



# Cardiovascular disrupting effects of bisphenols, phthalates, and parabens related to endothelial dysfunction: Review of toxicological and pharmacological mechanisms

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## ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. CVDs are promoted by the accumulation of lipids and immune cells in the endothelial space resulting in endothelial dysfunction. Endothelial cells are important components of the vascular endothelium, that regulate the vascular flow. The imbalance in the production of vasoactive substances results in the loss of vascular homeostasis, leading the endothelial dysfunction. Thus, endothelial dysfunction plays an essential role in the development of atherosclerosis and can be triggered by different cardiovascular risk factors. On the other hand, the 17 $\beta$ -estradiol (E2) hormone has been related to the regulation of vascular tone through different mechanisms. Several compounds can elicit estrogenic actions similar to those of E2. For these reasons, they have been called endocrine-disrupting compounds (EDCs). This review aims to provide up-to-date information about how different EDCs affect endothelial function and their mechanistic roles in the context of CVDs.

## 1. Introduction

### 1.1. Endothelial dysfunction

The endothelium is a single layer of endothelial cells (ECs) that lines the inside of blood vessels. It is an active tissue that plays a crucial role in the maintenance of vascular homeostasis (Sandoo et al., 2010). The endothelium has an important role in cardiovascular physiology and pathophysiology by regulating vascular tone, coagulation, fluid exchange, inflammation, and angiogenesis, among other processes (Panza et al., 1990; Martí et al., 2012; Maldonado et al., 2022). Damage to the endothelium leads to endothelial dysfunction, which is a predisposing factor for atherosclerotic layer formation that allows the development of various cardiovascular diseases (CVDs) such as myocardial infarction and stroke (Medina-Leyte et al., 2021; Björkegren and Lusis, 2022).

Endothelial dysfunction is a pathophysiological process caused by chronic exposure to different risk factors including toxins, immune alterations, diabetes, hypertension, dyslipidemias, oxidative stress, and smoking, among others (Jeon, 2021). These factors produce changes in the permeability of the endothelial layer, leading to the infiltration of

low-density lipoproteins (LDL) into the tunica intima layer of the endothelium. Subsequently, LDLs undergo oxidation, which enhances the process of endothelial dysfunction. As a consequence, the vascular surface becomes prothrombotic displaying a pro-inflammatory cellular and humoral environment (Jiang et al., 2022). In addition, there is an exacerbated production of adhesion proteins that leads to the recruitment of monocytes, lymphocytes, and platelets, as well as changes in the tissue microstructure (Medrano-Bosch et al., 2023). These physical, cellular, and biochemical modifications enhance the proinflammatory response, leading to chronic inflammation. In addition, recruited monocytes are activated by macrophages, which engulf oxidized LDLs. These activated macrophages also lead to foam cells that undergo apoptosis and release cholesterol particles, further enhancing the inflammatory state of the endothelium (Gui et al., 2022). All these mechanisms contribute to endothelial damage, inducing the migration of smooth muscle cells from the tunica media to the tunica intima, and promotion the secretion of collagen, which stabilizes the atheroma layer, (Fig. 1) (Jiang et al., 2022).

As a final event, endothelial dysfunction leads to loss of homeostasis with a significant reduction in vasodilator agents such as nitric oxide

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(NO), a sustained inflammatory response, increased vascular permeability, alterations in angiogenesis, and increased production of adhesion proteins. For these reasons, endothelial dysfunction might be considered a marker of subclinical atherosclerosis (Hadi et al., 2005).

It is important to mention that for the study of endothelial alterations including endothelial dysfunction and cardiovascular-associated pathologies, several studies have proposed the human umbilical cord as a useful methodological strategy (Mangana et al., 2021). The above is because the umbilical cord is an accessible source for ECs isolation. In addition, this model does not need specific ethical consent since there is no harm to the donors and it is considered a non-tumorigenic and less immunogenic model. Also, as a primary culture, the ECs derived from the human umbilical cord maintain native characteristics of endothelial tissue and its intracellular signaling pathways (Medina-Leyte et al., 2020).

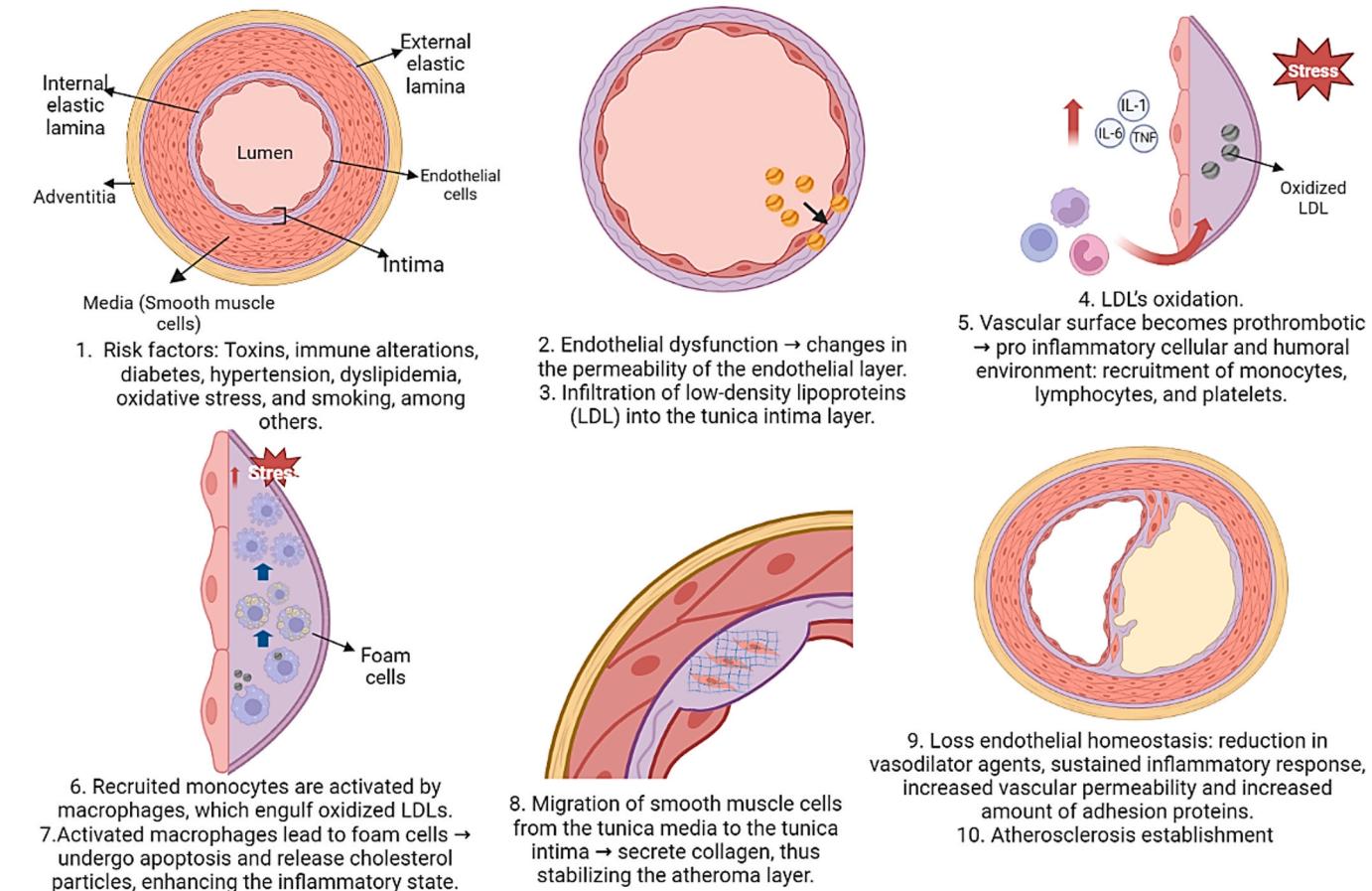
## 2. The role of estrogens in endothelial function

Estrogens are the principal sex steroid hormones produced from cholesterol in the ovaries, placenta, breast, adrenal glands, and peripheral adipose tissues in women as well as in the testis, adrenal glands, and peripheral adipose tissues in men (Heldring et al., 2007). Serum estradiol ( $E_2$ ) levels are approximately 4 times higher in women than

men.  $E_2$  is considered the most potent estrogen hormone in comparison to estriol, and estrone. Generally,  $E_2$  can promote the expression of genes by genomic mechanisms, through its interaction with the nuclear estrogen receptors ( $ER\alpha$  and  $ER\beta$ ), as well as non-genomic mechanisms, with the binding to the estrogen membrane-bound receptor, G protein-coupled estrogen receptor 30 (GPER1), which rapidly activates intracellular signaling. Both routes regulate the expression of different molecular targets (Fuentes and Silveyra, 2019). While  $E_2$  is responsible for the control of the female reproductive system, it also has pleiotropic effects in different organs (Knowlton and Lee, 2012; Fuentes and Silveyra, 2019).

On the other hand, one of the indications to postulate that  $E_2$  has an important role in endothelial homeostasis is the fact that women in menopausal stages have exacerbated effects and symptoms for different CVDs in comparison with their reproductive age counterparts (Mathews et al., 2019). Several cellular and animal experimental strategies, have shown  $E_2$  endothelial modulation role associated with the atherosclerotic process. In this sense,  $E_2$  promotes the upregulation of nitric oxide synthase (NOS) via both genomic and nongenomic mechanisms, increasing the levels of one of the most potent vasodilator agents, nitric oxide (NO) (Hayashi et al., 1995; McNeill et al., 2002). Additionally,  $E_2$  actions are often associated with the decrease of pro-inflammatory cytokines and chemokines involved in monocyte migration into the

# ENDOTHELIAL DYSFUNCTION



**Fig. 1.** Steps of endothelial dysfunction: The process of endothelial dysfunction begins with 1) the endothelium damage due to multiple factors, followed by 2) permeability changes of the endothelium begin, with the concomitant 3) lipoproteins infiltration. Next, 4) The lipoproteins undergo oxidation, favoring the atheroma layer, and 5) an inflammatory microenvironment is generated, where 6) monocytes and macrophages are recruited, and 7) macrophages turn into foam cells, which undergo apoptosis and release cholesterol particles, enhancing the inflammatory environment. Subsequently, 8) migration of smooth muscle cells occurs, leading to collagen secretion, which results in the atheroma layer stabilization. Finally, 9) there is loss of endothelial homeostasis, reduction of the vascular lumen, and 10) formal establishment of atherosclerosis. Abbreviations: interleukin (IL), tumor necrosis factor (TNF), low density lipoproteins (LDL). Created with BioRender.com.

subendothelial space, the modulation of low-density lipoprotein (LDL) oxidation, a decrease in endothelial permeability, cellular apoptosis, the production of reactive oxygen species (ROS), and an increase in proliferation of endothelial cells (Cho et al., 1999; Wagner et al., 2001; Florian and Magder, 2008; Oviedo et al., 2011; Chakrabarti et al., 2014).

### 3. Endocrine-disrupting compounds in the endothelium

Since multiple compounds found in the environment can interact with estrogen receptors, even without having a steroid structure, it is of interest to know their possible association with the endothelial dysfunction process and the development of CVDs.

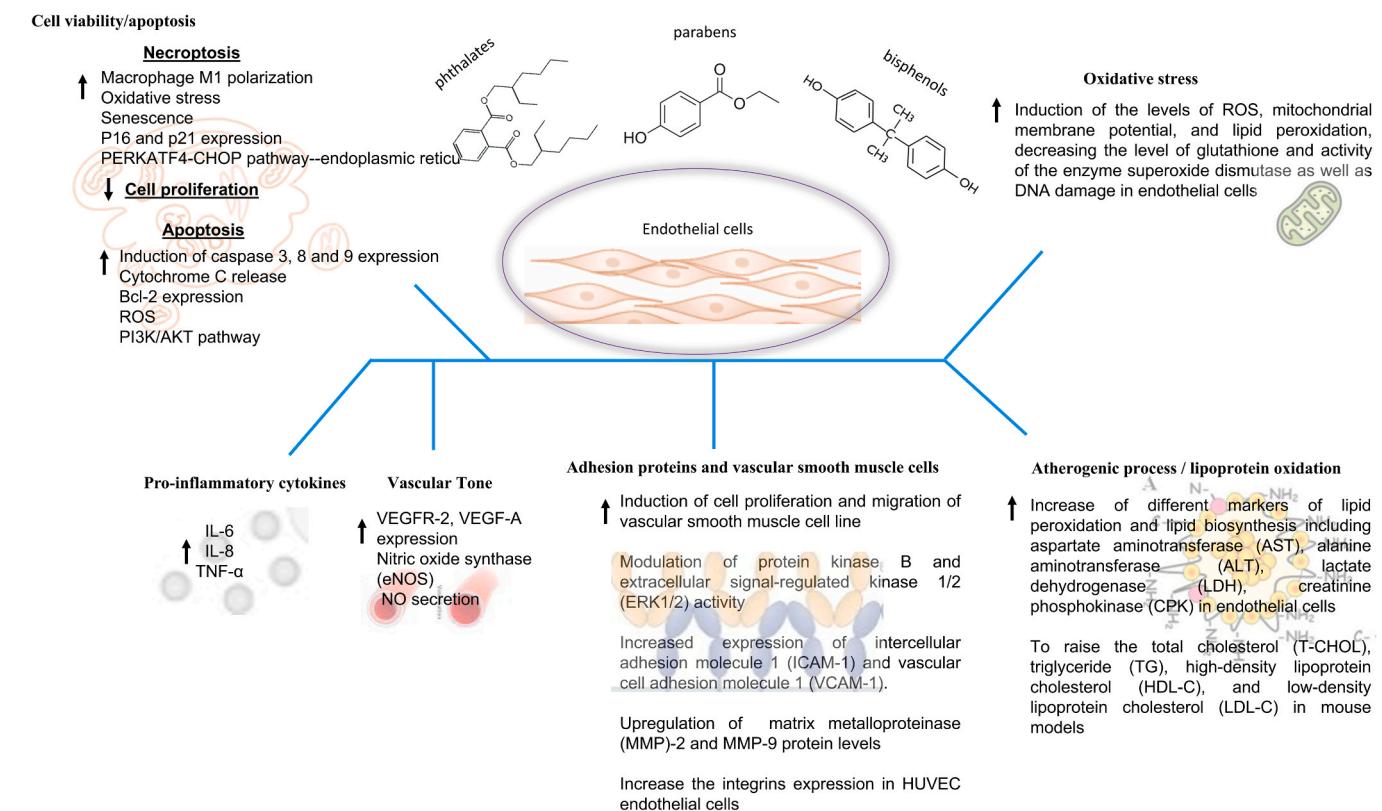
The US Environmental Protection Agency (EPA) has defined an EDC as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural bloodborne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process" (Diamanti-Kandarakis et al., 2009). Phthalates, bisphenols, and parabens are the EDCs most used in the industry and present in common-use products including cosmetics, food packaging, among many others (Almeida et al., 2018; Segovia-Mendoza et al., 2020; Luis et al., 2021; Wei et al., 2021). Human exposure to EDCs can occur through different routes including oral, inhalation, vaginal, or dermic absorption. There are many types of EDCs, however, bisphenols, phthalates, and parabens are the chemical compounds most used in personal, plastic packaging, medical, and other products that have been studied and associated with harmful health effects (La Merrill et al., 2020). Once entering the body, these compounds are processed through different metabolic routes. In this regard, bisphenols are conjugated with glucuronic acid, which is eliminated in the urine. Metabolism and elimination of phthalates involve complex

mechanisms, as these are metabolized to monoesters and eliminated in the urine as glucuronide conjugates. Similarly, parabens suffer hydrolysis at the ester bonds following glucuronidation reactions (Silva et al., 2003; Pellerin et al., 2022). Nevertheless, a fraction of the EDCs absorbed compounds can be stored in adipose tissue and then slowly released into the bloodstream. Regardless of the metabolic pathway, it has been reported that all of these compounds can bind to hormone receptors (Nowak et al., 2018).

The biological relevance of EDCs in multiple systems has been widely documented (La Merrill et al., 2020). In addition, their effects on the cardiovascular system and associations with CVD are a matter of current investigation (Campanale et al., 2020). Research on the effects of EDCs is not only situated in cellular models but is also carried out in pre-clinical and translational models, where their toxicological effects associated with different pathological conditions (including CVDs) are evaluated, due to their exposure in vulnerable stages of development (Lorigo and Cairrao, 2022).

In epidemiological studies, serum concentrations of different EDCs metabolites have been associated with increases in CVDs incidence (Kirkley and Sargis, 2014; Mariana and Cairrao, 2020). The most frequent health problems associated with these compounds are atherosclerotic plaques, hypertension, angina, coronary heart disease, and endothelial apoptosis (Ranciere et al., 2015; Bae et al., 2017; Medina-Leyte et al., 2021; Singh et al., 2021).

In the following section, the effects of EDCs including bisphenols, phthalates, and parabens in mechanisms associated with endothelial dysfunction are described. These have been summarized in Fig. 2 and Table 1.



**Fig. 2.** Endothelial dysfunction-associated mechanisms promoted by exposure to phthalates, parabens, and bisphenols. The exposure to different environmental contaminants such as phthalates, parabens, and bisphenols in endothelial cells has been related to alterations in cell viability and promotion of apoptosis, induction of a pro-inflammatory microenvironment, and deregulation of vascular tone and oxidative stress. These contaminants are also involved in the induction of adhesion molecule expression and smooth muscle cell migration in the different layers of the endothelium, resulting in the establishment of the atheroma layer and endothelial dysfunction.

**Table 1**

Effects of EDCs exposure in endothelial function.

Type of EDC	Doses	Cellular Function	Reference
Cell viability / apoptosis DEHP and mono-(2-ethylhexyl) phthalate (MEHP)	0, 6.25, 12.5, 25, 50 and 100 mM and 0–400 μM of each compound	Induction the apoptosis in human umbilical endothelial cells (HUVEC) Activation of caspase-3, -8 and -9 Increasing the Bax/bcl-2 mRNA protein ratio Induction of the cytochrome C releasing Promotion of the reactive oxygen species generation Activation of PI3K/AKT pathway	(Ban et al., 2014; Liu et al., 2017)
di-n-butyl phthalate (DBP) benzyl butyl phthalate (BBP) di-2-ethylhexyl phthalate (DEHP) diisodecyl phthalate (DIDP) di-n-octyl phthalate (DnOP) di-isobutyl phthalate (DINP)	1–200 mmol/L of each phthalate	decreased cell viability and proliferation of endothelial cells up-regulation of gene expression and inflammatory cytokine secretion	(Kruger et al., 2012)
BPA	BPA≤50 mg/kg and 25 mg/kg	Necroptosis in endothelial cells Inflammatory response up-regulation of M1 macrophage polarization increased oxidative stress Inducing aging and cellular senescence through induction of p16 and p21 expression Hyperactivation of PERKATF4-CHOP pathway (endoplasmic reticulum stress / unfolded protein response)	(Reventun et al., 2020; Moreno-Gomez-Toledano et al., 2021)
Pro-inflammatory cytokines di-(2-ethylhexyl) phthalate (DEHP) and MEHP	10, 100 or 1000 nM DEHP or MEHP	Induction of IL-8 secretion in human umbilical vein endothelial cells (HUVEC)	(Rael et al., 2009)
DEHP and MEHP	0, 5, 10, 25, 50 and 100 μM of DEHP or MEHP 500 mg/kg body weight of DEHP or MEHP for 4 weeks	The exposure to DEHP in apoE−/− mice showed increased levels of TNF-α, IL-1β, MCP-1, MIP-2, and IL-6. In addition, the levels of these cytokines were also increased in endothelial cell cultures (EAhy926)	(Zhao et al., 2016)
Vascular tone DEHP	300 mg DEHP/kg/day	The compound was administered to pregnant rats and the effects on the offspring were evaluated, the administration of DEHP from gestational day 14 until birth denoted alterations in blood pressure in the offspring	(Martinez-Arguelles et al., 2013)
DEHP	10 mg/kg/day	The effects of DEHP have also been corroborated in mice exposed to DEHP in dosages of 0.1/1/10 mg/kg/day of DEHP and 0.1/1/10 mg/kg/day of DBP for 6 weeks. Mice exposed to these compounds exhibit hypertension, elevated angiotensin-converting enzyme (ACE), and angiotensin II (AngII) expression levels, and significant downregulation of nitric oxide synthase (eNOS) and the level of NO regulation and expression, respectively	(Xie et al., 2019)
BPA	0.1 nM –1 μM	Increase the mRNA expression of the proangiogenic genes VEGF-2, VEGF-A in HUVEC cells Alterations in the endothelial nitric oxide synthase (eNOS) with the deregulation of NO production in endothelial cell cultures	(Andersson and Brittebo, 2012)
Phthalic acid	1763 mg/kg and 2981 mg/kg	The phthalic acid was administered to pregnant rats from the seventh day to the 16th day of pregnancy, the effects in the offspring were vascular dysfunction, increased oxidative stress, reduction of eNOS activity in the aorta. Additionally, increment in the heart rate and the wall thickness (tunica intima + tunica media) in the thoracic aorta in mature offspring were also found.	(Rahmani et al., 2016)
DEHP	30 mg/kg body weight during pregnancy and lactation	Maternal DEHP exposure causes reduction of eNOS activity, upregulation of angiotensin receptor type 1 receptor and increase hypertension in offspring of 8 weeks old	(Lee et al., 2016)
DEHP	1 μg/mL in water supplementation in mice for a 6-weeks experimental protocol	Decrement in heart rate and alterations in arterial pressure, Alteration of endothelin-1, angiotensin-converting enzyme, and eNOS gene expression	(Jaimes et al., 2017)
Adhesion proteins in endothelial cells and vascular smooth muscle cells DEHP	5, 10 and 25 μM of DEHP	Induction of cell proliferation and migration of vascular smooth muscle cell line Modulation of protein kinase B and extracellular signal-regulated kinase 1/2 (ERK1/2) activity Increased expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). Upregulation of matrix metalloproteinase (MMP)-2 and MMP-9 protein levels	(Kim, 2020)

(continued on next page)

**Table 1 (continued)**

Type of EDC	Doses	Cellular Function	Reference
DEHP	500 mg/kg body weight of DEHP for 4 weeks	Induces the upregulation of protein expression of ICAM-1, VCAM-1, and iNOS in the aortas of apoE <sup>-/-</sup> mice	(Zhao et al., 2016)
BPA, and BPS	10, 100 nM	Increase the integrins expression in HUVEC endothelial cells	(Kenda et al., 2022)
Atherogenic process / lipoprotein oxidation			
DEHP	500 mg/kg body weight of DEHP for 4 weeks	To induce hyperlipidemia, systemic inflammation, and atherosclerosis. In addition, DEHP promoted low-density lipoprotein (LDL) oxidation in the aortas of apoE <sup>-/-</sup> mice, which led to inflammation in endothelial cells as well as a significant increase in pro-inflammatory mediators. To increase the macrophage infiltration in white adipose tissue apoE <sup>-/-</sup> mice	(Zhao et al., 2016)
DEHP	Intraperitoneally administration 5, 50, and 200 mg/kg body weight for 30 consecutive days	To deregulate of lipid metabolism the cardiac tissue of BALB/c mice To increase different markers of lipid peroxidation and lipid biosynthesis including aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine phosphokinase (CPK) To raise the total cholesterol (T-CHOL), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) To increase the atherosclerotic lesions that contained cholesterol clefts and necrotic areas in the aortic root of apoE <sup>-/-</sup> mice	(Amara et al., 2019)
DEHP	100 mg/kg of DEHP administered in drinking water for 4, 8, and 12 weeks	To increase the atherosclerotic lesions that contained cholesterol clefts and necrotic areas in the aortic root of apoE <sup>-/-</sup> mice	(Zhou et al., 2015)
Oxidative Stress MEHP	0, 10, 20, and 40 mM	To augment the levels of ROS, mitochondrial membrane potential, and lipid peroxidation, decreasing the level of glutathione and activity of the enzyme superoxide dismutase as well as DNA damage in HUVEC cells	(Yang et al., 2017)
Polychlorinated biphenyls	0.3 μM	To induce the formation of ROS by the modulation of c-myc and AP-1, which are redox-sensitive transcription factors in endothelial cells	(Felty, 2011)

### 3.1. Cell viability/apoptosis

We previously described that as a part of endothelial dysfunction, cell death plays an important role. Regarding this fact, mono-(2-ethylhexyl) phthalate (MEHP), the active metabolite of di-(2-ethylhexyl) phthalate (DEHP) has been related to apoptosis in human umbilical endothelial cells (HUVEC) via induction caspase-3, -8 and -9 activation, increased ratio of Bax/bcl-2 mRNA protein expression, as well as cytochrome C release. In addition to increasing the ROS generation (Ban et al., 2014; Liu et al., 2017). The PI3K/AKT pathway has also been related to the effects of MEHP in endothelial cell apoptosis (Liu et al., 2017).

Other phthalates have also been linked with the decreased cell viability of endothelial cells. In line with this, the exposure to di-n-butyl phthalate (DBP), benzyl butyl phthalate (BBP), di-2-ethylhexyl phthalate (DEHP), di-isodecyl phthalate (DIDP), di-n-octyl phthalate (DnOP), and di-isonyl phthalate (DINP) in endothelial cells also decreased cell proliferation. In addition to the above, the up-regulation of gene expression and inflammatory cytokine secretion has been also reported after exposure to different phthalates in human endothelial cells (Kruger et al., 2012). Moreover, several reports have investigated the effects of *in utero* exposure to DEHP in rats and observed alterations in blood pressure in the offspring, a phenomenon related to hypertension and CVDs (Martinez-Arguelles et al., 2013). This also suggests a relationship between EDCs regulating endothelial vascular tone and subsequent CVD development.

Other types of endothelial cell damage and death, including necroptosis, have been reported after exposure to bisphenol A (BPA) at the endothelial level. This compound causes an inflammatory response, up-regulation of M1 macrophage polarization, and increased oxidative stress (Reventun et al., 2020), as well as aging and cellular senescence through p16 and p21 expression and the hyperactivation of PERKATF4-CHOP pathway, which is related to endoplasmic reticulum stress associated with the unfolded protein response (Moreno-Gomez-Toledano et al., 2021).

### 3.2. Pro-inflammatory cytokines

Pro-inflammatory cytokines are involved in many pathological processes, including endothelial damage and atherosclerosis. Their dysregulation is related to an increased risk of cardiovascular complications (Migliaccio et al., 2021). One of the most studied cytokines associated with the process of atherosclerosis and endothelial dysfunction is TNF $\alpha$ , which is involved in vascular tone, adhesion molecules expression, lipid metabolism, adipocyte function, and insulin signaling (Zhang et al., 2009). Concerning the above, the secretion of pro-inflammatory cytokines by endothelial cells due to the action of different EDCs has not been widely studied.

Some findings in other cell models may also relate to the proinflammatory function of EDCs in the endothelium. For instance, BPA and phthalates induced proinflammatory cytokines such as interleukin (IL)-1 $\beta$ , IL-6, and TNF $\alpha$  in a concentration-dependent manner in macrophages in cell culture models (Hansen et al., 2015; Huang et al., 2019). In addition, the pro-inflammatory role of BPA has also been reported in human mature adipocytes and stromal vascular fraction (SVF) cells, favoring the expression of IL-6, IL-8, monocyte chemo-attractant protein 1 $\alpha$  (MCP1 $\alpha$ ) via GPER1 activation (Cimmino et al., 2019). In addition, the effects of BPA related to inflammation can be linked with the induction of COX-2 expression via nuclear translocation of NF- $\kappa$ B and activation of mitogen-activated protein kinase (MAPK) by phosphorylation of ERK1/2 (Song et al., 2017).

On the other hand, exposure to phthalates in children has been related to an inflammatory state (Yang et al., 2014), but their role in endothelial cells has not been explored in depth. Experimental data have shown that endothelial human umbilical vein cells (HUVEC) exposed to DEHP and MEHP present an increase in IL-8 levels (Rael et al., 2009; Zhao et al., 2016). It has also been reported that the pre-treatment of DEHP (1 mg/mL) for 1 h to microvascular endothelial cells (HMECs) promotes TNF $\alpha$  expression (Guo et al., 2020). Additionally, in an animal model widely used as a pre-clinical model of atherosclerosis, such as apoE<sup>-/-</sup> mice (Jawien, 2012), exposure to DEHP showed increased levels of TNF- $\alpha$ , IL-1 $\beta$ , MCP-1, MIP-2, and IL-6 (Zhao et al., 2016). Following exposure to di-isonyl phthalate (DINP) for 14 days

(200 mg/kg/d), the pro-inflammatory cytokines interleukin IL-1 and TNF $\alpha$  were detected in mouse hepatic and renal tissues (Ma et al., 2014). Although these findings were not found in endothelial cells, it could be assumed that phthalates exposure favors an inflammatory condition, a physiological event that could also have repercussions at the endothelial level.

Related to the above, different research groups have studied the serum levels of different EDCs in people without a declared pathology, and in patients with different diseases, in which cancer patients stand out (Pazos et al., 2020; Wang and Qian, 2021; Segovia-Mendoza et al., 2022; Segovia-Mendoza et al., 2022; Zhang et al., 2022). It is noteworthy that other inflammatory biomarkers such as IL-6, IL-10, TNF $\alpha$ , MCP-1, C-reactive protein (CRP), and interferon- $\gamma$  (IFN- $\gamma$ ) have been associated with high serum levels of bisphenols, parabens, and phthalates in adults of reproductive age or menopause with different health conditions (Savastano et al., 2015; Aung et al., 2019; Ferguson et al., 2019; Haq et al., 2020; Jain et al., 2020; Trim et al., 2021; Lai et al., 2022; Requena et al., 2023). However, research on the effects of parabens is still limited. It is worth mentioning that bisphenols, phthalates, and parabens show an affinity for nuclear and membrane estrogen receptors, although they have opposite biological effects in the endothelium (Fuentes and Silveyra, 2019).

### 3.3. Vascular tone

The balance between vasodilator and vasoconstrictor molecules is what maintains endothelial homeostasis. Different substances are secreted by the endothelium or by other systems that control the vascular tone; for instance, NO, prostacyclin (PGI2), and endothelium-derived hyperpolarizing factor (EDHF) have vasodilator effects; in contrast, thromboxane (TXA2) and endothelin-1 (ET-1) elicit vasoconstrictor actions (Sandoo et al., 2010). In this sense, EDCs have shown significant hypertension, blood pressure, and cardio electrophysiology alterations in animal models (Wei et al., 2012; Martinez-Arguelles et al., 2013; Lu et al., 2018; Deng et al., 2019; Xie et al., 2019; Ramadan et al., 2020; Arenas, 2021). However, their effects on endothelial function are controversial (Arenas, 2021). Regarding this point, the range of nanomolar and micromolar (0.1 nM–1  $\mu$ M) BPA concentrations can increase the mRNA expression of the proangiogenic genes VEGFR-2, VEGF-A, and endothelial nitric oxide synthase (eNOS), and increase the production of NO in endothelial cells (Andersson and Brittebo, 2012). It should be noted that the range of concentrations tested can be extrapolated to concentrations of this compound reported in the serum of adults.

An indirect mechanism by which DEHP acts on endothelial dysfunction is by promoting plasminogen activator inhibitor type 1 in macrophage cultures. The exposure to DEHP (0, 50, 100 or 200 nM) in cultured macrophages can also modulate endothelial dysfunction by transforming the growth factor-b1/Smad/ signaling pathway (Yamaguchi et al., 2019). The above is relevant since atherosclerosis has been related to an active coagulation state (Borisoff et al., 2010). Macrophages and several tissue factors participate in the coagulation process, which together induces thrombin formation and promotes the sustained accumulation of macrophages in the vessels, giving rise to the atherosclerotic process (Moore et al., 2013).

In addition, prenatal exposure to phthalic acid, a phthalate precursor compound, in rats causes vascular dysfunction, increases oxidative stress, and reduces eNOS activity among the offspring (Rahmani et al., 2016). Of note, prenatal exposure to phthalic acid significantly increases both heart rate and wall thickness (tunica intima + tunica media) in the thoracic aorta in the mature offspring. The same study showed that phthalic acid exposure dramatically deregulates the eNOS activity in the aorta in the offspring (Rahmani et al., 2016). The effects of phthalic acid are shared with prenatal DEHP exposure in other experiments evaluated in the rat's offspring. DEHP causes a reduction of eNOS activity and upregulates the angiotensin receptor type 1 receptor (Lee et al., 2016). The DEHP effects have also been evaluated in an adult mice model

where the animals were exposed to DEHP in a drinking water supplementation scheme (1  $\mu$ g/mL) for six weeks and then the heart rate and arterial pressure were monitored. The authors mentioned that this dose of DEHP was considered because it falls within the clinical exposure range for a pediatric patient. The authors reported that DEHP causes a decrement in heart rate and alterations in arterial pressure, which were correlated with endothelin-1, angiotensin-converting enzyme, and eNOS gene expression alterations (Jaimes et al., 2017). The effects of DEHP have also been corroborated in mice exposed to DEHP dosages of 1 or 10 mg/kg/day, where the mice exposed to this compound exhibited hypertension, elevated angiotensin-converting enzyme (ACE), and angiotensin II (AngII) expression, and significant downregulation of eNOS and NO regulation and expression, respectively (Xie et al., 2019).

Interestingly, it has been reported that phthalates can also counteract the effects of drugs used to treat CVDs. Related to this concept, the pre-treatment of DEHP (1 mg/mL) for 1 h to microvascular endothelial cells (HMECs) abrogated the simvastatin-induced NO bioavailability and the endothelial cell-related vasodilation (Guo et al., 2020). The authors postulated that mechanistically, DEHP reduced the activation of transient receptor potential vanilloid type 1 (TRPV1), which is required for NO production by simvastatin in endothelial cells (Guo et al., 2020). In addition, the pre-treatment with DEHP increased the activity and expression of protein phosphatase 2B (PP2B), a negative regulator of TRPV1 activity (Guo et al., 2020). Together, the findings above support the harmful effects of different EDCs at the endothelial level, modulating vascular tone and predisposing to different CVDs.

### 3.4. Interrelation between adhesion proteins in endothelial cells and vascular smooth muscle cells

Coupled with endothelial dysfunction, changes in contractile capacity, collagen secretion, upregulation of adhesion molecules expression, and migration of endothelial and vascular smooth muscle cells (VSMCs) are considered (Marino et al., 2013; Afewerki et al., 2019). Concerning this, it has been described that phthalates such as DEHP induced cell proliferation and migration of vascular smooth muscle cell lines obtained from rat aortas in cell-culture experiments. The mechanisms associated with these changes have been related to the modulation of protein kinase B and extracellular signal-regulated kinase ½ (ERK1/2) activity, and an increased expression of both intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). The exposure to 50 nM of DEHP also upregulated the protein levels of matrix metalloproteinase (MMP)-2 and MMP-9 (Kim, 2020). Additionally, chronic exposure to DEHP in apoE $-/-$  mice resulted in the upregulation of protein expression of ICAM-1, VCAM-1, and inducible nitric oxide synthase (eNOS) in the mouse aorta (Zhao et al., 2016).

Regarding bisphenols exposure, both BPA and BPS at 10 and 100 nM have also been shown to increase the expression of different integrins in endothelial cells (Kenda et al., 2022). Using a novel experimental model, a recent study evaluated the modulation of other endothelial cell dysfunction markers in human endothelial cell cultures exposed to the serum-derived form of an occupational cohort of diesel engine testers. The results showed that chemokine 5 (CCL5) and the adhesion molecule VCAM were the most affected genes in addition to increased DNA leucocyte damage (Cheng et al., 2022), associated with endothelial cell dysfunction. Similar studies evaluating the effects of different EDCs from exposed subjects on healthy endothelial cell cultures would be an interesting methodological strategy to assess the mechanisms of indirect exposure to these compounds. Of note, it should be mentioned that other scientific models could be used to study endothelial dysfunction such as rat aorta artery (Rameshrad et al., 2016) or the umbilical cord (Wei et al., 2020, Lorigo and Cairrao, 2022). Similarly, these models could be applied to the study of endothelial disruption and interaction with VSMCs, as evidenced in some studies with phthalates (Liu et al., 2022; Wen et al., 2022), BPA (Ribeiro-Varandas et al., 2014; Easson et al., 2022). Both models allow the use of arteries with and without

endothelium, as well as the primary isolation of both types of cells.

### 3.5. Atherogenic process/lipoprotein oxidation

As described in the introductory section, endothelial dysfunction can lead to atherosclerotic plaque formation, decreasing the capillaries' lumen. This deregulation is generally what leads to the promotion of different CVDs. It is important to remark that the alterations of lipoprotein oxidation, macrophage infiltration, and a sustained inflammatory environment are conditions that promote and maintain atherosclerotic plaque (Libby et al., 2019). Different kinds of EDCs can evoke upregulation of lipid metabolism, specifically in free fatty acids and, high and low-density lipoproteins at both serum and liver levels (Jia et al., 2016; Ke et al., 2016; Bastos Sales et al., 2018; Xu et al., 2022; Li et al., 2023). These mechanisms have been associated with the interaction of EDCs with the peroxisome proliferator-activated receptor gamma (PPR $\gamma$ ), the modulation of signaling cascades such as the PI3K/AKT and JAK/STAT, and epigenetic alterations such as pre-programming of DNA methylation patterns (Jia et al., 2016; Ke et al., 2016). The epigenetic effects related to BPA exposure on endothelial cells have been little studied. About the above, BPA exposure (10 ng/mL and 1  $\mu$ g/mL) in Human Umbilical Vein Endothelial Cells (HUVEC) produces BPA global transcription deregulation, which has been related to epigenetic markers modulations such as histones, specifically H3K9me2 and H3K4me3. Both markers have an impact on endothelial cell senescence and a close relationship with related pathologies such as atherosclerosis (Ribeiro-Varandas et al., 2014). Supporting that, global histone methylation in human atherosclerotic plaques has been documented (Wei et al., 2020). In this sense, the H3K9me2 epigenetic marker has been significantly decreased in atherosclerotic lesions, highlighting its effects in endothelial dysfunction associated with atherosclerotic plaque formation (Greissel et al., 2015).

On the other hand, although phthalates can induce a negative effect on cardiovascular health, little research has been done to study the underlying epigenetic mechanisms leading to cardiovascular toxicity focusing on endothelial dysfunction (Sree et al., 2023).

Delving into the effects of EDCs exposure in the pathophysiology of atherosclerosis, experimental exposure to DEHP in apoE $^{-/-}$  mice for four weeks showed exacerbated hyperlipidemia, systemic inflammation, atherosclerosis, and macrophage infiltration in white adipose tissue (Zhao et al., 2016). In addition, DEHP promoted LDL oxidation in the aortas of apoE $^{-/-}$  mice, leading to inflammation in endothelial cells and a significant increase in pro-inflammatory mediators (Zhao et al., 2016).

Another finding related to the effects of DEHP, and dysregulation of lipid metabolism was documented in the cardiac tissue (Amara et al., 2019). For this purpose, DEHP was administered intraperitoneally at 5, 50, and 200 mg/kg body weight doses for 30 consecutive days in BALB/c mice. Different markers of lipid peroxidation and lipid biosynthesis including aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatinine phosphokinase (CPK) were found upregulated (Amara et al., 2019). In addition, total cholesterol (T-CHOL), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were also increased. Interestingly, the ratio of LDL-C to HDL-C was also elevated in mice treated with DEHP, which resembles the increased ratio observed in patients with atherosclerosis (Amara et al., 2019). DEHP has also been related to atherosclerosis establishment in female apoE $^{-/-}$  mice exposed to 100 mg/kg of DEHP for 4, 8, and 12 weeks. The above effect was denoted by the presence of atherosclerotic lesions that contained cholesterol clefts and necrotic areas (Zhou et al., 2015). Regarding the above, different mechanisms related to adipogenesis are implicated after exposure to different EDCs (Callaghan et al., 2021). However, one of the main mechanisms of action documented on how phthalates or bisphenols modulate the regulation of lipoproteins or various lipids is due to their interaction with PPAR $\gamma$

(Zhang et al., 2019).

### 3.6. Oxidative stress

Oxidative stress is an important pathophysiologic component of CVDs. This condition can be defined as an imbalance of NO and ROS. It is important to remark that oxidative stress may promote endothelial dysfunction, leading to cardiovascular complications (Higashi et al., 2014). Reported mechanisms that lead to the formation of oxidative stress are the deregulation of the enzymes nicotinamide-adenine dinucleotide phosphate oxidase, xanthine oxidase, cyclooxygenase, as well as mitochondrial electron transport, inactivation of the antioxidant system, and uncoupling of endothelial NO synthase (Higashi et al., 2014). Similarly, oxidative stress participates in LDL oxidation, which subsequently promotes an inflammatory environment, favoring the atherogenic process (Stocker and Keaney, 2004).

There are some reports about the related effects of different EDCs regarding oxidative stress and the endothelium. The exposure of MEHP (0, 10, 20, and 40 mM) increases the levels of ROS, mitochondrial membrane potential, and lipid peroxidation, decreasing the level of glutathione and activity of the enzyme superoxide dismutase. In addition, DNA damage was significantly observed, as denoted by p53 and p-Chk2 T68 protein expression increments, in HUVEC cells (Yang et al., 2017). ROS generation at hepatic, renal, and testicular levels can also be boosted after DINP exposure (200 mg/kg/d or 500 mg/kg/d) for 14–19 days (Ma et al., 2014; Qin et al., 2017). Notably, although these effects were not studied at the endothelial level, they indicate the oxidative damage evoked by EDCs in endothelial cells. Supporting the fact that EDCs have important consequences in the development of different CVDs and their relationship with oxidative stress, it has been described that exposure to polychlorinated biphenyls (another type of EDCs) at 0.3  $\mu$ M in endothelial cells (HMVEC) induces the formation of ROS by the modulation of c-myc and AP-1, which are redox-sensitive transcription factors (Felty, 2011).

Additionally, a reported mechanism by which polychlorinated biphenyls are involved in ROS production is the modulation of NADPH oxidase (Eum et al., 2009). BPA has also been shown to induce oxidative stress in neurons by modulating mitochondrial superoxide (Babu et al., 2013). These findings support the idea that BPA can have toxic effects at the cardiovascular level.

## 4. Clinical evidence

At the clinical level, exposure and high levels of bisphenols (Ranciere et al., 2015; Kataria et al., 2017), phthalates (Attina and Trasande, 2015; Valvi et al., 2015; Werner et al., 2015; Kataria et al., 2017; Ding et al., 2021), and parabens (Yin et al., 2023; Zhang et al., 2023) have been correlated with cardiovascular alterations, specifically in blood pressure, lipid metabolism, and hypertension and altered circulating levels of activated endothelial cell-derived microparticles in children (Chu et al., 2021). Interestingly, endothelial microparticles are considered biomarkers of endothelial and vascular alteration, since they are released in response to endothelium cell apoptosis, oxidative stress, and vascular inflammation, leading to atherosclerosis progression (Paudel et al., 2016).

Phthalates such as DEHP, and several of their metabolites, have been strongly associated with CVDs incidence and mortality. Interestingly, this association has been more evident in women than in men, however, other factors such as alcohol consumption, smoking status, physical activity, body mass index, and comorbidities including diabetes, and dyslipidemias need to be considered to make more precise statements (Ding et al., 2021; Zeng et al., 2022). In fact, very few reports have evaluated the dimorphic differences and effects of different EDCs and CVDs in both sexes, although it is widely known that CVD disproportionately affect males and females (Peters et al., 2019). Concerning the above, studies carried out only in the male population on the levels of

EDCs and the predisposition to develop CVDs can allow establishing that being overweight is an important factor that correlates with high levels of different phthalates, as well as increased triglyceride and decreased HDL cholesterol serum levels (Milosevic et al., 2017). Nevertheless, it seems very important to us to mention that in the population of children and young people between 9 and 19 years of age, different phthalates and their metabolites have been recently associated with increased blood pressure (Trasande and Attina, 2015; Hashemi et al., 2021). However, in the elderly population, high levels of phthalates have also been related to oxidative stress and CV damage (Dong et al., 2018). These data point out the importance of making specific measurements of the different EDCs and carrying out preventive schemes for the development of various diseases at different ages, with the main focus on CVDs.

On the other hand, high blood levels of mono-methyl phthalate, mono-isobutyl phthalate (MiBP), and BPA were related to carotid plaques. These findings were found in a large cohort of hypertensive adult women from Sweden. High levels of these EDCs were related to body mass index, blood glucose, blood pressure, HDL and LDL-cholesterol, serum triglycerides, and smoking lifestyle. The intima-media thickness (IMT) diameter was significantly modified in women with high levels of these contaminants. In addition, carotid plaques were particularly found in women with high levels of mono-methyl phthalate (Lind and Lind, 2011). In addition, clinical data correlating the proinflammatory actions of phthalates have been observed in pregnant women where urinary levels of these compounds and several markers of inflammation have been measured. The findings have shown that blood levels of IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$ , and oxidative stress were higher in women with high levels of various DEHP metabolites (Ferguson et al., 2014). The above implies that the physiological actions of different EDCs may also be shared at the endothelial level.

With the evidence exposed, it could be assumed that the different EDCs could be considered cardiovascular disruptors in the endothelial context, favoring future CVD events, as was suggested in recent years (Muscogiuri and Colao, 2017). Nevertheless, intending to counteract the effects of different EDCs, several research groups have proposed the consumption of phytochemicals, which opens up new lines of research about compounds jointly at the endothelial level (Kamaruddin et al., 2022). Concerning the above, phytochemicals can counteract harmful actions of agents that damage the endothelium. One example is curcumin, which inhibits the oxidation of LDLs as well as the formation of ROS induced by TNF $\alpha$  exposure in endothelial cells (Kim et al., 2007; Lee et al., 2010). Resveratrol is another phytochemical that has been shown to counteract the harmful effects of TNF $\alpha$  and cigarette smoke exposure on endothelial cells, in addition to counteracts the secretion of ROS and inflammatory and vasoconstriction markers such as ICAM-1, iNOS, IL-6, (Csizsar et al., 2006). It has also been proposed that the administration of phytochemicals in critical stages of development, such as the perinatal stage, attenuates the damage in multiple systems in the offspring of mice that were exposed to these compounds, highlighting the role of resveratrol associated with cardiovascular diseases, as the administration of this compound together with BPA in the perinatal stage prevents the progression of atherosclerotic lesions (Sirasanagandla et al., 2023).

## 5. Conclusion

This review exposes the mechanisms by which bisphenols, parabens, and phthalates cause endothelial dysfunction, predisposing to different CVDs. It is evident that the mechanisms by which these compounds act are multiple. The damage they cause has even been reported at the clinical level, not only in the adult population but also in the extremes of life, children, and older people. Therefore, it is necessary to disseminate the information to avoid its consumption and/or unnecessary exposure.

In addition, it is necessary to generate new lines of research jointly exposing compounds that allow counteracting the harmful effects of

EDCs. In the new generations of toxicologists and medical doctors, it should be required to include notions about the mechanisms these compounds impact and the pharmacological conditions in the therapeutics they may present.

It is even important to consider an emerging concept, such as indirect exposure to EDCs not only synthetic but also natural EDCs within a patient's clinical history, considering individuals close to a family and social environment as distribution vectors. Moreover, considerations of sex, gender, and hormonal status should be included in the research design and data interpretation, to evaluate mechanisms involving hormone receptors and potential implications for sex-specific effects.

## CRediT authorship contribution statement

The authors have the following roles: MSM: Conceptualization, writing the draft, funding acquisition, review & editing. CL: review & editing. PS: Conceptualization, review & editing, project administration.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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