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Article

Health Risks of Pesticides and Their Impact on the Immune System: A Review Article

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Abstract: In the last few decades, the demand for essential crops and vegetables has increased due to the increase in population worldwide. Thus, it was so important to produce and develop unlimited types of required pesticides and insecticides within the previous generation of these chemically manufactured products, as these substances eradicate undesirable insects, weeds, and fungi. Concerning the harmful effects of pesticides on human health is currently present in many nations. The harmful effects of the utilized pesticide on the health of individuals in different nations became a source of concern. that pesticides are intimately linked to immunological disorders and can cause cancer, respiratory illnesses, organ diseases, system failures, nervous system abnormalities, and asthma. The immunotoxicity of pesticides and insecticides that are either in use or forbidden, particularly their impact on leukocytes like macrophages, T cells, and B cells. To defend hosts, these immune cells are essential components of both the innate and adaptive immune systems.

Keywords: Pesticides, Toxicity, Immunological disorders, Populations

Introduction

The increment of food chain manufacturing to handle the rise in population and nutritional hunger is one of the major challenges in the world, using both wise and sustainable practices to address the related issues [1]. Applying pesticides is a double-edged sword when it is used in modern agriculture, as pesticides are chemically manufactured products utilized in minimizing and getting rid of pests and their populations, which are any plants, animals, or microorganisms that affect food, health, or comfort, as the Environmental Protection Agency (EPA) defines pesticide products [2-3]. Various types of pesticides are available for local and global use, such as pyrethroids, chlorophenyls, triazines, carbamates (CBs), organochlorines (OCs), organophosphates (OPs), and phthalimides, as these pesticides and their particles are readily found in the environment [4]. Exposure to pesticides could alter fundamental and/or minor functions in the mammal's immune system; among these effects, it can lead to severe disturbances, as previous studies show [5]. Pesticides are capable of causing severe

effects on the health of human beings (Figure 1), as the United States Environmental Protection Agency (USEPA) has noted, such as these effects are disorders of the immune and endocrine systems, inflammation, cancers, and metabolic issues [6].

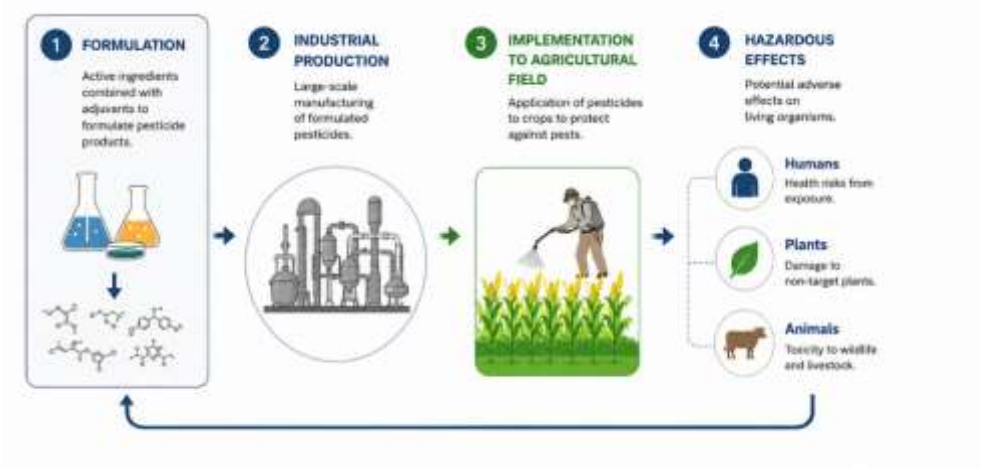

Figure 1. The diagram represents the workflow of the impact of pesticides on living beings.

Mammals immune system (especially in humans) can be classified into several branches, the first one is described as the innate system (non-specific for antigen), and the second one is the adaptive system (specific for antigen), including cell-mediated immunity and humoral immunity, as the elements of the Immune system are a unique diversity of cells that are divided into specialized cells, such as neutrophils, eosinophils, basophils, lymphocytes, and monocytes [7].

Allergies, such as rhinitis and asthma, can be highly induced by the use of chemical pesticides, as that leads to autoimmune diseases being triggered [8]. Direct contact with pesticides used in agricultural areas promotes health problems in the populations, especially with diseases of the respiratory tract, which were reported [9].

The mode of action of pesticides is not species-specific, by other means, they often cause elimination or harmful effects on organisms, including pests, insects, and weeds. The World Health Organization (WHO) and indicated by their research that pesticide exposure has caused serious diseases, with approximately 200,000 casualties and poisoning cases for a population of three million globally [10].

Modifications to immune system functions by pesticides, such as pesticide-induced immunotoxicity in immune cells, are linked to the disruption of immune cells' capacity for survival, proliferation, and differentiation [11]. Numerous mechanisms, including oxidative damage, mitochondrial dysfunction, endoplasmic reticulum stress (ER stress), alterations of the ubiquitin-proteasome system (UPS), and autophagy, have been documented as contributing to pesticide-induced impairment of the immune system. [12]. The immunotoxicity caused by Malathion (organophosphate pesticide), this type of pesticide has been widely used worldwide since it has harmful effects on the population's health, especially on the immune system functions, as it is hard to get rid of its concentrated chemical formula and its environmental effects [13]. The immunological response can be badly affected by the dose levels, time, and routes of exposure to the applied pesticide; it's extremely hard to get rid of the effects caused by chemical elements on the functional role of the immune system [14], pesticides, like Lambda-cyhalothrin (LCT), had harmful cellular effects, severe toxicity, and its shows signs of inflammatory action by interfering with the tissue membranes [15].

Mechanisms of Immunotoxicity Caused by Pesticides.

Direct Toxicity to Immune Cells.

Pesticides play an important role in modulating immune responses by altering the pathways and activities of immune cells, which act as a defensive barrier against potential illness, a phenomenon recognized as direct immunotoxicity [16].

Direct immunotoxicity can be altered by the activation or inhibition of the immune system workflow, glyphosate, for example is a typical pesticide (N (phosphonomethyl) glycine), is known to have systemic broad-spectrum uses; it's related to the family of organophosphate compounds [17], it can be metabolite in the environment by microbes and natural resistant plant by three methods like aminomethylphosphonic acid, glyoxylate, and methylphosphonic acid, these methods are recognized to have the ability to react with nucleophilic amino acids on the proteins level as it shows highly difficulty to detect [18]. Since the overuse of pesticide, it's easily found on agricultural products, water supplies, cattle, and poultry; thus, the risk of farm workers exposed to the chemical components of this pesticide was accumulated [19]. Oral, body dermal, and respiratory tract are considered the main routes of glyphosate absorption, although the minimal effect of adsorption through the skin remains the main route for workers to get exposed to the mentioned pesticide [20].

Neutrophils are one of the cell types of leukocytes; they are considered the first spot line of defense against any foreign matter, by chemotaxis signals, they are attracted to the site of infection to trigger the phagocytosis mechanisms, which are considered the main function of neutrophils [21]. Energy uptake by neutrophils is done by a process called glycolysis, which provides the continuity of its specific functions; thus, any changes in this pathway lead to alterations in the function of neutrophils, such as alterations that could be taken please by azurophilic releasing, neutrophil migration, and neutrophil cellular trap suppression [22].

Glyphosate and its related metabolites (AMPA, MPA) have been found to have a direct effect on the neutrophil's functions via the impact on the glycolysis pathway, such as the chemokine CXCL8/IL-8 and the formation of ROS (Reactive oxygen species), such an effect that may cause weakness in the response of neutrophils and overall impairment of functions [23].

Oxidative stress by ROS generation.

An unlimited number of pesticides have been shown to have a comparable effect, in which they promote the induction of a condition called oxidative stress in almost all cell types by reactive oxygen species [24]. The reactive oxygen species (ROS) refer to various substances that are often manufactured within the body, specifically with various substances such as cytokines and toxins, and stressors such as heat and disease, pesticides metabolites are the key entrance for the production of these ROS, as they have the capability of inducing oxidative homeostasis disruptions caused by aberrant redox states and antioxidant depletion [25]. Ros gains the ability to minimize the antioxidant grade and macerate the body's protection against oxidative harm to cells; thus, it has obviously high exposure to pesticides, is led to a significant imbalance, and causes an increase in the production of ROS and oxidative stress. For that reason, the cellular system will be unable to get rid of the defect [26].

The pesticide Cypermethrin is a pyrethroid chemical product with a wide range of uses in agricultural approaches, showing specific action towards insecticides, as it is a carcinogenic element for humans, and promotes high levels of ROS, which cause DNA deterioration and mitochondrial function damage [27]. The interaction with Cypermethrin finally resulted in impairment of both cellular structure and function by activating mitogen-activated protein kinase (MAPK) signaling pathways, leading to cell death [28].

Dysregulation of Cytokine.

Cytokines control the immune communications key, since cytokines have an effective role in the control, function, and recruitment of immune cells to respond to infections in site [29].

Under normal circumstances, cytokines maintain the host defense system organized and preserve the homeostasis of body tissues; nevertheless, any defect in cytokine response, and/or impairment in secretion levels may promote the initial signal of causing inflammation, followed by diseases [30].

Studies on various pesticides such as pyrethroids, organochlorines, and organophosphates were connected to immunotoxicity via methods that included harmful damage to the activities of different kinds of cytokines, in which these pesticide exposures will definitely lead to decrease lymphocytes numbers and induce the activities of allergic outcomes [31]. Both methyl parathion and chlorpyrifos were found to induce the production of inflammatory cytokines, including tumor necrosis factor alpha, interleukin-6, and interleukin -1 beta in human hepatocellular carcinoma (HepG2) [32].

Proinflammatory cytokines (TNF-α, IL-1β, and IL-6) and NADPH oxidase were induced in rats treated with dichlorvos, another organophosphate pesticide, over an extended period of time [33].

A study by Volker, et al., found that blood samples from farmers who were exposed to pesticides suffered from cellular deactivation, especially with interferon gamma (IFN-γ) and interleukin-2 (IL-2), while interleukin-4 (IL-4) was induced as a result of triggered inflammation [34].

Exposure to the following pesticides, atrazine and carbamates confirmed to have an impact on the immunological activity of the natural killer cells (NK), since these cells have a critical role in regulating immune responses by producing cytokines like IFN- γ, TNF- α , and defending against foreign invaders [35].

Hapten formation.

Haptens are chemical compounds with low molecular weight that lack the antigenicity properties and play a significant role as an immunogen inducer only in the case of binding to massive molecules [36]. Haptens and proteins can be conjugated to each other with the assistance of haptens' own carboxylic or amino groups, as an alternative path for haptens, carboxylic acid can be included for the same purpose as a reactive group [37].

Since pesticides have low molecular weight, they gain the ability to infiltrate the bodies of living beings into all cells and tissues, causing immunotoxicity to both the innate and adaptive systems [38]. Haptens react with pesticides in the manner of a foreign invader to the body, which can cause inflammatory action or allergy developing into a chronic or acute condition, since their role can be summarized into binding to toxic chemical components and inducing the immune response via the innate immune system [39]. The process of haptenation is described as two molecules binding to each other, one of which is (electrophilic) that binds to the side chain of an amino acid (nucleophilic), once this condition is met, the hapten molecule will be noticeable to the immune system, leading to the activation of a robust immune response [40].

Result

Pesticides and Autoimmune Diseases

Since environmental and genetic factors have a direct impact on the mechanisms by which genes function, autoimmune illnesses are thought to be multifactorial disorders that arise from these interactions [41]. Several studies have examined the potential significance of pesticides as risk factors for autoimmune illnesses, despite reports that a number of them, such as pentachlorophenol, chlordane, chlorpyrifos, and hexachlorobenzene, raise autoantibodies [42]. The physiological factors associated with the exposure to pesticides shows direct effect on the individual health and its immunity via affecting including the person genetics stability among with nutritional habits, pathological factors such as infectious diseases and enzymatic defects factors that can readily compromise the immune system activities, which is a labile system, many immunologically based systemic disorders, including autoimmune disorders rheumatological diseases, chronic inflammatory, metabolic syndrome, and neurodegenerative diseases [43].

There is mounting evidence that environmental variables play a part in the development of autoimmune diseases like systemic lupus erythematosus (SLE), a chronic condition that in some cases leads to death if not treated well [44]. Research has indicated links between SLE and pesticide exposure since the immune system components gain the ability to cause self-antigen targeting, leading to impairment in joints, kidney illness, and skin [45]. A positive result related to a study of farmworkers shows that high exposure to pesticides triggers the risk of SLE infection, indicated by the increase in antinuclear antibody (ANA), and the expansion of ANA after exposure to specific types of pesticides for a long period leads to the illness with SLE, especially with the risk of insignificant use of chemical synthesis compounds [46].

Rheumatoid arthritis (RA) is a type of autoimmune disease that affects populations worldwide, pesticide considered one of the causative agents of promoting RA; several studies mention that direct contact with pesticides, especially insecticides like guanidine and fonofos, contributes to the risk factors of RA [47]. The indication of autoimmune disease, especially with RA, can be detected with the presence of interleukin 6 (IL-6), a cytokine parameter that has an important role in immunity, acts as an anti-

inflammatory mediator, and its rise to high levels occurs in the case of exposure to pesticides, rather than not, also found to increase the release of IL-12, supporting the elevation of IL-6 [48].

Discussion

Populations prone to harmful pesticides.

Farm Workers

The high pesticide exposure timeline shows severe health outcomes. workers in the agriculture filed are considered worthwhile populations, according to their contribution to social and cultural elements, as well as exposure to hazardous product risks in farm work [49]. Since agricultural gain an important role in the food chain worldwide, it was obvious that keeping security levels in control away from the risk of damaging a variety of crops, the awareness of avoiding being affected by pesticides is required, especially when using personal protective equipment [50].

Agricultural farmers who exposed to pesticides have been linked to certain cancers, DNA damage, oxidative stress, neurological disorders, as well as respiratory, metabolic, and thyroid effects [51]. Conditions such as depression and poisoning signs were detected when farm workers were integrated with pesticides, since these harmful factors affect personal physiology, cognitive abilities, and mentality if not treated in the right time with suitable practices [52]. Chronic and/or acute toxicity symptoms appear after exposure to pesticides, depending on the route of pesticide application and period, symptoms can be determined when exposed to the same pesticide at different times, in which case [53]. Chronic conditions could lead to illnesses such as cancer and neurological disorders, while acute symptoms can be summarized in diarrhea, vomiting, and breathing issues [54].

Pregnant Women

Pregnant women are particularly vulnerable to the possible risks of pesticide exposure, both for the fetus and for themselves. The theory is supported by several studies conducted on expectant mothers [55].

For centuries, the potentially harmful effects of pesticides have been recorded, especially to pregnant women, since these effects lead to severe conditions for both the mother and her baby, such as condition the once who cause congenital malformation as a result of the synthetic chemical compounds of pesticides [56]. Studies took place in different countries with similar outcomes admit that urine samples from pregnant women in Bangladesh contain high levels of pesticides, which are associated with the defect of newborns low in weight, increased rates of premature birth, and reduced length relative to gestational age. Conversely, the result of urine samples from pregnant women located in Indiana, a US city, shows a high rate of the pesticide glyphosate [57-58].

In China, a practical study of 615 pregnant women indicated that for one year after, levels of pesticides like organophosphate and pyrethroids were connected for high rate of infertility cases among these pregnant women [59]. A scientific study focusing on the Current in-Use Pesticide (CUPs), especially with pregnant women, 345 women in the pre-pregnancy stage were included in the study, in Beijing, China. It found that the blood tests of these women were contaminated with a high concentration of pesticides, including organophosphate compounds, at higher levels of contamination [60].

Conclusion

Pesticides play a critical role in agricultural approaches since they have a direct influence on increasing crop yield and eliminating different types of pests and grasses. Pyrethroids and organophosphates are the most abundant groups of pesticides and have diverse and complex chemical structures, which are considered highly harmful to living beings and the environment. Pesticide exposure by the farming and consumer community is highly dangerous, since the ability of these synthetic chemical compounds to induce immunotoxicity, modifications on the basis of genetics material, autoimmune disorders, and congenital abnormalities in newborns. The mechanisms of immunotoxicity caused by pesticides have a great impact on alteration and modification of the cellular system. the immunotoxicity of pesticides effect is indicated to be target specific types of immune cells.

A comprehensive investigation into these mechanisms will provide a better understanding and enable the development of practical strategies to mitigate the harmful effects induced by pesticides.

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