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Review article

Pesticides induced oxidative stress in mammalian systems

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ABSTRACT

For over last two decades, the toxicological research has focused on pesticide-induced oxidative stress (OS) as a possible mechanism of toxicity. In fact OS is an outcome of a multistep process spanning from perturbations in the balance between the levels of oxidants / prooxidants and antioxidants (both enzymatic and non-enzymatic) to tissue damage leading to onset of several disease states and finally to apoptosis. The mechanism(s) of pesticides induced oxidative stress, however, is still not completely understood. Further, several other factors (called as risk factors) are thought to be associated with potentiation of the impact of pesticides induced oxidative stress in living systems and hence play crucial role in the evaluation of safety or toxicity of the pesticide concerned. In recent years several attempts have been made to understand pesticide induced OS in terms of monitoring alterations in various biochemical and molecular compositions in different organs of some experimental animal models by exposing them to varying acute and sub-acute doses of pesticides. It is important therefore to explore some plant products or drugs, which could help mitigate the adverse effects of reactive oxygen species (ROS) including free radicals (FR) produced due to pesticides exposure. This review presents an updated account of reported cellular and molecular events taking place in mammalian systems due to pesticide induced OS, factors influencing its toxicity, and its amelioration through application of various antioxidants.

Contents

1. Introduction

The information about cellular toxicity and tissue injury caused by the reactive oxygen species (ROS) including free radicals (FR) has been known to the scientific world for the last three decades. It has been shown that their continuous accumulation generates various adverse pathophysiological impacts on key tissues / an organ of the humans and animals and that is why they are known to be highly destructive in nature. Oxidative stress (OS) can be defined in terms of a shift of the balance between prooxidants and total antioxidants in the body towards the former. The ROS and free radicals (FR) have the ability to cause peroxidation of unsaturated lipids constituting the membrane of cells and depletion of cellular reserves of reducing elements (both enzymatic and non-enzymatic; jointly called as antioxidants defense system), which the body can produce indigenously. The FR are the chemical species, that are defined in terms of the atoms, or molecules which

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contain one or more unpaired electrons and that makes them several folds more reactive than their corresponding ions and FR continue to seek stabilisation by reacting with other micromolecules, failing which they may interact with biological macromolecules or tissues. Free Radicals have various chemical forms such as hydroxyl, superoxide, nitric oxide and lipid peroxyl radicals etc. The production of FR has been used in the genesis of toxicity of many man-made chemicals and drugs that are called as xenobiotics. The toxicity associated to these xenobiotics is the primary cause of development of different pathophysiological conditions which lead to number of diseases such as occurrence of neurodegeneration in Alzheimer's disease [1,2], aging, asthma, atherosclerosis, cataract, chronic inflammatory diseases of the gastrointestinal (GI) tract, diabetes, Parkinson's disease, neoplastic disease and several others [3].

The aerobic organisms including human beings utilise molecular oxygen for respiration and oxidation of nutrients through mitochondria, a powerhouse of the cell, as it generates energy for driving its physiological activities. As a consequence of the mitochondrial activity, highly reactive oxygen species (ROS) are generated. Reactive Oxygen Species comprise FR, H_2O_2 and peroxynitrite anion. Further, ROS elements may combine to form other toxic species such as peroxynitrite ($O=NOO^-$), a product of reaction between superoxide and nitric oxide radicals. The FR elements are highly unstable due to available electrons; they readily react with various cellular organic substrates such as lipids, proteins, membranes and DNA. Oxidation of these molecules can result into molecular damage which further leads to alterations in their normal biochemical / physiological functions. This event may therefore significantly contribute to onset of various disease states such as cancer and Alzheimer's etc. It also exerts profound impact on the body's aging processes. The factors, which may induce generation of FR and other ROS elements in the human body, include physical exercise, environmental stimuli such as ionising radiation from industry, sun exposure, cosmic rays and medical X-rays etc., environmental toxins and altered atmospheric conditions (such as hypoxia and hyperoxia). Certain drugs, ozone and nitrous oxide (primarily from automobile exhaust), sunlight, and various other industrial chemicals/ pollutants including heavy metals, smoke and different pesticides also induce FR and ROS element production in the human body, which are considered as one of the major causes of carcinogenesis [4].

The FRs is formed continuously in cells as a consequence of both enzymatic and non-enzymatic reactions [5]. As a consequence of oxidation of nutrients in mitochondria and production of ATP through electron transport chain (ETC), FRs are frequently generated. The main source of ROS *in vivo* is aerobic respiration, although ROS are also produced by peroxisomal β-oxidation of fatty acids, microsomal cytochrome P450 metabolism of xenobiotic compounds, stimulation of phagocytosis by pathogens or lipopolysaccharides, arginine metabolism, and tissue specific enzymes.

The FR elements primarily select three important cellular targets to attack in the living systems: (1) essential proteins which are oxidised resulting into diminution of sulfhydryls or thiols contents (2) DNA which is damaged via free radicals mediated oxidative reactions and serve as a precursor to cause cancer and (3) cellular membrane lipids consisting of poly unsaturated fatty acids, which rapidly react with FR and undergo peroxidation (LPO) finally leading to damage of the membrane. As a result, membrane permeability and its Ca^{2+} flux are increased. These events lead to damage of mitochondria, DNA and proteins, which in turn result into swelling of cells and finally the cell death due to apoptosis. The imbalances between the production of ROS/FR and antioxidant defenses in the body lead to a number of important health implications. If there are too many ROS or FR species or the level of antioxidants is depleted or a condition of failure to repair the oxidative damage has arisen, then a pathological condition, called as oxidative stress (OS) develops, and it may cause chronic and permanent damage to the body [6]. The list of ROS/FRs and their salient characteristics are already illustrated elsewhere [7,8].

The exposure of experimental animals or humans to some industrial chemicals including heavy metals has been shown to generate OS [7,8]. The application of pesticides in fields and for sanitary reasons is an essential evil. A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Though often misunderstood to refer only to insecticides, the term pesticide also applies to herbicides, fungicides, and various other substances used to control pests, the main targets of the pesticides. Pests are living organisms that occur where they are not wanted or that cause damage to crops or humans or other animals for examples insects, mice and other animals, unwanted plants (weeds), fungi, microorganisms such as bacteria and viruses, and prions. Under United States law, a pesticide is also any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant. The indiscriminate application of these chemicals has posed serious threat to the environmental health.

An extensive survey of available literature indicates that for the last two decades pesticide-induced OS has been considered as a possible mechanism of toxicity and hence it has been a focus of toxicological research even today. The pesticides have been shown to induce production of ROS by altering the balance between the oxidants / prooxidants and antioxidants through promoting lipid peroxidation (LPO) and depleting the antioxidative cellular reserves (both the enzymatic and non enzymatic) leading to a condition of OS. The range of its impact spans from tissue injury, and aging through apoptosis, to onset of various known/unknown diseases. However, the exact mechanism(s) of their action in mammalian systems has still not been completely understood. In present article, an endeavour has been made to present an updated account of reported information on pesticides induced OS, factors responsible for potentiation of its impact (risk factors), cellular and molecular events influenced by OS, in various key organs of mammalian systems and possible amelioration via application of certain plant products and drugs.

2. The role of antioxidants (AO) in maintaining health

Human body protects itself from the damages caused to it by FRs/ROS employing various defense mechanisms. The body cells primarily utilise its indigenous antioxidant defense system comprising FRs/ROS scavenging enzymes as the first line of defense and the sulfhydryl reserves (thiols), vitamins (A, C and E) and their precursors (such as β-carotene for vitamin A), and polyphenols as the second to combat ROS/FRs mediated toxicity to human health [9,10]. An antioxidant (AO) is a molecule that is capable of slowing down or preventing the oxidation of other molecules by ROS/FRs or any other chemical events. Oxidation is a chemical reaction which transfers electrons from a substance to an oxidizing agent and is able to produce free radicals. This is followed by chain reactions that produce apoptosis in cells. The AO molecules terminate these chain reactions by removing free radical (FR) intermediates, and inhibit other oxidation reactions by being oxidized themselves. This often results in AOs acting as reducing agents. Several AO substances have now been known so far that can provide an effective protection to the biological

macromolecules [11].

Various kinds of fruits, vegetables and medicinal plants have been examined for their AO's potential [12-14]. Many nutraceutical and food companies sell formulations of antioxidants as dietary supplementation and these are widely used by people [15] . The AOs differ in their affinity to the various FRs as well as in their binding site in the organism, for example, vitamin E is highly effective with the superoxide radicals but it is very weak in scavenging hydroxyl ions. Vitamin E is found on the surface of biological membranes and the blood lipids only, whereas in the fluid spaces vitamin C is the main AO. Glutathion also acts as an AO intracellularly and melatonin in the nerve cells. The AOs have thus been classified according to their affinity to FRs and tissue concentrations. There is no doubt that neither a common effective AO compound exists, nor a universal AO treatment [16], only some substances that scavenge certain FRs on defined cells or molecules are present.

Further, when determining the AO content of a tissue, plant or fruits in a peroxide system such as plums and bananas, red grapes were the most effective against FRs, whereas in a hypochlorite system the banana proved to be the weakest. Similarly, on examining some food additives (butylhydroxytoluene, trinatriumpolyphosphate, phenol, propylgallate, etc.) and spices (rosemary, red pepper and oregano as the best ones) a different rank order was established in the two mentioned systems, except Vitamin E, which proved to be the weakest one [17]. Garlic, carrots, apricots, onions, curry, citrus fruits etc. have good AO properties. The advantages of tea and fish consumption are undoubtedly proven, but the role of red wine in preventing FRs is still a debated topic. The results are controversial, but it was suggested that a moderate drinking of red wine (1-3dl daily) might be protective against FRs [18], and possibly against neoplastic diseases too. Each of these antioxidant nutrients, as discussed above, possesses specific and unique characteristics. They mostly function in synergistic manner in the body system in order to potentiate its overall antioxidant protection capability [19,20].

3. Adverse effects of antioxidant administration

The consumption of any of the antioxidants in plenty is not always safe. It is evident from the literature available that any AO can be transformed to a prooxidant, especially if given in a high dose and without proper supplementation of other AOs. The AO will be saturated when it is not able to step into the electron transport chain and it becomes a source of FRs. Probably this is the explanation of the failure of the "Natural" Cancer Prevention Trial [21]. Later it was experimentally proved that high doses of β-carotene produce superoxide radicals. It can, thus, be said: "a single antioxidant is not an antioxidant"[14]. Therefore a new term as "antioxidative stress" has also been coined. This includes all ill effects of AOs and their indirect disadvantages. For example, relatively strong reducing acids can have antinutrient effects if it binds to dietary minerals such as zinc in the gastrointestinal (GI) tract, which prevents it from being absorbed [22]. The beneficial effect of exercise by the induction of aortic catalase activity and endothelial NO synthase expression was counteracted by the administration of vitamin E [24]. This shows that an adaptative reaction may be hindered by the administration of an AO. Certainly the physiological FR reactions must not be blocked.

4. Application of antioxidants (AOs) in the therapy of other diseases

The exposure of animals or human beings to pesticides, heavy metals or introduction of any xenobiotics in the body increases FR generation, which in turn causes tissue injuries [7,8,25]. The administration of AOs has been found to be good in all kinds of ailments, in the form of the poly-AO therapy (N-acetylcysteine, selenium, Vitamin C+E, allopurinol and lazaroid combination)[26,27]. The application of AOs has been found to protect the animals from brain damages due to AOs [10,28]. Another antioxidant, allopurinol, which is able to scavenge superoxides generated by xanthine oxidase, has been found effective in treating the patients suffering from shock and respiratory distress syndrome [29]. In the course of the influenza, the ROS derived from the macrophages causes more damages than the influenza virus itself [30]. Hemila and Douglas (1999)[31] have shown that high doses of vitamin C (2000mg daily) are effective in acute respiratory infections. The combination therapy of AO compounds (vitamin C, coenzyme Q10, β-carotene) has proved to be effective in the therapy of different (toxic and infective) hepatic diseases [32,33]. The chronic pancreatitis was treated with selenium compounds [34]. Anti oxidative treatment, in addition, has also shown protective response against several neurologic and metabolic disorders including renal [9,35], haematological [36], autoimmune and gynaecologic ailments [37]. In the malignant cell lines, the pycnogenol, allicin and resveratrol showed greatest antitumour activity. Lockwood et al. [38] reported that a megadose of coenzyme Q10 and multivitamin therapy can prevent carcinogenesis, but this data has not been confirmed by other workers.

5.Pesticides

A pesticide is a substance or mixture of substances used to kill a pest. A pesticide may be a chemical substance, biological agent (such as a virus or bacteria), antimicrobial, disinfectant or device used against any pest. The FAO has defined the term of 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 which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term pesticides includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thining fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport [39]. Pests include insects, plant pathogens, weeds, molluscs, birds, mammals, fish, nematodes (roundworms) and microbes which compete with humans for food, destroy property, spread or are a vector for disease or cause a nuisance.

Pesticides include variety of different compounds such as insecticides (organochlorines, organophosphates, carbamates, pyrethroids to act as ovicides (substances that kill eggs), larvicides (substances that kill larvae) or adulticides (substances that kill adults)), herbicides (paraquat, diquat, 2,4-dichlorophenoxyacetic acid [2,4-D], gyphosate to control weeds), fungicides (dithiocarbamates, captan), fumigants (ethylene dibromide, methyl bromide), rodenticides (anticoagulants to control rodents), Algicides or algaecides for the control of algae, Avicides for the control of birds, Bactericides for the control of bacteria, Miticides or acaricides

for the control of mites, Molluscicides for the control of slugs and snails, Nematicides for the control of nematodes, Virucides for the control of viruses (e.g. H5N1) [40]. Most pesticides work by poisoning the pest. A list of the most commonly used pesticides, their mechanisms of actions, signs and symptoms and treatment are summarized in Table 1.

Table 1. Most common pesticides, mechanisms of actions, signs and symptoms and treatment

Class	Mechanism of action/ toxicity	Signs and symptoms	Treatment
Organochlorines Chlorobenzilate, Dicofol (Kelthane) Dienochlor(Pentac) Endosulfan, Lindane (Kwell)	Induction of hyperexcitable state in central and peripheral nervous system by disruption of normal flow of sodium and potassium across the axon membrane; may antagonize GABA-mediated inhibition in CNS	Seizures, headache, dizziness, nausea, vomiting, paresthesias, incoordination, tremor/twitching following topical treatment for lice/ scabies or accidental or intentional ingestion of liquid pesticide	1) Maintain and protect airway, (2) Ensure adequate oxygenation,(3) Seizure control with diazepam; adults, 5 to 10 mg, push over 2 to 5 min, intentional ingestion of liquid pesticide repeated every 10 min as necessary; children of <12 years, 0.04 to 0.2 mg/kg every 10 min, monitoring airway closely; lorazepam may be used as an alternative, (4) IV fluids with dextrose (5 to 10%) and thiamine (100 to 500 ng/L), (5) Dysrhythmias from rare myocardial irritant effect treated with lidocaine (1mg/ kg bolus, 2 to 4 mg/min continuous infusion)
Biocides Pyrethrins/ pyrethroids Allethrin, Cyfluthrin (Baythroid), Cypermethrin (Barricade, Cymbush, Cynoff, Demon), Deltamethrin, Dimethrin, Fenothrin, Fenvalerate, Permethrin (Ambush, Dragnet, Nix, Pounce), Remethrin	Pyrethrins are derived from chrysanthemums; pyrethroids are synthetic compounds with longer half-lives; both can produce toxic effects on the nervous system but are not well absorbed and are effectively and quickly detoxified by mammalian liver enzyme systems.	The most severe symptoms are seizures, though highly uncommon unless highly exposed (usually through ingestion of large quantities); tremor, incoordi-nation, salivation, vomiting; topical exposure can produce short-term paresthesias, especially of the hands and face; a small portion of the population (1 to 3%) is allergic to pyrethrins/ pyrethroids, symptoms ranging from nasal stuffiness to asthma.	(1) Skin decontamination by thorough washing with soap and water is suggested; vitamin E, oil preparations are effective in preventing and treating paresthesias; corn oil and petrolatum are less effective, (2) Seizures controlled with benzodiazepines, (3) Standard antiallergy therapy for hypersensitivity reactions.
Organo- phosphates Acephate (Orthene), Chlorphoxim (Baythion-C), Chlorpyrifos (Dursban, Lorsban), Diazinon,Dimethoate (Cygon, DeFend),Ethoprop (Mocap),Fenitrothion Sumithion), Fenthion (Baytex),Malathion (Cythion),Naled (Dibrome),Terbufos (Counter)	Inhibit cholinesterase leading to excess acetylcholine accumulation at the nerve endings	CNS--anxiety, seizures, skeletal nerve-muscle junctions, autonomic ganglia--twitching, tachycardia, muscle weakness (nicotinic effects); peripheral cholinergicneuroeffector junctions--"all faucets on"--sweating, salivation, diarrhea, tearing (muscarinic effects); miosis (pinpoint pupils) most commonly, but 15 percent have mydriasis secondary to epinephrine release from adrenals due to nicotinic receptor stimulation.	(1) Draw red cell cholinesterase and plasma pseudocholine-sterase levels before therapy, (2) Do not delay treatment while awaiting results, (3) Maintain and protect airway, (4) Supplemental oxygen, (5) Atropine (preservative-free, if possible), 2 to 5 mg every 15 min (adults and children of >12 years) until pulmonary symptoms controlled; children < 12 years, 0.05 to 0.1 mg/kg every 15 min; doses repeated as needed for symptom control (up to 24 h, taper dose), (6) Pralidoxime (2-PAM, Protopam) , 1 to 2g (adults) over 10 min, 20 to 50 mg/kg (<12 years) over 30 min; repeated in 1 to2 h and at 10- to 12-h intervals as needed for symptom control; alternatively: continuous infusion 10 to 20 mg/kg/h (up to 500 mg/h) after initial bolus and continued for 24 h, (7) Furosemide (Lasix), 40 to 160 mg for pulmonary congestion remaining after full atropinization.

Class	Mechanism of action/ toxicity	Signs and symptoms	Treatment
Carbamates Carbaryl (Sevin), Pirimicarb (Aphox, Rapid), Propoxur (Baygon), Timethacarb (Landrin), Other carbamates	Reversible cholinesterase inhibition (carbamoyl acetylcholinesterase[AChE] complex dissociates much more easily and quickly than OP-AChE complex)	Cholinergic crisis with "all faucets on"; CNS depression with coma, seizures, hypotonicity in serious toxic exposures	(1) Maintain and protect airway, (2) Optimizeoxygenation/supplemental oxygen, (3) Atropine (preferably or IM) Adults, children >12 years, 2.0 to 4.0 mg every 15 min until secretions controlled; children <12 years, 0.05 to 0.10 mg/kg every 15 min until secretions controlled; continue 2 to 12 h; continued signs of poisoning indicate need for more atropine, (4) Furosemide (Lasix), 40 to 160 mg, if basilar rales persist after atropinization (5) Pralidoxime not indicated in pure carbamate poisoning; may be necessary in mixed organophosphate/ carbamate poisoning or unknown poisoning with cholinergic syndrome.
Repellants Diethyltoluamide-- DEET (Muskol, Off!, Skeeter Beater, Skeeter Cheater, Skintastic for Kids, others)	Mechanism of toxicity unknown	CNS depression followed by seizures; rare unless applied excessively under occlusion; mild skin irritating effects with repeated use; corneal and mucosal irritation; nausea and vomiting with ingestion and, rarely, hypotension, tachycardia with heavy dermal exposure	(1) Decontamination, (2) Control of seizures with benzodiazepines (3) Supportive care
Biopesticides Bacillus thuringiensis Variety aizawai (Agree, Mattch) Variety israelensis (Aquabac, Skeetal) Variety kurstaki (Bactur, Dipel)	Wide range of products derived from several varieties of this organism; highly limited effects on mammalian systems	Mild irritative pulmonary symptoms in some involved in manufacturing process, not in mixers or appliers; theoretical risk of respiratory infection in immunocompromised individuals; single corneal ulceration reported, successfully treated with standard antibiotics; mild gastroenteritis with heavy ingestion.	(1) Symptomatic treatment following decontamination

CNS=central nervous system, IV=intravenous, IM=intramuscular, GABA-gama amino butyric acid, Source: [40]

Although the usage of pesticides is beneficial, there are also number of drawbacks, such as potential toxicity to humans and other animals. It has been reported that the indiscriminate application of various pesticides in agricultural and public health programs has caused severe environmental pollution and health hazards, including cases of human poisoning [40-47] . The use of pesticide raises a number of environmental concerns. Over 98% of sprayed insecticides and 95% of herbicides reach a destination other than their targeted species, including air, water, bottom sediments, food and non-target living systems. Pesticide drift occurs when pesticides that are suspended in the air as particles are carried by wind to other areas, potentially contaminating them. One of the causes of water pollution is pesticide, and some pesticides are persistent organic pollutants and contribute to soil contamination. Thus, these toxic chemicals have become an integral part of the ecosystem. Since these pesticides are chemically designed to act as poison to the pests (target species), they leave devastating effects on other living beings in the environment by intoxicating non-target organisms as well including humans leading to potential hazards to their health. Recently it has been demonstrated that pesticides and many other industrial chemicals may induce FRs production into the experimental animals, which possibly play an important role in causing the toxicity. It has been shown that pesticides may induce oxidative stress by producing FRs, enhancing lipid peroxidation (LPO), and causing drastic increase in the activities of antioxidant enzymes and pool of vital antioxidant components in mammalian systems [8,48-51]. The toxicology of various pesticides is presented by different workers [52-57].

5.1.Organophosphate pesticides

The word "organophosphates" refers to a group of insecticides or nerve agents acting on the enzyme acetylcholinesterase responsible for facilitating neurotransmission in many oraganisms. The term is used often to describe virtually any organic phosphorus (V)-containing compound, especially when dealing with neurotoxic compounds. Many of the so called organophosphates contain C-P bonds. For instance, sarin is O-isopropyl methylphosphonofluoridate, which is formally derived from phosphorous acid ($HP(O)(OH)_2$), not phosphoric acid ($P(O)(OH)_3$). Also, many compounds which are derivatives of phosphonic acid are used as neurotoxic organophosphates. The representative structure of organophosphate molecules is shown in

Figure1. Organophosphate pesticides

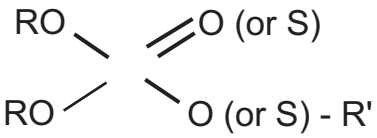

Figure1.Organophosphate pesticides (as well as sarin and VX nerve agent) irreversibly inactivate acetylcholinesterase (AChE) by making an ester bond with hydroxyl group of serine residue present at the active site of enzyme, which is essential to nerve function in insects, humans, and many other animals. The reaction can be displayed as following: $OP(OH)_3+ROHOP(OH)_2(OR)+H_2O$, where R represents the side chain of serine. Being a triprotic acid, phosphoric acid can form triesters whereas carboxylic acids only form monoesters. Esterification entails the attachment of organic groups to phosphorus through oxygen linkers. Being neuropoisons, these chemicals are also used as chemical warfare agents (nerve gases etc.). For instance, parathion, one of the first OPs commercialized, is many times more potent than malathion, an insecticide used in combating the Mediterranean fruit fly (Medfly) and West Nile Virus-transmitting mosquitoes. Organophosphate pesticides degrade rapidly by hydrolysis on exposure to sunlight, air, and soil, although small amounts can be detected in food and drinking water. Their ability to degrade made them an attractive alternative to the environmentally persistent organochlorines, such as DDT, aldrin and dieldrin. Although organophosphates degrade faster than the organochlorines, they have greater acute toxicity, posing risks to people who may be exposed to its large amounts. Some of the commonly used organophosphates include parathion, malathion, methyl parathion, chlorpyrifos, diazinon, dichlorvos, phosmet, tetrachlorvinphos, and azinphos methyl. The structural features of organophospahtes include (1) A terminal oxygen connected to phosphorus by a double bond, i.e. a phosphoryl group, (2) two lipophilic groups bonded to the phosphorus, and (3) a leaving group bonded to the phosphorus, often a halide.

Some of these compounds contain sulfur in place of oxygen at the terminus and are called as thiophosphoryl compounds. They bear P=S functionality and are much less toxic than related phosphoryl derivatives for example sarin, VX and tetrethyl phosphate. Thiophosphoryl compounds are not active inhibitors of acetylcholinesterase in either mammals or insects; in mammals, metabolism tends to remove lipophilic side groups from the phosphorus atom while in insects it tends to oxidize the compound, thus removing the terminal sulfur and replacing it with terminal oxygen, which allows the compound to more efficiently act as an acetylcholinesterase inhibitor. Within these requirements, a large number of different lipophilic and leaving groups have been used. The variation of these groups is one means of fine tuning with the toxicity of the compound. A good example of this chemistry are the p-thiocyanate compounds which use an aryl (or alkyl) group and an alkylamino group as the lipophilic groups. The thiocyanate is the leaving group.

5.2.Toxicity and poisoning by organophosphates

Organophosphates are potent nerve agents, functioning by inhibiting the action of AChE activity in nerve cells. They are one of the most common causes of poisoning worldwide, and are rarely used intentionally in suicides in agricultural areas. Their toxicity is not limited to the acute phase, however, their chronic effects have long been noted. Neurotransmitters such as acetylcholine (which is affected by organophosphate pesticides) are profoundly important in the brain's development, and many OPs have neurotoxic effects on developing organisms even from low levels of exposure.Other organophosphates are not toxic, yet their main metabolites, such as their oxons are toxic. Signs and symptoms of organophosphate poisoning include salivation, lacrimation, urinary incontinence, defecation, GI upset diarrhea/emesis and miosis.

5.3.Oxidative stress induced by organophosphates

Amal et al [58] have studied the effect of acute organophosphorus toxicity on the biomarkers of oxidative stress and apoptosis. They conducted biochemical assays for monitoring activities of true and pseudocholinesterase, catalase and caspase 3 as well as levels of glutathione, (GSH), and malonyldialdehyde (MDA) and found significant decrease in the levels of reduced glutathione and catalase and increase in the level of MDA in acute OP patients over controls. They observed a significant linear negative correlation between MDA and cholinestrases and a significant positive correlation between cholinestrases and catalase, and reduced glutathione (GSH). Thus they concluded that organophosphate in the patients induced production of OS as evidenced by the increased level of malondialdehyde (end product of lipid peroxidation) and decreased level of antioxidants (reduced glutathione and catalase). Serum MDA level is considered as an index of the general peroxidative damage to different tissues [59], GSH serves as a substrate in the glutathione peroxidase/ glutathione reductase system, with NADPH as a reductant, to detoxify lipid peroxidation. Depletion of GSH favours lipid peroxidation and consequently induces cell damage [60,61]. Catalase is one of the cellular defense mechanisms against cytotoxic oxygen species (H_2O_2). A decrease in its activity can lead to excessive accumulation of ROS resulting in initiation and propagation of lipid peroxidation. The impaired glutathione redox status could result in induction of apoptosis, as the activity of caspase-3 is elevated [60]. Also, the activity of cholinestrases correlated negatively with MDA levels and positively with glutathione and catalase levels in OP toxicity. Similar to these results, the observations recorded from different organs (liver, kidney, spleen, and brain) of rats exposed to sublethal concentrations of chlorpyrifos *(O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothionate,* CPF) through intramuscular route for 3 dyas revealed decrease in the levels of reduced glutathione (GSH) and consequent increase in oxidized glutathione (GSSG) levels, resulting in a significant decrease in GSH/GSSG ratio in all these rat tissues tested. However, the treatment of CPF exposed rats with antioxidant vitamins (vitamins A, E, and C) for 1 month, protected the antioxidant parameters [61] in experimental rats. The chlorpyrifos (a chlorinated organophosphate) has also been reported to induce OS into liver, kidney, brain and fetus of the pregnant rats. However, their treatment with butanolic extract of a plant, *Paronychia argentea,* offered considerable protection [62].

5.4.Pathophysiology of organophosphate poisoning

Organophosphates reversibly bind to and inactivate the enzyme acetylcholinesterase (AChE), inhibiting the breakdown of acetylcholine and leading to an excess of acetylcholine in cholinergic synapses. This excess acetylcholine initially overstimulates and then paralyzes cholinergic transmission. The bond between organophosphates and AChE becomes irreversible after a period of approximately 24 to 72 h, a process referred to as “aging”. Toxicity manifests in nicotinic and muscarinic effects in the central and peripheral nervous systems.

5.5.Clinical signs and symptoms of organophosphate poisoning

Acute signs can result within 1-12 h following inhalation or cutaneous absorption and more rapidly following ingestion. The clinical signs of organophosphate poisoning occur as a result of excess acetylcholine accumulation at the nerve endings, which mimics hyperactivity of the parasympathetic nervous system. Signs relative to the alimentary tract include excess salivation, lacrimation, abdominal pain, vomiting, intestinal hypermotility, and diarrhea. The muscarinic effects of acetylcholine cause bronchoconstriction and an increase in bronchial secretions. The nicotinic effects of acetylcholine consist of involuntary irregular, violent muscle contractions and weakness of voluntary muscles. Death occurs as a result of respiratory failure. Clinically affected animals may lose weight due to the inability to feed and drink because of muscular weakness. Clinical signs in birds include goose-stepping, ataxia, wing spasms, wing droop, dyspnea (difficulty in breathing), tenesmus (spasm of anal sphincter), diarrhea, salivation, lacrimation, ptosis (drooping) of the eyelids, and wing-beat convulsions. Non-fatal cases usually recover within 48h. Susceptibility to organophosphate toxicity varies greatly among individuals of any species and can be increased by frequent repeated mild exposure, which results in greater susceptibility due to exhaustion of the body's store of cholinesterase. No definite postmortem changes are seen and when present, are usually secondary to the symptoms and include pulmonary edema, asphyxia, gastroenteritis, and rarely kidney and liver degeneration.

5.6.Diagnosis of organophosphate poisoning

As postmortem findings are usually not revealing, diagnosis is usually made by laboratory analysis. The most reliable diagnostic test is the determination of AChE level in red blood cells, but it must be performed on fresh samples. The AChE levels can be determined on red blood cells (RBCs), whole blood or plasma. The analysis, which is usually used, is the detection of organophosphate degradation products in the stomach contents and liver and kidney tissue. Analysis of brain tissue for decreased AChE levels is also good if done within a few days following death.

5.7.Treatment of organophosphate poisoning and management

If organophosphate toxicity is diagnosed, treatment with atropine and 2-PAM (2-pyridine aldoxime methiodide) can alleviate some of the symptoms. Decontamination of the skin, stomach and eyes of the animal may be necessary, along with symptomatic treatment and respiratory support. Precautions should be taken to prevent drift or drainage of organophosphates to adjoining fields, pastures, ponds, streams or other premises outside the treated area.

6.Carbamates

Carbamate pesticides are derived from carbamic acid and kill insects in a similar fashion as organophosphate insecticides. Organocarbamate pesticides are one of several classes of insecticides, including compounds such as carbaryl, aldicarb, and zectran, which are not broad spectrum in ansecticidal function. They are widely used in homes, gardens and agriculture. Like the organophosphates, their mode of action is inhibition of cholinesterase enzymes, affecting nerve impulse transmission but they are relatively less toxic than organophosphates. The basic chemical structures of carbamate pesticides and their derivatives are shown in Figure 2.

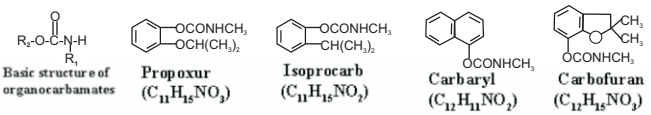

Figure 2. General structure of organocarbamate pesticides and their derivatives. R1, R2= aromatic or aliphatic moieties.

The first carbamate, carbaryl, was introduced in 1956 and more of it has been used throughout the world than all other carbamates combined. Because of carbaryl's relatively low mammalian oral and dermal toxicity and broad control spectrum, it is widely used against a variety of insect pests of cotton, fruits, vegetables, ornamental trees and shrubs, and animals and livestock. It is also used as a molluscicide as well as in lawn and garden settings, where as Aldicarb is released to soil as a systemic insecticide for soil use. Most of the carbamates are extremely toxic to Hymenoptera, and precautions must be taken to avoid exposure to foraging bees or parasitic wasps. Some of the carbamates (like aldicarb) are translocated within plants, making them an effective systemic treatment. Humans may be exposed to organocarbamate insecticides through contaminated air, soils, water, and food by inhalation, dermal contact, and ingestion exposure routes.

The persistence of organocarbamates in the environment varies with each individual compound and the chemical properties of the surrounding soils and water. The reported persistence of carbaryl ranges from nonpersistent in aerobic conditions, with effectiveness lasting from a few hours to several days, but rarely more than 12 weeks, to moderately persistent, with effectiveness ranging from 1 to 18 months. The reported persistence of aldicarb ranges from nonpersistent, with effectiveness lasting from a few hours to several days, but rarely more than 12 weeks, to persistent, retaining toxicity for years. Neither of these compounds binds strongly to soil and both have potential to leach to groundwater.

6.1.Toxicity of organocarbamates

The mode of action of the organocarbamates, like the organophosphates, is inhibition of AChE activity, which results in accumulation of endogenous acetylcholine, a chemical transmitter of neural impulses in nerve tissue and effector organs. This results in an over activity of cholinergic components of the autonomic nervous system, inhibition of neurotransmission process and development of titanic conditions or paralysis.

6.2.The clinical signs and symptoms of carbamate poisoning

These are similar to those caused by the organophosphate pesticides. The carbamate's principal route of entry is either by inhalation or ingestion or secondarily by the dermal route. Dermal exposure tends to be the less toxic route than inhalation or ingestion. For example, carbofuran has a rat oral LD50 of 8 mg/kg, compared to a rat dermal LD50 of >3,000 mg/kg body weight, making it much more toxic when ingested. The carbamates are hydrolyzed enzymatically by the liver and the kidneys excrete the degradation products. Respiratory depression combined with pulmonary edema is the usual cause of death from poisoning by carbamate compounds whereas with organophosphates, the signs and symptoms are based on excessive cholinergic stimulation. Unlike organophosphate poisoning, carbamate poisonings tend to be of shorter duration because the inhibition of nervous tissue AChE is reversible, and carbamates are more rapidly metabolised as well.

The commonly observed early signs and symptoms due to carbamates poisoning include muscle weakness, dizziness, sweating, eye tearing, coughing, and frequent bowel movements

and urination and slight body discomfort. The headache, salivation, nausea, vomiting, abdominal pain and diarrhoea are often prominent at higher levels of exposure. Contractions of the pupils with blurred vision, incoordination, muscle twitching and slurred speech have been reported. Breathing may become difficult, and muscles become weak. Rarely, shortness of breath or muscle weakness is fatal. Symptoms last hours to days after exposure to carbamates but can last for weeks after exposure to organophosphates. Mammalian toxicities for carbamate pesticides are demonstrated in Table 2 [63].

Table 2. Toxicity of carbamate pesticides to mammalian systems.

Common name	Rat oral LD50 (mg/kg body weight)	Rabbit dermal LD50 (mg/kg body weight)
Aldicarb	1	20
Carbaryl	500-850	>2,000
Carbafuron	8	>3,000
Fenoxycarb	16,800	>2,000
Methicarb	60-1,000 depending on product	>2,000 (rat)
Methomyl	30-34	>2,000
Oxamyl	5.4	2,960
Thiodicarb	66	>2000

Source: [63]

6.3.Diagnosis and treatment

The diagnosis of insecticide poisoning is based on the symptoms and on a description of the events surrounding the poisoning. Blood tests can confirm carbamate or organophosphate poisoning. If an insecticide might have contacted the skin, washing of the area is recommended followed by immediate start of medication. Atropine, given by vein, may relieve most of the symptoms. Pralidoxime (Trade Names: PROTOPAM), given by vein, can speed up recovery of nerve function, eliminating the cause of the symptoms.

6.4.Oxidative stress induced by organocarbamates

Very recently the effects of four carbamates, aldicarb and its metabolites (aldicarb sulfone and aldicarb sulfoxide) and propoxur on glutathione content and the activity of the enzymes involved in the sulfur-redox cycle in the mammalian cellular model CHO-K1 cells after 24h exposure have been determined by Elisi et al. [64]. They have shown that carbamate exposure resulted in (1) depletion of intracellular reduced glutathione (GSH) content, (2) no change in oxidized glutathione (GSSG) and (3) a decrease in GSH/GSSG ratio. They have further indicated that reduced levels of GSH were accompanied by the induction of glutathione reductase (GR) and glutathione peroxidase (GPx) activities after 24h exposure with each of the four carbamates into CHO-K1 cells. Since it is known that GSH plays critical role in preventing cytotoxicity via free radical scavenging, they suggested that treatment with high concentrations of carbamates might result in increase of oxidative stress in CHO-K1 cells [64].

In another study, the effects of carbofuran (CF, another carbamate pesticide) has been observed on the erythrocytes of rats keeping in view that RBCs are prone to oxidative stress due to the presence of hemoglobin in its centre and polyunsaturated fatty acids in its membrane lipids [65]. Oxidative stress (OS) is associated with increased osmotic fragility (OF) of erythrocytes. Organophosphate and organocarbamate pesticides are known to cause OS in erythrocytes. They have investigated the effect of a single sub-acute dose of carbofuran (CF), and ameliorating role of vitamin C on OF and OS in erythrocytes of Wistar rats. They observed a significant alteration in the mean erythrocyte fragility (MEF) due to pesticide treatment. They showed drastic increase in the activities of CAT and SOD and decrease in the GST activity in RBC´s membrane. The erythrocytes fragility as well as OS induced by pesticides got recovered near to normal by vitamin C treatment. Recently, chronic exposure to carbofuran via oral administration has been reported by Rai and Sharma 2007 [66] to generate reactive oxygen species (ROS) in rat brain and liver by exposing the animals (intra peritoneal, ip) to three subacute concentrations (0.2, 0.4 and 0.8 mg/kg body weight) equivalent to 10, 20, and 40%, respectively, of its LD50 (i.p.) for 24 h. The results demonstrated that carbofuran treatment at the 3 concentrations tested caused significant increase in lipid peroxidation (LPO). The increased oxidative stress at the same pesticide concentrations significantly induced activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase in rat brain; the impact on catalase being more marked only at high-pesticide doses (0.4 and 0.8 mg/kg body weight). Rat brain was more severely affected by carbofuran than liver. These results demonstrated that i.p. administration of carbofuran accelerated oxidative stress in rat brain in a dose-dependent manner.

Similar findings were reported by several other workers into different parts of rat brain and brain mitochondria of carbofuran treated rats resulting in not only rise in LPO and activities of antioxidative enzymes (SOD, GPx) and decrease in catalase activity but also it induced severe alterations in the motor functions (muscle strength), and cognitive behaviour (memory functions) of animals which could be ameliorated by treatment with sulfhydryl group containing compounds such as n-acetylcysteine, which is a precursor of glutathione biosynthesis [67-69] .

7.Organochlorines

Organochlorine pesticides have a long history of widespread use around the world. Because of high stability or extremely low degradation nature, these compounds are typically very persistent in the environment, and are known for accumulating in sediments, plants and animals. Some of the notable examples include DDT (dichlorodiphenyltrichloroethane) and its analogs (such as methoxychlor), dicofol, aldrin, endrin, heptachlor, endosulfan, chlordane, dieldrin, lindane, mirex, pentachlorophenol and others. The chemical structures of some of the organochlorines are illustrated in Figure 3.

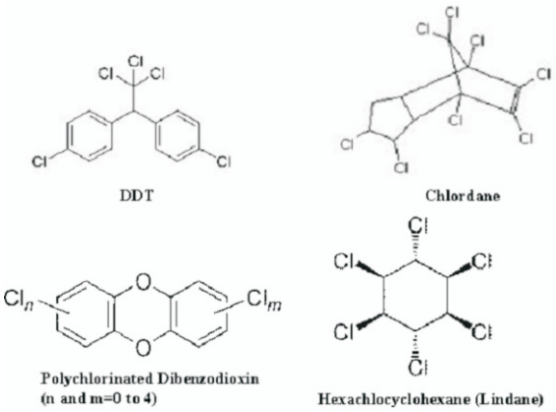

Figure 3. Molecular structure of some organochlorine compounds. The and can vary from 0 to 4.

These can be either hydrophilic or hydrophobic depending on their molecular structure. Many of these agents such as mirex, aldrin have been banned in various countries. Organochlorines have a wide range of both acute and chronic health effects, including cancer, neurological damage, and birth defects. Many organochlorines are also suspected to act as endocrine disruptors. Since, they are mostly liophilic in nature, so they tend to get deposited in fat depots or adipose tissue or even in blood and breast milk. Because of their chemical structure, organochlorines break down slowly (as the -C-Cl bond is highly resistant), build up in fatty and remain in our bodies for a long time. After repeated exposure when their concentration exceeds a critical level, they initiate development of disease processes through induction of central nervous system (CNS) or by altering the levels of neurotransmitters at the synaptic junctions.

Organochlorine pesticides are insecticides composed of primarily of carbon, hydrogen, and chlorine (at least one chloride group should be there covalently linked to the carbon). They break down slowly (half life in years, Table 3) and hence can remain in the environment for long time after application and in the organisms after exposure [70] . The most notorious organochlorine is the insecticide DDT (dichlorodiphenyl trichloroethane). Promoted as a "cure all" insecticide in the 1940s, DDT was widely used to control insects/pests to increase agricultural produce around the world for many years. It was also the chemical of choice for mosquito control; until the 1960s. DDT was applied as the primary weapon in the global "war against malaria" and still continues to be used for malaria control programmes in some countries. The commonly known organochlorines that have been banned in the U.S. include DDT, aldrin, dieldrin, toxaphene, chlordane and heptachlor. Others that are in main use include lindane, endosulfan, dicofol, methoxychlor and pentachlorophenol.

Table3. Environmental half-life of organochlorines in temperate soil

Insecticide	Half-life in soil (years)	95% disappearance (years)
Aldrin	0.3 to 3.0	3.0
Isobenzon	0.4 to 4.0	4.0
Heptachlor	0.8 to 3.5	3.5
Chlordane	1.0 to 4.0	4.0
Lindane	1.2 to 6.5	6.5
Endrin	2.2 to 7.0	7.0
Dieldrin	2.5 to 8.0	8.0
DDT	2.8 to 10.0	10.0

Source: [70]

7.1.Applications of organochlorines

Organochlorine pesticides are mostly used as insecticides. Specific uses take a wide range of forms, from pellet application in field crops to sprays for seed coating and grain storage. Some organochlorines are applied to surfaces to kill insects that land there. An example of this strategy is the spraying of interior home walls with DDT to control mosquitoes and the malaria they carry. This is the way DDT is applied in those countries that are still using the pesticide for malaria control. Other organochlorines - such as chlordane, heptachlor and pentachlorophenol - are used to treat wood to prevent pest damage. Some organochlorine pesticides are used on a wide array of crops. Endosulfan, for example, was first registered as an insecticide miticide in the U.S. in 1954. It is still in widespread use in the U.S. to control pests in vegetables, fruits, cereal grains, and cotton, as well as ornamental shrubs, trees, vines, and ornamental plants. Internationally, its use in African cotton production is common, and it is applied to control pests on cashew plantations in India.

Lindane is another organochlorine with a range of uses. In India lindane has been used to protect crop seeds from insects, for pest control in forests, on livestock and household pets for control of ticks and other pests, and in homes to control ants and other household pests. It is also the active ingredient in many medicated shampoos and soaps to control head lice and scabies. Lindane is now restricted to seed coating uses for a handful of grain crops, and continues to be used to control lice and scabies (except in California, where these uses were recently banned). Internationally, lindane is banned or severely restricted in 40 countries.

7.2.Oxidative stress induced by organochlorines

Koner et al [71] have shown that treatment of experimental animals with subacute doses of organochlorines induced OS in rats by evaluating the impact of DDT and lindane exposure on lipid peroxidation and antioxidant mechanisms in rats. They found that the oral administration of DDT and lindane dependently increased thiobarbituric acid reactive substance (TBARS) levels in serum after 8 wk of treatment. The activity of superoxide dismutase (SOD) in red blood cells (RBCs) also got increased by these compounds in dose dependent manner. They have also shown the protective effect of vitamin C on DDT and lindane induced lipid peroxidation and SOD activity. In another study, endosulfan has been reported to induce OS in rats heart as there was significant rise in the activities of SOD, glutathione peroxidase (GPx) and catalase (CAT) which could be prevented by use of vitamin E as an antioxidant [72] . Lindane and malathion treatment have also been shown to cause immunotoxicity in cell culture by inducing OS. Some workers [73,74] have demonstrated that acetofenate, an organochlorine insecticide treatment can cause macrophage apoptosis by inducing oxidative stress on mouse macrophage cell line RAW264.7. Their studies revealed that the increase of endogenous ROS and DNA damage co-mediating organochlorine pesticides-induced apoptosis in macrophages might be by the mitochondria and p53 signal pathway.

The role of dieldrin in hepatotoxicity of mouse through oxidative stress has previously been reported by Bachowski et al [75]. They observed that oxidative stress correlated with the induction of DNA S-phase synthesis in the experimental mouse. In the rat cerebral hemisphere, the effects of oral administration of hexachlorocyclohexane (HCH) on the extent of LPO and levels of antioxidant enzymes have been evaluated by Sahoo and coworkers [76]. They reported elevated level of LPX after 7 days of treatment in crude homogenate. The pesticide elicited a significant decrease in the activities of cytosolic total and CN- -sensitive superoxide dismutase (SOD) without any change in CN- -resistant SOD. They found decreased activities of cerebral catalase and glutathione peroxidase activity (both selenium-dependent and -independent isoenzymes) throughout the treatment period. Cerebral catalase and the level of glutathione content were decreased after 7 and 30 days of treatment, respectively. Hexachlorocyclohexane (HCH, lindane) caused elevation in the activity of glutathione reductase and content of ascorbic acid, due to the pesticide exposure. The different isomers of HCH (α-, β- and γ-HCH) and DDT exhibit the capability to alter the antioxidant parameters in tumour and surrounding tumour free tissues of female breast cancer patients when compared to controls [77]. Iscan et al [77] demonstrated that free-radical mediated OS was, at least partly, associated with organochlorine residues in human breast tumours. The involvement of the antioxidant enzymes (catalase and glutathione peroxidase) in defense against the genotoxicity induced by phosphamidon and dieldrin has been demonstrated in primary mouse lung fibroblast cultures [78]. These two pesticides

damaged DNA through the generation of reactive oxygen species and therefore produce OS. The catalase activity decreased only in the damage induced by phosphamidon, while glutathione peroxidase protected against damage induced by both phosphamidon and dieldrin. Simultaneous treatment with antioxidant inhibitors and pesticides resulted in a decrease in micronucleus frequency and cell number, due to apoptotic death. The clastogenic DNA damage produced by the two pesticides was found to be modulated by antioxidant enzymes and their inhibitors, which indicated the involvement of pesticides, induced OS in genotoxicity [78].

7.3.Clinical symptoms of organochlorine poisoning

Organochlorines contribute to many acute and chronic illnesses. Symptoms of acute poisoning include tremors, headache, dermal irritation, respiratory problems, dizziness, nausea, and seizures. Organochlorines are also associated with many chronic diseases. Studies have found a correlation between organochlorine exposure and various types of cancer, neurological damage (several organochlorines are known neurotoxins), Parkinson's disease, birth defects, respiratory illness, and abnormal immune system function. Many organochlorines are known or suspected hormone disruptors, and recent studies show that extremely low levels of exposure in the womb can cause irreversible damage to the reproductive and immune systems of the developing fetus.

8.Pyrethrins

Pyrethrins are available in different trade names such as Buhach, Chrysanthemum Cinerariaefolium, Ofirmotox, Insect Powder, Dalmation Insect Flowers, Firmotox, Parexan and NA 9184. Pyrethrin compounds have been used primarily to control human lice, mosquitoes, cockroaches, beetles and flies. Some "pyrethrin dusts," used to control insects in horticultural crops, are only 0.3% to 0.5% pyrethrins. Other pyrethrin compounds may be used in grain storage and in poultry pens and on dogs and cats to control lice and fleas. The basic chemical structure of pyrethrins and its derivatives are shown in Figure 4. Pyrethrins are natural insecticides produced by certain species of the chrysanthemum plant. The flowers of the plant are harvested shortly after blooming and are either dried and powdered or the oils within the flowers are extracted with solvents. The resulting pyrethrin containing dusts and extracts usually has an active ingredient content of about 30%. These active insecticidal components are collectively known as pyrethrins. The other sources of pyrethrin include Asteracea (ex Compositae) family: Calendula officinalis, Chrysanthemum cinerariaefolium, Chrysanhemum coccinum, Tagetes erecta, Tagetes minuta, Zinnia elegans, Zinia linnearis, etc [79,80] . The commercial plant, Chrysanthemum cinerariaefolium vis., also known as Dalmatian pyrethrum, is the principal source of pyrethrins.

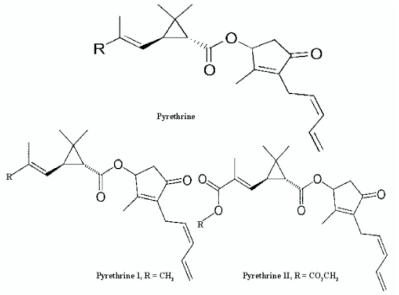

Figure 4. Chemical structure of pyrethrine compounds. In pyrethrin I, R=CH_3 and pyrethrin II, R=CO_2CH_3

8.1.Toxicity of pyrethrins

The natural pyrethrins are contact poisons, which quickly penetrate the nerve system of the insect. A few minutes after application, the insect cannot move or fly away. But, a "knockdown dose" does not mean a killing dose. Enzymes in the insect swiftly detoxify the natural pyrethrins. Thus, some pests will recover. To delay the enzyme action a lethal dose is assured, organophosphates, carbamates, or synergists are added to the pyrethrins. Semisynthetic derivatives of the chrysanthemumic acids have been developed as insecticides. These are called pyrethroids and tend to be more effective than natural pyrethrins while they are less toxic to mammals. One common synthetic pyrethroid is allethrin. Because of their low stability (high degradability in environment) and very high LD_{50} value to humans, pyrethrins have not been reported to show any teratogenic, mutagenic or carcinogenic effects in mammals. These molecules are not stored in the body. But inhaling their higher doses may show toxicity as such as allergy, asthmatic breathing, sneezing, nasal stuffiness, headache, nausea, incoordination, tremors, convulsions, facial flushing and swelling, and burning and itching sensations, central nervous system and immune system.

8.2.Oxidative stress induced by pyrethrins

A survey of literature indicates that not much work has been conducted on evaluation of pyrethrin induced OS in mammals. However, some available reports indicate that certain pyrethrins have the potential to generate OS in various key tissues of some mammalian systems as reviewed by Abdollahi et al [7]. The propensity of lambda-cyhalothrin (LTC) to induce OS in blood and brain of male Wistar rats and its possible attenuation by vitamin C has been reported. A significant increase of MDA levels in erythrocytes and brain were observed in LTC group compared to controls. Antioxidant enzyme activities in both tissues were modified due to LTC treatment. Administration of vitamin C recovered these parameters close to normal. Their results indicated the potential effects of LTC to induce oxidative damage in tissues and the ability of vitamin C to attenuate LTC-induced oxidative damage [81]. Exposure of deltamethrin has been shown to induce OS and cause perturbations in various biochemical parameters including LPO, antioxidant and neutrotransmission enzymes; the toxicity however, has been shown to be reduced by treatment with vitamin E [82]. In rats brain and liver, cypermethrin induced OS has been observed which got ameliorated by treatment with vitamin E or allopurinol [83]. In one report the use of vitamin E with selenium has been reported to protect the rats from cypermethrin induced OS [84]. The effects of treatment with the synthetic insecticide, cypermethrin, on plasma membrane fluidity, lipid peroxidation and antioxidant status in rat erythrocytes have been investigated in rats by Gabbianelli et al [85]. They reported that cypermethrin treatment caused significant decrease in erythrocyte membrane fluidity. Cypermethrin treatment also induced a significant increase in the lipid peroxidation. The increased OS resulted in a significant decrease in the acitivity of glutathione peroxidase. They proposed preferential localization of cypermethrin in the hydrophobic core of the membrane, where it increased lipid packing and consequently decreased membrane fluidity. In most these reports it has been proposed that rise in LPO and antioxidant enzymes/ molecules in different body tissues of mammalian systems exposed to pyrethrin could be part of a strategy to mitigate the adverse influence of ROS and free radicals generated due to pesticide stress.

9.Herbicides

A herbicide is the substance used to kill unwanted plants. Selective herbicides kill specific target plants by interfering with the growth while leaving the desired crop relatively unharmed. Some herbicides used to clear waste ground, industrial sites, railways and railway embankments are non-selective and kill all plant material with which they come into contact. The chemical structures of some herbicides are displayed in Figure 5. Some plants produce natural herbicides, such as the genus Juglans (walnuts) applied for total vegetation control (TVC) programs for maintenance of highways and railroads.

Herbicides may be divided into two broad categories (1) inorganic (such as copper sulfate, sodium chlorate, and sodium arsenite) and organic (such as chlorophenoxy compounds, dinitrophenols, bipyridyl compounds, carbamates, and amide herbicides). The first widely used herbicide was 2,4-dichlorophenoxyacetic acid (2,4-D) which is very selective in function. It is cost effective, still being used as a preferred herbicide over others such as atrazine and glyphosate. Based on their mechanisms of action, they have been classified as (1) acetyl coenzyme A carboxylase (ACCase, the enzyme catalysing the first step of lipid biosynthesis) inhibitors, (2) acetolactate synthase(ALS,catalysing the first step of branched chain amino acid synthesis) inhibitors (such as imazapic), (3) enolpyruvylshikimate 3-phosphate synthase enzyme (EPSPS, catalysing aromatic amino acids biosynthesis) inhibitors (such as glyphosate), and (4) Photosystem II inhibitors (such as atrazine). Some characteristics of representative herbicides are displayed in Table 4.

Table 4. Some characteristics of representative herbicides

Herbicide (type)	Control/Purpose	Acute Toxicity LD_{50}mg/kg
2,4-D (2,4-dichloro phenoxy acetic acid)	Systematic herbicide	3001,000: rats, Guinea pigs, rabbits
Acetochlor	Control of most annual grasses, some broadleaf weeds.Tolerant crops include corn, soybeans, peanuts, and sugarcane.	2,953: rat acute oral
Amitrole (triazine)	Broadleaf weeds and grasses in noncrop areas, generally low toxicity.	>5,000: male rats
Arsenic acid (inorganic)	Desiccation of cotton which is to be stripped	48: young rat 100: older rats
Atrazine	Widely used selective herbicide for broadleaf and grassy weeds.	No ill effects in rats, dogs with diet of 25 ppm
Dinosep (dinitrophenol)	Control of seedlings, not established perennial weeds except with repeat treatments. Applicable to variety of crops, except cruciferous crops.	58: rats
Diquat dipyridyl)	General aquatic herbicide; preharvest top killer or desiccant.	230: rats
Diuron (carbamate)	Low ratesbroadleaf and grass weeds in cotton, sugarcane etc. general weed killer at higher rates	3,400: oral rats
Glyphosate	Broad-spectrum herbicide Used in crop, noncrop, weed control	(Rabbit acute dermal, >5,000 mg/kg)
Metolachlor	Selective herbicide used to control annual grass weeds, yellow nut sedge, some broadleaf in corn, cotton, peanuts, and other crops	2,780: rat acute oral
Paraquat (dipyridyl)	Weed control during establishment of grass seed crops	138: male rats
Propanil (aromatic amide)	Grasses and broadleaf weeds in certain wheat crops (north) and rice (south)	1,870: rats

Source: [65,86]

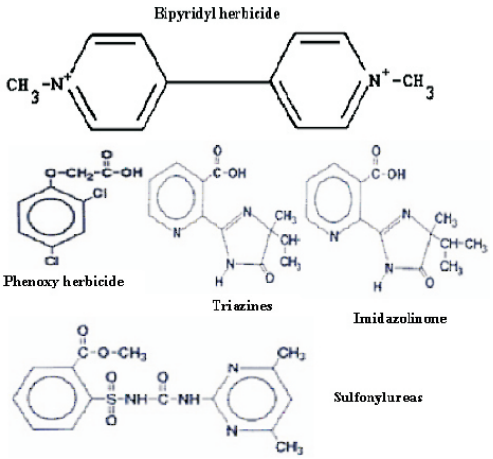

Figure 5. General molecular structures of some herbicides including dipyridyls

9.1.Toxicity of herbicides

Since plants and mammals differ in organization and physiology, it might be expected that herbicides would constitute only a slight chemical hazard to mammals. Whereas some herbicides have very low toxicities in mammals, others have considerable. A number of test species are used to appraise toxicity, and their sensitivities are graded as acute (short-term) LD_{50} values. The chlorophenoxy compounds 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) may be the most familiar herbicides. They have been used in agriculture (to eradicate broadleaf weeds) and to control woody plants in ditches and along highways. They act as growth hormones in many plants, and can evoke active plant growth in areas in which abnormal, twisted, or curtailed growth occurs. Massive doses of these chemicals may cause ventricular fibrillation in mammals. Lower doses may cause contact dermatitis and chloracne (a kind of severe dermatitis) in workers who have contact with 2,4,5-T (or 2,3,7,8-tetrachlorodibenzodioxin, or dioxin). Dinitrophenols (as alkali salts or aliphatic amine salts) exposure in humans may lead to nausea, gastric upset, rapid breathing, tachycardia (rapid heartbeat), cyanosis, and ultimately coma. Death or recovery occurs within 24h. Paraquat and diquat (1,1'-dimethyl-4.4'-bipyridilium derivatives), known as bipyridyl compounds appear to act via free radical mechanism, competing for and depriving plants of an essential reducing agent. The previous works showing mechanism of toxicity of these compounds have been reviewed [65]. These compounds are hazardous to human beings but to lesser extent as compared to other group of pesticides such as organochlorines, organophosphates and carbamates. The fatalities may include lung, liver, and kidney damage. Paraquat tends to become concentrated in the kidney, with the accumulation of toxic amounts in the lung being secondary to kidney damage.

It is a severe eye and moderate skin irritant, but is not significantly absorbed through intact skin. The toxicokinetic studies indicate that through oral route the LD_{50} values paraquat for male and female rats were 100 and 110mg/kg body weight, respectively. Through dermal route the values were 80 and 90 mg /kg body weight, respectively, for male and female rats. The LD_{50} value of paraquat through inhalation in rabbit (for 4h) has been reported to be 6.4mg/m^3. However, the guinea pig has been reported to be the most sensitive animal as LD_{50} value for this chemical has been reported to be less than one third (30 mg/kg) of the oral rout LD_{50} for rats. Men are also highly susceptible to these chemical species. However the exposure to diquat may lead to local and systemic effects. In severe and usually fatal cases, gastrointestinal mucosal ulceration, paralytic ileus, hypovolemic shock, acute renal failure, and coma have been reported [86]. The poisoning by these herbicides could be diagnosed by a qualitative urine test, gut decontamination in patients within 1h of ingestion of a life-threatening dose of >6g. The management of poisoning by these chemicals includes fluid and electrolyte replacement, hemofiltration and hemodialysis etc. [86]. a splice variant of p52shc/p46shc, a cytoplasmic signal transducer involved in the transmission of mitogenic signals from activated receptors to Ras. These workers have proposed that p66shc is part of a signal transduction pathway that regulates stress apoptotic responses and life span in mammals [91]. Paraquat is shown to be involved in triggering oxidative stress and dopaminergic cell death. Epidemiological studies suggest an increased risk for developing Parkinson's disease following chronic exposure to paraquat [92]. This compound was found to trigger stress in endoplasmic reticulum (ER), cell dysfunction, and dopaminergic cell death. The p23, a small co-chaperone protein is cleaved during ER stress-induced cell death triggered by paraquat. The blockage of the caspase cleavage site of p23 was found to be associated with decreased cell death [92]. The cellular glutathione peroxidase has been shown to protect the experimental mice against lethal OS induced by various doses of diquat [93].

The acute diquat (1,1'-ethylene, 2,2'-bipyridilium) toxicity in the rat has been shown to be associated with stimulation of net fluid secretion into the gastrointestinal (GI) tract. Rawlings et al [94] have explained that the mechanism of diquat toxicity in the small intestine as it involves redox cycling of the bipyridyl leading to a disturbance of biochemical function and oxidative stress by conducting in vitro experiments using varying diquat concentrations upto 1mM. They further suggested that diquat-induced fluid secretion in the rat small intestine was associated with redox cycling of bipyridyl leading to depletion of NADPH. According to Li and Sun [88] diquat induces OS in mice when injected through intraperitoneal (ip) route. The rise in hepatic glutathione peroxidase (GPX1) level in the diquat teated mice was attributed to its role in imparting protection against acute oxidative stress produced by herbicide. These workers indicated that normal GPX1 expression is necessary to protect mice against the lethality, hepatic protein oxidation, and elevation of plasma ALT activity induced by diquat. The mechanisms of toxicity, clinical features, and management of diquat ponisoning have been reviewed by Jones and Vale [86].

9.2.Oxidative stress induced by bipyridyl compounds

The toxicity of bipyridyl paraquat in mammals is presumed to be via generation of OS. The bipyridyl paraquat induced toxicity in human neuroblastoma SH-SY5Y cells related to dopaminergic pathogenesis has been reported to occur through OS and proteosomal dysfunction [74]. The experimental mice lacking the genes for various forms of SOD are highly sensitive to the toxic effects of this compound [87- 90]. One of such studies has reported that the p66shc adaptor protein controls oxidative stress response and life span in mammals exposed to paraquat [91]. The p66shc is a splice variant of p52shc/p46shc, a cytoplasmic signal transducer involved in the transmission of mitogenic signals from activated receptors to Ras. These workers have proposed that p66shc is part of a signal transduction pathway that regulates stress apoptotic responses and life span in mammals [91]. Paraquat is shown to be involved in triggering oxidative stress and dopaminergic cell death. Epidemiological studies suggest an increased risk for developing Parkinson's disease following chronic exposure to paraquat [92]. This compound was found to trigger stress in endoplasmic reticulum (ER), cell dysfunction, and dopaminergic cell death. The p23, a small co-chaperone protein is cleaved during

ER stress-induced cell death triggered by paraquat. The blockage of the caspase cleavage site of p23 was found to be associated with decreased cell death [92]. The cellular glutathione peroxidase has been shown to protect the experimental mice against lethal OS induced by various doses of diquat [93].

The acute diquat (1,1'-ethylene, 2,2'-bipyridilium) toxicity in the rat has been shown to be associated with stimulation of net fluid secretion into the gastrointestinal (GI) tract. Rawlings et al [94] have explained that the mechanism of diquat toxicity in the small intestine as it involves redox cycling of the bipyridyl leading to a disturbance of biochemical function and oxidative stress by conducting in vitro experiments using varying diquat concentrations upto 1mM. They further suggested that diquat-induced fluid secretion in the rat small intestine was associated with redox cycling of bipyridyl leading to depletion of NADPH. According to Li and Sun [88] diquat induces OS in mice when injected through intraperitoneal (ip) route. The rise in hepatic glutathione peroxidase (GPX1) level in the diquat teated mice was attributed to its role in imparting protection against acute oxidative stress produced by herbicide. These workers indicated that normal GPX1 expression is necessary to protect mice against the lethality, hepatic protein oxidation, and elevation of plasma ALT activity induced by diquat. The mechanisms of toxicity, clinical features, and management of diquat ponisoning have been reviewed by Jones and Vale [86].

10.Conclusions

With the advent of chemical pesticides having diverse nature, structures and biological activity as well as their indiscriminate application in the environment, the problem of ranking the hazards that each one poses has arisen. As mentioned above, the results of studies conducted in humans and animals have reported that pesticides induce OS which leads to development of different pathophysiological conditions of many diseases affecting the renal, haematological, immunity, gynaecological, neurological and metabolic functions. There is mounting evidence that chronic moderate exposure of pesticides is neurotoxic and increases risk of Parkinson's disease. More studies other than OP's and greater attention to disentangling the effects of different pesticides are needed. Therefore the usage of pesticides is required to be strictly monitored and regulated in order to control the frequent entry of such poisons into the environment, which causes serious risk to the health of humans and animals.

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11.References

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