PCPA Imidacloprid Comment
Pesticide Registration Branch
Calif. Department of Pesticide Registration
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EWG comments calling for an immediate end to imidacloprid pollution of California groundwater

The Environmental Working Group, or EWG, a nonprofit research and advocacy organization with offices in Sacramento, Minneapolis and Washington, D.C., objects to the pollution of California's groundwater with imidacloprid that continues due to the lack of adequate regulation by the California Department of Pesticide Regulation, or CDPR.

Imidacloprid is a neonicotinoid insecticide harmful to the nervous system. The detection of imidacloprid above the reporting limit of 0.05 parts per billion, or ppb, in 15 wells in Fresno, Santa Barbara and Tulare counties at concentrations ranging from 0.051 to 5.97 ppb[1] demonstrates the threat imidacloprid poses to California's precious groundwater supply, which is a source of drinking water for millions of people.

In this comment letter, EWG presents three key findings and recommendations:
1. The human health reference value used by CDPR disregards numerous studies showing imidacloprid toxicity at much lower concentrations.
2. The health-protective guideline value for groundwater should be developed based on the most sensitive studies and should include a tenfold children's health safety factor.
3. Imidacloprid pollution of California's ground water must stop immediately.

Details for these recommendations are listed below.

1. The human health reference value used by CDPR disregards numerous studies showing imidacloprid toxicity at much lower concentrations.

[1] DPR, 2021. Notice of imidacloprid residue detections in California groundwater and the Pesticide Contamination Prevention Act review process. California Notice 2021-08. September 21, 2021. Pesticide Registration Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Available online at: https://www.cdpr.ca.gov/docs/registration/canot/2021/ca2021-08.pdf

Following the detection of imidacloprid in water wells in Fresno, Santa Barbara and Tulare, a subcommittee of the CDPR's Pesticide Registration and Evaluation Committee held a public hearing in March and April 2022 to determine whether these detections meet the definition of pollution and whether the registration and use of imidacloprid as an agricultural pesticide should be allowed to continue.

Critical to the determination about whether imidacloprid pollutes California groundwater is whether the detected levels are a concern for human health. Therefore, it is critical that a human health reference level be determined based on the currently available science reflecting the most sensitive toxicological endpoint, as well as current and appropriate risk assessment guidelines.

EWG contends that a human health reference level of 283 ppb is not a health-protective value, and that it should not be used in the Pesticide Registration and Evaluation Committee's determination. The human health reference level set by CDPR in 2021[2] is based on a risk characterization document from 2006,[3] which used a 2001 developmental neurotoxicity study with a point of departure of 5.5 mg/kg per day. There are many toxicological assessments of imidacloprid in the peer-reviewed literature showing that doses far lower can cause harm in laboratory animals. This human health reference level is based on outdated science, and more recent publications on the toxicity of imidacloprid support use a much lower value to assess harm to human health.

2. A health-protective guideline value for groundwater should be developed based on the most sensitive studies and should include a tenfold children's health safety factor.

As reviewed by OEHHA[4] and supported by additional studies, and presented in Figure 1, peer-reviewed studies identified that imidacloprid exposure can cause

[2] DPR, 2021. Memorandum Subject: Updated risks from human exposure to imidacloprid residues in well water. P Lohstroh and S Koshlukova. April 13, 2021. Human Health Assessment Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, Calif.
Available at: https://www.cdpr.ca.gov/docs/emon/grndwtr/imidacloprid/imidacloprid_risks_memo.pdf
[3] DPR, 2006. Imidacloprid risk characterization document dietary and drinking water exposure. February 9, 2006. Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. Available at: https://www.cdpr.ca.gov/docs/risk/rcd/imidacloprid.pdf
[4] OEHHA, 2021. Memorandum: OEHHA's findings on the health effects of imidacloprid relevant to its identification as a potential groundwater contaminant. Sutherland-Ashley, K. February 18, 2022. Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

developmental neurotoxicity,[5] immunotoxicity[6] and glucose homeostasis,[7, 8, 9, 10] and its impact on the reproductive system, particularly the male reproductive system, affecting several parameters associated with sperm function.[11, 12, 13, 14, 15, 16, 17]

Epidemiological studies of real-world exposure to imidacloprid show harm, particularly to children. A systematic review published in 2017 indicated that imidacloprid exposure is associated with increased risk of autism spectrum disorder and adverse birth outcomes, such as birth defects of the brain.[18]

[5] Kara M, Yumrutas O, Demir CF, et al. (2015). Insecticide imidacloprid influences cognitive functions and alters learning performance and related gene expression in a rat model. Int J Exp Pathol 96: 332-337.
[6] Badgujar PC, Jain SK, Singh A, Punia JS, Gupta RP, Chandratre GA (2013). Immunotoxic effects of imidacloprid following 28 days of oral exposure in BALB/c mice. Environ Toxicol Pharmacol 35(3):408-418.
[7] Sun Q, Xiao X, Kim Y, et al. (2016). Imidacloprid promotes high fat diet-induced adiposity and insulin resistance in male C57BL/6J mice. J Agric Food Chem 64: 9293-9306.
[8] Sun Q, Qi W, Xiao X, et al. (2017). Imidacloprid promotes high fat diet-induced adiposity in female C57BL/6J mice and enhances adipogenesis in 3T3-L1 adipocytes via the AMPKalpha-mediated pathway. J Agric Food Chem 65: 6572-6581.
[9] Khalil SR, Awad A, Mohammed HH, Nassan MA (2017). Imidacloprid insecticide exposure induces stress and disrupts glucose homeostasis in male rats. Environ Toxicol Pharmacol 55: 165-174.
[10] Nimako C, Ikenaka Y, Okamatsu-Ogura Y et al. (2021). Chronic low-dose exposure to imidacloprid potentiates high fat diet-mediated liver steatosis in C57BL/6J male mice. J Vet Med Sci. 2021 Apr 3;83(3):487-500.
[11] Abdel-Rahman Mohamed A, Mohamed WAM, Khater SI (2017). Imidacloprid induces various toxicological effects related to the expression of 3beta-HSD, NR5A1, and OGG1 genes in mature and immature rats. Environ Pollut 221: 15-25.
[12] Bal R, Turk G, Tuzcu M, et al. (2012a). Assessment of imidacloprid toxicity on reproductive organ system of adult male rats. J Environ Sci Health B 47: 434-444.
[13] Bal R, Naziroglu M, Turk G, et al. (2012b). Insecticide imidacloprid induces morphological and DNA damage through oxidative toxicity on the reproductive organs of developing male rats. Cell Biochem Funct 30: 492-499.
[14] Bagri P, Kumar V, Sikka AK (2015). An in vivo assay of the mutagenic potential of imidacloprid using sperm head abnormality test and dominant lethal test. Drug Chem Toxicol 38: 342-348.
[15] Zhao G, Li J, Yang F, et al. (2021). Spermiogenesis toxicity of imidacloprid in rats, possible role of CYP3A4. Chemosphere 282: 131120.
[16] Saber TM, Arisha AH, Abo-Elmaaty AMA et al. (2021). Thymol alleviates imidacloprid-induced testicular toxicity by modulating oxidative stress and expression of steroidogenesis and apoptosis-related genes in adult male rats. Ecotoxicol Environ Saf. 2021 Sep 15;221:112435.
[17] Abdel-Razik RK, Mosallam EM, Hamed NA et al. (2021). Testicular deficiency associated with exposure to cypermethrin, imidacloprid, and chlorpyrifos in adult rats. Environ Toxicol Pharmacol. 2021 Oct;87:103724.
[18] Cimino AM, Boyles AL, Thayer KA, Perry MJ (2017). Effects of Neonicotinoid Pesticide Exposure on Human Health: A Systematic Review. Environ Health Perspect. 2017 Feb;125(2):155-162.

Figure 1. Toxicological findings from studies in the peer-reviewed literature and associated potential public health-protective concentrations compared to CDPRs' human health reference level. Figure and table information are adapted and modified (to include an additional children's health safety factor) from OEHHA's findings on the health effects of imidacloprid relevant to its identification as a potential groundwater contaminant.

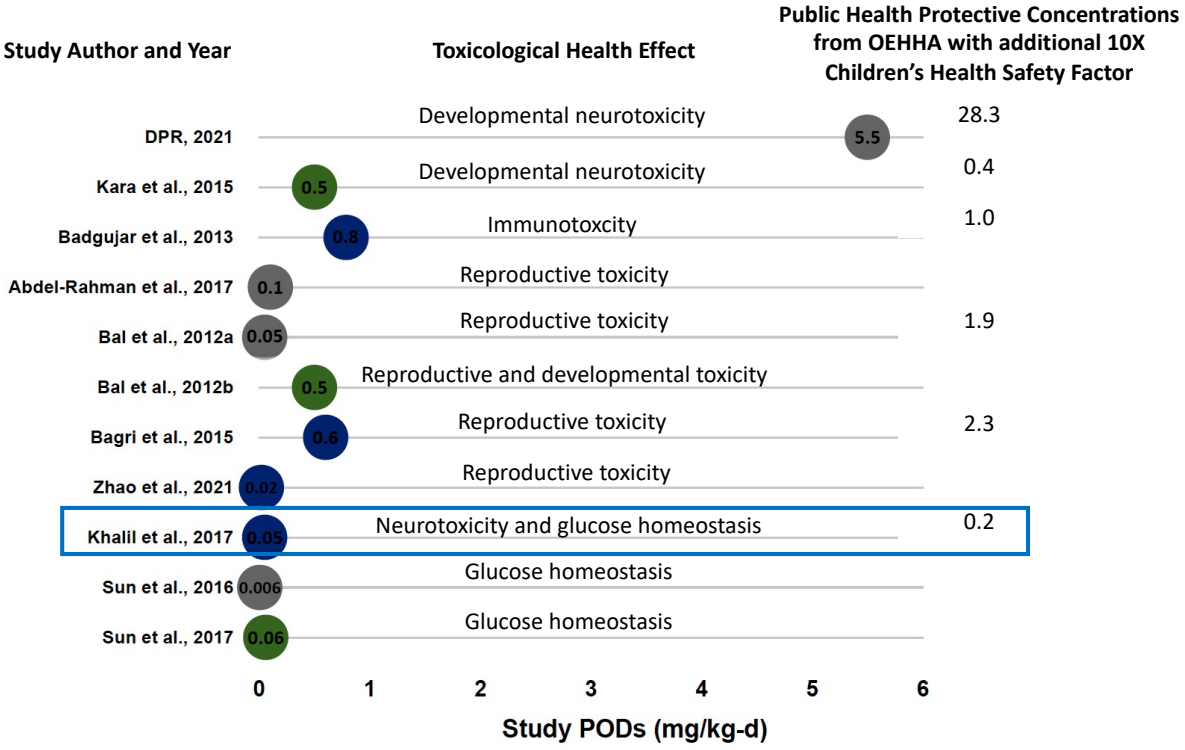

Figure legend: BMDL (blue data points); ENEL (grey data points); NOAEL (green data points). The blue box denotes the lowest derived value.

In presentations from the registrant during the hearing, the registrant inappropriately dismissed findings from these peer-review studies, which indicate harm from imidacloprid at doses lower than the current point of departure. Inclusion of these studies is extremely important, since toxicological effects at high and low doses may be different; low-dose exposures often represent real world exposure scenarios for humans; and the peer-review studies often investigated health effects not assessed in registrant-submitted studies.

Furthermore, there is the precedent of regulatory agencies using the studies presented in Figure 1 for assessing the risk of imidacloprid in water, namely by the

Wisconsin Department of Health Services[19] and Minnesota Department of Public Health.[20] For example, the Wisconsin Department of Health Services has proposed an enforcement standard of 0.2 ppb for imidacloprid based on the Sun et al. 2016 study that identified the impacts on metabolic parameters. This value would be in line with the public health concentration values derived by OEHHA for the Khalil et al. 2017 study, with an additional safety factor for children's health. Additionally, other studies support the idea that that imidacloprid can act as a metabolic disruptor, promoting lipid accumulation in cells,[21] and exposure in humans has been associated with being overweight or obese in adults.[22]

Therefore, a value no higher than 0.2 ppb should be used a screening value, a level more than 1,000 times lower than the value proposed by CDPR and supported by the registrant.

3. Imidacloprid pollution of California's ground water must end immediately.

The detection of imidacloprid in groundwater wells at levels that may cause harm to human health meets the definition of pollution put forth by the Pesticide Contamination Prevention Act. This calls for such pollution to be stopped immediately.

Although the CDPR's Pesticide Registration and Evaluation Committee hearing was specific to imidacloprid, it is a member of a group of pesticides known as neonicotinoids, which have a common mechanism of action for their insecticidal use and have toxicological effects that are similar in mammals and other species. In 2020, the National Toxicology Program published a review of neonicotinoid toxicity, reporting neurological and developmental effects as the most studied outcomes.[23]

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[19] Wisconsin Department of Health Services (WDHS, 2019). Recommended public health groundwater quality standards: scientific support documents for Cycle 10 substances. Publication P-02434V. June 2019. Available at: https://www.dhs.wisconsin.gov/publications/p02434v.pdf

[20] Minnesota Department of Health (MDH, 2020). Toxicological Summary for: Imidacloprid. Available at: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/imidasumm.pdf

[21] Mesnage R, Biserni M, Genkova D et al. (2018). Evaluation of neonicotinoid insecticides for oestrogenic, thyroidogenic and adipogenic activity reveals imidacloprid causes lipid accumulation. J Appl Toxicol. 2018 Dec; 38(12): 1483–1491.

[22] Godbole AM, Moonie A, Coughenour C et al. (2022). Exploratory analysis of the associations between neonicotinoids and measures of adiposity among US adults: NHANES 2015-2016. Chemosphere. 2022 Mar 31;300:134450.

[23] Boyd WA, Boyles AL, Blain RB et al. (2020). NTP Research Report on the Scoping Review of Potential Human Health Effects Associated with Exposures to Neonicotinoid Pesticides: Research Report 15. National Toxicology Program, Research Triangle Park, NC.

Since 2020, animal studies continue to show neonicotinoids harm the reproductive system, as well as affecting memory and behavior.[24, 25, 26]

Analyses of neonicotinoid residue data from the U.S. Department of Agriculture Pesticide Data Program indicated that neonicotinoids are widely detected in foods, and multiple residues from different neonicotinoids are often present on the same sample. Additionally, nearly 50 percent of the U.S. population has detectable levels of neonicotinoids, as measured in their urine, with children having higher levels of exposure.

Given the documented exposure to multiple neonicotinoids and shared toxicological properties of these insecticides, additional exposure to imidacloprid through water is a risk to human health.

In conclusion, it is essential that the subcommittee use the best available science to ensure that public health is protected from imidacloprid pollution of ground water. The committee must recognize the low dose effects of imidacloprid in its determination, and pollution of California's groundwater by imidacloprid must end. To protect Californians from unintended and damaging health impacts, we urge the branch and department to consider EWG's findings and recommendations seriously.

Submitted on behalf of the Environmental Working Group,

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[24] Liu Y, He Q, Xu Z et al. (2021).
Thiamethoxam Exposure Induces Endoplasmic Reticulum Stress and Affects Ovarian Function and Oocyte Development in Mice. J Agric Food Chem. 2021 Feb 17;69(6):1942-1952
[25] Shamsi M, Soodi M, Shahbazi A, Omidi A (2021). Effect of Acetamiprid on spatial memory and hippocampal glutamatergic system. Environ Sci Pollut Res Int
. 2021 Jun;28(22):27933-27941.
[26] Maeda M, Kitauchi A, Hirano T et al. (2021). Fetal and lactational exposure to the no-observed-adverse-effect level (NOAEL) dose of the neonicotinoid pesticide clothianidin inhibits neurogenesis and induces different behavioral abnormalities at the developmental stages in male mice. J Vet Med Sci. 2021 Apr 3;83(3):542-548