Endocrine disruptors in cosmetics: a review

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ABSTRACT

The body is regulated by the endocrine system; thus it is important that it is functional. However, we encounter more and more endocrine disruptors in our lives. As cosmetics represent daily exposure to many chemicals, concerns raise about the eventual presence of endocrine disruptors in cosmetics. Endocrine disrupting abilities of chemicals were widely investigated, as they can be found in food, materials, and environment. Considering the amount of data, one might find clear information with difficulty. The purpose of this review is to establish the state-of-the-art of endocrine disrupting properties of cosmetic ingredients. The method used was to read several articles related to skin penetration, nuclear receptor binding, epigenetic effects, adverse effects, and diseases. The toxic doses were not always found. The overall data was confronted to draw definite conclusion on the endocrine disruptor nature of each compound. If not enough information was found to bring out a sturdy conclusion, leads for further research were given. An overview of novel methods used to assess endocrine disruptors' effects was also done. The major studied compounds were not clearly identified as endocrine disruptors when applied topically because of the skin barrier. Synergism and inhibition effects between several endocrine disruptors must be a subject of further investigation because it represents the reality of cosmetic formulations. Epidemiological studies should also be conducted to better assess risks of the ingredients. Overall, cosmetic ingredients applied *via* cosmetics do not have endocrine disrupting effects.

Keywords: endocrine disruptors; cosmetics; parabens; phthalates; perfluorinated chemicals; aluminum salts; triclosan; organic UV filters; nanoparticles; fragrances; cyclic voltaic methylsiloxanes; nonylphenol; synthetic phenolic antioxidants; essential oils; phenoxyethanol; bisphenol A.

1. INTRODUCTION

The cosmetic market is constantly expanding with the continuous development of new products and the every-day use of make-up, skin care and hair care products worldwide. Cosmetics are composed of many ingredients that sometimes raise concern about their safety. Some of these ingredients are suspected to be endocrine disruptors (EDs).

According to the European Commission, an endocrine disruptor is "an exogenous substance that causes adverse health effects in an intact organism, or its progeny, consequent to changes in endocrine functions" [1]. The European commission then specified in 2017 that such a substance must show the adverse effects mentioned before, have an endocrine mode of action and the adverse effects must be a consequence of the endocrine mode of action [2]. Thus we will take a closer look at the actions of EDs on the human endocrine system.

The endocrine system is composed of glands that secrete hormones [3]. In simplified terms, hormones are messenger which carry signals to target organs [4]. A single hormone can have different effects on diverse tissues while different hormones can have diverse effects on the same tissue [3]. So that the hormone recognizes the target tissue and so that the tissue activates the right hormone, cells of target tissues have specific receptors of each hormone involved in the function of this tissue. Two types of receptors are able to bind hormones: i) nuclear receptors, which are protein in the cell's nucleus, structurally fitting suitable hormones like a docking-site [3] and ii) membrane receptors, to

which hormones bind to release another messenger [5]. The activation of receptors by hormones aims at regulating gene expression and its subsequent responses [6], [7]. Endocrine disruptors have the particularity to show similar properties to hormones, without being hormones. Thus, the human immune system is not able to prevent EDs from acting in the body [6].

We know that EDs can bind to several receptors even if our knowledge of some mechanisms is limited [6]. However, most of the harmful effects of EDs are known to be the consequence of their binding to diverse nuclear receptors (NRs) [8]. The nuclear receptors targeted by EDs are estrogen receptors (ERs), androgen receptor (ARs), thyroid receptors (TRs), estrogen-related receptors (ERRs), peroxisome proliferator-activated receptors gamma (PPARγ) and pregnane X receptors (PXRs) [6]–[13]. All nuclear receptors are composed of three major domains including one DNA-binding domain (DBD) and one ligand-binding domain (LBD) made of 12 α-helices [7], [8], [13]. Inside the LBD is a hydrophobic cavity named ligand-binding pocket (LBP) and composed of the helices H3, H7, H10 and H12. The binding of the LBP and the ligand can adopt different conformations enabled by the position of H12 and depending on the structure of the small molecule. Two predominant conformations can be adopted with EDs [7], [13]. Binding with an agonist adopts an active conformation allowing the receptor to interact with coactivators. On the contrary, binding with an antagonist leads to the adoption of an inactive conformation precluding any interactions with coactivators [7]. Binding with small molecules is the result of hydrogen bounds and Van Der Waals interactions and depends on the molecule and the NR. Because of chemical discrepancies between EDs and natural hormones, only few EDs can mimic the actions of their natural homologues and many act as antagonists, unable to cause the active conformation [7][13].

The differences between the NRs remain on their internal structure, made of helices and residues.

Estrogen receptors, ERα and ERβ, are the NRs of the sex-hormone estradiol (E2) which allows the growth and upkeep of tissues such as the uterus and mammary glands [9].

Androgen receptors are responsible for the development and maintenance of male reproductive system and influence the female reproductive system. They are the docking-sites of testosterone [9].

Estrogen-related receptor γ is an orphan receptor that is expressed in different tissues depending on the stage of development of the human being. It is mostly expressed in muscles, adipose tissues and central nervous system, and plays a role in regulating energy metabolism. ERRγ has the particularity to adopt the active conformation without binding any ligand [8].

The primary role of peroxisome proliferator-activated receptor γ is to regulate energy homeostasis, adipogenesis and lipid metabolism. PPARγ has a large LBP with allows many different ligands to bind in and the simultaneous binding of two or three molecules of phthalates and perfluorinated compounds [7].

Thyroid receptors and its hormones are essential to normal growth and development of humans. Thus, they are expressed is several tissues [9].

Finally, pregnane X receptors act as the protector of the endocrine system. PXRs detect increasing concentrations of EDs and trigger detoxifying pathways [9].

A consequence of binding NRs is the alteration of epigenetic marks [14]. Epigenetic marks accumulate during oogenesis in females and spermatogenesis in males, both on histones and on DNA, *via* histone modifications and DNA methylation respectively [15]. These mechanisms lead to gene expression and have the decisive role to store information in the genome during the critical window of development, which happens from preconception to early childhood [6], [14]–[16]. EDs, by crossing placenta [15], [16] and being into breast milk [12] during early-life, interfere with these mechanisms,

reprograming DNA, dysregulating gene expression and promoting diseases later in life [16]. Thus, it has been proven that EDs are the most harmful on pregnant women, fetus and newborns [5], [6], [11], [12], [17]. Additionally, data shows that early exposure to EDs can have effects on subsequent generations, with absence of direct contact with these compounds [17], [18]. This also due to the altered DNA-methylation and research is close to understand the mechanism by which the effects are transmitted to the third generation [19].

However, the conditions at which ingredient have endocrine disrupting effects are hard to determine because these compounds do not follow the well-known principles of toxicology. Firstly, the dose makes the poison, but not linearly. Indeed, the dose-response curves are non-monotonic U-shaped and inverted U-shaped curves, which means that very low doses can have strong effects, and that toxic effects doses are heavily determinable [5], [6], [20]. Secondly, the toxicity depends on the age of the victim. Adults need higher doses than children in the critical period of development to feel toxicity [6], [20]. Finally, combinations of EDs can promote synergism or inhibition of the particular effects of each EDs and the mechanisms of action of the mixtures are not predictable [5], [11].

To evaluate the toxicity of EDs in cosmetics, it is essential to consider their dermal route of exposure. An ED will only be toxic if it is diffused into the vascular system because it needs to reach NRs in tissues [21]. This means that it previously has to be absorbed over the three layers of the skin [11][22]. The epidermis is the outermost layer, covered by the stratum corneum (SC). Under is the dermis, and then the hypodermis. Metabolism can occur after SC penetration. Skin is both hydrophilic and lipophilic, precluding highly hydrophilic or highly lipophilic compounds to be absorbed [12], [23]–[25]. Moreover, skin penetration of one compound depends on the solvent of the formulation [12], [23], [24], [26], the presence of inhibitors or enhancers [12], [22], [23], [27], and the condition of the skin [11], [12], [22], [24], [25]. Thus, studying the dermal absorption, metabolism, and diffusion in the skin of EDs applied as ingredients of cosmetic formulations is inevitable to prove their toxicity.

This being said, we will now focus on distinguishing between the true and the false about endocrine disrupting activity of suspected cosmetic ingredients.

2. COSMETIC INGREDIENTS SUSPECTED TO BE ENDOCRINE DISRUPTORS

Several components of cosmetic products, synthetic and natural, are suspected to have endocrine disrupting activities. For each of them, we will consider its dermal permeation and metabolism, nuclear receptors it targets, and phenotypical effects observed, along with the respective doses.

Parabens

Parabens are p-hydroxybenzoic acid esters [11], [17] used as preservatives in many cosmetics such as body creams, sunscreens and antiperspirants. Their advantage is their high chemical stability, resistance to hydrolysis and low cost production [11], [12]. The most common parabens used in cosmetics are methylparaben (MP ; N°CAS: 99-76-3), ethylparaben (EP ; N°CAS: 120-47-8), propylparaben (PP ; N°CAS: 94-13-3) and butylparaben (BP ; N°CAS: 94-26-8) [11], [12], [28]. In Europe they are allowed at a maximum concentration of 0,4% used as a single acid and at maximum 0,8% in a mixture of parabens [1]. MP and PP have the GRAS (Generally Recognized As Safe) status is the USA when use up to 0,1% [29], [30]. They are not regulated in Canada [31]. In the latest version of the Handbook of Pharmaceutical Excipients, parabens are classified as non-teratogenic, non-mutagenic and non-carcinogenic [30].

The major source of human exposure to parabens is dermal application of cosmetics [32]. The penetration dose of parabens is contradicted. As highlighted by Darbre et al. [22] and Petric et al. [30], some studies demonstrated effective dermal absorption of parabens, and others low absorption rate of these compounds. More toxicokinetic and pharmacokinetic studies are needed to give a definite value. However, a mechanism of detoxification of parabens occurs in the skin, which consists in the hydrolysis of the ester bond [32], [33]. In spite of this, hydrolysis does not favor short-chained parabens [33]. Thus MP, EP, PP and BP are found in the body in their intact form [12], [22]. Petric et al. [30] reported in his review that some studies suggested an accumulation of parabens in the body because of this phenomenon, while others showed its unlikelihood due to the low dermal absorption of parabens. Thus the ability of parabens to cross the skin barrier is still indeterminate, all the more so as other cosmetic ingredients can enhance its absorption, such as nicotinamide, [27], [34] used for its effectiveness on sallowness, wrinkling, red blotchiness and hyperpigmented spots in aging skin [35].

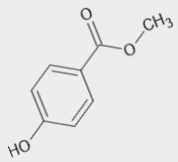
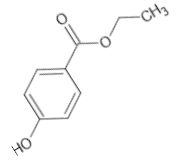
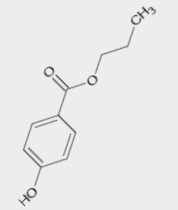
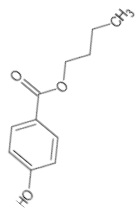
After having diffusing into the vascular system, parabens target some nuclear receptors. MP, EP, PP and BP have been defined as estrogen receptors agonists but between 10^4 and 10^6 times lower than E2 [11], [12], [17], [22]. Researches [12], [22] proved that they also act as androgen receptors antagonists, inhibiting testosterone's impact on gene expression. Additionally, they happen to be thyroid receptors antagonists, becoming obesogens [12], [22], [30]. Moreover, the anti-androgenic activity of butylparaben is enhanced when in mixture with BHT or BHA [36]. Any epigenetic modification has been observed in humans [17].

Parabens have been suspected to increase breast cancer risk because intact parabens have been found in several breast tumors [11], [37]. Although the ability of parabens to increase proliferation of breast cancer cells have been observed *in vitro*, [11], [32] it was not sufficient to prove that parabens as part of cosmetic formulations are responsible for breast cancer [11], [36]. Parabens and more notably EP and BP have been demonstrated as obesogens [17], [38] and disruptors of glucose metabolism,[12] increasing gestational diabetes mellitus risks [12], [32] and promoting adipogenesis [12], [28], [38]. Moreover, studies have been led to evaluate MP, EP and BP effects on male and female reproductive systems, but results are contradictory [30]. Hoberman et al. [39] found no correlation between testosterone levels, spermatogenesis and MP and BP administration. In another study [40], all four parabens decreased reproductive hormones concentration in girls, leading to delayed and dysfunctional sexual maturation. Generally, no conclusion can be drawn linking parabens and dysfunctional reproductive system [28].

Considering the few phenotypical effects of the use of a single paraben, these compounds are considered as safe. However, mixtures are not often considered in studies although synergism are typical phenomenon occurring with endocrine disruptors, all the more so as synergism may also happen in combination with parabens coming from food consumption. Overall, we lack representative data to truly assess endocrine disrupting activity of parabens, as shown in Table 1 [30].

Table 1: Endocrine disrupting effects of parabens

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects

Methylparaben N°CAS: 99-76-3 	- Max concentrations detected (body/face products, from 2013 to 2020): 3540 µg/g, 2880 µg/g [32] - From 0,02 % to 0,35% of the product composition [28],[30]	- ER agonist > 10^{-5} M [28] - AR antagonist > 10^{-5} M [28] - NOAEL: 1000 mg/kg bw/day [30] - NOAEL: 11,2 mg/kg bw/day [12]	- DD = 2,0 µg/ cm² [26] - 10% of the applied dose is absorbed intact, (3.63 mg on chest/breast *via* body lotion) [42] - 1,91 µg/cm² after 24h [12] - ASED: 0,0181-0,6611 mg/kg bw/day [12]	- ER agonist [11], [12], [17], [22] - AR antagonist [12], [22] - TR antagonist [12], [22]	- Present in breast cancer tumors [11], [12], [28], [30], [32], [37] - Linked to male and female infertility contradicted (yes: [30], [32]/no: [28], [30], [39]) - Decreases reproductive hormones levels in girls [40] - Increases risk of GDM, obesity and cancers [12], [17], [30], [32], [38]
Ethylparaben N°CAS: 120-47-8 	- Max concentration detected (body/face products, from 2013 to 2020): 379 µg/g [32] - From 0,04% to 0,35% of the product composition [28]	- NOAEL: 1000 mg/kg bw/day [30] - NOAEL: 250 mg/kg bw/day [12]	- 10% of the applied dose is absorbed in the intact form [42] - ASED: 0,0005-0,5162 mg/kg bw/day [12]	- ER agonist [11], [12], [17], [22] - AR antagonist [12], [22] - TR antagonist [12], [22]	- Present in breast cancer tumors [11], [12], [28], [30], [32], [37] - Linked to male and female infertility contradicted (yes: [30], [32]/no: [28], [30], [39]) - Decreases reproductive hormones levels in girls [40] - Increases risk of GDM, obesity and cancers [12], [17], [30], [32], [38]
Propylparaben N°CAS: 94-13-3 	- Max concentration detected (body/face products, from 2013 to 2020): 1540 µg/g [32] - From 0,01 % to 0,6% of the product composition [28],[30]	- NOAEL: 2 mg/kg bw/day [30] - NOAEL: 3,3 mg/kg bw/day [12]	- DD = 1,5 µg/cm² [26] - Up to 30% of the applied dose is absorbed in the intact form [42] - ASED: 0,015-0,438 mg/kg bw/day [12]	- ER agonist [11], [12], [17], [22] - AR antagonist [12], [22] - TR antagonist [12], [22]	- Present in breast cancer tumors [11], [12], [28], [30], [32], [37] - Decreases reproductive hormone concentrations in girls [40] - Increases risk of GDM, obesity and cancers [12], [17], [30], [32], [38]
Butylparaben N°CAS: 94-26-8 	- Max concentration detected (body/face products, from 2013 to 2020): 2 mg/g [32]	- AR antagonist > 10^{-5} M [28] - Adipogenic effects at 10^{-4} M [28] - NOAEL: 2 mg/kg bw/day [12], [30]	- 10% of the applied dose is absorbed in the intact form [42] - 0,24 µg/ cm² after 24h [12] - ASED: 0,0017-0,3124 mg/kg bw/day [12]	- ER agonist [11], [12], [17], [22] - AR antagonist [12], [22] - TR antagonist [12], [22]	- Present in breast cancer tumors [11], [12], [28], [30], [32], [37] - Linked to male and female infertility contradicted (yes: [30], [32]/no: [28], [30], [39]) - Decreases reproductive hormone concentrations in girls [40] - Increases risk of GDM, obesity and cancers [12], [17], [30], [32], [38]

NOAEL: No Observed Adverse Effects Level; DD: Dermal Delivery; GDM: Gestational Diabetes Mellitus; ASED: Aggregated Systemic Exposure Dose

Phthalates

Phthalates are esters of phthalic acid [43]. Diethylphthalate (DEP; N°CAS: 84-66-2) is the most commonly used in US and Canada [44] as solvent, vehicle for fragrances and anti-foaming agent in deodorants and perfumes [29], [45]. Dimethylphthalate (DMP; N°CAS: 131-11-3) is less common but used for its anti-stiffness properties in aftershave lotions and hair sprays [29], [45]. Dibutylphthalate (DBP; N°CAS: 84-74-2) is a famous plasticizer used in nail polishes [11], [17], [22], [29]. However, it has been banned in Europe in 2009, classified as a reproductive toxicant [1], [46]. Even though they are not regulated in North America, they are rarely used in this region nowadays [29], [31]. Di-(2-ethylexyl)phthalate (DEHP; N°CAS: 117-81-7) is forbidden in cosmetics [1], [31], yet it may appear in the composition of a final product due to a transfer from the packaging or during manufacturing

processes [11], [12], [43]. Generally, phthalates are incorporated in formulations at highest concentration of 1000 µg/g of product [22], [45].

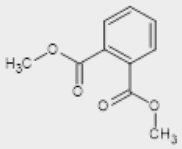
Intact DEP, DBP and DEHP are too lipophilic to cross the skin [22], [23], [47]. However, they are metabolized in the skin into their monoesters, which diffuses through the three dermal layers and are then detected in urines: DEHP is hydrolyzed into MEHP in dermis, DEP in mono ethyl phthalate (MEP) and DBP in mono butyl phthalate (MBP) [43]. Thus, we cannot affirm that phthalates themselves reach the vascular system and nuclear receptors.

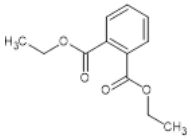
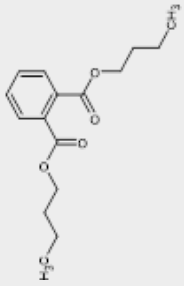
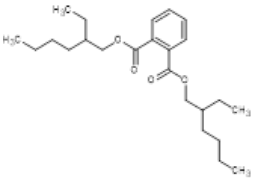
Still, phthalates demonstrate weak estrogenic activities [22], [43] and strong antiandrogenic activities [5], [17], [43]. They can activate PPARγ, altering thyroid hormone level, and thus being considered as obesogens [43]. DEHP has been demonstrated to be thyroid receptor antagonist [48].

Exposure to DBP was associated with an increased risk of breast cancer, yet the exposure was not representative of an application of cosmetic products [21], [43]. Other studies [9], [46] found an association between the metabolite of DBP and a decreased sperm quality. However, there is a need for further epidemiological studies to set up a clear link between male infertility and phthalate exposure *via* cosmetics [6], [49]. Much evidence shows epigenetic effects due to prenatal and infant exposure to phthalates [37]. Embryonic developmental problems and neurodevelopmental effects have been reported [17], [37]. Phthalate exposure leading to sex and thyroid hormones decrease have been linked with precocious puberty [11], body mass change in newborns [43] and gestational diabetes mellitus [43]. Prenatal exposure to phthalates may disrupt genital development in males and females and particularly sexual differentiation [6], [50]. Fetal phthalate exposure is responsible for testicular dysgenesis syndrome (TDS), precluding androgen action and thus causing male genital malformations [6], [17], [43]. Dutta et al. [43] reported that reproductive toxicity in females such as delayed puberty, increased risks of endometriosis, infertility and clinical pregnancy loss can be a consequence of DEHP exposure. A link between polycystic ovary syndrome and DEHP exposure is also suggested [51].

As demonstrated in Table 2, most of the endocrine disrupting effects of phthalates and their metabolites happen during the critical window of development. However, toxic doses need to be determined. The presence of DEHP in packaging needs further investigations as it may play a role in cumulative exposure to phthalates [46]. Finally, more epidemiological and transgenerational studies of DMP, DEP and their metabolites must be led to ensure endocrine properties of these compounds [17] as most of the adverse effects are observed with DBP and DEHP, which are forbidden ingredients.

Table 2: Endocrine disrupting effects of phthalates

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Dimethylphthalate N°CAS: 131-11-3 	Max concentration, 2021: 0,569 mg/L [45]	NOAEL not established for epigenetic effects [43]	- Metabolized in MMP [23], [43], [47] - DD = 0,8 µg/cm² [26]	- ER agonist [22], [43] - AR antagonist [5], [17], [43] - PPARγ agonist [43]	- Increases risk of GDM [43] - Increases risk of obesity [43] - Leads to adverse effects on male reproduction [11], [37], [49]

Diethylphthalate N°CAS: 84-66-2 	-Max concentration,2021: 0,475 mg/L [45] -Max concentration (2013, Canada): 25,5 mg/g (2,6%) [44]	- NOAEL not established for epigenetic effects [43] - sperm DNA damaged: MEP found at 443 ng/mL of urine [52]	- Metabolized in MEP [23], [43], [47] - AED > 1 µg/kg/day (4 cosmetics co-used) [53]	- ER agonist [22], [43] - AR antagonist [5], [17], [43] - PPARγ agonist [43]	- Body mass change in newborns [43] - Increases risk of GDM [43] - Increases risk of obesity [43] - Leads to adverse effects on male reproduction [11], [37], [49] - MEP alters sperm DNA [49]
Bibutylphthalate N°CAS: 84-74-2 	- Max concentration, 2021: 0,423 mg/L [45] - Max concentration (2013, Canada): 24,3 mg/g (2,4%) [44]	- 10 mg/g [43] - Lower doses cause more adverse effects than the highest dose (which is 3689 mg/kg bw/day) [54] - Breast cancer: > 10 mg/g [43]	- Metabolized in MBP [23], [43], [47] - In epidermis: 80 ± 65 µg/cm² [47] - MBP in the dermis: 1.9 ± 0.4 µg/cm² [47] - AED >10 µg/kg/day (14 cosmetics co-used) [53]	- ER agonist [22], [43] - AR antagonist [5], [17], [43] - PPARγ agonist [43]	- Increases breast and ovarian tumor cells, *in vitro* [21] - Increases risk of breast cancer [43] - Decreases sperm quality [9], [46] - Increases risk of GDM [43] - Increases risk of obesity [43] - Leads to adverse effects on male reproduction [11], [37], [49]
Di-(2-ethyexyl)phthalate N°CAS: 117-81-7 	Found only in 8 of 252 samples, only 8 of 252 at concentrations that are not specified [44]	NOAEL not established for epigenetic effects [43]	- Metabolized in MEHP [23], [43], [47] - AED > 1 µg/kg/day (3 cosmetics co-used) [53]	- ER agonist [22], [43] - AR antagonist [5], [17], [43] - PPARγ agonist [43] - TR antagonist [48]	- Polycystic ovary syndrome [51] - Body mass change in newborns [43] - Increases risk of GDM [43] - Increases risk of obesity [43] - Leads to adverse effects on male reproduction [11], [37], [49]

AED: Aggregate Exposure Dose

Perfluorinated chemicals

Perfluorooctanoic acid (PFOA; N°CAS: 335-67-1) and perfluorooctane sulfonic acid (PFOS; N°CAS: 1763-23-1) are two of the most common perfluoroalkyl substances (PFAs) used in cosmetics [11],[55], [56]. Their amphiphilic property makes them choice compounds in nail polishes and lotions to repel water, grease, stain and dirt [11], [55] as well as in foundations and concealers to smooth the skin [29][57]. Both are forbidden in EU since 2019, recognized as CMR C2, [58] but are neither regulated in Canada [31] nor in the USA [29]. The Food and Drug Administration (FDA) [29] is currently conducting research about their dermal absorption, the main obstacle to understand their toxicity in cosmetics.

As dietary intake is the first source of exposure to PFOA and PFOS, the contribution of dermal exposure to overall exposure is estimated to be less than 1 % [59]–[61]. Only one study [57] focused on skin absorption of PFOA. This study concluded that a quarter of the dose penetrated the skin, and half was retained in the skin layer. Moreover, the dermal absorption was 1,000 times higher at low pH, when the acid is not dissociated. Finally, it stated that perfluorinated chemicals are not metabolized, and that the major proportions of intact absorbed PFOA and PFOS were distributed in blood. The absorbed PFOA and PFOS then persist in the body for a long time [62]. Despite the relevance of this study, further research needs to be done to draw definitive conclusions.

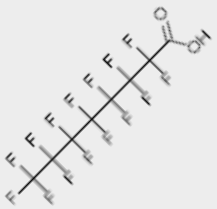
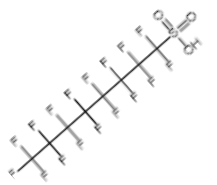
Several studies [55], [56], [59] proved that PFOA and PFOS activate PPARα and PPARγ. PFAs clearly acts as TR antagonists and alter hypothalamic-pituitary-thyroid axis, thus disturbing sex hormones and thyroid hormones productions [55], [57], [63]. The agonist binding to ERs is

contradicted. A review [55] explains disturbed sex hormones levels by an activation of estrogen receptors, while another [56] found no binding between PFOA and ERα and neither with ERβ.

PFOS is involved in decreasing birth weight when pregnant women are exposed to these compounds [11], [55], [59]. However, Mokra et al. [55] and White et al. [59] reported that a correlation between maternal exposure to PFOA and birth weight and length abnormalities is simultaneously suggested and denied. These effects may be linked with the impact of PFAs on thyroid hormones [62]. Thyroid disruption also manifests by hypothyroidism on both adults and children [62], [64]. Research suggests that PFOA and PFOS are obesogens for adults [59] but prenatal exposure leading to child obesity is uncertain [55]. Elevated total cholesterol as a consequence of high concentration of PFOS and PFOA in serum has been demonstrated [55], [61], [63]. Sun et al. [65] reported in his review that high plasma concentrations of PFOA and PFOS have been correlated to an increased risk of type 2 diabetes in some studies, while in another one they have been inversely correlated. In women, PFOA could increase risk of irregular menstrual cycle, delay pubertal development and increase time to pregnancy [59]. However, PFAs are not associated with earlier menopause [66]. In men, exposure to a combination of PFOA and PFOS could alter sperm quality [59]. Indeed, a decreased level of total testosterone has been observed, as well as several changes in other hormone levels [67].

Several effects have been observed in human exposed to PFOA and PFOS and are detailed in Table 3. Nonetheless, most of the studies were conducted by oral exposure *via* food and water as they constitute the major way of absorption of these chemicals. Thus, more representative research needs to be undergone to provide relevant cosmetic data, experimenting dermal exposure and mixtures of PFAs.

Table 3: Endocrine disrupting effects of perfluorinated compounds

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Perfluorooctanoic acid **N°CAS: 335-67-1** 	Detected between 0,79 and 3,09 ng/mL in blood samples in USA, EU and Australia [55]	- LOAEL (maternal dose): 0,01 mg/kg/day [59] - No doses for diabetogenic effects [65] - 19 g birth weight decrease with a 1ng/mL increase of PFOA [63]	23 to 25% penetrated and diffused in blood while are 45 % retained in the skin layers [57]	- PPARγ agonist [55], [56], [59] - PPARα agonist [55], [56], [59] - TR antagonist [55], [57], [63]	- Linked with abnormal birth weight and length (contradicted) [55], [59] - Hypothyroidism [62], [64] - Obesogenic in adults [59] - Elevates total cholesterol level [55], [61], [63] - Increases or decreases type 2 diabetes risk [65] - Irregular menstrual cycle, delayed puberty [59] - Decrease sperm quality and hormone levels [59], [67] ([59]: *via* food and water)
Perfluorooctane sulfonic acid **N°CAS: 1763-23-1** 	Detected between 0,36 and 8,59 ng/mL in blood samples in USA, EU and Australia [55]	No doses for diabetogenic effects [65]	Penetrated dose diffuses in blood [57]	- PPARγ agonist [55], [56], [59] - PPARα agonist [55], [56], [59] - TR antagonist [55], [57], [63]	- Decrease birth weight [11], [55], [59] - Hypothyroidism [62], [64] - Elevates total cholesterol level [55], [61], [63] - Increases or decreases type 2 diabetes risk [65] - Decrease sperm quality and hormone levels [59], [67] ([59]: *via* food and water)

Aluminum salts

The aluminum element is suspected to be endocrine disruptor. It can enter the body *via* topical application of cosmetics, as many of its salts are added in formulations. Aluminum salts are used in cosmetics as antiperspirants in underarm products or as pigments in lipsticks and sunscreens [11], [68], [69]. The most used aluminum salts in cosmetics are aluminum chloride (N°CAS: 7446-70-0) and its complexes, aluminum chlorohydrate (N°CAS: 12042-91-0) and its complexes, aluminum fluoride (N°CAS: 7784-18-4) and aluminum-zirconium complexes. Each of these compounds have specific regulations, recapitulated in Table 4 below.

Dermal absorptions of aluminum salts are rarely estimated. However, Darbre et al. [22] reported that aluminum could penetrate the skin in the aluminum chlorohydrate from and at a greater extent in damaged skin such as freshly waxed underarm skin.

Aluminum is a metalloestrogen, acting as an ERα agonist [22], [70]. It may also induce a stress proliferation and DNA deterioration [21].

Several studies confronted by Nicolopoulou-Stamati et al. [11] suggest a link between aluminum exposure and breast cancer. Indeed, aluminum has been detected in breast tissues and its aggregation is suspected to be a risk factor of breast cancer due to its ERα binding [69], [71]. On the contrary, Tietz et al. [69] reported that another study suggests that the aggregation of aluminum in breast tissue might be a consequence of breast cancer, instead of a cause. *In vitro*, increased breast cancer cells proliferation caused by aluminum has been observed but rather by stress proliferation [21]. Finally, it has been shown than aluminum can cross the placental barrier, exposing fetuses, and that it could be responsible for delayed puberty in boys and girls at high doses [69].

Regulated aluminum doses in cosmetics are considered as safe [69]. Its implication in breast cancer have not been clearly demonstrated and toxicological data mostly highlight its skin irritative property. However, studies suggest that adverse effects occur by an accumulation of aluminum in the body, combined with dietary intake. Thus, further research needs to be conducted to draw definitive conclusion about endocrine activity of aluminum as a cosmetic ingredient.

Table 4: Endocrine disrupting effects of aluminum salts

Compound [41]	EU legislation	USA legislation	Canada legislation	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Aluminum chloride N°CAS: 7446-70-0	Not regulated [1], [58]	Not regulated [29]	-Forbidden in aerosols or with other Al salts. -Max 15% antiperspirants. [31]	- Antiperspirant: max 2 mg_{Al}/kg bw/day - Sunscreens: max 0,02 to 0,16 mg_{Al}/kg bw/week (Al at 0,1% to 0,8 % in products) - Lipsticks: max 0,19 mg_{Al}/kg bw/week - Toothpaste: max 0,003 to 0,72 mg_{Al}/kg bw/week (Al at	LOAEL for delayed puberty: 50–500 mg/kg bw/day [69]		- Erα agonist -metallo-estrogen [22], [63]	- Breast cancer risk (suspect) [11], [21], [69]–[71] - Delayed puberty [69]
Aluminum chloride complexes	-Max 20% anhydrous -Max 5,4% with Zr -Forbidden in aerosols [1]	Not regulated [29]	Not regulated [31]					

Aluminum chlorohydrate N°CAS: 12042-91-0	Not regulated [1], [58]	Not regulated [29]	-Forbidden with other Al salts. -Max 25% anhydrous. [31]	0,02%to 4,5% in product) [69]		1.81 µg/cm² of intact skin VS 11.5 µg/cm² of stripped skin [22]		
Aluminum chlorohydrate complexes	Not regulated [1], [58]	Not regulated [29]	-Forbidden with other Al salts. -Max 25% anhydrous. [31]					
Aluminum fluoride N°CAS: 7784-18-4	Max 0,15% in oral products. [1]	Not regulated [29]	Not regulated [31]					
Aluminum zirconium complexes	-Max 20% anhydrous -Forbidden aerosols[1]	Forbidden in aerosols. [29]	-Max 20% anhydrous -Forbidden aeros. [31]					

LOAEL: Lower Observed Adverse Effects Level

Triclosan

5-chloro-2-(2,4-dihydroxyphenoxy)phenol (triclosan; N°CAS: 3380-34-5) is an antimicrobial agent used in many cosmetics [22], [72]. Europe [1] and Canada [31] set the maximum concentration of triclosan at 0,3% of the final products. The FDA [29] did not establish specific regulations for this preservative.

The primary exposure sources to triclosan in US and Canada are through ingestion and dermal contact [73]. Dermal absorption of triclosan has been widely studied. Overall, researches [22], [26], [72], [74]–[77] showed that less than 20% of the applied dose was absorbed through skin. Detailed penetrated doses are gathered in Table 5. In human, triclosan was detected in all layers of the skin, as well as in blood, urine and breast milk [72], [74], [77]. Yet because of its lipophilicity, the applied dose is mostly retained in the SC and thus only low doses reach the blood stream [26]. It was also found as sulfate metabolite within the first 4 hours and glucuronide metabolite after 8 hours in the stratum corneum and in the epidermis [74], [76]. However, triclosan can also enter through hair follicles, which pathway occurs minimal metabolism [76].

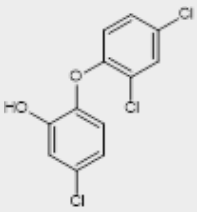
Because of its two phenol groups and its similar structure to thyroid hormones, an endocrine disrupting activity of triclosan was suspected [72], [78]. Nonetheless, the ED nature of triclosan is discussed. Several studies [22], [74] suggest ER, AR and TR bindings while others reported by Mihaich et al. [79] totally refute these hypothesis and no consensus has been reached yet. However, despite these contradictory and incomplete data, many evidence support the estrogenic activity of triclosan [78].

Carcinogenic potency of triclosan has not been reported by the International Agency for Research on Cancer (IARC) [72]. However, its presence has been confirmed in human breast cancer cells. Some studies [11], [72], [74] suggest a link between its estrogen activity and early breast cancer development. Besides, agreement on thyroid disrupting consequences has not been reached. Studies [80][81] also showed that triclosan may affect thyroid homeostasis and autoimmunity. Gestational and childhood exposure to triclosan could be the cause of these effects, inducing neurodevelopmental

problems and abnormal behaviors in children [75]. On the contrary, many studies [72]–[74], [78], [82] found no correlation between triclosan exposure and neurodevelopmental toxicity.

Overall, triclosan's endocrine toxicity has not been proven, as data from Table 5 demonstrates. Further research on nuclear receptors it could target, adequate human evidence and epidemiological studies need to be conducted [78], [83]. Moreover, low doses and long term exposure must be experimented so as to support evidence with realistic toxic doses [78]. Finally, a review [72] suggests that triclosan may be a concern in combined use on several cosmetics and personal care products.

Table 5: Endocrine disrupting effects of Triclosan

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
5-chloro-2-(2,4-dichlorophenoxy) phenol N°CAS: 3380-34-5 	- Max 0,3% allowed in EU and Canada [1], [31] -Estimated between 0,047 and 0,14 mg/kg bw/day [72]	-AR antagonist at 0,1 - 1 - 10 µmol/L [74] - NOAEL: 12 mg/kg bw/day [72]	-5,9 ± 2,1% of the applied dose (2% as a cream, 48h) [22] - 10% of the applied dose [75] -11,3% W/O, 7,65% deodorant [72] -2,06 % of the applied dose (20min, real-life scenario) and 18,38% (24h) [77] -Metabolized [74] -DD= 0,08 µg/cm². 1% of the applied dose in RF [26]	-ER agonist [22], [74], [78] -AR activity (yes: [22], [74]/ no: [79]) -TR activity (yes: [22], [74]/ no: [79])	-Breast cancer risk factor suspected [11], [72], [74] -Affects thyroid homeostasis and autoimmunity [77], [81] - Neurodevelopment dysregulation and child behavioral problems (yes: [81]/no: [72], [82])

Organic UV filters

Organic UV filters are used in various cosmetics to absorb solar UV radiation [11]. They can protect the skin from UVA or UVB or both [84]. They are not only used in sunscreens, but also in daily use cosmetics such as make-up, skin, lip and hair care products [75], [85]. Organic UV filters are mostly derivates of benzophenone, like benzophenone-1 (BP1; N°CAS: 131-56-6), benzophenone-2 (BP2; N°CAS: 131-55-5) and 2-hydroxy-4-methoxybenzophenone (oxybenzone; BP3; N°CAS: 131-57-7) which is the most commonly used [86]. Cinnamates such as octyl methoxycinnamate (octinoxate; OMC; N°CAS: 5466-77-3) and isopentyl-4-methoxycinnamate (amiloxate; IMC; N°CAS: 71617-10-2) are also widely used because of their high efficiency to absorb UVA and UVB [84]. Other compounds are incorporated in formulations like 4-methylbenzylidene camphor (enzacamene; 4-MBC; N°CAS: 36861-47-9), 3-benzylidene camphor (3-BC; N°CAS: 15087-24-8) and benzoic acid,2-hydroxy-,3,3,5-trimethylcyclohexyl ester (homosalate; HS; N°CAS: 118-56-9) [11], [22], [84]. Finally, 2 Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester (octocrylene; OC; N°CAS: 6197-30-4) and butylmethoxydibenzoylmethane (avobenzone; AB; N°CAS: 70356-09-1) are often used in combination as octocrylene stabilizes avobenzone [87]. The trio BP3-OMC-AB is also frequently used as a mixture in same cosmetics [85]. Most of these UV filters are regulated in EU [1], [88], [89] and USA [29], but not in Canada [31]. Detailed regulations are presented in the Table 6 below.

Skin permeation of UV filters is to be avoided to ensure safety of the consumer and preclude consequences of endocrine disruption, and they must adhere with high affinity to the SC to ensure effectiveness of UV protection [85].Thus, skin permeation of UV filters must be evaluated to certify both their effectiveness and safety. Several studies [75], [84], [85], [90] showed that BP3 did not meet these criteria, having low affinity for SC and rapidly penetrating the skin layers. BP3 can also undergo metabolism into BP1 in the skin [91]. OMC acts the same way in contact to skin, penetrating SC and the skin layers, reaching systemic circulation in one hour [85], [90]. 4-MBC, 3-BC and AB are also easily absorbed through the skin [84], [92]. As for octocrylene, studies [87][93] demonstrated that it has a very low dermal absorption. However, octocrylene slowly transforms into benzophenone which is a

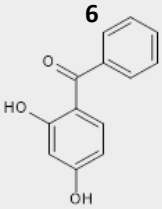
proven endocrine disruptor [87][93]. Overall, UV filters succeed in penetrating the skin. What matters the most is their accumulation in the body, due to their stability and lipophilicity, enhanced by their conditions of applications [84], [87]. Indeed, UV filters are used in sunscreens and cosmetics which are supposed to be reapplied several times a day, during a quarter of the year. Thus, realistic time of exposure to these cosmetics is between 6 and 12 hours a day. Therefore, this long exposure time may be a factor of bioaccumulation [85]. Finally, realistic amount of UV filters penetrating the skin is hard to establish, because of the unappropriated applicated dose of the products by consumers, estimated to be 0,5 mg/cm² instead of 2 mg/cm² [85].

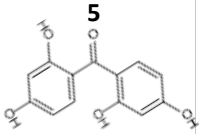
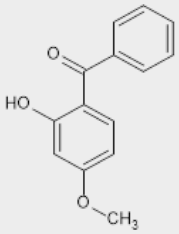
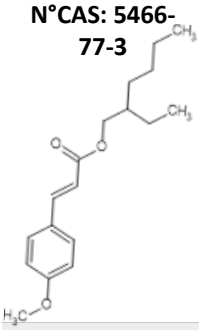
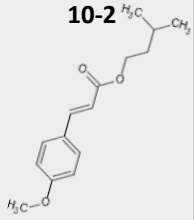
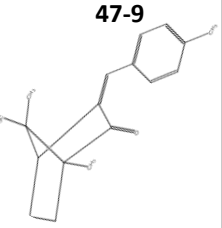
Aromatic structures of organic UV filters resemble other endocrine disruptors, and more notably BP3 and OMC that exhibit structures similar to estradiol [85]. Indeed, numerous evidence showed nuclear binding to these compounds [94]. Benzophenone derivates and homosalate act as agonists of ERs [84], [94], and 4-MBC, 3-BC, IMC, OMC and OC are antagonists of ERs [84]. All UV filters mentioned in this article have antagonistic androgen activities [84], [94]. Additionally, BP-1,2,3 and OMC act as agonists and antagonists of TR [84]. Finally, BP-3, cinnamates, benzylidene camphor derivates and octocrylene are progesterone receptor agonists [84], [94].

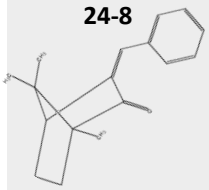
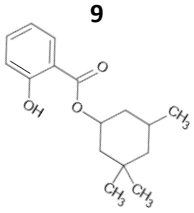
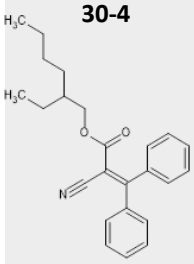
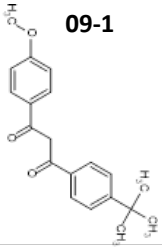
BP-3 may influence birth weight of boys and girls [11]. OMC has been detected in human breast milk. A decrease of sex hormones has been revealed, yet it cannot be extrapolated to humans [11]. Similarly, adverse effects on the reproductive system of animals are observed as a consequence of 4-MBC and 3-BC exposure [90]. Another study [95] warns that human exposure to these two cinnamate derivates may interfere with sperm function and thus impairing male infertility. No endocrine disruption caused effects has been observed following octocrylene exposure [87]. However, several adverse effects are the consequences of benzophenone exposure, the endocrine disruptor into which octocrylene slowly transforms as a raw material or in the final product [93].

Nuclear receptors targeted by UV filters have been widely studied and data is recapitulated in Table 6. However, a lack of epidemiological studies on human is visible. Moreover, mixtures of UV filters must be the subject of further investigation in order to provide more representative data [90], [92]. Thus, it is hard to conclude today on an obvious endocrine disrupting activity of these compounds when applied *via* cosmetics. Finally, it has to be noted that no evidence has been found concerning avobenzone, neither nuclear receptors it could target, nor endocrine disrupting induced effects. It is thus considered as safe.

Table 6: Endocrine disrupting effects of organic UV filters

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
BP1 **N°CAS: 131-56-6** 	Under 6% as a metabolite of BP3 allowed under 6% in EU and USA [29], [89]	-ER agonist from 10^{-4} to 10^{-6} M [96] -ER EC50 = 1,26 µM [96] -AR IC50 = 10 µM [96] -Cell proliferation from 0,1 to 1 µM [97]	Metabolite of BP3 [91]	-ER agonist -AR antagonist -TR agonist -TR antagonist [84]	-Breast cells proliferation [97] -Increases uterine weight (rats) [97]

BP2 **N°CAS: 131-55-5** 		-ER agonist from 10^{-4} to 10^{-7} M [96] -ER EC50 = 0,30 µM [96] -AR IC50 = 1,53 µM [96]	No data available on human skin penetration of BP2 [98]	-ER agonist -AR antagonist -TR agonist -TR antagonist [84]	Hyperthyroidism (rats) [98]
BP3 **N°CAS: 131-57-7** 	-Allowed under 6% in EU and USA [29], [89] -Daily mean intake (USA): 24,4 µg [22] -Max exposure estimated: 50 mg/kg bw [99]	-ER EC50 = 19,5 µM [96] -AR IC50 > 100 µM [96] -AR IC50 = 4,98 µM [100]	-0,01 mg/cm² in RF (0,5% of the 2,0 mg/cm² applied dose)[85] -10 % of the applied dose reaches blood stream [75] -Detected in plasma after 1-2h [85], [90] -In plasma > 0,5 ng/mL (applied dose < 2 mg/cm²) [92] -Metabolized in BP-1 [91] -1,0 ± 0,4 µg/cm² in RF (after 16h)[101]	-ER agonist -AR antagonist -TR agonist -TR antagonist -PR agonist [84]	-Increases birth weight of boys -Decreases birth weight of girls [11]
Octinoxate **N°CAS: 5466-77-3** 	-Allowed under 10% (EU) and 7,5% (US) [1], [29] -Max exposure estimated: 50 mg/kg bw [99]	Toxic doses reported on animals (rats)[84]	-Detected in plasma after 1-2h [90] -0,03 ±0,07 µg/cm² in RF (after 16h) [101] -Penetration from 0,2% to 4,5% of the applied dose. Systemic absorption: 0,002% [99] -Plasma concentration (2 mg/cm² applied): from 10 to 20 ng/mL [99]	-ER antagonist -AR antagonist -TR agonist -TR antagonist -PR agonist [84]	Decreases sex hormones in animals [11]
Amiloxate **N°CAS: 71617-10-2** 	-Allowed under 10% (EU) [1] -Max exposure estimated: 50 mg/kg bw [99]	Toxic doses reported on animals (rats)[84]	-Max skin penetration: 5% of the applied dose -Total amount absorbed estimated up to 2,56 mg/kg bw [99]	-ER antagonist -AR antagonist -PR agonist [84]	No effects reported
Enzacamene **N°CAS: 36861-47-9** 	-Allowed under 4% (EU) [1] -Max exposure estimated: 50 mg/kg bw [99]	-Estrogenic activity from 10 to 150 µM [102] -ER EC50 = 3,99 µM [103]	Plasma concentration (after 3-4h, 10% of formulation, 2 mg/cm² applied): 20 ng/mL [99]	-ER antagonist -AR antagonist -PR agonist [84]	-Adverse effects on reproductive system of rats and mice [90] -Alters sperm function, impairs male infertility [95]

3-benzylidene camphor N°CAS: 15087-24-8 	-Forbidden in EU [1] - Max exposure estimated: 50 mg/kg bw [99]	-Mammary cell proliferation from 6 to 10 µM -ER EC50 = 0,68 µM [103]	-Max skin penetration: 5% of the applied dose -Total amount absorbed estimated up to 2,56 mg/kg bw [99]	-ER antagonist -AR antagonist -PR agonist [84]	-Adverse effects on reproductive system of rats and mice [90] -Alters sperm function, impairs male infertility [95]
Homosalate N°CAS: 118-56-9 	-Allowed under 10% (EU) and 15% (US) [1], [29] - Max exposure estimated: 50 mg/kg bw [99]	-AR IC50 = 5,87 µM [100]	-Max skin penetration: 5% of the applied dose -Total amount absorbed estimated up to 2,56 mg/kg bw [99]	-ER agonist -AR antagonist [94]	No effects reported
Octocrylene N°CAS: 6197-30-4 	-Allowed under 10% (EU and USA) [1], [29] -Benzophenone exposure estimated > 100 mg/kg/day [93] - Max exposure estimated: 50 mg/kg bw [99]	No relevant doses found (benzophenone: toxic dose *via* dermal exposure is assessed on rabbits: 3,535 mg/kg) [41]	-In plasma > 0,5 ng/mL (applied dose < 2 mg/cm²) [92] - 0,05 % of the applied dose in RF [87] -2,9 ng/mL to 7,8 ng/mL in plasma (2 mg/cm² applied on 75 % of the body surface, concentrations from 2,35% to 10%) [87] -Below 0,01 µg/cm² in RF (after 16h) [101] -Metabolized in benzophenone [87], [93]	-ER antagonist -AR antagonist -PR agonist [84]	-No effects reported [87] -Many effects of BP (banned) have been reported [93]
Avobenzone N°CAS: 70356-09-1 	-Allowed under 5% (EU)and 3% (USA) [1], [29] - Max exposure estimated: 50 mg/kg bw [99]	Considered as safe [29]	In plasma > 0,5 ng/mL (applied dose < 2 mg/cm²) [92]	No studies	No effects reported

EC50: half maximal Effective Concentration; IC50: half maximal Inhibitory Concentration

Nanoparticles

Nanoparticles also raise concern today. Particularly, titanium dioxide (TiO_2; N°CAS: 13463-67-7) and zinc oxide (ZnO; N°CAS: 1314-13-2) are suspected, as they are UV filters. Unlike organic UV filters, metal oxide particles block and reflect solar radiations [11]. These ingredients are not only used as UV filters in sunscreens and lipsticks, but also as white pigments in eyeshadows, and for other properties in deodorants, shampoos and shaving foams [24], [104]. They are considered as safe under the maximum concentration of 25% in EU [1] and USA [29]. No regulation is defined in Canada [31]. Above this concentration, the anatase crystallographic form of TiO_2 induces oxidative stress [24].

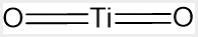
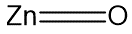
Overall dermal absorption of nanoparticles is low while they accumulate in the SC. However, TiO_2 and ZnO have been identified in the underneath layers of the skin and in blood stream in very low

quantities after prolonged exposure [104], [105]. The skin penetration of this sized particles is ongoing discussion [21].

No binding to any nuclear receptor has been reported. However, effects likely to be the consequences of an endocrine mode of action have been observed on animals such as pregnancy disruption and impaired fetus growth [11], [104]. No effects have been reported on humans [106].

Endocrine disrupting-like effects on animals have been observed but no NR targeted were reported and no effects on human occurred. Additionally, their low dermal absorption let us think that their toxicities as cosmetic ingredients are unlikely. Available data is presented in Table 7. Without further research, these compounds are considered as safe under the maximum concentrations set by governments. Ongoing studies will then enlighten us more on that matter.

Table 7: Endocrine disrupting effects of nanoparticles

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Titanium dioxide N°CAS: 13463-67-7 	Allowed under 25% of the product [1], [29]	No toxicity observed on humans	-Accumulation in the SC [25] -Detected in epidermis and dermis after prolonged application [105]	Not reported	Affects pregnancy and fetus development (rats, mice) [11], [104]
Zinc oxide N°CAS: 1314-13-2 	Allowed under 25% of the product [1], [29]	No toxicity observed on humans	<0,01% of the applied dose identified in blood stream (sunscreen twice a day, 5 days) [104]	Not reported	Affects reproduction and body weight (rats) [11], [104]

Fragrances

Fragrances are compounds used to mask any smell and give a special scent in cosmetics such as perfumes, hair care or body care products and even make-up [22], [107]. Nitromusks are concerning fragrances because of their structures [107]. Maximum concentration of musk xylene (N°CAS: 81-15-2) and musk ketone (N°CAS: 81-14-1) have been instituted in EU, depending on the containing product [1]. Musk xylene have been classified as a very Persistent very Accumulative (vPvA) compound by EU [22], [107]. Musk ambrette and musk tibetene have been forbidden both in EU [1] and Canada [31], and musk moskene (N°CAS: 116-66-5) is only forbidden in EU [1]. Benzyl salicylate (BS; N°CAS: 118-58-1) is allowed in EU [1], USA [29] and Canada [31] if it respects labeling legislations. However, BS has been recently classified as potential endocrine disruptor by the European Scientific Committee for Consumer Safety (SCCS) [108]. 2-(4-tert-butylbenzyl)propionaldehyde (also named lilial, lysmeral, lily aldehyde or butylphenylmethylpropional; N°CAS: 80-54-6) is suspected to have endocrine disrupting properties too [109].

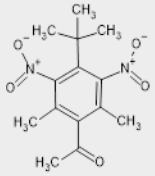
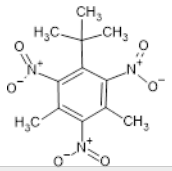
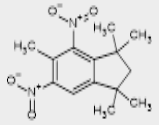
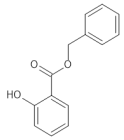
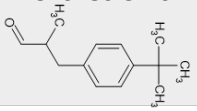
Although dermal absorption of these compounds has been barely studied, some studies [75], [107] state it is low. However, nitro musks have been detected in adipose tissues and breast milk [110], [111]. Research [107] suggests that inhalation is an important way of exposure to these compounds. BS and lilial dermal absorption are unknown, yet fragrances are used at low concentrations. Thus, repeated dermal exposure may be a concern [108]. Moreover, four metabolites of lilial, tert-butylbenzoic acid, lysmerol, lysmerylic acid, and hydroxylysmerylic acid are found in urine samples, suggesting a metabolism of lilial and an unlikely accumulation of this compound [109].

Their aromatic structures and lipophilicity lead us to believe that they have endocrine disrupting abilities. Hence, Kathryn et al. [107] reported that studies observed estrogenic activity of these compounds.

Significant increase in the proliferation of human breast cancer cells by 29% for musk xylene and by 97% for musk ketone has been observed [107]. However, this is insufficient proof to claim that musks are risk factor of breast cancer. Other findings also reported by Kathryn et al. [107] imply a potential impact of nitro musks on ovarian hormones natural function. As for lilial, it is suspected to alter fertility [109]. No relevant effects of BS have been reported.

Evidence on endocrine disrupting properties of fragrances is sparse and is summed up in Table 8. More studies on the estrogenic activity of these compounds, as well as their phenotypical effects are needed to assess their endocrine disrupting abilities. With no further study to confirm, these fragrances used at regulated doses are considered as safe.

Table 8: Endocrine disrupting effects of fragrances

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Musk ketone N°CAS: 81-14-1 	Low concentrations (in mixtures of fragrances incorporated in diverse products, secret trade) [29]	-Proliferation of breast cancer cells: 10 mmol/$L_{substance}$ [107] -Premenstrual syndrome: 24 ng/L_{blood} [107] Higher doses than without syndrome	10% of the applied dose reached circulation [75]	ER agonist suspected [22], [107]	-Increases by 97% proliferation of breast cancer cells -Premenstrual syndrome -Effect on hypothalamic-ovarian hormone pathway [107]
Musk xylene N°CAS: 81-15-2 	Low concentrations (in mixtures of fragrances incorporated in diverse products, secret trade) [29]	-Proliferation of breast cancer cells: 10 mmol/$L_{substance}$ [107] -Women infertility: 23,5 ng/L_{blood} [107] Higher doses than without syndrome	10% of the applied dose reached circulation [75]	ER agonist suspected [22], [107]	-Increases by 29% proliferation of breast cancer cells -Women infertility -Effect on hypothalamic-ovarian hormone pathway [107]
Musk moskene N°CAS: 116-66-5 	Low concentrations (in mixtures of fragrances incorporated in diverse products, secret trade) [29]	No doses available [107]	10% of the applied dose reached circulation [75]	ER agonist suspected [22], [107]	Effect on hypothalamic-ovarian hormone pathway [107]
Benzyl salicylate N°CAS: 118-58-1 	Low concentrations (in mixtures of fragrances incorporated in diverse products, secret trade) [29]	-NOAEL (all endpoints): 2500 ppm [108] -Most ER active doses from 1.10^{-4} to 2.10^{-4} M [108] -*In vivo*, expected to be ER agonist between 2 and 20 g/kg/day [108]	Very low absorption suspected [108]	-ER agonist suspected [22], [107] -Weak ER agonist [108]	No relevant effects reported
2-(4-tert-butylbenzyl) propionaldehyde N°CAS: 80-54-6 	Low concentrations (in mixtures of fragrances incorporated in diverse products, secret trade) [29]	No doses available [109]	Metabolized [109]	ER agonist suspected [22], [107]	May alter fertility [109]

Cyclic volatile methylsiloxanes cVMSs

Cyclic methylsiloxanes are common volatile silicones [22] used as spreading agents, hair conditioners, antistatic, emollient, humectant, solvent and viscosity controlling agents [112] in hair care products, deodorants and antiperspirants, nail polishes, lotions, skin cleansers and baby products [113]. The most frequently used cVMSs in cosmetic formulations is octamethylcyclotetrasiloxane (D4; N°CAS: 556-67-2) which has been recently forbidden in Europe, considered as CMR R2. [22], [58] Its mate decamethylcyclopentasiloxane (D5; N°CAS: 541-02-6) is it not regulated either in EU [22], [58] or in North America [29], [31]. Its concentration in cosmetic product can achieve 93% [114]. However, purity of D5 must be a center of attention because it may contain traces of D4 [112].

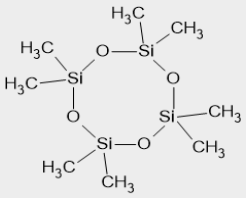
D4 can reach blood circulation after 24h of exposure, but at low dose [22]. It is mostly retained in SC yet then its diffusion and elimination are easy, making bioaccumulation unlikely [115], [116]. D5 also has a low dermal absorption. However, its bioaccumulation is discussed. A study [115] proved that its cumulative doses in SC and epidermis are high and its diffusion to the receptor fluid is low, risking a bioaccumulation. In contrast, a toxicological review [117] considers that potential bioaccumulation of D5 is unlikely.

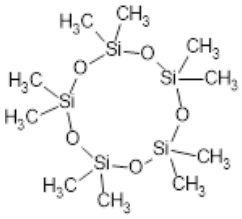
Several evidences [22], [114], [118] show that D4 and D5 are estrogen receptors agonists. An antiandrogenic activity of D4 is suspected but is a subject of disagreement [114].

D4 impairs the female reproductive system [22], [118] and has been classified as type 2 reprotoxic by EU [58]. Its implication in human uterine tumor has been observed on animals, yet it cannot be extrapolated to humans as this effect can be species-specific [116]. Similarly, D5 is a risk factor of uterine tumor growth in rates and is responsible for their aging reproductive system [117]. Thus no directly link to human endocrine system can be made. Additionally, these effects are observed after inhalation of the chemicals, not by dermal application [116], [117].

Several studies are led to assess toxicology of D4 and D5, as Table 9 shows. However, the main used exposure pathway is inhalation because of their volatility and low dermal absorption. Moreover, experiments are conducted on animals and results cannot be extrapolated to humans. Further epidemiological studies representative of human dermal exposure to D4 and D5 must be conveyed. According to the overall data, potential effects of D5 are not consequences of an endocrine disrupting ability.

Table 9: Endocrine disrupting effects of cyclic volatile methyl siloxanes

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Octamethylcyclotetrasiloxane **N°CAS: 556-67-2** 	-Concentration (2008): max 28% [114] -From 0,06% to 89% (concentrations in the product, 2011) [22]	No relevant toxic doses: determined for oral exposure and inhalation of rats and rabbits [116]	-0,02 % of the applied dose remained in the skin after 24h (29% in the dermis and 10% in adipose tissue) [22] -Max 0,3% of the applied dose in blood after 1h [22] -Cumulative dose in SC = 27,5 µg/cm²/24h [115] -Cumulative dose in epidermis = 6,4 µg/cm²/24h [115] -Percutaneous absorption: from 0,1% to 8,1% [115]	-Estrogen agonist [22], [114], [118] -Androgen antagonist (contradicted) [118]	-Impairs female reproductive system [22], [118] - Classified as CMR R2 by EU [58] -Generates uterine tumors in rats [116]

Decamethylcyclopentasiloxane **N°CAS: 541-02-6** 	-Concentration (2008): max 93% [114] -From 0,06% to 89% (concentrations in the product, 2011) [22]	No relevant toxic doses: determined for inhalation of rats [117]	-Max 0,05% of the applied dose in blood after 1h [22] -Cumulative dose in SC = 63,9 µg/cm²/24h [115] -Cumulative dose in epidermis = 29,9 µg/cm²/24h [115] -0,04 % of the applied dose (1g) totally absorbed after 24h [117] -Cumulative doses: neat = 0,1 µg/cm², in formulation = 0,3 µg/cm² [117]	Estrogen agonist [22], [114], [118]	-Generates uterine tumor in rats -Ages reproductive system of rats [117]

Nonylphenols

Nonylphenol ethoxylate (NPE; N°CAS: 9016-45-9) is part of the nonionic class of surfactants alkylphenol ethoxylate, used in cosmetics for cleansing purposes [22], [119]. NPE is not regulated by the European commission [1], FDA [29] or Canadian government [31]. However, the product of its microbial degradation 4-nonylphenol (NP; N°CAS: 104-40-5) is forbidden in EU since 2009 [1], [119].

Two studies [120], [121] evaluated skin penetration and absorption of NPE and NP. Both found that skin penetration is low, with most of the applied dose remaining in the SC. Then, absorption of NPE and NP in skin layers is even lower. One of them [121] observed that the absorbed dose was the highest for the lowest doses applied.

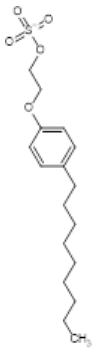
NP is definitely an estrogen receptors agonist [122]–[126]. Additionally, its ability to activate PPARγ and act as AR antagonists are suggested [119], [122], [123]. An alteration of TR function is also advanced [124].

The endocrine disrupting effects of NP are characterized by an alteration of sex hormones production [122], [127], [128]. A disruption of sexual development and reproduction may be a consequence, notably in males [122], [129]. Effects of NP on female infertility has not been well studied [127]. Additionally, NP is suspected to increase risks of endometrial pathology [130], breast cancer [123] and prostate cancer [125], even though Peremiquel-Trillas et al. [123] and Forte et al. [125] have not reached an agreement already. NP exposure during pregnancy and breast feeding may induce learning and memory alteration on the infant [131]. Lastly, some studies [38], [119] found that NP promoted adipogenesis and obesity on the offspring while exposed during pregnancy.

All available data about NPE and NP endocrine disrupting abilities are recapitulated in Table 10. With no further research, NPE cannot be considered as an endocrine disruptor. Yet considering the available evidence showing the nuclear receptors targeted by NP, we can indisputably state that this compound is an endocrine disruptor. However, we lack epidemiological studies to confirm that adverse effects occur on humans and as a consequence of an endocrine mode of action. Indeed, many of the reported effects were tested on animals [123], [127]. NPE is not an ED itself, yet its biological degradation that may occur in the body or in the raw material is considered as toxic. Thus, products containing NPE may be contaminated by NP and have an endocrine disrupting ability.

Table 10: Endocrine disrupting effects of nonylphenol

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects

4-nonylphenol **N°CAS: 104-40-5** 	Highest estimated exposure: 0,1 µg/kg/day [123]	-Increases estradiol production: 2,5 µg/mL and 5 µg/mL -Increases testosterone production: 5 µg/mL -Decreases progesterone production: 1 µg/mL, 2,5 µg/mL and 5 µg/mL -Decreases androstenedione production at 5 µg/mL [128]	- <1% of the applied dose penetrated SC and epidermis. 0,1% penetrated all skin layers after 8h [120] - <5% of the applied dose penetrated, it remained in SC. 1% of the applied dose = 0,3µg/cm², penetrated all skin layers after 8h [121]	-PPARγ agonist [119] -ER agonist [122]–[126] -AR antagonist [122], [123] -TR disruptor [124]	-Disrupts sex steroid hormone production (human) [128] -Disrupts sexual development and reproduction (fishes) [129] -Male infertility suspected [122] -3-fold increases risk of breast cancer (human) [123] -Endometrial pathology (not ED pathway supposed) [130] -Increases risk of prostate cancer (yes: [125]/ no:[123]) -Damages learning and memory (animals) [131] -Promotes adipogenesis and obesity (mice) [38], [119]
Nonylphenol ethoxylate **N°CAS: 9016-45-9** 	Highest estimated exposure: 0,1 µg/kg/day [123]	NPE is not toxic by itself. It is a degraded in NP.	- <1% of the applied dose penetrated SC and epidermis. 0,1% penetrated all skin layers after 8h [120] - <5% of the applied dose penetrated, it remained in SC. 1% of the applied dose = 0,3µg/cm², penetrated all skin layers after 8h [121]	No NR targeted	-Effects occur after application of NPE but as a consequence of its degradation in NP -3-fold increases risk of breast cancer (human) [123]

Synthetic phenolic antioxidants

Butylated hydroxyanisole (BHA; N°CAS: 25013-16-5) and butylated hydroxytoluene (BHT; N°CAS: 128-37-0) are synthetic phenolic antioxidants (SPAs) used in cosmetics [36], [132], [133]. Although they are not regulated [1], [29], [31], [58], they are suspected to be endocrine disruptors [36], [133]. Their concentrations in cosmetic are low and they are used in a lesser extent today, but they are still found in some formulations [132]. Hence, it is worth studying their endocrine disrupting potentials.

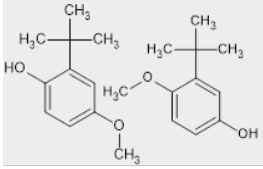
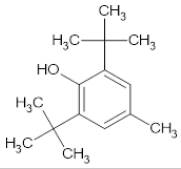
As BHA and BHT are mostly added in food, ingestion is the primary source of exposure to these compounds [36], [132]–[134]. Concerning cosmetic application, research [132] found that very low doses of BHT can penetrate the skin. Unfortunately, dermal absorption of BHA has not been studied. Yet what we know is that BHA and BHT are metabolized in the body in many compounds [133].Thus toxicity of the metabolites will be taken into account thereafter. An accumulation in adipose tissues of BHA and BHT have been observed when both compounds where present in the same formulation, suggesting an interaction between them [134].

Binding nuclear receptors has been proven. Indeed, they act as ER agonists [21], [133]. Alone, BHA and BHT have low antiandrogenic activity [36]. However, several studies [36], [134] found a synergism between both compounds, conferring high antiandrogenic activity to the mixture. Combinations with either propylparaben or butylparaben also led to stronger binding.

BHA exposure may lead to abnormal testicular development and inhibit testosterone production in males [134]. Similarly, Lanigan et al. [132] reported that BHT may be responsible for reproductive and development impairment. However, these effects were proved on animals only. Behavioral effects of BHA and BHT exposure are also observed on fetuses and small children [132], [135].

Even though the nuclear receptor binding of BHA and BHT are proved, human phenotypical effects are not well studied. Skin penetration of BHT may also need to be a subject of further investigation [132]. It seems important to highlight that synergism is a matter of concern in mixtures with these SPAs, and precautions need to be taken. Supporting data in presented in Table 11.

Table 11: Endocrine disrupting effects of synthetic phenolic antioxidants

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Butylated hydroxyanisole N°CAS: 25013-16-5 	From 0,0002% to 0,5% of the product composition [132]	Abnormal testicular formation at 100 µM (mice) [134]	No studies investigated dermal penetration of BHA. Mostly integrated *via* food [36], [132]–[134]	-ER agonist [21], [133] -Weak AR antagonist [36] -Strong AR antagonist combined with: BHT, butylparaben, propylparaben [36], [134]	-Causes abnormal testicular development and decreases testosterone production (mice) [134] -Behavioral changes on fetuses and small children [132], [135]
Butylated hydroxytoluene N°CAS: 128-37-0 	From 0,0002% to 0,5% of the product composition [132]	NOAEL for rats, not relevant [132]	- < 4 % of the applied dose penetrates the skin [132] -Mostly integrated *via* food [36], [132]–[134]	-ER agonist [21], [133] -Weak AR antagonist [36] -Strong AR antagonist combined with: BHA, butylparaben, propylparaben [36], [134]	- Causes reproductive and development impairment (rats and mice) [132] -Behavioral changes on fetuses and small children [132], [135]

Essential oils

Lavandula angustifolia oil (lavender essential oil; N°CAS: 8000-28-0/90063-37-9) and melaleuca alternifolia leaf oil (tea tree essential oil; N°CAS: 85085-48-9/8022-72-8/68647-73-4) are suspected to have endocrine disrupting properties [22]. These two essential oils are used in many cosmetics such as soaps, lotions, shampoos, hair care products and cologne for its scent and its skin-healing properties [22], [136]. They are not submitted to any specific regulations [1], [29], [31], [58].

Skin penetration of essential oils are not well studies, and its likely to be due to their complex compositions and recent craze. We know that dermal cosmetic application is one of many ways of exposure to these products. Indeed, essential oils are applied topically during massages but are also inhaled, as used in perfumes and ingested [136].

Nevertheless, lavender and tea tree essential oils proved *in vitro* their ER agonist binding [21], [136]–[138] and AR antagonist binding [21], [136]–[138]. Additionally, a TR antagonist action is suspected [21].

Clinically, several studies [136], [138] observed an abnormal breast growth and puberty in adolescents regularly exposed to lavender and tea tree oils. This is thought to be the result of disturbed balance between estradiol and testosterone levels, in agreement with ER and AR bindings [136]. Finally, nasal exposure to these essential oils is suspected to upregulate estradiol level during menopausal transition [139].

Lavender essential oil and tea tree essential oil clearly demonstrate endocrine disrupting activities, as shown in Table 12. However, they deserve further investigation to enlighten the toxic and skin penetrating doses, so as to understand whether these products are hazardous at doses found in cosmetics. Moreover, synergism of these oils has to be evaluated to better understand their effects. They are today both considered as safe.

Table 12: Endocrine disrupting effects of essential oils

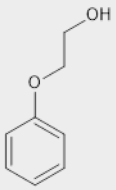
Compound [41], [136]	**Exposure**	**Toxic dose**	**Skin absorption**	**Nuclear receptors**	**Effects**
Lavender essential oil N°CAS: 8000-28-0 / 90063-37-9 Mixtures of chemicals.	Not estimated	-ER agonist: max 0,025% vol/vol [138], [140] -AR antagonist: max 0,005% vol/vol [138], [140]	No research has been conducted	ER agonist AR antagonist [21], [136]–[138]	-Changes estradiol and testosterone levels [136],during menopausal transition [139] -Abnormal breast growth and puberty [136], [138] -Pubertal gynecomastia[138], [140] and premature thelarche [138]
Tea tree essential oil N°CAS: 85085-48-9 / 8022-72-8 / 68647-73-4 Mixtures of chemicals.	Not estimated	-ER agonist: max 0,025% vol/vol [138], [140] -AR antagonist: max 0,005% vol/vol [138], [140]	No research has been conducted	ER agonist AR antagonist [21], [136]–[138]	-Changes estradiol and testosterone levels [136],during menopausal transition [139] -Abnormal breast growth and puberty [136], [138] -Pubertal gynecomastia[138], [140] and premature thelarche [138]

Phenoxyethanol

Since recently, phenoxyethanol (N°CAS: 122-99-6) raises concerns about its safety, because it is part of the glycol esters family, famous for its endocrine disrupting properties, in which all are forbidden [141]. This chemical is widely used in cosmetic products for its preservative properties and its pleasant smell [141], [142]. In 2009, its maximum concentration has been regulated at 1% in cosmetic products [1]. It is thus considered as safe under this concentration and is not regulated in North America [29], [31], [141].

Even though its rapid dermal absorption has been proven, potential endocrine disrupting activity have not been observed. All studies [141], [143] conducted gave inconsistent and irrelevant results. Neither nuclear receptor binding has been reported nor consequent effects under the maximal authorized dose. Supporting data is presented in the Table 13 below.

Table 13: Endocrine disrupting effects of phenoxyethanol

Compound [41]	**Exposure**	**Toxic dose**	**Skin absorption**	**Nuclear receptors**	**Effects**
2-phenoxyethanol N°CAS: 122-99-6 	Allowed under 1% (EU) [1], [141]	-NOAEL (development): 486 mg/kg/day -NOAEL (reproduction): 400 mg/kg/day [143]	-37% of the applied dose totally absorbed (within 24h, 1% in a rinse-off product) [141] -78% of the applied dose totally absorbed (within 24h, 1% in a leave-on product) [141] - Max 81% of the applied dose (leave-on product) [143] - Metabolized into 2-phenoxyacetic acid, in the skin, but mostly in liver [141]	Inconsistent results	No reported effects

Bisphenol A

Bisphenol A is a well-known endocrine disruptor (BPA; N°CAS: 80-05-7) forbidden as a cosmetic ingredient in EU [1] and Canada [31]. However, it is still used in packaging as an antioxidant, hardening agent, and stabilizer [144].

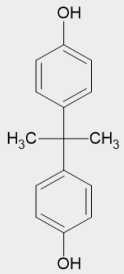
As it is part of the packaging, BPA might transfer to the products, and then penetrate the skin by topical application of the cosmetic. The final dose that succeeds in reaching the blood stream and coming from the packaging has not been determined yet [144]. However, we know that BPA is absorbed through the skin, and more readily in aqueous solutions [145], [146]. In the body, BPA is metabolized in 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP) [144].

Because of its phenolic rings, BPA is an ERα and ERβ agonist, and its metabolite MBP can bind these ERs with even higher affinities [5], [7], [17], [144]. BPA can also act as thyroid receptor antagonist [144], and bind ERRγ [144].

Due to its endocrine disturbing abilities, BPA is responsible for altering reproductive systems of males and females, leading to various diseases [11], [16], [144]. Additionally, BPA alters DNA methylation which causes neurobehavioral adverse effects on children [11], [17], [18], [144]. BPA also induces metabolic dysfunctions such as diabetes [11], [13], [43], [144], obesity [38] and cardiovascular diseases [13], [144]. Overall, the multigenerational and transgenerational effects of BPA *via* DNA methylation are often emphasized [11], [16]–[18].

Endocrine disrupting abilities of BPA are undeniable, as Table 14 shows. However, as BPA is not a cosmetic ingredient but a packaging component, the transferred dose from the packaging to the cosmetic that is later absorbed through skin must be determined. Yet regarding its low dose toxic effects, this compound must be avoided in packaging formulations to ensure safety of the consumer [144].

Table 14: Endocrine disrupting effects of bisphenol A

Compound [41]	Exposure	Toxic dose	Skin absorption	Nuclear receptors	Effects
Bisphenol A N°CAS: 80-05-7 	BPA transfers from the packaging to the product and then arrives on the skin *via* topical application. The final dose having taken this pathway has not been determined [144].	From 2 µg/kg/day [144]	- 0,022 µg/cm²/h [145] - 16-20% of the applied dose [146] - Metabolized in MBP [144]	- ERs agonist (BPA and MBP) [5], [7], [17], [144] -TR antagonist [144] - ERRγ agonist [144]	-Alters reproductive systems: male infertility, reduced spermatogenesis, polycystic ovarian syndrome, ovarian cysts, reduced libido, early puberty,.. [11], [16], [144] -Aggressive behavior, social anxiety and impaired memory of children [11], [16], [18], [144] -Increases risk of diabetes and GDM [11], [13], [43], [144] -Promotes adipogenesis [38] -Leads to cardiovascular diseases and hypertension [13], [144] -Alters liver and pancreas function [17], [144]

3. METHODS FOR STUDY OF ENDOCRINE DISRUPTORS' EFFECTS

As we can notice from available data detailed hereinabove, detecting the endocrine disrupting activity of compounds is hard, especially because it foils the classic toxicological laws [6], [20], [144]. It is all the more so challenging as for ethical reasons, tests on humans are not practiced and tests on animals are forbidden [147]. Additionally, effects might be species-specific, which means that *in vivo* models are not always representative of human exposure [21]. *In vitro*, *in vivo* and *in silico* alternative methods have been developed to overcome this difficulty.

To better understand endocrine disruptors' mode of action, *in vitro* methods were developed. To study epigenetic effects in response to chemical exposure, various cell systems are used [14], [22], [63], [148]. These methods analyze changes in DNA methylation, histone modifications and ncRNA, the seats of epigenetic alterations. Such techniques are used in the Reporter Genomic Methylation system (RGM) that traces DNA methylation *via* a minimal imprinted gene promoter driving a fluorescent protein [149]. The "Chemical Activated LUciferase gene eXpression" (CALUX test) is used to detect endocrine activity of chemicals, *via* cells that produce light in response to exposure to an ED [21]. Additionally, estrogenic activity of EDs can be assessed by biomarkers such as the CaBP-9k gene [150].

In vivo methods are attractive because they seem to be the most representative of human exposure to EDs. Zebrafish is a very interesting model to study EDs effects because of its dynamic endocrine system and its similar genes to ours. Less than 6 days-old zebrafish larvae and embryos are used because they are not considered as animals yet [151], [152]. Similarly, Japanese rice fish larvae hormonal activities are observed by fluorescence, enabled by a rapporteur gene. Androgenic, estrogenic and thyroidal activities can be detected by this method [21].

Moreover, *in silico* studies can predict endocrine disrupting activity of cosmetic ingredients. These computational methods [5], [153]–[155] consist in building 2D and 3D models of potential binding between a molecule and a nuclear receptor, based on molecular structures of ligands, nuclear receptors and binding energies.

While many alternatives have been developed, endocrine disrupting activities are still hard to study. Indeed, *in vivo* results extrapolation to humans implies exact similarities of hormonal mechanisms during early-stage of development [21]. Thus, combination of *in vivo*, *in vitro* and *in silico* methods would constitute sturdy evidence. However, as most of these alternatives are brand-new, time is needed before systematic tests of endocrine disrupting activity of cosmetic ingredients. Methods to assess complex mixture risks of endocrine disrupting activity also need to be developed as synergism of EDs can be even more toxic [9].

4. CONCLUSION

As endocrine disruptors are ubiquitous compounds nowadays, it is important to question their presence in cosmetics. Despite the important number of studies conducted on the subject, many relevant data is missing to properly conclude on endocrine disrupting activity of the compounds studied. Indeed, exposure through cosmetics is not as hazardous as dietary intake, as human skin constitutes an effective barrier to chemicals. Links between nuclear receptor binding and observed effects are weak, especially due to a lack of epidemiological studies. Adverse effects are hardly observed, mostly because of their delayed apparition and the complexity of detection of their causes. Fortunately, novel methods will facilitate research and enable relevant results. The latter will need to focus on synergism and inhibition of mixtures, as cosmetic formulations often gather several of the aforementioned ingredients. This aspect of endocrine disrupting activity will give further perspective to assess endocrine disruption of ingredients into the final cosmetic product.

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