March 20, 2023

NRDC Comments
On EPA's draft White Paper
'Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)'

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Attention: Natalie Bray, Pesticide Reregistration Division (7508M), Office of Pesticide Programs
Tel: (202) 566-2222; email address: *bray.natalie@epa.gov*.

These comments are submitted on behalf of NRDC and the 35 groups and individuals listed at the end of these comments, which include: farmworker advocates; environmental justice leaders; fenceline community representatives; health professionals; environmental health groups; grassroots activists; lawyers; scientists; and technical experts.

These comments are informed by the Louisville Charter for Safer Chemicals, which has been signed by more than 100 organizations, including many of those signed on to these comments.[1] We work for environmental and economic health and justice, which includes fully informed and engaged workers, families, and communities that have the right to know about the hazardous chemicals and pesticides that contaminate the places that we live, work, learn, and play.

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[1] Coming Clean, The Louisville Charter for Safer Chemicals: A Platform for Creating a Safe and Healthy Environment through Innovation, https://ej4all.org/about/louisville-charter (last updated in 2021).

DETAILED COMMENTS

1. **EDSP, The First 25 Years – A high throughput program that is slower and more expensive than traditional testing, with no results.**

Hormone systems, also called endocrine systems, are in all mammals, including humans, and birds, fish, reptiles, insects, and even plants. Endocrine systems regulate growth and development of the brain and nervous system, reproductive system, metabolism, and other critical functions throughout life. Endocrine disrupting chemicals (EDCs) interfere with this system by blocking, mimicking, or otherwise altering the normal hormone activity, with results that include infertility, developmental malformations, and neurological deficits.

Congress, EPA and the public were first alerted to the devastating environmental effects of EDCs by Rachel Carson in her 1962 book Silent Spring. Carson's work was carried forward by Dr. Theo Colborn (1927-2014), who many of us had the honor of working with. Dr. Colborn was the first to envision an Endocrine Disruptor Screening Program (EDSP) and worked tirelessly with scientists, lawmakers, and advocates to see her vision finally made real in 1996.[2]

The EDSP was established by the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA, with two directives: one to test chemicals; the other to act on the test results:

- Section 408(p)(3)(A) on testing of all pesticide chemicals for human endocrine-disruption activity;
- Section 408(p)(6) on taking appropriate action to protect public health when finding, through testing and evaluation, that a substance has human endocrine effects.

The same year, EPA convened a committee, the Endocrine Disruptor Screening and Testing Committee (EDSTAC), to advise it on implementation, and in 1998, received the committees' final report.[3]

The EDSP covers about 10 thousand chemicals, with some overlap of categories: pesticide active ingredients (1,200 a.i.'s); pesticide inert ingredients (2,500 chemicals, many of which have environmental and health hazards); and drinking water contaminants (6,000).

Below is a table of how EPA's progress - in both missed deadlines and flawed content – has stacked up to its legal requirements:

EDSP requirements of the 1996 FQPA law	EPA progress to date
Development of the program is to be no later than 2 years after FQPA is enacted.	1996-1998 EPA held 16 public meetings and workshops related to EDSP development.[5]

[2] Maffini MV, Vandenberg LN. Failure to Launch: The Endocrine Disruptor Screening Program at the U.S. Environmental Protection Agency. Front Toxicol. 2022 May 30;4:908439. doi: 10.3389/ftox.2022.908439.

[3] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-and-testing-advisory-committee-edstac-final

[5] EPA. Endocrine Disruptor Screening Program Federal Register Notices. Webpage updated Nov, 2022. https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-federal-register-notices

It must use "appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an [endocrine] effect in humans"...(see FQPA)[4]	
Substances to be screened "shall provide for the testing of all pesticide chemicals" and "may provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical"	2009 EPA finalized the list of the first group of 67 chemicals to be screened in the EDSP with the Tier 1 battery of assays (List 1; 50 pesticidal active ingredient and 2 inert ingredients).[6]
Implementation of the program not later than 3 years after enactment.	2009-2011 EPA issued test orders for Tier 1 screening, for 67 chemicals (List 1).[7] Ultimately, 15 were discontinued, leaving 52 pesticides subject to Tier 1 screening. 2012 EDSP begins transitioning to HT screens and computational toxicology methods. 2013 (17 years after FQPA) EPA announced its second final list of 107 chemicals (List 2; 41 a.i. pesticides and 86 SDWA chemicals, with some overlap) to be screened with the Tier 1 assay battery, but never issued test orders.[8] 2015 EPA made several announcements of final Tier 2 Test Guidelines, and its intention to issue Tier 2 test orders for 18 of the 52 List 1 chemicals,[9] but never issued any Tier 2 test orders.
Collection of information – the law specifies that the Administrator "shall issue an order to a registrant of a substance," and then registrants conduct the tests and submit the results to EPA.	In 2015, EPA completed Weight of Evidence (WoE) screening determinations for the List 1 chemicals as follows: for 20 EPA found, "no evidence for potential interaction with any of the endocrine pathways"; for 14 there was potential endocrine activity, but no more testing was needed; only 18 "potentially" need Tier 2 testing, but no Tier 2 test orders were ever issued (White Paper, p. 14).
Exemptions may be given "if the Administrator determines that the substance is anticipated not to produce any effect in humans" that is estrogenic	No exemptions were ever issued for any of the approximately 10 thousand chemicals covered by EDSP, including pesticides and drinking water contaminants (White Paper, p. 14).

[4] FQPA https://www.govinfo.gov/content/pkg/PLAW-104publ170/pdf/PLAW-104publ170.pdf

[6] https://www.regulations.gov/document/EPA-HQ-OPPT-2004-0109-0080

[7] https://www.regulations.gov/document/EPA-HQ-OPP-2009-0634-0001

[8] https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0477-0074

[9] https://www.regulations.gov/document/EPA-HQ-OPPT-2013-0171-0008

Suspension – the law states that if registrants fail to comply with test orders, the Administrator "shall issue a notice of intent to suspend the sale or distribution of the substance by the registrant" within 30 days.	No suspensions have issued for chemicals as a result of information gathered by EDSP.
Section 408(p)(6) of the FFDCA, as amended by the FQPA, requires that EPA take action if it finds, after testing and evaluation, that a substance disrupts the human endocrine system.	No regulatory actions have been taken to reduce or restrict the use of any pesticide or other chemical as a result of information gathered by EDSP. Regulatory failure is an inherent outcome of the flawed system, in which "Tier 2 testing is necessary to make a determination"[10] that the chemical may have endocrine activity, but EPA has not issued any Data Call-In (DCI) for Tier 2 testing studies for any pesticides or other chemicals.

EPA's failures have not gone unnoticed. Litigation has been filed on more than one occasion over EPA's failure to carry out its mandates pertaining to the endocrine screening program.[11] Just a few weeks before the release of the NAMs white paper, farmworker and environmental groups filed a lawsuit challenging EPA's failure to implement the EDSP by the statutory deadline and to test all pesticide chemicals for possible endocrine disruption.[12] The action draws attention to EPA's delays in completing testing for the pesticides it has recognized require further testing, its general failure to test pesticides, noting just 4% of pesticides have begun to undergo testing and almost half of those remain unfinished, and the apparent intentionality of these actions by the agency.[13]

EPA's own conclusion from its over 25-year investment in the EDSP acknowledge the program's failure to produce actionable information: "Of the approximately 10,000 EDSP substances, including pesticide active ingredients and other ingredients in formulated pesticide products (called 'inerts' though many have known toxicity) and chemicals found in sources of drinking water (covered under SDWA), only 67 (List 1) and 107 (List 2) chemicals have been prioritized for screening and potential testing to date. Based on the current pace of the Tier 1 screening assays, it could take decades to screen all 10,000 chemicals in the EDSP domain" (White Paper, p. 14). Given the past 25 years, even EPA's prediction of decades to screen the remaining 10,00 chemicals seems unrealistic, and certainly it will never meet the legal requirements for taking action to deliver any of the protections for farmworkers, communities, and

[10] "Where Tier 1 results, accepted alternatives, or OSRI indicate a potential for EAT activity, Tier 2 testing is necessary to make a determination that a substance may have an effect similar to that of a naturally occurring hormone." See EPA 2023 NAMs EDSP White Paper, p. 11

[11] *See* Natural Resources Defense Council v. Whitman, 2001 WL 1221774 (N.D. Cal. Sept. 24, 2001); *see also* Settlement Agreement, Natural Resources Defense Council v. Whitman, 2001 WL 1221774 (N.D. Cali Sept. 24, 2001) (No. C-99-3701)

[12] Alianza Nacional de Campesinas et al. v. U.S. Env't Prot. Agency, No. 4:22-cv-9030 (N.D. Cali filed Dec. 20, 2022).

[13] *See* Complaint at 2–3, 27–28, Alianza Nacional de Campesinas et al. v. U.S. Env't Prot. Agency, No. 4:22-cv-9030 (N.D. Cali filed Dec. 20, 2022).

families that Congress envisioned when it passed the law. (See a summary of the EDSP's history in the recent published paper, "Failure to Launch."[14])

Despite EPA's own detailed analysis of the programs failures, it doesn't seem to have provided any explanation of why it failed, or how this time will be different. The EPA Office of Inspector General issued two reports on EDSP failures, first in 2011 and then in 2021. The OIG 2021 report gives a deeply disturbing view of a program and Agency is far from its legal mandates:[15]

- Failed to implement corrective actions in response to the 2011 OIG report.
- Lack of strategic guidance documents on how to evaluate and use the information.
- Lack of performance measures:
    - Failure to assess progress against regulatory requirements;
    - Failure to communicate with internal and external stakeholders.
- Lack of internal controls to help ensure accountability and enhance transparency. Without these controls, "the EDSP cannot have reasonable assurance that program goals and objectives will be accomplished and that resources will be allocated efficiently and effectively" (OIG 2021 p. 17).
- Some EPA staff indicated that they were instructed to function as if the EDSP was eliminated from EPA's budget, despite the FY21 budget allocating $7.5 million to the program, which by that time had only four full-time staff (OIG 2021, p. 18, 21).
- OCSPP leadership abandoned EPA's established WoE approach for evaluation EDSP Tier 1 screening data, instead using an approach that has not been subjected to public review and comment or to review by the FIFRA Science Advisory Panel. The OIG report characterized this as having "an appearance of bias" (OIG 2021 p. 17).
- Lack of transparent internal and external communications (OIG 2021, p. 13-14).

The OIG 2021 report concludes that, "Without the required testing and an effective system of internal controls, the EPA cannot make measurable progress toward compliance with statutory requirements or safeguard human health and the environment against risk from endocrine-disrupting chemicals." (OIG 2021, p. 15). Importantly, the OIG identifies numerous serious process failures, and makes recommendations to improve the process. Yet, EPA's own 2021 New Approach Methods Work Plan notes that it still lacks any guidelines or policies to assure that NAMs will support regulatory decisions to limit or eliminate hazardous chemicals.[16] Instead, EPA's White Paper proposes new tests, the NAMs, which seems disconnected from its ongoing process failures and not responsive to the OIG recommendations.

If EPA moves forward with the use of NAMs – whether within EDSP or other programs – it will be essential for EPA to prove it can do the two things OIG identified as most critical: issue test orders; have an effective system of internal controls to implement the program and achieve EPA's mandate to take meaningful action and enforce regulatory safeguards to achieve human health and environmental protections. To move forward, EPA needs to stop treating NAMs like a science issue, and instead re-

[14] Maffini MV, Vandenberg LN. Failure to Launch: The Endocrine Disruptor Screening Program at the U.S. Environmental Protection Agency. Front Toxicol. 2022 May 30;4:908439. doi: 10.3389/ftox.2022.908439.

[15] EPA OIG 2021. EPA's Endocrine Disruptor Screening Program Has Made Limited Progress in Assessing Pesticides. EPA Office of the Inspector General. Report No. 21-E-0186. Available at: https://www.epa.gov/office-inspector-general/report-epas-endocrine-disruptor-screening-program-has-made-limited

[16] EPA, New Approach Methods Work Plan: Section III. Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions, at 12 (Dec. 2021), https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

structure the NAMs work to address the needs and concerns of fenceline communities, farmworkers and others. Meaningful engagement with environmental justice communities, environmental groups, farmworker groups, unions, health impacted groups and others, as recommended by OIG and the EDSTAC (see below), must be a part of this work.

2. Meaningful public engagement is long overdue.

EPA and other agencies must assure full transparency and conduct meaningful outreach to susceptible communities, whose interests in enhanced protection against pollution and chemical exposure will be directly impacted by the development and use of NAMs. Workers and impacted communities deserve a strong voice in how agencies use NAMs assays for hazard evaluation and risk assessment.

In its inception, the program was not EDSP, but EDSTP, with the now-absent letter T standing for "Testing." The federal stakeholder advisory group was the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC).[17] The 1998 EDSTAC final report including an entire chapter on 'Communications and Outreach', which recommended that EPA establish a communication and outreach strategy to include, "tailored information to be relayed through a variety of mechanisms. This would help to ensure that specific audiences – such as environmental justice organizations, 'downstream' industries, farm workers, and patient groups – who may not have the ability to access information via traditional means and who have varying levels of knowledge and interest in endocrine disruptor-related issues, have the opportunity to learn about the EDSTP and its results".[18] No plan was ever produced, according to the 2021 OIG report.

The 2021 OIG report devotes a substantial section to EPA's ongoing failure communicate with stakeholders (see 2021 OIG report, p. 13-14). OIG found that the EDSP lacks an effective process for even within-Agency coordination, had not published any technical documents for public review since 2015, and has only just produced its response to public comments received from its last public comment period in 2015.[19] Unfortunately, OIG's recommendation for EPA to update its website falls far short of what is required for full and meaningful public engagement.

The White Paper is an ongoing failure to engage the public and stakeholders. For example, none of the following words appear in the current White Paper: "communication"; "outreach"; "engagement"; "farmworker" or "farm"; "patient"; "fenceline" or "justice". The words "worker" and "cumulative" each appear only once, in the White Paper introductory paragraphs on the historical context. The word "community" appears once, discussing the scientific community (White Paper, p. 37). The word "stakeholder" appears three times in the White Paper, always about stakeholders that produce and use NAMs, nothing about those that are harmed by pesticides and hazardous chemicals (White Paper, pgs. 15, 32, 42).

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[17] Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) Final Report, 1998. https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-and-testing-advisory-committee-edstac-final

[18] EDSTAC report, 1998. P. 25. https://www.epa.gov/sites/default/files/2015-08/documents/chap7v14.pdf

[19] EPA 2023. Response to Public Comments on the Public Review Draft: "Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment" (2015). Posted by the Environmental Protection Agency on Jan 19, 2023. Docket EPA-HQ-OPP-2021-0756. https://www.regulations.gov/document/EPA-HQ-OPP-2021-0756-0003

The White Paper's only community engagement on NAMs appears to be with the regulated community, the scientific community, and the animal welfare community. For example, the website on its NAMs Work Plan (issued to the public December 2021) makes plain EPA's top priority is to reduce the use of vertebrate animals, in bold face in the title. Of the five priority areas that follow, top on the list is "evaluate regulatory flexibility" and the last to be listed is, "engage and communicate with stakeholders".[20] As more evidence that EPA seems to have limited its view of its community to federal agencies, regulated industry, and animal protection groups, it launched a webinar series through 2021-2023 co-organized with EPA and two animal welfare groups, PETA and PCRM (Physicians Committee for Responsible Medicine). The collaboration lists a dozen webinars to date, with speakers from government, industry and industry consultants, animal protection groups, and some academics.[21]

Why has EPA not established effective outreach and engagement with EJ perspectives, fenceline communities, farmworkers, labor and union representatives, environmental groups, disease impacted groups, and others in harm's way? Why does EPA fail to include those whose health and safety is threatened by weak chemical evaluations and failed chemical regulations? EPA has acknowledged that "vibrant stakeholder engagement and partnerships are the backbone of" EPA's environmental justice work and are "essential to achieving meaningful outcomes for overburdened communities."[22] The stated commitment to "early, ongoing and meaningful stakeholder engagement,"[23] has never been realized in EDSP, now in its third decade, or in EPA's NAMs work, now in its second decade. The White Paper neither proposes a public engagement plan, nor even identifies a need for one.

3. EPA's tiered testing approach should be a 'road to regulation' not an off-ramp from testing.

For the chemicals that "pass" Tier 1 screens, EPA does not require any additional testing or information and no regulatory actions are taken based on endocrine disruption. If these chemicals are already market-approved, the approval remains unaffected. This was the case for all of the 52 List 1 chemicals that were subjected to Tier 1 screening. In short, Tier 1 screens are used by EPA to identify chemicals that are <u>not</u> EDCs, akin to a safety finding for this adverse endpoint. The White Paper offers not one single sentence on chemicals that pass Tier 1 screening, other than that no further action is required, neither testing nor regulatory actions; this seems like a safety finding. EPA may protest by making a distinction between the semantic category of 'low priority' and 'not and EDC,' but in practice the EDSP and the White Paper treat them the same (see figure below from OIG report).

In contrast, for chemicals that fail the Tier 1 screen, EPA is adamant in the White Paper that no conclusions of harm can be drawn (see excerpts below).

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[20] EPA New Approach Methods Work Plan: Reducing Use of Vertebrate Animals in Chemical Testing. Last update January 23, 2023. https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-vertebrate-animals-chemical

[21] Webinar Series on the Use of New Approach Methodologies (NAMs) in Risk Assessment, 2018-2023. https://www.thepsci.eu/nam-webinars/

[22] EPA, EJ 2020 Action Agenda, at 10 (Oct. 2016), https://www.epa.gov/sites/default/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf.

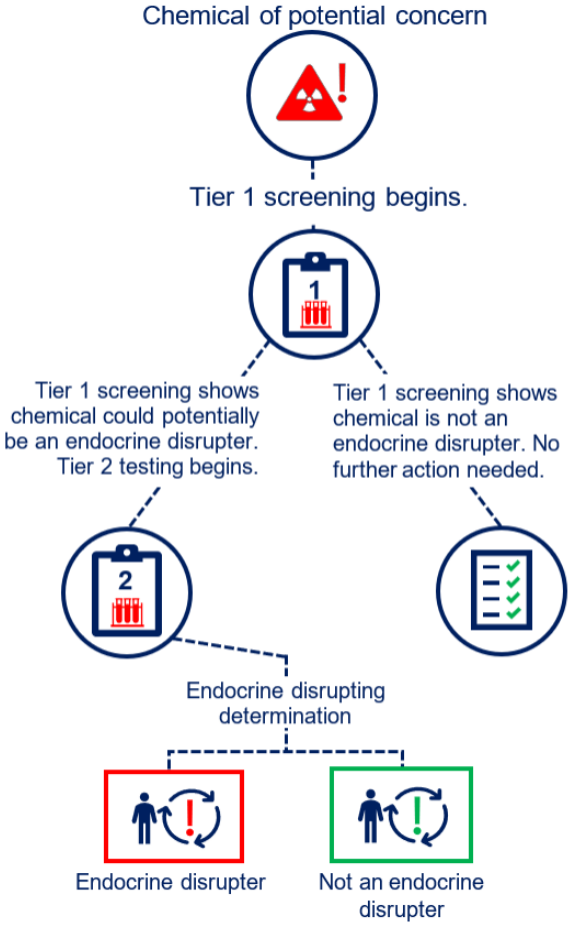
[23] EPA, EJ 2020 Action Agenda, at 10 (Oct. 2016), https://www.epa.gov/sites/default/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf.

See Figure from the EPA OIG 2021 report, p. 9, and excerpts from the White Paper:

- Screening [Tier 1] - "As these are preliminary assays, a positive result does not mean that a chemical substance may have an effect in humans, fish or wildlife that is similar to the effect produced by naturally occurring hormones." (White Paper, p. 11)

- Testing [Tier 2] - "Tests are designed to confirm and further define the results obtained in Tier 1 screens by identifying and establishing a dose-response relationship for any adverse effects..." (White Paper, p. 11)

- "For the EDSP, bioactivity (determined as part of Tier 1 screening) indicates that a chemical has the potential to alter endocrine function. However, confirming whether the chemical alters endocrine function and whether that altered function produces an adverse outcome cannot be determined without further testing (e.g., Tier 2 or other testing). It is important not to equate a determination of a chemical's bioactivity with a determination that a chemical causes endocrine disruption." (White Paper, p. 11)



Thus, EPA has constructed a decision tree whereby a determination of harm requires whole animal tests (Tier 2 tests), whereas a determination of safety can be made from NAMs (Tier 1 screens).

This sort of decision tree works with pharma because it is screening drugs before they are on the market. A drug in early research and development phase that passes Tier 1 screening will go on to Tier 2 type testing in whole animals, and passing that, on to clinical trials in people. For pharma, passing Tier 1 means it is safe enough to go on for further testing, safe enough to continue to invest resources in, safe enough to move forward with the hope of eventually getting market approval. **For pharma, passing Tier 1 screening in the first of many required safety findings before getting to market. For EPA it is the opposite – passing Tier 1 means avoiding testing, without imposing regulatory restrictions, for chemicals already in commerce, or on their way to commercialization**.

EPA's scheme assumes safety unless harm is proven, and then never issues test orders for the Tier 2 tests that could prove harm. With EPA's scheme, even the 9,950 chemicals that are never even screened are treated as safe for this endpoint, since EPA is neither making an EDC determination (which requires Tier 2 whole animal tests) nor taking any regulatory actions on any of the 10,000 chemicals subject to EDSP (based on Tier 1 NAM assays). EPA's approach is a violation of its legal mandate under FFDCA-FQPA to both test chemicals (Tier 2) AND also to act with the information (Section 408(p)(6)).

EPA has done neither. The EDSP is more than a screening mandate – metrics of success should include regulatory restrictions, cancellations, and bans to protect public health.

4. NAM results should be a one-way ratchet, to support or advance health protections.

When NAMs tests indicate that a chemical has a toxic effect, that should inform regulatory restrictions and other actions consistent with the toxicity of the chemical. However, due to their serious limitations and uncertainties, NAM are likely to miss most hazardous properties, and thus results should not be used identify chemicals as 'low priority' or otherwise shield them from regulatory restrictions or further testing. This is consistent with recommendations from scientific experts: "when prioritizing chemicals for further study for a particular biological outcome … positive results (i.e., results that indicate potential harm) in relevant bioassays could be used to identify chemicals of concern, whereas negative results (i.e., results that indicate a lack of potential harm) are not sufficient to conclude a lack of concern given the limitations of current *in vitro* methods to simulate *in vivo* metabolism or predict effects in different tissues and across different life stages."[24]

The use of NAMs as a one-way ratchet, as one stream of evidence, to strengthen, not weaken, health protections was recommended by the EPA Children's Health Protection Advisory Committee (CHPAC): "(NAMs) have the potential to provide needed data and could be used to establish potential hazards or upgrade overall hazard identification. However, due to important limitations, data from NAMs cannot be used to rule-out a specific hazard."[25]

5. Failure to require testing.

EPA has invested more than a decade of resources in the development and evaluation of high-throughput (HT) *in vitro* assays and *in silico* methods as NAMs, along with computational models, as screening assays, to: "accelerate the pace of screening, add efficiencies, decrease costs, and reduce animal testing" (White Paper, p. 5). These promises have not been realized. Moreover, EPA's approach has shifted the cost of testing from industry to the public.

EPA's failure to issue test orders to pesticide registrants was seen as a cause for celebration (of animal lives saved) by EPA managers when they hit 1,000 waivers for animal tests. Among critically important health and safety information that pesticide manufacturers no longer had to submit to EPA in the course of having its pesticide products approved, were: "90 percent of tests looking for developmental neurotoxicity; 92 percent of chronic cancer studies; and 97 percent of studies looking at how pesticides harm the immune system".[26] Pesticide manufacturers saved the cost of testing, and also the concern that such data may slow or restrict EPA's approval of its pesticide products.

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[24] Ginsberg GL, Pullen Fedinick K, Solomon GM, Elliott KC, Vandenberg JJ, Barone S Jr, Bucher JR. New Toxicology Tools and the Emerging Paradigm Shift in Environmental Health Decision-Making. Environ Health Perspect. 2019 Dec;127(12):125002. doi: 10.1289/EHP4745

[25] EPA Children's Health Protection Advisory Committee. Letter to EPA acting administrator on protecting children's health under amended TSCA: chemical prioritization. 2021. https://www.epa.gov/sites/default/files/2021-02/documents/2021.01.26_chpac_tsca_charge_response_letter.pdf

[26] Lerner S. 2021. The Department of Yes: How Pesticide Companies Corrupted the EPA and Poisoned America. The Intercept. June 30, 2021. Waiver data is from Dec 2011 to May 2018. https://theintercept.com/2021/06/30/epa-pesticides-exposure-opp/

It is not just the Pesticide Office and EDSP that avoids using its authority to require industry to conduct chemical tests. EPA has also largely failed to use its authority under TSCA Section 4 to require new testing data. It finally issued two test orders, and industry challenged them both in court. (Lanxess Corp. v. EPA challenges aquatic toxicity and consumer exposure tests for o-dichlorobenzene, which helps produce soaps, inks, and lubricants.[27] Vinyl Institute, Inc. v. EPA challenges environmental hazard tests of 1,1,2-trichloroethane, a solvent.[28] Meanwhile, communities in NC Cape Fear have petitioned EPA to issue test orders for 54 PFAS chemicals, but EPA has issued only two testing orders, for only one PFAS, and it's not on the list of 54 that the communities requested.[29]

Failing to require chemical testing cannot be solved by shifting testing requirements to another HT screening array. If EPA believes that its decades-long failure to hold industry accountable for its poisonous products is a problem that NAMs can solve, it should provide those details to the public. EPA should demonstrate that it has an effective internal control system, including plans, policies, and procedures to implement a strategy for both testing and for making decisions and taking health-protective action on test results. As the OIG report notes, without this, EPA cannot make progress on statutory compliance or on its mission to protect human health (OIG 2021 p. 20).

We recommend that EPA develop internal controls and accountability measures, in consultation with the EPA Office of Children's Health Protection (OCHP), the EPA Office of Environmental Justice & External Civil Rights, and the White House Environmental Justice Advisory Council, and subject to peer review and public engagement and comment.

6. NAMs are informative but limited testing methods.

High throughput (HT) assays –
HT assays are *in vitro* methods to provide rapid information about cell and sub-cellular activity in response to a chemical treatment. The method utilizes cells, or even sometimes just parts of cells such as proteins, maintained with nutritional liquid to keep the cells alive.

Not all chemicals are amenable to *in vitro* testing; for example, chemicals must be soluble in water and dimethyl sulfoxide (DMSO).[30] Existing methods do not work well for aryl flame retardants, polycyclic

[27] EPA. Modification to Order Under (4)(a)(2) of the Toxic Substances Control Act. August 5, 2022. https://www.epa.gov/system/files/documents/2022-03/9544-01_testorder_odcb_aa_signature.pdf

[28] Bloomberg News, July 2022. https://news.bloomberglaw.com/environment-and-energy/three-lawsuits-aim-to-shape-epas-use-of-chemical-test-orders

[29] Three Lawsuits Aim to Shape EPA's Use of Chemical Test Orders. Pat Rizzuto. Bloomberg News, July 22, 2022. https://news.bloomberglaw.com/environment-and-energy/three-lawsuits-aim-to-shape-epas-use-of-chemical-test-orders

[30] ToxCast Data Generation: Chemical Workflow. Updated January 2023 https://www.epa.gov/chemical-research/toxcast-data-generation-chemical-workflow

ToxCast Owner's Manual - Guidance for Exploring Data. 2018. https://www.epa.gov/sites/default/files/2018-04/documents/toxcastownermanual4252018.pdf

aromatic hydrocarbons (PAHs), 7α-ethinylestradiol, and 17β-estradiol that are not water soluble.[31] The White Paper doesn't mention these limitations. Also, some HT assays are proprietary commercial assays, with limited public access (White Paper, p. 32).

The cells are obtained one of two ways: either directly from an animal (usually from a rodent organ, such as rat liver, kidney, skin, heart, brain, or the cornea of an eye) or human (such as skin cells); or purchased from a company that grows cells in large batches (called cell lines) and sends them to researchers all over the world.

While cells removed from a rodent liver (called primary cell cultures) lack the biological ability of a functioning liver such as metabolism and blood flow, the cell lines grown in a lab are an even more distant approximation of a living system. That is because healthy cells, whether within a body or extracted and placed in a petri dish, will not continuously multiply; only cancer cells will do that. So, to produce them in large batches, the cell lines are manipulated to act like cancer cells. And, moreover, a cancer cell line that is mutated over time – just like real cancer cells – no longer resembles the organ it originally came from. These cell lines have names like CHO (Chinese Hamster Ovary cell lines) and HK-2 (derived from human kidneys), and the now infamous HeLa cells that was extracted without knowledge or consent from Ms. Henrietta Lacks' tumor almost 100 years ago and are still in use today.[32]

Some HT assays don't even have the biological complexity of a living cell. For example, many of the NAMs tests for endocrine disruptor activity employ a simple binding assay, to see whether the chemical binds to a hormone receptor protein.

Results are measured as changes in cellular bioactivity in response to chemical treatment. For example, the 18 high throughput assays that comprise the ER Model measure bioactivity at different sites along the ER pathway including receptor binding, receptor dimerization, chromatin binding of the mature transcription factor, gene transcription and changes in estrogen-receptor growth kinetics. Bioactivity (i.e., response) is measured using various detection methods (e.g., fluorescence, etc.) across a range of concentrations to examine potential concentration-response relationships, including no change across concentrations which EPA interprets as indicating no bioactivity.

Toxicology Forecaster (ToxCast) –
The high throughput assays are conducted with cells or subcellular constituents such as protein receptors maintained in fluid-filled wells on a multi-well plate small enough to fit in the palm of a person's hand. Each plate contains many wells (example, a 96-well or 384-well plate) laid out in a grid, making it amenable to robotics to automate the work of running the assays, injecting cells or test chemicals at desired concentrations across the wells in each plate. In this way, many chemicals – or even chemical combinations – across many concentrations, can be assayed over the course of a day.

ToxCast has ER and AR pathway model results for about 2,000 chemicals including pesticides, industrial and consumer products, food additives, and pharmaceuticals. The roughly 700 endpoints covered by the

[31] Truong L, Bugel SM, Chlebowski A, Usenko CY, Simonich MT, Simonich SL, Tanguay RL. Optimizing multi-dimensional high throughput screening using zebrafish. Reprod Toxicol. 2016 Oct;65:139-147. doi: 10.1016/j.reprotox.2016.05.015.

[32] The Legacy of Henrietta Lacks. https://www.hopkinsmedicine.org/henriettalacks/

HT ToxCast assays are conducted by contracted biotech companies outside of federal agencies or research labs (White Paper, p. 15).

A critical limitation is that EPA's ToxCast™ platform still does not include NAMs information for all the key characteristics of carcinogens, thus making it likely that it will miss chemicals that have the potential to cause breast cancer, testicular cancer and other hormone-related cancers through pathways that are not included in ToxCast.[33] In addition, epigenetic and transgenerational effects are not captured, both of which are critical pathways for many adverse endocrine effects.

Computational models –
Computational models (sometimes called '*in silico*' for silicon computer chips) integrate the information across the assays, to generate a mathematical estimate of whether or how much bioactivity was triggered by the chemical being evaluated, with 0 being none and 1 being a positive reference chemical (like estradiol in the ER model). The CompTox Chemicals Dashboard and InvitroDB are living databases and models that are regularly updated with new information from EPA research and external stakeholders, and includes proprietary models developed by industry.

In summary, NAMs tests are a lot like reaching into a haystack to find a harmful needle – you know when you've found one, but if you don't then maybe you didn't look in the right part of the haystack, or even in the right haystack.

For example, the ER Model as used by EPA missed nearly one-third of estrogenic chemicals (15 of 55 chemicals) when validated against in vivo estrogenic information from guideline-like studies. Estrogenic *in vivo* reference chemicals missed by the ER Model include methylparaben, triclosan, reserpine, permethrin, octamethylcyclotetrasiloxane, and gibberellic acid. Inconclusive chemicals cannot be specifically listed due to coded identities. For this discussion, false negatives include chemicals that were incorrectly identified as not having estrogenic activity and those reported to be inconclusive in the ER Model. In EPA's demonstration it treats inconclusive chemicals as either excluded from consideration or considered positive (having EDC activity) (White Paper, p. 24-25).[34] However, the reality is that when EPA evaluates Tier 1 information in the EDSP, that is not how EPA treats inconclusive results – they are treated as 'no effect' or excluded from consideration (just like the 9,950 chemicals that were never even screened) - thus biasing the EDSP outcomes towards the null, or false negatives.

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[33] Ginsberg GL, Pullen Fedinick K, Solomon GM, Elliott KC, Vandenberg JJ, Barone S Jr, Bucher JR. New Toxicology Tools and the Emerging Paradigm Shift in Environmental Health Decision-Making. Environ Health Perspect. 2019 Dec;127(12):125002. doi: 10.1289/EHP4745.

Iyer N, Pham N, Marty M, Sandy M, Solomon G, Zeise L. 2019. An integrated approach using publicly available resources for identifying and characterizing chemicals of potential toxicity concern: proof-of-concept exercise with chemicals that affect cancer pathways. Toxicol Sci169(1):14–24, PMID: 30649495, 10.1093/toxsci/kfz017.

Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, et al.2018. Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis39(4):614–622, PMID: 29562322, 10.1093/carcin/bgy031.

[34] Judson RS, Magpantay FM, Chickarmane V, Haskell C, Tania N, Taylor J, Xia M, Huang R, Rotroff DM, Filer DL, Houck KA, Martin MT, Sipes N, Richard AM, Mansouri K, Setzer RW, Knudsen TB, Crofton KM, Thomas RS. Integrated Model of Chemical Perturbations of a Biological Pathway Using 18 In Vitro High-Throughput Screening Assays for the Estrogen Receptor. Toxicol Sci. 2015 Nov;148(1):137-54. doi: 10.1093/toxsci/kfv168.

We recommend that NAMs should not be used to excuse chemicals from further testing, or to call them safe, given their significant limitations. EPA's own 2021 New Approach Methods Work Plan confirms these concerns: "…scientific challenges and gaps include inadequate coverage of potential biological targets and pathways, reduced or distinct xenobiotic metabolism in in vitro test systems, limited capabilities to represent the complex cellular, tissue, organ, and organism-level interactions, and a lack of robust integrated approaches to testing and assessment (IATAs)".[35] Put simply, NAMs cannot reliably measure key endocrine health outcomes including reproduction and neuroendocrine mediated growth and development, for which there are established rodent tests.

We are also concerned about lack of transparency for proprietary models and assays. We recommend that the models and methods used by the agency should be transparent and available for public evaluation. Data, code, and other information should be accessible throughout the process of evaluating new or existing chemicals.

7. NAMs could be employed to advance health protections across EPA programs.

Used appropriately, NAMs tests can provide important red flags of potential toxicity – find a few needles in the haystack. There are many ways that EPA could employ NAMs, with existing data and information, to strengthen chemical regulations and increase public protections. EPA could use NAMs with existing data and information to rapidly evaluate complex chemical mixtures.

Twenty-five years ago, the EDSTAC recommended that EPA prioritize the following chemical mixtures: chemical mixtures at hazardous waste sites; pesticide and fertilizer formulations; disinfection byproducts; gasoline chemicals; chemical contaminants found in breast milk.[36] EDSTAC made these recommendations to EPA in 1998, to set priorities for the EDSTP. How has EPA made progress on these priority mixtures? How will the EDSP address these priorities?

What is EPA's plan for identifying and then addressing the priorities of environmental justice communities, environmental groups, farmworker advocates, unions, health impacted groups and others at risk from pesticides and toxic chemicals?

8. Reducing animal testing should include advancing environmental and health protections.

NAMs can be used with additional existing public information right now to support EPA regulatory decisions across its programs: regulate chemical classes; use established methods to fill data gaps, including uncertainty factors, read-across, quantitative and non-quantitative structure activity relationship (SAR/QSAR) and category-based approaches; reduce known or suspected toxicants by promoting the elimination of unnecessary chemicals and supporting the development and use of safer substitutes. This could all be done if EPA made better use of existing data including from epidemiologic

[35] EPA, New Approach Methods Work Plan: Section IV. Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps, at 16 (Dec. 2021), https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

[36] Maffini MV, Vandenberg LN. Failure to Launch: The Endocrine Disruptor Screening Program at the U.S. Environmental Protection Agency. Front Toxicol. 2022 May 30;4:908439. doi: 10.3389/ftox.2022.908439.

studies, academic research, medical case reports, workplace incident reports, and spill and release information. See for example some recent reports and resources by European groups.[37]

When EPA identifies hazardous chemicals, it should eliminate harmful and unnecessary chemical uses, and promote the use of safer alternatives, consistent with EPA's commitment to the Principles of Green Chemistry and Green Engineering,[38] and to the Louisville Charter for Safer Chemicals, on safer substitutes and solutions for a non-toxic economy.[39]

Even with the above measures, EPA will continue to need animal models, including diverse rodent strains (e.g., collaborative cross, diversity outbred) and emerging vertebrate and invertebrate models (e.g., zebrafish, c. elegans) that are being developed through the NAMs work. This work will be valuable to inform policies and regulations that address individual and population diversity.

9. Conclusion – The measure of success new NAMs assays resides in their potential ability to be protective of the health of workers, communities, and ecosystems.

The Louisville Charter calls for a new chemical policy that "use[s] scientific data to support health-protective policies and practices," "ensure[s] the public and workers fully have the right-to-know, participate and decide in the decisions that impact their health because of the potential harm from toxic chemicals," and emphasizes "urgent action to stop production … of chemicals that are unsafe and/or accumulate in the environment and people."[40] EPA's current use of new NAMs as a blunt and unreliable instrument in a biased and broken framework is inconsistent with those foundational principles.

Importantly, the unavailability of NAMs data should not delay regulatory policies and practices that deliver health and safety protections for farmworkers, those living on the fenceline of hazardous chemical industries, and other environmental justice communities—often low-wealth and communities of color—who breathe, drink, and ingest toxic chemical pollution every day.[41] When EPA fails to identify

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[37] Joint letter to the EU Commission on the need for information in chemicals legislation signed by 22 NGOs. Feb 27, 2023. https://www.env-health.org/wp-content/uploads/2023/03/20230227-EEB-letter-to-Timmermans-and-relavant-Commissioners.pdf

No one likes animal tests. Here's how to reduce them. ChemSec: International Chemical Secretariat. March 1, 2023. https://chemsec.org/no-one-likes-animal-tests-heres-how-to-reduce-them

Chemical safety testing as part of a stronger REACH, protecting health & environment, promoting alternative methods. March 1, 2023. By Ninja Reineke. https://chemtrust.org/stronger-reach-alternative-methods/

Q&*A on animal testing and chemical safety assessments*. HEAL Health and Environment Alliance. Feb 27, 2023. https://www.env-health.org/qa-on-animal-testing-and-chemical-safety-assessments/

Chemical safety and animal welfare. What is at stake? ChemSec: International Chemical Secretariat. 2023. https://chemsec.org/publication/general-chemsec,reach/chemical-safety-and-animal-welfare-what-is-at-stake/

[38] EPA Green Chemistry. https://www.epa.gov/greenchemistry

[39] Transforming the Chemical Industry: Safer Substitutes and Solutions for a Non-Toxic Economy. Policy Paper #3, for the Louisville charter. Beverly Thorpe, Clean Production Action. July 2022. http://bit.ly/42uo9TZ

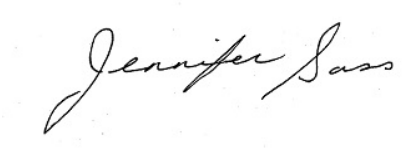
[40] Coming Clean, The Louisville Charter for Safer Chemicals: A Platform for Creating a Safe and Healthy Environment through Innovation, https://ej4all.org/about/louisville-charter (last updated in 2021).

[41] Report: Life at the Fenceline - Understanding Cumulative Health Hazards in Environmental Justice Communities. Environmental Justice Health Alliance for Chemical Policy Reform, Coming Clean, Campaign for Healthier Solutions.

critical adverse endpoints that are missed by Tier 1 screens (false negatives), these communities suffer the greatest harm.

The ultimate usefulness of new NAMs assays, and their measure of success, resides in their potential ability to be protective of the health of workers, communities, and ecosystems.

Respectfully,



Jennifer Sass, PhD
Senior Scientist,
Natural Resources Defense Council

(*Academic affiliation for identification purposes only and does not constitute institutional endorsement*.)

Jerry P Abraham, MD MPH CMQ
President, Los Angeles County Medical Association
Director & Chief Vaccinologist, Kedren Community Health Center, Inc., an FQHC,
Asst. Prof., Family Medicine & Psychiatry, Charles R. Drew University of Medicine & Science

Alaska Community Action on Toxics
Pamela Miller, Executive Director

Alliance of Nurses for Healthy Environments
Katie Huffling, DNP, RN, CNM, FAAN
Executive Director

John R. Balmes, MD
Professor of Medicine Emeritus
University of California, San Francisco
Professor of Environmental Health Sciences
School of Public Health
University of California, Berkeley

Linda S. Birnbaum, PhD, DABT, ATS
Scientist Emeritus and Former Director
National Institute of Environmental Health Sciences and National Toxicology Program
Scholar in Residence, Nicholas School of the Environment, Duke University

Breast Cancer Prevention Partners
Janet Nudelman

California Rural Legal Assistance Foundation
Anne Katten, MPH
Pesticide and Work Health and Safety Specialist

Center for Biological Diversity
Nathan Donley, PhD

Center for Food Safety
Jaydee Hanson

Clean+Healthy
Bobbi Wilding

Clean Production Action
Mark Rossi, PhD
Executive Director

September 2018. https://comingcleaninc.org/latest-news/in-the-news/report-life-at-the-fenceline-understanding-cumulative-health-hazards-in-environmental-justice-communities

Coming Clean
Maya Nye, PhD

Commonweal
Sharyle Patton
Director, Health and Environment Program

Earthjustice
Rashmi Joglekar, PhD
Patti Goldman, Senior Attorney

Environmental Working Group
Alexis Temkin, PhD

Farmworker Justice
Mayra Reiter, Project Director
Occupational Safety and Health

Farmworker Association of Florida
Jeannie Economos

Deborah Hirtz MD
Professor, Neurological Sciences and Pediatrics
University of Vermont School of Medicine

Arthur Lavin, MD, FAAP
Pediatrician, Cleveland, Ohio

Learning Disabilities Association
Tracy Gregoire

Moms for a Nontoxic New York
Kathleen Curtis, LRN
Founding Director

National Hispanic Medical Association
Elena Rios, MD, MSPH, MACP
President and CEO

Pesticide Action Network North America
Margaret Reeves, Senior Scientist

Physicians for Social Responsibility, San Francisco Bay
Robert M. Gould, MD

Beate Ritz, MD, PhD
University of California Los Angeles

Leslie Rubin MD
Break the Cycle of Health Disparities, Inc.
The Rubin Center for Autism and Developmental Pediatrics

Safer Chemicals Healthy Families
Toxic-Free Future
Liz Hitchcock, Director

Science and Environmental Health Network
Ted Schettler MD, MPH

Fatemeh Shafiei, PhD
Director of Environmental Studies &
Associate Prof. of Political Science
Spelman College

Tanya Khemet Taiwo, CPM, MPH, PhD
Assistant Professor, Department of Midwifery
Bastyr University

Sierra Club
Sonya Lunder, Senior Toxics Policy Advisor

Toxic Free NC
Alexis Luckey, Executive Director

Until Justice Data Partners
Monica E. Unseld, PhD, MPH
Executive Director

Ronald H. White, MST
Principal, RHWhite Environmental Health Consulting

R. Thomas Zoeller, PhD
Emeritus Professor of Biology
University of Massachusetts Amherst
Visiting Professor, Örebro University, Sweden