Journal of Natural Sciences Research
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.3, No.13, 2013
www.iiste.org

The Developmental and Physiological Interactions between Free Radicals and Antioxidant Defense System: Effect of Environmental Pollutants

R.G. Ahmed[1*], S. Incerpi[2], F. Ahmed[3], A. Gaber [1]
1. Division of Anatomy and Embryology, Zoology Department, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt
2. Department of Sciences, University of Roma Tre, Viale G. Marconi, 446, 00146 Roma, Italy
3. Microbiology and Immunology Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
* E-mails of the corresponding author: r_g_a_ahmed@yahoo.com & ahmedragab08@gmail.com

Abstract
This review explores the relation between antioxidant defense system and reactive oxygen species (ROS) during the development and shows the effect of environmental pollutants on this process. In normal state, the decline in levels of free radicals is coupled with increased antioxidant and the reverse is true, but there is a critical balance between them during the development. Also, redox signaling induced by environmental pollutants (stressors) involves both alterations in antioxidant defenses and accumulation of ROS leading to oxidative stress which acts as a critical pathophysiological mechanism. This disturbance has deleterious effect on male/female reproductive functions, on the development of the blastocysts and on the health of the embryos, newborns (perinatal life) and adulthood. Also, this overview shows that sperm, egg, zygote or blastocyst derived during the abnormal production of ROS due to environmental pollutants may result into offspring with high risk of any type of diseases producing developmental delay, embryopathy, teratogenic changes and apoptosis. These early insults may then lead to an increased rate of miscarriage and congenital anomalies depending on free radicals signaling and cell-death pathways. Thus, maintaining the balance between antioxidants and ROS during pregnancy or lactation period may modulate normal fetal/neonates growth and development, and may play an important role in a healthy life for the newborns. However, this argument is still ambiguous because of the difficulties of to what degree oxidants could participate as signaling molecules controlling fundamental and developmentally relevant cellular processes such as proliferation, differentiation, and death.
Keywords: Antioxidants, Reactive Oxygen Species, Development, Environmental Pollutants.

1. Introduction

In mammalian cells, antioxidant defenses consist of enzymatic antioxidants [superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and catalase (CAT) (Ames 1993; Piper 1995; Sardesai 1995; Betteridge 2000; Ahmed 2005 & 2012a; Ferrari *et al.* 2009; Makker *et al.* 2009; Matés *et al.* 2010; Garrel *et al.* 2010; Jain *et al.* 2011; Ahmed *et al.* 2012; Rahman 2012; Al-azzawie *et al.* 2013; Imosemi 2013) and non-enzymatic antioxidants [ascorbic acid (vitamin C), α-tocopherol (vitamin E), total thiol (t-SH), glutathione (GSH), carotenoids, flavonoids, and other antioxidants (Valko *et al.* 2007; Ahmed 2012a; Ahmed *et al*. 2012; Lombardo *et al*. 2013; Neeraj *et al.* 2013; Rossi *et al*. 2013)]. Specifically, enzymatic defenses are responsible for the scavenging of ROS, reactive nitrogen species (RNS), and their intermediates (Mruk *et al.* 2002; Ferrari *et al.* 2009; Makker *et al.* 2009; Garrel *et al.* 2010; Ziech *et al.* 2010; Ahmed 2012a; Ahmed *et al.* 2012; Petrulea *et al.* 2012; Rahman 2012; Kalyanaraman *et al.* 2012; Al-azzawie *et al.* 2013; El-Bahr 2013; Imosemi 2013; Neeraj *et al.* 2013; Poljšak and Milisav 2013).

Life on earth depends upon oxygen as the final acceptor of electrons in mitochondrial electron transport (Phillips 2003), but the process also generates toxic metabolites (Ahmed 2012a; Ahmed *et al*. 2012; Al-azzawie *et al.* 2013). ROS leak from mitochondria into the cytoplasm and nucleus where they cause cellular damage by oxidizing DNA, proteins, lipids, and carbohydrates (Mena *et al.* 2009; Garrel *et al.* 2010; Jain *et al.* 2011; Lushchak 2011; Small *et al.* 2012; El-Bahr 2013; Treidel *et al.* 2013). However, ROS/RNS are known to act as secondary messengers controlling normal physiological functions of the organism and therefore the production of nitric oxide ($NO^{\bullet}$) by nitric oxide synthase (NOS) and superoxide by nicotinamide adenine dinucleotide (phosphate) hydrogen (NAD(P)H) oxidase is tightly regulated by hormones, cytokines, and other mechanisms (Dröge 2002; Incerpi *et al.* 2007; Valko *et al.* 2007; De Vito *et al*. 2010 & 2013). This regulation involves signal transduction pathways regulating gene expression, cell replication, differentiation, and apoptotic cell death (Sen & Packer 1996; Suzuki *et al.* 1997; Finkel 1998; Andrieu-Abadie *et al.* 2001; Mena *et al.* 2009; Garrel *et al.* 2010; Lushchak 2011; Ahmed *et al*. 2012; Roopha & Latha 2013). In general, oxidative stress (OS) can be caused by excessive stimulation of NAD(P)H by cytokines, or by the mitochondrial electron transport chain and xanthine oxidase (Rizzo *et al.* 2007).

Many molecules relevant for development are sensitive to the action of ROS (Kheirat *et al.* 2013). Al-Gubory *et al.* (2010) recorded that ROS and antioxidants have been implicated in the regulation of reproductive processes (cyclic luteal and endometrial changes, follicular development, ovulation, fertilization, embryogenesis, embryonic implantation, and placental differentiation and growth) in both animal and human. Imbalances between ROS production and antioxidant systems induce OS that negatively impacts reproductive processes. Interestingly, the amount of ROS produced by embryos varies with the stage of development (Nasr-Esfahani *et al.* 1991; Favetta *et al.* 2007; Ahmed 2012a; Ahmed *et al*. 2012; Roopha & Latha 2013) and increases when embryos are produced *in vitro* compared to those derived *in vivo* (Goto *et al.* 1993). Moreover, Saker *et al.* (2008) and Ahmed (2012a) hypothesized that high levels of ROS during embryonic, fetal and placental development are a feature of pregnancy. In addition, oxygen radicals together with nitric oxide may regulate the circulation, energy metabolism, and the reproduction and remodelling of cells during the embryonic development (Rizzo *et al.* 2007; Ufer & Wang 2011; Ahmed 2012a; Ahmed *et al*. 2012).

However, how ROS may affect growth and differentiation of mammalian cell? Another question is how to protect the embryo from free radical damage, as exposure of early embryos to environmental oxygen concentrations? The answer to these questions is not known but some observations suggest that it is possible. Thus, we here review some of the interesting features about the interactions between antioxidants and ROS during development in different mammalian animal or species. We first present a concise introduction on ROS, antioxidants and then on different developmental periods, pregnancy outcomes and show the effect of different environmental pollutants to enable the reader to follow what is presently known on the interactions between them. There is a significant body of literature on some of the aspects considered in this review, but we will rather select reviews and more relevant articles when reporting on subjects not directly related to the main topic.

2. Oxidative Stress

OS is an imbalance between oxidants and antioxidants resulting from increased generation of oxidants and/or reduction in the amounts of antioxidants (Ahmed 2005; Ma 2009; Limón-Pacheco & Gonsebat 2009; Makker *et al.* 2009; Mena *et al.* 2009; Ahmed *et al*. 2012; Petrulea *et al.* 2012; Al-azzawie *et al.* 2013; Poljšak and Milisav 2013). OS includes a broad diversity of physiological and pathophysiological, endogenous and exogenous processes that affect the cellular oxidant/antioxidant balance (El-Bahr 2013; Treidel *et al.* 2013). We can take as an example the case of metal-induced oxidative damage (Limón-Pacheco & Gonsebat 2009; Ma 2009; Ahmed 2012a; Ahmed *et al*. 2012). Toxic metals, such as cadmium and chromium, induce OS in a variety of target cells via numerous actions that include directly damaging mitochondrial respiration, increased ROS generation via the Fenton reaction, lipid peroxidation (LPO), and reduction of intracellular antioxidants, such as GSH (Kasprzak 2002; Valko *et al.* 2005; He *et al.* 2007 & 2008; Ahmed 2012a,b). Several investigators (Mena *et al.* 2009; Lushchak 2011; Ahmed 2012a; Al-azzawie *et al.* 2013) undertook that OS within a physiological range is necessary for proliferative stimulation and perhaps the removal of aged cellular components while extensive OS damages the structure and function of tissues. Consequences of OS consist of modifications of cellular proteins, lipids, and DNA (Ahmed *et al*. 2012; Al-azzawie *et al.* 2013; Treidel *et al.* 2013). Modification of proteins, in turn, leads to the formation of carbonyl derivatives by direct oxidation of certain amino acid side chains and oxidation-induced peptide cleavage (Stadtman 1992), as well as modification of lipids leading to LPO (Mena *et al.* 2009; Ahmed *et al*. 2012; El-Bahr 2013). The hydroxyl radical ($^{\bullet}OH$) is the main player in oxidative DNA damage, changing purine and pyrimidine bases and deoxyribose sugar as well as cleaving the phosphodiester DNA backbone to give rise to DNA strand breaks (Ma 2009). Mitochondrial DNA is more sensitive to OS than nuclear DNA because of its proximity to the main source of ROS and a limited DNA repair capacity. Damaged mitochondria produce more ROS and set in motion a vicious cycle in which increasing DNA damage results in increased ROS production that in turn leads to more DNA damage (Mena *et al.* 2009). This vicious nature of oxidative damage may clarify in part why OS is usually associated with chronic diseases, such as neurodegeneration, chronic inflammatory disorders and various cancers.

3. Reactive Oxygen Species And Reactive Nitrogen Species: An Overview

ROS consist of a multiplicity of oxygen-derived small reactive molecules with diverse structures, including oxygen radicals, such as superoxide ($O_2^{\bullet-}$), $^{\bullet}OH$, peroxyl radical ($RO_2^{\bullet}$), and alkoxyl radical ($RO^{\bullet}$), and certain non radicals that are either oxidizing agents and/or are easily converted into radicals, such as hypochlorous acid ($HOCl^{-}$), ozone (O_3), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2) (Table 1). Some of these species, such as $O_2^{\bullet-}$ and $^{\bullet}OH$ radicals, are very unstable, whereas others, like H_2O_2, are relatively stable and freely diffusible (Ma 2009; Mena *et al.* 2009; Jain *et al.* 2011; Lushchak, 2011; Ahmed 2012a; Ahmed *et al*. 2012; Won *et al.* 2012; Al-azzawie *et al.* 2013; El-Bahr 2013; Kheirat *et al.* 2013; Treidel *et al.* 2013). $NO^{\bullet}$ and the strong oxidant peroxynitrite anion ($ONOO^{-}$) are known RNS. Wright *et al.* (2010) reported that $NO^{\bullet}$ acts in part by limiting inflammatory cell recruitment in the newborn lung. Furthermore, ROS and RNS play important roles in many

physiological processes, and are not only noxious byproducts of metabolism (Dröge 2002; Incerpi *et al.* 2007). ROS can be produced in several compartments and by multiple enzymes in cells (Ahmed *et al*. 2012; Treidel *et al.* 2013). In fact, most, if not all, enzymes that are capable of metabolizing oxygen are also capable of producing ROS (Ma 2009; Ahmed 2012a,b). Mitochondria consume about 90% of the body's oxygen to produce adenosine triphosphate (ATP) by oxidative phosphorylation. *In vitro* data show that 1–2% of the oxygen molecules consumed are converted to $O_2^{\bullet-}$ in mitochondria (Boveris & Chance 1973; Mena *et al.* 2009). Although *in vivo* rate of mitochondrial superoxide production is probable to be much less than this number, the majority of intracellular ROS can be returned to mitochondria (Staniek & Nohl 2000; St-Pierre *et al.* 2002; Won *et al.* 2012). Oxidative phosphorylation in mitochondria utilizes controlled oxidation of nicotinamide adenine dinucleotide hydrogen (NADH) to produce a potential energy from proton gradient across the mitochondrial inner membrane. The energy is then used to phosphorylate adenosine diphosphate (ADP) to ATP. Electrons resulting from NADH, along the respiratory chain, can directly react with oxygen and produce free radicals (Ma 2009). Productions of $O_2^{\bullet-}$ in mitochondria detected mainly in complex I (NADH dehydrogenase) and complex III (ubiquinone cytochrome c reductase), with the latter being the main site of ROS generation under normal metabolic events (Turrens 1997; Mena *et al.* 2009; Won *et al.* 2012).

Other enzymes related to OS are the expanding family of ROS-producing NADPH oxidases (NOXs), such as NOX1, NOX2, NOX3, NOX4, NOX5, and thyroid oxidases (DUOX1 and DUOX2) (Bedard & Krause 2007). Furthermore, Ma (2009) reported that NOX2 (gp91phox) is the prototype of NOX enzymes and is present mostly in neutrophils and other phagocytic cells. $O_2^{\bullet-}$ produced by NOX2 are critical in defense against microbes. Baehner & Nathan (1967) speculated that loss of the function of the NOX2 system is critical for chronic granulomatous disease, a human genetic disorder characterized by decreased bactericidal capability of phagocytes. Non-phagocytic NOXs produce $O_2^{\bullet-}$ and other radicals that may activate the cellular transformation or replicative senescence (Bedard & Krause 2007). These observations support the concept that, in addition to stochastically damaging macromolecules, ROS are used in normal cellular signaling and homeostasis (Mena *et al.* 2009). Additional sources of cytoplasmic ROS generation include cytochrome P450s, lipoxygenases, and one-electron reduction of quinones by NADPH: cytochrome P450 reductase. In this latter case, semiquinone radicals ($Q^{\bullet-}$) generated by enzymatic one-electron reduction cycle back to quinones and, at the same time, pass electrons to O_2 leading to the formation of $O_2^{\bullet-}$ radical. This futile cycling between quinone and semiquinone radical with concomitant generation of ROS contribute to the toxicities of several chemicals that have quinone moieties, such as doxorubicin and menadione (Enster1986; O'Brien 1991). Generally, ROS can be inactivated by other enzymes such as xanthine oxidase, cyclo-oxygenases, and lipoxygenases, CAT, SOD, GPx, but also other molecules may act as ROS scavenger such as peroxiredoxin (Prx) and thioredoxin (Trx).

4. Antioxidant Defense System: An Overview

The cellular redox status and antioxidant defense mechanisms are more sensitive and lower in the embryo compared to adults (Wells *et al.* 2009; Badham &Winn 2010; Davis & Auten 2010; Garrel *et al.* 2010; Ahmed *et al*. 2012; Imosemi 2013). Antioxidant defense mechanisms against free radical-induced oxidative damage include the following (Table 2): **(i)** catalytic removal of free radicals and reactive species by factors such as CAT, SOD, peroxidase and thiol-specific antioxidants; **(ii)** binding of proteins (e.g., transferrin, metallothionein, haptoglobins, caeruloplasmin) to pro-oxidant metal ions, such as iron and copper; **(iii)** protection against macromolecular damage by proteins such as stress or heat shock proteins; and **(iv)** reduction of free radicals by electron donors, such as GSH, vitamin E, vitamin C, bilirubin and uric acid (Halliwell & Gutteridge 1999; Ferrari *et al.* 2009; Garrel *et al.* 2010; Matés *et al.* 2010; Halliwell 2011; Ahmed 2012a; Ahmed *et al*. 2012; Rahman 2012). CATs, in animals, are heme-containing enzymes that convert H_2O_2 to water and O_2, and they are largely localized in subcellular organelles such as peroxisomes (Limón-Pacheco & Gonsebatt 2009; Ferrari *et al.* 2009; Ahmed *et al*. 2012). Mitochondria and the endoplasmic reticulum have little amount of CAT, thus, intracellular H_2O_2 cannot be eliminated unless it diffuses to the peroxisomes (Halliwell & Gutteridge 1999; Ahmed 2005; Halliwell 2011). On the other hand, several investigators (Biswas *et al.* 2009; Ferrari *et al.* 2009; Ahmed *et al*. 2012; Imosemi 2013; Neeraj *et al.* 2013) reported that GPx can remove H_2O_2 by coupling its reduction with the oxidation of GSH and it can also reduce other peroxides, such as fatty acid hydroperoxides. Limón-Pacheco & Gonsebatt (2009) detected these enzymes in the cytoplasm at millimolar concentrations and also in the mitochondrial matrix. Also, Kim *et al.* (2011) reported that SODs are metal-containing proteins that catalyze the scavenging of superoxide anion, generating hydrogen peroxide as a final product of the dismutation. Two SOD enzymes are found in the cell: SOD1 (Cu/ZnSOD) is a copper- and zinc-containing enzyme primarily localized in the cytoplasm and SOD2 (MnSOD) is a manganese-dependent enzyme in the mitochondrial matrix (Ahmed, 2005). SOD catalyzes the conversion of $O_2^{\bullet-}$ to H_2O_2, whereas CAT and GPx convert H_2O_2 to H_2O (Ma 2009; Ahmed *et al*. 2012). In addition, there is a new family of peroxide scavengers termed Prxs (Chae *et al.* 1999). Prxs can reduce peroxides in the presence of Trxs (Ahmed *et al.* 2006). Myeloperoxidase is present in the

granules of neutrophils and catalyzes the conversion of H_2O_2 and Cl^- to more reactive $HOCl^-$, which is critical for the bactericidal activity of neutrophils (Ma 2009). Importantly, Zhuang *et al.* (2010) hypothesized that Heme oxygenase (HO-1) is required for mouse postnatal lung alveolar development and that vascular expression of HO-1 is essential and protective during postnatal alveolar development.

Table 1. Overview about the molecules mediating oxidative stress and cell damage.

Name	Structure	Main reactions	Cell components attacked by ROS	References
Superoxide	$^{\bullet}O–O^-$	Catalysis of Haber–Weiß reaction by recycling ferrous and copper ions; formation of H_2O_2 or peroxynitrite.	Lipids: peroxidation of unsaturated fatty acids in cell membranes. - Oxidizing DNA or proteins.	Sies (1997), Sorg (2004), Ahmed (2012a) and Won *et al.* (2012)
Singlet oxygen	O=O	Reaction with double bonds, formation of peroxides; decomposition of amino acids and nucleotides.	Nucleic acids: base hydroxylation, cross-linkage, DNA strand scission.	Sorg (2004) and Mena *et al.* (2009)
Ozone	$^-O–O^+=O$	Oxidation of all kinds of biomolecules, especially those containing double bonds; formation of ozonides and cytotoxic aldehydes.	Oxidation of proteins, membrane lipids and DNA.	Löffler & Petrides (1988), Kanofsky (1989), Halliwell & Gutteridge (1999), Mathews-Roth (2000) and Halliwell (2011)
Hydroxyl radical	$^{\bullet}OH$	Hydrogen abstraction; production of free radicals and lipid peroxides; oxidation of thiols.	Inhibition of protein, nucleotide, fatty acid biosynthesis.	Taira *et al.* (1992) and Tyrrell (1995)
Hydrogen peroxide	HO–OH	Formation of $^{\bullet}OH$; enzyme inactivation; oxidation of biomolecules.	Proteins oxidation of sulfhydryl-containing enzymes (enzymes inactivation, DNA oxidation or LPO.	Sies (1997), Halliwell & Gutteridge (1999) and Halliwell (2011)
Nitric oxide	$^{\bullet}N=O$	Formation of peroxynitrite; reaction with other radicals.	Lipid, protein and DNA oxidation.	Dawson & Dawson (1996) and Halliwell & Gutteridge (1999)
Peroxynitrite	$O=N–O–O^-$	Formation of $^{\bullet}OH$; oxidation of thiols and aromatic groups; conversion of xanthine dehydrogenase to xanthine oxidase; oxidation of biomolecules.	Membrane-LPO, DNA damage and apoptosis and protein oxidation.	Pryor & Squadrito (1995), Squadrito & Pryor (1995) and Halliwell & Gutteridge (1999)
Hypochlorite	ClO^-	Oxidation of amino and sulphur-containing groups; formation of chlorine.	LPO, or oxidizing DNA or proteins.	Sies (1997), Halliwell & Gutteridge (1999), Klebanoff (1999) and Winterbourn *et al.* (2000)
Peroxyl radical	$R–O–O^{\bullet}$	Hydrogen abstraction; formation of radicals; decomposition of lipids and other biomolecules.	Carbohydrates depolymerization of polysaccharides.	Sorg (2004) and Ahmed (2005)
Hydroperoxide	R–O–OH	Oxidation of biomolecules; disruption of biological membranes.	Oxidation of proteins, membrane lipids and DNA by the peroxide ions.	Löffler & Petrides (1988) and Sorg (2004)
Copper and iron ions	Cu^{2+}, Fe^{3+}	Formation of $^{\bullet}OH$ by Fenton and Haber–Weiß reactions.	LPO, or oxidizing DNA or proteins.	Sies (1997) and Sorg (2004)

Table 2. Overview of endogenous antioxidants (Sorg 2004).

Antioxidant	Phase	Action
SOD	Hydrophilic	- Dismutation of O_2^- into H_2O_2 and O_2.
CAT	Hydrophilic	- Dismutation of H_2O_2 into H_2O and O_2.
GPx	Hydrophilic or lipophilic	- Reduction of R–OOH into R–OH.
GR	Hydrophilic	- Reduction of oxidized glutathione (GSSG).
GST	Hydrophilic	- Conjugation of R–OOH to GSH (→GS–OR).
Metallothioneins	Hydrophilic	- Binding to transition metals (= neutralisation).
Trxs	Hydrophilic	- Reduction of dithio acid (R-S-S-R) into thiol acid (R-SH).
GSH	Hydrophilic	- Reduction of R–S–S–R into R–SH. - Free radical scavenger. - Cofactor of GPx and GST.
Ubiquinol	Lipophilic	- Free radical scavenger (prevents LPO).
(Dihydro)lipoic acid	Amphiphilic	- ROS scavenger. - Increases antioxidant and phase II enzymes.
Ascorbic acid	Hydrophilic	-Free radical scavenger. -Recycles vitamin E. -Maintains enzymes in their reduced state.
Retinoids (vitamin A) and carotenoids	Lipophilic	-Free radical scavengers. - $^1O_2$ quencher.
Tocopherols	Lipophilic	-Free radical scavenger (prevents LPO). -Increases selenium absorption.
Selenium	Amphiphilic	- Constituent of GPx and Trxs.

On the other hand, nonenzymatic antioxidant molecules include vitamin E, vitamin A, vitamin C, GSH, estrogens, creatine (a nitrogenous compound), xanthophylls (yellow pigments related to carotene), flavonoids (aromatic oxygen heterocyclic compounds that are widely distributed in higher plants) (Rossi *et al*. 2013; Lombardo *et al.* 2013), metallothionein (cadmium-binding protein involved in heavy metal detoxification), taurine (an aminosulfonic acid) and its precursors, and other thiols, such as nonstructural polyunsaturated lipids (Van Poppel & van den Berg 1997; Lee 1999; Ahmed 2012a). For instance, lipid-soluble vitamin E and carotene may inhibit the oxidation of low-density lipoprotein (LDL) (Li *et al.* 1996), which can lead to cardiovascular diseases, atherosclerosis and cancer (Traber & Packer 1995). Vitamin E has also been shown to regulate signal transduction actions (Brigelius-Flohe & Traber 1999; Gopalakrishna & Jaken 2000; Ahmed 2012a), and contribute to spermatogenesis (Bensoussan *et al.* 1998). Bensoussan *et al.* (1998) speculated that vitamin E-deficient rats exhibited abnormal spermatogenesis with spermatids being the most advanced cell type presents. Generally, the antioxidants play an important role in the development of most biological systems, particularly cerebellum (Ahmed *et al.* 2012; Imosemi 2013) and cerebrum (Ahmed *et al.* 2012). However, the mechanism(s) by which other antioxidant molecules function in protecting cells from ROS- and RNS-induced damage is not completely recognized. Thus, the normal expressions and maturations of several antioxidant systems were summarized in table 3.

Table 3. Maturation of antioxidant system

Expression of antioxidants	Species	References
- The antioxidant defense mechanism is gradually developing with the advancement of pregnancy.	Rat	Zaken *et al.* (2000) and Ornoy *et al.* (2009)
- An abrupt drop in SOD activity at the perihatching stage.	Chick	Thomas *et al.* (1997)
- Marked expression vitamin E in the development of placental labyrinth trophoblast (throughout pregnancy).	Human	Jishage *et al.* (2001)
- Total antioxidant activity and CAT activity peaked in the brain, liver, heart muscle, skeletal muscle, kidneys, and blood serum at days 14 - 30 of development.	Rat newborns	L'vova & Abaeva (1996)
- Total SOD decreased on day 6, increased again on 10 day old, and remained constant thereafter. - Cu/ZnSOD levels were low at birth and reached adult levels on the 10th day after birth.		Shivakumar *et al.* (1991)

- SOD and Prxs are particularly abundant in oocytes and early embryos.	Human		Guérin *et al.* (2001) and Donnay & Knoops (2007)
- Obvious expression of GSH and its synthesizing enzymes, Cu/ZnSOD, MnSOD, and GPx in the oocyte and early embryo.			Guérin *et al.* (2001)
- Marked expression of GST at very early stages of embryonic development.	Toad		Anguiano (2001)
- Increased GPx in brain during the second half of the in ovo incubation period.	Embryonic chick		Wilson *et al.* (1992)
- Increased GSH during the first divisions of oocyte.	Human		Gardiner & Reed (1994)
- Increased GPx and CAT in liver during the final week before birth.	Both birds and mammals		Rickett & Kelly (1990) and Wilson *et al.* (1992)
- Decreased GPx and CAT in brain from gestation day (GD) 19 into postnatal day (PND) 2.	Rat		Del Maestro & McDonald (1987)
- The specific activity of GPx doubles and that of CAT falls 4-folds in brain during the final 2 weeks in ovo.	Embryonic chick		Wilson *et al.* (1992)
- Obvious expression of Cu/ZnSOD in late gestational and neonatal periods.	Rat		Del Maestro & McDonald (1987)
- Marked expression of MnSOD in embryonic brain.	Chick		Wilson *et al.* (1992)
- SOD is maintained at constant level during days 45-60 of gestation.	Guinea pig		Mishra & Delivoria-Papadropoulos (1988)
- Increased CAT, SOD and GPx during the course of egg and embryonic development.	Prawn *M. malcolmsonii*		Arun & Subramanian (1998)
- Increased SOD and whole body CAT and GPx in embryo.	Turbot *Scophthalmus maximus*		Peters & Livingstone (1996) and Livingstone (2001)
- Increased Cu/ZnSOD and GPx-1.	During pulmonary ontogenesis	Mouse	de Haan *et al.* (1994)
- Increased glucose-6-phosphate dehydrogenase (G6PDH), MnSOD, Cu/ZnSOD, CAT, and GPx.		Rat	Tanswell & Freeman (1984), Hass & Massaro (1987) and Hayashibe *et al.* (1990)
- Increased SOD, CAT, GPx, and decreased Cu/ZnSOD.		Guinea pig	Sosenko & Frank (1987), Rickett & Kelly (1990) and Yuan *et al.* (1996)
- Increased SODs (MnSOD, Cu/ZnSOD).		Human	Autor *et al.* (1976)
- GPx and Cu/Zn SOD are highly expressed in metabolically active tissues during embryogenesis.	Mouse		Baek *et al.* (2005), Schneider *et al.* (2006), Lee *et al.* (2008a) and Yon *et al.* (2008)
- Obvious expression of cytosolic Cu/ZnSOD and of Mn-SOD in germ cells of the testis.	Rat		Bauché *et al.* (1994) and Fujii *et al.* (2003)
- Marked expression of SODs, CAT and GPx in Leydig, peritubular myoid, and Sertoli cells.			Bauché *et al.* (1994) and Luo *et al.* (2006)
	Guinea pig		Kukucka & Misra (1993)
- Obvious expression of ascorbic acid content in the testes during the developmental phases.	human		Mukkadam (1980)
- An increasing trend of α-tocopherol, ascorbic acid, bilirubin, and GSH with gestational progress.	Human placental brush-border membrane (BBM)		Sen & Mukherjea (1998) and Qanungo *et al.* (1999)
- Marked expression of SOD, CAT, GPx and GR in term placental BBM and umbilical cord (UC) blood.	Human		Qanungo *et al.* (1999)
- High plasma ascorbate levels, and low total plasma antioxidant activity in preterm babies.			Gophinathan *et al.* (1994)
- Low GPx expression in erythrocytes of newborns.			Gross *et al.* (1967) and Whaun & Oski (1970)
- Vitamin E deficiency in the cord blood of full term and premature newborns.			Haga & Lunde (1978)
- Low membrane thiol groups in RBCs of the newborn infant.			Schroter & Bodemann (1970)
- Low GSH levels and SOD in erythrocyte of pregnant women at the third trimester.			Nakai *et al.* (2000) and Arikan *et al.* (2001)
- Obvious expression SOD, CAT and GPx in the lungs during late gestation.	Rabbits		Frank & Groseclose (1984)
- Marked expression of extracellular (EC)-SOD primarily intracellular (cytoplasmic) in newborns.	Human		Nozik-Grayck *et al.* (2000) and Auten *et al.* (2006)
- Increased SOD, CAT, GPx, and GR during gestation period.			Qanungo & Mukherjea (2000)
- High concentrations of the antioxidants taurine and vitamins A and E in fluid from the extra-embryonic			Jauniaux *et al.* (2003)

coelum at 5 weeks' gestation.			
- Increase in expression of CAT, Cu/ZnSOD and MnSOD in placental villi at approximately 12 weeks' gestation in tissue obtained prior to pregnancy termination.			Poston & Raijmakers (2004)
- Increased GR, GST, GPx, SOD, CAT, peroxidase (PO), lactoperoxidase (LP), and polyphenol oxidase (PPO).	In different brain regions with the age progress	Rat	L'vova & Abaeva (1996) and Ahmed (2005 & 2012b)
- Increased vitamin C, vitamin E, t-SH, and GSH.			Shivakumar *et al.* (1991) and Ahmed (2005 & 2012b)
- Increased GR, GST, GPx, SOD, CAT, PO, LP and PPO.		Mice	Hussain *et al.* (1995)
- Increased vitamin C, vitamin E, t-SH and GSH.			
- Fall in MnSOD activity in liver during the first week after hatching.	Chick		DeRosa *et al.* (1980) and Ahmed (2005)
- Obvious expression of GSH in early embryos.	Toad		Betteridge (2000) and Ahmed (2005)
- Marked expression of taurine and hypotaurine in the oviductal fluid.	Sow, goat, rabbit and cow		Lonergan *et al.* (1999)
- Taurine is a major component of the free amino acid pool.	In oviductal fluid	Murine	Dumoulin *et al.* (1992)
	In uterine fluid	Rabbit	Miller & Schultz (1987)
	In oocytes	Murine and rabbit	Schultz *et al.* (1981) and Miller & Schultz (1987)

5. Role Of ROS In Development

There is a clear balance between the functions of ROS and antioxidants to maintain homeostasis throughout development (Covarrubias *et al.* 2008; Ahmed 2012a; Ahmed *et al*. 2012; Kheirat *et al.* 2013). Moreover, Dennery (2010) reported that the disturbance in this balance leads to abnormalities that can have an impact on germ cells, the embryo, and the fetus and can have long-term consequences on the mature organism, depending on the timing of these conditions. Germ cells are particularly sensitive to changes in OS because of the high concentration of polyunsaturated fatty acids in sperm cells makes them highly susceptible to ROS (Kim & Parthasarathy 1998). Interestingly, OS affects multiple physiological processes, from oocyte maturation to fertilization, embryo development and pregnancy (Agarwal *et al.* 2006; Roopha & Latha 2013). Furthermore, human sperm is capable of producing low levels of H_2O_2 and $O_2^{\bullet -}$, which are critical factors to the capacitation process that allows the sperm to penetrate the zona pellucida of the ovum (Kim & Parthasarathy 1998). However, spermatozoa possess little capability to protect themselves against OS and they are susceptible to oxidative DNA damage (Aitken & Baker 2006). Several authors (Mena *et al.* 2009; Dennery 2010; Won *et al.* 2012) reported that the DNA damage occurs at both the mitochondrial and the nuclear levels, thereby impairing mitochondrial biogenesis and changing protein synthesis. This leads to proliferation-impaired embryonic development and/or increased morbidity in the offspring (Baker & Aitken 2005; Ahmed *et al*. 2012; Kheirat *et al.* 2013). When the uteroplacental circulation has been established and the placenta has become the source of nutrition and respiratory exchange, the embryo can better withstand OS because its antioxidant defenses are enhanced (Burton 2009). The level of programmed oxidative tone (redox switching) may change the fate of cells in the embryo toward proliferation, differentiation, apoptosis, or necrosis (Dennery 2010; Ahmed 2012a). A much reduced state results in proliferation, mild oxidation state leads to differentiation and further oxidation state causes cell death (Schafer & Buettner 2001; Lushchak 2011; Ahmed *et al*. 2012). Last, neuronal death, in a chick embryo model, was prevented by antioxidants, but their excessive levels were equally detrimental, suggesting that there is a set point for redox status at vital periods of development and that reductive stress is just as dangerous as OS (Castagne *et al.* 1999). The level of oxygen can also affect the differentiation and growth of the stem cells to a particular phenotype (Powers *et al.* 2008). This is mainly critical in the proliferation of pancreatic β cells, for example (Simmons 2006; Kheirat *et al.* 2013). Overall, these findings have important implications for the developing organism as they revealed that the level of oxidant stress and ROS can deeply influence development (Table 4).

Table 4. The interactions between the reactive oxygen species and development.

Remarks	Functions	Species	References
Presence of $NO^{\bullet}$	It is responsible for the regulation process of the sperm capacitation process.	Mouse	Herrero *et al.* (1997)
Blastocoel fluid contains amounts of H_2O_2 toxic to malignant pretrophectodermal cells.	It is important to the regulation process of blastocyst tissue mass by apoptosis.		Pierce et al. (1991)
Increased $^{\bullet}O_2^-$ levels in peri-implantation blastocyst.	It is required for the blastocyst hatching process.		Thomas *et al.* (1997)
H_2O_2 stimulates uterine contractions.	It is necessary for the peri-partum regulation of prostaglandin production.	Rat	Cherouny *et al.* (1988)
Increased $^{\bullet}O_2^-$ levels in day-5 uterus pregnancy.	It is responsible for the regulation process of vascular permeability at the initiation of implantation.	Mouse	Laloraya *et al.* (1989a,b)
High levels of $^{\bullet}O_2^-$ exhibit marked changes in the uterus during the oestrous cycle.	It is important to the regulation process of uterine oedema and cell proliferation.	Rat	Laloraya *et al.* (1991)
H_2O_2 or $^{\bullet}O_2^-$ reduce oxytocin-induced myometrial contractility.	It is essential to the uterine contraction.	Human	Warren *et al.* (2005)
Increased placenta tumor necrosis factor-α (TNF-α) levels.	It causes preeclampsia.		Wang & Walsh (1996)
Increased plasma leptin levels and placenta leptin mRNA.			Mise *et al.* (1998)
Increased placenta 8-isoprostane levels.			Walsh *et al.* (2000)
Increased placenta $^{\bullet}O_2^-$ concentrations.			Sikkema *et al.* (2001)
Increased placental and decidual protein carbonyl (PCa).			Zusterzeel *et al.* (2001)
Increased plasma PCa and H_2O_2 levels.			Tsukimori *et al.* (2008)
Increased serum and term placenta H_2O_2 levels.			Aris *et al.* (2009)
Increased plasma, UC blood and placental malondialdehyde (MDA) levels.	It causes intra-uterine growth restriction (IUGR).		Biri *et al.* (2007)
Increased serum MDA and 4-hydroxyalkenals concentrations.			Karowicz-Bilinska *et al.* (2007)
Increased plasma ROOH and PCa levels.			Saker *et al.* (2008)
Increased platelet $ONOO^-$ level			Nanetti *et al.* (2008)

6. Summary About The Effect Of Antioxidant System On Different Developmental Stages (Table 5).

Table 5. The interactions between the antioxidant system and development.

Remarks	Functions	Species or culture	References
I- Spermatogenesis			
Increased the GSH concentrations.	It is associated with sperm maturation.	Human	Covarrubias *et al.* (2008)
	It is required for sperm nuclear decondensation and formation of the male pronucleus.	Mammals	Dumollard *et al.* (2009)
Spermatid-specific thioredoxins (Sptrx1) has a distinctive distribution in the fibrous sheath.	It is important to the sperm tail elongation at late spermatogenesis.	Human	Yu *et al.* (2002)
Spermatid-specific thioredoxins (Sptrx3) is localized in the Golgi apparatus.	It is necessary for the spermatogenesis process.		Jimenez *et al.* (2004)
Marked expression of vitamin E.	It regulates the signal transduction events and participates in spermatogenesis.	Rat	Bensoussan *et al.* (1998), Palmer & Paulson (1999) and Gopalakrishna & Jaken (2000)
	It is one of the major membrane protectants against ROS and LPO in testis.	Human	Surai *et al.* (1998) and Akiyama (1999)
	It is important in maintaining the physiological integrity of testis, epididymis and accessory glands, which is critical in spermatoge spermatogenesis and sperm maturation thus improving sperm quality and quantity. It may have effect on sexual function by regulating the secretion of gonadotropin in anterior pituitary, then playing a positive role in promotion of spermatogenesis and semen motility.	Chicken	Cerolini *et al.* (2006)
Lack or deficiency of Vitamin E.	It causes abnormal spermatogenesis.	Both human and animals	Brigelius-Flohe & Traber (1999)
	It may lead to reproductive organ damage, such as degenerative spermatogonium, testicular damage and degeneration of the seminiferous tubules.	Rat	Wu *et al.* (1973) and Wilson *et al.* (2003)
Obvious expression of ascorbic acid.	It is important to the testicular differentiation (antioxidant in semen), integrity and steroidogenic functions and thus protects sperm from oxidative damage.	Rabbit	Luck *et al.* (1995), Salem *et al.* (2001), Castllini *et al.* (2003), Yousef *et al.* (2003) and Yousef (2005)
Marked expression of vitamins C and E.	It ameliorates oxidative stress-related testicular impairments in animal tissues.	Rat	Ghosh *et al.* (2002), Kujo (2004), Thews *et al.* (2005) and Marchlewicz *et al.* (2007)
Deficiency in ascorbic acid and vitamin E.	It results in disturbances in spermatogenesis.	Guinea pigs	Chinoy *et al.* (1986)
		rat	Bensoussan *et al.* (1998)
Vitamin A deficiency.	It results in male infertility due to the degeneration of most germ cells.	Both human and rat	Kim & Wang (1993)
Marked expression of selenoprotein phospholipid hydroperoxide glutathione peroxidase (PHGPx).	It plays a crucial role in mammalian male fertility (reduce the intracellular membrane phospholipid hydroperoxides).	Rat	Godeas *et al.* (1997)
Obvious expression of testicular γ-glutamyl transpeptidase (GGT), a membrane bound enzyme involved in amino acid transport across the plasma membrane.	It is essential to the metabolism of the antioxidant glutathione and, as such, is believed to be fundamental to the protection of cells against oxidative stress through the regulation of glutathione levels in Sertoli cell.		Hanigan & Ricketts (1993), Markey *et al.* (1998) and Ojha *et al.* (2006)
Marked expression of melatonin.	It simulates testis growth.	Mink	Maurel *et al.* (2002)
Obvious expression of taurine, GSH, GPx, CAT, and SOD.	It prevents oxidative damage in spermatozoa.	Bovine	Bucak *et al.* (2010)
Marked expression of hypotaurine and taurine.	It is important to gamete maturation and sperm capacitation, and has protective effects against	Cows and goats	Guérin & Ménézo (1995)

	peroxidative damage.		
II- Oogenesis			
Adequate or increase GSH concentrations.	It is necessary for the viability of oocytes and oocyte maturation.	Mammals	Knappen *et al.* (1999) and Fujii *et al.* (2005)
	It has been reported as a co-factor in thiol-disulfide exchange reactions in eggs and in the protection of protein-thiol groups (-SH).	Sea urchin	Sakia (1967) and Ahmed (2005)
Inhibition of GSH synthesis during oocyte maturation.	It gives rise to one-cell zygotes with one pronucleus and one set of condensed DNA.	Mammals	Perreault *et al.* (1988) and Sutovsky & Schatten (1997)
High SOD activity in growing and ovulated follicles.	It is important to the regulation of follicular development, ovulation and luteal functions.	Rat	Laloraya *et al.* (1989a,b)
Changes in the level of SOD in the uterus during the oestrous cycle.	It is responsible for the regulation of uterine oedema and cell proliferation.		Laloraya *et al.* (1991)
Inhibition of ovulation by SOD in human chorionic gonadotropin (hCG)-treated animals.	It may play role in the concentration of $\dot{O}_2^-$ in the mechanism of gonadotropin-induced ovulation.		Sato *et al.* (1992)
High SOD1 expression and activity in corpus luteum during early pregnancy.	It is necessary for the regulation of luteal function.	Human	Sugino *et al.* (2000)
SOD1-deficient.	It causes that oogenesis halted at the middle of follicle development.	Female mice	Matzuk *et al.* (1998)
Change in activities of SOD1, SOD2, GPX, GR and GST during oestrous cycle.	These effects may be linked to ROS generated in the luteal cells, and may be involved in the inhibition of apoptosis and maintenance of luteal steroidogenesis.	Ovine corpus luteum	Al-Gubory *et al.* (2005)
Enhanced SOD1, GPx and GST activities in corpus luteum during early pregnancy.	It is responsible for the rescue of corpus luteum from apoptosis.	Sheep	Al-Gubory *et al.* (2004)
Enhanced CAT and GPX activities and GSH levels in oviduct during the oestrous cycle.	It is important to the control of H_2O_2 during fertilization.	Cow	Lapointe & Bilodeau (2003)
Marked expression of CAT, Cu/ZnSOD, MnSOD, GPx, and γ-glutamylcysteine synthetase (GCS).	It protects the oocyte against peroxidative damage.	Rabbit	Li *et al.* (1993)
		Human and mice	El Mouatassim *et al.* (1999)
Obvious expression of GPx.	It provides insights on the regulation of ROS in the ovarian maturation process.	Shrimp	Ahmed (2005)
Marked expression of taurine in oviduct fluids.	It is an important protector of cells against accumulation of ROS when they are exposed to aerobic conditions.	Human	Miller & Shultz (1987) and Holmes *et al.* (1992)
III- Fertilizations, blastogenesis and organogenesis			
SOD1-deficient.	It causes a drastically compromised fertility.	Female mice	Matzuk *et al.* (1998).
Different superoxide scavengers.	It prevents the blastocyst from hatching, supporting the essential role of ROS in this process.	Mouse	Covarrubias *et al.* (2008)
A decline in antioxidant defence (GSH) and elevated oxidation of proteins, lipids, and DNA of mitochondria.	It may cause a decline of mitochondrial function that affects fertilization and development.	Mammals	Tarin (1996)
		Human	Wilding *et al.* (2001)
		Mice	Thouas *et al.* (2005)
Reduction of GSH and NADPH levels to 45%.	It results in an oxidation of the intracellular redox state.		Dumollard *et al.* (2007)
Recovery of GSH after depletion in two-cell and blastocyst-stage embryos.	It plays a protective role for GR in the GSH redox cycle.		Gardiner & Reed (1994)
Reduction in the GSH pool.	It may result in DNA damage, cell cycle, development arrest and increased susceptibility to oxidative damage.		Goto *et al.* (1992)
		Human	Messina & Lawrence (1989)
Marked expression of GSH.	It participates in various critical cellular processes including detoxification and the regulation of cellular proliferation and development.	Toad early embryos	Kosower *et al.* (1969)
		Black Sea animals	Alien & Balin (1989) and Rudneva (1999)
High uterine PO activity at the time of blastocyst attachment.	It is important to the protection process against deleterious H_2O_2 action.	Rat	Baiza-Gutman *et al.* (2000)

High glutathione S-transferase Mu2 (GSTm2) expression in the uterine epithelium.	It is responsible for the uterine preparation for blastocyst implantation.	Mouse	Ni *et al.* (2009)
Marked expression of ascorbic acid.	It plays critical roles in growth and fertility.	Petromyzon marinus	Moreau & Dabrowski (1998)
Obvious expression of vitamin A (retinol).	It is a fundamental for reproductive and proliferative processes.	Human	Baker *et al.* (2002) and Herrera *et al.* (2004)
	It may have some antioxidant effect by improving blastocyst development morphogenesis and differentiation.	Sheep	Maden (2000) and Livingston *et al.* (2009)
Marked expression of retinoid.	It plays important roles in many diverse biological functions such as cell growth and reproduction.		Livingston *et al.* (2009)
Protein-thiol group oxidation.	It delays cell division and embryonic development.	Mice	Goto *et al.* (1992)
Obvious expression of hypotaurine and taurine.	It is important to fertilization process and has protective effects against peroxidative damage.	Human	Guérin & Ménézo (1995)
Marked expression of hypotaurine.	It is important to the development of *in vitro*-fertilized embryos.	*In vitro* culture (hamster embryo)	Barnett & Bavister (1992)
Obvious expression of mineral element.	It is essential for organogenesis and tissue formation and therefore, their function in pregnancy is fundamental.	Dog	Vannucchi *et al.* (2007)
IV- Embryos and newborns			
Adequate or increase GSH concentrations.	It is associated with embryo maturation.	Human	Fujii *et al.* (2005) and Covarrubias *et al.* (2008)
Increased SOD activity during uterine deciduoma development.	It is responsible for the differentiation and control of decidual cell.	Rat	Devasagayam *et al.* (1990)
Decreased SOD activity and increased lipid peroxide in the endometrium of the late secretory phase.	It is important to endometrium shedding.	Human	Sugino *et al.* (1996)
SOD1 knock-out females exhibit marked increase in post-implantation embryo death.	Oxygen free radicals may cause abnormality of female reproduction in mammals.	Mouse	Ho *et al.* (1998)
Overexpression of CAT and/or SOD2.	It inhibits proliferation of vascular smooth muscle cell.	Human	Brown *et al.* (1999)
		Mice	Shi *et al.* (2004)
Obvious expression CAT, Cu/ZnSOD, MnSOD, GPx, and γ-GCS.	It protects the embryo against peroxidative damage.	Rabbit	Li *et al.* (1993)
		Human and mouse	El Mouatassim *et al.* (1999)
Enhanced CAT, SOD and GPx activities in placental and fetal tissues.	It is responsible for the protection process against ROS toxicity in the feto-placenal system.	Human	Qanungo & Mukherjea (2000)
Enhanced CAT and GPx, acivities, and GSH levels in placental tissue.	It enhances the control of H_2O_2 and stimulates of placental differentiation.		Jauniaux *et al.* (2000)
Enhanced GPx and GR activities.	It controls in the concentration of H_2O_2 and cell death during placental development.	Sheep	Garrel *et al.* (2010)
Early expression of GST isoenzymes in embryonic tissues.	It is important to the detoxification process of toxic compounds.	Human	van Lieshout *et al.* (1998)
A sudden increase of SOD, CAT, GPx, and GST.	It is necessary for the transformation process of embryonic to larval stage.	Larvae of *M. malcolmsonii*.	Arun & Subramanian (1998)
Antioxidants in feto-placental system and UC blood of neonates prevents oxygen damage.	It prevents LPO by trapping the oxygen free radicals and breaking the peroxidation chain reaction.	Human	Qanungo *et al.* (1999)
Deficiency in antioxidant metalloenzyme co-factors; Fe, Cu and Zn.	It leads to severe structural and functional abnormalities.	Chick embryo	Butler (1983)
Marked expression of vitamin A.	It is fundamental for embryo and fetal development.	Human	Baker *et al.* (2002) and Herrera *et al.* (2004)
Obvious expression of vitamin E.	It plays a crucial role in limiting membrane lipid autooxidation by scavenging free radicals or as a structural component of the cell membrane.		Burton *et al.* (1983) and Chow (1991)

Vitamin E deficiency in the cord blood of full term and premature newborns.	It has long been considered the main cause of susceptibility of the newborn erythrocyte to oxygen damage.		Haga & Lunde (1978)
Deficient selenium dependent GSH in newborns.	This susceptibility to oxidative stress presumably has deleterious consequences in cases of inborn error of metabolism.		Tubman *et al.* (1990) and Bracci & Buonocore (1998)
Deficiency in the trace metals selenium, copper and zinc, essential components of the antioxidant enzymes GPx and superoxide dismutase.	It may act in concert with plasma factors to produce the antioxidant handicap of the newborn.		Bracci *et al.* (1988)
Vitamin E-deficient mothers.	Tissues of pups born will be more sensitive to peroxidative damage.	Rat	Schinella *et al.* (1999)
Marked expression of hypotaurine and taurine.	It is important to the early embryonic development and has protective effects against peroxidative damage.	human	Guérin & Ménézo (1995)
Enriching the culture medium with taurine and melatonin.	It improves *in vitro* embryo production efficiency	Buffaloes	Manjunatha *et al.* (2009)
Obvious expression of taurine.	It may protect embryos from high K^+ concentrations in reproductive tract fluids.	mouse	Dumoulin *et al.* (1992)

7. General Diagram About The Interactions Between Antioxidants And ROS In Pregnant Dams And Their Offspring (Figure 1).

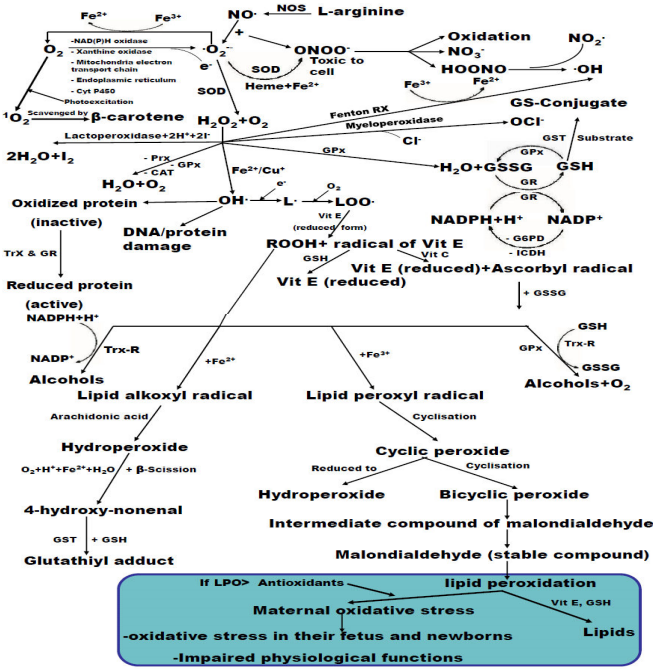

Figure 1. General diagram about the interactions between antioxidants and ROS in pregnant dams and their offspring.

8. Chemical Toxicity Associated With Oxidative Stress During Development

Environmental pollutants, such as compounds used in agriculture or deriving from vehicles, industries and human activities, can represent a major concern for human health since they are considered to be involved in many disease states with major public health significance (Braconi *et al.* 2011; Ahmed 2013). Also, Poljšak *et al.* (2011) reported that free radicals and ROS are involved in toxic mechanisms of action of certain air pollutants, metals, ionizing and nonionizing radiations, alcohols, and pesticides being implicated. A broad variety of pollutants in the aquatic environment have the capacity to give rise to toxic effects expressed as cellular OS (Farmen *et al.* 2010). In animals, the egg and larval stages are the most susceptible to environmental stress (Rudneva 1999; Menon & Rozman 2007). In addition, there were oxidative stress and DNA damage in a mercury exposure workers (Al-azzawie *et al.* 2013). Roopha & Latha (2013) reported that cadmium exposure-induced oxidative stress; delay in sexual maturation and impaired hormones in developing rat ovary. Epidemiological and experimental data indicate that the in utero exposure to environmental chemicals during pregnancy can mediate early embryonic losses, spontaneous abortion, fetal growth retardation and resorptions, decreased litter size, fetal malformations and low birth weight (Bajaj *et al.* 1993; Friedler 1996; Khattak *et al.* 1999; Buczynfiska & Tarkowski 2005), at least in part, via ROS production which damages cellular macromolecules and/or changes signal transduction (Wells *et al.* 2005). The teratogenicity of such chemicals depends upon their bio-activation by cytochrome P450 enzymes, prostaglandin H synthases and lipoxygenases, resulting in ROS-induced OS, and this in turn affects cellular macromolecules, leading to in utero embryonic and fetal death (Wells *et al.* 2005). Several consequences for human and animal reproductive systems are known as these chemicals disrupt endocrine function and contribute to alterations in growth and development (Sanderson 2006). In utero exposure to xenobiotics induces OS and fetal toxicity that may eventually cause cancer later in life (Wan & Winn 2006). Also, Fowler *et al.* (2008) reported that exposure of ovine fetus to prolonged low dose of environmental chemicals adversely affects fetal ovarian development, at least in part, through antioxidative pathways alteration and apoptosis induction. Xenobiotic substances are becoming an increasingly main environmental problem in sewage treatment systems and xenobiotics-enhanced OS may cause birth defects (Wells *et al.* 2009). In addition, Thompson and Bannigan (2008) speculated that environmental heavy metals have the potential to affect reproduction and development at every stage of the reproductive process. Methylmercury (MeHg) is a ubiquitous environmental pollutant to which humans can be exposed by eating contaminated food, particularly through the consumption of fish and fish products (Bourdineaud *et al.* 2008). Grandjean *et al.* (1997) undertook that MeHg has serious adverse effects on the development of the human central nervous system (CNS), particularly when exposure occurs prenatally. Moreover, MeHg is toxic through multiple mechanisms, including ROS formation (Sarafian & Verity 1991; Ali *et al.* 1992; Yee & Choi 1994), likely due to a less efficient ROS detoxifying system and lower activity of mitochondrial enzymes in tissue from young animals (Dreiem *et al.* 2005). Generally, Huang *et al.* (2010) reported that the hatching, survival, growth and antioxidant biomarkers of the flounder embryos and larvae were susceptible to the highest mercury concentrations and could thereby serve as potential biomarkers for evaluating mercury contamination in the aquatic environment. Also, Richetti *et al.* (2011) recorded that mercury chloride may cause a disturbance in the electric signal transmission, through alterations in cholinergic transmission, and also in the antioxidant competence of zebrafish brain tissue. In rat, the fluoride impaired OS and biometal deformations are synergistic that consecutively governs the neuronal damage and developing CNS no longer prevents exacerbations of fluoride (Narayanaswamy & Piler 2010). Prenatal exposure to other heavy metals, especially lead and cadmium, induces OS through impairment of the antioxidant defense systems in the brain, liver and kidney of the developing fetuses (Uzbekov *et al.* 2007; Chater *et al.* 2008a,b). Cadmium-enhanced ROS generation which considerably increased the oxidative products of proteins measured as carbonyls was effectively inhibited by zinc supplementation (Aravind *et al.* 2009; Zhang *et al.* 2011). In pregnant rats and fetuses, cadmium may induce OS in liver, kidney and placental tissues (Enli *et al.* 2010). Cadmium may generate the ROS and carbon-centered radical species by participation of both iron mediation through iron-catalyzed reactions and activation of Kupffer cells, the resident liver macrophages (Liu *et al.* 2008a). Cadmium induces autophagy in skin epidermal cells (Son *et al.* 2011). Also, cadmium initiates the caspase-independent death in mouse mesangial cells (Liu & Templeton 2008). Studies have demonstrated that ROS can induce or mediate the activation of the mitogen-activated protein kinase (MAPK) pathways (McCubrey *et al.* 2006). This mechanism is unclear. Because ROS can alter protein structure and function by modifying critical amino acid residues of proteins (Thannickal & Fanburg 2000), the oxidative modification of signaling proteins by ROS may be one of the plausible mechanisms for the activation of MAPK pathways. However, the precise molecular target(s) of ROS is unknown. The prevention of oxidative stress by antioxidants blocks MAPK activation after cell stimulation with cellular stimuli indicating the involvement of ROS in activation of MAPK pathways. The other observations provide a strong argument for activation of MAPK pathways by direct exposure of cells to exogenous H_2O_2 (Ruffels *et al.* 2004; Son *et al.* 2011). On the other hand, the mechanism of ROS-induced modifications in ion

transport pathways involves the inhibition of membrane-bound regulatory enzymes and modification of the oxidative phosphorylation and ATP levels (Su *et al.* 2007).
In addition, in goldfish, both chromium ions (III and VI) induced OS and affected the activity of antioxidant and associated enzymes (Kubrak *et al.* 2010). Moreover, sublethal waterborne zinc is an oxidative stressor in fish, and emphasizes the vital protective role of higher salinities in ameliorating the OS associated with zinc toxicity in estuarine teleost (Loro *et al.* 2012). Taken together, Kubrak *et al.* (2011) reported that exposure of goldfish to cobalt ions may result in the development of OS and the activation of defense systems. Impaired oxidant/antioxidant status is related to a variety of pregnancy complications, and the lead-induced OS may be one of the underlying mechanism(s) of preterm delivery and highlights the importance of evaluating the impact of persistent environmental pollutants on adverse pregnancy outcome (Ahamed *et al.* 2009). Rodríguez-Estival *et al.* (2011) speculated that certain physiologic disorders, attributed to lead exposure are related to the generation of OS. Collectively, the higher lead and cadmium concentrations in blood cause an increase of SOD activity (Wieloch *et al.* 2012). In rats, fluoride and ethanol exposure induces substantial changes in LPO, antioxidant defense, and morphology of intestine, which may affect its functions (Chauhan *et al.* 2011). Moreover, Hannas *et al.* (2010) demonstrated that nitrite elicits developmental and reproductive toxicity at environmentally relevant concentrations due likely to its intracellular conversion to nitric oxide. A mechanistic study in mice has shown that ROS may play a main role in benzene-mediated fetal hematotoxicity (Wan & Winn 2008; Badham & Winn 2010). Generally, several studies have focused on metal-induced generation of ROS in metal toxicity and carcinogenicity, underscoring the significance of OS in metal action in biological systems (Leonard *et al.* 2004; Valko *et al.* 2005 & 2006; Liu *et al.* 2008b). Metal overload reduces antioxidants in the cell by binding to reduced GSH, metallothioneins and Trxs (Ma 2009). Metal toxicity is related to their oxidative state and reactivity with other compounds (Koivula & Eeva 2010). In general terms, increased levels of antioxidant enzymes, in gill tissues of mussels, at some sites suffering from metal and organic pollution indicated a situation of OS that nevertheless did not appear to be harmful, since LPO levels showed no peroxidative damage (Fernández *et al.* 2010). Interestingly, in growing chicks, environmental intoxication causes an increase of lipoperoxidation and impairs the response of their immunological system (Kamiński *et al.* 2009).
During pregnancy, the contamination by xenooestrogen bisphenol-A (BPA) is confirmed by its presence in urine, blood, amniotic fluid and placental and fetal tissues (Vandenberg *et al.* 2007; Lee *et al.* 2008b). During the embryonic/fetal development, exposure of rodents to BPA induces tissue OS, ultimately resulting in maldevelopment of several organs as brain, kidney and testis (Kabuto *et al.* 2004), disturbances of postnatal reproductive functions (Rubin *et al.* 2001; Hong *et al.* 2005; Markey *et al.* 2005) and behaviorally sex difference (Palanza *et al.* 2008). Also, Gotti *et al.* (2010) reported that the alteration of the neuronal nitric oxide synthase expression may be one of the causes of the important behavioral changes noticed in bisphenol-exposed mice. Several actions have been proposed for the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and its congeners (Safe 1990; DeVito & Birnbaum 1994; Pohjanvirta & Tuomisto 1994; Van den Berg *et al.* 1994), where OS is being considered as one of the important ones (Stohs *et al.* 1990 & 1991). The administration of single acute doses of TCDD to laboratory animals induces the generation of ROS (Bagchi & Stohs 1993; Alsharif *et al.* 1994), LPO (Stohs *et al.* 1983 & 1990) and DNA damage (Wahba *et al.* 1988; Stohs *et al.* 1990), and decreases membrane fluidity (Alsharif *et al.* 1990) and GSH (Stohs *et al.* 1990) in liver and other tissues. These observations have been reported by the study of Slezak *et al.* (1999) who have demonstrated considerable increases in hepatic $O_2^{\bullet-}$ production and LPO as well as significant inhibition of the levels of GSH and α-tocopherol after seven days acute exposure of mice to TCDD. Also, long-term exposure of mice to TCDD leads to the induction of biomarkers of OS, including generation of ROS, LPO and DNA damage in liver and brain tissues (Hassoun *et al.* 1998; Alsharif *et al.* 1999; Tang *et al.* 1999; Slezak *et al.* 1999). Hassoun *et al.* (2000 & 2002) demonstrated that subchronic and chronic exposure of rats to TCDD leads to dose- and time-dependent increases in the production of ROS, LPO, and DNA damage in the whole brain tissue homogenate. TCDD, a potent developmental teratogen (Ahmed 2011) inducing OS and sublethal changes in multiple organs, provokes developmental chicken renal injuries (Lim *et al.* 2008). In rats, Hassoun *et al.* (2000) found that subchronic exposures to TCDD, 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) and 3,3',4,4',5-pentachlorobiphenyl (PCB126) cause a significant oxidative damage in liver and brain tissues, with more damage reported in the brain as compared to the liver tissues. Polychlorinated biphenyls (PCBs) have been shown to produce transient ROS in rat synaptosomes (Voie & Fonnum 2000), liver (Twaroski *et al.* 2001; Tharappel *et al.* 2008), cerebellar granule cells (Mariussen *et al.* 2002) and neutrophils (Narayanan *et al.* 1998). Even though the transduction pathways involved in the elevated ROS production in neurons are not well defined, several studies show that PCB exposure stimulates quick elevations in intracellular Ca^{2+}, suggesting that Ca^{2+}-mediated signaling pathways are potentially involved in neuronal adaptive and toxic responses (Shafer *et al.* 1996; Bemis & Seegal 2000; Inglefield *et al.* 2001; Lee & Opanashuk 2004). Prenatal-stress-induced neuronal damage in offspring is multifactorial, including oxidative damage in the developing brain (Madhyastha *et al.* 2013). In addition,

increasing evidence in animal models links TCDD and benzo[a]pyrene (BAP) with OS, and these compounds are easy to increase cancer risk in certain organs (Kim & Lee 1997; Yoshida & Ogawa 2000; Emre *et al.* 2007). BAP exposure leads to DNA and protein oxidation and alterations in SOD and CAT activities in liver and kidney (Kim & Lee 1997). Furthermore, Emre *et al.* (2007) reported that BAP administration alone, or together with ethanol, induces changes in GSH and MDA levels, and in SOD activity in the lung and brain with varying degrees of histological changes. In animal models, the unfavorable developmental events of in utero exposure to agents like thalidomide, methamphetamine, phenytoin, BAP, and ionizing radiation can be modulated by changing pathways that control the embryonic ROS balance, including enzymes that activate endogenous substrates and xenobiotics to free radical intermediates, antioxidative enzymes that detoxify ROS, and enzymes that repair oxidative DNA damage (Wells *et al.* 2009). Furthermore, Chen *et al.* (2006) observed that increased OS in blood samples from workers exposed to polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. Developmental polybrominated diphenyl ethers (BDE-99) exposure induces OS in the hippocampus of offspring by changing the activity of different antioxidant enzymes and producing free radicals (Cheng *et al.* 2009). Several investigators (KonKim *et al.* 2004; Marczynski *et al.* 2002; Singh *et al.* 2007) also revealed that increased oxidative DNA damage as well as up regulation of genes and proteins involved in OS occurs in individuals exposed to environmental air pollutants such as halogenated aromatic hydrocarbons, dioxins, and particulate matter. Moreover, Cavallo *et al.* (2006) speculated that occupational exposure to halogenated aromatic hydrocarbons has also been linked to oxidative DNA damage.

Pesticides are another example of agents that act as pro-oxidants and elicit actions in various tissues. In some cases, these prooxidant effects occur alongside pesticide-induced changes in target enzymes, many of which share in neurotransmitter metabolism (Limón-Pacheco & Gonsebatt 2009). Pesticide exposure of fish caused increase in MDA and fluctuated antioxidant system along with inhibited acetyl cholinesterase (AChE) (Sharbidre *et al.* 2011). For example, paraquat has been broadly studied as an OS inducer, and paraquat toxicity is thought to mainly result from ROS generation and alterations in redox cycling (Dinis-Oliveira *et al.* 2008). In rats, paraquat induces alterations in antioxidant systems in many tissues (e.g., liver, blood, kidney, lung), and its targets include GSH, GR, CAT, SOD, GPx, and GST (Aoki *et al.* 2002; Tomita *et al.* 2005; Ray *et al.* 2007). Malathion, an organophosphorus compound, is another example of a pesticide that induces OS in rats, resulting in generation of free radicals and changes in antioxidant systems in several organs (Akhgari *et al.* 2003). Also, exposure of laboratory animal to high concentrations of a single heavy metal might lead to its accumulation and potentially, oxidative damage (Halliwell & Gutteridge 1999). Parquet results in two potentially critical consequences relevant to the toxicity (Limón-Pacheco & Gonsebatt 2009): **(i)** production of ROS including $O_2^{\bullet-}$, H_2O_2 and $^{\bullet}OH$, and **(ii)** oxidation and reduction of reducing equivalents (NADPH, GSH, etc); both share in the initiation of OS and damage to the tissue. Arsenic induces a broad diversity of toxic and carcinogenic effects in humans, including cancers in skin, lung, bladder, kidney, and liver. There are reports also of skin lesions, nerve damage and cardiovascular lesions such as atherosclerosis (ATSDR 2007). Furthermore, Arsenic-mediated generation of ROS is a complex process that involves a variety of ROS including $O_2^{\bullet-}$, O_2, $RO_2^{\bullet}$, $NO^{\bullet}$, H_2O_2, dimethylarsinic peroxyl radicals, and the dimethylarsinic radical (Ma 2009). Severe oxidative damage to macromolecules causes cellular death. In addition, methyl parathion (MP), an organophosphate extensively applied in agriculture and aquaculture, mediates OS and alters the antioxidant defense system (Monteiro *et al.* 2009). Also, Stara *et al.* (2012) reported that the prolonged exposure of common carp (*Cyprinus carpio* L.) to simazine, an s-triazine herbicide normally present in aquatic environments, leads to excess of ROS formation resulting in oxidative damage to cell lipids and proteins and also inhibited antioxidant capacities. Several environmental pollutants engage signaling pathways that are activated in response to OS. Also, redox signaling caused by environmental stressors involves both changes in antioxidant defenses (such as decreases in GSH/GSSG ratio) and accumulation of ROS leading to OS (Mena *et al.* 2009). In general, antioxidant enzymes play vital roles in the protection against oxidative damage caused by environmental pollutants by scavenging high levels of ROS and have been quantified as OS markers (Nair *et al.* 2011). OS seems to be the essential aspect in the regulation of the apoptotic pathways triggered by environmental stressors (Franco *et al.* 2009). These biochemical alterations mediate a number of redox dependent processes such as oxidative protein modifications, oxidative DNA damage and changes in mitochondrial function which in turn trigger the activation of specific signaling cascades. These effects are dose- and age-dependent. Also, varying levels of metals and contaminants due to different age, gender, genetic susceptibility, diet were probably the main explanations for the species differences in antioxidant defense. Thus, understanding the pathways resulting in the initiation of antioxidant responses will allow development of strategies to protect against oxidative damage.

9.Diagram Of The Effect Of Environmental Pollutants On The Maternal ROS And Antioxidants During The Development Of Their Offspring (Figure 2)

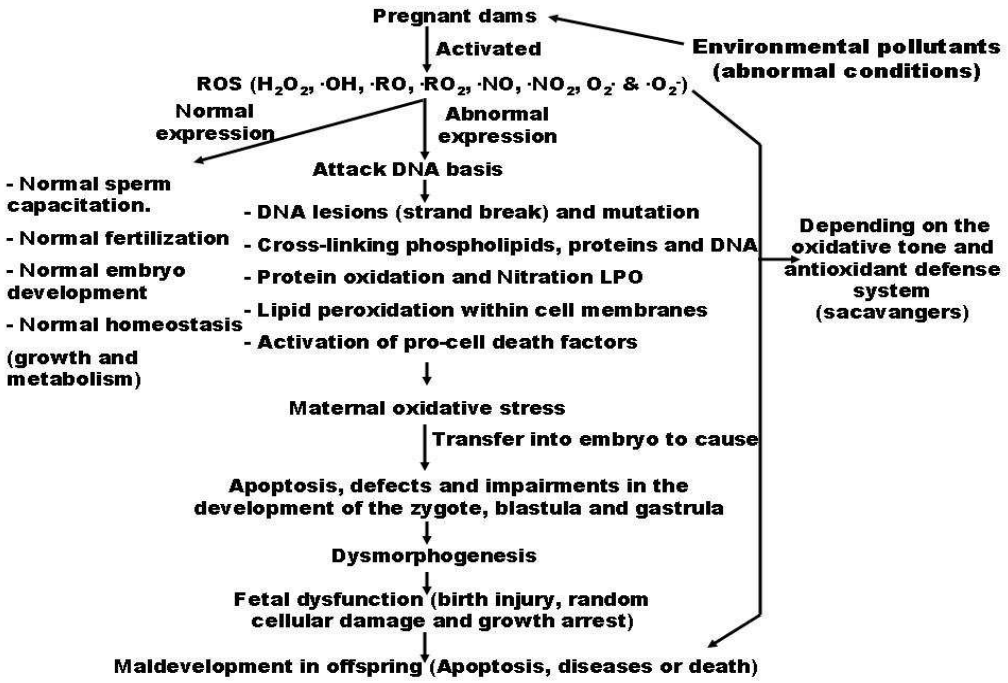

Figure 2. Diagram about the effect of environmental pollutants on both dams and their offspring

10. General Diagram About The Effect Of Environmental Pollutants On The Antioxidant-Reactive Oxygen Species System (Table 6 and Figure 3)

Table 6. Effect of environmental pollutants on the pro-oxidant/anti-oxidant balance in different species.

Environmental pollutants	Effect	Species	Reference
I- Aromatic hydrocarbons			
- TCDD	- It induces ROS and causes apoptosis via the activation of the aryl hydrocarbon receptor (AhR).	Zebra fish	Dong *et al.* (2001)
	- It induces the production of ROS, LPO and DNA damage.	Rat	Stohs *et al.* (1990) and Bagchi & Stohs (1993)
	- It causes a substantial increase in TBARS (thiobarbituric acid reacting substances) production in whole brain.		Hassoun *et al.* (2000 & 2003)
	- It causes a depletion of GSH, and inhibition of GPx activity.		Stohs *et al.* (1984), Hassan *et al.* (1985) and Vuchetich *et al.* (1996)
	- It induces oxidative stress.		Venkataraman *et al.* (2004)
		Bird	Hilscherova *et al.* (2003)
		Fish	Vega-Lopez *et al.* (2006)
		Hatchling chicken (*Gallus domesticus*)	Hilscherova *et al.* (2003)
	- It causes oxidative stress which following the production of reactive	Mice	Schetzer *et al.* (1998)
		Fish	Cantrell *et al.* (1996)

	oxygen species can cause embryolethality and teratogenicity.	Rat	Hassan *et al.* (1985)
	- It causes a significant increase in LPO in liver and adipose tissue on both day 1 and day 40 post-treatment.	Guinea pigs	Ashida *et al.* (1996)
- Dibenzo-p-dioxins (PCDDs)	- It produces ROS that overcome the protection afforded by antioxidant defense mechanisms, thereby leading to oxidative damage which is manifest by damage to tissue macromolecules including DNA, proteins and lipids.	Aquatic animals	Di Giulio *et al.* (1989)
- PCBs	- It decreases vitamin C content in testis.	Rat	Murugesan *et al.* (2005b)
	- It alters membrane bound ATPases and cholinergic function by inducing oxidative stress in different brain regions.		Venkataraman *et al.* (2008)
	- It is responsible for oxidative stress status and teratologic effects in embryos.	Chick	Jin *et al.* (2001)
	- It decreases the concentrations of antioxidant enzymes' activity and increases the concentration of LPO and H_2O_2 generation.	Rat	Muthuvel *et al.* (2006)
	- It induces ROS and oxidative stress.	Bird	Hoffman *et al.* (1996)
		Fish	Ruiz-Leal & George (2004)
- 2,3,7,8-tetrachlorodibenzofuran		Lake Sturgeon *(Acipenser fulvescens)*	Palacea *et al.* (1996)
- PeCDF	- It induces significant oxidative damage in the hepatic and brain tissues.	Rat	Hassoun *et al.* (2000)
- PCB 126	- It causes oxidative stress which is suggested by a similar decrease in GPx activities and increase in the oxidized to GSH ratio and in the LPO.	Birds (American kestrels)	Hoffman *et al.* (1996)
		Chicken eggs	Jin *et al.* (2001)
- PCB (Aroclor 1254)	- It increases H_2O_2 and LPO levels. - It declines the activity of GPx. - It decreases the level of vitamin C content and GSH. - It induces oxidative stress in brain by decreasing the activities of antioxidant enzymes.	Rat	Venkataraman *et al.* (2007)
	- It induces oxidative stress and decreases the activities of antioxidant enzymes in the ventral prostate and testicular Leydig and Sertoli cells.		Krishnamoorthy *et al.* (2005) and Murugesan *et al.* (2005a)
	- It induces cytotoxicity in brain.		Mariussen *et al.* (2002)
- A1242	- It induces production of ROS in a concentration-dependent manner.		
- BAP	- It leads to DNA oxidation, protein oxidation, and alterations in SOD and CAT activities.		Kim & Lee (1997)
- BPA	- It induces tissue oxidative stress, ultimately leading to underdevelopment of the brain, kidney and testis, and to disturbances of postnatal reproductive functions.		Hong *et al.* (2005)
		Mice	Kabuto *et al.* (2004) and Markey *et al.* (2005)

- Naphthalene (NAP)	- It produces $^{\bullet}OH$ and oxidative damage in liver	Freshwater goldfish (*Carassius auratus*)	Shi et al. (2005)
	- It induces LPO and tissue damage.	Mice	Bagchi *et al.* (2002)
	- It produces ROS which may lead to enhanced LPO, enhanced excretion of urinary lipid metabolites, as well as other cell-damaging effects, including membrane and DNA damage and glutathione depletion.	Rat	Vuchetich *et al.* (1996)
	- It results in elevated levels of serum lipid peroxides with a concomitant decrease in GSH levels in lenses, suggesting enhanced LPO.		Yamauchi *et al.* (1986)
	- It induces oxidative stress *in vivo* based on increased hepatic and brain LPO, GSH depletion, increased DNA-single strand breaks and membrane microviscosity, and elevated excretion of the urinary lipid metabolites MDA, formaldehyde, acetaldehyde and acetone.		Vuchetich *et al.* (1996)
	- It induces oxidative stress by producing ROS.	Marine organisms (crab and macroalga)	Collen *et al.* (2003), Lee & Shin (2003) and Vijayavel *et al.* (2004)
- Endrin	- It induces oxidative stress and tissue damage in the liver and brain tissues.	Mice	Bagchi *et al.* (2002)
	- It induces the production of $O_2^{\bullet -}$ by peritoneal macrophages as well as hepatic mitochondria and microsomes.	Rat	Bagchi *et al.* (1993a,b)
II- Pesticides			
- Organophosphorus	- It induces apoptosis in immune and neural cells via the mitochondrial pathway.	Human neuroblastoma cells	Carlson *et al.* (2000)
		Human lymphocytes	Das *et al.* (2006)
	- It causes oxidative attack in spermatozoa, including single- and double-DNA strand breaks, cross-links, chromosomal aberrations and DNA base oxidation.	Human	Hughes *et al.* (1996), Lopes *et al.* (1998), Twigg *et al.* (1998), Banerjee *et al.* (1999) and Ranjbar *et al.* (2002)
	- It induces oxidative stress.	Rat	Debnath & Mandal (2000) and Sharma *et al.* (2005)
- Chlorpyrifos	- It induces caspase dependent apoptosis associated to oxidative stress.	Human monocyte cell line U937	Nakadai *et al.* (2006)
- Dichlorvos		Human T cells	Li *et al.* (2009)
		Rat brain	Kaur *et al.* (2007)
		Mouse retina	Yu *et al.* (2008)
- Dichlorodiphenyldichloroethane (DDT)	- It induces apoptosis via GSH depletion and oxidative stress triggering the intrinsic mitochondrial apoptotic pathway.	Human T-cell leukemic line	Kannan *et al.* (2000)
		Human blood mononuclear cells	Perez-Maldonado *et al.* (2005) and Ahmed *et al.* (2008)
		Rat brain	Kaur *et al.* (2007)
- Endosulfan		Cultured rat Sertoli cells	Song *et al.* (2008)
- Dieldrin			

- Thiram	- It induces GSH depletion which is paralleled by protein carbonylation, LPO and subsequent apoptotic cell death.	Chinese hamster fibroblasts	Grosicka *et al.* (2005)
- Asmancozeb	- It induces oxidative stress, DNA damage and activation of the mitochondrial pathway of apoptosis.	Rat	Calviello *et al.* (2006)
- Piperonyl butoxide (PBO)	- It induces the increase of ROS and oxidative stress.		Muguruma *et al.* (2007)

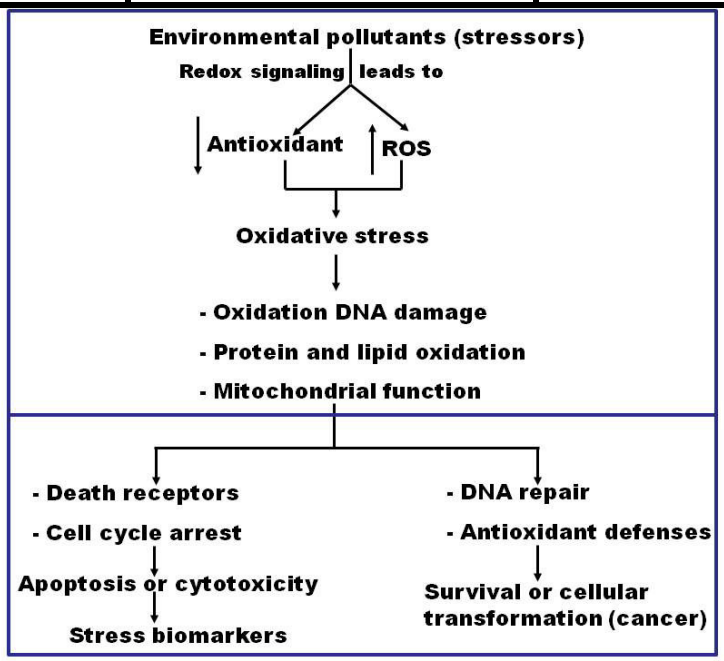

Figure 3. General diagram about the effect of environmental pollutants on the antioxidant-reactive oxygen species system.

11. Abbreviations

$^{\bullet}OH$ = Hydroxyl radical
$^{1}O_2$ = Singlet oxygen
AChE = Acetyl cholinesterase
ADP = Adenosine diphosphate
AhR = Aryl hydrocarbon receptor
ATP = Adenosine triphosphate
BAP = Benzo[a]pyrene
BBM = Brush-border membrane
BDE-99 = Polybrominated diphenyl ethers
BPA = Bisphenol-A
CAT = Catalase
CLO^{-L}= Hypochlorite
CNS = Central nervous system
Cyt P450 = Cytochrome P450
DDT = Dichlorodiphenyldichloroethane
DUOXs = Thyroid oxidases
EC-SOD = Extracellular superoxide dismutase
G6PDH = Glucose-6-phosphate dehydrogenase
GCS = γ-glutamylcysteine synthetase
GD = Gestation day
GGT = γ-glutamyl transpeptidase
GPx = Glutathione peroxidase
GR = Glutathione reductase
GSH = Reduced glutathione

GSSG = Oxidized glutathione
GST = Glutathione-S-transferase
GSTm2 = Glutathione S-transferase Mu2
H_2O_2 = Hydrogen peroxide
hCG = Human chorionic gonadotropin
HO-1 = Heme oxygenase
$HOCl^-$ = Hypochlorous acid
HOONO = Peroxynitrous acid
ICDH = Isocitrate dehydrogenase
IUGR = Intra-uterine growth restriction
$L^\bullet$ = Lipid radical
LDL = Low-density lipoprotein
$LOO^\bullet$ = Lipid peroxy radical
LP = Lactoperoxidase
LPO = Lipid peroxidation
MAPK = Mitogen-activated protein kinase
MDA = Malondialdehyde
MeHg = Methylmercury
MP = Methyl parathion
NADH = Nicotinamide adenine dinucleotide hydrogen
NADP = Nicotinamide adenine dinucleotide phosphate
NADPH = Nicotinamide adenine dinucleotide phosphate hydrogen
NAP = Naphthalene
$NO^\bullet$ = Nitric oxide
$NO_2^\bullet$ = Nitrite radical
NOS = Nitric oxide synthase
NOX = NADPH oxidases
$O_2^{\bullet-}$ = Superoxide
O_3 = Ozone
$ONOO^-$ = Peroxynitrite anion
OS = Oxidative stress
PBO = Piperonyl butoxide
PCa = Protein carbonyl
PCB126 = 3,3',4,4',5-pentachlorobiphenyl
PCBs = Polychlorinated biphenyls
PCDDs = Dibenzo-p-dioxins
PeCDF = 2,3,4,7,8-pentachlorodibenzofuran
PHGPx = Phospholipid hydroperoxide glutathione peroxidase
PND = Postnatal day
PO = Peroxidase
PPO = Polyphenol oxidase
Prx = Peroxiredoxin
$Q^{\bullet-}$ = Semiquinone radicals
RBCs = Red blood cells
RNS = Reactive nitrogen species
$RO^\bullet$ = Alkoxyl radical
$RO_2^\bullet$ = Peroxyl radical
R–O–OH = Hydroperoxide
ROS = Reactive oxygen species
R-SH = Thiol acid
R-S-S-R = Dithio acid
SH = Thiol group
SOD = Superoxide dismutase
Sptrx = Spermatid-specific thioredoxins
TBARS = Thiobarbituric acid reacting substances
TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin
TNF-α = Tumor necrosis factor-α
Trx = Thioredoxins

Trx-R = Thioredoxin reductase
t-SH = Total thiol
UC = Umbilical cord
Vitamin E = α-tocopherol

12. Research Agenda

- Identification of the proteins phosphorylated during sperm capacitation and acrosome reaction as well as proteins that appear to be regulated by a change in sulfhydryl content. These studies should improve the understanding of fertilizing ability by spermatozoa.
- Importance of polymorphisms in the antioxidant pathways for complications of pregnancy.
- The reciprocal regulation of signaling cascades and metabolic pathways during animal development, in which ROS will be a key player.
- The role of epigenetic processes (controlling gene expression) during different developmental periods.
- Understanding of both environmentally induced cytotoxicity/apoptosis and environmentally induced cellular transformation and maternal inflammation during pregnancy is necessary for a complete understanding of the human health consequences to environmental exposures.

13. Disclosure Statement

No actual or potential conflict of interest could inappropriately influence this work.

14. Funding

This work was supported by National Grant from the Research Center, Beni-Suef University, Beni-Suef, Egypt, and from the Italian Ministry for Education, University and Research, General Management for International Research.

15. Acknowledgments

The authors are grateful to Beni-Suef University and Roma Tre University for invaluable help.

16. References

Agarwal, A., Gupta, S., Sikka, S., 2006. The role of free radicals and antioxidants in reproduction. Curr. Opin. Obstet. Gynecol. 18, 325-332.

Ahamed, M., Mehrotra, P.K., Kumar, P., Siddiqui, M.K.J., 2009. Placental lead-induced oxidative stress and preterm delivery. Environ. Toxicol. and Pharmacol. 27(1), 70–74.

Ahmed, O.M., Ahmed, R.G., El-Gareib, A.W., El-Bakry, A.M., Abd El-Tawaba, S.M., 2012. Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: II-The developmental pattern of neurons in relation to oxidative stress and antioxidant defense system. Int. J. Dev. Neurosci. 30, 517–537.

Ahmed, R.G., 2005. Is there a balance between oxidative stress and antioxidant defense system during development? Medical J. of Islamic World Acad. of Sci. 15(2), 55-63.

Ahmed, R.G., 2011. Perinatal 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure alters developmental neuroendocrine system. Food Chem. Toxicol. 49, 1276–1284.

Ahmed, R.G., 2012a. Maternal-newborn thyroid dysfunction. In the Developmental Neuroendocrinology, pp. 1-369. Ed R.G. Ahmed. Germany: LAP LAMBERT Academic Publishing GmbH & Co KG.

Ahmed, R.G., 2012b. Postnatal heat stress and CNS maldevelopment. In the Histopathology and Pathophysiology, pp. 1-381. Ed R.G. Ahmed. Germany: LAP LAMBERT Academic Publishing GmbH & Co KG.

Ahmed, R.G., 2013. Early weaning PCB 95 exposure alters the neonatal endocrine system: thyroid adipokine dysfunction. J. Endocrinology 219(3), 205-15. doi: 10.1530/JOE-13-0302

Ahmed, R.G., Ma, Y.Y., Lee, S.H., 2006. Peroxiredoxins and neurodegeneration. Int. J. Zool. Res. 2(3), 226-241.

Ahmed, T., Tripathi, A.K., Ahmed, R.S., Das, S., Suke, S.G., Pathak, R., Chakraboti, A., Banerjee, B.D., 2008. Endosulfan-induced apoptosis and glutathione depletion in human peripheral blood mononuclear cells: attenuation by *N*-acetylcysteine. J. Biochem. Mol. Toxicol. 22, 299-304.

Aitken, R. J., Baker, M. A., 2006. Oxidative stress, sperm survival and fertility control. Mol. Cell. Endocrinol. 250, 66-69.

Akhgari, M., Abdollahi, M., Kebryaeezadeh, A., Hosseini, R., Sabzevari, O., 2003. 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. 22, 205-211.

Akiyama, M., 1999. *In vivo* scavenging effect of ethylcysteine on reactive oxygen species in human semen.

Nippon Hinyokika Gakkai Zasshi 90, 421-428.
Al-azzawie, H.F., Umran, A., Hyader, N.H., 2013. Oxidative stress, antioxidant status and DNA damage in a mercury exposure workers. British J. Pharmacol. and Toxicol. 4(3), 80-88.
Al-Gubory, K.H., Bolifraud, P., Germain, G., Nicole, A., Ceballos-Picot, I., 2004. Antioxidant enzymatic defence systems in sheep corpus luteum throughout pregnancy. Reprod. 128, 767-774.
Al-Gubory, K.H., Ceballos-Picot, I., Nicole, A., Bolifraud, P., Germain, G., Michaud, M., 2005. Changes in activities of superoxide dismutase, nitric oxide synthase, glutathione-dependent enzymes and the incidence of apoptosis in sheep corpus luteum during the estrous cycle. Biochem. Biophys. Acta 1725, 348-357.
Al-Guborya, K.H., Fowlerb, P.A., Garrel, C., 2010. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int. J. Biochem. & Cell Biol. 42, 1634-1650.
Ali, S.F., LeBel, C.P., Bondy, S.C., 1992. Reactive oxygen species formation as a biomarker of methylmercury and trimethyltin neurotoxicity. Neurotoxicol. 13, 637-648.
Alien, R.G., Balin, A.K., 1989. Oxidative influence on development and differentiation, an overview of a free radical theory of development. Free Rad. Biol. Med. 6, 631-661.
Alsharif, N.Z., Grandjean, C.J., Murray, W.J., Stohs, S.J., 1990. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced decrease in the fluidity of rat liver membranes. Xenobiotica 20, 979-988.
Alsharif, N.Z., Schlueter, W.J., Stohs, S.J., 1994. Stimulation of NADPH-dependent reactive oxygen species formation and DNA damage by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rat peritoneal lavage cells. Arch. Environ. Contam. Toxicol. 26, 392-397.
Alsharif, N.Z., Tang, L., Hassoun, E., Elmetwally, T., Pederson, C., Shara, M., 1999. Role of oxidative stress in the chronic toxicity of TCDD in C57BL, 6J female mice. Toxicologist 48, 218.
Ames, B.N., Shigenaga, M.K., Hagen, T.M., 1993. Oxidants, antioxidants and the degenerative diseases of aging. Proc. Natl. Acad. Sci, U.S.A., 90, 7915-7922.
Andrieu-Abadie, N., Gouaze, V., Salvayre, R., Levade, T., 2001. Ceramide in apoptosis signaling, relationship with oxidative stress. Free Rad. Biol. Med. 31, 717-728.
Anguiano, O.L., de Castro, A.C., de D'Angelo A.M.P., 2001. The role of glutathione conjugation in the regulation of early toad embryos tolerance to pesticides. Comp. Biochem. and Physiol. Part C 128, 35-43.
Aoki, H., Otaka, Y., Igarashi, K., Takenaka, A., 2002. Soy protein reduces paraquat induced oxidative stress in rats. J. Nutr. 132, 2258-2262.
Aravind, P., Prasad, M.N.V., Malec, P., Waloszek, A., Strzałka, K., 2009. Zinc protects *Ceratophyllum demersum* L. (free-floating hydrophyte) against reactive oxygen species induced by cadmium. J. of Trace Elem. in Medicine and Biol. 23(1), 50–60.
Arikan, S., Konukolu, D., Arikan, C., Akc¸ay, T., Davas, I., 2001. Lipid peroxidation and antioxidant status in maternal and cord blood. Gyneacol Obstet Invest 51,145-149.
Aris, A., Benali, S., Ouellet, A., Moutquin, J.M., Leblanc, S., 2009. Potential biomarkers of preeclampsia: inverse correlation between hydrogen peroxide and nitric oxide early in maternal circulation and at term in placenta of women with preeclampsia. Placenta 30(4), 342-347.
Arun, S., Subramanian, P., 1998. Antioxidant enzymes in freshwater prawn Macrobrachium malcolmsonii during embryonic and larval development. Comp. Biochem. and Physiol. Part B 121, 273-277.
Ashida, H., Enan, E., Matsumura, F., 1996. Protective action of dehydroascorbic acid on the Ah receptor-dependent and receptor-independent induction of lipid peroxidation in adipose tissue of male guinea pig caused by TCDD administration. J. Biochem. Toxicol. 11, 269-278.
ATSDR (Agency for Toxic Substances and Disease Registry), 2007. Toxicological profile for Arsenic. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
Auten, R.L., O'Reilly, M.A., Oury, T.D., Nozik-Grayck, E., Whorton, M.H., 2006. Transgenic extracellular superoxide dismutase protects postnatal alveolar epithelial proliferation and development during hyperoxia. Am. J. Physiol. Lung Cell. Mol. Physiol. 290, L32-40.
Autor, A.P., Frank, L., Roberts, R.J., 1976. Developmental characteristics of pulmonary superoxide dismutase, relationship to idiopathic respiratory distress syndrome. Pediatr. Res. 10, 154-158.
Badham, H.J., Winn, L.M., 2010. In utero exposure to benzene disrupts fetal hematopoietic progenitor cell growth via reactive oxygen species. Toxicol. Sci. 113(1), 207–215.
Baehner, R.L., Nathan, D.G., 1967. Leukocyte oxidase, defective activity in chronic granulomatous disease. Science J. 155(764), 835-836.
Baek, I.J., Yon, J.M., Lee, B.J., Yun, Y.W., Yu, W.J., Hong, J.T., Ahn, B., Kim, Y.B., Kim, D.J., Kang, J.K., Nam, S.Y., 2005. Expression pattern of cytosolic glutathione peroxidase (cGPx) mRNA during mouse embryogenesis. Anat. and Embryol. (Berl) 209, 315–321.
Bagchi, D., Balmoori, J., Bagchi, M., Ye, X., Williams, C.B., Stohs, S.J., 2002. Comparative effects of TCDD, endrin, naphthalene and chromium (VI) on oxidative stress and tissue damage in the liver and brain tissues of

mice. Toxicol. 175, 73-82.
Bagchi, M., Hassoun, E., Bagchi, D., Stohs, S., 1993a. Production of reactive oxygen species by peritoneal macrophages and hepatic mitochondria and microsomes from endrin-treated rats. Free Rad. Biol. Med. 14, 149-155.
Bagchi, M., Hassoun, E.A., Akubue, P.I., Bagchi, D., Stohs, S.J., 1993b. Comparative effects of endrin on the hepatic lipid peroxidation, DNA damage and nitric oxide production by peritoneal lavage cells from C57BL/6J and DBA/2 mice. Comp. Biochem. Physiol. 105C, 525-529.
Bagchi, M., Stohs, S.J., 1993. *In vitro* induction of reactive oxygen species by 2,3,7,8-tetrachlorodibenzo-p-dioxin, endrin and lindane in rat peritoneal macrophages and hepatic mitochondria and microsomes. Free Rad. Biol. Med. 14, 11-18.
Baiza-Gutman, L.A., Flores-S.nchez, M.M., D.az-Flores, M., Hicks, J.J., 2000. Presence of uterine peroxidase activity in the rat early pregnancy. Int. J. Biochem. Cell. Biol. 32, 255-262.
Bajaj, J.S., Misra, A., Rajalakshmi, M., Madan, R., 1993. Environmental release of chemicals and reproductive ecology. Environ. Health Perspect. 101(Suppl. 2), 125-130.
Baker, H., DeAngelis, B., Holland, B., Gittens-Williams, L., Barrett Jr., T., 2002. Vitamin profile of 563 gravidas during trimesters of pregnancy. J. Amer. College of Nutr. 21, 33-37.
Baker, M.A., Aitken, R.J., 2005. Reactive oxygen species in spermatozoa, methods for monitoring and significance for the origins of genetic disease and infertility. Reprod. Biol. Endocrinol. 3, 67.
Banerjee, B.D., Seth, V., Bhattacharya, A., Pasha, S.T., Chakraborty, A.K., 1999. Biochemical effects of pesticides on lipid peroxidation and free radical scavengers. Toxicol. Lett. 107, 33-47.
Barnett, D.K., Bavister, B.D., 1992. Hypotaurine requirement for *in vitro* development of golden hamster one-cell embryos into morulae and blastocysts, and production of term offspring from *in vitro*-fertilized ova. Biol. Reprod. 47, 297-304.
Bauché, F., Fouchard, B., Jégou, B., 1994. Antioxidant system in rat testicular cells. FEBS Lett. 349, 392-396.
Bedard, K., Krause, K.H., 2007. The NOX family of ROS-generating NADPH oxidases, physiology and pathophysiology. Physiol. Rev. 87(1), 245-313.
Bemis, J.C., Seegal, R.F., 2000. Polychlorinated biphenyls and methylmercury alter intracellular calcium concentrations in rat cerebellar granule cells. Neurotoxicol. 21, 1123-1134.
Bensoussan, K., Morales, C.R., Hermo, L., 1998. Vitamin E deficiency causes incomplete spermatogenesis and affects the structural differentiation of epithelial cells of the epididymis in the rat. J. Androl. 19, 266-288.
Betteridge, D. J., 2000. What is oxidative stress? Metabolism 49 (2), suppl. 1, 3-8.
Biri, A., Bozkurt, N., Turp, A., Kavutcu, M., Himmetoglu, O., Durak, I., 2007. Role of oxidative stress in intrauterine growth restriction. Gynecol. Obstet. Invest. 64(4), 187-192.
Biswas, S.K., Rahman, I., 2009. Environmental toxicity, redox signaling and lung inflammation: The role of glutathione. Mol. Aspects of Medicine 30(1–2), 60–76.
Bourdineaud, J.P., Bellance, N., Bard, G., Brhes, D., Fujimura, M., Gonzalez, P., 2008. Feeding mice with diets containing mercury-contaminated fish flesh from French Guiana, a model for the mercurial intoxication of the Wayana Amerindians. Environ. Health 7, 53-65.
Boveris, A., Chance, B., 1973. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. Biochem. J. 134(3), 707-716.
Bracci, R., Buonocore, G., 1998. The antioxidant status of erythrocytes in preterm and term infants. Semin. Neonat. 3, 191-197.
Bracci, R., Buonocore, G., Talluri, B., 1988. Neonatal hyperbilirubinemia. Evidence for a role of the erythrocyte enzyme activities involved in the detoxification of oxygen radicals. Acta Paediatr. Scand. 77, 349-356.
Braconi, D., Bernardini, G., Santucci, A., 2011. Linking protein oxidation to environmental pollutants: Redox proteomic approaches. J. of Proteomics 74(11), 2324–2337.
Brigelius-Flohe, R., Traber, M.G., 1999. Vitamin E, function and metabolism. FASEB J. 13, 1145-1155.
Brown, M.R., Miller, F.J., Li, Jr.W-G., Ellingson, A.N., Mozena, J.D., Chatterjee, P., Engelhardt, J.F., Zwacka, R.M., Oberley, L.W., Fang, X., Spector, A.A., Weintraub, N.L., 1999. Overexpression of human catalase inhibits proliferation and promotes apoptosis in vascular smooth muscle cells. Circ. Res. 85, 524-533.
Bucak, M.N., Tuncer, B.P., Sarzkan, S., Baspınar, N., Taspınar, T., Coyan, K., Bilgili, A., Akalın, P.P., Bleblebici, S., Aydos, S., Ilgaz, S., Sunguroglu, A., Ztuna, D., 2010. Effects of antioxidants on post-thawed bovine sperm and oxidative stress parameters, Antioxidants protect DNA integrity against cryodamage. Cryobiol. 61(3), 248-253.
Buczynska, A., Tarkowski, S., 2005. Environmental exposure and birth outcomes. Int. J. Occup. Med. Environ. Health 18, 225-232.
Burton, G.J., 2009. Oxygen, the Janus gas, its effects on human placental development and function. J. Anat. 215, 27-35.

Burton, G.W., Joyce, A., Ingold, K.U., 1983. Is vitamin E the only lipid-soluble chain breaking antioxidant in human blood plasma and erythrocyte membranes? Arch Biochem. Biophys. 221, 281-290.
Butler, E.J., 1983. Role of trace elements in metabolic processes. In, Physiology and Biochemistry of the Domestic Fowl. Ed by BM Freeman, Academic Press, London, pp 175-190.
Calviello, G., Piccioni, E., Boninsegna, A., Tedesco, B., Maggiano, N., Serini, S., Wolf, F.I., Palozza, P., 2006. DNA damage and apoptosis induction by the pesticide Mancozeb in rat cells: involvement of the oxidative mechanism. Toxicol. Appl. Pharmacol. 211, 87-96.
Cantrell, S.M., Hutz, L.H., Tillitt, D.E., Hannink, M., 1996. Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): The embryonic vasculature is a physiological target for TCDD-induced DNA damage and apoptotic cell death in medaka (*Oryzias latipes*). Toxicol. Appl. Pharmacol. 141, 23-34.
Carlson, K., Jortner, B.S., Ehrich, M., 2000. Organophosphorus compound-induced apoptosis in SH-SY5Y human neuroblastoma cells. Toxicol. Appl. Pharmacol. 168, 102-113.
Castagne, V., Lefevre, K., Natero, R., Clarke, P.G., Bedker, D.A., 1999. An optimal redox status for the survival of axotomized ganglion cells in the developing retina. Neurosci. J. 93, 313-320.
Castllini, C., Lattaioli, P., Dal, B.A., Minelli, A., Mugnai, C., 2003. Oxidative status and semen characteristics of rabbit buck as affected by dietary vitamin E, C and n-3 fatty acids. Reprod. Nutr. Dev. 43, 91-103.
Cavallo, D., Ursini, C.L., Bavazzano, P., Cassinelli, C., Frattini, A., Perniconi, B., Di Francesco, A., Ciervo, A., Rondinone, B., Iavicoli, S., 2006. Sister chromatid exchange and oxidative DNA damage in paving workers exposed to PAHs. Ann. Hyg. 50, 211-218
Cerolini, S., Zaniboni, L., Maldjian, A., Gliozzi, T., 2006. Effect of docosahexaenoic acid and α-tocopherol enrichment in chicken sperm on semen quality, sperm lipid composition and susceptibility to peroxidation. Theriogenol. 66, 877-886.
Chae, H.Z., Kang, S.W., Rhee, S.G., 1999. Isoforms of mammalian peroxiredoxin that reduce peroxides in presence of thioredoxin. Methods Enzymol. 300, 219-226.
Chater, S., Douki, T., Favier, A., Garrel, C., Sakly, M., Abdelmelek, H., 2008a. Influence of static magnetic field on cadmium toxicity, study of oxidative stress and DNA damage in pregnant rat tissues. Electromagn. Biol. Med. 27, 393-401.
Chater, S., Douki, T., Garrel, C., Favier, A., Sakly, M., Abdelmelek, H., 2008b. Cadmium-induced oxidative stress and DNA damage in kidney of pregnant female rats. CR Biol. 331, 426-432.
Chauhan, S.S., Ojha, S., Mahmood, A., 2011. Modulation of lipid peroxidation and antioxidant defense systems in rat intestine by subchronic fluoride and ethanol administration. Alcohol 45(7), 663–672.
Chen, H.L., Hsu, C.Y., Hung, D.Z., Hu, M.L., 2006. Lipid peroxidation and antioxidant status in workers exposed to PCDD/Fs of metal recovery plants. Sci. Total Environ. 372, 12-19.
Cheng, J., Gu, J., Ma, J., Chen, X., Zhang, M., Wang, W., 2009. Neurobehavioural effects, redox responses and tissue distribution in rat offspring developmental exposure to BDE-99. Chemosphere 75(7), 963-968.
Cherouny, P.H., Ghodgaonkar, R.B., Niebyl, J.R., Dubin, N.H., 1988. Effect of hydrogen peroxide on prostaglandin production and contractions of the pregnant rat uterus. Am. J. Obstet. Gynecol. 159(6), 1390-1394.
Chinoy, N.J., Mehta, R.R., Seethalakshmi, L., Sharma, J.D., Chinoy, M.R., 1986. Effects of vitamin C deficiency on physiology of male reproductive organs of guinea pigs. Int. J. Fertil. 31, 232-239.
Chow, C.K., 1991. Vitamin E and oxidative stress. Free Rad. Biol. Med. 11, 215-232.
Collen, J., Pinto, E., Pedersen, M., Colepicolo, P., 2003. Induction of oxidative stress in the red macroalga Gracilaria tenuistipitata by pollutant metals. Arch. Environ. Contam. Toxicol. 45, 337- 342.
Covarrubias, L., Hernández-García, D., Schnabel, D., Salas-Vidal, E., Castro-Obregón, S., 2008. Function of reactive oxygen species during animal development, Passive or active? Dev. Biol. 320, 1-11.
Das, G.P., Shaik, A.P., Jamil, K., 2006. Estimation of apoptosis and necrosis caused by pesticides *in vitro* on human lymphocytes using DNA diffusion assay. Drug Chem. Toxicol. 29, 147-156.
Davis, J.M., Auten, R.L., 2010. Maturation of the antioxidant system and the effects on preterm birth. Semin. in Fetal & Neonatal Medicine 15(4), 191-195.
Dawson, T.M., Dawson, V.L., 1996. Nitric oxide synthase, role as a transmitter/mediator in the brain and endocrine system. Annu. Rev. Med. 47, 219-227.
de Haan, J.B., Tymms, M.J., Cristiano, F., Kola, I., 1994. Expression of copper/zinc superoxide dismutase and glutathione peroxidase in organs of developing mouse embryos, fetuses, and neonates. Pediatr. Res. 35, 188- 196.
De Vito, P., Incerpi, S., Pedersen, J.Z., Luly, P., 2010. Atrial natriuretic peptide and oxidative stress. Peptides 31, 1412-1419.
De Vito, P., Incerpi, S., Affabris, E., Percario, Z., Borgatti, M., Gambari, R., Pedersen, J.Z., Luly, P., 2013. Effect of atrial natriuretic peptide on reactive oxygen species-induced by hydrogen peroxide in THP-1 monocytes: Role in cell growth, migration and cytokine release. Peptides. pii: S0196-9781(13)00306-9. doi: 10.1016/j.peptides.2013.09.002. [Epub ahead of print]

Debnath, D., Mandal, T.K., 2000. Study of quinalphos (an environmental oestrogenic insecticide) formulation (Ekalux 25 E.C.)-induced damage of the testicular tissues and antioxidant defense systems in Sprague-Dawley albino rats. J. Appl. Toxicol. 20, 197-204.
Del Maestro, R.F., McDonald, W., 1987. Distribution of superoxide dismutase, glutathione peroxidase and catalase in developing rat brain. Mech. of Ageing and Dev. 41, 29-38.
Dennery, P.A., 2010. Oxidative stress in development, Nature or nurture? Free Rad. Biol. Med. 49(7), 1147-1151.
DeRosa, G., Keen, C.L., Leach, R.M., Hurley, L.S., 1980. Regulation of superoxide dismutase activity by dietary manganese. J. Nutr. 110, 795-804.
Devasagayam, T.P., Sivabalan, R., Tarachand, U., 1990. Lipid peroxidation in the rat uterus during deciduoma induced cell differentiation. Biochem. Int. 21, 27-32.
DeVito, M., Birnbaum, L.S., 1994. Toxicology of the dioxins and related chemicals. In, Schecter, A. (Ed.), Dioxins and Health. Elsevier, New York.
Di Giulio, R.T., Washburn, P.C., Wenning, R.J., Winston, G.W., Jewell, C.S., 1989. Biochemical responses in aquatic animals: a review of determinants of oxidative stress. Environ. Toxicol. Chem. 8, 1103- 1123.
Dinis-Oliveira, R.J., Duarte, J.A., S.nchez-Navarro, A., Remio, F., Bastos, M.L., Carvalho, F., 2008. Paraquat poisonings, mechanisms of lung toxicity, clinical features, and treatment, Crit. Rev. Toxicol. 8, 13-71.
Dong, W., Teraoka, H., Kondo, S., Hiraga, T., 2001. 2,3,7,8-tetrachlorodibenzo-p-dioxin induces apoptosis in the dorsal midbrain of zebra fish embryos by activation of aryl hydrocarbon receptor. Neurosci. Lett. 303, 169-172.
Donnay, I., Knoops, B., 2007. Peroxiredoxins in gametogenesis and embryo development. Subcell. Biochem. 44, 345-355.
Dreiem, A., Gertz, C.C., Seegal, R.F., 2005. The effects of methylmercury on mitochondrial function and reactive oxygen species formation in rat striatal synaptosomes are age-dependent. Toxicol. Sci. 87, 156-162.
Dröge, W., 2002. Free radicals in the physiological control of cell function. Physiol. Rev. 82(1), 47-95.
Dumollard, R., Carroll, J., Duchen, M.R., Campbell, K., Swann, K., 2009. Mitochondrial function and redox state in mammalian embryos. Semin. Cell. Dev. Biol. 20(3), 346-353.
Dumollard, R., Ward, Z., Carroll, J., Duchen, M., 2007. Regulation of redox metabolism in the mouse oocyte and early embryo. Dev. 134(3), 455-465.
Dumoulin, J.C.M., Evers, J.L.H., Bras, M., Pieters, M.H.E.C., Geraedts, J.P.M., 1992. Positive effect of taurine on preimplantation mouse embryos *in vitro*. J. Reprod. Fertil. 94, 373-380.
El Mouatassim, S., Guérin, P., Ménézo, Y., 1999. Expression of genes encoding antioxidant enzymes in human and mouse oocytes during the final stages of maturation. Mol. Hum. Reprod. 5(8), 720-725.
El-Bahr, S.M., 2013. Biochemistry of free radicals and oxidative stress. Sci. Int. 1(5), 111-117.
Emre, M.H., Aktay, G., Polat, A., Vardt, N., 2007. Effects of benzo(a)pyrene and ethanol on oxidative stress of brain, lung tissues and lung morphology in rats. Chin. J. Physiol. 50, 143-148.
Enli, Y., Turgut, S., Oztekin, O., Demir, S., Enli, H., Turgut, G., 2010. Cadmium intoxication of pregnant rats and fetuses: Interactions of copper supplementation. Arch. of Medical Res. 41(1), 7–13.
Enster, L., 1986. Oxygen as an environmental poison. Chem. Scr. J. 26, 525-534.
Farmen, E., Olsvik, P.A, Berntssen, M.H.G., Hylland, K., Tollefsen, K.E., 2010. Oxidative stress responses in rainbow trout (*Oncorhynchus mykiss*) hepatocytes exposed to pro-oxidants and a complex environmental sample. Comp. Biochem. and Physiol. Part C: Toxicol. & Pharmacol. 151(4), 431–438.
Favetta, L.A., John, E.J.St., King, W.A., Betts, D.H., 2007. High levels of p66shc and intracellular ROS in permanently arrested early embryos. Free Rad. Biol. Med. 42, 1201-1210.
Fernández, B., Campillo, J.A., Martínez-Gómez, C., Benedicto, J., 2010. Antioxidant responses in gills of mussel (*Mytilus galloprovincialis*) as biomarkers of environmental stress along the Spanish Mediterranean coast. Aquatic Toxicol. 99(2), 186–197.
Ferrari, A., Lascano, C.I., Anguiano, O.L., D'Angelo, A.M., Venturino, A., 2009. Antioxidant responses to azinphos methyl and carbaryl during the embryonic development of the toad Rhinella (Bufo) arenarum Hensel. Aquatic Toxicol. 93(1), 37-44.
Finkel, T., 1998. Oxygen radicals and signalling. Curr. Opin.Cell. Biol. 10, 248-253.
Fowler, P.A., Dor, N.J., McFerran, H., Amezaga, M.R., Miller, D.W., Lea, R.G., 2008. In utero exposure to low doses of enviromental pollutants disrupts fetal ovarian development in sheep. Mol. Hum. Reprod. 14, 269-280.
Franco, R., Sánchez-Olea, R., Reyes-Reyes, E.M., Panayiotidis, M.I., 2009. Environmental toxicity, oxidative stress and apoptosis: Ménage à Trois. Mutat. Res. 674(1–2), 3–22.
Frank, L., Groseclose, E.E., 1984. Preparation for birth into an O_2-rich environment, the antioxidant enzymes in the developing rabbit lung. Pediatr. Res. 18, 240-244.
Friedler, G., 1996. Paternal exposures, impact on reproductive and developmental outcome. An overview.

Pharmacol. Biochem. Behav. 55, 691-700.
Fujii, J., Iuchi, Y., Matsuki, S., Ishii, T., 2003. Cooperative function of antioxidant and redox systems against oxidative stress in male reproductive tissues. Asian J. Androl. 5, 231-242.
Fujii, J., Iuchi, Y., Okada, F., 2005. Fundamental roles of reactive oxygen species and protective mechanisms in the female reproductive system. Reprod. Biol. Endocrinol. 3, 43-52.
Gardiner, C.S., Reed, D.J., 1994. Status of glutathione during oxidant-induced oxidative stress in the preimplantation mouse embryo. Biol. Reprod. 51, 1307-1314.
Garrel, C., Fowler, P.A., Al-Gubory, K.H. 2010. Developmental changes in antioxidant enzymatic defences against oxidative stress in sheep placentomes. J. Endocrinol. 205(1), 107–116.
Ghosh, D., Das, U.B., Misro, M., 2002. Protective role of α-tochopherol-succinate (provitamin-E) in cyclophosphamide induced testicular gametogenic steroidogenic disorders, a correlative approach to oxidative stress. Free Rad. Res. 36, 1199-1208.
Godeas, C., Tramer, F., Micali, F., 1997. Distribution and possible novel role of phospholipid hydroperoxide glutathione peroxidase in rat epididymal spermatozoa. Biol. Reprod. 57, 1502-1508.
Gopalakrishna, R., Jaken, S., 2000. Protein kinase C signaling and oxidative stress. Free Rad. Biol. Med. 28, 1349-1361.
Gophinathan, V., Miller, N.J., Milner, A.D., 1994. Bilirubin and ascorbate, antioxidant activity in neonatal plasma. FEBS Lett. 349, 197-200.
Goto, Y., Noda, Y., Mori, T., Nakano, M., 1993. Increased generation of reactive oxygen species in embryos cultured *in vitro*. Free Rad. Biol. Med. 15, 69-75.
Goto, Y., Noda, Y., Narimoto, K., Umaoka, Y., Mori, T., 1992. Oxidative stress on mouse embryo development *in vitro*. Free Rad. Biol. Med. 13, 47-53.
Gotti, S., Martini, M., Viglietti-Panzica, C., Miceli, D., Panzica, G., 2010. Effects of estrous cycle and xenoestrogens expositions on mice nitric oxide producing system. Ital. J. Anat. Embryol. 115(1-2), 103-108.
Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19, 417-428.
Grosicka, E., Sadurska, B., Szumilo, M., Grzela, T., Lazarczyk, P., Niderla-Bielinska, J., Rahden-Staron, I., 2005. Effect of glutathione depletion on apoptosis induced by thiram in Chinese hamster fibroblasts. Int. Immunopharmacol. 5, 1945-1956.
Gross, R.T., Bracci, R., Rudolph, N., 1967. Hydrogen peroxide toxicity and detoxif ication in the erythrocyte of newborn infants. Blood 29, 481-493.
Guérin, P., El Mouatassim, S., Menezo, Y., 2001. Oxidative stress and protection against reactive oxygen species in the pre-implantation embryo and its surroundings. Hum. Reprod. Update 7(2), 175-189.
Guérin, P., Ménézo, Y., 1995. Hypotaurine and taurine in gamete and embryo environments, de novo synthesis via the cysteine sulfinic acid pathway in oviduct cells. Zygote 3(4), 333-343.
Guérin, P., Tappaz, M., Guillaud, J., Menezo, Y., 1995. Demonstration of cysteine sulfinate decarboxylase (EC 4.1.1.29) in cultured oviduct epithelial cells in cows and goats. C.R. Acad. Sci. III. 318(5), 523-528.
Haga, P., Lunde, G., 1978. Selenium and vitamin E in cord blood from preterm and full-term infants. Acta Paediatr. Scand. 67, 735-739.
Halliwel, B., 2011. Free radicals and antioxidants - quo vadis? Trends Pharmacol Sci. 32, 125-130.
Halliwell, B., Gutteridge, J., 1999. Free radicals in biology and medicine. third ed., Oxford University Press, Oxford.
Hanigan, M.H., Ricketts, W.A., 1993. Extracellular glutathione is a source of cysteine for cells that express gamma-glutamyl transpeptidase. Biochem. J. 32, 6302-6306.
Hannas, B.R., Das, P.C., Li, H., LeBlanc, G.A., 2010. Intracellular conversion of environmental nitrate and nitrite to nitric oxide with resulting developmental toxicity to the crustacean *Daphnia magna*. PLoS One 5(8): e12453.
Hass, M.A., Massaro, D., 1987. Developmental regulation of rat lung Cu, Zn-superoxide dismutase. Biochem. J. 246, 697-703.
Hassan, M.Q., Stohs, S.J., Murray, W.J., 1985. Effects of vitamins E and A on 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced lipid peroxidation and other biochemical changes in the rat. Arch. Environ. Contam. Toxicol. 14, 437-442.
Hassoun, E.A., Al-Ghafri, M., Abushaban, A., 2003. The role of antioxidant enzymes in TCDD-induced oxidative stress in various brain regions of rats after subchronic exposure. Free Rad. Biol. Med. 35(9), 1028-1036.
Hassoun, E.A., Li, F., Abushaban, A., Stohs, S.J., 2000. The relative abilities of TCDD and its congeners to induce oxidative stress in the hepatic and brain tissues of rats after subchronic exposure. Toxicol. 145, 103-113
Hassoun, E.A., Wang, H., Abushaban, A., Stohs, S.J., 2002. Induction of oxidative stress in the tissues of rats

after chronic exposure to TCDD, 2,3,4,7,8-pentachlorodibenzofuran, and 3,3',4,4',5-pentachlorobiphenyl. J. Toxicol. Environ. Health A 65, 825-842.
Hassoun, E.A., Wilt, S.C., Devito, M.J., Van Bergelen, A., Alsharif, N., Birnbaum, L., Stohs, S.J., 1998. Induction of oxidative stress in the brain tissues of mice after subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Sci. 42, 23-27.
Hayashibe, H., Asayama, K., Dobashi, K., Kato, K., 1990. Prenatal development of antioxidant enzymes in rat lung, kidney, and heart, marked increase in immunoreactive superoxide dismutases, glutathione peroxidase, and catalase in the kidney. Pediatr. Res. 27, 472-475.
He, X., Chen, M.G., Ma, Q., 2008. Activation of Nrf2 in defense against cadmium induced oxidative stress. Chem. Res. Toxicol. 21(7), 1375-1383.
He, X., Lin, G.X., Chen, M.G., Zhang, J.X., Ma, Q. 2007. Protection against chromium (VI)-induced oxidative stress and apoptosis by Nrf2. Recruiting Nrf2 into the nucleus and disrupting the nuclear Nrf2/Keap1 association. Toxicol. Sci. 98(1), 298-309.
Herrera, E., Ortega, H., Alvino, G., Giovannini, N., Amusquivar, E., Cetin, I., 2004. Relationship between plasma fatty acid profile and antioxidant vitamins during normal pregnancy. Eur. J. Clin. Nutr. 58, 1231-1238.
Herrero, M.B., Goin, J.C., Boquet, M., Canteros, M.G., Franchi, A.M., Perez Martinez, S., Polak, J.M., Viggiano, J.M., Gimeno, M.A., 1997. The nitric oxide synthase of mouse spermatozoa. FEBS Lett. 411(1), 39-42.
Hilscherova, K., Blankenship, A.L., Nie, M., Coady, K.K., Upham, B.L., Trosko, J.E., Giesy, J.P., 2003. Oxidative stress in liver and brain of the hatchling chicken (*Gallus domesticus*) following *in vivo* injection with TCDD. Comp. Biochem. Physiol. Part C 136 (1), 29-45.
Ho, Y.S., Gargano, M., Cao, J., Bronson, R.T., Heimler, I., Hutz, R.J., 1998. Reduced fertility in female mice lacking copper zinc superoxide dismutase. J. Biol. Chem. 273, 7765-7769.
Hoffman, D.J., Melancon, M.J., Klein, P.N., Rice, C.P., Eisemann, J.D., Hines, R.K., Spann, J.W., Pendleton, G.W., 1996. Developmental toxicity of PCB 126 (3,3',4,4',5-pentachlorobiphenyl) in nestling American kestrels (*Falco sparverius*). Fundam. Appl. Toxicol. 34 (2), 188-200.
Holmes, R.P., Goodman, H.O., Shihabi, Z.K., Jarow, J.P., 1992. The taurine and hypotaurine content of human semen. J. Androl. 13, 289-292.
Hong, E.J., Choi, K.C., Jeung, E.B., 2005. Maternal exposure to bisphenol A during late pregnancy resulted in an increase of Calbindin-D9k mRNA and protein in maternal and postnatal rat uteri. J. Reprod. Dev. 51, 499-508.
Huang, W., Cao, L., Liu, J., Lin, L., Dou, S., 2010. Short-term mercury exposure affecting the development and antioxidant biomarkers of Japanese flounder embryos and larvae. Ecotoxicol. Environ. Saf. 73(8), 1875–1883.
Hughes, C.M., Lewis, S.E., McKelvey-Martin, V.J., Thompson, W., 1996. A comparison of baseline and induced DNA damage in human spermatozoa from fertile and infertile men, using a modified comet assay. Mol. Hum. Reprod. 2, 613-619.
Hussain, S., Slikker, W.Jr., Ali, S.F., 1995. Age-related changes in antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase and glutathione in different regions of mouse brain. Int. J. Dev. Neurosci. 13 (8), 811-817.
Imosemi, I.O., 2013. The role of antioxidants in cerebellar development. A review of literature. Int. J. Morphol. 31(1), 203-210.
Incerpi, S., Fiore, A.M., De Vito, P., Pedersen, J.Z., 2007. Involvement of plasma membrane redox systems in hormone action. J. Pharm. Pharmacol. 59, 1711-1720.
Inglefield, J.R., Mundy, W.R., Shafer, T.J., 2001. Inositol 1,4,5-triphosphate receptor-sensitive Ca^{2+} release, store-operated Ca^{2+} entry, and cAMP responsive element binding protein phosphorylation in developing cortical cells following exposure to polychlorinated biphenyls. J. Pharmacol. Exp. Ther. 297, 762-773.
Jain, S., Kumar, C.H.M., Suranagi, U.D., Mediratta, P.K., 2011. Protective effect of N-acetylcysteine on bisphenol A-induced cognitive dysfunction and oxidative stress in rats. Food Chem. Toxicol. 49 (6), 1404–1409.
Jauniaux, E., Gulbis, B., Burton, G.J., 2003. The human first trimester gestational sac limits rather than facilitates oxygen transfer to the foetus—a review. Placenta 24, S86-S93.
Jauniaux, E., Watson, A.L., Hempstock, J., Bao, Y.P., Skepper, J.N., Burton, G.J., 2000. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. Am. J. Pathol. 157, 2111-2122.
Jimenez, A., Zu, W., Rawe, V.Y., Pelto-Huikko, M., Flickinger, C.J., Sutovsky, P., Gustafsson, J-Å., Oko, R., Miranda-Vizuete, A., 2004. Spermatocyte/spermatid-specific thioredoxin-3, a novel Golgi apparatus-associated thioredoxin, is a specific marker of aberrant spermatogenesis. J. Biol. Chem. 279, 34971-34982.
Jin, X., Kennedy, S.W., Di Muccio, T., Moon, T.W., 2001. Role of oxidative stress and antioxidant defense in 3,3',4,4',5-pentachlorobiphenyl-induced toxicity and species-differential sensitivity in chicken and duck embryos. Toxicol. Appl. Pharmacol. 172, 241-248.
Jishage, K., Arita, M., Igarashi, K., Iwata, T., Watanabe, M., Ogawa, M., 2001. α-Tocopherol transfer protein is

important for the normal development of placental labyrinth trophoblasts in mice. J. Biol. Chem. 276, 1669-1672.
Kabuto, H., Amakawa, M., Shishibori, T., 2004. Exposure to bisphenol-A during embryonic/fetal life and infancy increases oxidative injury and causes under development of the brain and testis in mice. Life Sci. 74, 2931-2940.
Kalyanaraman, B., Darley-Usmar, V., Davies, K.J.A., Dennery, P.A., Forman, H.J., Grisham, M.B., Mann, G.E., Moore, K., Roberts II, L.J., Ischiropoulos, H., 2012. Measuring reactive oxygen and nitrogen species with fluorescent probes: challenges and limitations. Free Rad. Biol. Med. 52(1), 1–6.
Kamiński, P., Kurhalyuk, N., Jerzak, L., Kasprzak, M., Tkachenko, H., Klawe, J.J., Szady-Grad, M., Koim, B., Wiśniewska, E., 2009. Ecophysiological determinations of antioxidant enzymes and lipoperoxidation in the blood of White Stork Ciconia ciconia from Poland. Environ. Res. 109(1), 29-39.
Kannan, K., Holcombe, R.F., Jain, S.K., Alvarez-Hernandez, X., Chervenak, R., Wolf, R.E., Glass, J., 2000. Evidence for the induction of apoptosis by endosulfan in a human T-cell leukemic line. Mol. Cell. Biochem. 205, 53-66.
Kanofsky, J.R., 1989. Singlet oxygen production by biological systems, Chem. Biol. Interact. 70 (1-2), 1-28.
Karowicz-Bilinska, A., Kedziora-Kornatowska, K., Bartosz, G., 2007. Indices of oxidative stress in pregnancy with fetal growth restriction. Free Rad. Res. 41(8), 870-873.
Kasprzak, K.S., 2002. Oxidative DNA and protein damage in metal-induced toxicity and carcinogenesis. Free Rad. Biol. Med. 32(10), 958-967.
Kaur, P., Radotra, B., Minz, R.W., Gill, K.D., 2007. Impaired mitochondrial energy metabolism and neuronal apoptotic cell death after chronic dichlorvos (OP) exposure in rat brain. Neurotoxicol. 28, 1208-1219.
Khattak, S., K-Moghtader, G., McMartin, K., Barrera, M., Kennedy, D., Koren, G., 1999. Pregnancy outcome following gestational exposure to organic solvents, a prospective controlled study. JAMA 281, 1106-1109.
Kheirat, F., Merzouk, H., Boudilmi, N., Merzouk, S.A., Malti, A., Narce, M., 2013. Oxidative stress biomarkers in diabetic mothers and their newborns. Annals of Biol. Res. 4 (7), 73-80.
Kim, J.G., Parthasarathy, S., 1998. Oxidation and the spermatozoa. Semin. Reprod. Endocrinol. 16, 235-239.
Kim, K.B., Lee, B.M., 1997. Oxidative stress to DNA, protein, and antioxidant enzymes (superoxide dismutase and catalase) in rats treated with benzo(a)pyrene. Cancer Lett. 113, 205-212.
Kim, K.H., Wang, Z.Q., 1993. Action of vitamin A on the testis, role of the Sertoli cell. In, Russel, L.D., Grisworld, M.D. (Eds.), The Sertoli Cell. Cache River Press, Clearwater, FL, pp. 517-535.
Kim, B-M., Rhee, J-S., Park, G.S., Lee, J., Lee, Y-M., Lee, J-S., 2011. Cu/Zn- and Mn-superoxide dismutase (SOD) from the copepod *Tigriopusjaponicus*: Molecular cloning and expression in response to environmental pollutants. Chemosphere 84(10), 1467–1475.
Klebanoff, S.J., 1999. Myeloperoxidase. Proc. Assoc. Am. Physicians 111(5), 383-389.
Knappen, M.F.C.M., Zusterzeel, P.L.M., Peters, W.H.M., Steegers, E.A.P., 1999. Glutathione and glutathione-related enzymes in reproduction, a review. Eur. J. Obstet. Gynecol. Reprod. Biol. 82, 171-184.
Koivula, M.J., Eeva, T., 2010. Metal-related oxidative stress in birds. Environ. Pollut. 158(7), 2359–2370.
KonKim, M., Oh, S., Lee, J.H., Im, H., MiRyu, Y., Oh, E., Lee, J., Lee, E., Sul, D., 2004. Evaluation of biological monitoring markers using genomic and proteomic analysis for automobile emission inspectors and waste incinerating workers exposed to polycyclic aromatic hydrocarbons or 2,3,7,8-tetracholrodedibenzo-p-dioxins. Exp. Mol. Med. 36, 396-410.
Kosower, N.S., Song, K.R., Kosower, E.M., Glutathione, I.V., 1969. Intracellular oxidation and cellular injury. Biochem. Biophys. Acta 192, 23-28.
Krishnamoorthy, G., Murugesan, P., Muthuvel, R., Gunadharini, D.N., Vijayababu, M.R., Arunkumar, A., 2005. Effect of Aroclor 1254 on Sertoli cellular antioxidant system, androgen binding protein and lactate in adult rat *in vitro*. Toxicol. 212(2-3), 195-205.
Kubrak, O.I., Lushchak, O.V., Lushchak, J.V., Torous, I.M., Storey, J.M., Storey, K.B., Lushchak, V.I., 2010. Chromium effects on free radical processes in goldfish tissues: comparison of Cr(III) and Cr(VI) exposures on oxidative stress markers, glutathione status and antioxidant enzymes. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 152(3), 360-370.
Kubrak, O.I., Husak, V.V., Rovenko, B.M., Storey, J.M., Storey, K.B., Lushchak, V.I., 2011. Cobalt-induced oxidative stress in brain, liver and kidney of goldfish *Carassius auratus*. Chemosphere 85 (6), 983–989.
Kujo, S., 2004. Vitamin C, basic metabolism and its function as an index of oxidative stress. Curr. Med. Chem. 11, 1041-1064.
Kukucka, M.A., Misra, H.P., 1993. The antioxidant defense system of isolated guinea pig Leydig cells. Mol. Cell. Biochem. 126, 1-7.
Laloraya, M., Kumar, G.P., Laloraya, M.M., 1989a. Histochemical study of superoxide dismutase in the ovary of the rat during the oestrous cycle. J. Reprod. Fertil. 86, 583-587.
Laloraya, M., Kumar, G.P., Laloraya, M.M., 1989b. A possible role of superoxide anion radical in the process of

blastocyst implantation in Mus musculus. Biochem. Biophys. Res. Commun. 161, 762-770.
Laloraya, M., Kumar, G.P., Laloraya, M.M., 1991. Changes in the superoxide radical and superoxide dismutase levels in the uterus of Rattus norvegicus during the estrous cycle and a possible role for superoxide radical in uterineoedemaand cell proliferation at proestrus. Biochem. Cell. Biol. 69, 313-316.
Lapointe, J., Bilodeau, J.F., 2003. Antioxidant defenses are modulated in the cow oviduct during the estrous cycle. Biol. Reprod. 68, 1157-1164.
Lee, D.W., Opanashuk, L.A., 2004. Polychlorinated biphenyl mixture Aroclor 1254-induced oxidative stress plays a role in dopaminergic cell injury. Neurotoxicol. 25, 925-939.
Lee, I.M., 1999. Antioxidant vitamins in the prevention of cancer. Proc. Assoc. Am. Physicians 111, 10-15.
Lee, M.Y., Shin, H.W., 2003. Cadmium-induced changes in antioxidant enzymes from the marine alga Nannochloropsis oculata. J. Appl. Physiol. 15, 13-19.
Lee, S.R., Yon, J.M., Baek, I.J., Kim, M.R., Park, C.G., Lee, B.J., Yun, Y.W., Nam, S.Y., 2008a. Spatiotemporal expression of selenoprotein P gene in post-implantational mouse embryos. Int. J. Dev. Biol. 52, 1005-1011.
Lee, Y.J., Ryu, H.Y., Kim, H.K., Min, C.S., Lee, J.H., Kim, E., 2008b. Maternal and fetal exposure to bisphenol A in Korea. Reprod. Toxicol. 25, 413-419.
Leonard, S.S., Harris, G.K., Shi, X., 2004. Metal-induced oxidative stress and signal transduction. Free Rad. Biol. Med. 37(12), 1921-1942.
Li, D., Devaraj, S., Fuller, C., Bucala, R., Jialal, I., 1996. Effect of α-tocopherol on LDL oxidation and glycation, *in vitro* and *in vivo* studies. J. Lipid Res. 37, 1978-1986.
Li, J., Foote, R.H., Simkin, M., 1993. Development of rabbit zygotes cultured in protein-free medium with catalase, taurine, or superoxide dismutase. Biol. Reprod. 49, 33-37.
Li, Q., Kobayashi, M., Kawada, T., 2009. Chlorpyrifos induces apoptosis in human T cells. Toxicol. 255, 53-57.
Lim, J., Sanders, R.A., Yeager, R.L., Millsap, D.S., Watkins, J.B., Eells, J.T., Henshel, D.S., 2008. Attenuation of TCDD-induced oxidative stress by 670 nm photobiomodulation in developmental chicken kidney. J. Biochem. Mol. Toxicol. 22(4), 230-239.
Limón-Pacheco, J., Gonsebatt M.E. 2009. The role of antioxidants and antioxidant-related enzymes in protective responses to environmentally induced oxidative stress. Mutat. Res. 674, 137-147.
Liu, J., Goyer, R.A., Waalkes, M.P. 2008b. Toxic effects of metals. In C. D. Klaassen (Ed.), Casarett and Doull's Toxicology. The Basic Science of Poisons (pp. 931-979), 7 ed New York, McGraw-Hill Medical.
Liu, J., Qian, S.Y., Guo, Q., Jiang, J.J., Waalkes, M.P., Mason, R.P., Kadiiska, M.B., 2008a. Cadmium generates reactive oxygen- and carbon-centered radical species in rats: Insights from *in vivo* spin-trapping studies. Free Rad. Biol. Med. 45(4), 475–481.
Liu, Y., Templeton, D.M., 2008. Initiation of caspase-independent death in mouse mesangial cells by Cd^{2+}: involvement of p38 kinase and CaMK-II. J. Cell. Physiol. 217, 307–318.
Livingston, T., Rich, K., MacKenzie, S., Godkin, J.D., 2009. Glutathione content and antioxidant enzyme expression of *in vivo* matured sheep oocytes. Animal Reprod. Sci. 116, 265-273.
Livingstone, D.R., 2001. Contaminated-stimulated reactive oxygen species production and oxidative damage in aquatic organisms. Mar. Pollut. Bull. 42, 656-666.
Löffler, G., Petrides, P.E., 1988. Physiologische Chemie. 4 ed., p. 288, Springer, Berlin 1988, ISBN 3-540-18163-6 (in German).
Lombardo, E., Sabellico, C., Balducci, V., Hájek, J., Staňkova, V., Filipskringer, Berlin 198, Leone, S., Proietti Silvestri, I., Righi, G., Luly, P., Saso, L., Pedersen, J.Z., Incerpi, S., Bovicelli, P., 2013. Protection of cells against oxidative stress by nanomolar levels of hydroxyflavones indicates a new type of intracellular antioxidant mechanism. PLoS One 8 (4), e60796.
Lonergan, P., O'Kearney-Flynn, M., Boland, M.P., 1999. effect of protein supplementation and presence of an antioxidant on the development of bovine zygotes in synthetic oviduct fluid medium under high or low oxygen tension. Theriogenol. 51, 1565-1576.
Lopes, S., Jurisicova, A., Sun, J.G., Casper, R.F., 1998. Reactive oxygen species: potential cause for DNA fragmentation in human spermatozoa. Hum. Reprod. 13, 896-900.
Loro, V.L., Jorge, M.B., Silva, K.R., Wood, C.M., 2012. Oxidative stress parameters and antioxidant response to sublethal waterborne zinc in a euryhaline teleost *Fundulus heteroclitus*: protective effects of salinity. Aquatic Toxicol. 110-111, 187-193.
Luck, M.R., Jeyaseelan, I., Scholes, R.A., 1995. Ascorbic acid and fertility. Biol. Reprod. 52, 262-266.
Luo, L., Chen, H., Trush, M.A., Show, M.D., Anway, M.D., Zirkin, B.R., 2006. Aging and the brown Norway rat Leydig cell antioxidant defense system. J. Androl. 27, 240-247.
Lushchak, V.I., 2011. Environmentally induced oxidative stress in aquatic animals. Aquatic Toxicol. 101(1), 13–30.
L'vova, S.P., Abaeva, E.M., 1996. The tissue antioxidant system in the early postnatal development of rats. J.

Ontogenez 27 (3), 204-207.
Ma, Q., 2009. Transcriptional responses to oxidative stress, pathological and toxicological implications. Pharmacol. Ther. 125(3), 376-393.
Maden, M., 2000. The role of retinoic acid in embryonic and post-embryonic development. Proc. Nutr. Soc. 59, 65-73.
Madhyastha, S., Sahu, S.S., Rao, G., 2013. Resveratrol for prenatal-stress-induced oxidative damage in growing brain and its consequences on survival of neurons. J. of Basic and Clin. Physiol. and Pharmacol. 0(0), 1–10.
Makker, K., Agarwal, A., Sharma, R., 2009. Oxidative stress & male infertility. Ind. J. Med. Res. 129, 357-367.
Manjunatha, B.M., Devaraj, M., Gupta, P.S., Ravindra, J.P., Nandi, S., 2009. Effect of taurine and melatonin in the culture medium on buffalo *in vitro* embryo development. Reprod. Domest. Anim. 44(1), 12-16.
Marchlewicz, M., Wiszniewska, B., Baranowska-Bosiacka, I., Safranow, K., Kolasa, A., Glabiwski, W., 2007. Increased lipid peroxidation and ascorbic acid utilization in testes and epididumis of rats chronically exposed to lead. Biometals 20, 13-19.
Marczynski, B., Rihs, H.P., Rossbach, B., Holzer, J., Angerer, J., Scherenberg, M., Hoffmann, G., Bruning, T., Wilhelm, M., 2002. Analysis of 8-oxo-7,8-dihydro-2-deoxyguanosine and DNA strand breaks in white blood cells of occupationally exposed workers, comparison with ambient monitoring, urinary metabolites and enzyme polymorphisms. Carcinogenesis 23, 273-281.
Mariussen, E., Myhre, O., Reistad, T., Fonnum, F., 2002. The polychlorinated biphenyl mixture Aroclor 1254 induces cell death of rat cerebellar granule cells, the involvement of the N-methyl-Daspartate receptor and reactive oxygen species. Toxicol. Appl. Pharmacol. 179, 137-144.
Markey, C.M., Rudolph, D.B., Labus, J.C., Hinton, B.T., 1998. Oxidative stress differentially regulates the expression of gamma-glutamyl transpeptidase mRNAs in the initial segment of the rat epididymis. J. Androl. 19, 92-99.
Markey, C.M., Wadia, P.R., Rubin, B.S., Sonnenschein, C., Soto, A.M., 2005. Long-term effects of fetal exposure to low doses of the xenoestrogen bisphenol-A in the female mouse genital tract. Biol. Reprod. 72, 1344-1351.
Matés, J.M., Segura, J.A., Alonso, F.J., Márquez, J., 2010. Roles of dioxins and heavy metals in cancer and neurological diseases using ROS-mediated mechanisms. Free Rad. Biol. Med. 49(9), 1328-1341.
Mathews-Roth, M.M., 2000. Erythropoietic protoporphyria, treatment with antioxidants and potential cure with gene therapy. Methods Enzymol. 319, 479-484.
Matzuk, M.M., Dionne, L., Guo, Q., Kumar, T.R., Lebovitz, R.M., 1998. Ovarian function in superoxide dismutase 1 and 2 knockout mice. J. Endocrinol. 139, 4008-4011.
Maurel, D.L., Saad, M.M.B., Roch, G., 2002. Testicular activity is restored by melatonin replacement after suprachiasmatic nucleus lesion or superior cervical ganglionectomy in mink. J. Pineal Res. 32, 15-20.
McCubrey, J.A., Lahair, M.M., Franklin, R.A., 2006. Reactive oxygen species-induced activation of the MAP kinase signaling pathways. Antioxid Redox Signal 8(9-10), 1775-1789.
Mena, S., Ortega, A., Estrela, J.M., 2009. Oxidative stress in environmental-induced carcinogenesis. Mutat. Res. 674, 36-44.
Menon, J., Rozman, R., 2007. Oxidative stress, tissue remodeling and regression during amphibian metamorphosis. Comp. Biochem. and Physiol., Part C 145, 625-631
Messina, J.P., Lawrence, D.A., 1989. Cell cycle progression of glutathione depleted human peripheral blood mononuciear celt is inhibited at S phase. J. Immunol. 143, 1961-1974.
Miller, J.G.O., Schultz, G.A., 1987. Amino acid content of preimplantation embryos and fluids of the reproductive tract. Biol. Reprod. 36, 125-129.
Mise, H., Sagawa, N., Matsumoto, T., Yura, S., Nanno, H., Itoh, H., Mori, T., Masuzaki, H., Hosoda, K., Ogawa, Y., Nakao, K., 1998. Augmented placental production of leptin in preeclampsia: possible involvement of placental hypoxia. J. Clin. Endocrinol. Metab. 83(9), 3225-3229.
Mishra, O.P., Delivoria-Papadropoulos, M., 1988. Anti-oxidant enzymes in fetal guinea pig brain tissue during development and the effect of maternal hypoxia. Dev. Brain Res. 42, 173-179.
Monteiro, D.A., Rantin, F.T., Kalinin, A.L., 2009. The effects of selenium on oxidative stress biomarkers in the freshwater characid fish matrinxã, *Brycon cephalus* (Günther, 1869) exposed to organophosphate insecticide Folisuper 600 BR (methyl parathion). Comp. Biochem. and Physiol. Part C: Toxicol. & Pharmacol. 149(1), 40–49.
Moreau, R., Dabrowski, K., 1998. Body pool and synthesis of ascorbic acid in adult sea lamprey (*Petromyzon marinus*), an agnathan fish with gulonolactone oxidase activity. Proc. Natl. Acad. Sci. 95, 10279-10282.
Mruka, D.D., Silvestrini, B., Mo, M-y., Cheng, C.Y., 2002. Antioxidant superoxide dismutase - a review, its function, regulation in the testis, and role in male fertility. Contraception 65, 305-311.
Muguruma, M., Unami, A., Kanki, M., Kuroiwa, Y., Nishimura, J., Dewa, Y., Umemura, T., Oishi, Y.,

Mitsumori, K., 2007. Possible involvement of oxidative stress in piperonyl butoxide induced hepatocarcinogenesis in rats. Toxicol. 236, 61-75.
Mukkadam, J.K., 1980. Observations on ascorbic acid content and cholesterol in male reproductive tissues. Ind. J. Exp. Biol. 18, 1186-1188.
Murugesan, P., Muthusamy, T., Balasubramanian, K., Arunakaran, J., 2005b. Studies on the protective role of vitamin C and E against polychlorinated biphenyl (Aroclor 1254)-induced oxidative damage in Leydig cells. Free Rad. Res. 39(11), 1259-1272.
Murugesan, P., Senthilkumar, J., Balasubramanian, K., Aruldhas, M.M., Arunakaran, J., 2005a. Impact of polychlorinated biphenyl Aroclor 1254 on testicular antioxidant system in adult rats. Hum. Exp. Toxicol. 24, 61-66.
Muthuvel, R., Venkataraman, P., Krishnamoorthy, G., Gunadharini, D.N., Kanagaraj, P., Jone Stanley, A., Srinivasan, N., Balasubramanian, K., Aruldhas, M.M., Arunakaran, J., 2006. Antioxidant effect of ascorbic acid on PCB (Aroclor 1254) induced oxidative stress in hypothalamus of albino rats. Clin. Chim. Acta 365 (1-2), 297-303.
Nair, P.M.G., Park, S.Y., Choi, J., 2011. Expression of catalase and glutathione *S*-transferase genes in *Chironomus riparius* on exposure to cadmium and nonylphenol. Comp. Biochem. and Physiol. Part C: Toxicol. & Pharmacol. 154(4), 399–408.
Nakadai, A., Li, Q., Kawada, T., 2006. Chlorpyrifos induces apoptosis in human monocyte cell line U937. Toxicol. 224, 202-209.
Nakai, A., Oya, A., Kobe, H., 2000. Changes in maternal lipid peroxidation levels and antioxidant enzymatic activities before and after delivery. J. Nippon Med. Sch. 67, 434-439.
Nanetti, L., Giannubilo, S.R., Raffaelli, F., Curzi, C.M., Vignini, A., Moroni, C., Tanase, L., Carboni, E., Turi, A., Mazzanti, L., Tranquilli, A.L., 2008. Nitric oxide and peroxynitrite platelet levels in women with small-for-gestational-age fetuses. BJOG. 115(1), 14-21.
Narayanan, P.K., Carter, W.O., Ganey, P.E., Roth, R.A., Voytik-Harbin, S.L., Robinson, J.P., 1998. Impairment of human neutrophil oxidative burst by polychlorinated biphenyls, inhibition of superoxide dismutase activity. J. Leuk. Biol. 63, 216-224.
Narayanaswamy, M., Piler, M.B., 2010. Effect of maternal exposure of fluoride on biometals and oxidative stress parameters in developing CNS of rat. Biol. Trace Elem. Res. 133(1), 71-82.
Nasr-Esfahani, M.M., Johnson, M.H., 1991. The origin of reactive oxygen species in mouse embryos cultured *in vitro*. Dev. 113, 551-560.
Neeraj, Pramod, J., Singh, S., Singh, J., 2013. Antioxidants to the rescue of cell under invasion of free radicals – a review. Int. J. of Basic and Appl. Medical Sci. 3 (2), 190-200.
Ni, H., Yu, X.J., Liu, H.J., Lei, W., Rengaraj, D., Li, X.J., 2009. Progesterone regulation of glutathione S-transferase Mu2 expression in mouse uterine luminal epithelium during preimplantation period. Fertil. Steril. 91(5 Suppl.), 2123-2130.
Nozik-Grayck, E., Dieterle, C.S., Piantadosi, C.A., Enghild, J.J., Oury, T.D., 2000. Secretion of extracellular superoxide dismutase in neonatal lungs. Am. J. Physiol. Lung Cell. Mol. Physiol. 279, L977-L984.
O'Brien, P.J. 1991. Molecular mechanisms of quinone cytotoxicity. Chem. Biol. Interact. 80(1), 1-41.
Ojha, P., Dhar, J.D., Dwivedi, A.K., Singh, R.L., Gupta, G., 2006. Effect of antispermatogenic agents on cell marker enzymes of rat Sertoli cells *in vitro*. Contraception 73, 102-106.
Ornoy, A., Tsadok, M.A., Yaffe, P., Zangen, S.W., 2009. The Cohen diabetic rat as a model for fetal growth restriction, Vitamins C and E reduce fetal oxidative stress but do not restore normal growth. Reprod. Toxicol. 28, 521-529.
Palacea, V.P., Dick, T.A., Brown, S.B., Baron, C.L., Klaverkampal, J.F., 1996. Oxidative stress in Lake Sturgeon *(Acipenser fulvescens)* orally exposed to 2,3,7,8-tetrachlorodibenzofuran. Aquatic Toxicol. 35, 79-92
Palanza, P., Gioiosa, L., vom Saal, F.S., Parmigiani, S., 2008. Effects of developmental exposure to bisphenol A on brain and behavior in mice. Environ. Res. 108, 150-157.
Palmer, H.J., Paulson, K.E., 1997. Reactive oxygen species and antioxidants in signal transduction and gene expression. Nutr. Rev. 55, 353-361.
Perez-Maldonado, I.N., Herrera, C., Batres, L.E., Gonzalez-Amaro, R., Diaz-Barriga, F., Yanez, L., 2005. DDT-induced oxidative damage in human blood mononuclear cells. Environ. Res. 98, 177-184.
Perreault, S.D., Barbee, R.R., Slott, V.L., 1988. Importance of glutathione in the acquisition and maintenance of sperm nuclear decondensing activity in maturing hamster oocytes. Dev. Biol. 125(1), 181-186.
Peters, L.D., Livingstone, D.R., 1996. Antioxidant enzyme activities in embryologic and early larval stages of turbot. J. Fish Biol. 49, 986-997.
Petrulea, M., Muresan, A., Duncea, I., 2012. Oxidative stress and antioxidant status in hypo- and hyperthyroidism. In The Antioxidant Enzyme, Chapter 8, pp. 197-236. Ed M.A. El-Missiry. Croatia: Intech

Open Access Publisher.
Phillips, M., Cataneo, R.N., Greenberg, J., Gunawardena, R., Rahbari-Oskouia, F., 2003. Increased oxidative stress in younger as well as in older humans. Clinica Chimica Acta. 328, 83-86.
Piper, G.M., Jordan, M., Dondlinger, L.A., Adans, M.B., Roza, A. M., 1995. Peroxidative stress in diabetic blood vessels. Reversal by pancreatic islet transplantation. Diabetes 44, 884-889.
Pohjanvirta, R., Tuomisto, J., 1994. Short-term toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals, effects, mechanism and animals models. Pharmacol. Rev. 46, 483-549.
Poljšak, B., Milisav, I., 2013. Aging, oxidative stress and antioxidants. In Oxidative Stress and Chronic Degenerative Diseases - A Role for Antioxidants, Chapter 14, pp. 331-356. Ed by J.A. Morales-González. Croatia: Intech Open Access Publisher.
Poljšak, B., Jamnik, P., Raspor, P., 2011. Oxidation-antioxidation-reduction processes in the cell: Impacts of environmental pollution. Encyclopedia of Environ. Health 300–306.
Poston, L., Raijmakers, M.T.M., 2004. Trophoblast oxidative stress, antioxidants and pregnancy outcome—A Review. Placenta, 25, Suppl. A, Trophoblast Res., 18, S72-S78.
Powers, D.E., Millman, J.R., Huang, R.B., Colton, C.K., 2008. Effects of oxygen on mouse embryonic stem cell growth, phenotype retention, and cellular energetics. Biotechnol. Bioeng. J. 101, 241-254.
Pryor, W.A., Squadrito, G.L., 1995. The chemistry of peroxynitrite, a product from the reaction of nitric oxide with superoxide, Am. J. Physiol. 268, L699-L722.
Pulido, M.D., Parrish, A.R., 2003. Metal-induced apoptosis: mechanisms, Mutat. Res. 533, 227-241.
Qanungo, S., Mukherjea, M., 2000. Ontogenic profile of some antioxidants and lipid peroxidation in human placental and fetal tissues. Mol. Cell. Biochem. 215, 11-19.
Qanungo, S., Sen, A., Mukherjea, M., 1999. Antioxidant status and lipid peroxidation in human feto-placental unit. Clin. Chim. Acta 285, 1-12
Rahman, I., 2012. Pharmacological antioxidant strategies as therapeutic interventions for COPD. Biochim. Biophys. Acta. 1822(5), 714-728.
Ranjbar, A., Pasalar, P., Abdollahi, M., 2002. Induction of oxidative stress and acetylcholinesterase inhibition in organo Rahman phosphorous pesticide manufacturing workers. Hum. Exp. Toxicol. 21, 179-182.
Ray, S., Sengupta, A., Ray, A., 2007. Effects of paraquat on anti-oxidant system in rats. Ind. J. Exp. Biol. 45, 432-438.
Richetti, S.K., Rosemberg, D.B., Ventura-Lima, J., Monserrat, J.M., Bogo, M.R., Bonan, C.D., 2011. Acetylcholinesterase activity and antioxidant capacity of zebrafish brain is altered by heavy metal exposure. Neurotoxicol. 32(1), 116–122.
Rickett, G.M., Kelly, F.J., 1990. Developmental expression of antioxidant enzymes in guinea pig lung and liver. Dev. 108, 331- 336.
Rizzo, A.M., Adorni, L., Montorfano, G., Rossi, F., Berra, B., 2007. Antioxidant metabolism of Xenopus laevis embryos during the first days of development. Comp. Biochem. and Physiol., Part B 146, 94-100.
Rodríguez-Estival, J., Martinez-Haro, M., Monsalve-González, L., Mateo, R., 2011. Interactions between endogenous and dietary antioxidants against Pb-induced oxidative stress in wild ungulates from a Pb polluted mining area. Sci. of the Total Environ. 409(14), 2725–2733.
Roopha, D.P., Latha, P.C., 2013. Cadmium exposure-induced oxidative stress; delay in sexual maturation and impaired hormones in developing rat ovary. Oxidants and Antioxidants in Medical Sci. 2(3), 181-186.
Rossi, M., Caruso, F., Crespi, E.J., Pedersen, J.Z., Nakano, G., Duong, M., Mckee, C., Lee, S., Jiwrajka, M., Caldwell, C., Baffour, F., Karlin, D.A., Lidoff, G., Leone, S., Balducci, V., Miler, J., Incerpi, S., 2013. Probing antioxidant activity of 20-hydroxychalcones: Crystal and molecular structures, *in vitro* antiproliferative studies and *in vivo* effects on glucose regulation. Biochimie 95, 1954-1963.
Rubin, B.S., Murray, M.K., Damassa, D.A., King, J.C., Soto, A.M., 2001. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environ. Health Perspect. 109, 675-680.
Rudneva, I.I., 1999. Antioxidant system of Black Sea animals in early development. Comp. Biochem. Physiol., Part C 122, 265-271.
Ruffels, J., Griffin, M., Dickenson, J.M., 2004. Activation of ERK1/2, JNK and PKB by hydrogen peroxide in human SH-SY5Y neuroblastoma cells: role of ERK1/2 in H_2O_2-induced cell death. Eur. J. Pharmacol. 483(2-3), 163-173.
Ruiz-Leal, M., George, S., 2004. An *in vitro* procedure for evaluation of early stage oxidative stress in an established fish cell line applied to investigation of PHAH and pesticide toxicity. Mar. Environ. Res. 58 (2-5), 631-635.
Safe, S., 1990. Polychlorinated biphenyls (PCBs), dibenzo-pdioxins (PCDDs), dibenzofurans (PCDFs) and related compounds, Environmental and mechanistic considerations which support the development of toxic

equivalency factors (TEFs). CRC Crit. Rev. Toxicol. 21, 51-89.
Saker, M., Mokhtari, N.S., Merzouk, S.A., Merzouk, H., Belarbi, B., Narce, M., 2008. Oxidant and antioxidant status in mothers and their newborns according to birthweight. Eur. J. of Obstetr. & Gynecol. and Reprod. Biol. 141, 95-99.
Sakia, I.I., 1967. A ribonucleoprotein which catalyzes thioldisulfide exchange in the sea urchin egg. J. Biol. Chem. 242, 1458-1461.
Salem, M.H., Kamel, K.I., Yousef, M.I., Hassan, G.A., EL-Nouty, F.D., 2001. Protective role of ascorbic acid to enhance semen quality of rabbits treated with sublethal doses of aflatoxin B1. Toxicol. 162, 209-218.
Sanderson, J.T., 2006. The steroid hormone biosynthesis pathway as a target for endocrine disrupting chemicals. Toxicol. Sci. 94, 3-21.
Sarafian, T., Verity, M.A., 1991. Oxidative mechanisms underlying methylmercury neurotoxicity. Int. J. Dev. Neurosci. 9, 147-153.
Sardesai, V.M., 1995. Role of antioxidants in health maintenance. Nutr. Clin. Pract. 10, 19-25.
Sato, E.F., Kobuchi, H., Edashige, K., Takahashi, M., Yoshioka, T., Utsumi, K., 1992. Dynamic aspects of ovarian superoxide dismutase isozymes during the ovulatory process in the rat. FEBS Lett. 303, 121-125.
Schafer, F.Q., Buettner, G.R., 2001. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. Free Rad. Biol. Med. 30, 1191-1212.
Schetzer, H.G., Nebert, D.W., Puga, A., Ary, M., Sonntag, D., Dixon, K., 1998. Dioxin causes a sustained oxidative stress response in the mouse. Biochem. Biophys. Res. Commun. 253, 44-48.
Schinella, G.R., Marin, M.C., Alaniz, M.J.T., de Buschiazzo, P., Toumier, H.A., 1999. Antioxidant defence system and lipid peroxidation in lactating rats, ffect of dietary vitamin e during gestation and lactation. Nutr. Res. 19(5), 795-803.
Schneider, M., Vogt Weisenhorn, D.M., Seiler, A., Bornkamm, G.W., Brielmeier, M., Conrad, M., 2006. Embryonic expression profile of phospholipid hydroperoxide glutathione peroxidase. Gene Expression Patterns 6, 489-494.
Schroter, W., Bodemann, H., 1970. Experimentally induced cation leaks of the red cell membrane. On the mechanism of hemolysis in newborn infants. Biol. Neonate 15, 291-299.
Schultz, G., Kaye, P.L., McCoy, D.J., Johnson, M.H., 1981. Endogenous amino acid pool sizes in mouse eggs and preimplantation embryos. J. Reprod. Fertil. 61, 387-393.
Sen, A., Mukherjea, M., 1998. Modulation of bilayer fluidity by lipid peroxidation of human placental syncytiotrophoblast membranes during embryogenesis. Ind. J. Biochem. Biophys. 35, 216-223.
Sen, C.K., Packer, L., 1996. Antioxidant and redox regulation of gene transcription (see comments). FASEB J. 10, 709-720.
Shafer, T.J., Mundy, W.R., Tilson, H.A., Kodavanti, P.R., 1996. Disruption of inositol phosphate accumulation in cerebellar granule cells by polychlorinated biphenyls, a consequence of altered Ca^{2+} homeostasis. Toxicol. Appl. Pharmacol. 141, 448-455.
Sharbidre, A.A., Metkari, V., Patode, P., 2011. Effect of methyl parathion and chlorpyrifos on certain biomarkers in various tissues of guppy fish, *Poecilia reticulate.* Pesticide Biochem. and Physiol. 101(2), 132–141.
Sharma, Y., Bashir, S., Irshad, M., Gupta, S.D., Dogra, T.D., 2005. Effects of acute dimethoate administration on antioxidant status of liver and brain of experimental rats. Toxicol. 206, 49-57.
Shi, H., Sui, Y., Wang, X., Luoa, Y., Ji, L., 2005. Hydroxyl radical production and oxidative damage induced by cadmium and naphthalene in liver of *Carassius auratus*. Comp. Biochem. and Physiol., Part C 140, 115-121.
Shi, M., Yang, H., Motley, E., Guo, Z., 2004. Overexpression of Cu/Zn-superoxide dismutase and/or catalase in mice inhibits aorta smooth muscle cell proliferation. Am. J. Hypertens. 17(5), 450-456.
Shivakumar, B.R., Anandatheerthavarada, H.K., Ravindranath, V., 1991. Free radical scavenging systems in developing rat brain. Int. J. Dev. Neurosci. 9 (2), 181-185.
Sies, H., 1997. Oxidative stress, oxidants and antioxidants. Exp. Physiol. 82 (2), 291-295.
Sikkema, J.M., van Rijn, B.B., Franx, A., Bruinse, H.W., de Roos, R., Stroes, E.S., van Faassen, E.E., 2001. Placental superoxide is increased in pre-eclampsia. Placenta 22(4), 304-308.
Simmons, R.A., 2006. Developmental origins of diabetes, the role of oxidative stress. Free Rad. Biol. Med. 40, 917-922.
Singh, R., Kaur, B., Kalina, I., Popov, T.A., Georgieva, T., Garte, S., Binkova, B., Sram, R.J., Taioli, E., Farmer, P.B., 2007. Effects of environmental air pollution on endogenous oxidative DNA damage in humans. Mutat. Res. 620, 71-82.
Slezak, B.P., Hatch, G.E., DeVito, M.J., Diliberto, J.J., Slade, R., Crissman, K., Hassoun, E., Birnbaum, L.S., 2000. Oxidative stress in female B6C3F1 mice following acute and subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol. Sci. 54, 390–398.

Small, D.M., Coombes, J.S., Bennett, N., Johnson, D.W., Gobe, G.C., 2012. Oxidative stress, anti-oxidant therapies and chronic kidney disease. Nephrol. 17(4), 311–321.
Son, Y.O., Wang, X., Hitron, J.A., Zhang, Z., Cheng, S., Budhraja, A., Ding, S., Lee, J.C., Shi, X., 2011. Cadmium induces autophagy through ROS-dependent activation of the LKB1-AMPK signaling in skin epidermal cells. Toxicol. Appl. Pharmacol. 255(3), 287-296.
Song, Y., Liang, X., Hu, Y., Wang, Y., Yu, H., Yang, K., 2008. p,p'-DDE induces mitochondria mediated apoptosis of cultured rat Sertoli cells. Toxicol. 253, 53-61.
Sorg, O., 2004. Oxidative stress, a theoretical model or a biological reality? C. R. Biologies 327, 649-662.
Sosenko, I.R., Frank, L., 1987. Guinea pig lung development, antioxidant enzymes and premature survival in high O_2. Am. J. Physiol. Regul. 252, R693-R698.
Squadrito, G.L., Pryor, W.A., 1995. The formation of peroxynitrite *in vivo* from nitric oxide and superoxide. Chem. Biol. Interact. 96, 203-206.
Stadtman, E.R., 1992. Protein oxidation and aging. Sci. 257(5074), 1220-1224.
Staniek, K., Nohl, H. 2000. Are mitochondria a permanent source of reactive oxygen species? Biochim. Biophys. Acta 1460(2-3), 268-275.
Stara, A., Machova, J., Velisek, J., 2012. Effect of chronic exposure to simazine on oxidative stress and antioxidant response in common carp (*Cyprinus carpio* L.). Environ. Toxicol. Pharmacol. 33(2), 334-343.
Stohs, S.J., Alsharif, N.Z., Shara, M.A., Al-Bayati, Z.A., Wahba, Z.Z., 1991. Evidence for the induction of an oxidative stress in rat hepatic mitochondria by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Adv. Exp. Med. Biol. 283, 827-831.
Stohs, S.J., Hassan, M.Q., Murray, W.J., 1983. Lipid peroxidation as a possible cause of TCDD toxicity. Biochem. Biophys. Res. Comm. 111, 854-859.
Stohs, S.J., Hassan, M.Q., Murray, W.J., 1984. Effects of BHA, *d*-α-tocopherol and retinol acetate on TCDD-mediated changes in lipid peroxidation, glutathione peroxidase activity and survival. Xenobiotica 14, 533-537.
Stohs, S.J., Shara, M.A., Alsharif, N.Z., Wahba, Z.Z., Al-Bayati, Z.A.F., 1990. 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced oxidative stress in female rats. Toxicol. Appl. Pharmacol. 106, 126-135.
St-Pierre, J., Buckingham, J.A., Roebuck, S.J., Brand, M.D. 2002. Topology of superoxide production from different sites in the mitochondrial electron transport chain. J. Biol. Chem. 277(47), 44784-44790.
Su, Z., Limberis, J., Martin, R.L., Xu, R., Kolbe, K., Heinemann, S.H., Hoshi, T., Cox, B.F., Gintant, G.A., 2007. Functional consequences of methionine oxidation of hERG potassium channels, *Biochem. Pharmacol.*, 74(5), 702-711.
Sugino, N., Shimamura, K., Takiguchi, S., Tamura, H., Ono, M., Nakata, M., 1996. Change in activity of superoxide dismutase in the human endometrium throughout the menstrual cycle and in early pregnancy. Hum. Reprod. 11, 1073-1078.
Sugino, N., Takiguchi, S., Kashida, S., Karube, A., Nakamura, Y., Kato, H., 2000. Superoxide dismutase expression in the human corpus luteum during the menstrual cycle and in early pregnancy. Mol. Hum. Reprod. 6, 19-25.
Surai, P., Kostjuk, I., Wishart, G., Macpherson, A., Speake, B., Noble, R., Ionov, I., Kutz, E., 1998. Effect of Vitamin E and selenium supplementation of cockerel diets on glutathione peroxidase activity and lipid peroxidation susceptibility in sperm, testes, and liver. Biol. Trace Elem. Res. 64, 119-132.
Sutovsky, P., Schatten, G., 1997. Depletion of glutathione during bovine oocyte maturation reversibly blocks the decondensation of the male pronucleus and pronucleus apposition during fertilization. Biol. Reprod. 56, 1503-1512.
Suzuki, Y.J., Forman, H.J., Sevanian, A., 1997. Oxidants as stimulators of signal transduction. Free Rad. Biol. Med. 22, 269-285.
Taira, J., Mimura, K., Yoneya, T., Hagi, A., Murakami, A., Makino, K., 1992. Hydroxyl radical formation by UV-irradiated epidermal cells. J. Biochem. (Tokyo) 111(6), 693-695.
Tang, L., Alsharif, N.Z., Hassoun, E., Pederson, C., Shara, M., 1999. Role of oxidative stress in the subchronic toxicity of TCDD in C57BL, 6J female mice. Toxicologist 48, 218.
Tanswell, A.K., Freeman, B.A., 1984. Pulmonary antioxidant enzyme maturation in the fetal and neonatal rat. I. Developmental profiles. Pediatr. Res. 18, 584-587.
Tarin, J.J., 1996. Potential effects of age-associated oxidative stress on mammalian oocytes/embryos. Mol. Hum. Reprod. 2 (10), 717-724.
Thannickal, V.J., Fanburg, B.L., 2000. Reactive oxygen species in cell signaling. Am. J. of Physiol.: Lung Cell.and Mol. Physiol. 279(6), L1005-L1028.
Tharappel, J.C., Lehmler, H-J., Srinivasan, C., Robertson, L.W., Spear, B.T., Glauert, H.P., 2008. Effect of antioxidant phytochemicals on the hepatic tumor promoting activity of 3,3′,4,4′-tetrachlorobiphenyl (PCB-77). Food and Chem. Toxicol. 46(11), 3467–3474.

Thews, O., Lambert, C., Kelleher, D.K., Biesalski, H.K., Vaupel, P., Frank, J., 2005. Possible protective effects of alpha-tochopherol on enhanced induction of reactive oxygen species by 2-methoxyestradiol in tumors. Adv. Exp. Med. Biol. 566, 349-355.
Thomas, M., Jain, S., Kumar, G.P., Laloraya, M., 1997. A programmed oxyradical burst causes hatching of mouse blastocysts. J. Cell Sci. 110, 1597-1602.
Thompson, J., Bannigan, J., 2008. Cadmium, toxic effects on the reproductive system and the embryo. Reprod. Toxicol. 25, 304-315.
Thouas, G.A., Trounson, A.O., Jones, G.M., 2005. Effect of female age on mouse oocyte developmental competence followingmitochondrial injury. Biol. Reprod. 2, 366-373.
Tomita, M., Katsuyama, H., Okuyama, T., Hidaka, K., Minatogawa, Y., 2005. Changes in gene expression level for defense system enzymes against oxidative stress and glutathione level in rat administered paraquat, Int. J. Mol. Med. 15, 689-693.
Traber, M.G., Packer, L., 1995. Vitamin E, beyond antioxidant function. Am. J. Clin. Nutr. 62, 1501S-1509S.
Treidel, L.A., Whitley, B.N., Benowitz-Fredericks, Z.M., Haussmann, M.F., 2013. Prenatal exposure to testosterone impairs oxidative damage repair efficiency in the domestic chicken (*Gallus gallus*). Biol. Lett. 9(5), 20130684.
Tsukimori, K., Yoshitomi, T., Morokuma, S., Fukushima, K., Wake, N., 2008. Serum uric acid levels correlate with plasma hydrogen peroxide and protein carbonyl levels in preeclampsia. Am. J. Hypertens. 21(12), 1343-1346.
Tubman, T.R.J., Halliday, H.L., McMaster, D., 1990. Glutathione peroxidase and selenium levels in the preterm infant. Biol. Neonate 58, 305-310.
Turrens, J.F. 1997. Superoxide production by the mitochondrial respiratory chain. Biosci. Rep. 17(1), 3-8.
Twaroski, T.P., O'Brien, M.L., Larmonier, N., Glauert, H.P., Robertson, L.W., 2001. Polychlorinated biphenyl-induced effects on metabolic enzymes, AP-1 binding, vitamin E, and oxidative stress in rat liver. Toxicol. Appl. Pharmacol. 171, 85-93.
Twigg, J.P., Irvine, D.S., Aitken, R.J., 1998. Oxidative damage to DNA in human spermatozoa does not preclude pronucleus formation at intracytoplasmic sperm injection. Hum. Reprod. 13, 1864-1871.
Tyrrell, R.M., 1995. Ultraviolet radiation and free radical damage to skin. Biochem. Soc. Symp. 61, 47-53.
Ufer, C., Wang, C.C., 2011. The roles of glutathione peroxidases during embryo development. Front. Mol. Neurosci. 4, 12.
Uzbekov, M.G., Bubnova, N.I., Kulikova, G.V., 2007. Effect of prenatal lead exposure on superoxide dismutase activity in the brain and liver of rat fetuses. Bull. Exp. Biol. Med. 144, 783-785.
Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T.D., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. of Biochem. & Cell Biol. 39, 44-84.
Valko, M., Morris, H., Cronin, M. T. 2005. Metals, toxicity and oxidative stress. Curr. Med. Chem. 12(10), 1161-1208.
Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M., Mazur, M., 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem. Biol. Interact. 160, 1-40.
Van den Berg, M., DeJongh, J., Olson, J.R., 1994. The toxicokinetic metabolism of polychlorinated dibenzo-pdioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance for toxicity. CRC Crit. Rev. Toxicol. 24, 1-74.
van Lieshout, E.M., Knapen, M.F., Lange, W.P., Steegers, E.A., Peters, W.H., 1998. Localization of glutathione S-transferases alpha and pi in human embryonic tissues at 8 weeks gestational age. Hum. Reprod. 13, 1380-1386.
Van Poppel, G., van den Berg, H., 1997. Vitamins and cancer. Cancer Lett. 114(1-2), 195-202.
Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol A (BPA). Reprod. Toxicol. 24, 139-177.
Vannucchi, C.I., Jordao, A.A., Vannucchi, H., 2007. Antioxidant compounds and oxidative stress in female dogs during pregnancy. Res. Vet. Sci. 83, 188-193.
Vega-Lopez, A., Galar-Martinez, M., Jimenez-Orozco, F.A., Garcia-Latorre, E., Dominguez-Lopez, M.L., 2006. Gender related differences in the oxidative stress response to PCB exposure in an endangered goodeid fish (*Girardinichthys viviparus*). Comp. Biochem. Physiol. 146 (4), 672–678.
Venkataraman, P., Krishnamoorthy, G., Vengatesh, G., Srinivasan, N., Aruldhas, M.M., Arunakaran, J., 2008. Protective role of melatonin on PCB (Aroclor 1254) induced oxidative stress and changes in acetylcholine esterase and membrane bound ATPases in cerebellum, cerebral cortex and hippocampus of adult rat brain. Int. J. Dev. Neurosci. 26, 585-591.
Venkataraman, P., Muthuvel, R., Krishnamoorthy, G., Arunkumar, A., Sridhar, M., Srinivasan, N., Balasubramanian, K., Aruldhas, M.M., Arunakaran, J., 2007. PCB (Aroclor 1254) enhances oxidative damage in rat brain regions: Protective role of ascorbic acid. Neurotoxicol. 28, 490-498.
Venkataraman, P., Sridhar, M., Dhanammal, S., Vijayababu, M.R., Srinivasan, N., Arunakaran, J., 2004.

Antioxidant role of zinc in PCB (Aroclor 1254) exposed ventral prostate of albino rats. J. Nutr. Biochem. 15 (10), 608-613.
Vijayavel, K., Gomathi, D., Durgabhavani, K., Balasubramanian, M.P., 2004. Sublethal effect of naphthalene on lipid peroxidation and antioxidant status in the edible marine crab Scylla serrata. Mar. Pollut. Bull. 48, 429- 433.
Voie, O.A., Fonnum, F., 2000. Effect of polychlorinated biphenyls on production of reactive oxygen species (ROS) in rat synaptosomes. Arch. Toxicol. 73, 588-593.
Vuchetich, P.J., Bagchi, D., Bagchi, M., Hassoun, E.A., Tang, L., Stohs, S.J., 1996. Naphthalene-induced oxidative stress in rats and the protective effects of vitamin E succinate. Free Rad. Biol. Med. 21, 577-590.
Wahba, Z.Z., Lawson, T.A., Stohs, S.J., 1988. Induction of hepatic DNA-single strand breaks in rats by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Cancer Lett. 29, 281-286.
Walsh, S.W., Vaughan, J.E., Wang, Y., Roberts, L.J., 2000. Placental isoprostane is significantly increased in preeclampsia. FASEB J. 14, 1289–1296.
Wan, J., Winn, L.M., 2008. In utero exposure to benzene increases embryonic c-Myb and Pim-1 protein levels in CD-1 mice. Toxicol. Appl. Pharmacol. 228, 326–333.
Wan, J.,Winn, L.M., 2006. In utero-initiated cancer, the role of reactive oxygen species. Birth Defects Res. C Embryo Today 78, 326-332.
Wang, Y., Walsh, S.W., 1996. TNF alpha concentrations and mRNA expression are increased in preeclamptic placentas. J. Reprod. Immunol. 32(2), 157-169.
Warren, A.Y., Matharoo-Ball, B., Shaw, R.W., Khan, R.N., 2005. Hydrogen peroxide and superoxide anion modulate pregnant human myometrial contractility. Reprod. 130, 539-544.
Wells, P.G., Bhuller, Y., Chen, C.S., Jeng, W., Kasapinovic, S., Kennedy, J.C., 2005. Molecular and biochemical mechanisms in teratogenesis involving reactive oxygen species. Toxicol. Appl. Pharmacol. 207(2 Suppl.), 354-366.
Wells, P.G., McCallum, G.P., Chen, C.S., Henderson, J.T., Lee, C.J.J., Perstin, J., Preston, T.J., Wiley, M.J., Wong, A.W., 2009. Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer. Toxicol. Sci. 108(1), 4–18.
Whaun, J.M., Oski, F.A., 1970. Relation of blood cell glutathione peroxidase to neonatal jaundice. Pediatr. 76, 555-560.
Wieloch, M., Kamiński, P., Ossowska, A., Koim-Puchowska, B., Stuczyński, T., Kuligowska-Prusińska, M., Dymek, G., Mańkowska, A., Odrowąż-Sypniewska, G., 2012. Do toxic heavy metals affect antioxidant defense mechanisms in humans? Ecotoxicol. Environ. Saf. 78, 195-205.
Wilding, M., Dale, B., Marino, M., di Matteo, L., Alviggi, C., Pisaturo, M.L., Lombardi, L., De Placido, G., 2001. Mitochondrial aggregation patterns and activity in human oocytes and preimplantation embryos. Hum. Reprod. 16 (5), 909-917.
Wilson, J.X., Lui, E.M.K., DEL Maestro, R.F., 1992. Developmental profiles of antioxidant enzymes and trace metals in chick embryo. Mech. of Ageing and Dev. 65, 51-64.
Wilson, M.J., Kaye, D., Edward Smith, W., Quach, H.T., Sinha, A.A., Vatassery, G.T., 2003. Effect of vitamin E deficiency on the growth and secretory function of the rat prostatic complex. Exp. Mol. Pathol. 74, 267-275.
Winterbourn, C.C., Vissers, M.C., Kettle, A.J., 2000. Myeloperoxidase. Curr. Opin. Hematol. 7(1), 53-58.
Won, E-J., Rhee, J-S., Kim, R.-O., Ra, K., Kim, K.-T., Shin, K.-H., Lee, J-S., 2012. Susceptibility to oxidative stress and modulated expression of antioxidant genes in the copper-exposed polychaete *Perinereis nuntia.* Comp. Biochem. and Physiol. Part C: Toxicol. & Pharmacol. 155(2), 344–351.
Wright, C.J., Agboke, F., Chen, F., La, P., Yang, G., Dennery, P.A., 2010. Nitric oxide inhibits hyperoxia-induced NF-κB activation in neonatal pulmonary microvascular endothelial cells. Pediatr. Res. 68(6), 484–489.
Wu, S.H., Oldfield, J.E., Whanger, P.D., Weswig, P.H., 1973. Effect of selenium, vitamin E, and antioxidants on testicular function in rats. Biol. Reprod. 8, 625-629.
Yamauchi, T., Komura, S., Yagi, K., 1986. Serum lipid peroxide levels of albino rats administered naphthalene. Biochem. Int. 13, 1-6.
Yee, S., Choi, B.H., 1994. Methylmercury poisoning induces oxidative stress in the mouse brain. Exp. Mol. Pathol. 60, 188-196.
Yon, J.M., Baek, I.J., Lee, S.R., Kim, M.R., Lee, B.J., Yun, Y.W., Nam, S.Y., 2008. Immunohistochemical identification and quantitative analysis of cytoplasmic Cu/Zn superoxide dismutase in mouse organogenesis. J. Vet. Sci. 9(3), 233-240.
Yoshida, R., Ogawa, Y., 2000. Oxidative stress induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin, an application of oxidative stress markers to cancer risk assessment of dioxins. Ind. Health 38, 5-14.
Yousef, M.I., 2005. Protective effect of ascorbic acid to enhance reproductive performance of male rabbits treated with stannous chloride. Toxicol. 207, 81-89.
Yousef, M.I., Abdallah, G.A., Kamel, K.I., 2003. Effect of ascorbic acid and Vitamin E supplementation on

semen quality and biochemical parameters of male rabbits. Anim. Reprod. Sci. 76, 99-111.
Yu, F., Wang, Z., Ju, B., Wang, Y., Wang, J., Bai, D., 2008. Apoptotic effect of organophosphorus insecticide chlorpyrifos on mouse retina *in vivo* via oxidative stress and protection of combination of vitamins C and E. Exp. Toxicol. Pathol. 59, 415-423.
Yu, Y., Oko, R., Miranda-Vizuete, A., 2002. Developmental expression of spermatid-specific thioredoxin-1 protein, transient association to the longitudinal columns of the fibrous sheath during sperm tail formation. Biol. Reprod. 67, 1546-1554.
Yuan, H.T., Bingle, C.D., Kelly, F.J., 1996. Differential patterns of antioxidant enzyme mRNA expression in guinea pig lung and liver during development. Biochim. Biophys. Acta 1, 163-171.
Zaken, V., Kohen, R., Ornoy, A., 2000. The development of the antioxidant defense mechanism in young rat embryos *in vivo* and *in vitro*. Early Pregnancy, Biol. Med. 4, 110-123.
Zhang, Y., Sun, G., Yang, M., Wu, H., Zhang, J., Song, S., Ma, E., Guo, Y., 2011. Chronic accumulation of cadmium and its effects on antioxidant enzymes and malondialdehyde in *Oxya chinensis* (Orthoptera: Acridoidea). Ecotoxicol. Environ. Saf. 74(5), 1355–1362.
Zhuang, T., Zhang, M., Zhang, H., Dennery, P.A., Lin, Q.S., 2010. Disrupted postnatal lung development in heme oxygenase-1 deficient mice. Respiratory Res. 11, 142.
Ziech, D., Franco, R., Georgakilas, A.G., Georgakila, S., Malamou-Mitsi, V., Schoneveld, O., Pappa, A., Panayiotidis, M.I., 2010. The role of reactive oxygen species and oxidative stress in environmental carcinogenesis and biomarker development. Chemico-Biological Interact. 188(2), 334–339.
Zusterzeel, P.L., Rütten, H., Roelofs, H.M., Peters, W.H., Steegers, E.A., 2001. Protein carbonyls in decidua and placenta of pre-eclamptic women as markers for oxidative stress. Placenta 22(2-3), 213-219.