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REVIEW

Environmental pollutants and lifestyle factors induce oxidative stress and poor prenatal development




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Dr Kaïs H Al-Gubory is a senior scientist. During his 33-year career at the French National Institute for Agricultural Research, he developed his research in different units: physiology of lactation, animal physiology, endocrinology and embryonic development, developmental biology and reproduction. His research lies in understanding ovarian, luteal, uterine and placental physiology during pregnancy. He is engaged in the development and use of experimental surgery, animal models and live-cell imaging technology. Currently, his major research interest includes maternal environment and peri-implantation development, antioxidants and free radical biology, roles of antioxidants in prenatal developmental outcomes and fertility and peri-conception antioxidants nutritional therapies.

Abstract Developmental toxicity caused by exposure to a mixture of environmental pollutants has become a major health concern. Human-made chemicals, including xenoestrogens, pesticides and heavy metals, as well as unhealthy lifestyle behaviours, mainly tobacco smoking, alcohol consumption and medical drug abuse, are major factors that adversely influence prenatal development and increase susceptibility of offspring to diseases. There is evidence to suggest that the developmental toxicological mechanisms of chemicals and lifestyle factors involve the generation of reactive oxygen species (ROS) and cellular oxidative damage. Overproduction of ROS induces oxidative stress, a state where increased ROS generation overwhelms antioxidant protection and subsequently leads to oxidative damage of cellular macromolecules. Data on the involvement of oxidative stress in the mechanism of developmental toxicity following exposure to environmental pollutants are reviewed in an attempt to provide an updated basis for future studies on the toxic effect of such pollutants, particularly the notion of increased risk for developmental toxicity due to combined and cumulative exposure to various environmental pollutants. The aims of such studies are to better understand the mechanisms by which environmental pollutants adversely affect conceptus development and to elucidate the impact of cumulative exposures to multiple pollutants on post-natal development and health outcomes. 

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Introduction

Humans and wild and domestic animals are exposed to complex mixtures of various organic and inorganic environmental pollutants. Aquatic habitats throughout the world receive a great amount of pollutants due to industrial and agricultural activities as well as human and agricultural livestock waste inputs (Burkholder et al., 2007; Valavanidis et al., 2006). Many hazardous man-made chemicals have been voluntarily and involuntarily released into the environment and thus exposure of humans and wildlife to such pollutants has become inevitable. Industrial discharge, agricultural runoff, human and animal waste, municipal and domestic effluents, spillage of vessels and oil spill are the major sources of river, sea and ocean pollution. Exposure to various environmental pollutants may be difficult to avoid due to their ubiquitous occurrence in air, water, soil, vegetables, food, industrial and domestic products, plastic products, cosmetics and medication.

Epidemiological evidence indicates that prenatal and/or early life exposure to various environmental pollutants adversely affects conceptus (embryo/fetus and associated membranes) development and neonate health (Wigle et al., 2008). In reality, the conceptus, irrespective of maternal exposure pathways, is exposed *in utero* to multiple environmental pollutants during pregnancy that could adversely affect implantation and the developmental trajectory in a cumulative dose-additive manner (Rider et al., 2010). The main recognized disorders and complications linked to such exposure are embryonic mortality, fetal loss, intrauterine growth restriction, preterm birth, birth defects, childhood diseases, neuropsychological deficits, premature or delayed sexual maturation and certain adult cancers (Wigle et al., 2008). Developmental toxicity during pregnancy caused by various environmental pollutants has therefore become a major health concern.

Humans and animals are potentially exposed to a mixture of environmental pollutants that act on one or more organs through different and/or similar mechanisms of action. Endocrine disruptors that act by disparate mechanisms of toxicity to disrupt the dynamic hormone-dependent signalling pathways in differentiating tissues have been shown to produce cumulative dose-additive effects, regardless of the mechanism or mode of action of the individual mixture component (Rider et al., 2012). Multicomponent mixtures of endocrine-disturbing chemicals act as hormone mimics or antagonists, leading to disruption of oestrogen, androgen and other hormonal pathways (Kortenkamp, 2007). The toxicity of the combination of endocrine disruptors results from an antagonist mode of action of these chemicals, due to competitive ligand binding on oestrogen receptors (Li et al., 2012). Furthermore, one of the important mechanisms of action of environmental chemicals may involve reactive oxygen species (ROS)-induced oxidative stress (Luo et al., 2010; Ruder et al., 2008; Wells et al., 2009). Imbalance between ROS production and antioxidant ROS detoxification pathways is considered to be responsible for pregnancy-related disorders, such as embryonic mortality, early spontaneous abortion, intrauterine growth restriction, fetal death, premature delivery and low birthweight (Agarwal et al., 2012; Al-Gubory et al., 2010).

The susceptibility of the conceptus to developmental disturbances induced by environmental pollutants is related to the stage of development, the duration of exposition and the cumulative exposure dose. This might be pivotal in embryonic and fetal vulnerability towards toxicity of environmental contaminants. A weak antioxidant defence system renders the developing conceptus vulnerable to oxidative damage induced by *in utero* exposure to environmental contaminants. Indeed, antioxidant enzymes and detoxification pathways are not fully developed in the conceptus early in pregnancy (Al-Gubory and Garrel, 2012; Davis and Auten, 2010). Therefore, the association between environmental pollutants, oxidative stress and adverse prenatal development constitute a topic of interest in the field of reproductive medicine and fertility. This review focuses on the putative association between oxidative stress and adverse prenatal development caused by man-made chemicals and unhealthy lifestyle behaviours, particularly the notion of increased risk for developmental toxicity due to combined and cumulative exposure to various environmental pollutants.

ROS and oxidative stress

The generation of mitochondrial superoxide radical ($\text{O}_2^{\bullet-}$) is the first step in the formation and propagation of other ROS within cells and tissues. The production of $\text{O}_2^{\bullet-}$ occurs during the passage of electrons through the mitochondrial electron transport system during oxidative phosphorylation. The free radical $\text{O}_2^{\bullet-}$ is catalysed to hydrogen peroxide (H_2O_2) which in turn can be further catalysed to H_2O and O_2 (McCord and Fridovich, 1969). However, unconverted $\text{O}_2^{\bullet-}$ and H_2O_2 interact with each other via the iron-catalysed Haber–Weiss reaction to generate the hydroxyl radical (OH^{\bullet}). The free radical nitric oxide (NO^{\bullet}), generated from L-arginine in a reaction catalysed by NO synthases may also react with $\text{O}_2^{\bullet-}$ to produce peroxynitrite (ONOO^-). This is a powerful oxidant that can react with amino acids and alter the structure and function of proteins (Alvarez and Radi, 2003). Mitochondria are endowed with NO synthase and are a source of cellular NO and ONOO^- production (Valdez and Boveris, 2007). Cellular ONOO^- produced in response to physiological stress and environmental toxicants triggers oxidative DNA damage and apoptosis (Ahmad et al., 2009). ROS are also produced by various enzymic pathways, including membrane-bound NADPH oxidase, xanthine oxidase, the metabolism of arachidonic acid and the mitochondrial cytochrome P450 (Bedard and Krause, 2007; Zangar et al., 2004). In addition, ROS are generated in response to environmental chemicals (Lehnert and Iyer, 2002) and during transformation of xenobiotics and drugs, UV irradiation and inflammation (Jezek and Hlavatá, 2005). The cellular antioxidant mechanism requires therefore a tight control of $\text{O}_2^{\bullet-}$ and H_2O_2 production before their transformation to highly reactive ROS, mainly ONOO^- and OH^{\bullet} . Physiological concentrations of $\text{O}_2^{\bullet-}$ and H_2O_2 play important roles in cellular regulation through signal transduction pathways and gene expression involved in cell metabolism, growth, development and differentiation (Dennerly, 2007; Valko et al., 2007). In contrast, ROS overproduction induces oxidative stress, a state where increased ROS generation overwhelms

antioxidant protection and subsequently leads to oxidative damage of cellular macromolecules, including proteins, lipids and nucleic acids (Jezek and Hlavatá, 2005). The most important consequences of this oxidative damage are loss of enzyme activity, peroxidative cell membrane damage, DNA lesions and mutagenesis. Overall, the control of ROS production by antioxidants (Figure 1) is considered to be a double-edged sword (Buonocore et al., 2010).

ROS-scavenging systems

ROS are constantly produced during normal cellular energy production and metabolism in the mitochondria. The mitochondrial membranes contain the enzyme complexes (complexes I, II, III and IV) and the electron carriers (coenzyme Q and cytochrome c of the electron transport chain that play important role in adenosine triphosphate (ATP) production). Complexes I, II, and III are sources of $\cdot\text{O}_2^-$ and other ROS, mainly $\cdot\text{OH}$, $\cdot\text{NO}$, H_2O_2 and ONOO^- (Adam-Vizi and Chinopoulos, 2006). The main mitochondrial functions are the production of ATP and the control of ROS concentrations within a physiological range. Mammalian cells have elaborated interdependent enzymic and nonenzymic antioxidant systems that protect cellular structural integrity and functions against ROS damage by maintaining physiological concentrations of ROS (Jezek and Hlavatá, 2005). Antioxidant networks comprise copper- and zinc-containing SOD (Cu,Zn-SOD or SOD1) predominantly present in the cytoplasm (McCord and Fridovich, 1969) and manganese-containing superoxide dismutase (Mn-SOD or SOD2), located in the mitochondrial matrix (Weisiger and Fridovich, 1973).

These antioxidants catalyse the dismutation $\cdot\text{O}_2^-$ into H_2O_2 (McCord and Fridovich, 1969). Thus, they constitute the first enzymic step that plays a vital role in the control of cellular $\cdot\text{O}_2^-$ production. In turn, catalase (CAT), present in peroxisomes (Chance et al., 1979), and the glutathione-dependent antioxidant enzymes, selenium-containing glutathione peroxidases (Se-GPX), present in the mitochondrial matrix and the cytoplasm (Hayes and McLellan, 1993), both catalyse the conversion of H_2O_2 into H_2O . The ability of Se-GPX to reduce H_2O_2 is dependent on the activity of glutathione reductase which catalyses the reduction of the oxidized form of glutathione to the reduced glutathione (GSH) with NADPH as the reducing agent and is considered to be an essential enzyme for the GSH redox cycle that ensures adequate concentrations of GSH necessary for the maintenance of cells in a reduced state (Schafer and Buettner, 2001). Therefore, cellular enzymic and nonenzymic antioxidants are interrelated systems that interact with each other to control ROS production and maintain their physiological concentrations in biological systems (Figure 2).

Cumulative exposure to environmental pollutants and prenatal development outcome

Cumulative exposure to environmental pollutants can be defined as coexposure of an organism to more than one or multiple molecules from different sources that might occur by oral, inhalation and/or dermal pathways. Pregnancy outcome and neonatal health can be influenced by the preconception and prenatal maternal environment and, in turn, to multiple pollutants present *in utero*, mainly during early

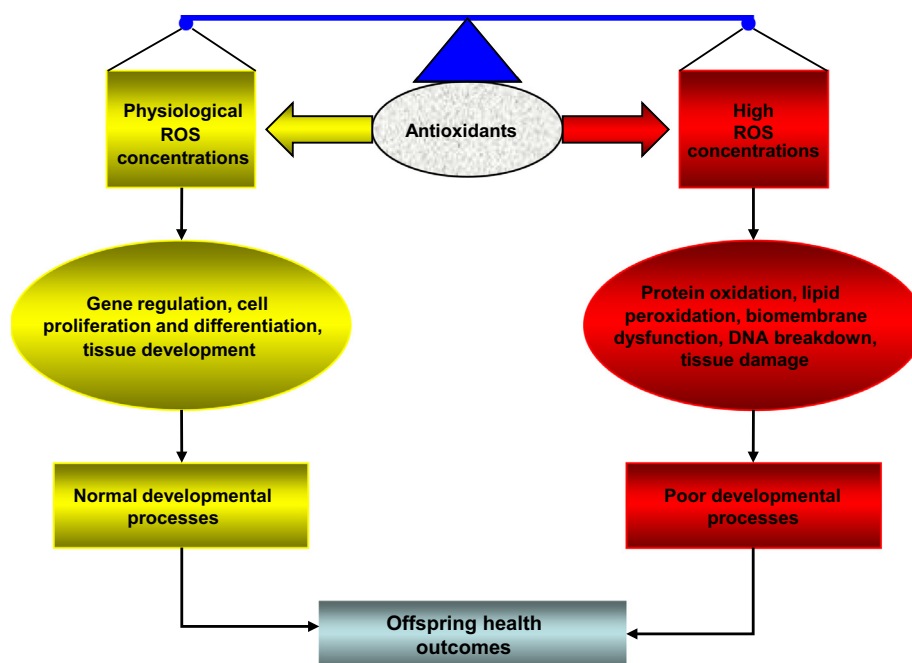


Figure 1 The control of reactive oxygen species (ROS) production by antioxidants is considered to be a double-edged sword. Physiological concentrations of ROS play important roles in normal developmental processes that positively impact newborn growth, development and health through gene regulation, cell proliferation and differentiation and tissue development, whereas high concentrations of ROS damage cellular macromolecules, lead to poor developmental processes and birth outcomes that negatively impact newborn growth, development and health.

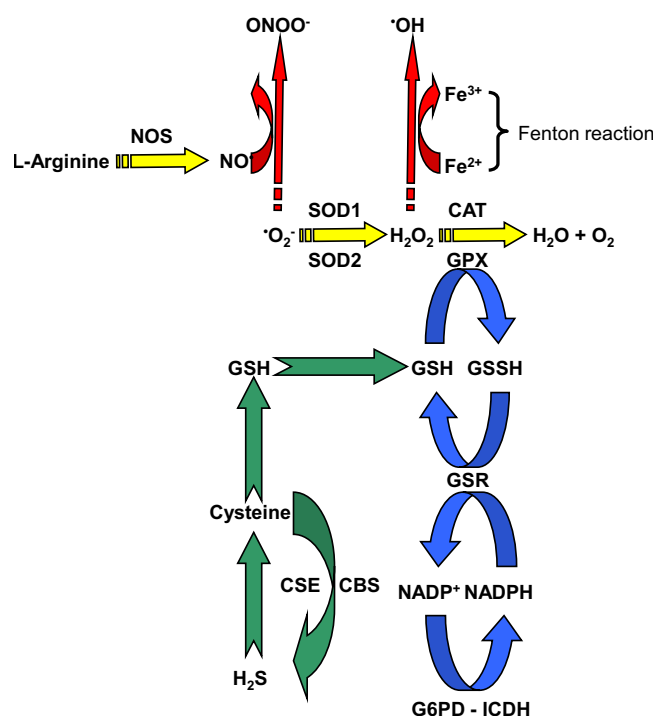


Figure 2 Overview of the enzymic and nonenzymic antioxidant pathways involved in the control of reactive oxygen species (ROS) production in biological systems. O_2^- = superoxide anion; OH = hydroxyl radical; CAT = catalase; CBS = cystathionine β -synthase; CDO = cysteine dioxygenase; CSD = cysteine sulphinatase decarboxylase; CSE = cystathionine γ -lyase; G6PD = glucose-6-phosphate dehydrogenase; GPX = glutathione peroxidase; GSH = reduced glutathione; GSR = glutathione reductase; GSSG = oxidized glutathione; ICDH = isocitrate dehydrogenase; NADP = oxidized nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; NOS = nitric oxide synthase; ONOO^- = peroxynitrite; SOD1 = copper-zinc superoxide dismutase; SOD2 = manganese SOD.

embryonic and fetal development. Most guideline animal studies to evaluate prenatal developmental toxicity focus on one chemical at a time to derive a no-observed-adverse-effect concentration. However, animal studies have shown that multicomponent mixtures of endocrine-disrupting chemicals have cumulative adverse effects on prenatal and post-natal development even when the individual chemicals occur in the mixture at low and ineffective concentrations (Christiansen et al., 2009, 2012; Crawford and deCatanzaro, 2012; Hass et al., 2012; Jacobsen et al., 2010, 2012; Rider et al., 2010; Yu et al., 2013). The possible mechanisms by which environmental pollutants exert their negative impact on the development involve divergent pathways including, but not limited to, disruption of hormonal signalling systems and epigenetic gene regulation, as well as induction of oxidative stress (Fleisch et al., 2012; Jain, 2012; Mrema et al., 2013; Ünüvar and Büyükgözü, 2012).

ROS imbalance and associated oxidative stress is a common finding across many different classes of environmental pollutants, including xenoestrogens, pesticides and heavy

metals, as well as unhealthy lifestyle factors, mainly tobacco smoke, alcohol and medical drugs, and may provide a common mode of action for potential adverse effects on prenatal development and health outcomes (Kovacic and Somanathan, 2006). Most aforementioned environmental pollutants could share a specific mode of developmental toxicity via enhancement of ROS generation and oxidative damage (Figure 3). The question of whether these compounds increase ROS production, induce oxidative damage to the developing embryo and fetus and adversely affects neonatal development and health remains open. The development of a basic research programme will benefit the field of reproductive medicine, particularly to progress towards designing effective therapeutic intervention strategies.

Environmental chemicals, oxidative stress and prenatal developmental outcomes

Exposure to human-made chemicals, mainly xenoestrogens (Maffini et al., 2006; Witorsch, 2002), pesticides (Dewan et al., 2013; Flocks et al., 2012; Knez, 2013; Pathak et al., 2008, 2010, 2011; Sharma et al., 2012) and heavy metals (Samuel et al., 2011; Stringari et al., 2008; Uzbekov et al., 2007) and the associated risk for prenatal development remains a major problem for maternal health and that of her offspring. The major concern with in-utero exposure to the aforementioned environmental chemicals is that they can disrupt reproductive function (Miller et al., 2004) and contribute to adverse prenatal developmental outcomes and birth defects (Buczyńska and Tarkowski, 2005). In-utero exposure to xenoestrogens, pesticides and/or heavy metals could result in abnormal ROS generation which ultimately leads to irreversible alteration of cellular macromolecules, affect the normal functioning of mitochondrial membranes and causes mitochondrial dysfunction, mitochondrial ROS-induced ROS release (RIRR) and apoptosis (Zorov et al., 2006). Damaged mitochondria produce high concentrations of ROS which enhance mitochondria-driven ROS propagation (or RIRR) via activation of an inter-mitochondrial signalling network (Park and Choi, 2012). Although mitochondrial RIRR, mitochondrial DNA damage and dysfunction may be the underlying mechanisms by which xenoestrogens (Moon et al., 2012; Ooe et al., 2005), pesticides (Lee et al., 2012; Ojha et al., 2011) and heavy metals (Stohs et al., 2001) exert their cellular toxicity, there is substantial evidence that the mitochondrion is an important target for many environmental contaminants (Meyer et al., 2013).

Cellular ATP is produced through mitochondrial oxidative phosphorylation. Mitochondria provide the ATP necessary for oocyte maturation and early embryogenesis (Van Blerkom, 2009, 2011). The mitochondrial DNA is susceptible to oxidative damage by the ever-increasing concentrations of ROS generated as a by product of mitochondrial oxidative phosphorylation. The control of O_2^- production and its downstream ROS by antioxidants within the mitochondria is a central element in the protection of embryonic cells against oxidative damage. The progressive development of the embryonic antioxidant capacity to support stage-specific process of early embryogenesis suggests that the developing embryo is capable of coping with ROS-induced

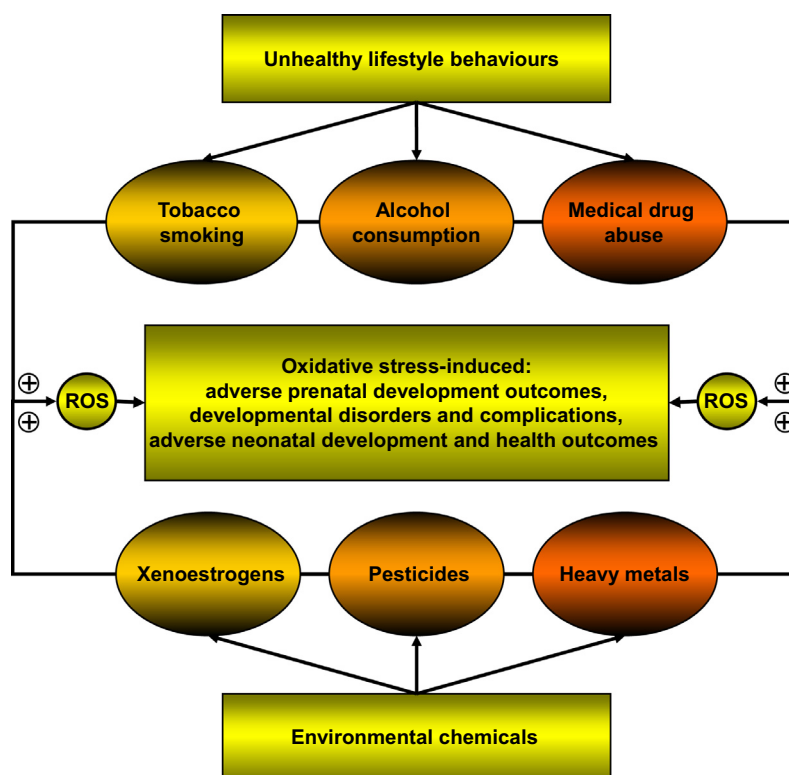


Figure 3 Environmental pollutants, mainly xenoestrogens, pesticides and heavy metals, as well as unhealthy lifestyle behaviours, mainly tobacco smoking, alcohol consumption and excessive medication, are the major factors that contribute to adverse prenatal development outcomes, developmental disorders and complications and neonatal development and health outcomes at least in part through the enhancement of reactive oxygen species (ROS)-induced oxidative stress.

oxidative damage (Zaken et al., 2000). Nevertheless, because of the weak embryonic antioxidant defence at the early stages of organogenesis (Ornoy, 2007), endogenous factors, mainly locally-produced mitochondrial ROS, and exogenous factors, including pollutant-induced mitochondrial ROS generation, may damage mitochondrial and nuclear DNA, adversely affect early embryogenesis and may compromise post-implantation prenatal development.

Xenoestrogens

Xenoestrogens, collectively referred to as endocrine disruptors, have the ability to mimic endogenous steroid hormones and interfere with endocrine processes (Singleton and Khan, 2003) and hereby block the action of oestrogens in reproductive tissues and organs. Xenoestrogens, mainly bisphenol-A (BPA), phthalates, parabens, tributyltin (TBT) and triclosan (TCS), are ubiquitous environmental contaminants because of their presence in plastics, food packaging and products, coatings for oral medication, cosmetic products and pharmaceutical personal care products, (Klingmüller and Alléra, 2011). The mutual actions of oestrogen and progesterone on their uterine receptors are essential to endometrial receptivity, embryonic implantation and the establishment of pregnancy. Animal experiments have shown that all of the aforementioned xenoestrogens are potentially hazardous to reproductive functions, conceptus implantation, development, survival and prenatal development

(Adeeko et al., 2003; Berger et al., 2007, 2008, 2010; Crawford and deCatanzaro, 2012; Ema et al., 1995; Fusani et al., 2007; Harazono et al., 1996, 1998; James et al., 2010; Rubin et al., 2001; Shaw and deCatanzaro, 2009; Si et al., 2012; Taxvig et al., 2008; Varayoud et al., 2011).

BPA, a plasticizer used in the production of polycarbonate plastic and epoxy resin, is a well-known endocrine disruptor (Maffini et al., 2006). BPA is an oestrogen-mimicking chemical with weaker affinity for oestrogen receptors than 17β -oestradiol (Welshons et al., 2003) and can be leached from plastic, food and beverage containers and widely spread in the environment and food chain. Exposure of women to BPA during pregnancy and prenatal contamination can be detected by its presence in maternal and umbilical cord blood, amniotic fluid, fetal and placental tissues (Le et al., 2008; Vandenberg et al., 2007). It is important to highlight that the adverse effects of preimplantation BPA exposure on embryonic implantation and the establishment of pregnancy in rodents depend on the dose and day of administration. Litter size was reduced after exposure of CF-1 mice on days 1–4 of pregnancy to daily BPA doses of 100 mg/kg/day (Berger et al., 2007). Exposure of CF-1 mice to BPA on days 1–4 of pregnancy to daily doses of 200 or 300 mg/kg/day has been shown to reduce the number of implantation sites (Berger et al., 2008), whereas no implantation sites were detected on day 4.5 of pregnancy when C57BL6 mice were exposed on days 0.5–3.5 of pregnancy to daily doses of 100 mg/kg/day (Xiao et al., 2011). The

number of implantation sites was found to be reduced when CF-1 mice received a dose of 300 mg/kg/day on day 0 or day 1 of pregnancy (Berger et al., 2008). Treatment of mice with doses of 4 mg BPA (122 mg/kg) and 9 mg TCS (262 mg/kg) on days 1–3 of pregnancy were found to be individually ineffective, whereas combination of these chemicals reduced the number of implantation sites (Crawford and Decatanzaro, 2012).

Although the aforementioned studies provide support for the ability of BPA to disturb embryonic implantation and pregnancy outcome, there is still a lot of controversy around developmental toxicity of BPA. Indeed, maternal oral exposure to low doses of BPA (2, 20 and 200 µg/kg/day) from day 7 of pregnancy to post-natal day 18 failed to adversely affect reproductive development, function and adult sex hormone-dependent behaviour in female rats (Ryan et al., 2010). These issues were highlighted in an editorial by Sharpe (2010). The results of Ryan et al. (2010) are in agreement with other studies that show a similar absence of adverse effects on reproductive development and function in female and male rats and mice when exposed orally to BPA at doses in excess of human exposure levels (Cagen et al., 1999; Ema et al., 2001; Howdeshell et al., 2008a,b; Tinwell et al., 2002; Tyl et al., 2002). The difference in results obtained by different laboratories worldwide could be explained, at least in part, by the use of different routes of BPA administration (Sharpe, 2010).

Although oxidative stress induced by exposure of mice to BPA during embryonic/fetal life is associated with underdevelopment of fetal brain, kidney and testis (Kabuto et al., 2004), the oxidative mechanism of action of BPA on conceptus implantation and development still remains to be elucidated. It is of interest to note that treatment of mice for 5 days with doses of BPA below the no-observed-adverse-effect concentration (0.05 and 1.2 mg/kg/day) has been shown to decrease the expression of GPX3 and increase hepatic concentrations of malondialdehyde, a product of lipid peroxidation, and ultimately leads to mitochondrial dysfunction and liver damage (Ooe et al., 2005).

Phthalates, used in the production of personal care products, plastics, food packaging and coatings for oral medication, and parabens and ubiquitously used as antimicrobial preservatives in a wide range of body care cosmetics, pharmaceuticals and foods, are potential endocrine-disrupting chemicals. There is substantial evidence from animal studies that phthalate exposure modulates circulating hormone concentrations and adversely affects reproductive physiology and the development of oestrogen sensitive target tissues (Kay et al., 2013). Exposure of rats on gestational days 14–18 to a mixture of phthalates suppresses the expression of genes responsible for cholesterol metabolism, inhibits fetal testosterone production and hereby induces male reproductive malformations (Hannas et al., 2011). Phthalates have been shown to be present in maternal blood after early exposure of pregnant rats and account for contamination of placental and fetal tissues (Singh et al., 1975) and amniotic fluid (Calafat et al., 2006). Exposure of rats to a mixture of butyl benzyl phthalate and the antiandrogenic pesticide linuron induces dose-additive adverse effects on male reproductive development (Hotchkiss et al., 2004). Furthermore, co-administration of chemically different phthalates to pregnant rats induces male reproductive malformations in

a cumulative dose-additive manner (Howdeshell et al., 2007, 2008a,b). Phthalates and their metabolites are present in human amniotic fluid (Silva et al., 2004) and urine (Casas et al., 2011). Exposure of rats to parabens during pregnancy has been shown to be associated with accumulation of parabens in maternal plasma, amniotic fluid, placenta and fetal liver (Frederiksen et al., 2008). It has been reported that human placental tissues collected at delivery contain methyl-, ethyl-, propyl- and butyl-paraben which are the most commonly used parabens in industrial applications (Jiménez-Díaz et al., 2011). This indicates that women are exposed to multiple parabens during pregnancy. The fact that parabens (Smith et al., 2012) and phthalate metabolites (Braun et al., 2012) are present in women's urine before and during pregnancy raises the question of human exposure to these endocrine-disrupting xenoestrogens and highlights the potential risk for developmental processes and offspring health outcomes.

Increased oxidative cellular damage through alteration of ROS-scavenging antioxidant enzymes has been suggested to be an underlying mechanism of phthalate and paraben toxicity. An in-vitro study using a cell line from monkey kidney showed that exposure to propylparaben for 24 h induces cell-cycle arrest and increases oxidative DNA damage (Martín et al., 2010). Exposure of mice to butyl cyclohexyl phthalate given orally at a dose of 100, 200 or 400 mg/kg/day for 5 consecutive days per week during 28 days has been shown to be associated with reduction in the enzymic activities of SOD and CAT in liver tissue (Yavaşoğlu et al., 2012). In-vivo administration of three different doses of butylparaben (40, 20 and 13.33 mg/kg/day) for 30 days induces lipid peroxidation through reduction in the enzymic activities of SOD, GPX and CAT in liver tissue (Shah and Verma, 2011). Feeding rats with chow containing 2% of mono-*n*-butyl phthalate for 3 days has been shown to induce oxidative DNA damage and ultimately leads to atrophy of the testis (Shono and Taguchi, 2014). Experimental data using developing fish embryos provide support for the concept that oxidative stress is an important mechanism in phthalate-induced developmental toxicity (Mankidy et al., 2013).

TBT has been used in marine paints and intensively applied as an antifouling agent. The major concern with TBT is that it leaks out from the paint, leads to the pollution of aquatic milieu and hence re-enters into the food chain. In spite of the fact that the International Maritime Organization called for a global prohibition of TBT by 2008 (<http://www.imo.org/OurWork/Environment/Anti-foulingSystems/Pages/Default.aspx>),¹ its accumulation in the sediment for almost the last four centuries cannot be without long-term effects on the marine ecosystem, food chain and prenatal development. Administration of TBT to rats during the post-implantation period increases the incidence of fetal malformation and loss (Ema et al., 1995). In addition, TBT increases the rate of implantation failure in rats after administration between days 0 and 7 (Harazono et al., 1998) or even between days 0 and 3 (Harazono et al., 1998) of pregnancy. Enlarged placenta, reduced fetal ossification and growth retardation were reported when rats

¹ www.imo.org/OurWork/.../Anti-foulingSystems/.../FOULING2003.pdf. Focus on IMO (International Maritime Organisation) – Anti-fouling systems.

were treated with TBT between days 0 and 19 of pregnancy (Adeeko et al., 2003). Exposure of rats to TBT during pregnancy has been shown to be associated with accumulation of TBT and its metabolite dibutyltin (DBT) in the placenta and fetal tissues (Cooke et al., 2008). Female offspring of mice exposed to low doses of tributyltin from day 6 of pregnancy through the period of lactation exhibit altered patterns of oestrous cyclicity in adulthood (Si et al., 2012). Although the mechanisms by which TBT induces developmental and reproductive toxicity have not been fully elucidated, TBT was reported to induce oxidative stress as demonstrated by an increase in hepatic ROS production, lipid peroxidation and DNA damage after exposure of rats to this environmental pollutant (Liu et al., 2006). In addition, exposure of developing zebrafish to TBT has been shown to induce apoptosis in the retinal neuron, at least in part, through ROS-induced oxidative stress (Dong et al., 2006). An in-vitro study using rat organotypic hippocampal slice cultures showed that TBT increased ROS production and lipid peroxidation and induced apoptosis, whereas when pretreated with antioxidants such effects have been removed (Ishihara et al., 2012).

TCS is used in almost all household items and personal care products as an antibacterial agent and it is increasingly found in wastewater and sewage sludge. Therefore, TCS is often present in the terrestrial environment mainly when sewage sludge is applied as fertilizer to agricultural land. It has been reported that TCS is one of the main environmental chemicals that contaminates surface water and accumulates in wastewater effluents, receiving rivers and lake sediment (Singer et al., 2002). The accumulation of TCS in the aquatic environment leads to contamination of animals (Fair et al., 2009). Recently, more attention is being paid to TCS as a potential toxicant because of its persistence in the terrestrial and aquatic environments. In the rat, exposure to TCS before mating, during pregnancy and lactation has been shown to impair maternal thyroid homeostasis and offspring pubertal development (Paul et al., 2012; Rodríguez and Sanchez, 2010). Exposure to TCS during pregnancy in rats has also been shown to induce maternal, fetal and early neonatal hypothyroxinaemia (Paul et al., 2012). Treatment of mice with high doses of TCS (523 and 785 mg/kg/day) just before blastocyst implantation has been shown to reduce the number of implantation sites, and a lower dose of TCS (262 mg/kg/day) given in combination with BPA (61 mg/kg/day) has the same adverse effect on embryonic implantation (Crawford and deCatanzaro, 2012). The underlying mechanism of TCS cytotoxicity is not clearly elucidated. Mitochondrial membrane damage is an early event leading to cell death by apoptosis and may be initiated by lipid peroxidation (Jezek and Hlavatá, 2005). Increased concentrations of lipid peroxides have been observed after exposure of freshwater mussels for 7 days to 580 ng TCS/l (Riva et al., 2012).

Pesticides

The use of pesticides in agriculture has caused serious environmental and health problems to the humans and animals. The intensive use of pesticides (herbicides, fungicides, insecticides, rodenticides) has led to the presence of these pollutants in human and animal diet. Plant products, mainly

fruit and vegetables, are contaminated by pesticide residues as a result of the intensive treatment of many crops (Keikotlhaile et al., 2010). Although pesticides are widely used in the world, China, the USA, France, Brazil and Japan are the largest pesticide producers and consumers (Zhang et al., 2011) and pesticides have become a major environmental and human health problem in India (Bhanti and Taneja, 2007), China (Zhou et al., 2012) and France (Nougadère et al., 2012), the first pesticide consumer in Europe (Zhang et al., 2011). In addition, soil and ground water contamination from agricultural runoff (Anderson et al., 2011; Bengtsson et al., 2007) expose grazing farm animals to various pesticides and raise the question of the potential adverse effects of such pollutants on welfare, health, fertility and reproductive performance of farm animals (Tiemann, 2008). The presence of organochlorine pesticides in human placenta (Lopez-Espinosa et al., 2007) has been shown to be associated with oxidative stress, intrauterine growth restriction and lower birthweight. Pesticide exposure has been shown to favour oxidative stress-induced lipid peroxidation and DNA damage in fish (Slaninova et al., 2009) and rodents (Koner et al., 1998; Sahoo et al., 2000), as well as in humans, mainly agricultural workers (Ranjbar et al., 2002; Rastogi et al., 2009; Shadnia et al., 2005) and pregnant women (Flocks et al., 2012; Pathak et al., 2008, 2010, 2011). Mammalian experimental studies with pesticides which directly linked developmental toxicity to ROS-induced oxidative stress are very scarce. Exposure of mice to tetrachlorodibenzodioxin, endrin or lindane given on day 12 of pregnancy at a dose of 30–60, 4.5 and 30 mg/kg body weight, respectively, has been shown to increase $\cdot\text{O}_2^-$ production and ultimately leads to fetal and placental oxidative damage as shown by induction of lipid peroxidation and DNA strand breaks (Hassoun and Stohs, 1996). Available experimental data from aquatic animals, such as fish, amphibians and invertebrates, provide support for the concept that oxidative stress is a highly important mechanism in pesticide-induced developmental toxicity (Pašková et al., 2011).

Heavy metals

Maternal exposure to heavy metals before and during pregnancy primarily occurs through the consumption of contaminated food and/or inhalation of contaminated air. Heavy metals are common environmental contaminants known for their adverse effects on prenatal development (Gundacker and Hengstschläger, 2012). Maternal exposure to cadmium (Cd) during pregnancy has been shown to be associated with early delivery and low birthweight (Kippler et al., 2012; Nishijo et al., 2002, 2004). Early embryonic development and implantation have also been identified as targets for Cd toxicity in experimental animals (Thompson and Bannigan, 2008). Environmental mercury (Hg) can be converted to methylmercury (MeHg) within microorganisms in aquatic sediments, allowing it to enter the food chain. Exposure to MeHg during pregnancy by the consumption of contaminated seafood may adversely impact prenatal developmental outcomes (Davidson et al., 2008). Exposure to heavy metal has been shown to induce ROS formation and oxidative damage to macromolecules

(Valko et al., 2005). However, the underlying mechanisms by which heavy metals induce oxidative stress and developmental toxicity remain to be fully characterized. Impairment of the ROS-scavenging antioxidant systems in the brain, liver and kidney of the developing rat fetuses is one established mechanism by which prenatal exposure to heavy metals induce oxidative stress (Dreiem et al., 2005; Uzbekov et al., 2007). Exposure of pregnant rats from embryonic day 9 to day 21 to Cd induces reproductive dysfunction through increased oxidative stress, as shown by an increase in H₂O₂ concentrations and lipid peroxidation and a decrease in activities of key ROS-scavenging antioxidant enzymes, namely SOD, CAT, GPX, glutathione reductase and glutathione-S-transferase (GST) (Samuel et al., 2011). Nuclear factor-erythroid 2-related factor (Nrf2) is a transcription factor that binds to antioxidant response elements to activate transcription. Activation of the Nrf2-antioxidant response element signalling pathway plays an important role in the expression of genes coding for protein involved in the control of ROS by enhancing cellular antioxidant capacity (Nguyen et al., 2009). Treatment of mouse embryonic fibroblast cells with 2.5 µmol/l MeHg and 5.0 µmol/l Cd for 24 h induces significant alterations in oxidative-related response pathways such as Nrf2-mediated oxidative stress response, GSH metabolism and metabolism of xenobiotics by cytochrome P450 (Yu et al., 2010).

Unhealthy lifestyle behaviours, oxidative stress and prenatal development outcomes

Tobacco smoking, alcohol consumption and/or drug abuse are major unhealthy lifestyle behaviours that adversely impact the female and male fertility (Anderson et al., 2010; Sharma et al., 2013). These lifestyle behaviours are known for their potential adverse effects on conceptus implantation, the establishment of pregnancy or prenatal development in humans (Kay et al., 2000; Thadani, 2002) and rodents (Huang et al., 2009; Wang et al., 2009; Wentzel and Eriksson, 2006; Wentzel et al., 2006). Increase ROS production and associated oxidative cellular damage induced by medical drugs, ethanol and cigarette smoke have been suggested to be an underlying mechanism of developmental toxicity (Kovacic and Somanathan, 2006).

Evidence-based data from epidemiological, clinical and experimental investigations indicate that exposure to tobacco smoke adversely affect steroidogenesis, embryo transport and endometrial receptivity (Dechanet et al., 2011), all contributing to implantation delay or failure and consequent early pregnancy loss. Exposure of whole mouse embryos *in vitro* to nicotine induces embryonic oxidative stress, apoptosis and malformations (Zhao and Reece, 2005). Preconception exposure of mice to cigarette smoke induces oxidative stress and compromises embryonic development (Huang et al., 2009). Exposure of pregnant rats to nicotine induces β-cell apoptosis in the fetal and neonatal pancreas through oxidative stress (Bruin et al., 2008). In-utero exposure to nicotine induces placental oxidative stress and inhibits fetal growth in rats (Wang et al., 2009). Active or passive smoking both causes oxidative stress by altering the balance between oxidants and antioxidants in

fetal cord blood (Aycicek and Ipek, 2008). Tobacco smoke is a complex mixture containing numerous toxic constituents (Borgerding and Klus, 2005). Different tobacco constituents increased oxidative stress and adversely affect cell proliferation and differentiation during embryonic development in pregnant female smokers (Feldes et al., 2013). One of the observed alterations in the antioxidant defence system is down-regulation of genes encoding glutathione S-transferases (GSTM1, GSTA1) which contribute to the GSH conjugation and GSH-dependent biotransformation of xenobiotics and many catalyse GPX (Board and Menon, 2013). It is important to highlight that young female smokers and those with a low education level are at risk for pregnancy-associated disorders and complications because of low antioxidant intake during pregnancy (Uusitalo et al., 2008).

Prenatal exposure of rats to ethanol induces hypothalamic oxidative stress and neuroendocrine alterations in offspring (Dembele et al., 2006). Chronic ethanol administration to pregnant mice (Wentzel and Eriksson, 2006) and rats (Wentzel et al., 2006) disturbs embryogenesis and increases fetal death and offspring malformation through enhancement of oxidative stress. In-utero combined exposure to cigarette smoke and alcohol results in an increase in lipid peroxidation and causes a parallel decrease in the activities of key antioxidant enzymes in the cerebral cortex and liver of mice offspring (Li and Wang, 2004). One of the main identified teratogenic mechanisms associated with medication use during pregnancy is oxidative stress (van Gelder et al., 2010). Phenytoin (Liu and Wells, 1994), thalidomide (Hansen and Harris, 2004), valproic acid (Defoort et al., 2006), almokalant, dofetilide, cisapride and astemizole (Danielsson et al., 2007) are the identified medical drugs known to induce oxidative stress. Generation of ROS and mitochondrial dysfunction are well-characterized relevant effects of medical drugs (Deavall et al., 2012).

Strategies against environmental pollutant-induced developmental toxicity

Many molecules present in animal and human diets have significant and specific antioxidant activity against ROS-induced oxidative stress in tissues and organs. Therefore, intervention strategies, such as antioxidant nutritional therapies, could benefit embryonic and fetal development, neonatal growth and health outcome. Maternal periconception nutrition may influence prenatal development and the course of the pregnancy. During the periconception period, the roles of dietary antioxidants on early developmental processes, mainly embryonic implantation, placentation and organogenesis, are of utmost importance (Cetin et al., 2010). Therefore, the therapeutic potential of periconception dietary antioxidants as an effective treatment of oxidative stress, female infertility and prenatal developmental disorders is of high interest in the field of reproductive biology and medicine. Healthful nutritional interventions (Henig et al., 2007, 2012), such as antioxidant therapy (Huang et al., 2007; Junovich et al., 2011; Nash et al., 2007), may provide sensible means to develop primary prevention strategies against adverse prenatal developmental outcome mediated by maternal exposure to environmental pollutants.

Conclusions

Although exposure to tobacco, alcohol and medical drugs can be reduced or even avoided during pregnancy, exposure to other contaminants, mainly xenoestrogens, pesticides and heavy metals, seems to be difficult to avoid due to their ubiquitous presence in the environment. Maternal exposure to xenoestrogens, pesticides and heavy metals before and during pregnancy occurs through the consumption of contaminated food, water and beverages that may affect developmental and health outcomes through ROS-induced oxidative stress (Figure 4).

Animal studies are often limited to the evaluation of developmental toxicity of one or a mixture of a few environmental pollutants. Nevertheless, the available research findings are relevant because they have alerted the scientific community, public authorities, industrial players and

the population at large regarding the adverse health impact following maternal exposure to various environmental pollutants. Therefore, the use of animal models is still necessary to examine the adverse effects of cumulative exposure to various ubiquitous pollutants on prenatal development. The aims of such studies are to better understand the mechanisms by which environmental pollutants adversely affect conceptus development and to elucidate the impact of cumulative exposures to multiple pollutants on post-natal development and childhood health outcomes. The adverse effect of several chemicals on prenatal development at environmental concentrations is still a matter of controversy. Therefore, the toxicity of certain chemicals has yet to be proven by further properly designed studies. Wildlife and human investigations and observations in the natural and/or altered environmental conditions will also be needed to understand if maternal periconception

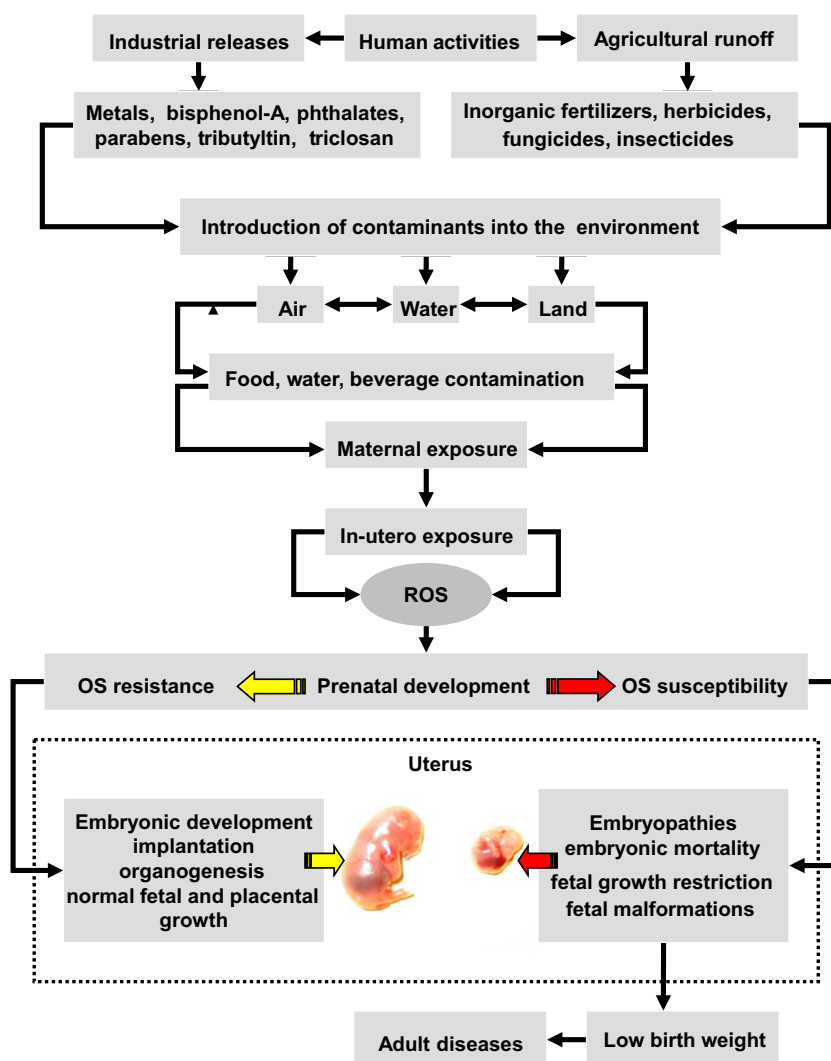


Figure 4 The links between environmental pollutants from various industrial and agricultural activities, reactive oxygen species (ROS), oxidative stress (OS), adverse prenatal developmental and health outcomes. The excessive production of ROS due to maternal exposure to various environmental chemicals early in pregnancy may exceed the capacity of conceptus antioxidant defence and ultimately lead to OS poor developmental processes and birth outcome that negatively impact newborn growth, development and health.

exposure to multiple environmental pollutants acts synergistically to adversely affect maternal reproductive health, fertility and prenatal development.

In the context of current climate change and food security (Gregory et al., 2005), as well as the constantly fluctuating environmental pollution (Rylander et al., 2011), minimizing environmental impacts on prenatal and post-natal development and health outcomes due to cumulative exposure to various pollutants is a challenge and requires the development of international applied research programmes and preventive strategies. The potential of dietary antioxidants as an effective treatment of oxidative stress may provide sensible therapeutic means against female infertility and adverse prenatal developmental outcome mediated by maternal exposure to environmental pollutants. In addition, communication campaigns to educate and to provide basic medical information will be necessary because a reduction in the cost of health care is an increasingly important economic imperative.

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