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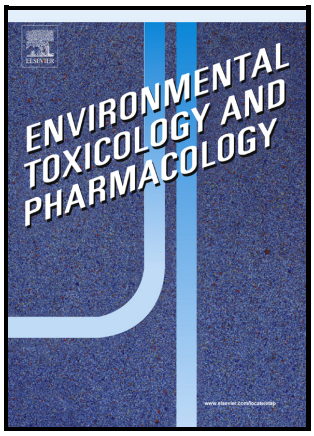

Cristina Lemini, Patricia Silveyra, Mariana Segovia-Mendoza

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

Cristina Lemini[1#], Patricia Silveyra[2#], Mariana Segovia-Mendoza[1#*]

[1] Departamento de Farmacología, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México, México.

[2] Department of Environmental and Occupational Health, Indiana University Bloomington, School of Public Health, Bloomington, IN, USA

*Correspondence to: Mariana Segovia-Mendoza (mariana.segovia@facmed.unam.mx)

#Cristina Lemini, Patricia Silveyra and Mariana Segovia-Mendoza, equally contributed to this work.

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 17β-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.

KEYWORDS: cardiovascular disease, endocrine disruptors, atherosclerosis, endothelial dysfunction, estradiol

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INTRODUCTION

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, van Zanten 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, Quyyumi et al. 1990, Marti, Gheorghiade et al. 2012, Maldonado, Morales 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, Zepeda-Garcia 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, Zhou 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, Simon-Codina 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, Zheng 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, (**Figure 1**) **(Jiang, Zhou 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 (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, Carr 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, Lorigo 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, Domínguez-Pérez et al. 2020)**.

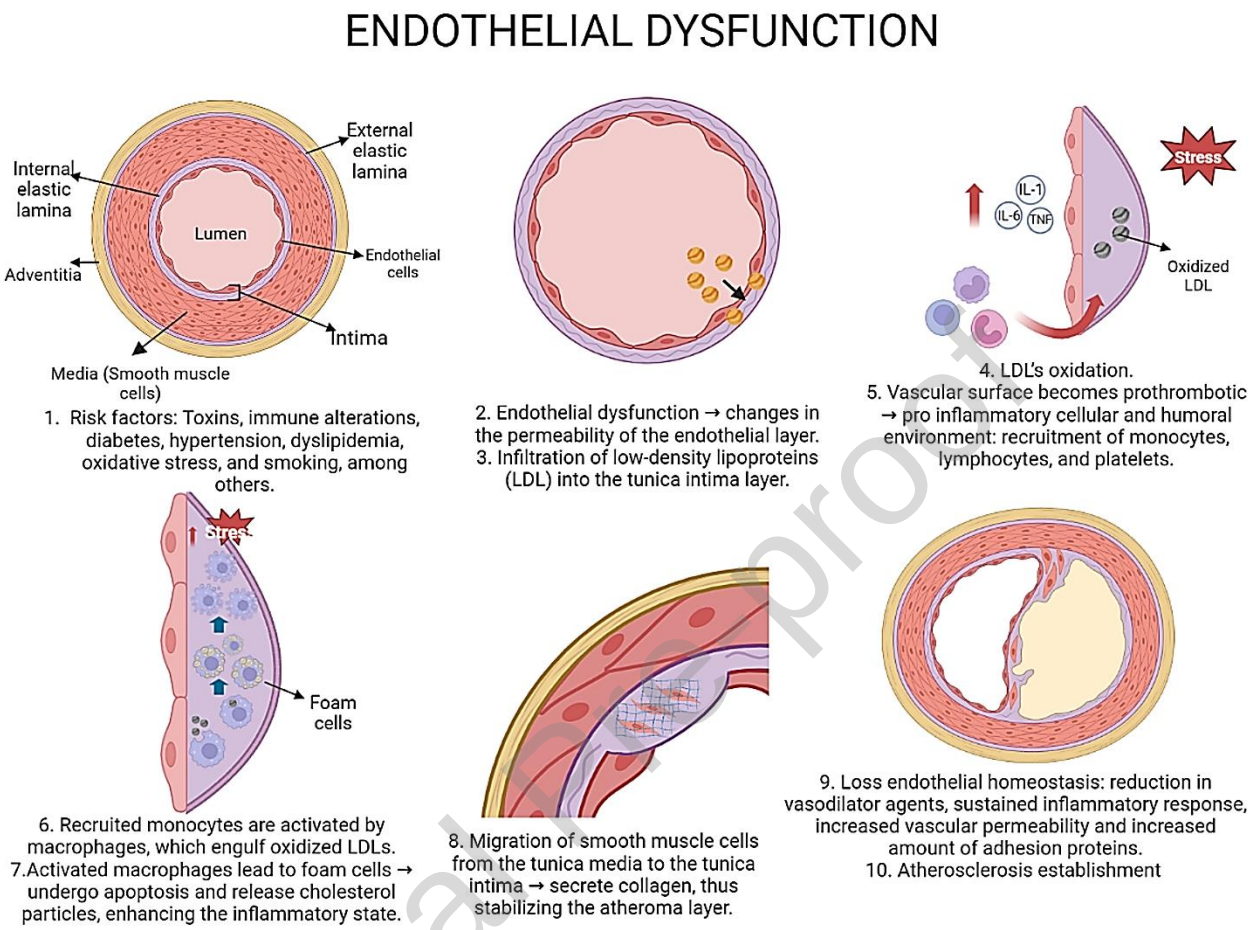

Figure 1. Steps of endothelial dysfunction: The process of endothelial dysfunction begins with 1) the endothelium damage due to multiple factors, followed by 2) permeability changes of the endothelium begin, with the concomitant 3) lipoproteins infiltration. Next, 4) The lipoproteins undergo oxidation, 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

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, Pike 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 (ERα and ERβ), 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, Subramanya 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, Yamada et al. 1995, McNeill, Zhang 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 subendothelial space, the modulation of low-density lipoprotein (LDL) oxidation, a decrease the endothelial permeability, cellular apoptosis, the production of reactive oxygen species (ROS), and an increase in proliferation of endothelial cells **(Cho, Ziats et al. 1999, Wagner, Schroeter et al. 2001, Florian and Magder 2008, Oviedo, Sobrino et al. 2011, Chakrabarti, Morton et al. 2014)**.

ENDOCRINE-DISRUPTING COMPOUNDS IN THE ENDOTHELIUM

Since multiple compounds found in the environment can interact with estrogen receptors, even without having a steroidal 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, Bourguignon 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, Raposo et al. 2018, Segovia-Mendoza, Nava-Castro et al. 2020, Luis, Algarra et al. 2021, Wei, Mortimer 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, Vandenberg 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, Barr et al. 2003, Pellerin, 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, Ratajczak-Wrona et al. 2018)**.

The biological relevance of EDCs in multiple systems has been widely documented **(La Merrill, Vandenberg et al. 2020)**. In addition, their effects on the cardiovascular system and associations with CVD are a matter of current investigation **(Campanale, Massarelli et al. 2020)**. Research on the effects of EDCs is not only situated in cellular models but is also carried out in preclinical 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, Lyons et al. 2015, Bae, Lim et al. 2017, Medina-Leyte, Zepeda-Garcia et al. 2021, Singh, Koshta 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 **Figure 2** and **Table 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, Fan et al. 2014, Liu, Jiang et al. 2017)**. The PI3K/AKT pathway has also been related to the effects of MEHP in endothelial cell apoptosis **(Liu, Jiang 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-isononyl 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, Cao 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, McIntosh 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, Sanchez-Esteban 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, Sanchez-Esteban et al. 2021)**.

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, Bimonte et al. 2021)**. One of the most studied cytokines associated with the process of atherosclerosis and endothelial dysfunction is TNFα, which is involved in vascular tone, adhesion molecules expression, lipid metabolism, adipocyte function, and insulin signaling **(Zhang, Park 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)-1β, IL-6, and TNFα in a concentration-dependent manner in macrophages in cell culture models **(Hansen, Bendtzen et al. 2015, Huang, Chang 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 1α (MCP1α) via GPER1 activation **(Cimmino, Oriente 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-κB and activation of mitogen-activated protein kinase (MAPK) by phosphorylation of ERK1/2 **(Song, Park et al. 2017)**.

On the other hand, exposure to phthalates in children has been related to an inflammatory state **(Yang, Hsieh 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, Bar-Or et al. 2009, Zhao, Hsiao et al. 2016).** It has also been reported that the pre-treatment of DEHP (1 mg/ml) for 1h to microvascular endothelial cells (HMECs) promotes TNFα expression **(Guo, Kuo et al. 2020)**. Additionally, in an animal model widely used as a pre-clinical model of atherosclerosis, such as apoE−/− mice **(Jawien 2012)**, exposure to DEHP showed increased levels of TNF-α, IL-1β, MCP-1, MIP-2, and IL-6 **(Zhao, Hsiao et al. 2016)**. Following exposure to di-isononyl phthalate (DINP) for 14 days (200 mg/kg/d), the pro-inflammatory cytokines interleukin IL-1 and TNFα were detected in mouse hepatic and renal tissues **(Ma, Yan 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, Palacios et al. 2020, Wang and Qian 2021, Segovia-Mendoza, Palacios-Arreola et al. 2022, Segovia-Mendoza, Palacios-Arreola et al. 2022, Zhang, Luo et al. 2022)**. It is noteworthy that other inflammatory biomarkers such as IL-6, IL-10, TNFα, MCP-1, C-reactive protein (CRP), and interferon-γ (IFN-γ) have been associated with high serum levels of bisphenols, parabens, and phthalates in adults of reproductive age or menopause with different health conditions **(Savastano, Tarantino et al. 2015, Aung, Ferguson et al. 2019, Ferguson, Cantonwine et al. 2019, Haq, Akash et al. 2020, Jain, Gupta et al. 2020, Trim, Hankinson et al. 2021, Lai, Liu et al. 2022, Requena, Pérez-Díaz 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)**.

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, van Zanten et al. 2010)**. In this sense, EDCs have shown significant hypertension, blood pressure, and cardio electrophysiology alterations in animal models **(Wei, Song et al. 2012, Martinez-Arguelles, McIntosh et al. 2013, Lu, Xu et al. 2018, Deng, Xie et al. 2019, Xie, Deng et al. 2019, Ramadan, Cooper 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 μM) 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, Sakamoto et al. 2019)**. The above is relevant since atherosclerosis has been related to an active coagulation state **(Borissoff, Heeneman 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, Sheedy 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, Soleimannejad 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, Soleimannejad 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, Chiang 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 µg/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, Swiercz 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, Deng 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 1h to microvascular endothelial cells (HMECs) abrogated the simvastatin-induced NO bioavailability and the endothelial cell-related vasodilation **(Guo, Kuo 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, Kuo 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, Kuo 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.

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, Guasti et al. 2013, Afewerki, Ahmed 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, Hsiao 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, Pečar Fonović 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, Pang 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, Babaei et al. 2016)** or the umbilical cord **(Wei, Yi 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, Qin et al. 2022, Wen, Kong et al. 2022)**, BPA **(Ribeiro-Varandas, Pereira et al. 2014, Easson, Singh 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.

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, Buring 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, Liu et al. 2016, Ke, Pan et al. 2016, Bastos Sales, van Esterik et al. 2018, Xu, Wu et al. 2022, Li, He et al. 2023)**. These mechanisms have been associated with the interaction of EDCs with the peroxisome proliferator-activated receptor gamma (PPRγ), the modulation of signaling cascades such as the PI3K/AKT and JAK/STAT, and epigenetic alterations such as preprogramming of DNA methylation patterns **(Jia, Liu et al. 2016, Ke, Pan 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 µg/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, Pereira et al. 2014)**. Supporting that, global histone methylation in human atherosclerotic plaques has been documented **(Wei, Yi 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, Culmes 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, Buddolla 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, Hsiao 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, Hsiao et al. 2016)**.

Another finding related to the effects of DEHP, and dysregulation of lipid metabolism was documented in the cardiac tissue **(Amara, Timoumi 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, Timoumi 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, Timoumi 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, Chen et al. 2015)**. Regarding the above, different mechanisms related to adipogenesis are implicated after exposure to different EDCs **(Callaghan, Alatorre-Hinojosa 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 PPARγ **(Zhang, Sun et al. 2019)**.

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, Maruhashi 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, Maruhashi 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, Gao 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, Yan et al. 2014, Qin, Tang 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 0.3μM 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, Andras et al. 2009)**. BPA has also been shown to induce oxidative stress in neurons by modulating mitochondrial superoxide **(Babu, Uppu et al. 2013)**. These findings support the idea that BPA can have toxic effects at the cardiovascular level.

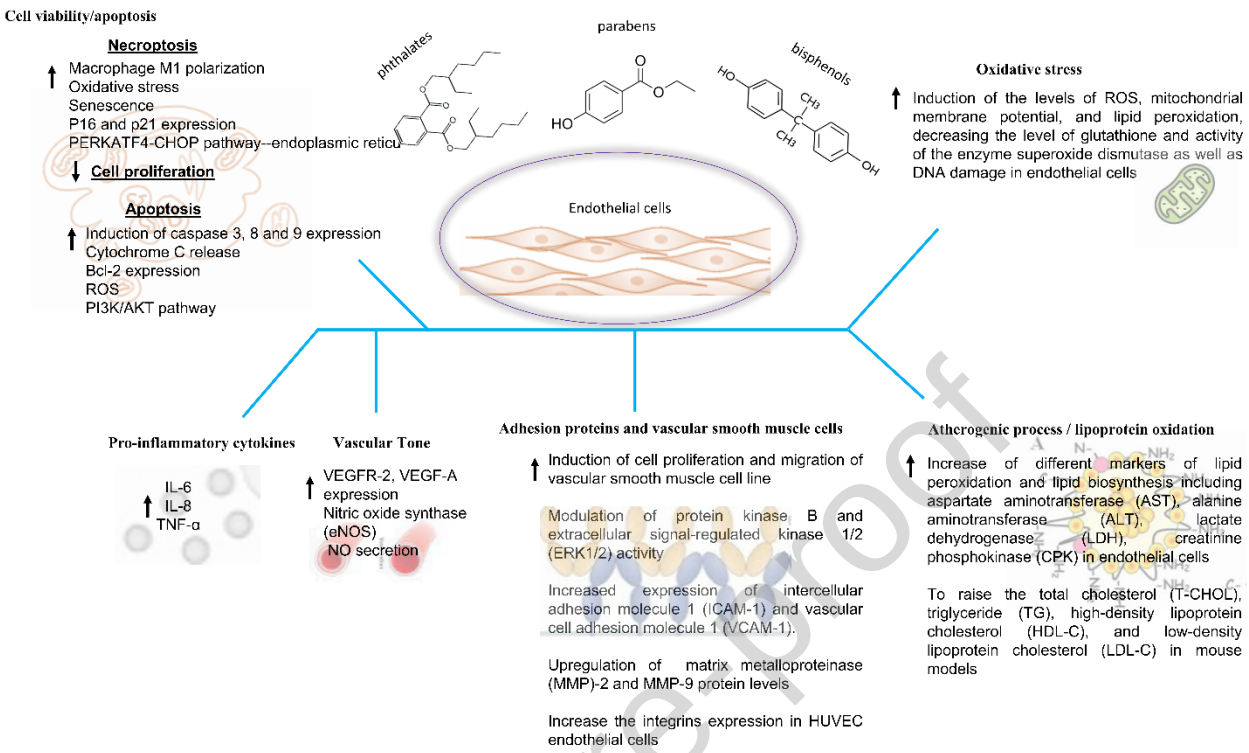

Figure 2. Endothelial dysfunction-associated mechanisms promoted by exposure to phthalates, parabens, and bisphenols. The exposure to different environmental contaminants such as phthalates, parabens, and bisphenols in endothelial cells has been related to alterations in cell viability and promotion 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, Fan et al. 2014, Liu, Jiang 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-isononyl phthalate (DINP)	1 to 200 mmol/L of each phthalate	decreased cell viability and proliferation of endothelial cells up-regulation of gene expression and inflammatory cytokine secretion	**(Kruger, Cao et al. 2012)**
BPA	BPA≤50mg/kg and 25 mg/kg	Necroptosis in endothelial cells Inflammatory response	**(Reventun, Sanchez-Esteban et al. 2020, Moreno-Gomez-Toledano, Sanchez-**

		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)	**Esteban et al. 2021)**
Pro-inflammatory cytokines			
di-(2-ethylhexyl) phthalate (DEHP) and MEHP	10, 100 or 1,000 nM DEHP or MEHP	Induction of IL-8 secretion in human umbilical vein endothelial cells (HUVEC)	**(Rael, Bar-Or 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 this cytokines were also increased in endothelial cell cultures (EA.hy926)	**(Zhao, Hsiao 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	**(Martinez-Arguelles, McIntosh et al. 2013)**

		alterations in blood pressure in the offspring	
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, Deng et al. 2019)**
BPA	0.1 nM –1 µM	Increase the mRNA expression of the proangiogenic genes VEGFR-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	**(Rahmani, Soleimannejad et al. 2016)**

		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.	
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, Chiang et al. 2016)**
DEHP	1µg/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, Swiercz 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).	**(Kim 2020)**

		Upregulation of matrix metalloproteinase (MMP)-2 and MMP-9 protein levels	
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−/− mice	**(Zhao, Hsiao et al. 2016)**
BPA, and BPS	10, 100 nM	Increase the integrins expression in HUVEC endothelial cells	**(Kenda, Pečar Fonović 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−/− 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−/− mice	**(Zhao, Hsiao 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	**(Amara, Timoumi et al. 2019)**

		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)	
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−/− mice	**(Zhou, Chen 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, Gao et al. 2017)**
Polychlorinated biphenyls	0.3μM	To induce the formation of ROS by the modulation of c-myc and AP-1, which are redox-sensitive	**(Felty 2011)**

	transcription factors in endothelial cells

CLINICAL EVIDENCE

At the clinical level, exposure and high levels of bisphenols **(Ranciere, Lyons et al. 2015, Kataria, Levine et al. 2017)**, phthalates **(Attina and Trasande 2015, Valvi, Casas et al. 2015, Werner, Braun et al. 2015, Kataria, Levine et al. 2017, Ding, Qi et al. 2021)**, and parabens **(Yin, Zhu et al. 2023, Zhang, 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, Wu 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, Panth 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, Qi et al. 2021, Zeng, Zhang 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 disproportionally affect males and females **(Peters, Muntner 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, Milic et al. 2017)**. Nevertheless, it seems very important to us to mention that in the population of

children and young people between 9-19 years of age, different phthalates and their metabolites have been recently associated with increased blood pressure **(Trasande and Attina 2015, Hashemi, Amin et al. 2021)**. However, in the elderly population, high levels of phthalates have also been related to oxidative stress and CV damage **(Dong, Chen 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-1β, IL-6, IL-10, and TNF-α, and oxidative stress were higher in women with high levels of various DEHP metabolites **(Ferguson, Cantonwine 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 phytocompounds, which opens up new lines of research about compounds jointly at the endothelial level **(Kamaruddin, Hakim Abdullah et al. 2022)**. Concerning the above, phytocompounds 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 TNFα exposure in endothelial cells **(Kim, Ahn et al. 2007, Lee, Lee et al. 2010)**. Resveratrol is another phytocompound that has been shown to counteract the harmful effects of TNFα 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, **(Csiszar, Smith et al. 2006)**. It has also been proposed that the administration of phytocompounds 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, Al-Mushaiqri et al. 2023)**.

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.

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Departamento de Farmacología, Facultad de Medicina, UNAM.

COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

The authors have the following roles:

MSM: Conceptualization, writing the draft, funding acquisition, review & editing

CL: review & editing

PS: Conceptualization, review & editing, project administration.

REFERENCES

Afewerki, T., S. Ahmed and D. Warren (2019). "Emerging regulators of vascular smooth muscle cell migration." Journal of Muscle Research and Cell Motility **40**(2): 185-196.

Almeida, S., A. Raposo, M. Almeida-Gonzalez and C. Carrascosa (2018). "Bisphenol A: Food Exposure and Impact on Human Health." Compr Rev Food Sci Food Saf **17**(6): 1503-1517.

Amara, I., R. Timoumi, E. Annabi, F. Neffati, M. F. Najjar, C. Bouaziz and S. Abid-Essefi (2019). "Di (2-ethylhexyl) phthalate induces cardiac disorders in BALB/c mice." Environ Sci Pollut Res Int **26**(8): 7540-7549.

Andersson, H. and E. Brittebo (2012). "Proangiogenic effects of environmentally relevant levels of bisphenol A in human primary endothelial cells." Arch Toxicol **86**(3): 465-474.

Arenas, I. A. (2021). "Invited Perspective: Phthalates and Blood Pressure: the Unknowns of Dietary Factors." Environ Health Perspect **129**(12): 121303.

Attina, T. M. and L. Trasande (2015). "Association of Exposure to Di-2-Ethylhexylphthalate Replacements With Increased Insulin Resistance in Adolescents From NHANES 2009-2012." J Clin Endocrinol Metab **100**(7): 2640-2650.
Aung, M. T., K. K. Ferguson, D. E. Cantonwine, K. M. Bakulski, B. Mukherjee, R. Loch-Caruso, T. F. McElrath and J. D. Meeker (2019). "Associations between maternal plasma measurements of inflammatory markers and urinary levels of phenols and parabens during pregnancy: A repeated measures study." Sci Total Environ **650**(Pt 1): 1131-1140.
Babu, S., S. Uppu, M. O. Claville and R. M. Uppu (2013). "Prooxidant actions of bisphenol A (BPA) phenoxyl radicals: implications to BPA-related oxidative stress and toxicity." Toxicol Mech Methods **23**(4): 273-280.
Bae, S., Y. H. Lim, Y. A. Lee, C. H. Shin, S. Y. Oh and Y. C. Hong (2017). "Maternal Urinary Bisphenol A Concentration During Midterm Pregnancy and Children's Blood Pressure at Age 4." Hypertension **69**(2): 367-374.
Ban, J. B., X. W. Fan, Q. Huang, B. F. Li, C. Chen, H. C. Zhang and S. Q. Xu (2014). "Mono-(2-ethylhexyl) phthalate induces injury in human umbilical vein endothelial cells." PLoS One **9**(5): e97607.
Bastos Sales, L., J. C. J. van Esterik, H. M. Hodemaekers, M. H. Lamoree, T. Hamers, L. T. M. van der Ven and J. Legler (2018). "Analysis of Lipid Metabolism, Immune Function, and Neurobehavior in Adult C57BL/6JxFVB Mice After Developmental Exposure to di (2-ethylhexyl) Phthalate." Front Endocrinol (Lausanne) **9**: 684.
Björkegren, J. L. M. and A. J. Lusis (2022). "Atherosclerosis: Recent developments." Cell **185**(10): 1630-1645.
Borissoff, J. I., S. Heeneman, E. Kilinc, P. Kassak, R. Van Oerle, K. Winckers, J. W. Govers-Riemslag, K. Hamulyak, T. M. Hackeng, M. J. Daemen, H. ten Cate and H. M. Spronk (2010). "Early atherosclerosis exhibits an enhanced procoagulant state." Circulation **122**(8): 821-830.
Callaghan, M. A., S. Alatorre-Hinojosa, L. T. Connors, R. D. Singh and J. A. Thompson (2021). "Plasticizers and Cardiovascular Health: Role of Adipose Tissue Dysfunction." **11**.
Campanale, C., C. Massarelli, I. Savino, V. Locaputo and V. F. Uricchio (2020). "A Detailed Review Study on Potential Effects of Microplastics and Additives of Concern on Human Health." Int J Environ Res Public Health **17**(4).
Chakrabarti, S., J. S. Morton and S. T. Davidge (2014). "Mechanisms of estrogen effects on the endothelium: an overview." Can J Cardiol **30**(7): 705-712.
Cheng, W., H. Pang, M. J. Campen, J. Zhang, Y. Li, J. Gao, D. Ren, X. Ji, N. Rothman, Q. Lan, Y. Zheng, S. Leng, Z. Hu and J. Tang (2022). "Circulatory metabolites trigger ex vivo arterial endothelial cell dysfunction in population chronically exposed to diesel exhaust." Particle and Fibre Toxicology **19**(1): 20.
Cho, M. M., N. P. Ziats, D. Pal, W. H. Utian and G. I. Gorodeski (1999). "Estrogen modulates paracellular permeability of human endothelial cells by eNOS- and iNOS-related mechanisms." Am J Physiol **276**(2): C337-349.
Chu, P. C., C. Wu and T. C. Su (2021). "Association between Urinary Phthalate Metabolites and Markers of Endothelial Dysfunction in Adolescents and Young Adults." Toxics **9**(2).
Cimmino, I., F. Oriente, V. D'Esposito, D. Liguoro, P. Liguoro, M. R. Ambrosio, S. Cabaro, F. D'Andrea, F. Beguinot, P. Formisano and R. Valentino (2019). "Low-dose Bisphenol-A regulates inflammatory cytokines through GPR30 in mammary adipose cells." J Mol Endocrinol **63**(4): 273-283.
Csiszar, A., K. Smith, N. Labinskyy, Z. Orosz, A. Rivera and Z. Ungvari (2006). "Resveratrol attenuates TNF-alpha-induced activation of coronary arterial endothelial cells: role of NF-kappaB inhibition." Am J Physiol Heart Circ Physiol **291**(4): H1694-1699.

Deng, T., X. Xie, J. Duan and M. Chen (2019). "Di-(2-ethylhexyl) phthalate induced an increase in blood pressure via activation of ACE and inhibition of the bradykinin-NO pathway." Environ Pollut **247**: 927-934.
Diamanti-Kandarakis, E., J. P. Bourguignon, L. C. Giudice, R. Hauser, G. S. Prins, A. M. Soto, R. T. Zoeller and A. C. Gore (2009). "Endocrine-disrupting chemicals: an Endocrine Society scientific statement." Endocr Rev **30**(4): 293-342.
Ding, S., W. Qi, Q. Xu, T. Zhao, X. Li, J. Yin, R. Zhang, C. Huo, L. Zhou and L. Ye (2021). "Relationships between di-(2-ethylhexyl) phthalate exposure and lipid metabolism in adolescents: Human data and experimental rat model analyses." Environ Pollut **286**: 117570.
Ding, S., W. Qi, Q. Xu, T. Zhao, X. Li, J. Yin, R. Zhang, C. Huo, L. Zhou and L. Ye (2021). "Relationships between di-(2-ethylhexyl) phthalate exposure and lipid metabolism in adolescents: Human data and experimental rat model analyses." Environmental Pollution **286**: 117570.
Dong, R., J. Chen, J. Zheng, M. Zhang, H. Zhang, M. Wu, S. Li and B. Chen (2018). "The role of oxidative stress in cardiometabolic risk related to phthalate exposure in elderly diabetic patients from Shanghai." Environ Int **121**(Pt 1): 340-348.
Easson, S., R. D. Singh, L. Connors, T. Scheidl, L. Baker, A. Jadli, H. L. Zhu and J. Thompson (2022). "Exploring oxidative stress and endothelial dysfunction as a mechanism linking bisphenol S exposure to vascular disease in human umbilical vein endothelial cells and a mouse model of postnatal exposure." Environ Int **170**: 107603.
Eum, S. Y., I. Andras, B. Hennig and M. Toborek (2009). "NADPH oxidase and lipid raft-associated redox signaling are required for PCB153-induced upregulation of cell adhesion molecules in human brain endothelial cells." Toxicol Appl Pharmacol **240**(2): 299-305.
Felty, Q. (2011). "Proteomic 2D DIGE profiling of human vascular endothelial cells exposed to environmentally relevant concentration of endocrine disruptor PCB153 and physiological concentration of 17beta-estradiol." Cell Biol Toxicol **27**(1): 49-68.
Ferguson, K. K., D. E. Cantonwine, T. F. McElrath, B. Mukherjee and J. D. Meeker (2019). "Corrigendum to "Repeated measures analysis of associations between urinary bisphenol-A concentrations and biomarkers of inflammation and oxidative stress in pregnancy" [Reprod. Toxicol. 66 (2016) 93-98]." Reprod Toxicol **90**: 166.
Ferguson, K. K., D. E. Cantonwine, L. O. Rivera-Gonzalez, R. Loch-Caruso, B. Mukherjee, L. V. Anzalota Del Toro, B. Jimenez-Velez, A. M. Calafat, X. Ye, A. N. Alshawabkeh, J. F. Cordero and J. D. Meeker (2014). "Urinary phthalate metabolite associations with biomarkers of inflammation and oxidative stress across pregnancy in Puerto Rico." Environ Sci Technol **48**(12): 7018-7025.
Florian, M. and S. Magder (2008). "Estrogen decreases TNF-alpha and oxidized LDL induced apoptosis in endothelial cells." Steroids **73**(1): 47-58.
Fuentes, N. and P. Silveyra (2019). "Estrogen receptor signaling mechanisms." Adv Protein Chem Struct Biol **116**: 135-170.
Greissel, A., M. Culmes, R. Napieralski, E. Wagner, H. Gebhard, M. Schmitt, A. Zimmermann, H. H. Eckstein, A. Zernecke and J. Pelisek (2015). "Alternation of histone and DNA methylation in human atherosclerotic carotid plaques." Thromb Haemost **114**(2): 390-402.
Gui, Y., H. Zheng and R. Y. Cao (2022). "Foam Cells in Atherosclerosis: Novel Insights Into Its Origins, Consequences, and Molecular Mechanisms." Front Cardiovasc Med **9**: 845942.
Guo, B.-C., K.-L. Kuo, C.-H. Chen, S.-L. Chen, T.-C. Tsou and T.-S. Lee (2020). "Di-(2-ethylhexyl) phthalate limits the pleiotropic effects of statins in chronic kidney disease patients undergoing dialysis and endothelial cells." Environmental Pollution **267**: 115548.
Hadi, H. A., C. S. Carr and J. Al Suwaidi (2005). "Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome." Vasc Health Risk Manag **1**(3): 183-198.

Hansen, J. F., K. Bendtzen, M. Boas, H. Frederiksen, C. H. Nielsen, A. K. Rasmussen and U. Feldt-Rasmussen (2015). "Influence of phthalates on cytokine production in monocytes and macrophages: a systematic review of experimental trials." PLoS One **10**(3): e0120083.
Haq, M. E. U., M. S. H. Akash, S. Sabir, M. H. Mahmood and K. Rehman (2020). "Human exposure to bisphenol A through dietary sources and development of diabetes mellitus: a cross-sectional study in Pakistani population." Environmental Science and Pollution Research **27**(21): 26262-26275.
Hashemi, M., M. M. Amin, A. Chavoshani, N. Rafiei, K. Ebrahimpour and R. Kelishadi (2021). "Relationship of Urinary Phthalate Metabolites with Cardiometabolic Risk Factors and Oxidative Stress Markers in Children and Adolescents." Journal of Environmental and Public Health **2021**: 5514073.
Hayashi, T., K. Yamada, T. Esaki, M. Kuzuya, S. Satake, T. Ishikawa, H. Hidaka and A. Iguchi (1995). "Estrogen increases endothelial nitric oxide by a receptor-mediated system." Biochem Biophys Res Commun **214**(3): 847-855.
Heldring, N., A. Pike, S. Andersson, J. Matthews, G. Cheng, J. Hartman, M. Tujague, A. Strom, E. Treuter, M. Warner and J. A. Gustafsson (2007). "Estrogen receptors: how do they signal and what are their targets." Physiol Rev **87**(3): 905-931.
Higashi, Y., T. Maruhashi, K. Noma and Y. Kihara (2014). "Oxidative stress and endothelial dysfunction: Clinical evidence and therapeutic implications." Trends in Cardiovascular Medicine **24**(4): 165-169.
Huang, F. M., Y. C. Chang, S. S. Lee, M. L. Yang and Y. H. Kuan (2019). "Expression of pro-inflammatory cytokines and mediators induced by Bisphenol A via ERK-NFkappaB and JAK1/2-STAT3 pathways in macrophages." Environ Toxicol **34**(4): 486-494.
Jaimes, R., 3rd, A. Swiercz, M. Sherman, N. Muselimyan, P. J. Marvar and N. G. Posnack (2017). "Plastics and cardiovascular health: phthalates may disrupt heart rate variability and cardiovascular reactivity." Am J Physiol Heart Circ Physiol **313**(5): H1044-H1053.
Jain, J., N. Gupta, R. Mathur, S. Nimesh and S. K. Mathur (2020). "A Study on Impact of BPA in the Adipose Tissue Dysfunction (Adiposopathy) in Asian Indian Type 2 Diabetes Mellitus Subjects." Indian J Clin Biochem **35**(4): 451-457.
Jawien, J. (2012). "The role of an experimental model of atherosclerosis: apoE-knockout mice in developing new drugs against atherogenesis." Curr Pharm Biotechnol **13**(13): 2435-2439.
Jeon, B. H. (2021). "Endothelial Dysfunction: From Pathophysiology to Novel Therapeutic Approaches." Biomedicines **9**(11).
Jia, Y., T. Liu, L. Zhou, J. Zhu, J. Wu, D. Sun, J. Xu, Q. Wang, H. Chen, F. Xu, Y. Zhang, T. Zhang, H. Liu and L. Ye (2016). "Effects of Di-(2-ethylhexyl) Phthalate on Lipid Metabolism by the JAK/STAT Pathway in Rats." Int J Environ Res Public Health **13**(11).
Jiang, H., Y. Zhou, S. M. Nabavi, A. Sahebkar, P. J. Little, S. Xu, J. Weng and J. Ge (2022). "Mechanisms of Oxidized LDL-Mediated Endothelial Dysfunction and Its Consequences for the Development of Atherosclerosis." Front Cardiovasc Med **9**: 925923.
Kamaruddin, N. A., M. N. Hakim Abdullah, J. J. Tan, V. Lim, L. Y. Fong, S. A. Abd Ghafar and Y. K. Yong (2022). "Vascular Protective Effect and Its Possible Mechanism of Action on Selected Active Phytocompounds: A Review." Evidence-Based Complementary and Alternative Medicine **2022**: 3311228.
Kataria, A., D. Levine, S. Wertenteil, S. Vento, J. Xue, K. Rajendiran, K. Kannan, J. M. Thurman, D. Morrison, R. Brody, E. Urbina, T. Attina, L. Trasande and H. Trachtman (2017). "Exposure to bisphenols and phthalates and association with oxidant stress, insulin resistance, and endothelial dysfunction in children." Pediatr Res **81**(6): 857-864.

Ke, Z.-H., J.-X. Pan, L.-Y. Jin, H.-Y. Xu, T.-T. Yu, K. Ullah, T. U. Rahman, J. Ren, Y. Cheng, X.-Y. Dong, J.-Z. Sheng and H.-F. Huang (2016). "Bisphenol A Exposure May Induce Hepatic Lipid Accumulation via Reprogramming the DNA Methylation Patterns of Genes Involved in Lipid Metabolism." Scientific Reports **6**(1): 31331.
Kenda, M., U. Pečar Fonović, J. Kos and M. Sollner Dolenc (2022). "The effect of endocrine disrupting chemicals on the vitronectin-receptor (integrin αvβ3)-mediated cell adhesion of human umbilical vein endothelial cells." Toxicology in Vitro **79**: 105275.
Kim, J. H. (2020). "Glucagon-like peptide-1 receptor agonist reduces di(2-ethylhexyl) phthalate-induced atherosclerotic processes in vascular smooth muscle cells." Physiol Res **69**(6): 1095-1102.
Kim, Y. S., Y. Ahn, M. H. Hong, S. Y. Joo, K. H. Kim, I. S. Sohn, H. W. Park, Y. J. Hong, J. H. Kim, W. Kim, M. H. Jeong, J. G. Cho, J. C. Park and J. C. Kang (2007). "Curcumin attenuates inflammatory responses of TNF-alpha-stimulated human endothelial cells." J Cardiovasc Pharmacol **50**(1): 41-49.
Kirkley, A. G. and R. M. Sargis (2014). "Environmental endocrine disruption of energy metabolism and cardiovascular risk." Curr Diab Rep **14**(6): 494.
Knowlton, A. A. and A. R. Lee (2012). "Estrogen and the cardiovascular system." Pharmacology & Therapeutics **135**(1): 54-70.
Kruger, T., Y. Cao, S. K. Kjaergaard, L. E. Knudsen and E. C. Bonefeld-Jorgensen (2012). "Effects of phthalates on the human corneal endothelial cell line B4G12." Int J Toxicol **31**(4): 364-371.
La Merrill, M. A., L. N. Vandenberg, M. T. Smith, W. Goodson, P. Browne, H. B. Patisaul, K. Z. Guyton, A. Kortenkamp, V. J. Cogliano, T. J. Woodruff, L. Rieswijk, H. Sone, K. S. Korach, A. C. Gore, L. Zeise and R. T. Zoeller (2020). "Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification." Nature Reviews Endocrinology **16**(1): 45-57.
Lai, C. C., F. L. Liu, C. Y. Tsai, S. L. Wang and D. M. Chang (2022). "Di-(2-ethylhexyl) phthalate exposure links to inflammation and low bone mass in premenopausal and postmenopausal females: Evidence from ovariectomized mice and humans." Int J Rheum Dis **25**(8): 926-936.
Lee, H. S., M. J. Lee, H. Kim, S. K. Choi, J. E. Kim, H. I. Moon and W. H. Park (2010). "Curcumin inhibits TNFalpha-induced lectin-like oxidised LDL receptor-1 (LOX-1) expression and suppresses the inflammatory response in human umbilical vein endothelial cells (HUVECs) by an antioxidant mechanism." J Enzyme Inhib Med Chem **25**(5): 720-729.
Lee, K.-I., C.-W. Chiang, H.-C. Lin, J.-F. Zhao, C.-T. Li, S.-K. Shyue and T.-S. Lee (2016). "Maternal exposure to di-(2-ethylhexyl) phthalate exposure deregulates blood pressure, adiposity, cholesterol metabolism and social interaction in mouse offspring." Archives of Toxicology **90**(5): 1211-1224.
Li, X., X. He, X. Lin, W. Li, J. Gao, N. Zhang, Y. Guo, Z. Wang, N. Zhao, B. Zhang and Z. Dong (2023). "Effects of bisphenols on lipid metabolism and neuro-cardiovascular toxicity in marine medaka larvae." Aquat Toxicol **259**: 106551.
Libby, P., J. E. Buring, L. Badimon, G. K. Hansson, J. Deanfield, M. S. Bittencourt, L. Tokgözoğlu and E. F. Lewis (2019). "Atherosclerosis." Nature Reviews Disease Primers **5**(1): 56.
Lind, P. M. and L. Lind (2011). "Circulating levels of bisphenol A and phthalates are related to carotid atherosclerosis in the elderly." Atherosclerosis **218**(1): 207-213.
Liu, C., Q. Qin, J. Xu, X. Li and H. Cong (2022). "Phthalate promotes atherosclerosis through interacting with long-non coding RNA and induces macrophage foam cell formation and vascular smooth muscle damage." Chemosphere **308**: 136383.
Liu, N., L. Jiang, X. Sun, X. Yao, X. Zhai, X. Liu, X. Wu, Y. Bai, S. Wang and G. Yang (2017). "Mono-(2-ethylhexyl) phthalate induced ROS-dependent autophagic cell death in human vascular endothelial cells." Toxicol In Vitro **44**: 49-56.
Lorigo, M. and E. Cairrao (2022). "Fetoplacental vasculature as a model to study human cardiovascular endocrine disruption." Mol Aspects Med **87**: 101054.

Lu, X., X. Xu, Y. Lin, Y. Zhang and X. Huo (2018). "Phthalate exposure as a risk factor for hypertension." Environmental Science and Pollution Research **25**(21): 20550-20561.
Luis, C., M. Algarra, J. S. Camara and R. Perestrelo (2021). "Comprehensive Insight from Phthalates Occurrence: From Health Outcomes to Emerging Analytical Approaches." Toxics **9**(7).
Ma, P., B. Yan, Q. Zeng, X. Liu, Y. Wu, M. Jiao, C. Liu, J. Wu and X. Yang (2014). "Oral exposure of Kunming mice to diisononyl phthalate induces hepatic and renal tissue injury through the accumulation of ROS. Protective effect of melatonin." Food and Chemical Toxicology **68**: 247-256.
Maldonado, F., D. Morales, C. Diaz-Papapietro, C. Valdes, C. Fernandez, N. Valls, M. Lazo, C. Espinoza, R. Gonzalez, R. Gutierrez, A. Jara, C. Romero, O. Cerda and M. Caceres (2022). "Relationship Between Endothelial and Angiogenesis Biomarkers Envisage Mortality in a Prospective Cohort of COVID-19 Patients Requiring Respiratory Support." Front Med (Lausanne) **9**: 826218.
Mangana, C., M. Lorigo and E. J. B. Cairrão (2021). "Implications of Endothelial Cell-Mediated Dysfunctions in Vasomotor Tone Regulation."
Mariana, M. and E. Cairrao (2020). "Phthalates Implications in the Cardiovascular System." Journal of cardiovascular development and disease **7**(3): 26.
Marino, F., L. Guasti, M. Tozzi, L. Schembri, L. Castiglioni, E. Molteni, G. Piffaretti, P. Castelli and M. Cosentino (2013). "Gene expression of adhesion molecules in endothelial cells from patients with peripheral arterial disease is reduced after surgical revascularization and pharmacological treatment." Int J Vasc Med **2013**: 412761.
Marti, C. N., M. Gheorghiade, A. P. Kalogeropoulos, V. V. Georgiopoulou, A. A. Quyyumi and J. Butler (2012). "Endothelial dysfunction, arterial stiffness, and heart failure." J Am Coll Cardiol **60**(16): 1455-1469.
Martinez-Arguelles, D. B., M. McIntosh, C. V. Rohlicek, M. Culty, B. R. Zirkin and V. Papadopoulos (2013). "Maternal in utero exposure to the endocrine disruptor di-(2-ethylhexyl) phthalate affects the blood pressure of adult male offspring." Toxicol Appl Pharmacol **266**(1): 95-100.
Mathews, L., V. Subramanya, D. Zhao, P. Ouyang, D. Vaidya, E. Guallar, J. Yeboah, D. Herrington, A. G. Hays, M. J. Budoff and E. D. Michos (2019). "Endogenous Sex Hormones and Endothelial Function in Postmenopausal Women and Men: The Multi-Ethnic Study of Atherosclerosis." J Womens Health (Larchmt) **28**(7): 900-909.
McNeill, A. M., C. Zhang, F. Z. Stanczyk, S. P. Duckles and D. N. Krause (2002). "Estrogen increases endothelial nitric oxide synthase via estrogen receptors in rat cerebral blood vessels: effect preserved after concurrent treatment with medroxyprogesterone acetate or progesterone." Stroke **33**(6): 1685-1691.
Medina-Leyte, D. J., M. Domínguez-Pérez, I. Mercado, M. T. Villarreal-Molina and L. Jacobo-Albavera (2020). "Use of Human Umbilical Vein Endothelial Cells (HUVEC) as a Model to Study Cardiovascular Disease: A Review." **10**(3): 938.
Medina-Leyte, D. J., O. Zepeda-Garcia, M. Dominguez-Perez, A. Gonzalez-Garrido, T. Villarreal-Molina and L. Jacobo-Albavera (2021). "Endothelial Dysfunction, Inflammation and Coronary Artery Disease: Potential Biomarkers and Promising Therapeutical Approaches." Int J Mol Sci **22**(8).
Medrano-Bosch, M., B. Simon-Codina, W. Jimenez, E. R. Edelman and P. Melgar-Lesmes (2023). "Monocyte-endothelial cell interactions in vascular and tissue remodeling." Front Immunol **14**: 1196033.
Migliaccio, S., V. M. Bimonte, Z. M. Besharat, C. Sabato, A. Lenzi, C. Crescioli and E. Ferretti (2021). "Environmental Contaminants Acting as Endocrine Disruptors Modulate Atherogenic Processes: New Risk Factors for Cardiovascular Diseases in Women?" Biomolecules **12**(1).

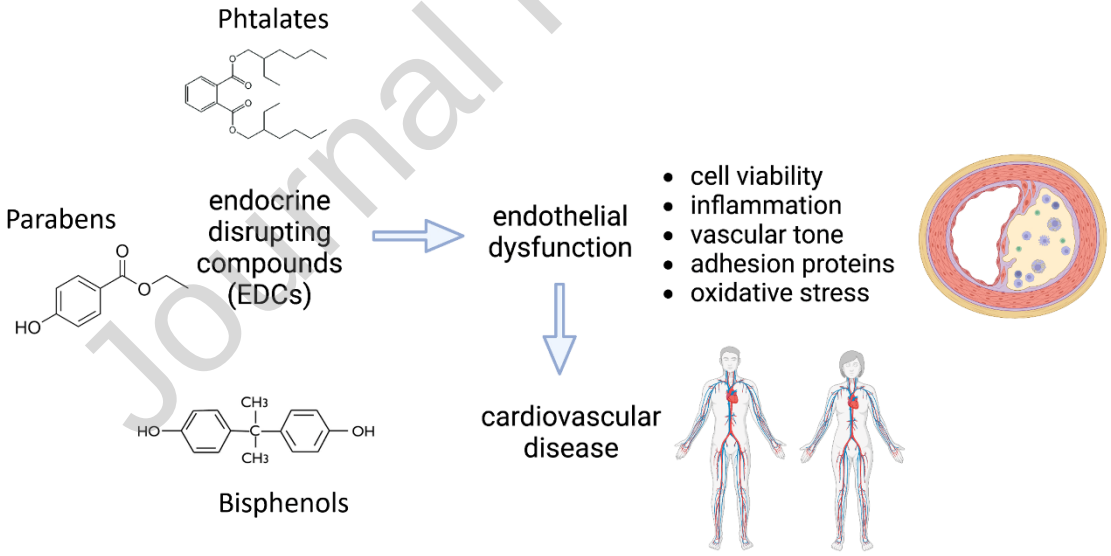
Milosevic, N., N. Milic, D. Zivanovic Bosic, I. Bajkin, I. Percic, L. Abenavoli and M. Medic Stojanoska (2017). "Potential influence of the phthalates on normal liver function and cardiometabolic risk in males." Environ Monit Assess **190**(1): 17.
Moore, K. J., F. J. Sheedy and E. A. Fisher (2013). "Macrophages in atherosclerosis: a dynamic balance." Nat Rev Immunol **13**(10): 709-721.
Moreno-Gomez-Toledano, R., S. Sanchez-Esteban, A. Cook, M. Minguez-Moratinos, R. Ramirez-Carracedo, P. Reventun, M. Delgado-Marin, R. J. Bosch and M. Saura (2021). "Bisphenol A Induces Accelerated Cell Aging in Murine Endothelium." Biomolecules **11**(10).
Muscogiuri, G. and A. Colao (2017). "Phtalates: new cardiovascular health disruptors?" Archives of Toxicology **91**(3): 1513-1517.
Nowak, K., W. Ratajczak-Wrona, M. Gorska and E. Jablonska (2018). "Parabens and their effects on the endocrine system." Mol Cell Endocrinol **474**: 238-251.
Oviedo, P. J., A. Sobrino, A. Laguna-Fernandez, S. Novella, J. J. Tarin, M. A. Garcia-Perez, J. Sanchis, A. Cano and C. Hermenegildo (2011). "Estradiol induces endothelial cell migration and proliferation through estrogen receptor-enhanced RhoA/ROCK pathway." Mol Cell Endocrinol **335**(2): 96-103.
Panza, J. A., A. A. Quyyumi, J. E. Brush, Jr. and S. E. Epstein (1990). "Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension." N Engl J Med **323**(1): 22-27.
Paudel, K. R., N. Panth and D.-W. Kim (2016). "Circulating Endothelial Microparticles: A Key Hallmark of Atherosclerosis Progression." Scientifica **2016**: 8514056.
Pazos, R., C. Palacios and A. Campa (2020). "Urinary Paraben Concentration and Its Association with Serum Triglyceride Concentration in 2013-2014 NHANES Participants: A Cross-Sectional Study." J Environ Public Health **2020**: 8196014.
Pellerin, È., F.-A. Pellerin, S. Chabaud, F. Pouliot, M. Pelletier and S. Bolduc (2022). "Glucuronidated Metabolites of Bisphenols A and S Alter the Properties of Normal Urothelial and Bladder Cancer Cells." **23**(21): 12859.
Peters, S. A. E., P. Muntner and M. Woodward (2019). "Sex Differences in the Prevalence of, and Trends in, Cardiovascular Risk Factors, Treatment, and Control in the United States, 2001 to 2016." Circulation **139**(8): 1025-1035.
Qin, Z., J. Tang, P. Han, X. Jiang, C. Yang, R. Li, M. Tang, B. Shen, W. Wang, C. Qin and W. Zhang (2017). "Protective effects of sulforaphane on di-n-butylphthalate-induced testicular oxidative stress injury in male mice offsprings via activating Nrf2/ARE pathway." Oncotarget **8**(47): 82956-82967.
Rael, L. T., R. Bar-Or, D. R. Ambruso, C. W. Mains, D. S. Slone, M. L. Craun and D. Bar-Or (2009). "Phthalate esters used as plasticizers in packed red blood cell storage bags may lead to progressive toxin exposure and the release of pro-inflammatory cytokines." Oxid Med Cell Longev **2**(3): 166-171.
Rahmani, A., K. Soleimannejad, M. R. Hafezi Ahmadi, K. Asadollahi and Z. Khalighi (2016). "Prenatal Exposure to Phthalic Acid Induces Increased Blood Pressure, Oxidative Stress, and Markers of Endothelial Dysfunction in Rat Offspring." Cardiovasc Toxicol **16**(4): 307-315.
Ramadan, M., B. Cooper and N. G. Posnack (2020). "Bisphenols and phthalates: Plastic chemical exposures can contribute to adverse cardiovascular health outcomes." Birth Defects Res **112**(17): 1362-1385.
Rameshrad, M., H. Babaei, Y. Azarmi and D. F. Fouladi (2016). "Rat aorta as a pharmacological tool for in vitro and in vivo studies." Life Sci **145**: 190-204.

Ranciere, F., J. G. Lyons, V. H. Loh, J. Botton, T. Galloway, T. Wang, J. E. Shaw and D. J. Magliano (2015). "Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence." Environ Health **14**: 46.
Requena, P., C. Pérez-Díaz, V. Mustieles, F. M. Peinado, J. León, F. M. Pérez-Carrascosa, H. Frederiksen, I. Salcedo-Bellido, R. Barrios-Rodríguez and J. P. Arrebola (2023). "Associations of circulating levels of phthalate metabolites with cytokines and acute phase reactants in a Spanish human cohort." Environmental Research **216**: 114470.
Reventun, P., S. Sanchez-Esteban, A. Cook, I. Cuadrado, C. Roza, R. Moreno-Gomez-Toledano, C. Munoz, C. Zaragoza, R. J. Bosch and M. Saura (2020). "Bisphenol A induces coronary endothelial cell necroptosis by activating RIP3/CamKII dependent pathway." Sci Rep **10**(1): 4190.
Ribeiro-Varandas, E., H. S. Pereira, S. Monteiro, E. Neves, L. Brito, R. B. Ferreira, W. Viegas and M. Delgado (2014). "Bisphenol A Disrupts Transcription and Decreases Viability in Aging Vascular Endothelial Cells." **15**(9): 15791-15805.
Ribeiro-Varandas, E., H. S. Pereira, S. Monteiro, E. Neves, L. Brito, R. B. Ferreira, W. Viegas and M. Delgado (2014). "Bisphenol A disrupts transcription and decreases viability in aging vascular endothelial cells." Int J Mol Sci **15**(9): 15791-15805.
Sandoo, A., J. J. van Zanten, G. S. Metsios, D. Carroll and G. D. Kitas (2010). "The endothelium and its role in regulating vascular tone." Open Cardiovasc Med J **4**: 302-312.
Savastano, S., G. Tarantino, V. D'Esposito, F. Passaretti, S. Cabaro, A. Liotti, D. Liguoro, G. Perruolo, F. Ariemma, C. Finelli, F. Beguinot, P. Formisano and R. Valentino (2015). "Bisphenol-A plasma levels are related to inflammatory markers, visceral obesity and insulin-resistance: a cross-sectional study on adult male population." J Transl Med **13**: 169.
Segovia-Mendoza, M., K. E. Nava-Castro, M. I. Palacios-Arreola, C. Garay-Canales and J. Morales-Montor (2020). "How microplastic components influence the immune system and impact on children health: Focus on cancer." Birth Defects Res **112**(17): 1341-1361.
Segovia-Mendoza, M., M. I. Palacios-Arreola, L. M. Monroy-Escamilla, A. E. Soto-Pina, K. E. Nava-Castro, Y. Becerril-Alarcon, R. Camacho-Beiza, D. E. Aguirre-Quezada, E. Cardoso-Pena, O. Amador-Munoz, J. J. Garduno-Garcia and J. Morales-Montor (2022). "Association of Serum Levels of Plasticizers Compounds, Phthalates and Bisphenols, in Patients and Survivors of Breast Cancer: A Real Connection?" Int J Environ Res Public Health **19**(13).
Segovia-Mendoza, M., M. I. Palacios-Arreola, L. Pavon, L. E. Becerril, K. E. Nava-Castro, O. Amador-Munoz and J. Morales-Montor (2022). "Environmental Pollution to Blame for Depressive Disorder?" Int J Environ Res Public Health **19**(3).
Silva, M. J., D. B. Barr, J. A. Reidy, K. Kato, N. A. Malek, C. C. Hodge, D. Hurtz, 3rd, A. M. Calafat, L. L. Needham and J. W. Brock (2003). "Glucuronidation patterns of common urinary and serum monoester phthalate metabolites." Arch Toxicol **77**(10): 561-567.
Singh, R. D., K. Koshta, R. Tiwari, H. Khan, V. Sharma and V. Srivastava (2021). "Developmental Exposure to Endocrine Disrupting Chemicals and Its Impact on Cardio-Metabolic-Renal Health." Front Toxicol **3**: 663372.
Sirasanagandla, S. R., M. Al-Mushaiqri, F. Al Ghafri, N. Al-Abri and I. Al-Huseini (2023). "Protective Effects of Perinatal Resveratrol on Bisphenol A Exposure-Induced Cardiovascular Alterations and Hepatic Steatosis in Adult Offspring Mice: A Histopathological Study." **13**(24): 13163.
Song, H., J. Park, P. T. C. Bui, K. Choi, M. C. Gye, Y. C. Hong, J. H. Kim and Y. J. Lee (2017). "Bisphenol A induces COX-2 through the mitogen-activated protein kinase pathway and is associated with levels of inflammation-related markers in elderly populations." Environ Res **158**: 490-498.
Sree, C. G., V. Buddolla, B. A. Lakshmi and Y. J. Kim (2023). "Phthalate toxicity mechanisms: An update." Comp Biochem Physiol C Toxicol Pharmacol **263**: 109498.

Stocker, R. and J. F. Keaney, Jr. (2004). "Role of oxidative modifications in atherosclerosis." Physiol Rev **84**(4): 1381-1478.
Trasande, L. and T. M. Attina (2015). "Association of exposure to di-2-ethylhexylphthalate replacements with increased blood pressure in children and adolescents." Hypertension **66**(2): 301-308.
Trim, A., S. E. Hankinson, S. Liu, A. H. Shadyab, J. Meliker, W. Bao, J. Luo, B. Liu, J. E. Manson, L. Tinker, C. Bigelow and K. W. Reeves (2021). "Biomarkers of phthalates and inflammation: Findings from a subgroup of Women's Health Initiative participants." Int J Hyg Environ Health **234**: 113743.
Valvi, D., M. Casas, D. Romaguera, N. Monfort, R. Ventura, D. Martinez, J. Sunyer and M. Vrijheid (2015). "Prenatal Phthalate Exposure and Childhood Growth and Blood Pressure: Evidence from the Spanish INMA-Sabadell Birth Cohort Study." Environ Health Perspect **123**(10): 1022-1029.
Wagner, A. H., M. R. Schroeter and M. Hecker (2001). "17beta-estradiol inhibition of NADPH oxidase expression in human endothelial cells." FASEB J **15**(12): 2121-2130.
Wang, Y. and H. Qian (2021). "Phthalates and Their Impacts on Human Health." Healthcare (Basel) **9**(5).
Wei, F., M. Mortimer, H. Cheng, N. Sang and L. H. Guo (2021). "Parabens as chemicals of emerging concern in the environment and humans: A review." Sci Total Environ **778**: 146150.
Wei, X., X. Yi, X. H. Zhu and D. S. Jiang (2020). "Histone methylation and vascular biology." Clin Epigenetics **12**(1): 30.
Wei, Z., L. Song, J. Wei, T. Chen, J. Chen, Y. Lin, W. Xia, B. Xu, X. Li, X. Chen, Y. Li and S. Xu (2012). "Maternal exposure to di-(2-ethylhexyl)phthalate alters kidney development through the renin-angiotensin system in offspring." Toxicol Lett **212**(2): 212-221.
Wen, Y., Y. Kong, G. Cao, Y. Xu, C. Zhang, J. Zhang, P. Xiao and Y. Wang (2022). "Di-n-butyl phthalate regulates vascular smooth muscle cells phenotypic switching by MiR-139-5p-MYOCD pathways." Toxicology **477**: 153279.
Werner, E. F., J. M. Braun, K. Yolton, J. C. Khoury and B. P. Lanphear (2015). "The association between maternal urinary phthalate concentrations and blood pressure in pregnancy: The HOME Study." Environ Health **14**: 75.
Xie, X., T. Deng, J. Duan, S. Ding, J. Yuan and M. Chen (2019). "Comparing the effects of diethylhexyl phthalate and dibutyl phthalate exposure on hypertension in mice." Ecotoxicol Environ Saf **174**: 75-82.
Xu, X., H. Wu, P. D. Terry, L. Zhao and J. Chen (2022). "Impact of Paraben Exposure on Adiposity-Related Measures: An Updated Literature Review of Population-Based Studies." Int J Environ Res Public Health **19**(23).
Yamaguchi, R., A. Sakamoto, R. Yamaguchi, M. Haraguchi, S. Narahara, H. Sugiuchi, T. Katoh and Y. Yamaguchi (2019). "Di-(2-Ethylhexyl) Phthalate Promotes Release of Tissue Factor-Bearing Microparticles From Macrophages via the TGFbeta1/Smad/PAI-1 Signaling Pathway." Am J Med Sci **357**(6): 492-506.
Yang, G., X. Gao, L. Jiang, X. Sun, X. Liu, M. Chen, X. Yao, Q. Sun and S. Wang (2017). "6-Gingerol prevents MEHP-induced DNA damage in human umbilical vein endothelia cells." Hum Exp Toxicol **36**(11): 1177-1185.
Yang, S. N., C. C. Hsieh, H. F. Kuo, M. S. Lee, M. Y. Huang, C. H. Kuo and C. H. Hung (2014). "The effects of environmental toxins on allergic inflammation." Allergy Asthma Immunol Res **6**(6): 478-484.
Yin, T., X. Zhu, I. Cheang, Y. Zhou, S. Liao, X. Lu, Y. Zhou, W. Yao, X. Li and H. Zhang (2023). "Urinary phenols and parabens metabolites associated with cardiovascular disease among adults in the United States." Environ Sci Pollut Res Int **30**(10): 25093-25102.

Zeng, G., Q. Zhang, X. Wang and K.-H. Wu (2022). "Low-level plasticizer exposure and all-cause and cardiovascular disease mortality in the general population." Environmental Health **21**(1): 32.
Zhang, C., Y. Luo, S. Qiu, X. Huang, K. Jin, J. Li, M. Yang, D. Hu, X. Zheng, Z. Jiang, M. Wang, X. Zou and Q. Wei (2022). "Associations between urinary concentrations of bisphenols and serum concentrations of sex hormones among US. Males." Environmental Health **21**(1): 135.
Zhang, H., Y. Park, J. Wu, X. Chen, S. Lee, J. Yang, K. C. Dellsperger and C. Zhang (2009). "Role of TNF-alpha in vascular dysfunction." Clin Sci (Lond) **116**(3): 219-230.
Zhang, L., W. Sun, X. Duan, Y. Duan and H. Sun (2019). "Promoting differentiation and lipid metabolism are the primary effects for DINP exposure on 3T3-L1 preadipocytes." Environ Pollut **255**(Pt 1): 113154.
Zhang, X., Y. Zhang, H. Lu, F. Yu, X. Shi, B. Ma, S. Zhou, L. Wang and Q. Lu (2023). "Environmental exposure to paraben and its association with blood pressure: A cross-sectional study in China." Chemosphere **339**: 139656.
Zhao, J. F., S. H. Hsiao, M. H. Hsu, K. C. Pao, Y. R. Kou, S. K. Shyue and T. S. Lee (2016). "Di-(2-ethylhexyl) phthalate accelerates atherosclerosis in apolipoprotein E-deficient mice." Arch Toxicol **90**(1): 181-190.
Zhou, W., M. H. Chen and W. Shi (2015). "Influence of phthalates on glucose homeostasis and atherosclerosis in hyperlipidemic mice." BMC Endocr Disord **15**: 13.

Graphical abstract



Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: