August 4, 2021

Environmental Working Group comments to the Environmental Protection Agency Docket ID: EPA-HQ-OPP-2015-0378
Subject: Draft human health risk assessment for tebuconazole

The Environmental Working Group, or EWG, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, Minn., San Francisco and Sacramento, Calif., submits comments to the Environmental Protection Agency urging the agency to limit the agricultural use of the fungicide tebuconazole to protect children's health.

The EPA itself has classified tebuconazole as a possible human carcinogen, and tebuconazole is toxic to the developing organism. In animal studies, exposure to tebuconazole caused malformations in nervous system development, changes in brain morphometric parameters, and decreases in motor activity.[1] Peer-reviewed studies have reported that tebuconazole alters testosterone production[2] and testicular morphometry.[3]

The European Union classifies tebuconazole as "suspected of damaging the unborn child," and a 2014 review by the European Food Safety Agency suggested that the chemical be classified as one that "may damage the unborn child."[4] Given the risk this pesticide poses to the developing fetus, the EPA must apply the full tenfold FQPA safety factor for all routes of exposure to tebuconazole.

In January 2020 EWG submitted comments to the EPA on a tebuconazole human health risk assessment that was conducted to support increases of tebuconazole tolerances in foods. At that time, EWG expressed concerns about the EPA's reduction of the FQPA

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[1] Environmental Protection Agency. Tebuconazole 7E8648 – HED Signed HH Risk Assessment October 18, 2019; Tebuconazole 7E8648 – HED Signed Acute-Chronic Risk Assessment October 16, 2019. https://www.regulations.gov/docket?D=EPA-HQ-OPP-2018-0094.

[2] Chen X, Zhu Q, Li X, Huang T, Wang S, Wang Y, Chen X, Lin Z, Ge RS. Pubertal exposure to tebuconazole increases testosterone production via inhibiting testicular aromatase activity in rats. Chemosphere 2019; 230: 519-526. https://doi.org/10.1016/j.chemosphere.2019.05.122.

[3] Machado-Neves M, Neto MJO, Miranda DC, Souza ACF, Castro MM, Sertorio MN, Carvalho TF, Matta SLP, Freitas MB. Dietary exposure to tebuconazole affects testicular and epididymal histomorphometry in 018-2377-6.

[4] European Food Safety Authority (EFSA). Conclusion on the peer review of the pesticide risk assessment of the active substance tebuconazole. EFSA Journal 2014; 12(1): 3485. https://www.efsa.europa.eu/en/efsajournal/pub/3485.

1436 U Street NW, Suite 100, Washington, DC 20009
p. 202.667.6982 | f. 202.232.2592
ewg.org

factor from tenfold to threefold, putting children's health at risk.[5] In the latest risk assessment, the EPA has inappropriately further reduced the FQPA Safety Factor to 1X.

EPA also proposed using a study with a higher No Observed Adverse Effect Level, or NOAEL, to set the point of departure for the development of the reference dose for tebuconazole. In its 2019 risk assessment, EPA used a registrant-submitted developmental neurotoxicity study for which only a LOAEL of 8.8 mg/kg could be identified, based on decreased body weight, absolute brain weights, and brain measurements, as well as motor activity.[6] The current risk assessment ignores these findings, with no explanation, and lists the NOAEL from the same study as 22 mg/kg, when in fact, based on previous EPA assessments, a true NOAEL is not available. EWG urges the EPA to use the previous point of departure of 8.8 mg/kg to develop the reference dose, and to use a full tenfold FQPA factor.

Furthermore, in the current updated risk assessment, the chronic population adjusted dose for the general population, including infants, is set five times higher than in the previous assessment, yet it does not use the most sensitive endpoint to set the threshold, as is standard toxicological practice. If the previous threshold with an additional safety factor for children's health – which is supported by the data – were used, then the EPA's current dietary exposure estimate of 0.03 mg/kg per day would exceed the more appropriate safe dose for children of 0.008 mg/kg per day by nearly four times.

Additionally, tebuconazole has toxicological hazards similar to other azole fungicides', as the EPA's assessment notes: "The toxicological effects of tebuconazole are consistent with those of other triazole-derivative chemicals. In particular, developmental toxicity and hepatocellular tumors are effects common to a number of these pesticides." Yet no cumulative risk assessment for the group of fungicides is performed or accounted for. This is a gross oversight, since multiple azole fungicides are used on the same crops and can be detected on the same individual samples of many popular foods, including raisins, a common snack for children, frozen cherries, peaches, and nectarines.

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[5] https://www.ewg.org/sites/default/files/testimony/Tebuconazole_EWG_comments_EPA_January2020.pdf.

[6] Environmental Protection Agency. Tebuconazole: Human Health Aggregate Risk Assessment for Establishment of Registrations and a Permanent Tolerance for Residues in/on Watercress, Add Greenhouse Tomato to Label and Crop Group Conversions/Expansions to *Brassica* Leafy Greens, Subgroup 4-16B, Except Watercress; Cottonseed, Subgroup 20C; Pome Fruit, Group 11-10, Stone Fruit, Group 12-12, Except Cherry; Small Vine Climbing Fruit, Except Fuzzy Kiwifruit, Subgroup 13-07F; Tropical and Subtropical Small Fruit, Inedible Peel, Subgroup 24A, Tree Nut, Group 14-12 and Sunflower, Subgroup 20B. October, 18, 2019.

In tests conducted by the Department of Agriculture from 2009 to 2019, azole fungicides commonly present on food included tebuconazole, propiconazole, tetraconazole, and fenbuconazle. An analysis of the most recent sampling of these fruits by the USDA showed that two or more azole fungicides could be found on 35 percent of raisins, 23 percent of frozen cherries, 10 percent of peaches and six percent of nectarines.[7]

The presence of multiple azole fungicides on a single sample of fruit is important from a toxicological perspective because evidence from the peer-reviewed literature shows that exposure to mixtures of azole fungicides can cause harms at doses lower than exposure to the individual compounds, especially for endpoints related to reproduction and development. In a study of the antiandrogenic effect of azole fungicides, mixtures of two fungicides were identified to have additive as well as synergistic effects.[8] Lastly, in mice exposed during pregnancy to the azole fungicides tebuconazole and epoxiconazole as well as three other endocrine-disrupting pesticides, the mixture – but not the individual compounds at the same dose – caused adverse effects on the male reproductive system in the offspring, affecting gestational length as well as offspring survival.[9,10]

In light of the observed sensitivity of young animals to tebuconazole exposure, the evidence of developmental neurotoxicity and endocrine disruption, and the likely exposure to multiple azole fungicides with similar health effects, we believe that to adequately protect children's health, the EPA must use a full tenfold safety factor in the risk assessment of tebuconazole and restrict the use of this fungicide.

Submitted on behalf of the Environmental Working Group.

Alexis Temkin, Ph.D.
Toxicologist

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[7] United States Department of Agriculture. Pesticide Data Program. https://www.ams.usda.gov/datasets/pdp.

[8] Christen V, Crettaz P, Fent K. 2014. Additive and synergistic antiandrogenic activities of mixtures of azol fungicides and vinclozolin. *Toxicology and Applied Pharmacology*. Sep 15;279(3):455-466. doi: 10.1016/j.taap.2014.06.025.

[9] Jacobsen RR, Christiansen S, Boberg J, Nellemann C, Hass U. 2010. Combined exposure to endocrine disrupting pesticides impairs parturition, causes pup mortality and affects sexual differentiation in rats. *Int J Androl*. Apr;33(2):434-42. doi: 10.1111/j.1365-2605.2009.01046.x.

[10] Hass U, Boberg J, Christiansen S, Jacobsen PR, Vinggaard AM, Taxvig C et al. 2012. Adverse effects on sexual development in rat offspring after low dose exposure to a mixture of endocrine disrupting pesticides. *Reprod Toxicol. Sep;34(2):261-74. doi: 10.1016/j.reprotox.2012.05.090.*