

Genetic and Epigenetic Changes Caused by Pesticide Exposure are Associated with the Development of Chronic Diseases in Humans: A Systematic Literature Review

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Abstract

Inadvertently, pesticides can poison humans or livestock through the mouth, skin and inhalation. Often without realizing it, these toxic chemicals enter a person's body without causing sudden pain and resulting in chronic poisoning. Some people are less efficient at metabolizing environmental chemicals, placing them at higher risk of disease. from parents to children, or occur randomly due to exposure to certain factors. The aim of this research is to examine the genetic and epigenetic changes caused by pesticide exposure that are associated with the development of chronic diseases in humans. This research uses a systematic literature review using Preferred Reporting Items for Systematic Reviews (PRISMA). The research results show that changes in the body can certainly affect health which are related to changes in the way genes work and the Three Basic Classes of Epigenetic Mechanisms Methylation is the process of adding chemical chains to the DNA structure. This cannot be separated from several mechanisms of action of pesticides in attacking humans, which results in the development of several chronic diseases in humans due to exposure to pesticides.

Keywords: Epigenetic, Genetic, Pesticide Exposure, Chronic Diseases.

Acknowledgments: Thanks to all parties who have participated in helping in the process until the completion of this research.

For citation:

Fitria, F., E. (2025). Genetic and Epigenetic Changes Caused by Pesticide Exposure are Associated with the Development of Chronic Diseases in Humans: A Systematic Literature Review. *Radinka Journal of Health Science*, 2(2), 295-304.

Introduction

Currently, the negative impacts of high use of pesticides in the agricultural environment have been felt, namely the emergence of pests and diseases, loss of germplasm, extinction of predators in the ecosystem and resistance to plant pest organisms. Not only that, but pesticide exposure targets enzymes and systems in pests that may be the same as systems or enzymes in humans, thereby posing a risk to human health and the environment. Indiscriminate and widespread use of pesticides causes various health problems. The health impacts caused by pesticides are not static because pests become resistant to newly used pesticides and can cause poisoning (Kalyabina et al., 2021). Disruptions in human body systems trigger cell cycle arrest or cell death resulting in acute or chronic health effects. These effects range from acute allergies to various types of cancer. (Boedeker et al., 2020) Chronic diseases caused by exposure to pesticides usually show slow disease progression but have long-term effects, resulting in increased mortality rates worldwide. The acute impacts are headaches and nausea, while the more serious impacts are inflammatory diseases (arthritis, vasculitis, glomerulonephritis), heart stroke, hemochromatosis, preeclampsia, and even death. The carcinogenicity of pesticides is influenced by various factors such as age, gender, smoking history, diet, education level, individual susceptibility, dose and duration of pesticide exposure, and pesticide absorption pathways (Wise et al., 2022).

Pesticides affect genetic material directly through the stimulation of structural and functional DNA damage, or indirectly disrupt cellular mitochondria, endoplasmic reticulum, and other factors involved in maintaining cell integrity. The majority of cellular components are attacked by ROS causing oxidation and fragmentation of nucleic acids, proteins, and lipids. ROS that escape detoxification cause DNA damage. Damaged DNA causes activation of the enzyme poly (ADP-ribose) which causes the breakdown of NAD⁺, so that NAD⁺ levels can be ignored, causing loss of cell function. DNA damage causes the formation of various modified bases (including thymine glycol, 5,6-dihydroxycytosine, 8-hydroxyguanine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine), sugar breakdown products such as erythrose, 2-deoxypentonic acid lactone, 2-deoxypentose-4-ulose, base free sites, and strand breaks. Free radicals attack sugar and base groups, resulting in oxidative damage to DNA, including changes or loss of nucleic acids (Shadfar et al., 2023). These ROS species are also formed as by-products of normal cellular metabolism as well as during exposure to mutagens such as ionizing radiation, UVA or H₂O₂ radiation and pesticides. Free radicals and ROS are considered the main factors of chronic diseases in humans (Jomova et al., 2023).

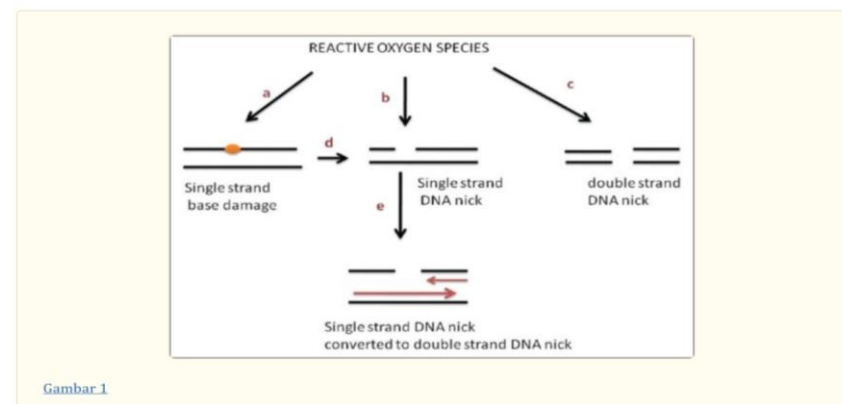


Figure 1. Reactive Oxygen Species (Reactive oxygen species (ROS) can cause various types of DNA damage (ac), single-stranded DNA breaks (ss), as in d. Some of the nicks may

persist during DNA synthesis, and may be converted into double-stranded DNA breaks (ds) (e). ROS attack can also cause direct dsDNA damage (c))

The mechanism of action of pesticides is very interesting. This varies due to differences in the use and distribution of each pesticide. There is a lot of information available regarding biological processes; however, limited data are available regarding the toxicology of pesticides in biological processes. The basic defense mechanism of cells against pesticides is antioxidant agents. These agents have the potential to donate electrons to neutralize free radicals. As discussed previously, organochlorines and organophosphates are the main types of pesticides used in agriculture; Apart from these two, pyrethroids, fungicides and herbicides are also powerful pesticides that cause bad effects. Different pesticides have different ways of working. Over the past two decades, our ability to measure genetic and epigenetic contributions to human behavior has increased several-fold. Although therapeutic manipulation of genetic and epigenetic factors remains largely beyond our reach, by better defining these contributions, we can more precisely delineate the effects of environment and gene–environment interactions-both of which offer malleable points of therapeutic intervention (Schiele et al., 2020). To achieve a better understanding of genetic and epigenetic factors, review human genetic structure and genetic variation, including single nucleotides, simple repeats, and copy number polymorphisms, as well as factors involved in epigenetic regulation, including DNA methylation, histone modifications, and factors involved in epigenetic regulation. and quaternary structure. Genetics and epigenetics can be related to environmental factors of exposure to pesticides.

There has been previous research conducted on pesticides (Lopes-Ferreira et al., 2022); (Hu et al., 2015), but there has been no research that has systematically reviewed the literature on Genetic and Epigenetic Changes Caused by Pesticide Exposure are Associated with the Development of Chronic Diseases in Humans. Based on the background above, the aim of this research is to study Genetic and Epigenetic Changes Caused by Pesticide Exposure are Associated with the Development of Chronic Diseases in Humans

Methodology

We conducted this research as a systematic review by following the PRISMA guidelines. The PRISMA guidelines provide several items that need to be considered in preparing a systematic review. In this study, we will mainly focus on several key items: Epigenetic, Genetic, Pesticide Chronic Diseases. This helps form the basis of our assessment. Initially, we collected the latest studies on genetic and epigenetic changes caused by pesticide exposure are associated with the development of chronic diseases in humans: a systematic literature review, based on a few selected keywords. Then, we apply eligibility criteria to the collection. We only selected literature published in 2015 or later to provide an overview of recent trends. In addition, we limit the types of literature, namely only literature in the form of journals and proceedings.

Results

The information offered is thorough, and impartial, and attempts to combine pertinent study findings. The steps of a systematic review of the literature involve developing research questions, searching the literature, screening and choosing relevant articles, filtering and choosing the best research findings, analyzing, synthesizing qualitative findings, and composing a research report. Writing background and study objectives, gathering research questions, scanning the literature, choosing articles, extracting articles, evaluating the caliber of basic studies, and synthesizing data are all steps in the systematic literature review research process.

Complete articles published in international journals from 2010-2023, indexed in databases, and themed genetic and epigenetic changes caused by pesticide exposure are associated with the development of chronic diseases in humans.

Table 1. Human Genetics

Source	Various health problems are related to changes in the way genes work.
(Benton et al., 2021); (Slavich et al., 2023)	Infection
(Katti et al., 2022); (Zeng et al., 2022)	Cancer
(Symington et al., 2018)	Nutrition during pregnancy

Changes in the body can certainly affect health. That is why researchers study these changes. The following are various health problems related to changes in the way genes work. Infection; Germs can change the way your genes work to weaken your immune system. That way, germs can survive in the body. For example, in *Mycobacterium tuberculosis*. Bacteria; this bacteria causes TB disease. infection with this bacteria causes changes in histones in several immune cells which result in "turning off" the IL-12B gene. Turning off the IL-12B gene will weaken your immune system and increase the survival of *Mycobacterium tuberculosis*. Cancer: Certain mutations make you more likely to get cancer. Likewise, some changes in the way genes work can increase the risk of cancer. For example, you have a mutation in the BRCA1 gene that prevents it from working properly, making you more likely to get breast cancer and other types of cancer. Likewise, increased DNA methylation, which results in decreased BRCA1 gene expression, can increase the risk of breast cancer and other cancers. The presence of cancer cells has increased DNA methylation in certain genes, the overall level of DNA methylation is lower in cancer cells compared to normal cells. Different types of cancer that look the same can have different DNA methylation patterns. Epigenetics can be used to help determine the type of cancer a person has. In addition, learning about this also helps doctors decide whether further cancer screening tests are needed. Nutrition during pregnancy; A pregnant woman's environment and behavior during pregnancy, such as whether she eats healthy foods, can change how the genes in the baby work. Some of these changes can persist for decades and may make children more likely to develop certain diseases.

Table 2. Epigenetics in Humans

Source	Three Basic Classes of Epigenetic Mechanisms
(Samantara et al., 2021); (Wu et al., 2023)	DNA Modification
(Alaskhar Alhamwe et al., 2018); (Handy et al., 2011)	Histone modifications
(Kaikkonen et al., 2011); (Gibney & Nolan, 2010)	Non-coding RNA

Three Basic Classes of Epigenetic Mechanisms Methylation is the process of adding a chain of chemicals to the DNA structure. So, this group is added to a certain location on the DNA, which then blocks the protein from attaching to the DNA so that reading the DNA will be hampered. This chemical group can also be removed through a demethylation process. Usually, methylation will turn off a gene and demethylation will turn on a gene. Histone modifications where DNA wraps around proteins called histones. Histones that are tightly wrapped around DNA are inaccessible to proteins that read genes. Some genes that wrap around histones will be turned off (off condition), and some genes that do not wrap proteins will remain on (on

condition). Chemicals can be added or removed from histones and turn these genes off or on. Non-coding RNA, namely DNA, is used as instructions to make coding and non-coding RNA. This RNA code is later used to make proteins. Non-coding RNA helps control gene expression by attaching to coding RNA, along with certain proteins, to break down the coding RNA so that it cannot be used to make proteins. Non-coding RNA also involves proteins to modify histones so they can activate or deactivate genes.

Table 2. Mechanism of Pesticide Action

Source	How Pesticides Work
(B.K & Dip, 2011); (Matsuzaki et al., 2023)	Pesticides attack the nervous system
(Giménez–Moolhuyzen et al., 2020); (O. Lalah et al., 2022)	Pesticides can inhibit the photosynthesis process
(Wang et al., 2021); (Paul et al., 2023)	Pesticides cause inhibition of cell division
(Benbrook, 2012);	Herbicides such as phenylamide inhibit the incorporation of uridine into RNA synthesis through hydrolysis of nucleotide bases.
(Gonçalves et al., 2021); (A., 2011)	Pesticides produce dangerous macromolecules

There are several mechanisms of action of pesticides in attacking humans: Pesticides can attack the nervous system as a mechanism of toxicity because the central nervous system of insects is similar to that of mammals. It inhibits enzyme action or enzyme production through changes in ion channels. Organophosphates (OPs) are a shining example of pesticide-induced ion channel dysfunction; This interferes with the flow of acetylcholine. OP inhibits the hydrolysis of acetylcholinesterase (ACHE), an enzyme that regulates neurotransmitters, thereby affecting the nervous system. OP forms a covalent bond with ACHE through phosphorylation of the serine hydroxyl group of ACHE; resulting in inactivation of ACHE and accumulation of acetylcholine in the nervous system. Acetylcholine accumulation affects receptors in the nervous system through excessive stimulation of muscarinic and nicotinic receptors. Excessive stimulation of these muscarinic and nicotinic receptors causes tachycardia, sinus bradycardia, hypertension, hypotension, heart rate variations, and heart muscle contractions, as well as cyanosis and increased serum levels of creatinine and lactate dehydrogenase.

Pesticides can inhibit the photosynthesis process. Herbicides, a type of pesticide, bind to protein (QA) D1 and inhibit electron transport by acting as an irreducible analogue of plastoquinone and inhibiting PQH 2. Paraquat, a common herbicide is known to interfere with photosynthesis through the formation of O₂ free radicals. Free radicals disrupt the electron gradient system, thereby affecting the transport of electrons to the final molecule and inhibiting the energy generation process. Pesticides cause inhibition of cell division by affecting the tubulin and microtubules that separate chromosomes during division. Herbicides such as phenylamide inhibit the incorporation of uridine into RNA synthesis through hydrolysis of nucleotide bases. The three types of RNA polymerase I, II, and III polymerase have different sensitivities to the toxic effects of these pesticides. RNA polymerase II is very sensitive to α -amanitin and organochlorines, whereas RNA polymerase I is less sensitive. However, RNA polymerase III was not affected by α -amanitin. Inhibition of RNA synthesis results in disruption of protein synthesis thereby affecting enzymatic function. In addition to the production of harmful macromolecules, pesticides affect molecular and biochemical processes, where the activity of DNA repair enzymes is inhibited and ultimately reduces DNA repair capacity. Much evidence provides scientists with the mechanisms of pesticides and disease development. All of the mechanisms above are thought to work synergistically and not individually.

Table 3. Pesticide Exposure is Associated with the Development of Chronic Diseases in Humans.

Source	Several Developments of Chronic Diseases in Humans Due to Exposure to Pesticides
(Mostafalou & Abdollahi, 2013); (Pedroso et al., 2022)	Carcinogenesis
(Gangemi et al., 2016); (Zeinali et al., 2022)	Immunotoxicity
(Dinca et al., 2023); (Davies et al., 2000)	Dcardiovascular
(Mrema et al., 2017); (Ghosh et al., 2022)	Reproductive Disorders

Pesticides via ROS play an important role in cancer prognosis. A number of investigations have proposed the participation of free radicals in mutation, transformation and carcinogenesis. Free radicals attack the double bonds of pyrimidine bases, abstracting hydrogen from sugars, resulting in cellular mutagenesis. Farmers who are exposed to pesticides are at risk of developing certain cancers, including leukemia, non-Hodgkin's lymphoma, soft tissue sarcoma, multiple myeloma, stomach and prostate malignancies, colorectal, endocrine gland, and brain cancer. Pesticide formulations can imitate hormones, causing hormonal disorders; pesticides mimic the female hormone estrogen which can block male hormones thereby causing

hormone-related cancers such as breast and testicular cancer. Based on evidence presented by many scientists, pesticide exposure is associated with lympho-hematopoietic cancer by alachlor, colorectal cancer by aldicarb, and breast cancer by chlorpyrifos. Carcinogenicity tests need to be applied to detect the carcinogenic effects of pesticides on men and women.

Pesticides are potential immunotoxic agents. They affect the immune system in two ways, either by decreasing or increasing the immune response. Immunocompetence, namely a decrease in the immune system's capacity to neutralize foreign particles can cause serious infections and increase the risk of cancer, while immune enhancement, namely an increase in the expression of the immune response can result in hypersensitivity, autoimmune diseases such as rheumatoid arthritis and autoimmune thyroid disease. The response of immune factors to exposure to various types of pesticides varies; for example, exposure to chlorpyrifos showed increased atopy and antibiotic sensitivity, while decreased CD5 cell proliferation in response to mitogens. Similarly, exposure to chlorodan increases hypersensitivity, allergic rhinitis, sinusitis, bronchitis, while decreasing CD45RA/T4 cell proliferation in response to mitogens, leading to various disease conditions. Pesticides play a role in lipid peroxidation which causes heart-related diseases. Polyunsaturated fatty acids are the main part of lipoproteins in the blood. Oxidation of these lipid components through lipid peroxidation via free radicals produced by pesticides plays an important role in atherosclerosis. Lipid peroxidation is a free radical process involving a source of free radicals that can act as second messengers or can directly react with other biomolecules. causes biochemical damage. Chronic exposure to pesticides is associated with an increased risk of coronary artery disease (CAD).

Pesticides can cause reproductive effects (infertility, malfunction) and developmental problems. Many pesticides such as DDT, chlorpyrifos, lindane, malathion, and aldicarb are known to cause reproductive disorders, with long-term effects. Pesticides disrupt the endocrine system causing changes in the secretion, binding, transportation and action of endocrine hormones, thereby causing side effects. Biological differences between male and female hormones are responsible for differences in susceptibility to the toxic effects of pesticides. Research has found a positive association between pesticide exposure and miscarriage (chlorophenoxy, sulfonyl ureas, and Dicamba), infertility (1,2-dibromo-3-chloropropane and DBCP), decreased sperm count/motility/count (DBCP), premature birth (atrazine and acid 4-(2,4-dichlorophenoxy) butyrate), stillbirth (carbamate), and defective spermatogenesis (carbaryl). Birth defects are functional and structural abnormalities that occur at birth or before birth, causing physical and mental disorders. Chemicals that cause birth defects are known as teratogens. Pesticides such as DDT and phenoxyherbicides are teratogens that can increase the incidence of congenital abnormalities. Exposure to pesticides by parents can also cause developmental toxicity in children such as increased risk of limb abnormalities, orofacial gaps/birthmarks (trifluralin, 2,4-D), premature birth, low birth weight, and learning difficulties in children.

Pesticides such as organophosphates, cyclodiene, pyrethrins, and organochlorines are known to attack the nervous system. The central and peripheral nervous systems are affected by pesticide exposure resulting in many chronic diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS). Many studies have found a high incidence of these diseases in workers exposed to pesticides. Pesticides affect the transmission of nerve signals by changing the function of ion channels. An increase in the influx of sodium ions or a decrease in the outflow of chloride ions causes depolarization of the nerve membrane, causing neuronal hyperexcitability. About Other Disorders: Worker exposure to pesticides has been linked to diabetes, chronic respiratory disease, chronic nephropathy, autoimmune disease, hyperglycemia/diabetes, and many other disorders. It is important to carry out biomonitoring in populations exposed to pesticides because pesticides cause serious health hazards.

Conclusion

Gene expression refers to the event that a protein is formed as a result of the instructions of a gene in a person's body. In contrast to genetic changes in general, epigenetic changes influence gene expression to "activate" and "deactivate" genes easily due to the environment and daily behavior, such as healthy lifestyle habits, smoking, exposure to pesticides and other external factors. You have to be careful about this because it can cause disease in humans. The government in public health agencies must continue to make efforts to prevent exposure to pesticides by providing outreach and providing tools to minimize the entry of dangerous substances caused by exposure to pesticides.

Conflicts of Interest

No conflicts of interest.

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