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Chapter

Endocrine Disrupting Chemicals in Cosmetics and Personal Care Products and Risk of Endometriosis

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Abstract

In the last years, the variety and consumption of cosmetics and personal care products (PCPs) have greatly increased, although the long-term adverse effects to low doses of chemicals used in their production and with proven hormone-mimicking properties have been still poorly addressed. Among these endocrine disrupting chemicals (EDCs), parabens, benzophenones, bisphenols, and phthalates are the most widely found in these products. Given the estrogenic-dependent nature of the endometrium, it has been hypothesized the potential contribution of these EDCs contained in cosmetics and PCPs in the risk of endometriosis. In this book chapter, we have summarized the current evidence supporting this hypothesis, highlighting epidemiological, *in vivo,* and *in vitro* studies that have addressed the potential influence of parabens, benzophenones, bisphenols, and phthalates in the origin and progression of this chronic feminine disease.

Keywords: cosmetics, personal care products, endometriosis, endocrine disruptors

1. Introduction

The term "cosmetic" has its origin from the Greek term "kosme'tikos," a noun to denote the art of beautifying the body [1]. Since ancient times, humans have searched for materials and developed many products to mainly enhance female beauty. Over the centuries, cosmetics have been developed and influenced by different ethnic traditions, from the times of the Pharaohs to the modern times [2]. Since then, physical appearance has been an inseparable part of daily human existence, improving their self-image and self-esteem. However, the esthetic concept of beauty has changed overtime, and beauty standards have been modified according to many factors such as social, ethnic, and religious belief influences [2]. Personal hygiene has been also part of human life since the ancient times. Traditionally related to hygiene habits during religious activities, the preparation of food, or the

Use	Products
Baby care products	Shampoo, lotion, oil, cream, talcum powder
Eyes	Eyebrow and eyeliner pencils, eye shadow, eye make-up remover, lash mascara
Skin care	Blush, powder, make-up base, make-up corrector, cream, lotions, face mask, face cleaner, skin toner, moisturizers
Lips	Lipstick, lip gloss, lip balm, lip liner
Hygiene	Soap, powder, oil, bath salts, shampoo, cleaning wipes
Deodorants and antiperspirants	Deodorants, antiperspirants
Hair	Hair dye, shampoo, coloured shampoo, hair spray, hair conditioner, hair lightener, permanent wave, hair straightener, hair lotion, hair wax
Nails	Base coat, nail polish, cuticle softener, nail polish remover, nail oil, nail glitter
Mouth	Toothpaste, mouthwash
Shaving	Shave balm, lotion, shaving cream/foam, soap
Tanning / UV protection	Oil, cream, sunscreen, suntan lotion
Hair removal	Depilatory wax/cream, oil
Skin lightening	Lightening cream
Feminine hygiene	Pads, panty liners, tampons, wipes, bactericidal creams and solutions

Table 1.
Most used cosmetics and personal care products.

prevention of diseases, hygiene practices have also greatly changed through the cultures and eras, from bathing facilities in the Roman period to modern synthetic products such as body lotions or hair tonics [3].

In the last years, the variety of cosmetics and personal care products (PCPs) have greatly increased (**Table 1**), in parallel to their manufacturing and consumption volumes in developed and developing countries. For example, the consumption of cosmetics and perfumery in Spain has consecutively increased in the last years, reaching a total of 1280 million units sold of these products and 770 million units exported during 2018. To date, the USA is the leader in the consumption of cosmetics and perfumery, with an amount of 78.6 billion euros, followed by China (52 billion euros), Japan (32 billion euros), and Brazil (28 billion euros) [4]. Despite the current beauty standards are not similar along cultures and ethnicities, it is acknowledged that women have a greater use of cosmetics and personal care products (PCPs) when compared with men [5], and therefore, potential adverse effect may affect predominantly to this population.

Table 1 summarizes the main types of cosmetics and PCPs commonly used worldwide.

2. Endocrine disruptors in cosmetics and PCPs

2.1 What is an endocrine disruptor?

The World Health Organization defines an endocrine disrupting chemical (EDC) as an exogenous substance or mixture of substances that alter one or more functions of the endocrine system and consequently cause adverse effects on the health of an intact organism or its progeny [6].

The main characteristics of exposure to EDCs are as follows [7–10]:

- There is no safe dose of EDCs. They act at low concentrations and in combination with endogenous hormones, making it difficult to establish a threshold level of no effect.

- Exposure to EDCs during periods of special vulnerability of the individual's development—pregnancy, lactation, puberty—causes damage with adverse effects throughout their lives and descendants.

- The curves that relate the exposure doses to EDCs with the adverse effect are not linear. The response does not always increase in the same proportion as the exposure dose.

- In general terms, individuals are not exposed to a single type of EDC but to a mixture of EDCs. Therefore, the effects are difficult to predict given the possible synergistic, additive, or antagonistic actions between chemical residues (the cocktail effect).

- As a result of exposure to EDCs in a certain individual, consequences can be observed in subsequent generations, due to either genomic involvement or epigenetic mechanisms. There is great difficulty in establishing a causal association because the effects observed after exposure can occur after long latency periods.

2.2 Sources and routes of exposure to EDCs

EDCs are distributed in the environment due to their widespread use. Depending on their resistance to physical, chemical, and biological degradation as well as their degree of liposolubility, EDCs can be divided into "persistent EDCs" and "non-persistent EDCs." In the case of persistent EDCs, low biodegradability, volatility, bioaccumulation in the trophic chain, and biomagnification are its most outstanding characteristics [11]. Furthermore, they can be transmitted to the offspring through the mother during pregnancy and lactation [12]. Since the 1970s, most countries have banned or severely restricted the production, handling, and disposal of the majority of them due to consistent evidence of their adverse effects at doses traditionally considered safe [13, 14]. Despite this, global population is suspected to be primarily exposed to these pollutants through diet, given the bioaccumulation pattern of these chemicals in the food chain [14].

On the other hand, non-persistent EDCs are less liposoluble, and therefore, they are prone to be metabolized and excreted rapidly [15, 16]. In addition to a variety of pesticides such as glyphosate or permethrins, this group includes bisphenol-A (BPA) and its analogues, parabens (PBs) [methyl- (MeP), ethyl- (EtP), propyl- (PrP), and butyl-paraben (BuP)], phthalates, and benzophenones (BPs). Currently, there is diverse evidence showing the presence of numerous EDC families (mainly phthalates, bisphenols, parabens, and benzophenones) in cosmetic products and PCPs [17–20]. However, contrary to most persistent EDCs, international regulation of their production, handling, and disposal is limited to a reduction in the concentrations of some specific compounds for those cosmetics in the EU market (EU 1004/2014). **Table 2** summarized the trade name, CAS number, and hormonal activity attributed to some of the most frequently used EDCs in cosmetics and PCPs.

Phthalates are used as a plasticizer in cosmetics and PCPs. The study carried out by Gao and Kannan [17] recently revealed that phthalates were found in >90% of the 77 feminine hygiene products analyzed. Mainly, they were found in all the tested pads, panty liners, tampons, and wipes. Furthermore, phthalates were also found in bactericidal creams and solutions, deodorant sprays, and powders. In another study, Guo and Kannan [18] showed that phthalates were also present in leave-on products, such as skin lotions, hair care products, perfumes, skin toners, deodorants, and creams. In this regard, detectable levels of phthalates were found in face creams, eyeliner creams, hand creams, sunscreens, lipsticks, and nail polish. These EDCs were also detected in products for dental hygiene and rinse-off

Compound	Acronym	CAS	Hormonal activities		
			Estrogenic	Anti-androgenic	Thyroid disruption
Bis(2-ethylhexyl) phthalate	DEHP	117-81-7		X	X
Diisononyl phthalate	DiNP	28553-12-0		X	
Dibutyl phthalate	DBP	84-74-2		X	
Diisobutyl phthalate	DiBP	84-69-5		X	
Benzyl butyl phthalate	BBP	85-68-7		X	
Dipentyl phthalate	DPP	131-18-0		X	
Di-n-hexyl Phthalate	DnHP	84-75-3		X	X
Di-n-octyl phthalate	DnOP	117-84-0		X	X
Bisphenol-A	BPA	80-05-7	X		
Methyl-paraben	MeP	99-76-3	X		
Ethyl-paraben	EtP	120-47-8	X		
Propyl-paraben	PrP	94-13-3	X		
Butyl-paraben	BuP	94-26-8	X		
Benzophenone-1	BP-1	131-56-6	X		
Benzophenone-3	BP-3	131-57-7	X		
Octamethylcyclotetrasiloxane	D4	556-67-2	X		
Ethylhexyl 4-methoxycinnamate	EHMC	5466-77-3	X		X
Bencilidene camphor	3-BC	15087-24-8			

Trade name, CAS number and demonstrated hormonal activities.

Table 2.
Most common endocrine disrupting chemicals in cosmetics and personal care products.

products (including body wash, shampoos, hair conditioners, face cleaners, and shaving gels).

In the case of the PB family, its main use in cosmetic products and PCPs is due to their antimicrobial properties [21]. It has been shown that the use of mixtures of paraben congeners allows the increase of their preservative capacity with the use of lower levels of each compounds [19]. Average daily application rates per women for face creams, hand or body lotions, facial cleansers, shampoos, and bath gel were 2.1, 8.7, 4.1, 12.8, and 14.5 g, respectively [22]. Yazar and Johnsson [20] carried out a study where they verified the composition of a series of 204 cosmetic products, which included shampoos, hair conditioners, liquid soap, wipes from different brands, and stores. The results showed that at least 44% of the analyzed cosmetics contained at least one PB congener. The PB that was found in the highest proportion was MeP (41% of the products), followed by PrP (25%). In the study carried out by Gao and Kannan [17], it was found that all feminine hygiene products contained at least one PB, and both MeP and EtP were found in >80% of these compounds, mainly in wipes, creams, bactericide solutions, deodorant sprays, and powders. Moreover, it has been reported that PBs were detected in 40% of the dental hygiene products analyzed and 60% in other types of daily hygiene products. MeP and PrP were the most detected compounds (40% of the analyzed samples), followed by BuP (~20%). The highest concentrations of MeP, EtP, PrP, and BuP ranged between 1040 and 8200 μg/g, which represent approximately 0.1–0.8% per product by weight [18]. Another study carried out in China [19] found PBs in all the categories of PCPs analyzed. Almost all creams, lotions, and face cleaners contained MeP and PrP, with concentrations of MeP slightly higher than PrP (2830 and 1560 μg/g, respectively). Their presence was greater in creams and lotions than in shampoos and body soaps.

BPs are used as ultraviolet (UV) filters. As shown in the study carried out by Rastogi [23], 75 sunscreen products from Europe and the USA tested contained levels of up to three UV filters. A recent study [24] verified the presence of BP-1 and BP-3 in 19.1% of their analyzed products (283 samples analyzed), especially in makeup products, which represented 45.2% of the products with the presence of BPs.

In addition to these three families, the chemical composition of cosmetics and PCPs also contains many other compounds, although with a lower percentage of the presence in these products. Among them, bisphenols, camphenes, dimethicones, and oxycinnamates can be found. Within these minority families, bisphenols are the one that are usually found in the greatest presence in cosmetic products. The main use of BPA is the manufacture of epoxy resins, obtaining polycarbonate plastics, which have great mechanical and thermal stability, as well as very good transparency [25], while the main use of the families of camphenes, dimethicones, and oxycinnamates is that they are used as preservatives in the manufacture of PCPs [26, 27]. Nevertheless, the concentrations of these substances in cosmetics and PCPs have been poorly addressed.

Contrary to persistent EDCs that mainly reach body internal compartments through diet, the main route of human exposure to non-persistent EDCs released from cosmetics and PCPs is mainly the dermal route [28]. Therefore, these EDCs avoid the first-pass metabolism, enhancing the bioavailability and therefore the biological effect of the parent compounds [15]. In this regard, several studies have related to the use of cosmetics and PCPs and internal levels of PB and BPs. For example, it has been recently found that levels of some PB and BPs in menstrual blood are related to the use of cosmetics [29]. Moreover, urinary concentrations of PBs were related to the use of hair products, deodorants, face, and hand creams [30]. Similarly, Larsson et al. [31] found higher levels of PBs and phthalates among those women with higher use of hygiene products.

2.3 Mechanisms of action of EDCs

EDCs act at very different levels of complexity, interfering a variety of hormone-signaling pathways. For instance, they can modify the circulating levels of hormones by acting on their synthesis, metabolism, or degradation. They can also reduce, increase, or interfere with the specific receptors for hormonal action and therefore affect the ability to respond to natural hormones [32]. In the particular case of EDCs that interfere in steroid hormone-related signaling pathways, the observed effects seem to be linked to the activation/blocking of nuclear receptors, which are the most common modes of action responsible for dose curves with non-monotonic response in experimental studies [33]. In fact, many EDCs released from cosmetics and PCPs have been evidenced to exert estrogenic and antiandrogenic activities in both *in vivo* and *in vitro* studies [34–40] (see **Table 2**).

An increasing number of studies have also linked exposure to EDCs with epigenetic changes in humans [41, 42]. An unexposed individual may show epigenetic changes due to (1) altered ovum or sperm after EDC exposure or (2) in utero exposure to EDCs. In this regard, it has been evidenced that fetal exposure to environmental pollutants with endocrine disrupting properties such as mirex, chlordane, or *p,p´*-DDE can cause epigenetic changes with transgenerational effects [43, 44]. This is also the case of bisphenol-A (BPA), and PBs, with epigenetic changes after prenatal and adolescence exposures to these chemicals [45, 46].

Furthermore, inflammation and oxidative stress have also been recently postulated as possible mechanisms of action of EDCs [47–50]. In this regard, oxidative stress, that is, the imbalance between the production of free radicals and the antioxidant capacity, has been shown to be enhanced after exposure to a variety of EDCs, including PBs and BPs [47, 49, 50]. For instance, human exposure to PB and BP has been linked to higher levels of lipid peroxidation [50, 51]. Moreover, local disruption of the antioxidant capacity has also been reported [47]. Although the underlying mechanisms are still poorly understood, it has been suggested that,

at least in part, EDCs might induce oxidative stress via estrogen receptor-α signaling pathways [52]. Moreover, EDC exposure has also been evidenced to trigger an inflammatory microenvironment [50, 53]. With an intimate relationship, both oxidative and inflammatory responses have also been suggested as crucial mechanisms beyond a variety of chronic diseases, as well as some gynecological conditions such as endometriosis [54, 55].

3. Potential adverse effects of EDC exposure

The consequences of exposure to EDCs seem to be different depending on age and gender (**Table 3**). In the case of men, EDC exposure is suspected to cause alterations in the development of the genitourinary system including cryptorchidism, testicular cancer, and infertility [56, 57]. Among women, the increase in hormone-dependent cancers (either breast or ovarian) [56] as well as uterine fibroids and endometriosis might also be related to inadvertent exposure to EDCs. Moreover, chronic conditions such as metabolic syndrome and its components (obesity, insulin resistance, hypertension, or dyslipidemia), neurobehavioral development disorders, and poor thyroid function are also on the list of possible effects of EDC exposure. In particular, in utero exposure to EDCs is believed to have consequences of such magnitude that they would hardly be suspected in studies of adult individuals. For example, in utero exposure to some EDCs has been linked to increased risk for breast cancer or endometriosis [58, 59]. This association gives maternal exposure some very particular peculiarities and places women of childbearing age in the limelight of most studies on endocrine disruption.

3.1 Use of cosmetics and PCPs and feminine diseases

Over the years and in parallel with the change in people's habits and lifestyle, numerous evidence has revealed that cosmetics could cause a variety of disease conditions in humans. For instance, women are suspected to have a greater risk for some chronic conditions such as obesity and metabolic syndrome than men [60], and in addition to physiological differences between genders, the greater female consumption of cosmetics and PCPs might also underlie this enhanced risk. Moreover, the consumption of cosmetics and PCPs might also be beyond the development of female-specific diseases such as breast or ovarian cancer. In this regard, Darbre [61]

Women	Girls	Boys	Men	Women / Men
Endometriosis	Precocious puberty	Cryptorchidism and hypospadias	Testicular cancer	Obesity
Breast / vaginal / ovarian / endometrial cancer	Early breast and pubic hair development	Reduction in semen quality	Prostate cancer	Diabetes
Uterine fibroids	Congenital malformations	Reduction in testosterone levels	Reduction in semen quality	Elevated blood pressure
Gestational diabetes and pregnancy-related outcomes	Low birth weight	Low birth weight	Reduction in testosterone levels	Dyslipidemia
Impaired ovarian function	Cognitive impairments	Cognitive impairments		
Polycystic ovary syndrome				
Reduced fertility				

Table 3.
Some adverse effects of EDCs in humans.

first alarmed scientific community about the potential effect of PCPs in breast cancer, suggesting that underarm cosmetic use might increase breast cancer. In fact, they detected a variety of EDCs including PBs in breast tumors, with higher concentrations in those samples from the axilla region, suggesting that their concentrations might be related to the application of deodorant products, body lotions, sprays, moisturizers, and sunscreen products in areas close to the human breast. However, current evidence on the relationship between cosmetic/PCP use and risk of cancer is not very conclusive. In this regard, in a case-control study comprised by 209 cases of breast cancer and 209 healthy controls, Linhart and Talasz [62] reported that the greater use of underarm cosmetic products was associated with increased risk of breast cancer. Contrary, a cohort study did not found any association between use of skincare products and risk of cancer of the breast and endometrium [63]. Another study carried out by McGrath [64] reported that those women with a higher use of antiperspirant products were diagnosed with breast cancer at an earlier age. Furthermore, it has been observed that long-term exposure to body care creams containing ethinyl estradiol may increase the risk of abnormal genital bleeding and breast cancer [65]. Interestingly, a case-report study found that synthetic hormones found in lotions used by the mother were present in very high concentrations in the hair of the girl [66].

However, the variety of products and differences in dosage, patterns of use, and individual susceptibility to specific product formulations pose great difficulties to detect a potential effect of cosmetic and PCP habits on human adverse effects [36, 61, 67–69]. Thus, the use of internal burden of EDCs seems to better reflect the magnitude of cosmetic and PCP use, independently of the type of product used or the dose applied. In this regard, urinary levels of PBs have been related to greater risk for breast cancer [70]. Some studies have also addressed the potential association between exposure to PCP-released EDCs and the origin and development of other female diseases. In this regard, the presence of trace levels of PBs was found in endometrial tissue samples suspected of being related to an increased risk of endometrial carcinoma [71]. Levels of PrP were also related to diminished ovarian reserve in a prospective cohort study of the US women seeking fertility treatment [72]. Regarding the development of sex characteristics during puberty, a recent study observed associations between levels of PBs and earlier development of the breasts and the pubic hair in girls. Moreover, earlier menarche was also related to higher levels of PBs [73].

Regarding BPs, *in vitro* studies have shown that exposure to BPs in rats and mice has been related to feminized sexual behavior and increased uterine weight [39, 74]. Two *in vivo* studies have also demonstrated the disturbance caused by BP in ovarian tissue [75, 76]. Santamaría and Abud [75] found that exposure to BP-1 and BP-3 disrupted early events in ovarian cells, such as germ cell development and disruption of crucial gene expression related to follicular assembly. Similarly, Shin and Go [76] reported the induction of BP-dependent metastasis in an *in vivo* model for ovarian cancer. Moreover, an epidemiological study has reported that urinary BP levels might be associated with blood pressure during pregnancy [77]. Similarly, higher BP levels were related to thyroid hormones and growth factors in pregnant women, as well as to reduced fetal growth [74].

Other hormonally active chemicals widely used in cosmetics are phthalates. Exposure to various congeners has been associated with the appearance of various female diseases. Exposure to di-(2-ethylhexyl) phthalate has been linked to an increased risk of preterm delivery [78–80] and intrauterine growth restriction [81]. Furthermore, it has also been associated with reduced total oocyte yield and a reduced probability of achieving pregnancy and live birth [82]. Other phthalate congeners, such as monoethyl phthalate and dibutyl phthalate, have also been linked to decreased fertility in women [79, 83].

Several investigations have also suggested the potential association between BPA exposure and adverse outcomes in women. For instance, it has been shown that elevated serum or urine BPA levels are associated with anovulation [84], lower antral follicle counts [85, 86], preterm birth [87], and infertility [88]. Moreover, increasing urinary BPA levels were associated with delayed menarche in adolescent girls [89, 90]. Furthermore, higher BPA levels have been associated with an increased risk of developing polycystic ovary syndrome [84, 91–93], ovarian failure [94], infertility [95], and fibroids [96, 97]. Triclosan, widely present in soaps, detergents, and toothpaste, has also been related to decreased fertility [98], although the currently available evidence is scarce.

3.2 Associations between PCP- and cosmetic-released EDCs and endometriosis

As mentioned above, detectable levels of PBs and BPs have been detected in endometrial tissue and menstrual blood [29, 71]. Trace levels of intact PBs were predominantly detected in endometrial carcinoma tissues (23%) in contrast to normal endometrium samples (2%), and thus, authors suggested that they might be related to an increased risk of endometrial carcinoma [71]. On the other hand, several PBs and BPs have been detected in menstrual blood samples, a biological sample in intimate contact with the endometrium [29]. Moreover, these menstrual blood concentrations of PBs and BPs were related to the magnitude of use of creams and cosmetics, evidencing that these EDCs from cosmetics and PCPs are capable of reaching a wide variety of biological matrices and thus might orchestrate, or at least contribute, to the development and progression of multiple gynecological diseases such as endometrial cancer and endometriosis.

Concerning endometriosis, the origin of endometriosis still remains unclear. To date, although various theories have been postulated to give a possible explanation for the origin of endometriosis [99–105], none of them consistently explains the onset and progression of the disease in deeper stages. Currently, it is known that it is a multifactorial disease in which genetic, epigenetic, immunological, hormonal, and environmental factors are involved [106]. Due to the suspected increase in the number of cases in the last decades [107], it is suspected that, in addition to the increased awareness among doctors and patients, environmental risk factors are suspected to also contribute to the onset and progression of this disease. This environmental hypothesis of the origin of the disease is also reinforced due to the estrogen-dependent nature of this pathology [53, 108].

Despite the growing public concern about human risks derived from the use of PCPs and cosmetics, there is little evidence on their influence on endometriosis (**Table 4**). To our knowledge, only one study has investigated the relationship between EDCs released from sunscreens and endometriosis. Concentrations of 2-hydroxy-4-methoxybenzophenone, 2,4-dihydroxybenzophenone, 2,2′-dihydroxy-4-methoxybenzophenone, 2,2′,4,4′-tetrahydroxybenzophenone, and 4-hydroxi-benzophenone were analyzed in urine samples collected from 600 women. The results obtained suggest that exposure to elevated levels of 2,4-dihydroxybenzophenone (BP-3) may be associated with a higher probability of a diagnosis of endometriosis [109]. As authors mentioned, these findings denoted an approximate 65% increase in the odds of an endometriosis diagnosis in women with the highest BP-3 concentration compared to women with lower concentrations.

Regarding BPA exposure, a recent meta-analysis revealed limited and contradictory epidemiological evidence regarding the contribution of BPA in the risk for endometriosis [110]. Thus, despite few studies have reported an absence of association between urinary levels of BPA and disease [111, 112], others reported increased risk for endometriosis [53, 113–115]. Even more, it has been recently suggested that

Ref.	EDCs	Study design	Matrix for exposure assessment	Population	Reported associations
109	Benzophenone (BP-1, BP-2, BP-3, BP-8, 4-OH-BP)	Epidemiological (cohort) ENDO study	Urine	N=600 Operative cohort: 473 Population cohort: 127	↑ urinary BP-3 levels → ↑ endometriosis risk
53	Bisphenol (BPA, BPS, BPF)	Epidemiological (case-control) EndEA study	Urine	N=124: 35 cases and 89 controls	↑ urinary BPA levels → ↑ endometriosis risk
111	Bisphenol (BPA)	Epidemiological (cohort) ENDO study	Urine	N=600 Operative cohort: 473 Population cohort: 127	No association
112	Bisphenol (BPA)	Epidemiological (cross-sectional)	Urine	N=140 women suspected of infertility	No association
114	Bisphenol (BPA)	Epidemiological (case-control)	Urine	N=430: 143 cases and 287 controls	↑ urinary BPA levels → ↑ non-ovarian pelvic endometriosis
115	Bisphenol (BPA)	Epidemiological (case-control)	Urine	N=100: 50 cases and 50 controls	↑ urinary BPA levels → ↑ endometriosis risk
113	Bisphenol (BPA)	Epidemiological (case-control)	Urinary and peritoneal fluid	N=128: 68 cases and 60 controls	↑ urinary BPA levels → ↑ endometriosis risk
116	Bisphenol (BPA)	*In vivo* study	-	136 mice	↑ urinary BPA levels → ↑ endometriosis risk
117	Bisphenol (BPA)	*In vivo* study	-	20 mice	↑ urinary BPA levels → ↑ endometriosis risk
108	Bisphenol (BPA, BPAF)	*In vivo* study	-	185 mice	↑ urinary BPA levels → ↑ atretic oocyte number
118	Phthalates (dBP, bBP, DEHP, dnOP)	Epidemiological (case-control)	Plasma	N=220: 85 cases and 135 controls	↑ urinary phthalate levels → ↑ endometriosis risk
111	Phthalates (mECPP, mCMHP, mEOHP, mEHHP, mEHP, mCPP, mMP, mEP, miBP, mBP, mCHP, mBzP, mNP, mOP)	Epidemiological (cohort) ENDO study	Urine	N=600 Operative cohort: 473 Population cohort: 127	↑ urinary phthalate levels → ↑ endometriosis risk
119	Phthalates (mEHHP, mEOHP, mBP, mBzP, mECPP)	Epidemiological (case-control)	Urine	N=88: 55 cases and 33 controls	↑ urinary phthalate levels → ↑ endometriosis risk
120	Phthalates (mEHP, mBP, mEP, mBzP)	Epidemiological (cross-sectional)	Urine	N=1227: 87 cases of endometriosis, 151 women with uterine fibroids and 1020 healthy women	No association
121	Phthalates (mEHP, mEHHP, mEOHP, mECPP, mBzP, mEP, miBP, mBP)	Epidemiological (case-control)	Urine	N= 287: 92 cases and 195 controls	No association
122	Phthalates (mMP, miBP, mBP, mCHP, mNP, mOP, mBzP, mEHP)	Epidemiological (case-control)	Urine	N= 52: 30 cases and 22 controls	No association

Benophenone-1 (BP-1), benzophenone-2 (BP-2), benzophenone-3 (BP-3), benzophenone-8 (BP-8), 4-hydroxybenzophenone (4-OH-BP), bisphenol A (BPA, bisphenol S (BPS), bisphenol F (BPF), bisphenol AF (BPAF), mono (2-ethyl-5-carboxyphentyl) phthalate (mECPP), mono-[(2-carboxymethyl) hexyl] phthalate (mCMHP), mono (2-ethyl-5-oxohexyl) phthalate (mEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), mono (2-ethylhexyl) phthalate (mEHP), mono (3-carboxypropyl) phthalate (mCPP), monomethyl phthalate (mMP), monoethyl phthalate (mEP), mono (2-isobutyl phthalate) (miBP), mono-n-butyl phthalate (mBP), mono-iso-butyl phthalate (miBP), monocyclohexyl phthalate (mCHP), monobenzyl phthalate (mBzP), monoisonoyl phthalate (mNP), and monooctyl phthalate (mOP), dibutyl phthalate (dBP), butyl benzyl phthalate (bBP), di-n-octyl phthalate (dnOP)

Table 4.
Studies exploring associations between exposure to cosmetics- and PCPs-released EDCs and endometriosis.

levels of oxidative stress might act as a mediation effect on the association between exposure to bisphenols and endometriosis risk [53]. Furthermore, exposure to BPA has not only been related to the onset of endometriosis, but it might be also involved in the progression of the disease [112, 114]. Moreover, these findings are supported by different experimental studies. In this sense, recent *in vivo* studies have evidenced in mouse models that exposure to bisphenols in adulthood was related to an increase in the growth of endometrial lesions and the number of atretic oocytes, the interruption of the ovarian steroidogenic pathway, an increase in periglandular fibrosis, and the upregulation of matrix remodeling enzymes [108, 116]. Another *in vivo* study revealed that prenatal exposure to BPA and other bisphenols caused a phenotype similar to endometriosis [117]. These experimental studies suggest that exposure to BPA could be related to the development and progression of endometriosis.

Other EDCs found in cosmetics and PCPs are phthalates. Several studies have explored the existing associations between exposure to these chemicals and endometriosis, showing conflicting results. One of the very first investigations reported higher concentrations of phthalates in women with a confirmed diagnosis of endometriosis [118]. Similarly, two studies evidenced an increased risk of endometriosis in women with higher levels of mono (2-ethylhexyl) phthalate [111, 119]. Conversely, few studies did not found any association between levels of urinary levels of any phthalate congener and enhanced risk for endometriosis [112, 120–122].

Currently, there are no studies that have explored the possible contribution of other EDCs released from cosmetics and PCPs (such as parabens, oxycinnamates, camphenes, and dimethicones) and the risk of endometriosis. Moreover, the combined effect of EDCs released from these products on endometriosis has not been addressed yet.

4. Conclusions

To date, there is still very limited evidence on the potential role of EDCs released from cosmetics and PCPs on the origin and development of endometriosis. In general terms, *in vitro*, *in vivo,* and epidemiological evidence is consistent with the endocrine-disrupting hypothesis set out in this chapter, indicating that EDCs might be in the causal pathway that leads to endometriosis. Nevertheless, in all published studies, the particular effect of specific EDCs was measured, without taking into account the possible synergistic or antagonistic effect that these chemicals can exert when they are present in a mixture. Thus, because its diagnosis is difficult and its treatment is mainly symptomatic, it is vitally necessary to establish preventive measures to avoid as far as possible the origin of this disease. Therefore, it is necessary to carry out well-conducted studies, with appropriate sample size and in which the "gold-standard" diagnosis serves to distinguish between cases and controls. Moreover, the combined effect of multiple EDCs on endometriosis should be addressed. These studies are needed to fully elucidate the potential disrupting properties of these PCP-released EDCs in the gynecological tissues. In this way, preventive measures could be established, the chemical composition of PCPs could be modified by other substances that are not endocrine disruptors, or the use of these cosmetics could be reduced as far as possible.

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Conflict of interest

The authors declare no conflict of interest.

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