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Pesticides and oxidative stress: a review

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Summary

The purpose of this paper is to provide a brief review of the current state of our knowledge regarding pesticides and oxidative stress. To this end, we performed a search of the literature using Medline/Index Medicus, EMBASE/Excerpta Medica, and Chemical Abstracts; most of the relevant citations were studied and summarized. In order to better understand the nature of oxidative stress, the principles of free radical production and the body's normal defense system are discussed. The pesticides are categorized and discussed according to their ability to produce lipid peroxidation or alter body antioxidant status. It is concluded that stimulation of free radical production, induction of lipid peroxidation, and disturbance of the total antioxidant capability of the body are mechanisms of toxicity in most pesticides, including organophosphates, bipyridyl herbicides and organochlorines.

key words: pesticides • oxidative stress • toxicity

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BACKGROUND

Reactive oxygen species and their highly destructive nature have been known for at least 30 years, but their diverse pathophysiological effects on vital organs are still of great interest. Oxidative stress can be defined most simply as the imbalance between the production of free radicals capable of causing peroxidation of the lipid layer of cells and the body's antioxidant defense. Free radicals are defined as atoms or molecules that contain one or more unpaired electrons. The toxicity of many xenobiotics is associated with the production of free radicals, which are not only toxic themselves, but are also implicated in the pathophysiology of many diseases. For example, there is extensive evidence for oxidative stress as an important mechanism of neurodegeneration in Alzheimer's Disease [1,2]. Other diseases include Parkinson's Disease, cataracts, atherosclerosis, neoplastic diseases, diabetes, chronic inflammatory diseases of the gastrointestinal tract, aging of skin, asthma, and many others [3]. A complete list of diseases in which oxidative stress possibly plays a role in the pathophysiology is presented in Table 1.

In many cases, the conclusion that free radical production is part of the pathomechanism follows the observation of increased amounts of free radical damage products, particularly markers of lipid peroxidation, in body fluids. It is important to remember, however, that lipid peroxidation inevitably accompanies cell death from any cause.

Extended occupational exposure to many environmental chemicals, such as cadmium and lead, may also cause oxidative stress, as a mechanism underlying the adverse effects in the biological system [4]. Pesticides represent one of the classes of chemicals that are intentionally released into the environment precisely because of their recognized potential to adversely affect biological systems, therefore they have been extensively studied for their toxic potential. Pesticide-induced oxidative stress has been also a focus of toxicological research for the last decade as a possible mechanism of toxicity. Several studies have been conducted to determine whether oxidative stress in humans or animals results from various agents in this group and is associated with their toxic effects. To understand the exact nature of oxidative stress, it is necessary to describe the principles of free radical production and the body's normal defense system.

The objective of this paper is to present a brief review of the state of our knowledge regarding pesticides and oxidative stress. To reach this objective, we performed a search of the literature using Medline/Index Medicus, EMBASE/Excerpta Medica, and Chemical Abstracts; all relevant citations were studied, and most of them were summarized. This article reviews the influences of pesticides, categorized by subgroups, on the oxidant-antioxidant system in animals and humans, and their known pathophysiology and complications. This information is discussed in different subgroups of pesticides separately.

FREE RADICALS AND OXIDATIVE STRESS

It is ironic that oxygen, an element indispensable for life, under certain situations has deleterious effects on the human body. Most of the potentially harmful effects of oxy-

gen are due to the formation and activation of a number of chemical compounds, known as reactive oxygen species, which have a high tendency to donate oxygen to other substances. Many such reactive species are free radicals, i.e. molecules with one or more unpaired electrons and therefore unstable and highly reactive. Free radicals have various chemical structures, such as hydroxyl, superoxide, nitric oxide and lipid peroxy radicals [5]. Seeking stability, radicals attack nearby molecules to obtain another electron and this damage the structure and function of the molecule. If free radicals are not inactivated, their chemical reactivity can damage all cellular macromolecules, including proteins, carbohydrates, lipids and nucleic acids [6,7]. For example, their destructive effect on LDL cholesterol is very likely responsible for arteriosclerosis [8]. Also, radicals have the ability to change the structure of DNA and serve as a precursor of cancer by inducing genotoxicity [9,10].

Free radicals and other reactive oxygen species are derived either from normal essential metabolism in the human body or from external sources, such as exposure to rays, ozone, cigarette smoking, certain drugs, pesticides, air pollutants and industrial chemicals. Free radical formation occurs continuously in cells as a consequence of both enzymatic and non-enzymatic reactions [6,7]. A complete list of causes of oxidative stress in the environment is presented in Table 2.

The balance between the production of free radicals and antioxidant defenses in the body has important health implications: if there are too many free radicals or too few antioxidants for protection, a condition of oxidative stress develops, which may cause chronic and permanent damage [11].

ANTIOXIDANTS

The human body has several mechanisms to counteract the damage caused by free radicals. The basic and the most prominent defense mechanism of the human body is antioxidant agents. The term antioxidant has been defined as any substance that delays or inhibits oxidative damage to a target molecule. These molecules are stable enough to neutralize free radicals by donating electrons. Today many compounds have been found to have antioxidant activity, but in the human body they can be categorized in two main systems. The main system of defense against damage from free radicals is the enzymatic system that opposes oxidation [12]. The body maintains pools of the antioxidant vitamins, such as vitamin E, vitamin C, and beta-carotene, the vitamin A precursor. This first defense system tries to handle all free radicals, but if the oxidative stress is far greater than the capacity of the system, the second line of defense (vitamins) may come into play. Vitamins scavenge and quench free radicals, but are oxidized and inactivated in the process. Each of these antioxidant nutrients has specific activities, and they often work synergistically to enhance the overall antioxidant capacity of the body [13].

PESTICIDES

Pesticides are compounds that are used to kill pests. They include compounds labeled as insecticides (e.g. organophosphates, organochlorines, carbamates), rodenticides (e.g.

Table 1. Diseases in which oxidative stress is possibly involved in the pathophysiology [78–82].

Disease category	Disease name
Autoimmune	Rheumatoid arthritis, immune-complex-mediated vasculitis, inflammatory bowel diseases
Eye	Cataract, age-related macular degeneration, retinopathy, cystic macular edema
GI tract	Hepatitis, pancreatitis, stomach, colitis
Kidney	Renal failure, renal interstitial fibrosis, nephropathy
Lung	Bronchial asthma, adult respiratory distress syndrome, cystic fibrosis, pneumonia, idiopathic pulmonary fibrosis, chronic obstructive pulmonary diseases
Neurodegenerative	Parkinson's, Huntington's, amyotrophic lateral sclerosis, progressive supranuclear palsy, Alzheimer's, multiple sclerosis, reflex sympathetic dystrophy, dementia, neuronal lipofuscinosis
Red cells	Sickle cell disease, anemia, aging, glucose-6-phosphate dehydrogenase activity, fetal/neonatal hypoxia, thalassemia, malaria infection
Skin	Contact dermatitis, atopic dermatitis, psoriasis, vitiligo
Vascular	Atherosclerosis, myocardial infarction, stroke, ischemic and reperfusion damage, focal cerebral ischemia, subarachnoid hemorrhage
Various	Trauma, cancer, burns, inflammatory conditions, multiple organ dysfunction, toxicity of xenobiotics

Table 2. Exogenous sources of free radicals [78,82].

Category	Compound
Drugs	Acetaminophen, clonazepam, clobazepam, ciprofloxacin, cyclosporin, tricyclic antidepressants, nitrofurantoin, troglitazone, bleomycin, doxorubicin, aminotriazole, hyperbaric oxygen, 3,4-methylenedioxyamphetamine (an illegal drug abused by some addicts)
Metal ions	Iron, copper, cadmium, nickel, chromium, mercury.
Pollutants	Asbestos fiber, mineral dust, ozone, carbon monoxide, nitric oxide, nitrogen dioxide, silica, some solvents, toxins, hypochlorite, sulfur dioxide, combustion, polychlorinated biphenyls, paraquat, diquat, plumbagin, juglone.
Radiation	Ultraviolet light, x-rays, gamma radiation.

anticoagulants), herbicides (e.g. paraquat, diquat, 2,4-dichlorophenoxyacetic acid [2,4-D]), fungicides (e.g. dithiocarbamates, captan), and fumigants (e.g. ethylene dibromide, methyl bromide) [14].

The widespread use of pesticides in public health and agricultural programs has caused severe environmental pollution and health hazards, including cases of severe acute and chronic human poisoning [14–21]. The introduction of new, more toxic and rapidly disseminating pesticides into the environment has necessitated accurate identification of their potential hazards to human health. These toxic chemicals have become an integral part of the ecosystem, although many of them are extremely toxic to mammals and other non-target creatures. However, the implications of pesticide residues for human health have yet to be comprehensively documented. Free radicals play an important role in the toxicity of pesticides and environmental chemicals. Pesticides may induce oxidative stress, leading to generation of free radicals and alteration in antioxidants, oxygen free radicals, the scavenging enzyme system, and lipid peroxidation [22,23].

The term “pesticides” is a general name that includes many chemicals, mostly in the classes of insecticides (organophosphates (OPs), organochlorines, carbamates and pyrethro-

ids) and herbicides (bipyridyl compounds). The toxicology of various pesticides is noted in Table 3.

BIPYRIDYL HERBICIDES

The bipyridyl herbicides exist in the market as paraquat, diquat, and mixtures of these two agents. Paraquat and diquat are highly potent systemic poisons. These herbicides are used throughout the world as contact herbicides and as crop desiccants on products such as cotton. Bipyridyl means that the structure contains two pyridine rings, aromatic rings in which one carbon atom is replaced by a nitrogen atom joined by an ethylene group. Paraquat is usually manufactured as a salt with chloride ion, and diquat with bromide. Paraquat is absorbed through the skin, gastrointestinal and respiratory tracts. Diquat, which is less toxic, is poorly absorbed through intact skin, and most cases of toxicity result from ingestion [14]. Free radical formation and the cellular consequences of bipyridyls have been the topic of a large number of surveys in medical literature over the past decade [24–36]. The basic mechanism of oxidative stress in bipyridyls is simple: they initiate a cyclic oxidation/reduction process. First, they undergo one electron reduction by NADPH (the major source of reducing equivalents for the intracellular reduction of paraquat [37]) to form free radicals that

Table 3. Toxicological characteristics of pesticide poisoning.

Chemical Basis	Examples	Site of toxicity	Major acute signs & symptoms
Chlorinated hydrocarbons	Methoxychlor, lindane, toxaphene, chlordane	Neurotoxin, CNS, kidney, liver	Apprehension, excitability, dizziness, headache, disorientation, weakness, paresthesia, convulsions
Organo-phosphates	Diazinon, malathion, parathion, chlorpyrifos, dichlorvos	Irreversible inhibition of red blood cell cholinesterase, acetylcholinesterase, plasma cholinesterase	Mild: fatigue, headache, blurred vision, dizziness, numbness of extremities, nausea, vomiting, excessive sweating and salivation, tightness in chest Moderate: weakness, difficulty talking, muscular fasciculations, miosis Severe: unconsciousness, flaccid paralysis, moist rales, respiratory difficulty, cardiac arrhythmias, and cyanosis
Carbamates	Aldicarb, carbaryl, carbofuran	Reversible inhibition of red blood cell acetylcholinesterase and plasma cholinesterase	Diarrhea, nausea, vomiting, abdominal pain, excessive sweating and salivation, blurred vision, difficulty breathing, headache, muscular fasciculations
Phosphine fumigants	Aluminum or zinc phosphide	Lungs, CNS, liver, kidney	Dizziness, headache, nausea, vomiting, dyspnea, pulmonary edema
Chlorophenoxy derivatives	2,4-D and 2,4,5-T	Skin, eyes, respiratory and GI tracts	Inhalation: burning sensation in the nasopharynx and chest, dizziness Ingestion: vomiting, esophagitis, abdominal pain, diarrhea, muscle stiffness and twitching, metabolic acidosis
Dipyridyls	Diquat, paraquat	Injury to epithelium, cornea, liver, kidney, and linings of GI and respiratory tract	Ingestion early: nausea, vomiting, 48–72 hours after exposure: oliguria, jaundice, cough, dyspnea, tachypnea, and pulmonary edema, convulsions, coma

adapted from ref [14]

donate their electron to O_2 , producing a superoxide radical; upon exhaustion of NADPH, superoxide reacts with itself and produces hydroxyl free radicals that lead to cell death [25]. Hydroxyl free radicals are highly toxic and react with lipids in cell membranes, a destructive process known as lipid peroxidation. The organ which is mostly involved is lung. The lung undergoes a biphasic injury pattern after paraquat exposure. The destructive phase, characterized by destruction of alveolar epithelium, results from the consequences of the redox cycle. Subsequently, a proliferative phase, regarded as a consequence of the destructive phase, produces additional destruction. In this second phase, normal epithelial cells are replaced by fibrous tissue, leading to massive pulmonary fibrosis, hypoxemia, and death. The damaging effects of PQ on lung tissue *in vivo*, and on isolated lung cells, are greatly potentiated at high oxygen concentrations, illustrating the importance of the reaction of the paraquat radical with O_2 *in vivo* [14,38].

PYRETHRIN AND PYRETHROID

Pyrethrins are natural insecticides derived from yellow *Chrysanthemum cinerariifolium* and *Tanacetum cinerariifolium*, and are among the oldest known insecticides, first used in the 1800s [39,40]. In addition, numerous synthetic derivatives known as pyrethroids have been produced, with greater chemical stability than the natural pyrethrins. Pyrethrin and pyrethroid aerosols are frequently used as automated insect sprays in public areas. Pyrethroid pesticides show high toxicity to a wide range of insects and low toxicity to mammals and birds, and rapid biodegradability. However, the liberal use of pyrethroids has increased the risk of into-

xication for non-target species, such as birds, animals and organisms present in soil and water. Pyrethroids exert their insecticide effects through delaying closure of the inward sodium channel of the nerve membrane. Several studies have indicated that pyrethroids induce oxidative stress [41–45]. Traces of this are evident in several organs, tissues, and cells, such as liver [41,43,45], brain [41,43,44], kidney [41] and erythrocytes [46,47]. The increase content of antioxidant enzymes, such as superoxide dismutase and catalase, which decomposes H_2O_2 , and glutathione (GSH) in erythrocytes is probably an initial adaptive response to increased oxidative stress in pyrethroid intoxicated rats [47].

Organophosphates

Organophosphates (OP) are cholinesterase-inhibiting chemicals used predominately as pesticides. They are also used as chemical warfare agents (nerve agents). OPs include all insecticides containing phosphorous derived from phosphoric acid, and are generally the most toxic of all pesticides to vertebrate animals. OPs and carbamates inhibit the function of carboxylic ester hydrolases, such as chymotrypsin, acetylcholinesterase (AChE), plasma or butyrylcholinesterase (BuChE), plasma and hepatic carboxylesterases (aliesterases), paraoxonases (asterases), and other nonspecific esterases within the body. The most prominent clinical effects of poisoning with OPs result from their inhibition of AChE [14–19]. Several studies have demonstrated oxidative stress induced by OPs in rats [48–52] and humans [22,53,54]. Lipid peroxidation is also evident in rat brains [51] and human erythrocytes [48,54]. OP-induced seizures have been reported, associated with oxidative stress [49]. It has also been shown that the acute tubu-

lar necrosis which accompanies OP toxicity is related to reactive oxygen species and lipid peroxidation [55].

Organochlorines

The organochlorines are insecticides that contain carbon, chlorine and hydrogen. They are also referred to as chlorinated hydrocarbons, chlorinated insecticides and chlorinated synthetics. The organochlorine insecticides may be divided into four distinct groups, including:

- DDT (dichlorodiphenyltrichloroethane) and related analogs (methoxychlor);
- cyclodienes (aldrin, endrin, heptachlor, dieldrin, chlordane, endosulfan, chlordane);
- hexachlorocyclohexane (lindane);
- related compounds.

Because they are so lipid soluble, these compounds are stored in fatty tissues, and repeated small exposures may result in accumulation and eventual clinical toxicity. Although all organochlorine insecticides are CNS stimulants, their exact mechanisms of action may vary. DDT and related compounds share a mechanism of action similar to the pyrethroids, whereas the cyclodienes, hexachlorocyclohexanes, toxaphene and related compounds are thought to exert their toxic effects through inhibition of gamma-aminobutyric acid [14].

DDT

DDT use was banned in the 1960s due to its hazards to the environment. Several studies have demonstrated that DDT and methoxychlor induce oxidative stress and lipid peroxidation [48,49]. Also, the adverse effects of methoxychlor on the male reproductive system have been described, consisting in by decreasing the antioxidant enzymes in the epididymal sperm of goats [56] and rats [57,58]

Hexachlorocyclohexane

Hexachlorocyclohexane (HCH) is the only organochlorine insecticide which is still widely used against pests and scabies. HCH is metabolized by the smooth endoplasmic reticulum cytochrome P₄₅₀ system. Lipid peroxidation has been proposed as a major molecular mechanism involved in tissue injury induced by lindane. In relation to HCH, microsomal induction by the insecticide could conceivably lead to alteration in the generation of O₂ by this subcellular fraction. Many studies have shown the oxidative effect of lindane in various organs of mammals, such as rat blood [59], brain [60,61], testis [62,63], and liver [59], and chick liver [62]; all these effects were duration- and age-dependent [64,65].

Increased lipid peroxidation, coupled with altered levels of GSH and oxygen free radical scavenging enzymes in the blood, are discussed in the light of oxidative stress [66]. Also there is support for the hypothesis that lindane inhibits uterine contractility and myometrial gap junctions by establishing an oxidative stress environment [67,68]. It is also interesting to note that lindane hepatotoxicity in hyperthyroid state, which involves enhancement in the oxidative stress status of the liver, is largely dependent on Kupffer cell function, which may involve generation of mediators leading to prooxidant and inflammatory processes [61].

Cyclodienes

It has clearly been demonstrated that these xenobiotics induce dose- and time-dependent oxidative stress and tissue damage in the liver and brain tissues of mice [69–72]. Several other studies have proved oxidative stress in mice, rats, stoats, and guinea pigs [73–76], induced by endrin. Also, endosulfan and dieldrin have been reported to induce oxidative stress [72]. Toxafene and related compounds are not widely used, but a change in the glutathione-redox balance by toxafene has been reported [77].

CONCLUSIONS

All reported studies in humans or animals support the idea that pesticides induce oxidative stress as a mechanism of their toxic action in the body. Regarding the involvement of oxidative stress in the pathophysiology of many debilitating chronic diseases in human, more attention to the reduction of pesticide usage in the environment is suggested.

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