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Daniela da Silva Lima

Environmental origins of obesity: are phthalates to blame?

Exposição ambiental e obesidade: o papel dos ftalatos

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Environmental origins of obesity: are phthalates to blame?

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Environmental origins of obesity: are phthalates to blame?

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Abstract

The pathophysiology of obesity development is complex and involves the interplay of genetic susceptibility, caloric intake and energy expenditure. Recent studies have hypothesized that metabolism and adipogenesis could also be disrupted by exposure to environmental contaminants, broadly designated as Endocrine Disrupting Chemicals (EDCs). Phthalates are a class of compounds widely used in the plasticizing industry and are among the suspected EDCs with obesogenic properties. The existence of conflicting results regarding the association of phthalate exposure and human obesity highlights the need for more thorough investigations. This review addresses this problematic, particularly focusing in potential confounding factors between studies. Phthalate distribution in the ecosystem, predominant routes of exposure, metabolism upon entering the human body and biomonitoring are here explored. The effect of early life exposure to phthalates on obesity parameters is also discussed and revealed discrepant results. The most consistent observation from epidemiological cross-sectional studies is the association of low molecular weight phthalates urinary levels in children and obesity. As for adults, epidemiological studies here reviewed have been inconclusive. Potential sources of discrepancies may be related to limited number of measurements of urinary metabolite levels, as well as age and other socio-demographic differences across populations. Longitudinal multi-ethnic studies, more frequent time-points for quantification of phthalate levels and longer follow-up periods would be important for the establishment of more accurate conclusions. Finally, the complexity of obesity pathways potentially affected by phthalates has been emphasized both by cell, animal and human studies and the existence of multiple mechanisms differentially affected cannot be ruled out.

Keywords: Phthalates, metabolic syndrome, plasticizers, obesity, EDCs

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1. Introduction

Over the last decades, obesity and overweight have become one of the major chronic health problems worldwide. It has been estimated that obesity alone has tripled between 1975 and 2016, and if the trend maintains, up to 60% of the world population will be overweight or obese by 2030 (Kelly et al., 2008). In 2016, excessive weight and obesity affected nearly 39% and 13% of the world's adult population, corresponding to 1.9 billion and 650 million adults, respectively (WHO, 2018). The consequences of such high prevalence are tremendous, since obesity is considered a major risk factor for other diseases, such as type 2 diabetes, cardiovascular diseases (stroke and coronary heart disease), musculoskeletal disorders and at least 13 types of cancer (Avgerinos et al., 2018; WHO, 2018). In children, this situation is even more alarming: in 2016, obesity or overweight affected 41 million children under the age of 5 years and over 340 million aged 5-19 (WHO, 2018). These numbers are particularly preoccupying, since it is known that obese children and adolescents tend to become obese adults and excess weight at early ages is associated with higher risk of cardiovascular, metabolic and malignant diseases in adulthood (Weihrauch-Bluher et al., 2018).

While obesity can generically be attributed to an energy imbalance between caloric intake versus caloric expenditure, the pathophysiology of its development appears to involve a complex interplay of multiple factors, from individual genetic predispositions to lifestyle habits (van der Klaauw and Farooqi, 2015). Additionally, there have been increasing reports suggesting that exposure to environmental agents could interfere with metabolism and adipogenesis, thus increasing the risk of obesity (Grun and Blumberg, 2006; Janesick and Blumberg, 2016; Nappi et al., 2016). These chemicals, broadly designated as Endocrine Disrupting Chemicals (EDCs), are defined as exogenous substances, or mixtures of

substances, that have the ability to interfere with endocrine systems, causing adverse health effects, either at the individual, or its progeny or (sub)populations (WHO, 2002). Among the EDCs with potential to be involved in the development of obesity are phthalates.

Phthalates are a group of chemical compounds widely used as plasticizers, in the production of rigid polymers such as polyvinyl chloride (PVC), and as fixatives in the cosmetic industry. Their use is so widespread, from toys, flooring, cables, medical devices, paints or personal care products, that it is not surprising that their production can reach up to over 213 000 tonnes per year in USA. (U.S. EPA, 2012). In Europe, every year one million tonnes of phthalates are produced, corresponding to 80% of all plasticizers and 95% of them are used in the production of PVC (ECPI, 2014).

Throughout the years, several studies have pointed an association between phthalates exposure and human obesity. However, while some epidemiological data have shown an association between phthalate levels and obesity markers, such as body mass index (BMI) and waist circumference in children (Hatch et al., 2008) for instance, others have found inverse or small relationships between exposure to phthalates and obesity markers (Buckley et al., 2016a; Buckley et al., 2016b). The inconsistency of the observed results highlights the need for a more thorough examination on the role of phthalates in obesity development.

Given the conflicting results described above and human continuous exposure to phthalates, it seems crucial to understand if phthalate exposure can be at least in part responsible for obesity pandemic. The purpose of this review is therefore to address the current state of knowledge regarding the role of phthalates in the development of obesity. Their sources, metabolism, routes of exposure, biomonitoring data, epidemiological studies and potential mechanisms of action will be here addressed and hopefully contribute to a better understanding of the problem.

2. Classification and sources

For the purpose of this review, the term phthalates designates dialkyl- or alkylaryl esters of the ortho-benzene di-carboxylic acid (phthalic acid) (Figure 1) (Correia-Sa et al., 2018; Lorz et al., 2000). The structure of the ester side chain confers them distinct chemical and biological properties and dictates their industrial applications (NRC, 2008). They can be subdivided into two groups based on their molecular weight: the low molecular weight (LMW) phthalates which include phthalates with one to four carbons in their ester side chain and the high molecular weight (HMW) phthalates comprising phthalates with 5 or more carbons atoms in their ester side-chain. The HMW phthalates are used as industrial plasticizers to increase softness, flexibility, elongation and durability of rigid polymers such as PVC (National Research Council Committee on the Health Risks of, 2008). Therefore, they can be found in a broad-spectrum of daily life objects such as floorings and wall coverings, cables, packaging materials, toys, synthetic leather clothes, among others. HMW phthalates include di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP) and diisodecyl phthalate (DiDP) (Correia-Sa et al., 2018) (Figure 1). DEHP is the most commonly used plasticizer in medical devices as tubings, catheters and bags for blood and parenteral nutrition (Koch and Calafat, 2009; U.S. EPA, 2012).

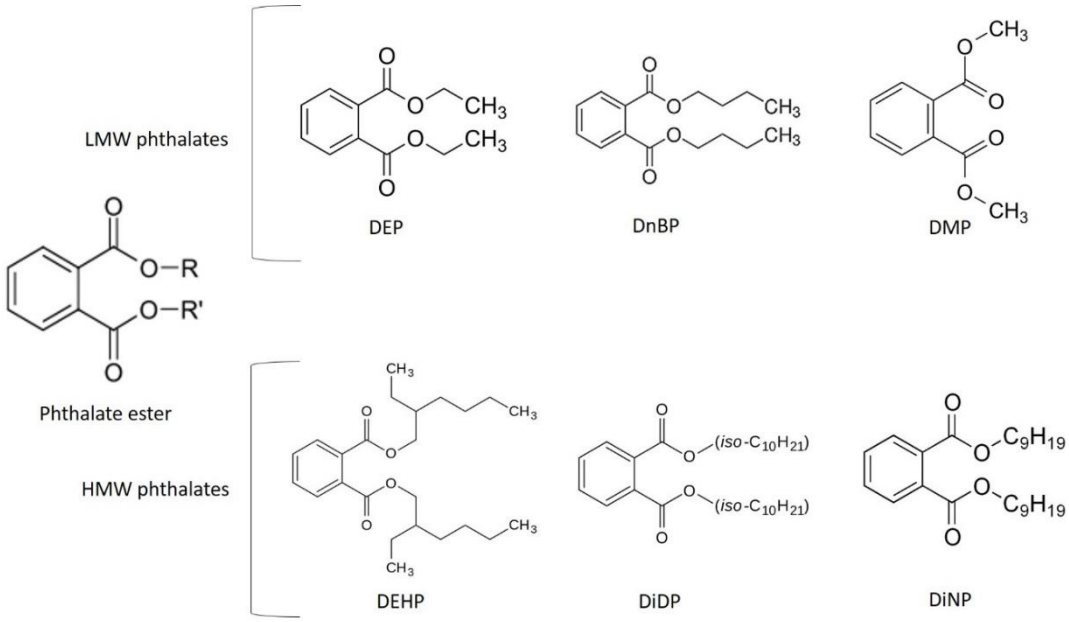

Figure1-General chemical structure of a phthalate ester (R and R' groups can be linear, branched, linear/branched or a cyclic ring) and chemical structure of 6 phthalates, grouped according to their molecular weight classification: Low Molecular Weight (LMW) and High Molecular Weight (HMW) phthalates.

LMW phthalates most commonly used are dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DnBP) (Figure 1), butyl benzyl phthalate (BBzP), and di-iso-butyl phthalate (DiBP) (Correia-Sa et al., 2018; NRC, 2008). They have plasticizing and solvent-like properties and in addition to PVC products, LMW phthalates are also used in medical devices, adhesives, paints, inks and enteric-coated tablets (Wittassek et al., 2011). DnBP is typically used in pharmaceutical formulations as enteric coating for medications (Katsikantami et al., 2016; Koch and Calafat, 2009). DMP, DEP and DnBP are mostly used in cosmetic and personal care products, as solvents and fixatives (Katsikantami et al., 2016; NRC, 2008).

In USA, DiNP reached the highest production volumes, followed by DiDP and DEHP (EPA, 2006). As for Europe, DiNP and DiDP have been progressively replacing DEHP and currently represent 60% of the total plasticizer market (Wittassek et al., 2011). Table 1 summarizes the main applications of most commonly used phthalates, displayed according to their molecular weight.

Table 1 - Most commonly used phthalates and their applications

Acronym	**Common name**	**Main uses**	**MW (g/mol)**	**Type**
DiDP	Diisodecyl phthalate	PVC plastic products, such as wires, cables, artificial leather, carpet backing, pool liners.	446.672	HMW
DiNP	Diisononyl phthalate	Garden hoses, pool liners, flooring tiles, tarps, and toys. Not used in medical devices and finds only limited use in food packaging.	418.618	HMW
DEHP	Di(2-ethylhexyl) phthalate	PVC plastic products, such as flooring, wallpaper, auto upholstery, raincoats, toys, food packaging, and medical devices (blood bags and tubings). Not used in toys intended for mouthing such as nipples or teething rings.	390.564	HMW
DnOP	Di-n-octyl phthalate	PVC plastic products, such as carpetback coating, floor tile, wire, cables, packaging films, adhesives, medical tubing and blood storage bags. Also used in cosmetics and pesticides.	390.564	HMW
BBzP	Butyl benzyl phthalate	Vinyl tiles (main use), food conveyor belts, artificial leather, automotive trim, and traffic cones.	312.365	LMW
DnBP	Di-n-butyl phthalate	Cosmetics, personal care products, cellulose plastics, solvent for dyes.	278.348	LMW
DiBP	Diisobutyl phthalate	Used in combination with other phthalates to produce nitrocellulose, cellulose ether, polyacrylate and polyacetate dispersions.	278.348	LMW
DEP	Diethyl phthalate	Solvent in products containing fragrances, such as perfumes, colognes, deodorants, soaps, shampoos, and hand lotions.	222.240	LMW
DMP	Dimethyl phthalate	Solid rocket propellants, plastics, and insect repellants	194.186	LMW

3. Exposure

Phthalates and polymers are not chemically bound, therefore, under appropriate conditions of pH and temperature, phthalates can leak out to the environment or enter directly in the human body (Katsikantami et al., 2016; Koch and Calafat, 2009). Even though phthalates are non-persistent chemicals, their widespread use renders them ubiquitous in the environment. Their volatility from moist soil surfaces and water is considered moderate, while mobility in soil and aquatic systems is low to moderate. In the environment, they are readily biodegraded but abiotic hydrolysis is considered negligible (EPA. 2006. U.S. Environmental Protection). In aquatic environments, due to their low solubility, they tend to associate to particles and accumulate in bottom sediments (Zhang et al., 2018). They have been detected in large river water and sediments across the globe (Domínguez-Morueco et al., 2014; Eremina et al., 2016; Liu et al., 2014; Sha et al., 2007), in water sediments and biota of lagoons (Adeogun et al., 2015), seawaters (Hassanzadeh et al., 2014; Martí et al., 2011; Zhang et al., 2018), wastewater treatment plants influent as well as effluent waters (Olujimi et al., 2012). The presence of these compounds has also been observed in water destined for human consumption, with bottled water displaying higher phthalate levels than tap water (Al-Saleh et al., 2011; Amiridou and Voutsa, 2011; Martine et al., 2013). However, the presence of phthalates like DEHP in bottled water has been attributed to laboratory background contamination, emphasizing the difficulty of reaching reliable measures for these compounds at ultra-trace level, when analyzing very pure matrices (Dévier et al., 2013). A comparison of phthalate levels in river and tap waters in Spain found DnBP to be the main pollutant and the only common compound in both samples (Domínguez-Morueco et al., 2014). Phthalates in soil have also been intensively analyzed in both agricultural and urban areas, particularly in China, where DnBP and DEHP predominate (Lü et al., 2018). Indoor

dust is another source of exposure to phthalates, with several reports highlighting DEHP as the most frequent compound (Guo and Kannan, 2011; Kanazawa et al., 2010; Kang et al., 2012; Wan-Li et al., 2014). The ubiquitous presence of phthalates in numerous plastic devices and laboratory equipment also prompts up the dangers of external contamination and highlights the need for careful interpretation of results (Koch and Calafat, 2009).

Ingestion is considered the main route of exposure to phthalates, particularly HMW such as DEHP (Trasande et al., 2013b; Zota Ami et al., 2016). Dermal and inhalation exposure are other potential sources of exposure, particularly for LMW phthalates (Koch et al., 2013; Weschler Charles et al., 2015). However, the relative contributions of the different sources of contamination to the total body burden at various ages is not known (NRC, 2008).

4. Metabolism

Upon entering the body, phthalate diesters are rapidly cleaved to their respective monoester, a process that can occur at numerous organs, such as skin, mouth, stomach, intestines or blood. Levels of parent compounds in blood are therefore residual or a result of background contamination (Koch and Calafat, 2009). The resulting alkyl ester can subsequently be oxidized or conjugated directly with glucuronic acid before suffering excretion through urine (Braun, 2017; Koch and Calafat, 2009). While LMW phthalates are typically hydrolyzed into monesters, HMW compounds suffer an additional oxidation process before excretion (Koch and Calafat, 2009). Table 2 summarizes main phthalates and respective metabolites. Even though phthalates can cross the placenta and have been detected in several biological matrices, such as amniotic fluid, breast milk and blood, their concentration reaches higher levels in urine, up to 5-20 times that in lipid-rich body compartments (NRC, 2008). Therefore, measurement of urinary polar metabolites is the most

frequent method for quantifying human exposure to phthalates (Braun, 2017; NRC, 2008). Given the fact that phthalates do not persist in the organism, as their half-lives is less than 24h, the ubiquitous detection of their metabolites indicates that exposure is widespread and relatively continuous (Braun, 2017).

Table 2 - Most commonly used phthalates and their main metabolites

Phthalate ester	**Type**	**Metabolite acronym**	**Common name**
DiDP	Primary	MiDP	mono isodecyl phthalate
	Secondary	MHiDP	mono hydroxy-isodecyl phthalate
	Secondary	MOiDP	mono oxoisodecyl phthalate
	Secondary	MCNP	mono carboxy-isononyl phthalate
	Secondary	MCiPeP	mono carboxy isopentyl phthalate
DiNP	Primary	MiNP	mono isononyl phthalate
	Secondary	MHiNP	mono hydroxy-isononyl phthalate
	Secondary	MOiNP	mono oxoisononyl phthalate
	Secondary	MCiOP	mono carboxy-isooctyl phthalate
	Secondary	MCiHxP	mono carboxy isohexyl phthalate
DEHP	Primary	MEHP	mono ethylhexyl phthalate
	Secondary	MEHHP	mono 2-ethyl-5-hydroxyhexyl phthalate
	Secondary	MEOHP	mono 2-ethyl-5-oxohexyl-phthalate
	Secondary	MECPP	mono 2-ethyl-5-carboxypentyl phthalate
	Secondary	MCMHP	mono 2-carboxymethylhexyl phthalate
DnOP	Primary	MnOP	mono-n-octyl phthalate
BBzP	Primary	MBzP	mono benzyl phthalate
DnBP	Primary	MnBP	mono n-butyl phthalate
	Secondary	MHBP	mono 3-hydroxybutyl phthalate
	Secondary	MCPP	mono 3-carboxypropyl phthalate
DiBP	Primary	MiBP	mono isobutyl phthalate
	Secondary	2OH-MiBP	mono 2-hydroxy-isobutyl phthalate
DEP	Primary	MEP	mono ethyl phthalate
DMP	Primary	MMP	mono methyl phthalate

5. Biomonitoring

The biomonitoring of phthalate metabolites urinary levels, conducted by the National Health and Nutrition Examination Survey (NHANES) and other studies, confirms the exposure to multiple phthalates by most people (CDC, 2009; Sathyanarayana et al., 2008; Wittassek et al., 2007). In Europe, levels of urinary phthalate metabolites show great variability among countries, probably reflecting different life-style habits, products used and market specificities (Hond et al., 2015). Southern European countries cluster (including Portugal and Spain) typically present higher levels of DEP and DEHP (Hond et al., 2015). Urinary metabolite levels in children appears to be higher than in adolescents or adults and seem to decrease with age (Becker et al., 2004; Koch et al., 2004; Silva et al., 2004). An exception to this trend is the metabolite of DEP, mono ethyl phthalate (MEP), which is found in higher levels in adults and seems to be associated with the use of DEP containing products such as detergents, soaps, shampoos and perfumes (Hartmann et al., 2018; Silva et al., 2004). While it remains unclear whether differences in urinary levels between adults and children result from different exposure or metabolism, children have been considered a group particularly susceptible to phthalates effects (NRC, 2008). Neonates in intensive care units, in particular, are considered a highly exposed group, due to medical devices containing phthalates (Weuve et al., 2006). Another cause of concern is the *in utero* exposure, as multiple phthalates have been detected in the urine of pregnant women (Adibi et al., 2008; Wolff et al., 2008).

Global phthalates body burden levels in different matrices has been reviewed recently by Katsikantami et al. (Katsikantami et al., 2016) which showed a decline over the past 15 years. They have estimated that levels of exposure in Europeans (median urinary levels of 209.06 μg/L) is similar to that of Americans (199.70 μg/L) but higher than Asians (125.25

μg/L). However, exposure to phthalates is still preoccupying particularly when it concerns children, since in 85% of the analyzed studies the exposition exceeded the reference maximum dose set by US EPA for DEHP (20 μg/kg bw/day).

In the European Union, concerns regarding developmental and/or fertility effects have led to the implementation of successively more restrictive legislation regarding the use of several phthalates, namely, DEHP, DnBP, BBzP, DiNP, DiBP and di-n-octyl phthalate (DnOP), in toys and childcare articles (Regulation (EC) No 1907/2006) (EC, 2006). Recently, new provisions were taken to restrict the use DEHP, DnBP, BBzP and DiBP in a concentration equal to or above 0.1% by weight, in all plasticized material by 2020 (EU, 2018).

It has been suggested that phthalate use restrictions in Europe may explain the decline in human urinary phthalates metabolites throughout the years (Koch et al., 2017). The analysis of 24-h urine samples collected between 1988 and 2015 in the German population has highlighted a 10 fold decrease in DEHP, DnBP and BBzP during this period (Koch et al., 2017). However, a global decrease was found in all phthalate metabolites, even for those without special legislation regarding its utilization, which may indicate a substitution of phthalates by other alternative compounds. DEHP appears to have been replaced by DiNP, even though its levels follow the trend of decrease observed for the other compounds. While a global trend to decrease has also been observed in the USA, levels of DiNP remain higher than in Europe (Koch et al., 2017). A recent analysis of plasticizers chemicals used in industry in Scandinavian countries between 2000 to 2014 confirms the decreasing trend in phthalate use, either those included in the authorized list or those from the restriction list, particularly since 2012 (Sackmann et al., 2018). Portugal seems to follow the same

decreasing trend in urinary phthalate levels, as children urine samples collected in 2014/2015 showed 2-3 times lower values than those reported in 2011/12 (Correia-Sa et al., 2018).

6. Epidemiological studies

6.1. Phthalates and childhood obesity

Several studies have suggested that EDCs may interfere at specific time-points of human development, such as gestation, infancy or early childhood, thereby disrupting critical processes for hormonal homeostasis. The repercussions of these early life events would only be observable later, resulting in changes in behavior, anatomy and physiology (Braun, 2017). There has been a growing interest in understanding whether this could be the case for phthalates. Herein we review the latest epidemiologic data on the effects of phthalate exposure on obesity at different age groups, from gestation to adolescence.

Regarding the effects of prenatal phthalate exposure and childhood obesity, prospective studies have provided variable conclusions. Valvi et al. used the population-based birth cohort INMA to study 391 Spanish mother–child pairs from the first trimester of pregnancy up to 7 years of age and observed sex-specific differences between the levels of urinary HMW phthalates during pregnancy and BMI at 7 years. In boys, higher levels of HMW phthalates were associated with lower BMI, while in girls were associated with higher BMI (Valvi et al., 2015). Sex-specific differences were also observed by Maresca et al., who used the New York City CCCEH longitudinal birth cohort to study the relationship of mother phthalate urinary levels in the third trimester of pregnancy and childhood body size up to 5 years of age. They reported an association of prenatal urinary levels of non-DEHP phthalate with lower BMI z-score, waist circumference and fat mass in boys but not in girls during early childhood (Maresca et al., 2016). However, other authors found no association between

maternal urinary non-DEHP phthalate levels and percent body fat in 4-9 years children of a New York City cohort and no evidence of differences according to the child's sex (Buckley et al., 2016b). Interestingly, in children from 3 prospective cohorts from United States, a positive association between the maternal urinary mono-3-carboxypropyl phthalate (MCPP), a non-specific metabolite of various phthalates, with childhood overweight/obesity status was observed (Buckley et al., 2016a). DEHP and its metabolites, on the other hand, were associated with lower BMI in girls, but not in boys, again suggesting sex-specific differences (Buckley et al., 2016a). In a French mother-child cohort that gave birth to boys, maternal urinary concentrations of MEP were positively associated with post-natal weight growth velocity from two to five years and BMI at five years (Botton et al., 2016). A study in Korea has analyzed two DEHP metabolites in newborn urine and umbilical cord and obesity related markers at early childhood. They concluded that higher levels of DEHP metabolites were associated with a decrease in Ponderal index (calculated as a relationship between mass and height) at birth and an increase in serum triglyceride levels of umbilical cord at birth, as well as an increase of body mass 3 months after birth (Kim et al., 2016). Recently, another prospective study using a cohort from an agricultural region of California with a large Mexican immigrant population has focused on the association of 11 phthalate metabolites levels, measured twice during pregnancy, with anthropomorphic features of children between 5 and 12 years of age (Harley et al., 2017). Higher levels of DEP, DnBP, BBzP, and DEHP were associated with higher BMI z-score, waist circumference z-score, and percent body fat at various ages. With the exception of DEP, in which the association was only found in boys, there was no sex-specific differences. In an attempt to identify periods of particular susceptibility to phthalates exposure, Shoaff et al., used a pregnancy and birth cohort study from Ohio to determine phthalate levels, prenatally and at six times from 1 to 8 years of age,

and correlate them with BMI, waist circumference and percent body fat at 8 years of age. While no association was observed with phthalate prenatal levels and excess adiposity, an inverse association was found between mono benzyl phthalate (MBzP) levels, both in pregnancy and childhood, with adiposity. The association of DEHP metabolites and MEP was variable according to the timing of exposure. MEP concentrations at 5 and 8 years of age were associated with higher child adiposity, but earlier childhood concentrations were not. Overall, in this cohort, there was no evidence of an obesogenic effect of prenatal phthalate exposure and positive associations between postnatal MEP and DEHP concentrations and obesity depended on the timing of exposure (Shoaff et al., 2017).

Other studies have focused on phthalate exposure in childhood and obesity. A cross-sectional analysis using data from NHANES 1999–2002 revealed different associations between phthalate metabolites and body mass, varying according to gender, age and type of metabolite. An inverse correlation was found between mono ethylhexyl phthalate (MEHP) and BMI in adolescent girls. As for children, no relevant associations were observed (Hatch et al., 2008). Teitelbaum et al observed that urinary concentrations of MEP and the sum of LMW phthalates in children aged 6-8 years old were associated with higher BMI and waist circumference measured one year later, among overweight children from a Hispanic and Black New York City cohort (Teitelbaum et al., 2012). A cross-sectional study involving 2,884 children 6–19 years of age enrolled in the 2003–2008 NHANES has highlighted positive association between LMW phthalate metabolites and the odds of overweight and obesity, but specifically among non-Hispanic blacks (Trasande et al., 2013a). A positive association was also observed for LMW phthalate concentrations in elementary school-aged girls from a multi-ethnic American cohort and BMI and waist circumference in all girls throughout 6 years of follow-up period (Deierlein et al., 2016a). Interestingly, a recent study

involving overweight/obese Portuguese children enrolled on a healthy versus a normal diet observed higher phthalate urinary metabolite levels in the regular diet group compared to the healthy diet group. The only exception was for the DEP metabolite MEP, which is consistent with the fact that the main route for DEP exposure is generally through personal care products and not through ingestion (Correia-Sa et al., 2018).

6.2. Phthalates and adult obesity

Regarding adult exposure to phthalates and obesity levels, several studies have also been conducted. A cross sectional analysis involving adult men participants of the NHANES 1999–2002 looked into mono-butyl phthalate (MBP), MEP, MEHP, MBzP, mono 2-ethyl-5-hydroxyhexyl phthalate (MEHHP) and mono 2-ethyl-5-oxohexyl-phthalate (MEOHP) urine levels and abdominal obesity. A statistical positive association was observed for several metabolites (MBzP, MEHHP, MEOHP, and MEP) and obesity parameters, suggesting a potential contribution of these compounds for the global burden of obesity (Stahlhut et al., 2007). Another cross sectional study using the same NHANES cohort and metabolite data confirmed the previously observed association of phthalates and obesity (BMI and waist circumference) in adult men (20-59). However, in women (20-59) a positive association was only observed for MEP and BMI. In fact, MEHP was inversely related to BMI in females of the (20-59) age group (Hatch et al., 2008). The observed associations did not seem to be caused by diet, as metabolite levels were not related to diet. This study has also observed higher metabolite levels in women than in males, for all metabolites. A study developed in Sweden analyzed phthalate serum metabolites (MEHP, MEP, mono isobutyl phthalate (MiBP) and mono methyl phthalate – (MMP)) in aged individuals (70 years), correlating them with obesity parameters measured by dual-energy X-ray absorptiometry (DXA) and

magnetic resonance imaging (MRI), two years later (Lind et al., 2012a). Only MiBP, in women, showed strong association with both DXA (waist circumference, total fat mass and trunk fat mass) and MRI measurements (subcutaneous adipose tissue). MMP concentrations were related to trunk fat mass and the trunk/leg-ratio measured by DXA in women and no significant associations were observed for males (Lind et al., 2012b). Phthalate metabolites were measured in adult obese individuals enrolled in weight loss programs in the Antwerp University Hospital, 3, 6 and 12 months after weight loss. Overall, a high variability was found and metabolite levels increased 3 to 6 months after weight lost. Given that the daily intake of phthalates remained constant throughout the study, the authors speculate that in addition to ingestion, other routes of exposure such as air and dust could be involved. No association with obesity parameters was observed (Dirtu et al., 2013).

Overall, epidemiological data here summarized are very variable, depending on the phthalate metabolites analyzed, the obesity outcomes used, the time of exposure studied, gender and age subgroups. Therefore, they do not provide sufficient evidence of an obesogenic effect caused by phthalate exposure. Reasons for discrepancy may rely on the time-points used to quantify phthalate levels and the fact that one-time urine measurement is often used as proxy of phthalate exposure. This may not correspond to continuous exposure levels, since phthalates are known for their short biological half-lives and rapid excretion (Janjua et al., 2008). Hence, specific metabolite and time-point associations may result from misclassification of exposure rather than a causal association (Shoaff et al., 2017). Furthermore, is has been suggested that phthalates mode of action may depend upon endogenous hormone levels, which vary according to age and gender. Grouping phthalates according to their molecular weights, although it is a classification frequently used, may lead

to the assumption that they have the same biologic action or potency which may be a source of confusion. It has also been suggested that there are considerable variation of sources and magnitude of exposure to specific phthalates according to age and other socio-demographic characteristics, both within and across populations (Deierlein et al., 2016b). Despite these limitations, cross-sectional studies have consistently shown an association of LMW phthalate urinary levels in children and obesity. However, one cannot rule out the existence of reverse causation, as it is possible that the biggest body surface of obese children may be related to a bigger surface of exposure to LMW phthalates in personal care products, thus increasing their urinary levels (Braun, 2017; Deierlein et al., 2016b). In order to clarify this, more longitudinal multi-ethnic studies would be necessary as well as the quantification of phthalate levels at more frequent time points and longer follow-up periods, particularly from the highly sensitive intrauterine period to childhood and adolescence.

Epidemiological data need to be carefully interpreted, since it's not possible to assess the isolate effect of a single compound when environmental exposure occurs in complex mixtures. Cell and animal studies are therefore crucial to characterize individual phthalate effects as well as to understand their mode of action. The analysis of the exposome as a way to include the effects of environmental exposures from the pre-natal period throughout an individual's life could also shed light to these questions.

7. Mechanism of action

The potential involvement of phthalates exposure in obesity development requires biological plausibility. However, to date, the mechanisms through which phthalates could interfere in obesity still remain elusive. Nevertheless, potential pathways involved could be subdivided into 3 major groups: 1) Interference with Nuclear Receptors (NR) involved in

energy balance; 2) Disturbance of neuroendocrine pathways and 3) Increase in oxidative stress.

7.1 Interference with NRs involved in energy balance

The abnormal activation of NR and subsequent activation of genetic cascades is the most well studied mechanism of action of EDCs (Casals-Casas et al., 2008). Several NR have been shown to be activated by phthalates, namely, the estrogen receptors (ERs), the peroxisome proliferator-activated receptor (PPAR) subtypes and xenobiotic sensors androstane and pregnane X receptor (Engel et al., 2017; Henley and Korach, 2006; Hurst and Waxman, 2003). Perhaps the strongest candidates involved in phthalate dysregulation are PPARs, a set of nuclear receptors involved in the regulation of lipid metabolism and energy homeostasis (Desvergne et al., 2009). Three types of PPARs have been identified in humans PPARα, PPARβ/δ and PPARγ. Despite their different functions, all three isotypes can be activated by phthalate monoesters, depending of the species, the cell type and the receptor, thus broadening the spectrum of consequences of this stimulation (Desvergne et al., 2009). While PPARγ is considered a key regulator for adipocyte differentiation and glucose metabolism, promoting adipogenesis, PPARα and PPARβ/δ are promotors of fatty acid catabolism (Casals-Casas and Desvergne, 2011). In fact, conflicting results regarding fat mass gain and phthalates exposure could ultimately be explained by differential activation of PPARs.

Several reports have suggested that phthalates obesogenic properties derive from the different potential of phthalates to activate PPARγ. For instance, MEHP, but not its parental compound DEHP, is able to bind to PPARγ ligand binding pocket in a similar way as its proposed natural ligand rosiglitazone (Feige et al., 2007). MEHP has further shown to promote adipogenesis directly by activating PPARγ and by inducing selective activation of

target genes in the mouse preadipocytes 3T3-L1 cell line (Feige et al., 2007; Hurst and Waxman, 2003). Using the same cell line, Pereira-Fernandes and collaborators confirmed that the obesogenic properties of the phthalates BBzP and DIBP are under PPARγ control (Pereira-Fernandes et al., 2013). However, despite the fact that phthalates are generally considered activators of these receptors, this is not always the case. For instance, using reporter gene assays to assess nuclear receptor activation by DiBP, DnBP and DEHP, it was shown that while DiBP and DnBP function as PPARγ agonists, DEHP displays antagonistic activities towards the same receptor (Simon et al., 2016). The demonstration of these effects on animal models would be of huge importance to clarify these knowledge gaps. However, it is well known that PPARs display species-specific regulatory modes, which make it difficult the extrapolation of results to human (Desvergne et al., 2009). In rodents, the activation of PPARα leads to proliferation of peroxisomes and liver carcinogenicity, an effect that was never observed in humans. PPARα humanized transgenic mice treated with the PPARα agonist fenofibrate display some effects similar to those observed in wild type mice, such as peroxisome proliferation, decreased serum triglyceride levels and induction of PPARα target genes involved in fatty acid metabolism, but these mice did not develop hepatomegaly or hepatocyte proliferation (Shah et al., 2007; Yang et al., 2008). Interestingly, exposure to DEHP protect mice from diet induced obesity via PPARα-dependent activation of hepatic fatty acid catabolism (Feige et al., 2010). This protection was lost when PPARα-humanized mice were used, suggesting species-specific differences in phthalates activation of PPARs and need of caution when extrapolating conclusions from animal models (Feige et al., 2010). A better understanding of phthalates effects on PPARs pathways is crucial given that it was recently demonstrated that exposure to plasticizers considered safe for use in food-contact material, such as DiNP and DiDP, at environmentally relevant doses cause lipid

accumulation through PPARγ regulation in 3T3-L1 mouse preadipocytes (Pomatto et al., 2018).

Other players which may be involved in energy balance disruption caused by phthalates are sex hormone receptors which signalization, although indirectly, may change fat deposition in a sex specific manner. The inhibition of androgens could potentially have an obesogenic effect (Stojanoska et al., 2017). It has been demonstrated that gestational exposure of male rats to several phthalates, such as DEHP, DiBP, DiNP, BBzP and DnBP, during the period of sex differentiation, led to a reduction of fetal testicular testosterone production (Hannas et al., 2011; Howdeshell et al., 2008). However, effects on weight were not assessed in these studies. Phthalates may also have antiandrogenic activity, as it has been suggested using the Hershberger assay in castrated male rats exposed to DEHP, DiNP or DnBP (Lee and Koo, 2007). In humans, exposure to high levels of DnBP and DEHP in factory workers has been associated with decreased free testosterone levels (Pan et al., 2006). *In vitro* reporter gene assays have shown that phthalates can either activate or inhibit ERα and ERβ, but can only inhibit androgen receptor (AR) (Engel et al., 2017). However, cell context needs to be considered before conclusions on phthalates effects on ERs can be inferred, as DEHP for example displays both strong agonistic and antagonistic activity towards ERs from different cell lines (Simon et al., 2016). In any case, the observed additive effect of phthalates mixtures on androgen production inhibition, in rodents, raises concerns regarding human populations, since exposure to phthalates typically involves multiple compounds and routes of exposure (Howdeshell et al., 2008; NRC, 2008).

Overall, the results described for cells, animals and human studies highlight the complexity of obesity pathways potentially affected by phthalates. One cannot exclude the existence of distinct biological mechanisms, differentially affected by different phthalates.

7.2 Disturbance of neuroendocrine pathways/signals

Body weight is under hypothalamus control, an integration center of internal metabolic stimulus that coordinates internal stimulus from leptin, ghrelin, insulin and neuropeptide Y (NPY) into appropriate effector responses regarding food intake (Migliarini et al., 2011). In scenarios of energy deprivation there is an increase in NPY, ultimately leading to a higher consumption of food (O'Shea and Gundlach, 1991). Contradictory results have been observed regarding the influence of phthalates in NPY. Masuo et al., describe that NPY gene expression increases in rats after neonatal exposure to DEHP (Masuo et al., 2004). An increase in orexigenic neuropeptides, including NPY, was also observed in male C3H/He mice exposed to DEHP, which is accompanied by an increase in food intake (Lv et al., 2016). However, there is insufficient evidence on the involvement of NPY and its modulation by phthalates in the development of obesity.

7.3 Increase in oxidative stress

Finally, it has been suggested that phthalates may increase oxidative stress, which may contribute to the establishment or development of obesity (Stojanoska et al., 2017). Animal studies revealed that DEHP can induce the formation of reactive oxygen species (ROS), increasing lipid peroxidation and thereby interfering with insulin signal transduction in adipose tissue, favoring glucose intolerance. However, there are no sufficient data to favor this hypothesis (Rajesh et al., 2013). Nevertheless, several human studies suggest that, in fact, the exposure to phthalates may be associated to an increase in oxidative stress (Hong et al., 2009; Kim et al., 2013; Tetz et al., 2013).

8. Conclusions

It is undeniable that major factors responsible for obesity are excess caloric intake, reduced levels of physical activity and genetic determinants. However, exposure to environment pollutants may play a role in predisposing to its development. This review summarizes current data regarding phthalate exposure and obesity in human populations. Most epidemiological data is scarce, restricted to specific populations, involves limited number of metabolite measurements and different times and concentrations of exposure, and therefore results obtained are not always in accordance, being difficult to draw definitive conclusions. The most consistent association found was between LMW phthalate levels and obesity in children, even though reverse causality cannot be ruled out. Larger studies, involving different populations, more frequent metabolite determinations and longer follow-up periods could help to shed light on this topic.

Cell and animal studies, despite their importance in deciphering the potential mechanism or mechanisms involved, have been inconclusive. Nevertheless, the most plausible mode of action is the abnormal activation of human nuclear receptors, either PPARs or sex steroid receptor AR. One cannot rule out the possibility of the simultaneous involvement of more than one pathway, as phthalates designate numerous compounds, each with their own characteristics and properties. In the environment, exposure occurs in complex mixtures via multiple routes, which also makes it difficult to assess individual compound effects. With the institution of stricter legislation regarding phthalates use, it is expected that exposure levels tend to decrease over the next years. Nevertheless, it is crucial to continue monitoring their effects, as well as the alternative products introduced in the market, in order to assure safety of human populations, particularly children and vulnerable groups as pregnant women.

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ANEXOS

1. Lista de acrónimos
2. Normas da revista
3. Highlights da revista

Lista de acrónimos

AR, androgen receptor

BBzP, butyl benzyl phthalate

DnBP, di-n-butyl phthalate

DEHP, di(2-ethylhexyl) phthalate

DEP, diethyl phthalate

DiBP, diisobutyl phthalate

DiDP, diisodecyl phthalate

DiNP, diisononyl phthalate

DnOP, di-n-octyl phthalate

DMP, dimethyl phthalate

EDCs, Endocrine Disrupting Chemcials

ERs, estrogen receptors

HMW, High Molecular Weight

LMW, Low Molecular Weight

MBP, mono butyl phthalate

MiBP, mono isobutyl phthalate

MBzP, mono benzyl phthalate

MCiHxP, mono carboxy isohexyl phthalate

MCiOP, mono carboxy-isooctyl phthalate

MCiPeP, mono carboxy isopentyl phthalate

MCMHP, mono 2-carboxymethylhexyl phthalate

MCNP, mono carboxy-isononyl phthalate

MCPP, mono 3-carboxypropyl phthalate

MECPP, mono 2-ethyl-5-carboxypentyl phthalate

MEP, mono ethyl phthalate

MEHP, mono ethylhexyl phthalate

MEHHP, mono 2-ethyl-5-hydroxyhexyl phthalate

MEOHP, mono 2-ethyl-5-oxohexyl-phthalate

MHBP, mono 3-hydroxybutyl phthalate

MHiDP, monohydroxy-isodecyl phthalate

MHiNP, mono hydroxy-isononyl phthalate

MiDP, mono isodecyl phthalate

MiNP, mono isononyl phthalate

MMP, mono methyl phthalate

MnBP, mono n-butyl phthalate

MnOP, mono-n-octyl phthalate

MOiDP, monooxoisodecyl phthalate

MOiNP, mono oxoisononyl phthalate

NPY, neuropeptide Y

NR, Nuclear Receptors

ROS, reactive oxygen species

PPAR, peroxisome proliferator-activated receptor

2OH-MiBP, mono 2-hydroxy-isobutyl phthalate

ENVIRONMENTAL RESEARCH

A Multidisciplinary Journal of Environmental Sciences, Ecology, and Public Health

AUTHOR INFORMATION PACK

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Highlights

- Phthalates are suspected endocrine disruptors with obesogenic properties
- Epidemiological data in different life stages reveals conflicting results
- Epidemiological association of urinary LMW phthalates and obesity in children
- Multiple mechanisms involved in obesity development can be affected by phthalates