

# Pesticide Toxicity and Oxidative Stress: A Review

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## ABSTRACT

**Oxidative stress is an imbalance in redox coupling in the body. Lack of antioxidants to scavenge the reactive oxygen species produces adverse effects on health. The causes for an imbalance in redox coupling are multi-factorial. Though, reactive oxygen species are beneficial in the body, excessive generation and lack of proper scavenging may pose a threat. Both internal and external factors may elevate the level. Environmental pollution is a major contributor. Man-made chemicals such as pesticides, heavy metals, and carbon combustion products are blamed. Chronic exposures lead to disease processes through oxidative stress. They mediate pro-inflammatory cytokines and produce free radicals. Pro-oxidant to antioxidant mismatch leads to the adverse effects. Nrf2 activates a number of genes that encode the antioxidants. Glutamate cysteine ligase is activated in response to Nrf2 and it is a key enzyme for GSH production. Nrf2 functionality protects the cells from environmental pollutants. Nrf2 mediates the antioxidant response due to chemical insults, translocated in the cell nucleus. Oxidative stress is known to induce a number of diseases such as genetic abnormalities, carcinogenesis, cardiovascular and respiratory diseases, neuro-degeneration - Parkinson's and Alzheimer's diseases. Pesticides are the major pollutants. Studies confirm oxidative stress and environmental pollution need to be addressed for public welfare.**

**Keywords:** oxidative stress, pesticide, Nrf2, antioxidant, pollution

## INTRODUCTION

Environmental pollution is a global phenomenon and the risks and outcomes on human health are a worrying factor. The present situation of pollution is a man-made calamity though the fact of benefit-risk ratio also needs to be weighed equally before complaining on the issue of pollution. From time immemorial, scientists, researchers and policy makers focused on improving the quality of life of people. New technologies, chemical products and medicines were able to increase the life expectancy over the years. Food and water are the basic needs of life; population explosion in turn potentiated the green revolution to increase the food production. Better yield, protection of farm yields from pesticides and other predators were the basic necessity. As a result, different chemicals and pesticide productions were made their way in view of supporting the green revolution. Pesticides are classified into insecticides, herbicides and fungicides based on their target of predator or pest. Over the years new formulations targeted specifically different breeds of pests with the mission of providing basic food need in the world for growing population. The benefit aspect of pesticides was hunger alleviation which is largely met but on the other hand; the risks of exposure, contamination of environment and short and long-term health issues of world population were a new challenge. Pesticides and its metabolites reach easily to every organ system including endocrine glands, reproductive, nervous, cardiovascular, immune, respiratory and renal systems which are the targets for the pesticides. Genetic anomalies and different types of cancers on exposed population challenged the scientific world. However, the researchers focus in finding

the basic mechanisms of pesticide toxicity at organ and cellular levels could yield future path to find solutions.

Chronic exposure to pesticides is directly linked to chronic diseases and mortality to an extent of 60%. According to WHO (2009)<sup>1</sup> reports, around 36 million people died due to the chronic diseases in the world. Pesticides results in production of reactive oxygen species which in turn brings down the antioxidant levels and their defense against oxidative damage in the cellular system. Lipids, proteins and nucleic acids are targeted due to the imbalance and cellular signalling pathways are affected. Oxidative stress and reactive oxygen species induce the long-term health effects such as carcinogenesis, neuro-degeneration, cardiovascular, respiratory, renal, endocrine and reproductive problems. When pesticides disturb the oxidative balance, they pave way for these diseases and homeostasis. Nrf2 is a leucine zipper protein which plays a role in expression of antioxidant proteins against the oxidative stress induced damage. Nrf2 function is maintaining the cellular homeostasis on exposure to oxidative stress due to chemical exposure. On exposure to different pesticides, Nrf2 expression is increased which protects against the oxidative damage.

Written informed consent was obtained from the patient to publish the case with its related pictures. A copy of the written consent is available for review by the Chief Editor of this journal.

### **Oxidative Stress**

Way back in year 2011 by Sies, based on Nernst formula, oxidative stress and imbalance in redox coupling are same and synonymous. According to Lushchak, oxidative stress in the cells is as result of transient and chronic elevation in reactive oxygen species that harms the normal cellular metabolism and the regulatory process hence adversely affecting the homeostatic balance<sup>2</sup>. Moses Gomberg has described the reactive oxygen species or free radicals almost

a century back which are constantly produced in in all the living systems<sup>3</sup>. Their role in varied pathological conditions and disease states were gradually proved over the years by constant research in this area, confirming the deleterious effects in biological systems of animal kingdom and human beings. Free radical scavenging enzyme superoxide dismutase discovery by McCord and Fridovich further strengthened the constant production of free radicals<sup>4</sup>. Though free radicals were thought as agents that produce only adverse effects in the body were disproved and were proved to be useful in attacking the infection producing organisms through activation of immunity and also in the endothelial derived relaxation in response to the production of nitric oxide by arginine and its good effects in the body. Though oxidative stress is dangerous, its positive effects and role in biological functions are thoroughly updated gradually. It is the imbalance and lack of natural scavenging system in combating the deleterious effects which mostly a subject of constant challenge in understanding the oxidative stress among the scientific discoveries.

Most of the reactive oxygen species (abbreviated as ROS) were produced in the mitochondria in eukaryotic organisms. More than 90% of oxygen in the body is converted into water by cytochrome oxidase by reduction process in the electron transport chain (ETC) through four-electron mechanism, but ROS were not released. Electron transport chain in eukaryotes was generally present at interior membrane of mitochondria but in prokaryotes in plasma membrane. Remaining 10% of oxygen is converted into superoxide anion, then to hydrogen peroxide ( $H_2O_2$ ) which is further yielding hydroxyl radical and anion by addition of an electron. Hydrogen ion from lipids and proteins initiates a chain reaction by abstraction. In the meantime  $O_2^-$  and  $HO^-$  are the major free radicals, in addition peroxide of proteins, lipids and nucleic acids also constitute their role as free radicals. Any toxic compounds in the biological system may induce an imbalance in the redox state. Toxic compounds such as heavy metals,

drugs and pesticides basically inhibit free radical scavenging enzymes such as superoxide dismutase and glutathione peroxidases while enhancing the generation of malondialdehyde and release of lactate dehydrogenases. Liver is a common target of such insults and generation of superoxide radicals resulting in oxidative stress. A variety of pesticides, organophosphates, chlorpyrifos, carbamates, benomyl and diazinon<sup>5, 6, 7</sup>. Diquat induced an increase in reactive oxygen species and long term oxidative stress in genetically CuZn superoxide dismutase enzyme genetic ablated has upregulated the thiol antioxidants mediated by redox sensitive Nrf2 transcription factor<sup>8</sup>. A soil fumigant, 1, 3 -dichloro-2-propanol (1, 3-DCP) induces hepatic toxicity through oxidative stress, nuclear translocation of Nrf2 with an expression of Nrf2 genes<sup>9</sup>. This clearly indicates that, pesticides induce oxidative stress along with translocation of Nrf2 gene expressions. Pesticides are known to induce disruption of endocrine and reproductive axis and a number of molecular mechanisms are disrupted such as enzymes involved in metabolic pathways, synthetic steps of hormones, membranous receptors and nuclear receptors. Pesticides which are also named as xenobiotics mediate their toxicity via the receptor interaction. These receptors are membrane receptors and nuclear receptors. In the nuclear receptors, xenosensors get activated mainly to initiate the metabolism of pesticide molecule so that it may be excreted. Secondly it also lead to the activation of different hormone receptors and the normal hormonal pathways are disturbed. Most of the pesticide induced toxicity is receptor and nuclear mediated in the organism. Around 127 pesticides are classified under endocrine disrupting chemicals which are in use for at least 55 to 60 years in the globe<sup>10</sup>. Promotion of oxidative stress by generation of reactive oxygen species and there by induction of apoptosis by activation of caspases as well as genetic mutation that have procarcinogenic

effects through epigenetic alterations, induction of oncogenes and suppression of tumour genes.

## **Pesticides**

Pesticides are artificially manufactured chemical compounds, developed to contain the pests such as different vectors of diseases, agricultural produces, and harmful plants. It may affect the growth of unwanted plants, helps to protect the yields of plants produce such as grains, fruits and vegetables. Overall, it arrests the pests, insects, and acts as a defoliant or desiccant. They are the toxic organic substances. Though pesticides were used very long back in history, 19th century documents the usage of them in human welfare in terms of better food production and health. Poisonous substance arsenic was in used against the insects. Gradually sulphur was also used as a pesticide. In 1873, Ziedler developed a compound dichlorodiphenyltrichloroethane, popularly called DDT and Paul Muller tested insect containing properties of same<sup>11</sup>. As the population of the globe was increasing, demand for food need to be met and around 1950s green revolution was initiated in Mexico to increase the agricultural produces. Since then a number of pesticides compounds were manufactured and marketed widely irrespective of their hidden potential towards adverse health effects. Based on their hazard, WHO classified pesticides into a number of different classes. Secondly based on the pest they control, pesticides are classified into different groups – insecticides, herbicides, rodenticides, nematocide, fungicide, acasicide and bactericide.

Based on their chemical nature, classified into:

- Organochlorines
- Organophosphates
- Carbamates
- Synthetic pyrethroid
- Microbial insecticides
- Insect growth regulators

Functional basis of classification of

pesticides was on the target organisms. Accordingly they are classified as shown in Table 1<sup>12</sup>.

**Table 1** Classification of pesticides based on the pests they target

Pesticide class	Target/Action	Example(s)
Acaricide	Mites	Aldicarb, Bifenazate
Algaecide	Algae	Copper sulphate
Attractant	Attracts wide range of pests	Pheromones
Avicide	Birds	Avitrol (aminopyridine)
Bactericide	Bacteria	Copper complexes, streptomycin
Bait	Wide range of organisms	Anticoagulants
Biopesticide	Wide range of organisms	Bacillus thuringiensis
Defoliant	Removes plant foliage	Tribufos
Desiccant	Removes water	Boric acid
Fumigant	Wide range of organisms	Aluminum phosphide
Fungicide	Fungi	Azoxystrobin, chlorothalonil
Herbicide	Weeds	Atrazine, glyphosate, 2,4-D
Insect growth regulator	Insects	Diflubenzuron
Insecticide	Insects	Aldicarb, Carbaryl, imidacloprid
Molluscicides	Snails, slugs	Metaldehyde
Nematicide	Nematodes	Aldicarb, fenamiphos
Piscicide	Fish	Rotenone
Plant growth regulator	Regulates plant growth	Gibberellic acid, 2,4-D
Predacide	Mammal predators	Strychnine
Repellent	Vertebrates and invertebrates	DEET, methiocarb
Rodenticide	Rodents	Warfarin
Silvicide	Trees	Tebuthiuron
Termiticide	Kills termites	Fipronil

All the different types of pesticide compounds have the potentiality to induce toxicity in normal cells of both animal and human and may pose long term threat to homeostasis in the body, thus disturbing the health. Earlier studies have proved evidences towards organophosphate induced oxidative stress in both in vivo and in vitro models of liver and brain. They increase the production of malondialdehyde by glutathione and superoxide dismutase inhibition and DNA strand break<sup>13</sup>. Endosulphan in low doses induce lipid peroxidation in a dose-dependent manner with simultaneous decrease in antioxidant status in liver and heart tissues<sup>14</sup>. Paraquat is capable of inducing oxidative stress by over expression of SOD enzymes, apoplastic reactive oxygen species, activation of NADPH oxidase complex and apoptosis<sup>15</sup>. Methyl parathion induces oxidative stress, damage of DNA and apoptotic cell death in human gingival fibroblasts which acts as a cytotoxic and genotoxic pesticide through generation of free radicals<sup>16</sup>. Methyl parathion has weak genotoxic and cytotoxic effects induced by a decrease in ascorbic acid in the testicular cell lines in rat model<sup>17</sup>.

### Exogenous Agents and Oxidative Stress

Oxidative stress is the results of production of reactive oxygen species (ROS) sometimes they are also have nomenclature as reactive oxygen intermediates (ROI). They are a result of metabolism of tissues. ROS act as signalling mediators as most of the time may be beneficial. Most of the exogenous substances may activate the production of these ROS. Cigarette smoke, UV radiation in the atmosphere, alcohol, drugs and cancer chemotherapeutic agents and radiotherapy treatments as well induce oxidative stress. Petroleum combustion products, heavy metals as well as pesticide particles and their metabolic end products too initiate the oxidative stress. Infections, tissue injury, and ischaemia also contribute in the elevated levels of ROS. Cigarette smoke is one of the exogenous agents that induce oxidative damage in cell line. Cigarette smoke induces oxidation of structural and functional components and also able to decrease the endothelial growth factors<sup>18, 19</sup>. In a recent study, Kau et al. (2016)

reported that, exposure to cigarette smoke has elevated the oxidative stress as indicated by the significant elevation in the MDA levels in orbital fibroblasts<sup>20</sup>. Exposure to smoking during gestational period has resulted in oxidative stress and hypoxia in BALB/c mice; antioxidant manganese superoxide dismutase activity was reduced with an increase in nitrotyrosine, a protein damage marker<sup>21</sup>. Pathogenesis of lung parenchymal cell population by smoking has a direct correlation with reactive oxygen species generation. In animal model, exposure to cigarette smoke has confirmed a reduction in superoxide dismutase, catalase and glutathione peroxidase with a simultaneous elevation in thiobarbituric acid levels in the lung tissues of mice<sup>22</sup>. E- Cigarette or vap is gaining more popularity among the adolescents and young generations as the perception of society at large as a reduced risk for higher levels of nicotine compared to the conventional cigarettes. Exposure of lung epithelial cells to e cigarette vapours resulted in higher levels of oxidative stress<sup>23</sup>. Few natural antioxidants such as icaritin was proved to decrease cigarette smoke induced oxidative stress by up-regulation of glutathione through P13K-AKT-Nrf2 dependent pathways. Host defense functions and redox homeostasis and mitochondrial biogenesis are possible by the transcription factor Nrf2 which is also a key element on metabolism and cell cycle processes. Heavy metal such as cadmium is a toxic compound that is present in the environment. Cadmium toxicity results in a decline in antioxidant status and an increased oxidative stress levels. When cadmium intoxicated rats were supplemented with proanthocyanidins, Nrf2 expression were increased in cardiac cells<sup>24</sup>. It is also speculated and proved that, neurodegenerative effects in Parkinson's disease is an outcome of oxidative stress leading into the loss of dopaminergic neurons. Heavy metals were basically are the root cause such as cobalt, iron and copper by generating reactive oxygen species that gradually deteriorate the functional ability of dopamine neurons<sup>25</sup>. Hepcidin is a hepatic antimicrobial peptide which helps in the absorption of iron which is generated by the

presence of xenobiotic and heavy metals, but the cells are protected and regulated by Nrf2 which defences against the hepcidin and extending its role as an antioxidant<sup>26</sup>. Another heavy metal, antimony induces oxidative stress in biological system leading to programmed cell death. Nrf2 is expressed in response to this toxicity which tries to nullify the apoptotic mechanism induced by antimony<sup>27</sup>. Heavy metals such as Pb, Cd, Ni, Al, Mn and Zn though are not directly generating reactive oxygen species in the biological system, they contribute indirectly in oxidative stress by NADPH oxidase system and the subsequent ROS produced affect the expression of genes, cell cycles and programmed cell death in both plant and animal cells. Heavy metals in the environment are a constant threat to mankind and along with petroleum combustion products which also enhances the oxidative stress and subsequent disease processes.

### **Pesticide Induced Oxidative Stress**

Agricultural workers those are continuously exposed for a long duration of pesticides had a remarkable decrease in antioxidant enzyme levels such as superoxide dismutase; in addition genetic polymorphism of paraoxonase-1 (PON1), glutathione S-transferases and cholinesterases metabolizing enzymes. It is clear in the literature that, pesticides generate oxidative stress by production of ROS which in turn decreases the antioxidant status. Oxidative stress is the major toxic pathway that affects the cell cycles and death on exposure to xenoestrogens. Exposure to environmental toxins is known to affect the neuro-physiological processes that may develop autistic spectrum of conditions. Pathogenesis of autism was speculated to be based on environmental toxins such as pesticides. Gestational stage exposure of mice to chlorpyrifos has resulted in an oxidative stress which led to the autism features exhibiting delay in functional and somatic growth at the postnatal stages<sup>28</sup>. Organophosphate compounds which are in common usage induce lipid peroxidation, nitric oxide synthase are activated that synthesizes nitric oxide which also forms a pro-oxidant damaging the normal

neurons. Exposure to diuron resulted in DNA damage through oxidative stress in both male and female germinal cell lines of Pacific oyster *Crassostrea gigas*<sup>29</sup>.

In aerobic organisms oxidative stress is a continuous process that keep generating reactive oxygen species. In normal conditions of health, ROS scavenging system is able to bring a balance by nullifying the toxic potential of these oxidative stress insults. If there is any imbalance in scavenging the oxidative stress, it may result in toxic effects at molecular, genetic and cellular levels. Mitochondria and endoplasmic reticulum, the two cell organelles along with cytochrome P450 which forms the electron transport chain in animal kingdom are the main molecules. In plants, chloroplasts function as alternative sources. In response to oxidative stress, a series of products are released which actually has a tissue damaging effect. As a marker of oxidative stress, lipid peroxidation products such malonyldialdehyde (MDA) thiobarbutyric acids, and 8-hydroxy-2-deoxyguanosine (8-OHdG) are released and in response to these, different antioxidant enzymes such as superoxide dismutase, GSH, catalase, xanthine oxidase, etc.

Organophosphate, organochlorine and fluorines, herbicides, carbamates and pyrethroids, etc. were known to generate oxidative stress. Organophosphate compounds inhibit the enzyme acetyl cholinesterases which favours the lipid peroxidation. This will follow ATPase activity disturbances. Prolonged exposure also depletes superoxide dismutase, GST, GPX, etc.<sup>30</sup> Depletion of glutathione S-transferase activity with an elevated hydroperoxide levels are also common in few vital organs on exposures. In our own previous studies, diazinon has elevated the level of oxidative stress in testis and endosulphan in the vital organs<sup>7, 14</sup>. In addition others study have also confirmed a reduction in  $\text{Na}^+/\text{K}^+$  - ATPase activities. Methyl parathion increased the MDA and a reduction in GSH and also in SOD. Chlorpyrifos, carbamates and monocrotophos have also increased the lipid

peroxidation with a reduction in CAT, SOD and GST levels in experimental models in different organs. Similarly paraquat, cypermethrin, atrazine rotenone and diurons have also depleted the antioxidant status with an increase in lipid peroxidation parameters.

### Antioxidants

Natural antioxidants are commonly found in the nature. Phytochemicals, enzymes and few vitamins are few of the antioxidants which generally are the plant sources. Some co-factors such as selenium, copper, zinc magnesium and iron are essential for the activity of antioxidant enzymes in the biological system. Few antioxidant enzymes are superoxide dismutase (SOD), catalases, glutathione peroxidases and reductases which are synthesized in the body. Dietary vitamins which are not synthesized also function as antioxidants such as vitamin A, C, and E, beta carotenes and folates. Some phytochemical molecules play an important role in the antioxidant properties mainly derived from plants. Polyphenols, flavonoids and carotenoids are few examples. Chlorpyrifos exposure is known to decrease SOD activity, catalase, glutathione reductase in experimental rats<sup>31</sup>. Dichlorvos and lindane treatment in brain tissues of the rats have significantly attenuated the concentrations of SOD, catalases and glutathione transferase activities which was reversed by ginger<sup>32</sup>. A mixture of pesticides-molinate, thiobencarb, linuron, phorate, primiphos methyl, fenvelerate and lambda – cyhalothrin treatment to *Drosophila* and analysis of CAT, GS and Mn-SOD genes by real time PCR exhibited a rise in their expressions with a concomitant increase in heat shock proteins (HSP26) and a decrease in HSP60 transcription<sup>33</sup>. Organophosphate, dichlorvos induced lipid peroxidation in human erythrocytes were attenuated by vitamin C and E, and a simultaneous beneficial effects on a series of antioxidant enzymes in in-vitro studies<sup>34</sup>. In a meta-analysis report, there was a higher antioxidant levels and lesser concentration of cadmium and pesticides in organic farming compared to that of non-organic practices<sup>35</sup>.

This is another fact that, pesticides and other heavy metals impact the antioxidant system in the food chain. Nuclear factor erythroid 2 - Nrf2, a NF- E2 transcription factor plays an important role in the oxidative stress induced by any chemical compounds. Chemical insults lead to exhaustion of glutathione and activate Nrf2 in the cell nucleus. This in turn affects the heme oxygenases. Nrf2 is a leucine zipper protein and activates a number of genes that encode the antioxidants. Glutamate cysteine ligase is activated in response to Nrf2 and it is a key enzyme for GSH production. Nrf2 functionality protects the cells from environmental pollutants. Nrf2 mediates the antioxidant response element which is expressed in response to chemical insults and is translocated in the cell nucleus. Nrf2 regulates the antioxidant related genes thereby both normal and adverse effects of oxidative stress will be nullified. Reactive oxygen species and nitrogen species are mainly neutralized by different antioxidants to maintain the redox balance in biological cells. Majority of afore-mentioned antioxidants are low molecular weight molecules which enable NADP<sup>+</sup>/NADPH and NAD<sup>+</sup>/NADH. NADPH further helps in the reduction process. Nrf2-Keap 1 signalling pathway provides the functional support in the antioxidant system. Nrf2 involves suppression and activation processes. A variety of molecules produce ARE gene such as environmental pollutants such as few pesticides, chemicals, therapeutic drugs, photochemical and few endogenous substances like nitric oxide through Nrf2. So Nrf2 is the key factor in homeostasis by regulatory control on antioxidant system on oxidative stress markers.

### **Pesticides – Oxidative Stress and Diseases**

In toxicology studies, pesticide induced oxidative stress is a major area of research as environmental factors that aggravate the disease processes due to the residues of these chemicals. Pesticides have deleterious effects on biological system and are able to generate oxidative stress. Though oxygen is the basic gas that is indispensable for sustaining life, it may be toxic

enabling the formation of toxic substances in the body. These chemicals are the reactive oxygen species which is able to transfer oxygen forming free radicals. These are unstable molecules with unpaired electrons. They have hydroxyl, lipid peroxy, and superoxide and nitric oxide moieties<sup>36</sup>. Since they are the unstable molecules, they attack the neighbouring like carbohydrates, proteins, nucleic acids and lipids to accept an electron and meantime producing a damaging effect. These adverse effects induce genotoxic effects and may lead to carcinogenic effects and also atherosclerosis and neurodegenerative problems and Parkinsonism<sup>37</sup>. These reactive oxygen species are generated either due to external insults or also due to normal biochemical metabolic functions. Pesticides, heavy metals, cigarette smoke, drugs, etc. are few of the common external insults. Oxidative stress is a common basis for many of the disease processes that may have chronic or permanent health effects. Few of the diseases in which oxidative stress was responsible for the pathophysiological changes are – autoimmune diseases, ophthalmic conditions like retinopathy, cataract, bronchial asthma, neurodegenerative diseases such as Parkinsonism, Alzheimer's, and dementia are the common among them. Various types of malignancies, cardiovascular diseases such as atherosclerosis, stroke, ischaemia, thalassaemia and inflammatory conditions to have their pathophysiological sequel which are directly correlated to the oxidative stress<sup>38</sup>.

Pro-oxidant to anti-oxidant imbalance lead to the intracellular damage, DNA, RNA was also targeted and these reactive oxygen species produce 8-hydroxy-2'-deoxyguanosine which may produce gene-mutations and nicks in the DNA. This may increase the carcinogenesis<sup>39</sup>. As genetic factors are contributing to the development of cancer, metabolic activities in cancer cells further enhances the generation of reactive oxygen species. Nrf2 in turn activates a number of genes that promote antioxidant enzymes and few immune and inflammation inducing genes. Nrf2 and its suppressor protein Keap 1 help to regulate the harmful oxygen

species but carcinogenesis and metastasis may also promote due to the ROS<sup>40</sup>. Secondly Ras pathways are also activated by oxidative stress which may induce point mutations and oncogenes. Subsequently oncogenic proteins will be over expressed and silencing of tumour suppressor genes. Oxidative stress is also the prime factors that induce inflammation and atherogenesis in blood vessels. It leads the development of fatty streaks in the vascular system. When mitochondrial respiratory chain is dysfunctional, it paves the way for the atherosclerosis. A number of mediators of oxidative stress are released from the dysfunctional mitochondria such as NADPH oxidases, xanthine, lipogenase, myeloperoxidase and nitric oxide synthases which are the causative factors in the formation of plaques and atherosclerosis. This is mainly affected whenever there is an imbalance in the pro-oxidant to antioxidant ratio<sup>41</sup>. Prolonged exposure to organophosphate compounds has been reported to accelerate the coronary blood vessel atherosclerosis by a decline in paraxonase activity. Cholesterolemia and increase in LDL are the two sources that promote premature atherosclerotic incidences and generally LDL is a major source having atherogenic potential. LDL once oxidized it enhances generation of monocyte colony stimulating factor by a series of steps. It leads to the formation of macrophages which helps in the uptake of LDL. Oxidized LDL promotes a number of biological activities and along with oxidative stress agents it promotes the atherosclerotic potential by the generation of NADPH oxidase, eNOS, myeloperoxidases xanthine oxidizes cyclooxygenase and oxidative phosphorylation in the mitochondria<sup>42</sup>.

Parkinson's disease is a neuro-degenerative disorder which keeps progressing over time. There is loss of dopamine secreting neurons in the selected nuclei of basal ganglia. Mitochondrial respiratory chain dysfunction which lead to the generation of ROS and in turn the toxic potential of these oxidative stress products lead to the neuronal cell death in substantia nigra in the corpus striatum. This neuronal loss is regulated by the microglia cells, when stimulated produce

ROS like superoxide and nitric oxide. This is the basis for inflammation of neurons and a neurodegenerative process in dopaminergic neurons. Further, dopaminergic neuronal dysfunction lead to the activation of microglia which release neuromelanin and a vicious cycle of loss of dopamine secreting cells are set in for the Parkinson's symptoms<sup>43</sup>. Overall, most of the pesticides which are discussed in this chapter generate the oxidative stress and are the basis for different diseases of cardiovascular, neuronal, respiratory, genetic, reproductive, and hepatic and many other system of the body.

## CONCLUSIONS

Pesticides are basically used for the purpose of mitigation of hunger, contain pests and diseases. Use of pesticide has impacted the hunger alleviation of the world. Along with its benefits, untoward health problems have been increased tremendously; genetic toxicity, carcinogenesis, mutations, infertility, respiratory, neurodegenerative and many more diseases are on a rise. It is alarming to confirm that, this health related adverse conditions are directly proportional to the environmental pollution and pesticides are blamed greatly. Scientific evidences prove the mediation of these toxicities is through an imbalance in the redox equilibrium and they constantly generate reactive oxygen species at cellular levels of living beings. Mediators of oxidative stress are released from the dysfunctional mitochondria; NADPH oxidases, xanthine, lipogenase, myeloperoxidase and nitric oxide synthases. Nuclear factor erythroid 2 - Nrf2, a NF- E2 transcription factor plays an important role in the oxidative stress induced by these chemical compounds. Chemical insults lead to exhaustion of glutathione and activate Nrf2 in the cell nucleus. This in turn affects the heme oxygenases. Nrf2 is a leucine zipper protein and activates a number of genes that encode the antioxidants. Glutamate cysteine ligase is activated in response to Nrf2 and it is a key enzyme for GSH production. Nrf2 functionality protects the cells from environmental pollutants. Nrf2 mediates



the antioxidant response element which is expressed in response to chemical insults and is translocated in the cell nucleus. Nrf2 regulates the antioxidant related genes thereby both normal and adverse effects of oxidative stress will be nullified. It is a major concern as many of the incurable health conditions and diseases are making their way in human life. Genetic defects, inborn errors, mutagenicity, infertility are of greater concern. Though benefit-risk ratio outweighs towards the benefit to mankind, the extent of health risk on exposure to pesticides need to be heavily relooked and measures to minimize the adversities need to be addressed in the 21st century for the greater cause of healthy human existence.

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