cosmetics

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*Review*

# Endocrine Disruption by Mixtures in Topical Consumer Products

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**Abstract:** Endocrine disruption has been gathering increasing attention in the past 25 years as a possible new threat for health and safety. Exposure to endocrine disruptor has been progressively linked with a growing number of increasing disease in the human population. The mechanics through which endocrine disruptors act are not yet completely clear, however a number of pathways have been identified. A key concern is the cumulative and synergic effects that endocrine disruptors could have when mixed in consumer products. We reviewed the available literature to identify known or potential endocrine disruptors, as well as endocrine active substances that could contribute to cumulative effects, in topical consumer products. The number of endocrine actives used daily in consumer products is staggering and even though most if not all are used in concentrations that are considered to be safe, we believe that the possibility of combined effects in mixtures and non-monotonic dose/response is enough to require further precautions. A combined in vitro approach based on existing, validated OECD test methods is suggested to screen consumer products and mixtures for potential interaction with estrogen and androgen hormone receptors, in order to identify products that could have cumulative effects or support their safety concerning direct endocrine disruption capabilities.

**Keywords:** endocrine disrupting chemicals; cosmetics; consumer products; safety; phthalates; preservatives; parabens; benzoic acid; triclosan; formaldehyde; sunscreens; PBA

## 1. Introduction

Although the concept of endocrine disruption has been the subject of research and papers since the early '90s [1–4], there is still little clarity about what an endocrine disruptor chemical (EDC) is and how to apply the EDC concept in formulating regulatory procedures to improve safety and human health.

This is particularly relevant for research fields such as the one related to the safety of consumer products, where screening for endocrine disrupting ingredients and mixtures requires a clear research path and definition [5].

The most widely accepted definition is the one provided by the WHO, according to which "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations." Existing literature however provides different interpretations of this definition and the different perception of what an adverse health effect is promotes different views. Articles range from considering any shifts in baseline endocrine hormone levels as an "adverse effect" to refuse to consider a substance as a potential endocrine disruptor unless it causes clear toxicity-related pathological effects [6,7].

Some literature discards the notion of a substance being an EDC if its dose/response effect is low compared to known and approved chemicals, such as Ethynilestradiol (used in contraceptive pills).

However, this approach does not consider the fact that the dose/response of many EDCs have been repeatedly stated to be non-monotonic [7–9], thus making a dose/response comparison impossible. Low-dose endocrine activity is to be expected [7–10]. Furthermore, the fact that a substance with endocrine biological activity is accepted for pharmaceutical use does not imply that its effect can be used as a comparison for other chemicals or mixtures. In the aforementioned example, the fact that Ethynilestradiol has been considered safe as a contraceptive does not imply that similar substances, or even ethynilestradiol itself, are to be considered safe overall. A substance with similar or even much lower effects on the reproductive cycle should still be regarded as an EDC when used outside this intended purpose. While a substance that blocks reproduction may be viewed as safe as an ingredient for a contraceptive, it is clear that a reduction or loss of fertility should be interpreted as an "adverse effect" when resulting from a mixture not specifically designed for this, such as a cosmetic, a medical device or a drug with another purpose.

Measuring adverse effects or EDCs according to the current definition can be extremely complex, as adverse effects can appear decades later, or in progeny, or even by accumulation after several generations [5,11]. Effects can be irrelevant in individuals or small cohorts but produce significant consequences in large populations (i.e., drops in fertility across animal species) and only be measured by epidemiological studies [12]. A further challenge is understanding just how EDCs are able to program an organism to produce pathological effects later in life or in future generations by acting during development. Current research is looking into epigenetic effects of EDCs to evaluate pathological programming [11,13,14].

Therefore, it is imperative to find a common definition of what an endocrine disruptor is and to design and validate methods to assess substances or mixtures for endocrine effects. Consequences of the Exposure to EDCs are varied and even "weak" endocrine active substances can have complex interactions and effects when supplied in mixtures [8,15,16]. As such, any mixture including two or more substances with potential endocrine activity should be regarded as a potential EDC and tested as such, since the non-linear, non-monotonic interaction of two or more ingredients can result in endocrine disruption even if the concentration of each of them has been proven safe individually [17].

Another concern is related to the accumulation of potential endocrine disruptors caused by their persistence, be it in the exposed organism or in the environment. The list of substances being screened as potential EDCs include several molecules that are extremely resistant to degradation, especially liposoluble chemicals. Several persistent organic pollutants have been linked with endocrine disruption [18] and substances that have been banned in most countries are still found to bioaccumulate in alarming concentration in several organisms, including humans, resulting in adverse reproductive effects.

On the other hand, it is clearly necessary to avoid demonizing a class of chemicals, or a category of products, based on the presence of endocrine agonists and antagonists in it. Doing so would lead to consider an almost unlimited number of compounds as EDCs.

The overall concern about endocrine disruptors is linked to three strands of evidence: the increasing incidence of several endocrine-related disorders in humans, the existing endocrine-related effects in the wildlife and the correlation between EDCs and known pathologies in laboratory studies.

The focus of the present article consists in reviewing the existing literature to provide an overview of EDCs and their effects, focusing on providing an overview of potential EDCs and endocrine active substances used in topical use consumer products such as cosmetics or medical devices, as well as the possible solutions to reduce the related health risks.

## 2. State of the Science and Regulatory Framework

To date, significant knowledge gaps exist concerning endocrine disruption. Screening known molecules for endocrine activity and endocrine disruption is a monumental work that will take several more years of work by the scientific community. Investigating the potential effect of mixtures and

combination of such molecules will take even longer. Epidemiological studies are long term by definition, especially when reproductive or generational effects are taken into account [12]. Linking known pathologies to endocrine disruption is also complex, due to the multifactorial nature of those pathologies themselves as well as to the intrinsic risks of such an analysis. The fact that exposure to endocrine disruptors is fundamentally ubiquitous worldwide generates bias in population analyses and epidemiological studies, especially since the lack of an unexposed "control" population increases the risk of confounding causality and simultaneity.

The existing regulatory framework concerning endocrine disruptors is therefore necessarily focused on validate agreeable methods to identify and test EDCs, on screening an increasing list of potential endocrine actives prioritizing them according to the likelihood of their action and secondary risk factors such as bioaccumulation and environmental persistence and on providing safety assessments for known substances.

The European Commission has a strategy on endocrine disruptors since 1999, which resulted in criteria to identify substances with endocrine disrupting properties being added to the Plant Protection Products Regulation (EC 1107/2009) and to the Biocidal Products Regulation (EU 528/2012) [19]. Additional references to EDCs were mead in regulation EC 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), in Regulation EC 1223/2009 on cosmetic products and in the EU Regulation on Food Contact Materials. The Commission and Member States continue to participate in the OECD—Endocrine Disruptor Testing and Assessment Task Force (EDTA), which was set up in 1998 with the goal of developing agreed test methods for endocrine disruptors.

The European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) subsequently provided a Guidance document for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 that was recently adopted in June 2018 [20]. This guideline also identifies a selection of substances falling under the REACH regulation, the cosmetics products regulation and the water framework directive, for which data are available.

Similarly, the US Environmental Protection Agency (EPA) promoted an Endocrine Disruptor Screening Program (EDSP) since 1996, with the combined objective of validating endocrine disruptor screening tests and setting a priority list of chemicals to undergo testing. The action resulted in a draft of the initial list of chemicals to be tested in 2007 and later in a finalized list for tier 1 screening in 2009.

The World Health Organization (WHO) also provided documents to support decision makers, including two "State of the Science on Endocrine Disruption Chemicals" documents in 2002 and 2013.

To date, it is however recognized that globally agreed test methods for endocrine disrupting effects do not yet exist, although scientific tools and laboratory methods are available [7]. Some OECD methods have been developed for in vitro screening: test guides no. 455, 456, 457, 458, (see Section 5). Furthermore, there are no viable laboratory models to screen for several human health effects and target organs at the same time.

Ongoing research will take many years to provide a complete response to EDCs and however complete the data on endocrine disrupting molecules may become, the need to test mixtures such as consumer products for cumulative effects will remain. Consequently, a key focus will have to be the validation of test methods to screen mixtures and finished products.

## 3. Endocrine Disruptors and Human Health

EDCs have been linked to a wide range of pathologies and long-term effects [21]. This include a wide range of direct endocrine and reproductive effects such as infertility, defects in gametogenesis, structural changes in sexual organs (endometriosis, hypospadias and so forth), alteration in the normal onset of puberty and puberty-related development. Further effects include alteration of the insulin response leading to diabetes, metabolic syndromes and obesity [22], as well as the promotion of breast, testicle and prostate cancer [23].

EDCs have also been investigated for their role in immune and autoimmune diseases and their developmental effect have been correlated to brain development problems and nervous system diseases such as Alzheimer, Parkinson and ADHD. Furthermore, a role of EDCs has been studied in correlation with the increasing incidence of asthma, hypertension and strokes [21,24,25].

Human disease trends investigated by the WHO showed a significant increase of reproductive problems and in EDCs-related cancer forms in the past 50 years (WHO State of the Science report, 2012) and a significant decrease in human fertility rates in several areas of the world. The potential effect of endocrine disruption in development and in the transmission of environment-derived cancer predisposition also plays a relevant role in the current epigenetic model of carcinogenesis [26]. Indeed, effects of endocrine disrupting chemicals may be transmitted to further generations through germline epigenetic modifications or from continued exposure of offspring to environmental exposure [21].

Several studies [18,27–29] linked EDCs to antiandrogenic effects and male sexual disorders, including loss of fertility. Existing circumstantial evidence in human and laboratory studies on animals point to the fact that pathologies such as cryptorchidism, hypospadias, testicular cancer and reduced semen quality may be linked to the exposure to androgen antagonists during fetal development, however further research is needed. The proven correlation between anti-androgenic and estrogenic EDCs and testicular dysgenesis in laboratory rats is not sufficient evidence of a similar impact on the human population.

Similarly, some EDCs were linked to decreased fertility and diminished ovarian reserves in women [30–34]. Animal studies confirmed that EDC exposure can affect mammary gland and uterine development, both in terms of timing and in terms of morphological changes and in silico analyses contributed to predict the mechanics behind this [16,35,36]. It is still debated however whether animal models can be accurate predictors of the effect of the same substances in humans. Data correlating EDCs to premature puberty and sexual development, adverse pregnancy outcomes and reproductive anomalies in human are still mostly missing, mainly because of the difficulties implied in relating exposure to substances and reliable measures of these parameters. Further reproductive effects of EDCs have been linked with lower weight at birth, premature birth, development effects and behavioral changes.

EDCs have also been linked with abnormal sex ratios in births, resulting in a disproportion of female births as compared to male births in humans. Similar sex ratios imbalances have been observed in sea organisms, including fishes and mollusks.

Epidemiological studies add to evidence that EDCs influence the risk of breast cancer [8,9,37–41], prostate cancer and testicular cancer [37,42,43]. The mechanics of this effect are not yet completely clear and will require further research.

The link between endocrine disruption and adverse effects on neurogenesis is not widely understood, although several insights were provided about action through several classes of receptors, with the best documented direct pathways being reported for nuclear steroid and xenobiotic receptors [44,45].

Animal studies investigated the effect of known or potential EDCs on neural development via direct or indirect effect on aromatase, estrogen receptors and androgen receptors [17,46–49]. Population studies concluded that similar effects exist in human, specifically linking thyroid disruptors during fetal development with cognitive and behavioral impairment [22,50–55] even at low doses.

Further roles of endocrine disruption have been found in relation to metabolic disorders, including alteration of cholesterol metabolism, weight gain, obesity [56–58] and type 1 and 2 diabetes [22,59].

Overall, the complex interaction of endocrine active substances and mixture can result in a wide range of adverse effects. In several cases, if endocrine disruptors are found in mixtures, cumulative action is suspected. The relevance of deepening the available knowledge about EDCs, their mechanisms of action and their potential combined effects is critical to understand their role in a wide range of key pathologies and devise safe policy to handle their use.

## 4. Endocrine Disruption of Natural Ecosystems and Animal Reproduction

Several known and potential endocrine disruptors are known to accumulate in the environment and persist in time. As such, EDCs have been linked with environmental effects, up to and including the drop in populations of several species, resulting in widespread effects on several ecosystems [1]. Indeed, it was the effects observed in animal populations and their correlation to environmental exposure to strong EDCs, that originally led to the identification of the concept of endocrine disruption and endocrine mediated adverse reproductive outcomes, eventually leading to the research of similar effects in humans [2].

The correlation with decline in wildlife population has been partially confirmed by the recovery of several species after restrictions were applied to the use and commercial distribution of some identified persisting pollutants. However, demonstrating the link between EDCs and population declines is extremely hard, due to confounding factors and to the complexity of identifying the specific role of endocrine disruptors among that of several other environmental and ecological factors.

It is theoretically possible that persisting EDCs could cause a drop in fertility in several species, thus contributing to the effect. Similar results of EDCs exposure have been confirmed in vitro in several species. The same could not be proven in wildlife species yet.

## 5. Endocrine Disruptors Testing: The OECD and US EPA Methods

Given the aforementioned role of EDCs in several pathologies and adverse effects, the need for shared, validated methods to identify potential endocrine disruptors and assess their effect is great. Specifically, methods to screen large numbers of substances or mixtures are a key concern.

Both the Organization for Economic Cooperation and Development (OECD) and the US Environmental Protection Agency (EPA) promoted new in vitro methods to screen large number of substances. The OECD methods focused on action pathways for endocrine disruptors, determining the activity of potential EDCs on individual elements of the endocrine system. The OECD has reviewed methods for most if not all known endocrine signaling pathways and axes and has proposed methods to screen substances or environmental samples for androgenic or estrogenic action in vitro. These methods resulted in the OECD 455, OECD 457 and OECD 458 guidelines for the determination of estrogenic and androgenic antagonists and agonists and OECD 456 for screening of steroidogenesis, specifically the production of 17ß-estradiol (E2) and testosterone (T). These in vitro screening methods are proposed as a quick analytical tool to screen large numbers of substances on specifically modified cell lines. The OECD has also proposed further testing methods in vivo, such as OECD Test. 443 for one-generation reproductive toxicity studies. In vitro screening methods are the most promising for the screening of the endocrine disruption potential of complex products and mixtures. Specifically, Test Guideline 455 uses a Stably Transfected TA assay using the Estrogen receptor alpha (ERα)-HeLa-9903 cell line, derived from a human cervical tumor, while Test Guideline 457, which used the BG1Luc4E2 cell line derived from a human ovarian adenocarcinoma, was recently deleted (Jan 2018) and a test method on MCH-7 mammary cancer cells has been nominated to replace it. Both the line used by OECD 455 and the one formerly used for OECD 457 were stably transfected with a responsive luciferase reporter gene to detect agonist or antagonist effects on ERα and ERβ by luminometer measurements. Test Guideline 458 uses a similar approach on the AR-EcoScreenTM to detect agonist and antagonist effects on Androgen Receptors (AR). Test Guideline 456 instead uses the H295R adreno-carcinoma cell line to detect any effects on steroidogenesis and specifically on the production of 17ß-estradiol (E2) and testosterone (T). Although these four test methods were originally designed to screen individual substances, they can be used in an integrated approach to exclude possible pathways of endocrine disruption on consumer products, thus allowing to screen mixtures for potential endocrine effects. Such an integrated approach could be used to evaluate topical products in order to increase customer safety by ruling off most, if not all, endocrine disruption effects.

Similarly, the US EPA has proposed several in vitro test methods (i.e., methods 890.1200, 1250, 1300 testing for effects on aromatase, estrogen receptor binding and estrogen receptor transcriptional

activation respectively) and in vivo on several animal models. A second tier of test guidelines is being published to assess one-generation, two-generation and development toxicity.

Overall, several screening methods have been proposed and, in some cases, approved [60]. It is however more relevant how the proposed methods were structured into a testing strategy focused on screening large numbers of substances in vitro, investigating samples in large numbers, before proceeding to in vivo studies to research in greater depth the actual effects and pathways of action of identified potential EDCs. Ongoing research needs a similar focused and structured approach in order to provide data and key information about the endocrine disrupting potential of the many substances yet to be confirmed as EDCs.

Further research strategy key focuses should include the development of easily applicable in vitro screening methods to test mixtures of endocrine active ingredients in consumer products, taking into account the potential cumulative interaction of combined substances. As previously mentioned, a combined approach using OECD test guidelines currently seems to be the best possible solution.

Further screening methods should be devised to verify the non-monotonic dose response of substances or mixtures, as well as the potential endocrine disrupting potential of metabolites and substances deriving from decomposition or internal reaction [17]. Furthermore, a direct receptor binding approach may be insufficient, as substances have been shown to act indirectly by interacting with hormone receptors and changing their response to their natural ligand [9]. This sort of insidious mechanisms will need to be considered to understand potential EDCs that do not rely on standard agonist/antagonist action.

The budding databases of known and potential EDCs promoted by several agencies will be an invaluable tool for the next required step, in which the focus will likely be shifting from identifying endocrine disrupting substances to testing the effect of mixtures and combined EDCs in products [61]. Similarly, several in silico tools and computer models are being devised in order to streamline the identification and prioritization of potential EDCs for further studies [35,62].

## 6. Endocrine Disruptors in Cosmetics

Given the potential endocrine disrupting effect of mixtures of endocrine active substances, it is critical to identify ingredients in finished products with endocrine effects. Even where those ingredients have been tested and confirmed not to produce adverse effects, cumulative action can result in endocrine disruption. Consumer products applied on the skin on a daily basis, such as cosmetics, topical medical devices and personal care products, are a potential source of combined endocrine actives and should be investigated extensively. Modern day cosmetics include fixatives, dyes, preservatives such as parabens, formaldehyde, glutaraldehyde, aromatic amine derivatives, metal salts, UV filters, phthalates, solvents, fragrance ingredients and more [63] Some of these compounds are key active of classes of products such as UV filters, while other have secondary roles in stabilizing formulations or as preservatives.

They can also contain contaminants deriving from raw materials or from packaging components, like phthalates, bisphenol A (BPA) or heavy metals. The current EU regulatory framework (Regulation EC No 1223/2009 on cosmetic products) provides an extensive list of banned ingredients or substances (Annex II), as well as limited ones (Annex III, IV, V, VI) while it does not contain a positive list of allowed ingredients. The Inventory of Cosmetic Ingredients filed by the European Commission (CosIng-accessible at https://ec.europa.eu) provides the correct INCI (International Nomenclature Cosmetic Ingredient), IUPAC and chemicals names to identify a cosmetic ingredient but it does not represent a positive list of authorized ones. The choice to use any ingredient or substance which is not banned or regulated as above is left to the manufacturer, provided the completion, before marketing, of a safety assessment procedure, the CPSR (Cosmetic Product Safety Report), as described in annex I of the Cosmetic Regulation. The CPSR is kept by the manufacturer itself (at an address specified on the cosmetic label) and shall be available for authorities in case of request but it is not required to be submitted for approval.

Most of the limited or regulated allowed ingredients (i.e., preservatives, sun filters, colors and dies) have been extensively studied in terms of toxicological impact both for humans and for the environment, including some potential endocrine disruption activity. These safety data and opinions are provided by regulatory and toxicological agencies such as the SCCS (Scientific Committee on Consumer Safety), the CIR (Cosmetic Ingredient Review), the EU Commission working groups, ECHA (European Chemicals Agency), EPA, FDA and so forth and are available also for many single chemicals or whole categories of chemicals widely used in cosmetics, even though not for all of them nor exhaustively. These opinions and guidelines, provide an assessment of safety when the investigated ingredients are used in the framework of allowed and described concentrations, with the required quality degree, for topical use finished products and according to the classification they are intended for (skin, mucosae, eye contour, hair, face, body, women, babies, rinsing or stay-on products etc.). It is also true on the other hand that for many ingredients used in cosmetics, toxicological information is still lacking or incomplete, especially when long-term effects are concerned. For a majority of these ingredients, the basic toxicity profile is very good as they either belong to GHS categories 4 and 5 and are thus known to be edible or inert, or there is a long history of safe human use, so that there may be no reason to suspect unknown toxic effects.

The testing ban for cosmetic ingredients, that came fully in force in 2013, forbids to perform any kind of testing on animals, including toxicity assays. Since testing for long term toxicity endpoints, like carcinogenicity or endocrine disruption is typically an investigation that requires complex organisms and several offspring generations, it is clear that this resulted in stop in producing more data of this kind and making it publicly available.

Nonetheless, in the past years the scientific community has made a great effort in characterizing endocrine disruptors and studying the potential endocrine impact of cosmetic ingredients and their degradation products individually. Several in vitro test methods have also been developed, to at least partially replace animal models for this purpose. Human epidemiological studies and observational studies were also evaluated, leading to critical findings and to a better understanding of the mechanism of action of several endocrine active molecules. Indeed, the large amount of work performed has led to the understanding of subtle risk factors, such as the fact that some apparently low toxicity compounds can degrade or be transformed by metabolic or environmental action into others with greater toxicological effects. Similarly, the non-monotonic nature of the dose/response of some compounds has been confirmed. Altogether, the results of this endeavor to understand characterize and regulate cosmetic ingredients led to a better understanding of direct and indirect endocrine disruption and to regulating and banning many potential endocrine active compounds. Our current focus is, however, the potential risk caused by yet incompletely understood interactions of diverse endocrine actives when present in mixtures and finished products, including their potential cumulative effects or synergistic action. Where the individual ingredients have been extensively studied and regulated as safe, a margin of risk still exist in combining safe ingredients with possible cumulative effects. The potential risk justifies the concern of unknown interactions even though direct impact may be less likely due to the existing precautions and regulations.

Since the priority in investigation has been directed towards food and environment, topical products seem not to be the greatest concern due to their topical route of exposure. The skin barrier indeed helps to reduce the risk of intake of EDCs that can be conveyed through cosmetics and other, topical products. We have to notice on the other hand that these products are used on a daily basis, without limits, assuming that they are 100% safe and also by the portion of the population who is at higher risk, like children, newborn babies and pregnant or breast-feeding women. An oil or a body cream can be spread all over the body of an infant for example, with a very high rate of absorption. A pregnant woman can use high SPF sunscreens all over the body, or oils/creams. Children use toothpastes and toiletries on a daily base. Even if cosmetic ingredients taken individually are considered to be safe, we cannot be completely aware of the cumulative effects. Also, we did not know in the past that some molecules could show ED effects at very low percentages (even at ppb

scale concentrations indeed) that require safety assessors to review the position of some ingredients (like for example UV filters, cyclic siloxanes, preservatives or fragrance components) or to reconsider the threat posed by some contaminants (like phthalates, BPA, pesticides or heavy metals). Other cosmetics or consumer products for topical use, like for example some medical devices, may be applied on mucosae in the genital area and have a direct effect on related organs. Also, products like toiletries and sunscreens, will be discarded in the environment and a particular attention should be payed when evaluating their safety of use without forgetting the safety for water- and soil-based ecosystems.

Cosmetic ingredients that are known or suspected to have any sort of endocrine action include several families of compounds. The following section will proceed to analyze some groups and substances individually.

### *6.1. Parabens*

Parabens (p-hydroxybenzoic acid esters) are used as antimicrobial preservatives and are so common in the environment that traces have been found in drinkable and mineral water samples [64]. The EU and ASEAN banned five parabens (isopropylparaben, isobutylparaben, phenylparaben benzylparaben; and pentylparaben) in 2014 and 2015 respectively. Other parabens still commonly employed in cosmetics because they were judged as safe include propyl-paraben ($C_{10}H_{12}O_3$), methyl-paraben ($C_8H_8O_3$), ethyl-paraben ($C_9H_{10}O_3$) and butyl-paraben ($C_{11}H_{14}O_3$). In vitro studies on the field demonstrated that these molecules can damage the DNA and interfere with the normal mitochondrial function [65]. Their ability to increase the proliferation of human breast cancer cells has also been demonstrated. However, a clear connection between parabens exposure and cancer risk has not been proved yet. Parabens have been demonstrated to act as weak xenoestrogens in animal models, although activity seems to increase with the length of the alkyl group. The administration of parabens in mice was also correlated to obesity and to epigenetic effects on the adipogenic process [66]. Similarly, paraben urinary concentration has been correlated to alterations in the serum concentrations of reproductive and thyroid hormone in humans (2). Butyl paraben has also been demonstrated to produce weak antiandrogenic effects in vitro, either alone or as a contributor to cumulative effects in mixtures [67]. Public opinion and the application of the precautionary principle have been leading several cosmetic manufacturers to look for other options to replace parabens with other preservatives.

The main factor used to support the safety of these molecules is the fact that their ability to activate estrogenic responses is extremely low and would require doses thousands of times higher than the ones used in consumer products. This consideration, despite being valid in itself, does not account for non-monotonic responses and mixture interactions [9].

Parabens, even if considered to be safe on their own, should still be regarded as endocrine active substances and as such should lead to further investigation when combined with other known EDCs or endocrine actives.

### *6.2. Other Preservatives/Antimicrobials*

The most relevant antimicrobial agent with endocrine active properties is without doubt Triclosan. This substance has been banned by the FDA in 2017 for unrelated concerns (lack of efficacy). Triclosan is considered as a weak potential endocrine disruptor and has been observed to bind the androgen receptor and estrogen receptor with both agonistic and antagonistic effects depending on model and cell type. Since it is extremely common in cosmetics, detergents and other consumer products, Triclosan is almost ubiquitous and exposure is constant and extensive over time [68,69]. It is currently classified as a contaminant of emerging concerns, mainly due to its demonstrated absorption as it has been detected in breast milk, blood and urine. The substance has been associated to increased fetal testosterone levels in humans [70] and higher weight at birth. A link with gestational diabetes mellitus has been indicated but is as yet unconfirmed. Further associations were researched and excluded with developmental obesity [71], while animal models showed links with hypothyroidism [72].

Both Triclosan and its equivalent triclocarban have also been demonstrated to inhibit human aromatase [73] and to be associated with diminished antral follicle counts in humans.

Another diffused cosmetic preservative, Benzoic Acid, has been shown to directly induce insulin and glucagon secretion after intravenous injection in an animal model [74], however earlier reports that the substance is uterotrophic and estrogenic to the rat and mouse a have not been confirmed [75].

Formaldehyde and paraformaldehyde are allowed in cosmetic products up to 0.2% when used as preservatives (even if Formaldehyde may be used up to 5% if used in nail hardeners) according to the Cosmetic Eu regulation 1223/09. However, some other preservatives such as Benzylhemiformal, Sodium Hydroxymethylglycinate, Bronopol, Diazolidinyl urea and Imidazolidinyl urea can decompose in aqueous and polar solvents to release some or all of their formaldehyde content [76]. There is currently no direct link between paraformaldehyde and endocrine disruption, however the monomeric form formaldehyde has been shown to have long-term low-dose effects on ovary function [77] and to damage spermatogenesis [78] in animal models and to be able to cross the placenta and affect differentiation and hormone functions in human cells [79] and as such should be regards as a potential endocrine active.

Quaternium-15 can also release low amounts of free formaldehyde according to the American Cancer Society and for this reason may be involved in potential risks, either acting as endocrine disruptors or working in synergy with other EDCs.

Climbazole has also been discussed in regard to potential endocrine disruption by the ECHA due to suspected reproduction effects but no agreement has been reached besides requesting further testing of the substance.

Other preservatives, such as o-Phenylphenol (OPP), sodium-OPP and potassium-OPP have been the subject of evaluation but data concerning their safety has been ruled too limited to predict or exclude health risks [80].

### *6.3. Fragrance Ingredients*

Synthetic fragrances include several substances that are currently being investigated as endocrine actives and thus potential EDCs. Substances such as musk xylene or musk ketone are very resistant to degradation and can thus accumulate in the environment in stable and, by now, almost ubiquitous forms. Specifically, musk xylene has been listed as a substance of high concern by the EPA and is both very persistent and capable of high levels of bioaccumulation.

According to available literature, nitro musks are not easily absorbed through the skin, with very low levels found in body fluids and excretion even after several hours from application. Data about nitro musks from animal studies are also conflicting, with studies reporting adverse effects on pregnancy and fertility in some species (i.e. zebrafish) and no related effects in other [81]. Nitro musks have been demonstrated to increase proliferation in vitro on human breast cancer cells [82], with secondary evidence of the mechanics being related to estrogen receptor response, although this does not imply cancerogenicity or endocrine disruption by itself.

Several nitro musks derivatives, including 4-NH2-musk xylene, 2-NH2-musk xylene and 2-NH2-musk ketone, have shown competitive binding of estrogen receptors as well. Despite the ongoing controversy, the European Union has established maximum authorized concentrations for musks ketone and xylene, (1.4% and 1.0% respectively) and banned them in oral products. Similarly, musks ambrette, tibetene and moskene were prohibited.

Isobornyl acetate, another widely used fragrance ingredient, has also been investigated for possible endocrine activity, however no direct correlation with adverse effects have been observed in animal studies [36].

Polycyclic musks such as HHCB (Galaxolide) and AHTN have also been object of several studies to assess its ability to bind and activate endocrine receptors, with conflicting results [83,84]. HHCB have been linked with steroidogenesis and transcriptional activation of Estrogen receptor alpha and beta in a cell type dependent way [85]. AHTN has been confirmed as a weak endocrine activator.

Other potential endocrine active in fragrances include diphenyl ether [86], several terpenes and essences and benzylacetate.

### 6.4. Cyclic Siloxanes

Cyclosiloxanes include very persistent, very bioaccumulative compounds. Among them, Siloxane D5 was classified as a substance of very high concern by the European Union. Siloxane D5 has been scheduled for limitation to 0.1% in wash-off cosmetics starting in 2020.

Cyclic silicone polymers based on cyclosyloxanes (Cyclomethicones) have been detected ubiquitously in the environment due to their use in medical and cosmetic products. Cyclomethicones have been proved to be toxic for aquatic organisms and cyclomethicones D4 and D5 among them are known to bioaccumulate in aquatic life in laboratory studies. Bioacumulation in wildlife still requires confirmation due to contradictive studies and data indicating decrease of siloxanes concentrations in the higher ranks of the food chain.

### 6.5. Alkyphenols

Alkyphenols are a family of organic compounds obtained by the alkylation of phenols. Alkyphenols are classified as xenoestrogens and the European Union has restricted the use of alkyphenols and among them nonylphenols specifically, due to its toxicity, persistence and possible bioaccumulation [80,87].

In the current list of priority substances to be analyzed as part of the European Commission strategy on endocrine disruptors, Nonylphenol and Octylphenol are both listed as medium priority molecules. Both are used as raw materials for detergents, emulsifiers, wetting agents and dispersion agents, as well as anti-oxidants. Both are also used as spermicides in contraceptive foams and are ubiquitous as components of plastic containers. Both are listed as biodegradable but are expected to bioaccumulate.

Production is prohibited and the substances are being replaced with alcohol ethoxylates Nonylphenols are capable of mimicking estradiol and bind the estrogen receptor only partially, resulting in a relatively weak effect. They have been known to bind the androgen receptor as well in fishes.

Possible effects of nonylphenols include feminization (in animal models), decrease in fertility and decreased survival (in fishes) [27]. In human, induction of the expression of placental and uterine proteins may be indicative of the compound's ability to permeate the placental barrier and reach the fetus during pregnancy. Effects on the placenta also include increased apoptosis and cytokine signaling alterations [88].

Nonylphenols also showed several metabolic effects, including obesogenic properties and possible hepatic stress. These substances have also showed to increase cell proliferation in estrogen-related cell cancer models and cell lines in vitro, although this does not imply carcinogenic properties.

In several animal models and in vitro studies, nonylphenol has been linked to severe adverse reaction, up to and including induction of neural stem cells death [89] in murine cell cultures, reduction of gonadal weight and induction of negative reproductive outcomes in vivo in mice [31]. The molecule has been associated with several endocrine receptors, including direct binding of the transthyretin receptor, estrogenic activity and anti-androgenic activity.

### 6.6. UV Filters

Several UV filters were either investigated for, or are suspected to have, some endocrine activity. These include 2-ethylhexyl 4-(dimethylamino)benzoate (Ethylhexyl dimethyl PABA, or Padimate O), Octinoxate (Ethylhexyl Methoxycinnamate) and benzophenones. Literature also pointed to nanoscale physical filters as potential substances with reproductive toxicity and endocrine effects [23,90], at least in animal models, although this does not necessarily imply action through an endocrine pathway.

Furthermore, recent population studies have demonstrated that large cohorts can be exposed to UV filters in the environment, even without direct administration and in seasons not associated with the use of sunscreens [91], pointing at the environmental ubiquity of some of these compounds.

The sunlight-mediated mutagenicity of Ethylexhyl dimethyl PABA has been demonstrated in yeasts as early as 1993 and photo carcinogenic activity has been hypothesized but has been disproved by several in vivo studies on murine models. The product may soon be delisted in the EU cosmetic regulation.

Benzophenone and its derivatives are already known to be pharmacologically active and have been demonstrated to bind the pregnane-X receptor. Benzophenone-2 has also been linked to estrogenic activity and developmental effects in zebrafish [92,93]. Most benzophenones indeed show endocrine action at some levels through the estrogen pathway.

Oxybenzone (Benzophenone-3) has been linked to breast morphology alterations through weak binding of Estrogen receptor alpha and alteration of the expression of the progesterone receptor in mammary epithelium in mice [94]. An association with modulation effects on sexual maturation was also made in humans [95], where the substance was linked with earlier menarche. The substance has also been shown to be absorbed by dermal uptake [96]. 4-hydroxy-Benzophenone was similarly correlated with expression of triiodothyronine (T3), thyroxine (T4), insulin-like growth factor I (IGF-I) and its binding protein IGFBP3 during pregnancy, resulting in statistically lower weight and size at birth [97]. Oxybenzone has also been linked to modulation of the expression of estrogen receptors alpha and beta, Gpr30 G protein coupled estrogen receptor and peroxisome proliferator-activated receptor gamma.

Homosalate (HMS) and Ethylhexyl-Methoxycinammate have also shown estrogenic activity on the estrogen receptor alpha [98]. ethylhexyl-Methoxycinnamate has also been showed to form Z-octyl-p-methoxycinnamate as part of its natural photodegradation due to the blocked UV light. This sub product has been linked with genotoxic effects. 4-methylbenzylidene camphor and 3-benzidene camphor are also estrogen receptor ligands [99]. On the other hand, Homosalate and 2-ethylhexyl 4-dimethylaminobenzoate (OD-PABA) were reported not to have endocrine disrupting effects in murine model studies [100]. Early life exposure to UV filters have also been linked to prostate gland development alterations in rats [101].

### *6.7. Phytosterols*

Several phytosterols from vegetal sources have been connected with endocrine effects. Coumestrol and resveratrol are both known to show very high affinity for estrogen receptors. A common source of phytosterols are soy extracts used in cosmetics, including soy isoflavones (genistein, daidzein and glycitein) and soybean oil. Soy isoflavones were reported to be natural selective estrogen receptor modulators with tissue specificity, resulting in estrogenic effects in some tissues and antiestrogenic effects in others. Genistein is considered the most endocrine active of soy derived compounds and is used as a natural substitute for estrogen replacement therapy in postmenopausal women.

Genistein has been reported to affect the development of the reproductive system [102,103] and other estrogen-sensitive tissues [104] in animal models. The substance has been also linked with behavioral effects and alterations of the reproductive development of offspring if administered to lactating animals [105]. Further effects may include alterations of the neurogenesis process in utero [106] and epigenetic modulation [107]. However, the studies focused on phytoestrogen exposure via dietary pathways, instead of administration through topical products. Despite the effects observed in animal models, soy and soy derivatives are mostly deemed safe for dietary consumption. The role of soy derived phytoestrogens in cosmetics would need to be investigated separately, especially in mixtures and formulations containing more known or potential endocrine actives.

Several other phytosterols are known or suspected to have endocrine effects. Serenoa repens is known and used for its antiandrogenic effects and is suspected to be able to induce effects on sexual

development and several extracts from other plants, such as licorice or Chinese peony [108], are known to display similar effects.

### *6.8. Skin Whitening Agents*

Some skin whitening agents used in cosmetics are known or suspected endocrine actives.

Kojic acid has been demonstrated to interfere with either iodine organification or iodine uptake by the thyroid, resulting in altered thyroid functions [109,110]. Another compound used in skin whitening is resorcinol, which, as previously mentioned, has similar effect on thyroid function and hormone production. A third compound used in similar products is arbutin, extracted from the Chinese yam plant. Arbutin has been shown to determine estrogenic effects, mainly mediated by estrogen receptors ERβ and GPR30 [111]. Literature about these 3 compounds is however still minimal.

### *6.9. Other Cosmetic Ingredients*

Several glycols are used as humectants in cosmetics. These compounds seem to display some level of endocrine action. Propylene glycol was loosely associated with disruption of reproduction through an insulin-related pathway in an animal model [112]. Both ethylene glycol and diethylene glycol were related to antiandrogenic and antiestrogenic activities [113]. Butylated hydroxyanisole (BHA), an antioxidant, has also been associated with weak estrogenic effects, reduced serum testosterone and abnormal reproductive organs development [114]. Literature and data are however limited and it is difficult to draw a conclusion regarding the safety of BHA when referring to its endocrine disrupting effect. The product might be associated with endocrine disrupting effects in human but evidence is lacking. Butylated hydroxytoluene (BHT), another related antioxidant, has also been loosely correlated with thyroid effects, however its weak anti-estrogenic effect was confirmed only in some cell lines and not in others [115]. P-phenylendiamine, a compound used in hair dyes, has been listed by the ECHA among the Substances of Very High Concern (SVHC) because of ED concerns, to be screened in the context of the impact assessment on criteria to identify endocrine disruptors. No definitive proof of endocrine disruptor effects is however currently available. Hair days also contain resorcinol, a compound that has been shown to cause thyroid dysfunction, effects on the central nervous system and alterations in the adrenal glands in animal studies [116–118].

### *6.10. Phthalates and Perfluorinated Chemicals*

Phthalates are occasionally used in personal-care products as vectors for fragrances, or as plasticizers for cellulose acetate [119]. However, their use as an ingredient is limited and are more commonly found in cosmetics as trace contaminants derived from packaging.

Phthalates have been linked as a family to several action pathways, including direct and indirect estrogenic and antiandrogenic effects, as well as modulation of the hypothalamus pituitary thyroid axis [120]. Great care should however be taken in correlating specific molecules to specific effects.

Substances such as diethyl-phthalate (DEP, $C_{12}H_{14}O_4$), dimethyl-phthalate (DMP, $C_{10}H_{10}O_4$) and dibutyl-phthalate (DBP, $C_{16}H_{22}O_4$) have been extensively used in the past. Today, the use of lower molecular weight phthalates is being phased out due to safety concerns, mainly linked to scientific evidences about their endocrine-disrupting potential. Low molecular weight phthalates have been correlated with cognitive, mental and behavioral effects including lower IQ, hyperactivity, attention problems and problematic social communication, as well as to adverse pregnancy outcomes and developmental alterations of the reproductive system [121]. A complete list of banned phthalates can be obtained from the European Commission database for information on cosmetic substances and ingredients (CosIng), which includes information from the Cosmetics Regulation (EC) No 1223/2009, the Cosmetics Directive 76/768/EEC, the Inventory of Cosmetic Ingredients as amended by Decision 2006/257/EC and the Opinions on cosmetic ingredients of the SCCS. The list was updated as recently as 24 April 2018.

Even when they are not used as ingredients, phthalates are fundamentally ubiquitous because of their use as plasticizers in plastics, leading to the presence of their metabolites to be found in humans and animals practically everywhere [122].

The low molecular weight phthalates are however being replaced with other molecules from the same family with longer carbon backbones, as those have been considered to be safer and less capable of penetrating the skin barrier. The most commonly used phthalate however, di-2-ethylhexyl phthalate (DEHP) have been linked with endocrine disrupting effects on the reproductive system due to his action as an androgen antagonist. DEHP has been correlated to lower fertility and sperm motility in males [90], to defective oocyte maturation [30,123], to anomalies in sexual development [122], to asthma [25], to breast cancer induction and to a wide range of other endocrine effects [124]. Recently, DEHP was categorized as a non-persistent endocrine disrupting compound by the world health organization (WHO). Dicyclohexyl phthalate has also been shown to modulate estrogen receptors in human breast cells, however this does not prove carcinogenic effects [125]. Phthalates and DEHP specifically, have been correlated to hypospadias, cryptorchidism and other male reproductive anomalies. Numerous studies of DEHP have shown changes in sexual function and development. More worryingly, DEHP has been reported to be able to increase the accumulation of other EDCs such as bisphenol A in reproductive tissues [123] indicating an indirect effect as a potential endocrine disruptor bioaccumulation promoter. A large study on male partners of subfertile couples found associations between monobutyl phthalate and below reference value sperm motility and sperm concentration. The correlation between phthalates and endocrine adverse effects is one of the more deeply investigate and proved to date. However, the different effects of longer chain phthalates and results of their safety assessment may indicate that some products within this family are indeed safer and thus it would be recommendable to test individual phthalates instead of condemning them as a whole.

With phthalates, perfluorinated chemicals (PFCs) have also been found in breast milk with a high endocrine disrupting risk on infants. Commonly PFCs found in lotions and nails polish include perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). In vitro, PFCs interfere with the function of sex hormone receptors and can also enter thyroid cells. It has been shown that in utero exposure to PFOS is negatively correlated with the birth weight of human female infants [121].

The presence of these molecules in personal care products and cosmetics reinforces the need to test products and mixtures extensively. Test methods for the known endocrine disruption pathways of phthalates may and could be applied to all mixtures containing them, regardless of concentration, in order to test for cumulative effects. The previously mentioned OECD 455 and 458 methods would be agreeable in this regards as quick in vitro methods for the initial screening of large numbers of formulas.

### *6.11. Bisphenol A*

Bisphenol A (BPA) is possibly the most studied endocrine active worldwide. According to EFSA "BPA poses no health risk to consumers of any age group (including unborn children, infants and adolescents) at current exposure levels." However, ECHA listed BPA as a substance of very high concern because of its endocrine disrupting capabilities. The most common use of BPA is as a precursor of several plastics and epoxy resins, including polycarbonates and vinyl derivatives. As such, BPA is found in a wide range of containers, accessories and primary packages and can leak in traces to the cosmetics and ingredients therein or in contact with. The molecule has been observed to bind both the alpha and beta nuclear estrogen receptors and to both mimic and antagonize estrogens, acting as a selective modulator [126]. It was also found to bind the androgen receptor, although at higher concentrations [127], glucocorticoid receptor (GR) and the thyroid receptor beta (TRβ) [128].

Today, some manufacturers have withdrawn BPA based plastic and materials, leading to the US FDA withdrawing its authorization to use it in baby bottles and infant food packaging based on market abandonment. The molecule is currently considered safe, due to the fact that although several

adverse effects in animals have been demonstrated, the possibility of such effects in humans is still controversial. Nonetheless, a recent study confirmed the transplacental transport of BPA, with likely accumulation in the fetal compartment and direct effect on the concentration of testosterone [129].

The correlation between BPA, diabetes and obesity [82,130,131], hormone dependent cancers and reproductive impairment is well documented in animals but still limited to case studies [132] and to controversial data in human. Several metabolites of BPA are also being investigated as suspected endocrine disruptors [133]. The molecule was originally considered to show weak affinity for the estrogen receptors, however recent studies have shown it to be rather more effective than previously thought. Nonetheless, while animal studies showed a clear activity of bisphenol A and its correlation with adverse effects on female fertility and pregnancy outcomes [22,48], human study results are still conflicting. Some studies seem to exclude adverse effects of BPA [32], while others report adverse effects on child development and behavior [50–52].

## 7. Discussion and Conclusions

The current toxicological data on endocrine disruptors is severely lacking [5], due to the huge list of substances to be tested and to how the effects of endocrine disruptors can cause adverse reactions decades later or in different generations. Furthermore, research about endocrine disruption still need to go deeper in the mechanics of endocrine effects and into the wider effects on more endocrine pathways and regulating enzyme that still need to be evaluated [5,134].

As such, despite a constantly growing list of known endocrine active substances and potential endocrine disruptors, there are no immediately available tools to evaluate how a complex product can affect the endocrine system. In silico tools are being developed and validated to this purpose but there are still several concerns about their reliability and their ability to detect the more complex and nuanced interactions in mixtures of endocrine actives and disruptors [35,38,135,136].

Similarly, many in vitro methods were proposed for the detection of endocrine activity and specific effects on endocrine pathways but only some of these methods are included into a validated regulatory framework and there is not a stand-alone screening method.

Further confusion is caused by the misunderstanding of what an endocrine disruptor is. A huge number of substances have some effects on the endocrine system but binding an endocrine receptor or affecting the concentration of an endocrine hormone is not a sufficient evidence to calcify a substance an EDC by itself, unless adverse effects can be proven [134]. An increase of hormone level does not constitute an endocrine adverse event by itself. The number of situations in which endocrine active substances are misclassified as endocrine disruptors is high. According to the most common misuse of the term, any food containing sugar would be considered as an endocrine disruptor, because it would increase insulin levels [7].

The number of potential endocrine active substances commonly used in consumer products and especially so in cosmetics, may be very high and the role of complex interaction and cumulative effects in mixtures is still too unclear to rule out potential endocrine adverse effects according to the concentration of individual ingredients. Some EDCs with very low activity are known or supposed to be able to act as multipliers for other endocrine actives by indirect modulatory effects [123]. While testing every existing product on the market for endocrine disruption is not feasible in the short term, a strategy to apply precautionary testing is needed in order to provide customer safety while EDCs research proceeds.

On the other hand, there is also a need to avoid the irrational consumers fear of class of chemicals, products or ingredients based on misconceptions about EDCs. Research should be linking endocrine disruption to specific ingredients and through specific pathways. Correlating an adverse effect to products or family of molecules without a mechanism of action, a clear link to the endocrine system and a list of the substances that cause the effect is pointless. When considering epidemiological data, they should be corrected for confounding factors such as economic, social or geographical

parameters and take into account the fact that several ingredients and substances have been banned in the meanwhile (i.e., chlorofluorocarbons in sprays).

The non-monotonic nature of most endocrine responses [137], together with the unclear interactions of endocrine actives, still needs an answer. While collecting more data from research on individual substances, a precautionary method should be applied to finished products aimed to be used by high risk categories (babies and children, pregnant and breast-feeding women) or in the genital area, or that can strongly effect the environment (toiletries, sunscreens), to benefit both the consumers and the manufacturers.

Cosmetic products and more generally consumer products, that fall in the above-mentioned categories, or that contain two or more known endocrine actives or substances listed as priority molecules for endocrine disruption testing, should undergo a pre-screening. In the current impossibility of assessing the effect of a mixture, testing the whole product as a potential endocrine active by use of OECD or other validated in vitro methods should at least provide an answer in term of estrogen or androgen activation and while the role of single substances will not be explored, the overall effect of the mixtures could be quantified.

In order to legitimize such a safety pre-screening strategy, an extensive literature search should be used to set agreed risk thresholds for acute and chronic changes in androgen, estrogen and other hormone levels. Cosmetics and consumer products are often applied several times daily for years or decades. In parallel, the development of tools for in silico and in vitro evaluation of mixtures and cumulative effects should be critical.

It is understandable that long term and complex cumulative effects of EDCs will require long term research and the analysis of epidemiological data in order to be fully understood, however short term protective strategies need to be prepared to ensure consumer safety in the meanwhile.

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