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# Roles of Free Radicals in the Toxicity of Environmental Pollutants and Toxicants

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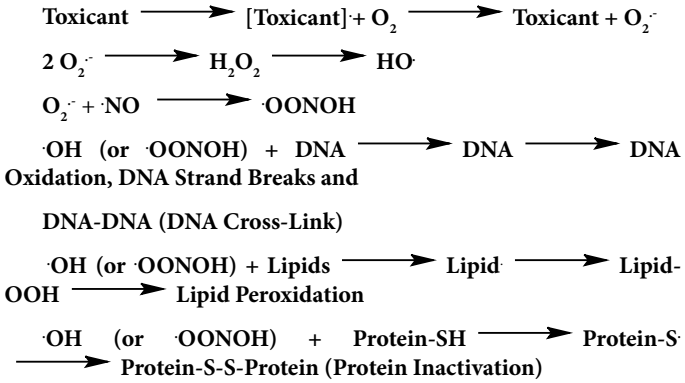
A vast body of evidence has been presented in the last decade indicating that various toxicants, both natural and man-made, present significant risk to human health. Health risks range from a simple allergy to the development of various types of cancers. The cost of prevention and treatment of these conditions/diseases is enormous and is escalating at a significant rate. The risk of people developing these conditions is far greater for those living in poor or underdeveloped countries than those living in developed countries due to the lack of understanding of health risks posed by toxicants to humans and/or lack of medical treatment in underdeveloped countries. However, there is a significant health risk from man-made toxicants in developed countries as more chemicals are synthesized every year, more food additives/preservative are used, and more automobile-based –petroleum-driven pollution is present in air.

Here I present a few examples of natural contaminants and a few examples of man-made synthetic compounds that pose significant risk to human health. I have chosen these toxicants (and environmental pollutants) because they have a common mechanism of toxicity and understanding of these mechanisms could result in both prevention and treatment. These toxicants/environmental pollutants range from metals (arsenic, copper, and lead), halogenated compounds (chloroform and carbon tetrachloride), air pollutants (ozone and sulfur dioxide, sulfur trioxide, hydrazines) and to various drugs (arsenic trioxide, and hydralazine) used as treatment for cancers and hypertension, respectively. The common theme with this wide range of toxicants is the biotransformation of these compounds in vivo and the generation of free radicals (oxidative stress). Although free radicals (molecules with unpaired electrons) are continuously generated during normal cell metabolism in vivo, they do not normally pose significant risks to human health as they are removed via extensive protective mechanisms (e.g., reduced glutathione, ascorbate and SOD) that are normally present in our body. In the absence or proper removable of free radical species formed (such as OH and NO radicals; commonly known as ROS and RNS) free radicals induce damage to critical proteins, lipids (lipid peroxidation) and DNA (formation of 8-oxo-deoxyguanosine, other oxidized DNA molecules, and DNA cross-links). It is generally believed that such damage if not properly repaired over a period of time could lead to tissue/organ toxicity, and may induce tumor formation.




## Scheme 1

Pathways for the formation of free radicals from toxicants/pollutants and subsequent damage to cellular macromolecules in the absence (or decreased levels) of antioxidant enzymes.

### Arsenic

Inorganic arsenic is found as a contaminant in soil, water and air. It is readily absorbed in humans and has been shown to induce formation of tumors in the bladder, prostate, liver and skin. Inorganic arsenic undergoes a series of methylation steps using S-adenosyl-L-methionine as the active methyl donor and it is believed that the methylated form of arsenic is the ultimate carcinogen in vivo [1,2]. Various mechanisms for arsenic toxicity have been proposed, including inhibition of critical enzyme functions (reactions of an SH group with arsenic) altering cellular signaling, affecting the glutathione redox system and production of free radicals. Several studies have shown that inorganic arsenic or its methylated form produce free radicals, resulting in an increase in the formation 8-oxo-deoxyguanosine, a biomarker of oxidative DNA damage. Formation of the OH radical has been shown directly from inorganic arsenic using spin-trapping techniques and electron spin resonance spectroscopy in both *in vitro* and *in vivo* in experimental models. Recent studies have confirmed formation of oxidized DNA using highly sensitive methods e.g., immuno-spin-trapping. The formation of oxidized DNA required biomethylation of inorganic arsenic and this DNA oxidation was found to be linked to an accelerated transformation to a cancer phenotype [2]. While other mechanisms for toxicity/carcinogenicity of arsenic cannot be discounted, it appears that the formation of free radicals and free radical-induced DNA oxidation plays a significant role in the formation of tumors in vivo.

### Haloalkanes

Haloalkanes formed from the reaction of chlorine with alkanes have been used in industry for many years as solvents, cleaners, anesthetics, and as antiseptics. It is believed some of these haloalkanes are also present as contaminants in drinking water and in chlorinated swimming pools. Haloalkanes in general are extremely hepatotoxic and are known human carcinogens. The mechanism of hepatoxicity induced by carbon tetrachloride has been extensively studied over the

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years [3]. Carbon tetrachloride is mostly metabolized by cytochrome P-450 (CYP2E1), however other isozymes of cytochrome P450 (CYPB1, CY2B2 and CYP3A) are also able to metabolize carbon tetrachloride. This cytochrome P-450—induced biotransformation of carbon tetrachloride results in the formation of a carbon-centered free radical (trichloromethyl radical) which by virtue of its reactivity binds covalently to many cellular macromolecules including DNA and cytochrome P-450 (suicidal inactivation). Formation of DNA adducts with carbon tetrachloride metabolites is believed to cause cancer formation. In the presence of oxygen, carbon tetrachloride radical reacts with lipids to form lipid peroxy radicals, resulting in lipid peroxidation and lipid degradation (liver steatosis). The hepatotoxicity of carbon tetrachloride is both dose- and time-dependent. Furthermore, it is synergistic with the presence of other pro-oxidants e.g. iron. Inhibitors of cytochrome P-450 appear to alleviate some of the toxicity. Furthermore, natural antioxidants may also be protective.

## Hydrazines

Hydrazines are environmental pollutants, are found in edible mushrooms, and are used in medicine. Hydrazines in general are toxic, and induce a variety of toxic insults, including liver toxicity, carcinogenicity and mutagenicity. Hydralazine, the least toxic of the hydrazines, induces DNA damage, causes severe forms of systemic lupus erythrematosus and increase the incidence of lung tumors in mice. Because of the significance of hydrazine derivatives as environmental pollutants, food contaminants, and their utility in medicine, a large volume of research has been carried out to elucidate mechanisms of toxicity of these compounds. Studies have shown that hydrazine derivatives generate free radicals upon oxidation (catalyzed by metal ions, cytochrome P-450 and peroxidases), causing DNA oxidation and damage [4]. Substituted hydrazines have been proposed to alkylate DNA by nucleophilic attack rather than via free radical generation. Nevertheless, DNA alkylation has been proposed to lead to carcinogenic events.

## Smog

A major health problem in the highly developed countries is a form of air pollution produced by the reaction of sunlight with hydrocarbons, nitrogen compounds, ozone and other gases primarily released in automobile exhaust. Smog is common in large urban areas, especially during hot, sunny weather, where it appears as a brownish haze that can irritate the eyes and lungs. The elderly and children as well as individuals with pre-existing heart or lung diseases are particularly at risk from breathing this smog. Various gases present in smog, e.g. nitric oxides, sulfur dioxide and ozone are well known oxidants and have been reported to induce organ and cellular damage via generation of free radical species. Nitric oxide rapidly reacts with molecular oxygen to generate highly reactive peroxynitrite, which is known to oxidize DNA, proteins and lipids. Sulfur dioxide reacts with water to generate sulfite (hydrated sulfur dioxide) which has been shown to generate sulfite ($^{\cdot}SO_3^-$) and sulfate ($^{\cdot}SO_4^-$) anion radicals catalyzed by human myeloperoxidases [5]. Sulfite is also used as food preservatives. Exposure to sulfite has been reported to induce allergenic reactions and bronchoconstriction in sensitive human populations. It is now believed that free radical formation from sulfite may be involved in damaging (oxidizing) sensitive proteins. Ozone is a toxic gas that is not naturally present at lower atmospheric levels. However, it is one of the primary pollutants present in photochemical smog. Ozone is a strong oxidizing agent and has been linked to lung inflammation, and alveolar epithelial damage. It has been suggested that these damages are initiated by free radicals formed from the decomposition of secondary ozonides, a reaction product of ozone with unsaturated lipids [6]. Ozone also has been reported to induce damage to cellular DNA via free radical mediated reactions.

While there are many other contaminants and chemicals that pose significant health risks, important questions remain unanswered as what to do to reduce/protect human health. Furthermore, since children are at much higher risk (more sensitive to toxicants) avoidance and protection from environmental toxicants becomes even more important. Various government agencies are involved in monitoring and enforcing clean air act. Additionally, these agencies are involved in identifications of various molecular and cellular mechanisms of action of pollutants/toxicants. While these agencies do an excellent work, enforcing and carrying out these tasks takes enormous amounts of time, money and sometimes is subject to political interference. Nevertheless, as a large percentage of environmental pollutants and toxicants undergo biotransformation (either oxidation or reduction in vivo) to generate toxic intermediates and some of which are converted into free radical species that induce various toxic insults, it is reasonable to assume that antioxidant (Vitamins A, C and E etc.) would play a significant role in reducing and/ or preventing toxicity in humans. In fact, recent studies indicate that a diet rich in antioxidants may play a major role in human health, especially in diabetic and heart diseases [7]. The importance of nutrition is now recognized as a major factor modulating toxicity of some toxicants and pollutants and it is believed that diet/nutrition can affect biotransformation as well as absorption of toxicants thus reducing the effective concentrations of toxic metabolites in vivo. Thus, it appears that identification of foods that are rich in antioxidants and foods that could negatively impact absorption/ metabolism of these toxicants would be easiest and least expensive way to reduce and prevent toxicity of these pollutants. Recently, "omics" of nutrition research (personalized- genetic- based nutrition science) has been proposed as an effective solution for many diseases, including toxic manifestations induced by various pollutants [8]. However, it is at its earliest development and a significant amount of research is needed for this to come to fruition.

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