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Review of Effect of Pesticides on Human Health

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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'. The Food and Agriculture Organization (FAO) has defined pesticide as: Any substance or mixture of substances intended for preventing, destroying, or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals, causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances that may be administered to animals for the control of insects, arachnids, or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant, or agent for thinning fruit or preventing the premature fall of fruit. Also used as substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

Agriculture is the largest consumer (around 85% of world production) of pesticides Figure 1 to chemically control various pests. Moreover, pesticides are also used in public health activitiesto 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. However, unintended exposure to pesticides can be extremely hazardous to humans and other living organisms as they are designed to be poisonous. 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. Even very low levels of exposure may have adverse health effects at early development. The physical makeup, behavior, and physiology of children make them more [1] susceptible to pesticides than adults. Pesticide exposure is linked with various diseases including cancer, hormone disruption, asthma, allergies, and hypersensitivity. A line of evidence also exists for the negative impacts of pesticide exposure Figure 2 leading to birth defects, fetal death, etc. On the basis of scientific evidence, the real, predicted, and perceived risks that pesticidespose 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.

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 Figure 3 routes. 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.

Types of Pesticides

Pesticides can be classified by various criteria such as chemical classes, functional groups, mode of action, and toxicity. The active ingredients of most pesticides are either organic (contain carbon) or inorganic (copper sulfate, ferrous sulfate, copper, lime, sulfur, etc.). The chemicals in organic pesticides tend to be more complex and less soluble in water than those of inorganic pesticides. Organic pesticides can be additionally Sub [2-5] divided into two groups: natural (produced from naturally occurring sources) and synthetic (artificially produced by chemical synthesis). Pesticides have different modes of action or ways to control the 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

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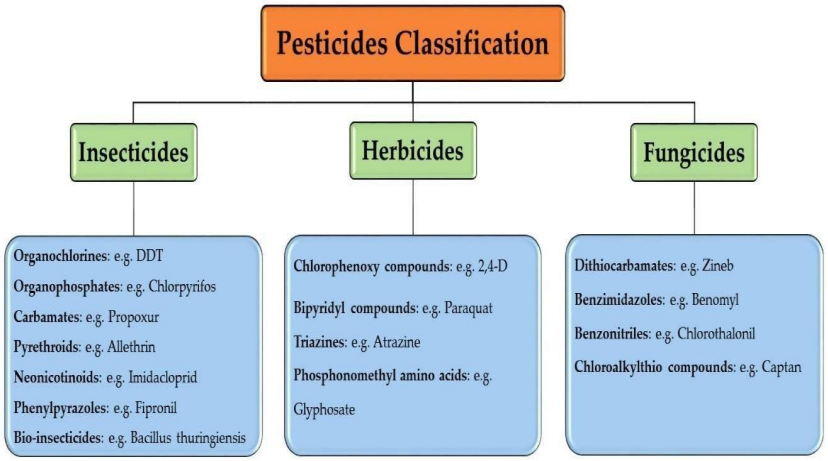

Figure 1: Classification of pesticides.

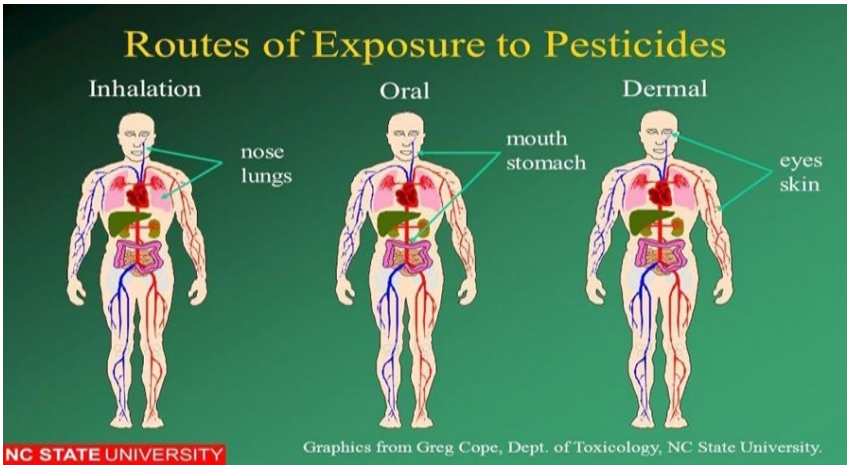

Figure 2: Different routes of pesticide exposure.

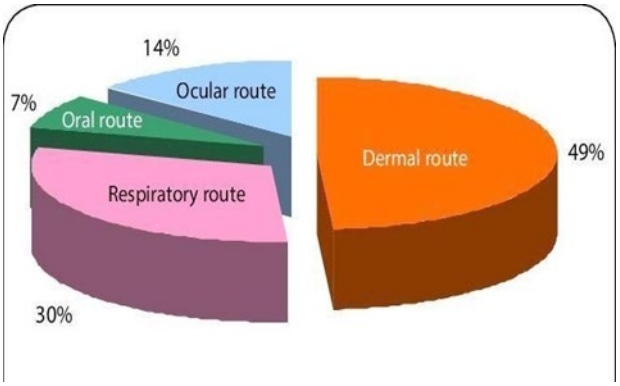

Figure 3: Routes of exposure to pesticide.

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 pesticidesare 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.

A. Insecticides

Neonicotinoids are a class of neuro-active insecticides chemically similar to nicotine. Imidacloprid, of the neonicotinoid family, is the most widely used insecticide in the world. In the late 1990s neonicotinoids came under increasing scrutiny over their environmental impact and were linked in a range of studies to adverse ecological effects, including honey-bee colony collapse disorder (CCD) and loss of birds due to a reduction in insect populations. In 2013, the European Union and a few non EU countries restricted the use of certain neonicotinoids.

Organophosphate and carbamate insecticides have a similar mode of action. They affect the nervous system of target pests (and non- target organisms) by disrupting acetylcholinesterase activity, the enzyme that regulates acetylcholine, at nerve synapses. This inhibition causes an increase in synaptic acetylcholine and over-stimulation of the parasympathetic nervous system. Many of these insecticides, first developed in the mid-20th century, are very poisonous. Although commonly used in the past, many older chemicals have been removed from the market due to their health and environmental effects (*e.g.* DDT, chlordane, and toxaphene). However, many organophosphates are not persistent in the environment. Pyrethroid insecticides were developed as a synthetic version of the naturally occurringpesticide pyrethrin, which is found in chrysanthemums. They have been modified to increase their stability in the environment. Some synthetic pyrethroids are toxic to the nervous system.

B. **Herbicides**

A number of sulfonylureas have been commercialized for weed control, including: amidosulfuron, flazasulfuron, metsulfuron-methyl, rimsulfuron, sulfometuron- methyl, terbacil, nicosulfuron, and triflusulfuron-methyl. These are broad-spectrum herbicides that kill plants weeds or pests by inhibiting the enzyme acetolactate synthase. In the 1960s, more than 1 kg/ha (0.89 lb/acre) crop protection chemical was typically applied, while sulfonylureates allow as little as 1% as much material to achieve the same effect.

a. **Biopesticides**

- Biopesticides are certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals. For example, canola oil and baking soda have pesticidal applications and are considered biopesticides. Biopesticides fall into three major classes: Microbial pesticides which consist of bacteria, entomopathogenic fungi or viruses (and sometimes includes the metabolites that bacteria or fungi produce). Entomopathogenic nematodes are also often classed as microbial pesticides, even though they are multi-cellular.
- Biochemical pesticides or herbal pesticides are naturally occurring substances that control(or monitor in the case of pheromones) pests and microbial diseases.
- Plant-incorporated protectants (PIPs) have genetic material from other species incorporated into their genetic material (*i.e.* GM crops). Their use is controversial, especially in many Euro country.

Impact of Pesticide Use in the Environment

As pesticides are designed to be toxic to particular groups of organisms, they can haveconsiderable adverse environmental effects on other living creatures as well as diverse mediaincluding air, soil, or water. The status of pesticide pollution in various environmental media(such as air, water, and soil) 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 theenvironment for years. Moreover, as such compounds have the ability to bioaccumulate andbiomagnify, they can be bioconcentrated by up to 70,000 fold relative to the initial concentration. Repeated application of pesticides leads to loss of biodiversity and increased pest resis-tance, while its effects on other species facilitate pest resurgence. It was estimatedthatN 95% of applied pesticides had the potential to impact non-target organisms and to become widely dispersed in the environment. Airborne pollution of pesticides may occur through pesticide drift (e.g., aerial spray drift) and post- application volatilization. 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. In one study, the ambient air concentrations of pesticides were measured from three potato farm sites in Prince Edward Island, Canada. The presence of the fungicide chlorothalonil was found ubiquitously at relatively high concentrations reflecting the effect of its repeated use onpotato 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, pϒ -DDE), Dichlorodiphenyldichloroethane (p,p'-DDD), and o,p'-DDT) in air averaged 1.24, 2.12, 0.36, and 7.67 ngm−3, respectively. At the Kaweah Reservoir, CA, USA, concentrations of chlorpyrifos werehighest in June (17.5 ng m−3), while those of chlorpyrifosoxon peaked in May (30.4 ng m−3). 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%). In a study [5-10] 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. In another study, the residues of OC pesticides in surface water were measured from2000 to 2002 at the Küçük Menderes River in Turkey. 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. Similar to other media, the status of pesticide pollution in soil media is ubiquitous.

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. Pesticides are distributed throughout the human body through the bloodstream but can be excreted through urine, skin, and exhaled air. 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.

A. Dermal Exposure

Dermal exposure is one of the most common and effective routes through which pesticide applicators are exposed to pesticides. Dermal absorption may occur as a result of a splash, spill, or spray drift, when mixing, loading, disposing, and/or cleaning of pesticides. 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, 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. 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 absorption than other areas of the body. As such, the rate at which dermal absorptionproceeds differs for each part of the body.

B. 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. 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. 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. Workers handling pesticides or equipment for their application can also consume pesticides if they do not wash their hands prior to eating or smoking. 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.

C. Respiratory Exposure

Due to the presence of volatile components of pesticides, their potential for respiratory exposure is great. Inhalation of sufficient amounts of pesticides may cause serious damage to nose, throat, and lung tissues. 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 isrecommended that pesticides should not be applied at air temperatures above 30 °C. Moreover, pesticides and with high vapor hazards should be applied with sufficient equipment for respiratory protection. The exposure levels of dialkyl phosphate 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 b 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. 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. The sum DAPs levels in hair samples of the sprayers were also significantly higher than thoseof control group (p b 0.001), confirming the effect of long-term exposure to OPPs. 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. 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 dithiophosphatedimethyl phosphate(3: IQI 3, 109.7). 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. 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.

D. 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. Granular pesticides pose a particular hazard to the eyes depending on the size and weight of individual particles. If pesticides are applied with power equipment, the pellets may bounce off vegetation or other surfaces at high velocity to cause significant eye damage. Eye protection is also needed when measuring for mixing concentrated or highly toxic pesticides. Protective face shields or goggles should be worn whenever spraying pesticides or to prevent eye contact with dusts.

Various Targets and Parameters

A. **Nerve and muscle targets**

1. **Cholinesterase inhibition**: Carbamate and organophosphate insecticides are used to control insects via inhibition of cholinesterase leading to overstimulation of insect nervous system. Such inhibition of acetylcholine esterase finally kills animals.

2. **Acetylcholine receptor stimulation**: Neonicotinoid insecticides and spinosad mimic the action of the neurotransmitter acetylcholine. They do not affect cholinesterase, but rather bind to acetylcholine receptors resulting in prolonged stimulation leading to insect death.

3. **Chloride channel regulation**: There are three mechanisms: activation of chloride channels (avermectins), inhibition of gamma-aminobutyric acid (GABA) receptor (organochlorine insecticides), and agonists of the GABA-gated chloride channel (bifenazate).

4. **Sodium channel modulators**: Pyrethrins and pyrethroids bind to sodium channels fixingthem in open state which leads to tremor, and eventually, to death.

A. **Growth and development targets**

1. Chitin synthesis inhibitors: There are hormonal substances that inhibit the synthesis of chitin in insects and therefore result in death at early life stages during embryonic development or molting.

2. Insect growth regulators: Insecticides of this group disrupt endocrine system affecting in this manner production of hormones needed for animal growth and development into imago. Insects poisoned by insect growth regulators do not receive the signal to metamorphose. Some of them were designed to mimic effects of juvenile hormone necessary to enter metamorphosis.

3. Nonspecific growth regulators: The exact mode of action of the growth regulators is not well understood. For example, hexythiazox kills before mite eggs can hatch and also kills some immature mites, but does not kill adult forms.

A. **Energy production targets**

1. **Electron transport inhibition**: Aliphatic type of organochlorine insecticides interferes with electron transport. They corrupt the ability of target organism to supply energy.

2. **Oxidative phosphorylation disruption**: Organotin miticides directly inhibit mitochondrial electron transport chain, whereas pyrroles uncouple electron transport and oxidative phosphorylation.

3. **Oxidative phosphorylation disruption**: Organotin miticides directly inhibit mitochondrial electron transport chain, whereas pyrroles uncouple electron transport and oxidative phosphorylation. This results in disability to produce ATP.

A. **Hematological and immunological parameters**

Blood is a special organ which is quickly exposed to absorbed chemicals. Blood parameters are known to be highly informative indicators of organism status and have many advantages over other tissue samples. Samples of blood can be obtained regularly from test organisms, thus allowing the use of a non-destructive (vital) approach for effective assessment. In most cases, blood serves as a medium for signaling in animals. Typically, hematological parameters are non-specific in their responses towards chemical stressors. Nevertheless, they may provide important information in effect-assessment studies. Disturbances in integrated functions can be detected, or strongly indicated, with rather simple analysis of blood parameters. Blood indices can be divided into primary and secondary parameters. The primary blood components include formed elements (e.g. red and white blood cells) and plasma with diverse constituents. The latter include nutrients, ions, enzymes, and hormones. Hemoglobin content and hematocrite are common hematological indices that change in many model systems exposed to xenobiotics. Although their levels can also be influenced by biological factors like animal size, gender, and environmental factors like temperature and seasonality, they are rather informative when dealing with pesticide intoxication. Under stress conditions (including pesticide-induced) these parameters can be elevated to increase oxygen carrying capacity and the supply of oxygen to the major organs in response to higher metabolic demands. However, most investigators reported a decrease in hemoglobin and hematocrit in pesticide-treated animals indicating anemia, hemolysis and erythropoiesis dysfunction. Hemolysis in human erythrocytes caused by chlorophenoxy herbicides was reported by Duchnowicz as a result of free radical production by phenols (probably, due to autoxidation) or/and their direct attack on cell structure. In 2005 Duchnowicz and colleagues found some protein damage in erythrocyte membranes which might result from the direct interaction of the investigated herbicide or an indirect effect, for example, via ROS-mediated oxidation.Several immunological parameters may also be potentially used as biomarkers of stress conditions, e.g. white blood cell (leukocyte) and lymphocyte status (measured as a blood cell or differential counts), non-specific defense factors (such as lysosomal activity and levels of acute phase proteins in body fluids), etc. Differential changes in leukocyte counts may be a sensitive indicator of environmental stress. For example, differential changes in leukocyte counts were found to be reliable markers of the stress caused by environmental factors. Decreases in lymphocyte numbers (lymphopenia) as a consequence of pesticide exposure have been reported for several fish species. Lymphopenia is often accompanied by concurrentincreases in monocytes and neutrophils occurring in response to stress exposure. Generally, immunological indices in the blood can supplement hematological parameters and help to clarify possible mechanisms of toxic impacts.

Impacts of Pesticides 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.

The General Types of Health Impact Caused By Pesticide Exposure:

A. **Cancer**

The link between pesticides and cancer Figure 4 has been reported by many studies. Results of aprospective cohort study with 57,310 pesticide applicators in USA indicated associations of two imidazolinone herbicides (imazethapyr and imazaquin) with bladder cancer. In another case control study (953 cases and 881 controls) of male agricultural workers in Egypt,increased risk of bladder cancer

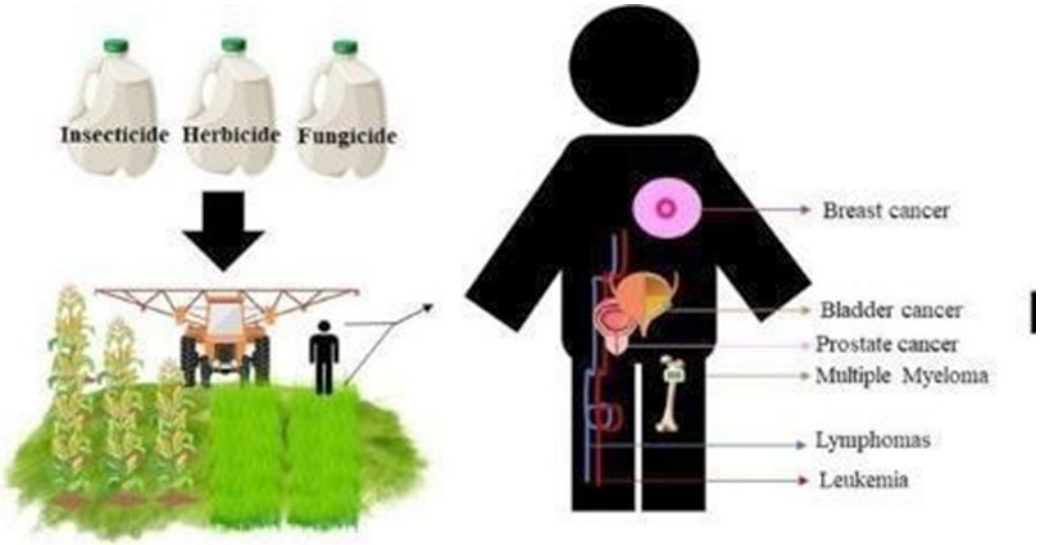

Figure 4: Different types of cancer caused by pesticides.

was associated with pesticide exposure (odds ratio (OR) = 1.68, 95% confidence interval (CI): 1.23 to 2.29) in a dose-dependent manner. 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 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. It was demonstrated that chlorpyrifos (CPF) in pesticides induced a redox imbalance that altered the antioxidant defense system in breast cancer cells. 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. 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. 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. 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. A case-control study including 1743 controls and 1169 cases was conducted in Australia from 2009 to 2011 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. 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. 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. In another case-control study, 400 cases and 800 controls were enrolled from different hospitals in Pakistan, 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. 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. 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 (N148 Bq m−3) had a significantly enhanced risk of hematologic cancer compared to those living in counties with the lowest (b74 Bqm−3) radon levels (HR=1.63, 95% CI:1.23–2.18). These authors also observed a statistically significant dose-response relationship (HRcontinuous=1.38, 95% CI:1.15–1.65 per 100 Bq m−3).

A. **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, immune suppression, or endocrine disruption. Also investigated the relationship between early life exposure to OPs and respiratory outcomes among 359 mothers and children in USA. They concluded that suchexposure 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). 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). 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. 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).

B. **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 itscomorbidities. 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)). 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). In some epidemiological studies, positive associations of T2DM risk with exposure to organochlorine pollutants were observed with different population. 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. 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 to3.54); and the herbicide 2,4,5-T/2,4,5-TP (HR = 1.59, 95% CI:1.00 to 2.51). 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.

C. **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; 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. 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. Based on an observation of dose-dependent increase in cellular αs levels, 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. 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. 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)]; 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.

D. **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.Studies of childhood leukemia, reported that ORs for acute lymphoblastic leukemia (ALL) for three types of pesticide exposure, shortly before conception, during pregnancy, and after birth, 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. 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). Exposures during pregnancy to unspecified residential pesticides, insecticides, and herbicides were positively associated with childhood leukemia. Turner 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. Studies between 1987 and 2009, statistically significant associations between childhood leukemia and pesticide exposure were observed (mRR: 1.74, 95% CI: 1.37–2.21). 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.

E. **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. In another study the role of pesticideson 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 Figure 5 test was higher in exposed subjects, with odds ratios ranging from1.35 to 5.60. Three independent studies on the prenatal exposure to OP pesticides and cognitive abilities on children reported lower IQ, poorer working memory and perceptual reasoning. 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 betweenage andlower cognitive function (Pinteraction b 0.01, 0.01, 0.03, b0.01, and 0.02, respectively). In a study in Rennes, France a total of 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.

F. **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. The 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.

Management of the Poisoned Patient

Incidence of acute poisoning is quite high in India. Most of these cases are either suicidal or homicidal. Accidental poisoning in children is quite frequent because of widespread use of insecticides and pesticides. In addition, episodes of large scale poisoning due to drug abuse (methanol) occur in regular frequency every year in our country. Careful and emergent management of vital life. supporting

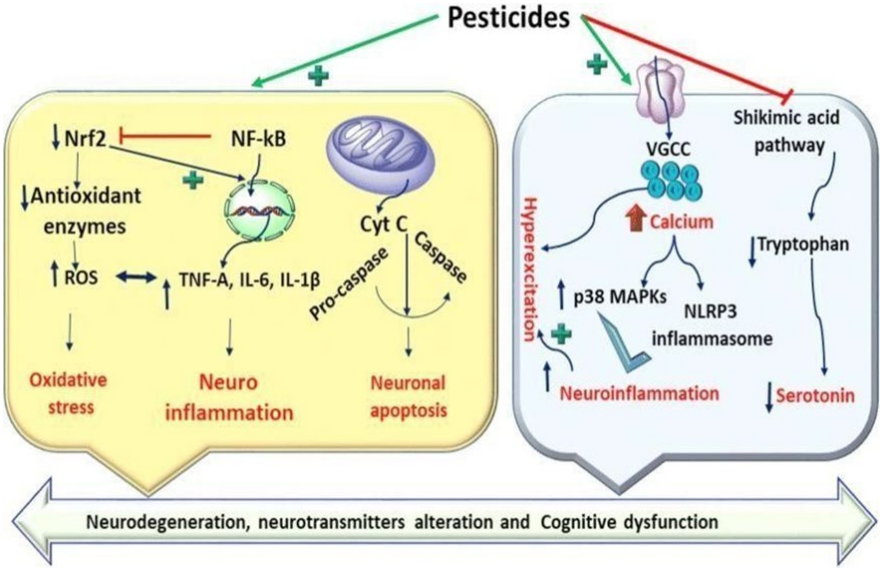

Figure 5: Cognitive effect produced by pesticides.

systems, alongwith 'decontamination and treatment of specific poison, result in improved survival of patients who reach the hospital alive These patients need 'intensive care of a well trained team of medical and paramedical personnel Role of well-trained personnel becomes all the more evident, and deficiencies a subject of severe criticism in the face of mass poisoning. Official recommendations are that district and regional poisoning treatment centres should be established but that remains to be implemented. In the absence of clear cut management drill, hospital personnel get overwhelmed with the number of poisoned patients and confusion and neglect reign the 'emergency' ward. Basic principles of management are discussed below.

General management: In the majority of cases of poisoning supportive measures alone are mainstay or treatment. Attempting to make a specfic toxicologic diagnosis first only delays the application of supportive measures that form the basis of poisoning treatment.

a. Management of vital systems: Respiratory and circulatory systems need immediate attention Respiratory airway must be kept patent, and needed, endotracheal intubation inserted and mechanical ventilation instituted. Circulation needs special attention, and assessed in relation urinary flow. Intravenous glucose (50 ml 50%) and if necessary, glucose- saline infusion may be given. Comatosed patient needs particular attention specially because of chances of airway obstruction convulsions, if any, must be controlled. With appropriate support for coma, shock, convulsions, respiration and circulation, most patients will survive the poisoning. Respiratory stimulants and analeptics are of no value, and are harmful in toxic

b. Toxicological diagnosis: Diagnosis of the offending poison is often possible from the history provided by the patient, relatives or friends. supportive evidence is provided by the physical examination of the patient. Classical signs and symptoms of common poisonings clinch the diagnosis. Laboratory investigations, e.g. arterial blood gases, serum glucose and electrolytes, renal function tests, ECG, and X-ray chest and abdomen may be helpful.

c. Decontamination: Decontamination procedures involve removing toxins from the skin and GIT. These should be instituted after initiating supportive therapy and toxicological diagnosis.

1. **Skin**: All clothes should be removed, and body washed, if necessary with soap and water with alcohol.

2. **GIT**: The place of gut decontamination is controversial specially when treatment isinitiated more than 1 hour after ingestion. During gut decontamination, it is essential toprotect the airways. Different steps are as follows:

- **Emesis**: Best emetic is syrup ipecac (30 ml). Apomorphine should not be used because of its persistent effect and propensity for CNS depression. Salt water and mustard are not recommended as emetics.

- **Gastric lavage**: It should be done in conscious patient or following endotracheal intubation. Warm 0.9% saline should be used. It is contraindicated in poisoning with corrosives or petroleum distillates.

- **Purgation**: Use of a suitable purgative should hasten removal of toxins from GIT and reduce absorption. Purgatives recommended are magnesium sulphate (10%), sodium sulphate (10%) or sorbitol (70%). The last one is the best as it does not provide sodium or magnesium. Oil based purgatives should never be used.

- **Activated charcoal**: Universal antidote (burnt toast, magnesium oxide and tannic acid) is of no value, and may be harmful. Activated charcoal, if given in sufficient amount, is useful as it binds many toxins and prevents absorption. It is not useful in poisoning due to acids and alkalies, ethanol, methanol, and iron. It is useful in poisoning with digitalis, barbiturates, carbamazepine and theophylline.

Specific antidotes

It is a misconception that there is an antidote for every poison. The opposite is true. Whether there is an antidote available or not, supportive therapy and decontamination are of vital importance. In case the offending poison has been identified, and an antidote is available, it should be used. Antidotes of commonly used drugs have been discussed under 'systemic pharmacology of the concerned drug.

Elimination of toxin

In cases of severe poisoning, it is imperative that the absorbed toxin, specially if it has a long half-life, be eliminated from the system. Again, in cases of massive overdosage, the elimination pathways with

limited capacities may be saturated. Circulatory failure further slows the processes.

a. Dialysis procedures: These are used for removing toxins that are eliminated through metabolic mechanisms which cannot be enhanced. Drugs with large V, are poorly removed by dialysis.

b. Peritoneal dialysis: Though this is a relatively simple technique but is insufficient in removing most drugs. It is effective in lithium and methanol poisoning, and also for salicylate removing poisoning in children.

1. **Haemodialysis**: This is more efficient than peritoneal dialysis. The efficiency of both these dialysis procedures is a function of the molecular weight, water solubility, protein binding and pharmacokinetics within the body compartments of the specific toxin. Dialysis medium may be fixed relation to the toxin. Haemodialysis also helps in correction of fluid and electrolyte imbalance due to intoxication.

2. **Haemoperfusion:** This procedure is being increasingly used. Blood is pumped from the patient via a venous catheter through a column of adsorbent material (activated charcoal or ion-exchange resin) and then recirculated to the patient. To prevent coagulation in the cartridge, heparin is administered systemically. This procedure removes many high Molecular-weight toxins that have poor water solubility. Affinity of the toxins for the adsorbent resin is a rate-limiting factor. Many types of haemoperfusion cartridges are being developed.

c. Exchange transfusion: It removes poisons affecting R.B.C.s, e.g. methaemoglobinaemia induced haemolysis. It is only feasible in small children.

Renal elimination: Some of the toxins are eliminated through urine. If the toxin is lipid soluble, its renal elimination may be pH-dependent. In such cases, alteration of urinary pH and forced diuresis (with frusemide) may hasten renal clearance. Urinary alkalinization (pH 7.5-8.5) and forced diuresis helps in poisoning with salicylates, phenobarbitone, and chlorophenoxy herbicides. Acidification (pH 5.5-6.5) of urine is helpful in amphetamine. However, in cases of renal insufficiency such methods may worsen fluid and electrolyte balance.

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 toreduce 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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