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POLICY BRIEF

CURRENT SCIENTIFIC LITERATURE SUGGESTS THE NEED FOR RE-EVALUATION OF EXISTING REGULATION REGARDING PYRETHROID INSECTICIDES, INCLUDING CYPERMETHRIN

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Pyrethroids are insecticide derivatives from a botanical compound produced by plants in the genus *Chrysanthemum*. Known as pyrethrum, this natural insecticide acts on voltage-sensitive ion channels within a neuron's membrane, where they delay channel closing and thereby overstimulate neurons, resulting in tremors and death in target insects (Shafer et al., 2005). In the pest control industry, pyrethrum derivatives have been chemically modified to increase their resilience to light degradation, allowing them to linger in the environment and continue pest control after application. Additionally, artificial pyrethroids like cypermethrin, allethrin, and permethrin have been altered to increase their toxicity to insect populations.

Though these toxins are advertised for their efficacy in controlling common insect pests, their potential impact on human health should not be ignored. It has been suspected that the pyrethroid cypermethrin may influence offspring neurodevelopment and risk for neuropsychiatric disorders like autism spectrum disorder, attention deficit hyperactivity disorder, and schizophrenia (Shafer et al., 2005). However, most recent interim reregistration of the pyrethroid cypermethrin by the US Environmental Protection Agency (EPA) does not address the pesticide's potential impact on neuropsychiatric risk. This brief literature review aims to summarize and publicize current research on cypermethrin and neurodevelopment, especially as it relates to cumulative risk in marginalized communities. Given the complex nature of neuropsychiatric disorders, and the numerous environmental factors that can contribute to risk for these diseases, future EPA decisions should consider available studies investigating the effects of exposure to pyrethroid insecticides, their impact on neurodevelopment, and the co-occurrence of their use with additional socioeconomic vulnerabilities.

Common Use of Cypermethrin

The chemical cypermethrin is common in domestic settings and is used in a variety of household products, including pest control sprays or foggers, pet collars, and insect repellants (*Reregistration Eligilibity Decision for Cypermethrin*, 2008). From recent data, of the approximate 1.0 million pounds of cypermethrin produced annually in the US, around 860,000 pounds are used in or around the home, with 110,000 pounds distributed for indoor pest control, and 750,000 pounds distributed for lawn and garden care. Usage of products containing cypermethrin concentrates in urban and residential areas (*Reregistration Eligilibity Decision for Cypermethrin*, 2008). Given the high volume of cypermethrin produced and used in the United States, it is the responsibility of the EPA to thoroughly investigate its risk for human health across all populations.

The majority of research cited in EPA registration documents concerns cypermethrin's impact on adult health. In domestic settings, research reflects that cypermethrin contamination resulting from normal household use is below its EPA-determined threshold of human toxicity. In commercial agriculture, there exists some regulation on the usage of ultra-concentrated cypermethrin crop treatments because of their impact on surrounding water and wildlife (*Reregistration Eligilibity Decision for Cypermethrin*, 2008). While regulation on the commercial use of cypermethrin is beneficial, a lack of acknowledgement of the compound's human health impact persists in domestic regulation. Particularly, inadequate consideration is given to pregnant and youth populations to which cypermethrin contamination could pose a risk during development.

Currently, children are exposed to the highest amount of cypermethrin relative to body weight. The EPA's 2021 revised human health risk assessment states that infants and toddlers aged 1-2 years old in residential areas are commonly exposed to 0.00071 milligrams cypermethrin per kilogram of body weight on a daily basis through food and drink (Collantes et al., 2020). This is the highest rate of dietary exposure of any age division in the US and is nearly a three-fold increase from the US average daily exposure of approximately 0.00026 milligrams cypermethrin per kilogram of body weight. The next highly exposed age groups are infants under one year of age at 0.00067 mg cypermethrin/ kg body weight per day and children aged 3-5 years old at approximately 0.00054 mg cypermethrin/ kg body weight per day (Collantes et al., 2020). Each of these highly exposed age groups is undergoing critical neurodevelopment that is essential for later neuropsychiatric health. While data on fetal exposure to cypermethrin during pregnancy is currently unavailable from the EPA, the effects of prenatal exposure to cypermethrin should also be considered, due to the importance of this developmental period.

Current Literature Regarding Cypermethrin and Human Development

Human studies have correlated prenatal pyrethroid exposure with low birth weight and poor infant growth, suggesting that pyrethroids may broadly interfere with fetal and child development. Eric Coker of the University of California—Berkeley and colleagues analyzed statistics from a broad cohort of new births at the Tshilidzini hospital in Thohoyandou, South Africa. Blood was collected voluntarily from women who entered the hospital in labor. Samples were then subjected to analysis for pyre-

throid metabolites *trans*-DCCA and *cis*-DCBA. After birth, children's weight and height were recorded and analyzed until age 2 years. Coker's team associated the high presence of *trans*-DCCA and *cis*-DCBA metabolites with lower BMI-for-age and weight-for-height across both male and female children (Coker et al., 2018). Guodong Ding and colleagues of Shanghai Jiao Tong University School of Medicine measured pyrethroid metabolites in women's urine at delivery and found that total levels were associated with a decrease in their infant's birth weight (Ding et al 2015). This information is disconcerting given the association of low birth weight with other adverse developmental outcomes in many human populations (Sandrine Hanan Aarnoudse-Moens et al., 2009). Additional studies have specifically examined the neurodevelopmental impact of prenatal pyrethroid exposure.

Research has correlated high *in utero* exposure to pyrethroids in general with neurodevelopmental delays based on early childhood patient examinations and developmental index scores. Deborah Watkins from the University of Michigan, Ann Arbor, analyzed urine samples from a variety of pregnant women in regions of Mexico City. These samples were subjected to biochemical assays to determine concentration of the pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA). Relatively high or low 3-PBA urine concentration was correlated to high or low pyrethroid exposure, respectively (Watkins et al., 2016). After birth, children underwent developmental examinations at twenty-four and thirty-six months of age. Cognitive and motor development was scored according to the Bayley Scales for Infant Development—Spanish Version (BSID-IIS). After examinations within this diverse cohort of mothers and children, Watkins and team found that lower cognitive BSID-IIS scores in toddlers correlated to higher levels of the metabolite 3-PBA in their mother's urine, suggesting that prenatal exposure to pyrethroids may produce neurodevelopmental delays in humans (Watkins et al., 2016).

Current neurobiological research in animal models has the capacity to reveal pyrethroids' mechanisms of toxicity during pregnancy and early development. Some studies also address how pyrethroid exposure may have additive effects with other maternal factors that are linked to higher risk for neuropsychiatric disorders in offspring. Benjamin Elser completed his Ph.D. in human toxicology at the University of Iowa under the mentorship of neurobiologist and practicing child psychiatrist Hanna Stevens. Their work has specifically examined the neurobiological repercussions of combined maternal stress and cypermethrin exposure during pregnancy, associating the combination of these two factors with a number of adverse developmental outcomes, including decreased fetal weight in line with the human studies completed by Coker, Ding, and their teams. Additionally, Elser and colleagues' work indicates that combined maternal stress and dietary cypermethrin exposure during pregnancy impairs embryonic brain development, resulting in reduced fetal forebrain volume (Elser et al., 2020). In these studies, maternal stress and cypermethrin exposure delayed the normal movement of neurons during crucial periods of neurodevelopment and induced changes in brain immune cells known as microglia. Perhaps most importantly, Elser and colleagues' work demonstrated that maternal stress increases maternal serum concentrations of cypermethrin (Elser et al., 2020), meaning that the stress experience of a subset of mothers who are also exposed to pyrethroids may put their children at greater risk for adverse developmental outcomes. Based on these data, it seems probable that a pregnant mother may be exposed to concentrations of cypermethrin that would not be harmful to offspring health when isolated from stress factors, but that may be increased to developmentally toxic levels in times of stress.

These studies should be noted by the EPA because they highlight the ways that the same cypermethrin exposure can affect subsets of human populations differently, leading to increased risk for neuropsychiatric disorders in communities that already face health disparities. Considering that environmental contamination already disproportionately targets low-income communities and communities of racial minorities (Gochfield & Burger, 2011), it is not in the best interest of public health for the EPA to continue exclusive use of data that is standardized for the general US population.

Policy Recommendations

Based on the available literature concerning pyrethroids generally and the specific pesticide cypermethrin, it is critical that the EPA take into consideration a few factors moving forward with reregistration in the future:

1. There is substantial peer-reviewed literature available concerning the consequences of maternal and offspring exposure to pyrethroids. A comprehensive analysis of these studies indicates that pyrethroids may lead to adverse neurodevelopmental outcomes.
2. Future policy needs to address the realistic use of pesticides in the home. Given that pyrethroids are broadly used in an uncontrolled domestic setting, product labeling must clearly state the potential risks associated with use.
3. Comprehensive data must be gathered on the exposure of low-income and socially disadvantaged communities to pyrethroids. Cypermethrin has been shown to have different effects on neurodevelopment in the presence of stress, indicating that it may target marginalized communities who are at greater risk for a variety of stress factors. When making future decisions on pyrethroid regulation, the EPA should thoughtfully consider the factors that may position certain communities at greater health risk and respond accordingly.

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