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Review

Exposure to pesticides and the associated human health effects

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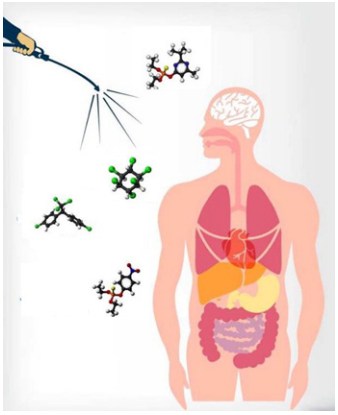
HIGHLIGHTS

- Pesticides are designed to function with reasonable certainty and minimal risk to human health.
- Pesticide exposure is however turned out to be linked with various diseases including cancer.
- In light of the significance of pesticide pollution, the general aspects of pesticides are assessed.
- The current state of knowledge regarding pesticide use and its detrimental impacts is described.

GRAPHICAL ABSTRACT



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ABSTRACT

Pesticides are used widely to control weeds and insect infestation in agricultural fields and various pests and disease carriers (e.g., mosquitoes, ticks, rats, and mice) in houses, offices, malls, and streets. As the modes of action for pesticides are not species-specific, concerns have been raised about environmental risks associated with their exposure through various routes (e.g., residues in food and drinking water). Although such hazards range from short-term (e.g., skin and eye irritation, headaches, dizziness, and nausea) to chronic impacts (e.g., cancer, asthma, and diabetes), their risks are difficult to elucidate due to the involvement of various factors (e.g., period and level of exposure, type of pesticide (regarding toxicity and persistence), and the environmental characteristics of the affected areas). There are no groups in the human population that are completely unexposed to pesticides while most diseases are multi-causal to add considerable complexity to public health assessments. Hence, development of eco-friendly pesticide alternatives (e.g., EcoSMART) and Integrated Pest Management (IPM) techniques is desirable to reduce the impacts of pesticides. This paper was hence organized to present a comprehensive review on pesticides with respect to their types, environmental distribution, routes of exposure, and health impacts.

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Contents

1. Introduction

Pesticides are one of the few toxic substances released deliberately into the environment to kill living organisms (e.g., weeds (herbicides), insects (insecticides), fungus (fungicides), and rodents (rodenticides)). Although the term pesticide is often misunderstood to refer only to insecticides, it is also applicable to herbicides, fungicides, and various other substances used to control pests' (Matthews, 2006).

Agriculture is the largest consumer (around 85% of world production) of pesticides to chemically control various pests. Moreover, pesticides are also used in public health activities to control vector-borne diseases (e.g., malaria and dengue) and unwanted plants (e.g., grass and weeds) in ornamental landscaping, parks, and gardens. They are also useful in suppressing or avoiding the proliferation of insects, pests, bacteria, fungi, and algae in electrical equipment, refrigerators, paint, carpets, paper, cardboard, and food packaging materials (Gilden et al., 2010). However, unintended exposure to pesticides can be extremely hazardous to humans and other living organisms as they are designed to be poisonous (Sarwar, 2015). They may also be harmful to people who are exposed to pesticides through occupational (or home) use, eating foods or liquids containing pesticide residue, or inhalation (or contact) of pesticide-contaminated air (Pimentel et al., 2013). Even very low levels of exposure may have adverse health effects at early development (Damalas and Eleftherohorinos, 2011). The physical makeup, behavior, and physiology of children make them more susceptible to pesticides than adults (Mascarelli, 2013).

Pesticide exposure is linked with various diseases including cancer, hormone disruption, asthma, allergies, and hypersensitivity (Van Maele-Fabry et al., 2010). A line of evidence also exists for the negative impacts of pesticide exposure leading to birth defects, reduced birth weight, fetal death, etc. (Baldi et al., 2010; Meenakshi et al., 2012; Wickerham et al., 2012). On the basis of scientific evidence, the real, predicted, and perceived risks that pesticides pose to human health (occupational and consumer exposure) and the environment are fully justified. In light of the environmental significance of pesticide pollution and its impact, this review has been organized to describe the general aspects of pesticides with respect to classification, the status of pollution, the transfer route, and the impacts on human health. The objective of this review is to conduct a systematic review of published studies (since 1999 to 2016) with respect to the use of pesticides and their detrimental impacts on human health and ecological systems.

2. Methodology

A comprehensive literature search was conducted to accurately describe the impact of pesticide exposure and its health outcome. To this end, the following data sources were utilized: Medline, EMBASE, Science direct, PubMed, psycINFO, and papers cited in those database. In light of the extensiveness of the existing literature on this topic as well as the availability of many reviews, we focused on studies published mainly from 2010 to the present. No restrictions on study type were applied while the search terms were organized by health effect and topic area. We did not restrict our search to papers written in English but also those presented in other languages (as long as English abstracts are available). After removing duplicate records, all remaining references retrieved from the literature search were screened by using only the title and abstract (when necessary and available).

After primary screening to remove records with irrelevant topics, a secondary screening was done to focus on the articles of our study interest. The results were organized according to health effect to assess the effect of exposure to cumulative or aggregate mixtures of pesticide. We also considered studies focusing not only on their impact but also on exposure route. The titles for each citation were screened and 272 articles were selected for the review of their abstracts. All abstracts were sorted to yield 121 publications for full review. After reviewing those full texts, only 87 studies were finally cited in the menu script. Overall, topics dealing with cancers associated with pesticide exposure are one of the most studied issues during the last decade. Distribution of the cited studies has been illustrated in Fig. 1.

3. Types of pesticides

Pesticides can be classified by various criteria such as chemical classes, functional groups, mode of action, and toxicity (**Garcia** et al., 2012). Table 1 provides classification of pesticides based on different criteria. The active ingredients of most pesticides are either organic (contain carbon) or inorganic (copper sulfate, ferrous sulfate, copper, lime, sulfur, etc.) (Gunnell et al., 2007). The chemicals in organic pesticides tend to be more complex and less soluble in water than those of inorganic pesticides (Debost-Legrand et al., 2016). Organic pesticides can be additionally subdivided into two groups: natural (produced from naturally occurring sources) and synthetic (artificially produced by chemical synthesis). Table 2 also displays the classification based on chemical structure. Pesticides have different modes of action or ways to control the

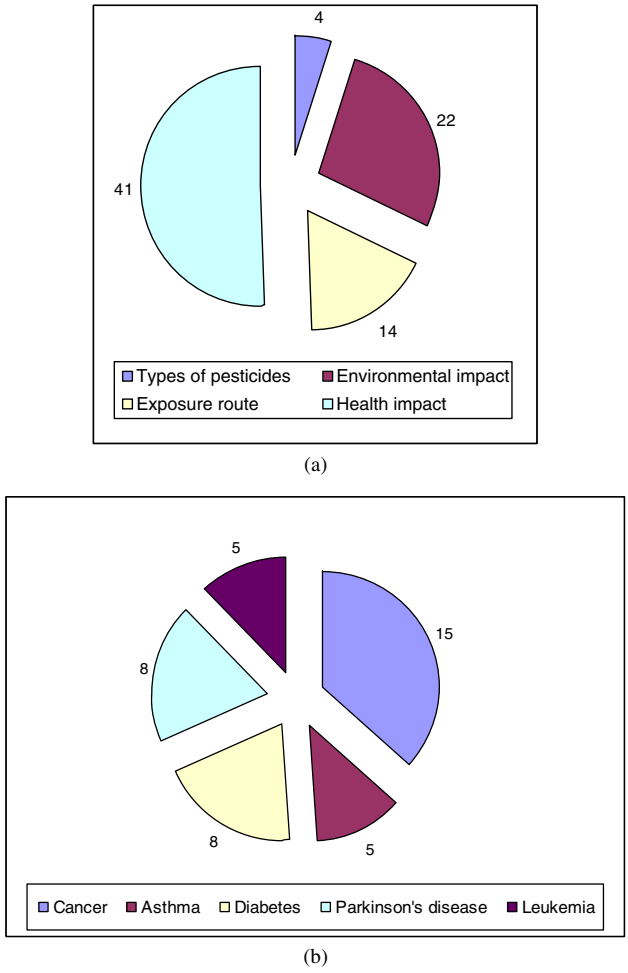


Fig. 1. Assortment of some key references used in this study: classification made according to (a) subject matter and (b) types of diseases.

target pest. Moreover, certain herbicides may simulate the function of plant growth regulators, while others may effectively control the capacity of a plant to convert light into food. Likewise, one fungicide may affect cell division, while others can be effective in slowing down the creation of certain compounds in the fungus. Pesticides are sometimes classified by the type of target pest for which they are applied. As a fungicide is used to control the growth of fungi, miticides, insecticides, and herbicides are used for mites, insects, and weeds, respectively. Insecticides are capable of killing insects by penetrating into their bodies via direct contact (dermal entry), oral, and/or respiratory entry. Herbicides are used to kill plants by direct contact and/or by killing the weeds when they are absorbed through the leaves, stems, or roots. Some pesticides are capable of moving into untreated tissues after being absorbed by plants or animals. Such insecticides or fungicides can penetrate throughout the treated plants to kill certain insects or fungi. Other pesticides have also been developed to influence the nervous system or to act on the endocrine or hormone systems of pests for their control (Mnif et al., 2011).

4. Impact of pesticide use on the environment

As pesticides are designed to be toxic to particular groups of organisms, they can have considerable adverse environmental effects on other living creatures as well as diverse media including air, soil, or water (Aktar et al., 2009). The status of pesticide pollution in various environmental media (such as air, water, and soil) is summarized in Table 3.

Table 1
Classification of pesticides.

(a) Based on toxicity criteria (WHO, World Health Organization, 2009)

Type	Toxicity level	LD_{50}[a] for the rat (mg/kg body weight)	
		Oral	Dermal
Ia	Extremely hazardous	<5	<50
Ib	Highly hazardous	5–50	50–200
II	Moderately hazardous	50–2000	200–2000
U	Unlikely to present acute hazard	5000 or higher	

(b) Based on target pest (Aktar et al., 2009)

Pesticide Type	Pest
Algicide	Algae
Avicide	Birds
Bactericide	Bacteria
Fungicide	Fungi
Herbicide	Weeds
Insecticide	Insects
Miticide	Mites
Molluscicide	Snails, slugs
Nematicide	Nematodes
Piscicide	Fish
Rodenticide	Rodents

(c) Based on the mode of formulation (Mascarelli, 2013)

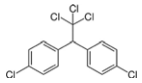
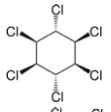
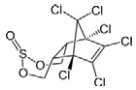
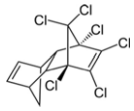
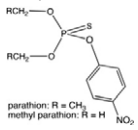
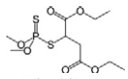
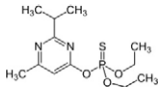
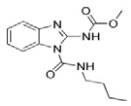
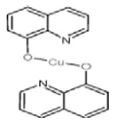
Physical state	Characteristics
Emulsifiable concentrates	Do not require constant agitation prior to each application.
Wettable Powders	Require constant agitation prior to each application
Granules	Obtained by mixing the active ingredient with clay
Baits	Obtained by mixing the active ingredient with food
Dusts	Dusts cannot be mixed with water and they must be applied dry

[a] LD_{50} is the amount of the substance required to kill 50% of the test population.

Some pesticides (e.g., aldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dieldrin, endrin, heptachlor, and hexachlorobenzene) contain persistent organic pollutants (POPs) that resist degradation and thus remain in the environment for years (Yadav et al., 2015). Moreover, as such compounds have the ability to bioaccumulate and biomagnify, they can be bioconcentrated by up to 70,000 fold relative to the initial concentration (Hernández et al., 2013a). Repeated application of pesticides leads to loss of biodiversity and increased pest resistance, while its effects on other species facilitate pest resurgence (Damalas and Eleftherohorinos, 2011). It was estimated that >95% of applied pesticides had the potential to impact non-target organisms and to become widely dispersed in the environment (**Simeonov et al., 2013**).

Airborne pollution of pesticides may occur through pesticide drift (e.g., aerial spray drift) and post-application volatilization (Rull and Ritz, 2003). Even indoors, air currents created by heating, cooling, and ventilation systems can be a mechanism for the spread of pesticides used in indoor environments. Pesticide use accounts for about 6% of the total tropospheric ozone level (Coxall, 2014). In one study, the ambient air concentrations of pesticides were measured from three potato farm sites in Prince Edward Island, Canada (White et al., 2006). The presence of the fungicide chlorothalonil was found ubiquitously at relatively high concentrations reflecting the effect of its repeated use on potato farms. In another study carried out in potato field sites in Prince Edward Island, Canada, the ground-level concentrations of carbofuran and methamidiphos in air were measured as 219 and 637 ng m^{-3}, respectively. The concentrations of these pesticides were identified as being of high concern in terms of potential exposure to wildlife. In the Taihu Lake region of China, concentrations of organochlorine (OC) pesticides (p,p′- DDT, Dichlorodiphenyldichloroethylene (p, p′ -DDE), Dichlorodiphenyldichloroethane (p,p′-DDD), and o,p′-DDT) in air averaged 1.24, 2.12, 0.36, and 7.67 ng m^{-3}, respectively (Qiu et al., 2004). At the Kaweah Reservoir, CA, USA, concentrations of chlorpyrifos were

Table 2
Classification of pesticide based on chemical structure.

Type	Example	Structure	Effect on pest
Organochlorines (five or more chlorine atoms)	DDT		Nervous system disruptors leading to convulsions and paralysis of the insect and its eventual death
	Lindane		
	Endosulfan		
	Aldrin		
Organophosphorous	Parathion		Nervous impulses fail to move across the synapse causing a rapid twitching of voluntary muscles and hence paralysis and death
	Malathion		
	Diaznon		
Inorganic	*Benomyl*		Predominantly stomach poisoning
	Oxine copper		

highest in June (17.5 ng m^{-3}), while those of chlorpyrifosoxon peaked in May (30.4 ng m^{-3}) (LeNoir et al., 1999).

Pesticide residues have been found in rain and groundwater as well. In a study conducted in Hungary, the most common contaminants in water were atrazine (6%), acetochlor (4%), propisochlor (1.5%), metolachlor (1.5%), diazinon (1%), and 2,4-D (1%) (Székács et al., 2015). In a study in Turkey, beta-Hexachlorocyclohexane (β-HCH), 4,4′-DDT, endrin ketone, and methoxychlor concentrations were found to be 0.281, 0.138, 0.120, and 0.102 μg L^{-1}, respectively, in drinking water samples (Bulut et al., 2010). In another study, the residues of OC pesticides in surface water were measured from 2000 to 2002 at the Küçük Menderes River in Turkey (Turgut, 2003). These authors found the highest concentration of heptachlor epoxide among organochlorine pesticides at 281 ng L^{-1} in river water.

Degradation and sorption are both factors that influence the persistence of pesticides in soil. The impacts of some pesticide compounds may last for decades, adversely affecting soil conservation and reducing biodiversity in the soil and soil quality (Jacobsen and Hjelmsø, 2014). Similar to other media, the status of pesticide pollution in soil media is ubiquitous, as described in Table 3.

5. Routes of pesticide exposure to human

Exposure to pesticides can occur directly from occupational, agricultural, and household use, while they can also be transferred indirectly through diet. Moreover, the general population may be exposed to pesticides due to their application on golf courses, around major roads, etc. The main routes of human exposure to pesticides are through the food chain, air, water, soil, flora, and fauna (Anderson and Meade, 2014). Pesticides are distributed throughout the human body through the bloodstream but can be excreted through urine, skin, and exhaled air (Damalas and Eleftherohorinos, 2011). There are four common ways pesticides can enter the human body: dermal, oral, eye, and respiratory pathways. The toxicity of pesticides can vary depending on the type of exposure such as dermal, oral, or respiratory (inhalation). As would be generally expected, the danger of pesticide contamination usually increases on the dosage (concentration) and critical periods in addition to toxicity of the chemical of interest (Meenakshi et al., 2012).

5.1. Dermal exposure

Dermal exposure is one of the most common and effective routes through which pesticide applicators are exposed to pesticides (Anderson and Meade, 2014). Dermal absorption may occur as a result of a splash, spill, or spray drift, when mixing, loading, disposing, and/or cleaning of pesticides (Salvatore et al., 2008). Absorption may also result from exposure to large amounts of residue. Pesticide formulations vary broadly in physicochemical properties and in their capacity to be absorbed through the skin (Beard et al., 2014), which can be influenced by the amount and duration of exposure, the presence of other materials on the skin, temperature and humidity, and the use of personal protective equipment (Macfarlane et al., 2013). In general, solid forms of pesticides (e.g., powders, dusts, and granules) are not as readily absorbed through the skin and other body tissues as liquid formulations. However, the hazard from skin absorption increases when workers are handling (e.g., mixing) concentrated pesticides (e.g., one containing a high percentage of active ingredients). Certain areas of the body (such as the genital areas and ear canal) are more susceptible to pesticide

Table 3
The status of pesticide pollution observed in various environmental media.

(a) Air

Pesticide	Mean (STDEV) concentration (ng m^{-3})	Study area	Location	Reference
Chlorothalonil	284 (60.9)	Potato field sites	Prince Edward Island, Canada	White et al., 2006
Metalaxyl (fungicide)	17.5 (8.92)			
α-endosulfan	11.7 (7.79)			
Carbofuran	219 (60.6)			Garron et al., 2009
Methamidophos	637 (108)			
p, p′-DDT	1.24 (1,14)	Taihu Lake bed	China	Qiu et al., 2004
p, p′-DDE	2.12 (1.27)			
p, p′-DDD	0.36 (0.34)			
o, p′-DDT	7.67 (1.79)			
Chlorpyrifos	17.5 (6.52)	Agricultural field	Kaweah Reservoir, CA, USA	LeNoir et al., 1999
Chlorpyrifos	30.4 (25.1)			

(b) Water

Pesticide	Mean (STDEV) concentration (ng L^{-1})	Study area	Location	Reference
Clopyralid	15.6 (10.3)	Carrot River	Canada	
2,4-D	16.8 (6.71)	Red River		
Clopyralide	20.9 (9.58)			Environment Canada, EC, 2015
Dicamba	3.78 (1.93)			
Metolachlor	23.7 (11.5)			
MCPA	10.5 (4.27)	Assiniboine River		
β-HCH	28.1 (17.3)	Drinking water	Afyonkarahisar province, Turkey	Bulut et al., 2010
Endrin keton	12.0 (4.75)			
Methoxychlo	10.2 (6.12)			
4,4′-DDT	13.8 (5.82)			
	50.0 (23.1)	River water	Turkey	Turgut, 2003
α-BHC	24.0 (10.9)			
β-BHC	121 (43.6)			
γ-BHC	198 (51.7)			
Heptachlor	281 (35.3)			
Simazine	300 (61.2)	Surface water	Traiguén river basin, Chile	Palma et al., 2004
Carbendazim	180 (24.3)			
Methylbenzotriazole	20.0 (11.9)	Ground waters	European Union	Loos et al., 2010
Bentazone	116 (21.5)			
Desethylterbutylazine	7 (1.67)			

(c) Soil

Pesticide	Mean concentration (g kg^{-1})	Study area	Location	Reference
Acetochlor	16.6 (4.76)	Field experiment	Portugal	Ferri et al., 2002
Acifluorfen	10.2 (3.28)		USA	Gaston and Locke, 2000
Fluometuron	13.9 (5.12)			Gaston et al., 2001
	30.1 (9.32)			Zablotowicz et al., 2000
	13.9 (7.18)			Locke et al., 2005
Norflurazon	13.9 (2.25)			
2,4-Dichlorophenol	27.0 (9.07)		Germany	Düring et al., 2002
Metolachlor	15.4 (5.53)		USA	Ding et al., 2002

absorption than other areas of the body (Dennis et al., 2010). As such, the rate at which dermal absorption proceeds differs for each part of the body (Fig. 2).

5.2. Oral exposure

The most severe poisoning may result when a pesticide is introduced through oral exposure. Oral exposure of a pesticide usually arises by accident due to carelessness or for intentional reasons (Damalas and Eleftherohorinos, 2011). The most frequent cases of accidental oral exposure were reported to occur when pesticides were transferred from their original labeled container to an unlabeled bottle or food container (Gilden et al., 2010). There are many cases in which people have been poisoned by drinking pesticides kept in soft drink bottles or after drinking water stored in pesticide-contaminated bottles (U.S. Environmental Protection Agency, USEPA, 2007). Workers handling pesticides or equipment for their application can also consume pesticides if they do not wash their hands prior to eating or smoking (U.S. Environmental Protection Agency, USEPA, 2007). Consequently, applicators should be carefully instructed on the handling of pesticides such as not to clear a spray line or nozzle by blowing through their mouth.

5.3. Respiratory exposure

Due to the presence of volatile components of pesticides, their potential for respiratory exposure is great (Amaral, 2014). Inhalation of sufficient amounts of pesticides may cause serious damage to nose, throat, and lung tissues (Damalas and Eleftherohorinos, 2011). However, the risk of pesticide exposure is in general relatively low when pesticides are sprayed in large droplets with conventional application equipment. However, if low-volume equipment is used to apply a concentrated material, the potential for respiratory exposure is increased due to the production of smaller droplets (Amaral, 2014). It is recognized that respiratory exposure to pesticides can be significant if applied in confined spaces (e.g., an unventilated storage area or greenhouse). In addition, with increased temperature, vapor levels of many pesticides increase to worsen such exposures. Thus, it is recommended that pesticides should not be applied at air temperatures above 30 °C (U.S. Environmental Protection Agency, USEPA, 2007). Moreover, pesticides

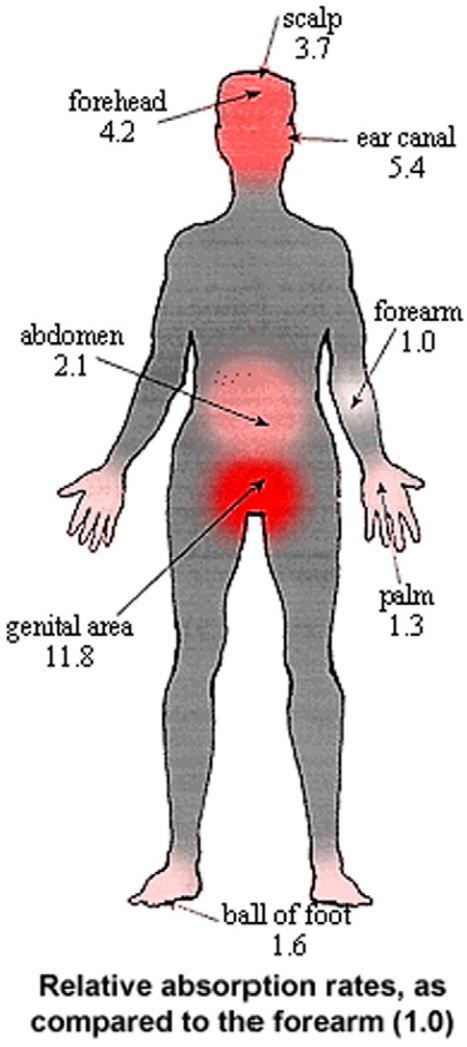


Fig. 2. Intensity of dermal exposure to pesticide on different parts of the body. (Source: Ministry of Agriculture, MOA, 2015)

with high vapor hazards should be applied with sufficient equipment for respiratory protection.

The exposure levels of dialkylphosphate metabolites (DAPs) were measured from three population groups in Thessaly, Greece such as the sprayers' group and two reference groups (rural and urban areas). Accordingly, the median DAP levels (μg g^{-1} creatinine) in the former (24.9 (range = 13.0–42.1)) were significantly ($p < 0.001$) higher than the latter two groups with 11.3 (range: 5.3–18.7) and 11.9 (range: 6.3–20.3), respectively (Koureas et al., 2014). Likewise, in a study carried out in Crete, Greece, elevated levels of DAPs were also found in hair and urine samples of those who sprayed organophosphorus pesticides (OPPs) occupationally in comparison to control group (Kokkinaki et al., 2014). The sum DAPs levels in hair samples of the sprayers were also significantly higher than those of control group ($p < 0.001$), confirming the effect of long-term exposure to OPPs (Kokkinaki et al., 2014). The analysis of amniotic fluid (AF) samples collected from 415 women during the second gestational trimester also confirmed that 97.8% of the samples were positive for at least one of the non-specific dialkyl-phosphate (DAPs) metabolites (Koutroulakis et al., 2014). From the hair samples of a rural Sri Lankan population, the median values (pg mg^{-1}) of several organophosphorus components were measured as: diethyl phosphate (83.3: IQI 56.0, 209.4), diethyl thiophosphate (34.7; IQI 13.8, 147.9), diethyl dithiophosphate (34.5: IQI 23.4, 55.2), and dimethyl phosphate(3: IQI 3, 109.7) (Knipe et al., 2016). High concentrations of organochlorine (up to 148 ng g^{-1} hair for the sum of PCB, DDT, and hexachlorocyclohexane (HCH) isomers) were found in samples from a group of Greek women who had occupational exposure to pesticides (Covaci et al., 2002). In another study, the analysis of rabbit hair also showed increasing levels for Cypermethrin (a synthetic pyrethroid used as an insecticide) metabolites over time with a dose-dependent relationship (Kavvalakis et al., 2014).

5.4. Eye exposure

The potential for chemical injury is high for tissues of the eye. Some pesticides were reported to be absorbed by the eyes in sufficient quantities to cause serious or even fatal illness (Gilden et al., 2010). Granular pesticides pose a particular hazard to the eyes depending on the size and weight of individual particles (Jaga and Dharmani, 2006). If pesticides are applied with power equipment, the pellets may bounce off vegetation or other surfaces at high velocity to cause significant eye damage (Fareed et al., 2012). Eye protection is also needed when measuring or mixing concentrated or highly toxic pesticides. Protective face shields or goggles should be worn whenever spraying pesticides or to prevent eye contact with dusts.

6. Impacts of pesticide use on human health

Studies suggest that pesticides may be related to various diseases including cancers, leukemia, and asthma. The risk of health hazards due to pesticide exposure depends not only on how toxic the ingredients are but also on the level of exposure. In addition, certain people such as children, pregnant women, or aging populations may be more sensitive to the effects of pesticides than others. Fig. 3 displays the general types of health impact caused by pesticide exposure.

6.1. Cancer

The link between pesticides and cancer has been reported by many studies. Results of a prospective cohort study with 57,310 pesticide applicators in USA indicated associations of two imidazolinone herbicides (imazethapyr and imazaquin) with bladder cancer (Koutros et al., 2015). In another case control study (953 cases and 881 controls) of male agricultural workers in Egypt, increased risk of bladder cancer was associated with pesticide exposure (odds ratio (OR) = 1.68, 95% confidence interval (CI): 1.23 to 2.29) in a dose-dependent manner (Amr et al., 2015). From a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina, USA, significant risks of bladder cancer and colon cancer were linked with imazethapyr, a heterocyclic aromatic amine herbicide (Koutros et al., 2009). Samanic et al. (2008) reported that women with occupational herbicide exposure had a significantly increased risk for meningioma relative to those who were never exposed (OR = 2.4, 95% CI: 1.4 to 4.3) in a hospital-based case–control study with 462 glioma and 195 meningioma patients in USA. From a population-based case–control study with 221 incident cases of brain tumors and 442 individually matched controls in France, exposure to pesticides exhibited a significant association with brain tumors

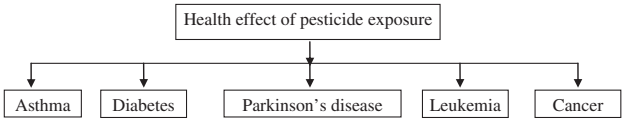


Fig. 3. Human health impact of pesticide exposure.

(OR = 2.16, 95% CI: 1.10 to 4.23) and gliomas (OR = 3.21, 95% CI: 1.13 to 9.11) (Provost et al., 2007).

It was demonstrated that chlorpyrifos (CPF) in pesticides induced a redox imbalance that altered the antioxidant defense system in breast cancer cells (Ventura et al., 2015). The main mechanism involved in the inhibition of cell proliferation induced by CPF is an increment of p-ERK1/2 levels mediated by H_2O_2 in breast cancer cells. Some OCs was found to be individually linked to breast cancer through their potential to exert oestrogenic effects on mammary cells (Rivero et al., 2015). In a study covering a female population from Tunisia, possible association between serum concentrations of organochlorine pesticides (polychlorinated biphenyls) and xenoestrogenic effects was investigated; accordingly, their positive link with breast cancer risk was observed (Arrebola et al., 2015). In a study covering 30,003 female spouses of OP pesticide applicators in North Carolina and Iowa, USA, an increased risk of several hormonally-related cancers including breast, thyroid, and ovary was reported (Lerro et al., 2015a). According to a meta-analysis of 13 case-control studies from Pubmed databases published between 1990 and 2005, there was a significantly positive association between occupational exposure to pesticides and all hematopoietic cancers as well as non-Hodgkin lymphoma (Merhi et al., 2007). A case-control study including 1743 controls and 1169 cases was conducted in Australia from 2009 to 2011 (El-Zaemey et al., 2013) in which an increased risk of breast cancer (OR = 1.43, 95% CI: 1.15 to 1.78) was seen among women who were exposed to pesticide spray drift. A case study in Brazil interviewed 110 women (age 20–35 years) diagnosed with breast cancer found an increased risk of breast cancer from residential use of pesticides during adulthood (Ortega-Jacome et al., 2010).

In a study conducted in USA, an increased risk of lung cancer was observed among acetochlor herbicide users (relative risk (RR) = 1.74, 95% CI: 1.07 to 2.84) and acetochlor/atrazine product mixtures (RR = 2.33, 95% CI: 1.30 to 4.17) compared to nonusers (Lerro et al., 2015b). From a cohort study of 168 urban pesticide applicators in Rome, Italy, increased risks of cancer such as gallbladder (standardized mortality ratios (SMR) 724, CI: 129 to 2279), liver (SMR 596, CI: 204 to 1365), and nervous system (SMR 529, CI: 144 to 1368) were observed (Giordano et al., 2006). In another case-control study, 400 cases and 800 controls were enrolled from different hospitals in Pakistan (Luqman et al., 2014), and the results indicated strong associations between pesticide exposure and lung cancer (OR = 5.1, 95% CI: 3.1 to 8.3).

However, International Agency for Research on Cancer (IARC) did not consider many pesticides as classifiable with respect to human carcinogenicity (group 3). However, evidence of carcinogenicity was noted by the U.S. Environmental Protection Agency (US EPA) and/or Canadian Pest Management Regulatory Agency (PMRA) in animal toxicity studies for alachlor, carbaryl, metolachlor, pendimethalin, permethrin, and trifluralin, thus supporting the biological plausibility of associations observed from these pesticides. The results of substantial mechanistic work suggested that pesticides are capable of inducing mutations in oncogenes while increasing their transcriptional expression in vitro (Vakonaki et al., 2013). Likewise, their studies on human population indicated the possible associations between pesticide exposure levels and mutation occurrence in cancer-related genes.

In a study focusing on long term genotoxic effect on rabbits exposed to the neonicotinoid pesticide imidacloprid (IMI), there were statistically significant differences in the frequencies of binucleated cells with micronuclei between control and exposed groups (Stivaktakis et al., 2016). However, there was no evidence to insist either dose-dependence or time-dependence of the genotoxic effect for such administered doses. According to an analytic cohort study, women living in counties with the highest mean radon concentrations (>148 Bq m^{-3}) had a significantly enhanced risk of hematologic cancer compared to those living in counties with the lowest (<74 Bq m^{-3}) radon levels (HR = 1.63, 95% CI:1.23–2.18) (Teras et al., 2016). These authors also observed a statistically significant dose-response relationship (HRcontinuous = 1.38, 95% CI:1.15–1.65 per 100 Bq m^{-3}).

6.2. Asthma

Several clinical and epidemiological studies have reported an association between pesticide exposure and symptoms of bronchial hyper-reactivity and asthma. Pesticide exposure may contribute to the exacerbation of asthma by irritation, inflammation, immunosuppression, or endocrine disruption (Hernández et al., 2011; Amaral, 2014). Raanan et al. (2015) also investigated the relationship between early-life exposure to OPs and respiratory outcomes among 359 mothers and children in USA. They concluded that such exposure could lead to respiratory symptoms consistent with childhood asthma. In a cross-sectional study covering female farm workers ($n = 211$) in Africa, the prevalence of ocular-nasal symptoms was positively associated with entering a pesticide-sprayed field (OR = 2.97; 95% CI: 0.93–9.50) (Ndlovu et al., 2014).

In another study with 926 pesticide applicators with active asthma in USA who completed enrollment questionnaires for the Agricultural Health Study (AHS), positive exacerbation-pesticide associations were observed for the herbicide pendimethalin (OR = 2.1) and for the insecticide aldicarb (OR = 10.2) (Henneberger et al., 2014). However, most pesticides are weakly immunogenic such that their potential to sensitize airways in exposed populations is limited, while only some pesticides are potent enough to damage the bronchial mucosa (Hernández et al., 2011). In a study covering 25,814 farm women in USA, any use of pesticides on the farm was found to be associated with atopic asthma (OR = 1.46; 95% CI: 1.14–1.87) (Hoppin et al., 2008).

6.3. Diabetes

Emerging scientific evidence suggests that diabetes should be affected by exposure to environmental pollutants. Exposure to pesticides, particularly organochlorines and metabolites, is suspected to impart a higher risk of developing type 2 diabetes and its comorbidities (Azandjeme et al., 2013). A systematic review of the literature indicated a positive association between diabetes and serum concentrations of several pollutants (such as polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs), PCBs, and several organochlorine pesticides (DDT, DDE, oxychlordane, trans-nonachlor, hexachlorobenzene, and hexachlorocyclohexane)) (Jaacks and Staimez, 2015). However, there were substantial limitations of the actual datasets, as most studies were cross-sectional. Only a few studies addressed selection bias and the confounding effect, while most estimates were based on exceptionally wide confidence intervals. A meta-analysis of 23 eligible articles concluded that exposure to organochlorine pollutants is associated with an increased incidence risk of type 2 diabetes (T2DM), such as polychlorinated biphenyls (PCBs) (OR = 2.14; 95% CI: 1.53–2.99) and *p,p′*-DDE (OR = 1.33; 95% CI: 1.15–1.54) (Tang et al., 2014). In some epidemiological studies, positive associations of T2DM risk with exposure to organochlorine pollutants were observed with different populations (Everett et al., 2007; Turyk et al., 2009). A cross-sectional study was performed among 116 pesticide sprayers and 92 nonexposed controls in Bolivia, abnormal glucose regulation (defined as HbA1c ≥ 5.6%) was found for 61.1% of sprayers relative to 7.9% of nonexposed controls (Hansen et al., 2014). In USA, a study was carried out covering 13,637 farmers' wives who were reported to have an experience of mixing or applying pesticides at enrollment (1993–1997). Accordingly, five pesticides were positively associated with incident diabetes ($n = 688$; 5%): three organophosphates (fonofos (HR = 1.56, 95% CI: 1.11 to 2.19), phorate (HR = 1.57, 95% CI 1.14 to 2.16), and parathion (HR = 1.61, 95% CI: 1.05 to 2.46)); the organochlorine dieldrin (HR = 1.99, 95% CI: 1.12 to 3.54); and the herbicide 2,4,5-T/2,4,5-TP (HR = 1.59, 95% CI: 1.00 to 2.51) (Starling et al., 2014). A total of 506 (4.5%) women out of 11,273 who were involved with agricultural pesticides (mixing or applying pesticides to crops or repairing pesticide application equipment) were reported to have gestational diabetes mellitus during pregnancy (OR = 2.2; 95% CI: 1.5–3.3) in USA AHS data (Saldana et al., 2007).

6.4. Parkinson's disease

Epidemiologic studies suggest that occupational exposure to pesticides might increase the risk of Parkinson's disease (PD). A French population-based case–control study (133 cases and 298 controls) examined quantitative aspects of occupational exposure to pesticides in relation with PD (Moisan et al., 2015); these authors found that pesticide exposure in vineyards was associated with PD (OR = 2.56; 95% CI: 1.31, 4.98). Likewise, it was also found that the risk of PD increased by 3% for every 1.0 μg L^{-1} of pesticide in groundwater (OR = 1.0 3; 95% CI: 1.02–1.04) in Colorado Medicare Beneficiary Database, USA (James and Hall, 2015). From a cohort study in the Netherlands in which 58,279 men and 62,573 women (aged 55–69 years) were enrolled; a possible linkage between PD mortality and occupational exposure to pesticides was observed (Brouwer et al., 2015). Based on an observation of dose-dependent increase in cellular αS levels, Chorfa et al. (2016) reported a relationship between PD and the use of certain pesticides (e.g., paraquat, rotenone, and maneb), insecticides (e.g., organophosphate, and three pyrethroids) and fungicides (e.g., thiophanate-methyl, fenhexamid, and cyprodinil). It was reported that chronic exposure to metals and pesticides is associated with the development of PD at a younger age relative to patients with no family history of the disease (Ratner et al., 2014). Moreover, they found that the duration of exposure was an important factor controlling the magnitude of such an effect.

According to meta-analyses of data from cohort and case-control studies, PD risk increased due to exposure to any types of pesticides, herbicides, and solvents; more specifically, an approximately two-fold increase in PD risk was seen from exposure to paraquat or maneb/mancozeb (Pezzoli and Cereda, 2013). In a population-based case-control study in USA, the frequent use of any household pesticide increased the odds of PD by 47% [odds ratio (OR) = 1.47, (95% confidence interval (CI): 1.13, 1.92)] (Narayan et al., 2013); moreover, the use of OP products increased the odds of PD even more strongly by 71% [OR = 1.71, (95% CI: 1.21, 2.41)], while use of organothiophosphate almost doubled the odds of PD. In a review study based on thirty-nine case–control studies, four cohort studies, and three cross-sectional studies, exposure to herbicides and insecticides was seen to considerably increase the risk of PD (Mark et al., 2012).

6.5. Leukemia

Exposure to pesticides is one of the most important causes of acute leukemia. In some previous studies, the effect of pesticide exposure on childhood leukemia was investigated. From 12 case–control studies of childhood leukemia, Bailey et al. (2015) reported that ORs for acute lymphoblastic leukemia (ALL) for three types of pesticide exposure, shortly before conception, during pregnancy, and after birth, were 1.39, 1.43, and 1.36, respectively.

In a case–control study in Iran, an occupational farmer was at significantly increased risk of developing acute leukemia in comparison to other jobs, especially for their children due to exposure to pesticides (Maryam et al., 2015). Meta-analysis of the 40 studies in France showed that the risk of lymphoma and leukemia increased significantly in children when their mother was exposed during the prenatal period (OR = 1.53; 95% CI: 1.22 to 1.91 and OR = 1.48; 95% CI: 1.26 to 1.75) (Vinson et al., 2011). Exposures during pregnancy to unspecified residential pesticides, insecticides, and herbicides were positively associated with childhood leukemia. Turner et al. (2011) found that such exposures during pregnancy were positively associated with childhood leukemia in their systematic review based on meta-analysis of previous observational epidemiologic studies. From 13 case-control studies published between 1987 and 2009, statistically significant associations between childhood leukemia and pesticide exposure were observed (mRR: 1.74, 95% CI: 1.37–2.21) (Van Maele-Fabry et al., 2011). However, the available data were not sufficient for causality ascertainment; hence, further study is needed to confirm the reliability of previous findings based on self-reporting, to examine potential exposure-response relationships, and to assess the toxicological impact of pesticides in more detail.

6.6. Cognitive effects

Despite growing evidence linking pesticide exposure to neurological diseases, epidemiological data on neurobehavioral effects of chronic pesticide exposure are limited. Plasma concentrations of 3 OC pesticides (p,p′-DDE, trans-nonachlor, and hexachlorobenzene) were measured among 989 men and women aged 70 years in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS), Sweden. The results showed that individuals with high levels of OC had about 3 times higher future risk of cognitive impairment than those with low levels of OC (Lee et al., 2016). In another study the role of pesticides on neurobehavioral performances in French vineyard workers was monitored a total of 929 workers aged between 42 and 57 years; accordingly, the risk for scoring low on a cognitive test was higher in exposed subjects, with odds ratios ranging from 1.35 to 5.60 (Baldi et al., 2010). Three independent studies on the prenatal exposure to OP pesticides and cognitive abilities on children reported lower IQ, poorer working memory and perceptual reasoning (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011). In other words, kids exposed to low levels of pesticides in utero face significant cognitive impairment later in life and PON1 may be an important susceptibility factor for these deleterious effects. Chronic exposure to OC pesticides among 644 participants (aged 60–85) in the National Health and Nutrition Examination Survey 1999–2002, USA was reported higher levels of β-hexachlorocyclohexane, trans-nonachlor, oxychlordane, and heptachlor epoxide modified the associations between age and lower cognitive function ($P_{interaction} < 0.01$, 0.01, 0.03, <0.01, and 0.02, respectively) (Kim et al., 2015). In a study in Rennes, France a total of 287 mother-child pairs were randomly selected from a cohort study found that low-level childhood exposures of two pyrethroid metabolites (3-PBA and cis-DBCA) is associated with a significant decrease in their cognitive performance, particularly in terms of verbal comprehension and working memory (Viel et al., 2015).

6.7. Other effects

Majority of pesticides including organophosphorous components are to affect the male reproductive system by such mechanisms as reduction of sperm activities (e.g., counts, motility, viability and density), inhibition of spermatogenesis, reduction of testis weights, damaging sperm DNA, and increasing abnormal sperm morphology (Mehrpour et al., 2014). Michalakis et al. (2014) reported that exposure to organophosphate and organochlorine pesticide may be a potential risk factor to induce hypospadias. Furthermore, pesticide exposure highlights the role of genetic polymorphisms in pesticide-metabolizing enzymes as biomarkers susceptible for developing adverse health effects (Hernández et al., 2013b).

7. Conclusion

Although pesticides are developed to prevent, remove, or control harmful pests, concerns of the hazards of pesticides towards the environment and human health have been raised by many studies. There are indeed many inherent problems in conducting large-scale experiments to directly assess the causation of the human health problems associated with the use of pesticides. However, the statistical associations between exposure to certain pesticides and the incidence of some diseases are compelling and cannot be ignored. Moreover, some members of the population have an inherent genetic susceptibility to pesticide-associated diseases and are thus likely to be more at risk than others. Evidence suggests that much of this exposure is presented as multiple mixtures of chemicals and that the toxic effect of such exposure is

unknown, particularly over longer time scales. It is very important to develop the precision and accuracy in the quantitation of pesticides along with improved safety profiles to reduce possibly adverse effects on human health and the environment. Furthermore, there should be a focus on determining what types of chemicals or formula are the most appropriate tools for environmental and ecological management of pests. Hence, natural bio-control agents, such as beneficial bacteria, viruses, insects, and nematodes, should be used for agricultural purposes. Moreover, both the public and private sectors such as government agencies, NGOs, and manufacturers should put much greater effort into research, product development, product testing and registration, and implementation of pesticide use strategies, while advocating public education concerning pesticides.

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