

March 03, 2021

Pesticide Re-Evaluation Division
Office of Pesticide Programs
Environmental Protection Agency,
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Re: EPA-HQ-OPP-2008-0850

Dear Members of the Office of Pesticide Programs,

The Endocrine Society appreciates the opportunity to comment on the proposed interim registration review decision for chlorpyrifos. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization dedicated to the understanding of hormone systems and the clinical care of patients with endocrine diseases and disorders. Our membership of nearly 18,000 includes researchers who are advancing our understanding of the effects of exposures to chemicals that interfere with hormone systems, also known as endocrine-disrupting chemicals (EDCs). As an endorsing organization for the original Project TENDR consensus statement¹, we fully support the letter submitted by project TENDR summarizing the evidence linking chlorpyrifos to neurodevelopmental harm and concluding that existing chlorpyrifos tolerances do not comply with the "reasonable certainty of no harm" standard in the Food Quality Protection Act (FQPA). Our comments below offer additional evidence for EPA to consider regarding the effects of chlorpyrifos on endocrine systems.

Detailed evidence of chlorpyrifos' harm to endocrine systems is included in EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals². The diverse impacts of chlorpyrifos and its metabolites on the endocrine system include:

- sex-specific male and female reproductive and developmental abnormalities^{3,4,5}
- altered thyroid hormone levels and associated behavioral changes^{6,7}

¹Bennett et al., *Environ Health Perspect.* 2016 Jul 1;124(7):A118-22. doi: 10.1289/EHP358.

² Gore A.C., et al., *Endocrine Reviews*, Volume 36, Issue 6, 1 December 2015, Pages E1–E150, <https://doi.org/10.1210/er.2015-1010>

³ Farag AT, Radwan AH, Sorour F et al (2010) *Reprod Toxicol.* <https://doi.org/10.1016/j.reprotox.2009.10.003>

⁴ Zidan NEHA, (2009). *Int J Pharmacol.* <https://doi.org/10.3923/ijp.2009.51.57>

⁵ Nishi and Hundal., 2013. *Food Chem Toxicol.*: <https://pubmed.ncbi.nlm.nih.gov/24140463/>

⁶ <https://www.sciencedirect.com/science/article/abs/pii/S0890623809003104?via%3Dihub> (accessed Feb 25, 2021)



- weight gain due to increase in adipose tissue⁸
- binding to sex hormone-binding globulin⁹
- anti-androgenic activity and inhibition of testosterone-stimulating increased weight of accessory sex organs¹⁰, reduced testosterone levels¹¹, and estrogen receptor binding¹²
- alterations in mammary gland structure¹³; also positive associations with breast cancer in humans^{14,15}.

Consistent with our understanding of the effects of chemicals on endocrine systems during development, many of the effects described above were observed at low doses and had long term effects. Similar impacts on wildlife have also been demonstrated¹⁶.

EPA's prior review and decisions regarding chlorpyrifos reveal a fundamental flaw in how the agency has historically evaluated chemical impacts on the endocrine system. As one of the first chemicals included in the Agency's Endocrine Disruptor Screening Program, manufacturers of chlorpyrifos submitted data from guideline studies along with a "weight of evidence" assessment in 2012. Based on this limited evidence from manufacturers, EPA previously concluded that "chlorpyrifos demonstrates no convincing evidence of potential interaction with the estrogen, androgen, or thyroid pathways". We strongly disagree with this conclusion given that many of the endpoints interrogated by guideline studies are not sufficiently sensitive and are not capable of capturing the biologically relevant effects routinely observed and published in academic scientific journals, including effects on developmental endpoints and important indicators of disease development later in life.

The Endocrine Society shares project TENDR's concerns regarding exposures to susceptible populations such as children and pregnant women. EPA should carefully consider the neurological and endocrine outcomes for these populations as well as the general public. Many crops in the US are authorized for chlorpyrifos use and affected drinking water sources shown to contain chlorpyrifos, meaning the public at large is continually exposed to chlorpyrifos via food and water.

⁷ Otenio et al., 2019. Drug and Chemical Toxicology: <https://www.tandfonline.com/doi/full/10.1080/01480545.2019.1701487?scroll=top&needAccess=true>

⁸ Meggs et al 2008. J of Medical Toxicology v3(3).

⁹ Hazarika J, Ganguly M, Mahanta R (2019) J Appl Toxicol. <https://doi.org/10.1002/jat.3789>

¹⁰ Kang et al., 2004. Toxicology, 199: 219-230.

¹¹ Kamijima et al, 2004. J. Occup. Health, 46:109-118.

¹² Hazarika et al, 2020: <https://link.springer.com/article/10.1007/s11224-020-01562-4>

¹³ Ventura et al., 2016.. J. Steroid Biochem Mol Biol.

¹⁴ Tayour et al., Environ Epidemiol. 2019 Oct; 3(5): e070. Published online 2019 Oct 14. doi: 10.1097/EE9.0000000000000070

¹⁵ Engel et al., Env. Health. Perspect. Vol. 125, No. 9 September 2017. <https://doi.org/10.1289/EHP1295>

¹⁶ Holzer et al., 2017 eLife: <https://pubmed.ncbi.nlm.nih.gov/29083300/>



We also note that occupational exposures and pesticide drift result in disproportionate impacts on agricultural communities, creating environmental justice concerns due to cumulative exposure to chlorpyrifos among other known or potentially hazardous chemicals.

In conclusion, there is ample evidence that chlorpyrifos has extensive effects on neurological and endocrine systems with demonstrated evidence of harm to humans and wildlife and we therefore endorse the statement that existing chlorpyrifos tolerances do not comply with the “reasonable certainty of no harm” safety standard in the FQPA. We urge EPA to carefully consider the totality of chlorpyrifos’ effects, including academic publications on its interference with endocrine systems.

Sincerely,

Gary D. Hammer, MD, PhD
President
Endocrine Society