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Office of Pesticide Programs
Environmental Protection Agency
Docket Center (EPA/DC), (28221T),
1200 Pennsylvania Ave. NW.,
Washington, DC 20460-0001.

Re: Draft Human Health Risk Assessment for Imidacloprid. Docket No: EPA-HQ-OPP-2008-0844

The U.S. Environmental Protection Agency (EPA) has completed its preliminary human health assessment for the neonicotinoid, imidacloprid, one of the most widely used insecticides in the U.S. Imidacloprid and other neonicotinoids are frequently detected in plants, water, and soil.[1,2] While the impacts of imidacloprid on insects and other invertebrate species are widely reported, impacts on mammals are less understood. Humans are exposed to imidacloprid in food and drinking water, and via treated plants, lawns, pets, and bedbug treatments.

This new assessment for imidacloprid finds evidence of neurotoxicity in laboratory animals. Tremors, decreased motor and locomotor activity, gait abnormalities, and decreases in forelimb and hindlimb grip strength have been observed in rats in studies following acute oral exposures. The doses at which these effects occurred were high, but these findings, along with others in the independent scientific literature, suggest a biological plausibility for, and association with, acute and chronic neurological effects as a result of exposures to imidacloprid.

A growing number of studies investigate the impacts of chronic neonicotinoid exposure to human health. Many of these studies report some association between neonicotinoids and neurological impairments. One 2016 study by Kimura-Kuroda et al., finds that "chronic neonicotinoid exposure alters the transcriptome of the developing mammalian brain in a similar way to nicotine exposure."[3] Neonicotinoids have been found to affect mammalian nicotinic acetylcholine receptors (nAChRs) in a way that is similar to the effects of nicotine. These receptors are of critical importance to human brain function, especially during

[1] Morrissey, C. A., Mineau, P, Devries, J, et al. 2015. Neonicotinoid contamination of global surface waters and associated risk to aquatic invertebrates: A review. *Environment International.* 74 (2015) 291–303
[2] Hladik, M.L. and Kolpin, D.W., 2016, First national-scale reconnaissance of neonicotinoid insecticides in streams across the U.S.A., *Environ. Chem.*, v. 13, pp. 12-20.
[3] Kimura-Kuroda, J, Nishito, Y, Yanagisawa, H et al. 2016. Neonicotinoid Insecticides Alter the Gene Expression Profile of Neuron-Enriched Cultures from Neonatal Rat Cerebellum. *Int J Environ Res Public Health.* 13(10): 987.

development and for memory, cognition, and behavior.[4] A review of the scientific evidence by Cimino et al. (2017) finds that there are reported associations between chronic neonicotinoid exposures and adverse developmental outcomes, including neurological effects, which support the reasonableness for these associations.[5]

Neurotoxic Sensitivity

In general, EPA finds imidacloprid does not pose a risk to human health. However, the assessment finds that for children under two years old, there is concern for exposures to pets treated with imidacloprid pet collars; for occupational handlers, on-farm seed treatment and seed planter exposure scenarios for certain crops (corn, cotton, canola, barley, millet, wheat, flax) need further refinement. Thus, the agency is reviewing and seeking more information to inform its risk assessment. For pet exposures, EPA is requesting information on the formulation of treated pet collars (solid, liquid, or combination), and a pet transferable residue study is sought to inform the assessment. The agency reports there is no increased prenatal susceptibility in developmental toxicity studies.

EPA has determined that the Food Quality Protection Act (FQPA) safety factor for infant and children can be reduced to 1X based on the exposure assessment conclusions. However, there is identified concern for children's exposure to imidacloprid from pet products. These exposures would include hand-to-mouth and dermal exposures. Although EPA believes the neurotoxic concern for imidacloprid is low, increasing the FQPA safety factor is warranted given the current uncertainty regarding exposures to pet products. This increase is supported by preliminary data that finds that imidacloprid may affect the developing mammalian nervous system, similar to that known to occur with nicotine, activating nAChRs antagonists, which can lead to neuronal proliferation, apoptosis, migration, differentiation, synapse formation, and neural-circuit formation, all of which are important in the developing brain.[6] One study finds significant neurobehavioral deficits and an increased expression of glial fibrillary acidic protein (GFAP) in several brain regions of rat offspring.[7] Already, imidacloprid has been identified as a weak agonist of human nicotinic receptors.[8] The available data are limited, even for EPA's risk assessment, and thus there is uncertainty around the potential for neurodevelopmental impacts. Increasing the safety factor would add an extra measure of safety for vulnerable populations (including infants, children, and pregnant women) while the science evolves.

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[4] Kimura-Kuroda J, Komuta Y, Kuroda Y, Hayashi M, Kawano H. 2012. Nicotine-like effects of the neonicotinoid insecticides acetamiprid and imidacloprid on cerebellar neurons from neonatal rats. *PLoS One* 7(2):e32432,

[5] Cimino AM, Boyles AL, Thayer KA, Perry MJ. 2017. Effects of neonicotinoid pesticide exposure on human health: a systematic review. *Environ Health Perspect*. 125:155–162

[6] Kimura-Kuroda J, Komuta Y, Kuroda Y, Hayashi M, Kawano H. 2012. Nicotine-like effects of the neonicotinoid insecticides acetamiprid and imidacloprid on cerebellar neurons from neonatal rats. *PLoS One* 7(2):e32432,

[7] Abou-Donia MB, Goldstein LB, Bullman S, et al. 2008. Imidacloprid induces neurobehavioral deficits and increases expression of glial fibrillary acidic protein in the motor cortex and hippocampus in offspring rats following in utero exposure. *J Toxicol Environ Health A*.;71(2):119-30.

[8] Li, P, Ann, J, Akk, G. 2011. Activation and modulation of human α4β2 nicotinic acetylcholine receptors by the neonicotinoids clothianidin and imidacloprid. *J Neurosci Res*. 89(8): 1295–1301.

Precautionary Stance Warranted

In 2013, the European Food Safety Authority (EFSA) concluded that acetamiprid and imidacloprid "may affect the developing human nervous system," proposed that "some guidance levels for acceptable exposure to the two neonicotinoids be lowered," and requested more research into the developmental neurotoxicity potential of these chemicals.[9] Specifically, EFSA finds,

> "[A]cetamiprid and imidacloprid may adversely affect the development of neurons and brain structures associated with functions such as learning and memory. [The panel] concluded that some current guidance levels for acceptable exposure to acetamiprid and imidacloprid may not be protective enough to safeguard against developmental neurotoxicity and should be reduced. These so-called toxicological reference values provide clear guidance on the level of a substance that consumers can be exposed to in the short- and long-term without an appreciable health risk."

After this conclusion, EFSA recommended changes to the toxicological reference values for acetamiprid and imidacloprid. For imidacloprid, the acute reference dose (ARfD) of 0.08mg/kg bw/day was proposed to be *lowered* to 0.06 mg/kg bw/per day. EFSA took this stance because the agency believed the data reviewed and health concerns raised by Kimura-Kuroda et al., (2012) was "legitimate." Currently, EPA's corresponding acute (and chronic) reference dose is 0.08mg/kg.

Other Toxicity Evidence

Some studies report that neonicotinoid pesticides impair mammalian reproduction and have developmental effects in mammals including reduced sperm production and function,[10] reduced pregnancy rates, higher rates of embryo death, stillbirth, and premature birth, and reduced weight of offspring.[11] Preliminary work involving clothianidin finds that the neonicotinoid negatively influences the expression of immune-related genes in a human cell line under control of the transcription factor NF-κB,[12] suggesting relatively unknown neuroimmune pathways in mammals that need further study. Other studies are reporting changes in sperm concentration and motility with imidacloprid exposure.[13,14] Beyond

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[9] https://www.efsa.europa.eu/en/press/news/131217

[10] Gu, Y, Li, Y et al. 2013. Reproductive Effects of Two Neonicotinoid Insecticides on Mouse Sperm Function and Early Embryonic Development *In Vitro.* PLoS One. 8(7): e70112.

[11] Cimino AM, Boyles AL, Thayer KA, Perry MJ. 2017. Effects of neonicotinoid pesticide exposure on human health: a systematic review. *Environ Health Perspect*. 125:155–162.

[12] Di Prisco, G, Iannaccone, M et al. 2017. The neonicotinoid insecticide Clothianidin adversely affects immune signaling in a human cell line. *Sci Rep*. 7: 13446.

[13] Hafez EM, Issa SY, AI-Mazroua MK, Ibrahim KT, Rahman SMA. 2016. The Neonicotinoid Insecticide Imidacloprid: A Male Reproductive System Toxicity Inducer-Human and Experimental Study. Toxicol open access 2: 109.doi:10.4172/tyoa.1000109.

[14] Lonare M, Kumar M, Raut S, et al. 2016. Evaluation of ameliorative effect of curcumin on imidacloprid-induced male reproductive toxicity in wistar rats. *Environ Toxicol*. 31(10):1250-63.

neurological effects, imidacloprid may have the ability to adversely impact other functions in mammalian systems, which warrants further review.

Cumulative Assessment

Finally, we urge the agency to conduct a cumulative risk assessment for the neonicotinoid class of pesticides. Currently, the agency's position is that it has not made a common mechanism of toxicity finding for imidacloprid and any other substance. We believe imidacloprid and the others in its class are good candidates for a cumulative risk assessment. There is structural similarity, and thus far, a common mode of action in mammalian systems,[15,16] based on their activity on nicotinic receptors. Given the widespread uses of neonicotinoids on major food commodities, residential sites, pets, and frequency in waterways, such an assessments is warranted due to the potential for low-level exposures to multiple neonicotinoids that can potentially cause a common toxic effect by a common mechanism leading to the same adverse health effect, according to EPA's guidance for identifying chemicals that have a common mechanism of toxicity.[17] We urge to agency to make a findings of common toxicity and complete a cumulative assessment.

Conclusion

Imidacloprid is ubiquitous, found in waterways, foods, and in a variety of residential products including treated ornamental plants. The human health data on imidacloprid is limited, but new evidence of potential harms is emerging in the independent scientific literature. To our understanding, the agency did not review the studies in the open literature. There is some preliminary evidence that imidacloprid can interfere with the developing mammalian brain that we believe warrant a precautionary approach until a more robust data set can be evaluated. Thus, the FQPA safety factor should be retained at 10X to protect vulnerable populations (infants, children and pregnant women) until uncertainties can be resolved. We advise EPA to monitor the scientific literature and update its assessment in the near future.

Respectfully,

Nichelle Harriott
Science and Regulatory Director

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[15] USEPA. 2016. Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose. Office of Pesticide Programs. Washington DC.

[16] USEPA. 1999. GUIDANCE FOR IDENTIFYING PESTICIDE CHEMICALS AND OTHER SUBSTANCES THAT HAVE A COMMON MECHANISM OF TOXICITY. https://www.epa.gov/sites/production/files/2015-07/documents/guide-2-identify-pest-chem_0.pdf

[17] USEPA. 2016. Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose. Office of Pesticide Programs. Washington DC.