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Review

Monitoring phthalate exposure in humans

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Abstract

The dialkyl- or alkyl/aryl esters of 1,2-benzenedicarboxylic acid, commonly known as phthalates, are high-production-volume synthetic chemicals and ubiquitous environmental contaminants because of their use in plastics and other common consumer products. Di-(2-ethylhexyl) phthalate (DEHP) is the most abundant phthalate in the environment. Humans are exposed to these compounds through ingestion, inhalation, and dermal exposure for their whole lifetime, since the intrauterine life. Public and scientific concern has increased in recent years about the potential health risks associated with exposure to phthalates. The main focus has moved away from the hepatotoxic effects to the endocrine disrupting potency of these chemicals. To date, although the consistent toxicologic data on phthalates is suggestive, information on sources and pathways of human exposure to phthalates is limited. Recently, exposure to phthalates has been assessed by analyzing urine for their metabolites. This approach is contrary to the determination of the parent phthalates in air, water and foodstuff and not subject to contamination. Furthermore, these metabolites and the parent phthalates are considered the toxic species. However, accurate methods and models for measuring the amount of phthalates absorbed by the various pathways of exposure have to be developed. In fact, a frequent biological monitoring of phthalates in body fluids and tissues would be highly advisable, both in helping physicians to perform health risk assessments for exposure in the general population and in guiding governments to provide regulations concerning the maximum allowed concentrations in the environment, plasticized products, medications and medical equipment.

Keywords: Human biological monitoring; General population; Phthalates; Primary and secondary phthalate metabolites; Endocrine disruptor; Fertility; Reproduction

Abbreviations: BBP, butylbenzylphthalate; BPD, bronchopulmonary dysplasia; DBP, di-*n*-butylphthalate; DEHP, di-(2-ethylhexyl)-phthalate; DEP, diethylphthalate; DiBuP, di-*iso*-butylphthalate; DIDP, diisodecylphthalate; DiNP, di-isononylphpthalate; DnBuP, di-*n*-butylphthalate; DnOP, di-*n*-octylphthalate; E2, 17β-estradiol; MBP, mono(*n*-butyl) phthalate; MEHP, mono-ethylhexyl phthalate; 5OH-MEHP, mono(2-ethyl-5-hydroxyhexyl)phthalate; 5oxo-MEHP, mono(2-ethyl-5-oxo-hexyl)phthalate; 2cx-MMHP, mono[2-(carboxymethyl)hexyl]phthalate; 5cx-MEPP, mono(2-ethyl-5-carboxypentyl)phthalate; NICU, Neonatal Intensive Care Unit; PA, phthalic Acid; PVC, polyvinylchloride; tdi, tolerable daily intake.

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Contents

1. Introduction

Phthalates are a family of industrial compounds with a common chemical structure, dialkyl or alkyl/aryl esters of 1,2-benzenedicarboxylic acid. Since about the 1930s phthalates have been used for a variety of purposes, including personal-care products (e.g. perfumes, lotions, cosmetics), paints, industrial plastics, and certain medical devices and pharmaceuticals [1–9]. Physical properties and therefore their field of application depend on the length and branching of the dialkyl or alkyl/aryl side chains (the alcohol portion of the ester). Some phthalates are commonly added to these commercial products to hold color or fragrance, to provide a film or gloss, or, in the case of some pharmaceuticals, to provide timed releasing. However, phthalates are primarily used as plasticizers to impart flexibility to an otherwise rigid polyvinylchloride (PVC) [1–4]. These plasticizers have been shown to elute at a constant rate from plastic products to the environment: Consequently they are widely distributed in the ecosystem and have been described as being among the most abundant man-made environmental pollutants. In particular, di-(2-ethylhexyl) phthalate (DEHP) is the most commonly used plasticiser. Globally, more than 18 billion pounds of phthalates are used each year and well above 2 million tons of DEHP alone are produced annually worldwide [10]. Other important phthalates production- and application-wise are diethylphthalate (DEP), dibutyl phthalate (DBP), di-*iso*- and di-*n*-butylphthalate (DiBuP, DnBuP), butyl-benzylphthalate (BBzP), di-isononylphpthalate (DiNP) or di-*n*-octylphthalate (DnOP) [11].

1.1. Phthalate exposure in humans

Humans are exposed to these compounds through ingestion, inhalation, and dermal exposure for their whole lifetime, since the intrauterine life [12–14]. Dermal and inhalative exposures are considered to be the major route of exposure to DEP that is found in hygiene products such as soap, shampoo, and conditioners. In contrast, for phthalates that are used mainly as plasticizers, such as DEHP, oral exposures predominate [15–17]. For certain subsets of the general population non-dietary ingestion (medical and occupational) or medical exposure is important. Exposure of the general human population to DEHP has been studied more in depth than other phthalates. It has been estimated to be in the range of 3 to 30 μg/kg of body weight/day (excluding occupational exposure, medical exposures, and nondietary ingestions in children), the major source being from residues in food [8,18–20]. These estimates already exceed chronic exposure levels believed to be tolerable for the general population. Preventive limit values, such as reference dose (RfD) of the US. Environmental Protection Agency (EPA) and tolerable daily intake (TDI) of the European Union, are 20 μg/kg of body weight/day and 37 μg/kg of body weight/day, respectively [21,22].

Higher exposures occur occupationally (up to about 700 μg/kg body weight/day, mainly by inhalation, based on current workplace standards) and in the medical settings through use of plastic tubing, IV bags, etc. (i.e. up to 457 μg/kg body weight/day for hemodialysis patients) [16,23].

Recently, it has been shown that general population can be exposed to DEHP to a much higher extent than