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Review article

A global assessment of phthalates burden and related links to health effects

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ABSTRACT

Phthalates are ubiquitous environmental contaminants which are used in industry as plasticizers and additives in cosmetics. They are classified as Endocrine Disrupting Chemicals (EDCs) which impair the human endocrine system inducing fertility problems, respiratory diseases, childhood obesity and neuropsychological disorders. The aim of this review is to summarize the current state of knowledge on the toxicity that phthalates pose in humans based on human biomonitoring studies conducted over the last decade. Except for conventional biological matrices (such as urine and serum), amniotic fluid, human milk, semen, saliva, sweat, meconium and human hair are also employed for the estimation of exposure and distribution of pollutants in the human body, although data are not enough yet. Children are highly exposed to phthalates relative to adults and in most studies children's daily intake surpasses the maximum reference dose (RfD) set from US Environmental Protection Agency (US EPA). However, the global trend is that human exposure to phthalates is decreasing annually as a result of the strict regulations applied to phthalates.

Contents

Abbreviations: 2OH-MiBP, mono 2-hydroxy-isobutyl phthalate; AC, abdominal circumference; AGD, anogenital distance; ASD, autism spectrum disorder; ATSDR, Agency for Toxic Substances and Disease Registry; BBzP, benzyl butyl phthalate; BMI, body mass index; BPD, biparietal diameter; BW, body weight; DBEP, di 2-n-butoxyethyl phthalate; DBP, di butyl phthalate; DCHP, di cyclohexyl phthalate; DEHP, di 2-ethylhexyl phthalate; DEEP, di 2-ethoxyethyl phthalate; DEP, di ethyl phthalate; DI, daily intake; DiBP, di isobutyl phthalate; DiDP, di isodecyl phthalate; DiNP, di isononyl phthalate; DiUP, di isoundecyl phthalate; DMEP, di-2-methoxyethyl phthalate; DMP, di methyl phthalate; DMPP, di 4-methyl-2-pentyl phthalate; DnHP, di n-hexyl phthalate; DnOP, di n-octyl phthalate; DnPeP, di n-pentyl phthalate; DPHP, di 2-propylheptyl phthalate; DPP, dipentyl phthalate; DTDP, di isotridecyl phthalate; EC JRC, European Commission Joint Research Center; ECPI, European Council for Plasticizers and Intermediates; EC SCENIHR, European Commission Scientific Committee on Emerging and Newly-Identified Health Risks; EDCs, endocrine disrupting chemicals; EU CSTEE, European Union Scientific Committee on Toxicity, Ecotoxicity and the Environment; FDA, Food and Drug Administration; FL, femur length; FT4, free T4; F_{UE}, urinary excretion factor; HC, head circumference; HDS, High DNA Stainability; HMW, high molecular weight; IQ, intelligence quotient; LBW, Low birth weight; LH, luteinizing hormone; LIN, linearity; LMW, low molecular weight; LOD, Limit of detection; LOQ, Limit of quantification; MBzP, mono benzyl phthalate; MCHP, mono cyclohexyl phthalate; MCiHxP, mono carboxy isohexyl phthalate; MCiOP or cx-MiNP or 7cx-MMeHP, mono carboxy-isooctyl phthalate; MCiPeP, mono carboxy isopentyl phthalate; MCMHP or 2cx-MMHP, mono 2-carboxymethylhexyl phthalate; MCNP or cx-MiDP, mono-carboxy-isononyl phthalate; MCPP, mono 3-carboxypropyl phthalate; MECPP or 5cx-MEPP, mono 2-ethyl-5-carboxypentyl phthalate; MEHHP or 5OH-MEHP, mono 2-ethyl-5-hydroxyhexyl phthalate; MEHP, mono ethylhexyl phthalate; MEOHP or 5oxo-MEHP, mono 2-ethyl-5-oxohexyl-phthalate; MEP, mono ethyl phthalate; MHBP or 3OH-MnBP, mono 3-hydroxybutyl phthalate; MHiDP or OH-MiDP, monohydroxy-isodecyl phthalate; MHiNP or OH-MiNP or 7OH-MMeOP, mono hydroxy-isononyl phthalate; MiBP, mono iso-butyl phthalate; MiDP, mono isodecyl phthalate; MMP, mono methyl phthalate; MnBP, mono n-butyl phthalate; MnOP, mono n-octyl phthalate; MiNP, mono isononyl phthalate; MnPeP, mono n-pentyl phthalate; MOiDP or oxo-MiDP, monooxoisodecyl phthalate; MOiNP or oxo-MiNP or 7oxo-MMeOP, mono oxoisononyl phthalate; MRL, minimum risk level; NICU, Neonatal Intensive Care Unit; PCOS, polycystic ovary syndrome; PE, phthalate ester; PM, phthalate metabolite; PVC, polyvinyl chloride; RfD, reference dose; SD, standard deviation; SHBG, sex hormone–binding globulin; T4, thyroxine; TDI, tolerable daily intake; TDS, testicular dysgenesis syndrome; US EPA, United States Environmental Protection Agency; VCL, curvilinear velocity; VSL, straight line velocity; WC, waist circumference; WHO, World Health Organization.

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1. Introduction

1.1. Phthalates in industry

Phthalates are the esters of 1,2-benzenedicarboxylic acid (o-phthalic acid) and their chemical structure consists of one benzene ring and two ester functional groups linked with two consecutive carbons on the ring (Fig. 1). Phthalates are produced by the reaction between an alcohol and the phthalic anhydrite. Alcohols that are used range from methanol and ethanol up to tridecanol (ECPI, 2014; Park et al., 2014). The hydrocarbon chains of the ester groups are obtained from the alcohol, they are either straight or branching and they are responsible for the name and the different properties among phthalates (Fernandez et al., 2012).

Phthalate esters (PEs) are classified into two distinct groups according to the length of their carbon chain. High molecular weight (HMW) phthalates include those with 7–13 carbon atoms in their carbon chain and low molecular weight (LMW) those with 3–6 carbon atoms in their backbone. The most common HMW phthalates are diisodecyl phthalate (DiDP), diisononyl phthalate (DiNP), di2-propylheptyl phthalate (DPHP), diisoundecyl phthalate (DiUP) and diisotridecyl phthalate (DTDP) and they are widely used in industry as plasticizers to increase softness, flexibility, elongation and durability of rigid polymers such as polyvinyl chloride (PVC). The plasticized products include wire and cables, flooring, truck tarpaulins, wall coverings, self-adhesive films or labels, synthetic leather, coated fabrics, roofing membranes and automotive applications (AgPU, 2006; Cao, 2010; ECPI, 2014; Wilkes et al., 2005).

LMW phthalates include dibutyl phthalate (DBP), diisobutyl phthalate (DiBP), butyl benzyl phthalate (BBzP) and di 2-ethylhexyl phthalate (DEHP), and are used in PVC products, as well as in medical devices, adhesives, paints, inks and enteric-coated tablets. Dimethyl phthalate (DMP) and diethyl phthalate (DEP), with one and two carbon atoms on their hydrocarbon chain respectively, are not classified in any group because they are not used as plasticizers, so they are not related to PVC. They are used as solvents and fixatives in fragrances, additives in cosmetics, medical devices, household and personal care products (AgPU, 2006; Carlstedt et al., 2013; Chou and Wright, 2006; ECPI, 2014; FDA, 2010; Frederiksen et al., 2013; Green et al., 2005; Koo and Lee, 2004; Philippat et al., 2012; Schettler et al., 2006; Schlumpf et al., 2010).

The interaction of the plasticizer with the polymer resin macromolecules is not permanent (Wilkes et al., 2005). So, under temperature variations and pH influence (Bošnir et al., 2007; Keresztes et al., 2013), phthalates are able to migrate from the plastic product to the

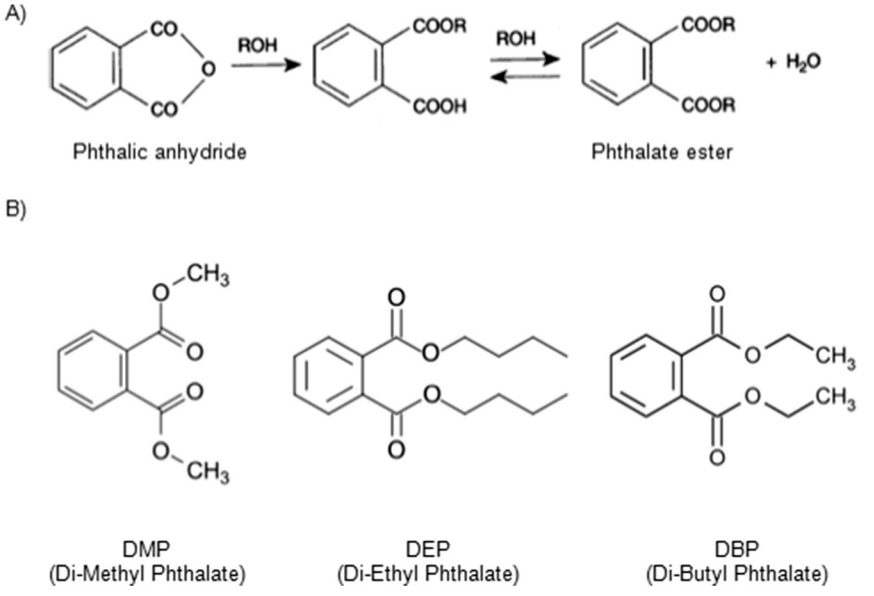

Fig. 1. A) The reaction between the phthalic anhydride and an alcohol (ROH) to produce a phthalate ester (Lorz et al., 2012). B) The structure of three Low Molecular Weight phthalates.

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