March 6, 2021

Ms. Patricio Biggio
Pesticide Re-Evaluation Division (7508P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Submitted via regulations.gov

Re: Pesticide Registration Review: Proposed Interim Decision for Chlorpyrifos; EPA-HQ-OPP-2008-0850-0964 (December 7, 2020).

Dear Ms. Biggio,

Established in 1933, CropLife America (CLA) represents the developers, manufacturers, formulators, and distributors of pesticides and plant science solutions for agriculture and pest management in the United States. CLA represents the interests of its member companies by, among other things, monitoring legislation, federal agency regulations and actions, and litigation that impact the crop protection and pest control industries and participating in such actions when appropriate. CLA's member companies produce, sell, and distribute virtually all the crop protection and biotechnology products used by American farmers.

CLA appreciates the opportunity to comment on the United States Environmental Protection Agency's (EPA or the Agency) Proposed Interim Decision (PID) for registration review of Chlorpyrifos. Our comments focus on the latest Human Health Risk Assessment for Chlorpyrifos and EPA's application of the Food Quality Protection Act (FQPA) 10x Safety Factor.

Although the most recent Human Health Risk Assessment for Chlorpyrifos was published on September 21, 2020, it relies on the 2015 "Literature Review on Neurodevelopmental Effects and FQPA Safety Factor Determination for the Organophosphates" and some additional studies (EPA, 2020). The Agency concluded that despite several years of study, the science addressing neurodevelopmental effects remains unresolved. This conclusion led to the application of a FQPA 10x Safety Factor in this registration review.

The 2015 literature review is based on a limited set of epidemiology studies, including studies from Columbia Center for Children's Environmental Health (CCCEH), Center for the Health Assessment of Mothers and Children of Salinas, and Mount Sinai School of Medicine, that are cited as evidence of neurodevelopmental effects in infants and children following exposure. However, the CCCEH study must be understood in the context of the FQPA's requirement that EPA consider the "validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue" (Federal Food, Drug, and Cosmetics Act, 2011).

Despite numerous requests, the researchers of the CCCEH study could not meet EPA's transparency needs nor agreed to the Agency's offers to anonymize the study data. This unwillingness to cooperate and provide raw data presents another reason why EPA should not adopt a 10x safety factor. In fact, due to numerous uncertainties and limitations with this study,

EPA's Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel advised against using it as a basis for drawing a definitive link between chlorpyrifos and neurodevelopmental effects or using it to establish new toxicological points of departure (POD) for exposures (Jenkins, 2012).

CLA has previously commented on additional flaws in these studies (CLA, 2015). More recent epidemiological studies from the US, France, and the Netherlands refute the conclusions of many of the studies in the 2015 literature review (Cartier et al., 2016; Donauer et al., 2016; Jusko et al., 2019). These three studies, like the Columbia study, followed children from birth to elementary school, but they did not show an adverse link between exposure and developmental outcomes.

In addition to the concerns with the use of the 2015 literature review for this registration review, we would also like to highlight specific concerns with the Human Health Risk Assessment which include:

- The evidence of alleged neurodevelopmental risks, beyond the known cholinesterase inhibition, for the adoption of the 10x safety factor for this registration review seems tenuous and at odds with other evidence. Newly released data from *in vitro* developmental neurotoxicity (DNT) assays developed by EPA's Office of Research and Development and the European Food Safety Authority support the conclusion that cholinesterase inhibition is the most sensitive toxicological endpoint for organophosphates chemicals (Masjosthusmann et al., 2020). The current body of research supports the conclusion that regulation of organophosphates using cholinesterase inhibition is protective to both pregnant mothers and their offspring. While we support EPA continuing to research these potential risks, we do not believe the evidence currently exists to justify adopting risk mitigation strategies before establishing the risk.

- The available toxicological databases for organophosphates are robust and include several high-quality guideline studies relevant to the evaluation of neurodevelopmental effects: rat multi-generation reproduction, rat and rabbit teratology, acute and sub-chronic neurotoxicity, comparative and age-related cholinesterase inhibition, and DNT studies. None of these studies have identified DNT effects below dose levels that cause cholinesterase inhibition. A review conducted by Makris and colleagues concluded that the Organization of Economic Cooperation and Development DNT guideline "represents the best available science for assessing the potential for DNT in human health risk assessment, and data generated with this protocol are relevant and reliable for the assessment of these end points" (Makris et al., 2009). They also reviewed the extensive history of international validation, peer review, and evaluation of the guideline methods using a wide variety of chemicals. The authors confirmed previous reports that the DNT guidelines can detect known human developmental neurotoxicants (Middaugh et al., 2003; Raffaele et al., 2010; Stanton & Spear, 1990). Among multiple *in vivo* DNT studies for organophosphates submitted to EPA in response to data call-ins, none identified DNT endpoints that were more sensitive than cholinesterase inhibition. These studies clearly demonstrate that regulating organophosphates based on cholinesterase inhibition protects from adverse health effects, including neurodevelopmental effects.

- The weight of evidence from available epidemiological research, including research published after the 2015 literature review used for this risk assessment, shows no link

between neurodevelopmental effects in humans and exposure to chlorpyrifos or other organophosphates. Many of the epidemiology studies used by EPA in the risk assessment have deficiencies that make them unsuitable for use in regulatory decision-making.

To conclude, the regulatory decisions made in this PID are based on studies that do not meet the legal standards of either reliable or publicly available data and perceived risks which in many instances are inconclusive. We strongly request the EPA to continue its research to validate the potential risks and revisit the literature review based on new data, information, and research that is now available before cancelling any registrations. Should you have any questions or comments, please feel free to contact me at mbasu@croplifeamerica.org or (202) 296-1585.

Sincerely,

Manojit Basu
Managing Director, Science Policy
CropLife America

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