September 20, 2021

Environmental Working Group comments to the Environmental Protection Agency Docket ID: EPA-HQ-OPP-2011-0840
Subject: Draft human health and ecological risk assessments for chlorothalonil

The Environmental Working Group, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, Minn., San Francisco and Sacramento, Calif., urges the Environmental Protection Agency to ban the use of chlorothalonil fungicide, following the lead of the European Union.

EWG has researched pesticide toxicity since 1993, especially the risks of pesticides to children's health. Exposure to chlorothalonil poses a particular risk for children's health because of the carcinogenic and endocrine-disrupting activity of this pesticide. Chlorothalonil is used on several crops in the U.S. From 2010 to 2017, approximately 10 to 12 million pounds of chlorothalonil were sprayed in several regions of the country every year, including California, the Midwest, Texas and the Southeast.[1] Tests conducted by the U.S. Department of Agriculture between 2009 and 2019 detected chlorothalonil on several fruits and vegetables, including celery, cucumbers, sweet bell peppers and summer squash.[2] It is also used on potatoes and has been detected in the air around residential homes near potato fields in Minnesota. [3]

EPA should prohibit uses of chlorothalonil based on the following rationale:

1. Dietary exposure to chlorothalonil exceeds levels of concerns, especially for children.
2. Chlorothalonil has carcinogenic and endocrine-disrupting properties that are not accounted for in the current risk assessment.
3. Chlorothalonil is toxic when inhaled.
4. There are issues with the current human health risk assessment that inflate the safe levels of exposure; EPA should apply the 10X FQPA children's health safety factor.
5. Chlorothalonil and its breakdown products, which have not been fully assessed for toxicity, can contaminate drinking water sources.
6. Chlorothalonil concentration estimates in the environment exceed levels of concern for several terrestrial and aquatic organisms.

In 2019, the EU did not reapprove chlorothalonil for registration with all uses of the fungicide ending in 2020. The main reasons for the ban were the potential for chlorothalonil breakdown products to cause DNA damage, which may be linked to increased cancer risk, and the capacity of both the parent and breakdown compounds to contaminate drinking water.

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[1] https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2017&map=CHLOROTHALONIL&hilo=L&disp=Chlorothalonil

[2] USDA. Pesticide Data Program. https://www.ams.usda.gov/datasets/pdp

[3] Pesticide Action Network North America. Pesticide Drift Monitoring in Minnesota June 13, 2006 – August 13, 2009. Technical Report. May 2012.

Other supporting information was severe health hazards associated with chlorothalonil, including its classification as "fatal if inhaled" and "may cause cancer," as well as harm to amphibians and fish.[4] The EPA should follow the lead of the EU and prohibit the use of the chlorothalonil.

Details and supporting information for EWG recommendation to ban chlorothalonil are listed below.

1. Dietary exposure to chlorothalonil exceeds levels of concerns, especially for children.

The EPA's current chronic dietary risk assessment, which includes contributions from food and drinking water, estimates concerning levels of exposure for all age groups, especially infants and children, which suggests strongly limiting the use of chlorothalonil.[5] Importantly, the safe level of exposure determined in the human health risk assessment does not include a 10X safety factor for children's health. If the 10X safety factor were applied, current dietary exposure levels estimated by EPA would be nearly 65 times higher than the safe threshold.

2. Chlorothalonil has carcinogenic and endocrine-disrupting properties that are not accounted for in the current risk assessment.

EWG disagrees with the EPA's threshold approach to carcinogenic risk assessment. The EPA refers to using a threshold approach, based on a 1998 Science Advisory Panel Decision. However, the California Office of Environmental Health Hazard Assessment, or OEHHA, published a cancer slope factor that can be used for risk assessment. Such an approach should be used, since the kidney tumors observed in the two-year carcinogenic study may have human relevance, as discussed in the European Food Safety Authority risk assessment. Additionally, a recent study found chlorothalonil could cause genomic damage to human peripheral lymphocyte cells.[6]

Lastly, in human studies, residential proximity (4000 meters) to chlorothalonil applications during pregnancy was associated with an increased risk for childhood central nervous system

[4] European Commission. Chlorothalonil; SANTE/10186/2018 Rev 1; 22 March 2019 https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=as.details&as_id=544
[5] U.S. EPA. Chlorothalonil: Revised Human Health Draft Risk ssesment for Registration Review. April, 09, 2021.
[6] Santovito A, Gendusa C, Ferraro F, Musso I, Costnazo M, Rubert S, Cervella P. (2018). Genomic damage induced by the widely used fungicide chlorothalonil in peripheral human lymphocytes. *Ecotoxicol Environ Saf. Oct;161:578-583. doi: 10.1016/j.ecoenv.2018.06.047.*

tumors.[7] The oral and inhalation slope factor for chlorothalonil as determined by the California OEHHA is 0.017 $(mg/kg\text{-}day)^{-1}$. The EPA should use this value in the carcinogenicity assessments of chlorothalonil.[8]

Recent studies in the peer-reviewed literature suggest chlorothalonil may be an endocrine-disrupting compound, but none of these studies is discussed in the human health risk assessment. Importantly, some of these studies observed endocrine-disrupting effects, including inhibiting spermatogenesis and ovarian development in mice, at doses below what EPA has determined to be safe.[9,10]

3. Chlorothalonil is toxic when inhaled.

Additionally, EWG strongly disagrees with the approach that the EPA risk assessment document took in characterizing the inhalation toxicity of chlorothalonil. EPA acknowledges the high toxicity demonstrated by chlorothalonil via the inhalation route, in which a level of exposure that did not have adverse effects could not be established from five studies submitted by the registrant. For certain applications of chlorothalonil, farmworkers are required to wear respirators, highlighting the risk to farmworkers posed by this pesticide. High inhalation toxicity is sufficient reason for the EPA to cancel registrations of chlorothalonil.

Instead of canceling chlorothalonil uses to protect public health, the EPA pesticide registration program decided to permit the use of a non-animal assay to assess the respiratory irritation potential of chlorothalonil. Given the severe inhalation toxicity of chlorothalonil, there are additional endpoints to consider besides irritation, such as long-term harm to the respiratory system.

Additionally, the EPA risk assessment inappropriately removed several uncertainty factors. Removal of the 10X interspecies factor is supported, since human cells were used in the assay. However, removal of the 10X intraspecies factor, to account for differences in response between individuals, is not, especially since EPA notes that increased sensitivity in the assay was observed when cells from multiple donors were used rather than a single donor.

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[7] Lombardi C, Thompson S, Ritz B, Myles C, Heck JE. (2021). Residential proximity to pesticide application as a risk factor for childhood central nervous system tumors. *Environmental Research*. https://doi.org/10.1016/j.envres.2021.111078

[8] https://oehha.ca.gov/chemicals/chlorothalonil

[9] Zhan P, Zhao Y, Zhang H, Liu J, Feng Y, Yin S et al. (2019). Low dose chlorothalonil impairs mouse spermatogenesis through the intertwining of Estrogen Receptor Pathways with histone and DNA Methylation. *Chemosphere*. Sep;230:384-395. doi: 10.1016/j.chemosphere.2019.05.029.

[10] Hao Y, Zhang H, Zhang P, Yu S, Ma D, Li L et al. (2019). Chlorothalonil inhibits mouse ovarian development through endocrine disruption. *Toxicol* Lett. Mar 15;303:38-47. doi: 10.1016/j.toxlet.2018.12.011. Epub 2018 Dec 23.

Finally, EPA did not apply the 10X FQPA safety factor for children's health, despite using weight and breathing rate estimates for an adult male, not a child, to convert the dose used in the cell assay to a dose that an individual would need to inhale to cause the same effect, and therefore did not account for children's increased susceptibility to harm from chlorothalonil exposure.

4. Protecting children's health by the application of the 10X FQPA Children's Health Safety Factor

EWG strongly disagrees with the reduction of the FQPA Safety Factor to 1X. As we have just described, recent studies published in the peer-reviewed literature suggest chlorothalonil can act as an endocrine disruptor during sensitive windows of development. As early as 2004, states including California, Connecticut, Massachusetts and New York petitioned EPA to retain the 10X factor, stating that "EPA did not have reliable data on which to base a deviation from the tenfold factor in that, among other things, it lacked data on cumulative risk of pesticides with a common mechanism of toxicity and endocrine disruptive effects, as required by the FQPA."[11]

Not only did EPA incorrectly deny this petition in 2006, but the new data that fills some data gaps highlighted in the petition also support the endocrine-disrupting potential of chlorothalonil, all of which warrant keeping the 10X safety factor.

In addition, as we have mentioned, in its analysis of inhalation toxicity for chlorothalonil, EPA did not account for children's smaller size and increased breathing rate.

Finally, studies in immune cells suggest chlorothalonil may harm the immune system, promoting inflammation.[12] High throughput screening assays suggest chlorothalonil may have neurotoxic potential,[13] and exposure to chlorothalonil during pregnancy, as estimated by residential proximity to agricultural fields where the pesticide is sprayed, is associated with an increased risk of childhood central nervous system tumors.[6] Together, these data support retaining the 10X FQPA children's health safety factor for chlorothalonil.

5. Chlorothalonil and its breakdown products pose a risk to drinking water sources.

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[11] Petition of New York, California, Connecticut and Massachusetts for Modification of Tolerances for Pesticide Chemical Residues Established in Reregistration Eligibility Determinations For The Following Chemicals: Alachlor EPA 738-R-98-020 (40 CFR 5 180.249); Chlorothalonil EPA 738-R-99-004 (40 CFR 5 180.275); Methomyl EPA 738-R-98-021(40 CFR 5 180.253); Metribuzin EPA 738-R-97-006 (40 CFR tj 180.332); Thiodicarb EPA 738-R-98-022 (40 CFR 180.407). December 17, 2004. https://oag.ca.gov/system/files/attachments/press_releases/04-145.pdf

[12] Weis G, Assmann C, Cadona F, Bonadiman B, Alves A, Machado A et al. (2019). Immunomodulatory effect of mancozeb, chlorothalonil, and thiophanate methyl pesticides on macrophage cells. *Ecotoxicol Environ Saf*. Oct 30;182:109420. doi: 10.1016/j.ecoenv.2019.109420.

[13] Kosnik M, Strickland J, Marvel S, Wallis D, Wallace K, Richard A et al. (2020). Concentration-response evaluation of ToxCast compounds for multivariate activity patterns of neural network function. *Arch Toxicol*. Feb;94(2):469-484. doi: 10.1007/s00204-019-02636-x.

EPA's dietary and drinking water assessment for chlorothalonil determined that estimated exposure to chlorothalonil from drinking water alone exceeds levels of concern. EPA's current modeling approach has improved significantly from previous versions, as it now includes more chlorothalonil breakdown products and accounts for all uses of chlorothalonil, and indicates that the highest estimated drinking water concentrations for groundwater were 2763 parts per billion.[14] In 2012, the United States Geological Survey detected chlorothalonil in 38 percent of surface and groundwater samples, and 41 percent of sediment samples from Idaho, Maine and Wisconsin.[15, 16]

Potential drinking water contamination was grounds for non-approval of chlorothalonil in the EU. A recent study in Switzerland found multiple chlorothalonil breakdown products in all groundwater sources sampled in the study, providing further evidence that historical and current uses of chlorothalonil can contribute to the contamination of drinking water sources.[17]

6. Chlorothalonil levels exceed levels of concern for several terrestrial and aquatic organisms.

EPA's ecological risk assessment for chlorothalonil found that anticipated levels of chlorothalonil in the environment could cause harm to birds, mammals, freshwater fish, amphibians, estuarine and marine fish, as well as aquatic invertebrates.[18] In several of these cases, all uses of chlorothalonil exceeded the levels of concern. Such ecological concerns were also identified in the European registration reviews of chlorothalonil, and ultimately led to the non-approval of the fungicide.

In conclusion, based on multiple lines of evidence demonstrating chlorothalonil toxicity, as summarized in this comments letter, the EPA should ban all uses of chlorothalonil.

Comments submitted on behalf of the Environmental Working Group,

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[14] U.S. EPA. Chlorothalonil Drinking Water Assessment for Registration Review. December 16, 2020.
[15] Reilly, T.J., Smalling, K.L., Orlando, J.L., and Kuivila, K.M., 2012, Occurrence of boscalid and other selected fungicides in surface water and groundwater in three targeted use areas in the United States: Chemosphere, v. 89, no. 3, p. 228-234, doi:10.1016/j.chemosphere.2012.04.023.
[16] Smalling, K.L., Reilly, T.J., Sandstrom, M.W., and Kuivila, K.M., 2013, Occurrence and Persistence of Fungicides in Bed and Suspended Solids from Three Targeted Use Areas in the United States: Science of the Total Environment, v. 447, p. 175-185, doi:10.1016/j.scitotenv.2013.01.021
[17] Kiefer K, Barder T, Minas N, Salhi E, Janssen E, von Gunten U, Hollender J. (2020). Chlorothalonil transformation products in drinking water resources: Widespread and challenging to abate. *Water Res.* Sep 15;183:116066. doi: 10.1016/j.watres.2020.116066.
[18] U.S. EPA. Chlorothalonil: Draft Ecological Risk Assessment for Registration Review. December 30, 2020.

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