# ENVIRONMENTAL EXPOSURES AND OXIDATIVE STRESS

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**Abstract**
Environment is one of the four major determining factors of human health, a factor to which all individuals are exposed, frequently beyond their control. Environmental xenobiotics, substances which are neither utilized nor neutralized in metabolism, are responsible for a wide variety of health damage, and a number of toxic mechanisms may be involved. Imbalance of oxidative and reductive processes at cellular level is one of them.
Oxygen-utilizing metabolism is the basic way of energy production for nearly all living creatures but it needs strict regulation and defensive mechanisms to prevent redox reactions from running false and producing reactive oxygen species (ROS). Presence of some ROS, such as hydrogen peroxide, is normal and is balanced by the cells' own antioxidant enzymes and compounds. Environmentally induced oxidative stress develops if the external agents promote the production of ROS, or reduce or deplete endogenous antioxidants.
The list of oxidative stress inducing environmental chemicals is long and includes heavy metals, pesticide agents, and some persistent organic pollutants. The list of diseases attributed to environmental oxidative stress is not less varied, and includes neurodegenerative diseases (Parkinson's etc.), diabetes (type 1 and type 2), cancers, reproductive problems and many more.
Metals cause oxidative stress first of all if they are capable of redox cycling. Fe, Mn, Cr etc. participate in ROS producing phenomena like Fenton reaction. This way they oxidize endogenous DNA, lipids and proteins, and the molecular damage can lead to mitochondrial dysfunction (further aggravating oxidative stress), carcinogenicity, and neurodegeneration. Other heavy metals like Hg, As and Cd, deplete cellular antioxidant pool, first of all reduced glutathione.
Organochlorines, phenoxy acids and organophosphates were shown to cause oxidative stress. The suggested consequences include preterm delivery and other fertility problems, neurodegenerative diseases (Parkinson's, Alzheimer's, etc.) and tumors. The effects of other persistent organics are partly overlapping with these.
It is generally assumed that consumption of antioxidants, in healthy diet or as food supplements, can protect against the ill effects of oxidative stress induced by xenobiotics. This, however, cannot be taken as a universal rule because several studies showed no effect or even a pro-oxidant action.
Oxidative stress is, finally, an important element in the pathomechanism of environmentally induced health damage, and is best prevented by reducing human exposure to harmful xenobiotics.

***Key words:*** *environmental hygiene; oxidative stress; pathomechanism; xenobiotics*

## Environmental xenobiotics

The role of environmental exposures in determining human health is more and more recognized. Most of the relevant exposures are of chemical nature, and the presence of the corresponding chemicals is mostly due to human activity.
Xenobiotics are chemical entities which are alien for the metabolism of the organism or species in question. They have no role, and are neither utilized as nutrients or energy sources nor efficiently neutralized or broken down (Hayes, 2001). This would suggest that xenobiotics are necessarily toxic; in fact the overlap of the set of xenobiotics and that of toxicants is high but not complete. Environmental xenobiotics are thought, or proven, to be responsible for a variety of human health problems as causative or contributing factors. In a broadened sense, natural substances can also be regarded as xenobiotics if they are unmanageable (and, hence, toxic) for another organism, but the environmental substances relevant for the problem of xenobiotics

and human health are typically artificial, or at least their presence is clearly caused by human activity.

## Oxidative stress: mechanisms and consequences

Oxidation of nutrient molecules is the way of energy production in all heterotrophic organisms including humans. Reactions with molecular oxygen are strongly exergonic, and provide a lot of useful energy on the one hand, but on the other hand several intermediates and by-products which themselves are oxidizing agents. Under healthy conditions, the presence of these reactive oxygen species (ROS) is efficiently counteracted by various cellular antioxidant systems (Sies, 1985). Redox balance is a major element of normal biochemistry at cellular and systemic level, and oxidative stress develops if this balance is lost.

Oxidative energy production is concentrated in the mitochondria. Electrons migrating along the electron transport chain are to reduce molecular oxygen to water; but ca. 1% of the electrons leaks from the chain prematurely, and converts $O_2$ molecule to superoxide anion ($O_2^-$), a ROS. Superoxide spontaneously converts to hydroperoxyl ($HO_2\cdot$), an oxidative free radical, or is metabolized to hydrogen peroxide ($H_2O_2$) by superoxide dismutase. This enzyme is found both in the cytoplasm (Cu,Zn-SOD), and in the mitochondrial matrix (Mn-SOD). $H_2O_2$ is another ROS, and is broken down by catalase and glutathione peroxidase. The latter also reduces lipid hydroperoxides, the products of $H_2O_2$ attacking unsaturated fatty acids.

Some ill consequences of oxidative stress come from direct reactions between ROS and biomolecules. Lipid peroxidation leads to damaged bilayers and disturbance of membrane functions such as synaptic transmission. Oxidized LDL cholesterol is especially prone to form atherosclerotic plaques. Enzymes are inactivated by oxidation of amino acid moieties or cofactors, and direct damage to DNA is also known. If the free radical-induced chain reaction involves base pair molecules in a strand of DNA, the DNA can become cross-linked (Marnett., 1999).

Oxidative stress is also a signal. Moderate oxidative stress leads to apoptotic cell death while a massive stress causes necrosis (Rice-Evans and Gopinathan, 1995). A leading theory (Harman, 1956) explains aging by ROS-induced damage to mitochondrial proteins and DNA, leading to more ROS produced and more damage done.

## Major groups of environmental xenobiotics and their relationship to oxidative stress

Metals are chemical elements which are not synthesized and broken down, only absorbed, used and excreted, by any living organism. If a metal is not irrelevant in terms of human health, it can be completely useless and toxic for the human organism (e.g. mercury, lead or cadmium) or can be an essential micronutrient but toxic when overdosed (manganese, chromium, copper, etc.). Many metals (first of all heavy metals) can be regarded as xenobiotics because they used to have minimal presence (and, hence, bioavailability) before man-made emission into the environment had begun. For some metals, this emission started ca. 5000 years ago when copper and tin, and not much later lead, started to be extracted from ores and turned to metal products. The environmental effects were not recognized in those times but the emissions from ancient mines and smelters can still be identified (Thevenon et al., 2011). Lead-containing alloys were made to kitchenware until the 19th century. Human toxicity was not obvious and the "food-preserving" effect of these dishes and cups, due to the antimicrobial action of the dissolved metals, was appreciated.

Manganese (Mn) finds practical application in a variety of alloys and compounds. A new application with direct human exposure is in magnetic resonance imaging for diagnostic use, in form of the contrast agent trisodium mangafodipir (Mn-DPDP, Teslascan). Atmospheric Mn load comes from man-made pollution. For all living organisms, Humans' daily Mn demand is 2-3 mg; it is a component in many enzymes, e.g. in one of the superoxide dismutases (Mn-SOD; Law et al., 1998) playing important role in counteracting oxidative stress.

Cadmium (Cd) has been used for industrial purposes since the 19th century. It has no biological function in higher-order organisms and is toxic even in small amounts. It is chemically related to zinc which explains several of its toxic effects. Applications resulted in significant workplace exposure and environmental contamination. Due to the toxic hazard involved, the use of Cd has been largely reduced in the last 20 years – but novel technologies and materials using Cd appeared in the meantime, like quantum dots. The presence of Cd in the elements of environment (air, soil, groundwater, etc.) is to a large part due to human activity, and the general population is exposed mainly by contaminated drinking water or food.

Denaturation of proteins is one of the general damaging effects of heavy metals. Glutathione-S-transferase, involved also in neutralizing peroxidated lipids, is inactivated by lead and cadmium (Planas-Bohne and Montserrat, 1992) Some of the toxic heavy metals (iron, chromium, manganese) are capable of redox cycling and catalyze reactions producing ROS, such as the Fenton reaction (Jomova and Valko, 2011). Most of the redox active (Fe and others) content of the cells is held safe in subcellular compartments or chelate complexes, and xenobiotics may cause oxidative stress and DNA damage indirectly by liberating Fe (Welch et al, 2002). If, however, a molecule (endogenous or xenobiotic) can bind a redox active metal it can counteract oxidative damage. ROS generated by metals attack fatty acids. Beside membrane destruction, malondialdehyde from peroxidation of polyunsaturated fatty acids is a bioimarker of oxidative stress.

Pesticides constitute an important group of organic environmental pollutants. They are applied for crop protection and for hygienic purposes in millions of tons yearly. First of all the chemically stable, persistent ones are notoriously toxic xenobiotics. Exposure can be job-related or indirect due e.g. to residues in food and drinking water. Beside acute toxicity, the role of chronic low-level exposure to pesticide agents is supposed to contribute to the development of several chronic non-infections diseases first of all in the nervous system. Various organophosphates were found to induce oxidative stress in rat brain (López-Granero et al., 2013) and Guinea pig liver (Al-Awthan et al., 2012) and the brain effect was paralleled by behavioral effects. Residues of organochlorine insecticides were connected to preterm delivery and elevated oxidative stress markers in exposed women (Pathak et al., 2010) and a phenoxy herbicide caused oxidative stress in the genitals of rats (Pochettino et al., 2013).

Organic solvents (mostly, halogenated hydrocarbon derivatives) have numerous industrial and home applications, resulting in frequent exposures. Liver and the central nervous system are the two main sites of damage. Oxidative stress plays a role at both sites (Malaguarnera et al., 2012; Crews and Nixon, 2009). Liver damage can be induced directly by free radical metabolites of solvent molecules, such as $CCl_3\cdot$ formed from $CCl_4$ by hepatic mitochondria (Tomasi et al., 1987). Alternatively, toxic inflammation of the liver can activate Kupffer and other RES cells to produce ROS (Malaguarnera et al., 2012) or the mitochondria can themselves be damaged by solvent molecules (Berson et al., 1998). In the brain, presence of ethanol was shown to induce free radical formation and liberation of sequestered Fe (Nordmann et al., 1990). For several other solvents, oxidative stress induction in the brain could not be verified in vivo (Chalansonnet et al., 2013). In workers exposed to aromatic hydrocarbons, biomarkers of exposure and of oxidative stress were elevated and seemed to be correlated (Kim et al., 2011.).

## Diseases caused by oxidative stress

The role of abnormal oxidation of biomolecules and cell constituents is supposed or proven in a number of diseases.

In Parkinson's disease, a definite group of dopaminergic neurons in the substantia nigra is gradually destroyed. These neurons are especially prone to oxidative damage due to locally active monoamine oxidase and the auto-oxidative character of dopamine (Alexi et al., 2000). In case of pesticide agents acting by free radical generation, like paraquat, or by mitochondriaal inhibition, like rotenone, the mechanism by which these contribute to causation of Parkinsonism is obvious; while for organochlorines, dithiocarbamates and pyrethroids, the mechanism responsible is still questionable (Brown et al., 2006; Dick, 2006).

In Alzheimer's disease, a number of oxidative stress markers have been detected (Markesbery, 1997) such as elevated level of redox metals and lipid peroxidation products.

The etiology of diabetes type I is still an open question. There are data, however, supporting that oxidative and/or nitrosative stress plays a role in destroying beta cells, and that children developing type I diabetes are deficient in blood urate, a major intrinsic antioxidant (Van Dyke et al., 2010). For type 2 diabetes, the role of persistent organic pollutants was proposed, causing mitochondrial dysfunction (Lowell and Shulman, 2005) and depletion of glutathione (Lee et al., 2008).

Cancers as a disease group are multicausal but the role of environmental (including workplace) exposures is doubtless. Beyond direct mutagenicity, xenobiotics can alter genetic information by generating abnormal metabolites such as malondialdehyde, coming from oxidative damage of polyunsaturated fatty acids and causing covalent modification of DNA (Marnett, 1999). ROS are thus cancer initiators but can also induce apoptosis to eliminate damaged cells (Valko et al., 2006).

## The questionable protective role of antioxidants

It has been generally supposed that antioxidants, mainly as natural constituents of food or food supplements, can protect the human organism against damages and diseases caused by oxidative stress. In reality, however, the results are all but clear. Careless application, e.g. overdosing, of an antioxidant is just another insult to cellular redox balance and, depending on the actual state of the latter, prooxidant effect of antioxidants, or excessive antioxidation (reductive stress) can be the final outcome. Moderate doses of vitamin C on the one hand seems to protect against gastric, colorectal and lung cancer, on the other hand it releases DNA-damaging derivatives from hydroperoxydated lipids (Valko et al., 2006). Vitamin E protects lipids against peroxidation but may reduce the effect of vitamin C. Also beta-carotene can act as a prooxidant in highly oxygenated environment.

## Conclusion

Oxidative stress is apparently an important element in the pathomechanism of various environmentally induced diseases. Reduced exposure and reasonable application of antioxidants are both important for a more efficient exposure.

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