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Submitted electronically via www.regulations.gov

Re: Docket ID EPA-HQ-OPP-2020-0263

**Comments of the Natural Resources Defense Council,
Earthjustice, and Pesticide Action Network North America
to the FIFRA Scientific Advisory Panel
to consider and review the use of new approach methodologies (NAMs)
to derive extrapolation factors and evaluate developmental neurotoxicity (DNT)
for human health risk assessment,
Sept 15-18, 2020**

Ms. Gibson:

We appreciate the opportunity to provide comments to the FIFRA Scientific Advisory Panel (SAP) on the use of New Approach Methodologies.

The Pesticide Office is calling a meeting of the FIFRA SAP on Sept 15-18, 2020, to invite peer review on the use of New Approach Methodologies (NAMs) to evaluate inter- and intra-species variability, and developmental neurotoxicity (DNT) in human health risk assessment. Our organizations have serious reservations about the proposed uses, and we urge the SAP to reject the proposal completely, to avoid undermining decades of work to protect the public from harmful chemicals.

As a preliminary matter, in response to an EPA FR Notice inviting public comments on its list of candidates to serve on the panel, our groups wrote to ask that EPA re-open the nomination period, and delay this FIFRA SAP meeting until at least the new year, 2021. Our concerns about conflicts of interest and the timing of review, relative to other in-process analyses, have not been addressed, so these comments renew our request to postpone the FIFRA SAP meeting. We have included our previous comments (EPA-HQ-OPP-2020-0263-0024) as an Appendix to these comments and incorporate by reference herein.

However, if the meeting does proceed as scheduled, the SAP should guard against unintended consequences that would likely result from an increased reliance on NAMs.

We are alarmed that EPA is proposing to reduce the default uncertainty factors (UFs) – interspecies, intraspecies, FQPA – and thus reduce important protections for farmworkers, pregnant women and children, and wildlife.[1]

[1] EPA: "As new approach methodologies (NAMs) can provide human relevant information that may be challenging to test in whole animals, EPA's OPP is also interested in using NAMs to reduce the reliance on default assumptions for risk assessment, including the application of 10X default uncertainty factors each for interspecies and intraspecies

EPA has selected the OP pesticides, including chlorpyrifos, as its first case study, because the risk estimates and regulatory decisions for every OP except chlorpyrifos is still based on cholinesterase inhibition (AChEi).[2]

EPA is asking the FIFRA SAP to consider an Exponent report funded by three agrochemical companies - AMVAC, FMC Corp, and Gowan – that concludes that there is, "very little evidence for effects among different subpopulations" with regards to intrahuman variability in acetyl cholinesterase (AChE) inhibition and suggests that the current 'intrahuman [pharmacodynamic] factor' of 3X is too high (Exponent report, p. 35-36).

EPA is asking two sets of charge questions to the SAP:

- First – can EPA use the results of NAM tests to determine if a pesticide may be DNT? Our response is that these tests are informative and should be used to complement more reliable information from whole animal and epidemiologic and other studies.
- Second – can EPA use an Exponent analysis funded by pesticide registrants to replace default pharmacodynamic (PD) interspecies and intraspecies factors with "data derived extrapolation factors" (DDEFs)? Exponent's analysis relies on the presumption that the active site on the AChE molecule has the same structure across species, and therefore has the same function, and the same PD activity. A memo from EPA ORD refutes this (Padilla memo, July 9, 2020). Even EPA's final charge question seems to doubt Exponent's analysis, noting that, "*The results were not consistent across the chemicals, ranging from 3% to 97% of the total variability due to differences in the replicate analyses".*

To the first set of charge questions regarding the use of NAMs information, we ask the SAP to recommend that the results of NAM tests should be used to strengthen or up-grade risk estimates, but not to down-grade or weaken them. To the second set of charge questions, regarding the Exponent paper, we ask the SAP to refute this analysis, as it relies on the false presumption that AChEi is the most sensitive endpoint, when both non-industry rodent studies and epidemiologic studies prove that it is not. Our detailed responses to the charge questions follow.

Documents discussed in these comments:

- Charge questions EPA-HQ-OPP-2020-0263-0018
- EPA Issue Paper EPA-HQ-OPP-2020-0263-0006
- EPA (Stephanie Padilla memo) on Exponent EPA-HQ-OPP-2020-0263-0005
- Exponent statistical analysis EPA-HQ-OPP-2020-0263-0013
- Comments of NRDC, Earthjustice, and PANNA on the nominees to this SAP, July 30, 2020. Docket ID EPA–HQ–OPP–2020–0263-0024

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extrapolations…. If appropriate, EPA's OPP may use such NAM information as part of a weight of evidence evaluation for the 10X Food Quality Protection Act (FQPA) Safety Factor." (EPA Issue Paper, p. 5, EPA-HQ-OPP-2020-0263-0006)

[2] EPA: "in vitro acetylcholinesterase (AChE) inhibition data has been generated for OP compounds. The OPP is considering the potential use of these data to develop interspecies and/or intraspecies data-derived extrapolation factors (DDEFs) in accordance with EPA's 2014 Guidance for Applying Quantitative Data to Develop DDEFs for Interspecies and Intraspecies Extrapolation." (EPA Issue Paper, p. 5)

DETAILED RESPONSE TO CHARGE QUESTIONS

NAMs for Developmental Neurotoxicity

CHARGE QUESTION 1. Using primary rat cortical neurons grown on microelectrode arrays (or MEAs), the EPA's Office of Research and Development has developed a network formation assay (NFA) to assess the potential impact of chemical exposure on neural network formation and function. Please comment on the strengths and limitations of using this assay to evaluate these endpoints as a component of neurodevelopment that may be susceptible to modulation by chemical exposure.

Strengths:
There is nothing inherently problematic with the use of MEAs to assess impacts to neuronal network formation. From the data presented by the Agency, the MEA evaluation appears to provide useful information about general neuronal activity, bursting, and connectivity. While these tests are not a panacea for understanding the full potential of chemicals to be developmentally neurotoxic, they do benefit from their ability to probe multiple molecular initiating events and cellular functions in relatively contained systems. These features make them particularly ripe for positively identifying chemicals with DNT potential.

Overarching Limitations:
Though the NFA assay has seemingly clear benefits, there are notable limitations that make them inappropriate for use in downgrading or weakening risk estimates and/or identifying chemicals without DNT activity. Significant limitations include but are not limited to the following:

- Lack of biological coverage - Important mechanisms for DNT (e.g., thyroid disruption, neuronal migration, neuronal subtype differentiation, oligodendrocyte differentiation, and oligodendrocyte maturation) are missing from the current (and proposed) battery of assays.
- Lack of metabolism – for many chemicals, particularly the chemicals tested in this OP case study, the active moiety of the chemical is the metabolite. Though some oxon metabolites were tested in this case study (e.g., chlorpyrifos oxon), the results of the tests demonstrated clear differences in activity based upon chemical state (i.e., metabolite versus parent). The lack of metabolic competence can limit the ability of these tests to determine the "true" biological activity of a particular substance in a whole animal system – including humans.[3]
- Differences between rat cortical and hPSC-derived MEAS – recent evidence reported in Hyvärinen et al, (2019) suggests that MEAs developed with human pluripotent stem cell derived neurons provide unique patterns of bursting (neuronal firing activity) relative to MEAs with rat cortical cultures.[4] While the potential species-related differences between

[3] Aschner M, Ceccatelli S, Daneshian M, Fritsche E, Hasiwa N, Hartung T, Hogberg HT, Leist M, Li A, Mundi WR, Padilla S, Piersma AH, Bal-Price A, Seiler A, Westerink RH, Zimmer B, Lein PJ. Reference compounds for alternative test methods to indicate developmental neurotoxicity (DNT) potential of chemicals: example lists and criteria for their selection and use. ALTEX. 2017;34(1):49-74. doi: 10.14573/altex.1604201. Epub 2016 Jul 25. PMID: 27452664; PMCID: PMC5250586.

[4] Hyvärinen, T., Hyysalo, A., Kapucu, F.E. *et al.* Functional characterization of human pluripotent stem cell-derived cortical networks differentiated on laminin-521 substrate: comparison to rat cortical cultures. *Sci Rep* **9**, 17125 (2019). https://doi.org/10.1038/s41598-019-53647-8

these cells does not prohibit the use of information from rat cortical MEAs, it does raise the possibility that the HFAs used by the Agency could miss important activity and/or potency relevant to human outcomes. To overcome this obstacle, the inclusion of default interspecies uncertainty factors remains a prudent practice.

- Emphasis on acute toxicity – identifying chemicals with acute toxicity is an important function of NAMs, but DNT substances are known to exert both acute and chronic effects. The inability to assess chronic effects of the chemicals being tested can result in a significant gap in knowledge about the effects of long-term exposures of chemicals substances on developing brains.
- The use of selectivity measures that decrease sensitivity and increase specificity – in order to fulfill its mandate to protect health and the environment, the agency should seek to develop tools that are more sensitive than specific. That is, assays such as the ones utilized in the white paper should seek to minimize false negatives (Type II error) while permitting increased levels of false positives (Type I error), so as to ensure a 'reasonable certainty of no harm' to people including sensitive individuals such as pregnant women and children. As noted by Harrill et al (2018) the inclusion of selectivity measures in developmental neurotoxicity assays shifts the outcome in the wrong direction, resulting in *decreased* sensitivity of a DNT assay battery from 87 percent to 68 percent and *increased* specificity from 71 percent to 93 percent.[5] These changes imply that the criteria used to distinguish non-specific cytotoxicity from DNT-relevant cell death are overly stringent and less health-protective.

<u>Reliability concerns:</u>

In addition to the technical limitations described above, the variability in the reproducibility of the MEA NFA for the test substances was quite alarming. The coefficient of variation (CV) for the DMSO vehicle control wells were greater than 20% in some cases. These values exceed the intra-plate test criteria set forth by the NIH HTS Assay Validation Manual (Iversen et al, 2012) – potentially limiting the acceptability of the data obtained from these assays.[6]

Reliability issues surfaced in the case study chemicals as well. Less than 50 percent of samples (10/21) had consistently positive or consistently negative results. These results significantly diminish the interpretability of the data obtained from these assays. While potential reasons for these missed results were given in the white paper (e.g., sample stability, culture preparations, temporal differences, and personnel changes), no additional details were provided on the ways in which the Agency will avoid these issues in the future and/or retest for reliability once the potential sources of error have been completed.

Finally, it is particularly concerning that the chlorpyrifos oxon produced mixed results in the MEA NFA assay. The chlorpyrifos oxon is an especially potent developmental neurotoxicant – one that has been

[5] Harrill JA, Freudenrich T, Wallace K, Ball K, Shafer TJ, Mundy WR. Testing for developmental neurotoxicity using a battery of in vitro assays for key cellular events in neurodevelopment. *Toxicol Appl Pharmacol*. 2018;354:24-39. doi:10.1016/j.taap.2018.04.001

[6] Iversen PW, Beck B, Chen YF, et al. HTS Assay Validation. 2012 May 1 [Updated 2012 Oct 1]. In: Markossian S, Sittampalam GS, Grossman A, et al., editors. Assay Guidance Manual [Internet]. Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK83783/

used previously for validation of HTS in vitro screens [Harrill, 2012; Frank 2017].[7] The inconsistency of the tests for this specific chemical is of grave concern, as is the Agency use of these data despite the expressed reasons for the observed discordance (i.e., experiments being performed in different years by different laboratory technicians). The use and interpretation of these data for developing PODs, AEDs, and UFs is extremely premature, given the significance of the reliability issues associated with this assay.

CHARGE QUESTION 2. The EPA's Office of Research and Development has used high content imaging (or HCI) with a variety of rat- and human-derived in vitro models to investigate the potential impact of chemical exposure on cell proliferation, apoptosis, neurite outgrowth, and synaptogenesis. Please comment on the strength and limitations of using the HCI assays to evaluate these endpoints as components of neurodevelopment that may be susceptible to modulation by chemical exposure.

Limitations:
Most of the HCI testing battery assays involve neuron-specific endpoints only. Critical processes are under-represented, or not represented at all, such as differentiation, migration, and myelination. This battery should also include examination of glia to widen the scope of DNT effects captured by these assays. Glial cells play a critical role in nervous system development and developing glia may be at least as sensitive to chlorpyrifos than neurons based on *in vivo* and *in vitro* evidence.[8]

As with the MEA NFA tests, the OP chemicals in the HCI assays had positive assay results (called hit-call responses) that indicated activity but were not scored as selective (Table 13 p. 48 of the issue paper). This is true of all of the OPs for at least one of the five HCI assays, indicating that there is a potential for false negatives even when positive hit-calls are recorded.

EPA concludes in the Issue Paper that there is consistency across both the MEA NFA assay and the HCI assays, based on a half dozen or so OP pesticides, indicating that, "if activity is observed in the HCI assays, it is also likely that the OP chemical will also be active in the MEA NFA" (EPA, p. 44). However, far more is known about OPs (such as the mechanism of action) than would be known about most chemicals and even most pesticides that could potentially be tested by this battery of assays. Using OPs, which are relatively well-characterized chemicals, as a case study provides valuable information, but more caution should be applied to over-interpreting the results and extrapolating findings to other chemicals. Important effects could be missed when screening new chemicals if the results of these tests are over-interpreted or relied upon to exonerate chemicals or down-grade toxicity concerns.

All of the OPs that were grouped in the first cluster (i.e., no effects or effects in 1-3 assay endpoints for HCI results-- see Figure 6, p. 43 of the issue paper) were oxon containing OPs. It's known that the chlorpyrifos oxon as well as chlorpyrifos can interact with signaling intermediates downstream from

[7] Frank CL, Brown JP, Wallace K, Mundy WR, Shafer TJ. From the Cover: Developmental Neurotoxicants Disrupt Activity in Cortical Networks on Microelectrode Arrays: Results of Screening 86 Compounds During Neural Network Formation. Toxicol Sci. 2017;160(1):121-135. doi:10.1093/toxsci/kfx169

Harrill JA, Freudenrich T, Wallace K, Ball K, Shafer TJ, Mundy WR. Testing for developmental neurotoxicity using a battery of in vitro assays for key cellular events in neurodevelopment. Toxicol Appl Pharmacol. 2018;354:24-39. doi:10.1016/j.taap.2018.04.001

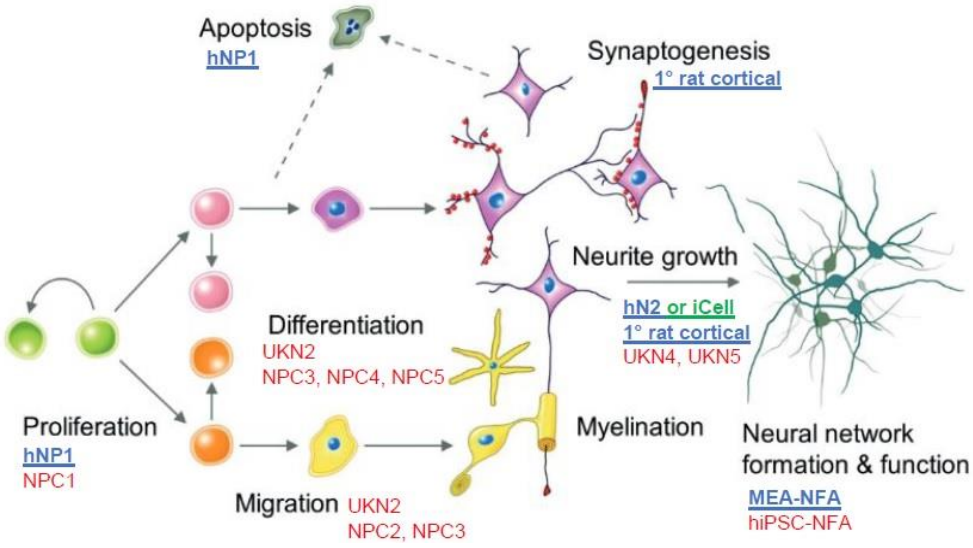
[8] Slotkin TA. Developmental Neurotoxicity of Organophosphates. In: *Toxicology of Organophosphate & Carbamate Compounds*. Elsevier; 2006:293-314. doi:10.1016/B978-012088523-7/50022-3

nicotinic and muscarinic cholinergic receptors.[8] The MEA NFA results for the oxon containing OPs also did not give clear results, indicating that the battery of tests provides useful information but also misses critical adverse from known neurotoxic compounds like the OP oxons grouped in the first cluster for HCI assay results.

CHARGE QUESTION 3. As discussed in Section 2.1 of the Agency's Issue Paper (EPA-HQ-OPP-2020-0263-0006), EPA has shifted its testing focus from the developmental neurotoxicity guideline study to more targeted testing due to several challenges associated with the study and its limited impact on human health risk assessments for pesticides. New approach methodologies (or NAMs) provide an opportunity to overcome some of these challenges by evaluating underlying critical processes of neurodevelopment and incorporating human relevant information. NAMs covering critical processes in neurodevelopment developed by EPA's Office of Research and Development and researchers funded by the European Food Safety Authority are presented in Table 3 and Figure 2 of the Agency's Issue Paper. Based on this information and considering the goal of developing a NAM testing strategy or an integrated approach to testing and assessment (or IATA) within the next year for evaluating developmental neurotoxicity to inform chemical risk assessments, please comment on whether the critical processes related to the evaluation of developmental neurotoxicity are reasonably covered by this NAM battery.

The effort presented in the white paper is still in development and is not ready to be used in risk assessment or regulatory decision-making.

The NAM battery addresses some, but not all critical processes related to DNT. As mentioned in the white paper, important mechanisms for DNT (e.g., thyroid disruption, neuronal migration, neuronal subtype differentiation, oligodendrocyte differentiation, and oligodendrocyte maturation) are missing from the current (and proposed) battery of assays See EPA Issue Paper, Figure 2, p. 21 adapted from Aschner et al (2016), reproduced here – the blue lettering indicates an assay described in EPA's issue paper with currently available data. Red and Green lettering indicates assays that do not have data (green) or are still under development (red) and are therefore not informative for this exercise. It is evident that critical processes are under-represented, or not represented at all, such as differentiation, migration, and myelination.



In addition, the proposed NAM battery does not address sex differences in brain development (sexually dimorphic brain regions), a pertinent area of investigation given the complex sexually-dimorphic mechanisms required for normal neurodevelopment,[9] and the substantive evidence supporting DNT to these mechanisms from chemical exposures.[10] Further, examining sex differences in DNT is highly relevant given the established association between sex and the prevalence of DNT-linked neurodevelopmental disorders like autism spectrum disorder (ASD prevalence is up to three times higher in males than females).[11] Neither of the proposed assay batteries accounts for sex differences in DNT. Both the MEA-NFA and HCI batteries fail to differentiate the sex of the rat pups from which primary cortical neurons are derived. Further, all human neuroprogenitor cells employed in the HCI assay battery were derived from the female WA09 human embryonic stem cell line.[12]

Additionally, it is currently unknown whether orthogonal assays are needed to confirm the impacts (or lack thereof) of chemical exposures on proliferation, apoptosis, migration, neuron differentiation, oligodendrocyte differentiation and maturation, neurite outgrowth, synaptogenesis, or network formation. This lack of confirmatory knowledge further prohibits the use of these tools to demonstrate a lack of DNT activity. While the integrated network of DNT processes created by EPA and EFSA represent a good starting place, it should not be considered sufficient for detecting all chemicals involved that act as development neurotoxicants.

The divergence away from specific adverse outcome pathways, at least in concept, is a positive one, but the proposed network still takes a relatively limited approach to the mechanisms by which DNT can arise. Efforts at UCSF and CalEPA are currently underway to systematically evaluate the key characteristics of DNT. In developing its approaches for using NAMs for DNT, EPA should consult with scientists engaged in the key characteristics work and incorporate this thinking into its models before moving forward with developing DNT-centered risk values for pesticide registrations.

EPA has failed to include assays for behavioral outcomes, which are particularly important metrics for identifying chemicals that act on multiple molecular processes and/or operate via extremely complex or unknown mechanisms. EPA acknowledges this in its Issue Paper, noting that, "an additional challenge to the interpretation of DNT data is the issue of correlating behavioral and/or neuropathological effects in the animal model to the myriad of complex neurological deficits seen in the human population ranging from subtle learning disabilities to neural tube defects" (EPA, p. 7). In other words, can these tests identify chemicals that will make it difficult for a child in elementary school to sit quietly in a desk and concentrate? By leaving out the zebrafish assay, EPA is leaving out the only NAM that accounts for

[9] McCarthy MM. Estradiol and the developing brain. Physiol Rev. 2008 Jan;88(1):91-124. doi: 10.1152/physrev.00010.2007.

[10] Dickerson SM, Cunningham SL, Patisaul HB, Woller MJ, Gore AC. Endocrine disruption of brain sexual differentiation by developmental PCB exposure. *Endocrinology*. 2011;152(2):581-594. doi:10.1210/en.2010-1103; Patisaul HB. Achieving CLARITY on bisphenol A, brain and behaviour. *J Neuroendocrinol*. 2020;32(1):e12730. doi:10.1111/jne.12730

[11] Halladay AK, Bishop S, Constantino JN, Daniels AM, Koenig K, Palmer K, Messinger D, Pelphrey K, Sanders SJ, Singer AT, Taylor JL, Szatmari P. Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority. Mol Autism. 2015 Jun 13;6:36. doi: 10.1186/s13229-015-0019-y.

[12] Harrill JA, Freudenrich T, Wallace K, Ball K, Shafer TJ, Mundy WR. Testing for developmental neurotoxicity using a battery of in vitro assays for key cellular events in neurodevelopment. Toxicol Appl Pharmacol. 2018;354:24-39. doi:10.1016/j.taap.2018.04.001

metabolism, includes DNT-relevant behavioral endpoints like learning and memory, and enables the simultaneous examination of DNT across all critical stages of neurodevelopment. Further, the zebrafish assay is an additional vertebrate model, thus adding genetic diversity to the standard rodent-derived assays.

Finally, the agency should not limit itself to mechanisms, pathways, or characteristics that are well-understood. In developing batteries for DNT, the agency should utilize emerging tools (e.g., zebrafish models) for the assessment of behavioral phenotypes associated with exposure to developmental neurotoxicants. There are other NAM tests still in development such as some z-fish transcriptomics assays that could be used to inform a DNT assessment. There are some primary cell assays (brains on chips) that may be used. None of these are currently available. There may be diversity outbred mice that may be fast ways to measure changes in the animal system without the need to examine structural changes in the brain. There is also a virtual tissue and virtual embryo models under development.[13]

CHARGE QUESTION 4. Organophosphate pesticides share the ability to inhibit the acetylcholinesterase enzyme, which prevents the breakdown of acetylcholine leading to neurotoxicity. Inhibition of acetylcholinesterase is the basis of current OP human health risk assessments. In order to compare the relative sensitivity of the MEA NFA and HCI assay results to doses that inhibit acetylcholinesterase in laboratory animals, in vitro to in vivo extrapolation (or IVIVE) approaches were used to approximate NAM administered equivalent doses for a subset of organophosphate pesticides. Please comment on the strengths and limitations of this comparison and whether there are alternative approaches for this evaluation.

The IVIVE approaches utilized by the Agency suffer from significant limitations. First, the AEDs derived from the IVIVE calculations were often several orders of magnitude higher than the BMDL10 estimates – which in some cases (e.g., chlorpyrifos) are known to be underestimates of the levels that cause harm in children. In particular, EPA has already determined that the neurobehavioral effects seen in both animals and human epidemiology is below the level that triggers AChE inhibition. Using AChE inhibition as the BMDL is insufficient to validate the sensitivity of the NAM assay on an insensitive endpoint of AChEi. See OEHHA's 2017 review, which is very thorough and very specific, noting that, "DNT effects were observed at doses that elicit minimal or no brain AChE inhibition" in registrant-sponsored and non-industry rodent studies, making DNT a more sensitive endpoint than AChE inhibition (OEHHA 2017, p. 4, 6).[14]

EPA's white paper cites for the reason for AEDs exceeding the BMDL10s is that the IVIVE calculations were based upon the *median individual in the general population*. This is a **completely** unacceptable

[13] See National Toxicology Program, NICEATM: Alternative Methods. https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/dev-tox/index.html

[14] Office of Environmental Health Hazard Assessment's (OEHHA) findings on the health effects of the active ingredient chlorpyrifos relevant to its review as a candidate toxic air contaminant (TAC). Summary: "OEHHA's analysis finds that the margin between modeled air concentrations of chlorpyrifos and the levels of chlorpyrifos exposure associated with health effects is not sufficiently protective. As is the case with the department's analysis, OEHHA's findings support the identification of chlorpyrifos as a TAC." Memo to Shelley DuTeaux from David Ting, December 12, 2017. Available online: https://oehha.ca.gov/media/downloads/pesticides/report/chlorpyrifostacfindings121217.pdf

model assumption for processes that impact developing brains. As the agency notes in the white paper on page 66:

> "*The AED_{50} values from DNT-NAM bioactivity presented for comparison, importantly, used the median individual in the general population for the HTTK-based IVIVE approach; accounting for interindividual variability (i.e., first order hepatic clearance, plasma protein binding, liver physiology, and glomerular filtration rate) and/or using a more sensitive individual or subpopulation would result in different AED values (indeed, lower values would result by using an estimate of a more toxicokinetically-sensitive individual)…Overall, the AED50 to BMD10/BMDL10 comparisons suggest that the doses required to achieve plasma concentrations (in the median individual in the general population) that demonstrate in vitro bioactivity relevant to DNT are higher than and in some cases approach the doses that have been associated with significant changes in AChE activity in rats.*" [p. 66]

The development of a model for DNT that does not utilize children as the subpopulation is nothing short of a complete and utter absurdity that is not only unfit for regulatory use but is an affront to scientific principles and thinking. By moving forward with its proposal to use these methods to strip away default UFs, EPA is abdicating its obligations under FQPA, including the obligations to "ensure that there is reasonable certainty that no harm will result to infants and children from aggregate exposure" to a pesticide and to account for pre- and post-natal toxicity. 21 U.S.C. § 346a(b)(2)(C)(ii).

DDEFs Using In Vitro AChE Inhibition Data

CHARGE QUESTION 5. In vitro acetylcholinesterase inhibition data have been generated for rats and humans to develop interspecies and intraspecies data-derived extrapolation factors (or DDEFs) for pharmacodynamics for 16 organophosphate compounds in accordance with EPA's 2014 Guidance for Applying Quantitative Data to Develop DDEFs for Interspecies and Intraspecies Extrapolation. Please comment on the strengths and limitations of these data. Please include in your comments a consideration of the study design and methods, appropriateness of the selected measures, sufficiency of reporting, and robustness of the data, including sample size.

See EPA memo from Stephanie Padilla, July 9, 2020 on the Exponent Whitepaper (EPA-HQ-OPP-2020-0263-0005).

An underlying argument made throughout the supplemental document is that similar 3D structures lead to similar interactions with AChE inhibitors due to similar amino acid sequences. However, Exponent failed to acknowledge many additional aspects of AChE structure that may have the potential to affect its function and activity. Therefore, the approach of aligning 3D structures and focusing solely on the catalytic site for reaching conclusions about PD parameters is not substantiated.[15]

[15] EPA, Padilla memo: "The supplemental document by Exponent (MRID 50773505) is a component of the data package submitted by the consortium of three agrochemical companies for the generation of DDEFs for several registered OPs (MRID 50773501-50773503). These studies were conducted to quantify potential differences, if any, in PD parameters between rats and humans and across the human population. These data have the potential to encompass potential post-translational modifications and potential mutations of concern that may have an impact on PD parameters in humans. However, the Agency has expressed concerns with the number of samples in these analyses and subsequently whether the sample set is sufficient to address the human population.

CHARGE QUESTION 6. Given the structure of correlated data, nonlinear mixed-effects models were used to analyze the in vitro inhibition data in order to calculate the interspecies and intraspecies pharmacodynamic DDEFs. The ratios of the biomolecular rate constants between species or subpopulation were estimated from the nonlinear mixed-effects models. For a number of chemical-specific datasets analyzed by Exponent, the fitted non-linear mixed model generated warning statements due to a full rank final Hessian matrix. Additionally, for several of the chemical-specific datasets analyzed, visual evaluation of diagnostic plots revealed severe outliers or a severe imbalance in the distribution of residuals leading to questionable model fit. (Note: Statistical analyses and results are presented in earlier reports from Exponent; however, the SAP should focus on the statistical analyses and results presented in the supplemental analysis (MRID 51182301) for their evaluation and comment.)

a. Please comment on the methods or techniques used in the nonlinear mixed-effects models.
No comment

b. Please comment on any concerns associated with the warning statements and model-fit issues and suggest, if necessary, methods or techniques for addressing such warning statements and model-fit issues.
No comment

CHARGE QUESTION 7. For the intra-species analyses, Exponent conducted stratified analyses, where the 18 human samples were subset into smaller groups to estimate the biomolecular rate constant ratios for these subgroups. EPA has concerns with the reliability of these stratified analyses due to the small sample sizes of the subgroups. Please comment on these analyses and their utility to evaluate intraspecies human variability in response to organophosphate exposure.

We share EPA staff concerns. Not only is the sample size too small to power the type of stratified analysis employed by Exponent, there are significant issues with the relative ratios of populations included in the analysis. Of the 18 samples, 14 were from people over the age of 10 (ranging from 10 – 60) and 4 cord blood samples. This represents a severe undercounting of populations (i.e., developing children) that are the most susceptible to the effects of OP exposures. Additionally, of the 18 samples, 13 were from white subjects, 3 from Black subjects, and 2 from Hispanic subjects. These samples completely exclude important U.S. ethnic groups and are not representative of exposure patterns observed in real-world settings.

EPA, Padilla memo: "The document provided an extensive summary of existing knowledge regarding AChE in rats and humans, including amino acid sequence alignments and 3D structures; however, it could benefit from discussion of additional aspects of AChE structure, beyond the catalytic site, that have the potential to affect its function and activity." Exponent fails to account for all the possible structural and functional differences outside of the catalytic site of the AChE molecule.

EPA, Padilla memo: Exponent relies on measurements of RBC AChE activity being used as a surrogate for nervous tissue AChE activity, but there is a sparsity of empirical evidence available to support or refute whether RBC AChE PD parameters accurately reflect brain AChE parameters.

Even for the chemicals for which there were no model fit issues, the sample sizes are so small and the interspecies variation so little (and absurdly skewed away from the most sensitive population) that it is impossible to interpret the results from these analyses in a reasonable or meaningful way.

CHARGE QUESTION 8. For intraspecies analyses, a limited subset of chemicals had three replicate analytical results on each of the four sources of human samples. The results from these analyses were used by Exponent to characterize the total variability of the estimates in terms of experimental variability and subject variability. The results were not consistent across the chemicals, ranging from 3% to 97% of the total variability due to differences in the replicate analyses. Please comment on the utility of these analyses.

Exponent's analysis claims to measure AChE inhibition kinetics across the human population, but the studies used very small numbers, and instead relies on the unsupported presumption that the 3D structure and sequence homology across species at the AChE catalytic site is enough to evaluate pharmacokinetic differences across the human population – it is not.

The Exponent document claims that mutations in some sites would not be expected to alter catalytic properties, but the publications that Exponent references show differences in activity of 2-7.5 times. Further, mutations may occur elsewhere on the AChE molecule, which are not considered by Exponent.

CONCLUSION

This SAP is being convened toward the end of the registration review process. EPA prioritized the OPs in that process because of the risks they pose to public health and of neurodevelopmental harm to children in particular. Under its work plans, EPA was scheduled to issue final risk assessments and safety findings for most if not all of the OPs by 2014-2015, but it has fallen short of the timelines it had set.[16] After extensive reviews of the weight of the evidence, including from gold standard epidemiology studies, EPA found that the OPs are associated with neurodevelopment harm to children at low level exposures than those that cause 10% cholinesterase inhibition, and EPA retained the FQPA tenfold safety factor because of this harm.[17] EPA has released preliminary or final human health risk assessments for the OPs using its standard risk assessment methodology and most retained the FQPA 10X. However, EPA used 10% red-blood cell cholinesterase inhibition to establish the point of departure, even though it is not a no-effect level; the harm to children's brains occurs from exposures below that level. These risk assessments find serious risks of concern from many, and for some OPs, the bulk, of uses of the pesticide. The risks of concern are from food, drinking water, pesticide drift, or worker exposures when they handle the pesticide or enter treated fields or for multiple of these routes of exposure.[18] This SAP is being asked to endorse new methods that would reduce or eliminate the risks

[16] *See, e.g.,* file:///C:/Users/pgoldman/Downloads/EPA-HQ-OPP-2009-0316-0010%20(1).pdf (work plan for phosmet); Other work plans available through individual pesticide searches at https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1.

[17] EPA. Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides (Sept. 15, 2015), at https://www.regulations.gov/searchResults?rpp=25&po=0&s=EPA-HQ-OPP-2016-0062-0055&fp=true&ns=true.

[18] For example, ethoprop poses risks of concern in food, drinking water, and drift, as well as to workers who handler the pesticide, at https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0560-0028; bensulide poses risks of

of concern, not by reducing the exposures, but by changing the methodology mid-stream. We urge the panel to reject this proposal and recommend that EPA not use the new methods to reduce safety factors and public health protections.

Respectfully,

Jennifer Sass, Ph.D., Senior Scientist, Natural Resources Defense Council
Kristi Pullen Fedinick, Ph.D. Director of Science and Data, Natural Resources Defense Council
Emily Marquez, Ph.D. Staff Scientist, Pesticide Action Network North America
Rashmi Joglekar, Ph.D. Staff Scientist, Earthjustice
Patti Goldman, Managing Attorney, Earthjustice

concern in food and drift, as well as to handlers, at https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0022-0019; phosmet poses risks of concern in food and drift, as well as to handlers and field workers, at https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0316-0022; and dimethoate poses risks of concern in food, drinking water, and drift, as well as to handlers and field workers, at https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0059-0027.

APPENDIX : COMMENTS ON THE SAP CANDIDATES, JULY 2020

July 30th, 2020

Comments submitted from
Natural Resources Defense Council,
Earthjustice, and Pesticide Action Network North America

On the FIFRA Scientific Advisory Panel;
Request for Nominations of Ad Hoc Expert Reviewers
to consider and review the use of new approach methodologies (NAMs)
to derive extrapolation factors and evaluate developmental neurotoxicity (DNT)
for human health risk assessment.

Docket ID EPA–HQ–OPP–2020–0263-0024

Submitted electronically via www.regulations.gov

We appreciate the opportunity to provide comments in advance of the selection of members to the FIFRA Science Advisory Panel on the use of new approach methodologies to derive extrapolation factors and evaluate developmental neurotoxicity for human health risk assessment.[19] Our groups have no direct or indirect financial or fiduciary interest in the manufacture or sale of any chemical or methodology that would be the subject of the deliberations of this Committee.

The work of this Panel will directly benefit pesticide companies and consultants

The work of this panel is to, "consider and review the use of new approach methodologies (NAMs) to derive extrapolation factors and evaluate developmental neurotoxicity for human health risk assessment." This panel will be the first FACA peer review of the application of these new methods by EPA to evaluate developmental neurotoxicity. Moreover, EPA specifically states in its Issue Paper that, "EPA's OPP is also interested in using NAMs to reduce the reliance on default assumptions for risk assessment, including the application of 10X default uncertainty factors each for interspecies and intraspecies extrapolations" (EPA Issue Paper, p. 5). That is, the Pesticide Office hopes to use information from NAMs to reduce or replace default uncertainty factors that have long been required to provide an added measure of protection for vulnerable and sensitive individuals. People needing protection include pregnant women and children, elders, people with chronic or underlying health conditions, and farmworkers and others with regular exposure to many pesticides and other harmful chemicals.

Of eight charge questions to be considered by the SAP, two of them pertain to default adjustment factors, for which the Pesticide Office is directing the SAP to consider a paper by Exponent, a company that is hired by industry to defend products and processes associated with harm to public health.[20] And,

[19] https://www.regulations.gov/docket?D=EPA-HQ-OPP-2020-0263

[20] Exponent - Supplemental Statistical Analysis of Organophosphorus (OP) Pesticides In Vitro Inhibition Study. Kelly Higgins, Leila Barraj, Risk Reiss. Exponent. Sponsors: AMVAC Chemical Corporation, FMC Corporation, Gowan Company. May 28, 2020. MRID: 51182301 EPA-HQ-OPP-2020-0263-0013

leaving no doubt what entities are served by Exponent's paper, it lists three agrochemical companies as sponsors: AMVAC Chemical Corporation; FMC Corporation; Gowan Company.

The Exponent industry report concludes that there is, "very little evidence for effects among different subpopulations" with regards to intrahuman variability in acetyl cholinesterase (AChE) inhibition and suggests that the current 'intrahuman [pharmacodynamic] factor' of 3X is too high (Exponent report, p. 35-36). If the Pesticide Office were to adopt the Exponent report findings, it would almost certainly lead to reductions in the default adjustment factors, reductions in risk estimates, and ultimately weakened pesticide regulations that benefit pesticide registrants, including those that sponsored the Exponent report. This would weaken health protections by the following actions: expanded pesticide approvals; increased allowable application rates; shortened re-entry intervals; reduced PPE requirements for farmworkers; increased residues in food and water.[21]

Request that EPA coordinate its efforts with the California EPA working group to identify key characteristics for neurotoxicants and developmental neurotoxicants

Given the far-reaching public health implications of this panel, it is alarming that the Pesticide Office seems to be rushing this through without coordination among the scientific community. Specifically, and most unfortunately, it has not coordinated its efforts with a major scientific initiative on exactly this issue, sponsored by California EPA and led by Professor Pamela Lein at UC Davis. This government-academic collaboration includes scientists from across the U.S., the European Union, Japan, and other countries, working together to understand the individual NAM tests, identify key characteristics of neurotoxicity and developmental neurotoxicity, and conduct a systematic review of test outcomes.[22] A published report is expected sometime at the end of this year or early 2021. And, yet, we were troubled to learn that the EPA Pesticide Office has not engaged in discussions with this working group, has not reached out to its members or to California EPA staff, and does not even list Dr. Lein among the candidates being considered for this panel, even though she would be among the most qualified to advise on this topic. In short, EPA's Pesticide Office is setting a timetable that will not benefit from the national dialogue on this subject, will not be aligned with the work of state agencies, and will not include input from the nation's leading experts on using NAMs to address developmental and neurotoxicity.

The Pesticide Office is delving into a novel – and highly questionable – use of NAMs to inform uncertainty and adjustment factors (EPA Issue Paper, p. 5). No government body has used NAMs for this purpose. Yet, the Pesticide Office is not only moving into unchartered scientific territory but is doing so without the benefit of California EPA's current scientific collaborations or established scientific principles of systematic review.

Additionally, the Pesticide Office is not following accepted scientific principles for systematic review adopted by the Institute of Medicine (IOM), the National Toxicology Program (NTP) and EPA's Integrated Risk Information System (IRIS) and endorsed by the NAS and other peer review bodies. In fact, the

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Michaels, D. The Triumph of Doubt: Dark Money and the Science of Deception. Oxford University Press, 2020. P. 3, 5-6.

[21] https://www.gpo.gov/fdsys/pkg/FR-2017-06-27/pdf/2017-13332.pdf

[22] Key Characteristics: A New Approach to Identifying Potential Toxicants, with Martyn Smith. Ashley Ahearn. The Researcher's Perspective, Vol. 2019, No. 1. Published:22 July 2019. https://doi.org/10.1289/EHP5776

Pesticide Office does not have such a systematic review framework or even systematic review guidelines.

The Pesticide Office's unimaginably fast timeline will prevent it from benefiting from the work of this international collaboration and will likely result in an SAP report that fails to capture the scientific consensus or the best thinking in this area, making it weak and of doubtful utility soon after it is completed.

Request that EPA postpone the SAP meeting until at least 2021, and align with the conclusions of the California EPA working group to identify key characteristics for both neurotoxicants and developmental neurotoxicants

In addition to requesting that EPA re-issue a call for public nominations – for at least one month, until September for the reasons below – we also ask that EPA delay the meeting of the panel. This panel is now slated for a 4-day public peer review meeting on Sept 15-18, 2020. We ask that EPA postpone the meeting until at least 2021, when the final report of the California EPA working group on key characteristics is expected to be published.

Once EPA issues invitations, the panelists will need time to prepare for the work of the panel. Experts that are affiliated with Universities or public health agencies will need extra time, due to pandemic-related duties that include digitizing classroom material to convert classes to online format and responding to pandemic-related health crises. It is for these reasons that EPA agreed to postpone its TSCA Advisory Committee peer review meeting of asbestos.[23] There are additional time and resource burdens that uniquely apply to people working in the field of public health or teaching at a University – people that are now almost absent from EPA's current list of candidates.

Request that EPA re-open public call for nominations until September

In a June 17, 2020 Federal Register Notice, EPA announced a two-week period, until July 2, for public nominations of ad hoc expert reviewers to serve on this FIFRA Science Advisory Panel. [24] We ask that EPA re-open the request for nominations, and we have included nominees in this letter. We make this request on the basis that the short two-week comment period failed to provide the public with a meaningful opportunity to comment. Under Section 4 of the Administrative Procedure Act, a federal agency is required to provide a meaningful opportunity for public comment on any proposed rule (5 USCS § 553). EPA has been clear that opportunities for comment must be meaningful in non-rulemaking processes as well. For example, on its National Environmental Policy Act (NEPA) website, EPA states, "Agencies are required to provide meaningful opportunities for public participation" during the NEPA process.[25] The comment period for nominations for this panel failed to provide meaningful public engagement for the following reasons:

[23] "EPA is postponing the Toxic Substances Control Act Science Advisory Committee on Chemicals (SACC) peer review virtual meeting scheduled for April 27-30, 2020, due to recent changes in the availability of members for this peer review." https://www.epa.gov/chemicals-under-tsca/april-27-30-2020-tsca-science-advisory-committee-chemicals-meeting-asbestos

[24] https://www.regulations.gov/document?D=EPA-HQ-OPP-2020-0263-0001

[25] How Citizens Can Comment and Participate in the National Environmental Policy Act Process, U.S. EPA, https://www.epa.gov/nepa/how-citizens-can-comment-and-participate-national-environmental-policy-act-process.

1. The nomination period was open for only two weeks, which is half the time EPA normally provides. For example, for the most recent SAP meeting on surface water monitoring, EPA published an FR notice on August 13 asking for nominations by September 12, 2019.[26]
2. Even one month is a short time to gather high quality nominations of experts with appropriate expertise in the areas of relevance for this panel, given the pandemic-related work disruptions that everyone across the nation is suffering, ranging from lack of childcare to illnesses and even deaths in families and among friends.
3. There are almost no candidates from academia (only 4 of the 21 candidates, 19%, list a university as their sole affiliation, see details below). This is likely due to EPA's 2017 directive restricting individuals with grant funding from serving on committees.
4. A comment period is not meaningful if the Agency has already made its decision and is unwilling to consider relevant or substantive points raised in public comments.[27]

Although this SAP's efforts will have wide-reaching impacts, discussed earlier in these comments, EPA received only two public submissions in response to its call for panel nominations – one from the pesticide industry, and one from an animal welfare group.[28] This alone is evidence that a meaningful public nomination process did not take place.

EPA must reopen the nominations process to comply with the law

EPA needs to reopen the nominations process to ensure that it complies with recent court decisions and the law. Recent court decisions and EPA's subsequent policy change require EPA to affirmatively reinstate and ensure implementation of its prior policies to make it clear when soliciting nominations for its scientific advisory committees that EPA grantees may serve.

On October 31, 2017, EPA issued a directive entitled titled "Strengthening and Improving Membership on EPA Federal Advisory Committees," which established a new "requirement that no member of an EPA federal advisory committee be currently in receipt of EPA grants, either as principal investigator or co-investigator, or in a position that otherwise would reap substantial direct benefit from an EPA grant." This directive reversed decades-long EPA policies that EPA funding did not preclude service on EPA's scientific advisory committees. Instead, EPA viewed participants in EPA-funded research as leaders in their fields who often have valuable expertise that can contribute to the integrity and rigor of peer reviews of science used by EPA.

In three separate lawsuits challenging the directive, a declaration from an EPA official who oversaw appointments to an EPA scientific advisory committee described the immediate effect of the directive. Declaration of Christopher Zarba (June 6, 2018). Before the directive, EPA staff "actively recruited qualified individuals from a range of backgrounds, including academia, non-profits, regulated industries, and trade associations," *id*. ¶ 13, and "the receipt of EPA grant funding did not disqualify an otherwise qualified scientist from service on EPA federal advisory committees," *id.* ¶ 15. In addition, EPA staff

[26] Federal Register / Vol. 84, No. 156 / Tuesday, August 13, 2019. ID: EPA-HQ-OPP-2019-0417-0001.

[27] Cf. Air Transport Ass'n of Am., Inc. v. Nat'l Mediation Bd., 663 F.3d 476, 487 (D.C. Cir. 2011).

[28] Comment submitted by Kristie Sullivan, Vice President for Research Policy, Physicians Committee for Responsible Medicine, ID: EPA-HQ-OPP-2020-0263-0004

Comment submitted by Cindy Smith, Chair, Coalition of Organophosphate (OP) Registrants, ID: EPA-HQ-OPP-2020-0263-0003

"placed very high priority on scientific expertise in relevant areas of science in the member selection process" and used peer-reviewed research and publications in specific areas of science as a primary indicator of scientific expertise. *Id*. ¶ 18. EPA viewed EPA grantees as having such expertise and being leaders in their field of inquiry: "A scientist serving as a principal investigator on a project funded by an EPA grant is, as a general matter, a leading expert in their field of study. This is because EPA grants are highly competitive and are awarded through rigorous internal and external peer-review." *Id*. ¶ 19. The directive became mandatory and effective immediately. It led EPA staff to remove EPA grant recipients from scientific advisory committees and to preclude consideration of such grantees for committee appointments. *Id.* ¶¶ 22-25.

An official with longstanding experience with EPA scientific advisory committees testified that to the damaging effects the directive had on the expertise and diversity of views on the scientific advisory committees:

> The bar on service by recipients of EPA grants has seriously damaged the ability of EPA to attract and appoint qualified scientists to serve on EPA federal advisory committees. Even as the Directive has more than doubled the turn-over on the committees, the bar on service by recipients of EPA grants shrinks the recruiting pool by disqualifying many top experts. The result is that many highly qualified experts were excluded from full consideration, limiting the range and depth of expertise and the diversity of perspectives available for the committees. ln the last round of appointments and removals, the SAB Staff Office was forced to pick from a significantly reduced candidate pool. This will inevitably compromise the quality of the SAB, CASAC, and other committees.
>
> When a committee needs particularized scientific expertise, excluding EPA grant recipients from consideration means that the qualified scientists who remain eligible will lack the diversity and balance of scientific perspectives essential to a high-quality review.

Id. ¶¶ 26, 27; *see also id*. ¶ 28 ("l know from conversations with EPA staff that many EPA employees now view the EPA 's federal advisory committees as having a strong bias.").

Two legal challenges to the directive prevailed. On February 10, 2020, the U.S. District Court for the Southern District of New York held that EPA acted arbitrarily and capriciously in adopting the directive because it failed to acknowledge or explain its sharp reversal of EPA's prior policies, provided no basis for believing EPA grantees had actual or perceived conflicts of interest, and failed to consider the effect of ousting EPA grantees on the overall balance of the memberships on the advisory committees. *NRDC v. EPA*, 2020 U.S. Dist. LEXIS 22855 (S.D.N.Y. Feb. 10, 2020). The court subsequently vacated the directive, meaning "the EPA may not categorically exclude EPA grant recipients from serving on advisory committees" and "must simply return to the standards that it historically applied until those standards were altered by the Directive." *NRDC v. EPA*, 1:19-cv-05174-DLC (S.D.N.Y. Apr. 15, 2020) at 3.

In April 2020, the D.C. Circuit Court of Appeals held that the directive was arbitrary and capricious because EPA failed to explain why it was departing from its longstanding policies. It also held that EPA violated applicable procedures requiring that any ethics rules that depart from those adopted by the

Office of Government Ethics be submitted to and jointly promulgated by that office. *Physicians for Soc. Responsibility v. Wheeler*, 956 F.3d 634 (D.C. Cir. 2020).[29]

Rather than appeal the Southern District of New York's vacatur order, EPA announced on June 24, that it will no longer apply this illegal policy.[30] As explained in EPA's press release, both court decisions influenced EPA's decision:

> The decision not to appeal the SDNY judgment was made in light of a related decision by the U.S. Court of Appeals for the District of Columbia Circuit issued in April. Based on that subsequent decision, EPA has determined that any blanket prohibition on the participation of EPA grant recipients as special government employees in EPA advisory committees should be promulgated as a supplemental ethics regulation with the concurrence of the Office of Government Ethics.

EPA also described the impact of its decision not to appeal:

> Because EPA has not promulgated such a regulation, the Agency will continue to follow the relevant policies as they existed before issuance of the 2017 Directive.

Because the directive had become so embedded in EPA's advisory committee appointment procedures and had become widely known both to EPA staff and the public, EPA had to instruct internal staff to reinstitute and apply the prior policies and screening procedures and it had to alert the public that it was inviting EPA grantees to become ad hoc committee members.

EPA's announcement came after EPA had published the Federal Register notice soliciting nominations for the upcoming SAP. It is, therefore is highly likely that EPA grantees and others who may nominate them would have believed EPA grantees were ineligible to serve on the SAP. In order to comply with the court rulings, EPA must affirmatively reinstate and ensure implementation of its prior policies and make it clear when soliciting nominations for its scientific advisory committees, like the SAP, that it is again welcoming nominations of EPA grantees. For this particular nomination process, EPA must reopen the process and publish a new notice in the Federal Register express describing the now-reinstated policies that govern nominations.

Conflicts of interest for *ad hoc* panel members must be publicly disclosed and avoided

EPA also has a duty under the Federal Advisory Committee Act (FACA) and the Federal Advisory Committee Act to transparently vet financial conflicts of interest that bias panel members toward undervaluing scientific evidence of health harms or adverse environmental impacts. Members of the community that review its regulatory priorities and health concerns must not financially benefit from lax or failed environmental safeguards.

[29]In between these two decisions, the U.S. Court of Appeals for the First Circuit overturned a lower court's decision and held that the directive is judicially reviewable. *Union of Concerned Scientists v. Wheeler,* 954 F.3d 11 (1st Cir 2020).

[30] https://www.epa.gov/newsreleases/epa-will-not-appeal-adverse-sdny-decision-regarding-october-31-2017-federal-advisory

The scientific credibility of the EPA is damaged by committees with real or perceived bias. The mission of the SAP is to provide credible and independent scientific analysis and peer review of the scientific and technical aspects of environmental issues to the EPA. EPA must ensure that no panel members have conflicts of interest and it must guard against a strong bias toward the perspective of regulated industries, which would undermine the credibility of the Agency and violate the Federal Advisory Committee Act. EPA should protect its objectivity, integrity, independence, and competence as its most valuable asset. The scientific credibility of the panel and the EPA is damaged by panels with real or perceived bias.

EPA committees must be composed in order to ensure that industry bias is publicly disclosed and avoided. FACA imposes requirements on agencies when they establish or utilize any advisory committee, like the SAP.[31] When an agency seeks to obtain such advice or recommendations it must ensure the advisory committee: is "in the public interest"[32]; is "fairly balanced in terms of points of view represented and the function to be performed"[33]; and will not be "inappropriately influenced by . . . any special interest, but will instead be the result of the advisory committee's independent judgment."[34]

These prohibitions call for special care with respect to the service on advisory committees of individuals whose employers or business would benefit financially from the committee's recommendations. Here the charge to the SAP is to review an industry paper and new methods that could be used to weaken default safety factors, which would benefit registrants and those who advocate to retain pesticide uses whose registrations may depend on such methods. In light of this charge, it is questionable whether any employee of or consultant to a registrant could serve on the SAP without skirting FACA's safeguards.

In addition to FACA's requirements, EPA must ensure that no individual SAP member has conflicts of interest or an appearance of such a conflict. Scientists who serve on EPA's scientific advisory committees are "special government employees," subject to federal conflict-of-interest statutes and regulations.[35] As such, they are subject to executive branch-wide conflicts of interest rules codified at 5 C.F.R. parts 2635-41.

The federal ethics statutes, 5 U.S.C. App. 4 and 18 U.S.C. §§ 201-209, as amended, are "intended to prevent an employee from allowing personal interests to affect his official actions, and to protect governmental processes from actual or apparent conflicts of interests."[36] The Office of Government Ethics (OGE) is charged with issuing conflicts of interest and ethics regulations for the executive branch.[37]

The General Services Administration (GSA), which is charged with issuing binding regulations to implement the Federal Advisory Committee Act,[38] has made the ethics rules applicable to agency

[31] 5 U.S.C. App. II, § 3(2).

[32] Id. App. II, § 9(2).

[33] Id. § 5(b)(2).

[34] Id. § 5(b)(3).

[35] Mem. Ethics Office General Counsel to Designated Agency Ethics Officials Regarding Federal Advisory Committee Appointments at 4 (Aug. 18, 2005); *Physicians for Social Responsibility*, 956 F.3d at 640.

[36] 5 C.F.R. § 2640.101.

[37] 5 U.S.C. App. 4 § 402(b)(1), (6).

[38] *See* 5 U.S.C. App. 2 § 7(c).

establishment and utilization of federal advisory committees. The GSA regulations direct agencies to "apply Federal ethics rules" to prospective members in the appointment process and to review members' "interests and affiliations . . . for conformance" with the regulations.[39]

The ethics rules identify conflicts of interest that preclude service as a special government employee and those that do not. Under the ethics rules, a financial interest can create an actual conflict of interest or an appearance of a conflict that disqualifies the individual from serving in a particular capacity. Individuals are disqualified from participating in a "particular matter" in which they have a financial interest, if the matter will have "a direct and predictable effect on that interest."[40] A direct and predictable effect is evident when there is a "close causal link" between the government action and a financial effect.[41] The financial effect does not need to take place immediately for a close causal link to be established.[42]

The SAP will review new methods being developed to reduce public health protection from toxic pesticides and organophosphates in particular. The SAP's recommendation and underlying methods, if adopted, would have a direct and predictable effect on any company that is a registrant of an OP or other pesticide likely to benefit from relaxed health protection. Such financial effects are real and not speculative. Accordingly, all employees of or consultant to such a company have conflicts of interest that preclude their service on the committee.

In addition to constituting a prohibited conflict of interest, such financial interests pose an impermissible appearance of a conflict. The ethics rules prohibit "any actions creating the appearance that they are violating the law or the ethical standards . . . [and] [w]hether particular circumstances create an appearance that the law or these standards have been violated shall be determined from the perspective of a reasonable person with knowledge of the relevant facts."[43] Allowing participation on the SAP by individuals with financial ties to registrants who will benefit from a weakening of current safety standards and methods creates such an appearance. The public would not envision that such self-dealing would occur in the name of independent scientific peer review.

EPA must strictly enforce its own ethics policies regarding disclosure and financial conflicts.[44] Effective disclosure policies and faithful implementation of ethics rules to avoid conflicts and appearances of conflicts play an essential role in protecting EPA and committee work products. If such interests are discovered later, it may seem that either the EPA or the individual was intentionally hiding this information from the public or stacking the SAP, thereby casting doubt on the Committee's work products, and on EPA's ability to identify conflicts and enforce its own policies.

Comments on specific candidates

<u>Chemical industry nominees who we oppose:</u>

[39] 41 C.F.R. part 102-3, subpt. C, App A; 41 C.F.R. § 102-3.105(h).

[40] 5 C.F.R. § 2635.402(c).

[41] *Id.* § 2635.402(b)(1).

[42] *Id.*

[43] 5 C.F.R. § 2635.101(b)(14); *see also Id.* § 2635.502(a) (stating that a special government employee should not participate in a matter where "a reasonable person with knowledge of the relevant facts" would "question his impartiality in the matter.").

[44] https://yosemite.epa.gov/sab/sabproduct.nsf/Web/ethics?OpenDocument

The candidate list of 21 nominees includes six individuals who are employed by the chemical industry, either directly or as a consultant. We oppose these nominees on the basis that they have direct or indirect financial conflicts, or that their clients and financial sponsors have not been disclosed. The financial interests of candidates must be fully disclosed so EPA and the public can accurately assess the candidate's perspectives, biases and financial conflicts. Committee membership should exclude experts with financial interests in the matter and must, under the conflict of interest rules, exclude any individual whose employer or business might predictably be affected by the matter under consideration.

While we do not intend to disparage the qualifications or personal or professional reputations of any of the candidates, we oppose the following six individuals due to their financial interests on behalf of the regulated industries that could be directly impacted by the deliberations of this Committee:

1. Harvey Clewell works for Ramboll US Corporation, a product defense company. The relationship between Ramboll and Dow Chemical is so close that Ramboll has employees on assignment at Dow Chemical.[45]
2. Penelope Fenner-Crisp is a private consultant. She was employed by the International Life Sciences Institute (ILSI) from 2000-2004, which represents the food industry, which has a direct financial interest in pesticide approvals. Her biography in the candidate list fails to identify any of her current or recent clients, and otherwise fails to identify any of her financial sources. Without this information, the public is unable to evaluate whether Dr. Fenner-Crisp has any direct financial conflicts, biases, or non-financial interests. Until this is made public, we oppose her nomination.
3. Daland Juberg is identified as a consultant on the candidate list. His candidate biography says he was employed by Dow AgroSciences from 2002 until last year, 2019. Just last year, he published a defense of chlorpyrifos that listed his affiliation as an employee of Corteva AgroSciences, and his email with Dow Chemical 'drjuberg@dow.com'.[46] Dr. Juberg also does not identify his financial sponsors and clients, but it is reasonable to presume that his employer, Corteva, which purchased the license for chlorpyrifos from Dow, is among them, leading to a direct financial conflict with the work of this panel.
4. John Lipscomb works for the Center for Tox and Environ Health (CTEH), an industry consulting company that provides product defense support for its clients, including litigation support and expert testimony, according to the 'Making Sense of Science' company webpage.[47] His biography in the candidate list fails to identify any current or recent clients or funding sources. Without this information, the public is unable to evaluate whether Dr. Libscomb has any direct financial conflicts, biases, or non-financial interests. Until this is made public, we oppose his nomination.

[45] See LinkedIn profile for Mackenzie Brownell, on assignment at Dow Chemical, 2018 to present. https://www.linkedin.com/in/mackenzie-brownell-123770157/

[46] Juberg DR, Hoberman AM, Marty S, Picut CA, Stump DG. Letter to the editor regarding "safety of safety evaluation of pesticides: developmental neurotoxicity of chlorpyrifos and chlorpyrifos-methyl" by Mie et al. (environmental health. 2018. 17:77). Environ Health. 2019 Mar 15;18(1):21. doi: 10.1186/s12940-019-0454-x. Erratum in: Environ Health. 2019 May 14;18(1):47. PMID: 30871546; PMCID: PMC6419458.

[47] https://www.cteh.com/service-detail/expert-services

5. Larry Sheets works for Bayer Crop Science. Bayer is a pesticide registrant with a direct financial interest in the deliberations of this panel. This represents a direct financial conflict.
6. Pamela Spencer works for Angus Chemical Company. Prior to that, Dr. Spencer worked for Dow Chemical Company for 30 years, indicating an industry bias, and an appearance of a conflict of interest. There may also be a direct conflict of interest, if Dr. Spencer continues any financial relationship with her long-time recent past employer or if her current employer has registrations that could be impacted by the SAP review. If this is the case, it should be disclosed.
7. Lisa Sweeney lists her affiliation as UES, Inc. which is a consulting company whose website says that it partners with government and industry customers, including the Air Force, aerospace companies, automakers, and the Department of Energy.[48] Her consulting listed in her biography includes work with TERA, the product defense consulting firm founded by industry favorite, Michael Dourson, who is TERA's Director of Science.[49] TERA's work to misrepresent the human health risks of DuPont's PFOA chemicals was so thoroughly discredited that both of North Carolina's Republican senators, Richard Burr and Thom Tillis, said they would oppose Dourson's nomination by President Trump for an EPA science position. On chlorpyrifos, the topic of this SAP, Dow Chemical hired TERA, resulting in TERA recommending a risk estimate that was 5,000 times less protective than the EPA's value.[50] Relevant to the work of this SAP, Sweeney and Dourson co-published an article together in 2010, in the industry journal Reg Tox Pharm, that proposed reducing the uncertainty factors that are the topic of this SAP.[51] Sweeney has an industry bias and potential conflict, and possibly a direct financial conflict with the matters to be discussed at this SAP. Her clients and financial interests should be publicly disclosed.

We recognize that industry experts have information that may be valuable to the deliberations of the federal advisory committees and the policies of EPA, including for example, technical, scientific, and market data. We therefore suggest that they avail themselves of the opportunity to present information to the SAP during the public comment period, which includes both a short oral and written comment opportunities.

<u>Animal rights groups representatives should be limited:</u>

We are not opposed to limited representation on the panel from animal rights groups, and we do not mean our comments to disparage the qualifications or personal reputations of any of the candidates listed below. However, we ask that participation from this stakeholder perspective be limited, given that they are all the same perspective. Of the five candidates below, two were quoted as supporters in the EPA 2019 memo announcing that Administrator Wheeler was cutting funds for animal tests - Clippinger

[48] https://www.ues.com/about

[49] Michaels, D. The Triumph of Doubt: Dark Money and the Science of Deception. Oxford University Press, 2020. P. 3, 5-6.

[50] Trump's Pick for EPA Safety Chief Argued Kids Are Less Sensitive to Toxins: If confirmed to the EPA, Michael Dourson will be in a position to set safety levels for many of the same chemicals his company was paid to defend. The Intercept. Sharon Lerner, October 3 2017.

https://theintercept.com/2017/10/03/epa-nominee-michael-dourson-toxic-chemicals/

[51] Hasegawa R, Hirata-Koizumi M, Dourson ML, et al. Proposal of new uncertainty factor application to derive tolerable daily intake. Regul Toxicol Pharmacol. 2010;58(2):237-242. doi:10.1016/j.yrtph.2010.06.006

and Sullivan – and two others – Hogberg and Smirnova – are both employed by the same center that was named in the same announcement as receiving EPA funds to develop NAMS.[52] We suggest that no more than one of the five candidates below be selected for the final panel:

1. Amy Clippinger, PETA
2. Helena Hogberg, Johns Hopkins University Center for Alternatives to Animal Testing
3. Lena Smirnova, Johns Hopkins University Center for Alternatives to Animal Testing
4. Kristi Sullivan, Physicians Committee for Responsible Medicine
5. Catherine Willett, Human Society International

Because we recognize that the above candidates have information relevant to the deliberations of this panel, we suggest that they present information during the public comment period.

<u>We are not opposed to the following nominees:</u>

We are not opposed to the following candidates *per se* but are concerned that the biographies and information provided by EPA does not include any information regarding potential direct or indirect financial conflict disclosure statements.

1. Veronica Berrocal, UC Irvine
2. Marion Ehrich, Virginia Tech
3. David Jett, NIH
4. Olga Naidenko, Environmental Working Group
5. Sherry Parker, WuXi App Tec
6. Aramandla Ramesh, Meharry Medical College
7. David Reif, NC State
8. Emily Reinke, US Army Public Health Center
9. Andrew Rubin, Cal DPR

We ask that all candidates be required to provide a disclosure statement to be made public so that EPA and the public can accurately assess the candidate's perspectives, biases and financial conflicts. The public statement need not be more than a few sentences, and should include relevant patents, employment, collaborations, consulting, and so on, that could be seen as possible competing interests. If no competing interests exist, then this should be stated in the public statement. The disclosure policy should address both financial and nonmonetary relevant competing interests, including back at least five years and any anticipated interests in the next five years such as future contracts, collaborations, and employment.[53] Committee membership should exclude experts with financial interests that could be impacted by the SAP review.

<u>Additional candidates for consideration:</u>

[52] Administrator Wheeler Signs Memo to Reduce Animal Testing, Awards $4.25 Million to Advance Research on Alternative Methods to Animal Testing

09/10/2019. https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance

[53] Sass J. Key elements of effective and practical disclosure policies for health science journals. Environ Health Perspect. 2009 Jun;117(6):A233. doi: 10.1289/ehp.12620. PMID: 19590660; PMCID: PMC2702421.

We are very concerned about the lack of environmental public health perspectives among the candidates. The topic of this SAP is not simply one of science, but about the appropriate application of science methods, data, and information to inform regulatory and policy decisions with the goal of protecting human health, including the most vulnerable among us. We recommend the following experts to serve on this SAP, with their affiliation and expertise noted:

- Margaret McCarthy, Professor, University of Maryland School of Medicine. Neuroendocrinology, neurodevelopment, neurotoxicology, key characteristics of neurodevelopment. See professional biosketch for details.[54]

- Heather Patisaul, Associate Dean of Research, Dept of Biological Sciences. NC State University. Neuroanatomical, neurobehavioral, neurotoxicology, and molecular testing methods. See professional biosketch for details.[55]

- Susan Schantz, Professor Emerita, Neuroscience Program, University of Illinois at Urbana-Champaign. Clinical and toxicological methods to evaluate neurotoxicity and neurobehavior, neurodevelopment and aging, epidemiology.

- Martyn Smith, Professor of Toxicology, Director of Superfund Research Program, University of California Berkeley. Key characteristics of carcinogens, key characteristics of neurotoxicants, epidemiology, environmental public health. See professional biosketch for details.[56]

- Christopher Portier, Professor, Dept of Toxicogenomics University of Maastricht. Molecular biology, risk assessment, bioinformatics, epidemiology, key characteristics of carcinogenesis, adverse outcome pathways, development, genomics, biostatistics. See professional biosketch for details.[57]

Conclusion: Reopen nominations and postpone SAP convening

As detailed in these comments, we recommend that the Pesticide Office re-consider this SAP in both content and timeline. We recommend that the Pesticide Office cancel this SAP until at least the new year, 2021, when it can fully consider information now under development by an international coalition that is using state-of-the-science systematic review methods to identify key characteristics of developmental neurotoxicity.

If the Pesticide Office disregards our recommendations and moves ahead with its current intention to present an industry-sponsored Exponent paper to the SAP to consider, the final product of the SAP will be of questionable value. Moreover, if the Pesticide Office selects the SAP members from this very limited candidate list, the panel will almost surely be industry-biased and publicly discredited. If either or

[54] https://www.medschool.umaryland.edu/profiles/McCarthy-Margaret/

[55] https://bio.sciences.ncsu.edu/people/hbpatisa/

[56] https://publichealth.berkeley.edu/people/martyn-smith/#:~:text=Martyn%20T.,public%20health%20and%20the%20environment.&text=Martyn%20T.,-Smith%20PhD%20is

[57] https://toxicogenomics-um.nl/staff/Chris-Portier

both of these events occur, the Pesticide Office will have wasted taxpayer's money and the time of the panelists.

Respectfully,

Jennifer Sass, Natural Resources Defense Council
Patti Goldman, Earthjustice
Emily Marquez, Pesticide Action Network North America