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

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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.

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[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)..

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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

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[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).

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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).

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[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.

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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

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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

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[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)

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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

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[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,

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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

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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

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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.").

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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

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[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

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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%

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[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.

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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]

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[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.

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- 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.

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[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.

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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.

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[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.

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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.)

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[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

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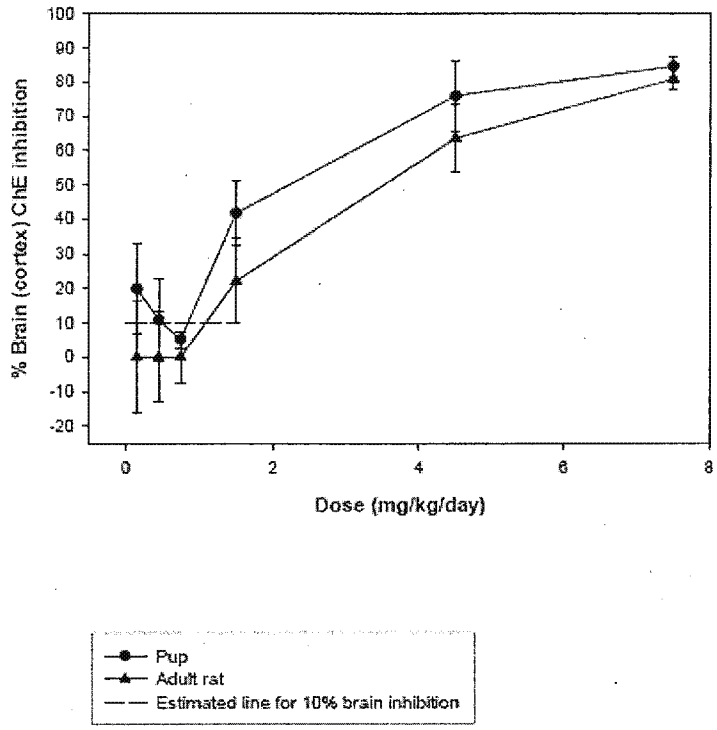
Figure I.B-3 Plot of chlorpyrifos data from Zheng et al (2000).



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

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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.

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[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

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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

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[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.

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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.

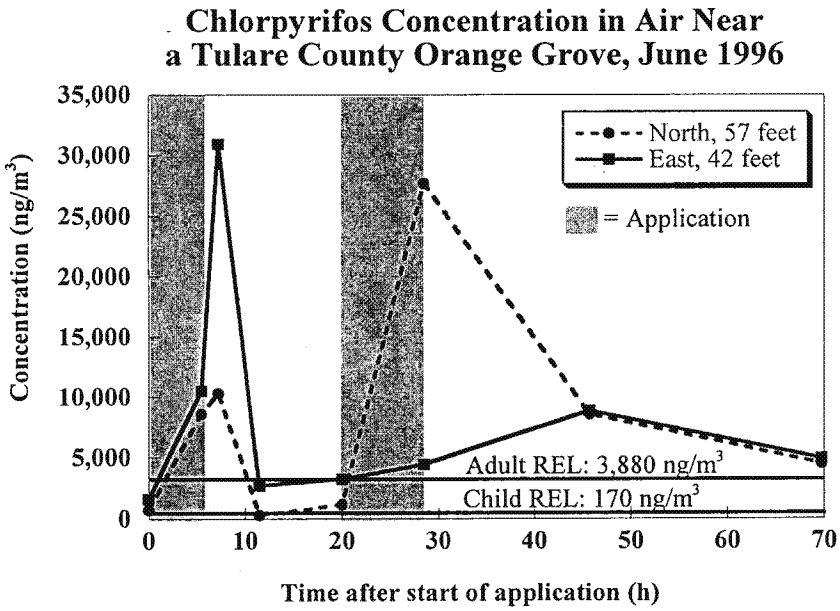

Figure 1: Chlorpyrifos air concentrations peaked approximately 2.5 hours after the end of the first application and again during the second application. Substantial volatilization continued for several days after application and exceeded 24-hour RELs for both adults and children for much of the sampling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

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

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.

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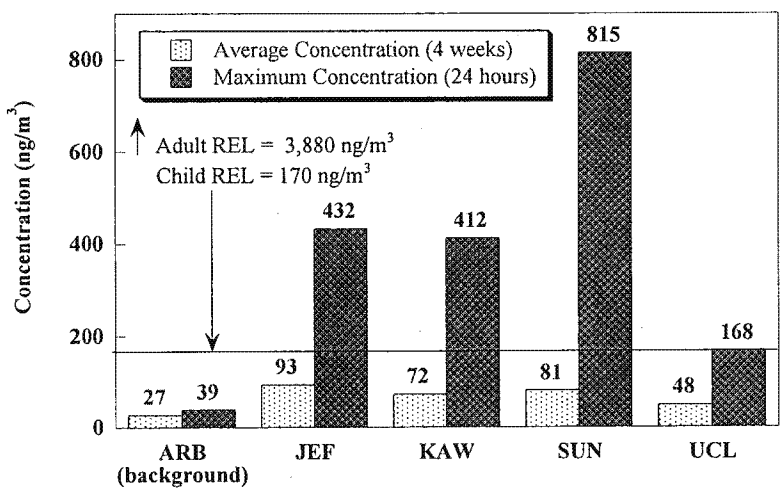
applications under different wind conditions (30,950 ng/m^3 vs. 27,700 ng/m^3) suggest that peak air concentrations may be quite predictable based on the vapor pressure of the pesticide, a fact consistent with other work in the peer-reviewed literature.[75]

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.

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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

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[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).

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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.

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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

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[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

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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.

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[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).

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Dated: 12 September 2007

cc: Administrator Stephen Johnson
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