Chapter

Pesticides and Human Health

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Abstract

Pesticides are used in managing pests and their use will continue in future because of food security and vector control. Most pesticides are potentially toxic to human beings resulting in severe health consequences. There is also evidence that parental exposure, as well as, exposure in early life or adolescence could increase the longer-term risks. Pesticide exposures have been linked to many human diseases such as Alzheimer, Parkinson, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, birth defects, attention deficit hyperactivity disorder, autism, diabetes, and obesity, respiratory diseases, organ diseases and system failures. People who are exposed to pesticides are at a greater risk to develop various cancers including non-Hodgkin lymphoma (NHL), leukemia, brain tumors, and cancers of the breast, prostate, lung, stomach, colorectal, liver, and the urinary bladder. The cell culture is an excellent experimental model reflecting human exposure to pesticides at a molecular level which is necessary to understand the hazards. Pesticide users should be aware of their risks and proper handling, as well as must use personal protective equipment which is effective in reducing damage to human health. Carcinogenic pesticides must be eliminated and sustainable and new approaches in pest management should be encouraged.

Keywords: pesticides, cancer, endocrine disruption, pesticide residues, toxicity

1. Introduction

A pesticide is any substance which is used to prevent, destroy or repel any pest from causing any damage. The term pest represents any living organism that may cause harm to human in respect to food competition, destruction of property and spread of disease. Pests include insects, rodents, microbes, fungi and weeds (unwanted plants), etc. of agricultural, medical and veterinary importance, and therefore, a pesticide can be an insecticide, an insect and plant growth regulator, a fungicide, an herbicide, a molluscicide, and an algaecide, etc. based on the target pest organism.

The major site of action for most pesticides are the nervous and endocrine systems and, therefore, are also potentially toxic to human with serious direct or indirect adverse health effects. Human beings are exposed to pesticides directly or indirectly. Direct exposure occurs during pesticide application process in agriculture, public health and livestock, and fumigation while indirect exposure involves ingestion of contaminated food and water, and inhalation of pesticides droplets from the drift. Children are more susceptible to pesticides than adults due to their physical makeup, behavior and physiology, and exposure to very low levels at early developmental stages can cause adverse health effects. Codex Alimentarius

committee and the Pesticide Data Program of the United States Department of Agriculture have established pesticide maximum residue limits in edible food which must be followed to avoid any health risks.

Pesticide exposures have been linked to the elevated incidence of human diseases such as cancers, Alzheimer, Parkinson, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, birth defects, attention deficit hyperactivity disorder, autism, diabetes, and obesity, respiratory diseases, organ diseases and system failures. People who are exposed to pesticides are at a greater risk to develop various cancers including non-Hodgkin lymphoma (NHL), leukemia, brain tumors, and cancers of the breast, prostate, lung, stomach, colorectal, liver, and the urinary bladder.

Pesticides cause genetic and epigenetic changes by involving various processes at cellular levels. Pesticides may be involved in endocrine disruption and induction of inflammatory signals which result in production of reactive oxygen species (ROS) causing oxidative stress. ROS disrupt the cellular functions of mitochondria and endoplasmic reticulum.

This chapter covers different types, importance and modes of action of pesticides. Human exposure to pesticides and pesticide residues in food are also discussed. Finally, the impacts of pesticide exposure on human health with focus on the major chronic health effects (neurotoxic, genotoxic and carcinogenic, and reproductive effects) and recent findings regarding health effects associated with exposure to common types of pesticides, i.e., organochlorines, organophosphates, carbamates, pyrethroids and neonicotinoids insecticides, fungicides and herbicides are discussed.

2. Types of pesticides and pesticide formulations

2.1 Types of pesticides

Pesticides can be classified based on chemical classes, functional groups, mode of action, and toxicity. The active ingredients of most pesticides are either organic (contain carbon) or inorganic (minerals e.g. copper sulfate, ferrous sulfate, copper, lime, sulfur, etc.). Organic pesticides are hydrophobic and more complex than those of inorganic pesticides. Organic pesticides can be natural (produced from naturally available sources) or synthetic (artificially produced by chemical synthesis in factories). The major types of pesticides used in agriculture, forestry, landscape, medical and veterinary sectors are listed in **Table 1**.

2.2 Pesticide formulations

Pesticides are sold as formulated products. Pesticide formulations are a combination of one or more active ingredients (a.i.) and several inert ingredients. Active ingredients control the pests. The inert ingredients help in solubility and stability of the product. A ULV (Ultra Low Volume) formulation need specialized spray equipment and the Ready-to-Use formulations are already diluted and are appropriate for indoor or small areas, for example, aerosols (A), granules (G), and most baits (B) [1].

Most liquid formulations are diluted with water according to the label directions. The three main types of liquid formulations are solutions, suspensions, and emulsions. A true solution is a mixture that cannot be separated by a filter or other mechanical means while a suspension is an even mixture of very small solid particles throughout a liquid and an emulsion is a mixture of droplets of one liquid

Type of pesticide	Active ingredient	Target pests
Insecticides	Natural and synthetic	Insect (6-legged) pests of agricultural, forestry, landscape, medical and veterinary importance
Miticides/acaricides	Natural and synthetic	Mites (8-legged) pests of agricultural, forest, landscape, medical and veterinary importance
Fungicides	Natural and synthetic	Fungal diseases (molds, mildews, rust) of agricultural, forestry and landscape importance
Herbicides	Natural and synthetic	Unwanted plants (weeds) of agricultural and landscape importance
Insect growth regulators	Synthetic	Disrupt the growth and reproduction of insect pests. IGR are species or genus specific.
Pheromones	Natural and synthetic	Attract and trap male insects and are often species-specific.
Plant growth regulators	Synthetic	Alter plants growth, e.g., induce or delay flowering
Algaecides	Natural and synthetic	Algae growing on different surfaces, e.g., patios
Molluscicides	Natural and synthetic	Slugs and snails of agricultural, forestry and landscape importance
Biopesticides	Natural	Can be insecticides, fungicides or herbicides
Antimicrobials	Synthetic	Microbes (mostly bacteria) of medical and veterinary importance
Rodenticides	Natural and synthetic	Rodents (mice, rats) in agriculture, landscape, building, storages and hospitals
Treated seeds	Synthetic	Seeds coated with an insecticide or fungicide or both to prevent damage from soil insect pests and fungus diseases
Wood preservatives	Synthetic	Pesticides to protect wood from insect pests, fungus and other diseases
Minimum risk pesticides	Natural and synthetic	Any pesticides which have been proven safe for human and are exempt from registration by any regulatory authorities

Table 1.
Major types of pesticides used in agriculture, forestry, landscape, medical and veterinary sectors. (adopted from: National Pesticides Information Center at http://npic.orst.edu/ingred/ptype/index.html).

in another liquid. Common Liquid Formulations are Emulsifiable Concentrate (E or EC), Solutions (S, CS), Emulsions in Water (EW), Flowables (F, L, or SC), Microencapsulated Pesticides (M or ME) and Aerosol (A).

In dry formulations the active ingredient is on the surface of a solid carrier, such as talc, clay, or ground corncobs. Common solid formulations include Granules (G), Wettable Powders (WP or W), Soluble Powder (SP or S), Water-Dispersible Granules (WDG) or Dry Flowables (DF Water-Soluble Bags/Packages (WSB) and Baits (B).

3. Importance of pesticides

The United Nations population division estimates 9.7 billion people by the year 2050 and to feed them, the Food and Agriculture Organization (FAO) of the United Nations estimates that an 80% increase in food production is necessary.

This increase in production will come from an increase in yields of crops as well as a decrease of damage to crops due to pests. There are approximately 9000 species of insects/mites (14% loss), 50,000 species of plant pathogens (13% loss) and 8000 weeds species (13% loss) worldwide [2]. Without pesticide application the pest losses to fruits, vegetables and cereals would reach 78%, 54% and 32%, respectively. Pesticides are, therefore, indispensable in agricultural production and there will be a need for pesticide based pest control and food security in the future. Pesticides are also used to control vector-born infectious diseases such as Zika virus, Lyme disease, and rabies, household pests like cockroaches, bed bugs, and as repellents etc. More than 1000 active ingredients are used in pesticides around the world to ensure food safety and prevention from pests and the highest amount (~45%) is spent on herbicides followed by insecticides, fungicides, and other types of pesticides.

4. Human exposure to pesticides and exposure risks

4.1 Human exposure to pesticides

Human beings get exposed to pesticides either actively through occupational exposure or passively through non-occupational exposure. Pesticides occupational exposure may occur during manufacturing, transportation, sale, and application process including exterminators. For example, in an incident of occupational exposure, 2800 workers were poisoned during malathion spray for malaria vector control in Pakistan [3]. Parents working in agriculture industry usually take pesticide contaminated clothing, equipment home, which has been associated with the development of cancers in their children.

Non-occupational exposure may include pesticides residues ingestion with contaminated food and water and inhalation of pesticides droplets from the air through drift from point of release or fumigation. Human beings are also exposed to residual indoor sprays and outdoor fogging of insecticides applied against insect pests of public health importance and homeowners exposed to structural pest control pesticides. Additionally, treatment of ectoparasites in pets, e.g. fleas, is also a source of exposure, especially for children.

Exposure through the intact skin (dermal exposure) is the most common route and may occur as a result of a splash, spill, or spray drift, during mixing, loading, disposing, and/or cleaning of application equipment especially when proper protective equipment are not used. Dermal absorption can be influenced by the amount/concentration, duration of exposure and temperature/humidity. Absorption is high through groin areas, the eyes and ear canal. Liquid formulations (e.g., emulsifiable concentrates) are readily absorbed through the skin compared to the solid formulations (e.g., powders, dusts, and granules).

Accidental ingestion of pesticides (oral exposure) occurs by drinking from unlabeled containers when pesticides are stored in food/drink container, water stored in pesticide-contaminated bottles, eating or smoking while, or after handling pesticides or through application equipment or pesticide residues in food and water. Inhalation of pesticides (respiratory exposure) may occur due to application of fumigants (which change into toxic gas after coming in contact with moisture in air) or presence of fine droplets in air (particle or vapor drift) after application of pesticides. Pesticides can enter blood stream after absorption through lungs.

Pesticides are distributed throughout the human body through the bloodstream and are excreted through urine, skin, and exhaled into air after metabolism. These pathways also determine the toxicity of any pesticide. Pesticides recognized as

persistent organic pollutant (POP) are fat soluble and are easily accumulated within the human fat-tissues, breast milk, and maternal blood placenta.

4.2 Pesticides exposure risks

The amount of risk from pesticide exposure depends on the toxicity and the exposure to the pesticide. Toxicity is a measure of how harmful or poisonous a pesticide is (causing sickness or other unwanted effects), while exposure is a measure of the contact (duration) with a pesticide. Toxicity of a pesticide is measured as lethal dose (LD_{50}). The LD_{50} value is the statistical estimate of a pesticide (mg/kg of body weight) which will kill 50% of the test animals within a stated period of time (24 hours to 7 days). The LD_{50} value also depends on the route of entry of a pesticide; oral LD_{50} for oral ingestion, dermal LD_{50} for skin contact exposure and Lethal Concentration (LC_{50}) for inhalation of fumigants and pesticide vapors.

A short term exposure or exposure to a single dose will cause acute toxicity with its health effects. Chronic toxicity results from repeated exposure to a pesticide over a longer period of time from several months to years. Hazard symbols, signal words and color on the primary display panel of a pesticide label are based on their dermal toxicity.

5. Pesticides modes of action

5.1 Insecticides

Insecticides Resistance Action Committee (IRAC) has classified insecticides into 32 groups based on their mode/site of action, in addition, there are 5 other types of insecticides with unknown modes of action. Most commonly used insecticides work at different sites in the nervous system of insects. Insecticides target the same sites of action in human nervous system and cause toxicity with adverse health effects. Carbamate (group 1A) and Organophosphate (OP) (group 1B) insecticides inhibit the enzyme Acetyl Choline Esterase (AChE) and cause hyper-excitation. AChE terminates the action of the excitatory neurotransmitter acetylcholine at the nerve synapses. Examples of pesticides inhibiting AChE include dichlorvos, malathion, phorate, carbaryl, carbofuran, etc. Cyclodiene organochlorine insecticides (OC) (group 2A) and phenylpyrazoles (group 2B) block the gamma amino butyric acid (GABA)-activated chloride channel causing hyper-excitation and convulsions. GABA is the major inhibitory neurotransmitter in insects. Examples of insecticides inhibiting GABA include endosulfan and fipronil. Synthetic pyrethroids and natural pyrethrins (group 3A) and DDT (group 3B) keep sodium channels open causing hyper-excitation and, in some cases, nerve blockage. Sodium channels are involved in the propagation of action potentials along nerve axons. Examples include deltamethrin and permethrin. Neonicotinoid insecticides (group 4A) bind to the acetylcholine site on nicotinic acetylcholine receptor (nAChRs) causing a range of symptoms from hyper-excitation to lethargy and paralysis. Examples include acetamiprid, clothianidin, imidacloprid, thiacloprid and thiamethoxam. Other groups of insecticides that work on nervous system includes those which allosterically activate nAChRs (e.g. spinetoram, spinosad) or glutamate-gated chloride channels (GluCls) (e.g. abamectin, emamectin benzoate), or allosterically inhibit the GABA-activated chloride channel and cause paralysis (e.g. broflanilide and fluxametamide). Glutamate is an important inhibitory neurotransmitter in insects. Other insecticides will block the nAChR ion channel or sodium channels, e.g. indoxacarb, cause nervous system shutdown and paralysis.

5.2 Fungicides

Fungicides inhibit fungal growth by interfering with critical cellular processes. Fungicide resistance action committee (FRAC) classify fungicides and bactericides into 50 groups based on the site of action. Within each group, there are target sites, which are the specific enzymes to which the fungicides bind. The different known target sites include nucleic acids metabolism, cytoskeleton and motor protein, respiration, amino acids and protein synthesis, signal transduction, lipid synthesis or transport/membrane integrity or function, sterol biosynthesis in membranes, cell wall biosynthesis, melanin synthesis in cell wall and host plant defense induction. Some fungicides and herbicides are considered endocrine disrupting pesticides.

5.3 Herbicides

Herbicides are pesticides that inhibit or interrupt normal plant growth and development. Herbicides are widely used in agriculture, landscape industry, and non-crop areas for weed management. Herbicides resistance action committee (HRAC) has classified herbicides into 27 groups. These include: growth regulators (synthetic auxins; auxin transport inhibitors), seedling growth inhibitors, photosynthetic inhibitors, amino acid synthesis inhibitors, lipid synthesis inhibitors, cell membrane disrupters, pigment inhibitors.

Growth regulator herbicides consist of the synthetic auxin and auxin transport inhibitory compounds and the most commonly used synthetic auxins include 2,4-*Dichlorophenoxyacetic acid* (2,4-D), fluroxypyr, dicamba, quinclorac, dichlorprop, MCPA (2-methyl-4-chlorophenoxyacetic acid), mecoprop and picloram. These are commonly used systemic herbicides which mimic the plant growth hormone auxin (indole acetic acid) [4]. Some of these synthetic auxin herbicides disrupt human hormonal system. Atrazine is also a commonly used photosynthetic inhibitor herbicide. Glyphosate (Roundup) is an amino acid derivative and inhibits synthase of EPSPS enzyme, which is involved in the synthesis of the aromatic amino acids (tyrosine, tryptophan, and phenylalanine). Paraquat (gramoxone) is an electron diverter, and as a respiratory inhibitor can be a significant risk to humans if inhaled or ingested.

6. Pesticide residues in food, water and air

6.1 Pesticide residues

'Pesticide residue' means any specified substance in food, agricultural commodities, or animal feed resulting from the use of pesticides. The term also includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities considered to be toxic. Application of pesticides during the production or storage of agricultural commodities result in pesticide residues in food (fruits, vegetables, grain, meat, etc). Pesticide residues are also found in the drinking water. Pesticide residues can build up to harmful levels through bioaccumulation and bio-magnification within the food chain.

WHO, in collaboration with FAO performs pesticide risk assessment to humans, both through direct exposure and through residues in food. The WHO core assessment group on pesticide residues review toxicological data and establish the acceptable daily intakes (ADIs) and acute reference doses (ARfDs) of pesticide residues for different commodities through a lifetime of food consumption. The ADIs are amount of pesticide residues which will not result in adverse health effects. Codex

Alimentarius Commission (the intergovernmental standards-setting body for food) establishes maximum residue limits (MRLs) for pesticides in food based on ADIs.

The MRL depends on the crop it is used on, and the same pesticide active ingredient may have different MRL values when used on different crops. Extraneous maximum residue limit (EMRL) refers to the maximum permitted limit of residues of mostly POP pesticides, which were previously used as pesticides but not registered any more, and residues arising from environmental contamination (including previous agricultural use) or residues from uses of these pesticides other than for agricultural purpose, e.g. DDT, Aldrin, etc.

6.2 Pesticide residues in food, water and air

There are several reports of pesticide residues detected on food exceeding the MRL values. For example, in India, vegetable samples were tested for the presence of OC, OP and pyrethroid insecticides, and 15.3% samples exceeded the MRL. In two Brazilian pesticide residue monitoring programs less than 3% of the samples had residue levels above the MRL. Pesticide residues were detected in 34% of samples of cereal grains collected throughout Poland and 3% samples contained residues over the maximum limit. A study from Maule Region (Talca, Chile) found pesticide residues on the fruits and vegetables schoolchildren brought as snack [5].

The pesticide residues detected in fruits and vegetables from Lithuania had multiple pesticides; 9 residues in grapes and tea, 5-9 residues in orange, mandarins, lemons, peaches, pears and 3-5 residues in pomegranates, plums, cucumbers, tomatoes and strawberries, and found that 2.6% samples exceeded the MRL values [6]. In a European Union study 14–23% of the samples had detectable residues of more than one active ingredient where 3.0–5.5% samples had residues levels above the MRL [7]. Exposure to multiple pesticide residues could be due to intake from a single food item containing multiple residues or from several food items each containing one or more residues. The combined toxic effects of two or more compounds can be independent, additive or synergistic.

Both recreational and medicinal cannabis samples contained high levels of residual pesticides and pesticides not legally allowed to be used on cannabis products in Oregon. Medicinal cannabis products were found to have mean levels of residual pesticides that were 3-12 times higher than recreational products, and 9 of the 50 pesticides identified were classified highly or extremely hazardous by the WHO [8].

Pesticide residues have been found in surface, groundwater and potable water samples from India [9]. Pesticide residues levels in river water and in drinking water samples in Turkey were significantly high compared with guideline values set by Turkey, EU and WHO as hazardous to human health [10]. Higher concentrations of pesticides in ambient air were recorded from potato farm sites in Prince Edward Island, Canada, Taihu Lake region of China and Kaweah Reservoir, CA, USA. A total of 87 pesticides were identified in the household dust samples from the rural Yakima Valley of Washington state, 47 of these have evidence of neurotoxicity included in the EPA list [11].

7. Impacts of pesticide use on human health

7.1 Acute health effects of pesticide exposure

The short-term acute adverse effects pesticide exposure on human health are stinging eyes, rashes, blisters, skin irritations, blindness, nausea, dizziness, diarrhea

and death. Exposure to pesticides in agricultural work can cause serious risks to the respiratory system causing chronic cough, dyspnea, wheezing and expectoration, decreased lung capacity, asthma, and bronchitis. These respiratory problems were found in workers in flower crops in Ethiopia, coffee plantations in Brazil and banana plantations in Costa Rica. In banana farming in Rio Grande do Norte (Brazil), the use of pesticides was related to the symptoms of burning in the throat and lungs, airway congestion, cramps, skin peeling, diarrhea, headache, chest pain, weakness, cough and skin irritation.

In banana production region of the Ribeira Valley (Brazil), workers (majority males, low schooling, mean age 39.6 years and 13.8 years of working time) had moderate obstructive disorder (10.0%) and mild obstructive disorder (13.3%) with decreased FEV1 (forced expiratory volume in 1 second) and FEV1/FVC (the ratio between forced expiratory volume in the first second and forced vital capacity and is very important for the detection of obstructive disorders). Similarly, exposures to mixtures (pollutants and pesticides) in children with asthma in California were also associated with reduced lung function measures FEV1 and FVC [12].

Many studies have found positive associations with pesticide exposure and children's respiratory and allergic effects such as asthma, wheezing, coughs, acute respiratory infections, hay fever, rhinitis, eczema, chronic phlegm, and lung function impairments. A study of school-age children with asthma in the agricultural community of Yakima Valley (Washington State) found that increase in exposures to OP insecticides was related with increase in LTE4 levels which was associated with a higher risk of asthma morbidity [13]. The neonicotinoid insecticides (e.g. imidacloprid, nitenpyram) are nicotinic receptors agonists and their exposure cause nausea, vomiting, muscle weakness, respiratory effects, headache, lethargy, and tachycardia.

7.2 Chronic effects of pesticide exposure

The long-term chronic adverse effects of pesticides exposure are cancers, birth defects, reproductive harm, neurological and developmental toxicity, immunotoxicity, and disruption of the endocrine system. The chronic effects of pesticides on human can be categorized into three major groups; neurotoxic effects, genotoxic and carcinogenic effects, and reproductive effects.

7.2.1 Neurotoxic effects

Neurotoxicity can be defined as any adverse effect on the central or peripheral nervous system caused by chemical, biological or physical agents. A developing nervous system in children (during replication, migration, differentiation, myelination of neurons, and synapse formation) is more susceptible to neurotoxic chemicals including pesticides. Chemicals (pesticides) can cause neuronal cell death by disruption of the cytoskeleton, induction of oxidative stress, calcium overload, or by damaging mitochondria. Most of the synthetic insecticides, some fungicides and herbicides, currently in use are neurotoxicants.

Pesticide molecules are small and lipophilic in nature, and can enter from blood to brain and then in neurons, glial cells and brain micro vessels. Pesticides can disrupt blood-brain barrier receptors in the central nervous system which enhance chronic toxicity and affect the receptor-mediated transcytosis. Neuronal cells are more susceptible to oxidative stress due to their high polyunsaturated fat content in the myelin sheaths, low anti-oxidative capabilities, enzymatic systems with transient metals that aid in the production of free radicals, and demand for high oxygen and glucose metabolism rate.

OPs and carbamates bind to and phosphorylate/carbamalate the AChE which causes accumulation of acetylcholine at cholinergic synapses causing overstimulation of muscarinic and nicotinic cholinergic receptors. Neuropsychiatric disorders, such as anxiety and depression, are observed in patients with acute and long-term poisoning from OPs. OPs may also cause an intermediate syndrome and OP-induced delayed polyneuropathy (OPIDP) 1-3 weeks after a single exposure. In carbamates, the AChE inhibition is reversible and acute intoxication is generally resolved within a few hours.

The OP insecticides can disturb the function of mitochondria by inducing oxidative stress in central nervous system through critical depletion of mitochondrial energy, the activation of proteolytic enzymes, and DNA fragmentation leading to apoptosis. The dysfunction of mitochondria and oxidative stress is responsible for several neurological diseases, including Parkinson's disease, seizure, cognitive dysfunction, attention and memory deficits, dementia, depression, and Alzheimer's disease. OP triggered induction of a xanthine oxidase may play a role in cognitive impairment.

In a study, increased inhibition of cholinesterase enzyme with increased exposure to OP insecticides was confirmed in both occupationally exposed (OE) and environmentally exposed (EE) groups of people. The OP exposure, mainly in the EE group, was associated with a diminished neuropsychological performance; general mental status, language, memory, attention, executive function, praxis and psychomotricity.

Acute poisoning due to exposure to OP (particularly chlorpyrifos) was reported with higher prevalence of peripheral polyneuropathy, and deterioration of cognitive functions (verbal fluency, and visual and auditory memory) was observed in agricultural workers and in inhabitants of rural agricultural areas. Exposure to OP insecticides in rural schoolchildren was associated with a lower processing speed in children and an IQ lower than expected for their age.

Exposure to type I pyrethroids cause tremor syndrome (behavioral arousal, aggressive sparring, increased startle response, and fine body tremor progressing to whole-body tremor, and prostration) while type II pyrethroids exposure cause salivation syndrome (profuse salivation, coarse tremor progressing to choreoatetosis, and clonic seizure). The poisoned cerebral cortex affect learning, memory, emotions, and movement. Pyrethroids exposure has been positively associated with hearing loss in U.S. adolescents. Pyrethroids exposure induced Tau protein malfunction which may be the mechanism underlying cognitive impairment. Paraquat, triazine and pyrazole (herbicides) through oxidative stress, raised influx of calcium and the stimulation of nitrogen oxide species, and aggravated Aβ amyloidogenesis cause cognitive impairment.

Exposure to endocrine disrupting chemicals (EDCs) including many pesticides can disrupt maternal thyroid imbalance which can result in permanent and lifelong neurodevelopmental consequences for their children, including attention-deficit disorder, autism spectrum disorder, and cognitive and behavioral dysfunction. Workers of fruit and seed export companies in a rural area of Santiago exposed to methyl bromide (CH3Br, a fumigant) had increased concentration of CH3Br in blood after application which resulted in a higher frequency of insomnia, headaches, paresthesias, mood swings, memory loss, and decreased concentration [14].

Parkinson's disease (PD) is characterized by progressive degeneration of dopaminergic neurons of the nigrostriatal pathway and the formation of alpha-synuclein (α-syn)-containing Lewy bodies. Dieldrin (OC) is selectively toxic to dopaminergic cells, disrupts striatal dopamine activity, and may promote α-syn aggregation while ziram (dithiocarbamate fungicide) increases the probability of synaptic vesicle release by dysregulation of the ubiquitin signaling system and increases excitability in both aminergic and glutamatergic neurons leading to PD.

7.2.2 Genotoxic and carcinogenic effects

A genotoxic agent can be a physical, chemical or biological agent that can interact with the genetic material (DNA) causing alterations, damage or ruptures, and those that interfere with enzymatic processes of repair, genesis or polymerization of proteins involved in chromosome segregation. These alterations could lead to impaired embryonic development or be the initial steps in the development of cancer. Pesticides exposure can cause genomic damage. Genetic damage caused by pesticides is broadly classified into three classes; (i) Pre-mutagenic damage like DNA strand breaks and DNA adducts (ii) gene mutations like insertion, deletion, inversion and translocation (iii) chromosomal aberrations, including loss or gain of whole chromosome (aneuploidy), deletion or breaks (clastogenicity), and chromosomal rearrangements.

Farmers exposed to pesticide mixtures in Greece had possible clastogenic (chromosome breakage cause mutation) and aneugenic (abnormal number of chromosomes) effect of pesticides on the genetic material. DNA methylation changes in the placenta were significantly associated with the maternal plasma concentrations of OCs in early pregnancy causing prenatal toxicity. OPs affect DNA methylation, induce the AChE gene expression and activate the NMDA glutamate receptors resulting in calcium influx in the post-synaptic neurons leading to degeneration.

Genetic damage has been reported from exposure to malathion (OP), carbofuran (carbamate), triflumuron (Insect growth regulator), imidacloprid, acetamiprid and thiamethoxam (neonicotinoid insecticides), pentachlorophenol (OC), Emamectin benzoate (used in agriculture, household, and veterinary medicine), and tembotrione (novel post-emergence herbicide) (**Table 2**).

Cancer is characterized by an uncontrolled cell growth with limitless replication, resistance to apoptosis, alteration of growth factors (GFs), resistance to chemotherapy, metastasis and angiogenesis. Cancer develops as a result of multifactorial complex interactions of genetic and lifestyle factors including, diet, stress, physical and biological agents, infections, and exposure to the hazardous chemical substances. Pesticides exposure acts as a stimulant to cancer and chronic low-dose is considered one of the important risk factors for the increasing cancer incidence. **Table 3** presents a list of pesticides suggesting carcinogenicity in different types of studies.

WHO Hazard Class	Band color	Signal word	Dermal LD_{50} (mg/Kg)	
			Solid formulation	Liquid formulation
Class Ia Extremely Hazardous	Red	VERY TOXIC	<10	<40
Class Ib Highly Hazardous	Red	TOXIC	10–100	40–400
Class II Moderately Hazardous	Yellow	HARMFUL	100-1000	400-4000
Class III Slightly Hazardous	Blue	CAUTION	>1000	>4000
Class U Products unlikely to present a hazard	Green			

Table 2.
Pesticides hazard classification by FAO.

Type of cancer	ToP	Name of pesticide	Type of study	Reference
Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)	OC	P,p'-DDT	Case control	[15]
		P,p'-DDE	Agricultural health	[16]
		HCH	Case control	
	MoC	Nonachlor/ trans-nonachlor hexachlorobenzene	Blood Agricultural health	
	OC	Mirex	Case control	
		Chlordane	Case control	
		Lindane	Case control	
	OP	Malathion	Case control	[17]
		Diazinon		
		Terbufos	Case control	[18]
		Dimethoate chlorpyrifos	Agricultural health	[15]
	PYR	Permethrin	Case control	[16]
	NPYR	Pyrethrum	Agricultural health	[17]
	PHE	2,4-D	Case control	[19]
		Mecoprop	Epidemiological	[20]
	CHL	Dichlorprop	Case control	[21]
	BNZ	Dicamba	Case control	[20]
	GLY	Glyphosate	Case control	[16]
Breast	OC	Pp'-DDT	Histopathology	[22]
		Pp'-DDD	Histopathology	[23]
		P,p′-DDE		
		β-HCH	Histopathology	[24]
		Heptachlor		
		Hexachlorobenzene		
	OP	Chlorpyrifos	MCF-7 breast cancer cells	[25]
		Malathion		
		Terbufos	Case control/MCF-7/ MCF-10F	[26]
		Diazinon		
		Dimethoate		
	PYR	Flucythrinate	AutoDock Vina 1.1.1	[27]
		Fluvalinate		
		Bifenthrin		
		Cyhalothrin		
		Cypermethrin		
	NEO	Thiacloprid imidacloprid	Hs578t cells	[28]
	PTH	Captan	Agricultural health	[29]
	GLY	Glyphosate	Case control	[30]

Prostate	OC	Pp'-DDT Lindane	Case-control	[31]
		Endosulfan	Human prostate cancer PC3 and DU145 cell	[32]
	OB	Methyl bromide	Agricultural health	[33]
	OP	Chlorpyrifos	Prostate epithelial lines	[34]
		Dimethoate	Agricultural health	[35]
		Malathion Carbaryl	Case-control	[31]
	PYR	λ-Cyhalothrin	Prostate epithelial lines	[34]
		Bifenthrin	PC3 human	[36]
		Deltamethrin	Prostate cancer cell	[37]
	QUI	Dichlone	Case control	[31]
	IMI	Prochloraz	PC-3 prostate cancer cells	[38]
	DIC	Vinclozolin		
	MoV	M2		
	CHL	2,4-D	Case control	[31]
		2,4-DB	Histopathology	[39]
		2,4,5-T		
	CHP	Picloram	Histopathology	[39]
	ORG	Cacodylic acid	Case control	[31]
	TRI	Simazine Atrazine	RM1 cells	[40]
	Mo2	2, 4-dichlorophenol (DCP)	Case control	[31]
	MoD	Dinoseb amine		
	GLY	Glyphosate	Prostate epithelial lines	[34]
Lung cancer	OP	Diazinon	Epidemiological	[41]
	PYT	Cypermethrin	Lewis lung cancer cells	[42]
	αCH	Acetochlor	Agricultural health	[43]
	TRI	Atrazine		
Bladder	IMZ	Imazethapyr imazaquin	Agricultural health	[44]
Hepatocellular carcinoma	OC	Pp'-DDT	Serum levels	[45]
		Pp'-DDE	Toxicological	[46]
	OC	Endosulfan	Human liver carcinoma cells (HepG2)	[47]
	CAR	Carbaryl	Toxicological	[46]
	BEZ	Fluopyram	Female rat	[48]
	BED	Carbendazim	Toxicological	[46]
	BEN	Dicamba	Agricultural health	[49]
	αCH	Acetochlor	Human liver carcinoma cells (HepG2)	[47]
Stomach	TRI	Atrazine	Agricultural health	[50]

Thyroid	OP	Malathion	Agricultural health	[51]
	TRZ	Penconazole	Agricultural health	[52]
	TRI	Atrazine	Agricultural health	[53]
		Amitrole	Nthy-ori-3-1 cell	[54]
Ovarian	OC	Pp'-DDT	Blood	[55]
		Pp'-DDE		
		β-HCH		
		Endosulfan		
	OP	Diazinon	Agricultural health	[51]
	PYR	λ-Cyhalothrin	BG-1 ovarian cancer cells	[56]
		Cypermethrin		
		Cyprodinil		
	HYD	Fenhexamid	Mouse model with transplanted BG-1 cells	[56]
Colorectal	OC	Pp'-DDE		[57]
		Endosulfan		
	OP	Chlorpyrifos	Human colorectal adenocarcinoma H508 cells	[58]
	CAR	Aldicarb		
	αCH	Acetochlor	Agricultural health	[51]
Brain	OP	Dichlorvos	Male albino Wistar rats	[59]

ToP, type of pesticide; OC, organochlorine insecticide; MoC, metabolites of chlordane; OP, organophosphate insecticide; PYT, pyrethroid insecticide; NPYT, natural pyrethroid insecticide; PHC, phenoxy-carboxylate herbicide; CHL, chlorophenoxy herbicide; BEN, benzoate herbicide; GLY, glycine herbicide; NEO, neonicotinoid insecticide; PHT, phthalimide fungicide; OB, organobromine insecticide; QUI, quinone algicide; IMI, imidazole fungicide; DIC, dicarboximide fungicide; MoV, metabolite of vinclozolin; CHP, chlorinated pyridine herbicide; ORG, organoarsenic herbicide; TRI, triazine herbicides; Mo2, metabolite of 2,4-D; Mod, metabolite of dinoseb dinitrophenol herbicide; αCH, α-chloroacetamides herbicide; IMZ, imidazolinones herbicides; CAR, carbamate insecticide/nematicide; BEZ, benzamide, pyramide fungicide; BED, benzimidazole fungicide; TRZ, triazole fungicide; HYD, hydroxyanilides fungicides.

Table 3.
List of Pesticides Suggesting Carcinogenicity in different types of studies.

7.2.2.1 Non-Hodgkin lymphoma and Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a diverse group malignancies and its incidence has increased worldwide. Patients with immune dysfunction are at a high risk to develop NHL. Studies have reported an elevated risk of NHL with exposure to several classes of pesticides. Terbufos (OP nematicide), dimethoate, malathion and chlorpyrifos (OP insecticide), and 2,4-D and dichlorprop (chlorophenoxy herbicides) have been associated with significant risk of developing HL.

7.2.2.2 Leukemia

Leukemia has been associated with occupational exposure with a higher risk in livestock farmers and golf course superintendents. The risk of chronic myelocytic leukemia (CML) and acute myeloblastic leukemia (AML) was found to be higher in women. Children whose parents used garden and indoor insecticides, or

whose mothers had been exposed while pregnant had increased rates of all types of leukemia. Children living on farms and those exposed to household pesticides have increased risk of leukemia. Association between occupational exposure to pesticides and chronic lymphocytic leukemia (CLL) has been reported from Spain. A nationwide study in France showed a moderate increase in incidence of childhood AL in municipalities where viticulture is common.

7.2.2.3 Brain cancer

Brain tumors are the most common solid tumors in children and the leading cause of cancer-related mortality during childhood. A positive association has been reported between parental occupational, prenatal or residential exposure, living on a farm, mothers living on farms, rural activity and childhood brain tumors. Increased risk for primitive neuroectodermal tumors (PNETs) was associated with maternal exposure living on pig or poultry farms. Exposure to pyrethroid formulations used to control mosquitoes and cockroaches at home also increase the risk of brain tumors.

7.2.2.4 Breast cancer

Breast cancer is the leading cause of cancer-related deaths among women. About 650 pesticides out of the 800 used worldwide can affect the functioning of the endocrine system and are called endocrine disrupting pesticides (EDPs). EDPs have the potential ability to act as tumor promoters and increasing risk of breast cancer. All women diagnosed with breast cancer between 1995 and 2005 in the city of Arica (geographic area that received massive aerial applications of malathion in 1980) were 5.7 times more likely to suffer from breast cancer compared to women diagnosed during the same period in the city of Iquique, Chile [14]. Several chemical classes of insecticides, fungicides and herbicides have been associated with breast cancer in women (**Table 3**).

7.2.2.5 Prostate cancer

Prostate cancer is the second most common cancer in men globally, and accounts for 7% of all cancers. More than 95% of cases of prostate cancer are androgen-dependent. The higher incidence of prostate cancer, at least in part, has been associated with the hormone disrupting pesticides and consistent positive associations between prostate cancer and pesticide exposure have been reported.

7.2.2.6 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the 6th most common cancer, and the 4th most common cause of cancer-related mortality. The major risk factors include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, aflatoxin contaminated foods, obesity, smoking and type 2 diabetes besides pesticides. Pesticides exposure has been associated with increased risk of developing HCC.

7.2.3 Reproductive effects

EDCs are emerging as one of the leading risks and are recognized as serious and urgent threats to public health. In laboratory studies, EDCs are reported to shorten gestation, alter intrauterine growth, and disrupt metabolic programming.

Prenatal exposure to EDCs can affect fetal neurodevelopment through disruption of peroxisome proliferator activated receptors, mainly estrogen receptors, and thyroid hormone receptors.

Failure of testosterone production in Leydig cells leads to failure of testosterone-bound androgen receptor-mediated gene transcription necessary for spermatogenesis. Many studies have shown that various pesticides decrease testosterone levels. Testosterone is required for the final stages of sperm maturation, so a decrease in intra-testicular testosterone is likely to impair fertility. Vinclozolin (fungicide) and chlorpyrifos (OP) can reduce testosterone production. Exposure to higher concentrations of OP and dialkyl phosphates (metabolites of OPs), p,p'-DDE, fenvalerate and atrazine (chlorotriazine herbicide) have been consistently associated with lower semen quality (sperm concentration, motility, and morphology).

A study of male children from a village of cashew plantations, where endosulfan (OC, EDC) had been aerially sprayed for more than 20 years, showed a delay in sexual maturity and an alteration in sex hormone synthesis. Endosulfan, in exposed mothers, can move via trans-placental route and breast feeding to children. Exposure during critical periods of development might contribute to decline conception rates and increased incidence of female reproductive disorders, such as altered cyclicity, endometriosis, fetal growth retardation, and pregnancy loss [60].

A high incidence of spontaneous abortions 81.02 / 1000 live newborns was reported in Valparaíso Region (agricultural area) compared to 9.5 /1000 live newborns in the rest of Chile. A 28% incidence of congenital malformations in live newborns was reported in the O'Higgins Region (agricultural area) compared to only 15% of cases in non-agricultural in Chile [14].

8. Conclusion

Pesticides are used in managing pests of agricultural and public health importance, and their use will continue in future because of food security and vector control. Additionally, pesticides are used at home in fumigation for structural pests and to mitigate household pest using aerosols or sprays. It is difficult to eliminate pesticides in the near future, but they should be used with care and caution. Most pesticides are potentially toxic to human beings resulting in severe health consequences including cancers.

Epidemiological evidence suggests that there is an increased incidence of different diseases including leukemia, lymphoma, and several other types of cancers in farmers, and those who are associated with application of pesticides. There is also evidence that parental exposure, as well as, exposure in early life or adolescence could increase the longer-term risks.

Since animal studies are problematic, expensive and often generate ethical problems, cell cultures are increasingly used as a model of research. Correctly conducted and properly selected, the cell culture is an excellent experimental model reflecting human exposure to different xenobiotics through all relevant routes. The cell cultures are also becoming more widely used to study the effect of pesticides on the human body at a molecular level, which is necessary to understand the hazards and determine the level of exposure.

Some pesticides (OCs) are no longer used worldwide due to their persistence and toxicity. However, their residues or metabolites are still found in food and water samples. The use of OPs and carbamate insecticides has been reduced since the arrival of newer chemistries in different parts of the world but most of them are still use around the world.

The workplace safety standards and proper pesticide management and storage must be implemented to reduce the risks posed to human health. Pesticide users should be aware of their risks and proper handling, as well as must use personal protective equipment which are effective in reducing damage to human health. To ensure healthy childhood growth, efforts should be made to develop comprehensive pesticides risk mitigation strategies and interventions to reduce children's exposure.

It is critical to achieve sustainable development in agricultural systems. Newer approaches in pest management have been developed which should be encouraged. For example, RNA interference- (RNAi-) based pesticides are emerging as a promising new biorational control strategy [61] and steam treatment at temperature of 150.56°C can kill 93.99% of nematode 97.49% of bacteria [62].

Future research need in the context of minimizing the impact on human health due to exposure to pesticides include an urgent need to eliminate the use of carcinogenic pesticides and to develop environmentally sound integrated pest management (IPM) strategies that use the minimum amount of pesticides. Such IPM strategies should aim at reducing the pesticides residues on food products and pesticides-free water and air.

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References

[1] University of Kentucky. PESTICIDE FORMULATIONS; Kentucky Pesticide Safety Education Program [Internet]. 2020. Available from: https://www.uky.edu/Ag/Entomology/PSEP/3formulations.html

[2] Pimentel D. Integrated Pest Management. In: Peshin, Rajinder, Dhawan AK, editor. 1st ed. Springer; 2009.

[3] USAID. Integrated Vector Management Programs for Malaria Vector Control. 2007. p. 524.

[4] HRAC. HRAC MODE OF ACTION CLASSIFICATION 2020 MAP [Internet]. 2020. Available from: https://www.hracglobal.com

[5] Muñoz-Quezada MT, Iglesias V, Lucero B, Steenland K, Barr DB, Levy K, et al. Predictors of exposure to organophosphate pesticides in schoolchildren in the Province of Talca, Chile. Environ Int [Internet]. 2012 Oct;47:28-36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0160412012001225

[6] Petraitis J, Jarmalaite I, Vaičiunas V, Uščinas R, Jankovskiene G. A review of research studies into pesticide residues in food in Lithuania. Zemdirbyste. 2013;100(2):205-12.

[7] Commission of the European Communities. Monitoring of Pesticide Residues in Products of Plant Origin [Internet]. 2008. p. 40. Available from: http://ec.europa.eu/food/fvo/specialreports/pesticide_residues/report_2006_en.pdf

[8] Evoy R, Kincl L. Evaluation of Pesticides Found in Oregon Cannabis from 2016 to 2017. Ann Work Expo Heal. 2020;64(7):770-4.

[9] Agarwal A, Prajapati R, Singh OP, Raza SK, Thakur LK. Pesticide residue in water—a challenging task in India. Environ Monit Assess. 2015;187(2).

[10] Koçyiğit H, Sinanoğlu F. Method validation for the analysis of pesticide residue in aqueous environment. Env Monit Assess. 2020;192(9):567.

[11] Bennett B, Workman T, Smith MN, Griffith WC, Thompson B, Faustman EM. Characterizing the Neurodevelopmental Pesticide Exposome in a Children's Agricultural Cohort. Int J Environ Res Public Health [Internet]. 2020 Feb 25;17(5):1479. Available from: https://www.mdpi.com/1660-4601/17/5/1479

[12] Benka-Coker W, Hoskovec L, Severson R, Balmes J, Wilson A, Magzamen S. The joint effect of ambient air pollution and agricultural pesticide exposures on lung function among children with asthma. Environ Res [Internet]. 2020 Nov;190:109903. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0013935120307982

[13] Benka-Coker W, Loftus C, Karr C, Magzamen S. Association of Organophosphate Pesticide Exposure and a Marker of Asthma Morbidity in an Agricultural Community. J Agromedicine [Internet]. 2020 Jan 2;25(1):106-14. Available from: https://www.tandfonline.com/doi/full/10.1080/1059924X.2019.1619644

[14] Zúñiga-Venegas L, Saracini C, Pancetti F, Muñoz-Quezada MT, Lucero B, Foerster C, et al. Exposición a plaguicidas en Chile y salud poblacional: urgencia para la toma de decisiones. Gac Sanit [Internet]. 2020 Jul; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0213911120301291

[15] Latifovic L, Freeman LEB, Spinelli JJ, Pahwa M, Kachuri L,

Blair A, et al. Pesticide use and risk of Hodgkin lymphoma: results from the North American Pooled Project (NAPP). Cancer Causes Control [Internet]. 2020;31(6):583-99. Available from: https://doi.org/10.1007/s10552-020-01301-4

[16] Alavanja MCR, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, et al. Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study. Akiba S, editor. PLoS One [Internet]. 2014 Oct 22;9(10):e109332. Available from: https://dx.plos.org/10.1371/journal.pone.0109332

[17] Kachuri L, Beane Freeman LE, Spinelli JJ, Blair A, Pahwa M, Koutros S, et al. Insecticide use and risk of <scp>non-Hodgkin</scp> lymphoma subtypes: a subset meta-analysis of the North American Pooled Project. Int J Cancer [Internet]. 2020 Jun 23;ijc.33164. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.33164

[18] Moura LTR de, Bedor CNG, Lopez RVM, Santana VS, Rocha TMB da S da, Wünsch Filho V, et al. Exposição ocupacional a agrotóxicos organofosforados e neoplasias hematológicas: uma revisão sistemática. Rev Bras Epidemiol [Internet]. 2020;23. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1415-790X2020000100428&tlng=pt

[19] Smith AM, Smith MT, La Merrill MA, Liaw J, Steinmaus C. 2,4-dichlorophenoxyacetic acid (2,4-D) and risk of non-Hodgkin lymphoma: a meta-analysis accounting for exposure levels. Ann Epidemiol [Internet]. 2017 Apr;27(4):281-289.e4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1047279717302466

[20] McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, et al. Non-Hodgkin's lymphoma and specific pesticide exposures inmen: Cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 2001;10(11):1155-63.

[21] Pahwa P, Karunanayake CP, Spinelli JJ, Dosman JA, McDuffie HH. Ethnicity and incidence of Hodgkin lymphoma in Canadian population. BMC Cancer [Internet]. 2009 Dec 11;9(1):141. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-9-141

[22] Ellsworth RE, Kostyniak PJ, Chi L-H, Shriver CD, Costantino NS, Ellsworth DL. Organochlorine pesticide residues in human breast tissue and their relationships with clinical and pathological characteristics of breast cancer. Environ Toxicol [Internet]. 2018 Aug;33(8):876-84. Available from: http://doi.wiley.com/10.1002/tox.22573

[23] He T-T, Zuo A-J, Wang J-G, Zhao P. Organochlorine pesticides accumulation and breast cancer: A hospital-based case–control study. Tumor Biol [Internet]. 2017 May;39(5):101042831769911. Available from: http://journals.sagepub.com/doi/10.1177/1010428317699114

[24] Arrebola JP, Belhassen H, Artacho-Cordón F, Ghali R, Ghorbel H, Boussen H, et al. Risk of female breast cancer and serum concentrations of organochlorine pesticides and polychlorinated biphenyls: A case-control study in Tunisia. Sci Total Environ. 2015;520:106-13.

[25] Zárate L V., Pontillo CA, Español A, Miret N V., Chiappini F, Cocca C, et al. Angiogenesis signaling in breast cancer models is induced by hexachlorobenzene and chlorpyrifos, pesticide ligands of the aryl hydrocarbon receptor. Toxicol Appl Pharmacol [Internet]. 2020 Aug;401:115093. Available from: https://

linkinghub.elsevier.com/retrieve/pii/S0041008X20302179

[26] Yang KJ, Lee J, Park HL. Organophosphate Pesticide Exposure and Breast Cancer Risk: A Rapid Review of Human, Animal, and Cell-Based Studies. Int J Environ Res Public Health [Internet]. 2020 Jul 13;17(14):5030. Available from: https://www.mdpi.com/1660-4601/17/14/5030

[27] Montes-Grajales D, Olivero-Verbel J. Structure-based Identification of Endocrine Disrupting Pesticides Targeting Breast Cancer Proteins. Toxicology [Internet]. 2020 Jun;439:152459. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300483X20300986

[28] Silva AMC, Campos PHN, Mattos IE, Hajat S, Lacerda EM, Ferreira MJM. Environmental exposure to pesticides and breast cancer in a region of intensive agribusiness activity in brazil: A case-control study. Int J Environ Res Public Health. 2019;16(20):1-10.

[29] Mills PK, Dodge JL, Bush J, Thompson Y, Shah P. Agricultural Exposures and Breast Cancer Among Latina in the San Joaquin Valley of California. J Occup Environ Med [Internet]. 2019 Jul;61(7):552-8. Available from: http://journals.lww.com/00043764-201907000-00003

[30] Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol. 2013;59:129-36.

[31] Band PR, Abanto Z, Bert J, Lang B, Fang R, Gallagher RP, et al. Prostate cancer risk and exposure to pesticides in British Columbia Farmers. Prostate. 2011;71(2):168-83.

[32] Wang Y, Guo Y, Hu Y, Sun Y, Xu D. Endosulfan triggers epithelial-mesenchymal transition via PTP4A3-mediated TGF-β signaling pathway in prostate cancer cells. Sci Total Environ [Internet]. 2020 Aug;731:139234. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0048969720327510

[33] Alavanja MC. Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort. Am J Epidemiol [Internet]. 2003 May 1;157(9):800-14. Available from: https://academic.oup.com/aje/article-lookup/doi/10.1093/aje/kwg040

[34] Potti A, Sehgal I. Exposure to pesticides increases levels of uPA and uPAR in pre-malignant human prostate cells. Environ Toxicol Pharmacol [Internet]. 2005 Feb;19(2):215-9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1382668904001383

[35] Pardo LA, Beane Freeman LE, Lerro CC, Andreotti G, Hofmann JN, Parks CG, et al. Pesticide exposure and risk of aggressive prostate cancer among private pesticide applicators. Environ Heal [Internet]. 2020 Dec 5;19(1):30. Available from: https://ehjournal.biomedcentral.com/articles/10.1186/s12940-020-00583-0

[36] Chien J-M, Liang W-Z, Liao W-C, Kuo C-C, Chou C-T, Hao L-J, et al. Ca 2+ movement and cytotoxicity induced by the pyrethroid pesticide bifenthrin in human prostate cancer cells. Hum Exp Toxicol [Internet]. 2019 Oct 17;38(10):1145-54. Available from: http://journals.sagepub.com/doi/10.1177/0960327119855129

[37] Lee H-H. Ca^(2+) Movement Induced by Deltamethrin in PC3 Human Prostate Cancer Cells. Chin J Physiol [Internet]. 2016 Jun 30;59(3):148-55. Available from: http://www.airitilibrary.com/Publication/alDetailedMesh?DocID=03044920-201606-201606290012-201606290012-148-155

[38] Thomas P, Dong J. Novel mechanism of endocrine disruption by fungicides through binding to the membrane androgen receptor, ZIP9 (SLC39A9), and antagonizing rapid testosterone induction of the intrinsic apoptotic pathway. Steroids [Internet]. 2019 Sep;149:108415. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039128X19300996

[39] Ansbaugh N, Shannon J, Mori M, Farris PE, Garzotto M. Agent Orange as a risk factor for high-grade prostate cancer. Cancer [Internet]. 2013 Jul 1;119(13):2399-404. Available from: http://doi.wiley.com/10.1002/cncr.27941

[40] Hu K, TIAN Y, DU Y, HUANG L, CHEN J, LI N, et al. Atrazine promotes RM1 prostate cancer cell proliferation by activating STAT3 signaling. Int J Oncol [Internet]. 2016 May;48(5):2166-74. Available from: https://www.spandidos-publications.com/10.3892/ijo.2016.3433

[41] Jones RR, Barone-Adesi F, Koutros S, Lerro CC, Blair A, Lubin J, et al. Incidence of solid tumours among pesticide applicators exposed to the organophosphate insecticide diazinon in the Agricultural Health Study: an updated analysis. Occup Environ Med [Internet]. 2015 Jul;72(7):496-503. Available from: http://oem.bmj.com/lookup/doi/10.1136/oemed-2014-102728

[42] Huang F, Chen Z, Chen H, Lu W, Xie S, Meng QH, et al. Cypermethrin Promotes Lung Cancer Metastasis via Modulation of Macrophage Polarization by Targeting MicroRNA-155/Bcl6. Toxicol Sci [Internet]. 2018 Jun 1;163(2):454-65. Available from: https://academic.oup.com/toxsci/article/163/2/454/4870159

[43] Lerro CC, Koutros S, Andreotti G, Hines CJ, Blair A, Lubin J, et al. Use of acetochlor and cancer incidence in the Agricultural Health Study. Int J Cancer [Internet]. 2015 Sep 1;137(5):1167-75. Available from: http://doi.wiley.com/10.1002/ijc.29416

[44] Koutros S, Silverman DT, Alavanja MCR, Andreotti G, Lerro CC, Heltshe S, et al. Occupational exposure to pesticides and bladder cancer risk. Int J Epidemiol. 2016;45(3):792-805.

[45] Zhao B, Shen H, Liu F, Liu S, Niu J, Guo F, et al. Exposure to organochlorine pesticides is an independent risk factor of hepatocellular carcinoma: A case–control study. J Expo Sci Environ Epidemiol [Internet]. 2012 Nov 14;22(6):541-8. Available from: http://www.nature.com/articles/jes201129

[46] Peyre L, Zucchini-Pascal N, de Sousa G, Luzy A-P, Rahmani R. Potential involvement of chemicals in liver cancer progression: An alternative toxicological approach combining biomarkers and innovative technologies. Toxicol Vitr [Internet]. 2014 Dec;28(8):1507-20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0887233314001246

[47] Huang T, Huang Y, Huang Y, Yang Y, Zhao Y, Martyniuk CJ. Toxicity assessment of the herbicide acetochlor in the human liver carcinoma (HepG2) cell line. Chemosphere [Internet]. 2020 Mar;243:125345. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0045653519325858

[48] Tinwell H, Rouquié D, Schorsch F, Geter D, Wason S, Bars R. Liver tumor formation in female rat induced by fluopyram is mediated by CAR/PXR nuclear receptor activation. Regul Toxicol Pharmacol [Internet]. 2014 Dec;70(3):648-58. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0273230014002165

[49] Lerro CC, Hofmann JN, Andreotti G, Koutros S, Parks CG, Blair A, et al. Dicamba use and cancer incidence in the agricultural health study: an updated analysis. Int J

Epidemiol [Internet]. 2020 May 1; Available from: https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa066/5827818

[50] Van Leeuwen JA, Waltner-Toews D, Abernathy T, Smit B, Shoukri M. Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991. Int J Epidemiol [Internet]. 1999 Oct 1;28(5):836-40. Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/28.5.836

[51] Lerro CC, Koutros S, Andreotti G, Friesen MC, Alavanja MC, Blair A, et al. Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study. Occup Environ Med [Internet]. 2015 Oct;72(10):736-44. Available from: http://oem.bmj.com/lookup/doi/10.1136/oemed-2014-102798

[52] Perdichizzi S, Mascolo MG, Silingardi P, Morandi E, Rotondo F, Guerrini A, et al. Cancer-related genes transcriptionally induced by the fungicide penconazole. Toxicol Vitr [Internet]. 2014 Feb;28(1):125-30. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0887233313001574

[53] Brasil VLM, Ramos Pinto MB, Bonan RF, Kowalski LP, da Cruz Perez DE. Pesticides as risk factors for head and neck cancer: A review. J Oral Pathol Med [Internet]. 2018 Aug;47(7):641-51. Available from: http://doi.wiley.com/10.1111/jop.12701

[54] Pan H, Xuan Q, Han D, Yin J, Wu S, Wang Q. [The change of cancer-related genes expression profile in Nthy-ori-3-1 cell induced by the pesticide amitrole]. Wei Sheng Yan Jiu [Internet]. 2016 Jul;45(4):558-62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29903322

[55] Tusha Sharma, Basu D Banerjee, Gaurav K Thakur, Kiran Guleria DM. Polymorphism of xenobiotic metabolizing gene and susceptibility of epithelial ovarian cancer with reference to organochlorine pesticides exposure. Exp Biol Med. 2019;244(16):1446-53.

[56] Go R-E, Kim C-W, Choi K-C. Effect of fenhexamid and cyprodinil on the expression of cell cycle- and metastasis-related genes via an estrogen receptor-dependent pathway in cellular and xenografted ovarian cancer models. Toxicol Appl Pharmacol [Internet]. 2015 Nov;289(1):48-57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0041008X15300752

[57] Song L, Liu J, Jin X, Li Z, Zhao M, Liu W. p, p′-Dichlorodiphenyldichloroethylene Induces Colorectal Adenocarcinoma Cell Proliferation through Oxidative Stress. Liu C, editor. PLoS One [Internet]. 2014 Nov 11;9(11):e112700. Available from: https://dx.plos.org/10.1371/journal.pone.0112700

[58] Lee WJ, Sandler DP, Blair A, Samanic C, Cross AJ, Alavanja MCR. Pesticide use and colorectal cancer risk in the agricultural health study. Int J Cancer [Internet]. 2007 Jul 15;121(2):339-46. Available from: http://doi.wiley.com/10.1002/ijc.22635

[59] KAUR P, RADOTRA B, MINZ R, GILL K. Impaired mitochondrial energy metabolism and neuronal apoptotic cell death after chronic dichlorvos (OP) exposure in rat brain. Neurotoxicology [Internet]. 2007 Nov;28(6):1208-19. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161813X07001659

[60] Milesi MM, Durando M, Lorenz V, Gastiazoro MP, Varayoud J. Postnatal exposure to endosulfan affects uterine development and fertility. Mol Cell Endocrinol [Internet].

2020 Jul;511:110855. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0303720720301556

[61] Mysore K, Hapairai LK, Sun L, Li P, Wang C-W, Scheel ND, et al. Characterization of a dual-action adulticidal and larvicidal interfering RNA pesticide targeting the Shaker gene of multiple disease vector mosquitoes. Abd-Alla AMM, editor. PLoS Negl Trop Dis [Internet]. 2020 Jul 20;14(7):e0008479. Available from: https://dx.plos.org/10.1371/journal.pntd.0008479

[62] Huh D-A, Chae WR, Lim HL, Kim JH, Kim YS, Kim Y-W, et al. Optimizing Operating Parameters of High-Temperature Steam for Disinfecting Total Nematodes and Bacteria in Soil: Application of the Box–Behnken Design. Int J Environ Res Public Health [Internet]. 2020 Jul 13;17(14):5029. Available from: https://www.mdpi.com/1660-4601/17/14/5029