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Review

The effects of phthalate ester exposure on human health: A review

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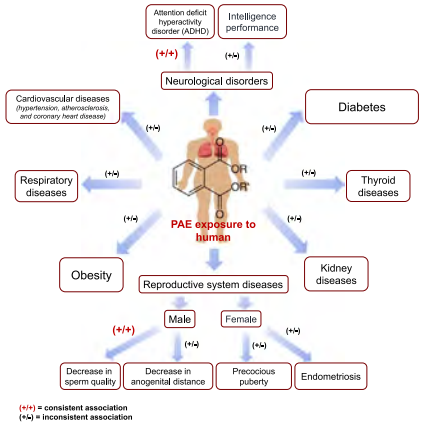
HIGHLIGHTS

- Associations between PAEs and lower sperm quality in males and *ADHD* in children were consistently revealed.
- Those associations were confirmed by cohort or longitudinal studies.
- Inadequate evidence of the association between PAE exposure and other human diseases.

GRAPHICAL ABSTRACT



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ABSTRACT

Phthalate esters (PAEs) are one of the most widely used plasticizers in polymer products and humans are increasingly exposed to them. The constant exposure to PAEs-contained products has raised some concerns against human health. Thus, the impacts of PAEs and their metabolites on human health require a comprehensive study for a better understanding of the associated risks. Here, we attempt to review eight main health effects of PAE exposure according to the most up-to-date studies. We found that epidemiological studies demonstrated a consistent association between PAE exposure (especially DEHP and its metabolites) and a decrease in sperm quality in males and symptom development of ADHD in children. Overall, we found insufficient evidence and lack of consistency of the association between PAE exposure and cardiovascular diseases (hypertension, atherosclerosis, and CHD), thyroid diseases, respiratory diseases, diabetes, obesity, kidney diseases, intelligence performance in children, and other reproductive system-related diseases (anogenital distance, girl precocious puberty,

Abbreviations: ACR, albumin/creatinine ratio; ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; B2M, β-2 microglobulin; BBzP, butyl benzyl phthalate; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CkiD, chronic kidney disease in children; DEHP, di-(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiBP, diisobutyl phthalate; DiDP, diisodecyl phthalate; DiNP, diisononyl phthalate; DMP, dimethyl phthalate; DnBP, dibutyl phthalate; DnOP, di-n-octyl phthalate; HOMA, homeostatic model assessment; IQ, intelligence quotient; LDL, low-density lipoprotein; MBP, monobutyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-(3-carboxypropyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, mono-ethyl phthalate; MMP, mono-methyl phthalate; MMPn, matrix metalloproteinase; MnBP, mono-n-butyl phthalate; NAG, *N*-acetyl-β-D-glucosaminidase; NHANES, National Health and Nutrition Examination Survey; PAEs, phthalate esters; PVC, polyvinyl chloride; T3, triiodothyronine; T4, thyroxine.

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PAE exposure
Health effects
Diseases

and endometriosis). Future studies (longitudinal and follow-up investigations) need to thoroughly perform in large-scale populations to yield more consistent and powerful results and increase the precision of the association as well as enhance the overall understanding of potential human health risks of PAEs in long-term exposure.

Contents

1. Introduction

The global use of plasticizers has increased substantially over recent decades in industrial products such as automotive products, textile fibers, electronic products, food packaging, and toys (Erythropel et al., 2014). The plasticizers are commonly added to polymer materials to improve their functionality (e.g., flexibility and durability) (Erythropel et al., 2014). Phthalate esters (PAEs) are the most important and widely used plasticizers (Erythropel et al., 2014) as they can enhance flexibility and elasticity, and therefore improving the quality of plastic polymers. In 2017, PAEs accounted for 65% of global plasticizer consumption, meanwhile, overall global consumption of PAEs is expected to grow at an average annual rate of 1.3% between 2017 and 2022 (Markit, 2018). In the United States, >470 million pounds of PAEs are annually produced and imported, make it the most frequently used plasticizer (EPA, 2012).

However, PAEs are easily released from those industrial products into the environment during their manufacture, storage, use, or disposal since they are not covalently bound to the plastic products such as polyvinyl chloride (PVC) (Koch et al., 2006). The previous study has shown that some PAE metabolites have been detected in nearly 80% of the population in the United States (Silva et al., 2004). The source of PAE uptake in humans, which includes foods (vegetables, edible crop, drinks) (Bošnir et al., 2007; Fu and Du, 2011; Liu et al., 2012; Zhang et al., 2019), personal care products (Romero-Franco et al., 2011; Nassan et al., 2017; Fisher et al., 2019), toys (Earls et al., 2003), air (as household dust and vapor) (Carlstedt et al., 2013; Promtes et al., 2019), home furnishings (Carlstedt et al., 2013), nutritional supplements to pharmaceuticals (Kelley et al., 2012), and medical instruments (Krishnan and Bhuvaneshwar, 2004; Chou and Wright, 2006), has been reported as routes of PAE exposure.

Exposure to certain PAEs is associated with disruption of the endocrine system and induces reproductive toxicity in animal studies (Richburg et al., 2002; Talsness et al., 2009; Shi et al., 2015; Xie et al., 2015; Zhang et al., 2015). PAEs can bind to molecular targets in the human body and interfere with hormonal homeostasis (Mariana et al., 2016), leading to different disorders in fetuses, infants, children, and adults (Katsikantami et al., 2016). PAEs are also suspected to interfere with biological processes in humans and wildlife, potentially causing teratogenicity, mutagenicity, and carcinogenicity even at very low concentrations (Becker et al., 2004; Caldwell, 2012). Thus, the use of PAEs has been restricted and strictly regulated. For instance, the EU (REACH Annex XVII and RoHS 2) has restricted six PAEs– benzyl butyl phthalate (BBP), di-n-butyl phthalate (DnBP), di-2-ethylhexyl phthalate (DEHP), di-isodecyl phthalate (DiDP), diisononyl phthalate (DiNP), and di-n-octyl phthalate (DnOP)–in toys and childcare since 1999. Meanwhile, DEHP, BBP, DnBP, and diisobutyl phthalate (DiBP) are restricted in electrical and electronic equipment (EEE) in Europe. In 2008, the US Consumer Products Safety Improvement Act (CPSIA) banned permanently for using three PAEs (BBP, DnBP, and DEHP) in children's toys and provisionally banned DiDP, DiNP, and DnOP. The global regulations for the use of PAE plasticizers are briefly presented in Supplementary Information S1.

Given the current trends have raised the health concerns of a large number of PAE-derived plasticizer products, it is important to deeply review the health impacts of such plasticizers. A summary and topical review on PAE effects to health effects (8 diseases) have not been comprehensively conducted yet. For instance, several papers only discussed the impact of PAE exposure on the individual or particular disease (Lyche et al., 2009; Huang et al., 2012; Holahan and Smith, 2015; Robinson and Miller, 2015; Mariana and Cairrao, 2020), summarizing the health impacts of only individual species of PAE (Posnack, 2014; Rowdhwal and Chen, 2018). Most reviews focused on cardiovascular diseases, reproductive system diseases, neurological disorders, thyroid diseases, and respiratory system diseases. In recent years, a number of scientific papers discussing the other possible harmful health outcomes of PAEs have experienced rapid growth, especially in kidneys, obesity, and the respiratory system. Thus, this paper attempts to bridge this gap and provide insights into 8 health outcomes of PAE exposure on humans through literature review.

2. Process of article selection

The literature search on the health effects of PAE plasticizers was conducted on the search engine of the PubMed database, as presented in Supplementary Information S2, highlighting the search terms used. Supplementary Information S3 summarizes the process of article selection. The initial search resulted in 2,103 retrievals (the selected articles were published from January 2000 to August 2020). Briefly, the total number of phthalate-related papers (shown in parentheses) associated with various health issues were as follows: thyroid diseases (195), respiratory tract diseases (257), obesity (265), reproductive system diseases (556), kidney diseases (345), neurological disorders (128), cardiovascular diseases (164), and diabetes (193). The first scan of titles and abstracts was carried out to limit the amount of potentially relevant papers to a total of 305 articles. The remaining potentially eligible full papers were reviewed and evaluated, resulting in a final inclusion of 103 articles. Meanwhile, Supplementary Information S4 presents the distribution of the selected 103 articles in each health issue, highlighting the cardiovascular (31%) and reproductive system diseases-related articles (31%) as the highest number of published articles until August 2020.

3. Type of PAEs

PAEs are fabricated by reacting phthalic anhydride with alcohol (s) with differing chain lengths ranging from C_1 (methanol) to C_{13} (tridecyl alcohol) (Saeidnia, 2014). Thus, PAEs can be divided into two main subgroups based on their carbon chain length: high-molecular-weight (HMW) with side-chain lengths of 7–13 carbons and low-molecular-weight (LMW) PAEs with the side-chain length of 3–6 carbons (Table 1) (NRC, 2009). The common HMW PAEs include DiDP, DiNP, di-2-propylheptyl phthalate (DPHP), and DEHP; HMW PAEs which are increasingly used in industry to enhance the flexibility and elasticity of rigid polymers (ECPI, 2014). Moreover, the addition of these HMW PAEs is also attributed to the improvement of the extensibility and durability of industrial products such as wires, cables, flooring, tarpaulin, wall coverings, synthetic leather, roofing membranes, and automotive-related materials (Wypych, 2012; ECPI, 2014; Katsikantami et al., 2016). Meanwhile, LMW PAEs include DnBP, DiBP, and butyl benzyl phthalate (BBzP), which are widely used in PVC products, such as medical equipment, adhesives, paints, inks, and enteric film ingots (ECPI, 2014). Other LMW PAEs, such as dimethyl phthalate (DMP) and diethyl phthalate (DEP), have 1–2 carbon atoms in their hydrocarbon chain, which are extensively utilized as solvents and fixing agents in perfumes as well as additives for medical devices, cosmetics, household products, and personal care products (Wypych, 2012; ECPI, 2014; Katsikantami et al., 2016). Among these PAE plasticizers, DEHP is the most widely used plasticizer in polymer products (Bošnir et al., 2007; Keresztes et al., 2013; HSDB, 2015).

4. Exposure route of PAEs

Humans are exposed to PAEs through multiple routes (dietary/oral/ingestion, dermal absorption, inhalation, and prenatal administration) and the most likely route varies by different PAE species (Wang et al., 2020). The major exposure route of most PAEs (such as DEHP) is oral/dietary exposure by food ingestion (Serrano et al., 2014). However, dermal absorption (through using personal care products) and inhalation are other routes to certain PAEs (Otake et al., 2004; Duty et al., 2005; Wang et al., 2020).

Dietary exposure to PAE has been revealed through several contaminated foods and drinks (Cirillo et al., 2011; Fierens et al., 2012; Alp and Yerlikaya, 2020). For instance, Fierens et al. (2012) revealed the presence of PAEs such as DEHP, DiBP, DnBP, and BBP in 400 food products sold in Belgian markets. The PAE contaminations occurred from the packaging materials of multiple foods (Fierens et al., 2012). Another study carried out in Turkey also demonstrated that PAEs (such as DEHP, DnBP, BBP, DiNP, DiDP, and DNOP) are present in foods as a result of migration from food packaging (Alp and Yerlikaya, 2020). Meanwhile, Cirillo et al. (2011) found the increasing concentrations of DEHP and DnBP in cooked foods before and after packaging were 113% and 125%, respectively. These results indicate that DEHP and DnBP are the most frequently used

Table 1
Type of PAEs and their metabolites.

CASRN	Common name	Category	Acronym	Primary metabolites	Secondary metabolites
131-11-3	Di-methyl phthalate	LMW	DMP	MMP	–
84-66-2	Di-ethyl phthalate	LMW	DEP	MEP	–
84-69-5	Di-isobutyl phthalate[d]	LMW	DiBP	MiBP	2OH-MBP and 3OH-MiBP
84-74-2	Di-n-butyl-phthalate[a,b,c,d]	LMW	DnBP	MnBP	3OH-MnBP, 4OH-MnBP, and MCPP
85-68-7	Butyl-benzyl-phthalate[a,b,c,d]	LMW	BBzP	MBzP	MCPP
84-61-7	Di-cyclohexyl phthalate	LMW	DCHP	MCHP	–
131-18-0	Di-n-pentyl phthalate[d]	LMW	DnPP	MnPP	–
26761-40-0	Di-isodecyl-phthalate[a,b,c,d]	HMW	DiDP	MiDP	–
610-09-3	1,2-Cyclohexane dicarboxylic acid, diisononyl ester	HMW	DINCH	MINCH	OH-MINCH, oxo-MINCH, and ex-MINCH
28553-12-0	Di-iso-nonyl phthalate[a,b,c,d]	HMW	DiNP	MiNP	MCiOP, MHiNP, and MOiNP
117-84-0	Di-n-octyl phthalate[b,c,d]	HMW	DnOP	MnOP	–
53306-54-0	Di-2-propylheptyl phthalate	HMW	DPHP	MPHP	OH-MPHP, oxo-MPHP, and ex-MPHP
117-81-7	Di-2-ethylhexyl phthalate[a,b,c,d]	HMW	DEHP	MEHP	MECPP, MCMHP, MEHHP, and MEOHP
84-75-3	Di-n-hexyl phthalate[a] (low or high)		DnHP	–	–

[a] Listed in California's Proposition 65 as a reproductive and developmental toxicant.
[b] Listed in California's AB1108.
[c] European Union banned as a phthalate softener in the manufacture of toys and childcare articles.
[d] U.S. Environmental Protection Agency's (EPA's) current management plan 2012.

plasticizer in food packaging and PAEs may migrate from food container into foods. PAE-contaminated foods are not only found in plastic packaged-foods, but also revealed in fresh vegetables, crops, and fruit. Fu and Du (2011) observed the presence of DEHP in 9 vegetables including potherb mustard, bok choy, celery, spinach, cabbage, leaf of the tube, lettuce, garlic, and edible amaranth, which the PAE contaminations were induced through the plastic film greenhouses containing PAE materials. Similar results have been reported by Ma et al. (2015), Wang et al. (2015a), Li et al. (2016), Zhang et al. (2018b), and Zhang et al. (2019) who revealed that PAE-contaminated vegetables and crops occurred through PAE-contaminated soils. Due to weak physical or chemical bonding between the polymer and PAEs, PAEs are easily released and accumulated in soils and waters as a result of oil leakage from agricultural machinery, dry and wet deposition from atmospheric air, and organic fertilizers through their root system (Przybylińska and Wyszkowski, 2016). Zorníková et al. (2014) revealed the presence of PAEs in every plant organ, from the roots, through the stem, to the seed, and led to negative impacts on soil quality, as well as potential adverse effects on human health. In addition, the presence of PAEs in a mother's body has been reported to be able to enter their breast milk (Kim et al., 2015b), and infant PAE exposure may due to ingesting monther's breast milk and infant formula containing PAEs (Mortensen et al., 2005; Kim et al., 2015b).

Finally, the non-dietary exposure to PAE is mainly via dermal absorption, inhalation, and parenteral administration. Dermal exposure to PAEs is mainly via cosmetics (Hubinger and Havery, 2006; Hubinger, 2010), lotions (Bi et al., 2013), and other personal care products (Romero-Franco et al., 2011; Fisher et al., 2019). Gong et al. (2016) reported that PAEs were detected at significantly higher levels in clothing-covered skin of the body compared with uncovered bare skin. Wang et al. (2020) also suggested that dermal absorption is also the main route for indoor exposure of PAEs (such as DiBP and DnBP). Meanwhile, exposure to PAEs through inhalation can be due to PAEs volatilized from PVC, nail polish, hair spray, and other PAEs-containing products (FDA, 2001). PAEs are semi-volatile compounds that are not covalently bound to polymeric matrixes; therefore, high temperatures in ambient air can increase PAE release rate from plastic products such as PVC flooring, which can lead to higher levels of PAEs in the air and environment (Bergh et al., 2010; Carlstedt et al., 2013; Koch et al., 2013). Recently, an exposure assessment has shown that the exposure of high level of DEHP in house dust of preschool children in Thailand was over reference dose (20 μg/g) set by the United States Environment Protection Agency (US EPA) (Promtes et al., 2019). Recently, Wang et al. (2020) reported that dust ingestion is the main exposure pathway for indoor exposure of PAEs, contributing 74.4% in pre-school children in Kindergarten in Beijing. Furthermore, PVC plastic has been widely used to manufacture medical devices, such as intravenous infusion and blood bags and infusion tubing, enteral and parenteral nutrition feed bags, nasogastric tubes, peritoneal dialysis bags, and tubing used devices for bypass, as well as neonatal intensive care nurseries (FDA, 2001; Krishnan and Bhuvaneshwar, 2004; Inoue et al., 2005). Thus, exposure to PAE through these routes also potentially occurred (FDA, 2001; Krishnan and Bhuvaneshwar, 2004; Inoue et al., 2005; Luo et al., 2014). Another non-dietary exposure to PAE was reported via sucking on toys or objects made with PAE-containing plastics (Sathyanarayana, 2008).

5. Metabolic pathway of PAEs

Once PAEs enter the body, they undergo a series of phase I hydrolysis and phase II conjugation reactions before they are subsequently excreted through sweat, feces, and urine (Hines et al., 2009; Axelsson et al., 2015). The 24 h-urinary excretion rate of PAE metabolites after oral administration has been reported, the fractional urinary excretion (f_{UE}) of different types of PAEs is presented in Supplementary Information S5 (Koch and Angerer, 2011). Briefly, the metabolism and elimination of PAEs are initiated by the hydrolysis of diesters to their respective monoesters. Subsequently, the alkyl chain of the resulting hydrolytic monoester can be modified by various oxidation reactions. In addition, both the hydrolytic monoester and the oxidized secondary metabolites can be conjugated with glucuronic acid and finally excreted in urine (Koch et al., 2006; Silva et al., 2006a; Silva et al., 2006b; Koch and Angerer, 2007). The hydrolyzed metabolites of DMP, DEP, and BBzP are mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), and mono-benzyl phthalate (MBzP), respectively, which are sufficiently hydrophilic that they are excreted without oxidation steps (Katsikantami et al., 2016). In particular, DnBP and DiBP are mainly excreted with hydrolyzed monoesters (84% and 70%, respectively, of the administered dose), and their total fraction in human urine is about 90% after 24-h oral administration. Moreover, HMW PAEs including DEHP, and DiNP are excreted with hydrolyzed monoesters and oxidative metabolites; however, only a small fraction of their metabolites are found in excretions. As the molecular weight of PAEs increases, the 24-h-excretion rate decreases. After oral exposure to DEHP and DiNP, 67% and 40% of the administered dose were subsequently excreted respectively (Koch et al., 2005; Koch and Angerer, 2007). Unmetabolized PAEs are also excreted in urine (Genuis et al., 2012; Jornet-Martínez et al., 2015). Unlike other contaminants that easily accumulate in the human body, PAEs are rapidly metabolized and eliminated within several hours (EPA, 2017); for example, the half-life of DEHP is estimated to be approximately 12 h (ATSDR, 2002). The PAEs and their metabolic pathways are briefly described in Figs. 1 and 2. Currently, PAEs and their metabolites have been detected in the circulatory system, breast milk, amniotic fluid, semen, and saliva (Ashley-Martin et al., 2014; Jornet-Martínez et al., 2015; Kim et al., 2015b; Katsikantami et al., 2016; Lin et al., 2016; Wang et al., 2016a). Additionally, PAEs were also detected in minor levels in adult adipose tissue related to human hair (Chang et al., 2013) and in fetal meconium (Li et al., 2013).

6. Health effects of PAEs

6.1. Reproductive system diseases

6.1.1. Male

6.1.1.1. Sperm quality. Multiple animal studies highlighted that PAE exposure has been linked to adverse effects on androgen-regulated reproductive development and suggested further study in human sperm (Mariana et al., 2016; Pant et al., 2011). In human, all epidemiological studies consistently revealed that PAE exposure is consistently associated with a decrease in sperm quality (Bloom et al., 2015; Pant et al., 2008; Wang et al., 2015b; Liu et al., 2012; Jurewicz et al., 2013; Wang et al., 2016a; Wang et al., 2015b) (Table 2). Among those studies, BBzP and its metabolite (MBzP) showed multiple severe effects on human sperm such as an increase in sperm aneuploidy, decrease in total sperm counts and concentrations, sperm head sizes, sperm curvilinear velocity and straight-line velocity, and percentage of abnormal heads and tails of sperm, further causing male infertility (Jurewicz et al., 2013; Bloom et al., 2015; Wang et al., 2016a). Along with it, DEHP and its metabolites (MEHP, MEHHP, MCMHP, and MEOHP) were highlighted by multiples studies, which synergistically revealed the adverse effects on sperm quality, including a decrease in semen volume, concentrations, total sperm counts, and testosterone level as well as increase in typical morphology such as percentage of abnormal heads of sperm, megalo head sperm morphology, sperm aneuploidy, sperm curvilinear velocity and straight-line velocity (Pant et al., 2008; Wang et al., 2015b; Wang et al., 2015c; Wang et al., 2016a; Jurewicz et al., 2013; Bloom et al., 2015). Particularly, in a longitudinal cohort study, Bloom et al. (2015) demonstrated that MEHP concentrations were positively associated with higher sperm motility. It is worth noting that PAEs are associated with a decrease in male sperm quality, which has been confirmed by a longitudinal cohort study (Bloom et al., 2015), raising the health concerns over the male population.

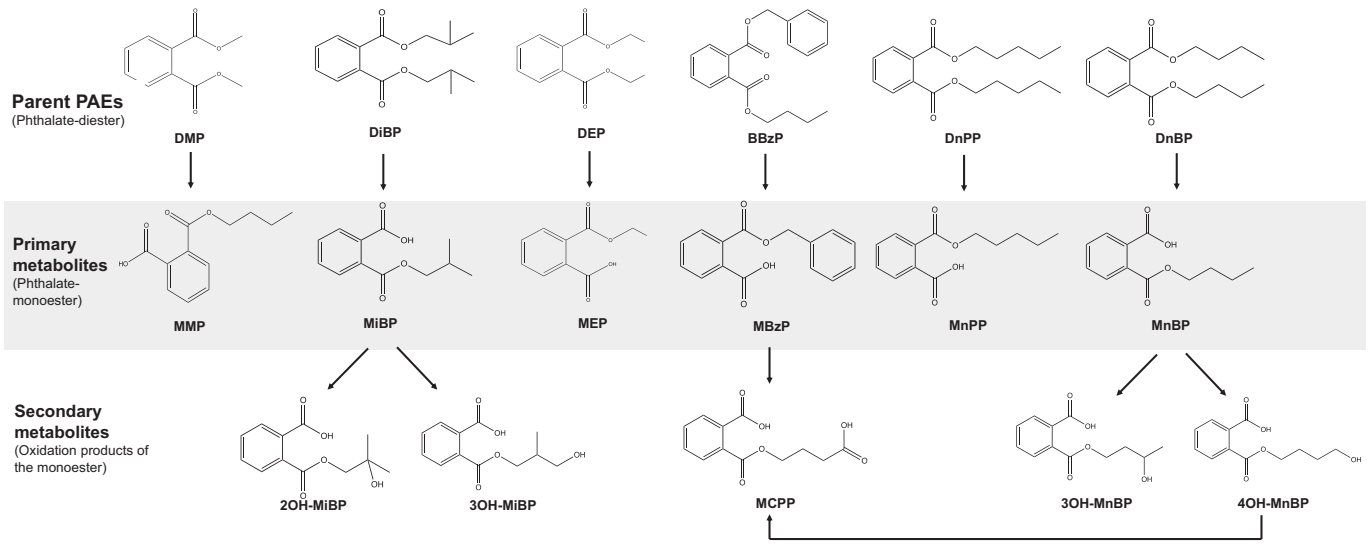

Fig. 1. Metabolic pathways of LMW PAEs. This highlights parent phthalates, primary (phthalate-monoesters), and secondary metabolites (oxidative metabolites).

6.1.1.2. Anogenital distance. Anogenital distance (AGD) is the distance from the anus to the base of the penis, and a reduced or short male AGD can be an indicator for genital malformations and reproductive disorders in adulthood (Schwartz et al., 2019). In the USA, Swan et al. (2005) studied AGD in 85 human male infants (2–36 months of age) in relation to their mother's urinary levels of 4 PAEs (MEP, MBP, MBzP, and MiBP). Afterward, a follow-up study with a larger sample (106 boys [85 from the previous study]) with available genital measurements and prenatal PAE exposure measurements have proved a significant inverse relationship between maternal urinary levels of PAE metabolites (MEP, MBP, MEHP, MEHHP, and MEOHP) and AGD (Swan, 2008). In Japan, Suzuki et al. (2012) observed the relationship between prenatal exposure to PAEs and AGD in 111 Japanese pregnant women (9th–40th-week gestation) and 7 urinary PAE metabolites (MMP, MEP, MnBP, MBzP, MEHP, MEHHP, and MEOHP). The result showed that only MEHP (DEHP monoester) had a weak but significant association with AGD, suggesting that prenatal exposure to DEHP affects the reproductive development in males. In 2015, Swan et al. (2015) conducted a prospective cohort study by recruiting pregnant women for analyzing AGD in newborns after PAE exposure in the first trimester of pregnancy. The result showed that three of DEHP metabolites (MEHP, MEOHP, MEHHP) have an inverse association between DEHP exposure and AGD in newborn boys, but not in girls, suggesting that phthalates affect male genital development and may have an impact on males during growth. Zarean et al. (2019) also found significant associations between the sum of DEHP ($\sum$DEHP) metabolites and risk of both shortened anopenile distance (AGDAP) and anoscrotal distance (AGDAS) in a meta-analysis study, and MBP, MEP, and MiBP were found to be associated with short AGDAP only. However, in Taiwan, Huang et al. (2009) conducted another study by measuring the 5 PAE levels (MBP, MEHP, MEP, MMP, MBzP) in urine and amniotic fluid of 33 male new-borns from Taiwanese mothers, reporting no association between those PAE levels and AGD. In Denmark, Jensen et al. (2016) performed a cohort study to observe the association between PAE exposure in late pregnancy of 245 Danish women and AGD in their male infants at 3 months of age. Both studies suggested no consistent association was observed between any prenatal PAEs and AGD.

The overall effects of PAE on the AGD are summarized in Supplementary Information S6. Taken together, the relation between PAEs and AGD reduction is inconsistently revealed throughout the studies. It may due to less sample size (Swan et al., 2005; Swan, 2008), which contributes to the variability of these studies. Therefore, large-scale epidemiological studies involving a larger population are suggested to examine in order to obtain a deep understanding of the health effects of PAEs on AGD.

6.1.2. Female

6.1.2.1. Precocious puberty. Precocious puberty means an abnormally early onset of puberty, where the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal (Wolff et al., 2010). This includes breast growth, pubic hair, and voice changes (Wolff et al., 2010). Most studies revealed inconsistent associations between PAE exposure (especially MEP, MiBP, MBP, MEHP, and its metabolites) and the appearance of precocious puberty in girls (Wolff et al., 2010; Shi et al., 2015; Zhang et al., 2015; Frederiksen et al., 2012) (Supplementary Information S7). Although Chou et al. (2009) and Zhang et al. (2015) revealed that MMP concentrations were significantly increased in girls with premature thelarche when compared with the control group, and might lead to the fast development of breasts, these results are not practical, since the sample sizes were too small (89 girls) (Chou et al., 2009). Meanwhile, Frederiksen et al. (2012) revealed no association between DiNP metabolites (such as MiNP, MHiNP, MOiNP, and MCiOP) and breast development. From these studies, there is not enough scientific evidence to prove the adverse effects of PAE exposure with early puberty in girls.

6.1.2.2. Endometriosis. Endometriosis is the abnormal growth of endometrial-like tissue outside the uterus and can lead to infertility and severe pelvic pain, as well as can be a cause of hormone-related changes of the endometrium and peritoneal cavity (Upson et al., 2013). Few studies are reporting the effects of PAEs on endometriosis, and most of these studies are case-control approaches as summarized in Supplementary Information S8, highlighting the results vary in each study. For instance, Reddy et al. (2006) collected serum samples from 85 Indian women with endometriosis and 135 normal women as controls, the results showed that concentrations of DnBP, BBzP, DEHP, and DnOP were significantly higher in the endometriosis cases as compared to the controls. Moreover, Kim et al. (2011) evaluated the plasma concentration of PAEs in 97 women with advanced-stage endometriosis and 169 control women, suggesting an association between MEHP and endometriosis. However, different result was reported by Huang et al. (2010) suggesting that there was a non-significant increase in MBP and MEHP in the endometriosis cases. In 2013, Upson et al.

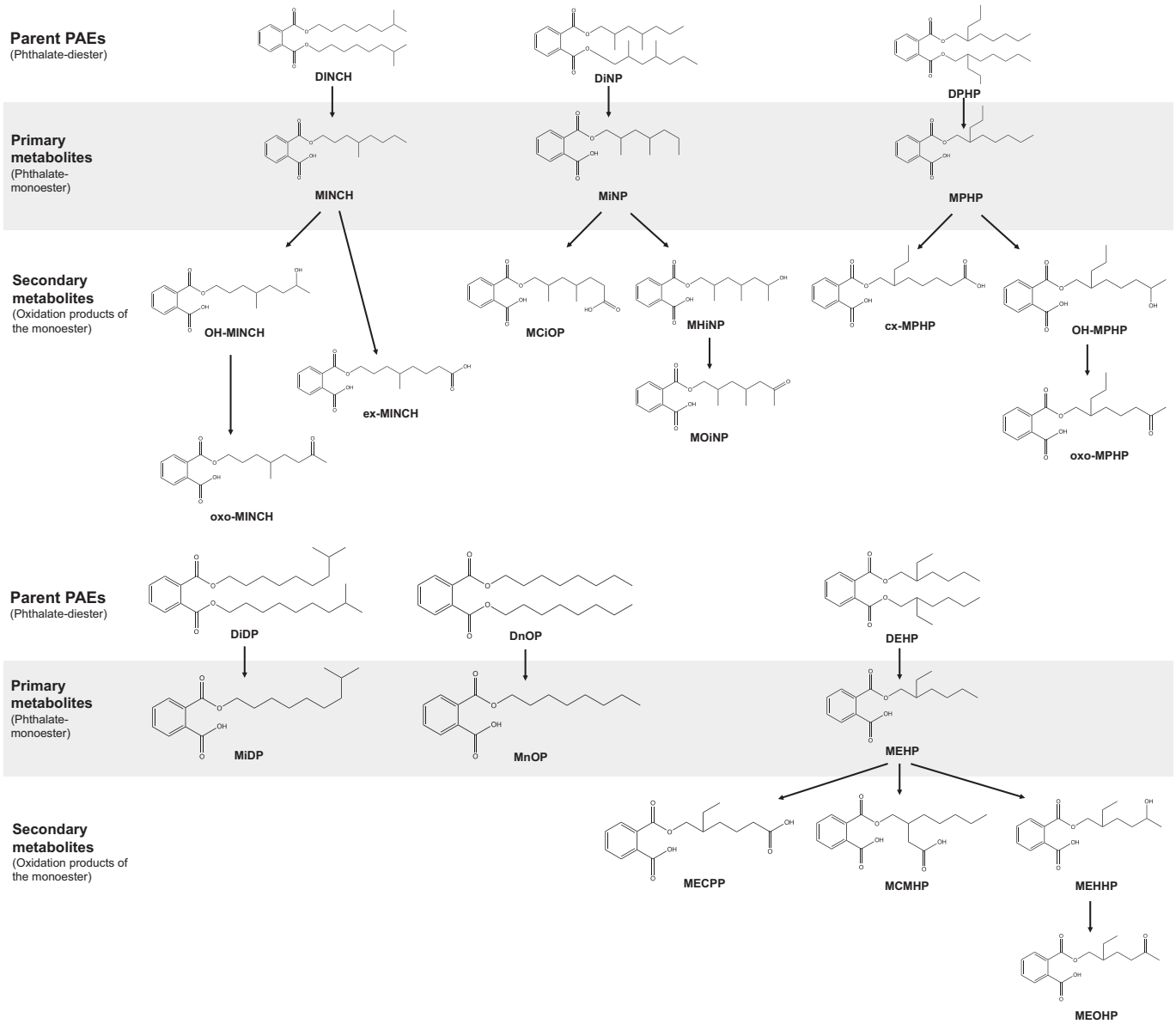

Fig. 2. Metabolic pathways of HMW PAEs. This highlights parent phthalates, primary (phthalate-monoesters), and secondary metabolites (oxidative metabolites).

(2013) monitored the concentrations of urinary PAE metabolites from 92 females (18–49 years) diagnosed with endometriosis and 195 controls. The results suggested a strong inverse association between urinary MEHP concentration and endometriosis risk, but a non-significant association between the urinary MBzP and MEP concentrations and increased endometriosis risk. Recently, Chou et al. (2020) evaluated the urinary concentrations of PAEs (MnBP, MEHP, MBzP, MEOHP, and MEHHP) from 123 women with positive endometriosis and 78 control patients, and revealed that only MnBP was associated with endometriosis. In 2010, Weuve et al. (2010) designed a cross-sectional study to evaluate the concentrations of the urinary PAE metabolites (MEHP, MBP, MEP, and MBzP) from 1,227 women (20–54 years of age). The results implied that MEP and MBzP were not appreciably associated with the risk of endometriosis, MBP was weakly associated with increased odds of endometriosis, whereas MEHP was found to be inversely associated with endometriosis. The authors argued that the inverse association between DEHP and endometriosis could be due to the ability of DEHP and MEHP to suppress estradiol levels, prolonged estrous cycles, and absence of ovulation (Weuve et al., 2010), that is in accord with previous study (Upson et al., 2013).

All things considered, most studies revealed inconsistent associations between PAEs and endometriosis. In addition, several studies were designed as case-control studies with very limited sample size, thus, further epidemiological studies with larger size are needed.

6.2. Cardiovascular diseases

Cardiovascular disease is one health hazard found to be a primary research target of PAE exposure (Jaimes 3rd et al., 2017; Muscogiuri and Colao, 2017). A series of previous studies revealed that high levels of serum PAE metabolite such as MEHP may have cardiotoxic effects in humans, suggesting that PAE exposure reduces human cardiac contractility (Barry et al., 1989; Barry et al., 1990; Mariana et al., 2016). Thus, it also became necessary to comprehensively evaluate the health effects of PAEs on the human cardiovascular system.

Table 2
Health effects of PAE exposure on sperm quality.

No.	PAEs and metabolites	Type	Location	Population	Model	Health effects	Association		References
1	DEP MEP	Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with an increase in sperm aneuploidy.	RC = 0.06 ($p = 0.004$) (a) and RC = 0.06 ($p = 0.007$) (b)	(+)	Jurewicz et al. (2013)
		Case-control	China	150 men	Pearson correlation	Positively correlated with straight-line velocity of sperm motion and movement.	$r = 0.232$, $p < 0.05$	(+)	Liu et al. (2012)
2	DnBP MnBP	Cross-sectional	China	1247 man	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in semen volume.	RC = 10%–9.5% (95% CI: −14, −5.0%), $p < 0.01$	(+)	Wang et al. (2016a)
		Case-control	China	150 men	Multivariate logistic regression	Associated with a decrease in sperm concentrations.	ORs = 6.8 (95% CI: 0.6–75.3) and 12.0 (95% CI: 1.01 to 143), $p = 0.05$	(+)	Liu et al. (2012)
		Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with an in sperm aneuploidy.	RC = 0.10 (p = 0.034) (a) and RC = 0.13 ($p = 0.010$) (b)	(+)	Jurewicz et al. (2013)
		Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with a decrease in straight-line velocity.	RC = −3.33 ($p = 0.020$) (a), RC = −4.11 (p = 0.007) (b)	(+)	Jurewicz et al. (2013)
		Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with a decrease in curvilinear velocity.	RC = −5.84 ($p = 0.013$) (a), RC = −6.56 ($p = 0.009$) (b)	(+)	Jurewicz et al. (2013)
		Cross-sectional	China	1040 men	Multivariate logistic and linear regression models	Associated with the below-reference sperm concentration.	OR = 2.01 (95% CI: 1.07, 3.79), $p = 0.06$	(+)	Wang et al. (2015c)
		Cross-sectional	China	1040 men	Multivariate logistic and linear regression models	Associated with the below-reference total sperm count.	OR = 1.80 (95% CI: 1.05, 3.08), p = 0.02	(+)	Wang et al. (2015c)
3	BBzP MBzP	Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with an increase in sperm aneuploidy.	RC = 0.07 ($p = 0.003$) (a), RC = 0.07 ($p = 0.008$) (b)	(+)	Jurewicz et al. (2013)
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in sperm curvilinear velocity.	RC = −0.98 (95% CI: −1.5, −0.42), $p < 0.05$	(+)	Wang et al. (2016a)
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in sperm straight-line velocity.	RC = −0.48 (95% CI: −0.81, −0.15), $p < 0.05$	(+)	Wang et al. (2016a)
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with an increase in the percentage of abnormal heads of sperm.	RC = 0.94 (95% CI: 0.26, 1.6), $p < 0.10$	(+)	Wang et al. (2016a)
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with an increase in the percentage of abnormal tails of sperm.	RC = 0.50 (95% CI: 0.16, 0.84), $p < 0.05$	(+)	Wang et al. (2016a)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm counts.	RC = −4.96 (95% CI: −28.53, −21.40)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm concentrations.	RC = −3.09 (95% CI: −25.52, −20.66)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with an increase in sperm head sizes.	RC = 1.03 (95% CI: 0.33, 1.74)	(+)	Bloom et al. (2015)
4	DiNP MiNP	Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with a decrease in sperm motility.	RC = −8.09 ($p = 0.012$) (a), RC = −9.05 ($p = 0.033$) (b)	(+)	Jurewicz et al. (2013)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm counts.	RC = −7.20 (95% CI: −12.11, −2.30)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm concentrations.	RC = −3.62 (95% CI: −6.98, −0.26)	(+)	Bloom et al. (2015)
6	DEHP	Cross-sectional	India	300 men	Pearson correlation	Correlated with the percent abnormal sperm.	$r = 0.18$, $p < 0.05$	(+)	Pant et al. (2008)
	MEHP	Cross-sectional	China	1040 men	Multivariate logistic and linear regression models	Associated with an increase in the percentage of abnormal heads of sperm.	RC = 3.18% (95% CI: 1.42, 4.95), $p < 0.01$	(+)	Wang et al. (2015c)

(continued on next page)

Table 2 (*continued*)

No.	PAEs and metabolites	Type	Location	Population	Model	Health effects	Association		References
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in semen volume.	RC = 10% (95% CI: −19, −2.7%), $p < 0.01$	(+)	Wang et al. (2016a)
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in sperm curvilinear velocity.	RC = −0.82 (−1.5, −0.10), $p < 0.05$	(+)	Wang et al. (2016a)
		Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in sperm straight-line velocity.	RC = −0.27 (−0.70, 0.16), $p < 0.05$	(+)	Wang et al. (2016a)
		Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with a decrease in testosterone level.	RC = −0.28 ($p = 0.030$) (a), RC = −0.29 ($p = 0.038$) (b)	(+)	Jurewicz et al. (2013)
		Case-control	Poland	269 men	Univariate (a) and multivariate logistic regression (b)	Associated with an increase in sperm aneuploidy.	RC = 0.11 ($p = 0.001$) (a), RC = 0.08 ($p = 0.005$) (b)	(+)	Jurewicz et al. (2013)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with higher sperm motility.	RC = 11.61 (95% CI: 0.70, 22.51)	(+)	Bloom et al. (2015)
	MEHHP	Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm counts.	RC = −2.85 (95% CI: −25.59, −20.11)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm concentrations.	RC = −2.20 (95% CI: −23.78, −20.05)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with an increase in sperm head sizes.	RC = 0.04 (95% CI: 0.00, 0.08)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with an increase in megalo head sperm morphology.	RC = 0.49 (95% CI: 0.02, 0.49)	(+)	Bloom et al. (2015)
	MCMHP	Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm counts.	RC = −2.89 (95% CI: −25.62, −20.17)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with a decrease in total sperm concentrations.	RC = −2.20 (95% CI: −24.05, −20.35)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with an increase in sperm head sizes.	RC = 0.04 (95% CI: 0.00, 0.08)	(+)	Bloom et al. (2015)
		Longitudinal cohort	USA	501 men	Linear or mixed linear regression models	Associated with an increase in megalo head sperm morphology.	RC = 0.72 (95% CI: 0.25, 1.20)	(+)	Bloom et al. (2015)
	MEOHP	Cross-sectional	China	1247 men	Multivariate linear regression and multivariable logistic regression	Associated with a decrease in semen volume.	RC = 18% (95% CI: −26%, −9.4%), $p < 0.01$	(+)	Wang et al. (2016a)

Notes:
(+): positive association.
(−): no association.
RC = regression coefficient (β = beta coefficient).
OR: odds ratio.
r = Pearson's correlation coefficient.
CI = confidence interval.

6.2.1. Hypertension

The effects of PAE exposure on hypertension have been studied across various age groups and populations as follows (Karle et al., 1997; Trasande et al., 2013a; Amin et al., 2018; Zhang et al., 2018a). In young children, a study at the Children's National Medical Center, USA revealed that DEHP has no significant cardiovascular effects in infants with therapy according to their heart rate, systolic blood pressure (BP), left ventricular shortening fraction, and stroke volume (Karle et al., 1997). In older children and adolescents, a cross-sectional study of children aged 6–19 years in the NHANES in 2003–2008 and 2009–2012 has found that the LMW PAEs commonly used in cosmetics and personal medical supplies were negatively associated with BP (Trasande et al., 2013a). In contrast, dietary exposure to PAEs (DEHP) was positively associated with higher systolic BP (Trasande et al., 2013a). In a later study, urinary DiNP and DiDP metabolites were confirmed to have a significant correlation with higher systolic BP, but they were not associated with high-density lipoprotein (HDL) (Trasande and Attina, 2015). Similarly, in a study of 242 children aged 6–18 years in Iran, MBP was significantly associated with elevated BP (Amin et al., 2018). Taken together, these results indicate that PAE exposure inconsistently induces hypertension effects in children.

In adults, a cross-sectional study of 474 participants in China reported that the median-exposed DEHP group exhibited significantly increased systolic BP (a 2.96 mmHg increase relative to the low-exposure group) and DMP and DEHP were also found to be associated with total cholesterol levels in serum (Zhang et al., 2018a). In pregnant women, Werner et al. (2015) observed a significant association between MBzP levels in maternal urine samples (collected at 16 and 26 weeks of

gestation) and the higher diastolic BP, as well as an increased risk of pregnancy-induced hypertensive diseases. In contrast, Lu et al. (2018) showed a negative association between diastolic BP and serum levels of phthalate metabolites. Overall, it may be said that the association between PAEs and hypertension is still inconsistent in both children and adults, and therefore further analysis is needed to elucidate the full effects of PAEs.

6.2.2. Atherosclerosis

Atherosclerosis is a known risk factor for cardiovascular disease (Frostegård, 2013) and also one of the characteristics of coronary heart disease (CHD) (Lind and Lind, 2011). Atherosclerosis is a chronic inflammatory process characterized by the deposition of fibrous tissue and fat in the elastic arterial intima, leading to thrombosis, structural damage marked by thickening and hardening of the vessel wall, and subsequent loss of elasticity and narrowing of the blood vessels (Wang et al., 2016b). As carotid-artery intima and media thickness (CIMT) has been positively associated with the prevalence of cardiovascular disease (O'Leary et al., 1999), it can be utilized as a parameter to assess the health effects of PAE exposure on the human cardiovascular system.

Over recent years, multiple animal studies have investigated the associations between PAEs and atherosclerosis (Shih et al., 2015; Zhao et al., 2016; Kim et al., 2015a). For example, Shih et al. (2015) found that rats exposed to DEHP had increased matrix metalloproteinase (MMPn)-2 and MMPn-9 expression compared with control rats, indicating that MMPn-2 and MMPn-9 might be inducers of atherosclerosis following DEHP exposure. In another study of rats by Zhao et al. (2016), those animals chronically exposed to DEHP for 4 weeks subsequently developed exacerbated hyperlipidemia, systemic inflammation, and atherosclerosis, and this treatment also promoted the oxidation of low-density lipoprotein (LDL), leading to the inflammation of endothelial cells and the increased accumulation of cholesterol in the liver. This study concluded that DEHP disturbs cholesterol homeostasis and deregulates the inflammatory response, thereby driving accelerated atherosclerosis. In an *in vitro* human cell study, Kim et al. (2015a) showed the occurrence of protein oxidation, aggregation, and degradation in human HDL following treatment with DEP, which also promoted foam cell formation via macrophage-mediated accelerated phagocytosis of LDL, as well as exacerbated cellular senescence in human dermal fibroblasts. Furthermore, this study uncovered that DEP treatment results in atherosclerosis and rapid aging effects through severe lipoprotein modification in human cells.

In the human study, Su et al. (2019b) showed that PAE exposures (MEHP, ΣDEHP, and MnBP) are strongly associated with thicker CIMT in adolescents and young adults in Taiwan. In addition, the association was not revealed in MEP and MMP (Su et al., 2019b). In another cross-sectional study, MBzP exposure was found to be associated with the echogenicity of the carotid intima-media, plaque, and CIMT (Wiberg et al., 2014). Although animal studies revealed both association and elaborated possible mechanism of PAEs on atherosclerosis, however, the evidence of health effects of PAE on atherosclerosis is still limited in epidemiological studies and lack of consistency. Therefore, more epidemiological studies (cross-sectional, case-control, and longitudinal or cohort study) are extremely necessary.

6.2.3. Coronary heart disease

Along with possible associations between specific PAE metabolites and cardiovascular risk factors have been reported, the associations between PAE exposure and coronary heart disease (CHD) become necessary to discuss. One study randomly recruited 180 participants from 336 CHD patients, as well as 360 non-CHD controls from hospitals, after matching for their age and sex, from 2008 to 2011 (Su et al., 2019a). The results revealed that the geometric mean of three DEHP metabolites (MEHP, MEHHP, and MEOHP) in the urinary samples of in-hospital CHD patients was significantly higher than those of patients being discharged. In addition, the urinary levels of MEHP, MnBP, and MiBP in 91 of the 180 CHD patients discharged after ≥3 days were higher than those of the controls. Among 451 participants, those with higher tertile levels of urinary MEHP, MnBP, and MiBP revealed an increased risk for CHD compared with those with the lowest tertile levels. These results were similar to the significant dose-response associations among CIMT, MEHP, ΣDEHP, and MnBP in a young population (Su et al., 2019a). Thus, MEHP and MnBP were found to be the influencing factors of cardiovascular disorders in young populations and CHD patients. Besides, plasma fibrinogen levels have been associated with the induction of CHD; therefore, they may be a risk factor or predictor of CHD (Song et al., 2015). Finally, using multivariate logistic regression analysis, only MEHP, MnBP, and MiBP were revealed to be positively associated with higher risk of CHD. Nevertheless, other 5 PAE metabolites (MEHHP, MEOHP, MMP, MEP, and MBzP) did not associate with CHD.

Although the study populations in this new observational report demonstrated that exposure to PAEs (mainly DEHP) could induce CHD, the data is still relatively limited, and association was inconsistently revealed. New longitudinal and experimental studies are necessary to validate the effects of each PAE species.

6.3. Thyroid disorders

Thyroid hormone (TH) is a key molecule that regulates the growth and differentiation of tissues or cells in the reproductive and central nervous systems; it also contributes to energy metabolism (Flamant and Samarut, 2003; Jugan et al., 2009). TH is also crucial for the growth and development of children (in which TH deficiency can induce growth retardation) and their central nervous system (Shi et al., 2012; Wu et al., 2017). To thoroughly evaluate the PAEs effects on human thyroid disorders, the levels of triiodothyronine (T3), free T3, and insulin-like growth factor 1 (IGF-1) are normally used for monitoring (Boas et al., 2010). As can be seen in Supplementary Information S9, most studies revealed the consistently positive associations between PAE exposures (MEP, MiBP, MBP, MBzP, MEHP, MEHHP, and MEOHP) with a decrease in free T3 and T4 in both girls and boys, suggesting that PAE may cause the thyroid disorders in children (Morgenstern et al., 2017; Weng et al., 2017; Huang et al., 2017). However, MEP and MEHP demonstrated positive associations in both children and adults (Huang et al., 2017; Wang et al., 2018; Huang et al., 2017), most PAE metabolites (MBP, MBzP, MEHHP) revealed negative effects on the adult TH system (Park et al., 2017; Huang et al., 2017). Taken together, although the results of these studies might support the existence of age differences (children and adults), the overall studies revealed inconsistent association. Furthermore, these present research studies still have several limitations, such as (1) several studies have a small human population (Huang et al., 2017); (2) uneven sampling distribution over graphical regions (Morgenstern et al., 2017; Weng et al., 2017); (3) PAE levels were measured by using a one-spot urine sample and cannot represent the long-term exposure (Morgenstern et al., 2017; Weng et al., 2017); and (4) low accuracy of PAE measurement (Morgenstern et al., 2017; Park et al., 2017; Weng et al., 2017).

6.4. Respiratory diseases

PAEs are ubiquitous environmental contaminants found in air, dust, and food, and may further lead to respiratory disorders in humans (Becker et al., 2004; Hoppin et al., 2013; Wang et al., 2014; Ku et al., 2015). Only fewer studies reported the associations between PAEs and respiratory disease (Hoppin et al., 2013; Beko et al., 2015; Bornehag et al., 2004; Ku et al., 2015) as can be seen in Supplementary Information S10. For instance, a cross-sectional study found associations between urinary levels of BBzP metabolites (MBzP) and asthma and hay fever in adults, but not in children (Hoppin et al., 2013). In contrast, multiple studies have reported positive relationships between PAEs (DnBP, BBzP, DEHP, MEHP) and asthma, rhinoconjunctivitis, or atopic dermatitis in children (Beko et al., 2015; Bornehag et al., 2004; Ku et al., 2015), suggesting inconsistency of the current results. Moreover,

prenatal and postnatal exposure to PAEs was reported to be associated with asthma occurrence in children (Ku et al., 2015).

Lack of consistency of associations between PAE metabolites and allergic symptoms (asthma) may be related to the age differences of the children used in each study. For instance, Hoppin et al. (2013) did not include children <6 years of age, while Ku et al. (2015) studied children 2, 5, and 8 years of age. Another possible explanation is that the relevant exposures for children are not those currently occurring but rather those that occurred earlier, such as prenatally as studied by Ku et al. (2015). Moreover, future studies should not only focus on the characterization of the temporal association between PAE exposure and outcome, but the researchers should also include allergen exposure to better understand the potential mechanisms by which PAEs may contribute to allergic outcomes in human.

6.5. Diabetes

In the animal study, PAEs interfere with a multitude of biochemical mechanisms, influencing the hormonal status and glucose homeostasis (Lin et al., 2011). A few studies have indicated that PAE exposure can cause oxidative stress and insulin resistance (IR) as a potential mechanism of type 2 diabetes mellitus (DM) (Kim et al., 2013). To further investigate the effects of PAEs on diabetes in human, Kim et al. (2013) recruited 560 elderly participants with a history of DM and analyzed their urine PAE metabolites, fasting blood glucose, and insulin levels before evaluating their insulin resistance using the insulin-sensitive HOMA (homeostatic model assessment) index. The results revealed that the molar sum of MEHHP and MEOHP was significantly related to the HOMA. These authors also demonstrated that malondialdehyde levels (a marker of oxidative stress) are involved in the HOMA increase following $\sum$DEHP exposure. However, Sun et al. (2014) suggested that PAE exposure may be only related to the risk of type 2 diabetes in middle-aged women, but not in older women. Trasande et al. (2013b) examined the associations of urinary DEHP in a cross-sectional study involving 766 fasting adolescents and revealed that DEHP was significantly associated with IR. However, insignificant association were shown in LMW PAEs (MEP, MBP, and MiBP) and HMW PAEs (MBzP and MCPP) (Trasande et al., 2013b). In a study of PAEs and diabetes, women with higher MnBP, MiBP, MBzP, MCPP, and ΣDEHP levels had a higher risk of developing diabetes than those with the lowest levels following the adjustment for potential confounders (James-Todd et al., 2012). Moreover, women in this study with MBzP and MiBP levels in the highest quartile had almost twice the odds ratio of developing diabetes compared with women in the lowest quartile.

The present research studies had several limitations including (1) small sample size (Kim et al., 2013); (2) PAE levels were conducted by using one-point time of urine and do not account for temporal changes in exposure levels, which led to modestly predictive of levels of PAEs (James-Todd et al., 2012; Trasande et al., 2013b). Future studies should examine multiple urine samples taken over time to better estimate long-term PAE exposure; (3) The result of the study participants were not representative of the general population (Sun et al., 2014); (4) Additionally, although several studies examined the association between PAEs and diabetes in a large sample size (James-Todd et al., 2012; Trasande et al., 2013b), there is still limited epidemiological evidence whether the association between some PAEs and diabetes existed. In addition, very few studies have evaluated the association between PAE metabolites, IR, and diabetes simultaneously (Kim et al., 2013; Trasande et al., 2013b). Future studies should longitudinally evaluate the association between PAE levels and markers of IR to better understand how PAEs could alter normal glucose metabolism and diabetes risk.

6.6. Obesity

PAE metabolites have biochemical activity including activation of perisome proliferator receptor and antiandrogenic effects, which contribute to the development of obesity (Halaby et al., 2015). Hence, the association between PAEs and obesity has been extensively studied in various populations (Hatch et al., 2008; Song et al., 2014; Harley et al., 2017; Xia et al., 2018) as supplemented in Supplementary Information S11.

6.6.1. Children

Wang et al. (2013) reported that urinary PAEs (MEHP and MEP) are positively associated with BMI or WC in 259 Chinese school children in a cross-sectional study. Xia et al. (2018) found a positive association between urinary MnBP levels and overweightedness/obesity in 149 children. However, MMP, MEP, MEHP, MEOHP and MEHHP were found to be not associated with obesity (Xia et al., 2018). Subsequently, in a study of 242 Iranian children aged 6–18 years, urinary PAE levels of MBzP, MBP, MMP, MEHP, and MEHHP were significantly associated with childhood obesity (Amin et al., 2018), as well MBzP and MEHP were related to triglyceride levels and obesity. In another study from the Breast Cancer and Environment Research Program, a total of 1,239 girls aged 6–8 years were assessed for urine metabolite levels, body height, weight, and WC annually during 2004–2007 (Deierlein et al., 2016). The results revealed that LMW PAEs (MEP, MBP, and MiBP) were positively associated with an increase in BMI and WC in these girls. Additionally, Zhang et al. (2014) reported that the urinary concentration of MBP was associated with obesity in boys in China.

Recently, obesity in children was also reported to be induced by PAE exposure during mother pregnancy. A comprehensive investigation was reported in a cohort study conducted by the Center for the Health Assessment of Mothers and Children of Salinas (Harley et al., 2017). Specifically, the levels of 11 PAE metabolites in the urine of 345 mothers during pregnancy were analyzed along with their children's height, weight, WC, and body fat percentage (children aged 5–12 years). The results revealed that DEP, DnBP, BBzP, and DEHP metabolites were strongly associated with BMI z-scores, WC z-scores, and body fat percentage in children of various ages. In particular, in the 12-year-old population, prenatal levels of DEP, DnBP, and DEHP metabolites were positively associated with overweight or obesity.

6.6.2. Adults

In the USA, Stahlhut et al. (2007) investigated the PAE exposures and their associations with obesity in adult US males (participant in the NHANES 1999–2002) and revealed that MBzP, MEHHP, MEOHP, and MEP were positively associated with an increase in WC and BMI, which is in inline with studies of Buser et al. (2014) and Hatch et al. (2008). In addition, MCNP, MCOP, and MEHP were also revealed to induce obesity (Buser et al., 2014). Recently, Li et al. (2020) conducted a cohort study for 942 elderly in China and revealed that urinary levels of MEOHP, MBP, MEP, and MMP were positively related to general obesity in males.

In a prospective case-control study of type 2 diabetes in 977 US women, Song et al. (2014) found that phthalic acid, MBzP, and MBP were associated with faster prospective weight gain in a dose-response trend, whereas other PAE metabolites (including MEP and MEHP) were not monotonically associated with bodyweight alterations. In addition, Lind et al. (2012) reported that MiBP was associated with increased fat deposition in the subcutaneous abdominal region in women. Meanwhile, Li et al. (2020) reported that MBP and MMP levels were eminently correlated with general obesity in adult females.

Taken together, relationships between PAE exposure and obesity on humans (children and adults) were inconsistently revealed, suggesting the need for more cohort or longitudinal studies. In addition, the current reports did not examine the possible mechanism involved in those relationships.

6.7. Kidney diseases

In the animal study, PAE exposure has been reported to lower kidney weight, and further inducing chronic progressive nephropathy in rats

(animal study) (David et al., 2000). Similarly, Wei et al. (2012) found that maternal rat exposure to PAE (DEHP) reduced the number of nephrons, increased glomerular volume, and resulted in a smaller Bowman capsule in DEHP-treated offspring at weaning, glomerulosclerosis, and interstitial fibrosis, further resulting in renal disease (Wei et al., 2012). However, the epidemiological studies demonstrated various results (Rais-Bahrami et al., 2004; Trasande et al., 2014) as supplemented in Supplementary Information S12.

In children, Trasande et al. (2014) revealed an approximately threefold increase in the metabolites of DEHP resulted in the albumin/creatinine ratio (ACR). However, no significant association was found between LMW PAEs and a higher ACR. Tsai et al. (2016) conducted a study of 184 children under the age of 10 who had consumed foods rich in DEHP and therefore received a relatively high DEHP exposure. They found that these exposures were significantly associated with the children's ACR. Moreover, children in the high-exposure group (DEHP intake >0.05 mg/kg/day) revealed a 10.4-fold increase in their risk of microalbuminuria relative to the low-exposure group (DEHP intake ≤0.02, but >0 mg/kg/day) following the adjustment for co-factors. In the Chronic Kidney Disease in Children (CKiD) study from the USA (Malits et al., 2018), the PAE levels in 538 children aged 1–17 years (the CKiD population) were lower than those in the control group. In the CKiD population, negative correlations were found between combined LMW PAEs or each of MMP, MBP, MiBP, MECPP, MEHHP, MEOHP, MBzP, MHxP (mono-hexyl phthalate), and MHpP (mono-2-heptyl phthalate) and the children's urine protein/urine creatinine ratio. However, some PAE metabolites (MMP, MiBP, MECPP, MEHHP, MEOHP, and MHpP) and the combined LMW PAEs were also positively correlated with the estimated glomerular filtration rate. Given the disparity in the results of these various studies, there is currently no clear and consistent association between PAEs and kidney disease in children.

In adults, Chen et al. (2019) revealed that three renal function parameters, namely, ACR, β-2 microglobulin (B2M), and *N*-acetyl-β-d-glucosaminidase (NAG), were positively associated with six PAE metabolites: MBzP, MEHP, MEOHP, MEHHP, MECPP, and MCMHP. Furthermore, the prevalence of hyperALBuria, hyperB2Muria, and hyperNAGuria, as well as potentially impaired renal function, was positively related to the MBzP, MEOHP, and MECPP levels in urine, respectively. In addition, co-exposure to MEP, MBzP, MEHP, MEOHP, MECPP, MEHHP, and MCMHP increased the risk of renal impairment. However, Kang et al. (2019) found that only MBP (not MiBP, MBzP, MECPP, MEHHP, MEOHP, MCMHP, and DEHP) revealed a significant positive association with higher ACR in women.

Conclusively, although animal studies have revealed a strong association between PAE exposure and kidney disease, there remains a lack of consistency in the results from the epidemiological studies (children and adults).

6.8. Neurological disorders

Several animal studies suggested that the higher levels of DEHP may have adverse effects on neurobehavioral parameters in mice (Tanaka, 2002; Tanaka, 2005) and zebrafish (Xu et al., 2020). Here, the neurological effects of PAE exposure on humans including attention-deficit/hyperactivity disorder (ADHD) and lowering intelligence performance are briefly discussed.

6.8.1. Attention-deficit/hyperactivity disorder

Attention deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children. The epidemiological studies reporting the health effects of PAE exposure on ADHD are listed in Table 3. Kim et al. (2009) initially conducted a cross-sectional study from 261 Korean children and found that DEHP was strongly associated with ADHD. Using a larger sample size, a total of 1,493 children from the NHANES, a cross-sectional study in the USA from 2001 to 2004 (Chopra et al., 2014) has shown that there were 112 children with attention deficit disorder (ADD), 173 with a learning disability, and 56 with both ADD and a learning disability. Among these disorders, ADD was reported to be positively associated with urine DEHP levels and HMW PAEs (MBzP, MCPP, MEHP, MEHHP, and MEOHP) after adjustment for potential risk factors. Additionally, Engel et al. (2018) demonstrated that maternal urinary concentrations of DEHP were monotonically associated with increased risk of ADHD in Norwegian children based on a case-control study.

Meanwhile, Kobrosly et al. (2014) performed a cohort study and revealed that higher prenatal urinary MBzP concentrations were positively associated with higher scores for oppositional/defiant problems and conduct problems in American boys, and associated with emotional symptoms in Canadian girls. Recently, Ku et al. (2020) also conducted a follow-up longitudinal cohort study and demonstrated that prenatal exposure to MEHHP, DEHP, and MBzP were associated with the behavioral characteristics of children, particularly temperamental traits associated with ADHD. The results of these cohort studies are consistent with previous cross-sectional studies in which the risk of ADHD symptoms was positively associated with urinary DEHP and BBzP metabolite concentrations in children (Kim et al., 2009; Chopra et al., 2014). In addition, we also highlight that these two PAE species (DEHP and its metabolites [MEHHP and MEOHP] as well as BBzP metabolites [MBzP]) were consistently revealed to induce ADHD, which have been confirmed by longitudinal cohort studies (Ku et al., 2020; Kobrosly et al., 2014), suggesting the health concern over human health.

6.8.2. Intelligence performance

Several epidemiological studies have reported that PAEs can interfere with the neurodevelopmental performance in children such as early psychological and psychomotor disorders, further leading to poor neurodevelopment, behavioral, and intelligence performance (Braun et al., 2013; Kim et al., 2018). Overall, the effects of PAE on human intelligence performance in epidemiological studies are still under debate (Supplementary Information S13). For instance, Li et al. (2019) conducted a longitudinal study and revealed that MBP and MiBP are positively associated with lower intelligence quotient (IQ) in children. However, most studies demonstrated an inverse association between PAE and lower children's IQ performance. For instance, a cross-sectional study was conducted by Choi et al. (2017) from 667 Korean children and revealed that IQ scores and children's vocabulary subscores were inversely associated with MEOHP, MEHP, and MBP. Similarly, Nakiwala et al. (2018) did not find any strong evidence of association between in-utero exposure to 11 PAEs (MEP, MBP, MiBP, MECPP, MEHHP, MEOHP, MEHP, MBzP, MCOP, MCPP, and MCNP) and verbal performance IQ among French boys, which is in line with the study of Kim et al. (2017) and Huang et al. (2015).

In a follow-up study, Factor-Litvak et al. (2014) observed the association between childhood IQ and maternal exposure to 4 PAEs (DnBP, DiBP, DEHP, and DEP), highlighting that maternal prenatal urinary metabolite levels measured in late pregnancy of DnBP and DiBP were inversely associated with deficits in children's intellectual development at age 7 years. In a longitudinal study of 430 pregnant women, Huang et al. (2015) found no significant association between maternal PAE exposure (MEHP, MEHHP, MEOHP) and children's IQ, which is in line with the study of Kim et al. (2017). However, van den Dries et al. (2020) recently performed a population-based birth cohort in Netherlands (1,282 mother-child pairs) to examine the association between pregnancy maternal urinary PAEs and nonverbal IQ in children 6 years of age. The results revealed that maternal PAE exposures (LMW PAEs [MMP, MEP, MBP, and MiBP] and HMW PAEs [MECPP, MEHHP, MEOHP, MCMHP, CPP, MBzP, mono-hexyl phthalate, and mono-2-heptyl phthalate=]) in early pregnancy were associated with a lower nonverbal IQ score in children. In addition, DnOP exposure in late pregnancy is inversely associated with lower nonverbal IQ scores in children. In summary, the current epidemiological studies revealed inconsistent associations between PAEs and human intelligence performance.

Table 3
Health effects of PAE exposure on ADHD.

No.	PAEs and metabolites	Type of study	Location	Population	Model	Health effects	Association		References
1	ΣDnBP	Cross-sectional	USA	143 children	Logistic regression	Associated with ADHD in children	OR = 2.5 (95% CI: 1.1, 5.6), $p < 0.05$	(+)	Chopra et al. (2014)
2	DiBP								
	MiBP	Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models	Associated with higher scores for inattention	RC = 0.27 (95% CI: 0.04, 0.50)	(+)	Kobrosly et al. (2014)
		Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models.	Associated with higher scores for rule-breaking behavior	RC = 0.20 (95% CI: 0.01, 0.38)	(+)	Kobrosly et al. (2014)
		Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models	Associated with higher scores for aggression	RC = 0.34 (95% CI: 0.09, 0.59)	(+)	Kobrosly et al. (2014)
		Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models	Associated with higher scores for conduct problems	RC = 0.39 (95% CI: 0.20, 0.58)	(+)	Kobrosly et al. (2014)
3	BBzP								
	MBzP	Longitudinal cohort	Taiwan	208 mother-child pairs	Logistic regression	Associated with ADHD in children	OR = 9.12 (95% CI: 1.07–78.06), $p < 0.05$	(+)	Ku et al. (2020)
		Cross-sectional	USA	143 children	Logistic regression	Associated with ADHD in children	OR = 2.7 (95% CI: 1.1, 6.4), $p < 0.05$	(+)	Chopra et al. (2014)
		Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models	Associated with higher scores for oppositional behavior	RC = 0.16 (95% CI: 0.01, 0.32)	(+)	Kobrosly et al. (2014)
		Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models	Associated with higher scores for conduct problems in boys	RC = 0.21 (95% CI = 0.06, 0.37)	(+)	Kobrosly et al. (2014)
4	ΣDEHP	Longitudinal cohort	Taiwan	208 mother-child pairs	Logistic regression	Associated with ADHD in children	OR = 3.28 (95% CI: 1.15–9.35), $p < 0.05$	(+)	Ku et al. (2020)
		Cross-sectional	USA	143 children	Logistic regression	Strongly associated with ADHD	OR = 2.4 (95% CI: 1.1, 5.3), $p < 0.05$	(+)	Chopra et al. (2014)
		Cross-sectional	Korea	261 children	Linear regression	Associated with ADHD in children	RC = *4.884* (SE = 1.728)	(+)	Kim et al. (2009)
		Longitudinal cohort	USA	153 mother-child pairs	Adjusted multiple regression interaction models	Associated with higher scores for somatic problems in children	RC = 0.15 (95% CI: 0.03, 0.28)	(+)	Kobrosly et al. (2014)
		Case-control	Norwegia	297 children	Logistic regression	Monotonically associated with increased risk of ADHD	OR = 2:99 (95% CI: 1.47, 5.49)	(+)	Engel et al. (2018)
	MEHHP	Longitudinal cohort	Taiwan	208 mother-child pairs	Logistic regression	Associated with ADHD in children	OR = 2.98 (95% CI: 1.05–8.48), $p < 0.05$	(+)	Ku et al. (2020)
	ΣHMW PAEs (MBzP + MCPP + MEHP + MEHHP + MEOHP)	Cross-sectional	USA	143 children	Logistic regression	Associated with ADHD	OR = 4.3 (95% CI: 1.6, 11.8), p < 0.01	(+)	Chopra et al. (2014)

Notes:
(+): positive association.
(−): no association.
OR = odds ratio.
RC = regression coefficient (β = beta coefficient).
CI: confidence interval.

7. Conclusions and future challenges

This work provided a comprehensive summary of the health effects of PAE exposure on humans. We found that studies in human populations revealed a consistent association between PAE exposure and decrease in sperm quality in males and ADHD-related behavior problems in children, which currently have been confirmed by cohort longitudinal studies (Bloom et al., 2015; Ku et al., 2020; Kobrosly et al., 2014). Of all the PAEs, most studies highlighted that DEHP and its metabolites are the ones which elicit the most health concern, especially in decreasing sperm quality in males (Bloom et al., 2015; Pant et al., 2008; Wang et al., 2015b; Wang et al., 2015c; Jurewicz et al., 2013; Wang et al., 2016a) and inducing symptoms of ADHD in children (Chopra et al., 2014; Engel et al., 2018; Kim et al., 2009; H.-Y. Ku et al., 2020), raising the health or safety concern as it has been the most popular PAE with more than two million tons produced annually.

In general, we found inadequate evidence of association (lack of consistency) between PAE exposure and cardiovascular diseases (hypertension, atherosclerosis, and CHD), thyroid diseases, respiratory diseases, diabetes, obesity, kidney diseases, intelligence performance in children, and other reproductive system-related diseases (anogenital distance, girl precocious puberty, and endometriosis). Lack of consistency may be due to several common limitations such as: several studies were conducted in small human populations, participants were not representative of the general populations, and concentration measurements of PAE metabolites were only conducted at the one-time point. Thus, the following recommendations for future research are put forward. Future studies need to be thoroughly performed using larger sample sizes and conducted in multiple sample measurements to yield more consistent and powerful results and increase the precision of the associations between PAE exposure and those health effects. Furthermore, more longitudinal and follow-up investigations are necessary to enhance the overall understanding of potential human health risks of PAEs in long-term exposure.

In addition, the measurements of PAE metabolites in the current studies were dominated by primary metabolites rather than oxidative

metabolites (secondary metabolites). This leads us to the question of "*is it sufficient to measure only urinary levels of primary PAE metabolites or should the oxidative metabolites also be measured? If both of them are measured in urine, are the sum of primary and secondary metabolites sufficient to interpret PAE exposure in epidemiological studies?*". Furthermore, accurate screening of some specific metabolism biomarkers to establish the association with particular human diseases should be another challenging part of confirming the molecular toxicity mechanism of PAE exposure. Finally, as multiple studies reported the effects of maternal PAE exposure on children, it is interesting to see whether PAEs have a genetic effect.

CRediT authorship contribution statement

Wei-Hsiang Chang: paper review & editing. **Samuel Herianto**: conceptualization and organized the article, writing the original draft, writing - review & editing, contributing for major revision. **Ching-Chang Lee**: resources and funding acquisition **Hsin Hung**: conceptualization, writing the original draft. **Hsiu-Ling Chen**: conceptualization and organized the article, writing, review, and final editing.

Declaration of competing interest

The authors declare that they have no competing financial interests or opposite opinions in this paper.

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Appendix A. Supplementary data

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