LULAC PETITIONERS' FEEDBACK ON THE ENVIRONMENTAL PROTECTION AGENCY'S CHLORPYRIFOS TOLERANCE REVOCATION RULE AND COMMENTS ON GROWERS' OBJECTIONS

Submitted Pursuant to 21 U.S.C. § 346a(g)(2)[1]

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INTRODUCTION

On August 18, 2021, after five lawsuits and numerous court orders, the most recent of which found that "EPA had abdicated its statutory duty" to ensure the safety of our food, *see League of United Latin American Citizens v. Regan*, 996 F.3d 673, 678 (9th Cir. 2021) ("*LULAC*"), EPA signed a final rule revoking all tolerances for chlorpyrifos residues on food. 86 Fed. Reg. 48,315 ("final rule" published August 30, 2021). EPA revoked the tolerances because "EPA is unable to conclude that the risk from aggregate exposure from the use of chlorpyrifos meets the safety standard." *Id*.

EPA's press release heralded this action:

> "Today EPA is taking an overdue step to protect public health. Ending the use of chlorpyrifos on food will help to ensure children, farmworkers, and all people are protected from the potentially dangerous consequences of this pesticide," said Administrator Michael S. Regan. "After the delays and denials of the prior administration, EPA will follow the science and put health and safety first."

The *LULAC* petitioners, along with other health, labor, and children's advocates, celebrate EPA's action.[2] As Administrator Regan's comment attests, it took far too long, but chlorpyrifos will finally be out of our food early next year. 86 Fed. Reg. at 48, 315 (final rule is effective October 29, 2021, and the tolerances will expire on February 28, 2022).

The content of the final rule, however, signals EPA's potential willingness to entertain petitions to reinstate some chlorpyrifos tolerances. EPA's 2021 final rule is expressly based on all the currently registered chlorpyrifos uses in the aggregate, concluding that the agency "cannot, at this time, determine that aggregate exposures to residues of chlorpyrifos ... are safe." 86 Fed. Reg. at 48,317, 48,333. However, it holds out the possibility that EPA might be able to find a discrete set of uses safe if significant changes were made to the registrations to add mitigation and impose geographic restrictions. *Id.* at 48,322, 48,333. It describes the Trump

[1] No fee is required because 21 U.S.C. § 346a(m)(3) prohibits the Administrator from collecting fees for objections through September 30, 2023.

[2] The *LULAC* petitioners are: LULAC, Natural Resources Defense Council, Pesticide Action Network North America, California Rural Legal Assistance Foundation, Farmworker Association of Florida, Farmworker Justice, GreenLatinos, Labor Council for Latin American Advancement, Learning Disabilities Association of America, National Hispanic Medical Association, Pineros y Campesinos Unidos del Noroeste, and United Farm Workers.

EPA's 2020 proposed interim registration review decision, which would retain about half the chlorpyrifos usage on certain crops in some geographic areas, as intended "to offer to stakeholders a way to mitigate the aggregate risk from chlorpyrifos." *Id*. at 48,322; *see* 85 Fed. Reg. 78,849 (Dec. 7, 2020) (seeking public comment on the 2020 Proposed Interim Registration Review Decision for Chlorpyrifos and 2020 Chlorpyrifos Human Health Risk Assessment).

The final rule indicates that a party wanting EPA to maintain a tolerance could ask it to do so through objections to the tolerance revocation rule. 86 Fed. Reg. at 48,316. We believe it would be inappropriate for EPA to entertain requests to maintain individual chlorpyrifos tolerances through the objections process. The full suite of chlorpyrifos tolerances are, in the aggregate, unquestionably unsafe, and that is the basis for the chlorpyrifos tolerance revocation rule. A request for an individual tolerance is a different action that must be supported by proof of safety of not only the individual tolerance, but also the aggregate effects of all other chlorpyrifos uses that EPA might consider retaining. And EPA could not act on such a request and make a safety finding without reviewing the entire chlorpyrifos record, including public comments, which it has not yet done. However, because EPA has suggested that entities seeking to maintain a tolerance could make such a request through the objections process, the *LULAC* petitioners submit this feedback pursuant to 21 U.S.C. § 346a(g)(2), the process for providing feedback referenced in EPA's Frequent Questions About the Chlorpyrifos 2021 Final Rule, ¶ 10, at https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule ("Frequent Questions").

It would defy both the law and the science for EPA to reinstate any chlorpyrifos tolerances. As explained in the 9th Circuit decision, EPA must find reasonable certainty of no harm to children from aggregate exposure in order to retain a chlorpyrifos tolerance. To do so, it must identify the greatest exposure that poses no risk of harm to children and ensure that children will not be exposed to higher levels of chlorpyrifos. 996 F.3d at 678, 680. The 9th Circuit held:

> The EPA has not determined, and on this record reasonably could not determine to a "reasonable certainty" that aggregate chlorpyrifos exposures under the current tolerances pose no risk of harm. Therefore, by statutory definition, the present tolerances are not safe.

Id. at 701.

EPA and its Scientific Advisory Panel have repeatedly found that chlorpyrifos causes learning disabilities and other neurodevelopmental harm to children at exposures below those that cause 10% acetylcholinesterase inhibition ("AChE" or "cholinesterase inhibition") in red blood cells ("RBC"). EPA, therefore, cannot find reasonable certainty of no harm to children based on 10% cholinesterase inhibition, as has been explained in great detail in the extensive comments submitted by scientists, states, health professionals, and farmworker and children's advocates on EPA's risk assessments, 2015 proposed revocation rule, and 2020 proposed interim registration review decision. These comments document the many ways EPA's risk assessments and 2020 interim registration review proposal do not protect children from neurodevelopmental harm that occurs at exposures below EPA's regulatory endpoint. The final tolerance revocation rule acknowledges that the comments raised the serious concern that using 10% cholinesterase inhibition as the regulatory endpoint "may not provide a sufficiently health protective human

health risk assessment given the potential for neurodevelopmental outcomes." 86 Fed. Reg. at 48,321. EPA did not respond to these comments in its August 2021 final rule and acknowledges that it must do so before considering requests to reinstate any chlorpyrifos tolerances or completing the chlorpyrifos registration review. *Id*. at 48,334. When it does so, the only scientifically plausible and legal conclusion will be that EPA is unable to find reasonable certainty of no harm to children from chlorpyrifos use on our food.

We are concerned, however, that entities seeking to retain chlorpyrifos tolerances will rely on the rule's unsupported use of 10% cholinesterase inhibition as the regulatory endpoint and treat it as precedent. We are also concerned that EPA might continue to use the unsupported regulatory endpoint in its future registration review actions on nonfood uses of chlorpyrifos or its registration review of other organophosphate pesticides.

Our concerns are borne out by the objections filed by 80 grower groups on October 19, 2021, asking EPA to stay and ultimately rescind the final revocation rule. The bulk of the growers' objections go to the implementation of the final rule on its economic impacts, which are beyond the scope of what can be addressed through the objections process. Growers' Objections at 1–4, 7–8. As the 9th Circuit held, Congress prioritized safety and protection of human health above all else when it passed the Food Quality Protection Act ("FQPA"), amending the Federal Food, Drug, and Cosmetic Act ("FFDCA"). 996 F.3d at 692. EPA must revoke tolerances of pesticides it cannot find reasonably certain to cause no harm generally and particularly to children. *Id*. at 678. While the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") is a risk-benefit statute, the FFDCA is not, contrary to the growers' objections. In addition to their broadside attack on the final rule in its entirety, the growers' objections seize upon the 2020 drinking water assessment, which uses an underprotective regulatory endpoint, to urge EPA to retain 11 crop uses of chlorpyrifos. Growers' Objections at 5, 7. Acceding to this request, however, would violate the FFDCA and the 9th Circuit's decision in *LULAC*.[3]

To ensure that EPA does not treat the final rule's regulatory endpoint as precedential for any such future decisions and to counter the growers' objections or objections from other entities seeking to retain chlorpyrifos tolerances, we are submitting these comments demonstrating why any continued use of an underprotective regulatory endpoint would violate the law and defy the record. Submitting this feedback through the objections process ensures that we can raise these issues in subsequent proceedings on this rule. *See* 86 Fed. Reg. at 48,316 (issues resolved in final rule cannot be raised in subsequent proceedings unless presented in objections).

As the preamble to the final rule indicates, EPA will not consider legal or factual issues presented in objections if the issue could reasonably have been raised in early proceedings. Accordingly, we will focus primarily on the 9th Circuit's decision in *LULAC* issued on April 29, 2021, and the rationale in the final rule.

[3] The Growers' Objections feature many crops and are signed by groups with interests in crops, including peanut, onion, corn, potato, sunflower, and rice, that are not the subject of the 2020 drinking water assessment or the 2020 proposed interim registration review decision that would retain some chlorpyrifos uses (based on an underprotective regulatory endpoint).

I. *LULAC* MAKES CLEAR THAT 10% CHOLINESTERASE INHIBITION IS NOT A SAFE EXPOSURE LEVEL FOR CHILDREN.

The core health issue before EPA and the courts has been the need to protect children from neurodevelopmental harm from low-level exposures to chlorpyrifos. In 2007, Natural Resources Defense Council and Pesticide Action Network of North America filed a petition to ban use of chlorpyrifos on food because of neurodevelopmental harm to children from exposures far lower than EPA's regulatory standard, 10% cholinesterase inhibition in RBC. Upon reviewing the growing body of scientific evidence, both EPA and its Scientific Advisory Panel ("SAP") repeatedly found that prenatal exposure to chlorpyrifos causes learning disabilities and other neurodevelopmental harm and that such harm occurs from chlorpyrifos exposures below those that cause 10% cholinesterase inhibition. Since it proposed revoking chlorpyrifos tolerances in 2015, EPA has been trying to find a daily exposure limit that would be reasonably certain to cause no neurodevelopmental harm across diverse populations and in sensitive subpopulations, specifically children. The 2021 final rule, like the Trump 2020 human health risk assessment and proposed interim registration review decision, however, abandons any attempt to find a safe exposure for children, even though the 2021 decision expresses EPA's continued concerns regarding neurodevelopmental effects. 86 Fed. Reg. at 48,322.

EPA's 14-year review of that harm, reinforced by the SAP's reviews and 9th Circuit decisions, established two guard rails on EPA's tolerance decisions, one scientific and the other legal. The scientific guard rail is that chlorpyrifos causes harm to children's brains at exposures below those that cause 10% cholinesterase inhibition, meaning that 10% cholinesterase inhibition is not the most sensitive endpoint. The legal guard rail is that EPA cannot make a reasonable certainty of no harm finding using 10% cholinesterase inhibition as the regulatory endpoint because it does not protect children from neurodevelopmental harm from lower exposures. The final rule acknowledges the scientific guard rail, but tries to evade the legal one by clinging to arguments that are at odds with EPA policies, the controlling statute, and the record, and that have been soundly rejected by the 9th Circuit.

The 9th Circuit confirmed that EPA cannot make a safety finding using 10% cholinesterase inhibition as the regulatory endpoint. The 9th Circuit recited the EPA and SAP findings beginning in 2008 when EPA found preliminarily in 2008 that chlorpyrifos played a role in neurodevelopmental harm at exposures below 10% cholinesterase inhibition and the 2008 SAP agreed. Specifically, a study conducted by the Columbia Center on Children's Environmental Health ("CCCEH") produced numerous peer-reviewed papers correlating chlorpyrifos exposures in pregnant women in New York public housing with reduced IQ and learning disabilities in their children, including attention deficit disorders, autism, and developmental delays. The 2008 SAP determined that the Columbia epidemiology studies are "epidemiologically sound" and "provided extremely valuable information" on the neurodevelopmental effects of chlorpyrifos. 996 F.3d at 683; *see also* 86 Fed. Reg. 48,320 (final rule reiterates that the Columbia study is epidemiologically sound and provides extremely valuable information). As the 9th Circuit observed, the 2011 preliminary human health risk assessment continued to use the 10% cholinesterase inhibition endpoint, but indicated EPA would need to ensure it is health protective for neurodevelopmental toxicity, 996 F.3d at 684, and the 2012 SAP

> opined with more certainty than the 2008 SAP that multiple "lines of evidence suggest that chlorpyrifos can affect neurodevelopment at levels lower than those associated with AChE inhibition, and that the use of AChE inhibition data may not be the most appropriate for ... assessment of the neurodevelopmental risks of chlorpyrifos."

996 F.3d at 700–01; *see also id.* at 684.

The final rule likewise references the 2012 SAP findings that the epidemiology studies "show some consistent associations relating exposure measures to abnormal reflexes in the newborn, pervasive development disorder at 24 or 36 months, mental development at 7-9 years, and attention and behavior problems at 3 and 5 years of age." 86 Fed. Reg. at 48,321. It notes that the 2012 FIFRA SAP concluded "that the RBC AChE inhibition remained the most robust dose-response data, though expressed significant concerns about the degree to which 10% RBC AChE inhibition is protective for neurodevelopmental effects, pointing to evidence from epidemiology, *in vivo* animal studies, and *in vitro* mechanistic studies, and urged the EPA to find ways to use the CCCEH data." *Id*.

The 2014 revised human health risk assessment, in the words of the 9th Circuit, "expressed greater certainty" that chlorpyrifos was causing neurotoxic harms to children and that "exposure was below the AChE inhibition-related point of departure." 996 F.3d at 685; *see also id*. at 701 ("'[C]hlorpyrifos likely played a role in the neurodevelopmental outcomes observed in these epidemiology studies.' Moreover, 'it is unlikely mothers enrolled in the [Human Cohort Studies] experienced [red blood cell] AChE inhibition.'") (quoting 2014 human health risk assessment).

As the 9th Circuit stated, the 2016 SAP "agree[d] that both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% red blood cell [AChE] inhibition." 996 F.3d at 686, 701. The final rule similarly acknowledges that the 2016 FIFRA SAP "expressed concern that 10% RBC AChE inhibition is not sufficiently protective of human health. Specifically, the FIFRA SAP stated that it 'agrees 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 (*i.e*., toxicity at lower doses).'" 86 Fed. Reg. at 48,321.

In the 2016 human health risk assessment, EPA reiterated the finding that "[t]he Columbia Study, 'with supporting results from the other [Human Cohort Studies] and the seven additional epidemiological studies reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition.'" 996 F.3d at 701. In the notice of availability making the 2016 risk assessment available for public comment, EPA expressly agreed with the 2016 and previous SAP findings "that there is a potential for neurodevelopmental effects associated with chlorpyrifos exposure to occur at levels below 10% RBC AChE inhibition." *Id*. at 688 n.85. EPA has never disavowed this finding, nor could it consistent with the extensive scientific record and EPA and SAP findings.

As the logical next step, EPA concluded in the 2016 risk assessment that "it was necessary to adopt an approach" that would protect against "any adverse effects that could occur

at lower doses." *Id*. at 688. Doing so is necessary because

> there is a potential for neurodevelopmental effects associated with chlorpyrifos exposure to occur at levels below 10% RBC AChE inhibition, and that [the] EPA's existing point of departure (which is based on 10% AChE inhibition), is therefore not sufficiently health protective.

Id. at 688 n.85.

The final rule does not attempt to find an exposure level that will be sufficiently health protective for children, even though it still expresses "concerns regarding potential neurodevelopmental effects." 86 Fed. Reg. at 48,322. EPA discarded the approach taken in the 2016 risk assessment because of uncertainties, without replacing it with an alternative approach that would ensure reasonable certainty of no harm to children. *Id*. But, as the 9th Circuit found, the 2016 risk assessment's finding that chlorpyrifos is unsafe is "consistent with more than a decade of EPA issue papers, revised human health risk assessments, and SAP proceedings." 996 F.3d at 702–03. Yet EPA simply cast it aside without trying to prevent low-level exposures that would cause neurodevelopmental harm to children by, for example, deriving a regulatory endpoint from animal toxicology studies that reported neurodevelopmental harm at doses that did not elicit meaningful cholinesterase inhibition, as California risk assessors have done. In the face of the unbroken EPA and SAP findings, beginning in 2008 and growing in strength over time, that exposures to chlorpyrifos at levels below those that cause 10% cholinesterase inhibition are linked to serious, life-long neurodevelopmental harm to children, EPA cannot find reasonable certainty of no harm at exposures that cause 10% cholinesterase inhibition.

II. UNSUPPORTED STATEMENTS PURPORTING TO DISPARAGE THE CAUSAL LINKAGE BETWEEN CHLORPYRIFOS AND NEURODEVELOPMENTAL HARM TO CHILDREN

The 2021 decision erroneously asserts that EPA has been unable to determine there is a causal linkage between chlorpyrifos exposure and neurodevelopmental harm to children. These unsupported statements are completely undercut by EPA's consistent conclusions that, as described by the 9th Circuit, "the available data support a conclusion of increased sensitivity of the young to the neurotoxic effects of chlorpyrifos and for the susceptibility of the developing brain to chlorpyrifos." 996 F.3d at 697.

A. Epidemiological Studies

EPA's asserted inability to find a causal linkage with respect to the Columbia studies is counter to the evidence before the agency and its own findings. 86 Fed. Reg. at 48,322 ("While EPA sought to verify the conclusions of the epidemiology studies conducted by Columbia University it has been unable to confirm the findings of the CCCEH papers or conduct alternative statistical analyses to evaluate the findings."); *id*. at 48,324 ("EPA remains unable to make a causal linkage between chlorpyrifos exposure and the outcomes reported by CCCEH investigators."). Disturbingly, EPA repeated the erroneous statement that "it has been unable to confirm the findings of the CCCEH papers" in its Frequent Questions document posted on its website (¶ 2).

These statements are utterly lacking in any support in the record and run counter to EPA's findings in its reviews of the science and its risk assessments, and the SAP's reviews of the science, including the Columbia studies, and the 9th Circuit decision. As the 9th Circuit explained, the 2012 SAP findings noted nine strengths in the Columbia studies along with some shortcomings and found overall that "[t]he strengths of the three studies support the Panel's conclusion." 996 F.3d at 684. The 9th Circuit quoted EPA's conclusions with respect to the three human cohort studies in its 2015 proposed revocation rule, *id*. at 686:

> [The] EPA has considered the strengths and limitations of these studies, and believes that random or systematic errors in the design, conduct or analysis of these studies were unlikely to fully explain observed positive associations between *in utero* [organophosphate] exposure and adverse neurodevelopmental effects observed at birth and through childhood (age 7 years). [The] EPA believes these are strong studies which support a conclusion that [organophosphates] likely played a role in these outcomes.

The 9th Circuit also quoted the 2016 risk assessment's conclusion that uncertainties

> "do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies ... represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements." "In summary," the EPA concluded that "the [Columbia Study], with supporting results from the other [two Human Cohort Studies] and the seven additional epidemiological studies reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition."

Id. at 687–88.

Even the 2020 risk assessment finds that chlorpyrifos harms children's brains at exposures below those that cause 10% cholinesterase inhibition, citing the Columbia and other cohort studies, along with the consistent findings of the SAP in 2008, 2012, and 2016. 2020 Revised Human Health Risk Assessment ("RHHRA") at 85–86, 88. EPA's 2019 denial of our objections likewise contains the same acknowledgement. 84 Fed. Reg. at 35,563–64. Statements to the contrary in the final tolerance revocation rule collide with the extensive record finding the opposite and are arbitrary and capricious.

B. Laboratory Animal Studies

The final rule makes a similar statement with respect to the laboratory animal studies correlating neurodevelopmental harm and exposures below those that cause 10% cholinesterase inhibition. 86 Fed. Reg. at 48,324 ("EPA has further concluded that the laboratory animal studies do not support a conclusion that adverse neurodevelopmental outcomes are more sensitive than 10% RBC AChE inhibition.").

This statement is at odds with EPA's actual review of the animal studies. Indeed, EPA noted that one study, in particular, "provides strong support for the conclusion that effects on the developing brain may occur below a dose eliciting 10% AChE inhibition" and EPA conducted an independent statistical analysis that confirmed the study's findings. 2020 RHHRA at 88. And as

explained below, the California Department of Pesticide Regulation ("CDPR") established a regulatory endpoint based on animal studies correlating neurodevelopmental harm to low-level exposures, found chlorpyrifos unsafe, and initiated cancellation proceedings, which phased out approximately 99% of chlorpyrifos use in California by the end of 2020.[4]

III. THE REGULATORY ENDPOINT USED IN THE FINAL RULE IS CONTRARY TO THE EVIDENCE AND THE 9TH CIRCUIT DECISION.

The final rule's rationale for using 10% cholinesterase inhibition as the regulatory endpoint runs run counter to the law, the record, and the 9th Circuit decision.

A. Difficulties in Pinpointing the Exposures That Cause Harm Do Not Justify Using an Underprotective Endpoint.

At its core, EPA tries to justify using 10% cholinesterase inhibition as the regulatory endpoint because of the challenges in identifying the specific lower exposures that cause neurodevelopmental harm. 86 Fed. Reg. at 48,322. The fact that such harm has occurred, however, means 10% cholinesterase inhibition is not a safe exposure level and EPA cannot find reasonable certainty of no harm to children from such exposures. As the 9th Circuit held, "[t]he EPA can find a tolerance safe only if there is 'a reasonable certainty' of 'no harm,' and for nearly a decade, the EPA and its SAPs have concluded that there is *not* a reasonable certainty of no harm." 996 F.3d at 700.

The final rule recites uncertainties in the science that the EPA embraced in denying the petition in 2017 and the objections in 2019. It lists uncertainties in the various studies, ignoring that the 2012 SAP found

> that multiple "lines of evidence suggest that chlorpyrifos can affect neurodevelopment at levels lower than those associated with AChE inhibition, and that the use of AChE inhibition data may not be the most appropriate for ... [assessing] the neurodevelopmental risks of chlorpyrifos."

Id. at 684.

And the final rule never acknowledges EPA's own finding in 2012 that any errors in the Columbia study likely underestimate, rather than overestimate, the risks to children. LULAC 2021 Comments at 17, quoting EPA's 2012 FIFRA SAP Issue Paper at 71 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0040-0002) ("EPA believes the possibility of under-estimation of effect size is more likely than factors that would lead to over-estimation of effect size.").

[4] CDPR, Final Toxic Air Contaminant Evaluation of Chlorpyrifos at 9–10 (July 2018), https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_final_tac.pdf; *see also* CDPR, Agreement Reached to End Sale of Chlorpyrifos in California by February 2020 (Oct. 9, 2019), https://www.cdpr.ca.gov/docs/pressrls/2019/100919.htm.

The final rule describes the difficulties in reconstructing the exposures in the Columbia study, even though it acknowledges that EPA followed the methodology laid out by the SAP and used the best available information and tools in reconstructing the dose in its 2014 and 2016 risk assessments. 86 Fed. Reg. at 48,324. And the 2016 risk assessment, which is the only EPA risk assessment designed to protect children from neurodevelopmental harm, found chlorpyrifos unsafe every way people are exposed, with children ages 1-2 years old exposed to 140 times safe levels in food alone, and it also found most drinking water exposures unsafe. 2016 RHHRA; 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016) (releasing the 2016 risk assessment for public comment).

The final rule takes the position that it cannot use the Columbia data in a risk assessment due to uncertainties in the dose-response relationship. 86 Fed. Reg. at 48,322, 48,325. However, the 9th Circuit refused to allow such uncertainties to justify retaining tolerances without making an affirmative finding that they are safe. It quoted the 2015 proposed revocation rule where EPA acknowledged

> "significant uncertainties ... about the actual exposure levels experienced by mothers and infant participants in the three children's health cohorts," but found that the measured exposures "are likely low enough that they were unlikely to have resulted in AChE inhibition."

996 F.3d at 686.

Given that EPA has, as the 9th Circuit noted, found chlorpyrifos "harmful at levels below the existing tolerances," *id*. at 691, and that EPA must use an exposure amount that poses no risk of harm in setting tolerances, *id*. at 680, using 10% cholinesterase inhibition as the regulatory endpoint will not ensure to a reasonable certainty that chlorpyrifos will cause no harm to children.

B. EPA Must Base Its Regulatory Endpoint on Neurodevelopmental Harm to Children Because That Is The Most Sensitive Endpoint.

The 2021 final rule identifies cholinesterase inhibition and effects on the developing brain as the most sensitive endpoints. 86 Fed. Reg. at 48,323. Because the harm to children's brains occurs at exposures below those that cause 10% cholinesterase inhibition, neurodevelopmental harm to children is the most sensitive endpoint and 10% cholinesterase inhibition is not a safe exposure level for children. It is EPA policy to use the most sensitive endpoint, called "point of departure," to ensure tolerances will be safe, as the final tolerance rule acknowledges. *Id*. at 48,317, 48,322.[5]

As the 9th Circuit explained, "[i]n setting chlorpyrifos tolerances, the EPA must determine the greatest exposure amount that poses no risk of harm, which is known as a 'point of

[5] EPA Office of Pesticide Programs, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment at 8 (Feb. 28, 2002), https://www.epa.gov/sites/production/files/2015-07/documents/determ.pdf.

departure.'" 996 F.3d at 680. EPA, therefore, cannot make a reasonable certainty of no harm finding based on exposures that produce 10% cholinesterase inhibition.

C. Uncertainties Surrounding the Mechanism By Which Chlorpyrifos Harms Children's Brains Do Not Justify Using An Underprotective Endpoint.

In reverting to 10% cholinesterase inhibition as the regulatory endpoint, the final rule refers to uncertainties about the mode of action by which chlorpyrifos harms children's brains. 86 Fed. Reg. at 48,324. The Growers' Objections likewise cite uncertainties about the mode of action as a reason to ignore the Columbia study. Growers' Objections at 6–7. EPA policy, however, does not require that EPA be able to identify the precise mechanism by which chlorpyrifos harms children's brains to be obligated to protect against such harm. *See* 2014 RHHRA at 48–49.

Indeed, the 9th Circuit squarely rejected an analogous argument:

> the EPA argues that it does not know *how* chlorpyrifos's neurotoxic effects harm infants and children. But that is not the question before the EPA. The question is *whether* chlorpyrifos causes such harms. Even if the mechanism is unknown, if a tolerance is unsafe, then the EPA must revoke it.

996 F.3d at 698. The court cited *American Trucking Associations, Inc. v. EPA*, 175 F.3d 1027, 1055 (D.C. Cir. 1999), which held that EPA was not required to prove "how particles actually interact with cells and organs to cause sickness and death" to find a correlation, *aff'd in part and rev'd in part on other grounds sub nom. Whitman v. Am. Trucking Assn's*, 531 U.S. 457, 121 S.Ct. 903, 149 L.Ed.2d 1 (2001). 996 F.3d at 698 n.142. The court also cited EPA's own finding that uncertainties surrounding the mechanism by which the effects occur and the precise window of susceptibility do not undermine or reduce confidence in the epidemiology studies. *Id.* at 687–88, citing 2016 RHHRA. EPA must protect children from adverse neurodevelopmental effects that occur at doses below those that cause cholinesterase inhibition, even if it has not yet identified the precise mechanism by which chlorpyrifos causes these effects.

D. Lack of Access to the Raw Data Does Not Justify Using An Underprotective Endpoint.

The final rule continues to use access to the raw data as a red herring. It cites the lack of public availability of the raw data as a reason not to use the Columbia study to set a regulatory endpoint for children. But it fails to grapple with the fact that public release of the raw data would violate the participants' personal privacy, Columbia offered to provide EPA with access to the raw data at a secure location many years ago, and a court has vacated a misguided Trump EPA rule that would have precluded the use of scientific studies when the raw data cannot be made public for privacy reasons. 996 F.3d at 699; *see* 86 Fed. Reg. 469 (Jan. 6, 2021), *vacated*

by Envtl. Def. Fund v. EPA, 2021 WL 402824 (D. Mont. Feb. 1, 2021), and 2021 WL 270246 (D. Mont. Jan. 27, 2021).[6]

The 9th Circuit eviscerated a similar rationale embraced by the Trump administration as a reason to delay revoking chlorpyrifos tolerances. It acknowledged reasonable concerns for the study participants' privacy and believed the fact that EPA's position as to the benefit of access to the data had flip-flopped over the years "suggests the weakness" of the argument. 996 F.3d at 699. Ultimately, however, the 9th Circuit determined that access to the raw data, like more information about the exposures in the Columbia study, "would not change the result in this case." *Id*. The court explained:

> This is because, while … lack of access to raw data might affect the weight the EPA accords to these studies, they are nowhere near enough to show that the studies are entirely unreliable. The FFDCA requires the EPA to consider the "information" that is "available" and to make a safety determination based on that information. In this case, … peer-reviewed cohort studies showing harms to infants' neurological development following their mothers' exposure to chlorpyrifos are available – even if the underlying data is not. The EPA speculates that it might find an error if the unspecified international standards were applied to the animal studies or if the data from the Human Cohort Studies were available. But that is all it is: speculation. Such speculation "runs counter to the evidence before the agency," so it cannot form the basis for denying the 2007 Petition.

Id. at 699–700 & n.149, citing 21 U.S.C. § 346a(d)(4)(A), and *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

IV. RETAINING THE FQPA TENFOLD SAFETY FACTOR IS INSUFFICIENT TO ENSURE REASONABLE CERTAINTY OF NO HARM TO CHILDREN.

In the final rule, EPA says it is "not ignoring or dismissing the extensive data concerning the potential for adverse neurodevelopmental outcomes," but "is addressing the uncertainties surrounding the potential for adverse neurodevelopmental outcomes by retaining the default 10X FQPA [Food Quality Protection Act] safety factor." 86 Fed. Reg. at 48,325. While EPA had to retain the FQPA tenfold safety factor based on the demonstrated harm to the developing brain and remaining scientific uncertainties, doing so is not sufficient to ensure reasonable certainty of no harm to children.

First, as explained above, 10% cholinesterase inhibition is not the most sensitive endpoint. As our comments on the 2020 proposed interim registration review decision and human health risk assessment explain,

> EPA itself has concluded that it is "unlikely" that pregnant women exposed to chlorpyrifos in epidemiologic studies experienced RBC AChE inhibition. 2014 HHRA at

[6] The Growers' Objections (at 6) assert that EPA needed to use the raw data to determine exposure levels and the mode of action, ignoring EPA policy, vacatur of the EPA rule, and the fact that Columbia provided EPA with access to the raw data years ago.

> 41. In 2014, the agency conducted a dose-reconstruction analysis "to help characterize the extent to which participants in the [Columbia University] cohort may or may not have experienced RBC AChE inhibition." *Id.* at 40. The analysis concluded RBC AChE inhibition was just 0.0012% for women applying chlorpyrifos and just 0.45% for women exposed after the pesticide was applied. *Id*. at 41. . . .
>
> The SAP reviewed this issue repeatedly and agreed with EPA's conclusions. In 2012, the SAP noted "multiple lines of evidence suggesting that adverse neurodevelopmental effects may be attributed to chlorpyrifos doses lower than those that elicit a 10% inhibition of AChE."[7] In 2016, it stated: "The Panel agrees 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 (i.e., toxicity at lower doses)."[8]

Second, because neurodevelopmental harm occurs below these low exposure levels, 10% cholinesterase inhibition is not a "no observable adverse effects level" or "NOAEL." Instead, it is a "low observable adverse effects level" or "LOAEL." Under EPA policy, which the final rule acknowledges at 86 Fed. Reg. at 48,323, the use of a LOAEL, instead of NOAEL, requires an additional uncertainty factor of 10X, but EPA did not include one.[9] Our 2021 comments raised this issue at page 21, but EPA has not responded to this or any of our other comments.[10]

Third, EPA did not determine that retaining the FQPA 10X safety factor, while still using 10% cholinesterase inhibition as the endpoint, would be sufficient to prevent neurodevelopmental harm to children. Nor could it given the scientific evidence, including EPA's 2016 risk assessment and California DPR's risk assessment, documenting harm to the developing brain at exposures that are more than an order of magnitude lower than those that cause 10% cholinesterase inhibition.

Again, we reviewed this evidence in our comments on the 2020 interim proposed registration review decision and human health risk assessment, which EPA has yet to address. Portions of those comments are inserted below:

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[7] 2012 SAP Report at 50.

[8] 2016 SAP Report at 18.

[9] EPA, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment at 9; EPA, A Review of the Reference Dose and Reference Concentration Processes at 4–44 (Dec. 2002), https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf.

[10] EPA reduced other safety factors based on a model developed by Dow-Corteva that tries to pinpoint the exposure that will cause 10% cholinesterase inhibition in various human populations. Because the model uses human data for different populations, EPA eliminated the 10X safety factor that accounts for uncertainties in extrapolating from animal studies to people and it shrunk the 10X safety factor that accounts for variations among human populations. Because harm to children's brain development occurred at exposures below those that cause 10% cholinesterase, our comments on the 2014 and 2020 risk assessments explain how shrinking safety factors based on Dow's model is underprotective. EPA has yet to address these comments.

EPA's 2016 Human Health Risk Assessment

> In 2016, EPA's risk assessment for chlorpyrifos found that acceptable levels of exposure to organophosphate pesticides based on harm to children's brain development are dramatically lower than acceptable levels based on >10% RBC AChE inhibition, which was used in EPA's 2014 risk assessment for chlorpyrifos. For the 2014 risk assessment, the agency derived population adjusted doses — the acceptable levels of exposure — for steady-state exposure to chlorpyrifos residues on food of 0.78 to 2.6 mcg/kg/day (Table 1). 2014 HHRA at 76. In 2016, when EPA assessed risks from chlorpyrifos based on neurodevelopmental toxicity, the population adjusted doses were 0.0012 to 0.002 mcg/kg/day — *three to four orders of magnitude* lower than when the acceptable level was based on >10% RBC AChE inhibition (Table 1). 2016 HHRA at 23.[11]
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> *Table 1: Steady-state Population Adjusted Doses (mcg/kg/day) for Food Exposure to Chlorpyrifos*

	AChE Inhibition (2014/2020)	Neurodevelopment (2016)
Infants	2.6	0.002
Children	2.5	0.0017
Youths	2.2	0.0012
Adults	0.78	0.0012

> . . .
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> The stark contrast in population adjusted doses, or acceptable levels, for 10% RBC AChE inhibition and neurodevelopmental toxicity in EPA's risk assessments indicate that continuing to base risk assessments for chlorpyrifos on the former endpoint is under-protective — even when the FQPA safety factor of 10X is retained. If the point of departure and thus the population adjusted dose for the neurodevelopmental toxicity of chlorpyrifos could be >1,000X lower than what EPA has derived for AChE inhibition, relying only on the FQPA safety factor of 10X to protect children from neurodevelopmental harm is plainly inadequate.

2021 Comments at 20–21.

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[11] In its 2020 chlorpyrifos human health risk assessment and in arguments made to the 9th Circuit, EPA has erroneously stated that the 2016 risk assessment used cord blood from the Columbia study and was the subject of criticism by the 2016 SAP. This is incorrect. A spring 2016 EPA white paper proposed using chlorpyrifos measurements in cord blood from the Columbia study and a 2% decline in working memory to establish a regulatory endpoint. A majority of the 2016 SAP disfavored using a single data point from a single study to establish the regulatory endpoint and instead urged EPA to reconstruct the exposure levels based on pest control methods used in the pregnant women's homes. EPA heeded this advice in the risk assessment it produced in the fall of 2016.

The Growers' Objections (at 6–7 & n.17) cite to the 2016 SAP's caution against this particular use of cord blood measurements from the Columbia study to make the utterly unsupported suggestion that the SAP recommended against any use of the three chlorpyrifos epidemiology studies as the basis for regulatory decisions.

California's 2018 Toxic Air Contaminant Evaluation

The California Department of Pesticide Regulation ("CDPR") also concluded that prenatal exposure to chlorpyrifos can elicit neurodevelopmental toxicity at levels of exposure that do not result in >10% RBC AChE inhibition. In 2018, when evaluating whether chlorpyrifos is a toxic air contaminant under California law, CDPR noted, "Recent in vivo animal studies provide evidence of neurotoxicity to developing organisms at chlorpyrifos doses below those causing cholinesterase inhibition."[12] The agency based its evaluation on developmental neurotoxicity rather than AChE inhibition: "These studies, along with epidemiological studies, are the impetus for CDPR considering developmental neurotoxicity as the critical endpoint for chlorpyrifos."[13]

CDPR considered five toxicologic studies reporting neurodevelopmental effects at low doses that did not elicit meaningful AChE inhibition.[14] It derived reference doses from them, found chlorpyrifos unsafe, and initiated cancellation proceedings, which phased out of 99% of chlorpyrifos use by the end of 2020.[15] Table 2 compares CDPR's references doses for neurodevelopmental toxicity from acute oral exposure to EPA's population adjusted doses for AChE inhibition from acute dietary exposure. CDPR's acceptable levels are 47-150X lower than EPA's, which further suggests that EPA's approach is under-protective of children's health.[16]

Table 2: Acute Reference Doses and Population Adjusted Doses (mcg/kg/day) for Chlorpyrifos

	CDPR (2018)	EPA (2014/2020)
Infants	0.1	15
Children	0.1	14
Youths	0.1	13
Adults	0.1	4.7

2021 Comments at 22–23.

The record is replete with reliable information confirming that retaining the FQPA tenfold safety factor, while still using 10% cholinesterase inhibition as the regulatory endpoint, could lead to exposures greater than a true safe exposure level by a thousand-fold or more.

[12] California Department of Pesticide Regulation ("CDPR"), Final Toxic Air Contaminant Evaluation of Chlorpyrifos at 9-10 (2018), https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_final_tac.pdf.

[13] *Id*.

[14] EPA, Chlorpyrifos: Review of 5 Open Literature Studies Investigating Potential Developmental Neurotoxicity Following Early Lifestage Exposure (2020).

[15] CDPR, Final Toxic Air Contaminant Evaluation of Chlorpyrifos at 9-10; *see also* CDPR, Agreement Reached to End Sale of Chlorpyrifos by February 2020 (Oct. 9, 2019), https://www.cdpr.ca.gov/docs/pressrls/2019/100919.htm.

[16] CDPR, Final Toxic Air Contaminant Evaluation of Chlorpyrifos at 82; 2014 HHRA at 75; 2020 HHRA at 34-35.

Retaining the FQPA tenfold safety factor using this endpoint provides an insufficient margin of safety for neurodevelopmental harm to children.

CONCLUSION

The final rule's unsupported use of an underprotective regulatory endpoint cannot legally or scientifically be used as precedent for retaining or establishing any chlorpyrifos tolerances. For all the above reasons, EPA cannot find, using 10% cholinesterase inhibition as the regulatory endpoint, even with the FQPA 10X, reasonable certainty of no harm to children.

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