Toxicity and Health Hazards of Pyrethroid Pesticides

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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 gained 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

Introduction

Similar 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 pyrethroids (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 market 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 Ca2+ 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 humans 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 developmental anomalies (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-dimethyl-cyclopropyl 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 neo-plastic 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 overdose 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.
2. Casida JE. Pyrethrum flowers and pyrethroid insecticides. Environ Health Persp 1980; 34:189-202. JSTOR, DOI: https://doi.org/10.2307/3428960

3. Shen MF, Kumar A, Ding SY, Grocke S. Comparative study on the toxicity of pyrethroids, a-cypermethrin and deltamethrin to Ceriodaphnia dubia. Ecotoxicol Environ Saf 2012; 78:9-13. DOI: https://doi.org/10.1016/j.ecoenv.2011.07.018

4. Chattopadhyay P, Banerjee G, Mukherjee S. Recent trends of modern bacterial insecticides for pest control practice in integrated crop management system. 3 Biotech 2017; 7(1):60. DOI: https://doi.org/10.1007/s13205-017-0717-6

5. Wakeling EN, Neal AP, Atchison WD. Pyrethroids and their effects on ion channels. In: Soundararajan, R., editor. Pesticides - Advances in Chemical and Botanical Pesticides [Internet]. London: IntechOpen; 2012. DOI: https://doi.org/10.5772/50330

6. Soderlund DM. Molecular mechanisms of pyrethroid insecticide neurotoxicity: Recent advances. Arch Toxicol 2012; 86(2):165-181. DOI: https://doi.org/10.1007/s00204-011-0726-x

7. Ramchandra AM, Chacko B, Victor PJ. Pyrethroid poisoning. Indian J Crit Care Med 2019; 23(Suppl 4):S267-S271. DOI: https://doi.org/10.5005/jp-journals-10071-23304

8. Shafer TJ, Meyer DA. Effects of pyrethroids on voltage-sensitive calcium channels: A critical evaluation of strengths, weaknesses, data needs, and relationship to assessment of cumulative neurotoxicity. Toxicol Appl Pharmacol 2004; 196(2):303-318. DOI: https://doi.org/10.1016/j.taap.2003.12.013

9. National Research Council (US) Committee on Pesticides in the Diets of Infants and Children. Pesticides in the Diets of Infants and Children. Washington (DC): National Academies Press (US); 1993. 7, Estimating Exposures. Available at: https://www.ncbi.nlm.nih.gov/books/NBK236273/

10. Bradberry SM, Cage SA, Proudfoot AT, Vale JA. Poisoning due to pyrethroids. Toxicol Rev 2005;24(2):93-106. DOI: https://doi.org/10.2165/00139709-200524020-00003

11. Thundiyil JG, Stober J, Besbelli N, Pronczuk J. Acute pesticide poisoning: A proposed classification tool. Bull World Health Organ 2008; 86(3):205-209. DOI: https://doi.org/10.2471/blt.08.041814

12. Bao W, Liu B, Simonsen DW, Lehmler HJ. Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general us adult population. JAMA Intern Med 2020; 180(3):367-374. DOI: https://doi.org/10.1001/jamainternmed.2019.0619

13. Shafer TJ, Meyer DA, Crofton KM. Developmental neurotoxicity of pyrethroid insecticides: Critical review and future research needs. Environ Health Perspect 2005; 113(2):123-36. DOI: https://doi.org/10.1289/ehp.7254

14. Wang Q, Shen JY, Zhang R, Hong JW, Li Z, Ding Z, Wang HX, Zhang JP, Zhang MR, Xu LC. Effects and mechanisms of pyrethroids on male reproductive system. Toxicology 2020 May 30; 438:152460. DOI: https://doi.org/10.1016/j.tox.2020.152460

15. Zhang X, Zhang T, Ren X, Chen X, Wang S, Qin C. Pyrethroids toxicity to male reproductive system and offspring as a function of oxidative stress induction: Rodent studies. Front Endocrinol (Lausanne) 2021; 12:656106. DOI: https://doi.org/10.3389/fendo.2021.656106

16. Skolarczyk J, Pekar J, Nieradko-Iwanicka B. Immune disorders induced by exposure to pyrethroid insecticides. Postepy Hig Med Dosw (Online) 2017; 71:446-453. DOI: https://doi.org/10.5604/01.3001.0010.3827

17. Silver KS, Du Y, Nomura Y, Oliveira EE, Salgado VL, Zhou BS, Dong K. Voltage-gated sodium channels as insecticide targets. Adv Insect Phys 2014; 46:389-433. DOI: https://doi.org/10.1016/B978-0-12-417010-0.00005-7

18. Pitler EM, Williams MT, Vorhees CV. Effects of pyrethroids on brain development and behavior: Deltamethrin. Neurotoxicol Teratol 2021; 87:106983. DOI: https://doi.org/10.1016/j.ntt.2021.106983

19. Hirano T, Suzuki N, Ikenaka Y, Hoshi N, Tabuchi Y. Neurotoxicity of a pyrethroid pesticide deltamethrin is associated with the imbalance in proteolytic systems caused by mitophagy activation and proteasome inhibition. Toxicol Appl Pharmacol 2021; 430:115723. DOI: https://doi.org/10.1016/j.taap.2021.115723

20. Sheets LP. A consideration of age-dependent differences in susceptibility to organophosphorus and pyrethroid insecticides. Neurotoxicology 2000; 21(1-2):57-63.

21. Godinho AF, Anselmo F, Horta DF. Perinatal exposure to type I and type II pyrethroids provoke persistent behavioral effects during rat offspring development. Med Res Arch 2017; 5(1):1-12.

22. Xi C, Yang Z, Yu Y, Li S, He J, El-Aziz TMA, Zhao F, Cao Z. Influence of perinatal deltamethrin exposure during rat offspring development on motor activity, learning and memory. Ecotoxicol Environ Saf 2022; 236:113460. DOI: https://doi.org/10.1016/j.ecoenv.2022.113460

23. Pitler EM, Sugimoto C, Gudelsky GA, Huff Adams CL, Williams MT, Vorhees CV. Deltamethrin exposure daily from postnatal day 3-20 in Sprague Dawley rats causes long-term cognitive and behavioral deficits. Toxicol Sci 2019; 169(2):511. DOI: https://doi.org/10.1016/j.taap.2021.115723

24. Di Consilvio E, Pistollato F, Mendoza-De Gyves E, Bal-Price A, Testai E. Integrating biokinetics and in vitro studies to evaluate developmental neurotoxicity induced by chlorpyrifos in human iPSC-derived neural stem cells undergoing differentiation towards neuronal and glial cells. Reprod Toxicol 2020; 98:174-188. DOI: https://doi.org/10.1016/j.reprotox.2020.09.010

25. Yang Y, Ma H, Zhou J, Liu J, Liu W. Joint toxicity of permethrin and cypermethrin at sublethal concentrations to the embryo-larval zebrafish. Chemosphere 2014; 96:146-154. DOI: https://doi.org/10.1016/j.chemosphere.2013.10.014
26. Paravani EV, Casco VH. Genotoxicity Induced by Cypermethrin in the Zebrafish Retina. In: Larramendy ML, Solonessi S, editors. Genotoxicity - A Predictable Risk to Our Actual World. London: IntechOpen; 2017. DOI: https://doi.org/10.5727/intechopen.72434

27. Farag MR, Alagawany M, Bilal RM, Gewida AGA, Dhma K, Abdel-Latif HMR, Amer MS, Rivero-Perez N, Zaragoza-Bastida A, Binnaser YS, Batsha GE, Naiel MAE. An overview on the potential hazards of pyrethroid insecticides in fish, with special emphasis on cypermethrin toxicity. Animals (Basel) 2021; 11(7):1880. DOI: https://doi.org/10.3390/ani11071880

28. Antwi FB, Reddy GV. Toxicological effects of pyrethroids on non-target aquatic insects. Environ Toxicol Pharmacol 2015; 40(3):9159-23. DOI: https://doi.org/10.1016/j.etap.2015.09.023

29. von Ehrenstein OS, Ling C, Cui X, Cockburn M, Park AS, Yu F, Wu J, Ritz B. Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: Population based case-control study. BMJ 2019; 364:k962. DOI: https://doi.org/10.1136/bmj.k962. Erratum in: BMJ 2019; 365:j4032.

30. Barkoski JM, Philippat C, Tacredi D, Schmidt RJ, Ozonoff S, Barr DB, Elms W, Bennett DH, Hertz-Picciotto I. In utero pyrethroid pesticide exposure in relation to autism spectrum disorder (ASD) and other neurodevelopmental outcomes at 3 years in the MARBLES longitudinal cohort. Environ Res 2021; 194:110495. DOI: https://doi.org/10.1016/j.envres.2020.110495

31. Addisie YA, Kruzska P, Troia A, Wong ZC, Everson JL, Kozel BA, Lipinski RJ, Malecki KMC, Muenke M. Prenatal exposure to pesticides and risk for holoprosencephaly: A case-control study. Environ Health 2020; 19(1):65. DOI: https://doi.org/10.1186/s12940-020-00611-z

32. Jurewicz J, Hanke W. Prenatal and childhood exposure to pesticides and neurobehavioral development: Review of epidemiological studies. Int J Occup Med Environ Health 2008;21(2):121-132. DOI: https://doi.org/10.2478/v10001-008-0014-z

33. Hyland C, Bradshaw PT, Gunier RB, Mora AM, Kogut K, Deardorff J, Sagiv SK, Bradman A, Eskenazi B. Associations between pesticide mixtures applied near home during pregnancy and early childhood with adolescent behavioral and emotional problems in the CHAMACOS study. Environ Epidemiol 2021; 5(3):e150. DOI: https://doi.org/10.1097/EE9.0000000000000150

34. Hyland C, Bradshaw P, Deardorff J, Gunier RB, Mora AM, Kogut K, Sagiv SK, Bradman A, Eskenazi B. Interactions of agricultural pesticide use near home during pregnancy and adverse childhood experiences on adolescent neurobehavioral development in the CHAMACOS study. Environ Res 2022; 204(Pt A):111908. DOI: https://doi.org/10.1016/j.envres.2021.111908

35. Gunier RB, Deardorff J, Rauch S, Bradshaw PT, Kogut K, Sagiv S, Hyland C, Mora AM, Eskenazi B. Residential proximity to agricultural pesticide use and risk-taking behaviors in young adults from the CHAMACOS study. Environ Res 2022; 215(Pt 2):114356. DOI: https://doi.org/10.1016/j.envres.2022.114356

36. Sutton P, Woodruff TJ, Perron J, Stotland N, Conry JA, Miller MD, Giudice LC. Toxic environmental chemicals: The role of reproductive health professionals in preventing harmful exposures. Am J Obstet Gynecol 2012; 207(3):164-173. DOI: https://doi.org/10.1016/j.ajog.2012.01.034

37. Brander SM, Gabler MK, Fowler NL, Connore RE, Schlenk D. Pyrethroid pesticides as endocrine disruptors: Molecular mechanisms in vertebrates with a focus on fishes. Environ Sci Technol 2016; 50(17):8977-8992. DOI: https://doi.org/10.1021/acs.est.6b02253

38. Marlatt VL, Bayen S, Castaneda-Cortès D, Delbès G, Grigorova P, Langlois VS, Martiniuk CJ, Metcalfe CD, Parent L, Rwigemera A, Thomson P, Van Der Kraa G. Impacts of endocrine disrupting chemicals on reproduction in wildlife and humans. Environ Res 2022; 208:112584. DOI: https://doi.org/10.1016/j.envres.2021.112584

39. National Research Council (US) Safe Drinking Water Committee; Thomas RD, editor. Drinking Water and Health: Volume 6. Washington (DC): National Academies Press (US); 1986. 2. Developmental Effects of Chemical Contaminants. Available at: https://www.ncbi.nlm.nih.gov/books/NBK219111/

40. Bao W, Liu B, Simonsen DW, Lehmler HJ. Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general us adult population. JAMA Intern Med 2020; 180(3):367-374. DOI: https://doi.org/10.1001/jamainternmed.2019.6019

41. Jin M, Li L, Xu C, Wen Y, Zhao M. Estrogenic activities of two synthetic pyrethroids and their metabolites. J Environ Sci (China) 2010; 22(2):290-296. DOI: https://doi.org/10.1016/s1001-0742(09)60107-8

42. Katragadda V, Adem M, Mohammad RA, Sri Bhasyam S, Battini K. Testosterone recuperates deteriorated male fertility in cypermethrin intoxicated rats. Toxicol Res 2020, 37(1):125-134. DOI: https://doi.org/10.1007/s43188-020-00046-1

43. Sharma P, Huq AU, Singh R. Cypermethrin-induced reproductive toxicity in the rat is prevented by resveratrol. J Hum Reprod Sci 2014; 7(2):99-106. DOI: https://doi.org/10.4103/0974-1208.138867

44. Kumar S, Gautam AK, Agarwal KR, Shah BA, Saiyad HN. Demonstration of sperm head shape abnormality and clastogenic potential of cypermethrin. J Environ Biol 2004; 25(2):187-190.

45. Piazza MJ, Urbanetz AA. Environmental toxins and their impact on spermatogenesis in male rodents and other study organisms. J Androl Reprod Toxicol 2019; 17:15557.20190016

46. Rattan S, Zhou C, Chiang C, Mahalingam S, Brehm E, Flaws JA. Exposure to endocrine disruptors during adulthood: Consequences for female fertility. J Endocrinol 2017; 233(3):R109-R129. DOI: https://doi.org/10.1530/JOE-17-0023

47. Shi X, Gu A, Ji G, Li Y, Di J, Jin J, Hu F, Long Y, Xia Y, Lu C, Song L, Wang S, Wang X. Developmental toxicity of cypermethrin in embryo-larval stages of zebrafish.
48. Meeker JD, Barr DB, Hauser R. Pyrethroid insecticide metabolites are associated with serum hormone levels in adult men. Reprod Toxicol 2009; 27(2):155-60. DOI: https://doi.org/10.1016/j.reprotox.2008.12.012

49. Sun J, Bai S, Bai W, Zou F, Zhang L, Su Z, Zhang Q, Ou S, Huang Y. Toxic mechanisms of 3-monochloropropane-1,2-diol on progesterone production in R2C rat Leydig cells. J Agric Food Chem 2013; 61(41):9955-9960. DOI: https://doi.org/10.1021/jf400809r

50. Young HA, Meeker JD, Martenies SE, Figueroa ZI, Barr DB, Perry MJ. Environmental exposure to pyrethroids and sperm sex chromosome disomy: A cross-sectional study. Environ Health 2013; 12:111. DOI: https://doi.org/10.1186/1476-069X-12-111

51. Radwan M, Jurewicz J, Wielgomas B, Sobala W, Piskunowicz M, Radwan P, Hanke W. Semen quality and the level of reproductive hormones after environmental exposure to pyrethroids. J Occup Environ Med 2014; 56(11):1113-1119. DOI: https://doi.org/10.1097/JOM.0000000000000297

52. Jurewicz J, Radwan M, Wielgomas B, Sobala W, Piskunowicz M, Radwan P, Bochenek M, Hanke W. The effect of environmental exposure to pyrethroids and DNA damage in human sperm. Syst Biol Reprod Med 2015; 61(1):37-43. DOI: https://doi.org/10.3109/19396368.2014.981886

53. Radwan M, Jurewicz J, Wielgomas B, Piskunowicz M, Sobala W, Radwan P, Jakubowski L, Hawula W, Hanke W. The association between environmental exposure to pyrethroids and sperm aneuploidy. Chemosphere 2015; 128:42-48. DOI: https://doi.org/10.1016/j.chemosphere.2014.12.077

54. Hu Y, Zhang Y, Vinturache A, Wang Y, Shi R, Chen L, Qin K, Tian Y, Gao Y. Effects of environmental pyrethroids exposure on semen quality in reproductive-age men in Shanghai, China. Chemosphere. 2020; 245:125580. DOI: https://doi.org/10.1016/j.chemosphere.2019.125580

55. Meeker JD, Barr DB, Hauser R. Human semen quality and sperm DNA damage in relation to urinary metabolites of pyrethroid insecticides. Hum Reprod 2008; 23(8):1932-1940. DOI: https://doi.org/10.1093/humrep/den242

56. Fernández-Cruz T, Álvarez-Silvaes E, Domínguez-Vigo P, Simal-Gándara J, Martínez-Carballo E. Prenatal exposure to organic pollutants in northwestern Spain using non-invasive matrices (placenta and meconium). Sci Total Environ 2020; 731:138341. DOI: https://doi.org/10.1016/j.scitotenv.2020.138341

57. Hashemi E, Malarkannan S. Tissue-resident NK cells: Development, maturation, and clinical relevance. Cancers (Basel) 2020; 12(6):1553. DOI: https://doi.org/10.3390/cancers12061553

58. Navarrete-Meneses MDP, Pérez-Vera P. Pyrethroid pesticide exposure and hematological cancer: Epidemiological, biological and molecular evidence. Rev Environ Health 2019; 34(2):197-210. DOI: https://doi.org/10.1515/reveh-2018-0070

59. Trosko JE, Chang CC. Mechanism of up-regulated gap junctional intercellular communication during chemoprevention and chemotherapy of cancer. Mutat Res 2001; 480-481:219-229. DOI: https://doi.org/10.1016/s0027-5107(01)00181-6

60. Rusiecki JA, Patel R, Koutros S, Bean-Breeaman L, Landgren O, Bonner MR, Coble J, Lubin J, Blair A, Hoppin JA, Alavanja MC. Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. Environ Health Perspect 2009; 117(4):581-586. DOI: https://doi.org/10.1289/ehp.11318

61. Tateno C, Ito S, Tanaka M, Yoshitake A. Effects of pyrethroid insecticides on gap junctional intercellular communications in Balb/c3T3 cells by dye-transfer assay. Cell Biol Toxicol 1993; 9(3):215-221. DOI: https://doi.org/10.1007/BF00755600

62. Chetrite G, Delalonde L, Pasqualini JR. Comparative effect of embryonic mouse fibroblasts (Balb/c-3T3) on the proliferation of hormone-dependent (T-47D) and hormone-independent (MDA-MB-231) human breast cancer cell lines. Breast Cancer Res Treat 1993; 25(1):29-35. DOI: https://doi.org/10.1007/BF00662398

63. Nagarjuna A, Jacob Doss P. Acute oral toxicity and histopathological studies of cypermethrin in rats. Indian J Anim Res 2011; 7(1):18-23.

64. George J, Shukla Y. Early changes in proteome levels upon acute deltamethrin exposure in mammalian skin system associated with its neoplastic transformation potential. J Toxicol Sci 2013; 38(4):629-642. DOI: https://doi.org/10.2131/jts.38.629

65. Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect 1998; 106 Suppl 3(Suppl 3):893-908. DOI: https://doi.org/10.1289/ehp.9810693

66. Bhojwani D, Yang JJ, Pui CH. Biology of childhood acute lymphoblastic leukemia. Pediatr Clin North Am 2015; 62(1):47-60. DOI: https://doi.org/10.1016/j.pcl.2014.09.004

67. Ding G, Shi R, Gao Y, Zhang Y, Kamijima M, Sakai K, Wang G, Feng C, Tian Y. Pyrethroid pesticide exposure and risk of childhood acute lymphocytic leukemia in Shanghai. Environ Sci Technol 2012; 46(24):13480-7. DOI: https://doi.org/10.1021/es303362a

68. Boettford P, Desai V. Exposure to permethrin and cancer risk: A systematic review. Crit Rev Toxicol 2018; 48(6):433-442. DOI: https://doi.org/10.1080/10408444.2018.1439449

69. Malley LA, Cagen SZ, Parker CM, Gardiner TH, van Gelder GA, Rose GP. Effect of vitamin E and other amelioratory agents on the fenvalerate-mediated skin sensitation. Toxicol Lett 1985; 29(1):51-58. DOI: https://doi.org/10.1016/0378-4274(85)90199-7

70. Yousef MI. Vitamin E modulates reproductive toxicity of pyrethroid lambda-cyhalothrin in male rabbits. Food Chem Toxicol 2010; 48(5):1152-1159. DOI: https://doi.org/10.1016/j.fct.2010.02.002

71. Galal MK, Khalaf AA, Ogaly HA, Ibrahim MA. Vitamin E attenuates neurotoxicity induced by deltamethrin in rats. BMC Complement Altern Med 2014; 14:458.
