

## Toxicity and Health Hazards of Pyrethroid Pesticides

Zisis Rah, Bayu Rustika\*

Brawijaya University, Jl. Veteran, Ketawanggede, Kec. Lowokwaru, Kota Malang, Jawa Timur 65145, Indonesia

\*: All correspondence should be sent to: Dr. Bayu Rustika

Authors' Contact: Zisis Rah, MSc, E-mail: [zisisrah@gmail.com](mailto:zisisrah@gmail.com); Bayu Rustika, PhD, E-mail: [drbrustika@gmail.com](mailto:drbrustika@gmail.com)

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**Worldwide, pyrethroid pesticides have been widely used in the control of agricultural pests and indoor pesticides, so they have an important impact on human daily life. The acute toxicity studies of pyrethroid pesticides have gotten many achievements and progress, but there is still no clear demonstration of its long-term chronic effects. This review presented the collection of published experiments, population surveys and laboratory tests on the long-term and chronic effects of pyrethroid pesticides. Typical research papers, and screened out the research progress in neurotoxicity, reproductive developmental toxicity, immunotoxicity and tumor research of pyrethroid pesticides. It can provide reference ideas for further research and development of harmless pesticides and pesticides.**

**Keywords:** Pyrethroid Pesticides; Health Hazard; Toxicity; Metabolism; Preventive Maneuvers

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### Introduction

**S**IMILAR to the natural pyrethrins in the genus *Pyrethrum*, pyrethroids are a class of organic chemical compounds that were developed by modifying the structure of natural pyrethrins and were developed in the 1970s (1). It has evolved into a new type of pesticide that has largely replaced organochlorine pesticides. Over 80 pyrethroid pesticide products have been registered, and pyrethroid pesticides have become the second most widely used insecticide pesticide. The photostability of pyrethroid pesticides is greater and they can retain the insecticidal activity of natural pyrethrins (2). The acute toxicity of pyrethroids to mammals is comparatively low (3). Ester pesticides have the advantages of high selectivity, high efficiency, low toxicity, rapid insecticidal, and less residue on crops and various insect pests, and they hold a significant mar-

ket share in contemporary agricultural production (4). The structure and mode of action are comparable to those of pyrethroids. They are toxic substances that disrupt axonal ion channels and impair nerve function (5). According to the presence of cyano groups in their structures, two types of pyrethroids can be categorized. Type I pyrethroid pesticides lack a cyano group in their molecular structure, whereas Type II pyrethroid pesticides contain a cyano group (6). Type II preparations are more stable in the environment (light, atmosphere and water) than Type I preparations. Consequently, preparations of type II pyrethroids, such as cypermethrin, deltamethrin, and fenvalerate are predominantly used as pesticides (7, 8).

However, as the overall use of pyrethroid pesticides has increased, more health issues have begun to emerge. As early as the 1990s, some Americans children were found to be exposed

to pesticides may be at risk for developing health issues. Therefore, the U.S. Environmental Protection Agency considered the cumulative exposure risk of infants and children when determining the maximum detectable level of pesticides in food (9). Acute symptoms of pyrethroid insecticide exposure in humans include dyspnea, cough, bronchospasm, nausea and vomiting, headache, as well as skin allergies (10, 11). Although exposure to pyrethroid pesticides has been linked to an increased risk of cancer, the long-term effects of pyrethroids are unknown, and studies have demonstrated that pyrethroid pesticides are neurotoxins, and neonatal and adult exposure to these pesticides may result in developmental neurotoxicity, reproductive toxicity, and immune toxicity (12-16).

## Neurotoxicity

The fundamental mechanism of action of pyrethroid pesticides involves voltage-sensitive sodium ion channels (17). To comprehend the function of pyrethroid-sensitive voltage-sensitive sodium ion channels in the neural development process, the duration and location of gene expression are helpful in understanding and explaining the developmental effects of exposure to the pesticide (18). In nerve cells, pyrethroids affect calcium, inositol phospholipid systems, and ion channels. Channel toxicity is characterized by low-dose activation and high-dose inhibition; the effect on Ca<sup>2+</sup> channels are also characterized by low-dose activation and high-dose inhibition, but the activation effect is weak, and the inhibition effect is prominent (19). Concerning whether the neurotoxic effects of pyrethroid pesticides are age-dependent, studies have demonstrated that toxicokinetics and non-toxic effect kinetics are significant factors in the differential susceptibility of young and elderly animals to this pesticide (20).

Studies have documented long-lasting behavioral and neurochemical alterations in animals exposed to pyrethroids. Godinho et al. showed that perinatal exposure to selected type I (d-allethrin) and type II (cypermethrin) pyrethroids resulted in physical and sensory-motor changes in weaned pups and persistent behavioral effects during offspring development, indicating that Cyp has a significant capacity to cause neurotoxicity over time (21). Another study found that rats exposed to cyhalothrin exhibited potential hyperactivity to avoid learning (22), whereas rats treated with deltamethrin did not exhibit hyperactivity (23). One study used a biologically based dose-response model to examine the relationship between high hydrochloric acid and developmental neurotoxicity, and they believed that, applied models can enhance the credibility of studies from animals to humans and can test whether the mode of action of a poison in animals is relevant to humans (24). In addition to studies conducted on rodents, pyrethroid pesticides are also neurotoxic to fish demonstrating that zebrafish contaminated with beta-cypermethrin displayed a curved body axis with some developing cyclops and erratic swimming behavior (25, 26). Farag et al. provided a summary of the toxic effects of pyrethroid pesticides on aquatic ecosystems and noted that cold water fish are more sensitive to this insecticide than warm water fish (27). As reviewed that aquatic insects' (both vector and non-vector) vulnerability is influenced by the biochemical and physiological conditions unique to aquatic habitats (28).

Cumulating evidence indicated that women whose children were exposed to pyrethroid pesticides before or during the first trimester of pregnancy were more likely to have children with autism spectrum disorder (29, 30). A case-control study showed that holoprosencephaly risk may be increased by exposure to personal, home, and agricultural pesticides during pregnancy (31). It is therefore plausible that pyrethroid pesticides pose a risk for neurodevelopmental disorders.

Not only are pyrethroid pesticides neurotoxic to animals, resulting in abnormal behavior and motor skills, but they also cause neurological disorders in neonates, making it difficult for adults to live and learn (32). Potential pesticide combination exposure revealed pesticide correlations with behavior disorders examined longitudinally into adolescence and young adulthood (33-35). Thus, it may be proven beyond a reasonable doubt that pyrethroid pesticides cause neurotoxicity since they interfere with brain development from an early age and persist into old age.

## Reproductive and Developmental Toxicity

Reproductive toxicity is associated with chemically hazardous substances that interfere with normal reproductive function. These harmful factors affect the reproductive system of adult men and pregnant women, causing developmental toxicity in themselves and their offspring (36). According to studies, pyrethroid ester pesticides may be endocrine disruptors (37), which can impair the endocrine function of animals and have estrogenic effects on the environment (38). Toxic substances can kill embryos prior to and after implantation, or malformations of various organs (39). The use of pyrethroid pesticides causes DNA damage, leading to an increase in the number of spermatozoa with deformed heads, followed by degeneration and death (40).

Cypermethrin and beta-cypermethrin have estrogenic effects on the environment (41). After entering the bodies of humans and animals, they mimic estrogenic effects or alter androgenic activity. Experiments on animals indicated that cypermethrin and beta-cypermethrin are toxic to male reproduction. For instance, adult male rats treated with varying doses of cypermethrin had reduced sperm counts in their semen or testes and decreased fertility, leading to a reduction in the litter size of female rats (42). Male mice exposed to cypermethrin had a decrease in testicular weight (43). There is a dose-response relationship between abnormal sperm heads and cypermethrin administration in mice (44). In female mice in the cypermethrin gavage test, it was discovered that the chemical can alter the reproductive organs of female mice, increase the weight of the ovary and uterus, and advance the vaginal opening (45, 46).

Pyrethroid pesticides are not only toxic to rodents' reproductive systems, but also to some fish. Beta-cypermethrin pesticides were found to have effects on zebrafish embryos when the gradient concentrations of beta-cypermethrin solutions were used to poison them (47). After pyrethroid pesticides were metabolized in vivo, biomarkers and sperm parameters were also strongly correlated (48).

The urine TCP (sodium 3,5,6-trichloropyridine-2-olate) was detected and found that it was not significantly correlated with sperm concentration and motility (49). However, a growing

body of evidence indicates that pyrethroid exposure in the environment is harmful to the quality of sperm in reproductive-aged men (50-54). Meeker demonstrated a correlation between pyrethroid insecticide urine metabolites [3-phenoxybenzoic acid (3PBA) and cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropyl carboxylic acid (CDCCA and TDCCA)] and decreased sperm DNA integrity (55). It was discovered that there are different concentrations of pyrethroid pesticide residues in the hair of pregnant women and the meconium of the unborn fetus when using the biomarker method to detect pregnant women exposed to pyrethroid pesticides (56).

Even while pyrethroid pesticides have low acute toxicity to mammals, long-term usage will nevertheless impair the reproductive systems of animals and humans to variable degrees, resulting in a loss in fertility, and some may pose a threat to offspring health.

### Immunotoxicity and Tumors

Accordingly, pyrethroid pesticides are immune system-resistant and may cause harm to the lymph nodes and spleen (16). The activation of the immune system by a rise in the number of generating cells and an increase in the activity of natural killer cells (NK) is also related with a decrease in the mass of the thymus and an increase in the mass of the mesenteric lymph nodes (57). Immune system circadian rhythm and cytokines play a role in the relationship between pyrethroid pesticides and tumors at the cellular level (58). Given the close relationship between gap junctions and intercellular communication and cancer (59), and there is evidence that the loss of intercellular communication between gap junctions is a crucial step in the development of cancer because of pyrethroid exposure (60). The chemical characteristics of pyrethroid pesticides disrupt gap junctions in cells (mouse embryonic fibroblast Balb/c3T3), which can result in liver cancer (61) and breast cancer (62).

Nagarjuna and Jacob Doss subjected rats to 41 mg/kg of cypermethrin and conducted toxicological experiments on the immune system at single, double, and repeated doses, and found that rats' duodenum, lungs, and testicles exhibited varying degrees of mild to severe pathological alterations (63). George and Shukla examined the influence of short exposure to deltamethrin on early protein expression alterations associated with neoplastic development in mouse skin, and found that five proteins (calcyclin, superoxide dismutase [Cu-Zn], carbonic anhydrase III, peroxiredoxin-2, and ubiquitin) may be involved in the neoplastic transformation of mouse skin epidermal cells and HaCaT cells by deltamethrin suggesting that the accumulation of ubiquitinated-calcyclin, which regulates deltamethrin-induced neoplastic alterations in skin, is caused by the suppression of proteasome activator protein (64).

Children are vulnerable to harmful environmental factors, including pesticides and pesticides, which increases the risk of childhood tumors (65). Acute lymphoblastic leukemia (ALL) is one of the most common types of childhood cancer (66). In a case-control study, 176 children aged 0 to 14 years with ALL were matched with 180 control children, and the urine metabolites (3-PBA, cis- and trans-DCCA) were analyzed, and 5 non-specific pyrethroid insecticide metabolites were detected in the urine (67), which raised the possibility that pyrethroid pesticide may increase the risk of ALL in children.

Although exposure to pyrethroid pesticide may increase the risk of immune system diseases and tumors, data on human cancer and pyrethroid insecticide exposure are limited as showed by a systematic analysis (68).

### Conclusion

The use of pyrethroid pesticides has become increasingly prevalent and has steadily permeated all aspects of human existence, beginning with agricultural production. How to properly deal with the migration and degradation of pyrethroid pesticides in the environment, as well as their effects on beneficial creatures and human health, is a crucial problem that modern medicine must address.

From the published data, we may infer that the long-term usage of pyrethroid pesticides will have a significant negative impact on human health. These pesticides are capable of entering the human body by direct contact and inhalation. It impairs the function of tissues and organs by acting on various tissues and organs. Children and women of childbearing age are both vulnerable groups; therefore, we must also address the problem of protecting these populations. In addition, evidence has indicated that vitamin E supplementation is advantageous for preventing the negative impact due to the exposure (69, 70), and it is efficacious against pyrethroid-induced endocrine problems and embryonic death (71). However, the aforementioned publications do not adequately demonstrate the development of research methodologies. Current study on human exposure to pyrethroid pesticides has uncovered that using biomarkers is the primary way for determining the relationship between pesticides and health effects. However, because the biomarkers themselves can be influenced by other substances within and outside the human body, it is required to establish a precise description of why pyrethroid pesticides are damaging to human health.

Regarding the safety of pesticide use, the overuse of pesticides should be avoided, pesticides should be used in accordance with the recommended methods to reduce residues, and agricultural producers and vulnerable groups should engage in early preventive measures to ensure environmental safety and human health. ■

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