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REVIEW ARTICLE

Phthalate exposure as a risk factor for hypertension

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Abstract

Phthalates are ubiquitous in environment. Hypertension is a major risk factor for cardiovascular diseases. Phthalate exposure is associated with hypertension in multiple studies. This review aims to summarize the scientific literature on associations between phthalate exposure and hypertension and discuss the mechanisms in the relationship. We identified and reviewed original articles published to March 2018, using PubMed and Web of Science to search the terms "phthalate(s)," "phthalic acid," "blood pressure," "high blood pressure," "hypertension," "prehypertension," and "cardiovascular disease." Findings were summarized based on the relevance to the themes, including presentation of main phthalates and their major metabolites as well as associations of phthalate exposure with blood pressure in epidemiological and experimental studies. We identified ten population-based investigations and five toxicological experiments. Epidemiological data underscored a possible correlation between phthalate exposure and hypertension in adults, whereas individual study in children stands on the opposite. Experimental studies mainly targeted the increasing effect of phthalates on blood pressure. This review suggested some underlying mechanisms of phthalate-associated hypertension. Considering the current evidence, phthalate might be risk factors of hypertension. However, the effect of phthalate exposure in early life on blood pressure in later life or adulthood is still unclear. Well-designed longitudinal and molecular mechanism studies are indispensable.

Keywords Phthalates · Blood pressure · Hypertension · Cardiovascular disease · Risk factor

Introduction

Concerns have been raised over the contributions of environmental exposure to the development of chronic diseases. Hypertension is a serious public health issue in global and attributed to the interactions of genetic and environmental factors. Ubiquitously, human is exposed to environmental phthalates through ingestion, inhalation, derma, and intravenous contact throughout daily life. Phthalates are toxicants for jeopardizing immune function, endocrine and reproductive systems, neural and physical development, and increased risk of cardiovascular disease (Ejaredar et al. 2015; Lind and Lind 2012; Pak et al. 2011; Trasande et al. 2013).

As high-production-volume synthetic chemicals, phthalates are extensively used in a variety of consumer products to prepare polyvinyl chloride. Phthalates are detectable in both environmental media and human samples. Consequently, it is unavoidable for populations to bear organ or system toxicities of phthalates.

The global annual production of phthalates is estimated to be 11 billion pounds (Sirivarasai et al. 2013). Generally, phthalates are divided into a high molecular weight phthalate (HMWP) and low molecular weight phthalate (LMWP), but both share common properties, such as their metabolism and industrial usage (Table 1). HMWP, consisting of diisononyl phthalate (DiNP), diisodecyl phthalate (DiDP), and di-2-ethylhexyl phthalate (DEHP), are widely used in food packaging, children's toys,

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Table 1 Main phthalates and their major metabolites

Parent compound	Abbreviation	Common industrial uses	Major metabolites	Abbreviation
Low molecular weight				
Dimethyl phthalate	DMP	Solid propellants, plastics, and insect repellents	Mono-methyl phthalate	MMP
Diethyl phthalate	DEP	Plastics, fragrances, cosmetics, and personal care products	Mono-ethyl phthalate	MEP
Dibutyl phthalate	DBP	Polyvinyl emulsions, adhesives, and coatings	Mono-*n*-butyl phthalate	MnBP
High molecular weight				
Benzylbutyl phthalate	BzBP	PVC, plastics, paints, coatings, adhesives, and printing inks	Mono-benzyl phthalate (some mono-*n*-butyl phthalate)	MBzP
			Mono-isobutyl phthalate	MiBP
Dicyclohexyl phthalate	DCHP	Rubbers, resins, polymers, nitrocellulose, polyvinyl acetate, and PVC	Mono-cyclohexyl phthalate	MCHP
Di-2-ethylhexyl phthalate	DEHP	Building products (wallpaper, wire, and cable insulation), car products (vinyl upholstery and car seats), clothing (footwear and raincoats), food packaging, children's products (toys and grip bumpers), and medical devices	Mono-2-ethylhexyl phthalate	MEHP
			Mono-(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
			Mono-(2-ethyl-5-oxohexyl) phthalate	MEOHP
			Mono-(2-ethyl-5-carboxypentyl) phthalate	MECPP
Diisobutyl phthalate	DiBP	Adhesives, cosmetics, industrial solvents, and glues	Mono-isobutyl phthalate	MiBP
Diisononyl phthalate	DiNP	PVC, inks, paints, and sealants (instead of DEHP)	Mono-isononyl phthalate	MiNP
Diisodecyl phthalate	DiDP	PVC plastics, covering on wires and cables, artificial leather, toys, carpet backing, and pool liners	Mono-(carboxynonyl) phthalate	MCNP
Di-*n*-octyl phthalate	DnOP	Polymer manufacturing, PVC, gloves, and flooring	Mono-(3-carboxypropyl) phthalate	MCPP
			Mono-*n*-octyl phthalate	MnOP

Source: http://www.cdc.gov/biomonitoring/ DBP_BiomonitoringSummary.html

PVC, polyvinyl chloride

medical devices, and building materials. LMWP, such as benzyl butyl phthalate (BBP or BzBP), dimethyl phthalate (DMP), diisobutyl phthalate (DiBP), diethyl phthalate (DEP), and dibutyl phthalate (DBP), are used in paints, adhesives, solvents, body-care products (cosmetics and perfumes), and medications (Guo and Kannan 2013; Hubinger 2010; Schettler 2006; Xu et al. 2010). Being not covalently bound with polyvinyl chloride, phthalates can leach, migrate, and volatilize over time into environmental media such as indoor air, atmosphere, and foodstuff (Ait Bamai et al. 2014). DEHP has the highest concentration in foodstuff: 329 μg/kg in meat product, 322 μg/kg in poultry, and 789 μg/kg in fish (Bradley et al. 2013). DEHP was detected at the highest level (5932 μg/kg) in fish products (Fierens et al. 2012). DEP was found at the highest concentration, ranging from 4.83 to 2250 ng/m^3 (median 152 ng/m^3), in indoor air samples collected from homes, offices, laboratories, schools, salons (hair and nail salons), and public places (Tran and Kannan 2015). The highest measured levels were DEHP 6.45 mg/L and DEP 9.80 mg/L in 9-month-old normal saline (Strac et al. 2013). Obviously, the dominant phthalate subclass varies in samples based on their application features. The concentration range of total phthalates in the ambient environment of e-waste dismantling areas were 0.31–2.39 mg/kg in soil and 1.81–5.77 mg/kg in plants (dry weight/DW) (Ma et al. 2013). Other data from soils at three e-waste sites, Fengjiang, Nanshan, and Meishu in Taizhou city in China, showed that total phthalate concentrations ranged from 12.57 to 46.67 mg/kg (Liu et al. 2009). Environmental pollutants from informal e-waste recycling area present a high exposure risk to local populations via direct and indirect contact (Awasthi et al. 2016). Populations are exposed to environmental phthalates from routes of ingestion, inhalation, derma, and intravenous contact throughout life, including intrauterine development. Our previous study measured five phthalates in umbilical cord blood samples near a world-class plastic industry, among which DEHP levels were the highest (645.59 μg/L), followed by DEP (258.67 μg/L) (Li et al. 2016). A Canadian study estimated that the daily exposure dose to DEHP through multiple sources, such as plasticizers, food packaging, plastic toys, and adhesives, was up to 9 μg/kg body mass/day in infants, 19 μg/kg body mass/day in toddlers, 14 μg/kg body mass/day in school-age children, and 6 μg/kg body mass/day in adults (Heudorf et al. 2007). This result hints at child susceptibility to environmental exposure. The inhalation dose of exposure to phthalates was estimated at 0.845, 0.423, 0.203, 0.089, and 0.070 μg/kg body mass/day for infants, toddlers, children, teenagers, and adults, respectively (Tran and Kannan 2015). Hence, inhalation may play a tiny role in human exposure to phthalates. Urine is the commonest specimen for monitoring phthalate exposure (Braun

et al. 2012). National Health and Nutrition Examination Survey (NHANES) concluded that children have higher urinary levels of both HMWP and LMWP metabolites than adults, because of child and younger toddler hand-to-mouth activities together with their increased dietary requirements per unit body mass (Silva et al. 2004). Apparently, children are more susceptible to environmental insults and are inclined to exhibit adverse health outcomes in later life or adulthood (Heacock et al. 2016). A systematic review has provided evidence on phthalate hazards in pregnant women and offspring (Zarean et al. 2016). Another finding suggests that intrauterine exposure to phthalate could cause metabolic disorders, which are closely associated with hypertension (Falkner 2015).

Hypertension, or high blood pressure, is the biggest single contributor to the global burden of disease and to global mortality. The aggregate effect of all the genetic loci on blood pressure to date is small. Environmental pollutants are linked to the pathogenesis of hypertension.

Primary hypertension is the most frequent class in adults. According to the World Health Organization (WHO), more than one in five adults worldwide have hypertension and the complications, accounting for 9.4 million deaths every year (Poulter et al. 2015). Over 30% of adults in many African countries have elevated blood pressure (BP) and the proportion is steadily increasing (Lim et al. 2012). In China, recent investigation indicates that 32.5% of adult participants (33.7% of men and 31.9% of women) have hypertension and 39.5% have prehypertension (Lewington et al. 2016). Furthermore, the prevalence of prehypertension in juveniles was 7.2% in China, 12.7% in the USA, and 11.1% in Poland; the prevalence of hypertension in juveniles was 3.1% in China, 5.4% in the USA, and 4.9% in Poland, respectively (Lee 2014; Ostrowska-Nawarycz and Nawarycz 2007). The prevalence rates ranged from 9.2 to 16.4% for prehypertension and 8.4 to 24.4% for hypertension in a longitudinal study in African pediatric populations (Kagura et al. 2015). Childhood BP values have been regarded as significant predictors of adult BP (Bao et al. 1995). Hypertension depends on a combination of genetic and environmental factors. The genetic discoveries so far explain only 3% of the heritability of blood pressure (Munroe et al. 2013). In addition, sufficient evidence attributes hypertension to obesity, insulin resistance, physical inactivity, increased levels of circulating angiotensin II, aldosterone, uric acid, and the higher dietary intake of sodium (Adrogue and Madias 2017; Perkins et al. 2016; Stea et al. 2014). Environmental heavy metals and persistent organic pollutants are noteworthy in the pathogenesis of hypertension through oxidative stress, inflammatory responses, and endocrine disruptions (Solak et al. 2016; Trasande and Attina 2015). A meta-analysis found that exposure to organic pollutants, including polychlorinated biphenyls, polybrominated diphenyl ethers, organochlorine pesticides, and dioxin-related compounds, can result in an increased risk of hypertension (Park et al. 2016).

Phthalate exposure associated hypertension has garnered greater concern in recent decades. Studies have analyzed the association of phthalate exposure and hypertension. Studies that have investigated the association between childhood exposure to phthalates and blood pressure (BP) endpoints have not reported consistent results (Trasande et al. 2013; Valvi et al. 2015). This review aims to summarize the scientific literature on associations of phthalate exposure with BP, as well as mechanisms connecting phthalates to hypertension, for example, oxidant stress, renin-angiotensin receptor changes, modification of vascular smooth muscle structure, and reactivity (Shih et al. 2015; Solak et al. 2016), and makes recommendations for future research.

Methods

We searched PubMed and Web of Science databases to find all published observational studies evaluating the relationship between phthalate exposure with hypertension using the free text and Medical Subject Headings terms "phthalate(s)," "phthalic acid," "blood pressure," "high blood pressure," "hypertension," "prehypertension," and "cardiovascular disease." The databases were searched to March 2018 and limited in English language. We only included original epidemiological reports and experimental studies, while excluded conference papers, editorials, reviews, letters, case reports, and case series. We screened titles and abstracts of papers, and then chose eligible papers. We identified ten population-based investigations and five toxicological experiments. Necessary information extracted from all eligible papers was tabulated: first author's last name, year of publication, country of the study, population studied, specimen type, analyzed phthalates, main findings, and covariates in studies.

Results and discussion

Epidemiological studies on phthalate exposure and hypertension

Table 2 summarizes eight cross-sectional studies on the association of phthalate exposure and altered BP. Cross-sectional data from Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS), conducted in Uppsala, Sweden, showed that serum mono-ethyl phthalate (MEP) was inversely associated with diastolic BP but not systolic BP in Caucasians aged 70 years after adjusting for confounders (Olsen et al. 2012). One community-based investigation in China adults demonstrated that there is no association of urinary phthalate with self-reported hypertension (Dong et al. 2017). Six other

Table 2 Cross-sectional studies on associations between phthalate exposure and blood pressure

Author and country	Study design/size	Population	Specimen type	Analyzed phthalates	Main finding	Covariates
Olsen et al. 2012 Sweden	Cross-sectional study $n = 1016$	Caucasians aged 70	Serum	MiBP, MMP, MEP, MEHP, MBzP, MINP, MOP, MCHP, MEOHP, MEHHP	The relation for MEP to diastolic BP remained *inversely* significant	Gender, BMI, serum cholesterol and triglycerides, smoking, and diabetes mellitus
Trasande et al. 2013 USA (NHANES)	Cross-sectional study $n = 2447$	Children aged 8–19 years	Urine	MEP, MEHP, MEHHP, MBP, MBzP, MiBP, MCPP, MEOHP, MECPP	Higher MEHP, MBP, MEHHP, and MEOHP levels were associated with SBP *z*-scores and MEP with prehypertension	Sex, caloric intake, television watching, poverty, parental education, serum cotinine, urine creatinine, BMI, ethnicity, and age
Shiue 2013 USA (NHANES)	Cross-sectional study $n = 10,537$	Non-institutionalized civilians ≥ 8 years old	Urine	MCNP, MCOP, MECPP, MnBP, MCPP, MCHP, MEP, MEHHP, MEHP, MnMP, MnOP, MBP, MiNP, MiBP, MEOHP	Higher MECPP, MnBP, and MnMP concentrations were significantly associated with increased risk of high BP in the general adult population	Urine creatinine, age, sex, ethnicity, and BMI
Shiue 2014 USA (NHANES)	Cross-sectional study $n = 20,293$	Non-institutionalized civilians ≥ 8 years old	Urine	MCNP, MCOP, MECPP, MnBP, MCPP, MEP, MEHP, MBP, MnMP, MiNP, MEOHP, MiBP, MEHHP	In men, MnMP and MnBP concentrations were associated with high BP. In women, urinary MCNP, MnBP, MEP, MBzP, MiBP, and MCPP concentrations were associated with high BP	Urine creatinine, age, sex, BMI, ratio of family income to poverty, and subsample weighting
Shiue 2014 USA (NHANES)	Cross-sectional study $n = 9756$	Non-institutionalized civilians ≥ 8 years old	Urine	MCNP, MCOP, MECPP, MnBP, MCPP, MEP, MEHP, MBP, MnMP, MiNP, MEOHP, MiBP, MEHHP	Higher MECPP, MnBP, MEHHP, MnMP, MEOHP, and MBP concentrations were associated with high BP	Urine creatinine, age, sex, ethnicity, BMI, and survey weighting
Trasande et al. 2015 USA (NHANES)	Cross-sectional study $n = 1329$	Children aged 8–19 years	Urine	MEP, MBP, MiBP, MMP, MBzP, MNP, MCPP, MCOP, MCNP, MEHP, MEHHP, MEOHP, MECPP	Increases in SBP *z*-scores emerged in multivariable modeling in association with urinary MEHHP, MEOHP, and MECPP, and MCOP, MNP, and MCNP	Urine creatinine, age, caloric intake, sex, poverty-income ratio, serum cotinine, BMI, ethnicity, and physical activity
James-Todd et al. 2016 USA (NHANES)	Cross-sectional study $n = 2719$	Men and non-pregnant and non-lactating women aged 20–80 years	Urine	MEP, MBzP, MnBP, MCPP, MiBP, total DEHP metabolites	Higher urinary ΣDEHP metabolite levels were associated with high BP	Urinary creatinine, age, sex, race/ethnicity, total caloric intake, education, physical activity, smoking, and poverty
Dong et al. 2017 China	Cross-sectional study $n = 2330$	Community population aged > 18 years	Urine	MMP, MEP, MnBP, MiBP, MBzP, MEHP, MEOHP, MEHHP, MECPP, MCMHP	*No* associations of urinary phthalate with self-reported hypertension	Age, sex, BMI, education, marriage, smoking, total calories and total fat

BMI, body mass index; *BP*, blood pressure; *SBP*, systolic blood pressure; *NHANES*, National Health and Nutrition Examination Surveys

epidemiological studies originated from NHANES, which found that multiple urinary phthalate metabolites are significantly positively related to higher BP, regardless of which demographic group is (James-Todd et al. 2016; Shiue 2013; Shiue 2014a; Shiue 2014b; Trasande and Attina 2015; Trasande et al. 2013; Werner et al. 2015). Trasande et al. found that higher urinary MEP levels were positively associated with prehypertension in children (8–19 years old) (Trasande et al. 2013).

Cross-sectional design cannot establish a causality. A single measurement may be inefficient to reflect long-term exposure. The outcomes (Dong et al. 2017; Olsen et al. 2012) differ from other six surveys due to their diverse ethnicities, because NHANES was conducted in a nationally representative human sample with mixed ethnicities (James-Todd et al. 2017). Also, self-reported hypertension rate may be lower defined and result in non-significant associations with phthalate exposure. Nevertheless, preponderant surveys are from the USA (NHANES), which might lessen the possibility for a conclusive and generalizable result. Future studies should be designed to understand the persisting risk throughout life from the environmental phthalate.

Table 3 lists two longitudinal surveys. One from the Health Outcomes and Measures of the Environment Study (HOME) reported that higher maternal urinary mono-benzyl phthalate (MBzP) concentrations were associated with increased diastolic BP at < 20 weeks gestation and a greater risk of pregnancy-induced hypertension at ≥ 20 weeks after controlling for confounders (Werner et al. 2015). Another from the Spanish population-based birth cohort study INMA (Infancia y Medio Ambiente Environment and Childhood) demonstrated that ΣHMWP and ΣLMWP metabolites are associated with lower systolic BP *z*-scores at 4 and 7 years of age in girls but not in boys, and no significant connection was shown with diastolic BP *z*-scores (Valvi et al. 2015).

Werner et al. (2015) evaluated when phthalates can increase maternal BP. This longitudinal study determined two measures of phthalate metabolites during pregnancy, whereas collected chart-derived BP measurement rather than research quality measures. It will more thoroughly assess how phthalates influence maternal and fetal health if pre-pregnancy health status is adjusted and markers of relevant biological pathways are added. Valvi et al. (2015) evaluated the causation of phthalate exposure and lower BP. It used the average concentrations measured in two spot-urine samples, lacked phthalate exposure levels in children and repeated measurements of BP at each child age. It will optimize relation assessment by using multiple spot-urine samples and adjusting potential confounders about postnatal exposure. Maternal hypertension during pregnancy can predict offspring BP rank at 21 years old (Mamun et al. 2012). Thus, more well-designed cohort studies are required to confirm or refute the current findings.

Table 4 outlines evidence for an association between phthalate metabolites and blood pressure in each demographic group. We can get an understanding that DEHP metabolites play the most important role in ΣHMWPm associations while ΣLMWPm action may be driven mainly by MEP. What's

Table 3 Prospective studies on associations between phthalate exposure and blood pressure

Author and country	Study design/size	Population	Specimen type	Analyzed phthalates	Main finding	Covariates
Werner et al. 2015 USA (HOME)	Prospective study $n = 369$	Women ≥ 18 years old, 16 ± 3 weeks gestation	Urine	MEP, MCPP, MBzP, ΣDEHP, and DBP metabolites	Maternal urinary MBzP concentrations at 16 weeks of gestation were associated with increased diastolic BP at < 20 weeks of gestation and risk of pregnancy-induced hypertension at ≥ 20 weeks of gestation	Maternal race, age at delivery, household income, education, marital status, serum cotinine concentration, weeks of gestation at blood pressure measurement, parity, BMI at 16 weeks of gestation, and previous use of BP medications
Valvi et al. 2015 Spanish (INMA)	Birth cohort study $n = 391$	Children aged 1, 4, and 7 years	Maternal urine	MEHP, MBzP, MEHHP, MEOHP, MEP, MnBP, MiBP, MECPP	ΣHMWPm and ΣLMWPm were associated with *lower* systolic blood pressure *z*-scores at 4–7 years of age in girls but not in boys, and no significant association was shown with diastolic BP *z*-scores	Child sex, exact age at examination, maternal nationality, delivery age, parity, education, social class, pre-pregnancy BMI, and smoking in pregnancy

BMI, body mass index; *BP*, blood pressure; *HOME*, Health Outcomes and Measures of the Environment Study; *INMA*, Infancia y Medio Ambiente Environment and Childhood; *ΣHMWPm*, the sum of low molecular weight phthalates metabolites; *ΣHMWPm*, the sum of high molecular weight phthalate metabolites

more notable is that the cross-sectional correlation between child BP and phthalate exposure is positive but the cohort investigation confirmed a negative relationship between early-life phthalate exposure and systolic BP at 4 and 7 years old.

Consequently, adults suffer from a consistent relationship of increased BP and phthalate exposure. However, old population is considered a negative association between diastolic BP and serum levels of phthalate metabolites. Possible reason is a divergence between the level of phthalate metabolites in urine and in serum (Frederiksen et al. 2010). Conclusions in children are inconsistent across these studies. It is less persuasive to conclude with the phthalate-associated hypertension in children and the elderly. Much more prospective studies are needed to validate these investigations.

Experimental studies on phthalate exposure and hypertension

Corresponding animal experimental studies are important for the interpretation of data derived from human investigations. The ability of phthalates to influence the formation and maintenance of elevated BP has been identified in animals. Of the five reports listed in Table 5, four found that DEHP exposure has the ability of elevating BP (Jaimes et al. 2017; Lee et al. 2015; Rahmani et al. 2016; Wei et al. 2012). However, Martinez-Arguelles et al. concluded that systemic BP decreased during the nighttime and diastolic BP decreased during the daytime and nighttime at postnatal day (PND) 200 after maternal exposure to 300 mg/kg/day DEHP from gestational day 14 until parturition (Martinez-

Table 4 Summary of associations between phthalate metabolites and blood pressure in each demographic group

Demographic groups	Phthalate metabolites	Health outcomes	References
Cross-sectional studies			
Children (< 18 years)	MEP	Prehypertension rate ↑	Trasande et al. 2013 and 2015
	MBP	SBP ↑	
	MEHP	SBP ↑	
	MEHHP	SBP ↑	
	MEOHP	SBP ↑	
	MECPP	SBP ↑	
	MCOP	SBP ↑	
	MNP	SBP ↑	
	MCNP	SBP ↑	
Adults (18–60 years)	MnMP	BP ↑	Shiue 2014; Shiue et al. 2014; James-Todd et al. 2016
	MnBP	BP ↑	
	MEP	BP ↑	
	MEHP	BP ↑	
	MEHHP	BP ↑	
	MEOHP	BP ↑	
	MECPP	BP ↑	
	MCNP	BP ↑	
	MBzP	BP ↑	
	MiBP	BP ↑	
	MCPP	BP ↑	
Old people (≥ 60 years)	MEP	Diastolic BP ↓	Olsen et al. 2012;
Prospective studies			
Pregnant woman (16 ± 3 weeks gestation)	MBzP	Diastolic BP at < 20 weeks gestation ↑; hypertension rate at ≥20 weeks gestation↑	Werner et al. 2015
Children (1, 4, and 7 years)	MEP	SBP at 4 and 7 years ↓	Valvi et al. 2015
	MEHP	SBP at 4 and 7 years ↓	
	MEHHP	SBP at 4 and 7 years ↓	
	MEOHP	SBP at 4 and 7 years ↓	
	MECPP	SBP at 4 and 7 years ↓	

BP, blood pressure; *SBP*, systolic blood pressure; ↑, increase; ↓, decrease

Table 5 Experimental studies on associations between phthalate exposure and blood pressure

Author/year	Species/strain	Phthalate	Administration	Measurement	Results (conc. phthalate)
Wei et al. 2012	Rats (Wistar)	DEHP (maternal exposure)	Pregnant rats were gavaged with 0.25 or 6.25 mg/kg DEHP from gestation day 0 through PND 21 (the end of lactation)	Tail-cuff plethysmography in weeks 15, 21, and 33	SBP increased (0.25 and 6.25 mg/kg/day) and diastolic BP increased (0.25 mg/kg/day) in 33-week-old offspring
Martinez-Arguelles et al. 2013	Rats (Sprague Dawley)	DEHP (maternal exposure)	Pregnant rats were gavaged with 300 mg/kg/day DEHP from gestational day 14 until parturition (PND 0)	Intravascular telemetric blood pressure transmitter probes at PND 60 and PND 200 (males)	SBP *decreased* during the nighttime, and diastolic BP decreased during the daytime and nighttime (300 mg/kg/day) at PND 200
Lee et al. 2015	Mice (C57BL/6)	DEHP (maternal exposure)	8-week-old female mice were gavaged with 30 mg/kg DEHP until their offspring weaned	Tail-cuff plethysmography in offspring at 8 weeks	There was a 20% increase in SBP, diastolic BP, and mean BP in offspring
Rahmani et al. 2016	Rats (Wistar)	Phthalic acid (maternal exposure)	Rats were gavaged with diets containing 1763 and 2981 mg/kg phthalic acid from the seventh day to the sixteenth day of pregnancy	Tail plethysmographic method at the end of the third month	Mean BP significantly increased to 1763 and 2981 mg/kg phthalic acid
Jaimes et al. 2017	Mice (C57BL/6)	DEHP	12-week-old male mice with drinking water containing DEHP/Captisol® (1 μg/4 mg/ml) for vehicle control, with a circulating MEHP level of 403 ± 28.8 ng/mL	BP transducer was placed in the left carotid artery and fed inferiorly to collect BP recordings for 3–4 days per week during total 6-week experiment	Basal SBP was slightly increased, and an exaggerated and delayed post-stress SBP recovery (+ 13%) in DEHP-treated animals

DEHP, di-(2-ethylhexyl) phthalate; *MEHP*, mono-2-ethylhexyl-phthalate; *BP*, blood pressure; *SBP*, systolic blood pressure; *PND*, postnatal day

Arguelles et al. 2013). The reduction in aldosterone levels at PND 60 could chronically disorganize water homeostasis, thus lessening BP at PND 200.

Phthalates exert an augmented effect on offspring BP in several lines of literature. However, a piece of the experimental study displayed inconsistent result. Unfortunately, Martinez-Arguelles et al. (2013) did not analyze any parameters in adult female offspring. Previous reports claimed that the adrenal response to prenatal exposure to DEHP is sex-specific, and a hypertensive response possibly induced by DEHP in the female offspring (Martinez-Arguelles et al. 2011). In further studies, the gender difference of response to prenatal phthalate exposure will be the subject. All the listed articles have also explored the biological mechanisms of maternal DEHP exposure in offspring's BP changes. Obviously, DEHP-induced BP alterations in offspring were analyzed most frequently because of DEHP's widespread use in consumer products. It is already clear that mono-2-ethylhexyl phthalate (MEHP) has a higher toxicity than DEHP (Feige et al. 2007; Laurenzana et al. 2016), but it is still unknown whether the cardiovascular toxicity observed in offspring is a result of the direct effects of the maternal transfer of phthalate or phthalate metabolites (Matsumoto et al. 2008; Posnack et al. 2012), which should be fully studied in future. The molecular mechanisms involved in the correlation between phthalate or their metabolites and the cardiovascular system need to be explored deeply.

Mechanisms of phthalate's effects on hypertension

Epidemiological data point to a reasonable correlation between phthalate exposure and abnormal BP. Experimental studies present basic mechanisms in favor of increased BP resulting from phthalates. Despite variations in study designs and end results among investigations, many published articles have identified the significantly positive association of phthalate exposure and hypertension (James-Todd et al. 2016; Shiue 2013; Shiue 2014a; Shiue 2014b; Trasande and Attina 2015; Trasande et al. 2013; Werner et al. 2015). Taken all together, some findings in human populations agreed with animal data, implying that phthalates and their metabolites play a remarkable role in BP enhancement. Different findings usually derive from dissimilar studies with different research objects and methods. The cause of primary hypertension is multifactorial. Obesity, insulin resistance, the activation of the sympathetic nervous system, alterations in sodium homeostasis, renin-angiotensin system changes, alterations in vascular smooth muscle structure and reactivity, high serum uric acid levels,

genetic factors, and fetal programming have already been published as contributors to hypertension (Grassi 2010; Raj and Krishnakumar 2013; Shih et al. 2015; Singh et al. 2010; Tomat and Salazar 2014).

Studies revealed that increased reactive oxygen species (ROS) and decreased nitric oxide (NO) are associated with vascular dysfunction, which promotes the prevalence of hypertension (Cunningham et al. 2013; Lytsy et al. 2013; Munoz et al. 2015; Xiao et al. 2011). Phthalic acid induces increased blood pressure, oxidative stress, and markers of endothelial dysfunction in rat offspring, which could be due to cardiac hypertrophy, aggravation in the thickness of the aorta wall, and higher levels of malondialdehyde, glutathione peroxidase, and vascular superoxide dismutase (SOD) enzymes (Rahmani et al. 2016). Oxidative stress may also play an important role in potential mechanisms of endothelial nitric oxide synthase (eNOS) uncoupling in cardiovascular diseases (Karbach et al. 2014). Maternal DEHP exposure can increase offspring BP, potentially through phthalate-induced deregulation of aortic eNOS phosphorylation and upregulation of angiotensin receptor II (AT_1R) expression in offspring (Lee et al. 2015). The activity of eNOS plays a vital role in physiologic BP regulation (Li et al. 2015). Reduction of eNOS expression impairing NO production by endothelial cells is a major factor for physiological and morphological changes in cardiovascular system, which, in turn, leads to hypertension (Afolayan et al. 2016). DEHP-treated animals exhibited sustained SBP elevation and had increased endothelin-1 and angiotensin-converting enzyme expression as well as decreased NOS3 gene expression, which may predispose these animals to vasoconstriction, vascular resistance, and autonomic dysfunction (Jaimes et al. 2017). DEHP exposure reduces circulating levels of aldosterone and testosterone and increases adrenocorticotropin and corticosterone levels (Martinez-Arguelles et al. 2011; Supornsilchai et al. 2007). In utero exposure to DEHP decreases circulating testosterone and aldosterone levels in adult male offspring and reduces the expression of the angiotensin II receptors in the adrenal gland (Martinez-Arguelles et al. 2013). Accordingly, impaired angiotensin-aldosterone system, autonomic dysfunction, and oxidative stress-mediated endothelial dysfunction may be of pathological relevance in phthalate-associated elevated BP.

Increasing evidence supports the inflammatory and immune pathogenesis of hypertension (Mattace-Raso et al. 2010; Rabinovitch et al. 2014; Solak et al. 2016). A new era of research is emerging on how the interactions between organismic internal environment and the external ambient environment dominate etiology. A prospective cohort study observed that most HMWP metabolites were associated with increases in interleukin-6 (IL-6), IL-10, C-reactive protein (CRP), and tumor necrosis factor α (TNF-α), but positive relationships existed between mono-(carboxynonyl) phthalate (MCNP) and IL-6, between mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) and IL-10 (Ferguson et al. 2014). Nevertheless, the veracities of these findings are doubtful for the small sample size. Analogously, serum CRP and TNF-α levels increased in adult male offspring exposed to 300 mg DEHP in utero (Campioli et al. 2014). Phthalates enhanced secretion of cytokines (IL-6, IL-10) and chemokine (CXCL8), while TNF-α secretion was impeded in macrophages cells, as was the decreased secretion of IL-2, IL-4, TNF-α, and interferon (IFN)-γ by T cells (Hansen et al. 2015). DEHP significantly increased the levels of TNF-α, IL-1β, IL-8, IL-6, and CXCL2, CXCL3, CXCL6, CCL3, MMP10, and CSF2 in THP-1 cells (Nishioka et al. 2012). Hence, phthalates may suppress cell differentiation and promote inflammatory processes in vivo. A study on spontaneously hypertensive rats showed a significant correlation between the intensity of the inflammatory cell infiltration and the severity of the BP elevation (Heijnen et al. 2014). Researchers found that the distribution of CRP, IL-6, and TNF-α was more likely to cause a higher prevalence of hypertension (Bautista et al. 2001; Bautista et al. 2005; Sung et al. 2003). This was confirmed in a pulmonary hypertension model that inflammation precedes vascular remodeling, a cause of vascular disease (Tamosiuniene et al. 2011). Based on the above discoveries, phthalate-induced inflammatory responses must be underlined in the etiological study of hypertension.

Prenatal exposure to phthalates is thought to alter the fetal programming of cardiovascular function and to heighten offspring risk of cardiovascular disease in later life (Ferguson et al. 2014; Graves et al. 2014). Prenatal phthalate exposure can alter the mRNA expression of placental fatty acid transport protein 1 and heart fatty acid binding protein, expressed in placenta and involved in the transfer of essential fatty acid between the mother and the fetus, which plays an important role in fetal development (Li et al. 2016; Xu et al. 2008). Data showed that maternal DEHP exposure impairs the offspring's renal development, resulting in a nephron deficit and elevated BP in later life (Wei et al. 2012). Research has demonstrated that early-life exposure to environmental toxicants adversely affects fetal growth and physical development after birth (Kazi et al. 2014). Details of the mechanisms, by which renal interstitial inflammation may cause hypertension, were recently reviewed elsewhere (Rodriguez-Iturbe et al. 2013). Indeed, initial BP is not independently associated with any single causative agent. A longitudinal community-based cohort study conducted in Framingham, Massachusetts, found that higher aortic stiffness measurements made up a proportion of higher risk factors of hypertension during a 7-year follow-up period in 1759 participants (Kaess et al. 2012). This indicates that the endocrine disruptor DEHP should be rationally evaluated as a risk factor for nephron genesis and onset of hypertension.

In addition, epigenetic modifications to DNA structure, the influence of non-coding RNAs, and histone modification are key players in hypertension development (Wise and Charchar 2016). Multiple lines of evidence from in vitro and in vivo models showed that phthalates are epigenetic toxicants, followed by phthalate-caused aberrant DNA methylation and expression levels mRNA along with protein (Singh and Li 2012). Many findings strongly hint that exposure to endocrine-disrupting chemicals may have cumulative adverse effects on future generations, and that these effects could be mediated by epigenetic mechanisms (Martinez-Arguelles and Papadopoulos 2016). However, it remains to be elucidated what are the impacts of epigenetic alteration on phthalate-induced hypertension or hypotension. Direct and specific epigenetic research concerning the BP regulation will provide further understanding.

In summary, the comprehensive mechanisms of phthalates significantly elevating BP in humans are not yet fully understood. Moreover, most studies concluded that phthalate exposure certainly increases BP, but did not refer to internal mechanisms. Naturally, integrated molecular evidence is needed to explicate their relationship and causality. Thus, the main mechanisms in the pathology of phthalate-associated hypertension could be the target of future research.

Conclusions and perspectives

Phthalates might be associated with the development of hypertension in adults. Its specific influence in children or the elderly is inconclusive. Oxidative stress, immune and inflammatory responses, autonomic dysfunction, impaired angiotensin-aldosterone system, renal dysfunction, and fetal programming might engage in phthalate-associated hypertension. Epigenetic studies on phthalate-induced hypertension may be the future concern. As a result, phthalate might be risk factors of hypertension.

Considering the current evidence, to promote public health and reduce the prevalence of hypertension, concurrent improvements should be made: (1) detect and treat elevated BP in high phthalate exposure risk groups; (2) minimize sources and routes of phthalate exposure in general populations by avoiding foods packaged and stored in plastics, personal care products containing phthalates, and polyvinyl chloride materials; (3) protect sensitive subpopulations, such as pregnant women, fetuses, infants, young children, and the elderly; (4) pay more attention to protect children from phthalate exposure because of their hand-to-mouth activities, immature body function development, and poor ability of excreting toxicants; and (5) clarify the exact relationship by well-designed longitudinal, molecular mechanism, and intervention trials to verify phthalate as the etiology of hypertension.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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