Chapter

Deleterious Effects of Banned Chemical Pesticides on Human Health in Developing Countries

Alaa Eldin Bayoumi

Abstract

Nowadays, large quantities of banned chemical pesticides are still in use illegally in various developing countries. The effect of these pesticides on humans, that is, children, adults, including pregnant women, either through chronic residential or occupational exposure, leads to various negative effects. This chapter focuses on the evidence of using the banned pesticides in developing countries and the occurrence of different diseases that affect the quality of life of the affected individuals either at the health, social, and/or labor level. The recorded diseases included obesity, diabetes, Alzheimer's, dementia, Parkinson's, asthma, chronic bronchitis, autism, erectile dysfunction, and psychological disorders as a result of chronic exposure to the banned pesticides. It was highlighted the identification of each disease, some epidemiological studies carried out in developing countries, and the mechanisms of action by which the pesticides are linked to each mentioned disease. In conclusion, it was discussed the major causes behind the incidence of such diseases and suggested suitable solutions that must be presented by the US Environmental Protection Agency, Food and Agriculture Organization among other bodies to the developing countries to avoid and overcome the occurrence of such diseases in the future.

Keywords: banned pesticides, human, exposure, developing countries

1. Introduction

Chemical pesticides are still considered as an essential tool used in the mass production of agricultural products in developing countries to control a wide range of pests, that is, insects, weeds, plant pathogens among others, and hence maintain high product quantity [1]. The consumption rate of chemical pesticides worldwide reached 2.4 megatons during 2006–2007 [2]. Pesticides have biological activity and toxic action on the targeted pests at the recommended concentration throughout various modes of action mechanisms exerted by the parent compounds and/or their metabolites [3]. If such concentration is exceeded through misuse or incorrect application, these pesticides become toxic to the non-target organisms, including humans [4].

Based on the enormous number of published studies related to the toxic effects of pesticides on non-targeted organisms and humans, some of these pesticides have

been banned in developed countries. The most famous banned compounds included organochlorine pesticides (OCPs) in the 1970s [5], some organophosphorus during 2001–2006 [6], certain carbamates insecticides [7], and specific synthetic pyrethroids and neonicotinoids insecticides, among others [8]. Globally, the total number of banned pesticides reached 460 compounds distributed between insecticides, fungicides, and herbicides among other groups of pesticides in 36 and 128 developed and developing countries, respectively [8]. The ban decision is based on various factors, such as a) the high toxicity of such pesticides to the non-targeted organisms (extremely hazardous, i.e., acute oral LD_{50} for the rat <5 mg/kg and highly hazardous, i.e., acute oral LD_{50} for the rat 5–50 mg/kg) [9], b) their carcinogenic effects on humans causing various types of cancer [10], and c) hazardous effects on environmental elements among other reasons such as effects on the endocrine system, that is, hormone disruptors [11].

Practically, the toxic effects of pesticides on mammals, including humans, are the sum of the results obtained by the studies carried out and extrapolation processes through decades from two major categories of studies, that is, *in vivo* and *in vitro*. The *in vivo* studies were carried out using laboratory animals that lead to an understanding of the toxicity mechanisms of the tested pesticides.

Also, it was studied both the toxicokinetics, toxicodynamics of chemical pesticides [12], teratogenicity [13], and carcinogenicity [14] using different mammalian models and affected humans in the epidemiological studies. With carcinogenic pesticides, they were classified into various categories, that is, carcinogenic, probably, possibly be carcinogenic to humans, or not classifiable as carcinogenic to humans [15]. Other studies of pesticides toxicity have been carried out depending on the response of different biomarkers [16], that is, hematological toxicity [17], nephrotoxicity [18], hepatotoxicity [19], neurotoxicity [20], oxidative stress, and DNA damage [21], pulmonary toxicity, reproductive and developmental toxicity and carcinogenesis biomarkers [22].

The *in vitro* toxicity studies have emerged through an approach that has been known as alternative methods, which is based on the application of a principle called (3Rs) designed by Russell and Burch [23] using animal organs, tissues, fertilized eggs, embryos, transplanted organs, such as liver, kidneys, brain, pancreas, and/or tissue pieces [24]. Also, the cell culture techniques, that is, primary cell cultures or cell lines were used as another approach of the alternative methods to understand the cytotoxic effects of xenobiotics including pesticides either at a biological level and/or biochemical level and explaining the genotoxic effects of the tested pesticides [25]. Through such alternative methods in association with the *in vivo* investigation, it was studied the mutagenicity, genotoxicity, and the effects of pesticides at the molecular level [26].

Regarding human health, exposure to different banned chemical pesticides may lead to consequent intoxication symptoms as a result of cellular, biochemical, and genetic effects, that is, congenital malformation, neurochemical and behavioral dysfunctions among others [27]. In developing countries, such as India, it was documented various negative effects resulted from human exposure to pesticides, that is, neurological, respiratory, dermal, and reproductive effects in addition to the impact on general health [28]. In other epidemiological studies related to the usage of banned chemical pesticides in developing countries, it was mentioned the percentages of chemical pesticides that caused a significant number of dead people annually as a result of pesticides intoxication [29]. The mentioned developing countries in such a chapter include India, Egypt, and African countries, Romania, Thailand, Taiwan,

Costa Rica, and Nicaragua among others. In Venezuela, it was recorded various serious problems due to exposure to pesticides either through environmental and/or occupational routes. Such exposure is due to limitations in the regulation acts related to the use of pesticides and lack of health and safety measures [30].

As specific pesticides, it was found that *in utero* exposure to organochlorine insecticides, that is, dichlorodiphenyltrichloroethane (DDT), dieldrin, endosulfan, heptachlor, dicofol, and methoxychlor was associated with neurodevelopmental effects in children [31]. Organophosphorus insecticides, such as parathion, dimethoate, monocrotophos, and chlorpyrifos among others, cause cardiovascular diseases [32]. Moreover, some banned pyrethroids insecticides such as fenvalerate, permethrin, and other compounds including certain metabolites causing DNA damage in human sperm [33] and developmental neurotoxicity [34]. As for banned neonicotinoid pesticides, that is, imidacloprid thiacloprid, they may cause breast cancer by increasing the expression of the aromatase enzyme. Other banned chemical pesticides, such as some triazine herbicides, were associated with breast cancer [35].

As for human exposure to pesticides via oral feeding, it was documented that consumption of contaminated foods by pesticide residues when exceeded the Acceptable Daily Intake (ADI) and/or the Maximum Residue Limits (MRL) values listed by the Codex Alimentarius may lead to various undesirable effects. Based on such type of exposure, high levels of pesticide residues and their metabolites in foodstuff could reach the human blood, including maternal blood, cord blood, placenta, breast milk, and children.

In the case of occupational exposure to pesticides, it was documented that such exposure occurs directly during various processes, such as manufacturing, transporting, storing, retailers, preparation, application by the user, re-entry into treated fields, harvest, and equipment cleaning. The exposure may be due to the misuse during the application of pesticides without protective equipment, which is considered economically expensive in developing countries. In addition, other routes of exposure may occur, such as exposure of children and/or pregnant women, which affects their fetuses.

In recent studies, it was found that all the mentioned negative effects of pesticides exposure are results of bad practices, that is, inadequate, unsafe, and handling applications without wearing the protective instrument. Also, it was reported that the lack of awareness of suitable pesticide use is considered as the main reason behind the occurrence of various diseases in the farmers' works in the Tu Ky district, Vietnam [36]. To overcome such types of problems, the Agricultural Pesticides Committee [APC] in Egypt, has been introduced around 10.000 licensed applicators in the agriculture fields and targets to reach 50.000 during the next years after their training in the suitable pesticides application procedures [37].

Based on the mentioned facts, this chapter has been focused on the most deleterious effects linked to chronic human exposure to various banned chemical pesticides that affect the exposed individuals with various diseases, that is, obesity, Alzheimer's, Parkinson's, asthma, chronic bronchitis, type 2 diabetes, autism, erectile dysfunction, and psychological disorder. Such diseases were selected in this chapter based on the fact that they are affecting the quality of life of the affected individuals either at the health, social, and/or labor level. Based on the lack of scientific and investigation background in most developing countries, the identification of each disease and the different mechanisms followed by the banned pesticides and/or their metabolites to exhibit these diseases either in pregnant women, their fetuses, children, and/or adults who were exposed to the banned pesticides were discussed.

2. Evidence of using banned pesticides in the developing countries

Practically, huge amounts of banned pesticides are still in use illegally in various developing and developed countries. Such banned pesticides include organochlorine insecticides, that is, DDT for controlling the public health pests [38] due to their cheap price, ease of production, lack of registration, and control measures systems for pesticides in some of these countries, besides the prevalence of the risk versus benefit theory [39]. Unfortunately, it was documented that the World Health Organization supported the reintroduction of DDT for malaria eradication in 2006 [40].

In agriculture, various published documents have been reported that a list of banned pesticides is still in use in developing countries [41]. For example, it was reported that the banned pesticides, such as chlorpyrifos, endosulfan, and cypermethrin, as insecticides, atrazine and glyphosate, as herbicides, are still in use in various provinces in Argentina in addition to Paraguay [42]. In addition, it was reported that many developing countries are still using the banned chemical pesticides that have been exported from the European Union after their banning in European countries [1].

Based on the export statistics from China Customs, the export volume of pesticides during the period of January to November 2015, African markets containing developing countries represented 13.9% of the total export of pesticides from China to 44 countries. The most exported banned pesticides include paraquat, glyphosate, 2,4-D-dimethylammonium, atrazine, glyphosate-monoammonium, tebuthiuron, as herbicides, lambda-cyhalothrin, imidacloprid, chlorpyrifos, dichlorvos, emamectin, as insecticides, mancozeb, metalaxyl+mancozeb, as fungicides. The top 10 countries by export value were Nigeria, South Africa, Ghana, Ivory Coast, Egypt, Kenya, Cameroon, Tanzania, Ethiopia, and Guinea. The amount of export value for these top 10 countries constitutes 85.9% of the total export value to Africa from China [43]. Moreover, some banned pesticides may be used in form of counterfeit and/or contraband pesticides either in developing or developed countries [44]. The decision toward the herbicide glyphosate has been taken by the Mexican Government to be a period of transition when sustainable alternatives will be promoted [8].

The decision to ban pesticides in developing countries is based on the published information by the USEPA and the European Union, while the executive decision will be in practical form by regulation and legislative acts present in some developing countries. For example, Egypt (Agricultural Pesticides Committee, APC), India, Malaysia, Philippines, Costa Rica, Mexico, Kenya, Bangladesh, and Indonesia, each of them has their regulation and legislative acts [28]. Other low-income countries have not any institutions related to pesticides in general, especially the agricultural ones, and hence their usage of the agricultural chemicals depends on the importing of these products from neighboring countries.

Also, the decision of banning pesticides in other developing countries may be retard to be in practice due to a lack of transparency and also depending on the availability of alternative pesticides in the market. In addition, the decision-makers in the developing countries may offer a period called a period of transition or grace period that may be reached for 6 months or more than 1 year as an expected period to consume the remaining stock of these banned pesticides. Such cases were already offered for the organophosphate insecticide chlorpyrifos, dimethoate, fipronil, alpha-cypermethrin, amitrole, carbendazim, iprodione, diazinon, carbosulfan, diuron, diniconazole among other pesticides, such as the case in Egypt and some other developing countries. During such grace period, the targeted pesticide[s] to be

banned is still in use, and hence the exposure processes, that is, farmers, unlicensed applicators, children, and/or pregnant women are continued.

At the governmental level of these countries, the most important question in the mentality of the decision-makers is related to the quantity of such pesticide[s], that is, where and how to treat the remaining amounts of such pesticide[s], that is, there is no possibility to withdrawing the remaining amounts that are still in the pesticide market. However, in a recent action taken by APC, based on the requirements of the European Commission, the MRLs of chlorpyrifos must not exceed 0.01 mg/kg of the exporting crops and such limits must be followed by the Agriculture Export Council [37]. In addition, it was decided to restrict the usage of such insecticides to control insect pests on nonedible crops, such as cotton, to control the desert locust and termites [37]. Unfortunately, from the practical viewpoint, despite such decisions, chlorpyrifos is still illegally available like other banned pesticides in the pesticide market in Egypt at least during the grace period. So, the use of banned pesticides at that moment is considered an inevitable fact either in Egypt or other developing countries.

3. Mechanisms of toxic action of some banned chemical pesticides

Depending on the chemical structure of the targeted banned chemical pesticides, it could classify the mechanisms of their action into two main categories, that is, neurotoxic action and hormone disruptors.

3.1 Neurotoxicity

Based on the published studies related to human diseases associated with exposure to banned chemical pesticides, it was found that most of these pesticides were neurotoxic compounds. The most famous classes of these pesticides are organochlorine, organophosphorus, carbamates, synthetic pyrethroids, and neonicotinoids insecticides. For organochlorine insecticides, that is, dichlorodiphenyltrichloroethane (DDT), cyclodiens, hexachlorocyclohexane, many studies have shown that its mode of action is based on a reduction in the transport of potassium ions, after blocking the sodium channels, and inhibiting the enzymes (Na^+ -K^+/Ca^{2+} -Mg^{2+}-ATPases), inhibiting the binding between calcium and calmodulin and then affecting the flow of neurotransmitters [45].

Regarding organophosphorus as parent compounds and/or their activated metabolites, such as [−oxon], the mechanisms of their actions depend on the irreversible inhibition of acetylcholinesterase by phosphorylating the amino acid serine in the esteratic site of the AchE enzyme [46], resulting in hyperstimulation of the cholinergic nerves, that is, muscarinic and nicotinic acetylcholine receptor [47]. Carbamate insecticides act as reversible inhibitors to acetylcholinesterase leading to various symptoms of toxicity [48].

As for the synthetic pyrethroids, their mechanisms of toxic action depend on inhibition of (Ca^{2+}, Mg^{2+}-ATPase) enzymes, binding to gamma-aminobutyric acid receptors in the chloride channels, and inhibition of the calmodulin protein that binds to calcium and thus increase the calcium ions that affect the flow of the neurotransmitters that lead to cause various symptoms of poisoning in humans [49]. In addition, it was documented that neonicotinoids insecticides, that is, imidacloprid act on nicotinic acetylcholine receptors, and hence stimulate these receptors at low doses while blocking such receptors at high doses leading to paralysis and death [50]. Also, some

fungicides exhibit neurotoxic action, which affects the peripheral nerves, the motor nerves, and the central nervous system that leads to different symptoms of poisoning [51]. Based on such toxic action observed in humans through different accidents, such fungicide has been banned in the 1970s [52].

3.2 Effects on the endocrine system

Based on the published studies, it was documented that various diseases, such as obesity, diabetes, and erectile dysfunction, have occurred as a result of exposure to various banned pesticides. It was reported that such diseases belong to the mechanisms of action of the mentioned pesticides within the endocrine system. Historically, in the 1970s, it had emerged the adverse effects of some chemical pesticides on the endocrine system through various modes of action and it was called for such pesticides the term (Hormone Disruptors) [53]. Such effects may be through the hormone-secreting gland, effects on the composition of the hormone itself, effects on its production and secretion rates, or that it is similar to it in composition or interfere with the hormone in its function by competing with it for binding to the hormonal receptors [54]. Many studies have shown that hormone disruptors cause many adverse health effects on humans, leading to various diseases [55]. Exposure to hormone disruptors maybe not be observable for many years. If the fetus is exposed to any of these disruptors during the pregnancy of the mother, then these substances cause adverse effects on many functions of this fetus that are not observed until after its birth and reaching puberty [56].

4. Diseases other than cancer caused by banned chemical pesticides

In the first two decades of this century, several studies that have been published and searched in MEDLINE [through PubMed] revealed the relationship between the exposure of humans, that is, farmworkers, unlicensed pesticide applicators, children, and/or pregnant women to different chemical pesticides and the emergence of various diseases other than cancer [57]. Such studies reported that these diseases do not appear until after reaching adulthood, which affects the quality of life of the affected individual[s] at the health, social, and labor level either in the present and/or the future.

4.1 Obesity

Obesity, that is, body mass index [BMI] ≥ 30.0 has been defined as a chronic disease that affects around 13% of the global population and 62% of people living in developing countries. These huge percentages lead to the death of 2.8 million individuals each year as a result of obesity [58]. Exposure to various classes of banned chemical pesticides and obesity are well documented in many published studies carried out in developed countries. For example, it was found that there was a positive linkage between maternal, prenatal, or postnatal exposure to pesticides and obesity, especially DDT as an organochlorine insecticide [59] and chlorpyrifos as organophosphorus pesticides [60]. Also, other classes of pesticides were found to be associated with the development of obesity, that is, bifenthrin as pyrethroid [61] and imidacloprid as neonicotinoid [62]. In addition, it was reported that exposure of pregnant women to pesticides through agricultural or industrial activities leads to overweight children [63].

Various mechanisms have been followed by pesticides to be associated with obesity. For example, increasing the adipocyte differentiation by quizalofop-*p*-ethyl, diazinon, imidacloprid, fipronil, and permethrin among others [64]. Also, it was documented that proliferation and alteration in the adipose function tissue lead to increasing the lipid uptake and alteration of the neuroendocrine control of feeding that affects the metabolism of nutrients [65]. Also, it was found that some pesticides, that is, organophosphate, carbamate, and organochlorines disrupt hormonal status through oxidative stress, which affects mitochondrial function, especially in the cellular metabolism of lipids, carbohydrates, and proteins [49]. Another theory proved that some pesticides are mimic the natural lipophilic hormone and altering the nuclear receptor transcription factor, which affects the key adipogenic factors, fat depot size, and function [66]. More recently it was reported that some pesticides are linked to obesity by affecting the gust microbiota, metabolic homeostasis by affecting the peroxisome proliferator-activated receptors (PPARs) and the thyroid hormone pathway, altering the fate of mesenchymal stem cells (MSCs), and dysregulation of sex steroid hormone [64].

4.2 Diabetes

Diabetes mellitus is a chronic disease with two main types, that is, Type 1 diabetes, which occurs in case of the pancreas does not produce enough insulin, and type 2 (T2D) or insulin resistance, which means that the body cannot effectively use the insulin it produces [67]. Diabetes, especially T2D, is a major cause of various diseases, such as cardiovascular disease [68], endometrial [69], prostate [70], and colon cancer [71] in addition to other diseases, that is, blindness, kidney failure, heart attacks, stroke and lower limb amputation [72].

The relationship between human exposure to the banned chemical pesticides and the occurrence of diabetes has been documented. Two studies in Korea found that low-dose background exposure to 10 OCPs, that is, HCH, HCB, heptachlor epoxide, *p,p′*-DDE, *p,p′*-DDD, *p,p′*-DDT, *o,p′*-DDT, oxychlordane, trans-nonachlor, and mirex were strongly associated with prevalent type 2 diabetes in Koreans people [73].

In Thailand, it was reported that endosulfan as an organochlorine insecticide, mevinphos an organophosphorus, carbaryl/Sevin as carbamate, and benlate as fungicides were positively associated with diabetes, as described in the case–control study carried out by Juntarawijit and Juntarawijit, [74]. In India, various pesticides including herbicides, that is, atrazine, butylate, 2,4,5-T, diazinon, fonofos, phorate, and parathion as organophosphorus insecticides, *p,p′*-DDT, *p,p′*-DDE, β-HCH, and oxychlordane as organochlorine insecticides were positively associated with hyperglycemia and diabetes [75]. In Egypt, it was found that lindane followed by *o,p′*-DDD, and *p,p′*-DDE as DDT metabolites as organochlorine compounds and malathion as organophosphate insecticide was strongly associated with type 1 diabetes in children, as reported in the preliminary study carried out by El-Morsi et al. [76].

As a mechanism of action by which the banned chemical pesticides induces diabetes, various specific studies have been proved that OCPs, as it is well known that these pesticides are lipophilic, hydrophobic, and highly resistant to metabolic degradation, so that, they are bioaccumulated in fatty tissues for many years, and their serum concentration is considered to be a good reflection of lifetime exposures [77].

However, it was documented that OCPs have variable molecular and cellular targets and thus they cannot be considered to have a single mode of action. Inflammation in adipose tissue, ectopic lipid accumulation [lipotoxicity] in liver, muscle, and

pancreas, and mitochondrial dysfunction caused by oxidative damage caused by OCPs lead to the development of insulin resistance and T2D [77]. Also, these pesticides may affect pancreatic β cells and trigger insulin resistance, thus impairing both lipid and glucose metabolism [78].

Besides, it is well known that *p,p′*-DDE is antiandrogenic and can bind to the androgen receptor and that DDT has estrogenic properties; both estrogen and androgen receptors are involved in the mediation of insulin sensitivity [79]. Another study showed that certain OCPs exposure can disrupt glucose homeostasis, which could contribute to the development of type 2 diabetes in the future [80]. As for banned organophosphorus pesticides, it was documented that exposure to sufficiently high levels of these compounds would be expected to result in increased accumulation of acetylcholine, potentially leading to overstimulation and eventual downregulation of its receptors and reducing insulin production [81].

4.3 Alzheimer's disease

Alzheimer's disease (AD) is the major form of dementia and is considered the fourth leading cause of death in the elderly. AD is the most common progressive neurological disease and results in an irreversible loss of neurons [82]. One of the most symptoms of AD is loss of short-term memory, speech problems, confusion, mood swings, self-care inability, and behavioral issues [83]. Few studies have been carried out in developing countries on the link between exposure to pesticides and AD. In India, it was found that OCPs, that is, β-HCH, dieldrin, and *pp′*-DDE are associated with the risk of AD in the north Indian population [84]. The same finding was reported with organophosphates insecticides [85].

In China, a positive association between pesticide exposure and AD, confirms the hypothesis that pesticide exposure is a risk factor for AD, as shown in the systematic review and meta-analysis carried out by Yan et al. [86]. One internal exposure investigation evaluated the relationship between serum dichlorodiphenyldichloroethylene (DDE) levels and AD, observing a 3.8-fold increase in serum levels of organochlorine metabolites of DDE in patients with AD when compared with control participants [87].

As mechanisms behind the occurrence of AD, it was found that such disease is a progressive neurodegenerative disorder associated with the loss of cholinergic neurons and the presence of excessive neuritic plaques containing amyloid β protein and abnormal tau protein filaments as neurofibrillary tangles [88]. Decreased level of acetylcholine in AD patients appears to be a critical element in producing dementia and memory disorders [89]. It was documented that various chemical pesticides cause uncoupled oxidative phosphorylation, which increases the levels of free radicals [90], which affect the mitochondrial function and hence increased the production of ROS and higher levels of oxidative stress that lead to cellular damage in form of synaptic linked with the development and progression of AD [91]. Baltazar et al. [92] found that various pesticides share many features, such as the ability to induce oxidative stress, mitochondrial dysfunction, α-synuclein fibrillization, and neuronal loss.

At *in vivo* level, various studies revealed that some pesticides may disrupt the metabolic pathways, such as the homeostasis of amyloid-β, causing a significant elevation in amyloid-β levels in the cortex and hippocampus, as well as increasing memory loss and reduced motor activity in experimental animals [93]. Thus, some researchers have documented that pesticide exposure is a potential risk factor for AD, and hence proved such results through several epidemiological studies [94].

Chin-Chan et al. [95] reported that some pesticides have been associated with AD due to their ability to elevate beta-amyloid [Aβ] peptide and the phosphorylation of Tau protein [P-Tau], causing senile/amyloid plaques and neurofibrillary tangles (NFTs) characteristic of AD. Tang et al. [96] showed the proposed neuropathological mechanisms that included oxidative stress through the reactive oxygen species [ROS] generated by pesticides, neuroinflammation enhancement that leads to amyloid-beta Aβ and tau protein expression, promotion of amyloidogenesis, such as amyloid plaque formation, DNA damage, and dysfunction of the brain-Gut axis. Like dementia, it was published in a nationwide population-based cohort study that revealed the relationship between exposure to pesticides and dementia [97].

4.4 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), having an overall prevalence ranging from 1 to 2 per 1000 people. PD is characterized by various motor dysfunctions, such as rigidity, bradykinesia, resting tremor, gait freezing, and postural reflex impairment, and neuropsychological dysfunctions, such as cognitive decline, depression, and sleep disturbance, all of which negatively affect patients' quality of life (QOL), as presented through the systematic review and meta-analysis carried out by Zhao et al. [98].

From an epidemiological viewpoint, the association between the use of pesticides and PD was first reported by Barbeau et al. [99]. Pesticides have been implicated as one of the most likely major environmental risk factors for PD [100]. In the case of the relation between pesticides and PD, it was documented that people exposed to pesticides at workplaces have a higher risk of PD than people exposed at home, and exposure at both workplaces and residences has the highest PD risk [101].

Occurrence of PD in developing and developed countries concerning the exposure to pesticides, the results of a study of the meta-analysis carried out by Ahmed et al. [102] showed that both types of countries suffered from such disease in a significant association with pesticide exposure. The pesticides linked with PD included trifluralin and paraquat as herbicides, maned and mancozeb as fungicides, diazinon, chlorpyrifos, parathion, β-HCH, permethrin, and dieldrin as insecticides. In another case–control study, paraquat was closely associated with a higher risk of developing PD [103].

Many mechanisms have been involved in the role of pesticides in PD development. Karen et al. [104] reported a significant reduction in the mitochondrial function in the *in vivo* synaptosome preparations, there was an increased dopamine turnover and decreased motor activity. In addition, dopaminergic neurotransmission was affected by exposure to permethrin. Also, dieldrin as organochlorine insecticide-induced apoptotic cell death alters dopamine levels and induces mitochondrial dysfunction and protein aggregation [105], while endosulfan inhibits proteasomal activity [106].

4.5 Respiratory disorder diseases

4.5.1 Asthma

Asthma is a common and global chronic inflammatory disease of the airways that affects children and adults characterized by variable and recurring respiratory symptoms (wheezing, breathlessness, chest tightness, and dry cough), airflow obstruction, and mucus hypersecretion hyperreactivity (AHR), all of which interfere

with breathing [107]. Several factors lead to asthma diseases, that is, genetic, allergic conditions, and multiple lifestyle factors in addition to low birth weight, prematurity, exposure to tobacco and indoor and outdoor air pollutants, and occupational exposure to chemicals, such as pesticides.

Two major types of epidemiological studies have been published concerning exposure to pesticides and linkage to asthma, that is, exposure of children and adults. For example, it was reported that occupational exposure to pesticides was associated with the prevalence of asthma [108]. In addition, children of farmers are at risk of pesticide exposure through various routes, that is, living close to agricultural fields, participating in farm work, and eating fruits and vegetables soon after harvest [109].

As for lower or middle-income developing countries, exposure of children to banned chemical pesticides was studied in Mexico [110], Brasil, [111], Costa Rica [112], Sri Lanka [113], and Lebanon [114]. As for exposure of adults through the occupational route, various studies have been carried out in different developing countries, such as Kenya [115], Ghana through a cross-sectional study [116], and Ethiopia on a large-scale cross-sectional study [117]. In Egypt, a published case–control study of adolescent pesticide applicators showed an association between exposure to OPs pesticides, chlorpyrifos, and reduction of lung function [118].

To investigate the relation between exposure to some specifically banned pesticides and the occurrence of asthma, Hoppin et al. [119] reported that paraquat as herbicide, dieldrin, heptachlor, lindane coumaphos, diazinon, parathion, DDT, and ethylene dibromide as insecticides, and captan as fungicide were associated with allergic and nonallergic asthma. In a recent ecological study carried out in Argentina, it was found a strong association between asthma in agricultural workers and occupational exposure to the herbicide glyphosate [120]. In another recent study carried out in Uganda, it was reported a strong association between organophosphate and carbamate insecticide exposure and disorder in lung function, including asthma among smallholder farmers [121]. As for OPs pesticides, it was demonstrated in the review published by Shaffo et al. [122] that exposure to various OPs pesticides, that is, bromofos, chlorpyrifos, diazinon, fenthion, malathion, and parathion were associated with asthma.

As a causal link between organophosphorus pesticides and asthma, mechanistic studies exhibited a blockage of autoinhibitory in the muscarinic receptors present in the parasympathetic nerves that innervate airway smooth muscle by which OPs induce airway hyperreactivity [122]. OPs disrupt the control of the respiratory function in the brain stem, which leads to central apnea.

4.5.2 Chronic bronchitis

Chronic bronchitis is long-term inflammation of the lining of the bronchial tubes. The most common symptoms include cough, mucus, wheezing, chest discomfort that leads to disability, severe infection in the airways, narrowing of the breathing tubes, and hence trouble to breathe. Globally, such disease is the third leading cause of death, that is, over 3 million in 2019. It was reported that more than 80% of the documented deaths by such disease are in low and middle-income developing countries [123].

Such disease is one of the most common diseases caused by several factors, such as exposure to pesticides [124]. For example, in a case–control study carried out in Lebanon, it was found that pesticide exposure was associated with chronic bronchitis [125]. In India, it was found a higher occurrence of chronic bronchitis, which

was associated with OP and carbamate pesticide exposures in agricultural workers [126]. In Vietnam, it was reported that 1499 Vietnam veterans who applied Agent Orange (the mixture of two equal parts of the herbicides 2,4-D and 2,4,5-T) showed a higher frequency of chronic respiratory diseases, such as chronic bronchitis [127]. Also, in Singapore, it was observed that pesticides were strongly associated with chronic bronchitis [128]. In the agricultural health study project, it was found that 16 pesticides were strongly associated with chronic bronchitis [129]. As mechanisms of action that are followed by the chemical pesticides to cause chronic bronchitis, it was documented that OPs as inhibitors to AChE, increase the acetylcholine quantity on nicotine and muscarinic receptors that lead to cholinergic over-expression on the smooth muscle of the airway hence causing broncho-constriction [130].

4.6 Autism

Autism has been recognized as the damage that occurred to many important areas of brain development. Autism has been defined as specific conditions of neurodevelopment that are characterized by specific, repetitive behavior, and difficulty in social communication. Also, autism is a condition in which a patient suffers from specific behavioral symptoms that result from many known and unknown biological factors based on brain dysfunctions that affect the developing brain's ability to handle information [131]. It has been observed that most children with autism suffer from difficulty in their ability to learn as a result of their mental retardation, although few of these children with autism have an average level of intelligence, although they sometimes suffer from epilepsy and audiovisual damage [132].

The statistics showed that there are 62 children with autism out of every 10.000 births [133]. It was found that there is an increase in the incidence of autism among children in many parts of the world and that many of these children were due to the exposure of their mothers during pregnancy to pesticides and other environmental pollutants, whether through direct exposure to pesticides during the application or non-direct exposure, such as the consumption of food contaminated with pesticide residues [134].

A study conducted by Shelton, et al. [135] showed that there is an increase in the risk rates of autism among children whose mothers lived near the fields where pesticides were applied. In some detail, Blatt et al. [136] reported the occurrence of disruption of the nerve conduction system of gamma-aminobutyric acid (GABA) by the action of some chemical pesticides, and it was found that there is a relationship between that and the incidence of autism in studies on the density of receptors in brain tissue. Also, the results of the study conducted by Lyall et al. [137] indicated that exposure to high levels of organochlorine pesticides during pregnancy was associated with autism in newborns. Also, it was documented in a cohort study that some exposure of pregnant women to pyrethroids leads to autism spectrum disorder (ASD) in their children [138]. Other pesticides cause autism, that is, metabolites of diazinon and chlorpyrifos as organophosphorus [139], besides organochlorines, pyrethroids, and carbamates insecticides [140].

Genetic analysis studies indicated that there are 206 genes appeared responsible for showing autism. This set of genes is present at many barriers in the human body, such as the blood–brain barrier, skin, intestine, placenta, and cellular barrier trophoblast. To reach this conclusion on the responsibility of these genes, the response of such genes to various chemical compounds was analyzed by the Comparative Toxicogenomics Database (CTD) [141].

4.7 Erectile dysfunction

Erectile dysfunction has been defined as a persistent inability to achieve or maintain an adequate erection for satisfactory complete sexual performance. Physiologically, penile erection is a neurovascular phenomenon that involves the coordination of three hemodynamic events, that is, elevated arterial inflow, relaxation of the sinusoidal smooth muscle, and decreased venous outflow. It also implies the interaction of the brain, nerves, neurotransmitters, and smooth and striated muscles. Any alteration in one or more of these components may affect the erectile tissue and cause erectile dysfunction [142]. Many factors play an important and major role in the pathogenesis of erectile dysfunction, such as exposure to pesticides [142].

It was established that sexual behavior in humans is controlled by hormonal and neural regulatory processes, therefore, some pesticides that act as hormone disruptors negatively affect the nature of the sexual relationship. Various studies showed that erectile dysfunction is responsible for infertility for up to 10% of the male population around the world, as mentioned in the review published by Kaur et al. [142].

In Egypt, Soliman et al. [143] conducted a study in the Damietta governorate. The results showed that there is a close relationship between chronic exposure to pesticides (DDT, and some organophosphorus and carbamates) and erectile dysfunction. Besides, it was possible to prove that acetamiprid as a neonicotinoid insecticide has the most damaging effect on erectile dysfunction due to the effect on several inhibitory pathways [144]. Also, it was demonstrated that some pesticides exert their effect on tunica albuginea, TA tissues (the fibrous envelope of connective tissue that surrounds the corpora cavernosa of the penis, TA composed of elastin and collagen, so, the effect on elastin leads to erectile dysfunction) [145].

It was established that some organophosphorus pesticides cause a decrease in the concentration of the male hormone, testosterone, through various mechanisms. Also, it was reported that the decrease of such hormone was related to inhibition in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [146]. Such inhibition occurs because organophosphorus pesticides inhibit the enzyme acetylcholine esterase and as a result, the level of the neurotransmitter acetylcholine increases and thus affects the inhibition of these hormones [147]. The pesticides were found to be responsible for the induction of apoptosis in Leydig cells, which were responsible for the secretion of 95% of the testosterone in the blood. Therefore, the death of these cells results in a significant reduction in the concentration of that hormone [148].

4.8 Psychological disorder

Various studies showed that there is a relationship between poisoning farmers with pesticides and the psychological problems that they suffer especially depressive disorders [149]. London et al. [150, 151] explained that many pesticides, especially organophosphorus, were associated with an increase in the occurrence of psychological problems, that is, depression, which has sometimes reached the suicide of some workers who were previously exposed to such pesticides. With depression, various studies showed the relationship between pesticides and decreasing serotonin levels in workers exposed to pesticides [152]. It is well established for the human being the relationship between the lowering in serotonin levels and depression [153]. At the experimental animal level, it was reported that some pesticides, that is, deltamethrin (pyrethroid insecticide) and acetamiprid (neonicotinoid insecticide) [154],

chlorpyrifos (organophosphorus insecticide), and cypermethrin (pyrethroid insecticide) [155] caused a decrease in serotonin and dopamine levels in rats.

Some studies showed links between exposure to pesticides and suicide rates, which has been reported by Faria et al. [156]. For example, it was reported that exposure to high levels of organophosphorus pesticides was associated with higher rates of suicide among workers exposed to these pesticides [157]. The same phenomenon has been recorded in many countries, such as Brazil [156] and Costa Rica [158].

In the case of the developing countries, as mentioned in the systematic review published by Gunnell et al. [159], it was estimated that the suicidal attempts due to pesticide toxicity ranged between 5200 and 21,910 in African countries. In Central America, especially, Belize, Costa Rica, El Salvador among other countries, it was documented that pesticides account for 31% of suicide cases in this region. In Eastern Mediterranean countries about 16.5% and 5629, in South East Asia, that is, India, Bangladesh, Sri Lanka, and Thailand, the proportion and annual total of pesticide suicides in this region reached 20.7% and 51,050, with a range of 47,720 to 82,680 cases.

5. Conclusions

Various developing countries are still using the banned chemical pesticides as a reason to the cheap price, ease of production or importation, and lack of both registration and control measures systems. Based on the aforementioned diseases caused by banned pesticides, exposure to such substances must be prevented as much as possible in developing countries. To continue the pest control process, an alternative method must be followed, that is, integrated pest management (IPM) strategies, using biopesticides to ensure that there are no residues of harmful chemical pesticides, whether they have been canceled or are still allowed to be used. The possibilities of getting rid of the large quantities of banned pesticides are technologically not available in all developing countries. Therefore, the developed countries must cooperate and the international institutions, organizations, and/or agencies, such as Food and Agriculture Organization (FAO) and the United States Environmental Protection Agency (USEPA) among others, must contribute to disbursing the material compensation and making alternative pesticides available to the developing countries. Such agencies must cooperate to overcome the problems related to using pesticides in developing countries that suffer from the import, export of banned pesticides, lack of training on the correct handling of pesticides, low pesticide education, lack of legislation, lack of enforcement of the available legislation, and absence of monitoring for pesticides residues on locally consumed products. The expected assistance from these bodies may be as providing safe equipment, education, training the farmers, and licensed pesticides applicators in the developing countries through various sustainable, not temporary programs.

In addition, the governments of developing countries must bear their responsibility to establish specialized bodies responsible for managing everything related to the use of pesticides, which have the authority to prevent the import of internationally banned pesticides, under the supervision of the relevant international bodies and to combat the counterfeit and contraband pesticides. So that, through following these suggested realistic practical solutions, it could possible to stop and prevent the continuation of using the banned pesticides at the international level. Following these policies, it may contribute positively to reducing the incidence of the aforementioned diseases and others associated with exposure to pesticides.

Author details

Alaa Eldin Bayoumi
Faculty of Agriculture, Department of Plant Protection, Ain Shams University, Shoubra El-Kheima, Cairo, Egypt

*Address all correspondence to: alaaeb@agr.asu.edu.eg

IntechOpen

References

[1] European Parliament. The Use of Pesticides in Developing Countries and their Impact on Health and the Right to Food. Belgium: Policy Department for External Relations, Directorate-General for External Policies of the Union; 2021. pp. 1-44. Available from: https://www.europarl.europa.eu/cmsdata/219887/Pesticides%20health%20and%20food.pdf [Accessed: August 12, 2021]

[2] Atwood D, Jones PC. Pesticides Industry Sales and Usage 2008-2012 Market Estimates. Washington DC, USA: U.S. Environmental Protection Agency; 2017. pp. 1-24

[3] Stenersen J, editore. Chemical Pesticides Mode of Action and Toxicology. 1st ed. USA: CRC Press; 2004. p. 296

[4] Damalas CA, Eleftherohorinos IG. Pesticide exposure, safety issues, and risk assessment indicators. International Journal of Environmental Research and Public Health. 2018;**5**:1402-1419. DOI: 10.3390/ijerph8051402

[5] Tsai WT. Organochlorine Insecticides. In: PH W, editor. Encyclopedia of Toxicology. 3rd ed. Cambridge, Massachusetts, USA: Academic Press; 2014. pp. 711-713

[6] Brenda, G. 2011 Pesticide Exposure in Womb Linked to Lower IQ, Health & Pregnancy. Atlanta, USA: WebMD; 2011. Available from: https://www.webmd.com/baby/news/20110421/pesticide-exposure-in-womb-linked-to-lower-iq#1 [Accessed: September 3, 2021]

[7] Cone M. Toxic Pesticide Banned after Decades of Use. New York, USA: Environ. Health News; 2010. Available from: https://www.scientificamerican.com/article/toxic-pesticide-banned-after-decades-of-use/ [Accessed: September 3, 2021]

[8] PAN, Pesticide Action Network International PAN International, Consolidated List of Banned Pesticides. New Taipei City, Taiwan: PAN International; 2021. Available from: https://pan-international.org/pan-international-consolidated-list-of-banned-pesticides/ [Accessed: August 15, 2021]

[9] WHO. The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification. Geneva: World Health Organization; Licence: CC BY-NC-SA 3.0 IGO. 2019 edition; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/332193/9789240005662-eng.pdf [Accessed: August 16, 2021]

[10] Alavanja MCR, Ross MK, Bonner MR. Increased cancer burden among pesticide applicators and others due to pesticide exposure. CA: a Cancer Journal for Clinicians. 2013;**63**(2): 120-142. DOI: 10.3322/caac.21170

[11] USEPA, Overview of Risk Assessment in the Pesticide Program. North Carolina, USA: EPA; 2021. Available from: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program [Accessed: August 27, 2021]

[12] Martin T, Thompson H, Thorbek P, Ashauer R. Toxicokinetic-Toxicodynamic modeling of the effects of pesticides on growth of *Rattus norvegicus*. Chemical Research in Toxicology. 2019;**32**(11):2281-2294. DOI: 10.1021/acs.chemrestox.9b00294

[13] Garcês A, Pires I, Rodrigues P. Teratological effects of pesticides in vertebrates: A review. Journal of Environmental Science and Health, Part B. 2020;**55**(1):75-89. DOI: 10.1080/03601234.2019.1660562

[14] Yadav H, Sankhla MS, Kumar R. Pesticides-induced carcinogenic & neurotoxic effect on human. Forensic Research & Criminology International Journal. 2019;7(5):243-245. DOI: 10.15406/frcij.2019.07.00288

[15] IARC, Monographs on the Identification of Carcinogenic Hazards to Humans. Lyon, France: IARC; 2021. Available from: https://monographs.iarc.who.int/agents-classified-by-the-iarc/ [Accessed: August 26, 2021]

[16] Anwar WA. Biomarkers of human exposure to pesticides. Environmental Health Perspectives. 1997;**105**(4):801-806. DOI: 10.1289/ehp.97105s4801

[17] Wafa T, Nadial K, Amel N, Ikbal C, Insaf T, Asma K, et al. Oxidative stress, hematological and biochemical alterations in farmers exposed to pesticides. Journal of Environmental Science and Health. Part. B. 2013;**48**(12):1058-1069. DOI: 10.1080/03601234.2013.824285

[18] Attia AM. Risk assessment of occupational exposure to pesticides. In: Linkov I, Ramadan AB, editors. Comparative Risk Assessment and Environmental Decision Making. Nato Science Series, IV, Earth and Environmental Sciences. Dordrecht: Springer; 2004. pp. 349-362. DOI: 10.1007/1-4020-2243-3_23

[19] Garcia-Garcia CR, Parron T, Requena M, Alarcon R, Tsatsakis AM, Hernández AF. Occupational pesticide exposure and adverse health effects at the clinical, hematological and biochemical level. Life Sciences. 2016;**15**(145):274-283. DOI: 10.1016/j.lfs.2015.10.013

[20] Kori RK, Jain AK, Yadav RS. Biomarkers: An essential gizmo in pesticide toxicity. Biomarkers. 2016;**2**:1-5. DOI: 10.21767/2472-1646.100009

[21] Muniz JF, McCauley L, Scherer J, Lasarev M, Koshy M, Kow Y. Biomarkers of oxidative stress and DNA damage in agricultural workers: A pilot study. Toxicology and Applied Pharmacology. 2008;**227**:97-107. DOI: 10.1016/j.taap.2007.10.027

[22] WHO. Biomarkers and Risk Assessment: Concepts and Principles. Geneva: Environmental Health Criteria; 1993. p. 155

[23] Russell WMS, Burch RL, editors. The Principles of Humane Experimental Technique. London: Methuen & Co. Limited; 1959. p. 238

[24] Liebsch M, Grune B, Seiler A, Butzke D, Oelgeschäger M, Pirow R, et al. Alternatives to animal testing: Current status and future perspectives. Archives of Toxicology. 2011;**85**(8):841-858. DOI: 10.1007/s00204-011-0718-x

[25] Rees KR. Cells in culture in toxicity testing: A review. Journal of the Royal Society of Medicine. 1980;**73**(4):261-264

[26] Tebourbi O, Sakly M, Rhouma KB. In: Stoytcheva M, editor. Molecular Mechanisms of Pesticide Toxicity, Pesticides in the Modern World - Pests Control and Pesticides Exposure and Toxicity Assessment. London, UK: InTech; 2011. Available from: https://www.intechopen.com/chapters/20786 [Accessed: August 24, 2021]. DOI: 10.5772/17952. ISBN: 978-953-307-457-3

[27] Lopez SL, Delia Aiassa D, Benitez-Leite S, Lajmanovich R, Mañas F,

Poletta G, et al. Chapter two: Pesticides used in south American GMO-based agriculture: A review of their effects on humans and animal models. Advances in Molecular Toxicology. 2012;**6**:41-75. DOI: 10.1016/B978-0-444-59389-4.00002-1

[28] Kesavachandran CN, Fareed M, Pathak MK, Bihari V, Mathur N, Srivastava AK. Adverse health effects of pesticides in agrarian populations of developing countries. Reviews of Environmental Contamination and Toxicology. 2009;**200**:33-52. DOI: 10.1007/978-1-4419-0028-9_2

[29] Abdou KA, Abo El-Atta HM. Epidemiology of pesticides in developing countries. Advances in Clinical Toxicology (ACT). 2018;**3**(1):1-8

[30] Rojas M, Weiss P, Rodríguez M, Agreda O. Determinants of pesticide poisonings in the central-western region of Venezuela. Chinese Society of Toxicology. 2003;7(4):16-16

[31] Eskenazi B, Marks AR, Bradman A, Fenster L, Johnson C, Barr DB, et al. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlo-rodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. Pediatrics. 2006;**118**(1):233-241. DOI: 10.1542/peds.2005-3117

[32] Hung DZ, Yang HJ, Li YF, Lin CL, Chang SY, Sung FC, et al. The long-term effects of organophosphates poisoning as a risk factor of CVDs: A nationwide population-based cohort study. PLoS One. 2015;**10**:e0137632. DOI: 10.1371/journal.pone.0137632

[33] Jurewicz J, Radwan M, Wielgomas B, Sobala W, Piskunowicz M, Radwan P, et al. The effect of environmental exposure to pyrethroids and DNA dam-age in human sperm. Systems Biology in Reproductive Medicine. 2015;**61**(1):37-43. DOI: 10.3109/19396368.2014.981886

[34] Shafer TJ, Meyer DA, Crofton KM. Developmental neurotoxicity of pyrethroid insecticides: Critical review and future research needs. Environmental Health Perspectives. 2005;**113**:123-136. DOI: 10.1289/ehp.7254

[35] Kettles MK, Browning SR, Prince TS, Horstman SW. Triazine herbicide exposure and breast cancer incidence: An ecologic study of Kentucky counties. Environmental Health Perspectives. 1997;**105**:1222-1227. DOI: 10.1289/ehp.971051222

[36] Huyen VH, Song NV, Thuy NT, Dung LP, Hoan LK. Effects of of pesticides on farmers' health in Tu Ky district, Hai Duong province, Vietnam. Sustainable Futures. 2020;**2**:1-26

[37] Agricultural Pesticide Committee, APC. Activities. Cairo, Egypt: Ministry of Agriculture; 2021. Available from: www.apc.gov.eg [Accessed: August 26, 2021]

[38] Van den Berg H. Global status of DDT and its alternatives for use in vector control to prevent disease. Environmental Health Perspectives. 2009;**117**:1656-1663. DOI: 10.1289/ehp.0900785

[39] Ecobichon DJ. Pesticide use in developing countries. Toxicology. 2001;**160**(1-3):27-33. DOI: 10.1016/s0300-483x(00)00452-2

[40] Rehwagen C. WHO recommends DDT to control malaria. BMJ. 2006;**333**(7569):622. DOI: 10.1136/bmj.333.7569.622-b

[41] Lucena RA, Allam MF, Jimenez SS, Villarejo ML. A review of environmental

exposure to persistent organochlorine residuals during the last fifty years. Current Drug Safety. 2007;**2**:163-172. DOI: 10.2174/157488607780598313

[42] Avila-Vazquez M, Maturano E, Etchegoyen A, Difilippo FS, Maclean B. Association between Cancer and environmental exposure to glyphosate. International Journal of Clinical Medicine. 2017;**8**:73-85. DOI: 10.4236/ijcm.2017.82007

[43] Erwin X. Briefing on Export of Pesticides to Africa from China in 2015. California, USA: AgNews; 2016. Available from: http://news.agropages.com/News/NewsDetail---17241.htm [Accessed: July 30, 2021]

[44] Bayoumi AE. Counterfeit pesticides. ACS Chemical Health & Safety. 2021;**28**:232-237. DOI: 10.1021/acs.chas.1c00010

[45] Coats JR. Mechanisms of toxic action and structure-activity relationships for organochlorine and synthetic pyrethroid insecticides. Environmental Health Perspectives. 1990;**87**:255-262. DOI: 10.1289/ehp.9087255

[46] Pope CN. Organophosphorus pesticides: Do they all have the same mechanism of toxicity? Journal of Toxicology and Environmental Health. Part B, Critical Reviews. 1999;**2**(2):161-181. DOI: 10.1080/109374099281205

[47] Abou-Donia MB. Organophosphorus ester-induced chronic neurotoxicity. Archives of Environmental Health. 2003;**58**(8):484-497. DOI: 10.3200/AEOH.58.8.484-497

[48] Karami-Mohajeri S, Abdollahi M. Toxic influence of organophosphate, carbamate, and organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: A systematic review. Human & Experimental Toxicology. 2010;**30**:1119-1140. DOI: 10.1177/0960327110388959

[49] Ecobichon DJ. Toxic effects of pesticides. In: Klaassen CD, editor. Casarett & Doull's Toxicology, the Basic Science of Poisons. 6th ed. New York, USA: McGraw Hill; 1996. pp. 763-810

[50] Gervais JA, Luukinen B, Buhl K, Stone D. Imidacloprid Technical Fact Sheet. Vol. 2012. Oregon State University, USA: National Pesticide Information Center; 2012. Available from: http://npic.orst.edu/factsheets/archive/imidacloprid.html. [Accessed: September 4, 2021]

[51] Bakir F, Rustam H, Tikriti S, Al-Damluji SF, Shihristani H. Clinical and epidemiological aspects of methylmercury poisoning. Postgraduate Medical Journal. 1980;**56**(651):1-10. DOI: 10.1136/pgmj.56.651.1

[52] Edwards R, Ferry DC, Temple WA. Fungicides and related compounds. In: Hayes WJ, Law ER, editors. Handbook of Pesticide Toxicology. Classes of Pesticides. Vol. 3. Cambridge, Massachusetts, USA: Academic Press; 1991. pp. 1409-1470

[53] Chmelíková E, Markéta S, Michal J, David N. Endocrine disruptors: General characteristics, chemical nature and mechanisms of action. A review. Medical Journal of Cell Biology. 2018;**6**(4):135-139. DOI: 10.2478/acb-2018-0022

[54] Mnif W, Hassine AIH, Bouaziz A, Bartegi A, Thomas O, Roig B. Effect of endocrine disruptor pesticides: A review. International Journal of Environmental Research and Public Health. 2011;**8**:2265-2303. DOI: 10.3390/ijerph8062265

[55] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R,

Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. Endocrine Reviews. 2009;**30**(4):293-342. DOI: 10.1210/er.2009-0002

[56] Meeker JD. Exposure to environmental endocrine disruptors and child development. Archives of Pediatrics & Adolescent Medicine. 2012;**166**(6):E1-E7. DOI: 10.1001/archpediatrics.2012.241

[57] Shah R. Pesticides and Human Health. London, UK: Licensee IntechOpen; 2020. Available from: https://www.intechopen.com/chapters/73921 [Accessed: August 25, 2021]

[58] Ng M, Flemeng T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the global burden of disease study 2013. Lancet. 2014;**384**:766-781. DOI: 10.1016/S0140-6736(14)60460-8

[59] Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, et al. Obesity pathogenesis: An Endocrine Society scientific statement. Endocrine Reviews. 2017;**38**:267-296. DOI: 10.1210/er.2017-00111

[60] Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA: a Cancer Journal for Clinicians. 2017;**67**(5):378-397. DOI: 10.3322/caac.21405

[61] Wei C, Wang X, Yao X, Xi F, He Y, et al. Bifenthrin induces fat deposition by improving fatty acid uptake and inhibiting lipolysis in mice. Journal of Agricultural and Food Chemistry. 2019;**67**(51):14048-14055. DOI: 10.1021/acs.jafc.9b06727

[62] Sun Q, Xiao X, Kim Y, Kim D, et al. Imidacloprid promotes high fat diet-induced adiposity and insulin resistance in male C57BL/6J mice. Journal of Agricultural and Food Chemistry. 2016;**64**:9293-9306. DOI: 10.1021/acs.jafc.6b04322

[63] OECD, Overweight and Obesity among Children and Adolescents. 2020. Available from: https://www.oecd-ilibrary.org/sites/7402dbb2-en/index.html?itemId=/content/component/7402dbb2-en [Accessed: August 9, 2021]

[64] Ren XM, Kuo Y, Blumberg B. Agrochemicals and obesity. Molecular and Cellular Endocrinology. 2020;**515**:110926. DOI: 10.1016/j.mce.2020.110926

[65] Mustieles V, Fernández MF, Martin-Olmedo P, Alzaga BG, et al. Human adipose tissue levels of persistent organic pollutants and metabolic syndrome components: Combining a cross-sectional with a 10-year longitudinal study using a multi-pollutant approach. Environment International. 2017;**104**:48-57. DOI: 10.1016/j.envint.2017.04.002

[66] Grun F, Blumberg B. Environmental obesogens: Organotins and endocrine disruption via nuclear receptor signaling. Endocrinology. 2006;**147**:50-55. DOI: 10.1210/en.2005-1129

[67] Guo S. Insulin signaling, resistance, and metabolic syndrome: Insights from mouse models into disease mechanisms. The Journal of Endocrinology. 2014;**220**:T1-T23. DOI: 10.1530/JOE-13-0327

[68] Adeva-Andany MM, Martínez-Rodríguez J, González-Lucán M, et al. Insulin resistance is a cardiovascular risk factor in humans. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2019;**13**:1449-1455. DOI: 10.1016/j.dsx.2019.02.023

[69] Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: A significant risk factor of endometrial cancer. Gynecologic Oncology. 2012;**125**(3):751-757. DOI: 10.1016/j.ygyno.2012.03.032

[70] Di Sebastiano KM, Pinthus JH, Duivenvoorden WC, Mourtzakis M. Glucose impairments and insulin esistance in prostate cancer: The role of obesity, nutrition and exercise. Obesity Reviews. 2018;**19**(7):1008-1016. DOI: 10.1111/obr.12674

[71] Cirillo F, Catellani C, Sartori C, Lazzeroni P, et al. Obesity, insulin resistance and colorectal Cancer: Could miRNA dysregulation play a role? International Journal of Molecular Sciences. 2019;**20**:2922. DOI: 10.3390/ijms20122922

[72] WHO, Diabetes. Geneva, Switzerland: WHO; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes [Accessed: August 15, 2021]

[73] Son HK, Kim SA, Kang JH, Chang YS, et al. Strong associations between low-dose organochlorine pesticides and type 2 diabetes in Korea. Environment International. Amsterdam: Elsevier; 2010;**36**:410-414. DOI: 10.1016/j.envint.2010.02.012

[74] Juntarawijit C, Juntarawijit Y. Association between diabetes and pesticides: A case-control study among Thai farmers. Environmental Health and Preventive Medicine. 2018;**23**(3):1-10. DOI: 10.1186/s12199-018-0692-5

[75] Gupta HPK, Pandey R, Anjum S. Occupational exposure to pesticide: A risk of diabetic neuropathy. Journal of Analytical Toxicology. 2018;**1**(14):1-5

[76] El-Morsi DA, Abdel Rahman RH, Abou-Arab AAK. Pesticides residues in Egyptian diabetic children: A preliminary study. Journal of Clinical Toxicology. 2012;**2**(6):1-5. DOI: 10.21608/mjfmct.2012.47773

[77] Lee SH, Kim Y, Kim HY, Kim YH, Kim MS, et al. Aminostyrylbenzofuran directly reduces oligomeric amyloid-ß and reverses cognitive deficits in Alzheimer transgenic mice. PLoS One. 2014;**9**:57-63. DOI: 10.1371/journal.pone.0095733

[78] Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock EJ, et al. Persistent organic pollutant exposure leads to insulin resistance syndrome. Environmental Health Perspectives. 2010;**118**:465-471. DOI: 10.1289/ehp.0901321

[79] Lind PM, Lind L. Endocrine-disrupting chemicals and risk of diabetes: An evidence-based review. Diabetologia. 2018;**61**:1495-1502. DOI: 10.1007/s00125-018-4621-3

[80] Han X, Zhang F, Meng L, Xu Y, Li Y, et al. Exposure to organochlorine pesticides and the risk of type 2 diabetes in the population of East China. Ecotoxicology and Environmental Safety. 2020;**190**:110125. DOI: 10.1016/j.ecoenv.2019.110125

[81] van Koppen CJ, Kaiser B. Regulation of muscarinic acetylcholine receptor signaling. Pharmacology & Therapeutics. 2003;**98**:197-220. DOI: 10.1016/s0163-7258(03)00032-9

[82] Goedert M, Spillantini MG. A century of Alzheimer's disease. Science. 2006;**314**:777-781. DOI: 10.1126/science.1132814

[83] Burns A, Iliffe S. Alzheimer's disease. BMJ. 2009;**338**:b158. DOI: 10.1136/bmj.b158

[84] Singh NK, Chhillar N, Banerjee BD, et al. Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population. Human & Experimental Toxicology. 2013;**32**(1): 24-30. DOI: 10.1177/0960327112456315

[85] Yadav SS, Singh MK, Yadav RS. Organophosphates induced Alzheimer's disease: An epigenetic aspect. Journal of Clinical Epigenetics. 2016;**2**(1):1-8. DOI: 10.21767/2472-1158.100010

[86] Yan D, Zhang Y, Liu L, Yan H. Pesticide exposure and risk of Alzheimer's disease: A systematic review and meta-analysis. Scientific Reports. 2016;**6**:32222. DOI: 10.1038/srep32222

[87] Richardson JR, Roy A, Shalat SL, von Stein RT, Hossain MM, et al. Elevated serum pesticide levels and risk for Alzheimer disease. JAMA Neurology. 2014;**71**(3):284-290. DOI: 10.1001/jamaneurol.2013.6030

[88] Breunig JJ, Guillot-Sestier MV, Town T. Brain injury, neuroinflammation and Alzheimer's disease. Frontiers in Aging Neuroscience. 2013;**5**:26. DOI: 10.3389/fnagi.2013.00026

[89] Nagele RG, Andrea MR, Anderson WJ, Wang HY. Intracellular accumulation of beta-amyloid (1-42) in neurons is facilitated by the alpha 7 nicotinic acetylcholine receptor in Alzheimer's disease. Neuroscience. 2002;**110**:199-211. DOI: 10.1016/s0306-4522(01)00460-2

[90] Lee J, Giordano S, Zhang J. Autophagy, mitochondria and oxidative stress: Cross-talk and redox signaling. Journal of Biochemistry. 2012;**441**:523-540. DOI: 10.1042/BJ20111451

[91] Wang X, Wang W, Li L, Perry G, et al. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochimica et Biophysica Acta. 2014;**1842**(8):1240-1247. DOI: 10.1016/j.bbadis.2013.10.015

[92] Baltazar MT, Dinis-Oliveira RJ, Bastos ML, et al. Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases–a mechanistic approach. Toxicology Letters. 2014;**230**:85-103. DOI: 10.1016/j.toxlet.2014.01.039

[93] Salazar JG, Ribes D, Cabré M, Domingo JL, et al. Amyloid beta peptide levels increase in brain of AβPP Swedish mice after exposure to chlorpyrifos. Current Alzheimer Research. 2011;**8**:732-740. DOI: 10.2174/156720511797633197

[94] Hayden KM, Norton MC, Darcey D, et al. Occupational exposure to pesticides increases the risk of incident AD: The Cache County study. Neurology. 2010;**74**:1524-1530. DOI: 10.1212/WNL.0b013e3181dd4423

[95] Chin-Chan M, Yepes JN, Vega BQ. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Frontiers in Cellular Neuroscience. 2015;**9**(124):1-22. DOI: 10.3389/fncel.2015.00124

[96] Tang BL. Neuropathological mechanisms associated with pesticides in Alzheimer's disease. Toxics. 2020;**8**(21):1-16. DOI: 10.3390/toxics8020021

[97] Lin JN, Lin CL, Lin MC, Lai CH, et al. Increased risk of dementia in patients with acute organophosphate and carbamate poisoning: A nationwide population-based cohort study. Medicine (Baltimore). 2015;**94**(29):e1187. DOI: 10.1097/MD.0000000000001187

[98] Zhao N, Yang Y, Zhang L, Zhang Q, et al. Quality of life in Parkinson's disease: A systematic review and

meta-analysis of comparative studies. CNS Neuroscience & Therapeutics. 2021;**27**:270-279. DOI: 10.1111/cns.13549

[99] Barbeau A, Roy M, Bernier G, Campanella G, Paris S. Ecogenetics of Parkinson's disease: Prevalence and environmental aspects in rural areas. The Canadian Journal of Neurological Sciences. 1987;**14**(1):36-41. DOI: 10.1017/s0317167100026147

[100] Wang A, Costello S, Cockburn M, et al. Parkinson's disease risk from ambient exposure to pesticides. European Journal of Epidemiology. 2011;**26**(7):547-555. DOI: 10.1007/s10654-011-9574-5

[101] Liu C, Liu Z, Zhang Z, Li Y, Fang R, et al. Scientometric analysis and visualization of research on parkinson's disease associated with pesticide exposure. Frontiers in Public Health. 2020;**8**(91):1-14. DOI: 10.3389/fpubh.2020.00091

[102] Ahmed H, Abushouk AI, Gabr M, Negida A, Abdel-Daim AM. Parkinson's disease and pesticides: A meta-analysis of disease connection and genetic alterations. Biomedicine & Pharmacotherapy. 2017;**90**:638-649. DOI: 10.1016/j.biopha.2017.03.100

[103] Shrestha S, Parks CG, Umbach DM, Barber MR, et al. Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses. Environmental Research. 2020;**191**:110186. DOI: 10.1016/j.envres.2020.110186

[104] Karen DJ, Li W, Harp PR, Gillette JS, Bloomquist JR. Striatal dopaminergic pathways as a target for the insecticides permethrin and chlorpyrifos. Neurotoxicology. 2001;**22**:811-817. DOI: 10.1016/s0161-813x(01)00063-8

[105] Kanthasamy AG, Kitazawa M, Kanthasamy A, Anantharam V. Dieldrin-induced neurotoxicity: Relevance to Parkinson's disease pathogenesis. Neurotoxicology. 2005;**26**:701-719. DOI: 10.1016/j.neuro.2004.07.010

[106] Wang XF, Li S, Chou AP, Bronstein JM. Inhibitory effects of pesticides on proteasome activity: Implication in Parkinson's disease. Neurobiology of Disease. 2006;**23**:198-205. DOI: 10.1016/j.nbd.2006.02.012

[107] Brozek G, Lawson J, Szumilas D, Zejda J. Increasing prevalence of asthma, respiratory symptoms, and allergic diseases: Four repeated surveys from 1993-2014. Respiratory Medicine. 2015;**109**:982-990. DOI: 10.1016/j.rmed.2015.05.010

[108] Baldi I, Robert C, Piantoni F, Tual S, et al. Agricultural exposure and asthma risk in the AGRICAN French cohort. International Journal of Hygiene and Environmental Health. 2014;**217**:435-442. DOI: 10.1016/j.ijheh.2013.08.006

[109] Hyland C, Laribi O. Review of take-home pesticide exposure pathway in children living in agricultural areas. Environmental Research. 2017;**156**:559-570. DOI: 10.1016/j.envres.2017.04.017

[110] Marks AR, Harley K, Bradman A, et al. Organophosphate pesticide exposure and attention in young Mexican-American children: The CHAMACOS study. Environmental Health Perspectives. 2010;**118**:1768-1774. DOI: 10.1289/ehp.1002056

[111] Asmus CIRF, Camara VM, Landrigan PJ, Claudio L. A systematic review of Children's environmental health in Brazil. Annals of Global Health. 2016;**82**:132-148. DOI: 10.1016/j.aogh.2016.02.007

[112] de Joode BVW, Mora AM, Lindh CH, et al. Pesticide exposure and

neurodevelopment in children aged 6-9 years from Talamanca, Costa Rica. Cortex. 2016;**85**:137-150. DOI: 10.1016/j.cortex.2016.09.003

[113] Kudagammana ST, Mohotti K. Environmental exposure to agrochemicals and allergic diseases in preschool children in high grown tea plantations of Sri Lanka. Allergy, Asthma and Clinical Immunology. 2018;**14**:1-5. DOI: 10.1186/s13223-018-0308-z

[114] Salameh PR, Baldi I, Brochard P, Raherison C, et al. Respiratory symptoms in children and exposure to pesticides. The European Respiratory Journal. 2003;**22**:507-512. DOI: 10.1183/09031936.03.00107403a

[115] Ohayo-Mitoko GJ, Kromhout H, Simwa JM, et al. Self reported symptoms and inhibition of acetylcholinesterase activity among Kenyan agricultural workers. Occupational and Environmental Medicine. 2000;**57**:195-200. DOI: 10.1136/oem.57.3.195

[116] Quansah R, Bend JR, Abdul-Rahaman A, et al. Associations between pesticide use and respiratory symptoms: A cross-sectional study in southern Ghana. Environmental Research. 2016;**150**:245-254. DOI: 10.1016/j.envres.2016.06.013

[117] Negatu B, Kromhout H, Mekonnen Y, Vermeulen R. Occupational pesticide exposure and respiratory health: A large-scale cross-sectional study in three commercial farming systems in Ethiopia. Thorax. 2017;**72**:1-8. DOI: 10.1136/thoraxjnl-2016-208924

[118] Callahan CL, Al-Batanony M, Ismail AA, et al. Chlorpyrifos exposure and respiratory health among adolescent agricultural workers. International Journal of Environmental Research and Public Health. 2014;**11**:13117-13129. DOI: 10.3390/ijerph111213117

[119] Hoppin JA, Umbach DM, London SJ, et al. Pesticide use and adult-onset asthma among male farmers in the agricultural health study. The European Respiratory Journal. 2009;**34**:1296-1303. DOI: 10.1183/09031936.00005509

[120] Avila-Vazquez M, Difilippo FS, Lean BM, Maturano E. Environmental exposure to glyphosate and risk of asthma in an ecological study. Global Journal of Medical Research. 2021;**21**(1):15-22. DOI: 10.34257/GJMRFVOL21IS1PG15

[121] Hansen MRH, Jørs E, Sandbæk A, Sekabojja D, et al. Organophosphate and carbamate insecticide exposure is related to lung function change among smallholder farmers: A prospective study. Thorax. 2021;**76**(8):780-789. DOI: 10.1136/thoraxjnl-2020-214609

[122] Shaffo FC, Grodzki AC, Fryer AD, Lein PJ. Mechanisms of organophosphorus pesticide toxicity in the context of airway hyperreactivity and asthma. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2018;**315**:L485-L501. DOI: 10.1152/ajplung.00211.2018

[123] WHO, Chronic Obstructive Pulmonary Disease (COPD). Geneva, Switzerland: WHO; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) [Accessed: August 27, 2021]

[124] Sprince NL, Lewis MQ, Whitten PS, et al. Respiratory symptoms: Associations with pesticides, silos and animal confinement in the Iowa farm family health and hazard surveillance project. American Journal of Industrial Medicine. 2000;**38**(4):455-462. DOI: 10.1002/1097-0274(200010)38:4<455::aid-ajim12>3.0.co;2-l

[125] Salameh PR, Waked M, Baldi I, Brochard P, Saleh BA. Chronic bronchitis and pesticide exposure: A case–control study in Lebanon. European Journal of Epidemiology. 2006;**21**(9):681-688. DOI: 10.1007/s10654-006-9058-1

[126] Chakraborty S, Mukherjee S, Roychoudhury S, et al. Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India. Journal of Occupational Health. 2009;**51**:488-497. DOI: 10.1539/joh.l9070

[127] Kang HK, Dalager NA, Needham LL, et al. Health status of Army chemical corps Vietnam veterans who sprayed defoliant in Vietnam. American Journal of Industrial Medicine. 2006;**49**(11):875-884. DOI: 10.1002/ajim.20385

[128] LeVan TD, Von Essen S, Romberger DJ, et al. Polymorphisms in the CD14 gene associated with pulmonary function in farmers. American Journal of Respiratory and Critical Care Medicine. 2005;**171**:773-779. DOI: 10.1164/rccm.200404-530OC

[129] Hoppin JA, Valcin M, Henneberger PK, Kullman GJ, et al. Pesticide use and chronic bronchitis among farmers in the agricultural health study. American Journal of Industrial Medicine. 2007;**50**(12):969-979. DOI: 10.1002/ajim.20523

[130] Tarmure S, Alexescu TG, Orasan O, Negrean V, et al. Influence of pesticides on respiratory pathology – A literature review. Annals of Agricultural and Environmental Medicine. 2020;**27**(2): 194-200. DOI: 10.26444/aaem/121899

[131] Landa RJ. Diagnosis of autism spectrum disorders in the first 3 years of life. Nature Clinical Practice. Neurology. 2008;**4**(3):138-147. DOI: 10.1038/ncpneuro0731

[132] Nazeer A, Ghaziuddin M. Autism Spectrum disorders: Clinical features and diagnosis. Pediatric Clinics of North America. 2012;**59**(1):19-25. DOI: 10.1016/j.pcl.2011.10.007

[133] Elsabbagh M, Divan G, Koh YJ, Kim YS, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Research. 2012;**5**(3):160-179. DOI: 10.1002/aur.239

[134] Liu J, Schelar E. Pesticide exposure and child neurodevelopment: Summary and implications. Workplace Health & Safety. 2012;**60**(5):235-243. DOI: 10.1177/216507991206000507

[135] Shelton JF, Hertz-Picciotto I, Pessah IN. Tipping the balance of autism risk: Potential mechanisms linking pesticides and autism. Environmental Health Perspectives. 2012;**20**(7):944-951. DOI: 10.1289/ehp.1104553

[136] Blatt GJ, Fitzgerald CM, Guptill JT, et al. Density and distribution of hippocampal neurotransmitter receptors in autism: An autoradiographic study. Journal of Autism and Developmental Disorders. 2001;**31**(6): 537-543. DOI: 10.1023/a:1013238809666

[137] Lyall K, Croen LA, Sjödin A, et al. Polychlorinated biphenyl and organochlorine pesticide concentrations in maternal mid-pregnancy serum samples: Association with autism Spectrum disorder and intellectual disability. Environmental Health Perspectives. 2017;**125**(3):474-480. DOI: 10.1289/EHP277

[138] Barkoski JM, Philippat C, Tancredi D, et al. In utero pyrethroid pesticide exposure in relation to autism spectrum disorder (ASD) and other neurodevelopmental outcomes at 3 years in the MARBLES longitudinal

cohort. Environmental Research. 2021;**194**:110495. DOI: 10.1016/j.envres.2020.110495

[139] Philippat C, Barkoski J, Tancredi DJ, et al. Prenatal exposure to organophosphate pesticides and risk of autism spectrum disorders and other non-typical development at 3 years in a high risk cohort. International Journal of Hygiene and Environmental Health. 2018;**221**(3):548-555. DOI: 10.1016/j.ijheh.2018.02.004

[140] Ongono JS, Béranger R, Baghdadli A, Mortamais M. Pesticides used in Europe and autism spectrum disorder risk: Can novel exposure hypotheses be formulated beyond organophosphates, organochlorines, pyrethroids and carbamates? - a systematic review. Environmental Research. 2020;**187**:109646. DOI: 10.1016/j.envres.2020.109646

[141] Carter CJ, Blizard RA. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol a, phthalates and many others in food, cosmetics or household products. Neurochemistry International. 2016;**101**:83-109. DOI: 10.1016/j.neuint.2016.10.011

[142] Kaur RP, Gupta V, Christopher AF, Bansal P. Potential pathways of pesticide action on erectile function a contributory factor in male infertility. Asian Pacific Journal of Reproduction. 2015;**4**(4):322-330. DOI: 10.1016/j.apjr.2015.07.012

[143] Soliman SS, Awad-Allah A, Ebied ZM. Erectile dysfunction in workers chronically exposed to pesticides and organic solvents in Damietta governorate. Mansoura Journal of Forensic Medicine & Clinical Toxicology. 2008;**16**(2):63-76

[144] Zhang JJ, Wang Y, Xiang HY, et al. Oxidative stress: Role in acetamiprid-induced impairment of the male mice reproductive system. Agricultural Sciences in China. 2011;**10**(2):786-796. DOI: 10.1016/S1671-2927(11)60063-1

[145] Najafi G, Razi M, Hoshyar A, et al. The effect of chronic exposure with imidacloprid insecticide on fertility in mature male rats. International Journal of Fertility and Sterility. 2010;**4**(1):9-16

[146] Ngoula F, Watcho P, Dongmo MC, et al. Effects of pirimiphos-methyl (an organophosphate insecticide) on the fertility of adult male rats. African Health Sciences. 2007;**7**(1):3-9. DOI: 10.5555/afhs.2007.7.1.3

[147] Slimani S, Boulakoud MS, Abdennour C. Pesticide exposure and reproductive biomarkers among male farmers from north-East Algeria. Annals of Biological Research. 2011;**2**:290-297

[148] Akingbemi BT, Ge RS, Klinefelter GR, et al. A metabolite of methoxychlor, 2,2-bis(p-hydroxyphenyl)-1,1, 1- trichloroethane, reduces testosterone biosynthesis in rat leydig cells through suppression of steady-state messenger ribonucleic acid levels of the cholesterol side-chain cleavage enzyme. Biology of Reproduction. 2000;**62**(3):571-578. DOI: 10.1095/biolreprod62.3.571

[149] Beard JD, Umbach DM, Hoppin JA, et al. Suicide and pesticide use among pesticide applicators and their spouses in the agricultural health study. Environmental Health Perspectives. 2011;**119**(11):1610-1615. DOI: 10.1289/ehp.1103413

[150] London L, Flisher AJ, Wesseling C, et al. Suicide and exposure to organophosphate insecticides: Cause or effect? American Journal of Industrial Medicine. 2005;**47**(4):308-321. DOI: 10.1002/ajim.20147

[151] London L, Beseler C, Bouchard MF, et al. Neurobehavioral and neurodevelopmental effects of pesticide exposures. Neurotoxicology. 2012;**33**(4):887-896. DOI: 10.1016/j.neuro.2012.01.004

[152] Kori RK, Mandrah K, Hasan W, et al. Identification of markers of depression and neurotoxicity in pesticide exposed agriculture workers. Journal of Biochemical and Molecular Toxicology. 2020;**34**(6):1-9. DOI: 10.1002/jbt.22477

[153] Cowen PJ, Browning M. What has serotonin to do with depression? World Psychiatry. 2015;**14**(2):158-160. DOI: 10.1002/wps.20229

[154] Gasmi S. Neurotransmission dysfunction by mixture of pesticides and preventive effects of quercetin on brain, hippocampus and striatum in rats. Toxicology and Environmental Health Sciences. 2020;**12**:203-212

[155] Ibrahim KA, Abdelrahman SM, Elhakim HKA, Ragab EA. Single or combined exposure to chlorpyrifos and cypermethrin provoke oxidative stress and downregulation in monoamine oxidase and acetylcholinesterase gene expression of the rat's brain. Environmental Science and Pollution Research. 2020;**27**(11):12692-12703. DOI: 10.1007/s11356-020-07864-8

[156] Faria NMX, Fassa AG, Meucci RD. Association between pesticide exposure and suicide rates in Brazil. Neurotoxicology. 2014;**45**:355-362. DOI: 10.1016/j.neuro.2014.05.003

[157] Meyer A, Koifman S, Koifman RJ, et al. Mood disorders hospitalizations, suicide attempts, and suicide mortality among agricultural workers and residents in an area with intensive use of pesticides in Brazil. Journal of Toxicology and Environmental Health. Part A. 2010;**73**(13-14):866-877. DOI: 10.1080/15287391003744781

[158] Wesseling C, de Joode B, Keifer M, London L, et al. Symptoms of psychological distress and suicidal ideation among banana workers with a history of poisoning by organophosphate or n-methyl carbamate pesticides. Occupational and Environmental Medicine. 2010;**67**(11):778-784. DOI: 10.1136/oem.2009.047266

[159] Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: Systematic review. BMC Public Health. 2007;**7**(357):1-15. DOI: 10.1186/1471-2458-7-357