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EPN Comments on EPA's White Paper "Endocrine Disruptor Screening Program (EDSP): Near-Term Strategies for Implementation"

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The Environmental Protection Network (EPN) harnesses the expertise of more than 600 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

I. Introduction

On October 27, 2023, EPA published a Notice in the Federal Register (88 FR 73841) (hereafter referred to as the "2023 FR Notice") that lays out a strategy for renewing the agency's work to implement the Endocrine Disruptor Screening Program (EDSP) mandated by the Federal Food, Drug, and Cosmetic Act (FFDCA). EPA's new proposed near-term plan is significantly different from the original EDSP. At least for the time being, EPA apparently is postponing the concept of a broad-based screening approach in favor of incorporating selected elements of the EDSP into pesticide registration and registration review for human health effects. Further, it focuses on conventional pesticide active ingredients. Other active ingredients, inert ingredients, and drinking water contaminants are not included. Effects on wildlife will not be routinely considered. The emphasis is on the statutory requirement to identify estrogen-active compounds with attention also to androgen. *In silico* and *in vitro* screening (New Assessment Methods or NAMs) will be used to set priorities and which can take the place of some Tier 1 assays for estrogen and androgen screening. Thyroid effects, as well as all other endocrine-mediated effects, will receive less attention until NAMs are developed for those effects.

The significant scaling back of the original EDSP is due to EPA's experience that chemical prioritization, the issuance of data call-ins (DCIs), and data review were overwhelming the resources available to carry out the program. Given the resource constraints for implementing the EDSP, EPN generally agrees with the steps presented in EPA's proposed strategy. Overall, they represent an appropriate prioritization of chemicals and agency resources. The strategy implicitly recognizes that EPA has legal duties to address its responsibilities beyond the EDSP program and that it must work with finite resources. The strategy also recognizes that some types of chemicals are more likely than others to affect endocrine systems adversely. Taking these realities into account, EPA's proposed strategy establishes priorities for what kinds of chemicals the agency will evaluate for potential endocrine effects in the near-term. The strategy also proposes to focus initially on assessing the potential for adverse outcomes in humans, rather than also trying to address non-target wildlife. Altogether, these seem like sensible choices.

Despite our general support for the near-term strategy, EPN does have some concerns about the proposal. EPN also feels there are several ways in which the proposed strategy could be modified to achieve even greater impact without devoting significantly more of EPA's limited resources to implementation of the EDSP.

II. Scope of the Near-Term Approach

The 2023 FR Notice contains a useful review of the statutory requirements imposed by section 408(p) of the FFDCA. EPA asserts that it already has completed three of the seven statutorily required actions — creation of an estrogen screening program, implementation of the screening program by August 1999, and reporting to Congress by August 2000[1]. The agency also states that, since inception of the EDSP, EPA has engaged in some ongoing work to address the remaining four actions required by section 408(p) — providing for the testing of all pesticide chemicals, identifying some chemicals for exemption from 408(p) requirements when appropriate, issuing test orders, and taking action to protect public health against substances with an endocrine-disrupting effect.[2]

In order to assess the proposed strategy, EPN thinks it useful to understand and be clear about which aspects of the EDSP will receive attention in the near-term, and which will receive lower or no priority. Therefore, EPN thinks it essential to compare the proposed strategy in terms of the scope with the approach EPA described when it first announced the EDSP (hereafter referred to as the 1998 FR Notice)[3]. As originally conceived, the EDSP had a very expansive scope. Initially, the EDSP effort planned to assess the potential of chemicals to affect three hormone systems: the estrogen (E), androgen (A), and thyroid (T) systems. EPA acknowledged that it might eventually consider other hormone systems. As required by section 408(p) of the FFDCA, EPA intended to address potential effects on all "pesticide chemicals." That term, defined in FFDCA section 201(q), includes both active ingredients and intentionally-added inert ingredients approved in registered pesticide products, as well as any pesticide ingredients not registered in the U.S., for which EPA has established tolerances or tolerance exemptions. Following the advice of its advisory committee, EPA developed and validated a two-tier screening and testing program designed to generate data that would address E, A, and T effects both in humans and in non-target wildlife species. Further, the agency also explained that it intended to use the registration review program mandated at the same time by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to assess pesticide active ingredients for their potential to disrupt the endocrine system and, if necessary, to take action to mitigate public health and environmental risks.

Finally, while the FFDCA imposed specific mandates on EPA regarding pesticide chemicals, the 1996 amendments adding section 1457 to the Safe Drinking Water Act (SDWA) also helped shape the EDSP. That provision states that "the Administrator may provide for testing under the screening program authorized by section 408(p) of the FFDCA in accordance with the provisions of section 408(p) of such Act, of any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance."[4]

A. Reaffirming the Long-Term Commitment to the Original Scope of the EDSP

The agency's 2023 FR Notice describes several ways in which the agency proposes to reorient its efforts on the EDSP. The new directions being proposed shift the focus to narrower aspects of the EDSP program than EPA originally described when it launched the EDSP. The 2023 FR Notice states that it "covers only

[1] See 88 Fed. Reg. 73843 - 44, Table 1 in section II. B of the 2023 FR Notice.
[2] *Id.*
[3] See the Notice announcing the "Endocrine Disruptor Screening Program," at 63 FR 42852 (August 11, 1998)
[4] 42 U.S.C. 300j-17.

the initial strategies that EPA is taking over the next several years to generate momentum toward its longer-term goal of timely addressing all its endocrine screening data needs."[5] In another location, the 2023 FR Notice repeats the agency's longer-term goal is "timely addressing all its endocrine data needs and decisions."[6] Further, the 2023 FR Notice states that EPA regards its proposed near-term strategy "as consistent with the policies in the 1998 FR Notice and thus [EPA] is not rescinding or modifying those policies."[7] These statements only imply that EPA still supports the vision for the EDSP program as described in its 1998 FR Notice.

While EPN feels that the overall EPA priorities for near-term EDSP work generally make sense, we recommend the agency find an early opportunity to make an express statement that EPA still stands behind the original scope of the EDSP effort. That statement should clarify that EPA remains committed to addressing the full range of chemicals and protected populations (both humans and non-target wildlife) described in the historical documents setting out the scope of the EDSP.

B. Broadening the Focus on Active Ingredients

The agency's 2023 FR Notice correctly notes that the law requires EPA to address "pesticide chemicals," a term that encompasses both pesticide active ingredients and intentionally added inert ingredients. EPA's notice announces that the agency will focus first on "conventional" active ingredients, including conventional active ingredients in currently registered pesticides, as well as any new conventional active ingredients that are proposed for registration under FIFRA. EPN suggests that this focus be broader.

EPN feels that a narrower focus on active ingredients is a wise way for EPA to obtain the greatest risk reduction "bang" for its scientific and regulatory "buck." Active ingredients are intentionally designed to have effects on pest species — in the words of FIFRA section 2(u): "destroying, repelling or mitigating any pest." Because there are great similarities in biological systems across species, it is possible, and even likely in most cases, that active ingredients would have effects on biological organisms that are not considered pests. In fact, data examined in the review of active and inert ingredients by the agency over the last fifty years amply demonstrate that, as a group, active ingredients are more toxic and more likely to cause adverse effects than are the chemicals used as intentionally added inert ingredients in pesticide products. (EPN notes that EPA has already acted to remove from pesticide products those intentionally added inert ingredients for which studies showed significant health hazards.)

Although the focus on both new and currently registered active ingredients seems sensible, EPN questions whether it is necessary or advisable to limit that focus to "conventional" active ingredients. Broadly speaking, EPA has organized its regulatory consideration of new and amended pesticide registrations into three large groups – "conventional" pesticides, "antimicrobial" pesticides, and "biopesticides." These groupings are based on either the products' pesticidal mode of action or the character of the target pests. The term "conventional pesticide" refers to any type of pesticide product other than an antimicrobial pesticide or biopesticide. The term encompasses many different types of pesticides, including agricultural use products, home use insecticides, and a variety of other product categories. "Conventional" is generally interpreted to apply to synthetic or man-made organic chemicals. "Biopesticides" have a "non-toxic mode of

[5] 42 U.S.C. 300j-17.
[6] 88 FR 73842, Section I. C. of the 2023 FR Notice
[7] *Id.*

action" and include genetically engineered "plant-incorporated protectants," as well as pheromone and similar agents. "Biopesticides" are more likely to be naturally-occurring substances rather than man-made compounds. "Antimicrobials," as the name implies, are designed to affect microbes, i.e., bacteria, viruses, and certain types of fungi.

Because of their inherent biological activity and often known toxicity, EPN recommends that EPA assess the endocrine disrupting potential of the active ingredients in antimicrobial pesticides using the same approaches as proposed for conventional active ingredients. EPA's reason for excluding antimicrobial active ingredients is, "Those ingredients span a wider range of uses and modes of action and can often present very different chemistries than conventional pesticides."[8] We find this rationale unpersuasive. EPN asserts that the universe of conventional active ingredients has as much or greater variation in both range of uses, modes of action, and chemistries as antimicrobial active ingredients. Unlike biopesticides, antimicrobial products can be as toxic as conventionals. In fact, at least one widely-used antimicrobial active ingredient, triclosan, is already known to be an endocrine disruptor. There are more, and EPA should seek to obtain screening data on antimicrobial active ingredients as it develops preliminary work plans in the course of its registration reviews of these chemicals.

EPN also recommends that the agency's near-term strategy for the EDSP include new inert ingredients. This could be easily integrated into the agency's existing framework for regulating the inert constituents of pesticide products. Currently, EPA requires a petition to establish a tolerance or an exemption from the requirement of a tolerance [FFDCA clearance] for every new inert ingredient that would be present in a food-use pesticide product. Such petitions must contain data that show the use of the new inert would be safe under the FFDCA. EPA should explain that, prospectively, petitions for new FFDCA clearances for inert ingredients must address the potential of the chemical to perturb the E, A, and T systems. Similarly, EPA should announce that all new, non-food use inerts must provide data adequate to assess the substance's potential to cause endocrine disruption. Moreover, because EPA receives only a small number of submissions seeking approval for new inerts each year, this would represent a very limited expansion of the overall effort. In fact, such new data requirements may discourage some submissions and actually reduce the demand on EPA's resources.

Finally, EPN notes that there are compounds that meet the definition of "pesticide chemical" and have so-called "import" tolerances or tolerance exemptions. Although these compounds are not present in pesticide products registered under FIFRA, they are covered by FFDCA section 408(p). EPA should decide when and how the agency will assess them and should inform the public of its position. EPN recommends that the agency require petitions for new import tolerances to address the chemical's potential to affect the E, A, and T systems. EPN recognizes that chemicals having existing import tolerances may not warrant the same priority as conventional active ingredients in registered products and the compounds discussed above.

C. Potential Endocrine Disruption in Non-Target Wildlife

The 2023 FR Notice indicates that EPA's near-term focus will be on protection of public health from risks of endocrine disruption. The 2023 FR Notice states that "Although the Agency will continue to address wildlife endocrine effects..., updates and activities relating to that work are on a longer-term timeline..."[9].

[8] 88 FR 73848, section III. B. of the 2023 FR Notice.
[9] 88 FR 73842, section I. C. of the 2023 FR Notice

There are sound policy and resource reasons for assigning a higher priority to protecting public health than protecting non-target wildlife. While EPN agrees generally with this priority, we think that EPA should address endocrine disruption risks to non-target wildlife when data point to such risk concerns. It was clear when EPA issued its 1998 FR Notice that the evidence of endocrine disruption was stronger in wildlife than in humans.

FFDCA section 408(p)(6) provides that EPA "shall, as appropriate, take actions under such statutory authority as is available . . . as is necessary to ensure the protection of public health." This language mandates protecting public health. FFDCA section 408(p)(1) gives EPA discretion to look beyond effects on humans to any "other endocrine effect as the Administrator may designate." Because the law makes protection of humans from endocrine disruption a mandatory duty, but protection against similar environmental impacts is discretionary, it is sensible to give greater attention to the potential of pesticides to harm humans. The 2023 FR Notice makes this priority operational by stating that EPA's Tier 2 testing will initially include only mammalian toxicity studies, but not the studies in fish, birds, and amphibians recommended by EPA's advisory committee. Reducing the number of studies required for Tier 2 testing will save resources both for the regulated community and also, importantly, for EPA. With smaller datasets to review for potential endocrine disruptors, EPA will have more resources to apply to determining whether and how to mitigate any risks revealed by the studies. EPN agrees that these are sound reasons to focus the near-term approach of the EDSP on protecting human health.

However, EPN recommends that the agency still plan to address risks to non-target wildlife posed by endocrine disruptors, at least in some situations, when risk mitigation can be achieved with efficient use of agency resources. The potential for risk to non-target wildlife species will always be on or near the front burner given EPA's responsibilities to make findings pursuant to the Endangered Species Act. Consequently, it would be wise for the agency to look for and address the potential for endocrine-disrupting chemicals to adversely affect listed species. EPN believes there is an efficient way to identify some endocrine-disrupting chemicals that have the potential to harm environmental receptors. EPA routinely conducts a search of the publicly-available scientific literature as part of its registration review process. The agency should ensure that the search is designed to capture studies (both peer-reviewed and gray literature) that contain useful information on the effects of pesticide chemicals on the hormone systems of various wildlife species. In fact, we already know that the public literature contains numerous articles that show adverse, endocrine-mediated effects in non-target wildlife. By incorporating broad search criteria into an existing search process, EPA could collect important information without significantly increasing the resources for its EDSP work.

It is not clear to EPN whether the Office of Pesticides Program (OPP) makes use of a formal vetted systematic review process for the identification and integration of peer-reviewed and gray literature and other non-registrant generated information into its risk assessments. We are aware that OPP participated with the Office of Research and Development (ORD), in the early stages of the development of the systematic review protocol that the Office of Pollution Prevention and Toxics (OPPT) is using in support of its preparation of risk evaluations in the TSCA Existing Chemicals Review program. However, we do not know if OPP has embraced its use in its risk assessment activities. If not, we highly recommend that it consider doing so in the EDSP. Although still in draft form, the *Systematic review protocol supporting TSCA risk evaluations for chemical substances, Version 1.0: A generic TSCA systematic review protocol with chemical-specific methodologies* provides a plethora of search terms relevant to the identification of information addressing environmental (and human health) hazards. The software tool SWIFT-Review is used to identify

peer-reviewed references that are predicted to be the most relevant for evaluating environmental and human health hazards, including endocrine effects. Search strings have been developed for the two hazard disciplines by ORD in collaboration with SWIFT-Review developer, Sciome, and search strategies for health hazards, including endocrine-mediated effects, are available online[10]. The search string used to identify potentially relevant peer-reviewed data references for evaluation of the environmental and human health hazard for the chemical of interest have been validated. OPPT's Data Gathering and Analysis Division is responsible for overseeing this element of the TSCA systematic review process. We recommend that OPP consult with them.

D. Addressing the EDSP Provision in SDWA

The 2023 FR Notice specifically states that the near-term strategy is designed "to help the Agency meet its obligations and commitments under the [FFDCA] . . . ."[11]. The FR Notice does not mention, much less address, the statutory provision of the SDWA that authorizes EPA to require testing of substances that may be present in drinking water. From its earliest days of crafting its policies for implementing the EDSP, the agency has always included some discussion of the SDWA component.

EPN believes there may well be ways in which the agency could use the procedures and authorities of both FFDCA and SDWA to address the goals of both statutes. Accordingly, EPN recommends that the near-term strategy should address how, if at all, EPA intends to implement the EDSP provision of SDWA. Priority Group 1 contains some conventional active ingredients that appear to meet the criteria in SDWA section 1457, for example, those for which national drinking water standards (MCLs) have been established, those for which non-regulatory Health Advisories have been derived, and those that have appeared on any of the six Contaminant Candidate Lists (CCLs). EPN recommends that, at the very least, EPA use information developed pursuant to the near-term strategy, when appropriate, in both its regulatory programs for pesticides and drinking water contaminants. EPN believes there may be even more opportunities for the EDSP program to address both FFDCA and SDWA program goals[12].

III. Prioritization and Timelines for Conventional Active Ingredients

The 2023 FR Notice contains a fairly detailed description of the plans for addressing the endocrine disrupting potential of the 459 currently registered, conventional pesticide active ingredients. The 2023 FR Notice discusses several groups of these 459 compounds:

1. 7 exempted chemicals;
2. 49 "List 1" chemicals;
3. 86 conventional active ingredients with "updated" reproductive toxicity data; and
4. the remaining 317 conventional active ingredients in registered pesticide products. As described below these 317 chemicals are further categorized into three priority subgroups, "Group 1," "Group 2," and "Group 3."

[10] https://www.sciome.com/swift-review/searchstrategies/
[11] 88 FR 73841
[12] See, e.g., EPN comment IV. E.

The 2023 FR Notice provides some additional information about the process and schedule for assessing the endocrine-disrupting potential of some of these six groups. The agency indicates that in Spring 2024 it will issue DCI notices requiring Tier 1 data on priority Group 1 chemicals. The 2023 FR Notice also says EPA will address the needs for additional screening and/or testing data on priority Group 3 chemicals as part of the routine registration review process of those active ingredients. The agency has also determined that it has adequate data to assess the endocrine-related human health risks of all but five of the 49 List 1 chemicals. The near-term strategy does not indicate, however, when EPA expects to move ahead on priority Group 2 chemicals or on the remaining five List 1 chemicals. Nor does the strategy explain when or in what new or existing process EPA will make determinations about the 86 chemicals for which it has reproductive toxicity studies using updated test methods[13].

The agency notes that it has already exempted seven (unidentified) active ingredients from further testing and evaluation using its authority in sec. 408(p)(4). EPN recognizes that there may be adequate data to conclude that a compound has no potential to cause endocrine disruption, and no further testing is needed. In such cases, an exemption is warranted. But, EPN recommends more transparency about the process of reaching such decisions.[14]

The 2023 FR Notice points out that there are 49 active ingredients that were identified as the first group of chemicals to be assessed using the Tier 1 battery data submitted following issuance of the 2009/2010 DCIs. They are referred to as "List 1" chemicals and are listed in the support document entitled "*Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions*." EPA has received and evaluated the Tier 1 data on these 49 chemicals and reached conclusions regarding the need for further testing in one or more Tier 2 studies, summarized in a document available through the docket[15]. EPA intends to complete the review of these 49 chemicals following the approach outlined in that document.

The agency proposes to take a different approach for another 86 active ingredients for which EPA already has either an extended one-generation reproductive toxicity study (EOGRT) or an updated two-generation reproductive toxicity study that was conducted after 1998, when the agency strengthened its guidance for such testing. For these 86 chemicals, the agency indicates it will use the available data to assess their potential to cause harm by disrupting human endocrine functions. EPN believes this would be appropriate for those four chemicals supported by an EOGRT study. However, EPN recommends that EPA should ensure it has adequate data on thyroid function to supplement the results of a study using EPA's updated 2-generation reproductive toxicity study methodology[16] if it has not already done so[17] before making an EDSP determination on the remaining 82 chemicals.

Apart from the three subgroups discussed above, there are 317 more conventional active ingredients that EPA plans to cover in the near-term. For them, EPA has laid out criteria that divide the 317 into three priority groups. Group 1 are those 30 chemicals that have shown positive results for potential E or A activity in ToxCast batteries of *in vitro* assays. The third group of 161 chemicals produced negative results for E and/or A in the ToxCast batteries. The second group contains 126 chemicals that have not been screened

[13] See, e.g., EPN comment IV. E.
[14] See EPN comment III. B.
[15] See 88 FR 73842 in section I. C. 3 of the Executive Summary of the 2023 FR Notice and Reference 3, "Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions."
[16] OPPTS 870.3800
[17] See EPN comment III. C.

in those ToxCast batteries. While EPN supports the use of the ToxCast results to set priorities for these 317 chemicals, EPN suggests the agency take other data into consideration in developing a more refined prioritization scheme[18].

A. Timeline for Addressing List 1 chemicals and the 86 Active Ingredients

A critical aspect of prioritization is to establish the sequence in which certain pieces of work will be performed. The 2023 FR Notice explains that EPA will treat the 142 active ingredients for which it has adequate screening and/or testing data differently from the remaining 317 active ingredients for which it needs more Tier 1 data. However, the 2023 FR Notice does not offer important details on when or how EPA will proceed. We are comfortable with the scientific approach to assessing the potential risk to humans of the List 1 chemicals. Using that process, the agency originally determined that five of the original 49 List 1 chemicals need additional follow-up work related to human health. Now they find that further testing is no longer needed. However, EPN thinks the strategy should clarify the timeline and process for completing the ecological (wildlife) assessment of those chemicals. Unlike chemicals assigned to priority Group 1 based on ToxCast results, List 1 chemicals have been evaluated more rigorously, with the full Tier 1 screening battery of 11 assays, and those studies have definitively shown whether the chemicals interact with the E, A, and/or T systems.

EPN also suggests that the near-term strategy spell out when EPA plans to examine the reproductive toxicity and other relevant studies available for the 86 chemicals. In composing a schedule for these 86 chemicals, the agency should consider whether there is a need for additional thyroid data[19]. EPA expects, absent an indication of significant toxicity in the available reproductive toxicity and other studies, the agency will perform EDSP assessments for these 86 chemicals no later than when it next conducts its Registration Review of the active ingredients. Further, if the agency decides additional data on thyroid function is needed, as EPN has recommended for all of the 86 chemicals currently lacking them, then we advise EPA to issue any necessary DCIs on a schedule that will align data submission with the plan for Registration Review of the 86 chemicals. However, one should be mindful of the possibility that the nature of all of the data may prompt the necessity to move a particular chemical up in the queue for consideration of the need for risk mitigation measures.

B. Exemption Determinations

FFDCA section 408(p)(4) authorizes the agency to issue an exemption for a "biological substance or other substance" "by order" if EPA "determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen." The agency staff have indicated that exemption requests typically are initiated inside the agency and are evaluated by a select team of EPA scientists who comprise the Endocrine Disruptor Screening Policy Committee (EDSPOC). Then the EDSPOC scientists produce a written explanation of any decisions to exempt a chemical from further testing and the memorandum is placed in the public docket for the chemical.

EPN recommends that the agency provide additional explanation of how – both the process and the criteria – the agency will determine whether to exempt a chemical from any further testing or evaluation of its

[18] See EPN comment III. C.
[19] *Id*.

potential to disrupt endocrine systems. The 2023 FR Notice invites the public to submit comments and other scientifically relevant information (OSRI) relating to priority Group 2 chemicals[20]. It also states that the agency plans to use some or all of such submissions to make determinations under FFDCA section 408(p)(4)[21].Thus the guidance would be particularly valuable in informing the public more fully about what types of data EPA would find useful in making exemption determinations.

With regard to process, EPN recommends that the agency take public comment on proposed exemption decisions; this could be done efficiently at the preliminary work plan stage of registration review. We do not recall this occuring with the seven aforementioned but unnamed chemicals. In addition, EPN recommends making final exemption orders public in a central location. Reviewing those orders, the public could then better determine how EPA generally makes its exemption determinations. Finally, EPN believes it would be advisable for EPA to issue and take public comment on general guidance for the exercise of authority under sec. 408(p)(4).

EPN has several recommendations concerning the criteria to guide exemption decisions. The agency's guidance, at a minimum, should clarify whether EPA will make exemption decisions based on a determination that a substance will not affect estrogen alone, or, as it did in issuing an exemption for citric acid, the agency will also consider the potential of the substance to affect A and T. This is unclear in the 2023 FR Notice. On one hand, the 2023 Notice states: "First, EPA will determine whether any of the active ingredients . . . are exempt from further testing under FFDCA section 408(p)(4) because the Agency has determined an active ingredient 'is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen.' <u>If so,</u> EPA will exempt the active ingredient and explain its decision"[22] (emphasis added). This language indicates that EPA will not consider potential effects on the A and T pathways. On the other hand, the 2023 FR Notice reports that the decision granting an exemption for citric acid was based on the conclusion that the compound did not affect E, A, or T systems. EPN endorses the latter, more expansive approach. Further, EPN recommends that the agency should issue exemptions based on criteria other than the availability of adequate testing for potential E, A, and T effects. The availability of data may justify a decision not to require further screening studies of potential E, A, or T effects, but it should not warrant an exemption from all requirements of section 408(p), including the possibility that EPA may issue future data requirements addressing endocrine endpoints other than E, A, and T. Instead, EPN believes that EPA should consider factors such as the mode of biological activity of a substance and whether a substance is naturally occurring and sufficiently ubiquitous as to produce significant exposure of both humans and non-target wildlife species.

C. <u>Thyroid Function Assessments for the 82 Chemicals Without an EOGRT Study</u>

The 2023 FR Notice states that there are 86 active ingredients for which updated reproductive toxicity studies are available. For four of these 86 chemicals, the agency has an EOGRT. For the other 82, EPA has an updated two-generation reproductive toxicity study that was conducted after 1998, when the agency strengthened its guidance for such testing. Because these studies directly evaluate a chemical's effects on a variety of endocrine-mediated effects, EPA proposes not to require the chemicals to be tested in Tier 1 assays. Rather, the agency will use the reproductive toxicity data directly in human health risk assessments.

[20] 88 FR 73852
[21] *Id.*
[22] 88 FR 73851

EPN does not fully support this approach. We agree that the results of EOGRT studies are adequate to support human health risk assessments for the effects of a chemical on the E, A, and T systems. We are aware, however, that the updated two-generation reproductive toxicity study does not include a requirement for measurements of thyroid-related endpoints (T4 and TSH). Thus, we think that the agency may lack information on these 82 chemicals' potential to adversely affect thyroid function. We understand that agency scientists think other routinely required studies may provide data adequate to assess T function. EPN therefore recommends that the agency explain what additional types of data it would typically deem adequate to assess effects on the thyroid system.

If, for any of the 82 chemicals, EPA concludes that neither the updated two-generation toxicity study alone nor additional studies provide adequate data to assess a chemical's effect on thyroid function, it would appear inefficient and inconsistent with the initial scope of the EDSP to proceed to risk assessment of those chemicals. (EPN would, of course, support risk assessment and risk mitigation for any chemical where existing study results point to significant risks.) Absent evident concerns, EPN instead recommends that the agency give high priority to obtaining thyroid data before going to risk assessment. Specifically, unless there are adequate data from other sources on thyroid function, EPN recommends that the agency require the Comparative Thyroid Assay (CTA) be conducted for those 82 chemicals not already possessing one. EPN believes that such an approach would enable EPA to eliminate the necessity of performing a second risk assessment to complete its EDSP review of the chemicals.

D. Refining the DCI Prioritization Scheme for Conventional Active Ingredients

EPA's prioritization of the 317 conventional active ingredients is based on the results of the short-term, high throughput assays comprising the E and A ToxCast batteries. Selected assays in ToxCast have been shown to be predictive of a chemical's ability to cause changes in the E or A systems. EPN agrees that using the ToxCast results to establish a hazard-based prioritization scheme is sound. Given the grounds for predicting that a chemical may disrupt the E or A or T pathways, it is responsible to gather more data to confirm the ability of the chemical to actually interact with the E or A (or T) system.

EPN is very supportive of the agency's plan to issue DCIs this Spring for Tier 1 studies to the registrants of the 30 active ingredients in priority Group 1. Further, EPN also believes that the agency should offer an opportunity for the public to nominate additional chemicals for inclusion in priority Group 1, based on information they may identify beyond the ToxCast E and A assay findings, particularly any that indicates the potential for a chemical to interact with the T system.

To the extent that preparing and obtaining clearance for so many DCIs becomes difficult — especially if EPA increases the number of DCIs in response to EPN's recommendations in comments III. A. and III. C. — EPN recommends that the agency establish a further priority within the group. Chemicals with positive E, A, and T results need Tier 1 testing more urgently than chemicals with red flags in one or two systems. Further, a chemical with flags for two endpoints should get higher priority than chemicals which are negative in all but one assay. To the extent that prioritization of staff work is needed, EPA could consider other, exposure-related criteria such as food vs. non-food use and volume of production.

IV. Process and Methods for EDSP Evaluation of Conventional Active Ingredients

The 2023 FR Notice describes what kinds of data EPA will use to make determinations about chemicals in the EDSP. EPN thinks that the agency's approach — to consider all available information in a weight-of-evidence approach — is fundamentally sound. The 2023 FR Notice also indicates that EPA will resume its EDSP efforts with priority Group 1, and the agency plans to issue DCIs for these chemicals this Spring. The timing of EDSP work on other chemicals is less clear because it appears to be tied to the schedule for EPA's consideration of the chemicals in Registration Review.

The approach to data requirements laid out in the FR Notice is generally consistent with earlier documents describing the kinds of studies EPA would use to assess the potential of chemicals to cause adverse effects on endocrine systems. The initial plan for the EDSP, laid out in 1998, called for a two-tier set of data requirements. The first, a "screening" tier, is a group of 11 studies, which would provide data to assess whether a chemical had the potential to interact with the E, A, or T systems. The second, a "testing" tier, included four or five studies that would yield data needed for quantitative risk assessment of adverse effects in humans and non-target species: either four studies, if the EOGRT was chosen to evaluate reproductive toxicity in mammalian species, or five studies, if the two-generation reproductive toxicity study was chosen as it would have to be accompanied by the comparative thyroid assay.

In January 2023, EPA issued a White Paper explaining that "two computational models that integrate bioactivity data from multiple *in vitro* assays, referred to as the ToxCast Pathway Models for estrogen and androgen receptors, . . . can serve as an alternative to four of the 11 assays" – (the two estrogen receptor binding assays, the androgen receptor binding assay and the uterotrophic assay)[23].

EPN agrees with the plan to merge EDSP evaluations with the Registration and Registration Review processes, to the extent feasible. The agency's and public's long history with these two regulatory processes will make the integration of EDSP evaluations more acceptable and efficient. As part of each process, EPN encourages the agency also to make and communicate determinations about whether a chemical is exempt from testing for potential endocrine-disrupting effects[24].

A. Public Comment Opportunity for the 49 List 1 Chemicals.

The 2023 FR Notice indicates that EPA plans to continue its assessment of the 49 "List 1" chemicals following the process outlined in its 2009 Federal Register Notice[25]. EPN recommends that EPA consider a new public comment opportunity to allow interested stakeholders to submit additional scientific information and analysis that would bear on the conclusions reached by the agency when EPA reviewed the results of Tier 1 screening of the List 1 chemicals. In the intervening 10-plus years, it is very likely there has been further research on some of the List 1 chemicals that would be pertinent to an assessment of the potential to disrupt the endocrine system. Alternatively, EPA could issue a Pesticide Registration (PR)

[23] 88 FR 73844; see also US EPA. Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP). December 12, 2022. https://www.regulations.gov/document/EPA-HQ-OPP-2021-0756-0002

[24] See also the comment in section III. B. regarding the need for greater transparency and for criteria to guide exemption decisions.

[25] See 74 FR 54422, October 21, 2009.

Notice or a FR Notice advising registrants that OSRI is considered reportable under FIFRA section 6(a)(2) and agency regulations at 40 CFR 159.195[26].

B. Requiring Registrants to Submit Potential Endocrine-Disrupting Information

The 2023 FR Notice states that "In this notice, EPA is requesting comments and the voluntary submittal of existing information on the [endocrine-disrupting] potential of the 30 priority Group 1 chemicals"[27] (emphasis added). EPN agrees that it would be useful to obtain any extant information about the endocrine-disrupting potential of chemicals in priority Group 1 and Group 2. Such information may change EPA's perception of the screening priority assigned to a particular chemical. This would be particularly useful for Group 2 chemicals that might be moved either to Group 1 or Group 3.

However, EPN suggests that the agency reframe the submission of certain types of existing information concerning the potential of a chemical to perturb endocrine systems as mandatory under FIFRA section 6(a)(2) and the implementing regulations at 40 CFR part 159. Specifically, 40 CFR 159.195(c) provides that: "The registrant shall submit . . . information, other than that described in Secs. 159.165 through 159.188, if the registrant has been informed by EPA that such additional information has the potential to raise questions about the continued registration of a product or about the appropriate terms and conditions of registration on a product." EPN regards the types of information that registrants might submit as ". . . information that has the potential to raise questions . . . about the appropriate terms and conditions of registration on a product." EPN thinks that whether and when additional data are needed to assess the endocrine disrupting potential of a chemical are "questions . . . about the appropriate terms and conditions of registration . . . ." All the agency would need to do is to issue a PR Notice identifying the specific additional types of information that it would find useful in determining the potential of a chemical to disrupt E, A, or T functions. (Pursuant to 40 CFR 159.158(a)(3), registrants ordinarily are not required to submit information found in certain types of publications. EPN, however, thinks that the authority in FIFRA section 6(a)(2), as implemented through 40 CFR 159.195(c), is broad enough so that EPA may require a registrant to submit designated types of publications in its possession.)

C. DCIs for Priority Group 1 Chemicals Should Address E, A, and T Effects

EPN found the 2023 FR Notice somewhat confusing with respect to the kinds of data that EPA will require in DCIs for priority Group 1 chemicals. In several places, the 2023 FR Notice states that EPA will address E, A, and T[28]. ("EPA will use the FIFRA registration and registration review processes to obtain data as needed to assess potential human estrogen, androgen, and thyroid effects.") However, in another passage EPA states it has created "a new framework for prioritizing estrogen and androgen data needs."[29]And, in describing its approach for the 30 priority Group 1 active ingredients, EPA writes: "EPA expects to accept Tier 2 data in response to the DCIs to assess [chemicals] for potential effects to the estrogen and androgen pathways. Thus, if EPA receives an acceptable two generation reproductive or EOGRT study, the study

[26] See EPN comment IV. B.
[27] 88 FR 73842; ES I. C.
[28] See, e.g., 88 FR 73845; Notice III. C.
[29] 88 FR 73842.

would fully satisfy the EDSP Tier 1 DCI for estrogen and androgen endpoints."[30] These passages seem to indicate that the agency may not receive data on potential thyroid effects.

The 2023 FR Notice devotes considerable attention to how the agency will assess the potential of chemicals to adversely affect the thyroid pathway[31]. From this, EPN understands the agency intends, as part of its near-term strategy, to require studies that will provide information on the potential of the chemicals to interact and/or adversely affect not only the E and A systems, but also the T system. EPN endorses this plan. EPN notes, however, this would mean that, in some cases, the recipient of a Group 1 DCI would need to supply additional data on thyroid effects, either from Tier 1 assays or from other sources[32]. Such an approach would be consistent with the original scope of the EDSP and would be the most efficient way to obtain and review the data needed to implement the program.

D. Pre-screening Priority Group 2 Chemicals with High-throughput Screening Batteries

As discussed earlier, EPN generally supports the agency's approach to determining the order in which it will evaluate chemicals for their potential to disrupt endocrine systems. One smart aspect of EPA's approach to establishing its priorities is the consideration of results from the agency's ToxCast research. The ToxCast program includes high-throughput assays that indicated whether a chemical had the potential to interact with E or A receptors. The 2023 FR notice proposes to give highest priority to further screening of conventional active ingredients that produced positive results in the E or A assays.

EPN suggests that EPA explore the possible use of high-throughput assays to generate additional data that might better inform its priorities. In our 2021 comments on the EDSP, EPN recommended that the agency use ToxCast to set priorities for further screening and testing[33]. That set of comments also noted that many pesticide chemicals have not been part of the ToxCast program, and therefore EPN strongly encouraged the agency to consider putting additional chemicals into the ToxCast program. EPN suggested several alternative regulatory approaches that EPA could use to generate the results. EPN still believes that further use of high-throughput assays could be useful in the overall EDSP program. There remains an urgency to developing a valid battery for T.

EPN recognizes that the situation in 2024 is different from the state-of-the-science in 2021. Some of the endocrine-related assays that at one time comprised the ToxCast batteries may no longer be commercially available. Others probably are. In addition, in the ensuing three years, researchers have developed new *in vitro* assays to characterize chemicals' biological activity. Given the large universe of pesticide chemicals and SDWA drinking water contaminants the agency must assess, getting better information to set priorities could be very valuable. Thus, we believe that EPA should determine what types of *in vitro* assays are currently commercially available, validated, and potentially useful for priority-setting, reinforcing the urgency for the development of the tool(s) for screening for T. If there appears to be such a reliable set of assays, EPN recommends that Priority Group 2 chemicals undergo evaluation with the new and upgraded batteries.

[30] 88 FR 73846.
[31] See 88 FR 848 - 49.
[32] See EPN comments III. C. and V. D.
[33] See https://www.environmentalprotectionnetwork.org/wp-content/uploads/2021/04/EPN-Letter-on-Endocrine-Disruptor-Screening-Program.pdf

(Again, we refer the agency to the regulatory options in our 2021 comments.) Chemicals could then be moved to Group 1 or Group 3, depending on the results.

E. SDWA Chemicals with Positive E or A ToxCast Screening Results

The presence of statutory provisions in both the FFDCA and SDWA relating to protection against risks posed by endocrine-disrupting chemicals has meant that the EDSP has been a cross-program effort since 1996. However, the 2023 FR Notice fails to mention the SDWA authority or to address how the agency is addressing the potential endocrine-disrupting effects of water contaminants to which substantial populations are exposed. EPN recommends that the Office of Water identify any chemicals that meet the criteria of SDWA section 1457 and that show positive results in the E or A batteries of the ToxCast program. Then EPA should issue DCIs for Tier 1 screening studies of those chemicals.

V. Additional EPN Comments

A. A Final Version of the Near-term Strategy is Needed

EPA staff have told EPN that the agency plans to revise its proposed near-term strategy in response to public comments received on the 2023 FR Notice, but the agency does not plan to issue a final version of its near-term strategy. EPN strongly recommends that EPA take the time to issue a public document explaining how it responded to public comment and describing what changes, if any, it will be making to its near-term strategy. There are several compelling reasons to do so.

EPN thinks that, for all its strengths, the 2023 FR Notice was not adequately clear on many important issues relating to the implementation of the EDSP. These comments, particularly those in section II identifying questions about the future scope of the program, reflect concerns that also are shared by other stakeholders. A final version of the near-term strategy would be useful for increasing the public's understanding of EPA's thinking about the important EDSP effort and in setting public expectations about the pace and scope of the program. Finally, capturing the agency's decisions about how it will move ahead to implement its statutory duties will be useful when a new administration takes responsibility for running EPA.

B. Clarifying the Relationship Between FFDCA 408(p) and FIFRA Registration Review Requirements

The 2023 FR Notice states that "the [FFDCA] statute does not specify when implementation [of the EDSP] ends nor steps for implementing the EDSP, and thus EPA views implementation as an ongoing activity . . .." However, EPA has said that it expects to implement the EDSP for currently registered, conventional active ingredients during the current 15-year Registration Review cycle. But, because of the agency's difficulties in moving ahead with the EDSP, EPA has not made determinations about the endocrine-disrupting potential of most chemicals being reassessed in the Registration Review process to date. Consequently, this is one reason that nearly all the regulatory documents issued by EPA in Registration Review are styled as "interim" decisions and contain a standard paragraph acknowledging that the EDSP assessment remains incomplete.

EPN agrees with the agency that FFDCA does not impose a timeline on the implementation of its obligation to issue test orders and to mitigate endocrine-mediated risks under the EDSP. In fact, these are

ongoing responsibilities. But the agency should address the question of whether FIFRA requires an EDSP assessment of pesticide active ingredients being evaluated as part of the current Registration Review cycle.

C. Developing New Criteria to Determine When a Chemical Should Be Taken "Out of Schedule"

EPN recognizes that there are strong reasons for EPA to adhere to the multi-step process that comprises a Registration Review. Knowing what scientific analyses, as well as when and what regulatory engagement will be needed, allows the agency to manage its resources with maximum efficiency. Thus, most of the time, it is prudent to concurrently examine all types of new studies submitted to support the Registration Review of a chemical. Likewise it is also sensible to try to address all types of risk issues at the same stage of the regulatory process.

However, EPN thinks that in some situations it may be advisable to depart from the existing Registration Review schedule and initiate an earlier and expedited risk assessment and risk management process. Although rare, it is possible a new study will indicate that a currently registered pesticide poses significant, albeit unanticipated, risks to human health or the environment. For example, this happened relatively recently with the active ingredient dacthal (DCPA). Because the near-term strategy envisions the submission of new Tier 1 and Tier 2 studies for some chemicals on a timeline independent of their place in the Registration Review schedule, it is possible such data might contain concerning results. Therefore we recommend that the agency develop criteria for when to advance the risk assessment and risk mitigation work of a chemical ahead of the schedule set for the chemical in Registration Review.

D. Amending the Human Health Data Requirements in 40 CFR 158.500

EPA's data requirements regulation for pesticide products, 40 CFR part 158, lays out the basic types of scientific information that an application for registration of a pesticide product. Subpart F, at 40 CFR 158.500, lists the types of toxicity data EPA requires for certain types of products, and also identifies a "guideline number" for the agency's guidance on how each type of study should be conducted in order to generate data that will satisfy the requirement. For "Reproduction and fertility effects," the regulation currently lists EPA Guideline 870.3800[34]. This guideline describes the two-generation reproductive toxicity study, not the EOGRT.

Because a study conducted using the methodology described in Guideline 870.3800 will not provide data on the effects of a chemical on the thyroid system, EPA should amend 40 CFR 158.500 to replace the reference to Guideline 870.3800 with a reference to a Guideline that describes the EOGRT[35]. This will save companies time and money and will reduce the workload for EPA, but garner more useful information. Alternatively, EPA could retain the existing guideline citation, but amend the guideline itself to add the thyroid component.

E. A Five-Year Near-Term Strategy Update

EPA apparently is committed to eventually implementing the full scope of the EDSP as described in the 1998 FR Notice. If so, and in order not to lose focus on that broader goal, EPN recommends that the

[34] See https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0156-0018

[35] See, e.g., the Organization for Economic Cooperation and Development's test guideline, TG443.

agency commit publicly to revisit all aspects of this near-term strategy, at a minimum, in five years. Undoubtedly, the agency's experience with its renewed efforts to implement the EDSP will have shown what works and what doesn't to identify and manage endocrine-mediated risks. In addition, further research by EPA and the broader scientific community will likely have generated new scientific methods and information that would offer ways to improve and/or expand upon the currently-proposed limited approach. This recommended reexamination of the agency's strategy should address priorities and timing for inclusion of existing food-use inerts, nonfood-use inerts, biopesticide active ingredients, and SDWA chemicals. This also should address endocrine-disrupting effects on non-target wildlife.

F. Expand the 2011 Weight of Evidence Guidance Document

Rigor, clarity and transparency are critical elements of a sound scientific assessment. Over the years, EPA has often been criticized for producing assessments lacking in these characteristics, as has much of the scientific enterprise. In the years since the EDSP was mandated in 1996, a number of tools based upon the principles of systematic review, as pioneered by the creators of the Cochrane Library, have become available. The use of these has been, and is being, shown to improve the quality and accessibility of complex science assessments. Two such internally-developed examples are the *ORD Staff Handbook for Developing IRIS Assessments* issued in 2022[36]. and OPPT's 2021 dra*ft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances*[37] Each has been peer reviewed by the National Academies of Sciences and by EPA-managed peer review panels (the Science Advisory Board for the ORD document and the Science Advisory Committee on Chemicals for OCSPP/OPPT). The two documents share and apply the same basic principles of systematic review, but also are tailored to be fit for the purpose for developing IRIS assessments and TSCA Risk Evaluations, respectively.

The TSCA systematic review protocol/framework provides a more useful model than the IRIS Handbook, as it addresses information categories covering a broader range of scientific disciplines, as well as how to handle data submitted in response to testing orders which are often claimed as Confidential Business Information (CBI) in addition to that available from the peer-reviewed and gray literature and other non-CBI sources (in OPP's case, the OSRI). But both ORD's and OPPT's protocols address the same major categories of effort: Literature searching and sorting; data extraction; data quality evaluation; assessment of bias; and evidence integration, using a weight of evidence (WOE) approach. The 2011 OPP WOE guidance[38] focuses primarily on this last step, but should be expanded to address the other areas as well.

G. Leveraging the REACH and EU Pesticides Authorization Programs to Improve EDSP Efforts

REACH stands for Registration, Evaluation, Authorization and Restriction of Chemicals. It became effective on June 1, 2007. REACH established a new legal framework to regulate the development and testing, production, commercialization, and use of chemicals. It has a very wide scope as it applies to all chemical substances that are manufactured or imported, placed on the market, or used within the European Union (EU). It is administered by the European Chemicals Agency (ECHA). Food-use pesticides, on the

[36] U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (2022). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-22/268, 2022.
[37] U.S. EPA, 2021. Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, Version 1.0: A generic TSCA systematic review protocol with chemical-specific methodologies. Office of Chemical Safety and Pollution Prevention, Washington, DC.
[38] https://www.regulations.gov/document/EPA-HQ-OPPT-2010-0877-0021

other hand, are regulated by the European Food Safety Authority (EFSA). Plant protection products are regulated by the EU member states and ECHA. Chemicals, food use pesticides, and plant protection products must all be tested and a dossier submitted for approval to the competent authority before the substance is permitted on the market.

REACH test data could be useful for the evaluation of pesticide inerts, biocides, and some non-food use pesticides. REACH testing requirements are based on the tonnage manufactured or imported into the EU. The data requirements fall into four groups: 1-10 tons, 10-100 tons, 100-1,000 tons, and over 1,000 tons. The vertebrate tests for each of the groups areas follows:

- 1-10 tons: acute oral toxicity
- 10-100 tons: skin and eye irritation (if necessary), *in vivo* genotoxicity (if triggered), acute inhalation toxicity, 28-day repeat-dose study, screening for reproductive/developmental toxicity, and short-term toxicity study in fish.
- 100-1,000 tons: Subchronic 90-day study, prenatal developmental toxicity in one species, extended one-generation study (if triggered), long-term study in fish.
- >1,000 tons: Chronic toxicity, developmental toxicity in a second species, EOGRT, carcinogenicity (if triggered).

The European Commission is updating the information requirements for the registration dossiers that companies have to provide for placing substances on the European market. This will ensure these dossiers have sufficient information to allow risk management of endocrine disruptors. Endocrine disruptors will have their own place as Substances of Very High Concern (SVHC). This replaces the situation where endocrine disruptors are of concern within other categories.

The EU's endocrine disruptor criteria[39] have been applied to new and pending dossiers for pesticides since November 2018. The criteria have also been applied to some maximum residue level determinations (MRLs, known as "tolerances" in the U.S.), and updates of 90 substances for ongoing MRL determination are published by EFSA.

Briefly, processes have been initiated or finalized for 95 active substances used in pesticides: 40 finalized; 26 on 'stop-clock', i.e., a period of up to 30 months to allow assessments to be completed; and 25 where 'stop-clock' has been resumed, while a few dossiers were withdrawn by the submitters. For the 40 dossiers where EFSA conclusions were finalized: 28 active substances were clearly identified as not being endocrine disruptors, six were identified as endocrine disruptors for human health, and three for non-target organisms (environment). There were a few others where no conclusion could be reached and additional data are needed. In one case for human health, a substance was banned for other reasons.

The European Commission has established the Endocrine Active Substances Information System[40], a freely-accessible web-based application, administered by the Joint Research Center of the European Commission.

[39] https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311
[40] https://echa.europa.eu/ed-assessment

EPA should look for ways to leverage the European Union's REACH program for endocrine disruption assessments. There are no food-use pesticides in the REACH database. However, inerts and drinking water contaminants are potentially covered. ECHA does not specifically require endocrine disruptor screening or testing. And, because REACH has production volume thresholds which dictate if and how much data must be submitted, many chemicals will be subjected to no or fewer testing requirements, including not having to submit reproductive toxicity studies.

ECHA cannot/does not share raw study data with EPA and other regulatory authorities or outside organizations because they are considered CBI, unless the submitter specifically releases them from that status. The REACH database consists of ECHA-generated summary reports of the studies submitted. These closely resemble OPP's Data Evaluation Records in the nature and level of detail and can be evaluated by EPA in the same manner as is done for the peer-reviewed and other literature in an OSRI submission.

These comments were developed by Penny Fenner-Crisp, William Jordan, and Gary Timm on behalf of EPN.