UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE ADMINISTRATOR

In re FIFRA Section 6(b) Notice of Intent to Cancel Pesticide Registrations for Chlorpyrifos Products	)	
Gharda Chemicals International, Inc. and Red River Valley Sugarbeet Growers Association, et al.,	)	**Docket No. FIFRA-HQ-2023-0001**
Petitioners.	)	

INTERVENORS' INITIAL PREHEARING EXCHANGES AND PRIMARY DISCOVERY

In accordance with the Tribunal's June 5, 2023, Order Scheduling Hearing and Prehearing Procedures, Intervenors[1] submit these prehearing exchanges and primary discovery.

A. and B. Witness Lists and Verified Written Statements

Intervenors do not intend to call witnesses at the hearing because the Tribunal's May 22, 2023, Order Granting Motion to Intervene made it clear that challenges to the validity of Respondent Environmental Protection Agency's ("EPA's") Chlorpyrifos; Tolerance Revocations Rule, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule") are beyond the scope of this proceeding. If the scope of this proceeding subsequently expands to include challenges to the Final Rule, Intervenors reserve the right to seek leave to file amended prehearing exchanges and primary discovery.

By way of further explanation, Intervenors indicated in their Motion to Intervene that they agreed with EPA that Petitioners Gharda Chemical International and Grower Organizations (together with Gharda, "Petitioners") may not lawfully challenge the Final Rule in this proceeding. Intervenors indicated, in the alternative, that if the Tribunal entertained such

[1] Intervenor organizations are League of United Latin American Citizens, Pesticide Action Network North America, Natural Resources Defense Council, California Rural Legal Assistance Foundation, Farmworker Association of Florida, Farmworker Justice, GreenLatinos, Labor Council for Latin American Advancement, Learning Disabilities Association of America, Pineros y Campesinos Unidos del Noroeste, Alianza Nacional de Campesinas, United Farm Workers, and United Farm Workers Foundation.

challenges, Intervenors would present evidence and argument that the Final Rule failed to afford children sufficient protection from learning disabilities and other neurodevelopmental harm. In opposing intervention, Petitioners argued that intervention would expand the scope of the issues in this case. This Tribunal disagreed because the Final Rule is the subject of an appeal to the Eighth Circuit Court of Appeals, that Court has "exclusive jurisdiction to affirm or set aside" the rule, 21 U.S.C. § 346a(h)(2), and "[a]ny issue as to which review is or was obtainable . . . shall not be the subject of judicial review under any other provision of law." *Id*. § 346a(h)(5). Accordingly, this Tribunal stated:

> [E]ven if it would ordinarily have had the authority to do so (a point Petitioners assume without support), this Tribunal cannot now adjudicate any issues related to the Final Rule's legality.
>
> There is, therefore, no present risk that Proposed Intervenors will be required to raise their alternative arguments.

Order Granting Motion to Intervene at 3 (May 22, 2023).

Relying on these limitations on this cancellation proceeding, Intervenors do not intend to call expert witnesses. If this Tribunal subsequently decides that the legality of the Final Rule may be adjudicated in this proceeding, Intervenors would seek leave to amend these prehearing exchanges and provide the identifies and verified written statements of one or more expert witnesses.

C. Intervenors' Exhibits

It is Intervenors' legal position that once EPA revoked all chlorpyrifos tolerances, cancellation of the associated food use chlorpyrifos registrations was legally required and foreordained. Accordingly, Intervenors believe the merits of this proceeding can be decided based on EPA's Final Rule revoking all chlorpyrifos tolerances and its denial of objections to that final rule, which are included in the Joint Exhibits being filed by EPA.

For context, Intervenors are submitting the 2007 Petition to Cancel Chlorpyrifos Tolerances and All Registrations that precipitated that rulemaking, EPA's proposed chlorpyrifos tolerance revocation rule, and its notice of data availability on that proposed rule. Intervenors Exhibits ("IX") 1-3. As explained above, the statements made in granting the motion to intervene make it clear that challenges to the validity of the Final Rule are not before the Tribunal at this time. Intervenors are submitting their feedback on the Final Rule, which they submitted through the objections process, to show that they preserved their argument that EPA's regulatory endpoint used in EPA's risk assessments and the Final Rule fails to protect children from neurodevelopmental harm from chlorpyrifos exposures, especially in utero, should the validity of the Final Rule become an issue in this proceeding. IX 4.

EXHIBIT	Intervenor Exhibit Number ("IX")
Petition to Revoke All Tolerances and Cancel All Registrations for the Pesticide Chlorpyrifos (Sept. 12, 2007)	**IX 1**
Chlorpyrifos; Tolerance Revocations, Notice of Proposed Rulemaking, 80 Fed. Reg. 69,080, 69,081 (Nov. 6, 2015)	**IX 2**
Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment, 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016)	**IX 3**
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) (Oct. 28, 2021)	**IX 4**

D. Matters on Which Official Notice May Be Taken

Under the Rules governing this hearing, official notice "may be taken of Agency proceedings, any matter judicially noticed in the Federal courts, and of other facts within the specialized knowledge and experience of the Agency." 40 C.F.R. § 164.81(e).

Intervenors request that the Tribunal take official notice of the following exhibits, which are all records of agency proceedings before EPA and thus entitled to official notice. The first two are being filed by Intervenors as IX 2 and 3 and the other three are being filed by EPA as Joint Exhibits ("JX") 1-3:

1. Chlorpyrifos; Tolerance Revocations, Notice of Proposed Rulemaking, 80 Fed. Reg. 69,080, 69,081 (Nov. 6, 2015), IX 2
2. Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment, 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016), IX 3
3. Chlorpyrifos; Notice of Intent to Cancel Pesticide Registrations, 87 Fed. Reg. 76,474 (Dec. 14, 2022) ("NOIC"), JX 1
4. Chlorpyrifos; Final Order Denying Objections, Requests for Hearings, and Requests to Stay the August 2021 Tolerance Final Rule, 87 Fed. Reg. 11,222 (Feb. 28, 2022), JX 2
5. Chlorpyrifos; Tolerance Revocations, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule"), JX 3

Taking official notice would authenticate these documents while allowing any party to offer reasonable disputes as to the truth of matters asserted therein to the extent relevant to this cancellation proceeding.

E. Interpretation Services

Intervenors do not plan to call any witnesses and therefore request no interpretative services.

F. Referral of Scientific Questions

Intervenors do not seek referral of any issues of scientific fact to the National Academy of Sciences.

Dated: July 14, 2023

Respectfully Submitted,

Patti A. Goldman
Noorulanne Jan
Earthjustice
810 3rd Avenue, Suite 610
Seattle, WA 98104
T: (206) 343-7340
pgoldman@earthjustice.org
njan@earthjustice.org

Counsel for Intervenors

PETITION TO REVOKE ALL TOLERANCES AND CANCEL ALL REGISTRATIONS FOR THE PESTICIDE CHLORPYRIFOS

Filed 12 September 2007

The Natural Resources Defense Council (NRDC) and Pesticide Action Network North America (PANNA) petition the U.S. Environmental Protection Agency (EPA) to revoke all tolerances and cancel all registrations for the pesticide chlorpyrifos. This petition is filed pursuant to 21 U.S.C. § 346a(d).

I. Introduction

Chlorpyrifos is one of the most widely used insecticides in the United States. It is used on various food and feed crops, on golf courses, as a non-structural wood treatment, and as an adult mosquitocide. Agriculturally, approximately 10 millions pounds are applied annually, with use on corn comprising the largest market (using approximately 5.5 million pounds ai). [1]

Chlorpyrifos belongs to a class of pesticides called organophosphates, which EPA has grouped together based on their common mechanism of toxicity. The devastating effects of this class of pesticides, originally designed as wartime nerve agents including sarin gas, are attributed to their inactivation of an enzyme called cholinesterase.[2] This enzyme is responsible for the timely deactivation of the nerve signaling protein acetylcholine.

Acetylcholine is a messenger of the nervous system, a "neurotransmitter," which carries the signal from a nerve cell to its target. Important targets of acetylcholine include muscles, sweat glands, the digestive system, and even heart and brain cells. In particular, acetylcholine signals activity of the "rest and digest" portions of the nervous system (the parasympathetic system) that stimulates digestion, slows the heart rate, and helps the body to conserve energy. The organophosphate pesticides, including chlorpyrifos, block the ability of cholinesterase to deactivate acetylcholine after its message is delivered. The resulting accumulation of acetylcholine causes over-activation of all its targets. Clinical symptoms of organophosphate poisoning can include: eye pupil contraction, increased salivation, nausea, dizziness, confusion, convulsions, involuntary urination and defecation, and, in extreme cases, death by suffocation resulting from loss of respiratory muscle control.

The state of the science identifying many various adverse health effects associated with dietary exposure to chlorpyrifos supports a ban on chlorpyrifos and revocation of all food tolerances. This petition summarizes the overwhelming scientific evidence that chlorpyrifos is too dangerous to be re-registered for food uses.

---

[1] "Chlorpyrifos Facts." EPA website, <www.epa.gov/oppsrrd1/REDs/factsheets/chlorpyrifos_fs.htm, 8 Mar 2007. All home uses of chlorpyrifos have been canceled "except ant and roach baits in child-resistant packaging." All uses for termite control were required to be phased out by December 31, 2005. IRED, p.71

[2] As chemical weapons, the production and stockpiling of organophosphate nerve agents are outlawed by the United Nations' 1993 Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction. ¶71(b)..

II. Legal Standard

EPA regulates pesticides under two statutes, the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 346a and the Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA), 7 U.S.C. § 136 *et seq.* The Food Quality Protection Act of 1996 ("FQPA") significantly amended both the FFDCA and FIFRA by mandating that health-based and child-protective standards drive decisions about acceptable levels of pesticide residues in food and the environment. FIFRA requires that pesticides must be registered to be sold in the United States.[3] EPA may not register a pesticide unless the chemical will perform its intended function without causing any "unreasonable adverse effects on the environment."[4]

The FFDCA, as amended by the FQPA, authorizes EPA to set tolerances (maximum allowable levels) for pesticide residues in food or to grant exemptions from the requirement to have a tolerance.[5] EPA 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."[6] The term "safe" means that "there is a reasonable certainty that no harm will result from aggregate exposure" to the pesticide, "including all anticipated dietary exposures and all other exposures for which there is reliable information."[7] A pesticide may not be used on a particular food unless there is a tolerance or exemption for that food.[8] The Food and Drug Administration and the U.S. Department of Agriculture are charged with enforcing these regulations by randomly sampling fruits and vegetables for exceedances of tolerances or use of unregistered pesticides or banned pesticides.

The FFDCA explicitly requires that EPA, in establishing a tolerance, must assess the risk that a pesticide poses to infants and children in particular.[9] Before EPA can establish a tolerance, the Agency shall "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure" to the pesticide, and shall "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children."[10] In ensuring that the statutory safety standard is met, EPA must consider available information concerning "the special susceptibility of infants and children," including "neurological differences between infants and children and adults, and effects of *in utero* exposure to pesticide chemicals."[11] EPA must also base its tolerance decision on available information about "food consumption patterns unique to infants and children" and the "cumulative effects on infants and children of [pesticides] that have a common mechanism of toxicity."[12] EPA acknowledges that, when setting

---

[3] 7 U.S.C. § 136a.
[4] 7 U.S.C. § 136a(c)(5)(C).
[5] 21 U.S.C. §§ 345a(b) & (c).
[6] *Id.* § 346a(b)(2)(A)(i).
[7] *Id.* § 346a(b)(2)(A)(ii).
[8] *Id.* § 346a(a)(1).
[9] *Id.* § 346a(b)(2)(C).
[10] *Id.* §§ 346a(b)(2)(C)(ii)(I) & (II).
[11] *Id.* § 346a(b)(2)(C)(i)(II).
[12] *Id.* §§ 346a(b)(2)(C)(i)(I) & (III).

new tolerances under the standard, it "must now focus explicitly on exposures and risks to children and infants."[13]

Furthermore, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children."[14] EPA can depart from this requirement and use a different margin of safety "*only if*, on the basis of *reliable data*, such margin will be safe for infants and children."[15]

Tolerance decisions are driven by the level of pesticide residue detected on food, which is the amount of pesticide that remains on a commodity after a pesticide is applied at a rate that meets or exceeds effective pest control.[16] They are "not based primarily on health considerations.... Their primary purpose is to ensure compliance with good agricultural practice."[17] On the other hand, reference doses (RfD), which represent the amount of pesticide residue that is safe for consumers to eat, are set, if at all, after tolerances. Based on residue data from food and drinking water and considering complexities, such as cooking, if the dietary exposure exceeds the RfD, EPA informs the registrant that the tolerance is unacceptably high. The registrant is tasked with proposing mitigation options, such as a lower application rate or cancellation of that use. As such, the pesticide control framework was established to maintain pesticide residues on food not at safe levels but at or below tolerance levels.

III. Factual Background

In 2001, EPA completed the chlorpyrifos aggregate assessment, called an Interim Reregistration Eligibility Decision (IRED), which revised, but retained, many of the pre-existing food tolerances (allowable residue limits on food).[18] In its 2002 comments on the IRED (Docket ID No. OPP-34203G), NRDC challenged the scientific limitations of the IRED, identified evidence of harm, and highlighted that there is inadequate evidence to establish a safe level at which infants and children will not suffer any developmental harm due to chlorpyrifos exposure. EPA never responded directly to NRDC's comments or other comments submitted by other public interest advocates, including the Pesticide Action Network North America (PANNA) and the New York Attorney General (Docket ID No. OPP-34203G).

---

[13] EPA, Fact Sheet: Protecting Children from Pesticides (Jan. 2002) (www.epa.gov/pesticides/factsheets/kidpesticide.htm) ("The 1996 Food Quality Protection Act set tougher standards to protect infants and children from pesticide risks.")

[14] 21 U.S.C. § 346a(b)(2)(C).

[15] *Id.* (emphasis added).

[16] J. Sass and S. Kegley. Call with EPA to discuss chlorpyrifos. From HED: Jack Housenger, Anna Lowit, and Tom Moriarty; from RD: Venus Eagle; from SRRD: Pete Caulkins, Margaret Rice, and Tom Myers; from OGC: Mark Dyner and Jon Fleuchaus. July 17, 2007

[17] Philip J. Landrigan and others, Pesticides In The Diets Of Infants And Children (Washington, D.C.: National Academy Press, 1993), 9.

[18] 66 Fed Reg 57073 (Nov 14, 2001) Organophosphate Pesticide; Availability of Chlorpyrifos Interim Risk Management Decision Document. IRED at 64-68.

In 2006, EPA completed the cumulative risk assessment (CRA) for all organophosphates (OPs), including chlorpyrifos, and reaffirmed the chlorpyrifos IRED without change, despite new, significant published studies that emerged during this time showing harm. Without addressing the comments by NRDC and other public interest advocates and without referencing much of the data that had been available since 2001, the Agency concluded that chlorpyrifos uses would be eligible for reregistration and that the current pesticide tolerances met the legal safety standard.[19] Because EPA failed to respond to any of NRDC's comments, this petition incorporates by reference the January 14, 2002 NRDC comments and those of other public health advocates.

According to EPA, tolerances are generally reassessed under two possible scenarios. First, an application to register a new use for a pesticide forces EPA to review the aggregate assessment and determine whether the new use 'fits' into the aggregate risk evaluation (i.e. the aggregate exposure from all use scenarios is at or below the RfD); second, during registration review, which occurs about every fifteen years, must reconsider the aggregate risk evaluation.[20] Tolerances are not reassessed based on new data, new science, or new evidence of harm. However, scientific evidence that has emerged since 2001 when the chlorpyrifos IRED was published reinforce the earlier science showing that exposure to chlorpyrifos causes many adverse health effects. In fact, both the weaknesses in the studies relied on by EPA in the IRED and the failure to incorporate evidentiary science since 2001 undermine EPA's decision to re-register chlorpyrifos and retain its tolerances. In this petition we summarize the pre-2001 data and identify relevant post-2001 scientific evidence relevant to the risk assessment of chlorpyrifos.

IV. A Risk Assessment Must Account for the Full Spectrum of Toxicity

The assessment of the health effects associated with particular pesticides includes both an aggregate assessment, which analyzes the risk from multiple routes of exposures (food, water, residential uses) to a single pesticide, and a cumulative assessment, which analyzes the risk from cumulative exposure to a class of pesticides that share a common mode of action. The Agency grouped chlorpyrifos with the other organophosphates to conducts its cumulative risk assessment. For the organophosphate cumulative assessment, EPA used the endpoint of plasma and red blood cell cholinesterase inhibition in dams to determine an acceptable maximum level of cumulative exposure to organophosphate pesticides (identified as a 10% effect level, or benchmark dose 10, BMD10).

Alternately, for the individual aggregate assessment of chlorpyrifos, EPA identified the critical endpoint as structural alterations in brain development in exposed rodent pups at

[19] Memo from Debra Edwards to Jim Jones, re: Finalization of Interim Reregistration Eligibility Decisions (IREDs) and Interim Tolerance Reassessment and Risk Management Decisions (TREDs) for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides, July 31, 2006.

[20] J. Sass and S. Kegley. Call with EPA to discuss chlorpyrifos. From HED: Jack Housenger, Anna Lowit, and Tom Moriarty; from RD: Venus Eagle; from SRRD: Pete Caulkins, Margaret Rice, and Tom Myers; from OGC: Mark Dyner and Jon Fleuchaus. July 17, 2007

the lowest dose tested to determine an acceptable maximum level of aggregate exposure to chlorpyrifos (identified as the RfD).[21] The Agency determined that there was demonstrated evidence of neuropathology and increased susceptibility following pre-natal exposure to chlorpyrifos.[22] Since the developmental neurotoxicity test (DNT) did not identify a no-effect level, and to account for possible non-cholinergic effects in the brain, EPA retained the FQPA factor of 10X.[23] However, this petition reviews scientific evidence that a 10X factor is insufficient, and, as explained below, no safe level of early-life exposure to chlorpyrifos can be supported.

For the organophosphate cumulative assessment, EPA used only the endpoint of cholinesterase inhibition in female rat brain at 21-days of exposure. The Agency argues that there was no evidence of differences between adults and pups for this endpoint and eliminated the FQPA factor by dropping it to 1X. However, as discussed below, the Agency's explanation for this decision does not reflect a true representation of the data used by EPA.

A. Genetic Evidence of Vulnerable Populations

As part of the risk calculation for a particular pesticide, EPA will often include an intra-species variability factor to account for the variation between different people's responses to the same exposure (both chemical and dose). The same dosage of chlorpyrifos may be very harmful to one person and have no effect on another person. This is because of individualized factors that include differences in nutritional status, health or disease status, activity level, lifestyle, exposure to other chemicals or agents, and inherent genetic differences in the activity of the enzymes that break down toxic chemicals in the body. Conventionally, the Agency uses a standard intra-species factor of 10X, presuming no more than a 10-fold difference in susceptibility across a diverse human population.

Paraoxonase (PON1) is a protein (enzyme) that behaves very differently from one individual to the next, and aids in recovering from pesticide toxicity. PON1 detoxifies many of the organophosphates, particularly chlorpyrifos, through catalyzing the hydrolysis of its toxic oxon metabolite. In other words, PON1 breaks down the toxic by-products of chlorpyrifos that are produced during its metabolism, so that they do not build up in the body. A slow-acting genotype of PON1 is less efficient at detoxifying the oxon and is therefore associated with increased pesticide toxicity.[24]

Published epidemiologic studies by Furlong and colleagues in 2003 and 2006 report that the age-related activity of PON1 may impair the ability for perinatal and juvenile animals

---

[21] IRED at 17

[22] IRED at 16

[23] Makris S, Raffaele K, Sette W, Seed J. A retrospective analysis of twelve developmental neurotoxicity studies submitted to the USEPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS). Draft 11/12/98. Available at http://www.epa.gov/scipoly/sap/meetings/1998/december/neuro.pdf

[24] Lee, BW, London, L, Paulauskis, J, Myers, J, Christiani, DC. Association Between Human Paraoxonase Gene Polymorphism and Chronic Symptoms in Pesticide-Exposed Workers. J Occup Environ Med, 2003 Feb; 45(2)

and humans to recover from pesticide toxicity.[25, 26] In fact, the authors reported in their 2006 paper a 164-fold variation in sensitivity to chlorpyrifos between the most sensitive newborn and the least sensitive mother.[27] Although EPA claims to have reviewed this study for the OP CRA , the study supports an intraspecies factor of over 164X whereas the Agency applied only a 10X intraspecies factor to all the organophosphates.[28] In the OP CRA,The Agency specifically acknowledged, and subsequently disregarded, the Furlong et al. study, instead relying on a 2002 study that used a physiologically-based pharmacokinetic (PBPK) model for chlorpyrifos to find that the "response was relatively insensitive to changes in oxonase activity at low doses." [29] Despite EPA's stated preference for human data, and despite the availability of significant informative data derived from unintentionally exposed people (occupational and environmental epidemiologic studies, human biomonitoring [internal dose], and human passive dosimetry [external measurements]), in this case the Agency relied on the model to support its assessment. PBPK models are only as reliable as the data used to design them; they are therefore meant to help bridge data gaps, not override robust data.

EPA's treatment of the PON1 studies with respect to the calculation of the intra-species uncertainty factor provides a stunning example of the Agency turning a blind eye to relevant, robust data. Furthermore, using an intra-species variability factor of 100X or higher – as the results from the Furlong study should prescribe – would drive the tolerances below practicable levels of detections. Practically, tolerances set below the level of detection available for the most sensitive detection methods makes the tolerance unenforceable. EPA should not have ignored the result of the Furlong study and should have applied an intra-species variability factor of at least 150X in the aggregate and cumulative assessments; practically, the Agency should revoke all tolerances for chlorpyrifos.

B. Long-Lasting Effects from Early Life Exposure in Children

Many studies published since 2001 report that fetal exposure to chlorpyrifos is more damaging than adult exposure.[30] Columbia University researchers published two studies

---

[25] Costa LG, Richter RJ, Li WF, Cole T, Guizzetti M, Furlong CE. Paraoxonase (PON 1) as a biomarker of susceptibility for organophosphate toxicity. Biomarkers. 2003 Jan-Feb;8(1):1-12. Review.

[26] Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. Pharmacogenet Genomics. 2006 Mar;16(3):183-90.

[27] Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. Pharmacogenet Genomics. 2006 Mar;16(3):183-90.

[28] CRA at Section I.B page 55

[29] Organophosphorus Cumulative risk assessment – 2006 Update, available at < http://www.epa.gov/pesticides/cumulative/2006-op/index.htm>, 55.

[30] Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, Whitehead R, Tang D, Whyatt RW. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics. 2006 Dec;118(6):e1845-59. Epub 2006 Nov 20.; Perera FP, Rauh V, Whyatt RM, Tang D, Tsai WY, Bernert JT, Tu YH, Andrews H, Barr DB, Camann DE, Diaz D, Dietrich J, Reyes A, Kinney PL. A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. Neurotoxicology. 2005 Aug;26(4):573-87. Review.; Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, Hoepner LA, Diaz D, Dietrich J, Reyes A, Tang D,

from a single New York City (NYC) cohort reporting on the effects of chlorpyrifos on birth outcomes[31] and child development.[32] The authors report on a cohort of NYC African American and Dominican women and babies enrolled over a number of years, that capture changes in exposure levels related to the 2000-2001 ban of chlorpyrifos for residential use. Decreases in birth weight and length were associated with cord blood levels of chlorpyrifos, and the follow-up of children when they reached age 3 showed that the more highly (prenatally) exposed children (chlorpyrifos levels of > 6.17 pg/g plasma) were significantly more likely to experience delays in cognitive and psychomotor development as well as attention problems, attention-deficit/hyperactivity disorder problems, and pervasive developmental disorder problems. The authors report that "the proportion of delayed children in the high-exposure group was five times greater for the Psychomotor Development Index and 2.4 times greater for the Mental Development Index, increasing the number of children possibly needing early intervention services."[33] The adverse effects on birth outcomes were no longer observed among the children in the cohort who were born after the ban took effect (Jan 2001) and concentrations in cord blood were significantly lower, underscoring the benefits of the ban. These data provide strong evidence that prenatal and early-life stage exposure to chlorpyrifos is associated with not only poor birth outcomes (lower birth weight and length), but also long-lasting, and possibly permanent, impaired cognitive development.

In addition to the sensitivity of early life exposures (pre- and peri-natal) to chlorpyrifos, there are data reporting that infants born to mothers with genetically low activity of the PON1 detoxifying enzyme may be an especially vulnerable population. Berkowitz and colleagues from Mount Sinai School of Medicine determined pesticide exposure in a cohort of over 400 women in NYC by a prenatal questionnaire and measurement of maternal blood and urinary metabolites and fetal cord blood. The authors correlated this self-reported exposure information with birth outcomes and found that maternal detectable chlorpyrifos exposure and low PON1 activity correlated with a significant, albeit small, reduction in newborns' head circumference.[34] The authors point to pre-established evidence that small head size is predictive of impaired cognitive ability to

---

Kinney PL, Perera FP. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect. 2004 Jul;112(10):1125-32; Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, Bernert T, Garfinkel R, Tu YH, Diaz D, Dietrich J, Whyatt RM. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect. 2003 Feb;111(2):201-5.

[31] Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, Hoepner LA, Diaz D, Dietrich J, Reyes A, Tang D, Kinney PL, Perera FP. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect. 2004 Jul;112(10):1125-32

[32] Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, Whitehead R, Tang D, Whyatt RW. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics. 2006 Dec;118(6):e1845-59. Epub 2006 Nov

[33] Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, Whitehead R, Tang D, Whyatt RW. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics. 2006 Dec;118(6):e1845-59. Epub 2006 Nov

[34] Berkowitz GS, Wetmur JG, Birman-Deych E, Obel J, Lapinski RH, Godbold JH, HOlzman IR, Wolff MS. 2004. *In Utero* Pesticide Exposure, Maternal Paraoxonase Activity, and Head Circumference, Env. Health Persp., 112(3):388-91

support their suggestion that the infants of mothers with low PON1 enzyme activity may be an especially vulnerable population.

EPA failed quantitatively to incorporate these important evidentiary data that were published since the 2001 IRED was completed, which report a significant association between real-world chlorpyrifos exposures and real, developmental harm resulting from pre-birth and early childhood exposures. As noted earlier, FQPA imposes a duty on EPA to "focus explicitly on exposures and risks to children and infants."[35] The failure to consider quantitatively the full spectrum of diverse impacts of chlorpyrifos exposure to fetuses is a direct violation of EPA's mandate.

C. No Safe Level in Rodent Developmental Neurotoxicity Study

As discussed above, a substantial body of scientific evidence demonstrates the fetotoxic, neurotoxic, and immunotoxic properties of chlorpyrifos and its oxon metabolite, associated with pre-natal and early life exposures. These exposures have been shown to result in long-lasting, possibly permanent damage to the nervous system. There is no evidence that there is a safe or acceptable level of exposure to chlorpyrifos during pre-birth and early life stages. In fact, EPA staff experts concluded in the EPA human health risk assessment of chlorpyrifos:

> "the weight of the evidence raises concern for an increase in both the sensitivity and susceptibility of the fetus or young animal to adverse biochemical, morphological, or behavioral alterations from chlorpyrifos treatment during brain development. With respect to cholinesterase inhibition, an increase in sensitivity of the young compared to adults was seen all along the dose response curve, even at relatively low doses. There is a clear differential response (2- to ~5-fold) in the young compared to the adult animal after an acute treatment to a relatively low dose of chlorpyrifos. There is also increased sensitivity found after repeated dosing (up to 9-fold), but at the LD10 [lethal dose that results in a 10% death rate] and MTD [maximum tolerated dose]. It is important to point out that *an uncertainty remains concerning the magnitude of the differential response*, given that newborn animals (less than PND 7) have not been characterized for sensitivity. *Results of multiple studies have consistently shown that the developing brain is susceptible to chlorpyrifos treatment.* Effects on the developing CNS that are indicative of the unique susceptibility to the young animal include changes in macromolecular synthesis, altered cell signaling and muscarinic receptor down regulation, as well as morphological alterations in brain development. An uncertainty remains regarding the NOAELs for the susceptibility effects. The

[35] EPA, Fact Sheet: Protecting Children from Pesticides (Jan. 2002) (www.epa.gov/pesticides/factsheets/kidpesticide.htm) ("The 1996 Food Quality Protection Act set tougher standards to protect infants and children from pesticide risks.").

effects observed raise a high degree of concern that the fetus or young animal is particularly susceptible to adverse outcome if exposed to chlorpyrifos."[36]

The assessment of EPA scientific experts points to substantial scientific evidence that early life exposures to chlorpyrifos are extensively more harmful than adult exposures, and that the magnitude of the differential response is uncertain. This assessment from EPA staff scientists strongly supports the use of the default 10X FQPA factor.

D. Endocrine Disrupting Effects

Thyroid hormone is essential for virtually every function in the body, including reproduction and neurodevelopment. Both animal and human studies have reported that chlorpyrifos may interfere with thyroid hormone function. In a 2006 study of sub-fertile men, chlorpyrifos exposure was associated with reduced levels of thyroid stimulating hormone (TSH) and thyroxine.[37] In a 2005 study of rat pituitary cells, which are normally stimulated to grow after exposure to thyroid hormone, cell growth was inhibited by co-exposure to chlorpyrifos.[38] In an earlier study (1998), exposure to chlorpyrifos in ewes was associated with reduced thyroxine (thyroid hormone) concentrations.[39] More troubling, these effects resulted from exposures at levels similar to those found in the general population, indicating that chlorpyrifos can reduce thyroid hormone and cause endocrine disruption at environmentally relevant levels. In addition to causing infertility, reductions in thyroid hormone concentrations, even at subclinical levels, can result in permanent neurological effects on the developing nervous system of a fetus or newborn.[40, 41]

Studies also indicate that chlorpyrifos can affect the reproductive hormones estrogen and testosterone. Chlorpyrifos is a weak estrogen-like substance.[42] Pituitary cells from the rat that are normally stimulated to grow after estrogen exposure were found to grow after chlorpyrifos exposure.[43] This growth was blocked by a potent estrogen receptor

---

[36] EPA. Human health risk assessment: Chlorpyrifos. June 8, 2000. p 131. emphasis is added.
[37] Meeker JD, Barr DB, Hauser R. 2006 Thyroid hormones in relation to urinary metabolites of non-persistent insecticides in men of reproductive age. Reprod Toxicol. 22(3):437-42.
[38] Ghisari M, Bonefeld-Jorgensen EC. 2005 Impact of environmental chemicals on the thyroid hormone function in pituitary rat GH3 cells. Mol Cell Endocrinol. 244(1-2):31-41
[39] Rawlings, N.C., Cook, S.J., Waldbillig, D., 1998. Effects of the pesticides carbofuran, chlorpyrifos, dimethoate, lindane, triallate, trifluralin, 2,4-d, and pentachlorophenol on the metabolic endocrine and reproductive endocrine system in ewes. J. Toxicol. Environ. Health A 54, 21–36.
[40] Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. 2003 Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study Clin Endocrinol 59(3):282-8.
[41] Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 341(8):549-55.
[42] Andersen, H.R., Vinggaard, A.M., Rasmussen, T.H., Gjermandsen, I.M., Bonefeld-Jorgensen, E.C., 2002. Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicol. Appl. Pharmacol. 179, 1–12.
[43] Ghisari M, Bonefeld-Jorgensen EC. 2005 Impact of environmental chemicals on the thyroid hormone function in pituitary rat GH3 cells. Mol Cell Endocrinol. 244(1-2):31-41

antagonist, suggesting that chlorpyrifos stimulates the growth of these pituitary cells via the estrogen receptor and is an estrogen agonist. In human studies, exposure to chlorpyrifos has been shown to be associated with lower levels of testosterone, poorer sperm quality, and increased sperm DNA damage.[44, 45]

Gonadotropin-releasing hormone (GnRH) is a hormone released by the hypothalamus. It acts as a primary regulator of reproduction by controlling the release of luteinizing hormone and follicle stimulating hormone from the pituitary gland, thereby ultimately controlling androgen and estrogen levels. In experiments with a cell line model for GnRH neurons, exposure to chlorpyrifos was found to alter the biosynthesis of GnRH, potentially disrupting the entire hypothalamic-pituitary-gonadal axis.[46]

According to the IRED, EPA did not consider the endocrine disrupting effects of chlorpyrifos because the development of an Endocrine Disruptor Screening Program (EDSP) has not been completed. As a consequence, it neglects analyzing an entire category of potential adverse health effects. In fact, the risk assessment omits a group of studies that, taken together, suggest that chlorpyrifos may be an endocrine disrupting chemical, capable of interfering with multiple hormones controlling reproduction and neurodevelopment.

There is precedent for the Agency to consider endocrine disrupting effects in a human health risk assessment in the absence of a final EDSP. For example, in the RED for atrazine, the Agency examined the potential endocrine disrupting effects of atrazine on amphibians, undermining any agency claim that existing studies of the endocrine disrupting effects cannot be considered in its human health risk assessments. Accordingly, given the studies suggesting that chlorpyrifos has the potential to cause endocrine disrupting effects, EPA should have quantitatively incorporated these endpoints in its risk assessment of chlorpyrifos.

E. Cancer risks

The 2004 National Institutes of Health Agriculture Health Study, a very robust prospective epidemiology study of pesticide applicators in the Midwest, reported chlorpyrifos-specific findings that have been ignored by EPA despite their high relevance to the risk analyses and registration decisions. The incidence of lung cancer was statistically significantly associated with both chlorpyrifos lifetime exposure-days and chlorpyrifos intensity-weighted exposure days. After adjusting for other pesticide exposures and demographic factors, "individuals in the highest quartile of chlorpyrifos lifetime exposure-days (>56 days) had a relative risk of lung cancer of 2.18 (95%

---

[44] Meeker JD, Ryan L, Barr DB, Hauser R. Exposure to non-persistent insecticides and reproductive hormones in adult men. Epidemiology 2006;17:61–8.
[45] Meeker JD, Singh NP, Ryan L, et al. Urinary levels of insecticide metabolites and DNA damage in human sperm. Hum Reprod 2004;19:2573–80.
[46] Gore AC 2002 Organochlorine pesticides directly regulate gonadotropin-releasing hormone gene expression and biosynthesis in the GT1-7 hypothalamic cell line. Mol Cell Endocrinol. 192(1-2):157-70.

CI=1.31-3.64), significantly higher than those with no chlorpyrifos exposure."[47] These data were not referenced in the final aggregate assessment of chlorpyrifos or the OP CRA, but are highly relevant and so should have been.

F. Potential adverse effects below 10% cholinesterase inhibition

The OP CRA evaluated the cumulative toxicity of chlorpyrifos and its related organophosphate pesticides assuming that if the Agency regulated so as to allow no more than a 10% level of cholinesterase inhibition (10% ChEI) in the female adult rodent brain, this would be protective of all adverse effects at all life stages. That is, the Agency presumed that there are no other adverse effects that occur with doses lower than the dose eliciting a 10% ChEI in the female adult rodent brain. However, scientific studies published both prior to and since the IRED was completed in 2001 have reported that fetal and newborn exposure to chlorpyrifos affects diverse cellular functions by mechanisms of toxicity that are independent of cholinesterase inhibition. This is important because while the systemic toxicity that results from cholinesterase inhibition is reasonably well characterized, it does not explain why rodents exposed pre- and perinatally seem to recover from cholinesterase inhibition relatively rapidly, yet display persistent and more severe damage to the central nervous system.[48] Accumulating scientific evidence points to non-cholinergic mechanisms that disrupt multiple brain targets.[49] Many of these critical targets are vulnerable even at doses below those that elicit 10-20% cholinesterase inhibition. Some of the relevant studies are listed below:

- Scientists first reported in 1994, and then confirmed in 2001 that chlorpyrifos inhibited the production of the cellular second messenger Cyclic Adenosine Monophosphate (cAMP) in rat brain.[50] This has serious implications for many important cellular functions. For example, cAMP is required for normal function of hormones like glucagon (increases blood sugar levels) and adrenaline (regulates the stress response by increasing heart rate, elevating blood sugar, and depressing the immune system). cAMP is also required for regulating normal calcium movement in the body. Disruption of normal cAMP function may be associated with progression of some cancer types, including melanoma.[51,52]

---

[47] Lee et al, Cancer Incidence Among Pesticide Applicators Exposed to Chlorpyrifos in the Agricultural Health Study, Journal of the National Cancer Institute, Vol 96, No. 23, December 1, 2004, p. 1781-9

[48] Slotkin TA, Cousins MM, Tate CA, Seidler FJ. Persistent cholinergic presynaptic deficits after neonatal chlorpyrifos exposure. Brain Res. 2001 Jun 1;902(2):229-43.

[49] Pope CN. Organophosphorus pesticides: do they all have the same mechanism of toxicity? J Toxicol Environ Health B Crit Rev. 1999 Apr Jun;2(2):161-81. Review.

[50] Huff RA, Corcoran JJ, Anderson JK, Abou-Donia MB. Chlorpyrifos oxon binds directly to muscarinic receptors and inhibits cAMP accumulation in rat striatum. J Pharmacol Exp Ther. 1994 Apr;269(1):329-35; Huff RA, Abu-Qare AW, Abou-Donia MB. Effects of sub-chronic in vivo chlorpyrifos exposure on muscarinic receptors and adenylate cyclase of rat striatum. Arch Toxicol. 2001 Oct;75(8):480-6.

[51] Dumaz N, Hayward R, Martin J, Ogilvie L, Hedley D, Curtin JA, Bastian BC,Springer C, Marais R. In Melanoma, RAS Mutations Are Accompanied by Switching Signaling from BRAF to CRAF and Disrupted Cyclic AMP Signaling. Cancer Res. 2006 Oct 1;66(19):9483-91.

[52] Abramovitch R, Tavor E, Jacob-Hirsch J, Zeira E, Amariglio N, Pappo O, Rechavi G, Galun E, Honigman A. A pivotal role of cyclic AMP-responsive element binding protein in tumor progression. Cancer Res. 2004 Feb 15;64(4):1338-46.

- Scientists reported in 2007 that in neonatal rats exposed to four daily doses of 1 mg/kg chlorpyrifos on days 1-4 after birth displayed life-stage and gender-specific alterations in the expression of genes important for nerve cell growth, cAMP-related cell signaling, programmed cell death (apoptosis), oxidative stress, and neurotransmitter synthesis. This dose and treatment regime is below the threshold dose that is associated with growth retardation and systemic toxicity and elicits less than 20% ChEI in exposed newborn rats.[53]
- In 2006, scientists reported that chlorpyrifos disrupted serotonin pathways in the developing rat brain at doses spanning the threshold for cholinesterase inhibition.[54] Interestingly, the study reported altered expression of transcription factors in both the forebrain (an area with many cholinergic neurons) and in the cerebellum (an area poorly innervated with cholinergic neurons), suggesting that there are severe impacts on non-cholinergic targets of chlorpyrifos in the brain, presumably through a non-cholinergic mechanism of toxicity.
- Scientists reported in 2006 an observed loss of non-cholinergic cerebellum neurons and permanent sensorimotor deficits in adult rodents exposed to chlorpyrifos *in utero,* demonstrating long-lasting effects from early life exposures to chlorpyrifos.[55] In this work, pregnant Sprague-Dawley rats were treated with 1.0 mg/kg daily dermal exposures to chlorpyrifos, and offspring were evaluated at 90 days after birth, corresponding to a human adult age. This study provides evidence that exposures during vulnerable windows of development can result in adverse impacts that extend into adulthood.
- In 2007, researchers reported that neonatal rats exposed to four daily doses of 1 mg/kg chlorpyrifos on days 1-4 after birth displayed regional alterations in the expression of the fibroblast growth factor family of genes across the brain and brain stem.[56] The proteins that are coded from these genes play critical roles in neural cell development, brain assembly and recovery from neuronal injury.

The broad spectrum of neurotoxic effects indicate that chlorpyrifos toxicity is far more complex than would be predicted if only its direct impairment of cholinesterase activity were considered.

---

[53] Slotkin TA, Seidler, FJ. 2007. Comparative developmental neurotoxicity of organophosphates in vivo: Transcriptional responses of pathways for brain cell development, cell signaling, cytotoxicity and neurotransmitter systems. Brain Res Bull, May 30;72(4-6):232-74. Epub 2007 Jan 25.
Crumpton TL, Seidler FJ, Slotkin TA. Developmental neurotoxicity of chlorpyrifos in vivo and in vitro: effects on nuclear transcription factors involved in cell replication and differentiation. Brain Res. 2000 Feb 28;857(1-2):87-98.

[54] Slotkin TA, Tate CA, Ryde IT, Levin ED, Seidler FJ. Organophosphate insecticides target the serotonergic system in developing rat brain regions: disparate effects of diazinon and parathion at doses spanning the threshold for cholinesterase inhibition. Environ Health Perspect. 2006 Oct;114(10):1542-6

[55] Abou-Donia MB, Khan WA, Dechkovskaia AM, Goldstein LB, Bullman SL, Abdel-Rahman A. In utero exposure to nicotine and chlorpyrifos alone, and in combination produces persistent sensorimotor deficits and Purkinje neuron loss in the cerebellum of adult offspring rats. Arch Toxicol. 2006 Sep;80(9):620-31. Epub 2006 Feb 16.

[56] Slotkin TA, Seidler FJ, Fumagalli F. Exposure to organophosphates reduces the expression of neurotrophic factors in neonatal rat brain regions: similarities and differences in the effects of chlorpyrifos and diazinon on the fibroblast growth factor superfamily. Environ Health Perspect. 2007 Jun;115(6):909-16. Epub 2007 Feb 27.

A review published in 2003 by Duke University Professor Abou-Donia of OP poisoning incidents includes clinical reports of long-term impairment of cognitive and neurobehavioral performance associated with long-term exposure to the pesticides.[57] Permanent clinical symptoms that have been reported includes anxiety and deficits in learning, memory, and concentration. [58] In addition, individuals exposed to low, subclinical levels of chlorpyrifos have reported persistent long-term deficits in concentration, word finding, and short-term memory.[59] Two separate studies in 1996 and 1997 reported clinical cases of long-term cognitive and neuropsychological deficits in sheep dipper workers exposed to organophosphate pesticides.[60, 61] Dr. Abou-Donia suggests that the observed long-term effects are more likely to be a result of neuronal cell damage and death from apoptosis and oxidative stress, rather than from transient cholinesterase inhibition. [62]

Neither EPA's aggregate risk assessment (IRED) nor the OP CRA cite or quantitatively incorporate the results of the aforementioned laboratory studies and clinical reports. Without quantitatively incorporating low-dose risks of non-cholinergic effects, EPA's contention that the acute and chronic dietary point of departures (BMD10) are protective is unproven and is likely to underestimate significantly the long-lasting impairments resulting from early life exposure to chlorpyrifos.

EPA ought to heed experts who warned: "the fact that alterations in neurodevelopment occur with organophosphate exposures below the threshold for cholinesterase inhibition reinforces the inadequacy of this biomarker [cholinesterase inhibition] for assessing exposure or outcome related to developmental neurotoxicity."[63] EPA's own Scientific Advisory Panel (SAP) in 2002 had raised the same concern, stating "reliance on a single biochemical assay to measure brain damage may become problematic."[64] Accordingly, the Agency must consider non-cholinergic neurotoxicity in the CRA and IRED assessments when establishing the safe level (RfD) and allowable commodity tolerances. Taking into consideration the full toxicity spectrum of chlorpyrifos will lead to the scientifically-defensible conclusion that it is too dangerous to be reregistered.

---

[57] Abou-Donia, MB. Organophosphorus ester-induced chronic neurotoxicity. Arch Environ Health, 2003; 58(8): 484-497

[58] *Id.*

[59] Kaplan JG, Kessler J, Rosenberg N et al. Sensory neuropathy associated with Dursban (chlorpyrifos) exposure. Neurology 1993; 43:2193-2196

[60] Beach JR, Spurgeon A, Stephens R, et al. Abnormalities on neurological examination among sheep farmers exposed to organophosphate pesticides. Occup Environ Med, 1996; 53(8): 520-525

[61] London L, Myers JE, Neil V, et al. An investigation into neurological and neurobehavioral effects of long-term agrochemical use among deciduous fruit farm workers in the Western Cape, South Africa. Environ Res, 1997; 73(1-2):132-145

[62] Abou-Donia, MB. Organophosphorus ester-induced chronic neurotoxicity. Arch Environ Health, 2003; 58(8): 484-497

[63] Slotkin TA, Tate CA, Ryde IT, Levin ED, Seidler FJ. Organophosphate insecticides target the serotonergic system in developing rat brain regions: disparate effects of diazinon and parathion at doses spanning the threshold for cholinesterase inhibition. Environ Health Perspect. 2006 Oct;114(10):1542-6.

[64] Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held June 26-27, 2002. Released on July 19, 2002, 26.

III. CRA Misrepresents Risks, Fails to Apply FQPA

The CRA failed to apply any FQPA factor to adjust for early life exposures, citing a 2000 study that EPA interprets to show no difference in response between pups and adult rats at the dose estimated to result in 10% inhibition.[65]

In addition to relying on limited data, EPA resorted to inaccurate interpretations of that data to support its decisions. EPA approached the determination of an FQPA factor by screening for data "which measured brain cholinesterase inhibition in juvenile and adult rats following repeat dosing."[66] For all organophosphate pesticides *except* chlorpyrifos, EPA then determined a benchmark dose. However, for chlorpyrifos, EPA used data from a paper by Zheng et al.[67] authored and provided by FIFRA SAP member Carey Pope, to identify a 10% brain cholinesterase inhibition point.[68] EPA relied solely on this one study to eliminate the FQPA factor for repeat exposures, stating that "at this dose, there is no difference in response between pups and adult rats." However, review of these data in both the original published manuscript, and as presented in the cumulative risk assessment, shows that there is an obvious difference between juvenile and adult responses to chlorpyrifos. (See Figure 1, below.)

---

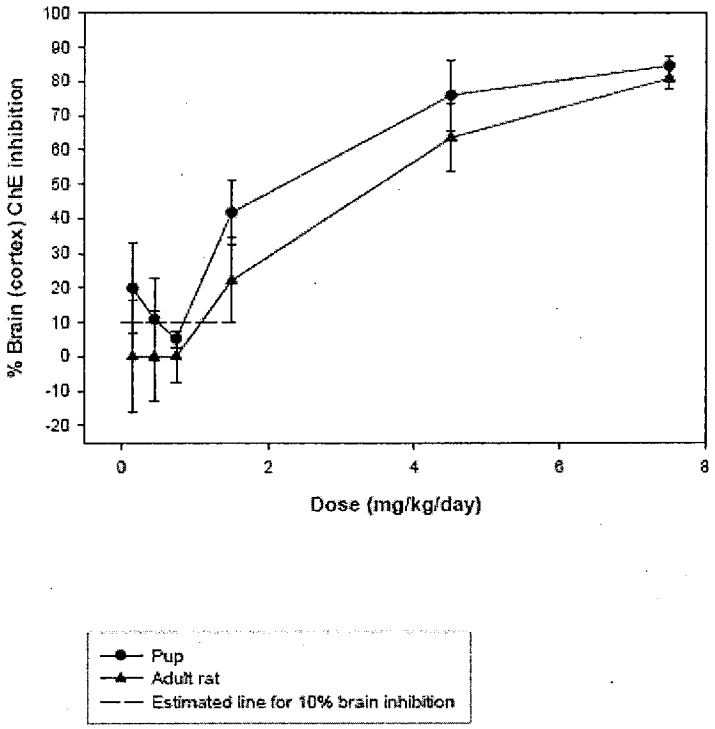
[65] *Id.*

[66] Organophosphorus Cumulative risk assessment – 2006 Update, available at < http://www.epa.gov/pesticides/cumulative/2006-op/index.htm>, 59.

[67] Zheng Q, Olivier K, Won YK, Pope CN. 2000. Comparative cholinergic neurotoxicity of oral chlorpyrifos exposures in preweaning and adult rats. Toxicological Sciences, 55(1): 124-132

[68] Oklahoma State University, Fig I.B-3, Cumulative Risk Assessment at 63

Figure I.B-3 Plot of chlorpyrifos data from Zheng et al (2000).



In fact, Zheng et al. report that neonates are more sensitive than adults to chlorpyrifos associated ChEI.

First, the authors observed that after acute chlorpyrifos exposure, neonates were much more sensitive than adults: "Following acute CPF [chlorpyrifos] exposure, more extensive ChE [cholinesterase] inhibition was noted in neonates than in adults (especially in the brain) with NOELs based on ChE inhibition in adult tissues being 1 to ≥10-fold higher than in neonates."[69] These results are consistent with many other reports in the scientific literature: "It is apparent from a number of studies that neonatal rats are more sensitive to acute toxicity following either oral or subcutaneous acute high dosages of CPF (Atterberry et al, 1997; Moser and Padilla, 1998; Pope and Chakraborti, 1992; Pope et al, 1991)." They also note that signs of toxicity and lethality generally develop several hours, rather than immediately, after an acute exposure to chlorpyrifos.

The authors also reported that neonates were more sensitive than adults following repeat exposure scenarios: "With repeat exposures, NOELs based on ChE inhibition in adults were only 0.2 - 2-fold higher than in neonates." However, using the endpoint of body

[69] Zheng Q, Olivier K, Won YK, Pope CN. 2000. Comparative cholinergic neurotoxicity of oral chlorpyrifos exposures in preweaning and adult rats. Toxicological Sciences, 55(1): 124-132

weight changes following repeat doses, the authors noted that "the NOEL for adults was 5-fold higher than for neonates."[70]

EPA has mischaracterized these data. Rather, these data support using a 10X FQPA factor based on acute exposures using brain cholinesterase endpoints, a 2X FQPA factor based on repeat exposures using brain cholinesterase endpoints, and a 5X FQPA factor based on repeat exposure using body weight endpoints. EPA has presented an incomplete and therefore inaccurate interpretation of these data to support for its decision to remove the FQPA factor altogether.

IV. Over-Reliance on Registrant Data

Chlorpyrifos is one of the most studied of all the organophosphate pesticides. And, as demonstrated above, all the evidence of adverse health effects arising from the exposure to chlorpyrifos supports banning all uses of chlorpyrifos and revoking all food tolerances. Yet, despite this plethora of publicly-available data, the Agency cherry picked the data, ignoring robust, peer-reviewed data in favor of weak, industry-sponsored data to determine that chlorpyrifos could be re-registered and food tolerances be retained. EPA's re-registration and tolerance reassessment decision is not scientifically defensible because it is based on a strained and biased interpretation of an incomplete data set.

As with all scientific inquiry, greater confidence is ascribed to results of studies that are repeatable, supplied by multiple lines of evidence, and drawn from multiple, well-designed, well-conducted studies of adequate statistical power. To that end, all of the studies identified in this petition are published and publicly-available in peer-reviewed scientific literature, indicating that they were subject to public and professional scrutiny and are therefore likely to be reliable. These data showing adverse impacts of chlorpyrifos and other organophosphate pesticides on fetal and childhood development from non-cholinergic effects satisfy all three prongs for strong scientific validity because they a) arise from multiple laboratories (independent lines of evidence), b) are based on studies *in vitro*, in whole animals, and in humans (multiple lines of evidence), and c) show agreement across studies regarding the reported adverse outcomes (repeatability) and the mechanisms of action (biological plausibility). These data fulfill the scientific criteria for establishing causality, highlighting the breadth of robust data available to, yet ignored by, the Agency regarding chlorpyrifos.

Where EPA should have relied on its strongest scientific evidence, it led off with its weaker database and relied on the odd claim of scant organophosphate data to justify its decision not to refine the intra-species factor. More egregiously, despite having data on chlorpyrifos, the Agency chose to ignore that data and retain a weak intra-species factor for chlorpyrifos. As illustrated by the PON1 study discussed in the previous section, the Agency chose to ignore strong evidence of harm at doses below those that inhibit cholinesterase, despite evidence of susceptibility in exposed children.

---

[70] Zheng Q, Olivier K, Won YK, Pope CN. 2000. Comparative cholinergic neurotoxicity of oral chlorpyrifos exposures in preweaning and adult rats. Toxicological Sciences, 55(1): 124-132

V. EPA Failed to Incorporate Inhalation Routes of Exposure

In its aggregate assessment, EPA considered exposures from food, drinking water, and residential uses of chlorpyrifos. However, for some populations that include children and pregnant women, inhalation of chlorpyrifos-contaminated air may be one, if not the most, significant source of chlorpyrifos exposure. Although EPA was advised of these public data prior to 2006, it failed to incorporate quantitatively this scientific evidence of air exposures into the aggregate assessment.[71]

Available monitoring data show that for volatile and semi-volatile pesticides (vapor pressure > 10^{-7} mm Hg at 20-25°C), post-application drift typically accounts for 80-95% of the total off-site airborne pesticide movement. Chlorpyrifos falls solidly into this category of pesticides, with a vapor pressure of 10^{-5} mm Hg. Air monitoring studies conducted by the California Air Resources Board (ARB) and by communities working with PANNA indicate that post-application volatilization typically peaks between two and 24 hours after the start of an application for volatile and semi-volatile pesticides and may persist for days above levels of concern. ARB published its work on air monitoring for chlorpyrifos in 1998.[72] PANNA published its chlorpyrifos air monitoring results for Lindsay, California in July 2006, before the finalization of the OP CRA.

A. State of California Data Documents Air Contamination

The California ARB has documented widespread presence of chlorpyrifos in the air using both near-field and ambient air monitoring.

1. Near-Field Monitoring

The California ARB measured air concentrations of chlorpyrifos near an orange grove treated with chlorpyrifos, with the application taking place during two separate events separated by a day.[73] Three-day, time-weighted average concentrations at the monitoring stations ranged from 5,312 to 8,112 ng/m^3 (depending on the location of the monitoring station). See Figure 1. Translation of these concentrations into Reference Exposure Levels (RELs) that take into account breathing rate and body weight indicated that these concentrations exceeded the acute 24-hour REL for a one-year-old child by a factor of 31

---

[71] PANNA provided EPA with the results of the ARB monitoring demonstrating problematic exposure from volatilization drift for multiple pesticides on several occasions, including in several formal comment letters to EPA on molinate (Docket ID # OPP-34232, included here by reference), several legal petitions,[71] in comments submitted to US EPA for the OP CRA docket in October of 2006 (Docket ID # EPA-HQ-OPP-2006-0618), and in a presentation to EPA staff (EFED and HED) on May 9, 2002. PANNA published a report presenting and analyzing the ARB data in May of 2003. S.E. Kegley, A. Katten, and M. Moses, *Secondhand Pesticides: Airborne Pesticide Drift in California*, Californians for Pesticide Reform (San Francisco, CA 2003),

[72] *Report for the Application and Ambient Air Monitoring of Chlorpyrifos (and the Oxon Analogue) in Tulare County during Spring/Summer 1996,* California Air Resources Board, Test Report #C96-040 and # C96-041, April 7, 1998, http://www.cdpr.ca.gov/docs/empm/pubs/tac/chlrpfs.htm.

[73] *Report for the Application and Ambient Air Monitoring of Chlorpyrifos (and the Oxon Analogue) in Tulare County during Spring/Summer 1996,* California Air Resources Board, Test Report #C96-040 and # C96-041, April 7, 1998, http://www.cdpr.ca.gov/docs/empm/pubs/tac/chlrpfs.htm.

to 48 and the acute 24-hour REL for adults by a factor of 1.4 to 2.1.[74] Concentrations of chlorpyrifos were still above both the adult and child RELs at the downwind site at the end of the monitoring period, at 4,900 ng/m^3 (29 times the child REL and 1.3 times the adult REL). These data indicate that those who live, work, or go to school near application sites risk acute nervous system toxicity from airborne exposure to this pesticide. The developing fetus, infants and children are especially at risk because their nervous systems are still developing.

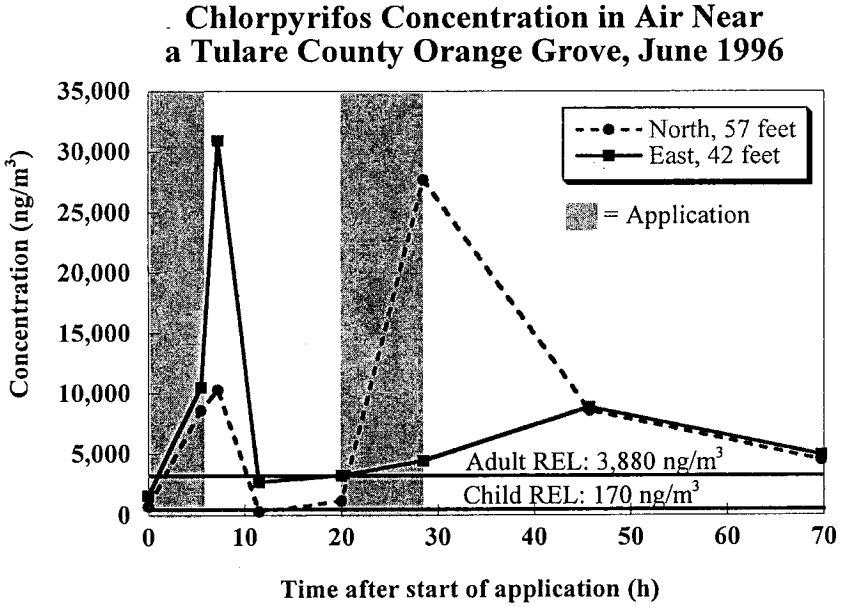


Figure 1: Chlorpyrifos air concentrations peaked approximately 2.5 hours after the end of the first application and again during the second application. Substantial volatilization continued for several days after application and exceeded 24-hour RELs for both adults and children for much of the sampling period.

ARB only conducted a single application site monitoring study for chlorpyrifos; however, the fact that the application occurred in two distinct time periods provides essentially two applications in one study. The similar peak concentrations observed for the two

---

[74] In order to compare observed concentrations of chlorpyrifos in air with concentrations likely to be associated with adverse effects, the US EPA inhalation NOAELs for acute and sub-chronic exposures to chlorpyrifos of 0.1 mg/kg-day (based on plasma and red blood cell cholinesterase inhibition)74 were used to calculate Reference Exposure Levels (RELs) for a sensitive receptor, a one-year-old infant weighing 7.6 kg, breathing on average 4.5 m^3 of air per day. This calculation takes into account the 10-fold intraspecies, 10-fold interspecies and 10-fold FQPA uncertainty factors used by US EPA for chlorpyrifos.

$$\text{Acute REL (ng/m}^3\text{)} = \frac{\text{Inhalation NOEL (mg/kg - day)} \times 10^6\,\text{ng/mg} \times \text{body wt. (kg)}}{(UF_{inter} \times UF_{intra} \times UF_{FQPA}) \times \text{breathing rate (m}^3\text{/day)}} = \frac{0.1\,\text{mg/kg - day} \times 10^6\,\text{ng/mg} \times 7.6\,\text{kg}}{(10 \times 10 \times 10) \times 4.5\,\text{m}^3\text{/day}} = 170\ \text{ng/m}^3$$

The calculated concentration is the equivalent of a concentration in air below which no adverse effects on cholinesterase inhibition are anticipated by US EPA. Note, however, that the developmental neurotoxicity observed for chlorpyrifos (see Section 1 above) is not mediated by cholinesterase inhibition and may occur at lower doses.

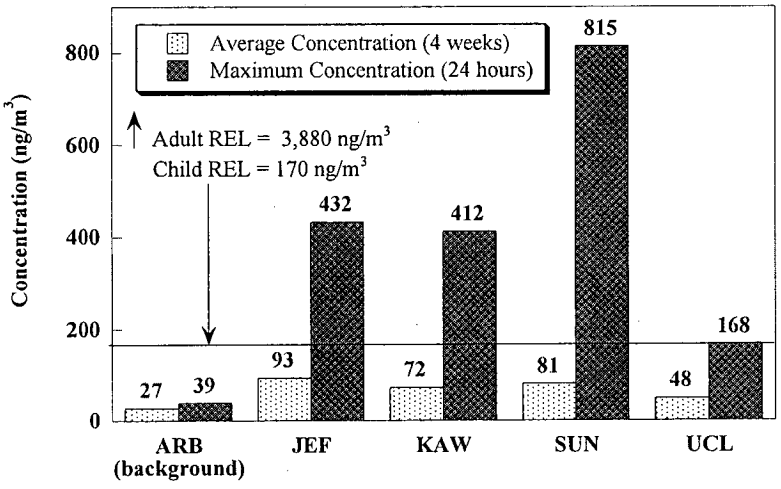
applications under different wind conditions (30,950 ng/m^3 vs. 27,700 ng/m^3) suggest that peak air concentrations may be quite predictable based on the vapor pressure of the pesticide, a fact consistent with other work in the peer-reviewed literature.[75]

The breakdown product chlorpyrifos oxon was observed in 100% of the samples, but the toxicity of this substance was not taken into account in this analysis because no RELs are available for comparison. However, because the oxon is more acutely toxic than the parent compound, neurotoxic effects associated with breathing air contaminated with both chlorpyrifos and its oxon at the measured levels will be greater than chlorpyrifos concentrations alone would suggest.

2. Ambient Monitoring

During the summer of 1996, the ARB sampled seasonal concentrations of chlorpyrifos in ambient air in Tulare County, California by placing monitoring stations on several schools that were somewhat distant from direct applications but located in regions of high use.[76] Monitoring occurred over the course of four and a half weeks, which serves as an estimate of sub-chronic exposure. Average concentrations over the full time frame of the monitoring study were below both adult and child sub-chronic RELs, averaging 38% of the one-year-old child REL over all sites. See Figure 2. The maximum measured 24-hour concentrations equaled or exceeded the 24-hour acute child REL at four of the five monitoring sites and ranged from 23% to 485% of the 24-hour acute child REL. The monitoring report was published by ARB in 1998, but was not incorporated into EPA's aggregate assessment.

Concentration of Chlorpyrifos in Ambient Air in Tulare County May 28-June 30, 1996



[75] JE Woodrow, JN Seiber, LW Baker, Correlation Techniques for Estimating Pesticide Volatilization Flux and Downwind Concentrations, *Envi. Sci. Tech.*, **1997,** 31: 523-529.

[76] *Report for the Application and Ambient Air Monitoring of Chlorpyrifos (and the Oxon Analogue) in Tulare County during Spring/Summer 1996,* California Air Resources Board, Test Report #C96-040 and # C96-041, April 7, 1998, http://www.cdpr.ca.gov/docs/empm/pubs/tac/chlrpfs.htm.

Figure 2: Chlorpyrifos concentrations in air in Tulare County, CA in Summer 1996 measured by the CA ARB. Averages are for 4 days per week of sampling over the 4-week period. Monitoring sites included ARB, the ARB office in downtown Visalia; JEF, Jefferson Elementary School in Lindsay; KAW, Kaweah School in Exeter; SUN, Sunnyside Union Elementary School in Strathmore; UCL, University of California, Lindcove Field Station.

Using these ARB data, scientists at the California Department of Health Services concluded in a peer-reviewed paper in 2002 that short-term chlorpyrifos exposure estimates exceeded the acute REL for 50% of children in the exposed general populations.[77] The researchers noted that farm workers and their children likely experience higher exposures and risks than individuals in the general population. Furthermore, "[p]esticide exposures and risks are characterized for the communities around the air monitoring locations. However, the potential for exposures in other residential areas clearly exist . . ." In addition, the authors indicate that census data suggest "a potential for exposures and risks, similar to those calculated in this risk assessment, for hundreds of thousands of people in California."[78]

B. Community Air Monitoring Shows Widespread Contamination

Since 2004, PANNA has been working with rural communities to conduct air monitoring at people's homes, schools and workplaces.[79] Chlorpyrifos is one of the primary pesticides that has been found in these communities. Data collected in Lindsay, California in June and July of 2004, 2005, and 2006, and in Washington State in 2006 demonstrate that daily exposure to chlorpyrifos can be substantial, and regularly exceeds the "acceptable" 24-hour acute dose for a one-year-old child established by the EPA. This information has been transmitted to EPA staff through personal communications with staff, presentations at public meetings, and in Spray Drift Work Group meetings. The 2004 and 2005 results from the Lindsay, California study were published on July 14, 2006.[80]

Of the 104 samples collected in Lindsay, California during the summer of 2004, 11% were above the 24-hour acute and sub-chronic child REL. The highest concentration observed for a 24-hour period was 1,340 ng/m^3 (7.9 times the 24-hour acute child REL). Of the 108 samples in the same area during the next summer (2005), 23% were above the 24-hour acute and sub-chronic child REL. The highest concentration observed for a 24-hour period in 2005 was 1,120 ng/m^3 (6.6 times the 24-hour acute child REL). These data are consistent with results obtained by the ARB for ambient air monitoring conducted in

[77] S. Lee, R. McLaughlin, M. Harnly, *et al.*, Community exposures to airborne agricultural pesticides in California: Ranking of Inhalation Risks, *Env Health Persp,* 2002, 110: 1175–84.
[78] S. Lee, R. McLaughlin, M. Harnly, *et al.*, Community exposures to airborne agricultural pesticides in California: Ranking of Inhalation Risks, *Env Health Persp,* 2002, 110: 1175–84.
[79] *Drift Catcher Results*, Pesticide Action Network, www.panna.org/campaigns/driftCatcherResults.html
[80] K Mills and SE Kegley, *Air Monitoring for Chlorpyrifos in Lindsay, California, June-July 2004 and July-August, 2005,* Pesticide Action Network North America (San Francisco, CA, July 14, 2006).

1996 (see above).

Although the observed 24-hour average concentrations were below the adult RELs, adults living in the houses where the monitoring stations were located experienced symptoms of acute OP poisoning. This observation suggests the following: 1) the NOELs EPA determined from industry toxicology studies are inaccurate and do not reflect the true toxicological endpoints; and/or 2) using a 24-hour averaging time does not protect people from poisoning resulting from shorter-term exposures at higher concentrations. In any case, it is clear that inhalation exposure is high enough to cause acute poisonings of bystanders and that EPA's failure to account for inhalation exposures in its aggregate risk assessment is a serious flaw in the risk assessment process.

C. Inhalation Exposure to Chlorpyrifos Far Exceeds Dietary Exposure

In areas of high chlorpyrifos use, inhalation is the primary source of exposure, dwarfing all other sources. A comparison of dietary exposure estimated by EPA for the most-exposed (99.9th percentile) children to inhalation exposure reported by ARB and PANNA from measurements in several different locations and seasons is illuminating.

The highest acute dietary exposures for infants are estimated by EPA to result in a dose that is 50% of the acute Population Adjusted Dose (PAD). In contrast, inhalation exposures estimated from ARB monitoring data indicate that infants living very close to an application site during the day the application takes place are exposed to a dose that is over 75 times higher than the acute PAD. The ambient air monitoring conducted in Lindsay, California and the Yakima Valley in Washington State[81] indicate that the highest 24-hour exposures (comparable to the 99.9th percentile acute dietary exposure) would result in a dose that ranges from 404–793% of the acute PAD. These data show that EPA is failing to account for the vast majority of exposure when it assumes inhalation exposure is zero for rural residents in areas of high chlorpyrifos use.

VI. Exporting Hazards

Unless chlorpyrifos is banned, and all tolerances cancelled, chlorpyrifos will continue to be used, often unsafely, in other countries thus creating a health and environmental hazard in those countries and on contaminated food re-entering the US. Although chlorpyrifos is listed as a "restricted use" pesticide in the US, it is exported in high volume: 7 to 9 million pounds annually since 1997 (8,570,694 in 2000).[82] Between 1997 and 2000, nearly 65 million pounds of severely restricted or forbidden pesticides in the US were exported; more than 22 tons per day – and more than half were exported to

[81] C Dansereau, SE Kegley, K Tupper, A Wang and M. Perez, *Poisons on the Wind: Community Air Monitoring for Chlorpyrifos in the Yakima Valley*, Farm Worker Pesticide Project and Pesticide Action Network North America (San Francisco, CA December 2006).

[82] Smith, C. 2001. Pesticide exports from U.S. ports, 1997-2000. *Int J Occ Environ Health,* 7(4): 266-274. Table 6, data from California EPA.

developing countries for agriculture use.[83] The International Labor Organization estimates that 60 to 90% of children estimated to be working in Africa (80 million), Asia (152 million), and Latin America (17 million) work in agriculture. These children are exposed to toxic pesticides in the fields, from drinking and washing water, through contaminated clothing, and in their homes.[84] The U.N. Commission on Human Rights stated that "[a]llowing the export of products recognized to be harmful is immoral."[85] The mitigation requirements in this IRED include respirators with an organic-vapor removing cartridge and a pesticide-approved prefilter, chemical-resistant outer-clothes, enclosed-cab machinery, emergency equipment readily available, and storage containments for discarding single-use chemically-resistant over-clothes. It is inconceivable that these are "readily available" to mixers, loaders, applicators, and fieldworkers in developing countries. US labeling requirements will have no mitigation effects for these men, women, and children workers. Cancellation of these dangerous pesticides is the most prudent and health-protective solution.

VII. Conclusion

Just a few months prior to the August, 2006 release of the CRA, the Local Presidents of EPA Unions representing scientists, risk managers, and related staff took the unusual step of sending a letter to Administrator Johnson expressing significant concerns about the EPA's risk analyses for organophosphates and identifying undue influence of pesticide registrants on its decision-making processes for these pesticides.[86] Particular concerns raised by the EPA Union leaders included the failure of EPA adequately to address exposures to infants and children who live near treated fields, including the children of farm workers. Moreover, the letter alerted Administrator Johnson that Pesticide Program staff "feel besieged by political pressure exerted by Agency officials perceived to be too closely aligned with the pesticide industry and former EPA officials now representing the pesticide and agricultural community; and by the USDA...."[87] The letter concluded that "until EPA can state with scientific confidence that these pesticides will not harm the neurological development of our nation's born and unborn children, there is no justification to continue to approve the use of the remaining OP [organophosphate] and carbamate pesticides."[88]

Separately, NRDC also voiced serious concerns about the limitations of the data set used by EPA for the aggregate and cumulative assessments.[89] Many of these concerns were discussed at length by the FIFRA SAP and reported in 2002. Two members of the panel "felt strongly that the studies presented by the Agency have limited application to

---

[83] article by C. Smith according to customs records

[84] US Newswire. 2001. U.N. human rights investigator deems U.S. export of banned pesticides 'immoral'. December 17, 16 :09. http://www.usnewswire.com

[85] U.N. Special Rapporteur Fatma Zora Ouhachi-Vesely. In : US newswire, December 17, 2001. op cit.

[86] Union Letter to EPA Administrator. May 24, 2006 http://www.nrdc.org/media/docs/060525.pdf

[87] Union letter at 3

[88] Union letter at 3

[89] NRDC comments on the Revised Cumulative Risk Assessment of the Organophosphate Pesticides. Docket OPP-2002-0230. April 28, 2002

understanding the effects of OP insecticides, specifically in children."[90] The SAP was also concerned about the failure to fully incorporate pre- and post-natal effects of organophosphates associated with children's brain function. The SAP reported that "[n]ot to include data on these outcomes excludes important variables in the assessment and therefore introduces important specification error. Wilson's work and the work of many others have shown that *systematically measured behavior may demonstrate toxicological effects at lower doses than those that yield phenotypic or biochemical alterations*."[91] Significantly, the SAP concluded that EPA's assessment contained "substantial measurement and specification errors, and as a consequence, underestimates the risk of OPs for child health."[92] In its final determinations, EPA failed to acknowledge these important limitations and chose not to adjust the uncertainty factors.

Without incorporating published literature describing the chronic impacts of long-term, low-level doses of organophosphate pesticides, particularly early-life exposures, EPA is making critical decisions about chlorpyrifos based on only a fragment of the whole story. Together with the decision to ignore robust data, this approach of deliberately selecting for the weakest data dumbs down the Agency's registration decision to the lowest common denominator.

Robust data shows that any use restriction on chlorpyrifos would still not be health-protective and that all food tolerances must be revoked. EPA's decision to reregister chlorpyrifos and retain food tolerances violates FIFRA and the FFDCA. EPA failed to consider important studies and improperly disregarded others. Furthermore, the Agency relied on a biased selection of available, weak data, in favor of the robust data, leading to an unsupported risk assessment.

As a result of EPA's actions, NRDC and PANNA members and their children are being exposed to unsafe levels of chlorpyrifos, and will continue to be as long as the chlorpyrifos registrations and food tolerances challenged in this petition remain in effect. We therefore request that EPA expedite its consideration of this petition in every way possible. If EPA intends to solicit public comment before making a decision on this petition, we request that the Agency do so promptly. EPA's past history of significant delay in responding to pesticide petitions and tolerance objections filed by NRDC constitutes a pattern and practice of unlawful agency inaction that harms NRDC and PANNA and its members.

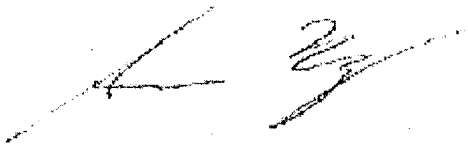
Based on all of the foregoing comments, NRDC and PANNA petition EPA to revoke all tolerances and cancel all registrations for the pesticide chlorpyrifos. We reserve the right to supplement this petition based on new information.

---

[90] Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held June 26-27, 2002. Released on July 19, 2002, 26.
[91] *Id* (emphasis is added).
[92] Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held June 26-27, 2002. Released on July 19, 2002 (emphasis is added).

Respectfully submitted,

Mae C Wu, Esq.
Jennifer Sass, Ph.D.
Natural Resources Defense Council
1200 New York Ave., NW, Suite 400
Washington DC, 20005
(202) 289-6868
(202) 289-1060 (fax)



Susan E. Kegley, Ph.D.
Pesticide Action Network, North America
49 Powell Street, Suite 500,
San Francisco CA 94102

Dated: 12 September 2007

cc: Administrator Stephen Johnson
General Counsel Roger Martella
James Gulliford
Debbie Edwards
Pete Caulkins
Bob Perliss
Tom Myers

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2015–0653; FRL–9935–92]

Chlorpyrifos; Tolerance Revocations

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: On August 10, 2015, the U.S. Court of Appeals for the Ninth Circuit ordered EPA to respond to an administrative Petition to revoke all tolerances for the insecticide chlorpyrifos by October 31, 2015, by either denying the Petition or issuing a proposed or final tolerance revocation. At this time, the agency is unable to conclude that the risk from aggregate exposure from the use of chlorpyrifos meets the safety standard of section 408(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Accordingly, EPA is proposing to revoke all tolerances for chlorpyrifos. EPA is specifically soliciting comment on whether there is an interest in retaining any individual tolerances, or group of tolerances, and whether information exists to demonstrate that such tolerance(s) meet(s) the FFDCA section 408(b) safety standard. EPA encourages interested parties to comment on the tolerance revocations proposed in this document and on the proposed time frame for tolerance revocation. Issues not raised during the comment period may not be raised as objections to the final rule, or in any other challenge to the final rule.

DATES: Comments must be received on or before January 5, 2016.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2015–0653 by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- *Mail:* OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001.
- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at *http://www.epa.gov/dockets/contacts.html.*

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *http://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: Dana Friedman, Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave NW., Washington, DC 20460–0001; telephone number: (703) 347–8827; email address: *friedman.dana@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

B. What should I consider as I prepare my comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through regulations.gov or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments.* When preparing and submitting your comments, see the commenting tips at *http://www.epa.gov/dockets/comments.html.*

C. What can I do if I wish the Agency to maintain a tolerance that the Agency proposes to revoke?

This proposed rule provides a comment period of 60 days for any interested person to submit comments on the agency's proposal. EPA will issue a final rule after considering the comments that are submitted. Comments should be limited only to the pesticide and tolerances subject to this proposal.

EPA's finding that it cannot determine if aggregate exposure from all existing uses of chlorpyrifos are safe, does not necessarily mean that no individual tolerance or group of tolerances could meet the FFDCA 408(b)(2) safety standard and be maintained. EPA's risk assessment supporting this proposed rule indicates that the primary source of risk comes from chlorpyrifos and chlorpyrifos oxon in drinking water in highly vulnerable watersheds (generally small watersheds where the land is agricultural and could be treated with chlorpyrifos (*i.e.,* heavily cropped areas)). However, as explained in this proposed rule, some uses of chlorpyrifos do not by themselves present risks of concern from either food or drinking water and are only a concern when aggregated with all exposures to chlorpyrifos. EPA therefore invites comments that address whether some tolerances or groups of tolerances can be retained. In that regard, in addition to information related to the safety of such tolerances, use site specific information pertaining to the pests targeted by chlorpyrifos, and the alternatives to chlorpyrifos for these pests, may help to inform the agency's final decision if EPA is able to conclude that some tolerances may be retained under the FFDCA safety standard. In addition, if EPA receives information that would allow it to better refine the location of at risk watersheds and protect such watersheds through appropriate product labeling restrictions, it is possible EPA could conclude that such mitigation would eliminate the need for some or all of the proposed tolerance revocations. It is important to stress, however, that because the FFDCA is a safety standard, EPA can only retain chlorpyrifos tolerances if it is able to conclude that such tolerances are safe.

After consideration of comments, EPA will issue a final regulation determining whether revocation of some or all of the tolerances is appropriate under section 408(b)(2). Such regulation will be subject to objections pursuant to section 408(g) (21 U.S.C. 346a(g)) and 40 CFR part 178.

In addition to submitting comments in response to this proposal, you may also submit an objection at the time of the final rule. If you anticipate that you may wish to file objections to the final rule, you must raise those issues in your comments on this proposal. EPA received numerous comments on its

December 2014 Revised Human Health Risk Assessment (RHHRA) (Ref. 1) related to the scientific bases underlying this proposed rule. In light of the U.S Court of Appeals for the Ninth Circuit's August 10, 2015 order in *Pesticide Action Network North America (PANNA)* v. *EPA,* No. 14–72794 (*PANNA*), compelling EPA to take this action by October 31, 2015, EPA has not addressed these prior comments in this proposed rule. Persons wishing to have EPA consider previously submitted comments on the RHHRA in connection with this proposal should submit a comment indicating that intention and identifying their earlier comments on the RHHRA. EPA will treat as waived any issue not raised or referenced in comments submitted on this proposal. Similarly, if you fail to file an objection to the final rule within the time period specified, you will have waived the right to raise any issues resolved in the final rule. After the specified time, issues resolved in the final rule cannot be raised again in any subsequent proceedings on this rule making.

II. Background

A. What action is the Agency taking?

EPA is proposing to revoke all tolerances for residues of the insecticide chlorpyrifos as contained in 40 CFR 180.342. This includes tolerances for residues of chlorpyrifos on specific food commodities (180.342(a)(1)); on all food commodities treated in food handling and food service establishments in accordance with prescribed conditions (180.342(a)(2) and(a)(3)); and on specific commodities when used under regional registrations (180.342(c)).

The agency is proposing to revoke all of these tolerances because EPA cannot, at this time, determine that aggregate exposure to residues of chlorpyrifos, including all anticipated dietary exposures and all other non-occupational exposures for which there is reliable information, are safe.

EPA's full risk conclusions supporting this proposal are set forth in the 2014 RHHRA for chlorpyrifos that EPA issued for public comment. That document, supporting materials, and the public comments on those documents are available in the chlorpyrifos registration review docket, EPA–HQ–OPP–2008–0850. While EPA's assessment indicates that contributions to dietary exposures to chlorpyrifos from food and residential exposures are safe, when those exposures are combined with estimated exposures from drinking water, as required by the FFDCA, EPA has determined that safe levels of chlorpyrifos in the diet may be exceeded for people whose drinking water is derived from certain vulnerable watersheds throughout the United States. This primarily includes those populations consuming drinking water from small water systems in heavily cropped areas where chlorpyrifos may be used widely.

B. What is the Agency's authority for taking this action?

EPA is taking this action, pursuant to the authority in FFDCA sections 408(b)(1)(A), 408(b)(2)(A), and 408(d)(4)(A)(ii). 21 U.S.C. 346a(b)(1)(A), (b)(2)(A), (d)(4)(A)(ii).

III. Statutory and Regulatory Background

A ''tolerance'' represents the maximum level for residues of pesticide chemicals legally allowed in or on raw agricultural commodities and processed foods. Section 408 of FFDCA, 21 U.S.C. 346a, authorizes the establishment of tolerances, exemptions from tolerance requirements, modifications of tolerances, and revocation of tolerances for residues of pesticide chemicals in or on raw agricultural commodities and processed foods. Without a tolerance or exemption, food containing pesticide residues is considered to be unsafe and therefore ''adulterated'' under FFDCA section 402(a), 21 U.S.C. 342(a). Such food may not be distributed in interstate commerce, 21 U.S.C. 331(a). For a food-use pesticide to be sold and distributed, the pesticide must not only have appropriate tolerances under the FFDCA, but also must be registered under FIFRA, 7 U.S.C. 136a(a); 40 CFR 152.112(g). Food-use pesticides not registered in the United States must have tolerances in order for commodities treated with those pesticides to be imported into the United States.

Section 408(d) of the FFDCA, 21 U.S.C. 346a(d), authorizes EPA to revoke tolerances in response to administrative petitions submitted by any person. Because EPA is unable to determine at this time that aggregate exposures to chlorpyrifos are safe, EPA is proposing to revoke these tolerances in response to a Petition from PANNA and the Natural Resources Defense Council (NRDC) to revoke all chlorpyrifos tolerances (Ref. 2). The timing of this proposal is the result of the August 10, 2015 order in the PANNA decision to respond to that petition by October 31, 2015. This proposal also implements the agency findings made during the registration review process required by section 3(g) of FIFRA (7 U.S.C. 136(a)(g)) which EPA is conducting in parallel with its petition response. That process requires EPA to re-evaluate existing pesticides every 15 years to determine whether such pesticides meet the FIFRA registration standard set forth in FIFRA section 3(c)(5), 7 U.S.C. 136a(c)(5). In part, that standard requires EPA to ensure that dietary risks from the pesticide meet the FFDCA section 408 safety standard. Section 408 directs that EPA may establish or leave in effect a tolerance for pesticide only if it finds that the tolerance is safe, and EPA must revoke or modify tolerances determined to be unsafe. FFDCA 408(b)(2)(A)(i) (21 U.S.C. 346a(b)(2)(A)(i)). Section 408(b)(2)(A)(ii) defines ''safe'' to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.'' This includes exposure through drinking water and all non-occupational exposures (*e.g.* in residential settings), but does not include occupational exposures to workers (*i.e.,* occupational).

Risks to infants and children are given special consideration. Specifically, pursuant to section 408(b)(2)(C), EPA must assess the risk of the pesticide chemical based on available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of in utero exposure to pesticide chemicals; and available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity.

(21 U.S.C. 346a(b)(2)(C)(i)(II) and (III)).

This provision further directs that ''in the case of threshold effects, . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.'' (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to ''use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.'' (21 U.S.C. 346a(b)(2)(C)). Due to Congress's focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years. For

convenience sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) are referred to throughout this proposed rule as the ''FQPA safety factor for the protection of infants and children'' or simply the ''FQPA safety factor.''

IV. Chlorpyrifos Background, Regulatory History, and Litigation

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide that has been registered for use in the United States since 1965. Currently registered use sites include a large variety of food crops (including fruit and nut trees, many types of fruits and vegetables, and grain crops), and non-food use settings (*e.g.,* golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products). Public health uses include aerial and ground-based fogger mosquito adulticide treatments, roach bait products and individual fire ant mound treatments. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for ant and roach baits in child-resistant packaging and fire ant mound treatments.

In 2006, EPA completed FIFRA section 4 reregistration and FFDCA tolerance reassessment for chlorpyrifos and the OP class of pesticides. Given ongoing scientific developments in the study of the OPs generally, EPA chose to prioritize the FIFRA section 3(g) registration review (the next round of re-evaluation following reregistration) of chlorpyrifos and the OP class. The registration review of chlorpyrifos and the OPs has presented EPA with numerous novel scientific issues that have been the subject of multiple FIFRA Scientific Advisory Panel (SAP) meetings since the completion of reregistration that have resulted in significant developments in the conduct of EPA's risk assessments generally, and, more specifically, in the study of chlorpyrifos's effects. These SAP meetings included review of new worker and non-occupational exposure methods, experimental toxicology and epidemiology, risk assessment approaches for semi-volatile pesticides and the evaluation of a chlorpyrifos-specific pharmacokinetic-pharmacodynamic (PBPK–PD) model.

A. Registration Review

In 2011, in connection with FIFRA registration review, EPA issued its Preliminary Human Health Risk Assessment (PHHRA) (Ref. 3) for chlorpyrifos that evaluated exposures from food, drinking water, other non-occupational sources, and occupational risk (such as risks to farmworkers applying chlorpyrifos and working in treated fields). At the time of the PHHRA, EPA had not yet performed an integrated weight of evidence analysis on the lines of evidence related to the potential for neurodevelopmental effects. The PHHRA indicated that for food alone, the acute and chronic dietary risk estimates for all populations assessed were below the level of concern. The residue of concern in treated drinking water is the chlorpyrifos oxon because chlorpyrifos transforms to the more toxic chlorpyrifos oxon in treated drinking water (*e.g.* chlorination). For drinking water alone, EPA had a concern for infant exposures to the chlorpyrifos oxon.

In December 2014, EPA completed the RHHRA for registration review (Ref. 1). The RHHRA represents a highly sophisticated assessment of hazard and exposure to chlorpyrifos and its oxon. The dietary risk assessment in the RHHRA provides the scientific support for this proposed rule. The approach EPA used for the chlorpyrifos dietary assessment and for this proposed rule can be described as follows: EPA conducted dietary exposure modeling using the Dietary Exposure Evaluation Model (DEEM) and the Calendex models (Ref. 4) to develop a probabilistic evaluation of human dietary consumption. Most of the pesticide food residue values used in those models were based upon U.S. Department of Agriculture's (USDA) Pesticide Data Program (PDP) monitoring data. Percent crop treated and empirical food processing factors were used where available. EPA then utilized a PBPK–PD model to calculate both acute (24 hour) and steady state (21 days (*i.e.,* the approximate time to reach steady state for most OPs)) points of departure (PoD) dose levels that represent the minimum amount of chlorpyrifos that presents a risk concern. (OPs exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. OP AChE studies of 2–3 weeks generally show the same degree of inhibition as those of longer duration (*i.e.,* up to 2 years of exposure). Therefore, a steady state assessment based on 21 days of exposure may be conducted in place of the traditional chronic assessment).

For chlorpyrifos, the risk of concern is 10% acetylcholinesterase inhibition (AChE) in red blood cells (RBC)—a precursor for adverse neurological symptoms—for both acute and steady state exposure durations. The PBPK–PD PoD predictions for each human lifestage exposure route and pathway were modeled separately (*e.g.,* for residential exposure *i.e.* dermal, inhalation and incidental oral calculations). PoDs are divided by the total uncertainty factors (which are used to account for potential differences in sensitivities within populations or extrapolations from test results in animals to effects on humans) to derive a population adjusted dose (PAD). There are potential risks of concern when the estimated dietary exposures exceed 100% of the PAD. For the food intake portion of the dietary assessment, the only potential residue of concern is chlorpyrifos (the oxon metabolite is not an expected residue on foods). EPA incorporated total uncertainty factors of 100X for adult females (a 10X FQPA safety factor and another 10X intra-species extrapolation factor since the PBPK–PD model does not include a component that specifically models pregnant women) and 40X for the other relevant populations (a 10X FQPA safety factor and another 4X intra-species data derived extrapolation factor) using the PBPK–PD model to account for potential metabolic and physiological differences between populations. The chlorpyrifos exposure values resulting from dietary modeling are then compared to the PAD to determine the portion of the ''risk cup'' that is taken up by exposures from food. In the case of chlorpyrifos, the RHHRA concluded that food and non-occupational exposures by themselves take up only a small portion of the risk cup and are therefore not a risk concern when considered in isolation.

For the drinking water portion of the dietary assessment, the chlorpyrifos oxon, which is more toxic than chlorpyrifos, is the residue of concern assumed to occur in drinking water. Based on available information regarding the potential effects of certain water treatments (*e.g.,* chlorination appears to hasten transformation of chlorpyrifos to chlorpyrifos oxon), EPA believes it is appropriate to assume that all chlorpyrifos in water is converted to chlorpyrifos oxon upon treatment. The chlorpyrifos oxon total uncertainty factors are 100X for adult females (10X FQPA safety factor and 10X intra-species extrapolation factor to account for potential differences between populations) and 50X for the other

relevant populations (10X FQPA safety factor and 5X intra-species data derived extrapolation factor) using the PBPK–PD model to account for potential metabolic and physiological differences between populations. See Unit VI.5 for how the intra-species factors for chlorpyrifos and chlorpyrifos oxon were derived. After considering food and residential contributions to the risk cup, EPA determined that drinking water concentrations to chlorpyrifos oxon greater than 3.9 ppb for a 21-day average would exceed EPA's Drinking Water Level of Comparison (DWLOC) and present a risk of concern. EPA's water exposure assessment indicated that multiple labeled use scenarios for chlorpyrifos exceed the DWLOC and therefore present a risk concern. On January 14 2015, EPA published a **Federal Register** Notice seeking public comment on the RHHRA.

EPA's drinking water analysis in the RHHRA also showed that the DWLOC exceedances are not expected to be uniformly distributed across the country. As a result, EPA began to conduct further analysis to look at the spatial distribution of Estimated Drinking Water Concentrations (EDWCs) at more refined geographic levels. This exercise demonstrated that chlorpyrifos applications will result in variable drinking water exposures that are highly localized and that the highest exposures generally occur in small watersheds where there is a high percent cropped area on which chlorpyrifos use could occur. Accordingly, following the development of the RHHRA in December 2014, EPA has continued working to develop a more refined assessment to examine EDWCs on a regional and/or watershed scale to pinpoint community drinking water systems where exposure to chlorpyrifos oxon as a result of chlorpyrifos applications may pose an exposure concern. At this time this more refined drinking water assessment that will allow EPA to better identify where at-risk watersheds are located throughout the country is not completed. Thus, we are not currently able to determine with any great specificity which uses in which areas of the country do or do not present a risk concern. EPA intends to update this action, as warranted, with any significant refinements to its drinking water assessment, and intends, to the extent practicable, to provide the public an opportunity to comment on the refined drinking water assessment prior to a final rule.

B. PANNA±NRDC Petition and Associated Litigation

In September 2007, PANNA and NRDC submitted to EPA a Petition seeking revocation of all chlorpyrifos tolerances and cancellation of all FIFRA registrations of products containing chlorpyrifos. In connection with both EPA's response to the Petition and the FIFRA registration review of chlorpyrifos, EPA has taken most of the complex and novel science questions raised in the Petition to the SAP for review and EPA has developed numerous new methodologies (including approaches to address pesticide drift, volatility, and the integration of experimental toxicology and epidemiology) to consider these issues.

While EPA agreed that these new methodologies were necessary to properly evaluate PANNA and NRDC's (Petitioners') claims, Petitioners have been dissatisfied with the pace of EPA's response efforts and have sued EPA in federal court on three separate occasions to compel a prompt response to the Petition. Although EPA has to date addressed 7 of the 10 claims asserted in the Petition by either issuing a preliminary denial or approving label mitigation to address the claim, on June 10, 2015, in the *PANNA* decision, the U.S. Court of Appeals for the Ninth Circuit signaled its intent to order EPA to complete its response to the Petition and directed EPA to inform the court how—and by when—EPA intended to respond. On June 30, 2015, EPA informed the court that, based on the results of its drinking water assessment, EPA intended to propose by April 15, 2016, the revocation of all chlorpyrifos tolerances in the absence of pesticide label mitigation that ensures that drinking water exposures will be safe. EPA proposed this time frame in part to accommodate the completion of a refined drinking water assessment that might allow EPA to identify high risk areas of the country where additional label mitigation could be put in place to address drinking water concerns. On August 10, 2015, the court rejected EPA's time line and issued a mandamus order directing EPA to ''issue either a proposed or final revocation rule or a full and final response to the administrative Petition by October 31, 2015.'' As a result of this order, EPA is issuing this proposed rule in advance of completing its refined drinking water assessment. In addition, EPA has had insufficient time to address comments received on the RHHRA. As a result, EPA may update this action with new or modified analyses as EPA completes additional work after this proposal. For any significant new or modified analyses, to the extent practicable, EPA intends to provide the public an opportunity to comment on that work prior to issuing a final rule.

V. EPA's Approach to Dietary Risk Assessment

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. A short summary is provided below to aid the reader. For further discussion of the regulatory requirements of section 408 of the FFDCA and a complete description of the risk assessment process, refer to References 5 and 6 respectively. To assess the risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps: (1) Identification of the toxicological hazards posed by a pesticide; (2) determination of the exposure ''level of concern'' for humans; (3) estimation of human exposure; and (4) characterization of human risk based on comparison of human exposure to the level of concern.

A. Hazard Identification and Selection of Toxicological Endpoint

Any risk assessment begins with an evaluation of a chemical's inherent properties, and whether those properties have the potential to cause adverse effects (*i.e.,* a hazard identification). EPA then evaluates the hazards to determine the most sensitive and appropriate adverse effect of concern, based on factors such as the effect's relevance to humans and the likely routes of exposure.

Once a pesticide's potential hazards are identified, EPA determines a toxicological level of concern for evaluating the risk posed by human exposure to the pesticide. In this step of the risk assessment process, EPA essentially evaluates the levels of exposure to the pesticide at which effects might occur. An important aspect of this determination is assessing the relationship between exposure (dose) and response (often referred to as the dose-response analysis). In evaluating a chemical's dietary risks, EPA uses a reference dose (RfD) approach, which first involves establishing a PoD—or the value from a dose-response curve that is at the low end of the observable data and that is the toxic dose that serves as the starting point in extrapolating a risk to the human population. In typical risk assessments, PoDs are derived directly

from laboratory animal studies, and then EPA extrapolates to potential effects on humans and human populations by applying both inter and intra-species uncertainty factors. Traditionally, EPA has used a 10X factor to address each of these uncertainties. In the case of chlorpyrifos and its oxon, however, EPA has used PBPK–PD modeling to estimate PoDs for all age groups using Data-Derived Extrapolation Factors (DDEF) rather than default uncertainty factors to address intraspecies extrapolation for some groups (Ref. 1). The PBPK–PD model accounts for PK (pharmacokinetic) and PD (pharmacodynamic) characteristics to derive age, duration, and route specific PoDs. Specifically, the following characteristics have been evaluated: exposure (acute, 21-day (steady state); routes of exposure (dermal, oral, inhalation); body weights which vary by lifestage; exposure duration (hours per day, days per week); and exposure frequency (*e.g.,* eating and drinking events per day). While the current PBPK–PD model accounts for age-related growth from infancy to adulthood by using polynomial equations to describe tissue volumes and blood flows as a function of age, the model does not include any descriptions on physiological, anatomical, and biochemical changes associated with pregnancy. Due to the uncertainty in extrapolating the current model predictions among women who may be pregnant, the agency is applying the standard 10X intra-species extrapolation factor for women of childbearing age.

Although the PBPK–PD model's use of data-derived extrapolation factors renders unnecessary the use of traditional inter- and intra- species uncertainty factors for evaluating most populations, as required by FFDCA section 408(b)(2)(C), EPA must also address the need for an additional safety factor to protect infants and children. That provision requires EPA to retain an additional 10-fold margin of safety unless EPA concludes, based on reliable data, that a different safety factor will be safe for infants and children. The PoDs calculated by the PBPK–PD model are then divided by the uncertainty factors to derive a PAD. There are potential risks of concern when the estimated dietary exposure exceeds 100% of the PAD.

B. Estimating Human Exposure Levels

Pursuant to section 408(b) of the FFDCA, EPA evaluated dietary risks for chlorpyrifos based on ''aggregate exposure'' to chlorpyrifos. By ''aggregate exposure,'' EPA is referring to exposure to chlorpyrifos residues by multiple pathways of exposure. EPA uses available data, together with assumptions designed to be protective of public health, and standard analytical methods to produce separate estimates of exposure for a highly exposed subgroup of the general population, for each potential pathway and route of exposure. For both acute and steady state risks, EPA then calculates potential aggregate exposure and risk by using probabilistic techniques to combine distributions of potential exposures in the population for each route or pathway. (Probabilistic analysis is used to predict the frequency with which variations of a given event will occur. By taking into account the actual distribution of possible consumption and pesticide residue values, probabilistic analysis for pesticide exposure assessments ''provides more accurate information on the range and probability of possible exposure and their associated risk values.'' (Ref. 7). In capsule, a probabilistic pesticide exposure analysis constructs a distribution of potential exposures based on data on consumption patterns and residue levels and provides a ranking of the probability that each potential exposure will occur. People consume differing amounts of the same foods, including none at all, and a food will contain differing amounts of a pesticide residue, including none at all). For dietary analyses, the relevant sources of potential exposure to chlorpyrifos are from the ingestion of residues in food and drinking water. EPA uses a combination of monitoring data and predictive models to evaluate environmental exposure of humans to chlorpyrifos.

1. *Exposure from food.* Acute and steady state dietary (food only) exposure analyses for chlorpyrifos were conducted using the Dietary Exposure Evaluation Model (DEEM) and Calendex software with the Food Commodity Intake Database (FCID). The DEEM–FCID model uses 2003–2008 food consumption data from the USDA National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). These current analyses reflect the latest available consumption data as well as more recent food monitoring and percent crop treated data. Both the acute and steady state dietary exposure analyses are highly refined. The large majority of food residues used were based upon USDA's PDP monitoring data except in a few instances where no appropriate PDP data were available. In those cases, field trial data or tolerance level residues were assumed.

DEEM–FCID also compares exposure estimates to appropriate RfD or PAD values to estimate risk. EPA uses these models to estimate exposure for the general U.S. population as well as subpopulations based on age, sex, ethnicity, and region. For its chlorpyrifos assessment, EPA used DEEM–FCID to calculate risk estimates based on a probabilistic distribution that combines the full range of residue values for each food with the full range of data on individual consumption amounts to create a distribution of exposure and risk levels. More specifically, DEEM–FCID creates this distribution by calculating an exposure value for each reported day of consumption per person (''person/day'') in the food survey, assuming that all foods potentially bearing the pesticide residue contain such residue at the chosen value. The exposure amounts for the thousands of person/days in the food survey are then collected in a frequency distribution.

The probabilistic technique that DEEM–FCID uses to combine differing levels of consumption and residues involves the following steps:

(1) identification of any food(s) that could possibly bear the residue in question for each person/day in the USDA food survey;

(2) calculation of an exposure level for each of the thousands of person/days in the USDA food survey database, based on the foods identified in Step #1 by randomly selecting residue values for the foods from the residue database;

(3) repetition of Step #2 one thousand times for each person/day; and

(4) collection of all of the hundreds of thousands of potential exposures estimated in Steps # 2 and 3 in a frequency distribution.

The resulting probabilistic assessment presents a range of exposure/risk estimates that can be compared to appropriate PADs to determine the safety of food exposures.

2. Exposure from water. EPA may use field monitoring data and/or simulation water exposure models to generate pesticide exposure estimates in drinking water. Monitoring and modeling are both important tools for estimating pesticide concentrations in water and can provide different types of information. Monitoring data can provide estimates of pesticide concentrations in water that are representative of the specific agricultural or residential pesticide practices in specific locations, under the environmental conditions associated with a sampling design (*i.e.,* the

locations of sampling, the times of the year samples were taken, and the frequency by which samples were collected). Further, monitoring data can reflect the actual use of a pesticide rather than the label rates. Although monitoring data can provide a direct measure of the concentration of a pesticide in water, it generally does not provide a reliable basis for estimating spatial and temporal variability in exposures because sampling may not occur in areas with the highest pesticide use, and/or when the pesticides are being used and/or at an appropriate sampling frequency to detect high concentrations of a pesticide that occur over the period of a day to several days.

Because of the limitations in most monitoring studies, EPA's standard approach is to use water exposure models as the primary means to estimate pesticide exposure levels in drinking water. EPA's computer models use detailed information on soil properties, crop characteristics, and weather patterns to estimate exposure in vulnerable locations where the pesticide could be used according to its label. (Ref. 8). These models calculate estimated water concentrations of pesticides using laboratory data that describe how fast the pesticide breaks down to other chemicals and how it moves in the environment at these vulnerable locations. The modeling provides an estimate of pesticide concentrations in ground and surface water. Depending on the modeling algorithm (*e.g.,* surface water modeling scenarios), daily concentrations can be estimated continuously over long periods of time, and for places that are of most interest for any particular pesticide.

As discussed in Unit VI.B. in greater detail, EPA relied on models developed for estimating exposure in both surface water and ground water. A detailed description of the models routinely used for exposure assessment is available from the EPA Office of Pesticide Programs (OPP) Water Models Web site: *http://www.epa.gov/oppefed1/models/water/.* The Surface Water Concentration Calculator provides a means for EPA to estimate daily pesticide concentrations in surface water sources of drinking water (a reservoir) using local soil, site, hydrology, and weather characteristics along with pesticide applications and agricultural management practices, and pesticide environmental fate and transport properties. EPA also considers percent cropped area (PCA) factors which take into account the potential extent of cropped areas that could be treated with pesticides in a particular area.

In modeling potential surface water concentrations, EPA attempts to model areas of the country that are highly vulnerable to surface water contamination rather than simply model ''typical'' concentrations occurring across the nation. Consequently, EPA models exposures occurring in small watersheds in different growing areas throughout the country over a 30-year period. The scenarios are designed to capture residue levels in vulnerable drinking water sources and are adjusted by PCA factors. The PCA is calculated from satellite derived land cover data to account for the area of watershed that is cropped.

EPA believes these assessments are likely reflective of a subset of the watersheds across the country that are used for drinking water supply, representing a drinking water source generally considered to be more vulnerable to frequent high concentrations of pesticides than most locations. For this reason, in its evaluation of chlorpyrifos, EPA has also begun to refine its assessment to evaluate drinking water risk at a regional and drinking water intake scale. While it is currently challenging to assess exposure on a local scale due to the unavailability of data and wide range of characteristics (*i.e.,* environmental factors such as soil, weather, etc. or others (*e.g.,* drinking water treatment process)) that affect the vulnerability of a given community drinking water system to chlorpyrifos oxon contamination, EPA developed a method to examine the potential geospatial concentration differences using specific examples for two Hydrological Unit Code (HUC) 2 Regions—HUC 2 Region 17: Pacific Northwest and HUC 2 Region 3: South Atlantic-Gulf, in order to identify use patterns in those regions that may result in EDWCs that exceed the DWLOC on a regional basis. There are 21 HUC 2 regions with 18 in the conterminous United States. These areas contain either the drainage area of a major river, or a combined drainage of a series of rivers. The average size is 177,560 square miles. Additional information can be found at *https://water.usgs.gov/GIS/huc.html.* The analysis used a number of modeling scenarios to represent all potential chlorpyrifos agricultural use sites. This analysis showed an overlap of potential chlorpyrifos use sites that may result in an exceedance of the DWLOC with watersheds that supply source water for community drinking water systems. In addition, this analysis shows that exposure is not uniform within a HUC 2 Region and that some watersheds present risk concerns while others do not. In general, the refined analysis confirms that smaller watersheds with high percent cropped areas are much more vulnerable than large watersheds. When this assessment is complete (*i.e.,* when EPA has completed this analysis for the rest of the country), it may provide EPA with a basis for tailoring its drinking water risk mitigation efforts through pesticide product labeling rather than revoking tolerances nationwide. Because of the *PANNA* decision on August 10, 2015 compelling EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA has not been able to complete its refined drinking water assessment for chlorpyrifos in advance of this proposed rule. As a result, this proposal relies only on the results of the national screen that do not provide a basis for more tailored risk mitigation. EPA is continuing to conduct its regional and water-intake level assessment and intends to update this action if warranted with the results of that assessment when it is completed. For any significant new or modified drinking water analyses, to the extent practicable, EPA intends to provide the public an opportunity to comment on the work prior to issuing a final rule.

3. *Residential and Other Non-Occupational Exposures.* EPA's ''residential'' assessments actually examine exposure to pesticides in both residential and other non-occupational settings (*e.g.,* homes, parks, schools, athletic fields or any other areas frequented by the general public). All residential uses of chlorpyrifos except ant and roach baits (in child resistant packaging) and fire ant mound treatments were voluntary cancelled by registrants in 2000. As such, the use of the term ''residential'' throughout this document does not connote there are residential uses, rather it is used interchangeable with ''non-occupational'' exposures. Exposures to pesticides may occur to persons who apply pesticides or to persons who enter areas previously treated with pesticides. Such exposures may occur through oral, inhalation, or dermal routes. For chlorpyrifos, the uses that could result in non-occupational exposures are the public health uses as an aerial and ground-based ultra-low volume (ULV) fogger for adult mosquito control, the fire ant mound treatments, the use in ant and roach bait stations, and foliar use on golf course turfgrass.

Non-occupational assessments are conducted through examination of significant exposure scenarios (*e.g.,*

children playing on treated lawns or homeowners spraying their gardens) using a combination of generic and pesticide-specific data. To regularize this process, OPP has prepared Standard Operating Procedures (SOPs) for conducting ''residential'' assessments on a wide array of scenarios that are intended to address all major possible means by which individuals could be exposed to pesticides in a non-occupational environment (*e.g.* homes, schools, parks, athletic fields, or other publicly accessible locations). The SOPs identify relevant generic data and construct algorithms for calculating exposure amounts using these generic data in combination with pesticide-specific information. The generic data generally involve survey data on behavior patterns (*e.g.,* activities conducted on turf and time spent on these activities), unit exposure, and transfer coefficient data to evaluate the transfer of pesticide to humans from a treated surface.

Typically, non-occupational risks are quantified by comparison of estimates of exposure to toxicological PoDs for each route of exposure as selected from laboratory animal studies. In the case of chlorpyrifos, the PBPK–PD model was used to derive age-, duration-, and route-specific human equivalent doses. Separate PoDs were calculated for residential exposures by varying inputs on types of exposures and populations exposed. Residential risk estimates, or margins of exposure (MOEs) were calculated with use of the scenario- and lifestage-specific PoDs by comparison to exposure estimates (doses) quantified with use of standard occupational and residential exposure assessment methodologies.

C. Selection of Acute and Steady State Dietary Exposure Level of Concern

Because probabilistic assessments generally present a realistic range of residue values to which the population may be exposed, EPA's starting point for estimating exposure and risk for its aggregate risk assessments is the 99.9th percentile of the population under evaluation. When using a probabilistic method of estimating acute and steady state dietary exposure, EPA typically assumes that, when the 99.9th percentile of exposure is equal to or less than the PAD, the level of concern has not been exceeded and dietary exposures are safe.

D. Aggregating Exposures and Deriving a Risk Estimate

In an aggregate risk assessment, pesticide exposures from relevant sources (*i.e.,* food, drinking water and non-occupational uses) are added together and compared to quantitative estimates of hazard (*e.g.,* PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, both the route and duration of exposures are considered. For chlorpyrifos, EPA has considered aggregate exposures and risks from combined food, drinking water, and non-occupational exposures. Residues in food consist of parent compound chlorpyrifos only, while concentrations in water are assumed to consist of chlorpyrifos oxon only. The acute aggregate assessment includes only food and drinking water while the steady state aggregate assessment includes exposures from food, drinking water, and non-occupational scenarios. Typically, in aggregate assessments, total dietary exposure (food and drinking water combined) are derived by incorporating both food residues and EDWCs in the dietary exposure model. In the chlorpyrifos RHHRA, only food exposures were derived from the dietary model. For drinking water exposure and risk, a DWLOC approach was used to calculate the amount of exposure which could occur without exceeding the risk level of concern (*i.e.,* the available space in the total aggregate risk cup for exposures to chlorpyrifos oxon in drinking water after accounting for exposures to parent chlorpyrifos from food and non-occupational scenarios). The calculated DWLOCs were then compared to the EDWCs of oxon modeled under a variety of conditions. When the EDWC is less than the DWLOC, there are no risk concerns for exposures to the pesticide in drinking water which also indicates aggregate exposures are not of concern. Conversely, when the EDWC is greater than the DWLOC, then potential risks of concern are identified.

VI. Aggregate Risk Assessment and Conclusions Regarding Safety

Consistent with section 408(b)(2)(D) of FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action. EPA's assessment of exposures and risks associated with chlorpyrifos use follows.

A. Hazard Identification and Endpoint Selection

This unit summarizes EPA's review of relevant data for extrapolating risk and its integrative analysis using multiple lines of evidence from experimental toxicology and epidemiology with respect to AChE/ChE inhibition (acetylcholinesterase/cholinesterase) and neurodevelopmental outcomes. This section also describes EPA's use of a robust PBPK–PD model for deriving PoDs and refined intra-species factors. Finally, this unit provides the quantitative results of the end-point selection process, including EPA's evaluation and application of the FQPA safety factor.

1. Background. Mode of action (MOA) and adverse outcome pathways (AOPs) provide important concepts and organizing tools for risk assessment. MOAs/AOPs describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events. An AOP further defines the initial step in the process as the molecular initiating event. Fundamentally, MOA and AOP are different terms for basically the same concept.

It is well established that AChE inhibition is the mode of action/adverse outcome pathway (MOA/AOP) for the cholinergic toxicity of OP pesticides, including chlorpyrifos. AChE breaks down acetylcholine (ACh), a compound that assists in transmitting signals through the nervous system. When AChE is inhibited at nerve endings by chlorpyrifos or another AChE inhibiting pesticide, the inhibition prevents the ACh from being degraded and results in prolonged stimulation of nerves and muscles. If a person has enough exposure to chlorpyrifos for poisoning to occur the physical signs and symptoms include headache, nausea, dizziness, blurred vision, slurred speech, excessive perspiration, salivation, vomiting, diarrhea, and muscle twitching. Severe exposure to chlorpyrifos can lead to convulsions, loss of bladder and bowel control, coma, difficulty breathing, pulmonary edema, muscle paralysis, and death from respiratory failure. Because AChE inhibition is the initiating event for this MOA/AOP, using AChE inhibition as a regulatory endpoint is protective of downstream cholinergic effects. Moreover, given the sensitivity of AChE inhibition data for OPs, using AChE inhibition to establish a regulatory point of departure has historically been considered to be protective of other potential toxicities. EPA uses a value of 10% AChE inhibition as a point of departure in its regulation of AChE inhibiting pesticides, including chlorpyrifos. EPA's analyses have demonstrated that 10% is a level that can be reliably measured in the majority of animal toxicity studies; is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity across the brain compartment; and is a response

level close to the background AChE level.

Newer lines of research on chlorpyrifos, notably epidemiological studies, have raised some uncertainty about EPA's historical risk assessment approach for chlorpyrifos with regard to the potential for neurodevelopmental effects that may arise from prenatal exposure to chlorpyrifos. This research is summarized in Unit VI.A.6.iii.

2. Summary of data evaluated for deriving PoDs. Chlorpyrifos and its oxon are widely studied and thus have an extensive database of scientific studies. Included in the database are: Studies developed by registrants pursuant to EPA guidelines, special studies conducted by the registrants, and studies in the public literature. These studies reflect different levels of biological organization (*e.g.,* metabolism, MOA/AOP, *in vitro* and *in vivo* experimental toxicology, biomonitoring, and epidemiology), various species (mouse, rabbit, dog, non-rodent, and human) and address multiple lifestages (fetal, postnatal, pregnant, and non-pregnant adult). The metabolism and pharmacokinetic (PK) profile of chlorpyrifos and its oxon have been extensively studied in *in vitro* systems, *in vivo* laboratory animals, as well as humans. Chlorpyrifos is bioactivated to the more toxic and potent AChE inhibitor, the oxon form. 3,5,6-trichloro-2-pyridinol (TCPy) is the major excreted metabolite and is used as the biomarker in PK, biomonitoring, and epidemiology studies. Diethylphosphate (DEP) is another metabolite often used in biomonitoring studies, but since it is produced by a number of OPs, DEP is not a specific marker for chlorpyrifos.

Summarized below are key findings from experimental toxicology studies on AChE inhibition as presented in detail in the June 2011 PHHRA and the December 2014 RHHRA. Readers should refer to those documents (Refs. 3 and 1) and their appendices in the public docket for this proposed rule for a complete summary of EPA's data review. Chlorpyrifos has also been evaluated for other adverse outcomes such as reproductive toxicity, developmental toxicity, cancer, genotoxicity, dermal toxicity, inhalation toxicity, and immunotoxicity. These adverse outcomes are less sensitive (*i.e.,* are likely to occur at higher doses) than AChE inhibition and neurodevelopmental effects, which form the scientific foundation of this proposed rule, and are thus not discussed in detail here. Concerns for neurodevelopmental effects provide the basis for retention of the FQPA safety factor and are summarized in Unit VI.A.6.

AChE inhibition remains the most robust quantitative dose response data for chlorpyrifos and thus continues to be the critical effect for the quantitative risk assessment. This approach is consistent with the advice EPA received from the FIFRA SAP in both 2008 and 2012 (Refs. 9 and 10) when EPA sought input specifically on the agency's approach to evaluating the toxicity of chlorpyrifos. EPA has conducted benchmark dose (BMD) analysis of numerous studies using empirical approaches previously endorsed by the FIFRA SAP (Ref. 11) and consistent with the 2006 OP cumulative risk assessment (Ref. 12) and other single chemical OP risk assessments. Details on AChE studies and related analyses can be found in Appendix 1 of the PHHRA (Ref. 3).

There are many chlorpyrifos studies evaluating AChE inhibition in red blood cell (RBC) or brain in multiple lifestages (gestational, fetal, post-natal, and non-pregnant adult), multiple species (rat, mouse, rabbit, dog, human), methods of oral administration (oral gavage with corn oil, dietary, gavage via milk), and routes of exposure (oral, dermal, inhalation via vapor, and via aerosol). In addition, chlorpyrifos is unique in the availability of ChE data from peripheral tissues in some studies (*e.g.,* heart, lung, liver). There are also literature studies comparing the *in vitro* ChE response to a variety of tissues (Ref. 13) which show similar sensitivity and intrinsic activity. Across the database, brain AChE tends to be less sensitive than RBC AChE or peripheral ChE. In oral studies, RBC AChE inhibition is generally similar in response to peripheral tissues (*e.g.,* liver, heart, and lung). Thus, the *in vitro* data and oral studies combined support the continued use of RBC AChE inhibition as the critical effect for quantitative dose-response assessment.

As with many OPs, female rats tend to be more sensitive than males to these AChE effects. For chlorpyrifos, there are data from multiple studies which provide robust RBC AChE data in pregnant, lactating, and non-pregnant female rats from oral exposure (*e.g.,* DNT, reproductive, and subchronic rats), respectively. The BMD_{10}/$BMDL_{10}$ values from these studies range from 0.05/0.04 to 0.15/0.09 mg/kg/day. (BMD_{10} is the estimated dose to yield 10% inhibition in RBC AChE inhibition compared to controls or background levels. The $BMDL_{10}$ is the lower 95% confidence limit on the BMD_{10}). Studies are available in juvenile pups which show age-dependent differences, particularly following acute exposures, in sensitivity to chlorpyrifos and its oxon. As discussed above, this sensitivity is not derived from differences in the AChE enzyme itself but instead is derived largely from the immature metabolic clearance capacity in the juveniles.

Multiple route-specific laboratory animal studies for the dermal and inhalation routes are available. Dermal AChE data are available from a 21-day study and 4-day probe study (Ref. 14) in rats which together establish a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg/day and a Lowest Observed Adverse Effect Level (LOAEL) of 10 mg/kg/day. Two subchronic inhalation toxicity studies (Refs. 15, 16, and 17) in the rat are available using vapor phase chlorpyrifos which show no ChE effects up to a concentration of 20.6 ppb (287 $\mu g/m^3$ or 0.082 mg/kg/day). Multiple acute inhalation studies are also available. In a special acute inhalation study, female rats were exposed by nose only (mass median aerodynamic diameter/geometric standard deviation was 1.9/1.51, respectively) to atmospheric concentrations of up to 53.9 mg/m^3 of particulate chlorpyrifos for six hours and allowed an additional 72 hours to recover (Refs. 18 and 19). Consistent and significant lung ChE inhibition were noted at the lowest concentration tested of 3.7 mg/m^3, which is a LOAEL. RBC and brain ChE inhibition were noted at $\geq$ 12.9 mg/m^3 and 53.9 mg/m^3, respectively, indicating they are less sensitive than lung and plasma ChE inhibition following acute inhalation exposures.

Since the 2011 PHHRA, two acute inhalation studies on the saturated vapor have been performed on the parent chlorpyrifos and chlorpyrifos oxon (Refs. 20 and 21). In these studies, female rats were exposed by nose only to a saturated vapor of chlorpyrifos or its oxon for 6 hours to a time-weighted concentration of 17.7 ppb (0.254 mg/m^3) (Ref. 20) or 2.58 ppb (35.3 $\mu g/m^3$) (Ref. 21), respectively. There were no statistically-significant decreases in ChE activity in the RBC, lung, brain, or plasma tissues. These acute studies along with the subchronic inhalation studies with vapor phase chlorpyrifos support a conclusion that acute exposure to the saturated vapor of chlorpyrifos or its oxon do not result in hazard due to AChE inhibition.

3. Durations of Exposure, Critical Windows of Exposure, & Temporality of Effects Relevant for AChE Inhibition. In risk assessment, exposure is evaluated in conjunction with the toxicology profile. More specifically, a variety of pharmacokinetic and pharmacodynamic factors are considered. In the case of

chlorpyrifos, exposure can occur from a single exposure (*e.g.,* eating a meal) or from repeated days of exposure (*e.g.,* worker, residential).

With respect to AChE inhibition, these effects can occur from a single exposure or from repeated exposures. Generally, for OPs, repeated exposures result in more AChE inhibition at a given administered dose compared to acute studies. Moreover, AChE inhibition in repeated dosing guideline toxicology studies with OPs show a consistent pattern of inhibition reaching steady state at or around 2–3 weeks of exposure in adult laboratory animals (Ref. 22). This pattern is observed with repeated dosing and is a result of an equilibrium between the amount of AChE inhibition and the production of new enzyme. As such, AChE studies of 2–3 weeks generally show the same degree of inhibition with those of longer duration (*i.e.,* up to 2 years of exposure). Thus, for most of the single chemical human health risk assessments for the OPs, EPA is focusing on the critical duration range from a single day up to 21 days (*i.e.,* the approximate time to reach steady state for most OPs). As described below, PoDs for various lifestages, routes, and scenarios have been derived at the acute and steady state durations. For this proposed rule, PoDs for various lifestages, routes, and scenarios have been derived at the acute and steady state durations.

4. Use of the Chlorpyrifos PBPK±PD Model to Establish PoDs. As described in detail in EPA's 2006 document entitled, ''Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment,'' (Ref. 23) PBPK modelling is a scientifically sound and robust approach to estimating the internal dose of a chemical at a target site and as a means to evaluate and describe the uncertainty in risk assessments. PBPK models consist of a series of mathematical representations of biological tissues and physiological processes in the body that simulate the absorption, distribution, metabolism, and excretion (ADME) of chemicals that enter the body. Examples of PBPK model applications in risk assessments include interspecies extrapolation, intra-species extrapolation, route-to-route extrapolation, estimation of response from varying exposure conditions, and high-to-low dose extrapolation. PBPK models can be used in conjunction with an exposure assessment to improve the quantitative characterization of the dose-response relationship and the overall risk assessment. These models can also be used to evaluate the relationship between an applied dose and biomonitoring data.

For a full discussion of the development and evaluation of the chlorpyrifos PBPK–PD model, please refer to the December 2014 RHHRA (Ref. 1) in the public docket for this rule.

As discussed above, in typical risk assessments, PoDs are derived directly from laboratory animal studies and inter- and intra-species extrapolation is accomplished by use of ''default''10X factors. In the case of chlorpyrifos and its oxon, EPA is using a PBPK–PD model as a data-derived approach to estimate PoDs. This model was originally developed by Timchalk and coworkers in 2002 (Refs. 24 and 25), partially funded by EPA Star Grants, and most recently supported by Dow AgroSciences. The PBPK–PD model for chlorpyrifos has been heavily peer reviewed through numerous scientific publications and a review by the FIFRA SAP (Ref. 26). All model code for the PBPK–PD model are provided in the public docket for the chlorpyrifos risk assessment. Developers of the chlorpyrifos PBPK–PD model sponsored a third-party quality assurance assessment to verify model parameter values and their respective sources. EPA has also done a quality assurance assessment of the model for human health risk assessment applications. (Ref. 27).

The chlorpyrifos PBPK–PD model includes the description of a molecular initiating event in the cholinergic toxicity MOA/AOP: AChE inhibition. Thus, the PBPK–PD model can be used to predict the dose metrics associated with cholinergic toxicity following chlorpyrifos exposure, *i.e.,* RBC and brain AChE inhibition. The model also predicts levels of chlorpyrifos, its oxon, and TCPy in various tissues, such as plasma and urine. Age-specific parameters are incorporated allowing for lifestage-specific evaluations from infant through adulthood. The model can be run in two modes: deterministic and variation. In the deterministic mode, the output accounts for human specific metabolism and physiology, thus obviating the need for the inter-species extrapolation factor for all age groups. In variation mode, distributions for 16 parameters, which are critical for determining human variations in RBC AChE inhibition, are incorporated and thus the output accounts for intra-species extrapolation for infants, toddler, youths, and non-pregnant adults. The approach to intra-species extrapolation is described in Unit VI.A.5.

With respect to AChE inhibition, as noted, EPA typically uses a 10% response level in its human health risk assessments. This response level is consistent with EPA's 2006 OP cumulative risk assessment (Ref. 12) and other single chemical OP risk assessments. As such, EPA has used the PBPK–PD model to estimate exposure levels resulting in 10% RBC AChE inhibition following single day (acute; 24 hours) and 21-day exposures for a variety of exposure scenarios. The model accounts for PK and PD characteristics to derive age, duration, and route specific PoDs (see Table 1 below). Separate PoDs have been calculated for dietary (food, drinking water) and residential exposures by varying inputs on types of exposures and populations exposed. Specifically, the following characteristics have been evaluated: Duration (acute, 21-day (steady state)); route (dermal, oral, inhalation); body weights which vary by lifestage; exposure duration (hours per day, days per week); and exposure frequency (events per day (eating, drinking)).

For each exposure scenario, the appropriate body weight for each age group or sex was modeled as identified from the Exposure Factors Handbook (Ref. 28) for residential exposures and from the NHANES/WWEIA Survey (Ref. 29) for dietary exposures.

EPA evaluated the following scenarios: dietary exposure to the oxon exposures via drinking water (24-hour and 21-day exposures for infants, children, youths, and female adults); exposure to chlorpyrifos exposures via food (24-hour and 21-day exposures for infants, children, youths, and female adults); 21-day residential exposures to chlorpyrifos via skin for children, youths, and female adults; 21-day residential exposures to chlorpyrifos via hand-to-mouth ingestion for children 1–2 years old; and 21-day residential exposures to chlorpyrifos via inhalation for children 1–2 years old and female adults.

For all residential dermal exposures to chlorpyrifos, EPA set the fraction of skin in contact with chlorpyrifos to 50% and assumed a daily shower (*i.e.,* washing off the chlorpyrifos) following chlorpyrifos exposure. All residential exposures were set to be continuous for 21 days. For residential exposures via golfing on treated turf, the daily exposure time is assumed to be 4 hours/day; for residential exposures via contact with turf following public health mosquitocide application, the daily exposure duration is assumed to be 1.5 hours. For residential inhalation exposures following public health

mosquitocide application, the exposure duration was set to 1 hour per day for 21 days. The exposure times selected are based on those recommended in the 2012 *Standard Operating Procedures for Residential Pesticide Exposure Assessment* (2012 Residential SOPs). (Ref. 30).

Summarized in Table 1 are the PBPK–PD model results used to estimate exposure levels resulting in 10% RBC AChE inhibition for each evaluated population.

TABLE 1—CHLORPYRIFOS PBPK MODELED DOSES (PODS) CORRESPONDING TO 10% RBC ACHE INHIBITION [1]

RA Type	Exposure pathway (all chlorpyrifos unless noted)	Infants (< 1 yr old)		Young Children (1–2 years old)		Children (Residential: 6–11 years old; Dietary: 6–12 years old)		Youths (Residential: 11–16 years old; Dietary: 13–19 years old)		Females (13–49 years old)	
		Acute	Steady state (21 day)	Acute	Steady state (21 day)	Acute	Steady state (21 day)	Acute	Steady state (21 day)	Acute	Steady state (21 day)
Dietary	Drinking Water (oxon conc, ppb).	1,183	217	3,004	548	7,700	1,358	4,988	878	5,285	932
	Food (ug/kg/day)	600	103	581	99	530	90	475	80	467	78
Residential (Golfers).	Dermal (ug/kg/day)						25,150		16,370		14,250
Residential (Mosquitocide Application).	Dermal (ug/kg/day)				187,000						38,650
	Oral (ug/kg/day)				101						
	Inhalation (concn. in air mg/m3).				2.37						6.15

[1] Empty cells are not populated because these exposure scenarios are either not relevant for the age group (*e.g.,* infants or 1–2 year olds golfing), or do not represent the most health protective life stage for assessment of a particular exposure scenario as recommended in the 2012 SOPs (*e.g.,* for mosquitocide exposure assessment, children 1 to < 2 years old result in a more protective assessment than infants).

5. Use of the Chlorpyrifos PBPK±PD Model to Extrapolate from Animals to Humans (Inter-species) and Among the Human Population (Intra-species). Once EPA determines the appropriate toxicological PoDs (Table 1), it then applies appropriate uncertainty factors or DDEFs to account for inter-species and intra-species variation, and to address the requirements of section 408(b)(2)(C) regarding the need for an additional margin of safety for infants and children. Specifically, the modeled doses (PoDs) in this table are divided by appropriate factors to establish PADs that are used for regulatory purposes. The PADs are presented in Unit VI.B.2.ii and iii, Tables 2 and 3.

In a typical risk assessment, the agency uses PoDs derived from laboratory animal studies. For these typical assessments, the agency must then extrapolate from animals to humans which is generally performed with a 10X inter-species factor. As noted above in Unit V.A., the output of the chlorpyrifos PBPK–PD model accounts for human specific metabolism and physiology, thus obviating the need for the inter-species extrapolation factor for all age groups.

EPA has, however, calculated a DDEF to address intra-species variation not accounted for in the output of the PBPK–PD model. Consistent with EPA's ''Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation'' (Ref. 31), when calculating a DDEF, EPA compares the administered doses leading to the response level of interest (10% change in RBC AChE inhibition) between a measure of average response and response at the tail of the distribution representing sensitive individuals. Dow AgroSciences has conducted an analysis to derive the oral doses that cause 10% RBC AChE inhibition in both adults and 6-month old infants. (Ref. 1 at 69–70). The ratio of the adult ED_{10} (effective dose) to the infant ED_{10} was then used to derive intraspecies extrapolation factors. In the subsequent Monte Carlo simulations, the target age group is six month old individuals. Based on the 1st percentile of the distributions being used to extrapolate human health, the DDEF for intraspecies extrapolation is 4X for chlorpyrifos and 5X for the oxon (Ref. 32) for all groups except women who are pregnant or may become pregnant.

While the current PBPK–PD model accounts for age-related growth from infancy to adulthood by using polynomial equations to describe tissue volumes and blood flows as a function of age, the model does not include any descriptions on physiological, anatomical and biochemical changes associated with pregnancy. Due to the uncertainty in extrapolating the current model predictions among women who may be pregnant, EPA is applying the standard 10X intra-species extrapolation factor for women of child bearing age.

6. Retention of the statutory 10X FQPA Safety Factor for purposes of this proposed rule for infants, children, youths, and women of childbearing age for all exposure scenarios. Section 408 of FFDCA provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base on toxicity and exposure unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses acceptable risk to humans.

In applying the FQPA safety factor provision, EPA has interpreted the statutory language as imposing a presumption in favor of applying an additional 10X safety factor (Ref. 33). Thus, EPA generally refers to the additional 10X factor as a presumptive or default 10X factor. EPA has also made clear, however, that the presumption can be overcome if reliable data demonstrate that a different factor is safe for infants and children. (Ref. 33). In determining whether a different factor is safe for infants and children, EPA focuses on the three factors listed in section 408(b)(2)(C)—the completeness of the toxicity database, the completeness of the exposure database, and potential pre- and post-natal toxicity.

In examining these factors, EPA strives to make sure that its choice of a safety factor, based on its weight-of-evidence evaluation, does not understate the risk to infants and

children. New lines of research on chlorpyrifos, notably epidemiological studies, have raised some uncertainty about EPA's risk assessment approach for chlorpyrifos with regard to the potential for neurodevelopmental effects that may arise from prenatal exposure to chlorpyrifos. Over the last several years, the agency has taken a stepwise, objective and transparent approach to evaluate, interpret, and characterize the strengths and uncertainties associated with all the lines of scientific information related to the potential for adverse neurodevelopmental effects in infants and children as a result of prenatal exposure to chlorpyrifos. The agency has evaluated multiple lines of evidence with regard to the potential for neurodevelopmental outcomes associated with exposure to chlorpyrifos. These are summarized below; full details of this analysis can be found in the RHHRA. Given the degree of uncertainty EPA has in the human dose-response relationship for neurodevelopmental effects, EPA is retaining the statutory 10X FQPA Safety Factor for purposes of this proposed rule for infants, children (including youths), and women of childbearing age (to address prenatal exposure to the fetus) for all exposure scenarios.

i. Neurodevelopmental outcomes in laboratory animals. There is a considerable and still-growing body of literature on the effects of chlorpyrifos on the developing brain of laboratory animals (rats and mice) indicating that gestational and/or postnatal exposure may cause persistent behavioral effects into adulthood. These data provide support for the susceptibility of the developing mammalian brain to chlorpyrifos exposure. Literature searches have been conducted and periodically updated by EPA to review papers addressing long-term outcomes from developmental exposure. This review has focused on studies in which chlorpyrifos was administered during gestation and/or the pre-weaning period and the offspring are examined at some time after weaning, and on studies using relatively low doses (*e.g.,* 1 mg/kg/day) that would not be expected to produce considerable brain AChE inhibition and resultant cholinergic toxicity.

There are substantial differences in the studies, including critical features of experimental design such as developmental period of exposure, dosing scenarios, testing methods, age at testing, and statistical analyses. Despite these differences, behavioral changes of some sort were reported in most studies. Given the wide array of testing that has been conducted, some variability is not unexpected and in fact, the consistency of finding neurological effects is striking. After presentation of these reviews, FIFRA SAP Panels (Refs. 9 and 10) have agreed that exposure to doses of 1 mg/kg/d and greater, during some developmental period, produce significant and long-term effects on animal behavior.

Many of these studies using various cognitive tests report perturbations of learning and/or memory, even though in a few cases these may be manifested as improved function. Several findings using specific test methods have been replicated across studies and laboratories, increasing confidence in the outcomes. Likewise, alterations in some domains, such as those describing anxiety and social interactions, are not fully consistent, but are still suggestive of long-term impacts on these behaviors. Motor activity measures, on the other hand, produce results as varied as the different measures of assessment. Taken together, these data provide evidence for more global alterations in neurobehavioral function rather than a specific profile of effects.

In these papers, testing was conducted at various times after weaning (adolescents to adults), and there is a presumption that the effects are permanent; however, no study has directly addressed this issue. Dose-response is not always evident, since many studies only use one dose, and of those using two or more doses, there is not always a monotonic response. There are differences in route of administration (oral, subcutaneous) and vehicle (corn oil, DMSO), but the outcomes do not provide obvious differences due to these factors. Likewise, the experimental literature has not consistently shown that any specific developmental period is critical overall to the long-term outcomes. For example, using one specific test cognitive changes were observed following gestational and early postnatal, but not late postnatal, exposures (Refs. 34, 35, 36, and 37). On the other hand, deficits have been reported using a different cognitive test following both gestational and late postnatal exposures (Refs. 38, 39, and 40). Similarly, some changes in anxiety and social behaviors were reported at both gestational and postnatal exposure periods. Unfortunately, no laboratory has provided systematic comparisons across exposure period, dosing regimen, and age of testing; such studies would improve understanding of the impact of these critical factors.

These studies have almost exclusively focused on doses that could produce some degree, however minimal, of AChE inhibition. For example, a number of papers use a dose of 1 mg/kg/d administered 1–4 days after birth, and this dose inhibits 5–10% of brain AChE in the pups when measured 2 hours after the last dose (*e.g.,* Refs. 34, 37, and 41). In another study of chlorpyrifos administered in feed to pregnant rats, the lowest intake of 0.36 mg/kg/d produced about 20–25% RBC ChE inhibition in the dams (Ref. 42). Currently there are no animal studies that support or dispute the potential for adverse neurodevelopmental outcomes at lower doses that do not inhibit AChE at any time, since this has not been adequately studied.

Overall, across the literature on neurodevelopmental outcomes and including most recent publications, there continue to be reports of effects on cognitive, anxiety/social behaviors, and motor activity. There are, however, inconsistencies in these effects with regards to dosing paradigms and gender-specificity. Studies report effects at doses that inhibit fetal/pup brain AChE activity to some degree, but there are also studies with no effects at the same doses. The broad profile of neurological effects that has been reported do not aid in the development of a specific AOP (AChE inhibition or other mechanisms), and existing experimental studies have not been designed to examine and track possible mechanisms from early initiating events to the final neurological outcome.

ii. Modes of action/adverse outcome pathways (MOA/AOP). Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events. A review of the scientific literature on potential MOA/AOP leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (Ref. 10) and updated for the December 2014 chlorpyrifos RHHRA (Ref. 1). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers including: AChE as a morphogen; cholinergic system; endocannabinoid system; reactive oxygen species; serotonergic system; tubulin, microtubule associated proteins, and axonal transport. However, no one pathway has sufficient data to be considered more plausible than the others. Among the available studies, there are effects which are either as or more sensitive than AChE inhibition. The fact that there are, however, sparse data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative

use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. The lack of an established MOA/AOP makes quantitative use of the epidemiology study in risk assessment challenging, particularly with respect to dose-response, critical duration of exposure, and window(s) of susceptibility. The agency will continue to monitor the scientific literature for studies on the MOA/AOP for neurodevelopmental effects.

iii. Epidemiology studies in mothers and children. In the chlorpyrifos RHHRA, EPA included epidemiologic research results from three prospective birth cohort studies. These include: (1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; (2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the ''Mt. Sinai Child Growth and Development Study'' (Mt. Sinai); and (3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. In these epidemiology studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Importantly, each of these cohorts evaluated the association between prenatal chlorpyrifos or OP exposure with adverse neurodevelopmental outcomes in children through age 7 years.

These studies reflect different types of exposed groups in the total population which strengthens the weight of the evidence considerations regarding this stream of information. The CCCEH Mother's and Newborn study and the Mt. Sinai Child Growth and Development study participants were likely exposed to OPs through the diet and through residential use of the pesticide for indoor pest control. In the residential setting, study populations were most likely exposed through indoor residential use of the pesticide during the study time period and additionally exposed to OPs via the oral route through ingesting residues in the diet and from hand-to-mouth contact with in-home surfaces, as well as possible dermal or inhalation exposure through contact with treated areas in the home environment (Refs. 43, 44, 45, and 46). In contrast, CHAMACOS cohort participants were employed as farm laborers or were residing in homes with farm laborers. The CHAMACOS study participants likely experienced exposure to OPs through the diet and from occupational exposure (primarily inhalation and dermal routes), as well as probable indirect take-home exposures (the ''tracking in'' of pesticide residues through shoes and clothing, augmented by poor hygiene practices) (Ref. 47). In each of the three U.S. children's health cohorts, 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* OP exposure and adverse neurodevelopmental effects observed at birth and through childhood (age 7 years). EPA believes these are strong studies which support a conclusion that OPs likely played a role in these outcomes.

These cohort studies each enrolled pregnant women during roughly the same time period, measured both environmental exposure to the pesticide during pregnancy and also measured biomarkers representing internal dose during pregnancy and at delivery, and prospectively assessed associations in their newborns and young children through age 7 years. Each study includes several hundred (approximately 100–400) mother-infant pairs; these sample sizes are sufficient to perform statistically valid analyses. Investigators from each study cohort utilized a similarly strong study design (prospective birth cohort); measured pesticide exposure using several different methods including environmental indicators as well as specific and non-specific biomarkers of OPs; ascertained developmental outcomes using validated assessment tools well-established in both clinical and research settings; and, measured, analyzed, selected and statistically adjusted for potentially confounding variables including socio-economic status and other environmental exposures using reasonable and appropriate methods. Limitations exist as well. These studies utilized a one-time measure (or the average of two measures) of chlorpyrifos or OP exposure to assess prenatal pesticide exposure throughout the gestational period, were unable to assess the influence of mixtures (co-occurring exposures in the relevant biological time window), and reflect a small sample size to fully evaluate the effect of more than one simultaneous exposure on neurodevelopment, *i.e.,* evidence of effect modification.

As noted, two major uncertainties in environmental epidemiology studies are the accurate and reliable measurement of exposure and potential confounding variables such as the influence of mixtures. The researchers with each of the three cohorts have provided supplemental methodological research to address these areas to the extent possible. Across the three children's health cohorts, study authors measured biomarkers of OP exposure. There is uncertainty as to the extent measurement of non-specific metabolites of OP or chlorpyrifos accurately reflects OP exposure; CCCEH and Mt. Sinai studies do not estimate post-natal exposure to chlorpyrifos among child participants, therefore the influence of early life and childhood OP exposure is unaccounted for in these analyses. The CHAMACOS cohort measured urinary levels of dialkyl phosphates (DAPs) in young children and did not observe negative significant associations in relation to neurodevelopment from post-natal exposure (Ref. 48). The CHAMACOS cohort investigators also measured AChE and butyl ChE as supplemental indicators of OP exposure.

Potential confounding bias is another major uncertainty within environmental epidemiology studies. Confounding variables, exposures that could be related to OP exposure and neurodevelopmental outcomes such as blood lead, may result in an incorrect epidemiological risk estimate. Across these cohort studies, investigators collected relevant information concerning demographic characteristics and other environmental exposures, and were, to the extent possible with the existing information, able to effectively hold constant the influence of these other variables when estimating the association between prenatal chlorpyrifos and adverse neurodevelopmental outcomes. Control of these variables is important to reduce the chances of a false positive study result. Overall, statistical analyses were judged to be appropriate and reasonable (not overly large number of statistical model variables) to the research question by EPA and expert Panel reviews (Refs. 9 and 10).

Researchers with both the Mt. Sinai and CHAMACOS cohorts evaluated neonatal neurological functioning in association with prenatal OP exposure; CCCEH did not conduct these measurements. To measure indices of abnormal neonatal behavior and/or neurological integrity, the Mt. Sinai and CHAMACOS authors used outcome measures derived from the Brazelton Neonatal Behavioral Assessment Scale

(BNBAS), a neurological assessment of 28 behavioral items and 18 primitive reflexes. This tool was administered to infants 2–5 days post-partum by trained neonatologists in the hospital setting using similar environmental conditions. The authors with both study groups observed an increased number of abnormal reflexes in relation to increasing measures of OP exposure (Refs. 49 and 50). Among the other 27 measures in the BNBAS, neither study group reported evidence of any other positive associations. The authors also observed evidence of potential effect modification by PON1 activity level in the relation between DAPs and neonatal neurodevelopment in which infants of mothers who are slower metabolizers have greater risk of abnormal reflexes (Refs. 49 and 50). However, EPA notes these studies are likely under-powered to make a statistically robust estimate of this statistical interaction.

Researchers across the three children's health cohorts utilized the Bayley Scales of Infant Development II (BSID–II) to generate a Mental Development Index (MDI) and a Psychomotor Development Index (PDI) to assess neurodevelopment in early childhood. In the CCCEH Mothers and Newborn study, Rauh *et al.* (Ref. 51) investigated MDI and PDI at 12, 24, and 36 months of age. Children were categorized as having either high (>6.17 pg/g) or low (≤6.17 pg/g) prenatal chlorpyrifos exposure, using categories informed by results of the previous study on birth characteristics (Ref. 52). Authors reported that the difference in MDI scores was ''marginally significant'' (p = 0.06) between the ''high'' and ''low'' exposed groups; the high exposed group scoring an average of 3.3 points lower than the low exposed (Ref. 51). Regarding the PDI score (motor skills), none of the 12 or 24 month PDI scores showed significant effects, but the 36 month score was significantly related to chlorpyrifos exposure. Researchers noted that the effects were most pronounced at the 36 month testing period. Within the 36 month testing period, the likelihood of highly exposed children developing mental delays were significantly greater (MDI: 2.4 times greater (95% CI: 1.12–5.08, p = 0.02) and PDI: 4.9 times greater (95% CI: 1.78–13.72; p = 0.002)) than those with lower prenatal exposure (Id.). Within the Mt. Sinai study, authors administered the BSID–II to participating children at 12 and 24 months and observed that prenatal total DAP metabolite level was associated with a decrement in mental development at 12 months among blacks and Hispanic children; however, these associations either attenuated or were non-existent at the 24-month visit (Ref. 52). In the CHAMACOS cohort, Eskenazi *et al.* (Ref. 53) observed that prenatal DAP levels were adversely associated with MDI, and at 24 months of age these associations reached statistical significance. In this study, neither prenatal DAPs nor maternal TCPy were associated with PDI (motor skills), nor did authors observe evidence of different risk by PON1 status. (Ref. 54).

With respect to the findings related to the autism spectrum, from CCCEH, Rauh *et al.* (Ref. 51) reported a statistically significant odds ratio for pervasive developmental disorder (PDD) (OR = 5.39; 95% CI: 1.21–24.11) when comparing high to low chlorpyrifos exposure groups. As described above, among 7–9 years old children in the Mt. Sinai Cohort (Ref. 55), there was no overall statistically significant association between maternal third trimester urinary DAP metabolite levels and reciprocal social responsiveness. However, some evidence of modification of the association between prenatal OP pesticide exposure and impaired social responsiveness in early childhood was observed by both race/ethnicity and child sex, with an association between diethyl alkylphosphate (DEAP) and poorer social responsiveness observed among black participants and boys. No association was observed among whites or Hispanics, among girls, or for DAP or dimethyl alkylphosphate (DMAP) biomarker levels. In the CHAMACOS cohort, Eskenazi *et al.* (Ref. 54) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p = 0.14), whereas Eskenazi *et al.* (Ref. 53) reported a statistically significant association between total DAP exposure and increased odds of PDD.

With respect to attention problems, Rauh *et al.* (Ref. 50) also investigated 36-month child behavior checklist (CBCL) (behavioral) scores. Significant differences were observed between the high and low chlorpyrifos exposure groups in the general category of attention-problems (p = 0.010), and in the more specific DSM–IV (Diagnostic and Statistical Manual of Mental Disorders version IV) scale for ADHD problems (p = 0.018). The CHAMACOS cohort also investigated attention problems in early childhood using three different assessment tools: maternal report of child behavior at 3.5 and 5 years of age; direct assessment of the child at 3.5 and 5 years; and by a psychometrician's report of the behavior of the child during testing at 5 years. In this study population, higher concentrations of OP metabolites in the urine of pregnant women were associated with increased odds of attention problems and poorer attention scores in their children at age 5 years. (Ref. 53).

To measure intelligence among school aged children, authors from each of the three children's health cohorts used the Wechsler Intelligence Scale for Children, 4th edition (WISC–IV). The instrument measures four areas of mental functioning: The Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index. A Full-Scale IQ score combines the four composite indices. WISC–IV scores are standardized against U.S. population-based norms for English and Spanish-speaking children. In the CCCEH Mothers and Newborn Study, Rauh *et al.* (Ref. 56) evaluated the relationship between prenatal chlorpyrifos exposure and neurodevelopment among 265 of the cohort participants who had reached the age of 7 years and had a complete set of data including prenatal maternal interview data, prenatal chlorpyrifos marker levels from maternal and/or cord blood samples at delivery, postnatal covariates, and neurodevelopmental outcome data (Ref. 56). While models were developed using continuous measures of both prenatal chlorpyrifos exposure and Wechsler scores, for ease of interpretation, investigators reported that for each standard deviation increase in exposure (4.61 pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory. In the Mt. Sinai study, prenatal maternal DEP urinary metabolite concentrations were associated with slight decrements in Full Scale Intelligence Quotient (FSIQ), Perceptual Reasoning, and Working Memory between the ages of 6 and 9 years, and difference in intelligence measures by putative PON1 status were also noted. (Ref. 52). Similarly, in the CHAMACOS cohort, Bouchard *et al.* (Ref. 57) observed evidence of an association between prenatal exposures to OPs as measured by urinary DAP (total DAP, DEP, and DMP) metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7. In this study, children in the highest quintile of maternal DAP concentrations had a statistically significant 7 point difference in IQ points compared with those in the lowest quintile.

To ascertain whether observed differences in neurodevelopment after prenatal chlorpyrifos exposure may be explained by differences in brain morphology between exposed groups,

the CCCEH study investigators compared MRI brain images between high and low chlorpyrifos exposed child study participants. (Ref. 58). Authors determined there were distinct morphological differences in brain areas associated with these neurodevelopmental outcomes. The pilot study included 40 child participants due to strict inclusion and exclusion criteria, and the high cost of performing the imaging studies on each child. EPA convened a Federal Panel of experts to perform a written peer-review of this study. (Ref. 59). The Federal Panel concurred with the authors' conclusions in general; however the Federal Panel also noted that significantly greater and more sophisticated MRI imaging studies would be needed to link the morphological changes indicated in this study with specific functional outcomes noted in the CCCEH IQ study. Therefore, while generally supportive of the epidemiologic findings, additional study is needed to make specific links with areas of brain development change.

In sum, across these three children's environmental health studies, authors consistently identified associations with neurodevelopmental outcomes in relation to OP exposure. There is evidence of delays in mental development in infants (24–36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to chlorpyrifos or OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2–4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.,* intelligence measures.

7. *Weight-of-Evidence Analysis Across Multiple Lines of Evidence.* The discussion above summarized key scientific information on two different adverse health outcomes: AChE inhibition and potential neurodevelopmental effects. The agency has conducted a weight-of-evidence (WOE) analysis utilizing the draft ''Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment'' in an effort to integrate this information in the development of an appropriate PoD for chlorpyrifos. That assessment focuses on two key scientific questions: (1) The degree to which scientific data suggest that chlorpyrifos causes long-term neurodevelopmental effects from fetal or early life exposure and (2) the degree to which adverse effects can be attributed to doses lower than those which elicit 10% inhibition of AChE, *i.e.,* the dose levels previously used for regulatory decision making.

i. *Dose-response relationships and temporal concordance.* Since the MOA(s)/AOP(s) is/are not established for neurodevelopmental outcomes, it is not possible to describe the concordance in key events or biological steps leading to neurodevelopmental outcomes. As such, the quantitative linkages between molecular initiating events, intermediate steps, and ultimately the adverse outcome (*i.e.,* neurodevelopmental effects) cannot be determined. Experimental toxicology studies in rodents suggest that long-term effects from chlorpyrifos exposure may occur. Due to the dose selections in most of these *in vivo* studies evaluating effects such as behavior and cognition, it is not known whether such adverse effects would be shown at doses lower than those which elicit 10% RBC AChE inhibition. It is notable, however, that comparing the lowest NOAEL observed in the *in vivo* animal studies (0.2 mg/kg/day; Ref. 60) for the neurodevelopmental outcomes to the repeated dosing reliable $BMDL_{10}$ ranging from 0.05–0.17 mg/kg/day for RBC AChE inhibition suggests that neurodevelopmental outcomes may occur in the same range as AChE inhibition in rat.

Within the epidemiology studies, the relationship in time between prenatal chlorpyrifos exposure and adverse neurodevelopmental outcomes is concordant. Specifically, with regard to the children's environmental health epidemiology studies, each of the three study cohorts utilized a prospective birth cohort study design in which mothers were recruited into study prior to the birth of the infants and development and identification of adverse effects; therefore, it is known with certainty that exposure preceded effect. In addition, because the time period under study within these cohorts, and specifically the CCCEH study, spanned the point in time in which pesticide manufacturers voluntarily cancelled the use of chlorpyrifos in the home environment, researchers were able to show the change in exposure before (high use period) and after (low/no use period) the period of removal of chlorpyrifos products from the residential marketplace. Moreover, prior to the voluntary cancellation there were >80% detectable levels of chlorpyrifos in cord blood but in the time period after the cancellation only 16% of the measured values were greater than the LOD; there was only one child born in the time period subsequent to the voluntary cancellation of chlorpyrifos in the residential marketplace for whom the cord blood chlorpyrifos level was in the upper-tertile of pre-cancellation exposure levels. The significantly reduced proportion of measured values greater than the limit of detection as well as the observation of an absence of an association between prenatal chlorpyrifos exposure and neurodevelopmental outcomes among infants born after the voluntary cancellation of chlorpyrifos support the hypothesis that chlorpyrifos is related to these outcomes. However, as noted by study authors, EPA, and the FIFRA SAP (Ref. 10), this could also be due to an inadequate sample size to detect a small to modest effect among the group of infants born after the voluntary cancellation.

With respect to the timing of exposure, the cord blood and other (meconium) measures from the CCCEH study provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the three children's health cohorts, particularly during the time period prior to the voluntary cancellation of indoor residential uses of chlorpyrifos, exposures measured in the range reported in the epidemiology studies (pg/g plasma) are likely low enough that they were unlikely to have resulted in AChE inhibition. The FIFRA SAP (Ref. 10) concurred with the conclusion that measured levels of chlorpyrifos among epidemiology study participants were unlikely to have resulted in AChE inhibition. The urinary TCPy concentrations among mothers were comparable to the general population levels measured in NHANES. Comparing cord blood concentrations with the concentrations in which AChE inhibition was observed in adult volunteers indicates AChE inhibition would likely not have occurred at levels observed in the epidemiology studies (6.17 pg/g). Therefore, while uncertainty exists as to actual chlorpyrifos exposure at (unknown) critical windows of exposure, EPA believes it is unlikely mothers enrolled in the birth cohort studies experienced RBC AChE inhibition (greater than 10%).

The biomarker data from the CCCEH studies are supported by EPA's dose reconstruction analysis using the PBPK–PD model, which support a conclusion that indoor application of chlorpyrifos, when used as allowed prior to cancellation from the residential

marketplace in 2000, likely would not have resulted in RBC AChE inhibition greater than 10% in pregnant women or young children.

ii. Strength, consistency, and specificity. As stated in the EPA neurotoxicity guidelines (Ref. 61), direct extrapolation of developmental neurotoxicity results from laboratory animals to humans is limited by the lack of knowledge about underlying toxicological mechanisms and the relevance of these results to humans. EPA notes consistencies across these two databases, although challenges of making a direct comparison between neurodevelopmental domain inter-species remain. It can be assumed that developmental neurotoxicity effects in animal studies indicate the potential for altered neurobehavioral development in humans, although the specific types of developmental effects seen in experimental animal studies may not be the same as those that may be produced in humans. However, considering the toxicological and epidemiological data in the context of three major neurodevelopmental domains (specifically, cognition, motor control, and social behavior), insights can be gained. For example, chlorpyrifos studies in rats and/or mice have reported impaired cognition (spatial learning and working memory; *e.g.,* Refs. 35 and 38); changes in locomotor activity levels (exploration, rearing; *e.g.,* Refs. 36 and 62); altered social interaction (aggression, maternal behavior; Refs. 63 and 64); and effects on brain morphometrics (Refs. 65 and 66). Similarly, epidemiologic investigations have reported effects on cognition (Bayley scale indices; Refs. 50 and 53), abnormal motor development in neonates (reflexes, Brazelton score; Refs. 49 and 48), altered social development (*e.g.,* ADHD; Refs. 50 and 67), and MRI brain scans (Ref. 68). It is notable that the laboratory animal studies vary in experimental designs such as species, strain, gender, dosing regimens (age, routes, vehicle), and test parameters (age, protocol). Likewise, observational epidemiology studies vary by population characteristics (race/ethnicity, socio-economic status (SES), and pesticide use/exposure profile), co-exposures (mix of chemicals, windows of exposure), and method of exposure and outcome assessment. Given the differences across laboratory animal and epidemiology studies, the qualitative similarity in research findings is striking.

In contrast, quantitatively, there are notable differences between animals and humans. Specifically, in animals, the doses most often used in the behavior studies (1 and 5 mg/kg/day) are sufficient to elicit approximately ≥10% brain AChE inhibition and ≥30% in RBC AChE inhibition, depending on the study design, age of the animal, and sampling time. In the epidemiology studies, based on the comparisons with biomonitoring data and the results of the dose-reconstruction analysis, it is unlikely that RBC AChE would have been inhibited by any meaningful or measurable amount, if any at all, and most likely none in the brain. This key difference in dose response between the experimental toxicology and epidemiology studies poses challenges in interpreting such data. There are a number of possible hypotheses such as: (1) Limitations of experimental laboratory studies which have limited statistical power due to relatively small sample sizes; (2) humans display a broader array of behaviors and cognitive abilities than rats, thus limiting the sensitivity of the rat studies; and (3) in the epidemiology studies, the timing of chlorpyrifos application and blood collections are not coupled—thus higher levels of blood chlorpyrifos were likely missed (albeit the results of the dose reconstruction analysis reduce the likelihood of this hypothesis).

In making a weight-of-the-evidence analysis, it is important to consider the strength of the statistical measures of association between prenatal chlorpyrifos exposure and adverse neurodevelopmental outcomes through childhood (epidemiology) and possibly into adulthood (animal studies). It is also important to consider the strength of the integrated qualitative and quantitative evidence, the consistency of the observed associations across epidemiology studies and considering both animal and human data support the conclusion that chlorpyrifos plays a role in adverse neurodevelopmental outcomes. While it cannot be stated that chlorpyrifos alone is the sole contributor to the observed outcomes (specificity), since other environmental, demographic or psychosocial exposures may also play a part in these outcomes, this does not obviate the contribution of prenatal chlorpyrifos exposure in the development of adverse neurodevelopmental outcomes as echoed by the FIFRA SAP (Ref. 10).

The CCCEH study, which measures chlorpyrifos specifically, provides a number of notable associations. Regarding infant and toddler neurodevelopment, the CCCEH authors also reported statistically significant deficits of 6.5 points on the Bayley Psychomotor Development Index (PDI) at 3 years of age when comparing high to low exposure groups (Ref. 50). Notably these decrements in PDI persist even after adjustment for group and individual level socioeconomic variables (Ref. 69). These investigators also observed increased odds of mental delay (OR = 2.4; 95% CI: 1.1–5.1) and psychomotor delay (OR = 4.9; 95% CI: 1.8–13.7) at age three when comparing high to low exposure groups. (Ref. 50). Rauh *et al.* (Ref. 50) also reported large odds ratios for attention disorders (OR = 11.26; 95% CI: 1.79–70.99), ADHD (OR = 6.50; 95% CI: 1.09–38.69), and PDD (OR = 5.39; 95% CI: 1.21–24.11) when comparing high to low chlorpyrifos exposure groups. (Ref. 50). EPA notes that the magnitude of these results are so large that they are unlikely to be affected by residual confounding although limited sample sizes resulted in imprecise estimates.

Decrements in intelligence measures were identified in relation to increasing levels of prenatal chlorpyrifos exposure. The CCCEH study reported statistically significant decreases of 1.4% in full scale IQ and 2.8% in working memory among seven-year olds for each standard deviation increase in chlorpyrifos exposure. (Ref. 56). These results persist even when performing sensitivity analyses including only those with detectable chlorpyrifos levels.

iii. Biological plausibility and coherence. Although MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes, the growing body of literature does demonstrate that chlorpyrifos and/or its oxon are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The lack of established MOA/AOP does not undermine or reduce the confidence in the findings of the epidemiology studies. The CCCEH study data are not considered in isolation, but rather are strengthened when considered in concert with the results from the other two cohort studies, as noted by the FIFRA SAP. (Ref. 10). As noted above, the CHAMACOS and Mt. Sinai cohorts that measured neurological effects at birth (the Brazelton index), observed a putative association with chlorpyrifos. (Ref. 48 and 49). Similarly, while not consistent by age at time of testing (ranging from 6 months to 36 months across the three cohorts), each cohort reported evidence of impaired mental and psychomotor development. Attentional problems and ADHD were

reported by both Columbia and CHAMACOS investigators. Finally, each of the three cohort study authors observed an inverse relation between the respective prenatal measures of OP and intelligence measures at age 7 years.

iv. Weight of evidence conclusions. Key issues being considered by the Agency in its weight-of-evidence evaluation of chlorpyrifos toxicity are (1) whether chlorpyrifos causes long-term effects from fetal or early life exposure and (2) whether adverse effects can be attributed to doses lower than those which elicit 10% inhibition of AChE—EPA's current regulatory point of departure for chlorpyrifos and other OPs. When taken together the evidence from (1) the experimental toxicology studies evaluating outcomes such as behavior and cognitive function; (2) mechanistic data on possible adverse outcome pathways/modes of action; and (3) epidemiologic and biomonitoring studies leads the agency to the following conclusions:

- Qualitatively, these lines of evidence together support a conclusion that exposure to chlorpyrifos results in adverse neurodevelopmental outcomes in humans, at least under some conditions.
- Quantitatively, the dose-response relationship of AChE inhibition across different life stages is established, but MOAs/AOPs for neurodevelopmental outcomes are not established.
- The database of *in vivo* animal toxicology neurodevelopmental studies on adverse outcomes includes only a small number of studies at doses lower than 1 mg/kg/day. Despite this, the agency noted that the BMD values in adult (pregnant and nonpregnant) female rats (0.05–0.15 mg/kg/day) are generally 10-fold or more lower than the doses where effects on neurodevelopmental outcomes in laboratory rats are observed.
- With respect to the mechanistic data, there are sparse data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence, which significantly limits their quantitative use in risk assessment.
- As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology study in risk assessment challenging, particularly with respect to dose-response, critical duration of exposure, and window(s) of susceptibility. Despite this uncertainty, the cord blood and other measures (meconium) provide evidence of exposure to the fetus during gestation. Moreover, exposure levels in the range measured in the epidemiology studies (pg/g) are likely low enough that they are unlikely to result in AChE inhibition, as supported by the dose reconstruction analysis of residential use prior to 2000 (although the agency has not investigated the degree to which exposure to multiple AChE-inhibiting pesticides indoors simultaneously could impact this conclusion).
- Given the totality of the evidence, the agency concludes that chlorpyrifos likely played a role in the neurodevelopmental outcomes reported in the CCEH study but uncertainties such as the lack of an established MOA/AOP for neurodevelopmental effects and the exposure to multiple AChE-inhibiting pesticides precludes definitive causal inference.
- In light of the uncertainties regarding the relationship of observed neurodevelopmental outcomes to AChE inhibition, EPA is retaining the 10X FQPA safety factor.

Following publication of the December 2014 RHHRA, EPA received public comments suggesting that the uncertainty surrounding the dose-response relationship for neurodevelopmental effects warranted the application of a larger safety factor than the statutory default 10X factor. The commenters suggested that EPA's assessment had failed to establish that, even with the retained 10X FQPA safety factor, exposures to chlorpyrifos will not result in adverse neurodevelopmental outcomes. Some of the commenters suggested that EPA evaluate available biomonitoring from the epidemiologic data to help assess whether these outcomes could in fact be occurring at levels below EPA's PAD that it is using for purposes of this proposed rule. EPA is currently in the process of evaluating the available biomonitoring; however, in light of the August 10, 2015 *PANNA* decision that orders EPA to respond to the PANNA–NRDC Petition not later than October 31, 2015, EPA has not been able to complete that evaluation in advance of this proposal. EPA is continuing its evaluation of the available biomonitoring and will update this action to reflect the results of that review, if warranted.

Further, EPA is aware that some commenters on EPA's RHHRA believe the PBPK–PD model used to derive PoDs is inappropriate for the evaluation of neurodevelopmental effects, given that there is no established association between AChE inhibition and long term adverse neurodevelopmental outcomes observed in recent epidemiology studies. While EPA's evaluation of biomonitoring from available human epidemiology studies will not help to further determine the MOA/AOP for these adverse neurodevelopmental outcomes, as noted, it will help EPA better assess whether the doses (PADs) EPA is proposing to use for regulatory purposes in this proposed rule are protective for potential adverse neurodevelopmental effects. While, as noted, that assessment is still not complete, because EPA is proposing to revoke all tolerances in this proposed rule based on its concern regarding AChE inhibition, it is unnecessary for EPA to determine at this time whether its current PADs bound the chlorpyrifos exposures measured in the epidemiology studies. In any case, as EPA completes its further evaluation it will update this action, as warranted.

B. Dietary Exposure and Risk Assessment.

The general approach for the chlorpyrifos dietary exposure and risk assessment is as follows: The PBPK–PD model was used to predict acute (24 hour) and steady state (21-day) PoDs which correspond to 10% RBC AChE inhibition for the lifestages relevant to chlorpyrifos risk assessment. The PoDs are then divided by the total uncertainty factor to determine the PAD.

For the dietary risk assessment for food only, the exposure values resulting from Dietary Exposure Evaluation Model (DEEM) and the Calendex model are compared to the PBPK–PD-based acute PAD and steady state PAD, respectively. When estimated dietary risk estimates exceeds 100% of the PAD there is generally a risk concern.

For the dietary assessment for water, a drinking water level of comparison (DWLOC) approach to aggregate risk was used to calculate the amount of exposure available in the total 'risk cup' for chlorpyrifos oxon in drinking water after accounting for any chloropyrifos exposures from food and/or residential use.

1. Residues of concern. The qualitative nature of the residue in plants and livestock is adequately understood based on acceptable metabolism studies with cereal grain (corn), root and tuber vegetable (sugar beets), and poultry and ruminants. The residue of concern, for tolerance expression and risk assessment, in plants (food and feed) and livestock commodities is the parent compound chlorpyrifos.

Based on evidence (various crop field trials and metabolism studies) indicating that the metabolite chlorpyrifos oxon would be not be present in edible portions of the crops (particularly at periods longer than the currently registered PHIs), it is not a residue of concern in food or feed at this

time. Also, the chlorpyrifos oxon is not found on samples in the USDA PDP monitoring program. In fact, from 2007 to 2012, out of several thousand samples of various commodities, only one sample of potato showed presence of the oxon at trace levels, 0.003 ppm where the LOD was 0.002 ppm, even though there are no registered uses of chlorpyrifos on potato in the U.S.

The oxon metabolite was not found in milk or livestock tissues in cattle and dairy cow feeding studies, at all feeding levels tested, and is not a residue of concern in livestock commodities.

Oxidation of chlorpyrifos to chlorpyrifos oxon can occur through photolysis, aerobic metabolism, and chlorination as well as other oxidative processes. Because of the toxicity of the oxon and data indicating that chlorpyrifos rapidly converts to the oxon during typical drinking water treatment (chlorination), the drinking water risk assessment considers the oxon as the residue of concern in treated drinking water and assumes 100% conversion of chlorpyrifos to chlorpyrifos oxon. (Ref. 70). This approach of assuming 100% conversion of chlorpyrifos to the more toxic chlorpyrifos oxon, is a conservative approach and thus protective of other likely exposure scenarios of chlorpyrifos only and chlorpyrifos and chlorpyrifos oxon.

The chlorpyrifos degradate TCPy is not considered a residue of concern for this assessment as it does not inhibit cholinesterase (a separate human health risk assessment has been performed for TCPy, which has its own toxicity database). TCPy (derived from triclopyr, chlorpyrifos, and chlorpyrifos-methyl) was previously assessed on June 6, 2002. (Ref. 71).

2. Dietary (food only) risk assessment. The general approach for the chlorpyrifos (food only) exposure and risk assessment can be described as follows: The PBPK–PD model was used to predict acute (24 hour) and steady state (21-day) PoDs which correspond to 10% RBC AChE inhibition for the index lifestages relevant to chlorpyrifos risk assessment (children of various ages which differ due to exposure pattern, and adult females of childbearing age). The PoDs are then divided by the total uncertainty factor to determine the PAD. For food, the residue of concern is chlorpyrifos (the oxon metabolite is not an expected residue on foods). The chlorpyrifos total uncertainty factors are 100X for adult females (10X FQPA SF and 10X intra-species extrapolation factor) and 40X for the other populations (10X FQPA SF and 4X intra-species extrapolation factor). For the dietary risk assessment for food only, the exposure values resulting from Dietary Exposure Evaluation Model (DEEM) and the Calendex model are compared to the PBPK–PD-based acute PAD and steady state PAD, respectively. The chlorpyrifos exposure values resulting from dietary modeling are compared to the PAD. Dietary exposures greater than 100% of the PAD are generally cause for concern and would be considered ''unsafe'' within the meaning of FFDCA section 408(b)(2)(B).

i. Description of residue data used in dietary (food only) assessment. Acute and steady state dietary (food only) exposure analyses for chlorpyrifos were conducted using the Dietary Exposure Evaluation Model (DEEM) and Calendex software with the Food Commodity Intake Database (FCID) (Ref. 90). This software uses 2003–2008 food consumption data from NHANES/WWEIA. The most recent previous dietary assessment was conducted in support of the 2011 PHHRA and the ongoing chlorpyrifos registration review. (Ref. 72). This current analysis reflect the latest consumption data as well as more recent food monitoring and percent crop treated data. These analyses were performed for the purpose of obtaining food exposure values for comparison to the chlorpyrifos doses predicted by the PBPK–PD model to cause RBC ChEI. The acute and steady state exposure analyses do not include drinking water which is assessed separately as discussed in Unit VI.2.B.

Both the acute and steady state dietary exposure analyses are highly refined. The large majority of food residues used were based upon U.S. Department of Agriculture's PDP monitoring data except in a few instances where no appropriate PDP data were available. In those cases, field trial data were used or tolerance level residues were assumed. The same data were used for both the acute and steady state analyses. EPA also considered percent crop treated information. Food processing factors from submitted studies were used as appropriate.

The acute and steady state dietary exposure assessment used percent crop treated information from EPA's Screening Level Usage Analysis (Ref. 73) to estimate chlorpyrifos exposures from the consumption of food. Reported percent crop treated ranged from <2.5% to 70%. 100% crop treated was assumed for many crops for which no usage data were available.

ii. Acute dietary (food only) risk assessment. Chlorpyrifos acute (food only) dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database DEEM–FCID™, Version 3.16, which incorporates consumption data from NHANES/WWEIA. This dietary survey was conducted from 2003 to 2008. Acute dietary risk estimates are presented below for the sentinel population subgroups for acute risk assessment: infants (<1 year old), children (1–2 years old), youths (6–12 years old) and adults (females 13–49 years old). The assessment of these index lifestages will be protective for the other population subgroups.

As Table 2 indicates, EPA believes that acute dietary risk from food only does not present a significant risk, as estimates are all far below 100% of the acute PAD for food (aPADfood) at the 99.9th percentile of exposure. The subgroup with the highest risk estimate was females (13–49 years old) at 3.2% aPADfood.

TABLE 2—ACUTE DIETARY (FOOD ONLY) EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS

Population subgroup	$aPoD_{food}$ [1] (ug/kg/day)	$aPAD_{food}$ [2] (ug/kg/day)	Food exposure [3] (ug/kg/day)	Percent of $aPAD_{food}$
Infants (<1 yr)	600	15	0.273	1.8
Children (1–2 yrs)	581	14	0.423	3.0
Youths (6–12 yrs)	530	13	0.189	1.4
Adults (Females 13–49 yrs)	469	4.7	0.150	3.2

[1] Acute point of departure; daily dose predicted by PBPK–PD model to cause RBC ChEI of 10% for acute dietary (food) exposures.

[2] aPAD = acute PAD = PoD (Dose predicted by PBPK–PD model to cause 10% RBC ChEI) ÷ total UF; Total uncertainty factor = 100X for females 13–49 years (10X intraspecies factor and 10X FQPA safety factor) and 40X for other populations (4X intraspecies factor and 10X FQPA safety factor).

[3] Acute food only exposure estimates from DEEM (at 99.9th percentile). Refined with monitoring data and %CT.

iii. Steady state detary (food only) risk assessment. A chlorpyrifos steady state dietary (food only) exposure analysis was conducted using Calendex-FCID™. EPA's steady state assessment considers the potential risk from a 21-day exposure duration using a 3-week rolling average (sliding by day) across the year. For this assessment, the same food residue values used in the acute assessment were used for the 21-day duration. In the Calendex software, one diary for each individual in the WWEIA is selected to be paired with a randomly selected set of residue values for each food consumed. The steady state analysis calculated exposures for the sentinel populations for infant, child, youths, and adult (infants <1 year, children 1–2 years, youths 6–12 years, females 13–49 years).

Calendex reported dietary exposures for each population subgroup at several percentiles of exposure ranging from 10th percentile to 99.9th percentile. Similar to acute risks, the dietary (food only) exposures for chlorpyrifos were all well below 100% ssPADfood (all populations, at all percentiles of exposure). Only the 99.9th percentile of exposure is presented in Table 3. For the steady state dietary (food only) exposure analyses, children (1–2 years old) was the population subgroup with the highest risk estimate at 9.7% of the ssPADfood at the 99.9th percentile of exposure.

TABLE 3—STEADY STATE DIETARY (FOOD ONLY) EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS

Population subgroup	$_{SS}$ PoD_{food} [1] (ug/kg/day)	$ssPAD_{food}$ [2] (ug/kg/day)	Food exposure [3] (ug/kg/day)	Percent of $ssPAD_{food}$
Infants (<1 yr)	103	2.6	0.186	7.2
Children (1–2 yrs)	99	2.5	0.242	9.7
Youths (6–12 yrs)	90	2.2	0.128	5.8
Adults (Females 13–49 yrs)	78	0.78	0.075	9.6

[1] Steady state point of departure; daily dose predicted by PBPK–PD model to cause RBC ChEI of 10% for steady state (21-day) dietary (food) exposures.

[2] ssPAD = Steady state PAD = PoD (Dose predicted by PBPK–PD model to cause 10% RBC ChEI) ÷ total UF; Total uncertainty factor = 100X for females 13–49 years (10X intraspecies factor and 10X FQPA safety factor) and 40X for other populations (4X intraspecies factor and 10X FQPA safety factor).

[3] Steady state (21-day) food only exposure estimates from Calendex (at 99.9th percentile). Refined with monitoring data and %CT.

As Tables 2 and 3 make clear, EPA does not believe that food exposures to chlorpyrifos by themselves present a significant risk of AChE inhibition. Based on the analysis above, EPA would therefore not be proposing the revocation of chlorpyrifos if dietary exposures were confined to food. As outlined below, however, EPA believes that for some portions of the country, food exposures, when aggregated with residential exposures and potentially more significant drinking water exposures, do present a significant risk concern and support revocation of all chlorpyrifos tolerances.

iv. Residential (non-occupational) exposure/risk characterization. As explained above in Unit V.B.3., in assessing dietary risk under the FFDCA, EPA must consider not only direct dietary exposure from food and drinking water, but also non-occupational exposures to the pesticide, such as residential exposure and bystander exposure from the use of agricultural pesticides. For simplicity, EPA refers to its assessment of all such exposures as its ''residential exposure assessment.'' For chlorpyrifos, the vast majority of residential use products were cancelled as of 2001. Current chlorpyrifos residential uses now include a granular fire ant mound use (commercial applicator only) and ant and roach bait in child-resistant packaging (homeowner applicator). Additionally, chlorpyrifos is labeled for public health aerial and ground-based fogger ULV mosquito adulticide applications and for golf course turf applications. For the purpose of residential exposure assessment, the parent compound chlorpyrifos is the residue of concern.

With respect to bystander exposure, EPA's worker protection standard prohibits using any pesticide in a way that will contact either workers or bystanders through spray drift. Further, in connection with EPA's 2012 spray drift evaluation, EPA imposed additional no-spray buffers to limit deposition of chlorpyrifos through drift in areas adjacent to agricultural fields where bystanders may be present following application. With respect to bystander exposure to volatilized (vapor form) chlorpyrifos following application, as noted in Unit VI.A., recently submitted rat acute toxicity studies of vapor phase chlorpyrifos along with available subchronic vapor phase inhalation studies support a conclusion that acute exposure to the saturated vapor of chlorpyrifos or its oxon do not result in hazard due to AChE inhibition. Accordingly, EPA concludes that with the additional no spray buffer restrictions, risk concerns to bystanders from spray drift have been eliminated and therefore bystander exposures are not included as part of EPA's aggregate risk assessment.

Residential Handler Exposure. EPA uses the term ''handlers'' to describe those individuals who are involved in the pesticide application process. EPA believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential (non-occupational) handlers are addressed somewhat differently by EPA as homeowners are assumed to complete all elements of an application without use of any protective equipment.

Based upon review of all chlorpyrifos registered uses, only the ant and roach bait products can be applied by a homeowner in a residential setting. Because the ant and roach bait products are designed such that the active ingredient is contained within a bait station, the potential for contact with the chlorpyrifos-containing bait material has been eliminated and therefore these products do not pose a risk concern.

Residential Post-Application Exposure. There is the potential for post-application exposures as a result of being in an environment that has been previously treated with chlorpyrifos. Chlorpyrifos can be used in areas frequented by the general population including golf courses and as an aerial and ground-based ULV mosquito adulticide applications made directly in

residential areas. Post-application exposure from residential fire ant mound treatment is not quantitatively assessed here as exposures are considered to be negligible and do not pose a risk concern; these products can only be applied professionally and EPA therefore does not anticipate direct non-occupational exposure with treated ant mounds.

In the RHHRA which supports this rule, EPA has updated the post-application exposure assessment to reflect: (1) Use of the PBPK–PD model for determining toxicological PoDs; (2) use of the 2012 Residential SOPs (Ref. 28); (3) use of the AgDISP model for estimation of airborne concentrations and residue dissipation following chlorpyrifos mosquito adulticide applications; (4) updated methodology for determining the airborne concentration of active ingredient following ground-based mosquito adulticide applications; and (5) use of updated body weights for all residential populations assessed.

In addition, EPA utilized only steady state durations of exposure in the updated residential assessment. The steady state endpoint selection for chlorpyrifos overlaps EPA's traditional short-term exposure duration endpoint selection and is considered health protective for both short- and intermediate-term exposures.

The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

Golf Course Use (Emusifiable Concentrate (EC) and Granular (G) Formulations)

- Children 6 to <11 years old, youths 11 to <16 years old, and adult post-application dermal exposure from contact with treated turf while golfing.

Public Health Mosquito Adulticide Use (Aerial and Ground Applications)

- Children 1 to <2 years old and adult post-application dermal exposure from contact with turf following the deposition of chlorpyrifos residues from public health mosquito adulticide application.
- Children 1 to <2 years old and adult post-application inhalation exposure from airborne chlorpyrifos following public health mosquito adulticide application.
- Children 1 to <2 years old post-application incidental oral (hand-to-mouth) exposure from contact with turf following the deposition of chlorpyrifos residues from public health mosquito adulticide application.
- Children 1 to <2 years old post-application incidental oral (object-to-mouth) exposure from contact with toys containing residues from turf following the deposition of chlorpyrifos residues from public health mosquito adulticide application.

The following assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. These assumptions and factors are described in detail in the updated occupational and residential exposure and risk assessment. (Ref. 74).

Exposure Duration: Residential post-application exposures to chlorpyrifos are assumed to be steady state (*i.e.,* 21 days or longer).

The application of mosquitocide in residential areas may result in the potential for post-application inhalation exposures. The aerosolized particulate remaining following application is assumed to persist for no longer than one hour in proximity of the application source and, accordingly, would be most appropriately defined as acute in duration. However, this assessment assumes that post-application inhalation exposures are steady state which is a highly conservative approach given how infrequently mosquitocides are repeatedly applied to the same locations and how rapidly aerosols dissipate after these types of applications. The parameters used to define this exposure scenario in the PBPK–PD model conservatively reflect daily, one hour exposures for 21 days.

Application Rates: In order to seek clarification of chlorpyrifos usage, the agency compiled a master use summary document reflective of the use profile of all active product labels. The document, among other information, presents all registered uses of chlorpyrifos and corresponding maximum single application rates, equipment types, restricted entry intervals (REIs), etc. This assessment assumes that the detailed information on application rates and use patterns presented in Appendix 9 (Master Use Summary Document) in support of the 2014 RHHRA will be implemented on all chlorpyrifos labels and is the basis of the occupational and residential risk assessment. If, for any reason, the final chlorpyrifos labels contain higher application rates, the actual risks posed by those products may exceed the risks estimated in this assessment.

Body Weights: The body weights assumed for this assessment differ from those used in 2011 residential exposure assessment and are based on the recommendations of the 2012 Residential SOPs. These body weights are the same as selected for derivation of PBPK–PD PoDs for use in assessment of residential exposures.

The standard body weights are as follows: Youths 11 to <16 years old, 57 kg; children 6 to <11 years old, 32 kg; and children 1 to <2 years old, 11 kg. For adults when an endpoint is not sex-specific (*i.e.,* the endpoints are not based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment. However, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used due to concerns for neurodevelopmental effects related to early life exposure to chlorpyrifos.

Post-application exposures from golfing have been assessed using the 2012 Residential SOPs and with use of exposure data from a chemical-specific turf transferable residue (TTR) study. The study was conducted with an emulsifiable concentrate, a granular, and a wettable powder formulation. Only the emulsifiable concentrate and granular data were used because there are no currently registered wettable powder formulations. The study was conducted in 3 states, California, Indiana and Mississippi, with use of the emulsifiable concentrate and wettable powder formulations. Exposure was estimated by normalizing Day 0 TTR measures from study application rates to the current maximum application rate allowable by the label. Chlorpyrifos oxon residues were not analyzed.

The post-application exposure potential from public health mosquito adulticide applications has been considered for both ground based truck foggers and aerial applications. For assessment of the mosquito adulticide use, the algorithms and inputs presented in the 2012 Residential SOP Lawns/Turf section were used coupled with the available TTR data described above. The deposition of chlorpyrifos from these applications are not based on the application rate alone, but also using the AgDISP (v8.2.6) model (aerial applications, the currently recommended model for assessment of mosquito adulticide applications) or empirical data (ground applications) to determine how much pesticide is deposited on residential lawns as a result of mosquito adulticide treatments at the maximum application rates for each. The TTR data are then used to determine the fraction of the total residue deposited following the mosquitocide application which can result in exposures to impacted individuals. Inhalation exposures are also estimated using AgDrift for aerial

application and a recently developed well-mixed box (WMB) model approach for outdoor foggers.

EPA used the AgDISP (v8.2.6) model to estimate the deposition of chlorpyrifos from aerial applications and the airborne concentration of chlorpyrifos following public health mosquitocide application. AgDISP predicts the motion of spray material released from aircraft, and determines the amount of application volume that remained aloft and the amount of the resulting droplets deposited on the surfaces in the treatment area, as well as downwind from the treatment area. The model also allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation risks to individuals residing in areas being treated by aerial application of chlorpyrifos. The aerial fraction of the mosquito adulticide application rate applied (0.010 lb ai/A) is 0.35 (*i.e.,* 35 percent of application rate is deposited on turf); and the airborne concentration at the breathing height of adults and children of chlorpyrifos 1 hour following aerial mosquito adulticide application is 0.00060 mg/m3.

EPA used empirical data to derive the ground-based deposition of chlorpyrifos following public health mosquitocide application. These data, conducted by Moore *et al.* (Ref. 75) and Tietze *et al.* (Ref. 76), measured the deposition of malathion via ULV ground equipment as applied for mosquito control. Based on these data, EPA used an off-target deposition rate of 5 percent of the application rate to evaluate ground-based ULV applications (*i.e.,* 5 percent of the target application rate deposits on turf). A value slightly higher than the mean values for both studies was selected because of the variability in the data and the limited number of data points. The adjusted application rate was then used to define TTR levels by scaling the available TTR data as appropriate.

In order to calculate airborne concentrations from ULV truck fogger applications, EPA used the 2012 Residential SOPs for Outdoor Fogging/Misting Systems, with minimal modification to the well-mixed box (WMB) model. The WMB model allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation exposure to individuals residing in areas being treated by ground application of chlorpyrifos. This methodology is a modification of the previous method used in the 2011 occupational and residential exposure assessment to evaluate post-application inhalation exposure resulting from truck mounted mosquito fogger. The revised methodology more accurately accounts for dilution.

Combining Residential Exposure and Risk Estimates. Since dermal, incidental oral, and inhalation exposure routes share a common toxicological endpoint, RBC AChE inhibition risk estimates have been combined for those routes. The incidental oral scenarios (*i.e.,* hand-to-mouth, object-to-mouth, and soil ingestion) should be considered inter-related, as it is likely that these exposures are interspersed over time and are not each occurring simultaneously. Combining all three of these scenarios with the dermal and inhalation exposure scenarios would be unrealistic because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 <2 years old are the dermal, inhalation, and hand-to-mouth scenarios (the highest incidental oral exposure expected). This combination should be considered a protective estimate of children's exposure to pesticides.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates. The assessment of steady state golfer post-application exposures (dermal only) to chlorpyrifos treated turf for the lifestages adults, children 6 to <11 years old, and youths 11 to <16 years old, results in no risks of concern (*i.e.,* children 6 to <11 and youths 11 to <16 years old, MOEs are ≥40; adults, MOEs are ≥100). For the assessment of post-application exposures from public health mosquitocide applications, no combined risks of concern were identified for adults (dermal and inhalation) and children 1 to <2 years old (dermal, incidental oral, and inhalation). A summary of risk estimates is presented in Table 4.

TABLE 4—RESIDENTIAL POST-APPLICATION NON-CANCER EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS

Lifestage	Post-application exposure scenario		Application rate [1]	State (TTR data)	Dose (mg/kg/day) [3]	MOEs [4]	Combined routes [5]	Combined MOEs [6]
	Use site	Route of exposure						
Adult (Females)	Golf Course Turf	Dermal	1.0 (Emulsifiable Concentrate).	CA	0.010	1,400	NA	NA
				IN	0.0069	2,100		
				MS	0.012	1,200		
				Mean	0.0095	1,500		
Youths 11 to <16 yrs old.				CA	0.010	1,600		
				IN	0.0069	2,300		
				MS	0.012	1,400		
				Mean	0.0096	1,700		
Children 6 to <11 years old.				CA	0.012	2,100		
				IN	0.0082	3,100		
				MS	0.014	1,800		
				Mean	0.011	2,200		
Adult (Females)			1.0 (Granular)	CA	0.0088	1,600		
Youths 11 to <16 yrs old.					0.0088	1,900		
Children 6 to <11 years old.					0.010	2,400		
Adult (Females)	Aerial and Ground Based ULV Mosquitocide Applications.	Dermal	0.010 (Aerial)	MS	0.00052	75,000	X	9,100
		Inhalation		NA	0.00060 (mg/m^3)	10,300	X	
Children 1 to <2 yrs old.	Mosquitocide Applications.	Dermal		MS	0.00088	210,000	X	2,300
		Inhalation		NA [2]	0.00060 (mg/m^3)	4,000	X	

TABLE 4—RESIDENTIAL POST-APPLICATION NON-CANCER EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS—Continued

Lifestage	Post-application exposure scenario		Application rate [1]	State (TTR data)	Dose (mg/kg/day) [3]	MOEs [4]	Combined routes [5]	Combined MOEs [6]
	Use site	Route of exposure						
		Hand-to-Mouth		MS	0.000018	5,600	X	
		Object-to-Mouth		MS	5.5×10^{-7}	180,000	NA	NA
		Soil Ingestion		NA [2]	1.2×10^{-7}	4,900,000	NA	NA
Adult (Females)		Dermal	0.010 (Ground)	MS	0.000074	520,000	X	1,200
		Inhalation		NA	0.0051 (mg/m^3)	1,200	X	
Children 1 to <2 yrs old.		Dermal		MS	0.00013	1,500,000	X	460
		Inhalation		NA	0.0051 (mg/m^3)	460	X	
		Hand-to-Mouth		MS	2.6×10^{-6}	39,000	X	
		Object-to-Mouth		MS	7.9×10^{-8}	1,300,000	NA	NA
		Soil Ingestion		NA [2]	1.7×10^{-8}	34,000,000	NA	NA

[1] Based on the maximum application rates registered for golf course turf and ULV mosquito adulticide uses.
[2] The airborne concentrations of chlorpyrifos following ULV mosquito adulticide applications was determined with use of the AgDISP (v8.2.6) model.
[3] Dose (mg/kg/day) equations for golfing and mosquitocide applications are provided in Appendices B and C (Ref. 1) of the updated occupational and residential exposures assessment. For calculation of doses (*i.e.,* dermal, hand-to-mouth, and object-to-mouth) from exposure to ULV mosquito adulticide, TTR data was used. The MS TTR data was selected for use because it is the worst case and, as a result, most protective of human health. Additionally, the fraction of chlorpyrifos residue deposited following mosquitocide application, 35% (0.35), was determined with use of the AgDISP (v8.2.6) model and used for dose calculation. The fraction of chlorpyrifos deposited following ground ULV application, 5% (0.050), is based on surrogate exposure data (malathion). For dose estimation from exposures to golfing on treated turf, on the TTR data was used. Doses have been presented for all State sites, including the mean of all State sites.
[4] MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day).
[5] X indicates the exposure scenario is included in the combined MOE; NA = Not applicable.
[6] Combined MOE = 1 ÷ (1/dermal MOE) + (1/inhalation MOE) + (1/incidental oral MOE), where applicable.

v. Aggregating exposures and developing the drinking water level of concern. Consistent with FFDCA section 408(b)(2)(D)(vi), EPA considers and aggregates (adds) pesticide exposures and risks from three major sources: Food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard, or the risks themselves can be aggregated. The durations of exposure identified for chlorpyrifos uses are acute and steady state. The acute aggregate assessment includes high end exposure values for food and drinking water but does not include residential exposure estimates. The steady state aggregate assessment includes food, drinking water, and residential exposures and for chlorpyrifos it is protective of the acute aggregate risks because examination indicates it results in higher risk estimates for all situations—so in effect acute residential exposures have also been considered in the aggregate risk assessment process.

For purposes of this proposed rule, EPA is using a DWLOC approach to aggregate risk. Under this approach, EPA calculates the amount of exposure available in the total 'risk cup' for chlorpyrifos oxon in drinking water after accounting for any chlorpyrifos exposures from food and/or residential use.

The DWLOC approach for this proposed rule uses a reciprocal MOE calculation method for adults (females of childbearing age) since the target MOEs are the same for all relevant sources of exposure, *i.e.,* 100X for residential dermal and for dietary food and water. This entails calculating the MOE for water (MOEwater) by deducting the contributions from food (MOEfood) and residential dermal exposure (MOEdermal) from the aggregate MOE (MOEagg) of 100. The aggregate MOE value is the same as target MOE (level of concern). The DWLOC is then calculated by dividing the PoDwater by the MOEwater. The general reciprocal MOE formula is as follows:

MOEagg = 1/((1/MOEwater) + (1/MOEfood) + (1/MOEdermal))

MOEwater = 1/((1/MOEagg) − ((1/MOEfood) + (1/MOEdermal)))

DWLOC= PoDwater/MOEwater

When target MOEs (levels of concern) are not the same across the relevant sources of exposure, the reciprocal MOE approach for calculating DWLOCs is not appropriate; instead an aggregate risk index (ARI) method is used. For purposes of this proposed rule, EPA therefore employed the ARI method for infants, children, and youths because the target MOEs for the relevant sources of exposure are not the same *i.e.,* the target MOE for dietary food and for residential dermal exposures is 40X while the target MOE for drinking water exposure is 50X. In this approach, the aggregate, or 'total', ARI value is assigned as 1 (EPA is generally concerned when any calculated ARIs are less than 1). Similar to the reciprocal MOE approach, the ARIs for food and dermal are deducted from the aggregate ARI to determine the ARI for water. The water ARI is multiplied by the target MOE for water to determine the calculated water MOE (MOEwater). The DWLOC is then calculated by dividing the PoDwater by the MOEwater. The general ARI method formula is as follows:

ARIs for food or dermal are calculated as ARIfood or dermal = (MOEfood or dermal)/(MOEtarget for food or dermal)).

ARIagg = 1/((1/ARIwater) + (1/ARIfood) + (1/ARIdermal))

ARIwater = 1/((1/ARIagg) − ((1/ARIfood) + (1/ARIdermal))); Where ARIagg = 1

MOEwater = ARIwater × MOEtarget.

DWLOC = PoDwater/MOEwater

Determination of Acute DWLOC. The acute aggregate assessment includes only food and drinking water. The acute DWLOCs were calculated for infants, children, youths, and adults and are presented in Table 5. The lowest acute DWLOC calculated was for infants (<1 year old) at 24 ppb. Acute exposures greater than 24 ppb are generally considered a risk concern and unsafe for purposes of FFDCA section 408(b).

TABLE 5—ACUTE AGGREGATE (FOOD AND DRINKING WATER) CALCULATION OF DWLOCS [1] [2]

Population	Food exposure (chlorpyrifos) [3]		Drinking water exposure (chlorpyrifos) [4]		Acute DWLOC [5] (ppb chlorpyrifos oxon)
	MOE	ARI	MOE	ARI	
Infants [1] (<1 yr)	2200	55	50	1.0	24
Children [1] (1–2 yrs)	1400	35	50	1.0	60
Youths [1] (6–12 yrs)	2800	70	50	1.0	150
Adults [2] (Females 13–49 yrs)	3100	NA	100	NA	53

[1] DWLOCs for infants, children and youths are calculated using the ARI (Aggregate Risk Index) approach since target MOEs are different for drinking water (chlorpyrifos oxon target MOE = 50) and for food and residential (chlorpyrifos target MOE = 40) exposure.
[2] DWLOCs for adults (females 13–49 years) are calculated using the reciprocal MOE approach since the target MOEs are the same for drinking water (chlorpyrifos oxon target MOE = 100) and for food and residential (chlorpyrifos target MOE = 100) exposure.
[3] FOOD: MOEfood = PoDfood (ug/kg/day) (from Table 4.8.4)/Food Exposure (ug/kg/day) (from Table 5.4.3). ARIfood = ((MOEfood)/(MOEtarget)).
[4] WATER (ARI approach): ARIwater = 1/((1/ARIagg) − ((1/ARIfood) + (1/ARIdermal))); Where ARIagg = 1 (Note: EPA is generally concerned when calculated ARIs are less than 1). MOEwater = ARIwater × MOEtarget. WATER (Reciprocal MOE approach): MOEwater = 1/((1/MOEagg) − ((1/MOEfood) + (1/MOEdermal))); Where MOEagg =Target MOE.
[5] DWLOC: DWLOC ppb = PoDwater (ppb; from Table 4.8.4)/MOEwater.

Determination of Steady State DWLOC. The steady state aggregate assessment includes dietary exposures from food and drinking water and dermal exposures from residential uses (dermal exposures represent the highest residential exposures). The steady state DWLOCs were calculated for infants, children, youths, and adults and are presented in Table 6. The lowest steady state DWLOC calculated was for infants (<1 year old) at 3.9 ppb. Exposures to chlorpyrifos oxon in drinking water at levels that exceed the steady state DWLOC of 3.9 ppb are therefore a risk concern and are considered unsafe for purposes of FFDCA section 408(b).

TABLE 6—STEADY STATE AGGREGATE (FOOD, DRINKING WATER, RESIDENTIAL) CALCULATION OF DWLOCS [1] [2]

Population	Food exposure (chlorpyrifos) [3]		Dermal exposure (chlorpyrifos) [4]		Drinking water exposure (chlorpyrifos oxon) [5]		Steady state DWLOC [6] (ppb chlorpyrifos oxon)
	MOE	ARI	MOE	ARI	MOE	ARI	
Infants [1] (<1 yr)	550	14	NA	NA	55	1.1	3.9
Children [1] (1–2 yrs)	410	10	NA	NA	55	1.1	10
Youths [1] (6–12 yrs)	700	18	1800	45	55	1.1	16
Adults [2] (Females 13–49 yrs)	1000	NA	1200	NA	120	NA	7.8

[1] DWLOCs for infants, children and youths are calculated using the ARI (Aggregate Risk Index) approach since target MOEs are different for drinking water (chlorpyrifos oxon target MOE = 50) and for food and residential (chlorpyrifos target MOE = 40) exposure.
[2] DWLOCs for adults (females 13–49 years) are calculated using the reciprocal MOE approach since the target MOEs are the same for drinking water (chlorpyrifos oxon target MOE = 100) and for food and residential (chlorpyrifos target MOE = 100) exposure.
[3] FOOD: MOEfood = PoDfood (ug/kg/day) (from Table 4.8.4)/Food Exposure (ug/kg/day) (from Table 5.4.4). ARIfood = ((MOEfood)/(MOEtarget)).
[4] DERMAL: MOEdermal = PoDdermal (ug/kg/day) (from Table 4.8.4)/Dermal Exposure (ug/kg/day) (from Table 6.2). ARIdermal = ((MOE dermal)/(MOEtarget)).
[5] WATER (ARI approach): ARIwater = 1/((1/ARIagg) − ((1/ARIfood) + (1/ARIdermal))); Where ARIagg = 1 (Note: EPA is generally concerned when calculated ARIs are less than 1). MOEwater = ARIwater × MOEtarget. WATER (Reciprocal MOE approach): MOEwater = 1/((1/MOEagg) − ((1/MOEfood) + (1/MOEdermal))); Where MOEagg = Target MOE.
[6] DWLOC: DWLOC ppb = PoDwater (ppb; from Table 4.8.4)/MOEwater.

vi. Estimating aggregate riskÐ comparing DWLOCs to estimated drinking water concentrations. In a DWLOC aggregate risk assessment, the calculated DWLOC is compared to the EDWC. When the EDWC is less than the DWLOC, there are no risk concerns for exposures to the pesticide in drinking water. Conversely, when the EDWC is greater than the DWLOC, there may be a risk concern. For chlorpyrifos, DWLOCs were calculated for both the acute and steady state aggregate assessments for infants, children, youths and adult females. However, for the national screening level drinking water assessment, only the steady state DWLOCs were compared to the modeled EDWCs (based on a national screen). The calculated steady state DWLOCs are much lower than those for the acute. For example, for infants, the lowest acute DWLOC is 24 ppb while the lowest steady state DWLOC is 3.9 ppb (Tables 5 and 6). Since the lowest DWLOC calculated for any duration or population was the 3.9 ppb steady state exposure value (infants), it is the concentration used for comparison to EPA's modeled EDWCs. Drinking water concentrations of chlorpyrifos oxon above 3.9 ppb may therefore be unsafe. Were EPA to conduct further analyses that compared all acute exposures to EDWC, it is possible that for some limited numbers of use scenarios, the EDWC could result in an exceedance of the acute DWLOC, but not the steady state DWLOC. However, because EPA is proposing to revoke all tolerances based on the steady state DWLOC, it is unnecessary to address that issue at this time.

EDWCs in Groundwater and Surface Water. EPA conducted a national screening level drinking water assessment for both groundwater and surface water, with focus on the agricultural uses. For both assessments, EPA calculated EDWCs for chlorpyrifos and chlorpyrifos oxon. Chlorpyrifos

EDWCs were multiplied by 0.9541 (molecular weight correction factor) and 100% (maximum conversion during water purification) to generate chlorpyrifos oxon EDWCs. EPA used a 100% conversion factor for the oxidation of chlorpyrifos to chlorpyrifos oxon as an approximation based on empirical bench scale laboratory data that indicate chlorpyrifos rapidly oxidizes to form chlorpyrifos oxon almost completely during typical water treatment (chlorination). (Ref. 77). There are limited data available on the removal efficiency of chlorpyrifos prior to oxidation or the removal efficiency of chlorpyrifos oxon during the drinking water treatment process. Based on community water systems survey showing that more than 75 percent of community water systems use chlorination to disinfect drinking water in the United States (Ref. 78), the assumption of exposure to chlorpyrifos oxon equivalent to 100% conversion of chlorpyrifos is not considered overly conservative. It is possible that some drinking water treatment procedures, such as granular activated carbon filtration and water softening (increased rate of chlorpyrifos oxon hydrolysis at pH > 9) could reduce the amount of chlorpyrifos oxon in finished drinking water; however, these treatment methods are not typical practices across the country for surface water.

While there is the potential to have both chlorpyrifos and chlorpyrifos oxon present in finished drinking water, no information is available to readily quantify how much of each form remains in the finished water. In the absence of available information, EPA conservatively assumes that 100% of chlorpyrifos that enters a drinking water treatment facility exists after treatment and that during treatment 100% of it converts to chlorpyrifos oxon.

Although chlorpyrifos oxon has a hydrolysis half-life of 5 days, the drinking water treatment simulation half-life for chlorpyrifos oxon is approximately 12 days. (Refs. 79, 80, and 81). Hydrolysis of chlorpyrifos oxon under simulated drinking water treatment processes is slower when compared to hydrolysis of chlorpyrifos oxon in water only; thus, the use of a half-life of 12 days under simulation. Therefore, once chlorpyrifos oxon forms during treatment, little transformation is expected to occur before consumption (during drinking water distribution). There are a wide range of treatment processes and sequences of treatment processes employed at community water systems across the country and there are limited data available on a community-water-system-specific basis to assess the removal or transformation of chlorpyrifos during treatment. These processes are not specifically designed to remove pesticides and pesticide transformation products including chlorpyrifos and chlorpyrifos oxon. In general, drinking water treatment processes, with the exception of activated carbon (Ref. 82), have been shown to have little impact on removal of conventional pesticides.

To illustrate the range of EDWC, two maximum label rate application scenarios were selected to represent high and low end exposures, *i.e.,* tart cherries at 5 applications totaling 14.5 pounds per acre per year, and bulb onions at a single application of one pound per acre per year, respectively. To estimate groundwater EDWCs for chlorpyrifos and chlorpyrifos oxon, EPA conducted a conservative Tier I assessment using SCI–GROW (Screening Concentration in Groundwater, version 2.3, August 8, 2003) and PRZM-Groundwater (PRZM–GW version 1.0, December 11, 2012), using the GW–GUI (Graphical User Interface, version 1.0, December 11, 2012). (Ref. 83). For this assessment, EPA used the results from the model (either SCI–GROW or PRZM–GW) that provided the highest EDWCs. Despite the conservative assumptions used in the Tier I models, as presented below in Table 7 estimated groundwater EDWCs are well below the DWLOCs and therefore do not represent a risk concern.

To calculate the national screening level surface water EDWCs for chlorpyrifos and chlorpyrifos oxon, EPA used the Tier II Surface Water Concentration Calculator (SWCC) version 1.106. The SWCC uses PRZM version 5.0+ (PRZM5) and the Variable Volume Water Body Model (VVWM). PRZM is used to simulate pesticide transport as a result of runoff and erosion from an agricultural field. VVWM estimates environmental fate and transport of pesticides in surface water. For the national screen, upper and lower bound exposure scenarios for surface water were modeled using the highest application rate (tart cherries), and the lowest application rate (bulb onions). This analysis showed that even with only one application, several chlorpyrifos uses may exceed the DWLOC at rates lower than maximum labeled rates (both single as well as yearly), including an application rate of one pound per acre per year. The analysis also showed that the DWLOC exceedances are not expected to be uniformly distributed across the country. The application of chlorpyrifos to tart cherries in Michigan resulted in concentrations that exceeded the drinking water level of concern (DWLOC); whereas, chlorpyrifos applications to bulb onions in Georgia resulted in concentrations below the DWLOC. To investigate with more specificity whether other chlorpyrifos application scenarios may result in concentrations that exceed the DWLOC, a screen (A risk assessment screen is a procedure designed to quickly separate out pesticides uses patterns that meet the safety standard from those that may not meet the safety standard) of all available surface water modeling scenarios was completed considering three different application dates and a single application at several different application rates that ranged from one to six pounds.

EPA also conducted a refined, but limited analysis of the spatial distribution of EDWCs at a regional level and at the drinking water intake level. This exercise demonstrated that chlorpyrifos applications will result in variable drinking water exposures that are highly localized, with concentrations of concern generally occurring in small watersheds where there is a high percent cropped area where chlorpyrifos use is expected.

Finally, EDWCs were also compared to monitoring data. This analysis showed that when modeling scenarios are parameterized to reflect reported use and EDWCs are adjusted to reflect percent cropped area, the EDWCs are within a range of 10x of the measured concentrations reported in the monitoring data. In addition, evaluation of the monitoring data further illustrates that exposures are highly localized. EPA is currently conducting a broader refined assessment that examines EDWCs on a regional and/or watershed scale to pin-point community drinking water systems where exposure to chlorpyrifos oxon as a result of chlorpyrifos applications may pose an exposure concern. As a result of the *PANNA* decision ordering EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA has not been able to complete that assessment in advance of this proposed rule. EPA is continuing that assessment and will update this action with the results of that assessment, as warranted.

Estimated Aggregate RiskÐNational Drinking Water Screen Results. To determine whether the EDWC exceeds the steady state DWLOC of 3.9 ppb, as noted above, EPA initially conducted a bounding estimate of exposure using a screening level national assessment approach. The results of that exercise are reported in Table 7 for Tier I groundwater and Tier II surface water model simulations.

TABLE 7—ESTIMATED DRINKING WATER CONCENTRATIONS RESULTING FROM THE USE OF CHLORPYRIFOS

Residue	Surface water				Groundwater
	1-in-10 Year peak concentration ppb	21-Day average concentration ppb	1-in-10 Year annual average concentration ppb	30 Year annual average concentration ppb	SCI–GROW Tier I concentration ppb
Michigan Tart Cherries					
Chlorpyrifos	129	83.8	39.2	29.7	0.16
Chlorpyrifos-oxon	123	80.0	37.4	28.3	0.15
Georgia Onion					
Chlorpyrifos	6.2	3.1	1.2	0.8	0.01
Chlorpyrifos-oxon	5.9	3.0	1.1	0.8	0.01

SCI–GROW resulted in higher EDWCs than PRZM–GW simulations.

As Table 7 makes clear, the surface water EDWCs for the high application rate Michigan tart cherry scenario significantly exceed the steady state DWLOC of 3.9 ppb for chlorpyrifos oxon, while the low application rate Georgia bulb onion scenario results in EDWC below the DWLOC. Given that the results of the initial bounding estimate showed these mixed results, EPA conducted a further evaluation of additional use scenarios to determine which chlorpyrifos uses do and do not exceed the DWLOC, based on a single application of chlorpyrifos per year at 1 and 4 pounds (where permitted by labeling) of chlorpyrifos per acre. The results for 1 and 4 pounds per acre are reported here as a representation of what EPA believes to be the range of likely chlorpyrifos applications, bearing in mind that chlorpyrifos can be applied at lower and higher single rates (*e.g.,* an application rate of 6 pounds per acre on citrus). This analysis showed that the current maximum application rate scenarios, as well as maximum single application rates for a wide range of chlorpyrifos use scenarios, may result in a 21-day average concentration that exceeds the DWLOC. Table 8 represents the use scenarios that resulted in exceedances of the DWLOC from a single application to the crop and it shows the estimated percentage of 21-day intervals over a 30-year period for which the average concentration is expected to exceed the DWLOC.

TABLE 8—NATIONAL SCREENING RESULTS USING DWLOC APPROACH—SCENARIO REPRESENTATION AND LABELED RATE COMPARISON FOR EXAMPLE USES THAT EXCEED THE DWLOC

Scenario	Highest 21-day average concentration ppb (application date)	21-Day exceedance count	Represented use site examples (maximum single application rate)
		Percent [a]	
1 lb a.i./A			
MScornSTD	16.5 at 1.0 lb a.i./A	21	Corn [2 lb a.i./A (aerial and ground)].
TXcornOP	13.9 at 1.0 lb a.i./A	13	Soybean [1 lb a.i./A (aerial); 2.2 (ground)].
ILcornSTD	14.6 at 1.0 lb a.i./A	16	
MScotton	19.8 at 1.0 lb a.i./A [e]	16	Cotton [1 lb a.i./A (foliar aerial and ground); seed treatment
NCcotton	14.4 at 1.0 lb a.i./A	25	permitted at 2.2 lb a.i./A].
TXcotton	15.1 at 1.0 lb a.i./A	8	
NYgrape	15.7 at 1.0 lb a.i./A	27	Grape [2.25 lab a.i./A (ground)].
TXsorghumOP	25.8 at 1.0 lb a.i./A	12	Wheat [1 lb a.i./A (aerial and ground)].
			Sunflower [2 lb a.i./A (aerial and ground)].
TXwheatOP	21.0 at 1.0 lb a.i./A	6	*Other Grains:*
			Sorghum [3.3 lb a.i./A (granular) [b]].
			Alfalfa [1 lb a.i./A (aerial and ground)].
PAVegetableNMC	21.1 at 1.0 lb a.i./A	18	Vegetables and Ground Fruit:
			Strawberry [2 lb a.i./A (aerial and ground)].
			Radish [3 lb a.i./A (ground) [d]].
			Pepper [1 lb a.i./A (ground)] Onion [1 lb a.i./A (ground)].
CAlettuce	12.8 at 1.0 lb a.i./A	8	
MEpotato	10.7 at 1.0 lb a.i./A	17	*Other Row Crops:*
NCsweetpotatoSTD	13.5at 1.0 lb a.i./A	9	Tobacco [2 lb a.i./A (aerial and ground)].
			Sugarbeets [2 lb a.i./A (granular) [b]].
			Peanuts [4 lb a.i./A (granular) [c]] Sweet Potato [2 lb a.i./A (aerial and ground)].
2 lb a.i./A			
MIcherriesSTD	19.6 at 2.0 lb a.i./A	42	Orchards and Vineyards (Tree fruit and Nuts):
GApecansSTD	20.7 at 2.0 lb a.i./A	12	Fruit and Nuts [4 lb a.i./A (ground)].
			Pecans [2 lb a.i./A (air); 4.3 (ground)].

TABLE 8—NATIONAL SCREENING RESULTS USING DWLOC APPROACH—SCENARIO REPRESENTATION AND LABELED RATE COMPARISON FOR EXAMPLE USES THAT EXCEED THE DWLOC—Continued

Scenario	Highest 21-day average concentration ppb (application date)	21-Day exceedance count	Represented use site examples (maximum single application rate)
		Percent [a]	
PAapples	29.1 at 2.0 lb a.i./A	11	Apple [2 lb a.i./A (air and ground)]. Peach [2 lb a.i./A (air); 3 (ground)].
NCPeanutSTD	21.0 at 2.0 lb a.i./A	21	Peanut: 2.0 lb a.i./A (aerial and ground) 4 lb a.i./A (granular ground).
FLCitrusSTD	10.1 at 2.0 lb a.i./A	6	Citrus: 6.0 lb a.i./A [ground including airblast]. 2.3 lb a.i./A (aerial).

[a] The highest percent of 21-day time periods where the average concentration exceeds the DWLOC. There are approximately 10,000 21-day time periods per 30 year simulation; however, it should be noted that not all scenarios contain exactly 30 years of weather data.
[b] (1.0 (air and ground)).
[c] (2.0 (air and ground)).
[d] Incorporated or in furrow otherwise (1.0 (air and ground)).
[e] A preplant seed treatment is permitted at 2.2 lb a.i./A and assumes 100% of the applied material washes off the seed coat in the field and is available for transport.

In summary, EPA's analysis shows that the current maximum single application rates for a wide range of chlorpyrifos use scenarios result in a 21-day average concentration that exceeds the DWLOC. And the analysis makes clear that exceedances may occur with considerable frequency.

Regional Screen. Although Table 8 makes clear that numerous labeled chlorpyrifos uses result in exceedances of the DWLOC on a national basis, EPA analysis indicates that exposure is likely to be highly localized. While it is currently challenging to assess exposure on a local scale due to the unavailability of data and wide range of characteristics (*e.g.,* environmental characteristics such as soil, weather, etc. or other variables such as drinking water treatment processes) that affect the vulnerability of a given community drinking water system to chlorpyrifos oxon contamination, EPA developed a method to examine the potential geospatial concentration differences for two Hydrological Unit Code (HUC) 2 Regions—HUC 2 Region 17: Pacific Northwest and HUC 2 Region 3: South Atlantic-Gulf, in order to identify use patterns that may result in EDWCs that exceed the DWLOC on a regional basis. (Ref. 84). This analysis considered all potential chlorpyrifos use sites within the HUC 2 regions based on the National Agricultural Statistics Service cropland data layers and survey data. For HUC 2 Region 17, only four chlorpyrifos use patterns were identified as a potential concern based on maximum single application rates of 1 and 4 pounds per acre. However, for HUC 2 Region 3, several chlorpyrifos use scenarios were identified that could exceed the DWLOC, based on the use of available scenarios.

Watershed Screen. The uses that exceeded the DWLOC from the regional screening exercise for HUC 2 Region 3 were further explored by utilizing the DWI watershed database. This analysis shows an overlap of potential chlorpyrifos use sites that may result in an exceedance of the DWLOC with watersheds that supply source water for community drinking water systems. In addition, this analysis shows that exposure is not uniform within a HUC 2 Region and that some watersheds are more vulnerable than others. Watershed vulnerability is expected to be greatest for smaller watersheds with high percent cropped areas. Smaller community water systems are generally more vulnerable due to short distribution times and the reliance of chlorination to treat source surface water as well as limited access to other treatment methods such as granular activated carbon.

As noted above, on August 10, 2015, the *PANNA* decision ordered EPA to issue either a proposed or final revocation rule or a full and final response to PANNA–NRDC administrative Petition by October 31, 2015. As a result of that order, EPA is issuing this proposed revocation in advance of completing its refined drinking water assessment. As a result, EPA may update this action with a new or modified drinking water analyses as EPA completes additional work after this proposal.

Monitoring Data Analysis. In EPA's PHHRA in 2011, the agency evaluated water monitoring data from the USGS National Water Quality Assessment Program (NAWQA), USEPA/USGS Pilot Reservoir Monitoring Program, USDA PDP, and California Department of Pesticide Regulation (CDPR). The monitoring data showed chlorpyrifos detections at low concentrations, generally not exceeding 0.5 µg/L. For example, USGS NAWQA, which contains an extensive monitoring dataset for chlorpyrifos and chlorpyrifos oxon, reports a peak chlorpyrifos detection of 0.57 µg/L in surface water with a detection frequency of approximately 15%. CDPR has detected chlorpyrifos concentrations greater than 1 µg/L in surface water on several occasions, with an observed peak chlorpyrifos concentration of 3.96 µg/L. Sampling frequencies in these monitoring programs were sporadic, however, and generally range from only once per year to twice per month.

Since the preliminary assessment, EPA has evaluated additional water monitoring data from Washington State Department of Ecology and Agriculture (WSDE/WSDA) Cooperative Surface Water Monitoring Program (Refs. 85 and 86), Dow AgroSciences (Ref. 87), and Oregon Department of Environmental Quality. The previously referenced data have also been re-examined to consider short-term exposure (*i.e.,* 21-day average concentrations) considering the importance of the single day exposure and the temporal relationship of exposure. A summary of all surface water monitoring data examined to date for chlorpyrifos are presented in Table 9. Some of the monitoring programs analyzed for chlorpyrifos oxon; however, the number of detections as well as the concentrations were generally much lower. Since the majority of the conversion of chlorpyrifos to chlorpyrifos oxon is

assumed to occur during drinking water treatment, and not in the environment, the monitoring data presented in Table 9 are limited to chlorpyrifos and not its oxon.

TABLE 9—SURFACE WATER MONITORING DATA SUMMARY FOR CHLORPYRIFOS

Monitoring data	Scale	Years of sampling (number of samples)	Detection frequency (%)	Maximum concentration (µg/L)
USGS NAWQA	National	1991–2012 (30,542)	15	0.57
California Department of Pesticide Regulation.	State	1991–2012 (13,121)	20	3.96
Washington State Department of Ecology and Agriculture Cooperative Surface Water Monitoring Program.	State	2003–2013 (4,091)	8.4	0.4
USDA Pesticide Data Program	National	2004–2009 (raw water; 1,178) 2001–2009 (finished water; 2,918).	0	na
USGS–EPA Pilot Drinking Water Reservoir.	National	1999–2000 (323)	5.3	0.034
Oregon Department of Environmental Quality.	Watershed (Clackamas)	2005–2011 (363)	13	2.4
MRID 44711601 (Ref. 87)	Watershed (Orestimba Creek)	1996–1997 (1,089)	61	2.22

In general, the monitoring data include sampling sites that represent a wide range of aquatic environments including small and large water bodies, rivers, reservoirs, and urban and agricultural locations, but are limited for some areas of the United States where chlorpyrifos use occurs. Also, the sampling sites, as well as the number of samples, vary by year. In addition, the vulnerability of the sampling site to chlorpyrifos contamination varies substantially due to use, soil characteristics, weather and agronomic practices. While almost all samples in the monitoring results are below EPA's lowest DWLOC (infant steady state exposures) of 3.9 ppb, none of the monitoring programs examined to date were specifically designed to target chlorpyrifos use (except the Registrant Monitoring Program Ref. 87); therefore, peak concentrations (and likely 21-day average concentrations) of chlorpyrifos and chlorpyrifos oxon likely went undetected in these programs. See Table 9 for a summary of the chlorpyrifos surface water monitoring data.

As a general matter, sampling frequency needs to be approximately equal to the duration of exposure concern. (Ref. 88). The chlorpyrifos monitoring data evaluated thus far also show that as sample frequency increases, so does the detection frequency. This is evident in the registrant-submitted monitoring data, as well as examination of individual sampling sites within the various datasets. The highest detection frequency noted for chlorpyrifos is for Marion Drain (a sample site in Washington), where 103 samples were collected between 2006 and 2008, with 53 chlorpyrifos detections (51%).

Therefore, while there is a large number of individual samples collected and analyzed for chlorpyrifos (or chlorpyrifos oxon) across the United States, it would not be appropriate to combine these data sources to generate exposure estimates or to use these datasets to represent exposure on a national or even regional basis. Thus, comparing the monitoring data results to the DWLOC would not be a reasonable approach for the reasons given above, including limited sample frequency, limited use information, and sampling site variability, on a national or even a regional basis. EPA believes that model estimated concentrations provide more suitable upper bound concentrations for chlorpyrifos and chlorpyrifos oxon.

Additionally, model simulations were completed to represent two different water monitoring datasets—WSDE/WSDA Cooperative Surface Water Monitoring Program (Refs. 85 and 86) and Dow AgroSciences (Ref. 87) Orestimba Creek. For both of these water monitoring programs, enough information was available, including chlorpyrifos use information as well as the PCA, to parameterize the model. In these simulations, the modeled EDWCs were similar to the measured concentrations. This suggests that the modeling results are not overly conservative and supports the use of the model to estimate chlorpyrifos oxon concentrations in drinking water.

As noted above, EPA is continuing to work to refine its drinking water assessment with the goal of pinpointing regions or watersheds where EDWCs may exceed the DWLOC. This effort would include completing the regional assessment presented here for all HUC 2 Regions and crop uses, as well as considering multiple applications per year. Because of the *PANNA* decision ordering EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA has not been able to complete this more refined drinking water assessment for chlorpyrifos in advance of this proposed rule. As a result, this proposal does not provide a basis for supporting a more tailored approach to risk mitigation. EPA is continuing to conduct its regional and water-intake level assessment and may update this action with the results of that assessment when it is completed.

Summary. EPA's examination of chlorpyrifos agricultural use across the country indicates that there are multiple uses of chlorpyrifos that may result in exposure to chlorpyrifos oxon in finished drinking water at levels that exceed the 21-day steady state DWLOC of 3.9 ppb for infants and children. EPA therefore believes that infants and children in some portions of the country are at some risk from cholinesterase inhibition. While there are uncertainties associated with the model input parameters for which conservative assumptions were made (*e.g.,* one aerobic aquatic metabolism half-life value multiplied by the uncertainty factor of three, stable to hydrolysis, 100% of the cropped watershed is treated, and use of the Index Reservoir as the receiving waterbody), the

modeling is sufficiently representative of some vulnerable water bodies that we cannot make a safety finding based on drinking water exposure. Comparison of model estimated concentrations with measured concentrations suggests that model estimates are consistent with measured concentrations when actual application rates and representative SWCC scenarios are considered and a PCA adjustment factor is applied to the model estimates. This modeling/monitoring comparison suggests that when growers use maximum application rates, or even rates much lower than maximum, chlorpyrifos oxon concentrations in drinking water could pose an exposure concern for a wide range of chlorpyrifos uses. However, these exposures are not expected to be uniformly distributed across the country. As noted, additional analyses are still being conducted in an effort to determine the community water systems where concentrations may be of concern. While that evaluation may ultimately lead to a more tailored approach to risk mitigation, at this point in time, based on the information before EPA, EPA cannot determine that current dietary exposures to chlorpyrifos are safe within the meaning of FFDCA section 408(b)(2)(A). Additionally, although EPA's current assessment indicates that the tolerances for food service and food handling establishments by themselves would not present an unsafe risk (since they do not result in drinking water exposure), because EPA must aggregate all dietary and non-occupational exposures to chlorpyrifos in making a safety finding under the FFDCA, EPA cannot find that any current tolerances are safe and is therefore proposing to revoke all chlorpyrifos tolerances. As noted, however, EPA is soliciting comment on whether it may be possible to retain some group of tolerances.

vii. Cumulative exposure/risk characterization. Section 408(b)(2)(D)(v) of the FFDCA provides that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from the pesticide's residues when considered together with other substances that have a common mechanism of toxicity. Chlorpyrifos is a member of the OP class of pesticides, which share AChE inhibition as a common mechanism of toxicity. The agency completed a cumulative risk assessment for OPs in connection with FIFRA reregistration and FFDCA tolerance reassessment (Ref. 10) which can be found on EPA's Web site *http://www.epa.gov/pesticides/cumulative/rraop/.* To the extent that chlorpyrifos tolerances and uses remain following this action, prior to the completion of the FIFRA registration review for chlorpyrifos and the OP class, OPP will update the OP cumulative assessment to ensure that cumulative dietary exposures to the OPs are safe.

C. When do these actions become effective?

EPA is proposing that the revocation of the chlorpyrifos tolerances for all commodities become effective 180 days after a final rule is published. The agency believes this revocation date will allow users to exhaust stocks and allow sufficient time for passage of treated commodities through the channels of trade. However, if EPA is presented with information that unused stocks would still be available and that information is verified, the agency will consider extending the expiration date of associated tolerances. If you have comments regarding stocks of remaining chlorpyrifos products and whether the effective date allows sufficient time for treated commodities to clear the channels of trade, please submit comments as described under **SUPPLEMENTARY INFORMATION.**

Any commodities listed in this proposal treated with the pesticides subject to this proposal, and in the channels of trade following the tolerance revocations, shall be subject to FFDCA section 408(1)(5), as established by FQPA. That section provides that, any residues of the subject pesticide in or on such food shall not render the food adulterated so long as it is shown to the satisfaction of the Food and Drug Administration that:

1. The residue is present as the result of an application or use of the pesticide at a time and in a manner that was lawful under FIFRA, and

2. The residue does not exceed the level that was authorized at the time of the application or use to be present on the food under a tolerance or exemption from tolerance. Evidence to show that food was lawfully treated may include records that verify the dates when the pesticide was applied to such food.

VII. International Residue Limits and Trade Considerations

The tolerance revocations in this proposal are not discriminatory and are designed to ensure that both domestically-produced and imported foods meet the food safety standard established by the FFDCA. The same food safety standards apply to domestically produced and imported foods.

In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and agricultural practices. EPA considers the international maximum residue limits (MRLs) established by the Codex Alimentarius Commission (Codex), as required by FFDCA section 408(b)(4). The Codex Alimentarius is a joint United Nations Food and Agriculture Organization/World Health Organization food standards program, and it is recognized as an international food safety standards-setting organization in trade agreements to which the United States is a party.

EPA also ensures that its tolerance decisions are in keeping with the World Trade Organization's Sanitary and Phytosanitary Measures Agreement. Consistent with that agreement, the effective date EPA is proposing for the revocation of chlorpyrifos tolerances in this proposed rule ensures that the tolerances will remain in effect for a period sufficient to allow a reasonable interval for producers in the exporting countries to adapt to the requirements of these modified tolerances.

VIII. Statutory and Executive Order Reviews

In this proposed rule, EPA is proposing to revoke specific tolerances established under FFDCA section 408. The Office of Management and Budget (OMB) has exempted this type of action (*e.g.,* tolerance revocation for which extraordinary circumstances do not exist) from review under Executive Order 12866, entitled ''Regulatory Planning and Review'' (58 FR 51735, October 4, 1993). Because this proposed rule has been exempted from review under Executive Order 12866, this proposed rule is not subject to Executive Order 13211, entitled ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355, May 22, 2001).

This proposed rule does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), or impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*). Nor does it require any special considerations as required by Executive Order 12898, entitled ''Federal Actions to Address Environmental Justice in Minority Populations and Low-Income

Populations'' (59 FR 7629, February 16, 1994); or OMB review or any other Agency action under Executive Order 13045, entitled ''Protection of Children from Environmental Health Risks and Safety Risks'' (62 FR 19885, April 23, 1997). However, EPA considered the best available science in order to protect children against environmental health risks and this proposed rule is consistent with EPA's 1995 Policy on Evaluating Health Risks to Children (*http://www2.epa.gov/sites/production/files/201405/documents/1995_childrens_health_policy_statement.pdf*), reaffirmed in 2013 (*http://www2.epa.gov/sites/production/files/201405/documents/reaffirmation_memorandum.pdf*).

This proposed rule does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note). In addition, the Agency has determined that this proposed rule will not have a substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled ''Federalism'' (64 FR 43255, August 10, 1999). This proposed rule directly regulates growers, food processors, food handlers, and food retailers, not States. This proposed rule does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). For these same reasons, the Agency has determined that this proposed rule does not have any ''tribal implications'' as described in Executive Order 13175, entitled ''Consultation and Coordination with Indian Tribal Governments'' (65 FR 67249, November 9, 2000).

I certify that this action will not have a significant economic impact on a substantial number of small entities under the Regulatory Flexibility Act (RFA), 5 U.S.C. 601 *et seq.* The small entities subject to this proposed action, which directly regulates growers, food processors, food handlers, and food retailers, include small businesses but not small government jurisdiction or small not-for-profit organizations as defined by the RFA.

For purposes of assessing the impacts of this proposed revocation on small businesses, a small business is defined either by the number of employees or by the annual dollar amount of sales/revenues. The level at which an entity is considered small is determined for each NAICS code by the Small Business Administration (SBA). Farms are classified under NAICS code 111, Crop Production, and the SBA defines small entities as farms with total annual sales of $750,000 or less.

Based upon the screening analysis completed (Ref. 89), EPA has determined that less than 39,000 of the 1.2 million small farms nationwide, or approximately 3% of all small farms, may be impacted by this proposed revocation. Of these, 38,000 have potential impacts of less than 1% of gross farm revenue. The analysis indicates that fewer than 1,000 small farms, or 0.1% percent of all small farms, may experience impacts greater than 1%, depending on the availability and cost of alternatives. Based on this analysis, EPA concludes that revoking all tolerances for chlorpyrifos will not have a significant economic impact on a substantial number of small entities. Details of this analysis are presented in EPA's analyses which can be found in the docket (Ref. 89).

IX. References

EPA has established an official record for this rulemaking. The official record includes all information considered by EPA in developing this proposed rule including documents specifically referenced in this action and listed below, any public comments received during an applicable comment period, and any other information related to this action, including any information claimed as CBI. This official record includes all information physically located in docket ID number EPA–HQ–OPP–2015–0653, any documents identified in this proposal, and documents referenced in documents in the docket. The public version of the official record does not include any information claimed as CBI.

1. U.S. EPA (2014). Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Available in docket number EPA–HQ–OPP–2008–0850, *http://www.regulations gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0195.*
2. The Petition from NRDC and PANNA and EPA's various responses to it are available in docket number EPA–HQ–OPP–2007–1005 available at *www.regulations.gov.*
3. U.S. EPA (2011). Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review. Available in docket number EPA–HQ–OPP–2008–0850, *http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0025.*
4. Information and software related to Dietary Exposure Evaluation Model and the Calendex models is available at *http://www.epa.gov/pesticides/science/deem/.*
5. For information related to Section 408 of FFDCA see *http://www2.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act.*
6. For information on the EPA's Office of Pesticide Programs risk assessment process see *http://www.epa.gov/pesticides/about/overview_risk_assess.htm.*
7. U.S. EPA (2000). Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern. Available at *http://www.epa.gov/oppfead1/trac/science/trac2b054.pdf.*
8. Information on the water exposure models used by EPA's Office of Pesticide Programs is available at *http://www.epa.gov/oppefed1/models/water/models4.htm.*
9. FIFRA Scientific Advisory Panel (2008). ''The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos.'' Report from the FIFRA Scientific Advisory Panel Meeting of September 16–19, 2008. Available: *http://www2.epa.gov/sap/fifra-scientific-advisory-panel-meetings.*
10. FIFRA Scientific Advisory Panel (2012). ''Scientific Issues Associated with Chlorpyrifos''. Available at: *http://www2.epa.gov/sap/meeting-materials-april-10-12-2012-scientific-advisory-panel.*
11. FIFRA Scientific Advisory Panel (2002). ''Organophosphate Pesticides: Preliminary OP Cumulative Risk Assessment.'' Information on how to obtain the meeting report is available at *http://www2.epa.gov/sap/fifra-scientific-advisory-panel-meetings.*
12. U.S. EPA (2006). Revised Organophosphorous Pesticide Cumulative Risk Assessment. Available at *http://www.epa.gov/pesticides/cumulative/2006-op/index.htm.*
13. Chambers, J.E. (2013). *In vitro* Sensitivity of Cholinesterase to Inhibition by Chlorpyrifos-oxon in Several Tissues of the Rat. College of Veterinary Medicine, Mississippi State University.
14. Calhoun LL, Johnson KA. (1988) Chlorpyrifos: 4-Day Dermal Probe and 21-Day Dermal Toxicity Studies in Fischer 344 Rats. MRID 40972801.
15. Corley, R.; Landry, T.; Calhoun, L.; *et al.* (1986) Chlorpyrifos: 13-Week Nose-only Vapor Inhalation Exposure Study in Fischer 344 Rats. MRID 40013901.
16. Corley, R.; Landry, T.; Calhoun, L.; *et al.* (1986) Chlorpyrifos: 13-Week Nose-only Vapor Inhalation Exposure Study in Fischer 344 Rats: Supplemental Data: Lab. MRID 40166501.
17. Newton, P. (1988) AThirteen Week Nose-Only Inhalation Toxicity Study of Chlorpyrifos Technical (Pyrinex) in the Rat. MRID 40908401.
18. Hotchkiss, J.; Krieger, S.; Brzak, K.; *et al.* (2010) Acute Inhalation Exposure of Adult Crl: CD (SD) Rats to Particulate Chlorpyrifos Aerosols: Kinetics of Concentration-Dependent Cholinesterase (ChE) Inhibition in Red Blood Cells, Plasma, Brain, and Lung. MRID 48139303.

19. U.S. EPA (2011) Chlorpyrifos: Review of the Comparative Cholinesterase (including chlorpyrifos oxon), special acute inhalation study and immunotoxicity studies (MRIDs 48139301, 48139303, 48139304). TXR No. 0055409.
20. Hotchkiss, J.; Krieger, S.; Mahoney, K.; *et al.* (2013) Nose-only Inhalation of Chlorpyrifos Vapor: Limited Toxicokinetics and Determination of Time-dependent Effects on Plasma, Red Blood Cell, Brain and Lung Cholinesterase Activity in Femal CD(SD): Crl Rats. MRID 49119501.
21. Hotchkiss, J.; Krieger, S.; Mahoney, K.; *et al.* (2013) Nose-Only Inhalation of Chlorpyrifos-Oxon Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain and Lung Cholinesterase Activity in Female CD(SD): Crl Rats. MRID 49210101.
22. U.S. EPA (2002). Revised Organophosphorous Pesticide Cumulative Risk Assessment. Available at *http://www.epa.gov/pesticides/cumulative/rra-op/.*
23. U.S. EPA (2006). Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. Available at *http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668.*
24. Timchalk, C., *et al.,* 2002a. Monte Carlo analysis of the human chlorpyrifos-oxonase (PON1) polymorphism using a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model. Toxicology Letters. 135, 51.
25. Timchalk, C., *et al.,* 2002b. A Physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for the organophosphate insecticide chlorpyrifos in rats and humans. Toxicological Sciences. 66, 34–53.
26. U.S EPA FIFRA Scientific Advisory Panel. (2011). ''Chlorpyrifos Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK–PD) Modeling linked to Cumulative and Aggregate Risk Evaluation System (CARES).'' Report from the FIFRA Scientific Advisory Panel Meeting of February 15–18, 2011. Available at *http://www2.epa.gov/sap/fifra-scientific-advisory-panel-meetings.*
27. U.S. EPA 2014. Chlorpyrifos: Quality Assurance Assessment of the Chlorpyrifos Physiologically Based Pharmacokinetic/Pharmacodynamic Model for Human Health Risk Assessment Applications. TXR No. 0056896. Available at *http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0843.*
28. U.S. EPA. Exposure Factors Handbook 2011 Edition (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R–09/052F, 2011. Available at *http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.*
29. NHANES/WWEIA survey and supporting documentation is available at *http://www.ars.usda.gov/Services/docs.htm?docid=13793.*
30. US EPA (2012). Standard Operating Procedures for Residential Pesticide Exposure Assessment available at *http://www.epa.gov/pesticides/science/USEPA-OPP-HED_Residential%20SOPs_Oct2012.pdf.*
31. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation Available at *http://www2.epa.gov/osa/guidance-applying-quantitative-data-develop-data-derived-extrapolation-factors-interspecies-and.*
32. Dow AgroSciences (2014), P. Price. Development of Chemical Specific Adjustment Factors for Chlorpyrifos and Chlorpyrifos Oxon Using Target Red Blood Cell Acetyl Cholinesterase Inhibition Levels of 10%, 5%, and 1%. Available at *http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0218.*
33. U.S. EPA (2002). Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment. Available at *http://www.epa.gov/oppfead1/trac/science/determ.pdf).*
34. Aldridge, J. E., Levin, E. D., Seidler, F. J., & Slotkin, T. A. (2005). Developmental exposure of rats to chlorpyrifos leads to behavioral alterations in adulthood, involving serotonergic mechanisms and resembling animal models of depression. Environ Health Perspect, 113(5), 527–531.
35. Icenogle, L. M., Christopher, N. C., Blackwelder, W. P., Caldwell, D. P., Qiao, D., Seidler, F. J., *et al.* (2004). Behavioral alterations in adolescent and adult rats caused by a brief subtoxic exposure to chlorpyrifos during neurulation. Neurotoxicol Teratol, 26(1), 95–101.
36. Levin, E. D., Addy, N., Baruah, A., Elias, A., Christopher, N. C., Seidler, F. J., *et al.* (2002). Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations. Neurotoxicol Teratol, 24(6), 733–741.
37. Levin, E. D., Addy, N., Nakajima, A., Christopher, N. C., Seidler, F. J., & Slotkin, T. A. (2001). Persistent behavioral consequences of neonatal chlorpyrifos exposure in rats. Brain Res Dev Brain Res, 130(1), 83–89.
38. Billauer-Haimovitch, H., Slotkin, T. A., Dotan, S., Langford, R., Pinkas, A., & Yanai, J. (2009). Reversal of chlorpyrifos neurobehavioral teratogenicity in mice by nicotine administration and neural stem cell transplantation. Behav Brain Res, 205(2), 499–504.
39. Jett, D. A., Navoa, R. V., Beckles, R. A., & McLemore, G. L. (2001). Cognitive function and cholinergic neurochemistry in weanling rats exposed to chlorpyrifos. Toxicol Appl Pharmacol, 174(2), 89–98.
40. Turgeman, G., Pinkas, A., Slotkin, T. A., Tfilin, M., Langford, R., & Yanai, J. (2011). Reversal of chlorpyrifos neurobehavioral teratogenicity in mice by allographic transplantation of adult subventricular zone-derived neural stem cells. J Neurosci Res, 89(8), 1185–1193.
41. Slotkin TA, Card J, Infante A, Seidler FJ. (2013) Prenatal dexamethasone augments the sex-selective developmental neurotoxicity of chlorpyrifos: Implications for vulnerability after pharmacotherapy for preterm labor. Neurotoxicol Teratol. 37:1–12.
42. Ohishi T, Wang L, Akane H, Itahashi M, Nakamura D, Yafune A, Mitsumori K, Shibutani M. (2013). Reversible effect of maternal exposure to chlorpyrifos on the intermediate granule cell progenitors in the hippocampal dentate gyrus of rat offspring. Reprod. Toxicol. 35:125–136.
43. Berkowitz, G. S., Obel, J., Deych, E., Lapinski, R., Godbold, J., Liu, Z., Wolff, M. S. (2003). Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. Environ Health Perspect, 111(1), 79–84.
44. Whyatt, R. M., Barr, D. B., Camann, D. E., Kinney, P. L., Barr, J. R., Andrews, H. F., . . . Perera, F. P. (2003). Contemporary-use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority mothers and newborns. Environ Health Perspect, 111(5), 749–756.
45. Whyatt, R. M., Garfinkel, R., Hoepner, L. A., Andrews, H., Holmes, D., Williams, M. K., . . . Barr, D. B. (2009). A biomarker validation study of prenatal chlorpyrifos exposure within an inner-city cohort during pregnancy. Environ Health Perspect, 117(4), 559–567.
46. Whyatt, R. M., Garfinkel, R., Hoepner, L. A., Holmes, D., Borjas, M., Williams, M. K., . . . Camann, D. E. (2007). Within- and between-home variability in indoor-air insecticide levels during pregnancy among an inner-city cohort from New York City. Environ Health Perspect, 115(3), 383–389.
47. Bradman, A., Whitaker, D., Quiros, L., Castorina, R., Claus Henn, B., Nishioka, M., . . . Eskenazi, B. (2007). Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. J Expo Sci Environ Epidemiol, 17(4), 331–349. doi: 10.1038/sj.jes.7500507.
48. Engel SM, Berkowitz GS, Barr DB, Teitelbaum SL, Siskind J, Meisel SJ, Wetmur JG, Wolff MS. Prenatal Organophosphate Metabolite and Organochlorine Levels and Performance on the Brazelton Neonatal Behavioral Assessment Scale in a Multiethnic Pregnancy Cohort. American Journal of Epidemiology. 2007;165:1397–1404.
49. Young, J. G., Eskenazi, B., Gladstone, E. A., Bradman, A., Pedersen, L., Johnson, C., . . . Holland, N. T. (2005). Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. Neurotoxicology, 26(2), 199–209. doi: 10.1016/j.neuro.2004.10.004.
50. Rauh, V. A., Garfinkel, R., Perera, F. P., Andrews, H. F., Hoepner, L., Barr, D. B., . . . Whyatt, R. W. (2006). Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics, 118(6), e1845–1859.
51. Whyatt, R. M., Rauh, V., Barr, D. B., Camann, D. E., Andrews, H. F., Garfinkel, R., . . . Perera, F. P. (2004).

Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect, 112(10), 1125–1132.
52. Engel, S. M., Wetmur, J., Chen, J., Zhu, C., Barr, D. B., Canfield, R. L., & Wolff, M. S. (2011). Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. Environ Health Perspect, 119(8), 1182–1188. doi: 10.1289/ehp.1003183.
53. Eskenazi, B., Marks, A. R., Bradman, A., Harley, K., Barr, D. B., Johnson, C., . . . Jewell, N. P. (2007). Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect, 115(5), 792–798. doi: 10.1289/ehp.9828.
54. Eskenazi, B., Huen, K., Marks, A., Harley, K. G., Bradman, A., Barr, D. B., & Holland, N. (2010). PON1 and neurodevelopment in children from the CHAMACOS study exposed to organophosphate pesticides in utero. Environ Health Perspect, 118(12), 1775–1781. doi: 10.1289/ehp.1002234.
55. Furlong, Melissa A., Engel, Stephanie M., Boyd Barr, Dana, Wolff, Mary S. Prenatal exposure to organophosphate pesticides and reciprocal social behavior in childhood. 2014. Environment International 70:125–131.
56. Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D. B., & Whyatt, R. (2011). Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect, 119(8), 1196–1201.
57. Bouchard, M. F., Chevrier, J., Harley, K. G., Kogut, K., Vedar, M., Calderon, N., . . . Eskenazi, B. (2011). Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect, 119(8), 1189–1195. doi: 10.1289/ehp.1003185.
58. Rauh, V. A., Perera, F. P., Horton, M. K., Whyatt, R. M., Bansal, R., Hao, X., . . . Peterson, B. S. (2012). Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci U S A, 109(20), 7871–7876. doi: 10.1073/pnas.1203396109.
59. The Federal Letter- Review of Chlorpyrifos Epidemiology Studies is available at *http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170.*
60. Billauer-Haimovitch, H., Slotkin, T. A., Dotan, S., Langford, R., Pinkas, A., & Yanai, J. (2009). Reversal of chlorpyrifos neurobehavioral teratogenicity in mice by nicotine administration and neural stem cell transplantation. Behav Brain Res, 205(2), 499–504.
61. U.S.EPA (1998). Guidelines for Neurotoxicity RiskAssessment. Available at *http://archive.epa.gov/raf/web/pdf/neurotox.pdf.*
62. Ricceri, L., Markina, N., Valanzano, A., Fortuna, S., Cometa, M. F., Meneguz, A., *et al.* (2003). Developmental exposure to chlorpyrifos alters reactivity to environmental and social cues in adolescent mice. Toxicol Appl Pharmacol, 191(3), 189–201.
63. Venerosi, A., Calamandrei, G., & Ricceri, L. (2006). A social recognition test for female mice reveals behavioral effects of developmental chlorpyrifos exposure. Neurotoxicol Teratol, 28(4), 466–471.
64. Venerosi, A., Ricceri, L., Rungi, A., Sanghez, V., & Calamandrei, G. (2010). Gestational exposure to the organophosphate chlorpyrifos alters social-emotional behaviour and impairs responsiveness to the serotonin transporter inhibitor fluvoxamine in mice. Psychopharmacology (Berl), 208(1), 99–107.
65. Hoberman, A. (1999) Developmental Neurotoxicity Study of Chlorpyrifos Administered Orally via Gavage to Crl: CDBR VAF/Plus Presumed Pregnant Rats: Report Supplement 2: Lab Project Number: 301–001: K–044739–109. Unpublished study prepared by Argus Research Laboratories, Inc. (MRID 44787301).
66. Chen X-P, Chen W-Z, Wang F-;S, Liu J-X. (2012) Selective cognitive impairments are related to selective hippocampus and prefrontal cortex deficits after prenatal chlorpyrifos exposure. Brain Res. 1474:19–28.
67. Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. (2010). Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides.Pediatrics. 2010 Jun;125(6):e1270–7. doi: 10.1542/peds.2009–3058.
68. Rauh, V. A., Perera, F. P., Horton, M. K., Whyatt, R. M., Bansal, R., Hao, X., . . . Peterson, B. S. (2012). Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci U S A, 109(20), 7871–7876.
69. Lovasi, G. S., Quinn, J. W., Rauh, V. A., Perera, F. P., Andrews, H. F., Garfinkel, R., . . . Rundle, A. (2011). Chlorpyrifos exposure and urban residential environment characteristics as determinants of early childhood neurodevelopment. Am J Public Health, 101(1), 63–70.
70. U.S. EPA (2014). Chlorpyrifos: Updated Drinking Water Assessment for Registration Review. Available in docket number EPA–HQ–OPP–2008–0850, *http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0198.*
71. U.S. EPA (2002). Aggregate Risk Assessment for Trichloropyridinol (TCP) Metabolite of Triclopyr (PC Code 116001), Chlorpyrifos (PC Code 059101), and Chlorpyrifos-methyl (PC Code 059102). Barcode D283101.
72. U.S. EPA (2011). Chlorpyrifos: Revised Acute (Probabilistic) and Chronic Dietary Exposure and Risk Assessments for Food only (with and without Food Handling Use included) and for Water Only for the Registration Review Action—Typical Use Rates/Water Included. D388166.
73. U.S. EPA (2014). Usage Report in Support of Chlorpyrifos (059101). Available at *www.regulations.gov* in docket number EPA–HQ–OPP–2008–0850.
74. U.S. EPA (2014). Chlorpyrifos: Updated Occupational and Residential Exposure Assessment for Registration Review. D424484. Available at *http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0196.*
75. J.C. Moore, J.C. Dukes, J.R. Clark, J. Malone, C.F. Hallmon, and P.G. Hester. Downwind Drift and Deposition of Malathion on Human Targets From Ground Ultra-Low Volume Mosquito Sprays; Journal of the American Mosquito Control Association; Vol. 9, No. 2 (June, 1993).
76. N.S. Tietze, P.G. Hester, and K.R. Shaffer. Mass Recovery of Malathion in Simulated Open Field Mosquito Adulticide Tests: Archives of Environmental Contamination and Toxicology; 26: 473–477 (1994).
77. Duirk, S. E.; Collette, T. W.; Degradation of Chlorpyrifos in Aqueous Chlorine Solutions: Pathways, Kinetics, and Modeling. Environ. Sci. Technol., 2006, 40(2), 546–550.
78. Community Water System Survey 2006; U.S. Environmental Protection Agency, Washington, DC 20460 May 2009 (survey data) available at *http://www.epa.gov/oppefed1/models/water/Development_and_Use_of_Community_Water_System.pdf.*
79. Tunink, A. Chlorpyrifos-oxon: Determination of hydrolysis as a function of pH, 2010. (MRID 48355201)
80. Wu, J.; Laird, D. A. Abiotic Transformation of Chlorpyrifos to Chlorpyrifos Oxon in Chlorinated Water. Environ. Toxcol. Chem., 2003, 22(2), 261–264.
81. Tierney, D. P.; Christensen, B. R.; Culpepper, V. C. Chlorine Degradation of Six Organophosphate Insecticides and Four Oxons in Drinking Water Matrix. Submitted by Syngenta Crop Protection, Inc. 2001. (MRID 45513501)
82. Progress Report on Estimating Pesticide Concentrations in Drinking Water and Assessing Water Treatment Effects on Pesticide Removal and Transformation: A Consultation. FIFRA Scientific Advisory Panel Meeting, September 29, 2000. Information on obtaining the report is available at *http://www2.epa.gov/sap/fifra-scientific-advisory-panel-meetings.*
83. To access EPA's water models go to *http://www.epa.gov/oppefed1/models/water/.*
84. Additional information related to HUCs can be found at *http://water.usgs.gov/GIS/huc.html.*
85. Sargeant, D., Dugger, D., Newell, E., Anderson, P., Cowles, J. Surface Water Monitoring Program for Pesticides in Salmonid-Bearing Streams 2006–2008 Triennial Report, February 2010 (Washington State Department of Ecology and Washington State Department of Agriculture) *https://fortress.wa.gov/ecy/publications/summarypages/1003008.html; http://agr.wa.gov/PestFert/natresources/docs/swm/2008_swm_report.pdf.*
86. Sargeant, D., Newell, E., Anderson, P., Cook, A. Surface Water Monitoring Program for Pesticides in Salmonid-Bearing Streams 2009–2011 Triennial

Report, February 2013 (Washington State Department of Ecology and Washington State Department of Agriculture) *http://agr.wa.gov/FP/Pubs/docs/377-SWM2009-11Report.pdf.*

87. Poletika, N.; Robb, C. (1998) A Monitoring Study to Characterize Chlorpyrifos Concentration Patterns and Ecological Risk in an Agriculturally Dominated Tributary of San Joaquin River: Lab Project Number: ENV96055. Unpublished study prepared by Dow AgroSciences and Paragon Research. (MRID 44711601).
88. U.S. EPA (2012). FIFRA SAP: Problem Formulation for the Reassessment of Ecological Risks from the Use of Atrazine, June 12–14, 2012, Docket Number: EPA–HQ–OPP–2012–0230 at *www.regulations.gov.*
89. U.S. EPA (2015). Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances. Available at *www.regulations.gov* in docket number EPA–HQ–OPP–2015–0653.
90. U.S. EPA (2014). Chlorpyrifos Acute and Steady State Dietary (Food Only) Exposure Analysis to Support Registration Review. Available at *www.regulations.gov* in docket number EPA–HQ–OPP–2008–0850.

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: October 28, 2015.

Jack E. Housenger,

Director, Office of Pesticide Programs.

Therefore, it is proposed that 40 CFR chapter I be amended as follows:

PART 180—[AMENDED]

■ 1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

§ 180.342 [Removed]

■ 2. Remove § 180.342.

[FR Doc. 2015–28083 Filed 11–5–15; 8:45 am]

BILLING CODE 6560–50–P

service fees listed in § 250.125 of this part for a pipeline ROW grant to install a new pipeline, or to convert an existing lease term pipeline into an ROW pipeline. An application to modify an approved ROW grant must be accompanied by the additional rental required under § 250.1012, if applicable. You must file a separate application for each ROW. The service fee for a pipeline ROW grant application is divided into two levels based on water depth, as shown in the following table:

Application type	Description
(1) Shallow water applications	Applications for a pipeline ROW grant for pipelines that will be located in their entirety within water depths of 1,000 feet or less.
(2) Deepwater applications	Applications for a pipeline ROW grant for pipelines, any portion of which will be located in water depths greater than 1,000 feet.

* * * * *

■ 7. In § 250.1303, revise paragraph (d) to read as follows:

§ 250.1303 How do I apply for voluntary unitization?

* * * * *

(d) You must pay the service fee listed in § 250.125 of this part with your request for a voluntary unitization proposal or the expansion of a previously approved voluntary unit to include additional acreage. Additionally, you must pay the service fee listed in § 250.125 with your request for unitization revision. The service fee for a request for unitization revision is divided into two levels, as shown in the following table:

Application type	Description
(1) Exhibits A and B	Applications for revisions to Exhibit A and/or Exhibit B or designation of Successor Unit Operators and/or Successor Unit Sub-operators.
(2) Exhibit C	Applications for revisions to Exhibit C.

[FR Doc. 2016–27500 Filed 11–16–16; 8:45 am]

BILLING CODE 4310–VH–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2015–0653; FRL–9954–65]

Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is announcing and inviting comment on additional information obtained and developed by EPA in conjunction with the proposed tolerance revocation for chlorpyrifos. This information includes the revised human health risk assessment and the drinking water assessment. It also includes EPA's issue paper and supporting analyses presented to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel's (SAP) meeting in April 2016 that addressed chlorpyrifos biomonitoring data and adverse neurodevelopmental outcomes, public comments received during the meeting, the FIFRA SAP's meeting minutes and the FIFRA SAP report. EPA is specifically soliciting comments on the validity and propriety of the use of all the new information, data, and analyses. EPA is accepting comment on the information and analysis, as well as reopening comment on any other aspect of the proposal or the underlying support documents that were previously available for comment. The EPA continues to seek comment on possible mitigation strategies, namely, use deletions, which might allow the EPA to retain a small subset of existing chlorpyrifos food uses. Commenters need not resubmit comments previously submitted. EPA will consider those comments, as well as comments in response to this notice, in taking a final action.

DATES: Submit comments on or before January 17, 2017.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2015–0653, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- *Mail:* OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001.
- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at *http://www.epa.gov/dockets/contacts.html.*

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *http://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: Dana Friedman, Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001; telephone number: (703) 347–8827; email address: *friedman.dana@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. How should I submit Confidential Business Information (CBI) to the Agency?

Do not submit this information to EPA electronically. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

II. Purpose of This Document

EPA is reopening the comment period on the proposed rule: Entitled ''Chlorpyrifos; Tolerance Revocations'' (80 FR 69080, November 6, 2015) (FRL–

9935–92), herein referred to as the ''proposed rule,'' for the purpose of obtaining public comment on the additional information and analyses announced in this document and which may be relevant to the development of a final action. EPA is also accepting comment on any other aspect of the proposal or the underlying support documents that were previously available for comment. As explained in the proposed rule, the timing of EPA's issuance of the proposal was dictated by an August 10, 2015 order by the U.S. Court of Appeals for the Ninth Circuit in *Pesticide Action Network North America (PANNA)* v. *EPA,* No. 14–72794. The *PANNA* decision directed EPA to respond by October 31, 2015 to PANNA and the Natural Resource Defense Council's (NRDC) petition to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations. As a result of that timing, EPA had not yet completed portions of its scientific assessment when it issued the proposed rule. Specifically, EPA noted that it issued the proposed rule in advance of completing a refined drinking water assessment and without conducting additional analysis of the hazard from chlorpyrifos in response to comments received on EPA's December 2014 Revised Human Health Risk Assessment. Accordingly, EPA noted in the proposed rule that it would update the proposal with any new or modified analyses, as EPA completed additional work after the proposal and, to the extent practicable, EPA would provide the public an opportunity to comment on that work prior to issuing a final rule. Consistent with that commitment, EPA is today seeking comment on the following documents that were not available for public comment during the prior comment period on the proposed rule: *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (2016);* the materials and final report from the 2016 Chlorpyrifos SAP; and *Chlorpyrifos Registration Review Drinking Water Assessment.*

EPA's revised analyses do not result in a change to the EPA's proposal to revoke all tolerances but it does modify the methods and risk assessment used to support that finding in accordance with the advice of the SAP. The revised analysis indicates that expected residues of chlorpyrifos on most individual food crops exceed the ''reasonable certainty of no harm'' safety standard under the Federal Food, Drug, and Cosmetic Act (FFDCA). In addition, the majority of estimated drinking water exposures from currently registered uses, including water exposures from non-food uses, continue to exceed safe levels even taking into account more refined drinking water exposures. Accordingly, based on current labeled uses, the agency's analysis provided in this notice continues to indicate that the risk from the potential aggregate exposure does not meet the FFDCA safety standard. EPA can only retain chlorpyrifos tolerances if it is able to conclude that such tolerances are safe. EPA has not identified a set of currently registered uses that meets the FFDCA safety standard because it is likely only a limited number of food uses alone, and in combination with predicted drinking water exposures, would meet the standard. Further, EPA has not received any proposals for mitigation that registrants may be willing to undertake that would allow the EPA to retain any of the tolerances subject to this rulemaking. EPA continues to seek comment on possible mitigation strategies, namely, use deletions, which might allow the EPA to retain a small subset of existing chlorpyrifos food uses.

EPA consulted the FIFRA SAP for scientific advice on its analysis of biomonitoring data at a meeting on April 19–21, 2016, at which time, the public also had an opportunity to provide comment. The FIFRA SAP was asked to address the use of the epidemiological study *The Mothers and Newborn Study of North Manhattan and South Bronx* performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University to establish a new toxicological endpoint and associated point of departure for chlorpyrifos based on observed adverse neurodevelopmental outcomes in children resulting from prenatal exposure to chlorpyrifos. While the residential uses that resulted in chlorpyrifos exposures in the CCCEH study were cancelled in 2000, EPA believes this study remains relevant in evaluating risks from exposure to currently registered uses. In its presentation to the SAP, EPA proposed to use biomonitoring data (cord blood concentrations) identified in the CCCEH study (Rauh *et al.,* 2006 and Rauh *et al.,* 2011) as the basis for its point of departure. The FIFRA SAP provided feedback indicating that it did not believe using the cord blood data from that study was appropriate to establish a new point of departure. The SAP's primary criticism was that there was not enough data on the relationship between cord blood concentrations at birth to exposures at and around the time of chlorpyrifos application to support its use in quantitative risk assessment. Further, the FIFRA SAP noted that EPA's assessment did not identify a particular window of exposure within the prenatal period linked to the effects reported. Generally, however, the FIFRA SAP agreed with the overall conclusion of the CCCEH study, *i.e.* the association between prenatal chlorpyrifos exposure and neurodevelopmental outcomes in children.

The final FIFRA SAP report provides a detailed account of the uncertainties associated with the agency's April 2016 proposed approach to selecting the point of departure and its use in quantitative risk assessment. It also outlines the SAP's concern that ''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 (RBC) acetylcholinesterase (AChE) inhibition'' (FIFRA SAP, 2016, p. 18). The FIFRA SAP recommended that EPA should derive the point of departure for neurodevelopmental effects using the ''estimated peak blood concentration or time weighted average blood concentration within the prenatal period'' (FIFRA SAP, 2016, p. 42).

After careful consideration of public comments and the SAP's recommendations, EPA has concluded the most appropriate path for reconciling the SAP's concerns is to follow through on the SAP's recommendation to use a time weighted average approach. The agency agrees with the 2016 FIFRA SAP (and previous SAPs) that there is a potential for neurodevelopmental effects associated with chlorpyrifos exposure to occur at levels below 10% RBC AChE inhibition, and that EPA's existing point of departure (which is based on 10% AChE inhibition), is therefore not sufficiently health protective.

As detailed in *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (2016),* in order to follow up on the SAP's recommendation that the point of departure should be based on blood concentrations at the time of exposure to chlorpyrifos (rather than based on cord blood at the time of delivery), EPA evaluated the most likely chlorpyrifos application method to determine peak exposures to the CCCEH study cohort experiencing neurodevelopmental effects in children. EPA contacted the technical pest advisor responsible for overseeing New York City's housing authority in order to confirm the application method used at the time the CCCEH study was conducted. Based on those conversations and a review of the

registered uses available during that period, EPA concluded that crack and crevice treatments were the most likely exposure pattern among those use patterns registered at the time of the study and therefore has used these exposures as the basis for a new point of departure.

EPA generally selects the dose at which no toxicological effects are demonstrated to ensure our regulatory endpoint reflects a level of exposure that does not present a risk concern. However, the CCCEH study only supported the determination of a lowest observed adverse effects level (LOAEL). In situations where the agency selects a POD from a study where a no observed adverse effects level (NOAEL) has not been identified, EPA generally will retain the Food Quality Protection Act (FQPA) safety factor of 10X to account for the uncertainty in using a LOAEL. The 2016 revised risk assessment retains this uncertainty factor for chlorpyrifos and also applies a 10X uncertainty factor for intraspecies variability because of the lack of sufficient information to reduce or remove this factor.

The external exposure was calculated based on the assumptions and methods outlined in the EPA's 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment and chemical-specific exposure data, where available. Specifically, the 2012 Residential SOPs, which were peer reviewed by the FIFRA SAP in October 2009, were used to predict the potential exposures which could have occurred to individuals in the cohort for the indoor crack and crevice pesticide use pattern.

EPA then used the chlorpyrifos physiologically based pharmacokinetic (PBPK) model to estimate the study cohort mothers' systemic dose related to the LOAEL by (1) determining time-weighted average (TWA) blood levels from women exposed to chlorpyrifos from indoor exposures to the cancelled crack and crevice use and (2) using the crack and crevice TWA blood level as the internal dose for determining points of departure for infants, children, and adults exposed to chlorpyrifos using current exposure potential. The use of the PBPK model to assess internal dosimetry from various exposure scenarios continues to be supported by the SAP. This applies to the crack and crevice scenario identified as the most likely exposure pattern in the CCCEH study, where women were potential exposed via the dermal, oral, and inhalation routes. The detailed rationale is presented in *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (2016).*

EPA has also completed, and is making available for public comment, *Chlorpyrifos Registration Review Drinking Water Assessment.* EPA conducted a national screening level drinking water assessment in 2014. Because of the court decision ordering EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA was not able to complete a more refined drinking water assessment for chlorpyrifos in advance of the proposed rule. Since that time EPA conducted the refined drinking water assessment with the intention of providing a basis for supporting a more tailored approach to risk mitigation. In the proposal, EPA proposed revoking all tolerances largely because the agency could not make a safety finding based on drinking water exposure in highly-vulnerable watersheds. EPA reasoned if it could better identify where such vulnerable areas might be, it could be possible for registrants to amend product labeling in ways that might make unnecessary some number of the proposed tolerance revocations.

Chlorpyrifos Registration Review Drinking Water Assessment serves to combine, update and complete the work presented in the 2011 and 2014 drinking water assessments for chlorpyrifos as part of the registration review process. This document specifically focuses on the exposure estimates for surface water. The 2014 assessment presented an approach for deriving more regionally-specific estimated drinking water exposure concentrations for chlorpyrifos and chlorpyrifos-oxon for two water resource regions, hydrologic unit code (HUC)-02. This assessment updates those exposure assessments and provides estimates for the remaining (*i.e.,* 19) HUC-02 regions. Urban uses, which had not previously been assessed, are included in this update. This assessment also includes statistical analysis of all available monitoring data for chlorpyrifos and chlorpyrifos-oxon. While this drinking water assessment is more refined than the previous assessments, as a general matter, the results did not allow for identification of many areas where potential exposures of concern to drinking water can be ruled out. As a result, this assessment does not significantly alter the conclusions in the proposed rule regarding drinking water exposure and continues to indicate potential exposure to chlorpyrifos or chlorpyrifos-oxon in finished drinking water across the country based on currently labeled uses. This is supported by both model estimated concentrations as well as measured chlorpyrifos concentrations in surface water across the United States.

Section IV of this Notice of Data Availability (NODA) describes all additional data and analyses and how they impact the EPA's proposal. Note, however, that this NODA does not provide an exhaustive presentation of the additional data and analysis that EPA is placing in the associated docket and seeking comment on. All the information subject to this notice can be accessed as described in section III of this notice.

EPA is providing notice on these additional analyses to provide an opportunity for the public to submit additional data or information for the agency's consideration as it develops the final rule. Since EPA is still in the process of deliberating the provisions of a final rule, EPA cannot definitively state whether this information will provide support for any provision of the final rule, or that the agency has determined that it is appropriate to rely on this information in developing the final rule.

On December 10, 2015, the Ninth Circuit issued a further order requiring EPA to complete any final rule and fully respond to the PANNA and NRDC petition by December 30, 2016. On June 30, 2016, EPA sought a 6-month extension to that deadline in light of the SAP's recommendation at the meeting and in order to allow EPA to fully consider the SAP's written report. The FIFRA SAP report was finalized and made available for EPA consideration on July 20, 2016. The court rejected EPA's request for a 6-month extension and ordered EPA to complete its final action by March 31, 2017 (an extension of 3 months). The court also announced that no further extensions to that date would be granted.

III. Where can the information identified in this document be found?

The information that EPA is be made available for public review and comment can be found in the following dockets: EPA–HQ–OPP–2015–0653, the docket for the proposed tolerance revocations, and EPA–HQ–OPP–2016–0062, the FIFRA SAP docket, which contains the Chlorpyrifos Issue Paper and supporting materials. Both dockets can be accessed through *http://www.regulations.gov.* As noted, EPA is also reopening the comment period to allow for comment on any aspect of the proposed revocation published on November 6, 2015 (80 FR 69080) (FRL–9935–92).

IV. What analysis and data are being noticed?

1. EPA is seeking comment on the following updates to the chlorpyrifos human health risk assessment: (1) Use of the crack and crevice scenario to derive an exposure level for women in the Columbia study; (2) using the LOAEL from the Columbia study and PBPK modeling to derive an endpoint for use in quantitative risk assessment; (3) use of the 10X uncertainty factor for intraspecies variability; (4) use of the 10X FQPA safety factor for LOAEL to NOAEL extrapolation (please include your rationale for any alternative values suggested for this factor). Its analysis is included in the *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (2016),* which is available in the chlorpyrifos tolerance revocation docket (EPA–HQ–OPP–2015–0653).

2. EPA is also making available for comment the issue paper and associated materials presented to the April 2016 FIFRA SAP and the final report of the SAP. The FIFRA SAP materials and final report are available in the FIFRA SAP docket (EPA–HQ–OPP–2016–0062).

3. EPA is also seeking comment on *Chlorpyrifos Registration Review Drinking Water Assessment,* a highly refined drinking water assessment that updates and completes the agency's examination of exposure through drinking water for all registered uses of chlorpyrifos. This assessment integrates regionally specific (*i.e.,* spatially relevant) estimated drinking water concentrations and an extensive evaluation of available surface water monitoring data for chlorpyrifos and chlorpyrifos-oxon. The assessment considers both agricultural and non-agricultural uses of chlorpyrifos, a sensitivity analysis for model estimated concentrations, and statistical evaluation of surface water monitoring data.

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: November 10, 2016.

Richard P. Keigwin, Jr.,

Acting Director, Office of Pesticide Programs.

[FR Doc. 2016–27552 Filed 11–16–16; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 271

[EPA–R07–RCRA–2016–0637; FRL–9955–24-Region 7]

State of Nebraska; Authorization of State Hazardous Waste Management Program

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: Nebraska has applied to the Environmental Protection Agency (EPA) for final authorization of revisions to its hazardous waste program under the Resource Conservation and Recovery Act (RCRA). EPA is proposing to grant final authorization to Nebraska.

DATES: Comments on this proposed action must be received in writing by December 19, 2016.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA–R07–RCRA–2016–0637, to *http://www.regulations.gov*. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from *Regulations.gov*. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.* on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit *http://www2.epa.gov/dockets/commenting-epa-dockets*.

FOR FURTHER INFORMATION CONTACT: Lisa Haugen, EPA Region 7, Enforcement Coordination Office, 11201 Renner Boulevard, Lenexa, Kansas 66219, phone number: (913) 551–7877, or email address: *haugen.lisa@epa.gov*.

SUPPLEMENTARY INFORMATION: In the final rules section of the **Federal Register**, EPA is authorizing the revisions by a direct final rule. EPA did not make a proposal prior to the direct final rule because we believe this action is not controversial and do not expect comments that oppose it. We have explained the reasons for this authorization in the preamble of the direct final rule. If no relevant adverse comments are received in response to this action, no further activity is contemplated in relation to this action. If EPA receives relevant adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed action. EPA will not institute a second comment period on this action. Any parties interested in commenting on this action should do so at this time. Please note that if EPA receives adverse comment on part of this rule and if that part can be severed from the remainder of the rule, EPA may adopt as final those parts of the rule that are not the subject of an adverse comment. For additional information, see the direct final rule which is located in the rules section of this **Federal Register**.

Dated: November 3, 2016.

Mark Hague,

Regional Administrator, Region 7.

[FR Doc. 2016–27683 Filed 11–16–16; 8:45 am]

BILLING CODE 6560–50–P

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]

DOCKET NUMBER EPA-HQ-OPP-2021-0523

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:

---

[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]

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

. . .

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.

[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.

Submitted by:

Patti A. Goldman
Earthjustice
810 Third Avenue, Suite 610
Seattle, WA 98104
T: (206) 578-5868
pgoldman@earthjustice.org

Attorney for LULAC Petitioners