No. 19-71979 & No. 19-71982
Consolidated

**UNITED STATES COURT OF APPEALS**
**FOR THE NINTH CIRCUIT**

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LEAGUE OF UNITED LATIN AMERICAN CITIZENS; *et al.*,
*Petitioners*,

STATE OF NEW YORK; *et al.*,
*Petitioners*,

v.

ANDREW WHEELER, Administrator, United States Environmental Protection Agency; and UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,
*Respondents*.

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ON PETITION FOR REVIEW OF THE ORDER OF THE ADMINISTRATOR OF THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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# BRIEF OF *AMICI CURIAE* AMERICAN ACADEMY OF PEDIATRICS, *ET AL.*, IN SUPPORT OF PETITIONERS

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Pursuant to Federal Rules of Appellate Procedure 26.1 and 29(a)(4)(A), *amici* state that they do not have any parent companies and no publicly-held company has a 10% or greater ownership interest in any of them.

Dated: December 13, 2019 */s/ Shaun A. Goho*
Shaun A. Goho

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## INTERESTS OF THE AMICI CURIAE[1]

*Amici* are organizations of healthcare professionals and scientists who have expertise in the health and wellbeing of children and the role of science in agency decision-making. *Amici* have a strong interest in the revocation of all tolerances for chlorpyrifos because exposure to currently allowable levels of chlorpyrifos has the potential to cause long-term neurological harm to children and because the decision represents a departure from science-based agency decision-making.

*Amicus* American Academy of Pediatrics ("AAP"), founded in 1930, is a national, not-for-profit organization dedicated to furthering children's health and the pediatric specialty. Over the past 88 years, as it has grown to include 66,000 pediatricians, the AAP has become a powerful voice for children's health through education, research, advocacy, and expert advice and has demonstrated a continuing commitment to protect the well-being of America's children.

*Amicus* Alliance of Nurses for Healthy Environments ("ANHE") is the only national nursing organization focused solely on the intersection of health and the environment. The mission of ANHE is to promote healthy people and healthy

[1] Pursuant to Federal Rule of Appellate Procedure Rule 29(a)(2), *amici* state that all parties have consented to or stated that they do not object to the filing of this brief. Pursuant to Federal Rule of Appellate Procedure 29(A)(4)(e), *amici* certify that no person or entity, other than *amici* or its counsel, made a monetary contribution to the preparation or submission of this brief or authored this brief in whole or in part.

environments by educating and leading the nursing profession, advancing research, incorporating evidence-based practice, and influencing policy. A key component of nursing practice is prevention, and thus ANHE supports efforts to reduce neurodevelopmental harm in infants and children through the elimination of chlorpyrifos exposure sources.

*Amicus* American Public Health Association ("APHA") champions the health of all people and all communities, strengthens the profession of public health, shares the latest research and information, promotes best practices, and advocates for public health policies grounded in research. APHA represents over 20,000 individual members and is the only organization that combines a 140-plus year perspective and a broad-based member community with an interest in improving the public's health. APHA has long advocated in support of protecting infants and children, farmers, farmworkers, and others from harmful pesticide exposure.

*Amicus* Migrant Clinicians Network ("MCN"), a global organization which serves over 10,000 constituents, supports clinicians to increase access to quality healthcare and reduce disparities for migrant farmworkers and other mobile, underserved populations. MCN's board of directors is comprised of a diverse group of professionals with experience in and a commitment to migrant health, including practicing clinicians, researchers, policy makers, and academics. MCN

also advocates on behalf of both migrant clinicians and the mobile populations they serve.

*Amici* Physicians for Social Responsibility ("PSR") and the San Francisco Bay Area Chapter of PSR are non-profit education and advocacy organizations who work to protect human life from the gravest threats to health and survival. As such, PSR combines the power of community activism with the knowledge and credibility of physicians and other health professionals to promote public policies that support human health. PSR seeks to protect vulnerable populations from the harmful impacts of pesticides such as chlorpyrifos.

*Amicus* Union of Concerned Scientists ("UCS") is a national nonprofit organization founded 50 years ago by scientists and students at the Massachusetts Institute of Technology. Its mission is to use rigorous, independent science to solve our planet's most pressing problems. UCS combines technical analysis and effective advocacy to create innovative, practical solutions for a healthy, safe, and sustainable future.

## SUMMARY OF ARGUMENT

Chlorpyrifos is an organophosphate pesticide, which in higher doses can cause acute, neurotoxic poisoning. The Environmental Protection Agency ("EPA") banned the residential use of chlorpyrifos in June 2000 but allowed agricultural use to continue. Since then, a significant body of evidence from both

epidemiological and animal studies has demonstrated that children are vulnerable to long-lasting, adverse cognitive and behavioral outcomes when exposed during pregnancy to chlorpyrifos at levels far below the current tolerances permitted by EPA. These data show that chlorpyrifos can alter the very structure of the brain itself, as well as result in an increased prevalence of attention deficit hyperactivity disorder and other behavioral problems.

In light of these findings, and after an extensive process involving independent peer review and multiple iterations of an integrated human health risk assessment, EPA proposed to prohibit the use of chlorpyrifos on food crops. The agency's decision to reverse course ignores its statutory duty to remove food tolerances for a pesticide if it cannot make an affirmative finding that they are safe and involves willfully blinding itself to the scientific evidence.

In particular, EPA's reliance on its alleged inability to review the raw data from a single epidemiological study is contrary to its best practices, including its commitment to using the best available science, its Peer Review Policy, and its weight-of-evidence approach to understanding scientific findings in the context of the larger body of peer-reviewed science. And without explanation, EPA ignored its previous conclusions regarding the need and utility of that study's raw data.

An agency may change its mind, but it must provide a rational reason for doing so. EPA has disregarded the science, the scientists, and its own past

conclusions. Its decision to leave the chlorpyrifos food tolerances in place is a textbook example of arbitrariness.

## ARGUMENT

### I. CHLORPYRIFOS HARMS CHILDREN'S BRAIN DEVELOPMENT AT LEVELS BELOW THOSE THAT CAUSE ACUTE TOXICITY

#### A. Chlorpyrifos Is an Organophosphate Pesticide That Historically Had Many Residential and Agricultural Uses

Chlorpyrifos is an organophosphate pesticide. Organophosphates, first developed as nerve agents during the Second World War, cause acute poisoning at high doses by affecting signaling between neurons. Typically, the brain propagates electrical signals along a network of neurons to communicate movement commands to the body's muscles, such as a command to start walking. This neuron-to-neuron signaling is achieved through use of a neurotransmitter, acetylcholine, which is released by the messenger neuron and read by the recipient neuron. An enzyme called acetylcholinesterase ("AChE") exists in the space between the neurons and breaks down the neurotransmitter, stopping the electrical signaling. Organophosphates, such as chlorpyrifos, hijack this enzyme, preventing AChE from performing its critical function.

Chlorpyrifos was first registered as a pesticide in the United States in 1965.[2] It was initially approved to treat food and feed crops; however, by 1987, half of all

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

chlorpyrifos produced was being used in non-agricultural settings.[3] Chlorpyrifos became one of the most common pesticides in the United States, with over 400 registered products.[4] In the 1990s, it was widely used in households to control cockroaches and termites.[5]

Beginning in the late 1990s, EPA took action to reduce residential exposures to chlorpyrifos. In 1997, EPA and the registrants agreed to eliminate indoor aerosols, foggers, pet shampoos, sprays, and paint additives as permissible products.[6] In 2000, the registrants and EPA agreed to phase out almost all remaining residential uses.[7] Chlorpyrifos may still be used, however, on food crops, golf courses, greenhouses, non-structural wood treatments, and for public health to control mosquito-borne illnesses.[8] 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

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[3] *Id.*

[4] *Id.*

[5] Philip J. Landrigan et al., *Pesticides and Inner-City Children: Exposures, Risks, and Prevention*, 107 (supp. 3) Envtl. Health Persp. 431, 432 (1999).

[6] EPA, *supra* note 2, at 3.

[7] *Id.*

[8] *Id.* at viii.

in 2012.[9] Because of the mounting evidence of harm, however, California and the European Union recently decided to end the agricultural use of the pesticide in 2020.[10]

### B. Prenatal Chlorpyrifos Exposure Is Directly Correlated with Adverse Brain Development and Cognitive Impairments

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. These studies have been performed by independent researchers, been subjected to peer review, controlled for possible alternative causes, used animal models and human cohorts, and almost invariably arrived at a convergent conclusion: relatively low levels of chlorpyrifos exposure early in life may result in severe, adverse neurodevelopmental outcomes.

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

[10] Press Release, Cal. Envtl. Prot. Agency & Cal. Dep't Pesticide Reg., Agreement Reached to End Sale of Chlorpyrifos in California by February 2020 (Oct. 9, 2019), https://calepa.ca.gov/2019/10/09/press-release-agreement-reached-to-end-sale-of-chlorpyrifos-in-ca-by-feb-2020/. Stephen Gardner, *EU to Ban Chlorpyrifos Pesticide Starting in February*, Bloomberg Env't (Dec. 6, 2019), https://news.bloombergenvironment.com/environment-and-energy/eu-to-ban-chlorpyrifos-pesticide-starting-in-february.

Experiments in rats in the late 1990s and early 2000s were the first to demonstrate an association of prenatal chlorpyrifos exposure with severe neurodevelopmental toxicity.[11] The experiments exposed rats *in utero* to high levels of chlorpyrifos. The rats exhibited lower birthweights, delayed reflexes, and reduced perception.[12] Although the initial experiments involved exposure levels known to cause acute toxicity, later experiments began studying the effects of chlorpyrifos exposure at subclinical levels. These studies found that even subclinical prenatal chlorpyrifos exposure resulted in marked effects on cognition and locomotion in rats.[13] Moreover, these effects were sex-dependent, suggesting that areas of the brain impacted by sex hormones were also affected by chlorpyrifos.[14]

Three long-term epidemiological studies in humans built on these results. Two of the studies, conducted by Columbia University[15] and the Mount Sinai

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[11] *See, e.g.*, S.M. Chanda & C.N. Pope, *Neurochemical and Neurobehavioral Effects of Repeated Gestational Exposure to Chlorpyrifos in Maternal and Developing Rats*, 53 Pharmacology Biochemistry & Behavior 771 (1996); Edward Levin et al., *Persistent Behavioral Consequences of Neonatal Chlorpyrifos Exposure in Rats*, 130 Brain Dev. Res. 83 (2001).

[12] Chanda & Pope, *supra* note 11, at 774–775.

[13] Levin et al., *supra* note 11, at 86–88.

[14] *Id.* at 87.

[15] 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"].

School of Medicine[16] ("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").[17] 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. Studies like these, that follow groups of people who differ with respect to certain factors and then track how these factors influence the rates at which particular outcomes occur, are known as prospective cohort studies, and are considered the "gold standard" in epidemiology.[18]

The Columbia Study followed 265 children in New York City born to non-smoking mothers, measuring chlorpyrifos umbilical cord blood levels at birth to

[16] 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"].

[17] 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"].

[18] Matthew Thiese, *Observational and Interventional Study Design Types: An Overview*, 24 Biochemia Medica 199, 204 (2014).

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.[19] 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 ("ADHD") and autism spectrum disorder ("ASD").[20]

In a follow-up, the researchers evaluated the same children at age seven.[21] 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

[19] Columbia Study 2006, *supra* note 15, at 1854–56.

[20] *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).

[21] 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"].

mothers exposed to lower chlorpyrifos levels.[22] Some of these changes were directly proportional to the dose of chlorpyrifos measured at birth.[23] In the higher chlorpyrifos exposure group, these changes in brain morphology were also directly correlated with a decrease in IQ scores.[24] Further, these children displayed a decrease in working memory directly proportional to their mothers' chlorpyrifos exposure levels.[25] Consistent with observations in animal models, *in utero* exposure disproportionately affected boys as compared to girls.[26]

By age eleven, the children with higher chlorpyrifos exposure were more likely to display mild or moderate tremors than those with lower exposure.[27] The neurodevelopmental effects observed in these children exposed *in utero* to chlorpyrifos persisted until adolescence.

As EPA stated in its 2016 Revised Human Health Risk Assessment ("HHRA"), a critical conclusion resulting from the Columbia Study was that even the children with higher chlorpyrifos exposure—where the most significant

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[22] Columbia Study 2012, *supra* note 21, at 7872.

[23] *Id.*

[24] *Id.* at 7872–73.

[25] Columbia Study 2011, *supra* note 21, at 1199.

[26] Columbia Study 2012, *supra* note 21, at 7875; *see also* Edward Levin et al., *Prenatal Chlorpyrifos Exposure in Rats Causes Persistent Behavioral Alterations*, 24 Neurotoxicology & Teratology 733, 736–37 (2002).

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

adverse neurodevelopmental effects were observed—likely had chlorpyrifos blood levels below those which would trigger EPA's safety threshold of 10% AChE inhibition. ER1261. 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. ER1261.

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.[28] Collectively, these studies suggested that prenatal chlorpyrifos exposure directly correlates with long-term adverse neurodevelopmental impacts.

### C. The Neurotoxic Effects of Chlorpyrifos Are Likely Caused by Other Mechanisms in Addition to AChE Inhibition

For many years, AChE inhibition was thought to be the exclusive mechanism for chlorpyrifos neurotoxicity. Operating under this assumption, EPA set chlorpyrifos tolerances based on the aggregate amount of pesticide that resulted in a 10% inhibition of AChE in the blood—the level of chlorpyrifos assumed to induce acute poisoning. Contrary to this assumption, multiple studies have since

[28] Mount Sinai Study, *supra* note 16, at 1886; CHAMACOS Study, *supra* note 17, at 188.

observed adverse effects from organophosphates at doses below those necessary to trigger 10% AChE inhibition and have identified other potential mechanisms of harm.

For example, chlorpyrifos directly influences the replication and differentiation of brain cells in rats.[29] Specifically, subclinical levels of chlorpyrifos in pre- and post-natal rats dramatically alter serotonin receptors and transporters critical to the proper development of the brain.[30] Moreover, neonatal subclinical chlorpyrifos exposure increases signaling molecules associated with inflammation in the developing brains of mice.[31] Chlorpyrifos also inhibits neurite cell outgrowth, which can lead to adverse neurological effects in humans.[32]

In rats, chlorpyrifos affects the structure of tubulin in cells.[33] Tubulin is an indispensable cellular component that provides a scaffold for the transport of

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[29] Justin Aldridge et al., *Serotonergic Systems targeted by Developmental Exposure to Chlorpyrifos: Effects During Different Critical Periods*, 111 Envtl. Health Persp. 1736 (2003).

[30] *Id.* at 1738–40.

[31] Jing Tian et al., *The Effect of HMGB1 on Sub-Toxic Chlorpyrifos Exposure-Induced Neuroinflammation in Amygdala of Neonatal Rats*, 338 Toxicology 95, 100–101 (2015).

[32] Verena Christen et al., *Developmental Neurotoxicity of Different Pesticides in PC-12 Cells* in vivo, 325 Toxicology & Applied Pharmacology 25, 25–26, 30 (2017).

[33] Xiangkun Yang et al., *Mass Spectrometric Quantitation of Tubulin Acetylation from Pepsin-Digested Rat Brain Tissue Using a Novel Stable Isotope Standard and*

molecules, including neurotransmitters. A recent molecular study recognized the ability of organophosphates to modify or cross-link tubulin.[34] Additionally, subclinical chlorpyrifos exposure in minnows results in a downregulation of NTRK1, a gene in humans that, when mutated, is associated with cognitive disabilities.[35] Finally, in mouse models, prenatal subclinical chlorpyrifos exposure results in an increase in the expression of genes that can trigger cell death.[36]

These data are particularly important given the finding in the Columbia Study that chlorpyrifos-exposed children exhibited morphological changes in their brains.[37] Inhibited neural cell growth and development, structural changes within the cell, and induced programmed cell death could explain these changes.

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*Capture by Anti-Peptide Antibody (SISCAPA) Method*, 90 Analytical Chemistry 2155 (2018).

[34] Lawrence M. Schopfer & Oksana Lockridge, *Chlorpyrifos Oxon Promotes Tubulin Aggregation via Isopeptide Cross-linking between Diethoxyphospho-Lys and Glu or Asp: Implications for Neurotoxicity*, 293 J. Biological Chemistry, 13577, 13577 (2018).

[35] Lilai Yuan et al., *Targeting Neurotrophic Factors and Their Receptors, But Not Cholinesterase or Neurotransmitter, in the Neurotoxicity of TDCPP in Chinese Rare Minnow Adults*, 208 Envtl. Pollution 670, 674 (2015).

[36] Maria Pallota et al., *Specific Effects of Chronic Dietary Exposure to Chlorpyrifos on Brain Gene Expression-A Mouse Study*, 18 Int'l J. Molecular Sci. 2467, 2473 (2017).

[37] *See supra* note 22 and accompanying text.

### D. Animal Models Demonstrate a Direct Effect Between Chlorpyrifos Exposure and Neurodevelopment Similar to Those Observed in Humans

Many animal model studies have supported the adverse neurodevelopmental effects discovered in the Columbia Study. A 2017 literature review found eight recent studies using animal models in which rodents exposed to chlorpyrifos *in utero* or as neonates suffered from significant cognitive impairments later in life.[38] These studies almost universally observed a decrease in spatial learning and memory in a sex-specific manner, similar to the findings of the Columbia Study.[39] While many of these animal studies were conducted at chlorpyrifos levels above 10% AChE inhibition, at least one study conducted at subclinical levels and observed similar defects in spatial learning and memory.[40]

[38] Richard Burke et al., *Developmental Neurotoxicity of the Organophosphate Pesticide Chlorpyrifos: From Clinical Findings to Preclinical Models and Potential Mechanisms*, 142 J. Neurochemistry 162, 167, 189–90 (2017).

[39] *Id.*

[40] *Id.*; *see also* Belen Gómez-Giménez et al., *Sex-Dependent Effects of Neurodevelopmental Exposure to Different Pesticides on Spatial Learning: The Role of Induced Neuroinflammation in the Hippocampus*, 99 Food Chemistry & Toxicology 153 (2017).

## II. EPA STAFF, WEIGHING ALL OF THE RELEVANT EVIDENCE, CONCLUDED IN 2016 THAT IT IS NOT REASONABLY CERTAIN THAT CHLORPYRIFOS RESIDUES ON FOOD CROPS ARE SAFE

### A. The Food Quality Protection Act Requires EPA to Revoke a Tolerance If There Is Not a Reasonable Certainty That No Harm Will Result

The Federal Food, Drug, and Cosmetic Act ("FFDCA") (as amended by the Food Quality Protection Act of 1996 ("FQPA")) provides EPA its authority to regulate certain pesticides that affect human health. Pub. L. 104–170, 110 Stat. 1489 (1996)). Under section 408 of the FFDCA, 21 U.S.C. § 346a, EPA sets "tolerances," or maximum levels, for pesticide residues on foods. In the absence of a tolerance, a food that contains a pesticide residue is considered to be "adulterated," may not be shipped in interstate commerce, and is subject to seizure by the federal government. *Id.* § 342.

In 1996, Congress amended section 408. These revisions established detailed standards for determining when tolerances are safe and integrated EPA's regulation of pesticide food residues under the FFDCA with the agency's registration and registration review of pesticides under Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). Section 408 now provides that "[t]he Administrator may establish or *leave in effect a tolerance* for a pesticide chemical residue in or on a food *only if* the Administrator determines that the tolerance is safe." *Id.* § 346a(b)(2)(A)(i) (emphasis added). "The Administrator shall modify

or revoke a tolerance if the Administrator determines it is not safe." *Id.* In making this safety determination, EPA must consider, among other things, "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue." *Id.* § 346a (b)(2)(D).

### B. In 2016, EPA Proposed to Revoke All Chlorpyrifos Tolerances

In 2007, Pesticide Action Network North America and Natural Resources Defense Council petitioned EPA to revoke all food tolerances for chlorpyrifos. ER1-24. In response, EPA expedited its pending FIFRA registration review of the pesticide. As part of its review, EPA sought independent advice from the FIFRA Scientific Advisory Panel ("SAP"). The SAP conducted general reviews of the new scientific literature concerning chlorpyrifos in 2008, ER775-852, and 2012, ER956-1030, and also reviewed EPA's risk assessment methodologies in 2009,[41] 2010,[42] and 2011.[43]

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[41] FIFRA SAP, *Field Volatilization of Conventional Pesticides* (Dec. 1-3, 2009) (EPA-HQ-OPP-2009-0687).

[42] FIFRA SAP, *Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment* (Feb. 2-4, 2010) (EPA-HQ-OPP-2009-0851).

[43] FIFRA SAP, *Chlorpyrifos Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Modeling Linked to Cumulative and Aggregate Risk Evaluation System (CARES)* (Feb. 15, 2011) (EPA-HQ-OPP-2010-0588-0038).

In December 2014, EPA released a HHRA based on the SAP's conclusions. ER184-714. In doing so, EPA followed the Agency's standard weight-of-evidence approach, *see* discussion *infra* Section III.B.2, synthesizing (1) experimental toxicology studies evaluating outcomes such as behavior and cognitive function, (2) mechanistic data on possible adverse outcome pathways/modes of action, and (3) epidemiological and biomonitoring studies. ER1132-1163. Upon reviewing the three key epidemiological studies, EPA stated it "believes these are strong studies which support a conclusion that chlorpyrifos likely played a role in" neurodevelopmental effects observed at birth and through childhood. ER216. Given that EPA cannot leave a tolerance in place unless "there is a reasonable certainty that no harm will result," 21 U.S.C. § 346a(b)(2)(A)(ii), in 2015, EPA proposed to revoke all tolerances for chlorpyrifos. ER1132-1163.

In April 2016, in response to the proposed tolerance revocations, the SAP met to review the key epidemiological studies' findings and EPA's incorporation of these studies into its rulemaking. Looking at the totality of the evidence, the SAP agreed 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." ER1198. The SAP concluded that the current tolerances for chlorpyrifos likely did not account for all biological mechanisms and might not be protective of human health.

EPA followed up on the SAP's review by issuing a revised HHRA in November 2016. ER1249-1289. This risk assessment again adopted the weight-of-evidence approach, considering four cohort epidemiological studies across twelve study citations that represented "different investigators, locations, points in time, exposure assessment procedures, and outcome measurements." ER1260. Based on this revised risk assessment, EPA concluded "that expected residues of chlorpyrifos on food crops exceed the safety standard under the" FFDCA and therefore left in place the proposal to revoke chlorpyrifos food tolerances.[44]

## III. EPA'S FINAL ORDER DOES NOT PROVIDE A RATIONAL EXPLANATION FOR ITS REJECTION OF THE RISK ASSESSMENT'S CONCLUSIONS

In July 2019, EPA issued a final order ("the Order") denying the 2007 petition. ER1a-14a. The Order states that the question of chlorpyrifos neurotoxicity remains too uncertain to reach a decision at this time. ER6a. In doing so, EPA ignores its statutory duty to remove the food tolerances if it cannot make an affirmative finding that they are safe and contradicts its previous conclusions from the 2016 risk assessment. 21 U.S.C. § 346a(b)(2)(A)(i).

[44] EPA, *Revised Human Health Risk Assessment on Chlorpyrifos*, https://19january2017snapshot.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos_.html (last updated on November 22, 2016).

Although an agency may change its mind, it must nonetheless "articulate a satisfactory explanation for its action." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). EPA cites its inability to review the raw data underlying the Columbia Study as the most significant cause for its reversal. ER9a. This justification is flawed for multiple reasons.

First, by requiring access to raw data as a precondition of including the study in its modeling, the Agency in effect implements the flawed Transparency Rule proposal, which has received extensive criticism from medical, public health, and research organizations on the grounds that it will result in the exclusion of good science from EPA policymaking processes. Second, EPA does not follow the Agency's own best practices nor the methods by which the scientific community assesses the reliability of scientific studies. And third, EPA's current reasoning contradicts, without explanation, the Agency's previous conclusion about whether it needed the Columbia Study's raw data. "The absence of a reasoned explanation for disregarding previous factual findings violates the [Administrative Procedure Act]." *Organized Vill. of Kake v. U.S. Dep't of Agric.*, 795 F.3d 956, 969 (9th Cir. 2015).

### A. EPA's Refusal to Consider the Columbia Study Effectively Implements Its Highly-Criticized Transparency Rule Proposal

In April 2018, EPA proposed a regulation speciously titled "Strengthening Transparency in Regulatory Science" ("Transparency Rule"). 83 Fed. Reg. 18,768

(Apr. 30, 2018). This proposed rule, if finalized, would prohibit EPA from relying on scientific studies in rulemaking unless the underlying data are "publicly available in a manner sufficient for independent validation." *Id.* at 18,768.

The Transparency Rule proposal has been widely criticized by leaders in scientific, medical, and public health professional communities. For example, a coalition of nearly 70 public health, medical, academic, and scientific groups expressed that "there are many credible scientific studies where the exposure of raw data to the public is infeasible, or would reveal confidential patient information," and that the proposal was "misguided and will not improve the quality of science used by EPA nor allow the agency to fulfill its mandate of protecting human health and the environment."[45] The editors of five leading scientific journals issued a joint statement in which they concluded:

> It does not strengthen policies based on scientific evidence to limit the scientific evidence that can inform them; rather, it is paramount that the full suite of relevant science vetted through peer review, which includes ever more rigorous features, inform the landscape of decision making. Excluding relevant studies simply because they do not meet rigid transparency standards will adversely affect decision-making processes.[46]

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[45] Press Release, Public Health, Medical, Academic, and Scientific Groups Oppose EPA Transparency Rule 1 (July 16, 2018), https://www.aaas.org/sites/default/files/s3fs-public/EPA%20Transparency%20Rule%20FINAL.pdf.

[46] Jeremy Berg et al., *Joint Statement on EPA Proposed Rule and Public Availability of Data*, Science (Apr. 30, 2018).

In sum, the transparency proposal is contrary to EPA's statutory authorities, would willfully blind the agency to the best available science, and is a formula for arbitrary and capricious decision-making. Nevertheless, EPA in effect implements this proposal in the Order by making access to raw data a prerequisite for a study's inclusion in the Agency's safety determination.

B. The Order Does Not Follow EPA's Best Practices

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.[47] Also, given variances in human genetics, epidemiological studies reduce interspecies uncertainty.[48] As summarized by EPA, epidemiological studies "better account for and represent actual population response to environmental chemicals than laboratory animals."[49]

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

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

[48] *Id.* at 17.

[49] *Id.*

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[50]—and include practices such as relying on the best available data, adopting a weight-of-evidence approach, and considering only peer-reviewed studies.

*1. The Order 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.[51] In the Order, EPA refers to the Columbia Study as "potentially the most relevant information regarding effects to humans." ER9a. Additionally, EPA acknowledges that "both the 2008 and 2012 SAP commented on the strengths of the [Columbia] epidemiologic studies and the value of the information they provide." ER10a. 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 data files. Since its inception, EPA has relied

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[50] 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"].

[51] *Id.* at 22.

on countless studies to support its regulatory decisions even when the underlying data were not available.[52] 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 polychlorinated biphenyls (PCBs), resulting in significant losses in protections for public health and the environment.[53]

Courts have repeatedly upheld EPA's reliance on studies even when the agency did not have access to the underlying data. For example, in a challenge to the 1997 National Ambient Air Quality Standards ("NAAQS") for ozone and particulate matter, industry challengers asked the court to "impose a general requirement that EPA obtain and publicize the data underlying published studies

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[52] 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).

[53] *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.

on which the Agency relies." *Am. Trucking Ass'ns v. EPA*, 283 F.3d 355, 372 (D.C. Cir. 2002). The Agency responded:

> [i]f EPA and other governmental agencies could not rely on published studies without conducting an independent analysis of the enormous volume of raw data underlying them, then much plainly relevant scientific information would become unavailable to EPA for use in setting standards to protect public health and the environment.

*Id.* The D.C. Circuit agreed with EPA, noting such data is often unavailable due to confidentiality agreements, and refused to impose an "impractical and unnecessary" requirement. *Id.*

Eight years later, the same issue resurfaced when EPA revised the primary and secondary NAAQS for lead. EPA included in its analysis a study connecting an exposure to lead with a decline in IQ scores. *Coal. of Battery Recyclers Ass'n v. EPA*, 604 F.3d 613, 623 (D.C. Cir. 2010). Again, industry petitioners criticized EPA for not obtaining the underlying raw data of the study. *Id.* The Petitioners attempted to distinguish their case from *American Trucking* because they were only seeking the data from a single study rather than multiple studies. The court rejected this argument and reaffirmed that requiring the data from even a single study is impractical and unnecessary. *Id.*

*2. The Order Ignores EPA's Previous Use of Weight-of-Evidence Analysis*

The Order 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." ER1260. 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.[54] A critical step in this guidance is the "incorporation" of epidemiological studies into a broader review of available data.[55] This step requires the Agency to analyze the "weight of the evidence" across all peer-reviewed studies.[56] 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.

This policy reflects the broader scientific community's understanding of how to assess the reliability of individual studies. While the Order and the Transparency Rule focus on the ability to reanalyze the data from a single study, the National Academy of Sciences recently explained that "[t]he robustness of

[54] *See* Epidemiological Framework, *supra* note 47, at 5.

[55] *Id.* at 12.

[56] *Id.*

science is less well represented by the replications between two individual studies than by a more holistic web of knowledge reinforced through multiple lines of examination and inquiry."[57] EPA's weight-of-evidence policy approach mirrors this professional best practice. In contrast, the Order ignores this method, focuses primarily on the Columbia Study, and fails to explain its deviation from EPA's prior holistic reasoning.

*3. The Order Ignores the Key Conclusions from Peer Review*

EPA's Peer Review Policy is one of the agency's most important procedures to ensure that the studies it uses meet the standards of the scientific and technical community.[58] Under this policy, EPA's major work products should, and are expected, to be peer reviewed, either externally or internally.[59] Through this process, independent experts provide the Agency with valuable, objective reviews of studies' strengths and weakness and give feedback on EPA's analysis.

The Peer Review Policy reflects the broader scientific community's best practices. Peer review has been the widely accepted method for ensuring high-

[57] National Academy of Sciences, *Reproducibility in Science* 143 (2019).

[58] EPA, *Peer Review Handbook 4th Edition* B-3 (Oct. 2015).

[59] *Id.* at 20.

quality results for the past three and a half centuries.[60] EPA has integrated the scientific community's peer-review standards into its policy since 1993.[61]

The Order, however, disregards the conclusions of the independent SAP's peer review. 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." ER1198. In the Order, EPA "acknowledges" this previous conclusion but decides otherwise, stating it "believes the shortcomings of the [Columbia Study] data identified raise issues . . . that direct against using the data for risk assessment at this time." ER9a.

This reasoning may "acknowledge" the agency's previous decision, but ignores the reasoning underlying it. By justifying its decision based on the uncertainties of a single study rather than the greater body of peer-reviewed scientific literature, EPA cherry picks the uncertainties but disregards a key conclusion from the independent, peer-review panel without explanation.

[60] Elsevier, *What is Peer Review?* (accessed Nov. 1, 2019) (https://www.elsevier.com/reviewers/what-is-peer-review).

[61] Information Quality Guidelines, *supra* note 50, at 11.

### C. The Order 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 Order 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. ER567-576. 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. ER569. 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. ER1252. The raw data was 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. ER570. 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." ER572. 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*." ER574 (emphasis added). As a result, EPA stated it was "no longer pursuing the request for the original analytic data file from [Columbia] researchers." ER567.

The Order does not reference this prior report nor its conclusions. Instead, EPA generically states it needs the raw data to "independently verify the validity and reliability of the results" and "believes it is necessary to first replicate the statistical analyses used in the studies to ensure their accuracy." ER9a. 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." ER572. EPA provides no explanation as to why it suddenly now questions the Columbia researchers' methods.

## CONCLUSION

Decades of scientific research suggest current tolerances for chlorpyrifos are not sufficiently protective of the health of children and infants. EPA's about-face is not supported by the scientific record and is contrary to its statutory mandate. By requiring access to the raw data of the Columbia Study, EPA ignores its best practices and its prior reasoning in this matter.

For the foregoing reasons, *amici* respectfully request that this Court vacate the Order and issue a writ of mandamus directing EPA to promulgate a final rule revoking chlorpyrifos tolerances.

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[62] The Emmett Environmental Law & Policy Clinic would like to acknowledge the contributions to this brief of Ryan Petty and Katherine Clements, students in the Clinic.

## CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 29(a)(4)(G), I hereby certify that the foregoing brief complies with the type-volume limitations in Federal Rules of Appellate Procedure 29(a)(5) and 32(a)(7)(b). It was prepared using Microsoft Word 2016 in Times New Roman 14-point font, a proportionally spaced typeface, and contains 6466 words.

*/s/ Shaun A. Goho*
Shaun A. Goho

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I hereby certify that I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/EF system on December 13, 2019. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

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