

**EVALUATION OF CHLORPYRIFOS
AS A TOXIC AIR CONTAMINANT**

Executive Summary

**Department of Pesticide Regulation
California Environmental Protection Agency**

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EXECUTIVE SUMMARY

Chlorpyrifos is a chlorinated organophosphorus (OP) ester used as an insecticide, acaricide, and miticide. Chlorpyrifos has major uses in California as an insecticide for nut trees, fruit, vegetable, and grain crops as well as non-food crop uses (e.g., golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products). Major use areas include the Central Valley, Central Coast region, and Imperial County. Use occurs year-round, with peak use during the summer. There are several dozen chlorpyrifos products registered by approximately 20 different companies. Methods of application allowed by labels include aerial, airblast, ground boom, chemigation, and others.

Chlorpyrifos first entered the comprehensive risk assessment process after being given a “High” priority status by the California Department of Pesticide Regulation (DPR) in 2011. Concerns originally focused on potential neurodevelopmental and neurobehavioral effects, genotoxicity and reproductive toxicity in rats, probable human exposure due to spray drift, possible hand-to-mouth exposure by children, and exposure through food and drinking water. The first draft risk assessment was published in December 2015. It was in that risk assessment that potential human exposure to spray drift (via inhalation or deposition) became a concern. As such, chlorpyrifos entered the formal evaluation process to determine the scientific evidence for listing it as a pesticide Toxic Air Contaminant (TAC) (CA Food & Agricultural Code §14021-14027).

Chlorpyrifos entered the formal TAC evaluation process and the first draft evaluation was published by DPR in August 2017. A subsequent revision was published in December 2017, which was reviewed by the Scientific Review Panel on Toxic Air Contaminants (SRP)¹. This 2018 final TAC evaluation reflects the SRP’s recommendation that DPR evaluate and identify the developmental neurotoxicity effects as the critical endpoint for the chlorpyrifos risk assessment.

This final TAC evaluation of chlorpyrifos reflects DPR’s thorough evaluation of the developmental neurotoxicity effects as the critical endpoint for the chlorpyrifos risk assessment. Recent *in vivo* animal studies provide evidence of neurotoxicity to developing organisms at chlorpyrifos doses below those causing cholinesterase inhibition. Effects noted include altered cognition, motor control, and behavior in rats and mice. These studies, along with epidemiological studies, are the impetus for DPR considering developmental neurotoxicity as the

¹ With the enactment of California's Toxic Air Contaminant Act, the Legislature created the statutory framework for the evaluation and control of chemicals, including pesticides, as toxic air contaminants (TACs) (Food & Agricultural Code §14021-14027). The statute defines TACs as air pollutants that may cause or contribute to increases in serious illness or death, or that may pose a present or potential hazard to human health. DPR is responsible for evaluating pesticides as TACs. The law defines specific steps DPR must follow for the identification, evaluation, and control of pollutants in ambient air in communities across California. One of those responsibilities is to extensively evaluate the potential adverse health effects of candidate pesticide TACs and estimate levels of exposure associated with their use. The SRP must review the risk assessment to determine if it is seriously deficient based upon a review of the scientific data, the procedures and methods used to support the data, and conclusions.

critical endpoint for chlorpyrifos. As such, DPR's Human Health Assessment (HHA) Branch conducted a chlorpyrifos risk assessment using developmental neurotoxicity as the endpoint based on in vivo animal findings. A target MOE of 100 was selected to be protective of human health. The target is comprised of 10x for interspecies sensitivity, 10x for intraspecies variability, and 1x for potential neurodevelopmental effects. The resulting points of departure (PoDs), reference doses (RfDs), and reference concentrations (RfCs) are also shown in Executive Summary Table 1.

Protecting against Developmental Neurotoxicity

Identification of a rigorous neurodevelopmental point of departure for chlorpyrifos would be strengthened by elucidation of a potential mechanism. Mammalian neurodevelopment is multifactorial and there are likely multiple pathways involved, some of which may be mediated via the classical cholinesterase toxicity pathway of binding and inhibiting acetylcholinesterase (AChE). Other potential mechanisms maybe covariates of this pathway, or may involve other key events at the molecular, cellular, and tissue level. While an adverse outcome pathway has not been elucidated at this time, it is important to note that developmental changes have been documented in experimental animal studies at chlorpyrifos levels below those that inhibit AChE. There is also evidence of potential associations between in utero exposure to chlorpyrifos and altered human growth and behavior later in life in the epidemiological studies. There are acknowledged uncertainties in the human evidence, including a lack of exposure-effect relationships, inconsistencies in reported outcomes across studies, and quantitative measures of chlorpyrifos exposure that vary from study to study.

As such, DPR considered protecting vulnerable subpopulations from chlorpyrifos exposure and the potential neurodevelopmental effects through the use of developmental neurotoxicity and AChE inhibition endpoints, the latter which can be considered a surrogate for developmental neurotoxicity when adjusted by an additional uncertainty factor (UF) of 10, as described below.

- 1) Point of departure based on neurodevelopmental effects.** Recent in vivo animal studies and human epidemiological studies have continued the investigations into the potential effects or associations of chlorpyrifos on neurodevelopment, growth, and behavior. HHA conducted a comprehensive review of recently available animal studies published from 2015 – 2018, especially focused on the potential for evidence of neurodevelopmental toxicity at low dose levels. Critical PoDs were established from animal studies reporting developmental neurotoxicity at dose levels that are generally considered lower than those necessary for AChE inhibition in red blood cells (RBC). As mentioned earlier, a target MOE of 100 was selected to be protective of human health. The target is comprised of 10x for interspecies sensitivity and 10x for intraspecies variability. There is no need for an additional UF for neurodevelopmental effects. The risk of exposures to inhalation and spray drift is exacerbated by consumption of food and drinking water in this approach.
- 2) Uncertainty factor of 10x applied to an AChE inhibition endpoint to account for the developmental neurotoxicity.** In its December 2017 Draft TAC Evaluation, DPR added an additional UF of 10x to account for more sensitive neurodevelopmental effects than AChE inhibition, the critical endpoint used to characterize the risk from chlorpyrifos exposure in that draft evaluation. Effects on cognition, motor control and behavior have been reported in

the human epidemiology and in vivo animal toxicology studies, the latter occurring at doses 10-fold lower than the threshold established for RBC AChE inhibition. However, neither the human epidemiological studies nor the in vivo animal studies available for our review at the time of the December 2017 draft were sufficient to derive critical PoDs for neurodevelopmental effects. Adding an additional 10x UF (resulting in a total UF of 100 when combined with the UF of 10 for variation in human sensitivity) would account for the possibility of neurodevelopmental effects, thus increasing the protection factor of the estimated RfCs and RfDs for chlorpyrifos. By increasing the total UF to 300 (see Appendix 3), DPR has further increased the protection factor and the conservativeness inherent in the chlorpyrifos proposed target RfCs and RfDs. Based on the AChE inhibition endpoint, inhalation resulting from spray drift is the exposure risk of concern.

The description of the uncertainties associated with each of these endpoints and a discussion of the weight of evidence is found in the Risk Appraisal Section.

The developmental neurotoxicity database for chlorpyrifos is evolving and currently contains five in vivo animal studies that permit the establishment of a critical oral no observed effect level (NOEL). As will be demonstrated below, the dose at which the neurodevelopmental effects occurred in these studies were similar regardless of the exposure window or the duration of the exposure. The most important implication of the five studies is that the threshold for chlorpyrifos-induced neurodevelopmental effects following exposure in early life may be 10-fold lower than the reported threshold of 1 mg/kg/day established for RBC AChE inhibition.

This final evaluation, as with the previous drafts, is intended to evaluate chlorpyrifos as a pesticide TAC as defined in the California Code of Regulations, Title 3, Section 6864. The determination of a pesticide TAC is based on the air concentration, either measured or modeled, that exceeds the RfC divided by 10. As explained in the Risk Appraisal section and Table 29 later in this document, chlorpyrifos meets the criteria of TAC designation by using either the developmental neurotoxicity endpoint or the AChE inhibition endpoint, even without the additional 10x uncertainty factor necessary to account for the fact that the developmental neurotoxicity effects occur at a lower level than AChE inhibition (see the August 2017 draft TAC evaluation of chlorpyrifos, available at https://www.cdpr.ca.gov/docs/risk/rcd/chlorpyrifos_draft_evaluation_2017.pdf).

Executive Summary Table 1. Points of Departure and Reference Dose or Concentrations used to evaluate the Risk from Exposure to Chlorpyrifos in Selected Population Subgroups for Developmental Neurotoxicity

Route	PoD ^a	RfD ^b or RfC
Uncertainty Factors (UF)		10 inter 10 intra 1 DNT
Acute Oral [mg/kg/day] Infants Children 1-2 Children 6-12 Females 13-49	0.01	0.0001
Acute Dermal [mg/kg/day]^c Infants Children 1-2 Children 6-12 Females 13-49	0.104	0.001
Acute Inhalation [mg/m³]^c Infants Children 1-2 Children 6-12 Females 13-49	0.405 0.459 0.624 0.862	0.004 0.005 0.006 0.009

^a Point of Departure (PoD): The critical acute oral PoD for chlorpyrifos is a no-observed effect level (NOEL) for developmental neurotoxicity in animals based on changes in cognition, motor control and behavior in rats and mice (Lee et al, 2015, Silva et al, 2017, Carr et al, 2017, Gómez-Giménez, 2017, 2018).

^b Reference Dose (RfD) or Reference Concentration (RfC): RfDs and RfCs are derived by dividing the appropriate PoD by the product of all uncertainty factors (UF).

^c Route to route extrapolation:

Dermal: Route specific dermal PoD: oral PoD in animals (mg/kg/day) / dermal absorption in human (9.6% ; Thongsinthusak, 1991).

Inhalation: Route specific inhalation PoD: oral dose mg/kg/day / [Breathing Rate (BR) m³/hr/Body Weight (BW) kg]; Oral PoD=0.01 mg/kg/day; Infants BR=0.188 m³/h BW= 7.6 kg; Children 1-2 yrs BR=0.283 m³/h BW=13 kg; Children 6-12 yrs BR= 0.417 m³/h, BW=26 kg; Females 13-49 yrs BR=0.833 m³/h, BW 71.8 kg (derived from Andrews and Patterson (2000) assuming 24-hr breathing rates of 0.59, 0.52, 0.38 and 0.28 m³/kg/24 hr for infants, children 1-2 yr, children 6-12 yr and females 13-49 yr, respectively.) [See Appendix 4.]