2. Oxidative damage improved by incidental additives and preservatives used in foods

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1. Introduction

Due to exponential increase of world population, and its increasing urbanization, it was necessary to increase the production and storage time of food. To this goal the agriculture, the livestock and the food processing industry have developed and been used several chemicals: the food additives. These compounds can be divided in two classes: incidental and intentional additives. Most of them are toxic, but below certain levels pose no hazard to human health. The concentration of these substances should be strictly controlled by government agencies to ensure food security. FAO (United Nations - Food and Agriculture Organization), WHO (United Nations - World Health Organization) FPC-NAS-USA (Food Protection Committee of National Academy of Science of USA), have established food protection standards for the proper use and limits of tolerance for these substances (de Man, 1999). In Brazil, since 1965 the presence of additives in
foods was regulated by various Laws and Regulations (Evangelista, 2000). The term food additive includes all nonnutritive substances or mixtures that are added to foods to improve or to maintain appearance, flavor, texture and increase storage time. These substances may or may not increase it nutritional capacity. Are also included the substances that are added during the food raw materials production, processing, packaging and storage. Most additives are very useful, allowing the use of seasonal surplus production, because they keep more time both the organoleptic as the sanitary food conditions. This is critical to the maintenance of food supply in the world today. Between the food additives, we chose to review the incidental additives and the food preservatives because both these groups show little toxicity threshold (Yost et al, 2004; Diaz et al, 2004). The incidental additives may be natural contaminants like toxins produced by microorganisms, and inorganic toxicants (e.g. Hg, Se, As and Pb ions) consumed in feeds by animals used as food sources, and dissolved in water used in the food processing (Sugár et al, 2013). In addition, agricultural chemicals (e.g. pesticides, fertilizers), chemicals derived from processing (e.g. by heat, ionizing radiation, smoking), packaging materials and inadvertent or accidental contaminants. The latter include preparation accidents or mistakes, contaminants from utensils, environmental pollution and contaminations during storage or transport (de Man, 1999; Cabrera-Vique and Mesias, 2013). Preservatives or antimicrobial agents are used to maintain the food sanitary quality during processing and the storage time (Davidson and Juneja, 1990). Between the preservatives there are inorganic compounds like sodium chloride, sulfites, nitrates, nitrites and hydrogen peroxide; organics like benzoic acid, parabens, sorbic acid and bacteriocins. As described above, the additives below the limits of tolerance established and under adequate control, pose no hazard to human health. But when present above the limits, these compounds can initiate or worse many acute and chronic diseases. Furthermore some of these compounds accumulate in the body that can cause long term damage.

**Incidental additives**

Organochlorine pesticides such as DDT, BHC and aldrin were widely used before the recognition of their toxicity and persistence. DDT was ban in the 1970s and over 90 countries signed the “Stockholm Convention on Persistent Organic Pollutants” in 2001 that was a commitment to eliminate the use of 12 organic pesticides (Daba et al, 2011). Despite of this, DDT has been used for preventing the spread of malaria in many countries, with the support of the WHO (Eskenazi et al, 2008). Aldrin and dielderin also has been recently found in soil (Westbom et al, 2008). Other
organophosphate pesticides like diazinon and malathion are commonly used in Agro-industries (Daba et al, 2011). These compounds are resistant to degradation and continue to be present in most food chains worldwide, mainly in animal based products like meat, fish and milk (Arguin et al, 2010). The exposition to these compounds, largely by dietary intake (Brock et al, 1998), has been related with arthritis, breast cancer and diabetes (Cox et al, 2007, Dorgan et al, 1999, Lee et al, 2007), neurobehavioral changes and DNA hypomethylation (Jurewicz and Hanke, 2008, Rusiecki et al, 2008). Pesticides and their metabolites have been detected in many foods like the based in meat, fish, eggs, vegetables (Schecter, 2010) and wheat (Daba et al, 2011).

Perfluorinated compounds (PFCs) are surfactants used to repel stain, grease and water. For example, PFCs may be used to keep food from sticking to cookware, to make sofas and carpets resistant to stains, to make clothes and mattresses more waterproof, and may also be used in some food packaging, as well as in some firefighting materials. These compounds are detected in food from various countries (Ericson et al, 2008, Schecter et al, 2010). Exposition to PFCs can lead to liver damage (Son et al, 2008), decreased fecundity and impaired sperm quality (Fei et al, 2009).

Polychlorinated polyphenyls were used in electrical systems, pesticides preparations, rubber industry, etc. (Penteado and Vaz, 2001). Their use was banned in USA in the 1970s (Garmon, 1982), but nowadays still been detected in various foods (Schecter et al, 2010). Exposition to these compounds has been associated to neurologic diseases, pubertal timing, growth abnormalities, endocrine disruption and cancers (Ribas-Fito, 2001, Guo et al, 1995, Schecter, 2010).

Recently Yang et al (2013) reported the contamination of Chinese children with melamine. This compound is a trimer of cyanamide used by industry to produce plastics, inks and paper. In 2008, more than 51,900 Chinese infants were contaminated by powder milk with melamine, and developed melamine-related urinary stones. This compound was used as fertilizer for crops, during the 1950s and 1960s and also may be used to adulterate the nitrogen composition of foods due it high nitrogen content.

Triazine herbicides, like ametryn, simazine, and atrazine have been used to control broad weeds and grasses at crops with great economic importance, like corn, pineapple, sugarcane, sorghum, artichokes, asparagus, beans and other deep-rooted crops (EPA). For humans and animals, the main access rout is the oral absorption (Singh et al, 2011). Many experiments reported the effects of triazine herbicides and their metabolites to vertebrate cells, inducing an oxidative stress process. Oxidative stress is related to the onset
and progression of many diseases like atherosclerosis, cancer, psoriasis, Alzheimer, hypertension, heart and liver diseases (Severi-Aguiar et al, 2013). Cyanogenic glucosides are bioactive compounds produced by plants as a defense against herbivores that break down to release hydrogen cyanide (HCN) (Gleadow and Woodrow, 2002). Many plants with importance to the food industry have these compounds like sorghum and cassava. Burns et al (2011) related high concentration of these compounds in cassava-derived foods read to eat in Australia cities. The lethal dose of cyanide to human is 1.5 mg/Kg body weight and for a child of 20 Kg body weight this concentration will be reached eating 40-240 g of cassava chips available in Melbourne. Cyanide oxidizes definitely the ferrous ion of hemoglobin, impeding the oxygen transport and can also inhibit the mitochondrial respiratory chain (Halliwell and Gutteridge, 2007).

Lead exposure have been related to the onset and progression of many diseases including neurological, cardiovascular, impaired renal function, hypertension, impaired fertility, adverse pregnancy outcomes, damage to teeth and to the hematopoietic system (Ciobanu et al, 2012; Zheng et al, 2013). Children are more vulnerable to low doses (Bierkens, 2011). Lead is derived from mining and processing activities, and presents potential risk to human and animal health mainly for the surrounding communities (Ricci, 2006).

For other communities, usual salt is an important font of lead. Salt used as a food additive and as a season in food industry and in domestic kitchen, is a font of essential and toxic metals like lead, cadmium, cooper, zinc, nickel and cobalt (Eftekhari et al, 2014). The maximum permitted level of lead in food grade salt is 2.0 μg/g (Codex, 2006), and literature reports a range of 0.01-5.8 μg/g for salt samples collected in Iran (Zarei, 2011), 0.5-1.64 μg/g in Turkey, Egypt and Greece (Soylak et al, 2008) and 0.03 μg/g in Brazil (Amorim and Ferreira, 2005).

Cadmium exposure induces osteoporosis, other bone damages, renal tubular dysfunction leading to renal failure (Ciobanu et al, 2012; Al-Rmalli et al, 2011; Engström et al, 2012) and several cancers mainly in liver (Satarug, 2012; Julin et al, 2012; Sawada et al, 2012). According to CODEX (2006), the maximum permitted level in food grade salt is 0,5 μg/g. Literature reports maximum concentration of cadmium: 0.65 μg/g in Iran (Jahed Khaniki, 2007), 0.03 in Brazil (Amorim and Ferreira, 2005) and Turkey, Egypt and Greece, (Soylak et al, 2008) in salt samples bought in the market. Besides salt, other sources of cadmium are cigarette and food (Starug, 2012). Cadmium, lead and mercury are reported in cereal samples, mainly rice grains, in several countries, due to water and soil contamination by pollution (Chamannejadian et al, 2013).
Mercury is one of the most toxic metals and the main route of food exposure is the consumption of freshwater and marine fish and related products (UNEP and WHO, 2008; Višnjevec et al, 2013). The major toxic effects observed on the central nervous system, mainly in the developing human fetus, leading to neuropsychological dysfunctions like impairment of language, attention and memory and to a lesser extent, visuospatial and motor functions (Stern and Smith, 2003; Debes et al, 2006; Grandjean et al, 1997). The effects of low level and mercury exposure of children and adults seems to lead to cardiovascular and immune system harms, although there are no conclusive evidences (Karagas et al, 2012).

Nickel ions are related to intestinal tract, liver and kidneys damages and neurological disorders (Elsagh, 2012; Zemanova et al, 2007). The literature reports up to 1.57 µg/g in salt (Solyak et al, 2008).

Copper, zinc and cobalt are essential ions at low concentrations, but in excessive levels can cause damage mainly to liver and kidneys (Zarei, 2011; Papagiannis et al, 2004). Excessive cobalt levels affect the fetus development and interfere with divalent ions actions as enzyme cofactors (Elsagh, et al 2012; Saulea, 2004). These metals are found in fish and salt. There are no guidelines on acceptable levels of Cu and Zn in fish suggested by FAO/WHO. However, based on the basis of the recommended daily dietary allowances (RDA) for safe consumption of fish muscle is established 50-350 mg of metal per 100 g of fish muscle (Papagiannis et al, 2004). For salt, the maximum permissible concentration is 2.0 µg/g (Codex, 2006). Literature reports concentration of 2.8 µg/g for Cu (Jahed-Kahaniki, 2007), 0.48 µg/g for Co (Solyak et al, 2008) and 6.34 µg/g for Zn in salts (Pourgheysari, 2012).

Mycotoxins are secondary metabolites of fungi that cause major damages to humans and other animals exposed to them. The mycotoxins of public health concern are: aflatoxins, fumonisins, trichothecene and ochratoxin A. Aflatoxins products of Aspergillus flavus and A. parasiticus, appear as contaminants in maize, peanuts, tree nuts, copra, spices and cotton seed (Wu et al 2014). Fumonisines products of Fusarium verticillioides, F. proliferatum and A. niger, contaminate maize (Missmer et al 2006). Trichothecene mycotoxins produced by F. graminearum and F. culmorum, contaminate maize, wheat, barley and oats (Sugita-Konishi and Nakajiima, 2010). Ochratoxin A produced by Penicillium verrucosum, A. ochraceus, A. carbonarius and A. niger contaminates maize, wheat, barley, oats, dried meats and fruits, coffee and wine (Ringot et al. 2006). Many human and animal diseases have been related to contact with mycotoxins, like hepatocellular carcinoma, acute aflatoxicosis, embryonic defects, growth impairment in children, immune system dysfunction and gastroenteritis (Wu et al 2014).
Intentional additives: Food preservatives

The Codex General Standard for Food Additives (CODEX STAN 192-1995) describes the food additives that have been assigned an Acceptable Daily Intake (ADI) or determined, on the basis of other criteria, to be safe by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Table 1 lists the substances described as preservatives by the CODEX.

Table 1. Preservatives and its safe use in foods.

<table>
<thead>
<tr>
<th>Preservative</th>
<th>Used in</th>
<th>Maximum use level (mg/Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid (glacial)</td>
<td>Cheeses, Vegetables (untreated, frozen, fermented), Egg products, Coffee and other grain beverages, Foods for infants and young children (^{(a)})</td>
<td>(a) 5000 Others (-) GMP*</td>
</tr>
<tr>
<td>Benzoates (benzoic acid, Na(^{+}), K(^{+}) and Ca(^{2+}) benzoates)</td>
<td>Foods and beverages based in: fruits, vegetables and cereal starches, Meat, poultry and game products (cured and dried, no heat treated), Fish and other sea food.</td>
<td>200 - 300 (depending on the product).</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>Whey based foods (excluding cheeses) (^{(b)}), Flour (^{(c)}),</td>
<td>(b) 100 (c) 75</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>Xylose, maple syrup and sugar toppings, Foods for infants and young children.</td>
<td>GMP*</td>
</tr>
<tr>
<td>Calcium propionate</td>
<td>Whey protein cheese.</td>
<td>300</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>Fruit juices and nectars.</td>
<td>GMP*</td>
</tr>
<tr>
<td>Dimethyl dicarbonate</td>
<td>Coffee, tea, herbal infusions, hot grain and cereal beverages (excluding cocoa), Wine (grape and others) and mead (^{(d)}), Cider and perry.</td>
<td>(d) 200 Others - 50.</td>
</tr>
</tbody>
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Table 1. Continued

<table>
<thead>
<tr>
<th>Additive</th>
<th>Foods</th>
<th>Use Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylenediamide tetracetates (Ca(^{2+}), Na(^{+}) and 2Na(^{+}))</td>
<td>Fruit based foods (spreads, dried, fermented, jams, jellies), ripe fruits and vegetables,</td>
<td>25 - 1000 (depending on the product).</td>
</tr>
<tr>
<td></td>
<td>Fruit and vegetable filling for pastries, cheese, ripened cheese, jams, jellies,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vegetable based food (frozen, fermented, cooked, fried), awake eggs,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fish and other sea food, Egg products, sausages, salads, food supplements,</td>
<td></td>
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<tr>
<td></td>
<td>table-top sweeteners, No alcoholic beverages (including coffee and tea),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beer, wines, spiruital (more than 15% alcohol), and other alcohol containing beverages.</td>
<td></td>
</tr>
<tr>
<td>Formic acid</td>
<td>Sauces(^{(e)}), Water based flavoured drinks (sport, energy and electrolyte drinks)(^{(f)}),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>((^{(e)}) 200, (^{(f)}) 100)</td>
</tr>
<tr>
<td>Hexamethylene tetramine</td>
<td>Ripened cheese</td>
<td>25</td>
</tr>
<tr>
<td>Hydroxybenzoates para- (ethyl and methyl)</td>
<td>Cheeses and analogs, Fat emulsions,</td>
<td>36 - 1500 (depending on the product).</td>
</tr>
<tr>
<td></td>
<td>Fruit and vegetable based products (cocoa included), Sauces,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vinegars, mustards, Chewing gum, Semi preserved fish and other sea food,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Water based flavoured drinks, coffee and tea, Alcoholic beverages like wine (other than grapes), spiruital and mead,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Snacks - potato, cereal, flour or starch based Processed nuts</td>
<td></td>
</tr>
<tr>
<td>Isopropyl citrates</td>
<td>Vegetable oils and fats, Lard tallow and other animal fats, Fat spreads (^{(g)}), Cured and dried meat, poultry and game products,</td>
<td>100 Others - 200</td>
</tr>
<tr>
<td></td>
<td>Water-based flavoured drinks. The maximum use level is 100 mg/Kg for fat spreads and 200 mg/Kg for the other.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. Continued

<table>
<thead>
<tr>
<th>Substance</th>
<th>Applications</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauric arginate ethyl ester</td>
<td>cheeses, dairy based desserts, fat spreads, dried fruit, fruit filling for pastries, Surface treated, peeled, cut and shredded fresh vegetables, Chewing gum, Cereal and starch products, Egg products, Seasonings, condiments, sauces and dips, Soups, salads, Water based drinks and the concentrates for its preparation (h).</td>
<td>(h) 50 Others - 200</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Ripened cheese (i), Grapes wine, cider and perry.</td>
<td>(i) GMP* others - 500</td>
</tr>
<tr>
<td>Natamycin (Pimaricin)</td>
<td>Cheeses (j), Processed (cured and dried) meat, poultry and game products: comminuted (k) or in whole pieces or cuts (l).</td>
<td>(j) 40 (k) 20 (l) 6</td>
</tr>
<tr>
<td>Nisin</td>
<td>Clotted cream (m), Cheeses (n), Starch based desserts (o).</td>
<td>(m) 10 (n) 12.5 (o) 3</td>
</tr>
<tr>
<td>Ortho-phenylphenols</td>
<td>Surface-treated fresh fruit.</td>
<td>12</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>Complementary foods for infants and young children.</td>
<td>GMP*</td>
</tr>
<tr>
<td>Propionic acid</td>
<td>Whey protein cheese.</td>
<td>300</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>Fermented vegetables, Seaweed products, Pasta and noodles (fresh (p) or dried), Egg products, Salt substitutes, Complementary foods for infants and young children, Coffee, tea, herbal infusions, cereal and grain beverages excluding cocoa.</td>
<td>(p) 6000 Others GMP*</td>
</tr>
<tr>
<td>Sodium propionate</td>
<td>Whey protein cheese.</td>
<td>300</td>
</tr>
<tr>
<td>-------------------</td>
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<td>-----</td>
</tr>
<tr>
<td>Sorbates (sorbic acid, sodium potassium and calcium sorbates)</td>
<td>Dairy based drinks and desserts, Rennented milk, Beverage whiteners, Cheeses, Fat spreads, emulsions and based deserts, Fruit, starch, cereal and vegetable based products (including cocoa), Chewing gum, Pastas and noodles, Egg products, Xylose, maple syrup, sugar toppings, Top table sweeteners, Sauces, seasonings and like products, salads, Soybean based products, Dietetic foods, Fruit juices and nectars, Water based flavoured drinks, Coffee, tea and based products, Cider perry, wine (grapes and other) Mead, Other alcoholic beverages, Snaks-potato, cereal, flour or starch based Processed nuts.</td>
<td>200-2000 (depending on the product).</td>
</tr>
<tr>
<td>Sulfites (sulfur dioxide, sodium sulfite, sodium hydrogen sulfite, sodium metabisulfite, potassium metabisulfite, potassium sulfite, calcium hydrogen sulfite, potassium bisulfite and sodium thiosulfate)</td>
<td>Fruit and vegetable based products, Flour, starches, pastas and noodles, Fish and other sea food products, White sugar, dextrose and fructose related products, Condiments and related products, Fruit and vegetable juice and nectars, wines (grapes and others), mead, alcoholic beverages, Snacks potato, cereal or starch based.</td>
<td>200 – 1000 (depending on the product).</td>
</tr>
</tbody>
</table>

*(GMP – Good manufacturing practice level).*
Preservatives are substances that prevent food spoilage by inhibiting unwanted microbial growth (Lück and Jager, 1997). The CODEX regulates its use only for the food described in the concentrations established. The use of preservatives in foods not mentioned in CODEX list is dependent on the legal authorization by competent authorities taking into account the technological needs and requires adequate toxicological control.

When the Maximum use level was established as GMP (Good manufacturing practice level), is the lowest quantity of the substance to accomplish its desired effect.

**Xenobiotics metabolism**

Depending of their chemical properties, mainly the oil/water partition coefficient, and the capacity to alter pH, the food additives, can cause damages to the gastrointestinal tract or absorbed and added to cells metabolism. Most substances used as food additives are identify as xenobiotics by the cellular metabolism. All cells are prepared to face these substances, but mainly of them are metabolized by the gut and liver. There are at least two metabolic pathways for neutralization and to facilitate the excretion of xenobiotics: the microsomal biotransformation and the complexation with suitable substances, mainly glycolic acid and reduced glutathione (GSH).

The microsomal biotransformation system, located at smooth endoplasmic reticulum, catalyzes the oxidation of substrates by O₂, performed by the cytochrome P450 (CYP) system superfamily. One oxygen atom enters the substrate and the other is reduced to H₂O, for this, a reducing agent is required and in liver is the NADPH, produced mainly by the pentose pathway (Halliwell & Gutteridge, 2007). The overall reaction is described by the equation below, where SH represents the substrate and RH₂ the reducing agent:

\[
\text{SH} + \text{O}_2 + \text{RH}_2 \rightarrow \text{SOH} + \text{R} + \text{H}_2\text{O}
\]

The CYP reaction produces a more water soluble product (SOH) increasing the possibility of excretion. Not always the biotransformation prevents the effects of xenobiotics, sometimes this process maintains or increases the harmfulness. So, the CYP reaction can be deployed multiple times to the same molecule.

Overload of CYP activity may induce electron leaking that reduces O₂ to the radical form O₂⁻ (superoxide radical). This reactive specie can start a cascade of oxidative reactions which leads to cell damage. To face this
situation the cells developed two antioxidant defense systems. The first is the enzymatic formed by the activity of the SOD (superoxide dismutase) enzyme that dismutes $2\text{O}_2^{-}$ to $\text{H}_2\text{O}_2$, and the enzymes that reduces $\text{H}_2\text{O}_2$ and other hydroperoxides. Catalase (CAT) and glutathione peroxidase (GPx) are the main enzymes that reduce $\text{H}_2\text{O}_2$ to water (Gandra et al, 2004).

Catalase has low affinity for $\text{H}_2\text{O}_2$ and reduced it only in high concentrations. To maintain the basal concentrations of hydroperoxides and $\text{H}_2\text{O}_2$ is the task of GPx. This enzyme uses reduced glutathione (GSH) as the reducing agent. This compound deserves further explanation because it importance to the cellular redox maintenance, and will be discussed below. The second line of antioxidant defense is constituted by molecules that are targets for the oxidative species, yielding more stable radicals or termination stable products. Other antioxidants chelate ions of transition metals, thereby inhibiting its action to catalyze the production of reactive species.

The molecular antioxidants have much chemical diversity and have very different origins. Vitamins A and E and carotenoids are lipophilic molecules, and the hydrophilic ascorbic acid (vitamin C), are provided by human diet. Urate and bilirubin are metabolic wastes that act as antioxidants in the plasma. Amino acid residues of proteins that can be dissociated at physiological pH, histidine ($\text{pK}_R = 6.0 \text{– free amino acid}$) and cysteine ($\text{pK}_R = 8.18 \text{– free amino acid}$) are also antioxidant groups. The $\text{–SH}$ groups present mainly in GSH and in the cysteine residues of proteins, can be easy oxidized by the oxidative species and can be reduced by the cellular antioxidant system. Thioredoxin and metallothionein are example of rich $\text{–SH}$ proteins. Determination of the $\text{–SH}/\text{S-S}$ ratio is a suitable tool to evaluate the antioxidant capacity of tissues and biological fluids (Halliwell and Gutteridge, 2007, Gandra et al 2004).

Other molecular antioxidants are the proteins that bind, carry and store ions of transition metals, avoiding their action as catalysts for Fenton reactions. This reactions produce reactive species, mainly the hydroxyl radical ($\text{OH}$). Examples of these proteins are: ferritin, transferrin, haptoglobin, hemopexin and ceruloplasmin.

The DNA repair system and the protein chaperones (HSP - Heat Shock Proteins) due to its ability to prevent damages to DNA and ensure the perfect folding of proteins are considered important part of the antioxidant defense system (Smolka et al 2000). In the literature have been attributed antioxidant properties to other biomolecules like melatonin, melanin and vegetal polyphenols. The latters are considered a significant proportion of antioxidants obtained from the diet (Halliwell and Gutteridge, 2007, Tessutti et al, 2013).
Reduced glutathione (GSH) is a tripeptide (γGlu-Cys-Gly) having antioxidant properties itself, and is the reducing substrate of the enzyme GPx family that detoxifies H₂O₂ and organic peroxides. Cells need to maintain high ratio GSH/GSSG and for this, the main system are the reduction of GSSG by the activity of the glutathione reductase (GR). NADPH, the reducing power used by GR is produced mainly by the pentose phosphate pathway. Diminishment in the activity of the enzyme glucose-6-phosphate dehydrogenase (G6PD) is related to lipid peroxidation in erythrocyte membranes (Alves et al, 2003, Corrêa-da-Silva et al, 2013).

Xenobiotics and their CYP metabolites can suffer complexation reactions to increase water solubility. Glucuronic acid and reduced glutathione (GSH) are the main substances that are used to complex xenobiotics. GSH is the substrate of the glutathione acyl transferase enzyme and the increasing activity induced by xenobiotics of this enzyme reduces the concentration of GSH (Alves et al, 2003).

Therefore, the biotransformation of xenobiotics leads to decrease of antioxidant capacity of cells and tissues. The CYP overload increases the oxidative attack and the complexation decreases GSH concentration that triggers the oxidative stress event (Halliwell and Gutteridge, 2007).

During the oxidative stress there is an increasing of oxidative damage to biological structures like membranes, hemoglobin, mitochondria and lipoproteins. In humans the oxidative stress, depending on its intensity, has been associated to the onset and progression of many diseases such as cancer, atherosclerosis, psoriasis, hypertension, Alzheimer, heart, kidney and liver diseases, and with important physiological processes like adaptation, exercise training and aging (Simonian and Coyle, 1996; Droge, 2002; Tessuti et al, 2013).

**Mitochondrial effects**

Reactive oxygen species (ROS) are generated during mitochondrial oxidative metabolism as well as in cellular response to xenobiotics, as described above. ROS is a collective term that broadly describes O₂-derived free radicals such as superoxide anions (O₂•⁻), hydroxyl radicals (HO•), peroxyl (RO₂•), alkoxyl (RO•), as well as O₂-derived non-radical species such as hydrogen peroxide (H₂O₂) (Halliwell and Cross, 1994). The mitochondrion is a major intracellular source of ROS. Of total mitochondrial O₂ consumed, 2% is diverted to the formation of ROS, mainly at the level of complex I and complex III of the respiratory chain, and is believed to be tissue and species dependent (Ames et al., 1993; Turrens, 2003). Mitochondria- derived O₂•⁻ is dismutated to H₂O₂ by manganese superoxide dismutase, and, in the presence
of metal ions, highly reactive HO• is generated via Fenton and/or Haber-Weiss reactions, inflicting significant damage to cellular proteins, lipids, and DNA (Sutton et al., 1989; Halliwell et al., 1989). Krebs cycle enzyme complexes, such as α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase have been implicated as significant mitochondrial O₂•− and H₂O₂ sources (Starkov et al., 2004). Notably, increased nicotinamide adenine dinucleotide (NADH) is linked to elevated H₂O₂ production by mitochondrial α-KGDH, and this elevated oxidant burden elicits further ROS production from mitochondrial complex I and accelerates cell death (Tretter et al., 2004). Other interesting mitochondrial ROS sources include p66Shc, an intermembrane space enzyme (Migliaccio et al., 2006), and monoamine oxidase, an outer membrane enzyme, and altered mitochondrial membrane potential (Korshunov et al., 1997) or matrix pH (Lambert et al., 2004). As major ROS generators, mitochondria are often targets of high ROS exposure with deleterious consequences, such as oxidative damage to mitochondrial DNA (Circu et al., 2009A). While elevated O₂•− and HO• associated with mtDNA damage have been implicated in cell apoptosis (Ricci et al., 2008), the precise mechanism whereby mtDNA damage mediates apoptotic signaling is incompletely understood and should provide a fruitful avenue for future investigation (Circu et al., 2009B). Cellular ROS sensing and metabolism are tightly regulated by a variety of proteins involved in the redox (reduction/oxidation) mechanism (Ray et al., 2012). Mitochondria have an efficient antioxidant defense system, represented by the enzymes superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, NAD(P)-transidrogenase, and other components such as glutathione (GSH), NADPH, vitamins E and C (Halliwell and Gutteridge, 1989; Vercesi, 1993). Under physiological conditions, the oxidant and antioxidant systems of the organelle are in equilibrium, but under conditions in which an excess of reactive oxygen species is produced and/or the antioxidant defense system is depleted, a state of oxidative stress is generated. When an increase in production of reactive oxygen species occurs, many oxidative changes of components of the mitochondrial membrane can occur, such as lipid peroxidation and oxidation of protein thiols, leading to the inner membrane permeabilization and mitochondrial dysfunction. The mitochondrial dysfunction is related to the diminishment in ATP availability, thereby worsening oxidative stress (Vercesi, 1993).

Conclusion

The use of food additives is essential to increase production and storage time of food, important strategies to face the crescent demand of food
worldwide. Most of these compounds may be toxic to humans and animals and its use needs to be properly controlled. International and national organizations led by FAO and WHO, determine the adequate concentration and in which food can be used each additive. If the use of these compounds is within these determinations, pose no hazard to human and animal health. But, the use of additives in amounts up the established maximum use level or in food not allowed can cause serious damages to human and animal health. Depending of its chemical properties, increasing concentrations of these substances can cause damage to gastrointestinal tract or enter the cells, behaving as xenobiotics. The xenobiotic and the products of its biotransformation process can increase the oxidative attack and decrease the antioxidant capacity of cells and tissues. This situation nominated oxidative stress, alters mainly the mitochondrial function and have been related to the onset and the progression of human and animal diseases.

References


