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Review of the Developmental Toxicity and Teratogenicity of Three Environmental Contaminants (Cadmium, Lead and Mercury)

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ABSTRACT

Heavy metals are among a large number of substances that exert adverse effects on embryonic development and human health. The large amount of heavy metals recently employed by modern industry produces a gradual increase of their concentrations in water, soils, and food. Embryos and fetuses are exposed every day to such toxic chemicals and other harmful substances in the air their mothers breathe, the food their mothers eat, the water their mothers drink, even in their mothers' milk. Exposure to these health hazards is putting embryos and newborns at risk for dangerous diseases and abnormal development. Even infant death and sudden infant death syndrome have been linked to toxic air. Therefore, the objective of this article was to illustrate the spectrum of developmental toxicity and teratogenicity (in experimental animals and human) resulting from exposure to cadmium, lead and mercury. A bibliography of many papers from different journals was generated from which appropriate data were presented. These data should provide a basis for predictions about types of malformations that might be expected in further studies and for judging postulated heavy metal-induced human birth defects. The following parameters were listed: 1) the developmental toxicity and teratogenicity of the chosen heavy metals (cadmium, lead and mercury) in experimental animal and human embryos, fetuses and newborns, 2) the mode of action and mechanism of their teratogenicity as well as the antagonism of their-induced teratogenic effects, 3) their transfer through placenta and breast milk, and 4) their bioaccumulation and toxicity in different body organs of vertebrates.

Keywords: Bioaccumulation, Developmental toxicity, Heavy metals, Placental transfer, Teratogenic effect.

CADMIUM

Cadmium (Cd) is an environmental pollutant that accumulates within the food web. The largest potential sources of Cd exposure for humans are food (meat, fish, grains, vegetables and fruits) and cigarette smoke (Koller, 1998).

1.1. Developmental Toxicity and Teratogenicity of Cadmium

Cadmium is teratogenic and embryotoxic causing different kinds of malformations and lethality in embryos and fetuses of vertebrate animals and human (reviewed by Webster, 1990; Domingo, 1994).

1.1.1. Developmental Toxicity and Teratogenicity of Cadmium in Experimental Animals

Early studies on laboratory animals reported that Cd at higher doses is a potent developmental toxicant (Yu *et al*., 1985). The teratogenic effects of Cd that were observed in fish, frog, chicks, mice, rats, hamster, and monkeys consisted of immunotoxic effects, central nervous system (CNS) anomalies, fetal growth retardation, skeletal defects, facial defects, limb abnormalities, body wall defects, visceral anomalies, developmental delay, delay of the reproductive functions of female offspring and death (Webster, 1990; Domingo, 1994; Chen and Hales, 1994, De *et al*., 1993; Gilani and Alibhai, 1990, Sunderman *et al*., 1991; Soukupova and Dostal 1991; Herkovits and Pérez-Coll, 1996; Salvatori *et al*., 2004, Fraysse *et al*., 2006).

In fishes, exposure to Cd during zebrafish embryonic development caused morphological malformations of organs and ectopic expression of genes involved in regulating developmental process. One of the most common developmental defects observed was altered axial curvature resulting from defects in the myotomes of the somites (Cheng *et al*., 2000). Also, trunk abnormalities resulting in distortions of body axis, reduced myotome formation, and altered axial curvatures were the predominant effects when zebrafish were exposed to Cd, either during the first 24 h of embryonic development or from 3–7 days of age after hatching (Blechinger *et al*., 2002). Furthermore, Cd-exposed zebrafish embryos exhibited abnormal somite patterning of the muscle fibers, and their notochords showed abnormal morphological features and failed to extend to the tail region (Chow and Cheng, 2003). Furthermore, in zebrafish embryo exposed to 100 µM Cd from 5 hours post fertilisation (hpf) to 28 hpf, varying degrees of gross developmental malformations, significantly higher numbers of apoptotic cells in the degenerating neural tube were observed by Chan and Cheng (2003).

In mice, Cd administered to mothers during gestation induced malformations of the neural tube, craniofacial region, limbs, trunk, viscera, and axial skeleton that vary in range and severity among inbred strains of mice (Hovland *et al*., 1999). If the embryos were exposed to Cd before neurulation stages (days 7 and 8 post coitus; p.c.), the most dramatic malformation was an opening in the anterior neural pore (exencephaly). If the exposure occured after the closure of the neural tube, there was a shift to rib and upper limb defects (Nakashima *et al*., 1988). They also concluded that a single dose of

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4 mg/kg body weight (BW) $CdCl_2$ (22 µmol Cd^{2+}) induced exencephaly without affecting the general rates of embryo survival. Neonatal mice exposure to a moderate dose of 50 ppm Cd increased the Cd level in the brain (Gupta *et al.*, 1993), in contrast to gestational exposure, which did not lead to elevated Cd levels in the brain (Murthy *et al.*, 1986). Cd administered to pregnant mice increased DNA damage and activated the apoptotic pathway (Fernández *et al.,* 2003).

In rat, Cd administration during organogenesis at doses of 1-40 mg/kg BW impaired implantation, decreased litter size, significantly increased fetus anomalies and external malformations, reduced metacarpus ossification, produced resorptions and caused embryonic and fetal death (Baranski *et al.* 1982; 1983). Fetal growth retardation and congenital malformations in the offspring of Cd-exposed (0.04–4 mg/kg BW or 60–180 ppm) rats were also reported (Baranski, 1987). Prenatal exposure to a teratogenic Cd dose induced -in the survivor animals- several deleterious effects in their development as well as in adult sexual behaviors (Dogra *et al*., 2001). *In utero* exposure of rats to Cd on gestation day (GD) 12 and 17 resulted in significant mammary gland growth changes at post natal day (PND) 35 (Johnson *et al.*, 2003). Cd treatment during organogenesis of rats induced external malformations; abnormal ossification and reduced male and female sexual behavior (Salvatori et *al.*, 2004).

In chick embryo 50 µl of Cd acetate (at 60-hr incubation) caused embryolethality (35%), ventral body wall defect with malpositioned lower limbs (40%), cell death in lateral plate mesoderm, somites, and neuroepithelium, and weight reduction in survivors (Thompson and Bannigan, 2001). In hamster, when Cd sulfate (2 mg/kg) injected on GD 2 the resulting embryos exhibited craniofacial dysmorphogenesis; significant resorption rates and external, internal, and skeletal abnormalities, e.g., exencephaly, cleft lip, cleft palate, renal agenesis and both unilateral and bilateral microanophthalmia, encephalocele (Gale and Horner, 1987).

1.1.2. Developmental Toxicity and Teratogenicity of Cadmium in Human

In the case of human pregnancy, the Cd passage to offspring from their mothers depends on the particular developmental stage, maternal smoking habit, and the relationship between maternal and fetal zinc status (Kuhnert *et al*, 1988). Maternal exposure to Cd is associated with low birth-weight (Frery *et al.*, 1993).

1.2. Cadmium Bioaccumulation and Transfer through the Placenta and Breast Milk

Cadmium administered to pregnant animals is possibly transferred to the fetus via the placenta, and to neonates through the milk. In mice, the Cd level in the brain was increased after neonatal exposure to a moderate dose of 50 ppm Cd (Gupta *et al.*, 1993), in contrast to gestational exposure, which did not lead to elevated Cd levels in the brain (Baranski, 1987). of the small amount of Cd that passed from mother to offspring during gestation and lactation, the major portion was transferred during lactation, while the placenta restricted the entry of Cd into the fetus (Whelton *et al.*, 1993). The transfer of Cd to milk was also restricted (Bhattacharyya, 1983). Interestingly, when fetuses were directly exposed *in utero* to $CdCl_2$ at levels exceeding that of maternal doses, no effects were seen, thus indicating a mechanism of Cd toxicity involving the placenta (Levin *et al.*, 1981). Although pharmacokinetic studies showed that Cd did not readily reach the fetus, it was accumulated in high concentrations in the placenta (Zadorozhnaja *et al*. 2000). Also, Cd accumulation in the mouse gut endoderm occurs until the closure of the vitelline duct (day 9 p.c.), producing anterior neural tube defects (NTDs) (Fernandez *et al*., 2004). Although relatively low, the transfer of Cd through maternal milk, it represented the primary route of offspring exposure when rodents were exposed during both gestational and lactational periods (Petersson and Oskarsson, 2000). The short- and long-term immunotoxic effects of neonatal exposure to environmentally relevant levels of Cd through maternal milk were also reported (Pillet *et al*., 2005).

1.3. The Mode of Action and Mechanism of Cadmium Developmental Toxicity and Teratogenicity

Cadmium at sufficiently high dosages was found in the trophoblast cells of the rat placenta leading to a decrease in blood flow, decrease in oxygen and nutrient transport, and could cross the placental barrier resulting in fetal death (Sonawane *et al.*, 1975). Cd is an interesting example for analysis of the mechanisms of teratogen-induced NTDs because of the time dependency, the pattern of malformations it can induce, and its tendency to accumulate specifically in the anterior visceral endoderm (AVE) (Dencker, 1975). Cd bounded to high molecular weight proteins such as albumin is freely transported to the yolk-sac cavity and hence to the gut lumen through the vitelline duct, after which it is absorbed by the AVE. Closure of the vitelline duct around day 9 p.c. shifted the retention of Cd from AVE to the mammalian chorioallantoic placenta and this correlateed with a shift in the pattern of malformations from exencephaly to digital defects (Ferm and Carpenter, 1968).

The toxic and teratogenic effects of Cd may be mediated by altered metabolism of Zn and Cu (Sorell and Graziano, 1990). Adequate availability of both Zn and Cu is essential for normal growth and development (Feller and O'Dell, 1980). Zn is a cofactor for many reactions in the organisms and, as a result, it is possible

that part of the action of Cd is caused by an exchange with Zn in some enzymes (Torra *et al*., 1994). Gestational exposure to oral Cd levels of >50 ppm in the drinking water resulted in decreased Zn and Cu levels in the fetal brain (Baranski, 1987), kidney and intestine (Sowa and Steibert, 1985), and in these tissues of neonates (Baranski, 1986) and adult offspring (Roelfzema *et al.*, 1989) as well as in the fetal liver and kidney of rats (Ishitobi and Watanabe, 2005). Also, the developmental stage, during which exposure takes place, was found as a critical factor for embryonic risk assessment of Cd (Goyer, 1996). It was reported that Cd interfered with the integrity of the hypothalamic–pituitary–gonadal axis of rats causing reduction of male and female sexual behaviors (Lafuente, 2000).

An estrogen-like activity for Cd was suggested by Garcia-Morales *et al.* (1994), who showed that Cd mimiced the effects of estrogens by decreasing the level of estrogen receptor (ER) mRNA and transcription of the ER gene. It was also demonstrated that Cd activated ER-α through interaction with the hormone-binding domain of the receptor, to which it binds with high affinity, thereby blocking the binding of estradiol (Stoica *et al.*, 2000). In addition, female offspring that were exposed *in utero* to 0.5 μg/kg or 5 μg/kg Cd experienced an earlier onset of puberty (indicated by earlier vaginal opening) as well as increases in the epithelial area and number of terminal end buds in the mammary glands (Johnson *et al.*, 2003). There is evidence suggesting that Cd^{2+} binds covalently to N7 centers of adenine and guanine, and that it can form intrastrand bifunctional adenine-thymine (AT) adducts, suggesting a direct attack on the DNA molecule (Hossain and Huq, 2002).

1.4. The Antagonism of Cadmium, Induced Developmental Toxicity and Teratogenicity

Cadmium teratogenesis was inhibited by mercaptoacrylic acid (Ferm and Hanlon, 1987) and Zn supplementation prior to Cd administration prevented several of the gross teratogenic effects observed when Cd was added alone (Warner *et al*., 1984). Also, Zn pretreatment protected against the lethal, teratogenic, and growth-retarding effects of Cd, as well as ectodermal changes and cell death (Fernández *et al.,* 2003). Recently, gene expression changes induced in the mice embryos 5 and 10 hrs after maternal Cd exposure in the absence or presence of Zn pretreatment revealed that the nine genes with a transcriptional response induced by Cd, none of which was influenced by Zn pretreatment, and two genes induced only by combined maternal Cd exposure and Zn pretreatment (Kultima *et al*., 2006). They proposed that the teratogenic effects of Cd may be secondary to toxicity in extraembryonic tissues, and that the primary protective role of Zn may not be to reverse Cd-induced transcription in the embryo.

LEAD

Lead (Pb) is a developmental immunotoxicant which through human exposure results in immune function changes and has the potential to adversely affect human health. It has many uses in industry including pipes, paints, enamels, glazes, motor industry and others. The major hazard in industry arises from the inhalation of dust and fume but the organic compounds may also be absorbed through the skin.

2.1. Developmental Toxicity and Teratogenicity of Lead

Developing individuals (embryos, fetuses and children) are the most susceptible populations to Pb. Exposure to low levels of Pb during early development was found to produce long-lasting cognitive and neurobehavioral deficits in children and experimental animals (Alfano and Petit, 1982; Bellinger *et al.*, 1989; Cory-Slechta *et al.*, 1992; Bourljeily and Suszkiw, 1997, Murphy and Regan, 1999; Moreira *et al.*, 2001 and Canfield *et al.*, 2003; Jaako-Movits *et al.*, 2005; Heidmets *et al.*, 2006).

2.1.1. Developmental Toxicity and Teratogenicity of Lead in Experimental Animals

In mice, Pb administered throughout full gestation resuted in persistent effects in the immune system of the offspring (Chen *et al*., 1999). Also, mice exposed to Pb continuously beginning at approximately 6 days prior to birth showed significant decrease in their blood Pb levels 2 weeks after weaning, despite continued exposure as adults (Jennifer *et al*., 2000). Neonatal exposure of male mice to Pb reduced fertility in the sexually mature animals, without reducing the sperm count, but with an effect on the number of testicular macrophages and somatic cells. The presence of the increased number of DNA fragments in the testes indicated an increase in apoptosis, which might resulted from Pb -induced oxidative stress (Beata *et al.,* 2005).

In Fischer 344 rats, exposure to Pb during embryonic development produced persistent immune changes at concentrations that did not affect the adult rat's immune system (Miller *et al*., 1998). Morphometric analyses following developmental Pb exposure to pregnant rats produced a decrease in hippocampal (Hi) pyramidal neurons spine density (Kiraly and Jones, 1982), a reduction in the dendritic fields of dentate granule cells (Alfano and Petit, 1982), and a decreased elaboration of mossy fiber terminals (Campbell *et al.*, 1982). Following developmental Pb exposure *in vitro*, age-related impairment of long-term depression (LTD) in area CA1 and dentate gyrus (DG) of rat Hi was reported by Sui *et al.* (2000). Pb is widely known for its capacity to cause reproductive toxicity in male and female rats. With respect to females, Pb exposure during pregnancy

and the neonatal period caused a delay in sexual maturity, irregular estrus, and reduced numbers of corpora lutea (Dearth, *et al*., 2002). Developmental Pb exposure induced persistent inhibition of neurogenesis and altered the pattern of differentiation of newly born cells in the DG of rat Hi, which could, at least partly, contributed to behavioral and cognitive impairments observed in adulthood (Jaako-Movits *et al*., 2005). Early post-natal Pb exposure induced persistent changes in the number of Poly-Sialated Neural Cell Adhesion Molecule (PSA-NCAM) expressing cells of rat, which could be, at least, partly the basis of impairments in the learning and memory formation, which follows low-level Pb exposure (Heidmets *et al*., 2006).

In the unchallenged and visally stressed chicks, Pb exposure during different windows of chick embryonic development resulted in different immunotoxic outcomes in the juvenile (Lee *et al.,* 2002). For example, low-level exposure to Pb had a direct effect on the developing chicken immune system, which was evident even during a postnatal infection. Furthermore, some of the changes were observed only when chicks were stressed by the viral infection. To evaluate the capacity of Pb to alter thymic function in juvenile chickens following embryonic exposure, chicken eggs were treated with lead acetate (400 µg/egg) on embryonic development (E12) with and without thymulin supplementation (Lee and Dietert, 2003). They suggested that Pb can directly influence thymocyte function in the absence of the thymic microenvironment.

2.1.2. Developmental Toxicity and Teratogenicity of Lead in Human

Maternal bone Pb levels may serve as a useful biological marker of long-term fetal Pb exposure over the course of pregnancy (Sanin *et al*., 2001). For example the higher Pb levels of maternal patella bone, tibia bone and cord blood resulted in lower infant birth weight and lower growth rate from birth to one month of age (Gonzalez-Cossio *et al*., 1997). Also, the skeletal contribution to blood Pb levels increased from 9% to 65% during pregnancy (Gulson *et al*., 1997). Persistent immune changes were evident after a pulsed *in utero* exposure to Pb either early or late in gestation. However, the effects of the exposure differed depending upon the timing of the exposure and the gender of the offspring (Dietert *et al*., 2000). Chronic exposure to Pb during perinatal or early postnatal development produced CNS impairments as indicated by behavioral, physiological and biochemical measures (Lanphear *et al.*, 2001). Low Pb levels, between 10 and 20 µg/dl, were considered to be of low concern but clinical studies showed that even with low blood Pb level, it produced disruption of CNS impairing children's ability to think, concentrate and learn, attentional dysfunction, growth retardation, language deficits, and other behavioral problems (Bernard, 2003; Lidsky and Schneider, 2003). Also, even very low Pb blood levels, defined as lower than 10 µg/dl were reported to induce harmful behavioral effects and, therefore, are not safe (Canfield *et al.*, 2003). Functional impairment of the developing brain was reported at blood Pb level as low as 10–15 µg/dl in children and <20 µg/dl in rodents (Bellinger *et al.*, 1989). In a population of men exposed occupationally to Pb with blood Pb levels >40 µg/dL, the quality of sperm and the birth rates among their wives were significantly reduced (Bonde *et al.*, 2002).

2.2. Lead Bioaccumulation and Transfer through the Placenta and Breast Milk

Lead can be stored in the liver after chronic exposure and it can affect the hepatic tissue of pups during pre- and post-natal development. The Hi is reported to be the primary target of Pb toxicity in the brain of rats as it is the location where the metal is found to selectively accumulate (Bielarczyk *et al.*, 1996). Pb is also accumulated in the bone and may be mobilised during pregnancy and lactation (Silbergeld, 1991). Human male reproductive organs have marked capacity to accumulate Pb, they are greatly affected by exposure to Pb in early childhood (Qintanilla-Vega *et al.*, 2000). Also, Pb readily crosses the placenta and accumulates in foetal tissue over the period of gestation where it competes with other ions for transport of proteins (Semczuk and Semczuk-Sikora, 2001). Maternal transfer of Pb was more efficient than oral adult exposure and substantial Pb transfer was occured both transplacentally and lactationally (Jennifer *et al*., 2000). During infancy, breast feeding is a source of Pb exposure (Pb mobilized from bones is excreted in milk) (Corpas *et al.*, 2002).

2.3. The Mode of Action and Mechanism of Lead Developmental Toxicity and Teratogenicity

The developing nervous system is recognized as a primary site for Pb-induced toxicity. Pb toxicity produced behavioral and cognitive effects in both developing and adult animals (Cory-Slechta *et al*., 1992). It interacts with the gastrointestinal absorption of calcium, iron, and zinc. It is known to impair cerebral growth, alter the number of synapses per neuron, and causing hypomyelination of the nervous system (Nichols and McLachlan, 1990). The constant differentiation of common progenitor cells from conception through embryonic development makes the fetus a more susceptible target for certain toxicants, such as Pb (Dietert *et al.*, 2000). In early childhood, oral exploratory behavior is a major mechanism of Pb exposure, and children absorb Pb through ingestion. In general, developing organisms are exposed to higher concentrations of Pb than adult organisms, and a newborn exposure accumulates more Pb than during adult life. Furthermore, in developing tissues, protective

mechanisms against heavy metal toxicities are not well developed. These factors predispose the infant during the period of early childhood to a heightened sensitivity to Pb toxicity (Corpas *et al.*, 2002).

2.4. The Antagonism of Lead -Induced Toxicity and Teratogenicity

Adding 2% tannic acid (wt/wt) to ground food of mice containing 3% lead acetate antagonized the toxic effect of Pb (Peaslee and Einhellig, 1977). The affinity of tannic acid for heavy metals is suggested as a reason for this protective effect. Also, supplementation with Ca and Zn reduces Pb-induced behavioral impairments, suggesting a protective effect by competing with Pb for similar binding sites and by decreasing the gastrointestinal absorption and tissue accumulation of Pb (Peraza *et al*., 1998). Also, the nutritional supplementation with Ca or Zn greatly reduces the Pb-induced behavioral impairments in young and adult mice, and may well be beneficial to human children at risk of Pb exposure (Sidhu and Nehru, 2003). Appropriate Ca levels are essential to maintain and activate nerve cell function, but Pb causes derangement of Ca flux in the extra- and intracellular spaces, which leads to central nervous system degeneration. Therefore, both Ca and Zn alter the kinetics of Pb toxicity and reduce the Pb burden on the body, thereby confirming that intake of Ca or Zn nutrients may be beneficial in preventing the toxic effects of Pb (Rantham *et al*., 2006).

MERCURY

Mercury (Hg) is mutagenic, teratogenic, carcinogenic, and embryotoxic. It may enter the body as organic salt, inorganic salt or as elemental Hg. Some developmental and behavioral effects from Hg vapor were found at levels considerably below that required for similar effects by methyl mercury (MeHg) (Fredriksson *et al*., 1996). Fish and marine products, drinking water, cereals, vegetables, and meat are believed to make important contributions to MeHg burden in man, while dental amalgams are implicated in the release of Hg vapor.

3.1. Developmental Toxicity and Teratogenicity of Mercury

All forms of Hg administered to animals were found to result in developmental problems such as spontaneous abortion, stillbirths, and congenital malformations (reviewed by Steffek *et al*., 1987; Schuurs, 1999).

3.1.1. Developmental Toxicity and Teratogenicity of Mercury in Experimental Animals

Female white Rats exposed prenatally to Hg vapor (2.5 mg/m^3, 6 h/day for 21 days before fertilization and over GD 7–20), died within 6 days after birth (Baranski and Szymczyk, 1973). At higher concentrations (6-8 mg/m^3) Hg caused an increased incidence of resorptions, decreased litter size, and decreased birth weight in the mouse (Khayat and Dencker, 1982). Maternal toxicity was observed only in animals exposed to the highest Hg concentrations (8 mg/m^3), and was manifested primarily as a decrease in body weight gain and mild nephrotoxicity. On the other hand, effects of Hg vapor (8 mg/m^3) on embryonic rat development were characterized mainly by CNS or behavioral disturbances rather than gross malformations (Danielsson *et al*., 1993). The next lower concentration (4 mg/m^3) caused only mild maternal toxicity and had no effect on resorptions, litter size, or birth weight. Exposure to 1.5 mg/m^3 Hg vapor for 1 or 3 h/day over GD 6–11 or 13–18 altered levels of nerve growth factor and its receptors on PND 21 and 60, suggesting that gestational exposure to Hg could alter trophic factor's regulation of brain development (Söderström *et al*., 1995). Exposure to 1.8 mg/m^3 Hg vapor over GD 11–14 and GD 17–20 (1 or 3 h/day) produced behavioral changes in offspring such as hypoactivity at three months, reduced habituation to activity chambers at seven months, followed by hyperactivity at 14 months of age (Fredriksson *et al*., 1996). However, gestational exposure to 4 mg/m^3 Hg vapor for 2 h/day over GD 6–15 did not alter compound nerve action potentials, nerve conduction velocity, cortical or cerebellar somatosensory potentials, brainstem auditory evoked responses, or visual evoked potentials in male or female offspring when tested as adults (Morgan *et al*., 2002). Levels up to 4 mg/m^3 Hg vapor produced neuroanatomical changes in adult animals, and altered cognitive and motor function after birth (Herr *et al*., 2004).

Exposure of pregnant squirrel monkeys to 500–1000 µg Hg/m^3 increased the variability in the performance of offspring in concurrent random-interval schedules of reinforcement. One of the treated monkeys underwent electroretinographic examination. No changes in the rod or cone response of this monkey were observed (Newland *et al*., 1996).

3.1.2. Developmental Toxicity and Teratogenicity of Mercury in Human

Earlier studies of human exposures to methyl mercury (MeHg) showed that the fetus is exclusively susceptible to MeHg poisoning (Spyker *et al*., 1972). Very low levels of exposures to Hg have caused inhibition of DNA & RNA synthesis (Khera, 1979), spontaneous abortions and birth defects (Marsh *et al*., 1980); reduction of blood's ability to transport oxygen to fetus, and transport of essential amino acids and nutrients including magnesium, zinc and Vit B12 (Boadi *et al*., 1992); infertility (Dickman *et al*., 1998); teratogenic/ DNA damage (Boyd *et al*., 1991). The fetal Hg content after maternal inhalation of Hg vapor was found to be over 20 times that for maternal exposure to an

equivalent dose of inorganic Hg (Warfvinge *et al*., 1994). A significant correlation between number of amalgam fillings of the mother and the level of Hg in the fetus, infants, and young children were reported by Drasch *et al*. (1994). Also, Hg from amalgam in the blood of pregnant women crosses the placenta and appears in amniotic fluid and fetal blood, liver, and pituitary gland within 2 days of amalgam placement. The highest levels of Hg are usually found in the pituitary gland of the fetus which affects development of the endocrine, immune, and reproductive systems (Warfvinge *et al*., 1994).

3.2. Mercury Bioaccumulation and Transfer through the Placenta and Breast Milk

The kidney is the primary depository of Hg after inhalation of Hg vapor and nephrotoxicity is a common sign of human Hg intoxication. Relatively high Hg concentrations were found in the brains of exposed pregnant rats that may in part be attributed to the direct uptake of Hg via the nasal mucosa and retrograde transport transynaptically into the brain (Tjalve and Henriksson, 1999). Because of the short transit time from the lungs to the brain, almost all the Hg vapor arrives at the brain unoxidized (Hursh *et al*., 1980). The Hg readily crosses the blood-brain barrier (BBB) and is oxidized in the brain to Hg^{2+}, a form that does not easily re-cross the blood-brain membrane. Various forms of Hg can pass the BBB and damage the cerebral microvascular endothelial cells, an essential part of the BBB (Albrecht, 1996). Mercury neurotoxicity causes a variety of neurological and behavioral effects in humans including central hearing loss, vestibular dysfunction, autism, mental deterioration, speech difficulty, impaired vision, weakness of the extremities and ataxia, and in some cases has proven to be fatal (Myers *et al*, 1995; Musiek and Hanlon, 1999). The level of Hg in umbilical cord blood, meconium, and placenta is usually higher than that in mother's blood (Ramirez *et al*., 2000). Because it is highly lipid soluble, Hg readily penetrates the placental barrier and is taken up by fetal tissues and accumulates in brain, liver, and kidney of newborns (Lutz *et al*., 1996; Morgan *et al*., 2006).

Breast milk is found to increase the bioavailability of inorganic Hg, which is excreted to milk from blood at a higher level than organic Hg (Yang *et al*., 1997). The main mechanism of transfer was found to be binding to albumin. For populations without high fish consumption, dental amalgams are the main source of Hg in breast milk and the fetus. This is because Hg from amalgam is stored in the breast milk and the fetus up to 8 times more than the mother's tissues and it crosses the placenta as suggested by Vimy *et al*. (1990). Furthermore, organic forms of Hg are found to be excreted into the animal milk (Nielsen and Anderson, 1995) and human breast milk (Grandjean *et al*., 2003).

3.3. The Mode of Action and Mechanism of Mercury Developmental Toxicity and Teratogenicity

Mercury vapor exposure caused impaired cell proliferation in the brain and organs, resulting in reduced volume for cerebellum and organs and subtle deficiencies (Drasch *et al*., 1994). In the brain, MeHg is converted to inorganic Hg most likely by *in situ* demethylation (Vahter *et al*, 1985). Prenatal/early postnatal exposure to Hg affected level of nerve growth factor in the brain and caused imbalances in development of the brain (Söderström *et al*., 1995). Exposure of developing neuroblastoma cells to sub-cytotoxic doses of Hg oxide resulted in lower levels of neurofilament proteins than unexposed cells (Abdulla *et al*., 1995). Also, organic and inorganic Hg were reported to disrupt ion channel functions (which play a crucial role in cellular homeostatsis) and, in turn, affected processes such as synaptic transmission and growth cone elongation (Sirosis and Atchison, 1996).
On the other hand, Hg is as an endocrine system disrupting substance in animals and human, preferentially accumulating in and disrupting function of the pituitary gland (Nylander *et al*., 1989); hypothalamus and thyroid gland (Lindqvist, 1996); disrupting or blocking enzyme production processes (Markovich and James 1999); glucose transfer (Boadi *et al*., 1992); and many hormonal functions (Gerhard *et al*., 1998) at very low levels of exposure. Different teratogenic effecs of Hg were corelaed to its inhibitory effects on DNA & RNA synthesis (Boyd *et al*., 1991; O'Halloran, 1993); reduction of blood's ability to transport oxygen to fetus, and transport of essential amino acids and nutrients including magnesium, zinc and Vit B12 (Boadi *et al*., 1992); reduced iodine uptake, inhibited ATP activity, and hypothyroidism (Kawada *et al*., 2001). Mercury readily deposits in mitochondria, and selective disruption of the mitochondrial electron transport chain was suggested as a specific mechanisms by which MeHg induce the formation of free radicals and lipid peroxidative stress (Konigsberg *et al.*, 2001).

3.4. The Antagonism of Mercury -Induced Toxicity and Teratogenicity

In the literature, a few studies on the antagonism of Hg-induced toxicity and teratogenicity are available. For example, zink was found to prevent Hg-induced testicular damage in mouse (Orish *et al*., 2001). In the developing brain, *in vivo* and *in vitro* MeHg exposure caused apoptosis and necrosis of neurons, destruction of glial cells and the inhibition of axonal development with distinct morphological and molecular features (Heidemann *et al.*, 2001). The organoselenium compound ebselen (2-phenyl-1,2-benzisoselenazole-3[2]-one), a lipid-soluble seleno-organic compound that is a potent anti-oxidant agent, was found to be a neuroprotective in pre-clinical studies and in a variety of

in vitro and *in vivo* animal models of neuropathological conditions, including exposure to methylmercury (Farina *et al.*, 2003; Moretto *et al*., 2005).

CONCLUSION

Cadmium, mercury and lead are among many other environmental toxic elements that are well known embryo/fetal toxicants causing different kinds of malformations and lethality in embryos and fetuses of experimental animals and human. The teratogenic effects of Cd, Pb and Hg that were observed in fish, frog, mice, rats, hamster, chicks, monkeys and human consisted of immunotoxic effects, CNS anomalies and functional impairment of the developing brain, fetal growth retardation, skeletal defects, facial defects, limb abnormalities, body wall defects, visceral anomalies, developmental delay, delay of the reproductive functions of male and female offspring and death. Different teratogenic effects of such heavy metals were corelated to the absence of the protective mechanisms against heavy metal toxicities; their inhibitory effects on DNA & RNA synthesis; reduction of blood's ability to transport oxygen to fetus, and transport of essential amino acids and nutrients including magnesium, Zn, Cu and Vit B12. Placental and maternal milk transfer (especially in human) of these metals indicates a potential risk in pre-natal and post-natal life for their infants. Because of the increased incidence of such environmental contaminants in human food; fetal exposure of such metals might pretense a potential risk in embryonic and infancy life of human.

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بحث مرجعى عن تسمم النمو الجنينى والتشوهات الخلقية بثلاثة من الملوثات البيئية (الكادميوم و الرصاص والزئبق)

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الملخص العربـــى

تعتبر المعادن الثقيلة من بين عدد كبير من المواد التي لها أثار سلبية على النمو الجنينى والصحة البشرية. ولقد أدى الكميات الكبيرة من المعادن الثقيلة التي إستخدمت مؤخرا فى الصناعة الحديثة إلى زيادة تدريجية فى تركيز تلك المعادن فى المياة والتربة والغذاء. وتتعرض يوميا الأجنة فى مراحل تكوينها المختلفة لمثل هذه المواد الكيميائية السامة وغيرها من المواد الضارة فى الهواء الذى تتنفسه والغذاء الذى تأكله والماء الذى تشربه أمهاتهم، والذى يظهر في حليب أمهاتهم. إن التعرض لهذه المخاطر الصحية تعرض الأجنة والمواليد لمشاكل الإصابة بأمراض خطيرة والنموغير الطبيعي. و من المعتقد أن موت الأطفال حديثى الولادة ومتلازمة الموت المفاجئ للأطفال الرضع قد تكون نتيجة لتلوث الهواء بمواد سامة. لذا فان الهدف من هذا البحث المرجعى هو توضيح مقدار التسُمم أثناء التكوين الجنينى والتشوهات الخلقية (في حيوانات التجارب والإنسان) الناتجة عن التعرض للرصاص والكادميوم والزئبق.

إستعرض البحث نتائج عدد كبير من الأبحاث المنشورة فى عديد من المجلات العلمية .ذلك لأن البيانات المأخوذة من تلك الأبحاث ينبغي أن تشكل أساسا لأنواع التشوهات المتوقعة فى المزيد من الدراسات على حيوانات التجارب والتى يمكن من خلالها التكهن بأنواع العيوب الخلقية التي قد تسببها المعادن الثقيلة للإنسان. لذلك، فإن هذا البحث يعطى ملخصا عن الأتى: (1) توضيح مقدار التسمم أثناء التطور الجنينى والتشوهات الخلقية الناجمة عن الرصاص والكادميوم والزئبق فى أجنة وصغار حيوانات التجارب والإنسان، (2) طريقة تأثير وآلية حدوث التشوهات الخلقيه مع ذكر كيفية التقليل أو التخلص من التشوهات الخلقيه الناجمة من تلك المعادن، (3) إنتقال تلك المعادن عن طريق المشيمة وحليب الثدي، (4) تراكمها البيولوجى وسميتها في مختلف أعضاء الفقاريات.