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January ##, 2024

Office of Pesticide Programs
Environmental Protection Agency, (28221T)
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Re: Endocrine Disruptor Screening Program (EDSP); Near-Term Strategies for Implementation [EPA–HQ–OPP–2023–0474]

Dear Madam/Sir,

These comments are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

The Environmental Protection Agency's (EPA) proposal for modifying its approach to the implementation of the Endocrine Disruptor Screening Program (EDSP) is an abrogation of its responsibilities under the *Food Quality Protection Act/Federal Food, Drug, and Cosmetic Act* (FQPA/FFDCA) as well as the *Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA) and *Safe Drinking Water Act* (SDWA). Limiting the scope of EDSP to humans, certain pesticide active ingredients only, and limiting the types of data to assess endocrine disruption (ED) effects is counter to the Congressional intent and requirements in these statutes. It is also a reversal of the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) advice and the agency's original EDSP implementation policy and science decisions.[1,2]

A historical context is needed to understand the broader Congressional intent with directives in FQPA and the EDSTAC recommendations for implementing the required EDSP. Evidence that synthetic chemicals can mimic or otherwise interfere with natural hormones has

[1] Federal Register (1998a). Endocrine Disruptor Screening Program. 63:42852 (August 11, 1998).

[2] Federal Register (1998b). Endocrine Disruptor Screening Program: Statement of Policy; Notice 63:71542 (December 28, 1998).

existed for over half a century.[3,4,5,6,7] Although early attention was given to estrogen mimics, it soon became apparent that the homeostatic function of the endocrine system can be disrupted at many sites and hormone systems. Estrogen doesn't function in isolation and its influence is interdependent on an array of signaling and metabolic compounds and processes.

A seminal point in the history of endocrine disruption investigations was the signing in 1972 of the Great Lakes Water Quality Agreement between Canada and the United States due to existing concerns and visible impacts of pollution in the Great Lakes. The Agreement gave the Canada/U.S. International Joint Commission (IJC) the responsibility for cleanup and reporting to the U.S. Congress and Canadian Parliament on a biennial basis. This precipitated further investigations into human and wildlife health in and around the Great Lakes. The wildlife/human connection in vulnerability to endocrine anomalies was apparent with animals at the top of the Great Lakes food web suffering increasing losses, disturbing reports of behavioral and intelligence problems in the infants and children of otherwise healthy mothers who ate fish from the lakes were reported.[8,9,10] The IJC Science Advisory Board requested a report on the state of the environment of the entire Great Lakes ecosystem and that stimulated Theo Colborn, PhD to champion the emerging issue that would later be identified as "endocrine disruption."[11] In the report, adverse health effects observed in affected birds, fish, mammals, and reptiles in the Great Lakes included:

- Reproductive impairment or loss of fertility
- Eggshell thinning, a disturbance of endocrine-controlled calcium metabolism
- Metabolic changes that led to wasting and early death even before chicks hatched or fry could swim up
- Birth defects such as crossed bills and clubbed feet
- Abnormal thyroid and male and female sex glands in almost all animals examined
- Abnormal thyroid hormone production in all fish and birds studied

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[3] Bitman, J., Cecil, H.C., Harris, S.J., & Fries, G.F. (1968). Estrogenic activity of o, p-DDT in the mammalian uterus and avian oviduct. *Science*, *162*, 371–372.

[4] Bitman, J., & Cecile, H.C. (1970). Estrogenic activity of DDT analogs and polychlorinated biphenyls. . *Journal of Agricultural and Food Chemistry*, *18*, 1108–1112.

[5] Nelson, J.A., Struck, R.F., & James, R. (1978). Estrogenic activities of chlorinated hydrocarbons. . *Journal of Toxicology and Environmental Health*, *4*, 325–339.

[6] McLachlan, J.A. (Ed.). (1980). *Estrogens in the environment*. Amsterdam: Elvesier.

[7] Hertz, R. (1985). The estrogen problem. Retrospect and prospect. . In J.A. McLachlan (Ed.), *Estrogens in the environment. II. Influences on development*. (pp. 1–11). New York: Elsevier North Holland.

[8] Fein, G.G., Jacobson, J.L., Jacobson, S.W., Schwartz, P.M., & Dowler, J.K. (1984). Prenatal exposure to polychlorinated biphenyls: Effect on birth size and gestational age. *Journal of Pediatrics*, *105*, 315–320.

[9] Jacobson, J.L., & Jacobson, S.W. (1988). New methodologies for assessing the effects of prenatal toxic exposure on cognitive functioning in humans. In M.S. Evans (Ed.), *Toxic contaminants and ecosystem health: A great lake focus*. (pp. 373–388). New York: John Wiley & Sons.

[10] Daly, H.B. (1992). The evaluation of behavioral changes produced by consumption of environmentally contaminated fish. In R.L. Isaacson, & K.F. Jensen (Eds.), *The vulnerable brain and environmental risks, vol. 1: Malnutrition and hazard assessment*. (pp. 151–171). Baltimore: University of Maryland.

[11] Colborn, T. (1988). Great Lakes Toxics Working Paper. Government of Canada, Department of the Environment [Contract Number KE 144–7-6336; 103 pp.].

- Behavioral changes in birds, such as lack of parenting, nest inattentiveness, males forming fraternities rather than establishing territories and attempting to mate, and female/female pairing
- Immune suppression, evidenced by increased rates of internal and external parasitism
- Transgenerational exposure, where the maternal animals were passing the persistent organochlorine chemicals in their bodies to their offspring before they were born, through their blood in utero in mammals, or with fish and birds through the liver to their eggs before they were laid.

Subsequently, the Conservation Foundation in Washington, DC, and the Institute for Research on Public Policy, Ottawa, Ontario, released a book, *Great Lakes, Great Legacy?*, that called for urgent action by federal, state, provincial, and local governments in both Canada and the United States.[12]

A group of diverse wildlife and human health experts later met at the Wingspread Center in Racine, Wisconsin, for a conference titled, "Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection." The findings by wildlife biologists in birds, fish, and mammals exposed to organochlorine contaminants in the Great Lakes were similar to pathologies in organs and offspring noted in humans exposed to an estrogenic pharmaceutical diethylstilbestrol (DES).[13] DES was widely prescribed from the 1950s to 1970s for the purposes of preventing miscarriages and also to be used more broadly to enhance growth of poultry and cattle. However, it was not until the early 1970s that young women born to mothers who had taken DES reached puberty and had begun to show an abnormally high incidence of adenocarcinoma of the vagina that the long-term and transgenerational consequences of the xenoestrogen became known and documented.[14] By the end of the meeting in Racine, WI, the term "endocrine disruption" was officially coined to collectively describe the adverse perturbations to hormonally regulated processes and a consensus statement was crafted by participants that "man-made chemicals that have been released into the environment have the potential to disrupt endocrine systems of animals including humans".[11]

[12] Colborn, T., Davidson, A., Green, S.N., Hodge, R.A., Jackson, C.I., & Liroff, R.A. (1990). *Great lakes, great legacy?* Washington, DC/Ottawa, Ontario: The Conservation Foundation/The Institute for Research on Public Policy, 301.

[13] Colborn, T., Clement, C. (eds.) (1992). Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing Co., Inc. (Mehlman MA, ed. Advances in Modern Environmental Toxicology, vol. 21). 403 pp.

[14] Herbst, A., Ulfelder, H., & Paskanzer, D.C. (1971). Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *New England Journal of Medicine*, *284*, 878–881.

Endocrine disruption as a phenomenon has been critically reviewed by several authors.[15,16,17,18] A common thread weaving across these reviews is the notion that chemicals that may disrupt the endocrine systems of humans and wildlife may be pervasive in contaminating their habitats. A pandemic of alleged endocrine-related disorders from attention deficit and hyperactivity disorder (ADHD), autism, diabetes, obesity, childhood cancers, testicular cancer in young men, infertility, male dysgenesis syndrome, hypospadias, low sperm count, loss of semen volume and sperm quality, and increased risk of testicular and prostate cancer had been reported and alleged to be due to endocrine-disrupting chemicals (EDCs). All these disorders have been increasing in incidence and can allegedly be traced back to some purported prenatal exposure to EDCs.[19,20,21,22]

Public awareness of these concerns increased in the 1990s largely through the efforts of Dr. Theo Colborn and the World Wildlife Fund.[23,24,25] This increased public awareness led to a number of international activities and need for congressional intervention. Internationally, at the request of member countries and the international industry, the Organization of Economic Cooperation and Development (OECD) initiated in 1996 the Special Activity on Endocrine Disrupters Testing and Assessment with the objective of providing a set of internationally recognized and harmonized test guidelines and testing and assessment strategies for regulatory application. The European Commission also commenced actions to regulate endocrine-disrupting substances in 1996. The Community Strategy for Endocrine Disrupters (COM(1999)706) was adopted in 1999, and this was later revised in 2004 (SEC(2004)1372) and in 2007 (SEC(2007)1635). In this strategy, short-term action (establishment of a list of priority substances for further evaluation), mid-term action (test method development and research implementation), and long-term action (consideration of methodologies for risk assessment and

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[15] Crisp, T.M., Clegg, E.D., Cooper, R.L., Wood, W.P., Anderson, D.G., Baitke, K.P., Hoffman, J.L., Morrow, M.S., Rodier, D.J., Schaeffer, J.E., Touart, L.W., Zeeman, M.G., & Patel, Y.M. (1998). *Environmental Health Perspectives*, *106*, 11–56.

[16] NRC [National Research Council]. (1999). *Hormonally active agents in the environment*. Washington, DC: National Academy Press.

[17] Damstra, T., Barlow, S., Bergman, A., Kavlkock, R., & Van der Kraak, G. (2002). *Global assessment of the state-of-the-science of endocrine disruptors*. Geneva, Switzerland: World Health Organization.

[18] Ottinger, M.A., & vom Saal, F.S. (2002). Impact of environmental endocrine disruptors on sexual differentiation in birds and mammals. In D.W. Pfaff, A.P. Arnold, A.M. Etgen, & S.E. Fahrbach (Eds.), *Hormones, brain and behavior*. (vol. 4) (pp. 325–383). New York: Elsevier Science and Technology Books.

[19] Charbonneau, J.P., & Koger, S.M. (2008). Plastics, pesticides and PBDEs: Endocrine disruption and developmental disabilities. *Journal of Developmental and Physical Disabilities*, *20*, 115–128.

[20] Cottrell, E.C., & Ozanne, S.E. (2007). Developmental programming of energy balance and the metabolic syndrome. *The Proceedings of the Nutrition Society*, *66*, 198–206.

[21] Newbold, R.R., Padilla-Banks, E., Jefferson, W.N., & Heindel, J.J. (2008). Effects of endocrine disruptors on obesity. *International Journal of Andrology*, *31*, 201–207.

[22] Sharpe, R.M., & Skakkeback, N.E. (2008). Testicular dysgenesis syndrome: Mechanistic insights and potential downstream effects. *Fertil Steril*, *89*(Suppl.), e33–e38.

[23] Colborn, T. (1988). Great Lakes Toxics Working Paper. Government of Canada, Department of the Environment [Contract Number KE 144–7-6336; 103 pp.].

[24] Colborn, T., vom Saal, F.S., & Soto, A.M. (1993). Developmental effects of endocrine-disrupting chemicals in wildlife and humans. . *Environmental Health Perspectives*, *101*, 378–384.

[25] Colborn, T., Dumanoski, D., & Meyers, J.P. (1996). *Our stolen future: Are we threatening our fertility, intelligence, and survival? A scientific detective story*. New York: Plume/Penguin Books.

risk management) have been described for eventual implementation. Also, in European Union's REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) on June 1, 2007, substances "having endocrine disrupting properties" that are also identified from scientific evidence as causing probable serious effects to humans and/or wildlife were mentioned as a condition to be authorized as a Substances of Very High Concern and regulated accordingly.

Japan similarly responded to emerging concerns with a strategic plan referred to as "SPEED'98" (Strategic Programs on Environmental Endocrine Disruptors), later published in May 1998 (http://www.env.go.jp/en/chemi/ed/speed98/sp98.html). Its specific activities to better address EDCs were (1) promotion of field investigations into the state of environmental pollution and effects on fish and wildlife; (2) promotion of research and method development; (3) promotion of environmental risk assessment, environmental risk management, and information sharing; and (4) efforts to strengthen international networks. Also, the Ministry of Environment has hosted the annual International Symposium on Endocrine Disruptors since 1998. In addition, bilateral joint research projects were pursued with the UK, the Republic of Korea, and the United States. Japan's efforts have been continued through ExTEND 2005, 2010, 2016, and 2022 (Extended Tasks on Endocrine Disruption).

In the United States, in response to the lobbying and heightened public awareness, two laws were passed by Congress in 1996, the FQPA that amends FIFRA and the FFDCA and amendments to the SDWA. EPA was directed to test all pesticide ingredients (active and inert) and drinking water contaminants, to which a substantial population may be exposed, to determine whether they have estrogenic or other endocrine activity. Under the amended FFDCA, EPA was explicitly directed to develop an endocrine screening program that uses appropriate validated test systems and other scientifically relevant information to determine whether certain substances may have an effect on humans that is similar to effects produced by a naturally occurring estrogen or such other endocrine effects as the Administrator may designate (21 U.S.C. 346a(p)). While the language may seem prescriptive, this statutory language provides significant latitude for how EPA would develop endocrine-specific test methods to implement the EDSP and allow for inclusion of other hormone systems and vertebrates beyond humans--recognizing that EPA is the "Environmental Protection Agency" and not the "Human Protection Agency". FIFRA, which FQPA amends, requires the agency to use appropriate evidence to assess risk to both human health and the environment and determine that prospective pesticides will not pose unreasonable risk to either.

In 1998, after external expert consultations and scientific peer reviews, EPA established the EDSP as a two-tiered screening and testing program to implement the statutory requirements of FFDCA section 408(p) (21 U.S.C. 346a) by considering endocrine bioactivity differently from endocrine adversity.[26,27] Under Tier 1 EDSP testing, a battery of screening-level assays is employed to identify substances that have the potential to interact with the estrogen,

[26] Federal Register (1998a). Endocrine Disruptor Screening Program. 63:42852 (August 11, 1998).

[27] Federal Register (1998b). Endocrine Disruptor Screening Program: Statement of Policy; Notice 63:71542 (December 28, 1998).

androgen, and thyroid hormonal systems that are themselves interconnected. The determination of endocrine biological activity is to be made based on a weight of evidence (WOE) approach, taking into account data from the full battery of Tier 1 screening-level assays and other available scientific information that will inform the decision of whether additional Tier 2 testing is warranted. The indication that a substance may potentially interact with a hormone system, however, is insufficient to establish that the chemical will cause adverse effects on human or ecological populations.

Tier 2 test methods include longer term, more definitive studies that are designed to identify any biologically adverse endocrine-related effects caused by exposure to the substance; these Tier 2 test methods also serve to establish a quantitative relationship between the dose and the hormonal adverse effect. Recognizing that, within a full chemical risk assessment, the endocrine endpoint is one of many different health endpoints, the most sensitive, lower dose endpoint, whether it be endocrine related or not, will serve as the regulatory point of departure (POD) that is protective of all subsequent health/ecological effects manifested at higher doses.

The EDSP Tier 1 battery was designed to work as a whole with all of the screening assays. The basis for selecting an assay to include in the battery involved two principal aspects: (1) the capacity of an assay to detect estrogen-, androgen-, and/or thyroid-mediated effects by various modes of action including receptor binding (agonist and antagonist) and transcriptional activation, steroidogenesis, and hypothalamic-pituitary-gonadal (HPG) or hypothalamic-pituitary-thyroid (HPT) feedback, and (2) the degree that in vitro and in vivo assays complemented one another in the battery as summarized. The rat pubertal assays were deemed insufficient alone to fully assess potential estrogen, androgen, or thyroid disrupting activity. In addition, the amphibian in vivo assay was selected for the screening battery based on its cross taxa relevance and capacity to detect certain direct and indirect effects on thyroid function (HPT regulation and feedback) not detectable by the other Tier 1 battery assays. Thus, the robustness of the proposed battery is based on the strengths of each assay and their complementary nature within the battery to detect the broad effects on the E, A, and T and other interrelated hormonal systems.

New alternative methods (NAMS) developed to help speed up the EDSP screening effort such as the ER and AR pathway models may suffice as alternatives to the Tier 1 in vitro ER and AR assays and the non-intact in vivo ER assay (uterotrophic assay), however their use may be limited to only priority setting. These NAMs were developed out of the ToxCast[28] and Tox21[29] EPA programs. ToxCast/Tox21 data are available for assessing the ER pathway model and AR pathway model utility in comparison to the EDSP Tier 1 battery of assays completed for the initial set of chemical pritoritized for testing (EDSP List 1). Of the 52 EDSP List 1 chemicals, 49 of

[28] Dix, DJ; Houck, KA; Martin, MT; Richard, AM; Setzer, RW; Kavlock, RJ. (2007). The ToxCast program for prioritizing toxicity testing of environmental chemicals. Toxicol Sci 95: 5-12.

[29]Thomas, RS; Paules, RS; Simeonov, A; Fitzpatrick, SC; Crofton, KM; Casey, WM; Mendrick, DL. (2018). The US Federal Tox21 Program: A strategic and operational plan for continued leadership. ALTEX 35: 163-168. http://dx.doi.org/10.14573/altex.1803011

these have ER pathway model data and 39 of the 52 chemicals have AR pathway model data. All List 1 chemicals with ER or AR pathway data were determined to show no activity in the ER pathway model and only 8 were positive in the AR pathway model. The 52 List 1 chemicals were selected based on human exposure metrics, and although all were negative in the ER pathway model assays and 31 of 39 chemicals were negative in the AR pathway model assays, nevertheless, the majority of the List 1 chemicals (32 of 52) showed interaction with one or more of the estrogen, androgen, and thyroid pathways based on the EDSP Tier 1 intact animal assays (rat, fish, and frog). Of note, the majority of the List 1 chemicals demonstrating endocrine activity in the intact animal assays were active in all 3 pathways, demonstrating the interconnected aspects of an intact endocrine system. Given that the EDSP List 1 screening findings with the ER and AR pathway models had limited ability to detect endocrine disrupting activity as revealed in the Tier 1 in vivo assays, the pathway models should not substitute for the intact Tier 1 animal assays in screening. Further, since the List 1 chemicals were selected based on being the most prone for human exposure, it may be argued that priority setting based on exposure metrics and other scientifically relevant information (OSRI) would be more appropriate for prioritizing those chemicals most important to screen for their endocrine disrupting risks. In vitro assays are very good for evaluating well understood mechanisms (e.g., receptor binding), but in vivo assays with intact HPG/HPT axes are needed for efficiently screening complex and integrated disrupting processes plausibly caused by a substance interfering with hormone synthesis, transport, metabolism, excretion, receptor-mediated action or other non-receptor mediated endocrine pathway.[30]

While defining endocrine perturbations may seem simple, federal agencies have continued to grapple with the fundamental definition of whether EDCs should include adaptive or enduring outcomes. In many cases, adaptive effects are defined as those that are temporary or effects that reflect the system's ability to compensate and overcome adverse effects from perturbation by homeostatic mechanisms, while enduring effects are those effects that are irreversible and permanent and have long-term impacts on the function of the organ or organism. A single perturbation or disruption of an endocrine pathway may have multiple effects, as the endocrine toxicity is an interconnected biological response. As a consequence, endocrine disruptors can interfere with the synthesis, and/or action, and/or transport, and/or metabolism of estrogens, androgens, thyroid hormones, as well as other pathways, including glucocorticoids, vitamin D, prolactin, insulin, vitamin A, and others. EDCs can interfere with the normal functioning of the hormonal system at multiple points to affect complex cellular processes such as growth and metabolism in various ways. For example, estrogen exerts its effect by acting on at least two major receptor types, but other kinds of receptors mediate estrogen action as well. The actions of a hormone in one cell type are almost always different from those in another cell type. Hormone receptors must interact with a variety of "helper" proteins called "coregulators" in order to exert their effects; different combinations of

[30] Manibusan, M.K. and Touart, L.W. (2017) A comprehensive review of regulatory test methods for endocrine adverse health effects. *Critical reviews in toxicology*, *47*(6), pp.440-488.

coregulators exist in different tissues of the body. Some chemicals have been shown to change the way the hormone receptor can interact with the coregulators, leading to complex effects on development and physiology, which is why general toxicity studies are able to detect effects that are systemic and broadly encompassing of multiple organ toxicities.[31] Thus the mandate in FQPA "…to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen" is to an extent fanciful since estrogens and/or estrogen disruptors affect a myriad of reproductive health functions and non-reproductive processes in skeletal, cardiovascular, and nervous systems in humans and wildlife. Hence the caveat "or such other effects as [EPA] may designate" was added by Congress to the statute. Moreover, mechanisms by which EDCs exert their pathophysiological effects have not yet been fully elucidated in human or wildlife studies.[32]

Endocrine pathways are largely conserved across species and, thus, are not species- or taxa- specific. For example, the EDSP Tier 1 includes screening-level assays in the amphibian system to capture thyroid-specific changes due to exposure to EDCs. The generalized vertebrate HPT axis, including the liver and peripheral tissues and the thyroid follicular cell, can be affected at several sites, including inhibition of iodide uptake at the sodium-iodide symporter (NIS); inhibition of the iodinating activity of thyroid peroxidase (TPO); increased elimination via upregulation of deiodination and conjugation reactions; competitive displacement of TH from carrier proteins in the blood, such as transthyretin; and altered local deiodination at the tissue level.

It is well known that thyroid endocrinology in particular is well conserved across vertebrate taxa. This includes aspects of thyroid hormone synthesis, metabolism, and mechanisms of action. Thyroid hormones are derived from the thyroid gland through regulation of the HPT axis, which is controlled through a complex mechanism of positive and negative feedback regulation. Activation of the HPT is initiated with the synthesis of the tripeptide thyrotropin-releasing hormone (TRH). TRH is produced throughout the hypothalamus; however, neurons located within the paraventricular nucleus of the hypothalamus are the primary site of TRH production. Multiple pathways contribute to the synthesis of thyroid-releasing hormone, including thyroid hormone signaling through feedback mechanisms; leptin and melanocortin signaling; body temperature regulation; and cardiovascular physiology. Each pathway directly targets thyroid-releasing hormone neurons, which integrate multiple inputs and provide a mechanism to establish set points for thyroid-releasing hormone production and the thyroid axis at appropriate levels, dependent upon physiological demands. Based on the similarities of endocrine pathways across vertebrate species, it is well understood that the ecological assays (the frog assay in particular) are often more sensitive and equally relevant to mammalian assays

[31] EEA [European Environment Agency] (2012). The Impacts of Endocrine Disrupters on Wildlife, People and Their Environments—The Weybridge+15 (1996–2011) Report. EEA Technical Report 2/2012, 112 pp.

[32] Sharma, A., Mollier, J., Brocklesby, R.W., Caves, C., Jayasena, C.N. and Minhas, S. (2020). Endocrine-disrupting chemicals and male reproductive health. *Reproductive medicine and biology*, *19*(3), pp.243-253.

in informing risk assessors of whether a chemical has the ability to perturb and cause adverse endocrine outcomes in the human population and vice versa.

FQPA essentially amends FIFRA to ensure potential endocrine disrupting effects are considered in agency risk assessments to fulfill the FIFRA mandate that a pesticide registration will not cause unreasonable adverse effects. This applies to humans and wildlife and to all pesticide chemicals as defined in FIFRA including "all active and pesticide inert ingredients of such pesticide" (21 U.S.C. 231(q)(1)). SDWA adds drinking water contaminants as well.

In summary, the agency cannot limit EDSP to only humans and conventional pesticide active ingredients without violating the statutory requirements enumerated in FIFRA, FQPA, and SDWA. The agency should make use of all available scientifically relevant endocrine disruption research findings and also be wary of deviating from established international efforts for screening/testing endocrine disruptors that incorporate human and wildlife relevant studies. Recognizing that mammalian data inform potential endocrine disruption in other vertebrate taxa (avian, amphibian, fish) and vice versa, the agency should not decouple the mammalian from other vertebrate assays in EDSP screening. There are more than 50 different ecological and mammalian assays included in the OECD Conceptual Framework for screening/testing endocrine disrupting effects, and there are additional assays being developed in other parts of the world for submission to OECD for consideration as well. So, the agency should not limit the range or types of data to be used as FQPA prescribes "using appropriate validated test systems and other scientifically relevant information". It is appropriate that the agency allow existing EDSP Tier 2 equivalent post-98 rat two-generation or an Extended One-Generation Reproductive Toxicity (EOGRT) study data to satisfy EDSP considerations for human risk assessments, but such Tier 2 equivalent data for wildlife species are largely absent. Therefore, the full breadth of EDSP Tier 1 battery assays is generally needed to justify requiring the longer term, animal intense and taxa specific Tier 2 eco tests. It should also be understood that under FIFRA there is an inherent presumption of risk, a pesticide is presumed to pose an unreasonable risk until reliable data demonstrate otherwise. If the agency lacks the data and/or resources to fully evaluate endocrine risks to human health and wildlife, then the agency is obliged to suspend or deny any pesticide registration until the agency has sufficient data to demonstrate no unreasonable adverse endocrine risk per the mandate in FIFRA. Further, it is not the agency but pesticide registrants that have the burden to demonstrate with adequate data that their products will <u>not</u> pose unreasonable adverse effects, including the inherently presumed endocrine disrupting effects.

Respectfully,

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