August 31, 2026

Via EPA E-Filing System and Federal eRulemaking Portal

Office of the Hearing Clerk
U.S. Environmental Protection Agency
Office of Administrative Law Judges
1200 Pennsylvania Avenue, NW, Mail Code 1900R
Washington, DC 20460

RE: Environmental Working Group's Objections to Chlormequat Chloride; Pesticide Tolerances, 91 Fed. Reg. 39,489 (June 30, 2026) (Docket No. EPA-HQ-OPP-2021-0290)

Dear Hearing Clerk:

Pursuant to section 408(g) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 346a(g), and 40 C.F.R. part 178, the Environmental Working Group (EWG) objects to EPA's June 30, 2026 final rule revising 40 C.F.R. § 180.698(a) (Final Rule).

EWG objects to the Final Rule's revisions to 40 C.F.R. § 180.698(a), including the tolerances it establishes or modifies, and alternatively requests the narrower relief described below. The Final Rule was published on June 30, 2026, and establishes August 31, 2026, as the deadline for filing objections. EWG's objections are therefore timely.

EWG requests that EPA revoke the revisions adopted in the Final Rule and revoke the underlying tolerances, consistent with the request EWG made in our 2023 comments to EPA, unless and until EPA can make the safety findings required by FFDCA section 408 on a complete and reliable record. In the alternative, EWG requests that EPA modify the challenged tolerances to levels supported by a lawful, child-protective assessment. EWG also requests that EPA stay the operation of the challenged revisions while these objections are pending pursuant to 21 U.S.C. § 346a(g)(1).

I. Preliminary Matters

A. EWG and the Interest Affected

EWG is a 501(c)(3) nonprofit research and policy organization dedicated to protecting human health and the environment, including through independent research and advocacy concerning pesticide residues in food. EWG, its staff, supporters, and the public they serve consume oat, wheat, barley, and triticale-based foods, including foods commonly eaten by infants and children, that may contain chlormequat residues under the challenged tolerances. EWG is therefore adversely affected by the Final Rule. EWG also participated in the underlying proceeding, including through comments submitted on April 24, 2023 (EPA-HQ-OPP-2021-0290-0026), and July 25, 2023 (EPA-HQ-OPP-2021-0290-0118).

B. Scope of the Objections

Chlormequat chloride is a plant growth regulator for which EPA first established tolerances on imported oats, wheat, barley, and certain animal products in 2018, increasing some of those tolerances in 2020. In a separate registration decision issued in connection with the Final Rule, EPA approved the first outdoor food uses of chlormequat on domestically grown wheat, triticale, barley, and oats. The Final Rule establishes and modifies the corresponding food tolerances. EPA received 41,666 public comments on the proposed registration decision, including comments from EWG and other public-health, environmental, agricultural, and industry stakeholders.

In comments dated April 24 and July 25, 2023, EWG explained that chlormequat chloride is a reproductive and developmental toxicant whose effects were not adequately accounted for in EPA's risk assessment; that its presence in foods commonly consumed by children raises concerns for children's health; and that chlormequat is not necessary to produce oats and other grains. EWG further explained that EPA did not adequately account for relevant peer-reviewed literature or evidence of immunotoxicity and neurotoxicity, failed to require a developmental neurotoxicity study, and did not apply the additional safety factors EWG maintained were necessary in light of the available dose-response data. As explained in the objections below, EPA's response does not adequately resolve these studies, data gaps, and safety-factor concerns.

C. Fee Waiver

EWG is a nonprofit research and policy organization with no financial interest in the outcome of this proceeding. Pursuant to 40 C.F.R. § 180.33(l) and EPA Pesticide Registration Notice 98-8, EWG respectfully requests waiver of the objection filing fee prescribed by 40 C.F.R. § 180.33(i) and required by 40 C.F.R. § 178.25(a)(5). EWG has no financial interest in this action, and waiver of the fee would promote the public interest.

II. Legal Standard

Under FFDCA Section 408(b), EPA "may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe," and "shall modify or revoke a tolerance if the Administrator determines it is not safe." 21 U.S.C. § 346a(b)(2)(A)(i). "Safe" means the Administrator "has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." *Id*. § 346a(b)(2)(A)(ii). In assessing safety, EPA must consider, among other things, "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue." *Id*. § 346a(b)(2)(D)(i). EPA must also consider available information concerning the relationship between study results and human risk, dietary consumption patterns among major consumer subgroups, aggregate exposure levels, and differences in sensitivity among major identifiable subgroups. *Id.* § 346a(b)(2)(D)(iii), (iv), (vi)–(vii).

The Food Quality Protection Act of 1996 imposes additional, mandatory child-protective requirements. EPA must "ensure that there is a reasonable certainty that no harm will result to

infants and children from aggregate exposure" to a pesticide chemical residue and must "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children." 21 U.S.C. § 346a(b)(2)(C)(ii)(I)–(II). For threshold effects, EPA must apply "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure… to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." *Id.* § 346a(b)(2)(C). EPA may use a different margin "only if, on the basis of reliable data," that margin "will be safe for infants and children." *Id*.

III. Objections

As required by 40 C.F.R. § 178.25(a), EWG specifies below, with particularity, the provisions of the Final Rule to which it objects, the basis for each objection, and the relief sought. EWG objects to the Final Rule's establishment and modification of tolerances for chlormequat chloride residues in or on wheat, triticale, barley, oats, and associated food and livestock commodities under 40 C.F.R. § 180.698(a), on each of the following grounds.

Objection 1: The reduction of the FQPA children's safety factor from 10X to 1X is not supported by reliable data

Section 408(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFDCA) requires EPA to ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to a pesticide and that a 10X safety factor applies unless reliable data shows a lower margin to be safe. Within the Final Rule EPA found that 1-2 year olds are the population subgroup with the highest exposure levels with exposure reaching 76 percent of the cPAD, the Agency's level of concern. Using the legally required 10X children's safety factor would indicate that exposure for 1 to 2 years would be 760 percent of the cPAD.

EPA's stated rationale for dropping the 10X safety factor is database completeness. In the HED memorandum (September 23, 2025, EPA-HQ-OPP-2021-0290-0188), EPA states, "At this time, the toxicological database is considered complete." EPA then contradicts that statement in noting that chlormequat is classified as EDSP "Group 2" supported by a reproduction study conducted under previous guidelines that "may not have evaluated all endocrine-related endpoints that have been added to the current guideline." EPA's review framework requires a case by case evaluation against the added endpoints and that has not been completed. Additionally the immunotoxicity study was waived, the subchronic neurotoxicity study was waived and no developmental neurotoxicity study was required. In all three cases the studies were waived in part based on an EPA prediction of what the unperformed study would have shown. The three studies EPA relied on to make the arguments against childhood susceptibility, a no-effect and two highest dose only results do not have the ability to indicate unique developmental susceptibilities. Chlormequat studies have found decreased fertility, reduced litter size and weight as well as delayed development. Reduced litter size and delayed development do not have parental analogues. Of significant importance is the lack of an updated systematic literature search

that goes beyond the March 2021 registration review assessment.

Objection 2: EPA has not adequately accounted for aggregate exposure by evaluating measured human biomonitoring data

In 2023 EWG submitted comments to the dockets that referenced the lack of any human epidemiological data reviewed by EPA alongside near universal detection of chlormequat in samples collected in the United Kingdom and Sweden. In 2024, EWG co-authored a peer-reviewed research study of U.S. adults finding chlormequat in 77 of 96 urine samples with a 90% detection rate in samples from 2023. While similar concentrations were detected in samples from 2017-2022, samples from 2023 showed a statistically significant increase in concentrations. EPA included no direct exposure assessment with monitoring verification needed to adequately assess aggregate exposure.

Objection 3: The poultry and egg tolerances are not supported by adequate residue characterization

EPA found the poultry metabolism study inadequate, noting no reference standards were included in the size-exclusion analysis and the extracted unknowns accounted for 20.6 to 57.1 percent of the total radioactive residue. The poultry and egg tolerances should be withdrawn until there is a scientifically complete and defensible characterization of the metabolism.

Objection 4: Inconsistent codified regulatory text with EPA's conclusions

The codified text at 40 C.F.R. § 180.698(a) was not updated to reflect EPA's agreement that the residue definition is the sum of chlormequat and its salts as chlormequat cation. Triticale grain is registered but has no allowable tolerance and not included in tolerance Table 1. While barley bran and wheat bran have listed tolerances, oat bran is not included in the tolerance Table 1 but listed at 80 ppm in Section IV. B. Wheat straw is listed at 70 ppm in Table 1 and 80 ppm in Section IV. B.

IV. Requested Relief

For the foregoing reasons, EWG respectfully requests that EPA:

A. Revoke the revisions to 40 C.F.R. §180.698(a) adopted through the Final Rule and revoke the tolerances, consistent with the request EWG made in our 2023 comments to EPA, until EPA makes the safety findings required by FFDCA section 408 on a complete and reliable record;
B. In the alternative, modify the challenged tolerances to levels supported by a lawful chronic population adjusted dose with the FQPA children's safety factor retained at 10X and stay the operation of the challenged revisions while these objections are pending;
C. Before establishing, modifying, reestablishing, or leaving in effect the challenged

tolerances:require completion of the developmental neurotoxicity, subchronic neurotoxicity, and immunotoxicity studies necessary to resolve the identified data gaps; conduct a case-by-case endpoint evaluation for endocrine disruption;conduct an updated systematic literature search covering publications since March 2021; and conduct a reasoned, public, and data-supported assessment of:

1. the appropriate point of departure and uncertainty factors; including how the reported adverse developmental effects observed at 5 mg/kg-bw/day bear on the protectiveness of the chosen NOAEL of 5 mg/kg-bw/day;
2. the additional FQPA safety factor;
3. the relevant animal-toxicity, measured human biomonitoring data and published urinary chlormequat concentrations, and food-residue data; and
4. the safety of aggregate exposure for infants and children, as required by 21 U.S.C. § 346a(b)(2)(C);

D. If EPA does not revoke the challenged tolerances, correct the codified text at 40 C.F.R. §180.698(a), including the cation-based residue definition EPA adopted, resolution of the missing triticale grain and oat bran tolerances, and reconciliation of the wheat straw level with Unit IV.B;
E. Waive the objection filing fee pursuant to 40 C.F.R. § 180.33(l) and EPA Pesticide Registration Notice 98-8; and
F. Issue an order stating the action taken on each objection and setting forth any resulting revision to the tolerance regulation, as required by 21 U.S.C. § 346a(g)(2)(C).

V. Filing Information and Reservation

EWG identifies Docket No. EPA-HQ-OPP-2021-0290 on the first page and will submit this filing to the Hearing Clerk in the manner specified by EPA and place a non-confidential copy, with its exhibits, in the public docket. No confidential business information is included. EWG incorporates the cited docket materials and attached exhibits to the extent permitted by 40 C.F.R. part 178. EWG preserves all objections and arguments fairly encompassed by this filing and requests leave to supplement the record if EPA identifies a curable procedural deficiency or if necessary to respond to material placed in the record after the filing deadline.

Respectfully submitted,

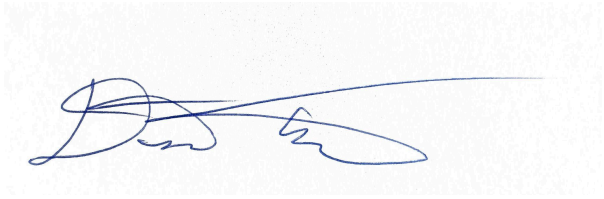

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Exhibit List

Exhibit A: EWG's April 24, 2023 Comments (EPA-HQ-OPP-2021-0290-0026)

Exhibit B: EWG's July 25, 2023 Comments on EPA's Proposed Registration of Chlormequat Chloride for Food Uses (EPA-HQ-OPP-2021-0290-0118)

Exhibit C: EPA, "Response to Public Comments on EPA's Registration Decision to Approve the First Outdoor Food Uses on Wheat, Triticale, Barley, and Oats for Chlormequat Chloride," posted July 2, 2026 (EPA-HQ-OPP-2021-0290-0189)

Exhibit D: Alexis M. Temkin et al., "A Pilot Study of Chlormequat in Food and Urine from Adults in the United States from 2017 to 2023," *Journal of Exposure Science & Environmental Epidemiology* 34, 317–321 (2024)

Exhibit E: EPA Health Effects Division, "Response to Public Comments on Tolerances and the Proposed First Food Uses for Chlormequat Chloride in the United States," September 23, 2025 (EPA-HQ-OPP-2021-0290-0188)

Exhibit A

April 24, 2023

Environmental Working Group comments to the Environmental Protection Agency Docket ID: EPA-HQ-OPP-2021-0290; 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 on the Document ID: EPA-HQ-OPP-2021-0290-0011; Receipt of a Pesticide Petition Filed for Residues of Pesticide Chemicals in or on Various Commodities February 2023

The Environmental Working Group, 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 requested tolerances for chlormequat chloride and to revoke previously approved tolerances for chlormequat chloride in oats, wheat, barley, and animal products, and not allow new uses of chlormequat in the U.S.

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. This decision paved the way, ultimately, 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 to impact fertility, harm the reproductive system, and alter growth and development in animal studies.

EWG is recommending the EPA not approve the currently petitioned tolerances for chlormequat chloride, revoke the previously approved tolerances, and not allow new uses of chlormequat in the U.S. Our recommendations are based on the following:

1. Chlormequat chloride is a reproductive and developmental toxicant, which is not accounted for in the current EPA risk assessment.
2. The presence of chlormequat chloride in foods commonly consumed by children puts children's health at risk.
3. Chlormequat chloride is not necessary to produce oats and other grains.

Details and information that support EWG's recommendation not to approve chlormequat tolerances are listed below.

[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-found-popular-oat-based

Chlormequat chloride is a reproductive and developmental toxicant, and exhibits neurotoxicity, which are not accounted for in the current EPA risk assessment.

Since the 1980s there have been reports, summarized in the peer-reviewed literature, showing that exposure to chlormequat during pregnancy, at environmentally relevant concentrations through controlled dosing experiments or using chlormequat treated animal feed, can harm reproduction in both pigs and rodents.[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] Importantly, the doses at which these effects occur in animal studies are in some cases 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 NOAEL was available, yet the 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 cause altered growth and metabolism during development.[6] These two aspects indicate that in the human health risk assessment for chlormequat, EPA should apply a 10X FQPA safety factor for children's health, based on the developmental effects of chlormequat exposure, and another 10X for extrapolation of a LOAEL to a NOAEL. Furthermore, acute neurotoxic effects were observed in the registrant studies, yet no developmental neurotoxicity study was available, suggesting the database on chlormequat toxicity is not complete.

The presence of chlormequat chloride in foods commonly consumed by children puts children's health at risk.

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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 chlorocholinechloride-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.

EWG has researched the presence of pesticides, particularly glyphosate, in oat-based products since 2018. Our results found glyphosate in nearly all conventional oat-based products, with most exceeding safety thresholds recommended by EWG scientists.[8] Upon learning of EPA's recent approval of tolerances for chlormequat in imported oats, EWG continued testing oat-based products, this time in 2022 for the presence of chlormequat. In our tests, we found chlormequat in all but one of 13 conventional oat-based products, with the highest levels detected in popular Quaker products as well as General Mills Cheerios.[1] These levels did not exceed EPA tolerances. But given the faults of the risk assessment highlighted in the previous section, the safety thresholds set by EPA do not adequately protect children's health.

Additionally, in Sweden and the U.K., chlormequat can be detected in 100 percent of the individuals sampled and at concentrations higher than other pesticides with known health effects in human populations, including chlorpyrifos.[9,10] Shockingly, despite widespread exposure in the human population and harmful effects at low doses in animal studies, no epidemiological studies exist investigating the potential adverse health effects in humans. This large data gap prevents a full understanding of chlormequat toxicity.

Chlormequat chloride is not necessary to produce oats and other grains.

The use of chlormequat and introduction of chlormequat into the food supply in not just the U.S. but also Canada is a relatively new phenomenon. Oats and grains have been grown in North America for decades without the use of chlormequat. Further still, in EWG tests of conventional oat-based infant food, chlormequat was rarely detected. Furthermore, one study that investigated switching from a conventional to an organic diet, found the levels of chlormequat dropped rapidly and significantly in human urine samples.[11]

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[8] Environmental Working Group. Complete Results of EWG's 2018 Glyphosate Tests in Oat Cereals and Snacks. 2018. https://www.ewg.org/sites/default/files/u352/EWG_Glyphosate-2_Table_Full_C02.pdf

[9] Galea KS, MacCalman L, Jones K, Cocker J, Teedon P, Cherrie JW, van Tongeren M. Urinary biomarker concentrations of captan, chlormequat, chlorpyrifos and cypermethrin in UK adults and children living near agricultural land. J Expo Sci Environ Epidemiol. 2015 Nov-Dec;25(6):623-31. doi: 10.1038/jes.2015.54. Epub 2015 Sep 16. PMID: 26374656; PMCID: PMC4611359.

[10] Norén E, Lindh C, Rylander L, Glynn A, Axelsson J, Littorin M, Faniband M, Larsson E, Nielsen C. Concentrations and temporal trends in pesticide biomarkers in urine of Swedish adolescents, 2000-2017. J Expo Sci Environ Epidemiol. 2020 Jul;30(4):756-767. doi: 10.1038/s41370-020-0212-8. Epub 2020 Feb 24. PMID: 32094458; PMCID: PMC8075908.

[11] Rempelos L, Wang J, Barański M, Watson A, Volakakis N, Hoppe HW, Kühn-Velten WN, Hadall C, Hasanaliyeva G, Chatzidimitriou E, Magistrali A, Davis H, Vigar V, Średnicka-Tober D, Rushton S, Iversen PO, Seal CJ, Leifert C. Diet and food type affect urinary pesticide residue excretion profiles in healthy individuals: results of a randomized controlled dietary intervention trial. Am J Clin Nutr. 2022 Feb 9;115(2):364-377. doi: 10.1093/ajcn/nqab308. PMID: 34718382.

In conclusion, given the large data gaps that prevent a full understanding of the toxicity of chlormequat, the available studies that indicate low dose exposure to chlormequat can harm reproduction and development, and the presence of chlormequat in children's food and foods eaten by pregnant people, we believe strongly that the EPA should not approve the petitioned tolerances, should revoke previously approved tolerances and should not allow new uses of chlormequat in the U.S.

We appreciate the opportunity to comment.

Alexis Temkin, PhD
Senior Toxicologist
Environmental Working Group

Exhibit B

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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Environmental Working Group

Exhibit C

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

Response to Public Comments on EPA's Registration Decision to Approve the First Outdoor Food Uses on Wheat, Triticale, Barley, and Oats for Chlormequat Chloride (Docket ID: EPA-HQ-OPP-2021-0290)

This document summarizes the U.S. Environmental Protection Agency's (EPA) responses to public comments received in response to the Notice of Receipt (NOR) of an application to register pesticide products containing the active ingredient chlormequat chloride and the proposed decision to unconditionally register new products containing chlormequat chloride under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3(c)(5).

On August 31, 2021, and October 27, 2021, EPA published the NOR in the *Federal Register* announcing that EPA had received an application to add uses for wheat, triticale, barley and oats and providing a 30-day public comment period. One comment was received from the Center for Food Safety on November 30, 2021.

On August 24, 2021, and October 21 2021, EPA published a Notice of Filing (NOF) in the *Federal Register* announcing that EPA had received a petition under the Federal Food, Drug, and Cosmetic Act (FFDCA) requesting that EPA establish tolerances for residues of chlormequat chloride on wheat, triticale, barley and oat commodities and providing a 30-day public comment period. Comments were received from the public, the National Association of Wheat Growers and National Barley Growers Association and the Center for Food Safety.

An additional NOF was published on March 24, 2023 to establish tolerances on aspirated grain fractions and livestock feed commodities and also provided a 30-day public comment period. A comment was submitted by the Environmental Working Group.

On April 26, 2023, EPA announced a proposed decision to grant new uses and new product registrations for one technical product and one end-use product containing chlormequat chloride under (FIFRA) Section 3(c)(5). EPA received several requests to extend the comment period for this decision. In response to the requests, the Agency extended the comment period for 60 days. During the comment period, the Agency received over 40,000 comments from stakeholders including non-governmental organizations, academic and medical professionals, the US Department of Agriculture (USDA), and members of the general public. Most comments came from mass mailer campaigns, and approximately 168 unique substantive comments were received from various stakeholders.

A number of literature citations, publications, website links, papers and draft papers were submitted to the docket. Supporting materials from stakeholders and the Agency can be found in

the EPA's public docket for the proposed new uses of the active ingredient chlormequat chloride docket (EPA-HQ-OPP-2021-0290) at www.regulations.gov. The Agency considered all these comments and submissions and responded to the substantive comments in this document and documents specific to the human health or environmental fate and effects comments. The comments and submissions received to the public docket resulted in changes to the Agency's risk assessments or the mitigation in the proposed decision document.

Comments on the NOR and EPA's Responses

A. Comments from the Center for Food Safety (CFS)

a. EPA-HQ-OPP-2021-0290-0009: Comments from CFS are summarized below.

i. CFS opposes the registration of the new uses and associated tolerances. Granting these uses will significantly increase domestic use.

ii. CFS has cited the agency's legal obligations under FIFRA Section 3. "Under Section 3(c)(5) of FIFRA, EPA shall register a pesticide only if the agency determines that the pesticide "will perform its intended function without unreasonable adverse effects on the environment" and that "when used in accordance with widespread and commonly recognized practice[,] it will not generally cause unreasonable adverse effects on the environment." And "….under Section 3(c)(7) of FIFRA "for a period reasonably sufficient for the generation and submission of required data," but only if EPA also determines that the conditional registration of the pesticide during that time period "will not cause any unreasonable adverse effect on the environment, and that use of the pesticide is in the public interest."

iii. CFS has also commented that under the Endangered Species Act (ESA) Section 7, the agency must consult with the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS). Section 7(a)(2) of the ESA requires every federal agency to consult the appropriate federal fish and wildlife agency (*i.e.*, the FWS in the case of land and freshwater species and the NMFS in the case of marine species) to "insure" that the agency's actions are not likely "to jeopardize the continued existence" of any listed species or "result in the destruction or adverse modification" of critical habitat.[1] The ESA's implementing regulations broadly define agency action to include "all activities or programs of any kind authorized, funded or carried out … by federal agencies," including the granting of permits and "actions directly or indirectly causing modifications to the land, water or air."[2] A species' "critical habitat" includes those areas identified as "essential to the conservation of the species" and "which may require special management considerations or protection."[3]

[1] 16 U.S.C. § 1536(a)(2); *see also* 50 C.F.R. § 402.01(b).
[2] 50 C.F.R. § 402.02 (emphasis added).
[3] 16 U.S.C. § 1532(5)(A).

EPA is required to review its actions "at the earliest possible time" to determine whether the action may affect listed species or critical habitat.[4] To facilitate compliance with Section 7(a)(2)'s prohibitions on jeopardy and adverse modification, the ESA requires each federal agency that plans to undertake an action to request information from the expert agency "whether any species which is listed or proposed to be listed [as an endangered species or a threatened species] may be present in the area of such proposed action."[5] If FWS/NMFS advises the agency that listed species or species proposed to be listed may be present, the agency must then prepare a biological assessment for the purpose of identifying any such species that are likely to be affected by the proposed agency action.[6]

If, based on a biological assessment, an agency determines that its proposed action may affect any listed species and/or their critical habitat, the agency generally must engage in formal consultation with FWS/NMFS.[7] At the end of the formal consultation, FWS/NMFS must provide the agency with a "biological opinion" detailing how the proposed action will affect the threatened and endangered species and/or critical habitats.[8] If FWS/NMFS concludes that the proposed action will jeopardize the continued existence of a listed species or result in the destruction or adverse modification of critical habitat, the biological opinion must outline "reasonable and prudent alternatives" to the proposed action that would avoid violating ESA section 7(a)(2).[9] Pending the completion of formal consultation with the expert agency, an agency is prohibited from making any "irreversible or irretrievable commitment of resources with respect to the agency action which has the effect of foreclosing the formulation or implementation of any reasonable and prudent alternative measures."[10]

iv. Under the Federal Food, Drug and Cosmetic Act (FFDCA), the agency must determine the proposed tolerance level will cause no harm to humans from exposure to chlormequat chloride.
v. A review of studies by European regulators revealed a host of reproductive and developmental effects, including evidence of hormone disruption. Despite this, the agency has not screened chlormequat chloride for potential endocrine disruption.
vi. CFS commented that The Agency failed to require additional neurotoxicity testing.
vii. CFS commented that chlormequat chloride is registered for use on grains in Europe, the U.K., Canada, and other countries, which Codex have established corresponding tolerances. About 65% of winter wheat and

[4] 50 C.F.R. § 402.14(a).
[5] 16 U.S.C. § 1536(c)(1); *see also* 50 C.F.R. § 402.12(c).
[6] *Id.*
[7] 50 C.F.R. § 402.14.
[8] 16 U.S.C. § 1536(b); 50 C.F.R. § 402.14.
[9] 16 U.S.C. § 1536(b)(3)(A).
[10] 16 U.S.C. § 1536(d).

50% of winter barley and oats are treated with products containing chlormequat chloride in the United Kingdom (Spink *et al*. 2004), while 70% of the winter wheat in the European Union as a whole is treated with it (Sorenson and Danielsen 2006). To facilitate import of chlormequat chloride-treated grains from these countries, the EPA has established import tolerances that do not apply to domestically-grown grains. Granting the requested tolerances and approving the proposed new uses will likely lead to an astronomical rise in domestic use of this chemical. Torner *et al*. (1999) cite typical application rates of 0.5 to 2 kg/ha (.45 to 1.79 lbs/acre) in Europe. EPA has granted experimental use permits with permitted application rates for wheat, barley/oats, rye/triticale, and grasses grown for seed of 1 lb/acre, 1.27 lbs/acre, 1-1.27 lbs/acre, and 1.34-4 lbs/acre, respectively (EPA 3/16/21, Table 3.3, p. 11). If 70% of the U.S. wheat, oats and barley that went on to be harvested in 2020 were treated at a rate of 1 lb/acre, 28 million lbs of chlormequat chloride would have been applied that year (40 million harvested acres in 202 * 70% * 1 lb/acre). This would represent a 28,000-fold increase over the current 1,000 lbs/year.

viii. CFS commented on the tolerance level/tolerance creep and increased exposure.

ix. CFS expressed concerns with the persistence of chlormequat chloride and uncertainty regarding the extent to which sorbed residues may represent a potential route of exposure.

x. CFS expressed concerns that the pesticide risk assessments should include an analysis of potential risks to soil-dwelling organisms. The petitioners included in their submission a 2021 petition regarding assessment of soil-dwelling organisms.

b. EPA Response

i. With respect to CFS's comments regarding domestic use and exposure, the acute and chronic dietary (food and drinking water) exposure and risk estimates for the general U.S. population and all population subgroups are below the Agency's levels of concern. As such, there is reasonable certainty that no harm will result to the general population, or to infants and children, from aggregate exposure to chlormequat chloride residues. In conducting the acute and chronic dietary risk assessments, EPA conservatively assumed 100 percent crop treated (PCT) for all crops and average field trial values. The PCT is defined as the percent of acres treated with a given pesticide relative to the total number of acres grown. The commenter has provided no information to support a conclusion that the proposal to modify existing tolerances for residues is not safe.

ii. EPA agrees that the Agency has an obligation under ESA section 7(a)(2) to assess the potential impacts to listed species and designated critical habitats (CH) and, where appropriate, to consult with the Services on this

registration decision. EPA is obligated to engage in a formal consultation if it has determined may affect and likely to adversely affect (MA-LAA) a listed species and/or CH. If, however, the agency determines that the action is may affect but not likely to adversely affect (MA-NLAA), then the agency is only obligated to engage in an informal consultation.

In 2025, EPA prepared a Biological Evaluation (BE) that assesses the potential effects on listed species and designated critical habitats. For species where EPA proposed to make a MA-LAA determination, EPA also predicted the potential likelihood of future jeopardy (J) for listed species and adverse modification (AM) of designated critical habitat ("J/AM"), consistent with 50 C.F.R. § 402.40(b)(1). The BE also includes EPA's assessment of how EPA identified mitigations to address any potential likelihood of future J/AM.

The BE makes LAA determinations for 433 species and 130 designated critical habitats and NLAA determinations for 712 species and 350 designated critical habitats from the use of chlormequat chloride on oats, barley, triticale, and wheat. The BE predicts that there is no potential likelihood of future J/AM from these uses based on the mitigations incorporated into the final labeling. The BE also makes no effect (NE) determinations for all listed species and designated critical habitats from indoor use of chlormequat chloride in greenhouses.

iii. Based on the BE, EPA has initiated consultation with the Services. However, EPA has also determined that moving forward with this registration action during consultation is appropriate. Consistent with ESA section 7(a)(2) and 7(d), EPA has determined that this action—taking into account the mitigations and the term on the registrations ensuring that any additional or different mitigations identified by the Services during the consultation process are added expeditiously to the registrations—will not make an irreversible or irretrievable commitment of resources that has the effect of foreclosing the development or implementation of any reasonable and prudent alternative measures. EPA's rationale for this determination is presented in the agency's "Endangered Species Act Section 7(d) Consistency Determination with Respect to the Application for the Registration of Products Containing the Chlormequat Chloride for New Uses on Wheat, Triticale, Barley, Oats and Meat Commodities" available in Docket ID# EPA-HQ-OPP-2021-0290.

iv. (iv. -vi.) With respect to CFS comments regarding harm to humans from exposure to chlormequat chloride, reproductive and developmental effects, neurotoxicity testing, and tolerance level/tolerance creep please refer to "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat

Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

v. See iv.

vi. See iv.

vii. EPA acknowledges that domestic uses under the proposed use will also increase exposure. However, the increases projected by CFS are largely speculative at this time and are not based on current U.S. (domestic) use. The ecological risk assessment of chlormequat chloride to support the FIFRA registration decision and subsequent Biological Evaluation under the ESA evaluates the maximum labeled rates for use of chlormequat chloride on cereals (USEPA, 2022*a* available in Docket ID# EPA-HQ-OPP-2021-0290). The FIFRA assessment estimates exposure for non-target organism specifically for use on cereals and assumes 100 PCT.

The BE relies on use data layers (UDLs) for barley, oats, triticale and wheat. The UDLs represent the potential locations of chlormequat chloride applications in contiguous United States (CONUS) and the non-lower 48 states/territories (NL-48 includes: Hawaii, Alaska, Puerto Rico, U.S. Virgin Islands, Guam, the Northern Mariana Islands and American Samoa). The UDLs are "buffered" in all directions based on the farthest distance from the treated sites where effects on listed species or designated CH are reasonably expected to occur due to spray drift, erosion, and/or runoff exposure. Although the extent to which chlormequat chloride use may fluctuate in the future depending on market penetration, EPA conservatively assumes that all the specific areas currently cropped with cereal grains are treated.

viii. See iv.

ix. With respect to CFS's comment regarding persistence and sorbed residues, the risk assessment characterizes chlormequat chloride as being persistent with residues sorbing to soil. Based on current guidance and the extraction methods used in the soil and aquatic metabolism studies (MRIDs 50747527, 50747528, 50747529), EPA considered these residues bound to the soil as not a potential source of exposure for the purposes of risk assessment. When calling this chemical persistent, the commenter is only referring to the upper bound aerobic soil metabolism half-life measured and is not considering the full range of data measured. While CFS cites a paper by Barraclough *et al*. 2005, the paper is not a primary source of data but rather a review and would not constitute a source of data to inform EPA ecological risk assessment. However, EPA considered the Barraclough *et al.* paper in the development of EPA's *Guidance for Addressing Unextracted Pesticide Residues in Laboratory Studies*

(USEPA 2014). Although the ecological risk assessment characterizes chlormequat chloride as a persistent compound, the assessment discusses submitted terrestrial field dissipation studies where the compound was applied to bare soils in Kansas (MRID 50747530[11]), North Dakota (MRID 50747531[12]), California (MRID 50747532[13]) and Washington (MRID 50747533[14]). In those studies, the dissipation half-lives of the compound ranged from 9 to 33 days in the total soil profile with the parent compound remaining in the surface layer (0 – 7.5 cm) of the soil plots in three of the four study areas. Therefore, while laboratory-based studies indicate that the compound is stable to abiotic degradation and slowly undergoes biotic metabolism, field-based studies suggest that there are situations where field dissipation rates may differ from degradation rates in laboratory studies. This is consistent with model input parameter guidance[15] since degradation studies are designed to only examine a single route of degradation but field dissipation studies consider multiple routes of degradation and transport simultaneously.

x. CFS expressed concerns that the pesticide risk assessments should include an analysis of potential risks to soil-dwelling organisms. CFS included a 2021 petition regarding assessment of such organisms. EPA is still considering the 2021 petition, and this response is not intended to be a response to the petition. Soils represent a complex biological environment which is typically organized into generic soil horizons and transitional horizons.[16] The organisms which make up this environment are diverse and can contribute to a wide range of ecosystem services (*e.g.,* nutrient

[11] Malekani, K. and S. Kang. 2018a. Terrestrial Field Soil Dissipation of Chlormequat Chloride SL Formulation on Bare Ground in Kansas State. Unpublished study performed by Smithers Viscient, Wareham, Massachusetts; sponsored and submitted by Eastman Chemical Company, Kingsport, Tennessee (pp. 1, 3). Smithers Viscient Study No.: 14105.6125. Analytical Phase Study No.: 14105.6126. Experiment initiation May 16, 2017, and completion October 12, 2017 (p. 11). Final report issued November 27, 2018.

[12] Malekani, K. and S. Kang. 2018b. Terrestrial Field Soil Dissipation of Chlormequat Chloride SL Formulation on Bare Ground in North Dakota State. Unpublished study performed by Smithers Viscient, Wareham, Massachusetts; sponsored and submitted by Eastman Chemical Company, Kingsport, Tennessee (pp. 1, 3). Smithers Viscient Study No.: 14105.6129. Analytical Phase Study No.: 14105.6130. Experiment initiation May 9, 2017, and completion October 6, 2017 (p. 11). Final report issued November 27, 2018.

[13] Malekani, K. and S. Kang. 2018c. Terrestrial Field Soil Dissipation of Chlormequat Chloride SL Formulation on Bare Ground in California State. Unpublished study performed by Smithers Viscient, Wareham, Massachusetts; sponsored and submitted by Eastman Chemical Company, Kingsport, Tennessee (pp. 1, 3). Smithers Viscient Study No.: 14105.6119. Analytical Phase Study No.: 14105.6105. Experiment initiation May 3, 2017, and completion September 29, 2017 (p. 11). Final report issued November 15, 2018.

[14] Malekani, K., and S. Kang. 2018c. Terrestrial Field Soil Dissipation of Chlormequat Chloride SL Formulation on Bare Ground in Washington State. Unpublished study performed by Smithers Viscient, Wareham, Massachusetts; sponsored and submitted by Eastman Chemical Company, Kingsport, Tennessee (pp. 1, 3). Smithers Viscient Study No.: 14105.6127. Analytical Phase Study No.: 14105.6128. Experiment initiation May 15, 2017, and completion October 12, 2017 (p. 11). Final report issued November 15, 2018.

[15] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/nafta-guidance-evaluating-and-calculating

[16] Soil Science Society of America, Inc., 2022. Glossary of Soil Science Terms. https://www.soils.org/files/publications/soils-glossary/appendix-2.pdf

cycling, soil formation, stabilization); however, protection goals are typically developed in terms of specific ecosystem services which are to be protected, and protection goals have not been well defined for soil organisms. Such protection goals must consider dispersal abilities and biological characteristics that can vary widely both spatially and temporally within the soil horizons and their transitional zones, and influence recovery/recolonization. Without specific goals it is not possible to provide guidance on developing specific tests for evaluating effects and acceptability criteria for studies with such organisms. Guidance has not yet been developed on estimating exposure to such organisms within the soil profile.

Consistent with evaluating other biological communities, the representativeness of test species, interspecies variability, soil variability, recovery, establishing exposure-effect relationships, and extrapolating those effects from laboratory to field are challenges in establishing a risk assessment process for soils.[17] Recovery of these species can be influenced by insensitive dormant stages (*e.g.,* seeds; ephippia; spores) which may not be directly influenced by pesticide use, life history traits, or voltinism (*i.e.,* number of generations per year). Additionally, the capacity for soil organisms to migrate can vary widely and influence protection goals. While EPA's current risk assessment process does not include nor require data from soil-dwelling organisms in part 158 of data requirements, as with other taxa, when such data are required or are available which meet data quality standards, EPA considers these data in assessing hazard. Therefore, given the reasons articulated in this response, at this time EPA is not planning to add additional testing requirements with which to assess a soil health endpoint which has yet to be defined.

Comments on the NOF and EPA's Responses

A. Comments from the Environmental Working Group

a. **EPA-HQ-OPP-2021-0290-0026:** Comments from the Environmental Working Group are summarized below.

i. Chlormequat chloride is a reproductive and developmental toxicant, and exhibits neurotoxicity, which are not accounted for in the current EPA risk assessment.

ii. The presence of chlormequat chloride in foods commonly consumed by children puts children's health at risk. There are huge data gaps that prevent a full understanding of the toxicity.

iii. The presence of chlormequat chloride in foods commonly consumed by children puts children's health at risk.

[17] European Food Safety Authority. 2016. Scientific Opinion addressing the state of the science on risk assessment of plant protection products for in-soil organisms. EFSA Journal. EFSA-Q-2011-00978. doi: 10.2903/j.efsa.2017.4690

b. **EPA Response:** Refer to "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290 regarding literature review, adverse health effects (including reproductive, developmental and neurotoxicity), as well as an explanation of how the current assessment is protective of children's health.

B. **Comments from CFS**
   a. **EPA-HQ-OPP-2021-0290-0007 and EPA-HQ-OPP-2021-0290-0008:** Comment submitted by CFS (Part 1 of 2); and Comment submitted by CFS (Part 2 of 2)
   b. **EPA Response:** Comments have been previously addressed in this document's Comments on the NOR and EPA's Reponses (section A. Comments from the Center for Food Safety (CFS)).

Comments on the Proposed Decision (April 26, 2023) and EPA's Responses

A. EPA-HQ-OPP-2021-0290-0171 and EPA-HQ-OPP-2021-0290-0172: General opposition to the proposed registration from members of the public

Comment Summary
Multiple comments from stakeholders (including two mass mail campaigns sponsored by CFS and EWG) requested the EPA to not approve the use of chlormequat chloride on wheat, triticale, barley, and oats claiming adverse effects to human health. Specific concerns included disrupting fetal growth, changing bone development, altering metabolism, delaying development during puberty, affecting male fertility, decreasing testosterone levels, and harming the nervous system.

EPA Response:
For comments regarding potential adverse health effects, please refer to the document "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

B. EPA-HQ-OPP-2021-0290-0055 and EPA-HQ-OPP-2021-0290-0060: USDA Comment

In general, USDA commented in support of the registration of chlormequat chloride and was supportive of the proposed mitigation measures. The comment describes benefits including increased grain yield and decreased lodging (*i.e.,* bending of stems near the ground) for barley and wheat. Further, the comment stated that the uses would complement micronutrient and biofertilizer application under drought and salinity stress conditions. USDA also provided information about how the application of chlormequat

chloride can provide other improved physical characteristics in small grains such a delayed apical development and stem elongation resulting in higher grain yields.

EPA Response:
The Agency acknowledges that USDA is supportive of EPA approving these chlormequat chloride registrations. EPA generally agrees with USDA that chlormequat chloride can reduce lodging and potentially increase yield in small grain crops. EPA also agrees that applications of chlormequat chloride can provide more desirable physical characteristics in small grains.

C. EPA-HQ-OPP-2021-0290-0057: American Academy of Pediatrics (AAP) Comment

The AAP believes that the EPA's proposed decision to approve the requested tolerances for chlormequat on food crops will negatively affect the health and well-being of infants and children. In the human health risk assessment for chlormequat, the EPA should seriously examine its pediatric and reproductive toxicity. At a minimum, EPA should at least apply the FQPA-required 10X child-protective safety factor, based on the developmental effects of chlormequat exposure. The apparent omission of this factor in the current risk assessment is concerning.

EPA Response: Refer to responses to comments regarding providing adequate protection for infants and children in the document "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

D. EPA-HQ-OPP-2021-0290-0068: Taminco Comments

Taminco Comment #1:
EPA proposed setting a plant-back interval of 12 months for leafy vegetables and root crops. An assessment of the Total Radioactive Residues shows that no inadvertent residues of concern (being chlormequat chloride) would be present in rotated leafy vegetables and root crops. Therefore, a plant-back interval of 0 days rather than 12 months would be more appropriate.

EPA Response:
The Agency concurs with Taminco's comment. A plant-back interval (PBI) for leafy vegetable and root and tuber crops is not required (see memorandum "Reassessment of Plant-Back Intervals for Rotated Crops Recommended in the Human Health Risk Assessment for the Section 3 Registration of Chlormequat Chloride on Wheat, Triticale, Barley, and Oats. Abbreviated Residue Chemistry Review", S. Piper, D468147, 08/23/2023) available in Docket ID# EPA-HQ-OPP-2021-0290.

Taminco Comment #2:
EPA concluded that several unknowns were inadequately characterized/identified in the

poultry metabolism study and that these unknowns should therefore be included in the residue definition for poultry matrices. However, from plant and rat metabolism studies it is known that the parent compound chlormequat chloride readily degrades to choline chloride and glycine betaine, which are natural compounds in many living organisms.

EPA Response:
Refer to "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID EPA-HQ-OPP-2021-0290.

Taminco Comment #3
Growers have expressed concerns regarding the restrictions when wind speeds exceed 10 miles per hour. EPA should consider amending the proposed drift management statement: "Do not apply when wind speeds exceed 10 miles per hour at the application site." to read "Do not apply when wind speeds exceed 15 miles per hour at the application site. If the windspeed is greater than 10 miles per hour, apply with the nozzle height no more than 2 feet above the ground or crop canopy."

EPA Response:

EPA agrees with Taminco's comment. A wind speed restriction of 10 miles per hour or less would allow for less available time to make applications as compared to a 15 miles per hour or less wind restriction. Depending on the local wind conditions, wind speed restrictions could prevent timely application of chlormequat chloride and complicate crop management.

EPA is revising the current proposed statements for all applications to " Do not apply when wind speeds exceed 15 miles per hour at the application site. " This revision will allow for additional opportunity to apply the product as compared to the previous restriction of 10 miles per hour or less. Additional mandatory spray drift label restrictions are updated and included on the end use label.

Taminco Comment #4:
The current tolerance expression for chlormequat chloride is as chlormequat chloride (§ 180.698), which is in line with the tolerance expression set by Pest Management Regulatory Agency (PMRA) and the European Commission. The residue definition by CODEX is as chlormequat cation. Both chlormequat cation and chlormequat chloride are used throughout EPA's evaluation documents. While these differences in expression of residues do not impact the proposed decision, we note them here for the Agency's consideration in the future.

EPA Response:
Refer to "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

E. EPA-HQ-OPP-2021-0290-0139: Center for Biological Diversity (CBD) Comment

CBD commented that they agreed with CFS that before approving new uses for chlormequat chloride, EPA must fulfill its duties under the ESA section 7(a)(2). Specifically, EPA must determine whether these new uses "may affect" any ESA-protected species or critical habitats.

EPA Response:
Comments have been previously addressed in this document's Comments on the NOR and EPA's Reponses (section A. Comments from the Center for Food Safety (CFS)).

F. EPA-HQ-OPP-2021-0290-0065: Beyond Pesticides (BP) Comments

BP Comment #1:
BP states that chlormequat is an unnecessary addition to the other pesticides on market and for use on wheat, triticale, barley, and oats. Specifically, BP raises concerns that there is a lack of evidence addressing the adverse health effects in the general population.

EPA Response:
EPA recognizes that there are other plant growth regulators (PGRs) available for use in wheat, triticale, barley, and oats. The main alternative identified by EPA is trinexapac-ethyl. Environmental conditions influence the performance of PGRs so multiple options can assist users by providing flexibility. EPA identified benefits for chlormequat chloride compared to trinexapac-ethyl, including a wider application window and effectiveness at lower temperatures.

The decision to approve this new use is in alignment with FIFRA section 3(c)(5), which states:

> "The Administrator shall not make any lack of essentiality a criterion for denying registration of any pesticide. Where two pesticides meet the requirements of this paragraph, one should not be registered in preference to the other. In considering an application for the registration of a pesticide, the Administrator may waive data requirements pertaining to efficacy, in which event the Administrator may register the pesticide without determining that the pesticide's composition is such as to warrant proposed claims of efficacy. If a pesticide is found to be efficacious by any State under section 24(c) of this Act, a presumption is established that the Administrator shall waive data requirements pertaining to efficacy for use of the pesticide in such State."

Regarding health effects, refer to "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

BP Comment #2:
BP states that EPA's risk assessments should consider the inadvertent biological effects of chlormequat chloride on the potential for both crop losses and harmful effects of

microbial toxins.

EPA Response:
In terms of "inadvertent biological effects" and as noted in an earlier response, EPA completed an ecological risk assessment (ERA) of the proposed new uses of chlormequat chloride.[18] That assessment evaluated the potential for adverse effects to terrestrial plants based on toxicity data across multiple monocotyledonous and dicotyledonous species of plants/crops. Consistent with the use of chlormequat chloride as an herbicide, the ERA identified risks of concern for terrestrial plants, and mitigations have been proposed to reduce exposure for non-target plants. With respect to concerns regarding the potential effects of chlormequat chloride on microbial toxins/soil-borne plant pathogens, at this time, EPA's current risk assessment process does not include such an assessment of soil health as protection goals have not been formally defined but are critical toward designing an appropriate risk assessment process and assessing impacts to ecosystem services. Such protection goals would include the ecological entity, the attribute to be protected, the magnitude of the effects, the temporal and spatial scales of the effect. However, as with other taxa, when data are available which meet data quality standards, EFED considers these data in assessing hazard. Although EPA is not assessing impacts to soil health, mandatory spray drift mitigation measures are included on the label to reduce non-target exposure.

The commenter has not provided any information/data on which "inadvertent biological effects" are resulting in crop losses from the application of the PGR and potential effects of soil-borne microbial toxins. The risk assessment is also clear that monocotyledonous (monocot) plants, which include wheat, triticale, barley, and oats to which chlormequat chloride would be applied, are less sensitive than dicotyledonous (dicot) plants. While dicots have definitive 25% inhibition concentration (IC_{25}) values, studies with monocots had non-definitive (>) IC_{25} values and where the maximum percent effect (*i.e.*, reduction in growth) was 6%. Although there are potential risks of concern for dicots, based on the available data, there are no potential risks of concern for monocots on which the compound is registered for use. Additionally, consistent with the search of the Incident Data System (IDS) in support of the ERA in July 2021, no incidents have been reported in the IDS as of October 28, 2025, nor are there any aggregated incident reports. While the absence of incident reports cannot be construed as the absence of incidents, such reports provide a line of evidence with which to ground truth previous assessments. EPA encourages BP to provide data to substantiate their concerns relative to chlormequat chloride.

BP Comment #3:
BP states the potential impacts on the endocrine system, gene transcription, and neurotoxicity investigations should focus on potential disruption of the endocrine, neurodevelopmental, and gut microbiome systems.

EPA Response:

[18] USEPA. 2021. Chlormequat Chloride: Ecological Risk Assessment for the Proposed Section 3 New Uses on Wheat, Triticale, Barely, Oats, and Grasses Grown for Seed. DP Barcode 460105.

Refer to "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

BP Comment #4:
BP states that the impact of low-level exposure to combinations of pesticides and other environmental contaminants need consideration as effects are unknown. *In vitro* human cell lines using metagenomic, transcriptomic, and metabolomic techniques can improve the chances of identifying harmful unknown effects.

EPA Response:
Refer to responses to comments regarding co-exposures in the document "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290**.**

G. EPA-HQ-OPP-2021-0290-0118: Environmental Working Group (EWG) Comments

Comment Summary
EWG provided a detailed response to EPA's proposed action. EWG raised several specific concerns why EPA should not approve the first outdoor food uses of chlormequat chloride on wheat, triticale, barley, and oats grown in the U.S or establish U.S. tolerances for those same crops.

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

EWG states that EPA did not adequately consider the immunotoxic effects of chlormequat chloride when it waived the required immunotoxicity study. According to EWG, evidence of chlormequat immunotoxicity exists in the peer-reviewed literature.

EWG states that 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 addition, EWG states that studies that have screened chemicals for properties of developmental neurotoxicants have identified other quaternary ammonium compounds as potential developmental neurotoxicants, like diquat, which EPA considered to be a compound that is structurally similar to chlormequat.

EWG states that EPA should apply additional safety factors to adequately protect children's health. EWG states that EPA 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. According to EWG, if an appropriate point of departure was selected and applied the 10X FQPA safety factor, the resulting safe level would be exceeded by the dietary exposure estimates.

EPA Response:
Refer to responses to comments regarding providing adequate protection for infants and children in the document "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID# EPA-HQ-OPP-2021-0290.

H. EPA-HQ-OPP-2021-0290-0140 and EPA-HQ-OPP-2021-0290-0141: CFS Comment

CFS's submission includes their prior comments and reference materials previously submitted to EPA on the (1) receipt of application for the new uses of chlormequat chloride (submitted Nov. 26, 2021); (2) petition to establish tolerances for residues of chlormequat chloride on various grains and meat commodities (submitted Nov. 22, 2021); and (3) proposed interim registration review decision for chlormequat chloride (submitted on Dec. 20, 2021 to EPA Docket EPA-HQ-OPP-2015-0816). A number of literature citations, publications, papers and draft papers were included in CFS's comment.

EPA Response:

Regarding (3), please note that registration review was occurring during the time the comment was submitted. The Agency is only addressing comments received to the docket that relate to the proposed use of chlormequat chloride on wheat, triticale, barley, and oats. For the registration review decision, responses to comments are viewable at www.regulations.gov under the docket ID # EPA-HQ-OPP-2015-0816.

The Agency considered the documents CFS submitted in our responses to comments. Comments have been previously addressed in this document's Comments on the Proposed Decision (April 26, 2023) and Comments on the NOF and EPA's Responses. Additionally, subject-specific response to comments memoranda by the Environmental Fate and Effects Division (EFED) and the Health Effects Division (HED) can be found in the public docket ID# EPA-HQ-OPP-2021-0290.

I. EPA-HQ-OPP-2021-0290-0058: National Association of Wheat Growers (NAWG) Comments

NAWG Comment #1:
NAWG states chlormequat chloride is a proven tool to protect yields by reducing lodging in wheat, while also reducing costs. Given the low levels of concern that chlormequat chloride presents to the environment and human health, some of the mitigations are excessive. NAWG is concerned that limiting application to days with no more than ten miles per hour wind speeds is not feasible. This requirement would limit the ability to use the product so much as to make it ineffective. NAWG encourages the EPA to expand the maximum wind speed allowable to make the label more effective for farmers.

EPA Response:

The Agency agrees with NAWG that chlormequat chloride can reduce lodging in wheat which can lead to reduced yield losses in grains. For response to the wind speed restrictions, see above response to comment from Taminco (Section D).

NAWG Comment #2:
NAWG is concerned with the 12-month plant-back interval restriction that would apply to Adjust SL for use on leafy vegetables and root crops. According to NAWG, this requirement is unnecessary and not backed by the rotational crop study results showing that no chlormequat chloride residues would be present in rotated leafy vegetables and root crops.

EPA Response:
See the response below in Section J.

J. EPA-HQ-OPP-2021-0290-0063: National Barley Growers Association (NBGA) Comment

NBGA Comment:
NBGA urges EPA to approve this registration without further delay. NBGA is concerned with the proposed 12-month plant-back interval restriction that would apply to leafy vegetables and root crops. According to NBGA, this requirement is unnecessary and not backed by the rotational crop study results showing that no chlormequat chloride residues would be present in rotated leafy vegetables and root crops. An overly long plant-back interval restriction would needlessly inhibit a grower's options for rotational crops.

EPA Response:
In response to plant-back interval comments by NAWG and NBGA, refer to "comments concerning pesticide residues" in the document "Chlormequat Chloride: Health Effects Division (HED) Response to Public Comments on the Proposed First Food Uses for Chlormequat Chloride in the United States." available in Docket ID #EPA-HQ-OPP-2021-0290.

Exhibit D

Journal of Exposure Science & Environmental Epidemiology www.nature.com/jes

BRIEF COMMUNICATION OPEN

Check for updates

A pilot study of chlormequat in food and urine from adults in the United States from 2017 to 2023

Alexis M. Temkin[1]✉, Sydney Evans[1], Demetri D. Spyropoulos[2] and Olga V. Naidenko[1]

Chlormequat chloride is a plant growth regulator whose use on grain crops is on the rise in North America. Toxicological studies suggest that exposure to chlormequat can reduce fertility and harm the developing fetus at doses lower than those used by regulatory agencies to set allowable daily intake levels. Here we report, the presence of chlormequat in urine samples collected from people in the U.S., with detection frequencies of 69%, 74%, and 90% for samples collected in 2017, 2018–2022, and 2023, respectively. Chlormequat was detected at low concentrations in samples from 2017 through 2022, with a significant increase in concentrations for samples from 2023. We also observed high detection frequencies of chlormequat in oat-based foods. These findings and chlormequat toxicity data raise concerns about current exposure levels, and warrant more expansive toxicity testing, food monitoring, and epidemiological studies to assess health effects of chlormequat exposures in humans.

IMPACT:

- This study reports the detection of chlormequat, an agricultural chemical with developmental and reproductive toxicity, in the U.S. population and U.S. food supplies for the first time. While similar levels of the chemical were found in urine sampled from 2017 to 2022, markedly increased levels were found in samples from 2023. This work highlights the need for more expansive monitoring of chlormequat in U.S. foods and in human specimens, as well as toxicological and epidemiological study on chlormequat, as this chemical is an emerging contaminant with documented evidence of low-dose adverse health effects in animal studies.

Keywords: Biomonitoring; Pesticides; Endocrine disruptors; Children's health

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INTRODUCTION

Chlormequat chloride is an agricultural chemical first registered in the U.S. in 1962 as a plant growth regulator. Although currently only allowed for use on ornamental plants in the U.S, a 2018 decision by the U.S. Environmental Protection Agency (EPA) permitted the import of foods, primarily grains, treated with chlormequat [1]. In the European Union, the United Kingdom and Canada, chlormequat chloride is approved for use on food crops, primarily wheat, oats, and barley. Chlormequat acts to decrease stem height, thereby reducing the likelihood of crops bending over, which can make harvesting difficult. In the UK and European Union, chlormequat is often the most detected pesticide residue in grains and cereals, as documented by monitoring surveys spanning several years [2, 3].

Despite being approved for use on crops in Europe and parts of North America, chlormequat exhibits concerning toxicological properties, as documented in historical as well as more recently published laboratory animal studies. In the early 1980s, the impacts of chlormequat exposure on reproductive toxicity and fertility were first described by Danish pig farmers who observed reproductive declines in pigs raised on chlormequat treated grains [4]. These observations were later investigated in controlled laboratory experiments on pigs and mice, whereby female pigs fed chlormequat treated grain exhibited disrupted oestrus cycling and difficulty mating compared to animals on a control chlormequat-free diet [4]. Additionally, male mice exposed to chlormequat via diet or drinking water during development exhibited decreased fertilization capacity of sperm in vitro [5]. More recent reproductive toxicity studies on chlormequat show delayed onset of puberty, reduced sperm motility, decreased weights of male reproductive organs, and decreased testosterone levels in rats exposed during sensitive windows of development, including during pregnancy and early life [6–8]. Developmental toxicity studies also suggest that chlormequat exposure during pregnancy can dysregulate fetal growth and metabolism [9]. Other investigations did not find impacts of chlormequat on reproduction in female mice, male pigs, or a subsequent investigation of fertilization capacity in male mice developmentally and postnatally exposed to chlormequat [4, 10, 11]. Equivocal evidence in the toxicological literature on chlormequat may be due to differences in doses tested and outcomes measured as well as selection of model

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organism and the sex of laboratory animals. Consequently, further investigation is warranted.

Although recent toxicological studies indicate impacts of chlormequat on development, reproduction and the endocrine systems, the mechanism(s) by which these toxicological effects occur is not well understood. Some studies indicate that chlormequat likely does not act through well characterized mechanisms of endocrine disrupting chemicals, including through estrogen or androgen receptors and does not alter aromatase activity [12]. Other evidence suggests chlormequat may elicit adverse effects through altered steroid biosynthesis and induction of endoplasmic reticulum stress [8, 13].

While chlormequat is prevalent in commonly consumed foods in Europe, only a relatively small number of biomonitoring studies assessing human exposure to chlormequat exists. Chlormequat has a short half-life in the body of about 2–3 h, with a large fraction of experimental doses being excreted within 24 h based on studies involving human volunteers [14]. In general population samples from the United Kingdom and Sweden, chlormequat was detected in the urine of nearly 100 percent of study participants at frequencies and concentrations considerably higher than for metabolites of other pesticides such as chlorpyrifos, pyrethroids, thiabendazole, and mancozeb [14–17]. Studies in pigs indicate that chlormequat can also be detected in serum, as well as transferred into milk, but these matrices have not been investigated in humans or other laboratory animal models, although the potential presence of chemicals associated with reproductive harm in serum and milk has important implications for exposures during pregnancy and to infants [18].

In April 2018, the U.S. EPA published acceptable food tolerance levels for chlormequat chloride in imported oat, wheat, barley, and some animal products, which permitted the import of chlormequat into the U.S. food supply. The allowable levels were then increased for oats in 2020. To characterize the impact of these decisions regarding the emergence and prevalence of chlormequat in the U.S. adult population, this pilot study measured levels of chlormequat in urine of individuals from three geographic regions within the U.S. from 2017 to 2023, as well as levels of chlormequat in oat and wheat-based products purchased in the U.S. in 2022 and 2023.

MATERIALS AND METHODS

Human urine samples

To measure chlormequat in urine from people residing in the U.S., convenience samples from three geographical regions collected between 2017 and 2023 were used. Twenty-one urine samples, collected on an Institutional Review Board (IRB)-approved protocol in 2017 from consenting de-identified pregnant women at time of delivery, were obtained from the Medical University of South Carolina (MUSC, Charleston, South Carolina, USA). Samples were stored at 4 °C for up to 4 h prior to being aliquoted and frozen at −80 °C. Twenty-five adult urine samples, were purchased in November of 2022 from Lee Biosolutions, Inc (Maryland Heights, Missouri, USA), representing single time point samples collected from October 2017 through September 2022, provided from volunteers (13 male and 12 female) collected in Maryland Heights, Missouri. The samples were stored at −20 °C immediately after collection. Additionally, 50 urine samples, collected in June of 2023 from volunteers in Florida (25 male, 25 female), were purchased from BioIVT, LLC (Westbury, NY, USA). Samples were stored at 4 °C until all samples were collected prior to being aliquoted and frozen at −20 °C. The supplier companies obtained necessary IRB approval for work with human samples and obtained consent for collection of the samples. No personally identifiable information was provided with any of the samples that were tested. All samples were shipped frozen for analysis. Detailed sample information can be found in the Supplementary information, Table S1.

Analytical methodology

Chlormequat was quantified in human urine samples by LC MS/MS at the HSE Science and Research Laboratory (Buxton, United Kingdom) following the methodology published by Lindh et al. 2011 with slight modifications [14]. Briefly, the samples were prepared by mixing 200 µL of unfiltered urine with 1.8 mL of 0.01 M ammonium acetate containing an internal standard. The samples were then extracted using HCX-Q columns conditioned with methanol, then 0.01 M ammonium acetate, washed with 0.01 M ammonium acetate, and eluted into methanol with 1% formic acid. Samples were then loaded onto a C18 LC column (Synergi 4 µ Hydro-RP 150 × 2 mm; Phenomenex, UK) and separated using an isocratic mobile phase consisting of 80:20 0.1% formic acid: methanol at a flow rate of 0.2 mL/min. Mass spectrometry selected reaction monitoring transitions are described in Lindh et al. 2011. The limit of detection was 0.1 µg/L, as reported in other studies [14].

Chlormequat concentrations in urine were reported as µmol chlormequat per mol creatinine and converted to µg chlormequat per g creatinine, as expressed in previous studies (multiplied by 1.08).

Oat (25 conventional and 8 organic) and wheat-based (9 conventional) food samples purchased at U.S. grocery stores in the Washington, DC metro area from June and August 2022, and February and May 2023 were tested for chlormequat by Anresco Laboratories, LLC (San Francisco, CA, USA). Samples were analyzed based on published methodologies with modifications [19]. The LOD/LOQ were set at 10/100 ppb and 3/40 ppb for oat samples from 2022 and for all wheat and oat samples from 2023 respectively. Detailed sample information can be found in the Supplementary information, Table S2.

Statistical analysis

Urinary chlormequat concentrations were grouped together based on geographic location and collection year except for two samples from Maryland Heights, MO collected in 2017, that were grouped with the other 2017 samples from Charleston, SC. Samples that were below the limit of detection for chlormequat were treated as LOD divided by the square root of two. The data were not normally distributed, therefore a Kruskal-Wallis nonparametric test with Dunn's multiple comparisons test was used to compare the medians between groups. All calculations were done in GraphPad Prism (Boston, MA).

RESULTS

Chlormequat was detected in 77 of 96, or 80% of all urine samples. Detection frequencies were higher in 2023 samples compared to 2017 and 2018 to 2022 samples with 16 of 23, or 69%, 17 of 23, or 74% and 45 of 50, or 90% of samples with detections, respectively (Table 1). The concentrations of chlormequat detected were comparable between the two groups before 2023, while the concentrations detected in 2023 samples were significantly higher than previous years samples (Fig. 1A, B). The concentrations among detectable samples ranged from 0.22 to 5.4, 0.11 to 4.3, and 0.27 to 52.8 µg chlormequat per g creatinine for 2017, 2018–2022, and 2023 samples, respectively. The median values from all samples were 0.46, 0.30, and 1.4 for 2017, 2018–2022, and 2023 samples, respectively (Table 1). These data indicate likely continuous exposure given the short half-life of chlormequat in vivo, with low levels from 2017 to 2022 and higher exposure levels in 2023.

Food samples purchased in the U.S. from 2022 and 2023 show detectable levels of chlormequat in all but two of 25 conventional oat-based products, with concentrations ranging from non-detectable to 291 µg/kg, indicating a high prevalence of chlormequat in oats. Median levels were similar between samples collected in 2022 and 2023, at 90 and 114 µg/kg respectively. Only one sample out of eight organic oat-based products at detectable chlormequat at 17 µg/kg. We also observed low concentrations of chlormequat in two of nine wheat-based products tested, at 3.5 and 12.6 µg/kg (Table 2).

DISCUSSION

This is the first report of urinary chlormequat measurements in adults residing in the U.S., and any population outside of the United Kingdom and Sweden. A time-course of pesticide

Table 1. Comparison of urinary chlormequat concentrations across studies.

Study (Location)	Collection Year	Sample Number	Detection Frequency (N)	Range (μg chlormequat per g creatinine)	Median	LOD (μg/L chlormequat)
Present (Florida, USA)	2023	50	90% (45)	ND - 52.8	1.4	0.1
Present (Missouri, USA)	2018–2022	23	74% (17)	ND - 4.3	0.3	0.1
Present (South Carolina, USA and Missouri, USA)[a]	2017	23	69% (16)	ND - 5.4	0.46	0.1
Noren et al. 2019 (Sweden)	2017	196	100% (196)	NA - 35.8	0.86	0.01
Galea et al. 2015 (United Kingdom)	2011–2012	140	~99% (NA)	NA - 388.2	15.1	0.6
Lindh et al. 2011 (Sweden)	2010	100	100% (100)	0.4–30.2	2.9	0.1

NA indicates value was not reported in the study, *ND* none detected.
[a]Two samples from Missouri were collected in 2017.

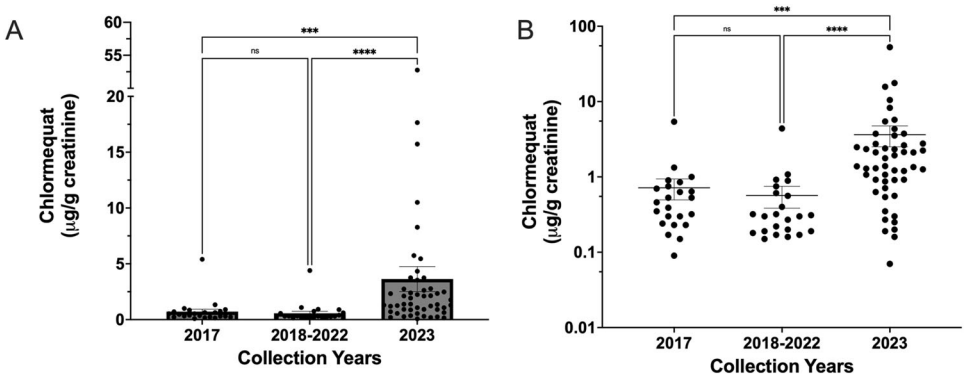

Fig. 1 Chlormequat concentrations in urine from individuals residing in the U.S. at three time points. Chlormequat concentrations for each individual urine sample are represented by single dots with bars at the mean and error bars representing +/- standard error. Urinary concentrations of chlormequat are expressed as μg chlormequat per g creatinine on a linear scale (**A**) and log scale (**B**). Kruskal-Wallis nonparametric ANOVA with Dunn's multiple comparisons test was used to test statistical significance (***$p < 0.001$, ****$p < 0.0001$).

Table 2. Chlormequat in oat and wheat-based products purchased in U.S. grocery stores.

Food Type (Year)	Number of Samples Tested	Samples With Detections	Range	Median (μg/kg or ppb)	LOD/LOQ (μg/kg or ppb)
Conventional Oat-based products (May 2023)	12	11 (92%)	ND - 209	114	3/40
Conventional Oat-based products (June and August 2022)	13	12 (92%)	ND - 291	90	10/100
Organic Oat-based products (2023)[a]	8	1 (12.5%)	ND - 17	ND	3/40
Conventional Wheat-based products (February 2023)	9	2 (22%)	ND - 12.6	ND	3/40

ND none detected.
[a]One organic sample was purchased in 2022; individual sample results can be found in Table S2.

biomonitoring in over 1000 adolescents from Sweden documented 100 percent detection frequencies of chlormequat from 2000 to 2017. The median concentrations in 2017 were 0.86 μg chlormequat per g creatinine and appeared to decrease over time, the highest median level was 2.77 in 2009 [16]. In the UK from 2011 to 2012, biomonitoring detected much higher median concentrations at 15.1 μg chlormequat per g creatinine, and while these samples were collected from people residing in an agricultural area, there were no differences in exposure when levels were compared before and after chlormequat spray events [15]. Compared to these previous studies in Europe, the median levels measured in our study of U.S. samples from 2017 to 2022 were lower, while the median level in 2023 samples were comparable to samples from Sweden, and lower than UK samples (Table 1).

Differences in exposure between these different regions and time points likely reflects differences in agricultural practices and regulatory status of chlormequat, ultimately impacting chlormequat levels in the food supply. For instance, the significantly higher concentrations of chlormequat in the 2023 urine samples compared to earlier years may reflect the likely recent introduction of chlormequat into the U.S. food supply due to EPA regulatory action changes involving chlormequat, including establishing limits on chlormequat in food in 2018 and raising those limits for oats in 2020. These actions permitted import and sale of agricultural products that had been treated with

chlormequat, for example from Canada. The time-lag between EPA regulatory changes and elevations in chlormequat concentrations found in the 2023 urine samples could be explained by several scenarios such as delays in adoption of agricultural practices that use chlormequat, delays in U.S. companies establishing trade agreements and exhausting old product stocks, and/or delays in individuals purchasing oats given the long expiration dates on oat products.

To determine if the concentrations observed in U.S. urine samples were reflective of potential dietary exposure to chlormequat, we measured chlormequat in oat and wheat-based food products purchased in the U.S. in 2022 and 2023. Oat products contained chlormequat more frequently than wheat products and the amount of chlormequat in different oat products varied, with a median level of 104 ppb, perhaps owing to sourcing from the U.S. versus Canada, potentially representing differences between products made with or without chlormequat-treated oats. Comparatively, in food samples from the United Kingdom, chlormequat is far more prevalent in wheat-based products such as bread in which 90% of samples collected in the UK between July and September 2022 had detectable levels of chlormequat with a median concentration of 60 ppb. Similarly, chlormequat was detected in 82% of UK oat samples from the same time with median concentrations of 1650 ppb, more than 15 times higher than in U.S. samples, which may explain the higher urinary concentrations observed in UK samples [20].

Our biomonitoring results indicate exposure to chlormequat before 2018, despite there being no established food tolerances set for chlormequat. Although there is no monitoring of chlormequat in food products in the U.S., and no historical data available for concentrations of chlormequat in foods sold in the U.S., we suspect these exposures were likely dietary given the short half-life of chlormequat. Additionally, natural formation of chlormequat from choline precursors in wheat products and egg powder has been shown to occur under high temperatures such as those used during food processing and production, resulting in chlormequat concentrations between 5 and 40 ng/g [21]. Our food testing results indicate chlormequat levels in some samples, including one organic oat-based product, were similar to those reported in the study of naturally forming chlormequat, while many other samples were higher. Thus, our pre-2023 levels observed in urine could be a result of dietary exposure to chlormequat from formation via food processing and production. And the 2023 levels observed could be due to a combination of dietary exposure to chlormequat from spontaneous formation as well as imported products agriculturally treated with chlormequat. Differences in chlormequat exposure in our samples could also be due to geographic locations, differing dietary patterns, or occupational exposure from uses of chlormequat in greenhouses and nurseries.

Our study indicates that a greater sample size and more diverse sampling of processed foods for chlormequat is needed to fully assess potential dietary sources of chlormequat in the low exposure individuals. Future studies that include the analysis of historical urine and food samples, dietary and occupational questionnaires, and continued monitoring of chlormequat in the U.S. food supply for both conventional and organic foods, as well as samples for biomonitoring would help elucidate the determinants of total chlormequat exposure in the U.S. population.

It remains to be determined whether chlormequat levels in U.S. urine and food samples may rise in the coming years. In the U.S., chlormequat is currently only allowed in imported oat and wheat products, but domestic agricultural uses on non-organic crops are currently under review by the U.S. EPA. It is possible that if such domestic uses were approved, combined with widespread adoption of agricultural practices that utilize chlormequat abroad and domestically, chlormequat levels would likely continue to increase in oats, wheat, and other grain foods, leading to higher levels of exposure for the U.S. general population.

Current chlormequat concentrations in urine from this study and others suggest that individual sample donors were exposed to chlormequat at levels several orders of magnitude below the reference dose (RfD) published by the U.S. EPA (0.05 mg/kg bw/day) and the acceptable daily intake (ADI) value published by the European Food Safety Authority (0.04 mg/kg bw/day). However, we note that published toxicological studies on chlormequat suggest reevaluation of these safety thresholds may be warranted. For instance, animals exposed to doses lower than the current RfD and ADI, of 0.024 and 0.0023 mg/kg bw/day in mice and pigs respectively, exhibited reduced fertility [4]. In another toxicological study, exposure during pregnancy at a dose equivalent to the No Observed Adverse Effect Level (NOAEL) of 5 mg/kg that was used to derive the U.S. EPA reference dose, caused altered fetal growth as well as metabolism and body composition in neonatal mice [9]. Additionally, the regulatory thresholds do not consider the adverse effects of mixtures of chemicals that may impact the reproductive system, which have been shown to cause additive or synergistic effects at doses lower than for individual chemical exposures [22], raising concerns about the potential health effects associated with current exposure levels, especially for individuals on the higher end of exposure in general populations of Europe and the U.S.

This pilot investigation into an emerging chemical exposure within the U.S. indicates that chlormequat chloride is present in the U.S. food supply, primarily in oat-based products, and is detectable in a majority of urine samples collected from nearly 100 individuals in the U.S., suggesting continuous exposure. Additionally, trends in these data suggest that exposure levels have increased and might continue to increase in the future. Given the toxicological concerns associated with chlormequat exposure in animal studies, and widespread exposure to the general population, in European countries, and now also likely in the U.S., monitoring of chlormequat in foods and people, in conjunction with epidemiological and animal studies, is urgently needed to understand the potential health harms of this agricultural chemical at environmentally relevant exposure levels, particularly during pregnancy.

DATA AVAILABILITY

The data generated and analyzed in this study can be found within the article and supplemental information with more detailed information available upon request to the corresponding author.

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AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study, acquiring of samples and data, analysis and interpretation of results, and drafting and revision the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICA APPROVAL

All human materials were collected with informed consent and in accordance with the standards of the Internal Review Board. No identifying information was provided to the authors, with the exception of women at delivery (to D.D.S.). However, no identifying information was conveyed to the reader in this publication.

ADDITIONAL INFORMATION

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Exhibit E

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: September 23, 2025

SUBJECT: **Chlormequat Chloride:** Health Effects Division (HED) Response to Public Comments on Tolerances and the Proposed First Food Uses for Chlormequat Chloride in the United States.

PC Code: 018101	**DP Barcode:** D467033, D468329
CAS No.: 999-81-5	**Task Group No.:** 00661766
Decision No: 564252, 562939	**Parent Case No.:** 00478775
Petition No.: 45728-GU	**Registration No.:** N/A
Risk Assessment Type: N/A	**Regulatory Action:** Response to Comments
TXR No.: N/A	**Reg. Review Case No.:** N/A
MRID No.: N/A	**40 CFR:** 180.698

FROM: Adrian Britt, Occupational and Residential Exposure Assessor/Risk Assessor

Adrian Britt

Sheila Piper, Dietary Assessor/Chemist (for)

Cynthia Browning, Toxicologist

Risk Assessment Branch VI (RAB6)

Health Effects Division (7509T)

THRU: Rick Fehir, Ph.D., Acting Branch Supervisor

Risk Assessment Branch VI

Health Effects Division (7509T)

TO: Yasmin Bowers, Risk Manager

Kristy Crews, Product Manager

Cynthia Giles-Parker, Branch Chief

Fungicide Branch, Registration Division (RD, 7505T)

The U.S. Environmental Protection Agency's (EPA) received public comments in response to the Notice of Receipt (NOR) of an application to register pesticide products containing the active ingredient chlormequat chloride and of EPA's proposed decision to unconditionally register new products containing chlormequat chloride under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3(c)(5). The original submitted comments and related materials can be found under the Docket ID EPA-HQ-OPP-2021-0290. The Registration Division (RD) of the EPA has asked the Health Effects

Division (HED) to respond to public comments specifically related to human health and the human health risk assessment prepared for this Section 3 registration of chlormequat chloride on wheat, triticale, barely, and oats. The public comments addressed in this memo were submitted by the American Academy of Pediatrics (AAP), Beyond Pesticides (BP), Center for Food Safety (CFS), the Environmental Work Group (EWG), and Tamico LLC. As multiple comments discussed similar concerns, this document combines comments by topic and provides responses in a collective manner. HED thanks the AAP, BP, CFS, EWG and Tamico LLC for their comments and provides responses below.

The conclusions conveyed in this assessment were developed consistent with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: EPA's Scientific Integrity Policy. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: Approaches for Expressing and Resolving Differing Scientific Opinions.

Comments regarding dietary exposure

Comment Summary: The CFS remarked that chlormequat chloride is commonly detected in grains and grain products such as cereals.

EPA Response: EPA agrees that detectable residues are found in/on registered cereal grains and is applied at various growth stages and a range of preharvest intervals depending on the country the pesticide is registered. Chlormequat chloride, a plant growth regulator, is registered in Canada, as well as in Northern and Southern Europe including Germany, Italy, Spain, and France for treating cereal grains. Before allowing the use of a pesticide on food crops, the EPA sets a tolerance, or maximum residue limit, which is the amount of pesticide residue allowed to remain in or on each treated food commodity. The tolerance is the residue level that triggers enforcement actions if exceedance of this level is detected. The dietary risk assessment utilized to establish the U.S. tolerances for chlormequat chloride is conservative, using maximum (i.e., tolerance-level) residues, field trial data designed to reflect use patterns that lead to the highest possible residues, high-end estimates of drinking water, and an assumption of 100 percent crop treated (i.e., every single acre of a particular crop in a given area has been treated with chlormequat chloride) to generate overestimates of dietary exposure. The U.S. tolerances being established for chlormequat as part of the Section 3 registration are consistent with international standards, including the European Union (EU) and Canadian maximum residue levels (MRLs) on barley, oat, and wheat grain. The residues that were detected in cereal grains are well below these respective tolerance levels, and thus are considered within lawful limits (D467413, A. Britt, 25-SEPT-2023).

Comments regarding literature review

Comment Summary: The EWG stated that EPA did not adequately search for or account for studies in the peer-reviewed literature on chlormequat toxicity.

EPA Response: As part of registration review for chlormequat chloride (D457479, S. Piper, 16-MAR-2021), a broad survey of the literature was conducted to identify studies that report toxicity following exposure to chlormequat chloride via exposure routes relevant to human health pesticide risk assessment not accounted for in the Agency's chlormequat chloride toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 60 studies from the literature. During title/abstract and/or full text screening of these studies, one study was identified as containing potentially relevant information (either quantitative or qualitative) for the chlormequat chloride human health risk assessment. Following a full text review of the identified relevant study, it was determined that this study does not contain any novel findings or reveal adverse health effects at doses that would impact the risk assessment. The points of departure (PODs) utilized in the risk assessment to evaluate potential risk from chlormequat chloride exposure are based on the most sensitive adverse health effects observed in relevant and acceptable toxicological studies. The most sensitive effect is the adverse health effect that occurs at a dose lower than those associated with other adverse effects observed in the studies appropriate for each specific exposure scenario. Thus, the PODs utilized by the EPA are protective of any observed adverse health effects from chlormequat chloride exposure.

Comments regarding providing adequate protection for infants and children

Comment 1: The AAP commented that the EPA's proposed decision to approve the requested tolerances for chlormequat on food crops will negatively affect the health and well-being of infants and children. Toxicological findings strongly suggest that chlormequat is likely dangerous for infants and children. The AAP stressed that the EPA has a responsibility and a legal duty under the Food Quality Protection Act (FQPA) to protect children against the toxic effects of pesticides, especially those such as chlormequat that exhibit developmental and reproductive toxicity (Huang D, et al., 2017; Xiao Q, et al., 2021; Hou X, et al., 2018).

EPA Response: EPA's review of chlormequat chloride toxicity data, including rat and rabbit developmental studies and a two-generation rat reproduction study, found no evidence of increased susceptibility in pre- or postnatal animals compared to adults, meaning that the fetuses and pups were not more sensitive to the treatment than the adults. The prenatal developmental rat study (MRID 42246604) produced clinical signs such as salivation, decreased motor activity, ataxia, and lacrimation in maternal animals at the highest dose tested of 180 mg/kg/day. One or more of these clinical signs were observed typically after the single oral dose. However, no developmental effects were observed at 180 mg/kg/day and no adverse maternal or developmental effects were observed at lower doses. In the prenatal developmental toxicity study in rabbits (MRID 46715205), there were no adverse maternal or developmental effects observed up to the highest dose tested (12 mg/kg/day). The two-generation reproduction study in rats (MRID 46715206) showed maternal, reproductive, and offspring effects at 255 mg/kg/day, which was the highest dose tested in this study. At 255 mg/kg/day maternal rats showed decreased body weight, tremors and hypersensitivity. Decreased fertility and decreased mean litter size, pup body weight and delayed pup development were seen at the same dose. No adverse effects (including reproductive effects) were seen at lower doses in this study.

The PODs selected for dietary and incidental oral exposure risk assessment are based on the most sensitive health effects observed in the toxicology database, which were not developmental or reproductive effects. The No Observed Adverse Effect Level (NOAEL) of 100 mg/kg selected as the POD to evaluate acute (i.e., single dose) dietary exposure to chlormequat chloride was based on functional observational battery (FOB) effects (e.g., tremors, salivation, decreased body temperature) and decreased motor activity observed in the acute neurotoxicity study (MRID 50182001) and is protective of the effects seen at 180 mg/kg/day in the rat developmental toxicity study described above. The NOAEL of 5 mg/kg/day selected as the POD to evaluate chronic dietary and incidental oral exposures of chlormequat chloride was based on increased salivation and diarrhea observed in a chronic dietary study (MRID 46715201). This chronic dietary and incidental oral POD is 2 times lower than the highest dose tested in the rabbit developmental study (no effects seen), and 36 times lower than the Lowest Observed Adverse Effect Level (LOAEL) of the rat developmental study. Additionally, this POD is approximately 50 times lower than LOAEL established in the two-generation rat reproduction study. Thus, the PODs utilized for dietary and oral risk assessment are below levels that could potentially induce developmental and reproductive effects. In addition, the developmental and reproduction studies in the toxicology database have clear NOAELs, providing confidence in the Agency's understanding of the dose response of chlormequat chloride.

The Agency also conducted an incident data review as part of registration review for chlormequat chloride (D457479, S. Piper, 16-MAR-2021). This incident data review showed no human chlormequat chloride incidents have been reported in the Incident Data System (IDS) or the NIOSH Sentinel Event Notification System for Occupational Risk (SENSOR).

The Agency notes that the AAP cited several published literature studies for the Agency's consideration. Although the studies cited by AAP may not meet the criteria for inclusion in accordance with the Agency's literature guidance, a preliminary review of the studies was performed. This review identified no information that would change the selected PODs for the chlormequat chloride human health risk assessment. A summary of the studies in relation to the current PODs is provided below:

1. **Huang et al., 2017 "The skeletal developmental toxicity of chlormequat chloride and its underlying mechanisms":** In Huang et al., 2017, an investigation into the impact of chlormequat chloride on rat skeletal development was undertaken. Rats from postnatal day 23 to 70 were exposed to chlormequat chloride daily by gavage at doses of 0, 75, 150, and 300 mg/kg/day. The authors concluded that chlormequat chloride influenced bone size, density, and related markers following exposure to the high dose (300 mg/kg/day). Gene expression alterations were also noted at 150 mg/kg/day. However, these gene expression alterations are of questionable adversity. No effects were observed at 75 mg/kg/day, the lowest dose tested. The current POD for chronic dietary and incidental exposures (NOAEL = 5 mg/kg/day) is 30 times lower than the dose at which gene expression alterations were observed and thus protective of any effects observed in this study.

2. **Xiao et al., 2021 "Effects of prenatal chlorocholine chloride exposure on pubertal development and reproduction of male offspring in rats":** In Xiao et. al., 2021, an investigation was undertaken to examine potential impacts of prenatal exposure to chlormequat chloride on pubertal development and the reproduction of male offspring in rats. The authors identified decreased testosterone levels in serum at doses ≥ 75 mg/kg/day

(lowest dose tested) and delays in preputial separation and reduced sperm motility at doses ≥ 137.5 mg/kg/day in male offspring. The authors found chlormequat chloride had no influence on the reproductive performance of pregnant rats at any dose level tested. The most sensitive endpoint in the study was statistically significant reduced levels of serum testosterone in male offspring. Reduced testosterone levels should be evaluated taking into consideration the totality of the data; however, the current chronic dietary and incidental oral POD (5 mg/kg/day) is protective of these effects, being 15 times lower than the lowest dose that impacted testosterone levels in offspring in this study (75 mg/kg/day).

3. **Hou et al., 2018 "Pubertal chlorocholine chloride exposure inhibits testicular testosterone synthesis by down-regulating steroidogenic enzymes in adult rats":** In Hou et al., 2018, researchers investigated the effects of pubertal exposure to chlormequat chloride on testicular testosterone synthesis in male rats. Chlormequat chloride was administered at doses of 0, 75, 150, and 300 mg/kg/day from postnatal day 23–70. The authors suggest that pubertal chlormequat chloride exposure reduced body weights at doses higher than 150 mg/kg/day, elicited increased percentage of seminiferous tubules with spermatogenic cells in the 75 and 150 mg/kg/day groups, decreased testicular absolute weights in the 75 and 300 mg/kg/day groups (but not 150 mg/kg/day), reduced sperm motility in the 150 mg/kg/day group, and decreased testicular testosterone levels at doses all doses tested. The chronic dietary and incidental oral POD (5 mg/kg/day) is 15 times lower than the dose at which testicular changes were observed (75 mg/kg/day; lowest dose tested) and thus, protective of any effects observed in this study.

To ensure the safety of the food supply for human consumption, EPA regulates the use of pesticides registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and, under the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA establishes regulatory thresholds, called 'tolerances,' identifying the amount of a pesticide that may remain in/on foods without the food being classified as adulterated and, for example, subject to seizure. Dietary risk assessments take into account the pesticide's toxicity, use pattern (how much is used and how often), and the amount of pesticide residue that remains in/on the food commodity. These assessments account for the differences in diets and size among age groups. The information on potential pesticide exposure (from food and drinking water) to infants, children and other subgroups is combined with toxicity information to determine potential risks posed by pesticide residues. Risk estimates that are greater than 100% of the population-adjusted doses (PADs) are deemed of concern and thus, unacceptable. More information on how tolerances are generally established by the EPA can be found at https://www.epa.gov/pesticide-tolerances/setting-tolerances-pesticide-residues-foods.

The dietary risk assessment utilized to establish the U.S. tolerances for chlormequat chloride is conservative and overestimates dietary exposure (D467413, A. Britt, 25-SEPT-2023). Unrefined acute (using proposed tolerance residue levels) and partially refined chronic (utilizing average field trial values of residue levels on/in food commodities) dietary assessments, both assumed 100% crop treated for all commodities and a high-end estimate of drinking water concentration. These dietary assessments found that exposure and risk estimates do not exceed HED's level of concern (< 100% of the acute or chronic population-adjusted doses (PADs) for the general U.S. population and all population subgroups, including infants and/or children) (D467413, A. Britt, 25-SEPT-2023). This approach to the dietary assessments was utilized to capture high end estimates of potential exposure

and ensure that even under such exposure conditions, the exposure and risk estimates do not exceed HED's level of concern for any population subgroup.

Comment 2: Several comments were received requesting that the FQPA 10X safety factor be retained in the human health risk assessment based on the developmental effects of chlormequat exposure. One commenter expressed concern that the risk assessment supporting the proposed rule on chlormequat does not pay sufficient attention to the particular exposures and unique vulnerabilities of infants and children, advising the EPA to seriously examine its pediatric and reproductive toxicity.

EPA Response: At this time, the toxicological database is considered complete. EPA has thoroughly reviewed the toxicity database of chlormequat chloride, including developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats, as well as a comprehensive literature search as described above. EPA's review of chlormequat chloride toxicity data found no evidence of increased susceptibility in developing or young animals compared to adults, meaning that the developing and young animals were not more sensitive to the treatment than the adults. There is no evidence of increased susceptibility/sensitivity of pre- or postnatal animals following exposure to chlormequat chloride in the available toxicological database. The two-generation reproduction study in rats conducted a thorough examination of parental, reproductive, and offspring effects, with clearly established NOAELs and LOAELs, which provides confidence in the EPA's understanding of the reproductive effects induced by chlormequat chloride and the dose at which they occur.

The FQPA SF of 10X was reduced to 1X based on the following considerations: (1) the completeness of the toxicity database including adequate studies to assess the potential susceptibility in developing or young animals (developmental and reproduction studies); (2) there is no evidence of increased quantitative or qualitative susceptibility to developing or young animals as compared to adults following pre- or post-natal exposure to chlormequat chloride; (3) the endpoints chosen for risk assessment are protective of the potential neurotoxicity seen in the chlormequat chloride database; and (4) exposure estimates are conservative (e.g., based on tolerance levels and assuming 100% crop treated) and unlikely to underestimate risk. The reproductive and offspring effects in the two-generation rat reproduction study had clear NOAELs and LOAELs and the toxicological PODs chosen for risk assessment are protective of the observed effects.

Comments regarding potential adverse health effects

Comment 1: BP states "The potential impacts on the endocrine system, gene transcription, and neurotoxicity investigations should focus on potential disruption of the endocrine, neurodevelopmental, and gut microbiome systems."

EPA Responses:

Endocrine System

In the Endocrine Disruptor Screening Program (EDSP); Near-Term Strategies for Implementation federal register notice (FRN)[1], the EPA describes near-term strategies to help the Agency meet its

[1] https://www.federalregister.gov/documents/2023/10/27/2023-23721/endocrine-disruptor-screening-program-edsp-near-term-strategies-for-implementation-notice-of

obligations and commitments under the Federal Food, Drug, and Cosmetic Act (FFDCA), which requires, among other things, that EPA screen for and protect against endocrine effects in humans. An important part of these obligations and commitments is the EDSP, which EPA established in 1998 as a two-tier endocrine screening and testing process for pesticides and other chemicals.

The near-term strategies emphasize leveraging existing endocrine data that are routinely obtained through the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration and registration review to determine whether additional human health-related endocrine data are needed to make decisions under FFDCA section 408(p). Therefore, a primary focus of the near-term strategies is to identify situations where available data can clearly meet the needs for making decisions under FFDCA section 408(p). For example, EPA will generally be able to rely on data provided by a reproduction toxicity study performed under current guidelines (OPPTS 870.3800 Reproduction and Fertility Effects; OECD Test Guideline 443 Extended One Generation Reproductive Toxicity Study) to make FFDCA section 408(p) decisions for estrogen and androgen pathways without seeking additional data. In sum, as explained in the FRN, existing data can still be used to inform FFDCA section 408(p) decisions and review and evaluation of available endocrine-related data for this purpose will take place consistent with the prioritization framework described in the FRN.

Specifically, and as described in the FRN and supporting documentation, EPA developed and is applying a framework for prioritizing conventional pesticide cases currently in registration review for which a reproduction toxicity study conducted under the current updated guideline was not available at the time EPA prepared the prioritization. These pesticides are generally supported by a reproduction toxicity study performed and found acceptable under a previous guideline. Studies performed under previous guidelines include endocrine-related measures; however, they may not have evaluated all endocrine-related endpoints that have been added to the current guideline. As a result, the reproduction toxicity studies performed under a previous guideline need to be evaluated on a case-by-case basis along with any available OSRI. In the FRN, EPA further encouraged the public to submit any relevant estrogen, androgen, and thyroid data for pesticide active ingredients currently in registration review. The public may also submit any explanations for why additional endocrine data are necessary or unnecessary to inform the Agency's findings under FFDCA section 408(p) for potential endocrine effects in humans.

Among conventional pesticide active ingredients in registration review, chlormequat chloride is prioritized in the FRN and supporting documentation as a "Group 2" active ingredient. It is supported, at a minimum, by the required toxicity data identified in 40 CFR Part 158, including the two-generation reproduction toxicity study, to support registration under FIFRA. In response to the FRN request for comments, the registrant submitted comments indicating, an intent to submit four EDSP Tier 1 studies voluntarily. Those studies were subsequently submitted to the Agency for review. The studies included two *in vitro* assays (steroidogenesis assay (MRID 52478801) and aromatase assay (MRID 52478802)) and two *in vivo* assays in the rat (Hershberger assay (MRID 52478803) and uterotrophic assay (MRID 52478804)). HED has completed its review of these assays and found that they were acceptable and conducted according to EPA or OECD guidelines. In the steroidogenesis and aromatase assays, chlormequat chloride did not alter the production of estradiol and/or testosterone in these test systems. Similarly, chlormequat chloride did not induce a positive response in androgen- or estrogen-sensitive tissues in the Hershberger or uterotrophic assays, respectively. Moreover, effects in the two-generation reproduction toxicity study were limited to a relatively high dose (255 mg/kg/day) The

negative findings from these four EDSP Tier 1 studies and risk assessment PODs that are well below levels tested for developmental effects (where there were no adverse effects observed) and well below any effects observed in the two-generation rat reproductive study collectively demonstrate that the current database for chlormequat chloride shows no potential for adverse effects to the estrogen or androgen pathways in humans from the proposed uses when used according to the label. Furthermore, several studies in the database for chlormequat chloride (including subchronic studies in the rat and chronic studies in the dog, rat and mouse) evaluated thyroid toxicity and there were no adverse thyroid effects observed related to thyroid hormone perturbations, demonstrating that the current database for chlormequat chloride shows no potential for adverse effects to the thyroid pathways in humans from the proposed uses when used according to the label. As noted in the near-term FRN, EPA will review all of the available data and information during registration review to confirm the sufficiency of data to support its FIFRA and FFDCA section 408(p)decisions for all uses of chlormequat chloride.

Neurotoxicity

Although potential evidence of neurotoxicity was observed in the database, clear NOAELs were identified for the potential neurotoxic effects and the selected endpoints and PODs for human health risk assessment are protective of the observed effects. As a result, HED has not required additional data regarding developmental neurotoxicity.

Gut Microbiome

Although gut microbiomes are not evaluated directly in guideline studies, the stomach and gastrointestinal tract are examined in several studies by gross evaluation and histopathological investigations. There are no indications in these studies that exposure to chlormequat chloride induces gross or histopathological effects on the stomach or gastrointestinal tract.

Comment 2*:* Several comments expressed concern that chlormequat is a low-dose reproductive toxin. These comments stated that chlormequat residues are concerning because chlormequat chloride is a reproductive toxin that has adverse effects at extremely low levels in animal models. These comments state that Torner et al (1999) found that low-level exposure of pregnant mice and their offspring to chlormequat chloride impacted the sperm of the male offspring such that in vitro fertilization tests showed far lower fertilization and oocyte cleavage rates than did sperm from control males. The comments identify another source that claimed that similar effects were observed at chlormequat doses on the order of 0.024 mg/kg bw (Sorensen and Danielsen 2006). The comments also refer to a pig experiment where sows were exposed to low levels of chlormequat in treated wheat and are claimed to have experienced impaired reproduction through disruption of estrous (Danielsen et al. 1989 [in Danish], described in Sorensen and Danielsen 2006). Xiagedeer et al. (2020) was also cited which claimed chlormequat disrupted the embryonic growth of offspring, with adverse postnatal effects, when female rats were exposed to 5 mg/kg bw during gestation.

The comments continued, stating that the noted reproductive effects in three species occur at doses lower than the NOAELs upon which EPA based its toxicological reference values for acute and chronic exposure to this compound, based solely on registrant testing, demonstrating that EPA has greatly underestimated the toxicity of chlormequat. The commenters further state that the same still holds for the somewhat lower safety thresholds established in the European Union.

EPA Response: Although potential evidence of reproductive toxicity was observed in the database, clear NOAELs were identified for the potential reproductive effects and the selected endpoints and PODs for human health risk assessment are protective of the observed effects. EPA has reviewed the toxicity database of chlormequat chloride, including developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats and a comprehensive literature search. In a rat two-generation reproduction study (MRID 46715206), evidence of reproductive (decreased fertility indices) and offspring toxicity (decreased mean litter size, body weight, and delayed development) was observed at 255mg/kg/day. These effects occurred at the same doses causing parental toxicity which was consistent with potential neurotoxic signs observed in adult animals throughout the database. As offspring and parental effects were observed at the same dose, there is no evidence of increased susceptibility to chlormequat chloride in offspring. The developmental study in rabbits saw no effects in maternal animals or offspring up to 12 mg/kg/day (highest dose tested) and there were no developmental effects observed in the rat developmental toxicity study up to 180 mg/kg/day (highest dose tested). The NOAEL used for chronic dietary and incidental oral risk assessment is 5 mg/kg/day and this POD is 50 times lower than the dose that induced adverse effects in the rat two-generation reproduction study. EPA therefore considers this toxicological endpoint and all others chosen for risk assessment to be protective of the observed effects.

In addition, after a preliminary review of the studies cited by the CFS, no studies were identified that would change the selected PODs for the chlormequat chloride human health risk assessment and thus EPA disagrees with commenters who state that these studies should be used to establish a basis for risk assessment. To support these findings, the following conclusions are offered from our preliminary review of each study cited by CFS:

1. **Torner et al., 1999 "Influence of chlorocholine chloride-treated wheat on selected in vitro fertility parameters in male mice":** In Torner et al., 1999, it was stated the animals had a daily intake of 0.024 mg/kg body weight of chlormequat chloride through a diet of chlormequat chloride treated wheat, but this cannot be verified without supporting evidence. There is a lack of information on the methodology used to determine the dose in chlormequat chloride treated wheat (HPLC, GC, etc.) and it is unclear what doses the animals received. Additionally, the study lacks information on test material purity and composition. Moreover, only a single dose was tested, which is insufficient to establish a dose response relationship. Typically, a minimum of three doses is required to establish a reliable trend in response to various levels of treatment. These deficiencies make this study unacceptable for use in risk assessment.

2. **Danielsen (1989) and Sorensen and Danielsen (2006) "Effects of the plant growth regulator, chlormequat, on mammalian fertility":** The full Sorensen and Danielsen 1989 study is not available in English. A 2006 review article is available and provides a discussion of the Danielsen (1989) study. However, this review article is not the primary source of the data. This cited review article is considered unacceptable for use in risk assessment according to the criteria as outlined in HED's open literature guidance[2].

[2] US EPA. 2012. Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment. https://www.epa.gov/sites/default/files/2015-07/documents/lit-studies.pdf

3. **Xiagedeer et al. (2020) "Maternal chlormequat chloride exposure disrupts embryonic growth and produces postnatal adverse effects":** In this study, pregnant rats were given oral doses of chlormequat chloride at 5 mg/kg of body weight during the entire pregnancy period (from gestational day 0 to gestational day 20). The impact on embryonic growth and growth regulators was evaluated on gestational day 11 and the post-natal growth and development of the offspring was examined on postnatal day 7. The study does not provide information on the purity or composition of the test substance. Additionally, only a single dose was tested, which is insufficient to establish a dose response relationship. Typically, a minimum of three doses is required to establish a reliable trend in response to various levels of treatment. These deficiencies make this study unacceptable for use in risk assessment.

Comment 2: EWG states that EPA did not adequately consider the immunotoxic effects of chlormequat chloride when it waived the required immunotoxicity study. According to EWG, evidence of chlormequat immunotoxicity exists in the peer-reviewed literature. Several studies were cited within the comment to support this position

EPA Response: The HASPOC recommended waiving the immunotoxicity study (TXR 0057329, S. Gallagher, 27-JAN-2016) (TXR 0057428, V. Chen, 14-JUL-2016). This decision included the following considerations: (1) the toxicology database for chlormequat chloride does not suggest that the immune system is a primary target; (2) for other registered quaternary ammonium herbicides, the immune system is not a primary target and these chemicals did not elicit immunotoxic effects in guideline studies; and (3) an immunotoxicity study is not likely to identify a lower POD or a more sensitive endpoint for human health risk assessment.

In addition, after a preliminary review of the studies cited by the EWG, no studies were identified that would change the selected PODs for the chlormequat chloride human health risk assessment. To support these findings, the following conclusions are offered from our preliminary review of each EWG cited study:

1. **Olson LJ, et al., 1984 "Influence of feeding chlorocholine chloride and glyphosine on selected immune parameters in deer mice, *peromyscus maniculatus*":** In Olson LJ, et al., 1984, researchers tested how exposure to the plant growth regulators, chlorocholine chloride (chlormequat chloride) and glyphosine, could affect immunomodulatory effects after feeding to deer mice (Peromyscus maniculatus) for 28 days. Cyclophosphamide (positive control) and saline were included as controls. Chlormequat chloride feeding levels were equivalent to 1, 10, 20, 40 and 80 mg/kg mouse/day. The parameters assessed were: spleen plaque forming cell assays, hemolysin titers, white blood cell counts, bone marrow cellularity, hematocrits, plasma proteins, and spleen, liver, kidney, thymus and body weights. Bone marrow cellularity, expressed as the number of bone marrow nucleated cells/g of femur produced slight, but non-significant deviations from controls for chlormequat chloride treated groups. Hematocrit values also did not vary significantly from saline controls. The most sensitive effect elicited by dietary exposure to chlormequat chloride identified by the authors was protein level variations in the 80 mg/kg/day treatment group. Even if considered adverse, the chronic dietary POD of 5 mg/kg/day selected by EPA for human health risk assessment of chlormequat chloride is 16 times lower.

2. **Fairbrother A, et al., 1984 "Effects of ingestion of chlorocholine chloride and cyclophosphamide on Venezuelan equine encephalitis virus infections in deer mice (*peromyscus maniculatus*)":** In Fairbrother A, et al., 1984, researchers investigated the effects of chlorocholine chloride (chlormequat chloride) and cyclophosphamide (CP), a known immunosuppressant (positive control), on the ability of deer mice (Peromyscus maniculatus) to resist challenge with a sublethal dose of Venezuelan equine encephalitis virus. Briefly, chlormequat chloride was continuously delivered in the feed at 1, 10, 20 or 40 mg/kg/day; CP at 20 mg/kg body wt/day for 23 days. Mice were bled daily for 7 days and at selected intervals from 8 to 63 days post inoculation for viremia (presence of the virus in the bloodstream) and antibody titer determinations. Mice consuming food containing chlormequat chloride at 1 mg/kg/day had mean viremia titers significantly lower than control (virus alone, no chlormequat chloride) titers on days 2 and 3 post-inoculation. Viremia titers of mice consuming food with 10, 20, or 40 mg/kg/day were never significantly different from controls, therefore, chlormequat chloride did not show a dose-dependent effect on viremia duration or titers compared to controls. Higher doses of chlormequat chloride had no effect on mean viremia titers. As a result, there were no adverse effects seen in this study and the chronic dietary POD of 5 mg/kg/day selected by EPA for human health risk assessment is 8 times lower than the highest dose tested in the cited study.

   Huang D et al., 2016 "The effects of chlormequat chloride on the development of pubertal male rats": In Huang D. et al., 2016, chlormequat chloride was administered to rats daily by gavage on postnatal days 23–60 at doses of 0, 75, 150 and 300 mg/kg/day. The results showed that body weight and the length of the right femur were significantly decreased only at the highest dose tested (300 mg/kg/day). Symptoms such as salivation, lachrymation and tremor were observed by the authors in rats from the 300 mg/kg/day treated group within one hour after exposure and disappeared after three hours. Body weights were significantly reduced in the 300 mg/kg/day treated group compared to those of the control group throughout the whole exposure period. There were no apparent differences in body weights in the 75 and 150 mg/kg/day treated groups. Gross necropsies and histological examinations of the tissues from liver, kidneys, spleen, testes and brain showed that the developmental toxicity of chlormequat chloride in weanling rats was a decreased body weight gain; no other specific organ was affected. The most sensitive effects elicited by dietary exposure to chlormequat chloride identified by the authors were salivation, lachrymation, and tremor, as well as decreased body weight and length of the right femur at 300 mg/kg/day. The chronic dietary POD of 5 mg/kg/day selected by EPA for human health risk assessment for chlormequat chloride is 60 times lower than this dose**.**

   Xiao et al., 2021 "Chlormequat chloride induced testosterone secretion inhibition mediated by endoplasmic reticulum stress in primary rat Leydig cells": Xiao et al. 2021 is a mechanistic study, in that it investigates the molecular pathway of testosterone secretion inhibition. Given the mechanistic nature of the study, the data would need to be evaluated in context with related results from other studies. It is also not appropriate to directly compare *in vitro* cellular data against PODs derived from *in vivo* animal studies due to toxicokinetic and potentially toxicodynamic differences between the

experimental models that would need to be accounted for. Although this study may qualitatively inform the hazard characterization, it would not quantitatively impact the risk assessment.

Comment 3: EWG states that 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 addition, EWG states that studies that have screened chemicals for properties of developmental neurotoxicants have identified other quaternary ammonium compounds as potential developmental neurotoxicants, like diquat, which EPA considered to be a compound that is structurally similar to chlormequat.

EPA Response: The developmental neurotoxicity (DNT) study is a conditionally required study that uses an information-based approach for requiring additional testing (https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158/subpart-F). The HASPOC previously evaluated the neurotoxic potential of chlormequat chloride to inform the need for a subchronic neurotoxicity study. A subchronic neurotoxicity study was recommended to be waived by the HASPOC (TXR 0057329, S. Gallagher, 27-JAN-2016) (TXR 0058602, J. Hale, 27-JUN-2023). There is a low degree of concern for the potential neurotoxic effects of chlormequat chloride because: 1) clear NOAELs were identified for the neurotoxic effects in available studies; 2) no neurotoxicity was observed in the subchronic neurotoxicity (SCN) studies of structurally similar chemicals (including diquat); 3) there is no concern for increased life stage susceptibility; 4) the dog is the most sensitive species in the database; in rats, potential neurotoxic effects occurred at dose levels 20 times higher than in the dog; 5) a subchronic neurotoxicity study in the rat, which is a less sensitive species than the dog, is not likely to identify a lower POD or a more sensitive endpoint for the risk assessment; 6) the short- and intermediate-term occupational handler inhalation risk estimates are not of concern and greater than 10 times the level of concern (LOC) of 30 (i.e., margins of exposure (MOEs) ≥ 300) at baseline attire (i.e., no respirator); and 7) the unrefined acute dietary (food and drinking water) and partially refined chronic dietary (food and drinking water) exposure and risk estimates for the general U.S. population and all population subgroups are below HED's LOC.

The need for a DNT study is based on a weight-of-evidence approach that incorporates current knowledge of neurotoxicity and developmental toxicity. EPA has reviewed the toxicity database of chlormequat chloride, including developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats. There was no increased quantitative or qualitative susceptibility observed in developing or young compared to the adult animals in the rat and rabbit developmental studies and the rat two-generation reproduction study. Additionally, clear NOAELs have been established for the potential neurotoxic effects observed and the endpoints and PODs selected for human health risk assessment are protective. Furthermore, a DNT study was not required for diquat, which EPA considered to be a structurally similar compound to chlormequat chloride. Considering all the available information, a DNT study was not required for chlormequat chloride.

Comments about co-exposures

Comment Summary: Several commenters expressed concern that co-exposure to different compounds can aggravate adverse health effects.

EPA Response: Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to chlormequat chloride and any other substances. For the purposes of this action, therefore, EPA has not assumed that chlormequat chloride has a common mechanism of toxicity with other substances.

In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis.[3] This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[4] and conducting cumulative risk assessments (CRA)[5].

Chlormequat chloride is a quaternary ammonium compound. As part of the ongoing process to review registered pesticides, the Agency intends to apply this framework to determine if the available toxicological data for chlormequat chloride suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

Comments regarding tolerance creep

Comment 1: CFS expressed opposition to new use registrations for chlormequat chloride, raising concern as to whether the amount used was higher than needed to accommodate the intended use of chlormequat to strengthen stalks of the pertinent grain crops: wheat, barley, oats, and triticale. There was also concern for whether proposed tolerances and MRLs are in line with those established by Canada.

EPA Response: The recommended tolerances are based on the submitted data, which reflect the proposed use, and the OECD tolerance calculation procedure. There are established Codex (4 ppm) and European (15 ppm) MRLs for chlormequat chloride in/on oat grain. Canada has established an MRL on oat grain at 40 ppm and the HED-recommended tolerance is harmonized with Canada. For wheat and barley grain, there are established Codex (2 ppm) and European (7 ppm) MRLs, respectively for chlormequat chloride. Canada has established an MRL on wheat grain at 5 ppm and 8 ppm for barley grain and the HED recommended tolerances that are harmonized with Canada. Furthermore, the recommended tolerances are supported by the Agency's dietary risk assessment, which evaluates risk based on potential exposure to chlormequat chloride through food and drinking water. The dietary risk assessment did not result in any risks of concern.

Comment 2: CFS expressed concern that high tolerances encourage bad agricultural practice and increase chlormequat exposure. They discuss how the timing of application of chlormequat is an important factor for its effectiveness and state that exposure could be considerably reduced if applications were restricted to earlier growth stages (before GS31-32).

[3] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
[4] Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)
[5] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

EPA Response: EPA agrees that the timing of application is important for the plant growth regulator. For chlormequat chloride, the application rate/timing for the registered uses on cereal grain is to apply a single application at a dose rate of 1 lb ai/A between GS 31 – 32 (the 1- to 2-node stage) no later than GS 39 or apply a split application at a dose rate of 0.55 lb ai /A between GS 12 and GS 30 followed by a second application of 0.44 lb ai/A between GS 31 –32. These application rates and timing of application are on listed on the registered labels. As enforcement tools, tolerances represent the highest amounts of pesticides that are allowed in food, and those levels are not expected to be exceeded when pesticides are applied in accordance with their labels. EPA tolerances are derived from field trial studies depicting the maximum application rate and shortest pre-harvest interval to ensure compliance with the label. Consequently, EPA disagrees with the statement that high tolerances encourage bad agricultural practices. The dietary risk assessments demonstrate that chlormequat chloride exposure from the registered uses resulted in dietary exposure risk estimates that are well below HED's level of concern for the general U.S. population and all population subgroups.

Comments concerning pesticide residues

Comment 1: A commenter questioned the EPA proposal for setting a plant-back interval of 12 months for leafy vegetables and root crops. This was based on an assessment of the Total Radioactive Residues that shows that no inadvertent residues of concern (being chlormequat chloride) would be present in rotated leafy vegetables and root crops. Therefore, a plant-back interval of 0 days rather than 12 months would be more appropriate.

EPA Response: Upon reconsideration of the available data, the Agency concurs with this point. A plant-back interval (PBI) for leafy vegetable and root and tuber crops is not required (see memorandum "Reassessment of Plant-Back Intervals for Rotated Crops Recommended in the Human Health Risk Assessment for the Section 3 Registration of Chlormequat Chloride on Wheat, Triticale, Barley, and Oats. Abbreviated Residue Chemistry Review") (D468147, S. Piper, 23-AUG-2023).

Comment 2: A submitted comment stated that the EPA concluded that several unknowns were inadequately characterized/identified in the poultry metabolism study and that these unknowns should therefore be included in the residue definition for poultry matrices. However, plant and rat metabolism studies show that the parent compound chlormequat chloride readily degrades to choline chloride and glycine betaine, which are natural compounds in many living organisms.

EPA Response: For the poultry metabolism study, there were inadequate characterization/ identification of several unknowns. Solvent-extractable unknowns from liver, kidney, muscle, and egg yolk accounted for 20.6- 57.1% of the total radioactive residue (TRR) and contained substantial amounts of radioactivity (0.025-0.169 ppm). The results indicated that the components resolved using Method 1 (Method 1; reverse phase high-performance liquid chromatography (HPLC) had sufficiently similar molecular weights that they could not be resolved into more than one or two components using Method 2 (Method 2; HPLC using a size exclusion column (SEC). Although the study suggest that these unknowns were naturally occurring polymeric materials of high molecular weight, no reference standards were included in the HPLC determination using a SEC analysis that would allow for estimation of molecular size vs. retention time. Aside from HPLC SEC analysis, which only indicated that these unknowns were of similar molecular size, no further characterization/identification was

attempted. Given the percent of the TRR accounted for by these polar unknowns and their associated residue levels, additional characterization/identification of these unknowns is required.

Also, the feeding study was conducted to monitor parent only and ratio of the parent plus the three major unknowns identified from the poultry metabolism study. For the purposes of human health risk assessment, the ratio of the parent plus the three major unknowns were used to determine a total the residue estimate for poultry tissues and eggs. This was derived by adding the unknowns found in the poultry metabolism study for each tissue and multiplying these totals by the expected parent residue from the feeding study. These adjustment factors were incorporated in the dietary risk assessment for poultry tissues and eggs to ensure it accounted for all the residues of concern.

Comment 3: A commenter noted that the current tolerance expression for chlormequat chloride is as chlormequat chloride (§ 180.698), which is in line with the tolerance expression set by PMRA and the European Commission. The residue definition by CODEX is as chlormequat cation. Both chlormequat cation and chlormequat chloride are used throughout EPA's evaluation documents. While these differences in expression of residues do not impact the proposed decision, the commenter notes them for the Agency's consideration in the future.

EPA Response: The Agency concurs with the point raised. The sum of chlormequat and its salts expressed as chlormequat cation is the residue definition for both tolerance enforcement and risk assessment for plants and livestock. This decision was concluded for the purposes of harmonization with CODEX. The latest risk assessment reflects this change (D467413, A. Britt, 25-SEPT-2023).

REFERENCES

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D457479, S. Piper, 16-MAR-2021. Chlormequat Chloride. Draft Human Health Risk Assessment for Registration Review.

D467413, A. Britt, 25-SEPT-2023. Chlormequat Chloride. Second Revision of the Human Health Risk Assessment for the Section 3 Registration Action for a New Use on Wheat, Triticale, Barley, Oats, and Grasses Grown for Seed.

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