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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 oxygen 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 peroxyl 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, clonazine, closapine, ciprofloxacin, cyclosporin, tricyclic antidepressants, nitrofuratoin, troglitazone, bleomycin, doxorubicin, aminotriazole, hyperbaric oxygen, 3,4-methylenedioxymethamphetamine (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 pyrethroids) 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 intoxication 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 butyrilcholinesterase (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, chlordecone);
- 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 P_{450} 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 O_2 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, stouts, and guinea pigs [73–76], induced by endrin. Also, endosulfan and dielderin 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.

REFERENCES:

1. Butterfield DA: Amyloid beta-peptide (1–42)-induced oxidative stress and neurotoxicity: implications for neurodegeneration in Alzheimer's disease brain. A review. Free Radic Res, 2002; 36: 1307–13
2. Butterfield DA, Lauderback CM: Lipid peroxidation and protein oxidation in Alzheimer's disease brain: potential causes and consequences involving amyloid beta-peptide-associated free radical oxidative stress. Free Rad Biol Med, 2002; 32: 1050–60
3. Zarkovic N. 4-Hydroxynonenal as a bioactive marker of pathophysiological processes. Mol Aspects Med, 2003; 24: 281–91
4. Abdollahi M, Bahreini-Moghadam A, Emami B et al: Increasing intracellular cAMP and cGMP inhibits cadmium-induced oxidative stress in rat submandibular saliva. Comp Biochem Physiol C, 2003; 135: 331–36
5. Cochranc CG: Cellular injury by oxidants. Am J Med, 1991; 92: 235–305
6. Halliwell B: Free radicals, antioxidants and human disease: Curiosity, causes or consequence. Lancet, 1994; 344: 721–724
7. Halliwell B: Free radicals and antioxidants: A personal view. Neut Rev, 1994; 52: 235–65
8. Rumley AG, Paterson JR: Analytical aspects of antioxidants and free radical activity in clinical biochemistry. Ann Clin Biochem, 1998; 35: 181–200
9. Lioi MB, Scarfi MR, Santoro A et al: Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures *in vitro*. Mutat Res, 1998; 403: 13–20
10. Banerjee BD, Seth V, Ahmed RS: Pesticide-induced oxidative stress: perspectives and trends. Rev Environ Health, 2001; 16: 1–40
11. Harman, D: Aging and oxidative stress. JI.FCC, 1999; 10: 24–47
12. Halliwell B, Gutterdge JMC: The antioxidants of human extracellular fluids. Arch Biochem Bio Phys, 1990; 280: 1–8
13. Sies H, Stan LW: Vitamins E and C, carotene and other carotenoids as antioxidants. Am J Clin Neut, 1998; 62: 13152–212
14. Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J: Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning, Williams & Wilkins, Maryland, 1997; 1614–63
15. Abdollahi M, Jafari A, Jalali N: Chronic toxicity in organophosphate-exposed workers. MJIRI, 1995; 9: 221–25
16. Abdollahi M, Jafari A, Jalali N et al: A New approach to the efficacy of oximes in the management of acute organophosphate poisoning. Irn J Med Sci, 1995; 20: 105–109
17. Abdollahi M, Balali M, Akhgari M et al: A survey of cholinesterase activity in healthy and organophosphate-exposed populations. Irn J Med Sci, 1996; 21: 63–66
18. Abdollahi M, Jalali N, Sabzevari O et al: A retrospective study of poisoning in Tehran. J Toxicol Clin Toxicol, 1997; 35: 387–393

19. Abdollahi M, Jalali N, Sabzevari O et al: Pesticide poisoning during an 18-month period (1995–1997) in Tehran, Iran. Irn J Med Sci, 1999; 24: 77–81
20. Jalali N, Pajoumand A, Abdollahi M, Shadnia S: Epidemiological survey of poisoning mortality in Tehran during 1997–1998. Toxicol Lett, 2000; Suppl. 1/116: P309
21. Pajoumand A, Jalali N, Abdollahi M, Shadnia S: Survival following severe aluminum phosphide poisoning. J Pharm Pract Res, 2002; 32: 297–299
22. Banerjee BD, Seth V, Bhattacharya A, Pasha ST, Chakraborty AK: Biochemical effects of some pesticides on lipid peroxidation and free-radical scavengers. Toxicol Lett, 1999; 107: 33–47
23. Etemadi-Aleagha A, Akhgari M, Abdollahi M: A brief review on oxidative stress and cardiac diseases. Mid East Pharmac, 2002; 10: 8–9
24. Smith LL, Rose MS, Wyatt I: The pathology and biochemistry of paraquat. Ciba Found Symp, 1978; 65: 321–341
25. Smith LL: Mechanism of paraquat toxicology in lung and its relevance to treatment. Hum Exp Toxicol, 1978; 6: 31–36
26. Onyeama HP, Ohema FW: A literature review of paraquat toxicity. Vet Hum Toxicol, 1984; 26: 494–502
27. Houze P, Baud FJ, Mouy R et al: Toxicokinetics of paraquat in humans. Hum Exp Toxicol, 1990; 9: 5–12
28. Petry TW, Wolfgang GH, Jolly RA et al: Antioxidant-dependent inhibition of diquat-induced toxicity *in vivo*. Toxicology, 1992; 74: 33–43
29. Tinco R, Parsonnet J, Halperin D: Paraquat poisoning in southern Mexico: a report of 25 cases. Arch Environ Health, 1993; 48: 78–80
30. Pinheiro R: Oxidative stress response of Kluyveromyces marxianus to hydrogen peroxide, paraquat and pressure. Appl Microbiol Biotechnol, 2002; 58: 842–47
31. Ranjbar A, Pasalar P, Sedighi A, Abdollahi M: Induction of oxidative stress in paraquat formulating workers. Toxicol Lett, 2002; 131: 191–94
32. Yumino K: Paraquat- and diquat-induced oxygen radical generation and lipid peroxidation in rat brain microsomes. J Biochem (Tokyo), 2002; 131: 565–70
33. Ikeda K, Kumagai Y, Nagano Y et al: Change in the concentration of vitamins C and E in rat tissues by paraquat administration. Biosci Biotechnol Biochem, 2003; 67: 1130–31
34. Chen CM, Wang LF, Su B, Hsu HH: Methylprednisolone effects on oxygenation and histology in a rat model of acute lung injury. Pulm Pharmacol Ther 2003; 16: 215–20
35. Kim HS, Manevich Y, Feinstein SI et al: Induction of 1-cys peroxiredoxin expression by oxidative stress in lung epithelial cells. Am J Physiol Lung Cell Mol Physiol, 2003; 285: L363-L369
36. Perez FJ, Maureira V: Inactivation *in vivo* of basic peroxidase and increased content of H2O2 in grapevine leaves post treatment with DTT and paraquat. J Plant Physiol, 2003; 160: 645–50
37. Suntres ZE: Role of antioxidants in paraquat toxicity. Toxicology, 2002; 180: 65–77
38. Jones GM, Vale JA: Mechanisms of toxicity, clinical features, and management of diquat poisoning: a review. J Toxicol Clin Toxicol, 2000; 38: 123–28
39. Casida JE: Pyrethrum flowers and pyrethroid insecticides. Environ Health Perspect, 1980; 34: 189–202
40. Dorman D, Beasley V: Neurotoxicology of pyrethrin and the pyrethroid insecticides. Vet Hum Toxicol, 1991; 33: 238–43
41. Gupta A: Effect of pyrethroid-based liquid mosquito repellent inhalation on the blood-brain barrier function and oxidative damage in selected organs of developing rats. J Appl Toxicol, 1999; 19: 67–72
42. Kale M: Lipid peroxidative damage on pyrethroid exposure and alterations in antioxidant status in rat erythrocytes: a possible involvement of reactive oxygen species. Toxicol Lett, 1999; 105: 197–205
43. Giray B: Cypermethrin-induced oxidative stress in rat brain and liver is prevented by vitamin E or allopurinol. Toxicol Lett, 2001; 118: 139–46
44. Vontas JG: Glutathione S-transferases as antioxidant defence agents confer pyrethroid resistance in Nilaparvata lugens. Biochem J, 2001; 357: 65–72
45. Gabbianelli R, Falcioni G, Nasuti C, Cantalamessa F: Cypermethrin-induced plasma membrane perturbation in erythrocytes from rats: reduction of fluidity in the hydrophobic core and in glutathione peroxidase activity. Toxicology, 2002; 175: 91–101
46. Spiteller G: Enzyme lipid peroxidation: a consequence of cell injury. Free Rad Biol Med, 2002; 21: 1003–1009
47. Kale M, Rathore N, John S, Bhathagar D: Lipid peroxidative damage on pyrethroid exposure and alteration in antioxidant status in rat erythrocytes. A possible involvement of reactive oxygen species. Toxicol Lett, 1999; 105: 197–205
48. Gultekin F: The effect of organophosphate insecticide chlorpyrifos-ethyl on lipid peroxidation and antioxidant enzymes (*in vitro*). Arch Toxicol, 2000; 74: 533–538
49. Gupta RC: Depletion of energy metabolites following acetylcholinesterase inhibitor-induced status epilepticus: protection by antioxidants. Neurotoxicology, 2001; 22: 271–282
50. Gupta RC: Nitric oxide modulates high-energy phosphates in brain regions of rats intoxicated with diisopropylphosphorofluoridate or carbofuran: prevention by N-tert-butyl-alpha-phenylnitrone or vitamin E: Arch Toxicol, 2001; 75: 346–56
51. Verma RS: Chlorpyrifos-induced alterations in levels of thiobarbituric acid reactive substances and glutathione in rat brain. Indian J Exp Biol, 2001; 39: 174–77
52. Akhgari M, Abdollahi M, Kebryaeezadeh A et al: Biochemical evidence for free radical-induced lipid peroxidation as a mechanism for subchronic toxicity of malathion in blood and liver of rats. Hum Exp Toxicol, 2003; 22: 205–11
53. Ranjbar A, Pasalar P, Abdollahi M: Induction of oxidative stress and acetylcholinesterase inhibition in organophosphorous pesticide manufacturing workers. Hum Exp Toxicol, 2002; 21: 179–82
54. Dantoine T, Debord J, Merle L, Charmes JP: Roles of Paraoxonase 1 in organophosphate compounds toxicity and in atherosclerosis. Rev Med Interne, 2003; 24: 436–42
55. Poovala VS, Huang H, Salahudeen AK: Role of reactive oxygen metabolites in organophosphate-induced renal tubular cytotoxicity. J Am Soc Nephrol, 1999; 10: 1746–52
56. Gangadharan B: Effect of methoxychlor on antioxidant system of goat epididymal sperm *in vitro*. B Asian J Androl, 2001; 3: 285–88
57. Koner BC: Organochlorine pesticide-induced oxidative stress and immune suppression in rats. Indian J Exp Biol, 1998; 36: 395–98
58. Latchoumycandane C: The effect of methoxychlor on the epididymal antioxidant system of adult rats. Reprod Toxicol, 2002; 16: 161–72
59. Simon-Giavarotti KA: Enhancement of lindane-induced liver oxidative stress and hepatotoxicity by thyroid hormone is reduced by gadolinium chloride. Free Radic Res, 200*2;* 36: 1033–39
60. Sahoo A: Acute hexachlorocyclohexane-induced oxidative stress in rat cerebral hemisphere. Neurochem Res, 1998; 23: 1079–84
61. Sahoo A: Mediation of oxidative stress in HCH-induced neurotoxicity in rat. Arch Environ Contam Toxicol, 2000; 39: 7–12
62. Samanta L: Age-related differences of hexachlorocyclohexane effect on hepatic oxidative stress parameters of chicks. Indian J Exp Biol, 1997; 35: 457–61
63. Samanta L: Age-related changes in rat testicular oxidative stress parameters by hexachlorocyclohexane. Arch Toxicol, 1999; 73: 96–107
64. Videla LA, Barros SB, Junqueira VB: Lindane-induced liver oxidative stress. Free Radic Biol Med, 1990; 9: 169–79
65. Bainy AC, Silva MA, Kogake M et al: Influence of lindane and paraquat on oxidative stress-related parameters of erythrocytes *in vitro*. Hum Exp Toxicol, 1994; 13: 461–65
66. Banerjee BD: The influence of various factors on immunotoxicity assessment of pesticides chemicals. Toxicol Lett, 1999; 107: 21–31
67. Krieger TR: Antioxidants prevent gamma-hexachlorocyclohexane-induced inhibition of rat myometrial gap junctions and contractions. Biol Reprod, 2001; 64: 537–47
68. Iscan M, Coban T, Cok I et al: The organochlorine pesticide residues and antioxidant enzyme activities in human breast tumors: is there any association? Breast Cancer Res Treat, 2002; 72: 173–82
69. Bagchi D, Hassoun EA, Bagchi M, Stohs SJ: Protective effects of antioxidants against eldrin–induced hepatic lipid peroxidation, membrane microviscosity DNA damage and excretion of urinary lipid metabolites. Free Rad Biol Med, 1993; 15: 217–22
70. Bagchi M, Ghosh S, Bagchi D et al: Protective effects of lazaroid U74389F (16-desmethyl tirilazad) on endrin-induced lipid peroxidation and DNA damage in brain and liver and regional distribution of catalase activity in rat brain. Free Radic Biol Med, 1995; 19: 867–72
71. Stevenson DE: Effect of dietary antioxidants on dieldrin-induced hepatotoxicity in mice. Toxicol Lett, 1995; 75: 177–83
72. Bachowski S, Xu Y, Stevenson DE: Role of oxidative stress in the selective toxicity of dieldrin in the mouse liver. Toxicol Appl Pharmacol, 1998; 150: 301–9
73. Numan IT: Endrin-induced depletion of glutathione and inhibition of glutathione peroxidase activity in rats. Gen Pharmacol, 1990; 21: 625–28
74. Hassan MQ: Endrin-induced histopathological changes and lipid peroxidation in livers and kidneys of rats, mice, guinea pigs and hamsters. Toxicol Pathol, 1991; 19: 108–14

75. Hincal F: Induction of lipid peroxidation and alteration of glutathione redox status by endosulfan. Biol Trace Elem Res, 1995; 47: 321–26

76. Hassoun EA, Bagchi D, Stohs SJ: TCDD, endrin and lindane induced increases in lipid metabolites in maternal sera and amniotic fluids of pregnant C57BL/6J and DBA/2J mice. Res Commun Mol Pathol Pharmacol, 1996; 94: 157–69

77. Bayoumi AE, Perez-Pertejo Y, Ordonez C et al: Changes in the glutathione-redox balance induced by the pesticides heptachlor, chlordane, and toxaphene in CHO-K1 cells. Bull Environ Contam Toxicol, 2000; 65: 748–55

78. Lachance PA, Nakat Z, Jeong WS: Antioxidants: an integrative approach. Nutrition 2001, 17: 835–38

79. Stohs SJ: The role of free radicals in toxicity and disease. J Basic Clin Physiol Pharmacol, 1995; 6: 205–28

80. Goodyear-Bruch C, Pierce JD: Oxidative stress in critically ill patients. Am J Crit Care, 2002; 11: 543–51

81. Fuchs J, Zollner TM, Kaufmann R, Podda M: Redox-modulated pathways in inflammatory skin diseases. Free Radic Biol Med, 2001;30: 337–53

82. Kashihara N, Sugiyama H, Makino H: Implication of apoptosis in progression of renal diseases. Contrib Nephrol, 2003;139: 156–72

83. Gudelsky GA, Yamamoto BK: Neuropharmacology and neurotoxicity of 3,4-methylenedioxymethamphetamine. Methods Mol Med, 2003;79: 55–73

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