ISSN 2664-4169 (Print) & ISSN 2664-7923 (Online)
South Asian Research Journal of Biology and Applied Biosciences
Abbreviated Key Title: South Asian Res J Bio Appl Biosci

| Volume-6 | Issue-2 | Mar-Apr -2024 | **DOI: 10.36346/sarjbab.2024.v06i02.002**

Review Article

The Effect of Pesticides on Public Health: A Review

Zaid Naji Hassan[1], Rasha Sattam Hameed[1], Maan Abdul Azeez Shafeeq[1*]

[1]Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq

***Corresponding Author:** Maan Abdul Azeez Shafeeq
Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq

Article History
Received: 11.02.2024
Accepted: 23.03.2024
Published: 01.04.2024

Abstract: Due to the widespread use of pesticides in agriculture and other contexts, human exposure to them persists. Despite premarket animal testing, epidemiologic studies show that current exposures are linked to dangers to the well-being of people. Within this analysis, we outline the current pathways for pesticide exposure and provide an overview and assessment of the epidemiologic research on adult neurotoxicity and carcinogenicity associated with pesticides. Assessing the hazards that pesticides bring to human health will be improved by a deeper comprehension of exposure patterns, the underlying diversity among people, and the connections between animals' toxicological data and their effects on human health. Public health policymakers will be able to evaluate the risks of exposure to pesticides to human health more precisely if epidemiological studies are improved and combined with toxicology data.

Keywords: Pesticides, Public Health, Cancer, Organochlorine, Organophosphate, Carbamates.

INTRODUCTION

To feed the growing population and combat vector-borne diseases, pesticides are essential. They also provide cotton fiber, tobacco, and food. Unfortunately, most pesticides that are used wind up in the environment and harm the health of unprotected industrial and agricultural workers. Skin, lung, and gut contamination are the three main entry points for pesticides [1].

Both acute and chronic severe health consequences, which can happen months or years after exposure, can be brought on by pesticides. According to [2], examples of long-term health impacts include malignancies, birth deformities, neurological damage, endocrine system disturbance, stinging eyes, rashes, blisters, blindness, nausea, dizziness, and diarrhea.

A substantial amount of epidemiology data links pesticide exposure to cancer, with a focus on child cancer that results from direct exposures to nonage and patriarchal influences. Leukemia and brain cancer exhibits are very strong. Still, there are also exhibits of neuroblastoma, affiliation with non-Hodgkin lymphoma, Wilm's tumor (kidney), and Ewing's sarcoma (a disease of the bone tissue). In addition to malignancies of the breast, lung, multiple myeloma, non-Hodgkin lymphoma, leukemia, ovary, pancreatic, prostate, renal bladder, stomach, colon, rectal, lip, connective tissue, brain, and testicles, multiple adult malignancies have been connected to pesticide exposure [3].

According to [4], epidemiological studies have linked many cancer types to the primary functional groups of pesticides, herbicides, insecticides, fungicides, fumigants, and chemical groups such as carbamate, organochlorine, and organophosphate insecticides.

Additionally, numerous researchers have noted a connection between pesticide use and human sterility, attributing this to the free radicals that pesticides produce, which cause oxidative stress and consequent reproductive disorders like follicular atresia, impaired folliculogenesis, defects in the estrous cycle, and other birth defects in women [5]. Additionally,

pesticides have cytotoxic effects on sperm by decreasing men's ability to fertilize sperm and their motility, directly affecting the organism's reproductive physiology and fertility [6].

1- PESTICIDES AND CANCER

1-1- Mechanism of Cancer-Inducing by Pesticides

Cancer is a diverse collection of diseases that may originate in various organs or tissues of the body due to the uncontrolled growth of abnormal cells. It is the second highest cause of mortality accounting for almost 9.6 million deaths globally in 2018, which accounted for each of every six fatalities. Men are more likely to develop lung, prostate, colorectal, stomach, and liver cancers than women are to develop breast, colorectal, lung, cervical, and thyroid cancers [7].

Reactive oxygen species (ROS) produced by pesticides are thought to play a major role in the initiation and spread of cancer. Free radicals may have a role in mutations, cellular alterations, and the development of malignant tumors, according to many studies [8].

Farmers exposed to pesticides are more likely to have some cancers because the double bond of the pyrimidine base is attacked by free radicals, which causes cellular alterations. According to [9], these cancers include brain cancer, colon cancer, stomach and prostate cancers, non-Hodgkin's lymphoma, soft tissue sarcoma, multiple myeloma, and leukemia.

Hormone abnormalities can result from pesticide compositions that mimic hormones. According to [10], pesticides can imitate the female hormone estrogen, which may interfere with male hormones and raise the risk of hormone-related cancers such as testicular and breast cancers.

Alachlor is linked to lympho-hematopoietic cancer, aldicarb is linked to colorectal cancer, and chlorpyrifos is linked to breast cancer, per the research of multiple scientists [11].

1-2- Carcinogenicity of Organochlorine (OC)

Organochlorine (OC) pesticides are synthetic compounds widely employed in agriculture and the chemical industry. They belong to a class of compounds termed derivatives of chlorinated hydrocarbons.

These compounds have a reputation for being very dangerous, bioaccumulating, and decomposing slowly. Although many of the chemicals that comprise OC were banned in developed countries, the use of these agents has increased [12].

1-2-1- Carcinogenicity of Lindane, DDT, and 2, 4-Dichloro Phenoxy Acetic Acid

Several studies conducted in various countries have provided strong evidence in humans for the carcinogenicity of lindane, particularly in non-Hodgkin lymphoma. For example, the US Agricultural Health Study, which included a large prospective cohort and a thorough exposure assessment, discovered that occupational exposure to lindane at higher levels was significantly associated with an increased risk of non-Hodgkin lymphoma. Comparably, lindane exposure was consistently associated with a lower incidence of non-Hodgkin lymphoma in population-based case-control studies conducted in the mid-western USA and Canada [13].

In more than 100 cohort and case-control studies from various nations, associations between DDT exposure and cancer have been examined. In China, nested and population-based case-control studies found significant, dose-related associations between blood DDT levels and liver cancer after adjusting for potential confounders [14].

Positive correlations were found in several cohort and case-control studies conducted in North America and Europe regarding non-Hodgkin lymphoma [15].

DDT or DDE was found to have a positive correlation with testicular cancer in several case-control studies conducted in the USA and Europe [16].

1-3- Carbaryl Carcinogenicity

Originally licensed for use on cotton by the US Environmental Protection Agency (EPA) in 1959, the carbamate insecticide Carbaryl (1-naphthyl methylcarbamate), also marketed as Sevin, is a broad-spectrum pesticide [17].

A carbamate pesticide, carbamate usage for carbaryl is numerous in commercial, residential, and agricultural contexts. It has been associated in the past with NHL (non-Hodgkin lymphoma), with farmers having a 30% to 50% higher risk of NHL [18].

1-3: Spouses of Pesticide Applicators' Usage of Organophosphate Insecticides and the Prevalence of Cancer

OPs are phosphoric acid amides, esters, or thiol derivatives. These substances are widely utilized for household uses, veterinary care, horticulture, forestry, and the prevention of vector-borne illnesses. Human head lice, scabies, and crab lice are all treated with several OPs [19, 20].

OPs are widely used in the agricultural industry to eliminate pests like caterpillars, aphids, locusts, leaf miners, fire ants, and thrips. According to [21], these insecticides increase the amount and quality of agricultural goods.

The following OPs are highly valued flame retardants and plasticizers in public spaces: tris-(2-chloro, 1-methyl-ethyl) phosphate, tris-(2-chloroethyl) phosphate, tri-n-butyl phosphate, tri-iso-butyl phosphate, triphenyl phosphate, and tris-(butoxy ethyl) phosphate [22].

Irreversible inhibitors of cholinesterase, such as acetylcholinesterase, and organophosphorus pesticides cause hyperstimulation of cholinergic nerves, and nicotinic and muscarinic cholinergic receptors, for example [23].

Organophosphorus insecticides were the most common type of insecticide in the world in the 1980s, accounting for 71% of the global market in 1987. However, because of their toxicity to mammals and persistence in the environment, their use decreased to approximately 52% in 1999 and 13% in 2013 [24].

Dichlorvos, parathion, and tetrachlorvinphos are classified as possibly carcinogenic to people (group 2B) by the International Agency for Research on Cancer, but malathion and diazinon are classified as likely carcinogenic to humans (group 2A). Additionally, parathion is listed by the US Environmental Protection Agency as a possible human carcinogen [23].

Several OP insecticides have been linked to an increased risk of cancer in epidemiological studies. These studies include case-control studies conducted in the USA, Canada, and Italy; nested case-control studies involving farm workers in California and structural pest control workers in Florida; and, more recently, an investigation of certified pesticide applicators within the prospective cohort of the Agricultural Health Study (AHS). Researchers from the AHS have connected the use of terbufos, chlorpyrifos, and diazinon to lung cancer; leukemia, terbufos, fonofos, and malathion; and non-Hodgkin lymphoma (NHL) in general and several subtypes in particular [25].

Moreover, there has been a rise in the occurrence of aggressive prostate cancer in men using terbufos, fonofos, and malathion applicators. While numerous studies have concentrated on farmers' exposure during work, it is important to note that organophosphate (OP) insecticides are also extensively used by individuals involved in the management of pests as part of their occupation, as well as by the general population for residential purposes. The research on the use of OPs and cancer incidence has primarily focused on predominantly male populations [26].

1-4- Glyphosate Carcinogenicity

Of all herbicides, glyphosate is a broad-spectrum chemical that is now produced in the largest quantities. It is found in about 750 distinct items used in forestry, household, urban, and agricultural applications. With the advent of genetically modified crop varieties resistant to glyphosate, its application has significantly increased. Food, water, and the air during spraying have all been shown to contain glyphosate. There was little proof that glyphosate causes cancer in people. Heightened dangers of non-Hodgkin lymphoma were found in occupational exposure case-control studies carried out in the USA,14 Canada,6, and Sweden [27].

In a study where mice were subjected to an initiation-promotion test, a glyphosate formulation was found to encourage the development of skin tumors. The presence of glyphosate in the blood and urine of farm workers suggests that it is being absorbed by the body. Glyphosate is broken down by soil microbes into aminomethylphosphoric acid (AMPA), as reported by FAO/WHO in 2015.

Human intestine microbial metabolism is suggested by the finding of blood AMPA following poisonings. Both in vitro human and animal cells and in mammals, glyphosate and glyphosate formulations caused chromosomal and DNA damage. After glyphosate formulations were sprayed on residents of multiple towns, increases in blood indicators of chromosomal damage (micronuclei) were observed in one research.16 mutagenesis tests on bacteria came up negative. In vitro and rodent oxidative stress was caused by glyphosate, glyphosate formulations, and AMPA. “Probably carcinogenic to humans” (Group 2A) is how the Working Group classified glyphosate [28].

1-5- Dieldrin and Aldrin Carcinogenicity

Before they were outlawed in the US in 1987 over worries about the environment and public health, in corn fields, dieldrin, and aldrin were commonly employed insecticides. Dieldrin primarily functions as a xenoestrogen and also

interferes with androgenic pathways. In vitro, dieldrin was introduced to human breast cancer cells MCF-7 (Michigan Cancer Foundation-7), and the cells proliferated and grew more quickly [27].

Dieldrin exposure in utero and the neonatal period enhanced the incidence of breast cancer in experimental rats. Dieldrin-mediated alterations in BNDF and cell signal receptor expression are likely the mechanism behind this effect. Breast tissue of a heroin addict, A 1998 cohort research by the Copenhagen Centre for Prospective Studies found a link between Dieldrin and higher incidence, aggressive tumor incidence, and breast cancer mortality. The study's findings indicated a rise in breast cancer risk that is dose-related. It also found a clear correlation between blood Dieldrin levels and tumor grading and staging [28].

1-6- Carbamates Pesticides Carcinogenicity

The Role of CM-induced immunosuppression in carcinogenicity the idea that the immune system could recognize and destroy tumor cells was developed more than a century ago. A multitude of data from animal models and compelling data from human patients suggest that there is a functional cancer immunosurveillance process that inhibits the growth of many different types of native and transplanted cancers [29].

Additionally, it has become clear that the immune system can promote the growth of tumors. The notion of immunity's dual involvement in the intricate relationships between tumors and their hosts led to an improvement in the cancer immunosurveillance theory, which is now known as cancer immunoediting [30].

The three stages of chemically induced immunotoxicity are called the three stages of cancer immunoediting (elimination, equilibrium, and escape) [31].

First, removal: immune surveillance for cancer,
Second, homeostasis: a stage of tumor dormancy in which immunity and tumor cells establish a dynamic balance that controls tumor growth, third, this is the point at which tumor cells either show decreased immunogenicity or use a variety of potential immunosuppressive strategies to weaken the body's defenses against the tumor, causing the tumors to grow larger and larger.

2- PESTICIDES AND BREAST CANCER

Insecticides like Dieldrin and Aldrin were often used in maize fields until the late 1980s. However, in 1987, the United States outlawed them because of health and environmental risks. Dieldrin inhibits androgenic pathways in addition to acting primarily as a xenoestrogen. Dieldrin increased the development and proliferation of human breast cancer cells MCF-7 (Michigan Cancer Foundation-7) when added to the cells in vitro [27].

Dieldrin exposure during pregnancy and neonatal stages in experimental rats led to a higher incidence of breast cancer in these animals. Dieldrin-mediated alterations in BNDF and cell signal receptor expression are likely the mechanism behind this increase in the incidence of breast cancer. Breast tissue is used in heroin [28].

Dieldrin has been connected to increased rates of aggressive tumors, mortality from breast cancer, and incidence of the disease, according to 1998 cohort research by the Copenhagen Centre for Prospective Studies. The study's findings indicated an increase in breast cancer risk that was dose-related (adjusted odds ratio of 2.05). Additionally, this investigation found a direct correlation between blood Dieldrin levels and tumor grading and staging [32].

Malathion and other pesticides, such as chlordane, were linked to a higher risk of breast cancer, particularly in young women or those with early cancer development. This link was found by [33], in a registry-based case-control study of farm labor union members in California that examined breast cancer. The study looked at 128 newly diagnosed cases of breast cancer and 640 cancer-free controls.

An increased incidence of breast cancer was found in women exposed to 2, 4, and 5-triclorophenoxypropionic acid, according to a big prospective cohort investigation conducted by Engle *et al*., to assess the relationship between insecticides and the incidence of breast cancer in spouses with agricultural field employment [34].

Serum concentrations of DDE [1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene], a primary DDT metabolite [1,1′-(2,2,2-trichloro-ethylidene) bis (4-chlorobenzene), and breast cancer have been compared in a case–control analyses of ten prospective cohort studies [35, 36].

Epidemiological research frequently relates hormone-dependent cancer risks to pesticide exposure in the environment. Women with breast cancer have had their fat samples tested for high levels of PCBs, DDE, and DDT. Women with elevated blood DDE levels are thought to be four times more likely to develop breast cancer. A recent epidemiological

study conducted in Spain from 1999 to 2009 reveals that 2,173 (81%) of the 2,661 occurrences of breast cancer in females that were documented were in locations with high pesticide exposure [36].

Comparable research has shown associations between immune system impairment and elevated levels of residues of organochlorines in certain malignant tissues. Numerous further research supports the idea that exposure to pesticides affects breast cancer risk, but few of them are truly definitive because of some inconsistent data throughout the investigation [37].

3-PROSTATE CANCER

Numerous studies consistently show a connection between pesticide exposure and prostate cancer showing a higher risk among agricultural populations compared to the general population. For instance, in a multi-site case-control study conducted in five rural areas in Italy between 1990-92, farmers exposed to organochloride pesticides, particularly DDT, exhibited a statistically significant increase in prostate cancer rates. Similarly, according to studies conducted in the USA and Sweden, commercial pesticide applicators and farmers have a somewhat to significantly elevated risk of developing prostate cancer compared to the general population [38 and 39].

4- LEUKEMIA

Farmers are overrepresented in leukemia studies, although this overrepresentation is often minor (10% to 40%), and no discernible pattern of risk for any particular histologic type has been found. Leukemia encompasses a wide range of hematopoietic cancers, affecting both adults and children and coming in both acute and chronic forms. Below is a summary of the etiologic data that links the use of pesticides and other agricultural exposures to distinct leukemia subtypes. Pesticide use was linked to chronic lymphocytic leukemia (CLL) in a population-based case-control research carried out in northeastern Italian farming and animal raising region. Exposure to pesticides, namely organophosphates, carbamates, and DDT, may contribute to the correlation between CLLs and labor in farm animal breeding [40].

Hairy-cell leukemia (HCL) is a rare type of chronic leukemia affecting B-lymphoid cells. Limited epidemiologic research has shown a notable link between HCL and exposure to organophosphate insecticides [41].

5- CHILDHOOD PESTICIDE EXPOSURE AND CANCER

Exposure to children typically takes place at home, and there is a strong correlation between the levels of exposure in adults and kids. This is due to the parents' exposure can impact their offspring [42].

Moreover, pediatric leukemia may have its origin during fetal development due to genetic mutations in hematopoietic stem cells, which could be triggered by maternal exposure to specific substances. Such damage could result in the transformation of normal cells into malignant ones, ultimately contributing to the onset of the disease [43].

The public's concern over children being exposed to pyrethroids has grown in recent years. Studies have shown that children are exposed to these agents in a variety of ways, and their urine contains their metabolites. Data from observational exposure measurement studies conducted in the United States in 2012 examined children's exposure to pyrethroids in media, including food, food dust, floor wipes, urine, and/or air, were reviewed. The findings indicated that pyrethroid exposure affected the majority of youngsters (67–100%), as evidenced by the presence of urinary 3-PBA. According to this review, children were probably exposed to low concentrations of several pyrethroids from a variety of sources, including food, but mostly permethrin and cypermethrin [44].

Due to a variety of physiological, dietary, and developmental issues, children are more vulnerable. 17 epidemiological case-control studies from the USA, Canada, Mexico, Japan, France, Brazil, and Germany were included in a 2010 systematic review and meta-analysis. Found a significant correlation between the risk of leukemia and exposure to residential pesticides during pregnancy and childhood. However, the examined research did not consistently specify the type of pesticide. Pyrethroids and childhood leukemia have been linked in papers that have expressly mentioned them [45, 46].

6- EFFECT ON ENDOCRINE GLANDS

Pesticides that disrupt the endocrine system are commonly used worldwide for agricultural, municipal, home, and medical purposes. Human exposure to these compounds has raised concerns due to their toxic properties and potential impact on hormonal-related health conditions. While most studies have focused on the exposure and toxicity of individual compounds, it is essential to also consider the accumulation of exposure and the existence of pesticide byproducts to multiple pesticide residues. In some instances, these by-products can pose greater risks than the original compounds. For instance, a study demonstrated that aldicarb-sulfoxide caused varying effects on heart rate at different concentrations, unlike aldicarb itself [47, 48].

A different research study indicated that the axons of methyl-parathion, chlorpyrifos, and diazinon were found to be 10 to 15 times more harmful to sperm DNA compared to their original compounds, as reported by [49].

For instance, laboratory studies have verified that 2,4-dichlorophenoxyacetic acid (2,4-D), a widely employed organophosphate herbicide, enhances the growth of cells sensitive to androgens [50].

In soil, plants, and animal species, vinclozolin breaks down into several metabolites. The process of hydrolytic breakdown yields two products: 2-[carbamoyl-(3,5-dichlorophenyl) oxy]. It has been discovered that the anti-androgenic compounds -2-methyl-3-butenoic acid and 3′,5′-dichloro-2-hydroxy-methylbut-3-enalide mediate the deleterious effects of vinclozolin [51].

Moreover, it is essential to consider the collective impact of pesticides When evaluating the risks associated with these substances in combination could lead to heightened toxic effects beyond what would be anticipated from individual compounds. For instance, in a mixture containing equal amounts In vitro experiments, the activation of the androgen receptor (AR) was blocked by three pesticides: prochloraz, methiocarb, and deltamethrin. Additionally, when simazine and tribenuronmethyl were introduced alongside these pesticides, changes in adrenal gland weight and modifications changed the expression of genes linked to AR in castrated rats receiving testosterone treatment in a live animal study [52].

Human fetuses, babies, and children have more susceptibility than adults, making age a particularly sensitive factor [53]. A large portion of the harm produced occurs throughout gametogenesis and the early stages of the fetus's development by EDC, while the effects might not be felt until maturity; Furthermore, due to the mother's fat reserves being mobilized during pregnancy and lactation, fetuses and infants receive higher doses. Infants are particularly susceptible to prenatal, and exposure to endocrine-disrupting herbicides after birth which can have a variety of detrimental health effects, including delayed effects on central nervous system functioning and potential long-term effects on intellectual function [54, 55].

6-1- Thyroid Effect by Pesticides

Epidemiological studies have found connections between thyroid-stimulating hormone (TSH) and/or thyroid hormones (TH) based on exposure to various persistent and non-persistent pesticides. Likewise, research suggests that pesticides could disrupt thyroid function by impacting the hypothalamic-pituitary-thyroid (HPT) axis in multiple ways: controlling central regulation, iodine absorption, TH production, and distribution, or the interaction of TH with membrane transporters or receptors. As a result, both in Europe and the US, interest in the effects of pesticides on the HPT axis is growing. 2013, according to [56], the European Food Safety Agency (EFSA) found that 101 of the 287 pesticides it analyzed may harm thyroid function.

Organophosphorus toxicants affect hormone receptors, hormone synthesis, hormone secretion and metabolism, and other aspects of the hypothalamus-pituitary-thyroid axis, which results in dysregulated thyroid hormone levels [57].

There are two categories of possible impacts of organophosphorus toxicants on thyroid hormones: direct effects and indirect effects. This involves disrupting the binding of thyroid hormones to their receptors (TH-r) in target cells, interfering with the binding of transport proteins to thyroid hormones, and interfering with the binding of TSH hormone to its receptors (TSH-r) in the thyroid, in addition to the suppression of thyroid hormone synthesis. Additionally, these toxicants can interfere with the activity and function of the enzyme’s thyroid peroxidase and deiodinase [58].

Interfering with the liver's activity and function is another way that organophosphorus toxicants indirectly impact thyroid hormones. This interference impedes the processes of detoxification, biotransformation, and metabolism in addition to interfering with the liver's synthesis and metabolism of transport proteins [59].

6-2- Diabetes and Pesticides

The 'diabetes epidemic' has escalated to a point where it is causing significant health and economic impacts, particularly in developing countries. While traditional risk factors for diabetes have typically focused on genetics and lifestyle, there is a growing emphasis on lifestyle interventions and the exploration of new pharmaceutical treatments to address the disease. However, emerging evidence suggests a connection between environmental pollutants, notably pesticides, and the development of insulin resistance and Type 2 diabetes. With a substantial rise in pesticide usage globally, the impact of these chemicals on glucose metabolism is too significant to ignore, potentially indicating a link to the development of diabetes [60, 61].

6-3- Pancreas Hormones Effect by Pesticides

Excessive activation of insecticides' cholinergic receptors can result in disruption of insulin and glucagon secretion, possibly as a result of damage to pancreatic tissue. Therefore, insecticides that affect either the level of

acetylcholine or its receptors by inhibiting acetylcholinesterase (such as organophosphates and carbamates) or by functioning as agonists (such as neonicotinoids) on nicotinic acetylcholine receptors have the potential to encourage the pancreas to release insulin. Studies have demonstrated that rats exposed to the organophosphate insecticide malathion have higher blood insulin levels. But according to a different study, malathion exposure reduced the amount of insulin secreted in response to glucose and occasionally caused degenerative alterations in the islets of Langerhans [55, 56].

7- REPRODUCTIVE EFFECTS OF PESTICIDE EXPOSURE

The hypothalamic-pituitary-gonadal axis regulates the production of sex hormones. The anterior pituitary gland releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in reaction to the pulsatile release of gonadotropin-releasing hormone from the brain. Certain pesticides, including methoxychlor, endosulfan, toxaphene, Kepone, DDT, fenarimol, alachlor, pentachlorophenol, fenvalerate, and chlordecone, have been discovered as estrogen agonists. On the other hand, some pesticides, such as vinclozolin, O, P-DDT, and p, p-dichlorodiphenyldichloroethylene (DDE), may have both estrogenic and androgenic qualities, or they may have antiandrogenic effects. Furthermore, it has been demonstrated that in primary cultures of human ovarian granulosa cells, the fungicide methyl-2-benzimidazole carbamate decreases the generation of estradiol [62-64].

Pesticides used in EDCs can function as endocrine disruptors, disrupting the hormonal balance in both men and women and potentially causing subfertility [65].

Improper activity of brain acetylcholinesterase (Ache) and levels of monoamines, caused by the use of OP insecticides in agricultural environments, have been linked to hindered gonadal development and changes in hypothalamic and pituitary endocrine functions. These insecticides have been shown to impact reproductive function, as well as the production and activity of hormones that control spermatogenesis. Lower testosterone levels can affect sperm count and quality, as well as cause erectile dysfunction and decreased libido [66].

Organophosphate (OP) pesticides act as phosphoric or thiophosphoric acid esters, which have deleterious consequences. By hindering the Ache enzyme's function, men's exposure to OP pesticides may alter the composition and functionality of sperm, which may ultimately lower the quality of human semen and result in infertility.

These insecticides work by inhibiting Ache activity in the brain and disrupting pituitary gonadotropin. At high doses, OP insecticides have been demonstrated to have toxic effects on sperm cells, diminishing both their fertilization capacity and motility [67].

7-1- Male Sterility and Pesticide Exposure

When exposed to male rats, atrazine has been shown to have estrogenic and antiandrogenic properties, which may diminish the levels of testosterone in their testicles. Additionally, Lindane can intercalate into the sperm membrane, potentially impeding sperm response to progesterone in laboratory settings. Furthermore, Lindane hinders steroidogenesis by decreasing cholesterol transfer mediated by the steroidogenic acute regulatory (StAR) protein [68].

The concentration of testosterone is decreased by azole fungicides (such as ketoconazole) because they hinder the enzymatic activity of 17a-hydroxylase and 17, 20-lyase. Research conducted in laboratory settings on certain pesticides like fenarimol, prochloraz, imazalil, and dicofol suggests that these pesticides block the transformation of androgens into estrogens by inhibiting CYP 19 aromatase [69].

Atrazine has also been discovered to decrease semen quality in workers exposed to atrazine. Atrazine leads to an increase in sperm abnormalities, DNA damage, and nuclear immaturity [70].

Benomyl, a fungicide with a long history of use, is known for its effectiveness [71]. This chemical, along with its main metabolite carbendazim, acts as microtubule poisons that have low toxicity towards animal organs, except for the reproductive system in men. Benomyl has been shown to decrease testicular and epididymal weights, as well as reduce epididymal sperm counts and fertility [72], evaluated its primary effects on the testis at moderate to low doses, revealing its ability to cause the shedding of germ cells according to the stage.

Carbendazim attaches to tubulin subunits, causing a significant reduction in microtubules within the Sertoli cells. These impacts extend to the division of germ cells, resulting in the elongating spermatids' aberrant head development [73].

When it comes to agricultural chemicals that are toxic to male reproductive systems, dibromochloropropane (DBCP) is the most well-studied. Studies have shown that occupational exposure to DBCP can result in oligospermia, a higher prevalence of spontaneous abortions in azoospermia wives of exposed workers, damage to the germinal epithelium, genetic alterations in sperm (such as double Y bodies), male subfertility, hormonal abnormalities, and a changed sex ratio

in kids [74]. Male employees who produce DBCP have been found to have lower sperm counts and elevated serum levels of FSH and LH [75].

Small and lipophilic, DBCP is easily transported from blood to the testis and germ cells via the blood–blood barrier. In some target tissues, DBCP has been demonstrated to metabolize into cytotoxic metabolites. The microsomal cytochrome P450 system plays a major role in the metabolism of DBCP. The biotransformation of DBCP into metabolites is facilitated by liver enzymes which subsequently pass through the bile and urine. Glutathione S-transferases in the testicular seminiferous tubules change DBCP into a cytotoxic, reactive episulfonium ion. Single-strand breaks in DNA can result from this metabolite's covalent binding to DNA. This pathophysiologic effect most likely explains why DBCP is particularly hazardous during the spermatogenic cycle [76].

7-2- Effect of Pesticides on Female Fertility

By changing an individual's antioxidant defense system's effectivity, oxidative stress damages the physiology of female reproduction. Many toxicants, primarily pesticides, modify this defense mechanism, leading to a range of disorders associated with lifestyle choices. Reproductive disorders such as impaired folliculogenesis, follicular atresia, implantation defects, spontaneous abortions, endometriosis, and fetal and other birth defects are linked to an imbalance in the antioxidant defense system caused by pesticidal toxicity-induced oxidative stress. This, in turn, directly affects the organism's reproductive physiology and fertility [77].

Some pesticides have the potential to upset the hormonal balance necessary for the reproductive system to function properly, which may have detrimental consequences on the reproductive system. Additionally, these herbicides might disrupt the female hormone system. Prior research has mostly concentrated on interaction with the androgen and/or estrogen receptor, although exposure to pesticides can affect hormone function in a variety of other ways as well.

Review topics include hormone synthesis, hormone release and storage, hormone transport and clearance, hormone receptor recognition and binding, hormone post-receptor activation, modulation of hormone concentrations, anomalies in the ovarian cycle, and decreased fertility. Pesticide exposure has been linked in epidemiological research to developmental malformations, disruptions in the menstrual cycle, decreased fertility, longer time to pregnancy, spontaneous abortion, and stillbirths. The disturbance of female hormone function may or may not be the source of these outcomes. Since pesticides are composed of many different substances with varying structures and levels of toxicity, several of the aforementioned mechanisms likely play a role in the pathophysiological pathways explaining the role of pesticide exposure in ovarian cycle disturbances, ultimately leading to problems with fertility and other reproductive effects [78, 79], found a correlation between women's decreased fertility and DDT exposure.

In a 2004 study [80], investigated the relationship between menstrual cycle features and pesticide exposure. They found that women who worked with pesticides that were thought to be hormonally active were 60–100% more likely than women who had never worked with pesticides to have long cycles, missed periods, and intermenstrual bleeding.

According to the findings of two studies on the delay in conception experienced by female greenhouse workers, female workers in floral greenhouses may be less fecundable, and pesticide exposure may play a role in the causal chain. According to another study, women who worked in industries related to agriculture or were around pesticides were more likely to become infertile.

Women who worked with chemicals suspected of being hormonally active were shown to be 60–100% more likely to develop long cycles, missed periods, and intermenstrual bleeding than women who had never worked with pesticides. According to the findings of two studies on the delay in conception experienced by female greenhouse workers, female workers in floral greenhouses may be less fecundable, and pesticide exposure may play a role in the causal chain. According to several studies [81-83], women who worked in industries related to agriculture or were exposed to pesticides were more likely to become infertile.

7-2-1- Disturbance of the Hormonal Cycle in Women Every Hormone is Unique in Them

Chemical structures are synthesized using a variety of routes involving countless steps. The synthesis of a hormone can be interrupted by one item or link, which could result in the hormone's production being disrupted or acquiring altered features. Certain pesticides, like prochloraz, fenarimol, and other imidazole fungicides, can stop the conversion of androgens to estrogens by inhibiting CYP19 aromatase in vitro, which inhibits the manufacture of estrogens. According to a 2006 hypothesis by Vinggaard *et al*., substances that might block aromatase activity in vitro could be able to alter localized levels of androgen and estrogen in vivo [84].

A physiological method for deactivating xenobiotics that may not always result in toxicity is aromatase stimulation. In vitro, aromatase activity is induced by the pesticide's atrazine, simazine, and propazine (2-chloro-triazine herbicides) [85].

Furthermore, heptachlor may function as an inducer of testosterone 16-alpha and 16-beta hydroxylases, while the insecticides methomyl, pirimicarb, propamocarb, and iprodione can only marginally increase aromatase activity [86].

8- EFFECT OF PESTICIDES ON THE IMMUNE SYSTEM

Western countries have shown through epidemiological evidence that the prevalence of diseases linked to immune response modifications, like cancer, some autoimmune diseases, and asthma, is rising to the point where it cannot be solely attributed to better diagnoses. There is some worry that this trend may be caused, at least in part, by altered or new patterns of chemical exposure, especially pesticide exposure [87].

Workers in chemical plants who were exposed to pesticide dust regularly, such as captan and carbendazim, demonstrated disruptions in their humoral and cellular immune systems [71, 72].

It has been observed that immunomodulation of the organophosphate (OP) insecticide chlorpyrifos increases multiorgan autoantibodies and CD26 cells while decreasing CD5+ cells and the mitogenesis response to phytohemagglutinin and concanavalin A [82].

Following a pest control operation, exposure to synthetic pyrethroid cypermethrin tended to decrease immunoglobulins (IgG, IgM, and IgA), complement components C3c and C4, acute phase protein α-acid glycoprotein (AAG), and lymphocyte subpopulations CD3+, CD4+, and CD20+ [83].

Researchers discovered that when European pesticide workers in agriculture were exposed to a mixture of pesticides, including ethylenebisdithiocarbamate (EBDC) fungicides, their levels of complement and IgG4 increased but their levels of IgA fell. Workers in chemical plants who were exposed to pesticide dust regularly, such as captan and carbendazim, demonstrated disruptions in their humoral and cellular immune systems [84].

9- CONTAMINATION WITH PESTICIDES IN IRAQ AND OTHER RELATED COUNTRIES

In several Arab nations, crop sample contamination by organic chemicals has become a serious issue. Cucumber and tomato samples from Palestine, Jordan, and Egypt showed varying degrees of contamination. Jordanian grapes and Egyptian and Pakistani vegetable produce were found to have high levels of contamination. In recent years, there have been several reports of poisoning incidents and plant food contamination in Morocco, Egypt, Iraq, Saudi Arabia, Sudan, Syria, Jordan, the United Arab Emirates, Pakistan, and Yemen. Additional in-depth research on this issue revealed the build-up of these organic pollutants in food consumers' bodies as well as in farm laborers who handle agricultural products directly. This issue most likely arose as a result of environmental pesticide abuse or misuse. These pollutants were categorized as substances that ranged from mildly to highly hazardous. There could be negative health impacts from these substances [75].

The muscles of Indian shad, shrimp, and cyprinids (Barbus xanthopetrus) that were caught from the Shatt al-Arab River exhibited comparatively greater residual levels of ΣDDT, endrin, and dieldrin [85].

In a 2020 study by [74], on farmers' exposure to pesticides in Alsulaimania, a governorate in northern Iraq, the researchers discovered that when respondents were asked about the PPE they used, gloves were the most frequently used item (88.24%) which is a positive sign for self-defense, but he also noted some really dangerous signs, since 98.04% of the respondents maintained the pesticides for the upcoming season.

Even though farmers kept their pesticides in a room specifically meant for their farming equipment, kids could easily get them. When pesticides are improperly stored, there is a risk to the health of both users and non-users, such as children. Furthermore, among the respondents, there was also an observation of pesticide containers being discarded.

Luckily, none of the farmers poisoned the pesticide containers; instead, they were all tossing the empty canisters. (Numerous studies have shown that when pesticide containers are used again to store food, pesticide residues may remain and pose a serious health danger to farmers and their families [86, 87].

As an alternative, the responders to this survey disposed of the empty containers in a variety of ways, including burning them, burying them underground, and throwing them in the street's trash. The most likely reason for this haphazard disposal was a lack of policy standards [88], state that throwing empty containers on the street poses health hazards and pollutes the environment.

Cleaning the equipment after pesticide applications could also be a substantial source of exposure, according to [89]. When asked where they cleaned their pesticide-spraying equipment after using it outside their plastic dwellings, all survey participants (100%) answered in the affirmative. According to [88], the discharge of pesticide waste may harm livestock through contaminated feed and water by pesticide residue. During the observation study, it was noted that the majority of farmers herded cattle near their plastic houses.

In a different investigation [90], assessed the levels of pesticide residues in animal milk in the Baghdad Governorate and discovered that DMT residues were present at high significant values. This suggests that consuming milk from these animals may pose a health risk to humans.

CONCLUSION

Chemicals known as pesticides play a crucial role in controlling agricultural pests and keeping animals and humans from contracting diseases from these pests. Because of the substantial health hazards associated with both short- and long-term exposure, they are extremely harmful despite their significance.

The most serious dangers are those associated with the generation of reactive oxygen species (ROS), which can disrupt endocrine, cause cancer, impair fertility, and harm the immune system.

Research conducted in Iraq and its surrounding nations has shown a dramatic rise in the amount of pesticide residues collected in meat, vegetables, and water. This suggests that there may be a human health risk associated with these residues.

ACKNOWLEDGMENTS

The authors would like to thank Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad-Iraq for its support in the present work.

REFERENCES

1. Pluth, T. B., Zanini, L. A. G., & Battisti, I. D. E. (2019). Pesticide exposure and cancer: an integrative literature review. *Saúde em debate*, *43*, 906-924.
2. Varghese, J. V., Sebastian, E. M., Iqbal, T., & Tom, A. A. (2021). Pesticide applicators and cancer: a systematic review. *Reviews on Environmental Health*, *36*(4), 467-476.
3. Yadav, H., Sankhla, M. S., & Kumar, R. (2019). Pesticides-induced carcinogenic & neurotoxic effect on human. *Forensic Research & Criminology International Journal*, *7*(5), 243-245.
4. Bassil, K. L., Vakil, C., Sanborn, M., Cole, D. C., Kaur, J. S., & Kerr, K. J. (2007). Cancer health effects of pesticides: systematic review. *Canadian Family Physician*, *53*(10), 1704-1711.
5. Bhardwaj, J. K., Mittal, M., Saraf, P., & Kumari, P. (2018). Pesticides induced oxidative stress and female infertility: a review. *Toxin Reviews*.
6. Lwin, T. Z., Than, A. A., Min, A. Z., Robson, M. G., & Siriwong, W. (2018). Effects of pesticide exposure on reproductivity of male groundnut farmers in Kyauk Kan village, Nyaung-U, Mandalay region, Myanmar. *Risk management and healthcare policy*, 235-241.
7. WHO, G. (2010). The WHO recommended the classification of pesticides by hazard and guidelines for classification in 2009.
8. Dennis, L. K., Lynch, C. F., Sandler, D. P., & Alavanja, M. C. (2010). Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural heath study. *Environmental health perspectives*, *118*(6), 812-817.
9. Douabul, A. A., Al-Saad, H. T., & Al-Rekabi, H. N. (1987). Residues of organochlorine pesticides in environmental samples from the Shatt Al-Arab River, Iraq. *Environmental pollution*, *43*(3), 175-187.
10. Alavanja, M. C., Hoppin, J. A., & Kamel, F. (2004). Health effects of chronic pesticide exposure: cancer and neurotoxicity. *Annu. Rev. Public Health*, *25*, 155-197.
11. Lerro, C. C., Koutros, S., Andreotti, G., Friesen, M. C., Alavanja, M. C., Blair, A., & Freeman, L. E. B. (2015). Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. *Occupational and environmental medicine*, *72*(10), 736-744.
12. Jayaraj, R., Megha, P., & Sreedev, P. (2016). Organochlorine pesticides, their toxic effects on living organisms, and their fate in the environment. *Interdisciplinary toxicology*, *9*(3-4), 90-100.
13. Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., & Soerjomataram, I. B. F. (2020). International agency for research on cancer 2020. *Glob Cancer Obs Cancer Today*, *419*, 1-2.
14. Peña, D., Pontillo, C., García, M. A., Cocca, C., Alvarez, L., Chiappini, F., & Randi, A. (2012). Alterations in c-Src/HER1 and estrogen receptor α signaling pathways in the mammary gland and tumors of hexachlorobenzene-treated rats. *Toxicology*, *293*(1-3), 68-77.
15. Grove, R., & Sanchez, O. (2022). Human Exposure to Environmental Pollutants and Associations with Non-Hodgkin Lymphoma: A Review. *Exposure and Health*, *14*(1), 99-109.

16. Burns, C., Bodner, K., Swaen, G., Collins, J., Beard, K., & Lee, M. (2011). Cancer incidence of 2, 4-D production workers. *International Journal of Environmental Research and Public Health*, *8*(9), 3579-3590.
17. Zheng, T., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Zhang, Y., & Blair, A. (2001). Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. *Journal of Occupational and Environmental Medicine*, *43*(7), 641-649.
18. Idriss, S., & Levitt, J. (2009). Malathion for head lice and scabies: treatment and safety considerations. *Journal of drugs in dermatology: JDD*, *8*(8), 715-720.
19. McDuffie, H. H., Pahwa, P., McLaughlin, J. R., Spinelli, J. J., Fincham, S., Dosman, J. A., & Choi, N. W. (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: a cross-Canada study of pesticides and health. *Cancer Epidemiology Biomarkers & Prevention*, *10*(11), 1155-1163.
20. Rajak, P., Ganguly, A., Sarkar, S., Mandi, M., Dutta, M., Podder, S., & Roy, S. (2021). Immunotoxic role of organophosphates: An unseen risk escalating SARS-CoV-2 pathogenicity. *Food and Chemical Toxicology*, *149*, 112007.
21. Chen, M. W., Santos, H. M., Que, D. E., Gou, Y. Y., Tayo, L. L., Hsu, Y. C., & Huang, K. L. (2018). Association between organochlorine pesticide levels in breast milk and their effects on female reproduction in a Taiwanese population. *International Journal of Environmental Research and Public Health*, *15*(5), 931.
22. Andresen, J. A., Grundmann, A., & Bester, K. (2004). Organophosphorus flame retardants and plasticizers in surface waters. *Science of the total environment*, *332*(1-3), 155-166.
23. Sparks, T. C. (2013). Insecticide discovery: an evaluation and analysis. *Pesticide biochemistry and physiology*, *107*(1), 8-17.
24. Sparks, T. C., & Nauen, R. (2015). IRAC: Mode of action classification and insecticide resistance management. *Pesticide biochemistry and physiology*, *121*, 122-128.
25. Lerro, C. C., Koutros, S., Andreotti, G., Friesen, M. C., Alavanja, M. C., Blair, A., & Freeman, L. E. B. (2015). Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. *Occupational and environmental medicine*, *72*(10), 736-744.
26. Seesen, M., Lucchini, R. G., Siriruttanapruk, S., Sapbamrer, R., Hongsibsong, S., Woskie, S., & Kongtip, P. (2020). Association between organophosphate pesticide exposure and insulin resistance in pesticide sprayers and nonfarm workers. *International Journal of Environmental Research and Public Health*, *17*(21), 8140.
27. Andersen, H. R., Vinggaard, A. M., Rasmussen, T. H., Gjermandsen, I. M., & Bonefeld-Jørgensen, E. C. (2002). Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. *Toxicology and applied pharmacology*, *179*(1), 1-12.
28. Cameron, H. L., & Foster, W. G. (2009). Developmental and lactational exposure to dieldrin alters mammary tumorigenesis in Her2/neu transgenic mice. *PLoS One*, *4*(1), e4303.
29. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *cell*, *144*(5), 646-674.
30. Dunn, G. P., Old, L. J., & Schreiber, R. D. (2004). The three Es of cancer immunoediting. *Annu. Rev. Immunol.*, *22*, 329-360.
31. Dhouib, I., Jallouli, M., Annabi, A., Marzouki, S., Gharbi, N., Elfazaa, S., & Lasram, M. M. (2016). From immunotoxicity to carcinogenicity: the effects of carbamate pesticides on the immune system. *Environmental Science and Pollution Research*, *23*, 9448-9458.
32. Høyer, A. P., Grandjean, P., Jørgensen, T., Brock, J. W., & Hartvig, H. B. (2000). Dieldrin as a Risk Factor for Breast Cancer and for Increased Mortality Once Breast Cancer Is Detected. *Journal of Clinical Epidemiology*, *2002*(53), 323-330.
33. Mills, P. K., & Yang, R. (2005). Breast cancer risk in Hispanic agricultural workers in California. *International journal of occupational and environmental health*, *11*(2), 123-131.
34. Engel, L. S., Hill, D. A., Hoppin, J. A., Lubin, J. H., Lynch, C. F., Pierce, J., & Alavanja, M. C. (2005). Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. *American journal of epidemiology*, *161*(2), 121-135.
35. Cohn, B. A., La Merrill, M., Krigbaum, N. Y., Yeh, G., Park, J. S., Zimmermann, L., & Cirillo, P. M. (2015). DDT exposure in utero and breast cancer. *The Journal of Clinical Endocrinology & Metabolism*, *100*(8), 2865-2872.
36. Kass, L., Gomez, A. L., & Altamirano, G. A. (2020). Relationship between agrochemical compounds and mammary gland development and breast cancer. *Molecular and cellular endocrinology*, *508*, 110789.
37. Alavanja, M. C., Sandler, D. P., Lynch, C. F., Knott, C., Lubin, J. H., Tarone, R., & Blair, A. (2005). Cancer incidence in the agricultural health study. *Scandinavian journal of work, environment & health*, 39-45.
38. Multigner, L., Ndong, J. R., Giusti, A., Romana, M., Delacroix-Maillard, H., Cordier, S., & Blanchet, P. (2010). Chlordecone exposure and risk of prostate cancer. *J Clin Oncol*, *28*(21), 3457-3462.
39. Cardona, B., & Rudel, R. A. (2020). US EPA's regulatory pesticide evaluations need clearer guidelines for considering mammary gland tumors and other mammary gland effects. *Molecular and cellular endocrinology*, *518*, 110927.
40. Morgan, M. K. (2012). Children's exposures to pyrethroid insecticides at home: a review of data collected in published exposure measurement studies conducted in the United States. *International journal of environmental research and public health*, *9*(8), 2964-2985.
41. Malagoli, C., Costanzini, S., Heck, J. E., Malavolti, M., De Girolamo, G., Oleari, P., & Vinceti, M. (2016). Passive exposure to agricultural pesticides and risk of childhood leukemia in an Italian community. *International journal of hygiene and environmental health*, *219*(8), 742-748.
42. Merhi, M., Raynal, H., Cahuzac, E., Vinson, F., Cravedi, J. P., & Gamet-Payrastre, L. (2007). Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case–control studies. *Cancer Causes & Control*, *18*, 1209-1226.

43. Villaverde, J. J., Sevilla-Morán, B., López-Goti, C., Sandín-España, P., & Alonso-Prados, J. L. (2017). An overview of nanopesticides in the framework of European legislation. *New Pesticides and Soil Sensors*, 227-271.
44. Küster, E., & Altenburger, R. (2007). Suborganismic and organismic effects of aldicarb and its metabolite aldicarb-sulfoxide to the zebrafish embryo (Danio rerio). *Chemosphere*, *68*(4), 751-760.
45. Kim, H. J., Park, Y. I., & Dong, M. S. (2005). Effects of 2, 4-D and DCP on the DHT-induced androgenic action in human prostate cancer cells. *Toxicological Sciences*, *88*(1), 52-59.
46. Mnif, W., Hassine, A. I. H., Bouaziz, A., Bartegi, A., Thomas, O., & Roig, B. (2011). Effect of endocrine disruptor pesticides: a review. *International journal of environmental research and public health*, *8*(6), 2265-2303.
47. Reffstrup, T. K., Larsen, J. C., & Meyer, O. (2010). Risk assessment of mixtures of pesticides. Current approaches and future strategies. *Regulatory Toxicology and Pharmacology*, *56*(2), 174-192.
48. Hardell, L., van Bavel, B., Lindström, G., Eriksson, M., & Carlberg, M. (2006). In utero exposure to persistent organic pollutants to testicular cancer risk. *International journal of andrology*, *29*(1), 228-234.
49. Wilson, V. S., Lambright, C. R., Furr, J. R., Howdeshell, K. L., & Gray Jr, L. E. (2009). The herbicide linuron reduces testosterone production from the fetal rat testis during both in-utero and in-vitro exposures. *Toxicology Letters*, *186*(2), 73-77.
50. Yang, F. W., Li, Y. X., Ren, F. Z., Luo, J., & Pang, G. F. (2019). Assessment of the endocrine-disrupting effects of organophosphorus pesticide triazophos and its metabolites on endocrine hormones biosynthesis, transport, and receptor binding in silico. *Food and chemical toxicology*, *133*, 110759.
51. Leemans, M., Couderq, S., Demeneix, B., & Fini, J. B. (2019). Pesticides with potential thyroid hormone-disrupting effects: a review of recent data. *Frontiers in endocrinology*, *10*, 468622.
52. Rashidi, M. A., MAHABADI, H. A., & KHAVANIN, A. (2020). Evaluation of the effects of chronic exposure to organophosphorus pesticides on thyroid function. *Asia Pacific Journal of Medical Toxicology*, *9*(2).
53. Swaminathan, K. (2013). Pesticides and human diabetes: a link worth exploring. *Diabetic medicine*, *30*(11), 1268-1271.
54. Rashidi, M. A., MAHABADI, H. A., & KHAVANIN, A. (2020). Evaluation of the effects of chronic exposure to organophosphorus pesticides on thyroid function. *Asia Pacific Journal of Medical Toxicology*, *9*(2).
55. Pournourmohammadi, S., Farzami, B., Ostad, S. N., Azizi, E., & Abdollahi, M. (2005). Effects of malathion subchronic exposure on rat skeletal muscle glucose metabolism. *Environmental Toxicology and Pharmacology*, *19*(1), 191-196.
56. Pournourmohammadi, S., Ostad, S. N., Azizi, E., Ghahremani, M. H., Farzami, B., Minaie, B., & Abdollahi, M. (2007). Induction of insulin resistance by malathion: Evidence for disrupted islets cells metabolism and mitochondrial dysfunction. *Pesticide biochemistry and physiology*, *88*(3), 346-352.
57. Alengebawy, A., Abdelkhalek, S. T., Qureshi, S. R., & Wang, M. Q. (2021). Heavy metals and pesticide toxicity in agricultural soil and plants: Ecological risks and human health implications. *Toxics*, *9*(3), 42.
58. Kojima, H., Takeuchi, S., & Nagai, T. (2010). Endocrine-disrupting potential of pesticides via nuclear receptors and aryl hydrocarbon receptor. *Journal of Health Science*, *56*(4), 374-386.
59. Band, P. R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R. P., & Le, N. D. (2011). Prostate cancer risk and exposure to pesticides in British Columbia farmers. *The Prostate*, *71*(2), 168-183.
60. Garey, J., & Wolff, M. S. (1998). Estrogenic and antiprogestagenic activities of pyrethroid insecticides. *Biochemical and Biophysical Research Communications*, *251*(3), 855-859.
61. Oduma, J. A., Okelo, D. O., Odongo, H., & Makawiti, D. W. (2006). The pesticide heptachlor affects steroid hormone secretion in isolated follicular and luteal cells of rats. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *144*(1), 76-84.
62. Sengupta, P., & Banerjee, R. (2014). Environmental toxins: Alarming impacts of pesticides on male fertility. *Human & experimental toxicology*, *33*(10), 1017-1039.
63. Swan, S. H. (2006). Semen quality in fertile US men about the geographical area and pesticide exposure. *International Journal of Andrology*, *29*(1), 62-68.
64. Hess, R. A., & Nakai, M. (2000). Invited Reviews-Histopathology, of the male reproductive system induced by the fungicide benomyl. *Histology and histopathology*, *15*(1), 207-224.
65. Jaiswal, A., Parihar, V. K., Kumar, M. S., Manjula, S. D., Krishnanand, B. R., Shanbhag, R., & Unnikrishnan, M. K. (2005). 5-Aminosalicylic acid reverses endosulfan-induced testicular toxicity in male rats. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *585*(1-2), 50-59.
66. Hwang, K., Eisenberg, M. L., Walters, R. C., & Lipshultz, L. I. (2013). Gonadotoxic effects of DBCP: A historical review and current concepts. *The Open Urology & Nephrology Journal*, *6*(1).
67. Bretveld, R. W., Thomas, C. M., Scheepers, P. T., Zielhuis, G. A., & Roeleveld, N. (2006). Pesticide exposure: Is the hormonal function of the female reproductive system disrupted? *Reproductive Biology and Endocrinology*, *4*, 1-14.
68. Pizzorno, J. (2018). Environmental toxins and infertility. *Integrative Medicine: A Clinician's Journal*, *17*(2), 8.
69. Vinggaard, A. M., Hnida, C., Breinholt, V., & Larsen, J. C. (2000). Screening of selected pesticides for inhibition of CYP19 aromatase activity in vitro. *Toxicology in vitro*, *14*(3), 227-234.
70. Corsini, E., Liesivuori, J., Vergieva, T., Van Loveren, H., & Colosio, C. (2008). Effects of pesticide exposure on the human immune system. *Human & experimental toxicology*, *27*(9), 671-680.
71. Oleksiivna, M. E., & Olegovich, Z. A. (2021, April). ALLERGIC REACTIONS AS A SELECTIVE RESPONSE OF THE HUMAN IMMUNE SYSTEM TO THE INFLUENCE OF CHEMICALS. In *The 8th International scientific and*

practical conference "Science and education: problems, prospects, and innovations" (April 28-30, 2021) CPN Publishing Group, Kyoto, Japan. 2021. 866 p. (p. 81).

72. Schettler, T., Solomon, G., Kaplan, J., & Valenti, M. (2003). Generations at risk: how environmental toxicants may affect reproductive health in California. *Brisbane, CA: George Lithograph*.
73. Aroonvilairat, S., Kespichayawattana, W., Sornprachum, T., Chaisuriya, P., Siwadune, T., & Ratanabanangkoon, K. (2015). Effect of pesticide exposure on immunological, hematological and biochemical parameters in Thai orchid farmers—a cross-sectional study. *International journal of environmental research and public health*, *12*(6), 5846-5861.
74. Chatterjee, S., Basak, P., Chaklader, M., Das, P., Pereira, J. A., Chaudhuri, S., & Law, S. (2013). Pesticide-induced marrow toxicity and effects on marrow cell population and on hematopoietic stroma. *Experimental and Toxicologic Pathology*, *65*(3), 287-295.
75. El-Nahhal, Y. (2004). Contamination and safety status of plant food in Arab countries. *J Appl Sci*, *4*(3), 411-7.
76. Prahl, M., Odorizzi, P., Gingrich, D., Muhindo, M., McIntyre, T., Budker, R., & Feeney, M. E. (2021). Exposure to pesticides in utero impacts the fetal immune system and response to vaccination in infancy. *Nature communications*, *12*(1), 132.
77. Rijal, H. B., Yoshida, K., Humphreys, M. A., & Nicol, J. F. (2021). Development of an adaptive thermal comfort model for energy-saving building design in Japan. *Architectural Science Review*, *64*(1-2), 109-122.
78. Damalas, C. A. (2021). Farmers' intention to reduce pesticide use: The role of perceived risk of loss in the model of the planned behavior theory. *Environmental Science and Pollution Research*, *28*(26), 35278-35285.
79. Al-Zahra, A., & Ahmed, A. J. (2018). Impacts of processing heat treatments on deltamethrin and bifenthrin residues in human breast milk and raw milk from different animals. *Iraqi Journal of Veterinary Sciences*, *32*(1), 27-31.
80. De Roos, A., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., & Blair, A. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occupational and environmental medicine*, *60*(9), e11-e11.
81. Farr, S. L., Cooper, G. S., Cai, J., Savitz, D. A., & Sandler, D. P. (2004). Pesticide use and menstrual cycle characteristics among premenopausal women in the Agricultural Health Study. *American journal of epidemiology*, *160*(12), 1194-1204.
82. Che'Ya, N. N., Mohidem, N. A., Roslin, N. A., Saberioon, M., Tarmidi, M. Z., Arif Shah, J., & Man, N. (2022). Mobile computing for pest and disease management using spectral signature analysis: A review. *Agronomy*, *12*(4), 967.
83. Idrovo, A. J., Sanìn, L. H., Cole, D., Chavarro, J., Cáceres, H., Narváez, J., & Restrepo, M. (2005). Time to first pregnancy among women working in agricultural production. *International archives of occupational and environmental health*, *78*, 493-500.
84. Ji, B. T., Silverman, D. T., Stewart, P. A., Blair, A., Swanson, G. M., Baris, D., & Hoover, R. N. (2001). Occupational exposure to pesticides and pancreatic cancer. *American journal of industrial medicine*, *39*(1), 92-99.
85. Karashdeep Kaur, K. K., & Rupinder Kaur, R. K. (2018). Occupational pesticide exposure, impaired DNA repair, and diseases.
86. Malagoli, C., Costanzini, S., Heck, J. E., Malavolti, M., De Girolamo, G., Oleari, P., & Vinceti, M. (2016). Passive exposure to agricultural pesticides and risk of childhood leukemia in an Italian community. *International journal of hygiene and environmental health*, *219*(8), 742-748.
87. Salazar-Arredondo, E., de Jesús Solís-Heredia, M., Rojas-García, E., Hernández-Ochoa, I., & Quintanilla-Vega, B. (2008). Sperm chromatin alteration and DNA damage by methyl-parathion, chlorpyrifos, and diazinon and their oxon metabolites in human spermatozoa. *Reproductive Toxicology*, *25*(4), 455-460.
88. Sánchez-Gervacio, B. M., Bedolla-Solano, R., Rosas-Acevedo, J. L., Legorreta-Soberanis, J., Valencia-Quintana, R., & Juárez-López, A. L. (2021). Pesticide management by subsistence farmers in Mexico: baseline of a pilot study to design an intervention program. *Human and Ecological Risk Assessment: An International Journal*, *27*(4), 1112-1125.
89. Talibov, M., Sormunen, J., Hansen, J., Kjaerheim, K., Martinsen, J. I., Sparen, P., & Pukkala, E. (2018). Benzene exposure at workplace and risk of colorectal cancer in four Nordic countries. *Cancer epidemiology*, *55*, 156-161.
90. Woo, S., Yum, S., Kim, D. W., & Park, H. S. (2009). Transcripts level responses in a marine medaka (Oryzias javanicus) exposed to organophosphorus pesticide. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *149*(3), 427-432.