No. 17-71636

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

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

STATE OF NEW YORK; et al., Intervenors

v.

SCOTT PRUITT, ADMINISTRATOR OF UNITED STATES ENVIRONMENTAL PROTECTION AGENCY, AND THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,
Respondents

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

BRIEF OF *AMICI CURIAE* HEALTH PROFESSIONAL ORGANIZATIONS IN SUPPORT OF PETITIONERS

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CORPORATE DISCLOSURE STATEMENT

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.

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INTERESTS OF THE *AMICI CURIAE*[1]

Amici are organizations of healthcare professionals who have expertise in the health and wellbeing of infants, children, and the families of migrant farmworkers. These groups are all disproportionately impacted by the toxic effects of pesticides as compared to the general population. *Amici* have a strong interest in supporting petitioners' challenge to revoke all tolerances for chlorpyrifos because many scientific studies have demonstrated that exposure to low levels of chlorpyrifos during pregnancy can result in long-term, irreversible neurological harm to children.

Amicus the 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 environments by educating and leading the nursing profession, advancing research, incorporating evidence-based practice, and influencing policy. Nurses are in every community and see first-hand the negative health impacts of exposures to pesticides such as chlorpyrifos. A key component of nursing practice is

[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.

prevention, and thus ANHE supports efforts to reduce neurodevelopmental harm in infants and children through the elimination of chlorpyrifos exposure sources.

Amicus the American Academy of Pediatrics ("AAP"), founded in 1930, is a national, not-for-profit organization dedicated to furthering the interests of children's health and the pediatric specialty. Since its inception, the membership of the AAP has grown from the original group of 60 physicians specializing in children's health to 66,000 pediatricians. Over the past 88 years, 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. The AAP has engaged in broad and continuous efforts to prevent harm to the health of infants, children, adolescents, and young adults caused by exposure to pesticides and other chemical exposures.

Amicus the 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 in Federally Qualified Health Centers and other healthcare delivery sites 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. Agricultural use of chlorpyrifos throughout the United States can expose farmworkers, their families, and rural communities to unsafe levels of the pesticide. Because migrant populations make up a large proportion of these communities, failing to eliminate chlorpyrifos tolerances would threaten MCN's constituents and the migrant populations they serve with an increased chance of irreversible neurological damage.

Physicians for Social Responsibility ("PSR") and the San Francisco Bay Area Chapter of PSR ("SF Bay Area PSR") are non-profit education and advocacy organizations whose mission states: "Guided by the values and expertise of medicine and public health, Physicians for Social Responsibility works 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. In this regard PSR seeks to protect vulnerable populations from the harmful impacts of pesticides such as chlorpyrifos, which scientific evidence has indicated can cause neurological harm in infants and children with even low-dose exposure.

SUMMARY OF ARGUMENT

Chlorpyrifos is an organophosphate pesticide, which in higher doses can cause acute, neurotoxic poisoning. Pesticides are regulated by the Environmental Protection Agency ("EPA"), in part under the Federal Food Drug and Cosmetic Act ("FFDCA"). In light of mounting evidence that children are more susceptible to harm from pesticides and other toxic chemicals than adults, Congress in 1996 unanimously amended the FFDCA with the Food Quality Protection Act ("FQPA"). The FQPA added significant safeguards for children's health in the pesticide approval process. It required, for the first time, that EPA account for the increased susceptibility of children when creating risk assessments. Applying these new safety standards in consort with new data, 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 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, EPA proposed to revoke all tolerances for chlorpyrifos in 2016. EPA has since reversed its position. In doing so, EPA has ignored the conclusions of a vast array of scientific data, as well as its own previous findings, that current chlorpyrifos tolerances do not sufficiently protect the health of children.

ARGUMENT

I. CHILDREN ARE MORE SUSCEPTIBLE TO TOXIC CHEMICALS, INCLUDING CHLORPYRIFOS, THAN ADULTS

A. Chlorpyrifos is an Organophosphate Pesticide that Historically had many Residential and Agricultural Uses

Chlorpyrifos, the chemical that is the subject of this litigation, is an organophosphate pesticide. Organophosphates, which were first developed as nerve agents during the Second World War, can cause acute poisoning at high doses by inhibiting a cellular enzyme called acetylcholinesterase ("AChE").

Acetylcholine, the normal target for AChE, is a neurotransmitter. The release of acetylcholine triggers muscle contraction and other critical central nervous system functions. Once acetylcholine has served its purpose, AChE's function is to break down the neurotransmitter. By inhibiting AChE, chlorpyrifos and other organophosphates lead to a buildup of acetylcholine, causing symptoms including nausea, headaches, muscle spasms, and death.

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 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 1997, the registrants and EPA agreed to reduce residential exposures to chlorpyrifos. Specifically, indoor aerosols, foggers, pet shampoos,

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[2] EPA, Interim Reregistration Eligibility Decision for Chlorpyrifos 3 (2001), *available at* https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-059101_1-Jul-06.pdf.

[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).

sprays, and paint additives were all eliminated as permissible products due to the potential for acute poisoning in children.[6] In 2000, the registrants and EPA agreed to phase out almost all remaining residential uses of chlorpyrifos.[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]

B. Epidemiological Research Starting in the 1970s Demonstrated that Children are more Susceptible than Adults to Toxic Chemicals

For decades, EPA and other agencies carried out risk assessments for toxic chemicals, including organophosphates, by studying the exposure patterns and health status of an adult, usually male.[9] In particular, scientific data used as the basis for regulatory decisions was often based on health findings in adult humans from epidemiology studies and in adult animals from direct exposure studies.[10]

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

[7] *Id.*

[8] *Id.* at viii.

[9] *See* National Research Council, *Pesticides in the Diets of Children and Infants* (1993) (AR 2180). For sources contained in the Petitioners' Excerpts of Record ("ER"), *amici* provide a parallel citation to the ER when first citing a document. If a source is contained within the Administrative Record ("AR"), but not the ER, then *amici* provide a parallel citation to the AR.

[10] *See id.*

Beginning in the 1970s, however, groundbreaking epidemiological studies demonstrated that children were more susceptible to toxic chemicals than adults.[11] A seminal study measured blood lead concentrations in all age groups within one mile of a smelting plant and found that children consistently possessed higher blood lead concentrations than similarly situated adults.[12]

Lead is a particularly potent neurotoxicant, and this mounting body of research resulted in a variety of statutory and regulatory actions. For example, EPA phased out lead from all grades of gasoline and limited the lead content of paints.[13] In 1986, Congress also limited the lead content of drinking water pipes, fittings, and fixtures.[14] These actions produced immense public health benefits; the benefits to children in health and education from the phase out of leaded gasoline alone are estimated at approximately $350 million per year.[15]

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[11] *See* Philip J. Landrigan et al., *Epidemic Lead Absorption Near an Ore Smelter – The Role of Particulate Lead*, 292 New Eng. J. Med. 123 (1975).

[12] *See generally id*.

[13] *See* Jack Lewis, *Lead Poisoning: A Historical Perspective* (1985), https://archive.epa.gov/epa/aboutepa/lead-poisoning-historical-perspective.html.

[14] *See generally* Safe Drinking Water Act Amendments of 1986, Pub. L. No. 99–359 (codified at 42 U.S.C. §§ 300f–300j); *see* 42 U.S.C. § 300g–6 (limiting the use of lead in drinking water pipes, fittings, and fixtures).

[15] *See* EPA Office of Policy Analysis, *Costs and Benefits of Reducing Lead in Gasoline: Final Regulatory Impact Analysis* (1985).

Continued research in the 1980s and 1990s demonstrated that children, especially those developing *in utero*, were also more susceptible than adults to another neurotoxicant, mercury.[16] Congress then commissioned a five-year National Academy of Sciences ("NAS") study, which established that children were more vulnerable than adults to pesticides as well.[17]

This report identified three primary reasons for children's increased susceptibility. First, they have greater exposure: infants and children drink more water, eat more food, and breathe more air per pound of body weight than do adults.[18] Second, because of their immature metabolisms, children may not have the enzymes needed to break down and remove toxic chemicals.[19] Third, they have "special windows of vulnerability" where "exposure to a toxicant can permanently alter the structure or function" of their bodies.[20] Their nervous and endocrine systems are especially sensitive at certain stages of development.[21]

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[16] *See, e.g.*, David Marsh et al., *Fetal Methylmercury Poisoning: Relationship Between Concentration in Single Strands of Maternal Hair and Child Effects*, 44 Archives Neurology 1017 (1987).

[17] *See generally* National Research Council, *supra* note 9.

[18] National Research Council, *supra* note 9, at 3.

[19] *See id.* at 38–41.

[20] *Id*.

[21] American Academy of Pediatrics, *Letter to EPA Administrator Gina McCarthy* (Jan. 17, 2017) ("[T]he nervous and endocrine systems have particular sensitivity to environmental toxicants at certain stages of growth.").

C. Congress Responded to this Research by Enacting Greater Protections for Children in the Food Quality Protection Act

In response to the NAS report's findings, Congress unanimously amended the Federal Food, Drug, and Cosmetic Act ("FFDCA") with the Food Quality Protection Act of 1996 ("FQPA"). In the FQPA, Congress added strong protections for infants and children,[22] requiring EPA for the first time to design risk assessments for pesticide tolerances that reflected the increased susceptibilities of these vulnerable populations. 21 U.S.C. § 346a(b)(2)(C). For example, the FQPA requires that EPA use an additional 10x safety factor when setting tolerances to account for the increased susceptibility of infants and children, thereby reducing the permissible levels of pesticide residue on food crops. 21 U.S.C. § 346a(b)(2)(C)(ii)(II). EPA may only reduce this safety factor if "reliable data" demonstrate that the reduction "will be safe for infants and children." *Id.* More generally, the FQPA requires EPA to set pesticide tolerances that would "ensure . . . there is a reasonable certainty that no harm will result to infants and children from aggregate exposure" to the pesticide. 21 U.S.C. § 346a(b)(2)(C)(ii).

[22] For a summary of the numerous safety enhancements in the FQPA, see Opening Br. Pet'rs at 5–7.

D. EPA Subsequently Banned Residential Uses of Chlorpyrifos

In 2000, EPA banned the residential use of chlorpyrifos.[23] EPA based its decision in part on the more stringent safety requirements of the recently passed FPQA.[24] The agency also relied on new testing data that showed greater chlorpyrifos toxicity to the brains of newborn rats, as well as evidence of acute organophosphate poisoning in children.[25] EPA, however, allowed the agricultural use of chlorpyrifos to continue.

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

Since EPA's decision in 2000, a substantial body of research has established that chlorpyrifos causes significant neurodevelopmental harms in children at lower doses, and through different mechanisms, than previously understood. These studies have been performed by numerous, independent laboratories, survived peer-review, controlled for possible alternative causes, used a variety of animal models and human cohorts, and almost invariably arrived at a convergent

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[23] EPA Office of Pesticide Programs, *Human Health Risk Assessment: Chlorpyrifos* (June 8, 2000), *available at* https://archive.epa.gov/scipoly/sap/meetings/web/pdf/hed_ra.pdf.

[24] *See* Andrew Revkin, *E.P.A., Citing Risks to Children, Signs Accord to Limit Insecticide,* N.Y. Times, June 9, 2000, http://www.nytimes.com/2000/06/09/us/epa-citing-risks-to-children-signs-accord-to-limit-insecticide.html; *see also* EPA Office of Pesticide Programs, *supra* note 23.

[25] EPA Office of Pesticide Programs, *supra* note 23.

conclusion: even relatively low levels of chlorpyrifos exposure early in life can result in severe, adverse neurodevelopmental outcomes.

A. Prenatal Chlorpyrifos Exposure is Directly Correlated with Adverse Brain Development and Cognitive Impairments

Experiments in rats in the late 1990s and early 2000s were the first to demonstrate that exposure to chlorpyrifos during the early stages of brain development could result in persistent behavioral and cognitive impairment.[26] The earliest experiments involved exposing rats *in utero* to high levels of chlorpyrifos. The exposed rats exhibited lower birthweights, delayed reflexes, and reduced perception.[27] Although these experiments involved exposure levels known to cause acute toxicity, later experiments began studying the effects of chlorpyrifos exposure at lower, subclinical levels, i.e., those that do not produce acute signs of toxicity. These studies found that even subclinical chlorpyrifos exposure during pregnancy resulted in marked effects on cognition and locomotion in rats after

[26] *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 Development Res. 83 (2001).

[27] *See* Chanda & Pope, *supra* note 26, at 774–775.

birth.[28] Moreover, these effects were sex-dependent, implying that areas of the brain impacted by sex hormones were also affected by chlorpyrifos.[29]

Three long-term epidemiological studies in humans built on these results. In 1997, President Clinton issued Executive Order 13,045, which directed federal agencies to "make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children." Exec. Order No. 13,045, 3 C.F.R. 198 (1998). In response, EPA and the National Institute of Environmental Health Sciences ("NIEHS") jointly established the Children's Environmental Health and Disease Prevention Research Centers program to study the impact of environmental exposures on children's health.[30] Through this program, starting in the late 1990s the agencies funded three prospective cohort studies that have examined the connection between early exposure to organophosphate pesticides, including chlorpyrifos, and adverse neurodevelopmental outcomes in children. In a prospective cohort study, researchers screen and collect demographic, environmental, and medical data from pregnant mothers and then follow the health and development of their children to

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[28] Levin et al., *supra* note 26, at 86–88.

[29] *Id.* at 87.

[30] EPA & NIEHS, *EPA/NIEHS Children's Environmental Health and Disease Prevention Research Centers: Impact Report* 8 (2017), https://www.epa.gov/sites/production/files/2017-10/documents/niehs_epa_childrens_centers_impact_report_2017_0.pdf.

assess the impact of certain factors, including exposure to toxic chemicals. Such studies are considered the "gold standard" in epidemiology.[31]

Two of the funded studies, conducted by Columbia University[32] and the Mount Sinai School of Medicine[33] ("Columbia Study" and "Mount Sinai Study," respectively), followed urban-dwelling 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").[34] In all three studies, researchers began by enrolling and taking baseline exposure measurements on pregnant women. In the intervening years, the scientists have conducted measurements and tests on the children at regular intervals. The children are now in their teens and the studies continue to this day.

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

[32] Virginia Rauh et al., *Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life*, 118 Pediatrics 1845 (2006) (AR 2188) [hereinafter "Columbia Study 2006"].

[33] Stephanie Engel et al., *Prenatal Exposure to Organophosphates, Paraxonase 1, and Cognitive Development in Childhood*, 119 Envtl. Health Persp. 1182 (2011) (AR 2190) [hereinafter "Mount Sinai Study"].

[34] 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 specifically measured chlorpyrifos exposure. It followed 265 children in New York City born to non-smoking mothers, measuring chlorpyrifos umbilical cord blood levels at birth to reflect prenatal exposure, and the researchers followed up with a series of cognitive and behavioral tests at various points in the child's life.

The first major result from the study was the observation that, at age three, the higher a child's *in utero* exposure to chlorpyrifos, the lower their performance in motor and mental development tests.[35] At the same age, children exposed to higher levels of chlorpyrifos were also more likely to develop attention problems including attention deficit hyperactivity disorder ("ADHD") and pervasive developmental disorder ("PDD").[36]

In a follow-up study, the researchers evaluated the same children at age seven.[37] This time, the scientists found that children exposed to higher levels of chlorpyrifos had noticeable changes in brain morphology compared to those

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[35] *See* Columbia Study 2006, *supra* note 32, at 1854–56.

[36] *Id.* at 1154.

[37] Virginia Rauh et al., *Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide*, 119 Envtl. Health Persp. 1196 (2011) (AR 2194) [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) (AR 2196) [hereinafter "Columbia Study 2012"].

exposed to lower chlorpyrifos levels.[38] Moreover, some of these changes were directly proportional to the dose of chlorpyrifos measured at birth.[39] In the higher chlorpyrifos exposure group, these changes in brain morphology were also directly correlated with a decrease in IQ scores.[40] Further, these children displayed a decrease in working memory that was again directly proportional to chlorpyrifos levels.[41] Consistent with observations in animal models, boys were disproportionately affected by chlorpyrifos exposure as compared to girls.[42]

By age eleven, the same higher chlorpyrifos exposure children were more likely to display mild or moderate tremors relative to the lower chlorpyrifos exposure children.[43] In other words, the neurodevelopmental effects observed in these children exposed *in utero* to chlorpyrifos persist until adolescence, suggesting that the cognitive and motor impairments may be irreversible.

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[38] Columbia Study 2012, *supra* note 37, at 7872.

[39] *Id.*

[40] *Id.* at 7872-73.

[41] Columbia Study 2011, *supra* note 37, at 1199.

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

[43] Virginia Rauh et al., *Prenatal Exposure to the Organophosphate Pesticide Chlorpyrifos and Childhood Tremor*, 51 NeuroToxicology 80, 83–84 (2015) (AR 2204).

The two other prospective cohort studies—carried out at the University of California–Berkeley, and Mount Sinai School of Medicine—did not look specifically at chlorpyrifos but at exposure to organophosphate pesticides more generally. Both studies found an association between prenatal organophosphate exposure and cognitive impairments in early childhood.[44] Moreover, the Mount Sinai study demonstrated that certain genetic minorities may be more susceptible to organophosphate-induced cognitive impairments than the general population.[45] These studies all show that prenatal chlorpyrifos exposure is directly correlated with significant, possibly irreversible, adverse neurodevelopment later in life.

B. The Neurotoxic Effects of Chlorpyrifos are Likely Caused by Other Mechanisms in Addition to AChE Inhibition

As described above, *see* Section I.A, *supra*, one mechanism of action for chlorpyrifos is to inhibit the enzyme AChE. 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 amount of pesticide that resulted in a 10% inhibition of AChE in the blood—effectively, the level of chlorpyrifos required to induce acute poisoning.

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[44] *See* Mount Sinai Study, *supra* note 33, at 1886; CHAMACOS Study, *supra* note 34, at 188.

[45] Mount Sinai Study, *supra* note 33, at 1884–86.

Perhaps the most alarming discovery of the Columbia Study was the fact that even the children with higher chlorpyrifos exposure—where the most significant adverse neurodevelopmental effects were observed—all had chlorpyrifos blood levels far below those which would trigger EPA's safety threshold of 10% AChE inhibition. This result had two major implications: 1) children were suffering from significant adverse neurodevelopmental effects through a biological mechanism independent of AChE inhibition; and 2) the safety threshold used by EPA to set tolerances was, in fact, *not protective* of the health of infants and children.

The Columbia Study findings have resulted in a substantial body of research in animal models that both confirms the observation that adverse neurodevelopmental effects occur at subclinical chlorpyrifos levels and identifies some possible AChE-independent mechanisms of neurotoxicity. These mechanisms implicate the processes underlying brain development, the transport of neurotransmitters, and cell death.

For example, chlorpyrifos directly influences the replication and differentiation of brain cells in rats.[46] Specifically, subclinical levels of chlorpyrifos in pre- and post-natal rats dramatically alter serotonin receptors and

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

transporters, which are critical to the proper development of the brain in early life.[47] Moreover, neonatal subclinical chlorpyrifos exposure increases signaling molecules associated with inflammation in the developing brains of mice.[48] Chlorpyrifos also inhibits neurite cell outgrowth, which can lead to adverse neurological effects in humans.[49]

In rats, chlorpyrifos also affects the structure of tubulin in cells.[50] Tubulin is an indispensable cellular component that provides a scaffold for the transport of molecules, including neurotransmitters. Additionally, subclinical chlorpyrifos exposure in minnows results in a downregulation of NTRK1, a gene in humans that, when mutated, is associated with cognitive disabilities.[51] Finally, in mouse

[47] *See id.* at 1738–40.

[48] *See* 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).

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

[50] *See* Xiangkun Yang et al., *Mass Spectrometric Quantitation of Tubulin Acetylation from Pepsin-Digested Rat Brain Tissue Using a Novel Stable Isotope Standard and Capture by Anti-Peptide Antibody (SISCAPA) Method*, 90 Analytical Chemistry 2155 (2018).

[51] *See* 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).

models, prenatal subclinical chlorpyrifos exposure results in an increase in the expression of genes that can trigger cell death.[52]

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

III. THESE STUDIES REINFORCE EACH OTHER AND SUPPORT THE CONCLUSION THAT EXISTING CHLORPYRIFOS FOOD TOLERANCES ARE NOT SAFE

EPA justified its reversal on the petition to revoke chlorpyrifos tolerances by stating that "the science addressing neurodevelopmental effects [of chlorpyrifos] remains unresolved" and that it would delay re-evaluation "to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos." 82 Fed. Reg. 16,581, 16,583 (Apr. 5, 2017) (ER 27). In reality, the research demonstrating adverse neurodevelopmental outcomes resulting from subclinical chlorpyrifos exposures is founded on a significant body of well-established science, which EPA itself

[52] *See* 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).

recognized in 2016.[53] This research provides ample support for the conclusion that the continued agricultural use of chlorpyrifos is unsafe. At a minimum, it makes it clear that EPA cannot affirmatively conclude "that there is a reasonable certainty that no harm will result from aggregate exposure to" chlorpyrifos. 21 U.S.C. § 346a(b)(2)(A)(ii).

A. The Prospective Cohort Studies Controlled for Alternative Confounding Factors

To establish reasonable cause and effect relationships based on epidemiological data, researchers must control for confounding factors. Confounding factors are extrinsic effects that may "confound" the result. Here, the three human epidemiological studies incorporated numerous controls for confounding factors. The Columbia Study, for example, controlled for childhood tobacco smoke exposure using self-reported tobacco residential use, confirmed by measuring blood levels of a byproduct of environmental tobacco smoke.[54] It also controlled for the possible adverse health status of the mother—selecting only those free of diabetes, hypertension, known HIV infection, and documented or

[53] *See* EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016) (ER 1257–62) [hereinafter "RHHRA"] ("[T]here is a breadth of information available on the potential adverse neurodevelopmental effects in infants and children as a result of prenatal exposure to chlorpyrifos."); 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016) (ER 1290, 1291) (proposing to revoke all tolerances based on the RHHRA).

[54] Columbia Study 2006, *supra* note 32, at 1847.

reported drug use[55]—and controlled for the education level and IQ of the mother.[56] Finally the Columbia Study controlled for a number of additional factors, including gestational age at birth and gender.

After controlling for many possible confounding factors, the Columbia Study still revealed a statistically significant, dose-dependent effect between chlorpyrifos levels and cognitive impairments and behavioral disorders.[57] Even if there were a hypothetical, confounding factor that the researchers did not analyze, it would have to correlate *exactly* with the chlorpyrifos dose-response relationship observed, which is highly unlikely. The CHAMACOS and Mount Sinai studies, which reached similar conclusions, collected and controlled for demographic information like that collected in the Columbia Study.[58]

B. Animal Models Demonstrate a Direct Effect Between Chlorpyrifos Exposure and Neurodevelopment Similar to those Observed in Humans

The adverse neurodevelopmental effects associated with chlorpyrifos discovered in the Columbia Study have been supported by a significant number of animal model studies. A recently-published literature review found eight recent

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[55] *Id.*

[56] *Id.* at 1851.

[57] *Id.* at 1853–54.

[58] CHAMACOS Study, *supra* note 33, at 182–183; Mount Sinai Study, *supra* note 34, at 1182–83.

studies using animal models in which rodents exposed to chlorpyrifos *in utero* or as neonates suffered from significant cognitive impairments later in life.[59] 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.[60] While many of these animal studies were conducted at chlorpyrifos levels above 10% AChE inhibition, at least one study was conducted at subclinical levels and observed similar sex-dependent defects in spatial learning and memory.[61] In addition, one study that was performed on guinea pigs—which the authors described as the most relevant animal model for human organophosphate exposure—observed similar impacts on brain morphology to those found in the Columbia Study.[62] Ultimately, the significant adverse effects on brain development and morphology observed in the Columbia Study, as well as the sex-specific cognitive impairment also observed in the CHAMACOS and Mount Sinai studies, have been supported by direct exposure experiments performed in animal models.

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[59] *See* 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).

[60] *Id.*

[61] *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).

[62] *See* Burke et al., *supra* note 59, at 171–72.

C. After an Exhaustive Literature Review, EPA Found that Current Chlorpyrifos Tolerances are not Protective

In light of the mounting evidence demonstrating that current chlorpyrifos tolerances were not sufficiently protective of the health of infants and children, in 2015 EPA proposed to revoke all tolerances for chlorpyrifos. 80 Fed. Reg. 69,080 (Nov. 6, 2015) (ER 1133). EPA consulted with the FIFRA Scientific Advisory Panel ("SAP") to evaluate the findings of the Columbia Study as well as the current state of the scientific literature concerning the effects of chlorpyrifos on neurodevelopment. 81 Fed. Reg. at 81,050 (ER 1291). The SAP generally supported the Columbia Study's conclusion that there is an "association between prenatal chlorpyrifos exposure and neurodevelopmental outcomes in children" at subclinical levels. *Id.* EPA agreed with the SAP's evaluation and found that the existing standard based on 10% AChE inhibition was "not sufficiently health protective." *Id.*

Because the Columbia Study did not identify a chlorpyrifos level at which no adverse developmental effects would occur, EPA instead used the level at which the lowest observed adverse effects occurred and retained the FQPA-mandated 10x safety factor to account for this uncertainty. 80 Fed. Reg. at 69,082, 69,089 (ER 1135, 1142). EPA also used a second 10x safety factor to account for variability among people's response and exposure to chlorpyrifos. *Id.*; 81 Fed. Reg. at 81,050 (ER 1291). The SAP agreed that the use of this additional 10x

safety factor was appropriate.[63] EPA then developed the new reference dose using a sophisticated model that estimated the time-weighted average of the blood concentration of chlorpyrifos in the Columbia Study mothers. 81 Fed. Reg. at 81,050–51 (ER 1291–92). After applying this new standard, EPA found that current tolerances resulted in an unsafe level of chlorpyrifos residue in food and drinking water.[64] Accordingly, EPA proposed to revoke all tolerances for chlorpyrifos. 81 Fed. Reg. at 81,050 (ER 1291).

D. Studies that do not Observe a Correlation Between Subclinical Chlorpyrifos Exposure and Neurodevelopment Suffer from Serious Experimental Design Flaws

In 2017, EPA abruptly reversed course and denied the 2007 petition to revoke chlorpyrifos tolerances. 82 Fed. Reg. at 16,583 (ER 27). The agency justified its decision by stating that "the science addressing neurodevelopmental effects remains unresolved." *Id.* This is not correct. The numerous studies demonstrating significant adverse neurodevelopmental outcomes in infants and children present substantial evidence that current chlorpyrifos tolerances are not safe. There is a small handful of studies in the literature that observe little or no effect on neurodevelopmental outcomes. These studies, however, all suffer from

[63] FIFRA Scientific Advisory Panel Minutes (Apr. 19–21, 2016), at 61 (ER 1234).

[64] *See* EPA, *supra* note 53; EPA, Chlorpyrifos Refined Drinking Water Assessment for Registration Review (Apr. 14, 2016) (AR 2136).

significant experimental design flaws which undermine the reliability of their conclusions.

1. Urine Metabolite Biomarkers do not Necessarily Correlate with Actual Chlorpyrifos Levels in Blood

One study examined the correlation between maternal chlorpyrifos levels and ADHD in their children and did not observe an effect.[65] Unlike the Columbia Study, however, these researchers did not directly measure chlorpyrifos levels in maternal blood samples.[66] Instead they measured a metabolite specific to chlorpyrifos, TCPY.[67] The problem with using this biomarker is that chlorpyrifos can naturally degrade into TCPY in the environment.[68] As a result, observed TCPY levels in urine or blood could be a result of maternal exposure either to chlorpyrifos itself or to TCPY. Therefore, use of this biomarker may dramatically overestimate exposures to chlorpyrifos, confounding the observed null results.[69]

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[65] Gamola Fortenberry et al., *Urinary 3, 5, 6-Trichloro-2-Pyridinol (TCPY) in Pregnant Women from Mexico City: Distribution Temporal Variability, and Relationship with Child Attention and Hyperactivity*, 217 Int'l J. Hygiene Envtl. Health 405 (2014).

[66] *Id.* at 409.

[67] *Id.*

[68] *See* Burke et al., *supra* note 59, at 164.

[69] *See id.* ("In cases in which the amount of TCPY absorbed from external sources overwhelms the amount of TCPY produced by the in vivo breakdown of [chlorpyrifos], blood or urine levels of TCPY do not accurately correlate with levels of [chlorpyrifos] absorbed and, consequently, do not correlate with the magnitude of the biological effects of [chlorpyrifos].")

2. AChE Rapidly Turns over in Cells

While EPA has relied on AChE inhibition as the standard for setting safety tolerances, there are significant problems with using this enzyme as a biomarker of chlorpyrifos toxicity. One problem is that AChE rapidly turns over in the cell.[70] As such, measurements taken later in time may dramatically underestimate chlorpyrifos exposure.[71] For example, one study that did not observe a correlation between exposure, AChE activity, and defects in locomotion measured AChE activity a full 24 hours after chlorpyrifos exposure.[72] Rapid turnover of AChE in the brain could underestimate any AChE-dependent chlorpyrifos toxicity and confound these results. In this study, even when chlorpyrifos exposure did not affect locomotion, it still induced adverse social and behavioral effects.[73] Moreover, as explained above, *see* Sections II.A–C, *supra*, numerous studies in humans and animal models have strongly suggested that there are other mechanisms of chlorpyrifos toxicity independent of AChE inhibition. EPA's

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[70] *See id.* at 167.

[71] *See id.*

[72] *See id.* (citing, e.g., Aldina Venerosi et al., *A Social Recognition Test for Female Mice Reveals Behavioral Effects of Developmental Chlorpyrifos Exposure*, 28 Neurotoxicology & Teratology 466 (2006).

[73] *See* Venerosi et al., *supra* note 72, at 469.

reliance on AChE inhibition as the benchmark in setting chlorpyrifos tolerances fails to capture these other modes of action.[74]

3. Certain Behavioral Tests may not be Sufficiently Sensitive to Detect the Cognitive Domains Affected by Chlorpyrifos

One study that did not detect learning or memory deficits in rats exposed prenatally to chlorpyrifos requires several important caveats.[75] First, the study was performed by scientists at Dow Chemical Company, one of the registrants for chlorpyrifos. Second, this study was performed years before the specific cognitive effects of chlorpyrifos were identified. Third, and related to the second caveat, the cognitive tests that the Dow researchers used may not have been sufficiently sensitive to detect abnormalities in the specific cognitive domains identified by the Columbia Study.[76]

For example, a subsequent study by a different research group also observed a lack of chlorpyrifos-induced effects using a test similar to that used by the Dow group.[77] However, when they used a test that measured a *different* form of

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[74] *See* Burke et al., *supra* note 59, at 173–75.

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

[76] *See* Burke et al., *supra* note 59, at 167.

[77] *See id.* (citing Xiao-Ping Chen et al., *Selective Cognitive Impairments are Related to Selective Hippocampus and Prefrontal Cortex Deficits after Prenatal Chlorpyrifos Exposure*, 1474 Brain Res. 19 (2012)).

cognition, chlorpyrifos exposure resulted in a statistically significant impairment.[78] As the researchers observed, because their "results suggest that cognitive deficits induced by prenatal exposure are function-specific, the negative results reported by [the Dow study] have to be interpreted with a great deal of caution."[79]

In summary, the handful of studies finding no effect all contain significant shortcomings and do not undermine the plethora of scientific evidence that chlorpyrifos exposure in the early stages of life results in significant adverse neurodevelopmental outcomes. As such, the scientific literature on the neurodevelopmental impacts of chlorpyrifos does not support a conclusion that existing food tolerances for the pesticide are safe.

CONCLUSION

Congress, in passing the FQPA, made the safety of children and infants paramount when EPA makes regulatory decisions related to pesticides. Decades of scientific research demonstrate that current tolerances for chlorpyrifos are not sufficiently protective of the health of children and infants. EPA was correct when it proposed to revoke all tolerances for chlorpyrifos. EPA's current about-face on chlorpyrifos safety is not supported by the scientific record. The agency cannot bury its head in the sand at the expense of children who are exposed to unsafe

[78] *See id.*

[79] *Id.*

levels of chlorpyrifos.

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

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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 2013 in Times New Roman 14-point font, a proportionally spaced typeface, and contains 6,144 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 February 13, 2018. 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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