Emmett Environmental Law & Policy Clinic
HARVARD LAW SCHOOL

6 Everett Street, Suite 5116
Cambridge, MA 02138
617.496.2058 (tel.)
617.384.7633 (fax)

February 5, 2021

By Electronic Submission to www.regulations.gov

Acting Administrator Jane Nishida
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Docket ID No. EPA–HQ–OPP–2017–0750

Re: COMMENTS ON PROPOSED INTERIM REGISTRATION REVIEW DECISION FOR CHLORPYRIFOS AND REVISED DRAFT HUMAN HEALTH RISK ASSESSMENT, 85 FED. REG. 78,849 (DEC. 7, 2020).

On behalf of Scott Belcher, David C. Bellinger, Linda S. Birnbaum, Gemma Calamandrei, Aimin Chen, Richard A. Fenske, Philippe Grandjean, Russ Hauser, Irva Hertz-Picciotto, Bruce Lanphear, Pamela J. Lein, Axel Mie, Devon Payne-Sturges, Frederica Perera, Virginia A. Rauh, Laura Ricceri, Beate Ritz, Christina Rudén, Robert Sapolsky, Theodore Slotkin, Elsie M. Sunderland, Charles V. Vorhees, and Robin M. Whyatt, the Emmett Environmental Law & Policy Clinic at Harvard Law School respectfully submits these comments on the proposed Interim Registration Review Decision for Chlorpyrifos and the revised draft Human Health Risk Assessment (HHRA), as announced and opened for comments in 85 Fed. Reg. 78,849 (Dec. 7, 2020). We urge the Environmental Protection Agency (EPA) to reverse the proposed registration decision and revise the HHRA. In particular, we highlight two bases for calling into question the decision to use 10% red blood cell acetyl cholinesterase (AChE) inhibition as the basis for the toxicological point of departure. First, a recently-published re-evaluation of the Hoberman et al. animal study provides evidence of effects on brain morphometry at exposure levels lower than those that cause AChE inhibition. Second, the HHRA's refusal to rely on the findings of a key epidemiological study based in part on EPA's inability to review the raw data from that study is irrational and contrary to EPA's longstanding commitment to rely on the best available science.

I. BACKGROUND

Chlorpyrifos is an organophosphorus pesticide. Organophosphorus compounds were first developed as insecticides prior to World War II, and then adapted as nerve agents during the

war.[1] They cause acute poisoning at high doses by affecting signaling between neurons that use acetylcholine as neurotransmitter. A chlorpyrifos metabolite inhibits the enzyme AcetylCholinEsterase (AChE) that is no longer able to hydrolyze the neurotransmitter, thus blocking the signal. However recent and separate lines of evidence indicate that, especially in case of developmental exposures, chlorpyrifos affects a variety of neuronal targets and processes that are not directly related to AChE. In addition, interference with basic processes implicated in synapse development and function occurs at low doses and at AChE inhibition well below the EPA's safety threshold of 10%.

Chlorpyrifos has been registered for use as a pesticide in the United States since 1965. Because of mounting evidence of harm, however, EPA started phasing out residential uses of chlorpyrifos in the late 1990s. In 1997, EPA and the registrants agreed to eliminate indoor aerosols, foggers, pet shampoos, sprays, and paint additives as permissible products.[2] In 2000, the registrants and EPA agreed to phase out almost all remaining residential uses.[3] Chlorpyrifos may still be used on food crops, golf courses, greenhouses, non-structural wood treatments, and for public health to control mosquito-borne illnesses.[4] Despite the residential phase-out, chlorpyrifos has remained the most broadly used organophosphate insecticide ingredient in the United States, with between 5 to 8 million pounds used on crops in 2012.[5]

Since the residential use phase-out in 2000, a substantial body of research has indicated that chlorpyrifos may cause significant neurodevelopmental harms in children at lower doses and through different mechanisms than previously understood. Of particular importance are three long-term epidemiological studies. Two of the studies, conducted by Columbia University[6] and the Mount Sinai School of Medicine[7] ("Columbia Study" and "Mount Sinai Study," respectively), followed children in New York City. The third study was conducted by the University of California–Berkeley and followed the children of farmworkers in the Salinas Valley in California ("CHAMACOS Study").[8] In all three studies, researchers began by screening and collecting demographic, environmental, and medical data from pregnant mothers. For the past twenty years, they have followed the health and development of the children to assess the impact of certain factors, including exposure to toxic chemicals.

---

[1] Lucio G. Costa, *Organophosphorus Compounds at 80: Some Old and New Issues*, 162 Toxicological Sci. 24 (2018).

[2] EPA, *Interim Reregistration Eligibility Decision for Chlorpyrifos* 3 (2001).

[3] *Id.*

[4] *Id.* at viii.

[5] EPA, *Pesticide Industry Sales and Usage 2008–2012 Market Estimates* 18 (2017).

[6] Virginia Rauh et al., *Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life*, 118 Pediatrics 1845 (2006) [hereinafter "Columbia Study 2006"].

[7] Stephanie Engel et al., *Prenatal Exposure to Organophosphates, Paraxonase 1, and Cognitive Development in Childhood*, 119 Envtl. Health Persp. 1182 (2011) [hereinafter "Mount Sinai Study"].

[8] Lauren Stein et al. *Early Childhood Adversity Potentiates the Adverse Association Between Prenatal Organophosphate Pesticide Exposure and Childhood IQ: The CHAMACOS Report*, 56 NeuroToxicology 180 (2016) [hereinafter "CHAMACOS Study"].

The Columbia Study followed 254 children in New York City born to non-smoking mothers, measuring chlorpyrifos umbilical cord blood levels at birth to reflect prenatal exposure. The first major observation from the study was that, by age three, higher *in utero* exposure to chlorpyrifos correlated with lower performance in motor and mental development tests.[9] At the same age, children of mothers with higher levels of chlorpyrifos exposure were more likely to develop neurodevelopmental disorders including attention deficit hyperactivity disorder symptoms and symptoms of pervasive developmental disorder..[10]

The researchers later evaluated the same children during their elementary school years.[11] This time, the scientists found that children of mothers exposed to higher levels of chlorpyrifos had noticeable changes in brain morphology compared to those from mothers exposed to lower chlorpyrifos levels.[12] Some of these changes were directly proportional to the dose of chlorpyrifos measured at birth.[13] In the higher chlorpyrifos exposure group, these changes in brain morphology were also directly correlated with a decrease in IQ scores.[14] Further, these children displayed a decrease in working memory directly proportional to umbilical cord blood or maternal blood chlorpyrifos concentration.[15] Consistent with observations in animal models, *in utero* exposure disproportionately affected boys as compared to girls.[16]

By age eleven, the children with higher chlorpyrifos exposure were more likely to display mild or moderate arm tremors than those with lower exposure.[17] The neurodevelopmental effects observed in these children exposed *in utero* to chlorpyrifos persisted at least until adolescence.

As EPA stated in its 2016 Revised Human Health Risk Assessment, a critical conclusion resulting from the Columbia Study was that even the children with higher chlorpyrifos exposure—where the most significant adverse neurodevelopmental effects were observed—

---

[9] Columbia Study 2006, *supra* note 6, at 1854–56.

[10] *Id.* at 1854. The 2006 Columbia Study uses the DSM-IV classifications and states "[s]ignificant chlorpyrifos effects were found for attention problems, ADHD problems, and pervasive developmental disorder (PDD) problems." In 2013, the American Psychiatric Association released its updated DSM-V, which converts PDD diagnoses into ASD diagnoses. *See* American Psychiatric Association, *DSM-V Fact Sheets: Autism Spectrum Disorder* 1 (2013) ("Anyone diagnosed with one of the four pervasive developmental disorders (PDD) from DSM-IV should still meet the criteria for ASD in DSM-5) (accessible at https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/dsm-5-fact-sheets).

[11] Virginia Rauh et al., *Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide*, 119 Envtl. Health Persp. 1196 (2011) [hereinafter "Columbia Study 2011"]; Virginia Rauh et al., *Brain Anomalies in Children Exposed Prenatally to a Common Organophosphate Pesticide*, 109 Proc. Nat'l Acad. Sci. 7871 (2012) [hereinafter "Columbia Study 2012"].

[12] Columbia Study 2012, *supra* note 11, at 7872.

[13] *Id.*

[14] *Id.* at 7872–73.

[15] Columbia Study 2011, *supra* note 11, at 1199.

[16] Columbia Study 2012, *supra* note 11, at 7875; *see also* Edward Levin et al., *Prenatal Chlorpyrifos Exposure in Rats Causes Persistent Behavioral Alterations*, 24 Neurotoxicology & Teratology 733, 736–37 (2002).

[17] Virginia Rauh et al., *Prenatal Exposure to the Organophosphate Pesticide Chlorpyrifos and Childhood Tremor*, 51 NeuroToxicology 80, 83–84 (2015).

likely had chlorpyrifos blood levels below those which would trigger EPA's safety threshold of 10% AChE inhibition.[18] This result suggested both that the safety threshold used by EPA to set tolerances may not be sufficiently protective and that the neurodevelopmental effects resulted from a biological mechanism independent of AChE inhibition.[19]

The two other prospective cohort studies—the CHAMACOS Study and the Mount Sinai Study—looked at exposure to organophosphate pesticides more generally. Both studies found an association between prenatal organophosphate exposure and cognitive impairments in early childhood.[20]

Collectively, these studies suggested that prenatal chlorpyrifos exposure directly correlates with long-term adverse neurodevelopmental impacts. Their findings have been bolstered by other recent research.[21] Accordingly, the authors of a 2018 scientific review concluded that "[c]ompelling evidence indicates that prenatal exposure at low levels [of organophosphate pesticides, including chlorpyrifos] is putting children at risk for cognitive and behavioral deficits and for neurodevelopmental disorders." [22] Based in part on such studies, California and the European Union in 2020 prohibited virtually all agricultural uses of chlorpyrifos.[23]

II. A RE-EVALUATION OF HOBERMAN (1998) IDENTIFIED EFFECTS ON BRAIN MORPHOMETRY AT EXPOSURE LEVELS LOWER THAN THOSE CAUSING ACHE INHIBITION

In Mie et al. 2018,[24] the authors (who are some of the signatories of this comment letter) re-evaluated certain aspects of the Hoberman 1998 laboratory study,[25] which has formed part of the

[18] EPA, *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review* 13 (2016).

[19] *Id.* ("[T]he use of 10% RBC AChE inhibition for deriving PoDs for chlorpyrifos may not provide a sufficiently protective human health risk assessment.").

[20] Mount Sinai Study, *supra* note 8, at 188.

[21] *See, e.g.*, Janie F. Shelton et al., *Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study*, 122 Envtl. Health Persp. 1103 (2014); Pamela Wofford et al., *Community Air Monitoring for Pesticides. Part 3: Using Health-based Screening Levels to Evaluate Results Collected for a Year*, 186 Envtl. Monitoring Assessment 1355 (2014).

[22] Irva Hertz-Picciotto et al., *Organophosphate Exposures During Pregnancy and Child Neurodevelopment: Recommendations for Essential Policy Reforms*, 15 PLoS Med. e1002671 (2018), https://doi.org/10.1371/journal.pmed.1002671.

[23] *Chlorpyrifos Cancellation*, Cal. Dep't Pesticide Regul., https://www.cdpr.ca.gov/docs/chlorpyrifos/index.htm (last visited Feb. 1, 2021); *Chlorpyrifos & Chlorpyrifos-methyl*, European Comm'n, https://ec.europa.eu/food/plant/pesticides/approval_active_substances/chlorpyrifos_chlorpyrifos-methyl_en (last visited Feb. 1, 2021); European Food Safety Authority, *Statement on the Available Outcomes of the Human Health Assessment in the Context of the Pesticides Peer Review of the Active Substance Chlorpyrifos*, 17(8) EFSA Journal e05809 (2019), https://www.efsa.europa.eu/en/efsajournal/pub/5809.

[24] Axel Mie, Christina Rudén, & Philippe Grandjean, *Safety of Safety Evaluation of Pesticides: Developmental Neurotoxicity of Chlorpyrifos and Chlorpyrifos-methyl*, 17 Envtl.ironmental Health77 (2018), https://pubmed.ncbi.nlm.nih.gov/30442131/.

[25] A.M. Hoberman, *Developmental Neurotoxicity Study of Chlorpyrifos Administered Orally via Gavage to Crl: CD® BR VAF/Plus® Presumed Pregnant Rats*, Argus Research Laboratories, Inc. MRID 44556901 (1998).

evidence base for EPA's assessments of chlorpyrifos for over 20 years. EPA appears to have overlooked certain effects in its evaluations of the Hoberman study. The Mie et al. re-evaluation highlights these overlooked effects.

In particular, the authors identified a previously unrecognized effect of developmental chlorpyrifos treatment on the cerebellum in offspring of rats at all dose levels tested. This effect was highly statistically significant, consistent between sexes, selective for one brain region, consistent with a monotonic dose-response relationship, and present in the absence of maternal systemic toxicity at low- and mid-dose. The study was performed under good laboratory practices and was judged guideline-compliant by EPA, with the exception of a lack of certain data for offspring on postnatal day 65.[26] Of note, at no point was AChE inhibition observed in low- and mid-dose fetuses or pups in any compartment in a satellite study; effects on offspring brain morphometry in the low- and mid-dose groups are therefore not secondary to AChE inhibition.[27]

We propose that these observations are indicative of developmental neurotoxicity (DNT) at all dose levels tested. We further urge EPA to consider this evidence when revising the HHRA, just as the Hoberman 1998 study has been considered in previous HHRAs. We provide some of the detailed results and considerations supplemental to the Mie et al. study as an appendix.

We suggest that EPA should establish a point of departure for the HHRA based on these observed brain morphology effects. In addition, we urge EPA to provide a separate risk assessment for that point of departure. Given the severity of the effect, and the fact that a benchmark dose level can obviously not be established because the effect is apparently fully developed at the lowest dose tested, extra safety factors may need to be considered. More generally, we endorse the recommendation that EPA use "approaches to quantify risks for all health effects, both cancer and noncancer, at all anticipated levels of exposures" in its risk assessments.[28]

III. THE HHRA ARBITRARILY AND IRRATIONALLY DECLINES TO RELY ON THE EPIDEMIOLOGICAL EVIDENCE

As recognized by EPA and the larger scientific community, epidemiological studies play an important role in health and safety regulation. For example, epidemiology allows researchers to study the actual relationship between pesticide exposure in the real world and health outcomes.[29] Also, given variances in human genetics, epidemiological studies reduce interspecies

[26] EPA, *Chlorpyrifos Toxicology Data Review*, Tox. Review No. 014014 (2000), https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-059101_3-Mar-00_427.pdf.

[27] Joel L. Mattsson et al., *Lack of Differential Sensitivity to Cholinesterase Inhibition in Fetuses and Neonates Compared to Dams Treated Perinatally with Chlorpyrifos*, 53 Toxicological Sciences 438 (2000).

[28] USCF Program on Reproductive Health and the Environment, *Executive Summary: Strengthen EPA and Its Mission to Protect Public Health*, https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/UCSF%20PRHE%20EPA%20Executive%20Summary%20v4.pdf.

[29] EPA, *Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides* 4 (2016) [hereinafter "Epidemiological Framework"].

uncertainty.[30] As summarized by EPA, epidemiological studies "better account for and represent actual population response to environmental chemicals than laboratory animals."[31]

One challenge of relying on human epidemiological studies, however, is that the underlying data may be protected by confidentiality agreements with study participants or otherwise unavailable to regulators. Given these studies are of immense value in the regulatory process, EPA has adopted policies to ensure the validity of the epidemiological studies on which it relies, even when the underlying data are unavailable. These policies reflect the Agency's longstanding commitment to information quality—a principle integral to EPA's mission[32]—and include practices such as relying on the best available data, adopting a weight-of-evidence approach, and considering only peer-reviewed studies.

Rather than following this time-tested approach, the HHRA disregards the conclusions of a key epidemiological study based in large part on EPA's inability to review the researchers' raw data. This decision reflects the fundamentally flawed approach embodied in the "Strengthening Transparency in Regulatory Science" rule, which was recently struck down in federal court. Just as EPA has abandoned its defense of that rule, it should reverse the HHRA's decision to ignore the findings of the Columbia study.

A. The HHRA Is Not Based on the Best Available Science

EPA's longstanding practice is to rely on the "best available science" as the basis for its decision-making.[33] As recently as 2019, EPA referred to the Columbia Study as "potentially the most relevant information regarding effects to humans." 84 Fed. Reg. at 35,563. Additionally, EPA acknowledged that "both the 2008 and 2012 SAP commented on the strengths of the [Columbia] epidemiologic studies and the value of the information they provide." *Id.* at 35,564. Despite this recognition, EPA arbitrarily ignores the study, in violation of its own best practices and the standards of the scientific community.

EPA and the scientific community have methods to assess the quality of scientific studies without access to their raw data. Since its inception, EPA has relied on countless studies to support its regulatory decisions even when the underlying data were not available.[34] If access to raw data had been necessary, EPA would have been unable to rely on key studies demonstrating the negative health effects from contaminants such as lead, radionuclides, mercury, and

[30] *Id.* at 17.

[31] *Id.*

[32] EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* 5 (2002) [hereinafter "Information Quality Guidelines"].

[33] *Id.* at 22.

[34] For a partial list of scientific studies using confidential raw data and cited by EPA, *see* Emmett Environmental Law & Policy Clinic, *Comments on Proposed Rule, Strengthening Transparency in Regulatory Science, 83 Fed. Reg. 18,786* (Apr. 20, 2018), Attachment 1 (Aug. 7, 2018) (accessible at http://clinics.law.harvard.edu/environment/files/2018/08/Harvard-Comments-re-Docket-ID-No.-EPA-HQ-OA-2018-0259.pdf).

polychlorinated biphenyls (PCBs), resulting in significant losses in protections for public health and the environment.[35]

B. The HHRA Ignores EPA's Previous Weight-of-Evidence Analysis and the Conclusions of the FIFRA SAP's Peer Review

The new HHRA also ignores that the 2016 HHRA was not based on the Columbia Study alone. Rather, EPA previously adopted a weight-of-evidence approach that considered all of the evidence before the agency, including epidemiological studies representing "different investigators, locations, points in time, exposure assessment procedures, and outcome measurements."[36] Consequently, EPA found that the trends across all studies suggested the existing tolerances might not be safe.

This approach was consistent with EPA's guidance and best practices. In 2016, EPA issued guidance on the effective integration of epidemiological studies into its risk assessments.[37] A critical step in this guidance is the "incorporation" of epidemiological studies into a broader review of available data.[38] This step requires the Agency to analyze the "weight of the evidence" across all peer-reviewed studies.[39] This approach looks at trends throughout findings from independent cohorts and from different times and places, and compares epidemiological data to animal-model data and molecular-pathway research.

In addition, the HHRA disregards the conclusions of the peer review by the independent FIFRA Scientific Advisory Panel (SAP). Using the weight-of-evidence approach, the SAP had concluded that "both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% [RBC AChE] inhibition."[40] In the HHRA, EPA quotes this language[41] but does not address it or otherwise act on its implications.

---

[35] *Id.*; *see also* Envtl. Data & Governance Initiative, *Public Protections Under Threat at the EPA: Examining Safeguards and Programs that would have been blocked by H.R. 1430* (2017), https://envirodatagov.org/wp-content/uploads/2017/03/Public-Protections-under-Threat-at-the-EPA.pdf; Envtl. Prot. Network, *Comments of the Environmental Protection Network on EPA's Proposal entitled "Strengthening Transparency in Regulatory Science," Appendix C: The Potential Devastating Health Impacts of the Proposal* (2018), https://www.environmentalprotectionnetwork.org/wp-content/uploads/2018/08/EPN-Comments-on-Censored-Science.pdf.

[36] EPA, *supra* note 17, at 12.

[37] *See* Epidemiological Framework, *supra* note 29, at 5.

[38] *Id.* at 12.

[39] *Id.*

[40] FIFRA SAP, *FIFRA Scientific Advisory Panel Minutes No. 2016-01: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Chlorpyrifos: Analysis of Biomonitoring Data* 25 (2016).

[41] HHRA at 86.

C. The HHRA Ignores EPA's Previous Conclusion That It Did Not Need Access to the Columbia Study's Raw Data

With regard to the Columbia Study in particular, the HHRA fails to acknowledge EPA's previous conclusion that access to that study's raw data would be unhelpful. In an appendix to the 2014 risk assessment, EPA described an April 2013 meeting with the Columbia researchers.[42] This document explains the reasons EPA sought access to the raw data, the researchers' responses, and EPA's conclusion that the Columbia Study raw data was in fact not necessary.

EPA initially believed the data would be helpful for a few key reasons. First, EPA sought data on direct exposure levels measured in the cohort study's mothers. After meeting with the researchers, EPA discovered that these measurements did not exist.[43] The researchers suggested surrogate sources of information to answer EPA's questions, and so EPA subsequently used a time-weighted average, as supported by the SAP, to derive the pesticide exposure levels of the mothers in the study.[44] The raw data were not necessary for this purpose.

Second, EPA was interested in obtaining data about the study participants' exposure to lead, to rule out the possibility of a confounding factor.[45] In response, the researchers showed EPA their statistical analyses, demonstrating no correlation between lead exposure and the observed effects. The researchers explained that chlorpyrifos and lead likely affect the brain differently and would result in different MRI patterns. Following these discussions, EPA stated that "lead exposure did not likely confound (bias or render incorrect) the observed association between chlorpyrifos exposure and neurodevelopment in this study population."[46] Again, EPA had no need to access the raw data.

As a result of these discussions, EPA concluded that "*access to the raw data would either not provide answers to EPA's questions or that the information EPA sought could be obtained without analyzing the raw data*."[47] As a result, EPA stated it was "no longer pursuing the request for the original analytic data file from [Columbia] researchers."[48]

The HHRA does not reference this prior report nor its conclusions. Instead, EPA generically states that, "without the availability of the raw data, EPA remains unable to verify the reported findings of the [Columbia] papers" and that "EPA and interested stakeholders are unable to

[42] *See* EPA, *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review* 384–93 (2014).

[43] *Id.* at 386.

[44] EPA, *supra* note 18, at 4.

[45] EPA, *supra* note 42, at 387.

[46] *Id.* at 389.

[47] *Id.* at 391 (emphasis added).

[48] *Id.* at 384.

conduct alternative statistical analyses to evaluate the robustness and appropriateness of the approaches used by the investigators."[49]

Neither of these justifications stands up to scrutiny. First, as discussed above, EPA previously used alternative methods, such as peer review and a weight-of-evidence approach, to ensure the validity and reliability of the Columbia Study. This approach was consistent both with EPA's guidance and the best practices of the scientific community at large. Second, EPA had already determined the statistical analyses of the Columbia Study authors were reliable. Specifically, in its 2013 report, EPA observed that the Columbia researchers "utilized best practices in statistical analysis of epidemiological data."[50] EPA provides no explanation as to why it now questions the Columbia researchers' methods. Indeed, the HHRA acknowledges that "EPA does not have a specific reason to believe that [the Columbia researchers] have inappropriately handled the data or statistical analysis."[51]

D. The HHRA's Refusal to Consider the Columbia Study Repeats the Errors of the Transparency Rule

On January 6, 2021, EPA published a regulation entitled "Strengthening Transparency in Pivotal Science Underlying Significant Regulatory Actions and Influential Scientific Information," 86 Fed. Reg. 469 (Jan. 6, 2021), which was sometimes referred to as the "Transparency Rule." Under this regulation, "when promulgating significant regulatory actions or developing influential scientific information," EPA was required to "determine which studies constitute pivotal science and give greater consideration to those studies determined to be pivotal science for which the underlying dose-response data are available in a manner sufficient for independent validation." *Id*. at 470. Accordingly, it purported to adopt an approach similar to that embodied in the HHRA—providing lesser weight to scientific studies whose raw data were not available—across a broad swath of EPA's scientific and regulatory actions.

As explained in a comment letter on the proposed version of the Transparency Rule joined by some of the signatories of this letter, the rule:

> does not address any identified problem, is unauthorized by any statute, is inconsistent with scientific best practices and statutory authorities and mandates, will impose substantial costs, and has not been adequately explained . . . . Most fundamentally, the [rule] . . . will prevent EPA from relying on the best available science, thereby undermining its ability to protect public health and the environment.[52]

[49] HHRA at 89-90.

[50] EPA, *supra* note 42, at 389.

[51] HHRA at 89.

[52] Emmett Environmental Law & Policy Clinic, *Comments on Strengthening Transparency in Regulatory Science, Supplemental Notice of Proposed Rulemaking, 85 Fed. Reg. 15,396 (Mar. 18, 2020)* (EPA-HQ-OA-2018-0259-12464), http://clinics.law.harvard.edu/environment/files/2020/05/Emmett-Clinic-Transparency-Supplemental-Notice-Comments-FINAL.pdf.

The Transparency Rule would have dramatically reduced EPA's reliance on epidemiological studies in particular, because researchers are frequently unable to disclose the raw data from those studies due to confidentiality and privacy concerns.

In response to a lawsuit filed by the Environmental Defense Fund, on February 1, 2021, a federal judge in the U.S. District Court for the District of Montana struck down the Transparency Rule, vacating it and remanding the action to EPA.[53] EPA should follow up on this decision by revising the chlorpyrifos HHRA to incorporate the findings of the Columbia study into a weight-of-evidence, as it did in the 2016 HHRA.

* * *

In sum, we urge EPA to reverse its draft registration decision and revise the HHRA to reflect the multiple lines of evidence suggesting that chlorpyrifos causes DNT at exposure levels below those that cause AChE inhibition. Thank you for your attention to these comments.

BY:

Shaun A. Goho, Acting Director
Emmett Environmental Law & Policy Clinic
Harvard Law School

ON BEHALF OF (affiliations provided for identification purposes only):

Scott Belcher
Department of Biological Sciences
Center for Human Health and the Environment
North Carolina State University

David C. Bellinger
Department of Neurology
Boston Children's Hospital
Harvard Medical School

Linda S. Birnbaum
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

Gemma Calamandrei
Director, Centre for Behavioral Sciences and Mental Health
Italian National Health Institute (ISS), Rome (Italy)

Aimin Chen
Professor of Epidemiology

[53] *Envtl. Def. Fund v. U.S. EPA*, No. 4:21-cv-00003-BMM, ECF No. 38 (D. Mont. Feb. 1, 2021).

Department of Biostatistics, Epidemiology and Informatics
Perelman School of Medicine, University of Pennsylvania

Richard A. Fenske
Professor Emeritus, Environmental and Occupational Health Sciences
University of Washington School of Public Health

Philippe Grandjean
Adjunct Professor of Environmental Health
Department of Environmental Health, T.H. Chan School of Public Health
Harvard University
and
Professor of Environmental Medicine
University of Southern Denmark

Russ Hauser MD, ScD, MPH
Chair, Department of Environmental Health
Frederick Lee Hisaw Professor of Reproductive Physiology
Professor of Environmental and Occupational Epidemiology
Harvard T.H. Chan School of Public Health
Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School

Irva Hertz-Picciotto
Director, Environmental Health Sciences Core Center
Professor and VC for Research, Department of Public Health Sciences
MIND Institute Program on Epidemiology of Autism and Neurodevelopment
University of California, Davis

Bruce Lanphear, MD, MPH
Simon Fraser University
Vancouver, BC

Pamela J. Lein
Professor of Neurotoxicology
Department of Molecular Biosciences
UC Davis School of Veterinary Medicine

Axel Mie
Department of Environmental Science
Stockholm University
Stockholm, Sweden
and
Department of Clinical Science and Education, Södersjukhuset
Karolinska Institutet
Stockholm, Sweden

Devon Payne-Sturges
Associate Professor
Maryland Institute for Applied Environmental Health
School of Public Health, University of Maryland, College Park

Frederica Perera
Professor of Public Health
Director Translational Research and Founding Director
Columbia Center for Children's Environmental Health
Mailman School of Public Health, Columbia University

Virginia A. Rauh
Professor and Vice Chair, Heilbrunn Department of Population and Family Health
Mailman School of Public Health, Columbia University

Laura Ricceri
Senior Researcher, Centre for Behavioral Sciences and Mental Health
Italian National Health Institute (ISS), Rome (Italy)

Beate Ritz
Professor of Epidemiology, Environmental Health, and Neurology
FSPH and SOM UCLA

Christina Rudén
Professor in Regulatory Toxicology,
Stockholm University

Robert Sapolsky
John A. and Cynthia Fry Gunn Professor
Departments of Biology, Neurology and Neurological Sciences, Neurosurgery
Stanford University

Theodore Slotkin
Professor of Pharmacology & Cancer Biology
Professor in Psychiatry & Behavioral Sciences
Professor in Neurobiology
Duke University Medical Center

Elsie M. Sunderland
Gordon McKay Professor of Environmental Chemistry
Harvard John A. Paulson School of Engineering and Applied Sciences
Harvard University

Charles V. Vorhees
Professor, Dept. of Pediatrics, University of Cincinnati

Division of Neurology
Cincinnati Children's Research Foundation

Robin M. Whyatt
Professor Emeritus
Department of Environmental Health Sciences
Mailman School of Public Health, Columbia University

APPENDIX – METHODS AND RESULTS SUPPLEMENTING MIE ET AL. (2018)[54]

Statistical methods and results:

The authors expressed cerebellar height relative to brain weight, as the test laboratory has done for some but not all brain regions in supplement 3 to Hoberman 1998, and in a peer-reviewed publication[55] based on the same study. Data were analyzed separately for sexes using one-way ANOVA with dose group as a factor, followed by Dunnett's test if p(ANOVA)<0.05.

The results of the statistical tests were:

Males: p(ANOVA)<0.0001, p(high dose vs control)= 0.24, p(mid dose vs control) = 0.00064, p(low dose vs control) <0.0001.

Females: p(ANOVA)=0.00031, Dunnett's test p(high dose vs control)= 0.995, p(mid dose vs control) = 0.0028, p(low dose vs control) =0.0039

The apparent absence of an effect at high dose can be explained by the fact that the effect on cerebellum height at all dose levels tested is paralleled by a decreased brain weight, observed at high dose only. A figure summarizing the data has been shown in Mie 2018.

Brain weight in male low-and mid-dose pups at PND11

An apparent inconsistency in the absolute cerebellum height between low- and mid-dose males and females on PND 11 is resolved when cerebellar height is expressed relative to brain weight (see figure 1 in Mie 2018). The slightly higher brain weights in the male low and mid dose group, compared to control, are apparently a chance event: PND 11 morphometrics were performed in 6 pups per sex per dose group. The mean body weight of the male morphometrics PND 11 pups were 23.2 ± 0.8, 28.3 ± 2.3, 26.5 ± 2.2, and 18.8 ± 5.6 g for control, low, mid and high dose groups, respectively, i.e. pups in the low and mid dose groups had a higher body weight compared to controls. For comparison, body weights in a larger group (Subset 4, n=20 per dose group per sex) at the same age were 24.4 ± 2.1, 25.6 ± 3.2, 25.4 ± 2.4, 19.8 ± 4.2 g for male pups on PND 11. Thus, apparently by coincidence, animals with higher than usual body weights were selected for the low and mid dose groups for PND 11 morphometrics.

Absence of behavioral effects

The only valid positive control study provided in Hoberman 1998 is a DNT study of lead nitrate, performed in accordance with the EPA DNT test guidelines from 1991. The DNT properties of lead are well described, yet this positive control study did not identify any DNT effects of lead nitrate. Thus, the ability of this test laboratory to reliably test for DNT is not demonstrated.

---

[54] Axel Mie, Christina Rudén, & Philippe Grandjean, *Safety of Safety Evaluation of Pesticides: Developmental Neurotoxicity of Chlorpyrifos and Chlorpyrifos-methyl*, 17 Envtl.ironmental Health77 (2018), https://pubmed.ncbi.nlm.nih.gov/30442131/.

[55] J.P. Maurissen et al., *Lack of Selective Developmental Neurotoxicity in Rat Pups from Dams Treated by Gavage with Chlorpyrifos*, 57 Toxicological Sci. 250 (2000).

There is thus low confidence in the reported absence of e.g. behavioral effects in the DNT study of chlorpyrifos.

Processing of neuropathology samples

The test laboratory has argued that the apparent effects of CPF on the cerebellum in low- and mid-dose PND 11 pups are an artifact, because these samples were said to have been processed with a delay, conditional to findings in the high dose group.[56] However,

- The method description in Hoberman 1998 specifies a delayed processing of low- and mid-dose samples, in case of effects at high dose, for PND 65 but not for PND 11;
- Maurissen 2000 is explicit that PND 66, but not PND11, offspring brains were processed in a sequential way conditional to effects of observed at high dose;
- There is no rationale why all dose groups for both sexes were analyzed on PND 11, if a tiered approach had actually been used; and
- The observed effects were selective for the cerebellum, and shrinking due to a delayed processing would affect all brain regions.

Thus, we believe that effects should be interpreted as treatment-related. We also suggest that EPA should evaluate the adequacy of our analytical approach, i.e. expressing a brain region relative to brain weight, in light of a presentation that Dow AgroSciences had at a meeting with the Health Effects Division of the EPA Office of Pesticide Programs on March 6th, 2000.

Age groups PND 11 vs PND 65

An effect of treatment on the cerebellar height was observed at PND 11 but not on PND 65. It is however not possible to establish the true reversibility of these effects. Rather, compensation should be suspected, which is regarded adverse.[57].

Benchmark dose

Because the effect on the cerebellum height appears fully developed at the lowest dose tested, a benchmark dose level can obviously not be established. Thus, due to the severity of the effect, extra safety factors may need to be considered, or associations of CPF exposure and neurodevelopmental outcomes from epidemiological studies could be used for establishing a point of departure.

[56] D.R. Juberg et al., *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)*, 18 Envtl. Health 21 (2019).

[57] OECD, *Series on Testing and Assessment, Number 43: Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment* (2008).