November 22, 2021

Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460–0001

RE: Comments on Pesticide Petition PP 0F8857 to Establish Multiple Tolerances for Residues of Chlormequat Chloride on Various Grains and Meat Commodities

EPA Docket EPA-HQ-OPP-2021-0290

Center for Food Safety appreciates the opportunity to comment on the above-named matter on behalf of itself and its 970,000 members and supporters. Center for Food Safety (CFS) is a public interest, nonprofit membership organization with offices in Washington, D.C., San Francisco, California, and Portland, Oregon. CFS's mission is to empower people, support farmers, and protect the earth from the harmful impacts of industrial agriculture. Through groundbreaking legal, scientific, and grassroots action, CFS protects and promotes the public's right to safe food and the environment. CFS has consistently supported comprehensive EPA review of registered pesticides and individual inert ingredients.

Taminco US LLC has petitioned EPA to register new uses of the plant growth regulator, chlormequat chloride, on barley, oat, triticale and wheat grains; and to establish new U.S. tolerances for this compound in or on these raw agricultural commodities, as well as in the meat and meat byproducts of cattle, goats, hogs, sheep and poultry, additionally in eggs and milk.

Center for Food Safety (CFS) strongly opposes the new use registrations and the associated tolerances. These comments focus on the tolerances. We will submit a second set of comments on the requested new use applications that provide further information and analysis.

INTRODUCTION

Chlormequat chloride is a plant growth regulator that inhibits gibberellic acid, a hormone that promotes plant stem elongation. Treatment leads to thicker, shorter stems. At present, chlormequat is registered for use only on ornamentals, mostly indoors in greenhouses, with limited outdoor use on containerized plants in shadehouses (EPA 3/26/21). It is not registered for use on a single crop intended for food or feed; and with usage totaling about 1,000 lbs/year nationwide (EPA 2/25/16), Americans and the nation's environment have very limited exposure to chlormequat from domestic use.

WASHINGTON D.C. OFFICE: 660 Pennsylvania Ave, SE, #402, Washington, DC 20003, T (202) 547-9359, F (202) 547-9429
CALIFORNIA OFFICE: 303 Sacramento St, 2nd floor, San Francisco, CA 94111, T (415) 826-2770, F (415) 826-0507
PACIFIC NORTHWEST OFFICE: 2009 NE Alberta St, Suite 207, Portland, OR 97211, T (971) 271-7372
www.centerforfoodsafety.org office@centerforfoodsafety.org

However, chlormequat is registered for use on grains in Europe, the U.K., Canada and other countries, which along with Codex have established corresponding tolerances. In fact, about 65% of winter wheat and 50% of winter barley and oats are treated with products containing chlormequat in the United Kingdom (Spink et al. 2004), while 70% of the wheat in the European Union as a whole is treated with it (Sorensen and Danielsen 2006). To facilitate import of chlormequat-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 (0.45 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 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 would have been applied that year (40 million harvested acres in 2020 * 70% * 1 lb/acre). This would represent a 28,000-fold increase over the current 1,000 lbs/year.

RELEVANT LEGAL STANDARDS

The Federal Food, Drug, and Cosmetic Act

Federal Food, Drug, and Cosmetic Act (the FFDCA)[1] prohibits the introduction of "adulterated" food into interstate commerce.[2] The Act requires that where use of a pesticide will result in any pesticide residue being left on food, EPA must either set a "tolerance" level for the amount of allowable pesticide residue that can be left on the food, or set an exemption of the tolerance requirement.[3]

EPA has a duty under the FFDCA to ensure that the proposed tolerance level of chlormequat residue will cause "no harm" to humans, particularly infants and children "from aggregate exposure" to chlormequat.[4] The FFDCA mandates EPA to "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."[5] For a tolerance level to be "safe," the statute requires EPA determine "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."[6] "Aggregate exposure" includes not only dietary exposure through food consumption, but also includes "exposures through water and residential uses."[7]

---

[1] 21 U.S.C. § 301 *et seq*.
[2] 21 US.C. § 331.
[3] 21 U.S.C. § 346a(1).
[4] 21 U.S.C. § 346a(b)(2)(A).
[5] 21 U.S.C. § 346a(b)(2)(A)(i).
[6] 21 U.S.C. § 346a(b)(2)(A)(ii).
[7] *Natural Res. Def. Council v. Whitman*, No. C 99-03701-WHA, 2001 WL 1221774 (N.D. Cal. Nov. 7, 2001).

COMMENTS

Chlormequat is frequently detected in grains

Chlormequat chloride is one of the most frequently detected pesticide residues in European countries where it is used. In Denmark, chlormequat was detected in 87% and 83% of cereals tested in 1997 and 1998 (Granby and Vahl 2001), while 44 of 48 samples of wheat produced in the UK in 2002 contained chlormequat residues (Spink et al. 2004). In the European Union as a whole, chlormequat was by far the most frequently quantified pesticide in wheat in 2015, with 49% percent of samples testing positive, while in 2016, the EU detected chlormequat residues in 34% of rye samples (EFSA 2017, EFSA 2018).

Chlormequat chloride is extremely persistent. It is stable to hydrolysis and photolysis in water, and is not expected to degrade on the surface of sprayed leaves (EPA 3/26/21). Thus, it is not surprising that it turns up frequently not only in raw cereal commodities, but also in processed cereal products. In the EU, chlormequat was by far the most frequently detected pesticide in wheat flour, with 48% of samples testing positive in 2014 (EFSA 2016). In the UK, an astounding 88% (125 of 142) of bread and related bakery goods tested positive for chlormequat in the third quarter of 2018.

Chlormequat is a low-dose reproductive toxin

These residues are concerning because chlormequat chloride is a reproductive toxin that has adverse effects at extremely low levels in animal models. 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. This occurred at chlormequat doses on the order of 0.024 mg/kg bw (Sorensen and Danielsen 2006). A pig experiment revealed that sows exposed to even lower levels of chlormequat in treated wheat experienced impaired reproduction through disruption of estrous (Danielsen et al. 1989 [in Danish], described in Sorensen and Danielsen 2006). Xiagedeer et al. (2020) found that chlormequat disrupted the embryonic growth of offspring, with adverse postnatal effects, when female rats were exposed to 5 mg/kg bw during gestation.

These reproductive effects in three species occur at doses lower than the NOAEL's upon which EPA based its toxicological reference values for acute and chronic exposure to this compound, based solely on registrant testing. Indeed, in some animal studies, effects were observed at levels lower than the reference values themselves (aRfD = 1 mg/kg/day, cRfD = 0.05 mg/kg/day), demonstrating that EPA has greatly underestimated the toxicity of chlormequat. The same still holds for the somewhat lower safety thresholds established in the European Union.

However, even with the inflated and unsafe reference doses established in the European Union (aRfD = 0.09 mg/kg/day; acceptable daily intake = 0.04 mg/kg/day), the EU finds potential short-term consumer risks from exposure to some food items bearing residues of chlormequat (EFSA 2017, p. 83). Even in the U.S., chlormequat chloride is regarded as an "extremely hazardous substance." See 40 C.F.R. § 355.

It is clear that the proposed tolerances would lead to unsafe exposures to this highly toxic compound, and must not be granted.

Tolerance creep

CFS opposes the new use registrations, and establishment of any domestic tolerances for chlormequat, as the risks to human health of exposure far exceed any minor agronomic benefits. However, even if one were to consider some tolerances justified, those proposed by Taminco are far higher than are "needed" to accommodate the intended use of chlormequat to strength stalks of the pertinent grain crops: wheat, barley, oats and triticale.

The proposed tolerance for wheat of 5 ppm far exceeds past and current maximum residue levels (MRL's) established by other countries and Codex: just 1 ppm in Canada, a major wheat-producing nation, and a 2 ppm Codex MRL (EPA 3/16/21, Appendix A.5). The disparity for barley is even greater. Canada's MRL of 0.1 ppm and the 2 ppm Codex MRL for barley are 80-fold and 4-fold, respectively, below the Taminco-proposed tolerance of 8 ppm (Ibid). Most unacceptable is the proposal for a 40 ppm tolerance in or on oats. The Codex MRL is just 4 ppm, one-tenth that value, while the UK not long ago and perhaps today had/has a nearly equivalent MRL of 5 ppm (Spink et al. 2004).

High tolerances encourage bad agricultural practice and increase chlormequat exposure

Chlormequat residue testing carried out at three sites in the UK during the 2002-03 growing season revealed widespread contamination of wheat, barley and oats, but at levels substantially below then-prevailing tolerances, and even farther below the vastly inflated tolerances proposed by Taminco (Spink et al. 2004).

Two key factors driving high residue levels are application rate and timing (Ibid). As one would expect, higher rates lead to higher residues. However, the timing of application is even more important.

Spink et al. (2004) found that chlormequat residue levels in wheat, oats and barley grain increased sharply as the time of application advanced to later growth stages. Teittinen (1975) found vastly increased chlormequat residues in wheat when 2.5 kg/ha was applied 65 days before harvest (3.2 mg/kg) vs. 98 days before harvest (0.16 mg/kg). Likewise with application of 0.69 to 1.38 kg/ha in oats, chlormequat residues increased from 0.23-0.33 mg/kg when applied at growth stages GS31/32 to 1.68-2.0 mg/kg when applied at GS45 (Gans et al. 2000, Tables 2 and 3).

While applications of chlormequat to grains were limited to GS31/32 in the past (Spink et al. 2004), EPA has approved experimental use permits in which applications are made as late as GS39 (EPA 3/16/21, Table 3.3, p. 11). Exposure to chlormequat could be considerably reduced if applications were restricted to earlier growth stages. Spink et al. (2004) found that changing the application timing from GS31 to an earlier growth stage – late tillering – dramatically reduced chlormequat residues without impacting performance. The same authors also found no benefit of chlormequat to barley.

These findings suggest that the ultra-high tolerances proposed by Taminco would encourage growers to make applications of chlormequat at far later growth stages than is recommended by agronomists, dramatically increasing exposure to this reproductive toxin.

Co-exposure aggravates adverse effects

In Sweden, chlormequat chloride was found in 100% of urine samples from Swedish adolescents in 2000, 2004, 2009, 2013 and 2017, with roughly 200 samples each year (Noren 2020, Table 3). The last thing we need in the U.S. is exposure to still another reproductive toxin.

The increased exposure to residues of this reproductive toxin that would ensue from granting the proposed tolerances would occur against a backdrop of exposure to a multitude of other such toxins, particularly other anti-androgens. Low-level co-exposures to multiple chemicals frequently have additive effects on common target tissues, a result which EPA scientists have found sometimes holds true even if components of the mixture have dissimilar mechanisms of toxicity (e.g. Rider et al. 2010). This means that safety thresholds established for individual substances may well not be protective in the real world of co-exposure to multiple chemicals (Kortenkamp et al. 2007, Nordkap et al. 2012).

This evidence is particularly strong for anti-androgenic compounds. Numerous animal studies show that in utero exposures to mixtures often have additive and occasionally synergistic adverse effects on a range of male reproductive endpoints, even when components of the mixture are administered at levels at or well below the individual NOAELs (Christiansen et al. 2009, Rider et al. 2010). As would be predicted from the dose addition principle, EPA research scientists found that the doses of individual chemicals needed to adversely affect male reproductive tract development decrease with increasing number of anti-androgens in the mixture (Conley et al 2018).

Sperm counts and quality have been declining for decades, with an over 50% reduction in sperm counts in men in developed countries from 1973 to 2011 (Levine et al. 2017). Scientists attribute this decline in large part to increasing exposure to environmental chemicals, including pesticides (Martenies and Perry 2013, Gore et al. 2015, Chiu et al. 2015).

CONCLUSION

The putative benefit of applying chlormequat to grains is far outweighed by the costs to human health of granting the proposed tolerances. CFS urges EPA to deny all of Taminco's proposed domestic tolerances for chlormequat chloride.

Bill Freese, Scientific Director
Center for Food Safety

REFERENCES

Chiu Y-H et al. (2016). Intake of Fruits and Vegetables with Low- to-Moderate Pesticide Residues Is Positively Associated with Semen-Quality Parameters among Young Healthy Men. The Journal of Nutrition 146(5): 1084-92.

Christiansen S et al. (2009). Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. Environmental Health Perspectives 117(12): 1839-46.

Conley JM et al. (2019). Mixed “anti-androgenic” chemicals at low individual doses produce reproductive tract malformations in the male rat. Toxicological Sciences 164(1): 166-178.

Danielsen, V., Larsen, A. E. and Binder, M. (1989) CCC- behandlet hvede som foder til gylte og 1. lægssøer (CCC-Treated Wheat as Feed for Gilts and First Parity Sows). Statens Husdyrbrugsforsøg, Meddelelse nr. 749, 4 pp (in Danish).

EFSA (2018). The 2016 European Union report on pesticide residues in food. European Food Safety Authority, EFSA Journal 2018; 16(7): 5348. Available at: https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5348.

EFSA (2017). The 2015 European Union report on pesticide residues in food. European Food Safety Authority, EFSA Journal 2017; 15(4): 4791. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/4791.

EFSA (2016). The 2014 European Union report on pesticide residues in food. European Food Safety Authority, EFSA Journal 2016; 14(10): 4611. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/4611.

EPA (3/26/21). Chlormequat Chloride: Draft Ecological Risk Assessment for Registration Review, EPA, EPA-HQ-OPP-2015-0816-0018, March 26, 20121.

EPA (3/16/21). Chlormequat Chloride: Draft Human Health Risk Assessment for Registration Review, EPA, EPA-HQ-OPP-2015-0816-0019, March 16, 20121.

EPA (2/25/16). BEAD Chemical Profile for Registration Review: Chlormequat Chloride (018101), Biological and Economics Analysis Division, EPA, EPA-HQ-OPP-2015-0816-0003, February 2, 2016.

Gans W, Beschow H and Merbach W (2000). Growth regulators for cereal and oil crops on the basis of 2,3-dichloroisobutyric acid and chlormequat chloride and residue analyses of both agents in the grain of oat. J. Plant Nutr. Soil Sci. 163: 405-410.

Gore AC et al. (2015). EDC-2: The Endocrine Society’s Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocrine Reviews 36(6): E1-E150.

Granby K and Vahl M (2001). Investigation of the herbicide glyphosate and the plant growth regulators chlormequat and mepiquat in cereals produced in Denmark. Food Addit Contam 18(10): 898-905.

Kortenkamp A et al. (2007). Low-level exposure to multiple chemicals: reason for human health concerns? Environmental Health Perspectives 115(1): 106-114.

Levine H et al. (2017). Temporal trends in sperm count: a systematic review and meta-regression analysis. Human Reproduction Update 23(6): 646-659.

Martenies SH and Perry MJ (2013). Environmental and occupational pesticide exposure and human sperm parameters: a systematic review. Toxicology 307: 66-73.

Nordkap L et al. (2012). Regional differences and temporal trends in male reproductive health disorders: semen quality may be a sensitive marker of environmental exposures. Molecular and Cellular Endocrinology 355: 221-230.

Noren E et al. (2020). Concentrations and temporal trends in pesticide biomarkers in urine of Swedish adolescents, 2000–2017. Journal of Exposure Science & Environmental Epidemiology 30: 756-767.

Rider CV, Furr JR, Wilson VS, Gray LE Jr (2010). Cumulative effects of *in utero* administration of mixtures of reproductive toxicants that disrupt common target tissues via diverse mechanisms of toxicity. International Journal of Andrology 33(2): 443-462.

Sorensen MT and Danielsen V (2006). Effects of the plant growth regulator, chlormequat, on mammalian fertility, International Journal of Andrology 29: 129-133.

Spink J, Berry PM, Wade AP and White EM (2004). Effects of timing and dose on residues of chlormequat in wheat, barley and oats. Project Report No. 334, Home-Grown Cereals Authority, United Kingdom, April 2004. Available at: https://ahdb.org.uk/effects-of-timing-and-dose-on-levels-of-chlormequat-in-wheat-barley-and-oats.

Teittinen, P (1975). Chlormequat (CCC) in growing spring wheat in Finland. Annales Agriculturae Fenniae 14: 1-56.

Torner H et al. (1999). Influence of chlorocholinechloride-treated wheat on selected in vitro fertility parameters in male mice. Reproductive Toxicology 13: 399-404.

Xiagedeer B et al. (2020). Maternal chlormequat chloride exposure disrupts embryonic growth and produces postnatal adverse effects. Toxicology 442: 152534.