

March 19, 2003

Via electronic transmission to: oppt.ncic@epa.gov

Docket ID No. OPPT-2002-0066
Document Control Office (7407M)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
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**Re: Request for Comment on EPA's Proposed Chemical Selection Approach
for the Initial Round of Screening Under the Endocrine Disruptor
Screening Program**

These comments are submitted on behalf of the more than 750,000 members and supporters of People for the Ethical Treatment of Animals (PETA) and the more 100,000 members of Earth Island Institute (EII), who are very concerned about the suffering of animals in laboratory toxicity studies mandated by the U.S. Environmental Protection Agency (EPA). Our organizations have grave concerns regarding the scope and composition of the agency's Endocrine Disruptor Screening Program (EDSP), in view of the EPA's radical departure from the very straightforward Congressional mandate under which the EDSP was established,¹ as well as the EPA's continued failure to adequately incorporate animal protection principles into the program.² In its current form, the EDSP threatens to be the largest animal testing program in U.S. history. Bearing these concerns in mind, our organizations submit the following responses to the questions posed in the EPA's December 30, 2002 *Federal Register* notice:

A. Overall Approach for Selecting the Initial Set of Chemicals to Undergo Tier 1 Screening

1. *Focusing on the subset of chemicals subject to a statutory mandate for screening.*

We agree. The scope of the EDSP should be consistent with, and limited to, the Congressional mandate under which it was established. Expansion of the EDSP beyond the statutory language of the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Safe Drinking Water Act (SDWA), whether for the selection of the initial set of chemicals to undergo Tier 1 screening or in subsequent phases of the program, is strongly discouraged.

2. *Limited use of effects information.*

PETA and EII strongly disagree. The EPA needs to consider both the probable level of human

¹ The EPA's development of multiple animal-based ecotoxicological studies is a total departure from its Congressional mandate "to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen..." Likewise, the agency's continued consideration of "87,000 substances as potential candidates for testing under the EDSP" is not consistent with the EPA's narrow discretionary authority to "provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such a substance."

² The EPA's inappropriate expansion of the EDSP beyond the mandate provided by Congress threatens to greatly increase the amount of animal testing that is carried out. At the same time, the agency continues to overlook promising non-animal screening systems, such as *in vitro* serum protein binding, thyroid biochemistry, and vitellogenin induction, while aggressively pursuing the development of numerous redundant animal-based assays, some of which could easily kill more than 2,000 animals for every chemical tested (i.e., Tier 2 tests).

exposure to a chemical as well as all existing data regarding its known properties and health/ecological effects in determining, first, whether there is 'value added' from further testing of any kind, and if so, the relative priority that should be assigned to such testing. As the EPA has acknowledged, the quantity of existing information will vary depending on the type of chemical in question. However, given that the EPA is only obligated to screen "pesticide chemicals" under the EDSP, and these substances are generally quite 'data rich,' it is imperative that the EPA give careful consideration to the abundance of existing information for these substances—particularly data from studies that examine endocrine-relevant endpoints and which suggest the presence or absence of endocrine-mediated adverse effects.

Retesting pesticide active ingredients under the EDSP, as it is currently designed, is unlikely to provide any new insight into the effects of these chemicals that would alter the manner in which they are currently regulated. The current data specifications under 40 CFR Part 158 already require that all pesticide active ingredients undergo dozens of separate animal-based toxicity studies, which collectively kill upwards of 9,000 rats, fish, birds, mice, hamsters, and dogs. Given the enormous quantity of information available for these chemicals, we are dumbfounded by the EPA's suggestion that "...it has not yet been established how the available data might be confidently used to predict the endocrine disruption potentials of [pesticide] chemicals" (p. 79617). If this is indeed the case, why has a two-generation rodent reproduction study—a required endpoint for all food-use pesticide active ingredients—been proposed as the 'definitive' Tier 2 test to evaluate adverse effects to human health under the EDSP? Likewise, if indeed the agency does not feel that it can confidently predict the endocrine disruption potential of chemicals using this type of study, why persist in adding more endpoints to this study, let alone continue to develop four additional chronic/multigenerational reproduction studies in multiple taxonomic groups, as the Tier 2 testing battery?

If, as is implied later in the *Federal Register* notice, the EPA's hesitation in relying on existing information stems from a perceived lack of mechanistic data regarding a chemical's mode of action, this 'gap' could be filled most efficiently and appropriately through the selective use of mechanistic Tier 1 assays (i.e., avoiding a 'one size fits all' mindset that would call for a full Tier 1 screening battery to be performed). Given the range of endocrine-related endpoints now assessed under the revised OPPTS multigenerational reproductive toxicity guideline, the only endpoint that may not be fully characterized in the current toxicity database for pesticide active ingredients is that of thyroid disruption/toxicity.³ Accordingly, the assessment of pesticide active ingredients under the EDSP should occur only where evidence of endocrine-mediated adverse effects is equivocal,⁴ and should generally be limited to a mechanistic assessment of chemical interactions with the thyroid gland. Furthermore, we strongly urge that such testing be performed using *in vitro* assay systems.⁵

The *Federal Register* notice also identifies "high production volume (HPV) chemicals with some pesticidal inert uses" as being an additional target for screening under the first phase of the EDSP (p. 79614). Of the approximately 2,100 chemicals used only as 'inert' ingredients in

³ Bearing in mind that every registered pesticide is required to undergo tolerance reassessment, and that this process is already well underway, it is reasonable to assume that data consistent with revised 1998 OPPTS Test Guidelines will be available for all pesticide active ingredients by the time the EDSP comes on-line.

⁴ Where existing data suggest that noted adverse effects result from an endocrine-mediated mode of action, a chemical should be exempted from further testing and proceed directly to risk assessment.

⁵ Langley C. *Draft Detailed Review Paper on In Vitro Thyroid Screening Assays for Hormonally Active Chemicals*, 64 pp. People for the Ethical Treatment of Animals, Norfolk, Virginia, 2003.

pesticide formulations, an estimated 600 are also HPV chemicals, which places them under the jurisdiction of both the Office of Pesticide Programs (OPP) and the Office of Pollution Prevention and Toxics (OPPT), each with its own separate data specifications.

Until recently, all pesticide inert ingredients were subject to EPA's *1987 Inerts Policy*, which mandated the submission of data from nine to 14 animal-based toxicity studies. Information regarding the presence/absence of endocrine-mediated adverse effects could be 'mined' from histopathological examinations of reproductive and other endocrine organs in pre-existing subchronic (90-day) feeding studies in dogs and rodents, as well as the myriad of observations carried out in existing rodent developmental toxicity studies. In June 2002, the EPA amended its risk assessment strategy for pesticide inert ingredients with the publication of a *Guidance Document on the Methodology for Determining the Data Needed and the Types of Assessments Necessary to Make FFDCA Section 408 Safety Determinations for Lower Toxicity Pesticide Chemicals* (hereinafter, *2002 Guidance Document*). This new strategy bears little resemblance to the *1987 Inerts Policy*, borrowing instead from the Screening Information Data Set (SIDS), the same battery of toxicity endpoints being collected under OPPT's HPV Chemical Challenge Program. The SIDS battery includes one or more screening studies to assess reproductive toxicity, i.e., a one-generation study, a combined repro/developmental study, or a combined subacute/repro/developmental study. The toxicology database for inerts and HPV chemicals also commonly includes a number of wildlife/ecotoxicity effects data, including studies in fish, avian, and invertebrate species.

Clearly, a review of existing information on pesticide inert/HPV chemicals must be undertaken prior to making any decisions regarding what additional testing, if any, is considered necessary and appropriate in the context of the EDSP. For example, chemicals reassessed according to the methodology described in the *2002 Guidance Document* and placed on List 1 (a) or 1 (b) should be exempted from further assessment, including screening under the EDSP. Other exemptions should include the more than 400 pesticide inert ingredients currently classified by the EPA as being of "minimal concern" (i.e., FIFRA List 4 inerts), as well as all chemicals that are "generally recognized as safe" by the U.S. Food and Drug Administration (FDA GRAS), of which an estimated 176 are currently being used in pesticide formulations. List 2 determinations, per the *2002 Guidance Document*, would presumably trigger the collection of SIDS-type toxicity data, and these data should be assessed on a case-by-case basis vis-à-vis further testing for endocrine effects. Finally, List 3 determinations, which would presumably trigger the generation of a complete Part 158 database, should be dealt with in a manner consistent with the assessment of pesticide active ingredients (as discussed above).

With respect to the generation of SIDS-type data under OPPT and OPP programs, we strongly urge EPA program offices to ensure that chemicals are not subject to duplicative or redundant testing for the same or similar endpoint. An example of the type of scenario that should be prevented would be for an HPV chemical/pesticide inert to undergo a screening-level reproductive toxicity study (675 to 1,300 animals) under either OPPT's HPV program or OPP's inerts reassessment strategy, and later be required to undergo one or more multigenerational reproduction studies (2,500+ animals) under the EDSP. Such needless duplication could be prevented through early and careful coordination among the program offices. PETA therefore calls on the EPA to defer 'lower tier' testing for chemicals that are certain/likely to be subject to multigenerational and/or higher-tier testing under the EDSP, and strongly urges the agency to publish specific guidance on this matter, particularly in view of the fact that the HPV and inerts reassessment programs are already well underway.

In addition to reviewing the standard slate of health and ecological effects data, the EPA must also give special consideration to a substance's inherent physical-chemical properties, as well

as its capacity to persist and bioaccumulate in the environment. With respect to the former, all polymers, strong acids and bases, and chemicals with a molecular weight of 1,000 daltons or greater should be categorically exempt from screening under the EDSP. Likewise, a chemical's capacity to bio-persist should be given considerable weight when establishing priorities for further assessment, i.e., with less bio-persistent substances being assigned lower, or no, priority for screening under the EDSP. Given the relationship between bio-persistence and human/environmental exposure assessment, it is astounding that this issue was not discussed or even raised in the EPA's *Federal Register* notice.

3. *Focus on human exposure; no separate criteria pertaining to exposure of ecological receptors.*

We agree with this approach, and with the EPA's rationale that focusing on "human exposure will also capture many chemicals with widespread environmental exposures to other organisms."

4. *Deferring consideration of nominations from the public.*

We agree. Once again, we strongly urge the EPA to limit the scope of the EDSP to pesticide chemicals, per its statutory mandate. This would effectively preclude the expansion of the EDSP to include a large number of non-pesticidal chemicals, as well as the bureaucracy associated with soliciting and evaluating a myriad of chemical nominations. If, however, the agency elects to utilize its discretionary authority and expand the program to non-pesticidal chemicals, it must be able to demonstrate (1) "that a substantial population may be exposed to the substance," and (2) that the substance "may have an effect that is cumulative to an effect of a pesticide chemical" [21 USC 346a(p)(3)]. Ensuring that these criteria are satisfied must take precedence over political and other forces driving the retesting of chemicals for endocrine effects.

5. *Defer testing of mixtures.*

We agree, and in fact, urge the EPA to rule out the testing of mixtures altogether. Given that the agency is only required to screen "pesticide chemicals," and these substances would be examined as individual ingredients or groups of structurally/chemically similar compounds, there would be no value in testing formulated products or other mixtures as well. Likewise, the expansion of the EDSP to include other individual chemicals, let alone mixtures, is simply and completely impossible. For example, supposing that the EPA decided to test just 10 percent of non-pesticidal chemicals in the TSCA inventory—approximately 8,000 substances—in combinations of three. The product of this exercise would be 85 billion different chemical combinations to be tested. Assuming further that one million different combinations could be tested per year (undoubtedly an over-estimate), it would take 85,000 years to carry out this testing.⁶ In other words, the expansion of the EDSP to provide for the testing of mixtures would result in an astronomical cost—both economic and in terms of animal suffering and death—with no foreseeable benefit in terms of improved protection of human health or the environment.

6. *Excluding chemicals that are no longer produced or used in the United States.*

We agree. There is no benefit to retesting chemicals that are no longer produced or used in the U.S., as they fall outside the regulatory jurisdiction of the EPA or any other U.S. agency,

⁶ "Modern Environmental Protection, Part 4." *Rachel's Environment & Health Biweekly*, 2000 Sep, 707, 5 pp.

thus precluding the possibility of any meaningful regulatory or risk mitigation response to whatever data might be generated. We therefore strongly urge the agency to strengthen its stated position "that such chemicals would not warrant high priority for testing at this time" (p. 79618) by categorically exempting chemicals that are no longer produced or used in the U.S. from screening or testing under the EDSP at any time.

7. *Number of chemicals to be selected for the initial testing list.*

Given the continually evolving science of endocrine disruption and development and validation of assay systems for its evaluation, our organizations strongly urge the EPA to limit the number of chemicals selected for this initial screening exercise to the greatest extent possible, at least until non-animal screening methods are validated and in place for all hormone types under consideration.

8. *Integration of lists generated by the pesticide active ingredient approach and the pesticide inert approach.*

Notwithstanding the fact that different chemicals will be assigned different priority levels for screening, an overriding consideration should be to screen physically/chemically related substances as a group rather than individually. The EPA should establish chemical categories up-front by grouping as many pesticide active ingredients and inert/HPV chemicals as possible into batches according to structural/molecular similarities. Every effort should be made to avoid testing chemicals individually. Once this process has been completed, the agency should review existing data for all chemicals/batches to determine whether there is evidence of an endocrine-mediated effect. Where such evidence exists, the EPA should forego additional testing under the EDSP and proceed to risk management. Additionally, for batched chemicals, it should be assumed that a similar effect(s) would likely be observed for other chemicals in the same batch, per the agency's procedures for data bridging. Alternatively, for chemicals/batches for which there is no existing evidence of an endocrine-mediated effects, the EPA should proceed using the prioritization processes outlined in its *Federal Register* notice.

B. & C. Approach for Selecting Pesticide Active Ingredients and Inert/HPV Chemicals

The EPA's proposed approach is acceptable, provided that all steps outlined above are completed first.

D. Other Comments

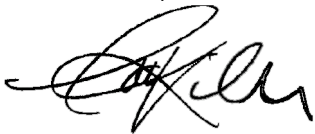
- The EPA states on several occasions its intent to "exclude from the first group of chemicals to undergo Tier 1 screening any chemical for which the available effects information clearly shows an endocrine-mediated effect. Such chemicals would be considered for proposed Tier 2 tests, mechanistic or special studies, or hazard assessment" (p. 79614, 79617). We concur that such chemicals should not be required to undergo Tier 1 screening, and urge the EPA to exempt these chemicals from further testing altogether, and instead, proceed directly to hazard assessment. If indeed existing information "clearly shows an endocrine-mediated effect," there is no value-added in carrying out further, extensive testing in Tier 2-type multigenerational studies. Likewise, "mechanistic or special studies" should only be considered if (1) they have been formally scientifically validated, and (2) there is a compelling reason to believe that the results of such a study would substantially alter the manner in which a chemical is regulated.

- In a similar vein, the EPA appears to be considering exempting apparently non-endocrine-active chemicals (e.g., FIFRA List 4 inerts, FDA GRAS chemicals, high molecular weight polymers, etc.) from Tier 1 screening only in the first phase of the EDSP (p. 49617). As stated previously, if these chemicals are generally considered to pose little or no risk, they should be categorically exempt from screening or testing under the EDSP.

- On a more general note, we strongly believe that the entire exercise being proposed in the EPA's *Federal Register* notice is highly premature. What if, for example, a validation study determines that the 'revised' rodent multigenerational reproduction study, complete with additional 'endocrine endpoints,' is only marginally or no more sensitive than the existing rodent 2-generation study? Presumably then, the revised study could be abandoned and the current study would become the *de facto* test for endocrine disruptive effects in humans. On the positive side, this could preclude the retesting of a pesticide chemical in a Tier 2 rodent test, as data for this endpoint should already exist and be regarded as sufficient. But at the same time, data from a 2-generation study would override and thus render moot all data generated under the Tier 1 screening exercise as currently proposed. Assuming that approximately 190 animals would be killed to generate a full Tier 1 battery,⁷ it is conceivable, therefore, that nearly 19,000⁸ could be killed for the sake of generating data that would, in all likelihood, have little or no impact on the manner in which a chemical is regulated. In the meantime, the generation of Tier 1 data without the potential to confirm or refute the results could leave chemicals in regulatory 'limbo' for months or years, pending the outcome of lengthy Tier 2 validation studies. In view of these considerations, we strongly urge the EPA to delay any *de novo* screening or testing of chemicals until validated Tier 1 and Tier 2 studies are in place. Additionally, the EPA should not begin any testing under the EDSP until non-animal methods are in place for all hormone types—including thyroid.

We appreciate the EPA's attention and responsiveness to our input. Please feel free to contact the undersigned with any questions or concerns at TroyS@peta.org or 757.622.PETA.

Sincerely,



Troy Seidle
Science Policy Advisor

⁷ Purchase IHF. Personal communication.

⁸ Assuming 100 chemicals screened using the full Tier 1 screening battery, which uses approximately 190 animals.