September 26, 2019

Environmental Working Group Comments to the Environmental Protection Agency
Docket ID EPA-HQ-OPP-2013-0305
Subject: Imazalil Reregistration Review

Environmental Working Group, or EWG, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, San Francisco and Sacramento, Calif., objects to the Environmental Protection Agency's proposed interim registration decision for the carcinogenic pesticide imazalil. Imazalil is commonly used as a post-harvest fungicide and, according to tests conducted by the Department of Agriculture, is detected on more than 80% of oranges and grapefruit sold in the U.S.

Imazalil targets the liver and thyroid and is a known endocrine disruptor. In 1999, EPA classified imazalil as "likely to be carcinogenic to humans." EPA's proposed decision on imazalil leaves children in America at risk of exposure to harmful levels of this pesticide in foods children eat frequently, such as oranges. This decision should be revised, and strong measures should be taken to protect children from imazalil in the diet.

EWG has researched pesticide toxicity since 1993, bringing public attention to the risks of pesticides to children's health. These comments point out three key aspects of the EPA's proposed decision that should be corrected:

1. EPA should set the maximum allowed imazalil levels, also called tolerances, on the basis of cancer risk of this pesticide.
2. EPA should address the harm that imazalil can pose to children's health due to its endocrine-disrupting properties.
3. EPA should use a full tenfold Food Quality Protection Act children's health safety factor for imazalil risk assessment.

Section 1: EPA should set imazalil tolerances to protect against cancer risk

Upon review of the EPA's proposed interim registration decision for imazalil, EWG concluded that EPA incorrectly used a non-cancer endpoint for defining the safe level of chronic exposure for this pesticide, also called a reference dose. According to EPA's definition, an acceptable reference dose should be "an estimate … of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."[1] For imazalil, EPA

[1] U.S. EPA. Basic Information about the Integrated Risk Information System https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system Accessed September 26, 2019.

developed the chronic dietary reference dose using as the point of departure the concentration of 10.8 mg/kg/day, defined by EPA as the No Observed Adverse Effect Level in a rat study. This departure point corresponds to a chronic reference dose of 0.108 mg/kg/day, which translates to a total allowable amount of 7.56 mg/day for a statistical definition of adult body weight of 70 kg.

In EWG's assessment, the one-in-one-million (10^{-6}) cancer risk benchmark is a more appropriate health benchmark for chronic imazalil exposure. Such a benchmark can be calculated based on the cancer slope factor of 6.1×10^{-2} $(mg/kg/day)^{-1}$ that EPA developed. Based on this slope factor, an intake of no more than 1.15 micrograms per day (μg/day) would correspond to a 10^{-6} risk level. This maximum intake level is more than three orders of magnitude lower than what the EPA's current approach for imazalil allows. EWG urges EPA to use a cancer-based benchmark for setting up allowable tolerance levels for imazalil in food.

Section 2: EPA should address imazalil's harm to the endocrine system

EPA proposed decision incorrectly dismisses the potential harm that imazalil exposure can pose to the endocrine system. Imazalil's effects on the thyroid may impact the neurodevelopment of the fetus and the young child. Further, recent research discovered that imazalil can suppress testosterone and estrogen biosynthesis and act as an androgen-receptor antagonist, and such effects can have life-long adverse health consequences.[2] These health risks due to imazalil are not adequately assessed in the EPA registration decision, a severe flaw that should be remedied.

Section 3: EPA should use a full tenfold children's health safety factor for imazalil

EWG objects to the EPA's decision to discard the Food Quality Protection Act tenfold children's health safety factor for the human health risk assessment of imazalil. Given the

[2] Egbuta C, Lo J, Ghosh D. 2014. Mechanism of inhibition of estrogen biosynthesis by azole fungicides. Endocrinology. 155(12): 4622-8. http://doi.org/10.1210/en.2014-1561; Gaudriault P, Mazaud-Guittot S, Lavoué V, Coiffec I, Lesné L, Dejucq-Rainsford N, Scholze M, Kortenkamp A, Jégou B. 2016. Endocrine Disruption in Human Fetal Testis Explants by Individual and Combined Exposures to Selected Pharmaceuticals, Pesticides, and Environmental Pollutants. Environ Health Perspect. 125(8): 087004. http://doi.org/10.1289/EHP1014; Kugathas S, Audouze K, Ermler S, Orton F, Rosivatz E, Scholze M, Kortenkamp A. 2016. Effects of Common Pesticides on Prostaglandin D2 (PGD2) Inhibition in SC5 Mouse Sertoli Cells, Evidence of Binding at the COX-2 Active Site, and Implications for Endocrine Disruption. Environ Health Perspect. 124(4): 452-9. http://doi.org/10.1289/ehp.1409544; Orton F, Rosivatz E, Scholze M, Kortenkamp A. 2011. Widely used pesticides with previously unknown endocrine activity revealed as in vitro antiandrogens. Environ Health Perspect 119(6): 794–800. http://doi.org/10.1289/ehp.1002895

cancer risk and the endocrine-disrupting potential of imazalil, EPA should apply the full tenfold safety factor for chronic and acute risk assessment of this pesticide.

In conclusion, Environmental Working Group urges EPA to revise the agency's proposed interim registration decision for imazalil, addressing the current proposal's serious shortcomings, and taking strong measures to protect children's health from this highly toxic fungicide.

Submitted on behalf of the Environmental Working Group,

Olga V. Naidenko, Ph.D.
EWG Vice President, Science Investigations