

Developmental and Reproductive Toxicant Identification Committee  
Office of Environmental Health Hazard Assessment  
Proposition 65 Implementation Office  
P.O. Box 4010, MS-58D  
1001 I Street  
Sacramento, California 95814

October 24, 2017

**Re: Consideration of Chlorpyrifos for possible Prop 65 listing based on developmental toxicity**

Dear Chairperson Gold and Developmental and Reproductive Toxicant Identification Committee Members,

The following comments are submitted on behalf of the undersigned individuals and organizations, none of whom have any financial interest in the topic of these comments.

The U.S Environmental Protection Agency (EPA)'s previous risk assessments make clear the potential for adverse health effects in children after fetal exposure to chlorpyrifos, one of the most commonly used organophosphate pesticides (OP).<sup>1</sup> EPA concluded that the observed neurodevelopmental impacts in children following prenatal chlorpyrifos exposures occur at levels below those that trigger cholinesterase inhibition in the pregnant mother.<sup>2</sup>

Data from toxicological studies has found disruption in neuronal development, neurotransmitter systems and synaptic formation as well as behavioral and cognitive impairments in test animals following perinatal chlorpyrifos exposure, including at exposure levels below those that cause cholinesterase inhibition.<sup>3</sup>

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<sup>1</sup> USEPA, "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review.," December 29, 2014, 1–531; USEPA, "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review.," (Washington DC, 20460, November 3, 2016).

<sup>2</sup> USEPA, "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review.."

<sup>3</sup> Theodore A Slotkin, "Guidelines for Developmental Neurotoxicity and Their Impact on Organophosphate Pesticides: a Personal View From an Academic Perspective.," *Neurotoxicology* 25, no. 4 (June 2004): 631–40, doi:10.1016/S0161-813X(03)00050-0;

Justin E Aldridge, Frederic J Seidler, and Theodore A Slotkin, "Developmental Exposure to Chlorpyrifos Elicits Sex-Selective Alterations of Serotonergic Synaptic Function in Adulthood: Critical Periods and Regional Selectivity for Effects on the Serotonin Transporter, Receptor Subtypes, and Cell Signaling.," *Environmental Health Perspectives* 112, no. 2 (February 2004): 148–55;

Justin E Aldridge et al., "Developmental Exposure of Rats to Chlorpyrifos Leads to Behavioral Alterations in Adulthood, Involving Serotonergic Mechanisms and Resembling Animal Models of Depression.," *Environmental Health Perspectives* 113, no. 5 (May 2005): 527–31, doi:10.1289/ehp.7867;

Theodore A Slotkin and Frederic J Seidler, "The Alterations in CNS Serotonergic Mechanisms Caused by Neonatal Chlorpyrifos Exposure Are Permanent," *Developmental Brain Research* 158, no. 1 (August 2005): 115–19, doi:10.1016/j.devbrainres.2005.06.008;

Edward D Levin et al., "Persistent Behavioral Consequences of Neonatal Chlorpyrifos Exposure in Rats," *Developmental Brain Research* 130, no. 1 (September 2001): 83–89, doi:10.1016/S0165-3806(01)00215-2;

In dozens of epidemiologic studies, OP pesticide exposure during fetal development has been linked to developmental abnormalities of primitive reflexes in newborns, increases in mental and motor delays among preschoolers, ADHD in childhood, and decreases in working memory, verbal comprehension, perceptual reasoning, and full-scale IQ among elementary-school age children (see references for published reviews and study summaries).<sup>4</sup> Applications of OP pesticides on agricultural fields within 1.5 km of homes where pregnant women resided was associated with an increased risk of autism spectrum disorders in their children, with the strongest associations seen for chlorpyrifos exposures.<sup>5</sup>

A small preliminary prospective birth cohort study found chlorpyrifos in umbilical cord blood to be associated with volumetric changes in the brain measured by magnetic resonance imaging among school-age children. These changes were present in regions responsible for attention, receptive language processing, social cognition, and regulation of inhibition, suggesting neuroanatomic alterations that may underpin the behavioral and cognitive deficits associated with chlorpyrifos.<sup>6</sup>

Similarly, arm tremors seen in children at age 11 years following prenatal chlorpyrifos exposure,<sup>7</sup> as well as delayed synaptic development observed in rats<sup>8</sup> underscore how impacts on the central and peripheral nervous system from intrauterine exposure can be enduring and may include latent effects.

As environmental health experts, we are concerned that further evidence of harm may emerge as studies continue to follow children with documented fetal exposure or of those exposed postnatally.

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Richard D Burke et al., “Developmental Neurotoxicity of the Organophosphorus Insecticide Chlorpyrifos: From Clinical Findings to Preclinical Models and Potential Mechanisms.,” *Journal of Neurochemistry* 142, no. 2 (August 2017): 162–77, doi:10.1111/jnc.14077.

<sup>4</sup> Gonzalez-Alzaga B, Lacasana M, Aguilar-Garduno C, Rodriguez-Barranco M, Ballester F, Rebagliato M, et al. A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. *Toxicol Lett.* 2014;230(2):104-21.

Munoz-Quezada MT, Lucero BA, Barr DB, Steenland K, Levy K, Ryan PB, et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: a systematic review. *Neurotoxicology.* 2013;39:158-68.

EPA US. EPA Revised Human Health Risk Assessment on Chlorpyrifos. December 2014. Docket ID EPA-HQ-OPP-2008-0850-2014. Available at: <http://www.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos>

Koureas M, Tsakalof A, Tsatsakis A, Hadjichristodoulou C. Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes. *Toxicol Lett.* 2012;210(2):155-68.

<sup>5</sup> Janie F Shelton et al., “Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: the CHARGE Study,” *Environmental Health Perspectives*, June 23, 2014, doi:10.1289/ehp.1307044.

<sup>6</sup> V A Rauh et al., “Brain Anomalies in Children Exposed Prenatally to a Common Organophosphate Pesticide,” *Proceedings of the National Academy of Sciences* 109, no. 20 (May 15, 2012): 7871–76, doi:10.1073/pnas.1203396109.

<sup>7</sup> Virginia A Rauh et al., “Prenatal Exposure to the Organophosphate Pesticide Chlorpyrifos and Childhood Tremor.,” *Neurotoxicology* 51 (December 2015): 80–86, doi:10.1016/j.neuro.2015.09.004.

<sup>8</sup> Marina Bjørling-Poulsen, Helle Raun Andersen, and Philippe Grandjean, “Potential Developmental Neurotoxicity of Pesticides Used in Europe.,” *Environmental Health* 7, no. 1 (October 22, 2008): 50, doi:10.1186/1476-069X-7-50.

Given the astounding rate of brain growth during gestation (on average, 250,000 new neurons formed per minute),<sup>9</sup> along with myelination and further brain development postnatally, opportunities for permanent damage are enormous.

In conclusion, chlorpyrifos warrants Prop 65 listing because, as described above, it has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity in both animal models and human epidemiologic studies.

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<sup>9</sup> Elysia Poggi Davis and Donald Pfaff, "Sexually Dimorphic Responses to Early Adversity: Implications for Affective Problems and Autism Spectrum Disorder.," *Psychoneuroendocrinology* 49 (November 2014): 11–25, doi:10.1016/j.psyneuen.2014.06.014.

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