July 25, 2023

Environmental Working Group comments to the Environmental Protection Agency Docket ID: EPA-HQOPP-2021-0290; EPA's Memorandum Supporting the Proposed Registration Decision to Approve the First Outdoor Food Uses on Wheat, Triticale, Barley, and Oats for Chlormequat Chloride and the Petition to Establish U.S. Tolerances for Residues of Chlormequat Chloride in or on Wheat, Barley, and Oats and Secondary Residues in Meat, Milk, Poultry and Eggs

The Environmental Working Group, or EWG, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, San Francisco and Sacramento, Calif., urges the Environmental Protection Agency not to approve the first outdoor food uses of chlormequat chloride on wheat, triticale, barley, and oats grown in the U.S. Further, no U.S. tolerances should be established for those same crops.

In 2018, the Environmental Protection Agency allowed chlormequat chloride on imported oats, wheat, barley, and some animal products, with tolerances increased on some of these commodities in 2020. In April 2023, the agency proposed to allow domestic applications of chlormequat chloride on these crops, justifying the decision with the same flawed data used in previous assessments of the public health risks associated with chlormequat use.

The 2018 decision paved the way for the introduction into the U.S. food supply of a new agricultural chemical, one with very concerning toxicity, as documented by recent EWG tests of oat-based products purchased in 2022.[1] The levels of chlormequat found in cereals and oat-based products are concerning for children's health, because low doses of chlormequat have been shown in animal studies to affect fertility, harm the reproductive system, and alter growth and development.

EWG is urging the EPA not to allow new uses of chlormequat in the U.S., not to approve the domestic tolerances for chlormequat chloride, and revoke the previously approved import tolerances. Our recommendations are based on the following concerns about the 2023 Revised Human Health Risk Assessment for Chlormequat Chloride:

[1] Evans S, Temkin A, Naidenko O. EWG Investigation: Dangerous agricultural chemical chlormequat found in popular oat-based products. January 31, 2023. Environmental Working Group. https://www.ewg.org/research/ewg-investigation-dangerous-agricultural-chemical-chlormequat-foundpopular-oat-based

1. **EPA did not adequately search for or account for studies in the peer-reviewed literature on chlormequat toxicity, which shows low dose reproductive and developmental effects.**
2. **EPA did not adequately consider the immunotoxic effects of chlormequat chloride.**
3. **EPA failed to require a developmental neurotoxicity study for chlormequat chloride, which should have been required given extensive evidence of the neurological effects from exposure to chlormequat.**
4. **EPA should apply additional safety factors to adequately protect children's health.**

Listed below are details and information that support EWG's recommendation not to approve new uses of chlormequat chloride.

EPA did not adequately search the peer-reviewed literature for studies on chlormequat toxicity, which show low dose reproductive and developmental effects.

As EWG emphasized in previous comments submitted to the EPA in April 2023, since the 1980s reports have shown that exposure to chlormequat during pregnancy can harm reproduction in both pigs and rodents. As summarized in the peer-reviewed literature, these effects occur at environmentally relevant concentrations, and were observed in controlled dosing experiments or when using chlormequat treated animal feed.[2,3] Subsequent published studies, from 2016 to 2022, have also documented the harmful effects of chlormequat exposure, especially on the male reproductive system, the hormone system, and on growth of the developing fetus in rodent models.[4,5,6,7,8]

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[2]Sorensen MT, Danielsen V. Effects of the plant growth regulator, chlormequat, on mammalian fertility. Int J Androl. 2006;29(1):129-33.

[3] Torner H, Blottner S, Kuhla S, Langhammer M, Alm H, Tuchscherer A. Influence of chlorocholine chloride-treated wheat on selected in vitro fertility parameters in male mice. Reprod Toxicol. 1999;13(5):399-404.

[4] Huang D, Wu S, Pan Y, Meng Q, Chu H, Jiang J, Shang L, Hao W. The effects of chlormequat chloride on the development of pubertal male rats. Environ Toxicol Pharmacol. 2016 Oct;47:92-99. doi: 10.1016/j.etap.2016.09.002. Epub 2016 Sep 4. PMID: 27653211.

[5] Hou X, Huang D, Meng Q, Zhang Q, Jia L, Wang S, Cheng Z, Wu S, Shang L, Jiang J, Hao W. Pubertal chlorocholine chloride exposure inhibits testicular testosterone synthesis by down-regulating steroidogenic enzymes in adult rats. Toxicol Lett. 2018 May 15;288:17-24. doi: 10.1016/j.toxlet.2018.02.015. Epub 2018 Feb 12. PMID: 29447956.

[6] Xiagedeer B, Hou X, Zhang Q, Hu H, Kang C, Xiao Q, Hao W. Maternal chlormequat chloride exposure disrupts embryonic growth and produces postnatal adverse effects. Toxicology. 2020 Sep;442:152534. doi: 10.1016/j.tox.2020.152534. Epub 2020 Jul 2. PMID: 32622971.

[7] Xiao Q, Hou X, Kang C, Xiagedeer B, Hu H, Meng Q, Jiang J, Hao W. Effects of prenatal chlorocholine chloride exposure on pubertal development and reproduction of male offspring in rats. Toxicol Lett. 2021 Oct 15;351:28-36. doi: 10.1016/j.toxlet.2021.08.005. Epub 2021 Aug 16. PMID: 34411681.

[8] Xiao Q, Hou X, Kang C, Xu L, Yuan L, Zhao Z, Meng Q, Jiang J, Hao W. Chlorocholine chloride induced testosterone secretion inhibition mediated by endoplasmic reticulum stress in primary rat Leydig cells. Toxicol Lett. 2022 Mar 1;356:161-171. doi: 10.1016/j.toxlet.2021.12.018. Epub 2021 Dec 25. PMID: 34958886.

The materials published by the agency did not make clear whether the EPA searched the peer-reviewed literature on chlormequat toxicity for studies that would impact the selected point of departure or application of safety factors in the 2023 revised human health risk assessment. Had the EPA searched the peer-reviewed literature, it would have found many studies assessing chlormequat chloride toxicity, described above, the findings of which could have influenced the decisions taken in the current risk assessment document. Notably, many of the studies described adverse effects occurring at doses lower than the current reference dose set by the EPA, at 0.05 mg/kg body weight per day. In early studies in pigs and mice, doses of 0.0023 and 0.024 mg/kg body weight per day, respectively, of chlormequat lowered fertility.[2,3] In another peer-reviewed study, no No Observed Adverse Effect Level, or NOAEL was available, yet the Lowest Observed Adverse Effect Level or LOAEL of the study, 5 mg/kg body weight per day, was at the same dose as the point of departure used in EPA's assessment and caused altered growth and metabolism during development.[6]

In the 2021 human health risk assessment to support registration review of chlormequat chloride, one section (Appendix A.3) details the literature review that EPA performed and the studies identified during that search.[9] That search incorrectly returned only one study, which EPA dismissed. But, notably, a similar section is absent from the 2023 assessment, despite the previous literature search having been conducted at the end of March 2020. Since then, a study has been published assessing the effects on male reproductive development of chlormequat exposure during pregnancy.[7] This study is highly relevant to EPA's risk assessment, the findings of which warrant retaining the 10X FQPA Safety Factor.

EPA did not adequately consider the immunotoxic effects of chlormequat chloride.

EPA justifies waiving the required immunotoxicity study by stating in the 2023 HHRA, "No immunotoxicity study was available; however, no evidence of immunotoxicity was observed in the chlormequat chloride database."[10] However, evidence of chlormequat immunotoxicity exists in the peer-reviewed literature. In deer mice, exposure to chlormequat resulted in several indications of immunotoxic effects, including reduced thymus weights, reduced white blood cell counts, reduced plasma proteins, reduced spleen plague forming cells and reduced spleen lymphocytes.[11] In another study, chlormequat exposure reduced the number of antibodies produced in

[9] Environmental Protection Agency. Chlormequat Chloride Draft Human Health Risk Assessment for Registration Review. March 16, 2021.
[10] Environmental Protection Agency. Chlormequat Chloride. Revised Human Health Risk Assessment for the Section 3 Registration Action for a New Use on Wheat, Triticale, Barley, Oats, and Grasses Grown for Seed. April 12, 2023. Page 6.
[11] Olson LJ, Hinsdill RD. Influence of feeding chlorocholine chloride and glyphosine on selected immune parameters in deer mice, Peromyscus maniculatus. Toxicology. 1984 Mar;30(2):103-14. doi: 10.1016/0300-483x(84)90121-5. PMID: 6710535.

response to exposure to a virus in mice.[12] Importantly, many of these effects occurred at doses of 1 mg/kg bodyweight per day, which is lower than EPA's currently selected point of departure of 5 mg/kg bodyweight per day.

EPA failed to require a developmental neurotoxicity study for chlormequat chloride, which should have been required given extensive evidence of the neurological effects from exposure to chlormequat.

In the HHRA, EPA notes that neurotoxic effects are the most consistently observed toxicological endpoint across animal studies, stating, "Decreases in body weight and signs of neurotoxicity (e.g., ataxia, salivation, decreased body temperature) were consistently observed in the available oral repeat dosing studies in rats, mice, and dogs and in the acute neurotoxicity study in rats."[13] In addition, studies that screen chemicals for properties of developmental neurotoxicants have identified other quaternary ammonium compounds as potential developmental neurotoxicants, like diquat,[14] which EPA considered to be a compound that is structurally similar to chlormequat.[15] Lastly, while no epidemiological studies exist assessing chlormequat toxicity, several reported human poisonings by chlormequat ingestion have been reported, indicating acute neurotoxic effects in humans.[16] Given the observed neurotoxic effects in adult animals and humans, and predicted developmental neurotoxic effects of similar compounds, it can be concluded that the database on chlormequat toxicity is not complete and that a developmental neurotoxicity study should be required.

EPA should apply additional safety factors to adequately protect children's health.

Studies published in the peer-reviewed literature show developing animals' higher susceptibility to the toxic effects of chlormequat chloride, compared to adult animals. While EPA states this is not the case, the previous sections of these comments have outlined numerous studies in the peer-reviewed literature that are relevant to chlormequat

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[12] Fairbrother A, Yuill TM, Olson LJ. Effects of ingestion of chlorocholine chloride and cyclophosphamide on Venezuelan equine encephalitis virus infections in deer mice (Peromyscus maniculatus). Toxicology. 1984 May 1;31(1):67-71. doi: 10.1016/0300-483x(84)90156-2. PMID: 6729837.

[13] Environmental Protection Agency. Chlormequat Chloride. Revised Human Health Risk Assessment for the Section 3 Registration Action for a New Use on Wheat, Triticale, Barley, Oats, and Grasses Grown for Seed. April 12, 2023. Page 15.

[14] Krug AK, Balmer NV, Matt F, Schönenberger F, Merhof D, Leist M. Evaluation of a human neurite growth assay as specific screen for developmental neurotoxicants. Arch Toxicol. 2013 Dec;87(12):2215-31. doi: 10.1007/s00204-013-1072-y. Epub 2013 May 14. PMID: 23670202.

[15] Environmental Protection Agency. Chlormequat chloride: Summary of Hazard and Science Policy Council (HASPOC) Meeting of October 27, 2016: Recommendation on the Requirement for Acute Neurotoxicity and Developmental Neurotoxicity Studies. November 16, 2016.

[16] Nisse P, Majchrzak R, Kahn JP, Mielcarek PA, Mathieu-Nolf M. Chlormequat poisoning is not without risk: Examination of seven fatal cases. J Forensic Leg Med. 2015 Nov;36:1-3. doi: 10.1016/j.jflm.2015.08.001. Epub 2015 Aug 13. PMID: 26318380.

toxicity as it relates to children's health. Exposure to chlormequat during pregnancy in several studies indicated that adverse effects were seen in the offspring at doses that did not cause maternal toxicity.[2,3,6,7]

In conclusion, EPA has failed to account for the risks to children's health from chlormequat exposure, despite numerous peer-reviewed papers showing increased susceptibility to chlormequat during development. Importantly, EPA used a refined dietary exposure, estimating infants and children were the most highly exposed populations, at 0.03 mg/kg bw per day. If EPA had used an appropriate point of departure and applied the 10X FQPA safety factor, the resulting safe level would be exceeded by the dietary exposure estimates. Furthermore, some studies observed impacts on fertility at doses far lower that EPA's estimated exposures, even for adults.

Therefore, EPA should not approve the new uses of chlormequat on oats, barley, wheat, and triticale grown in the U.S., nor approve U.S. tolerances on these crops, and remove the current import tolerances.

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