February 26, 2024

Environmental Working Group comments to the Environmental Protection Agency Docket ID: EPA–HQ–OPP–2023–0474; Endocrine Disruptor Screening Program: Near-Term Strategies for Implementation

The Environmental Working Group, or EWG, a nonprofit research and policy organization headquartered in Washington, D.C., urges the Environmental Protection Agency to strengthen the implementation strategies for the Endocrine Disruptor Screening Program (EDSP), to better identify pesticides as endocrine disruptors. A more robust and effective EDSP is necessary in order to adequately protect public health.

Since the inception of the EDSP in 1998, the agency has largely failed to meet its commitments to protect the public from endocrine disrupting pesticides. Even for pesticides where data call-ins were issued nearly a decade ago, as was the case with the herbicide DCPA (also known as dacthal), the manufacturers took an extremely long time to provide the requested studies to the agency, the results of which ultimately indicated serious risks to public health.

In order to protect public health from the adverse health effects associated with exposure to pesticides that act as endocrine disruptors, EWG is urging the agency to consider the following suggestions in its strategies to implement and "rebuild" the EDSP in accordance with latest research on endocrine disruptors:

1. The EPA must acknowledge the evolution in understanding of endocrine disrupting mechanisms, and utilize this understanding in its assessments.
2. The EPA must use all data available to assess endocrine disrupting properties, especially that which is published in the peer-review literature.
3. The EPA can begin protecting public health by adding additional uncertainty factors for pesticides where indication of endocrine disruption exists even though data gaps remain.
4. The EPA must only use new approach methodologies, or NAMs, to prioritize pesticides for further research, not to deem a chemical free of endocrine disrupting effects.

The EPA must acknowledge the evolution in understanding of endocrine disrupting mechanisms, and utilize this understanding in its assessments.

The goal of the EDSP is to identify endocrine disrupting chemicals and regulate them appropriately to protect public health. Since the passage of the Food Quality Protection Act in 1996 our scientific understanding of endocrine disruption has evolved

significantly. The first science advisory panel in 1996 tasked with making recommendations to EPA on endocrine disruptor screening established estrogen, androgen, and thyroid systems as the focus of EDSP screening, yet specifically mentioned that the field of endocrine disruption is "rapidly developing" and emphasized the need for the program to incorporate these developments. Of course, estrogen, androgen and thyroid pathways remain key mechanisms by which endocrine disrupting chemicals exert toxic effects, but other frameworks such as the key characteristics of endocrine disruptors should be incorporated into screening efforts made by the agency. According to the study by La Merrill and co-authors (2020) the key characteristics of endocrine disruptors are:

1) interacts with or activates hormone receptors;
2) Antagonizes hormone receptors;
3) Alters hormone receptor expression;
4) Alters signal transduction in hormone-responsive cells;
5) Induces epigenetic modifications in hormone-producing or hormone-responsive cells;
6) Alters hormone synthesis;
7) Alters hormone transport across membranes;
8) Alters hormone distribution or circulating hormone levels;
9) Alters hormone metabolism or clearance; and,
10) Alters fate of hormone-producing or hormone-responsive cells.

Importantly, only three of these characteristics (1, 2 and 6) are evaluated in guideline studies specified in FIFRA or Tier 1 and Tier 2 testing in the EDSP. However, these characteristics as well as others have been investigated for a number of chemicals by academic laboratories, making the peer-reviewed literature a rich source of information on endocrine disrupting potential of pesticides. Therefore, the EPA's current implementation strategy is not a complete picture of endocrine disrupting mechanisms, and the Agency should seek information to fill these data gaps in the peer-reviewed literature.

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As one of its implementation strategies, EPA is currently proposing to use existing mammalian data to evaluate the *in vivo* endocrine disrupting effects of pesticides through the registrant submitted studies submitted to the agency that are stipulated under 40 Code of Federal Regulations (CFR) Part 158.

However, there are several deficiencies in these studies and the available data that limit the utility of this approach. These studies are often outdated and don't cover low dose exposures for which endocrine disrupting chemicals are known to exert effects. Foundational to the EDSP was EPA's ability to request specific toxicity data with the

knowledge of endocrine disruption mechanisms of action in mind, registrant studies were not designed with this purpose. As such, the agency describes the endpoints relevant to endocrine disruption that the updated two-generation reproductive toxicity study or extended one generation reproductive toxicity study (EOGRT) (Table 3).

The last time the Reproduction and Fertility guidelines were updated was 1998, and while several important endpoints were added to these guidelines, other important endpoints are notably missing, like histopathology and assessment of the mammary gland, evaluation of circulating hormone levels, assessment of the thyroid, and many other key characteristics of endocrine disruptors. While some of these deficiencies are accounted for in the EOGRT study, like circulating hormone levels and thyroid impacts, the mammary gland is still only assessed as an optional tissue, neither study investigates adipose tissue, and, shockingly, only three pesticides have an extended one generation study, and hundreds of pesticides do not have either study, meaning this proposed strategy will likely miss several potential EDCs. Additionally, a recent investigation found that EPA pesticide risk assessments often inappropriately dismissed adverse effects observed in the mammary gland from Part 158 toxicity studies.

To highlight how the current approach may inappropriately mischaracterize or incorrectly deprioritize pesticides for further data requests, we briefly discuss EPA's approach to "Group 3" chemicals. EPA has grouped 161 active ingredients into "Group 3 cases", those that do not have sufficient registrant toxicity data and are not positive in estrogen and androgen pathway models (ToxCast Scores), that EPA has identified as low priority for further data and assessment. The agency simultaneously acknowledges that these ToxCast pathway models only cover 4 of the 11 assays identified for EDC screening purposes. However, the peer-reviewed literature in the PubMed database identifies multiple research studies that have described endocrine disrupting effects for several of these pesticides, such as acetamiprid and clothianidin, which can activate the G protein-coupled estrogen receptor, and fludioxonil, which blocks the androgen receptor, and also exhibits estrogen receptor-dependent breast cancer cell proliferation. Other studies have shown acetamiprid can inhibit testosterone synthesis.

To address these data gaps, the agency must not solely rely on the ToxCast scores and registrant data, but use all data available, especially that which is published in the peer-reviewed literature to systematically review pesticide active ingredients for endocrine disrupting effects.

The agency can begin protecting public health by adding additional uncertainty factors where data gaps exist or indication of endocrine disruption exists.

The agency has identified "Group 1 cases" and those pesticides that lack updated animal reproductive toxicity data but were identified as "active" in estrogen and androgen pathway assays and is prioritizing these chemicals for data call ins to fully assess their endocrine disrupting potential. The agency acknowledges that these tests are quite long to perform, which could leave the public unprotected. It could take several years for these

data to be generated and EPA must act on group 1 chemicals immediately by applying additional uncertainty factors towards these chemicals. It is imperative that EPA avoid a similar situation as DCPA, where the public was left unprotected from this chemical while data was being generated that ultimately showed harmful effects at low doses of exposure and serious risks to health.

The EPA must only use new approach methodologies, or NAMs, to prioritize pesticides for further research, not to deem a chemical free of endocrine disrupting effects.

As described in the previous section, EPA is essentially claiming that Group 3 cases are low priority and likely not endocrine disruptors. This is a gross misinterpretation of how data generated from NAMs should and could be used. EPA routinely says that evidence of bioactivity in NAMs does not mean a chemical *is* an endocrine disruptor and will require further whole animal tests. Yet, EPA insinuates that the absence of bioactivity is enough to deem a chemical free of endocrine disrupting potential, despite evidence that validation studies on NAMs routinely indicate that they do not have 100 percent concordance with *in vivo* studies, and in some cases can miss chemicals that impact estrogen signaling pathways *in vivo*.

At the current state of research on new approach methodologies, these methods are not yet sufficiently robust to provide scientific certainty that this testing avoids both false positives and false negatives. Extensive validation would be necessary before the new approach methodologies testing can be considered as a benchmark approach to determine whether a pesticide *can act as* an endocrine disruptor. Given that this scientific field has not yet reached the level of reliability necessary for public health protection, EWG urges the EPA to refrain from using NAM test data to dismiss endocrine toxicity concerns for any substance, including pesticides.

In summary, strengthening the Endocrine Disruptor Screening Program is an essential step that the EPA must make to protect public health. Given the widespread exposures to endocrine disrupting pollutants from dietary sources and the environment, EWG urges the EPA to take a precautionary approach with respect to endocrine disrupting chemicals in general, and in particular for pesticides associated with endocrine disruption.

Sincerely,

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