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Dr. Michal Ilana Freedhoff
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Mail code: 7101M
U. S. Environmental Protection Agency
1200 Pennsylvania Ave. N.W.
Washington, DC 20460

Re: The Endocrine Disruptor Screening Program

Dear Dr. Freedhoff:

The Environmental Protection Network (EPN) is an organization comprised of over 550 U.S. Environmental Protection Agency (EPA) alumni volunteering their time to protect the integrity of EPA, human health, and the environment. On behalf of EPNmembers, I am writing today to request that EPA consider reactivating the Endocrine Disruptor Screening Program (EDSP) and to suggest how EPA can fulfill its statutory obligation to screen pesticide chemicals for their potential to cause effects through interaction with the estrogen hormone system. We believe our suggestions are scientifically sound and capable of being implemented in a timely and less resource-intensive manner than the approach EPA used in the past.

EPA paused the EDSP in late 2015, after announcing the availability of some new screening technologies and completion of three Tier 2 test guidelines. The last actions EPA took were the release of their review of Tier 1 screening results on 52 pesticide chemicals and the release of estrogen receptor bioactivity data on 1,800 chemicals. Recognizing the slow pace and the significant staffing and other resources needed to implement the Tier 1 screening phase of the program, EPA determined that it needed to develop an alternative approach, but was unable to do so during the Trump administration. Now, however, with greater resources proposed in the President's request for FY22 discretionary funding, and an administration fully committed to addressing its statutory responsibilities, this could be the time to begin a more efficient process for screening chemicals for endocrine disrupting effects. We recognize that this would require additional resources, and we hope this information will be useful in your deliberations.

In 1996, Congress enacted the Food Quality Protection Act, (FQPA, P.L. 104-170), which requires EPA to "develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate." Because EPA has not yet required screening of all pesticide active ingredients (PAIs) and inert ingredients for estrogenic effects, EPA has only issued interim decisions in its registration review program. This and the potential for unaddressed health and environmental effects of endocrine disrupting chemicals

prompt us to send you this letter. Below, we will provide a brief history of the EDSP and our recommendations for efficiently screening chemicals for endocrine disrupting effects.

Early History of the EDSP

In the early 1990's, there arose a concern that chemicals present in the environment were acting like the natural hormone estrogen, leading to a variety of adverse effects seen in humans (e.g., precocious puberty in girls, cryptorchidism, testicular cancer, and decreased sperm counts in males, etc.) and fish and wildlife (e.g., intersex fish, shortened penises in alligators and river otters, changes in behavior in some birds, and decreased fertility). These concerns led Congress to include a provision in the 1996 FQPA requiring EPA to screen pesticide chemicals for their potential to act as estrogens. In the same year, the Safe Drinking Water Act (SDWA) Amendments (PL 104-182) authorized EPA "to use the estrogenic substances screening program created in the Food Quality Protection Act to provide for testing of substances that may be found in drinking water if the Administrator determines that a substantial population may be exposed to such substances." EPA responded to the mandate in the FQPA by forming the external stakeholder Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC).

EDSTAC recommended expanding the screening program to include additional endocrine hormone systems, specifically androgen, because it believed that some of the effects ascribed to estrogen were in fact anti-androgenic effects, and thyroid, because thyroid function also has profound effects on early development. EDSTAC also recommended that EPA expand the screening program to include fish and wildlife since some of the most convincing evidence of endocrine disruption had been observed in non-human species, and EPA's pesticide program has a mandate to protect the environment as well as human health. EDSTAC recommended a priority setting process and a two-tier screening and testing program. Tier 1 was designed to detect interactions of substances with the three endocrine systems. Tier 2 was designed to confirm the interactions, identify adverse effects, and provide quantitative data that could be used to assess the risks the chemical posed. Chemicals testing positive in Tier 1 would be tested in Tier 2. The assays comprising the two original tiers are listed below.

<u>Tier 1</u>

In Vitro Assays

- Estrogen Receptor Binding/Reporter Gene Assay
- Androgen Receptor Binding/Reporter Gene Assay
- Steroidogenesis Assay with minced testis

In Vivo Assays

- Rodent 3-day Uterotrophic Assay
- Rodent 20-day Pubertal Female with thyroid
- Rodent 5-7-day Hershberger Assay
- Frog Metamorphosis Assay
- Fish Gonadal Recrudescence Assay

In addition, EDSTAC recommended some alternative assays including the Placental Aromatase assay and the Pubertal Male with thyroid.

Tier 2

Two-Generation Mammalian Reproductive Toxicity Study
Avian Reproduction Test
Fish Life Cycle Test
Mysid Life Cycle Test
Amphibian Development and Reproduction Test

To meet the FQPA requirement that EPA use only validated test procedures, EPA developed guidelines for each test procedure and conducted a program to validate each in conjunction with the Organization for Economic Cooperation and Development.

Implementation of Screening

The First List
In October 2009, EPA issued a Data Call-In (DCI) notice under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) sec. 3(c)(2)(B) to obtain the Tier 1 screening data on 67 List 1 chemicals. List 1 was mainly composed of PAIs that were selected on the basis of the potential for, and anticipated magnitude of, exposure. Six chemicals were subsequently removed from the list because they no longer met the criteria for inclusion. Nine others dropped off the list after the DCI was issued because the manufacturers chose to cancel their registrations altogether.

Of the 52 chemicals evaluated, 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 already had enough information to conclude that they did not pose unacceptable risks to components of the three hormone systems. All 18 of the remaining chemicals showed potential interaction with the thyroid pathway, 17 with the androgen pathway, and 14 with the estrogen pathway. These chemicals were recommended for additional testing in the original Tier 2 testing battery, but no DCI was ever issued to require Tier 2 testing.

The Second List
EPA published a second list of chemicals for Tier 1 screening in 2014. This list included a large number of pesticide chemicals, two perfluorocarbon compounds (PFAS), and four pharmaceuticals (erythromycin, nitroglycerin, quinoline, and lindane (which was also a pesticide)). It also consisted of an array of other chemicals, including those used for industrial manufacturing processes, plasticizers, and in the production of pharmaceutical and personal care products (PCPs). Of 109 identified chemicals, 41 are PAIs and 68 are chemicals identified under the SDWA. No DCI or other action was taken to obtain screening data on these chemicals.

Development of Priority Setting Tools and Second-Generation Screens

EPA recognized that the original Tier 1 battery was resource-intensive and time-consuming and would require more than 100 years at the rate List 1 was screened to screen the estimated 10,000 plus chemicals and pesticides to which humans and the environment were exposed. In addition to the concerns that the

original Tier 1 battery was slow and costly, there were concerns from the animal welfare community about the numbers of animals that such an effort would entail. To make the screening more manageable, EPA's Office of Research & Development (ORD), working with the Office of Chemical Safety and Pollution Prevention (OCSPP), developed computational methods to prioritize chemicals for screening. These efforts were expanded through the Toxcast and Tox21 programs to include high-throughput *in vitro* screens (HTPS) that would become alternatives to some of the Tier 1 assays. Currently, 18 HTPS and the estrogen receptor (ER) pathway model can substitute for the ER *in vitro* binding assay, ER transcriptional activation assay, and the uterotrophic assay. Eleven HTPS and the androgen receptor (AR) pathway model can substitute for the AR i*n vitro* binding, AR transcriptional activation, and the Hershberger assays. In addition, a high-throughput version of the H295R assay has been developed that can replace the original H295R assay for steroidogenesis. HTPS for aromatase also exist. The FIFRA Scientific Advisory Panel has reviewed the ER- and AR- HTPS and their associated pathway models, as well as the HTPS aromatase and steroidogenesis assays, and has determined that the test methods are valid and provide a scientifically reliable basis for screening chemicals for their potential to interact with the estrogen and androgen receptors. This leaves the pubertal female, pubertal male, and fish short-term reproduction assays without full HTPS replacements. It should also be noted that the HTPS assays that would replace the thyroid component of the assays in the Tier 1 battery are still under development.

Proposed Path Forward

1. Decide on the assays to be used. Although FQPA only requires the screening of pesticide chemicals for effects on the estrogen system, we recommend implementing the use of the validated high-throughput screening batteries for ER and AR and the aromatase and steroidogenesis assays, since these individual assays and batteries have been validated and are reliable, inexpensive, and faster to complete than the original Tier 1 battery. This represents a departure from the 2014 EDSP Management Plan, which proposed the issuance of DCIs for Tier 1 screening in sync with registration review. The speed and low cost of the HTPS approach obviate the need for such a phased approach. EPA should add screening for thyroid effects when the work on developing a valid, reliable, inexpensive, and quick thyroid-effects screening battery is completed.

2. Establish the priority order in which substances will be screened. We recommend that EPA establish a priority-based approach for screening that addresses the types of chemicals to be evaluated, starting with four broad priority categories in the following order:
    - Pesticide active ingredients based on greater concern for active ingredients due to their biological activity and the Federal Food, Drug, and Cosmetic Act (FFDCA) sec. 408(p) mandate.
    - Intentionally added inert ingredients in pesticide products because FFDCA sec. 408(p) requires all "pesticide chemicals" to be assessed.
    - Substances meeting SDWA criteria because Congress explicitly gave EPA the authority to screen and test these substances.
    - Other industrial chemicals regulated under the Toxic Substances Control Act (TSCA). EDSTAC recommended the inclusion of TSCA chemicals, and some TSCA chemicals have already been identified as endocrine disruptors. Adding them would also be a demonstration

of EPA's commitment to diminish the use of whole animal toxicity testing, which TSCA addresses.

EPA may also find it useful to set priorities *within* these four categories if it is impractical to conduct screening for all chemicals in a group at the same time if, for example, laboratory capacity becomes a constraint.

3. Determine the most appropriate approach for obtaining the necessary initial screening data. We have identified three options for carrying this out.

Option 1: Require the regulated entities to conduct the screening. This is what EPN recommends, and it is consistent with Congressional policy as expressed in both FIFRA and TSCA, which places the burden for testing costs on the entities that benefit from the commercial use of the chemicals. There are two options for imposing data requirements on regulated entities:

- Data Call-In notices under FIFRA sec. 3(c)(2)(B) can be used for PAIs and intentionally added inert ingredients contained in currently US-registered pesticide products, some of which could also be SDWA or TSCA chemicals.
- Test Orders, Rules, or Negotiated Test Orders issued under TSCA sec. 4 can be used for TSCA chemicals and SDWA chemicals that are not pesticide chemicals.

There may be substances that meet the criteria in SDWA that may not be amenable to testing under FIFRA or TSCA, e.g., pharmaceuticals and legacy pesticide chemicals that remain in the environment but are not in any currently registered pesticide product. FFDCA also gives EPA authority to issue screening and testing requirements. Except for companies that manufacture food-use pesticides that are not registered in the US, it is unlikely that the FFDCA would succeed in getting entities to conduct studies if the entities cannot be reached under FIFRA. These substances may need to be tested under Option 3.

There will be significant administrative costs for both the agency and companies, if EPA imposes ER and AR data requirements on the regulated entities.

- EPA will need to obtain clearances under the Paperwork Reduction Act for any DCIs and actions taken under TSCA. EPA will need to issue DCIs, test orders, negotiate consent orders, or conduct rulemaking for any test rules.
- Companies will need to respond to DCIs, test orders, and test rules.
- EPA must allow companies to cite results from existing studies, including EPA's, results from Low-Throughput Tier 1 assays, results from Tier 2 assays, and Other Scientifically Relevant Information (OSRI).
- Processing company responses to DCIs and Test Rules, particularly reviewing responses that cite existing information, will impose significant burdens on EPA.
- Companies that produce the same chemical will probably elect to form testing consortia for their chemical. While this is a common cost-sharing mechanism, it also requires considerable resources to set up and administer. Additional complications arise when the test substances are intentionally added inert ingredients.

Option 2: If EPA imposes data requirements on regulated entities, a series of public-private

partnerships for generating required data could be an alternative approach to chemical-specific, private-entity consortia. Instead of individual, chemical-specific consortia, EPA could enter into agreement(s) with appropriate industry trade associations—e.g., CropLife America, American Chemistry Council, etc.—whereby the trade associations contribute funding to perform the testing on multiple chemicals, and together, the trade associations and EPA oversee the execution of the studies through a network of private contract labs. This option would increase the burden on EPA, but EPA's oversight of the conduct of the screeningassays and data analysis might ensure more consistent, better quality data.

Option 3: EPA could conduct the screening itself. Obviously, this is the most resource intensive for EPA and would probably be beyond EPA's budget and personnel resources if used widely, although the imposition of fees to cover the costs could be considered. (This might require legislation and/or rulemaking.) We regard this option as the least desirable choice.

4. Consider the need to develop and publish updated/revised criteria, as appropriate, for determining how EPA will interpret and use the results of the initial screening batteries of testing.
    - Develop and publish updated/revised criteria for determining whether a battery is "negative" or "positive."
    - Develop and publish updated/revised criteria for determining what type(s) of additional toxicity testing is required for substances that screen "positive" (see the next section).
    - For all substances, update EPA's endocrine disruptor database with the results of screening and testing.
    - For active ingredients that screen "negative" in the ER battery and/or AR battery and aromatase and steroidogenesis assays, also include that information in an updated Registration Review document and, where appropriate, remove the "interim" status from the regulatory determination.

Some Considerations for Tier 2

Undoubtedly, the HTPS screening assays and associated endocrine pathway models will identify some chemicals as having the potential to interact with the estrogen and androgen (and possibly thyroid) hormone systems, and EPA will need to determine how best to obtain the data sufficient to assess whether such effects pose risks of concern. While we do not propose a specific strategy for obtaining such data, we do offer some thoughts about what the agency may wish to consider in fashioning such a strategy. Our thoughts fall into three general categories: the adequacy of existing data, whether to investigate potential endocrine effects of pesticide chemicals and other substances only on humans or to include non-target wildlife, and how to manage the imposition of data requirements efficiently.

The Tier 2 battery of assays includes an enhanced two-generation rat reproductive toxicity study. The EPA/Organisation for Economic Co-operation and Development (OECD) test guideline for conducting the study [OECD TG 416] is quite similar to the current guideline for standard reproductive toxicity studies in rats [OPPTS 870.3800]. The Tier 2 version differs only by the inclusion in the post-mortem analysis of a small number of additional tissues and measurement of blood thyroid hormone levels. Thus, to the extent

that a chemical has already undergone testing using a protocol that follows the guideline for a standard reproductive toxicity study, it may be unnecessary to require it to be retested using the Tier 2 guideline for that study. This is a science policy issue that must be addressed.

Second, EPA should consider whether to pursue data for assessing risks to both humans and non-target wildlife. Some of the substances that show endocrine activity may have use patterns that involve limited or no environmental release and therefore would result in little, if any, exposure to non-target wildlife. Potential for exposure should factor into what tests are required in Tier 2. Requiring the fish life cycle, avian reproduction, mysid life cycle, and amphibian development and reproduction tests in such cases should not be a high priority. Further, as noted earlier, FFDCA section 408(p) only requires that EPA evaluate pesticide chemicals for their potential to affect humans, and gives the agency discretion to consider effects on non-target wildlife. However, EPA does have a broad obligation to protect non-human species as well as humans. So, EPA should consider how to weigh its mandatory and discretionary duties with respect to pesticide chemicals.

Lastly, EPA should consider how various approaches to obtaining required data would affect agency resources. As a practical matter, it would not be feasible for EPA to perform the testing needed to generate data usable for quantitative risk assessment on all substances that display activity in the screening batteries. The full Tier 2 battery is very expensive and time-consuming, and the total cost would far exceed EPA's budget. Thus, imposing the data requirements on the regulated industry is the better approach. EPA has express statutory authority by which it can require regulated entities to conduct the Tier 2 studies. The strongest tools are the Data Call-in authority in FIFRA sec. 3(c)(2)(B) and the test order/rule authority in TSCA sec. 4. Each provision applies only to particular entities and establishes specific procedural steps that EPA and the respondents must follow—procedures that impose a certain level of burden on both the respondents and the government. For EPA, these burdens include issuing DCIs and test order/rules, addressing waiver requests, tracking compliance, and more. The greater burdens on EPA, however, will come as agency scientists have to review the completed studies. The agency should consider whether devoting resources to the scientific review of data submitted in response to DCIs and test order/rules would complement or compete with other priority activities.

The Bottom Line

In summary, EPA should expeditiously initiate the initial round of screening for estrogenic, anti-estrogenic, androgenic, and anti-androgenic effects by issuing DCIs to registrants for PAIs and follow the above priority order for other chemicals.

Respectfully submitted,

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Executive Director
Environmental Protection Network

This letter was prepared by EPN members: Gary Timm (former Project Manager and Senior Technical

Advisor, Endocrine Disruptor Screening Program), Dr. Penny Fenner-Crisp (former Division Director, Deputy Office Director and Senior Science Advisor, Office of Pesticide Programs), and William Jordan (former Deputy Director for Programs, Office of Pesticide Programs). They are available for further conversation if desired by EPA officials.