July 8, 2019

Environmental Working Group Comments to the Environmental Protection Agency
Docket ID: EPA-HQ-OPP-2014-0175
Subject: Registration Review Draft Risk Assessment for Thiabendazole and Salts

Environmental Working Group (EWG), a nonprofit research and policy organization with offices in Washington, D.C.; Minneapolis, Minn.; San Francisco; and Sacramento, Calif., is submitting comments on the Environmental Protection Agency's registration review assessment for thiabendazole, a fungicide and an antimicrobial chemical. EWG has researched pesticide toxicity since 1993, bringing public attention to the risks of pesticides to children's health.

In this letter, EWG identifies two key areas where the EPA's human health risk assessment for thiabendazole needs to be strengthened. Specifically, EWG finds that in its draft risk assessment, the Agency has disregarded this fungicide's potential cancer risk and failed to fully consider its risks to children. To address these shortcomings, EWG urges the EPA to:

> ***First**, conduct a comprehensive evaluation of thiabendazole's cancer risk using the Key Characteristics of Carcinogens and the Hallmarks of Cancer frameworks; and,*
> ***Second**, include a 10x Food Quality Protection Act safety factor to take into the account data pointing to the greater health risks that children can face from thiabendazole.*

Details and additional information in support of EWG comments and recommendations are listed below.

Section 1. Thiabendazole in the food supply and other exposure sources

Thiabendazole residues are relatively common on fresh fruit. According to the U.S. Department of Agriculture, or USDA, Pesticide Data Program (USDA 2019), 63 percent of apples tested in 2016 had thiabendazole residues on them. In addition, USDA reported that thiabendazole are found in applesauce, grapefruit, oranges, pears, potatoes and sweet potatoes. These tests analyzed produce that had been washed and peeled just as shoppers would do for each type of produce. The USDA results thus reflect the exposure of the general public, and particularly children, to pesticides in the diet.

The EPA registration of thiabendazole also allows the pesticide's uses for seed treatment on a variety of crops; residential uses as an antimicrobial ingredient; and a preservative in household items such as paints, adhesives, caulks, sealants and textiles. These residential

applications, particularly in textiles, may result in incidental oral exposure in settings where children younger than two may mouth thiabendazole-treated textiles.

Section 2. Potential cancer risk associated with exposure to thiabendazole

The EPA last assessed the cancer data of thiabendazole in 1999, and no subsequent new review of thiabendazole's carcinogenicity has been published (EPA 1999; EPA 2019). In the 1999 assessment, the EPA reviewed the results of a two-year study of chronic toxicity and carcinogenicity in rats that were submitted to the EPA by the thiabendazole manufacturer ("the registrant") in 1993. EPA found that "the issue of concern is the occurrence of thyroid follicular cell adenomas in male and female rats" (EPA 1999). EPA concluded that thiabendazole interferes with the thyroid-pituitary homeostasis, an essential process for the overall balance of the endocrine system (EPA 1999). The agency also noted that thiabendazole may increase genomic instability, specifically by its ability to induce aneuploidy, or the altered number of chromosomes following the cell division process (EPA 2019). Similar results have been reported in peer-reviewed scientific studies (Santovito 2011).

In the 2019 draft human health assessment, the EPA summarized its view of thiabendazole carcinogenicity as "likely to be carcinogenic at doses high enough to cause a disturbance of the thyroid hormonal balance" and "not likely to be carcinogenic at doses lower than those which could cause a disturbance of this hormonal balance."

EWG strongly disagrees with the EPA's narrow assessment, which failed to take into the account the past two decades of research on cancer development pathways, expressed in the Hallmarks of Cancer framework (Miller 2017) and the Key Characteristics of Carcinogens framework (Guyton 2018). The contemporary understanding of carcinogenesis extends far beyond the outdated dichotomy between genotoxic and non-genotoxic carcinogens and focuses on how individual chemicals can affect multiple cellular pathways that can trigger or promote cancer growth.

For example, even if a chemical does not damage DNA directly, it may nonetheless alter DNA repair and cause genomic instability, thereby leading to carcinogenic, or cancer-promoting, effects. Further key pathways that may be affected by chemicals associated with cancer include suppression of the immune system, epigenetic alterations, oxidative stress, and other hallmark mechanisms that enable carcinogenesis.

EWG urges the EPA to conduct a comprehensive evaluation of thiabendazole's cancer risk using the Key Characteristics of Carcinogens and the Hallmarks of Cancer frameworks. For a pesticide assessed in 2019, it is not sufficient to quote a 1999 review of a study completed in 1993. Until a comprehensive re-analysis is conducted and

published, the cancer risks of thiabendazole should not be dismissed, and this pesticide should be classified as associated with an elevated cancer risk.

Section 3. Risk assessment for thiabendazole should include a 10x children's safety factor

As we summarized in Section 2, EWG disagrees with the EPA's decision to dismiss the cancer risk of thiabendazole. Moreover, because of thiabendazole's potential harm to the thyroid, it should be classified as an endocrine-disrupting chemical. Both the elevated risk of cancer and harm to the thyroid should initiate the use of a 10x safety factor for thiabendazole, as authorized by the Food Quality Protection Act, or FQPA. As the EPA noted in the dietary assessment for thiabendazole, children between the ages of one and two are the most exposed population subgroup. Young children are highly vulnerable to the effects of endocrine-disrupting chemicals that can affect a variety of body systems and functions, from the reproductive system development to metabolism, neurodevelopment, and cancer risk later in life.

To protect children's health from this pesticide, EWG thus urges the EPA to include the full 10x FQPA factor in the thiabendazole assessment for all routes of exposure.

Submitted on behalf of the Environmental Working Group,

Olga Naidenko, Ph.D.
Vice President, Science Investigations
Environmental Working Group
1436 U St. NW
Suite 100
Washington, DC 20009

References

EPA. 1999. Cancer Assessment Review Committee Meeting on Thiabendazole. Accessed at https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-060101_6-May-99_109.pdf

EPA 2019. Thiabendazole and Salts: Draft Human Health Risk Assessment in Support of Registration Review. March 28, 2019.

Guyton KZ, Rieswijk L, Wang A, Chiu WA, Smith MT. 2018. Key Characteristics Approach to Carcinogenic Hazard Identification. Chem Res Toxicol. 31(12):1290-1292.

Miller MF, Goodson WH, Manjili MH, Kleinstreuer N, Bisson WH, Lowe L. 2017. Low-Dose Mixture Hypothesis of Carcinogenesis Workshop: Scientific Underpinnings and Research Recommendations. Environ Health Perspect. 125(2):163-169.

Santovito A, Cervella P, Delpero M. 2011. In vitro aneugenic effects of the fungicide thiabendazole evaluated in human lymphocytes by the micronucleus assay. Arch Toxicol. 85(6):689-93.

USDA 2019. Pesticide Data Program. Agricultural Marketing Service. http://www.ams.usda.gov/datasets/pdp