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Prenatal plus postnatal exposures to phthalates and child health risks

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Abstract

Phthalates are a class of chemicals predominantly used as plasticizers in many plastics since the 1930's, in a wide variety of manufacturing applications and consumer products. Given their extensive use and their leakage from plastics, they are ubiquitous environmental contaminants with potential detrimental health effects. Di(2-ethylhexyl)phthalate (DEHP) is the most commonly used phthalate plasticizer. There is widespread exposure to phthalates in the general population and therefore it is important to investigate the toxic potential of these compounds. In particular, phthalate exposure has been shown to cause developmental and reproductive anomalies in animal models, and there is concern that these compounds may be causing adverse effects on human reproductive health. Phthalate effects are suspected to be much more severe after in uterus exposure. Phthalate esters are considered endocrine disruptors that interfere with the endocrine balance and development of the mammalian testis, thus exerting harmful effects on mammalian reproduction and fertility. Health risk assessments for the phthalate exposure of the general population should be performed and current PVC plasticizers, especially the ones used for infants should be replaced with high quality materials.

Introduction

Phthalates are a class of chemicals used as solvents, additives and predominantly plasticizers to make the polyvinylchloride (PVC) flexible and appropriate for different uses available since the 1930's. They are in a wide variety of manufacturing applications and consumer products (Tab.1). Di-[2ethylhexyl]-phthalate (DEHP) is the most commonly used phthalate plasticizer, but other phthalates have been produced and are on the market [1-3]. Above 150 million tons of phthalates are produced annually worldwide. However, by 2010, the worldwide annual production of plastics will be more than 300 million tons [4,5]. Phthalates are not chemically bound to PVC and leach out from the polymer into the environment over time, thus becoming ubiquitous environmental contaminants. Humans are exposed to phthalates through ingestion, inhalation, and dermal exposure from several different sources for their whole lifetime since intrauterine life [1].

Prenatal exposure

There is cumulating evidence that the intrauterine life is the most sensitive stage of life in which we are exposed to the potential toxicity of the phthalates [6,7]. Phthalates have been shown to cause foetal death, malformations, liver injury, teratogenicity, peroxisome proliferation and particularly reproductive toxicity in laboratory animals [1,6,8].

Mechanisms of action

The possible mechanisms of action by phthalates remain largely obscure. However, these chemicals have been shown to disrupt the endocrine system of humans and wildlife by mimicking or antagonizing the functions of natural hormones. They interfere with the programming of normal endocrine-signalling pathways during pre- and neonatal life, thus leading to adverse consequences later on [9].
In addition, phthalates have been shown to activate a subset of metabolic sensors, such as the peroxisome proliferators-activated receptors (PPARs). PPARs are known to be involved in the physiological and pathological events occurring during the placentation [10]. Moreover, phthalates-induced PPARs activation may alter the testicular function by several mechanisms [11,12] and as PPARs have been shown to be major regulators of lipid and glucose metabolism, contribute to the development of obesity and insulin resistance [13].

Human studies

Human studies are limited, but suggestive, reporting associations between phthalate exposure and foetal/ neonatal health risks.

First of all, several phthalates or their metabolites reach the human foetus and are able to affect foetal health [7]. In particular, associations between antenatal phthalate exposure and a shorter pregnancy duration [14-16] as well as a low birth weight [17] have been reported. To this regard, we hypothesized a potential role of prenatal phthalate exposure in determining chorioamnionitis, a foetal inflammatory response syndrome, the leading cause of foetal/neonatal morbidity and mortality [6, 18]. In addition, it has been shown that DEHP may interfere with signalling related to the timing of parturition [19] and a significant association between prenatal phthalate exposure and lower expression of the placental genes reflecting trophoblast differentiation has been observed [20]. These observations suggest that prenatal phthalate exposure may adversely affect not only pregnancy duration, but pregnancy itself.

Moreover, maternal phthalate exposure has been shown to be correlated with a shortened anogenital distance and impaired testicular descent in the males children. In the above mentioned study, median phthalate metabolite concentrations were below those found in one- quarter of the female population in the US, thus suggesting that prenatal phthalate exposure at environmental levels can adversely affect male human reproductive tract development [21].

To this regard, phthalates can affect fetal and neonatal testis differentiation, inducing male rat reproductive tract malformations, as well as testicular changes similar to those reported in testicular digenesis syndrome in humans [22,23]. Furthermore, it has been shown that prenatal phthalate exposure may be associated with less male-typical play behaviour in boys, thus altering androgen-responsive brain development in humans [24]. In addition, phthalates impair germ cell development in the human foetal testis [25]. On the other hand, DEHP alters the expression of a number of genes, many of which are critical for foetal development [26]. Moreover, DEHP is a highly potent and uniquely selective agonist of human constitutive androstane receptor splice variant, (CAR) 2 that regulates the expression of genes involved in xenobiotic metabolism in the liver [27]. Furthermore, DEHP interaction with human Granulocytes leads to multiple and independent effects, including ROS production [28]. Finally, Di-n-butyl phthalate exposure may affect thyroid activity in pregnant women [29], while behavioural domains commonly found in children clinically diagnosed with conduct or attention deficit hyperactivity disorders have been shown to be associated with prenatal phthalate exposure [30].

Postnatal exposures

However, unfortunately the phthalate exposure does not end with the end of pregnancy. In particular, according to the Food and Drug Administration (FDA), neonates in the neonatal intensive-care unit (NICU) environment, due to their small body size, physical condition, the multiple medical devices -related DEHP exposure (Tab. 1), represent a population at a particularly high risk [31,32].

Phtalate sources
Foodstuffs
Food packaging
Household Products
Personal care and consumer products (including baby care products)
Car Products
Medical devices
Pharmaceuticals

Table 1. Sources of exposure to phthalates.

In addition, it has been recently shown that newborns undergoing intensive medical interventions are exposed to DEHP up to 100 times more than the set values [33,34]. To this regard, it has been reported that there is an increased incidence of hepatoblastoma (HB) among very low birth weight (VLBW) infants. This correlation depends on the intensity of medical care. Thus, considering the high DEHP exposure for this population in the NICU environment and that DEHP is an hepatocarcinogen in animal model, we hypothesized a potential role of DEHP exposure in increasing HB risk in this category of patients [35,36]. it has also been documented that the use of DEHP-free infusion systems decreased the risk for cholestasis in newborns [37]. However, exposure to phtalates can also occur via two basic foods for the infants'nutrition, such as formula and breast milk. To this regard, we have recently documented phthalate exposure through breast milk in southern Italian infants [38]. For this reason, although the potential adverse effects of pre- and postnatal exposures to phthalates in humans need to be more in depth investigated in future studies, we believe that an immediate action to replace the current PVC plasticizers is required considering the availability of higher quality materials on the market.

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