Risks Associated with Cosmetic Ingredients

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Perspective - Opinion

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Abstract

The media and social networks often echo fears about the potential toxicity of cosmetics and the dangers they pose to the environment. Dermatologists may be asked about these topics, but despite regulatory labelling constraints and the proliferation of specialized sites and applications, they do not always have access to reliable information. It is for this reason that we are providing the present overview of current knowledge on the subject.

Keywords: cosmetic, endocrine disruptor, benzophenone, benzylidene camphor, zinc oxide, aluminum, preservatives, essential oil, phthalates, contact eczema

Introduction

Many apps, news sites and press articles alert consumers to the risks of cosmetics. This information is necessary, but it is widely dispensed, without much explanation, which leads consumers to change over for example to products considered natural that they feel are less harmful to them than conventional cosmetic products. However, as we will see, some natural products can also be harmful to health. For this reason, we present a synthetic overview of the risks and dangers of cosmetics. For the sake of clarity, the potential dangers of cosmetic ingredients will be classified here under several headings: by type of cosmetics (sun-care products, exfoliants, etc.), by ingredient type (phthalates, parabens, etc.), and by type of risk posed (endocrine disruptors, contact allergens, etc.).

In preparing this overview, we conducted searches of the PubMed-Medline database and of the non-specific Google search engine using the following keywords: *cosmetics AND endocrine disruptors, cosmetic AND cancer, sunscreens AND toxicity, sunscreens AND endocrine disruptor, preservatives AND endocrine disruptor, essential oil AND toxicity, essential oils AND endocrine disruptor, cosmetic AND coral, sunscreen AND coral, plastic AND endocrine disruptor, phthalate AND endocrine disruptor, bisphenol AND endocrine disruptor;* then, for each ingredient cited in the article: *name AND endocrine disruptor, name AND toxicity, name AND contact dermatitis*. European labels and regulatory texts were examined for each group of ingredients (CL).

Potential toxicity

General introduction

The toxicity of any given substance differs according to whether it enters the corneal layer but remains there (penetration), whether it passes from one layer of the epidermis to another (permeation), or whether it diffuses into the vascular system (resorption). For example, an endocrine disruptor will only be toxic to humans if it is resorbed. Most of the scientific data on cosmetic ingredients is derived from exposure of cells or animals to a particular ingredient, and this data is not directly transposable to humans. Moreover, data obtained *in vivo* come mainly from oral exposure; however, for topical ingredients, it is rarely known with great precision to what extent they are absorbed and pass into the systemic circulation. Finally, studies on penetration or resorption normally focus on healthy skin and it is difficult to extrapolate the findings of such studies to damaged skin, skin that is under constant aggression from ultraviolet (UV) radiation, or skin presenting chronic dermatosis that disrupts the barrier effect of the corneal layer.

In addition, toxicity data relate to individual ingredients. Regarding finished products, this knowledge must be modified in line with variations that may be introduced by cosmetic manufacturing technologies and relevant conditions of application. Thus, it is necessary to take into account the concentration of the substance in the finished product, whether or not the product is rinsed off, the area of exposed skin, the degree of occlusion and hairiness of the skin at the site of exposure, and whether the product can be absorbed through the gastrointestinal tract.

In infants and young children, the ratio between body surface area and body weight is low, resulting in higher blood concentration of resorbed cosmetics than in adults. Skin lesions increase the risk of penetration. The occlusion produced by diapers, on the other hand, can increase percutaneous penetration by a factor of 5 to 10, which means that recommendations concerning cosmetic ingredients and concentrations thereof in infants require adaptation.

Endocrine disruptor effects

Definition

According to the World Health Organization (WHO), endocrine disruptors (ED) are substances or mixtures that impair the functions of the endocrine system and cause harmful health effects on an intact organism or its descendants. Thus, exposure to ED can have life-long effects, or even consequences for the next generation. EDs work by mimicking natural hormones, altering their metabolism or binding to their cellular receptors, thereby blocking endogenous hormone-receptor bonding [1]. Their action covers all living organisms, whether human or animal, such as aquatic fauna.

Most ED effects have been evaluated following oral exposure of a living organism to a substance. There are no studies of ED-induced risk to which an organism has been exposed solely via cutaneous application.

The effects vary from one substance to another and, for the same substance, from one exposed species to another. It should also be noted that not all substances having reproductive toxicity are necessarily EDs. For example, ethanol has a direct toxic effect on the reproductive organs but does not interact with the endocrine system and is therefore not classified as an ED.

Regulatory considerations

In regulatory terms, the definition of EDs remains under discussion. In 2002, the Endocrine Disruptor Testing and Assessment (EDTA) protocol specified five different levels of investigation for the detection of ED substances: Level 1, data is available and computer models are used to sort and classify substances and mechanisms in order of priority; Level 2, *in vitro* tests provide information on mechanisms and signalling pathways; Level 3, *in vivo*

tests have been conducted on signalling mechanisms and pathways; Level 4, *in vivo* tests provide information on harmful effects with regard to the entire body; Level 5, *in vivo* tests have investigated the adverse effects of endocrine disruptors on the life cycle of organisms.

At European level, the European Chemicals Agency (ECHA) has put in place the REACH regulation governing the registration, evaluation, authorization and restriction of chemicals in order to better protect human health and the environment from chemical risks, while promoting competitiveness within the European Union's chemicals industry. It encourages alternative methods for assessing substance hazards with a view to reducing the number of animal trials. Regulation (EC) No. 1907/2006 of 18 December 2006 (REACH) includes a special authorization and restriction system for substances considered to be of “extreme concern" i.e. carcinogenic, mutagenic and reprotoxic (CMR), for persistent or bioaccumulation-prone substances, and for substances with ED properties for which there is scientific evidence of probable serious effects on human health or the environment. Risk assessment is thus a shared responsibility between the European regulatory and industrial agencies. Industry must provide data and risk assessments concerning the use of chemicals. The public authorities are then responsible for verifying and analysing the information submitted.

The criteria for identifying ED substances have been further refined in other texts that do not directly concern cosmetic ingredients. Regulation (EC) No. 1107/2009 of 21 October 2009 established the rules governing the authorization of phytopharmaceuticals (products used to treat agricultural crops), as well as the marketing, use and control thereof within the European Union. It states that "*an active substance can only be approved if it is not considered to have disruptive effects on the endocrine system, which can be harmful to humans, unless exposure to it is negligible*." Finally, Regulation 528/2012 of 22 May 2012 concerns the marketing and use of biocides (substances or reparative actions designed to

destroy, repel or render harmless pests, prevent their action or combat them, by means of chemical or biological action). This text states that active substances with endocrine-disrupting properties potentially harmful to humans may not be approved.

Methods for study of ED effects

EDs are studied *in vitro* or in animals, especially rodents, and their effects are subsequently extrapolated to humans. Carcinogenic potential in the mammary gland is also studied. A substance may be an ED for one animal species but not for another. In the same species, there may be differences: certain EDs, for example, will have an impact on the larvae of some fish but not of others. It is of course very difficult to determine whether substances that have an ED impact on fish larvae or rodents will also have such an effect in humans. Findings in animal models are extended to human health on the basis of the precautionary principle. By 2021, the National Health Safety Agency (ANSES) will draw up a list of EDs, enabling them to be classified as "suspect," "presumed" or "proven" [2]. It appears necessary to require that all "proven" EDs be banned from cosmetic formulations.

Some studies have shown that these chemicals can stimulate or reduce the activity of a hormone without necessarily disrupting the functioning of the endocrine system [2-4].

Different tests are used for cosmetics. One method that has become common is the use of larvae of the Japanese rice fish *(Oryzias latipes)* (https://www.watchfrog.fr/). The method turns on the reactions of this organism to the substances being studied, without affecting the normal physiology of the fry (transgenesis). The rapporteur gene enables fluorescence of the larva depending on measured hormonal activity: whether androgenic (spiggin gene), estrogenic (choriogenin gene), or thyroidal (the TH/bZIP gene, which is a marker for metamorphosis). Tests are carried out on very young larvae (from D0 to D15) in order to be permitted as an alternative method, since at this stage of development the larvae are not

considered laboratory animals. Extrapolation to humans of the results of exposure to EDs on rice fish larvae implies that the hormonal mechanisms of the early developmental stages in humans are identical to those of adult rice fish and that these mechanisms have been preserved through the evolution of species, from fish to humans.

The Chemical Activated LUciferase gene eXpression bio-test (CALUX test) used to evaluate "potential ED action" of ingredients and blends (finished products) is carried out in *vitro.* CALUX cells produce light in response to exposure to supposed ED products (Berthold Technologies). Some countries, such as the Netherlands, have set limits for cocktails of substances in aquatic environments based on responses to these bio-tests.

An ED effect on an animal species does not necessarily prove that the substance exerts the same effect in humans, and we lack a specific model to determine the potential ED effects of substances in humans [4-7]. Vitellogenin, a lipoprotein produced in the liver of oviparous female vertebrates such as fish, is considered a biomarker of the ED effect in *Gammarus fossarum* and *Eurytemora affinis.* For example, 3-(4-methylbenzyledene)-camphor (4-MBC) increases hepatic vitellogenin in the fathead minnow and rice fish but has no effect on zebrafish [5,6].

In any event, numerous studies, of which the results are summarized in Table 1, show that ED has an effect on numerous animal species (particularly aquatic fauna) and potentially on human beings.

The question arises of the link between ED and risk of breast cancer. Some EDs such as phthalates may have a role in triggering endometriosis [8]. The results of the study by Jeong et al. suggest that in order to determine whether a link exists between ED and risk of breast cancer, *in vitro* analysis should now be carried out of interference by ED with the five most suspect genes, namely ESR1 (oestrogen receptor 1), TP53 (tumour protein p53),

NCOA1 (nuclear receptor coactivator 1), AKT1 (AKT serine/threonine kinase 1), and BCL6 (B-cell CLL/lymphoma). To date, certain EDs have been reported as likely to act on the growth of MCF-7 cells derived from a breast cancer cell line.

Carcinogenic effects

Phtalates

In vitro, phthalates exert a proliferative action on cancer cell lines of mammary and ovarian tumours [10].

Parabens

Parabens are weakly absorbed following application on skin*; in vitro,* their estrogenic potency increases with the length and branching of their alkyl side chains (methyl < ethyl < propyl < butyl < isobutyl), although it remains weak, being one thousand to one million times less potent than 17-estradiol [10]. Hydroxybenzoic acid, a metabolite common to all parabens, appears to be inactive *in vitro.*

In vitro, parabens, chiefly butyl-paraben (BP), cause DNA damage, alter epithelial cells in the human breast, and increase the migratory and invasive properties of breast cancer cells. It has been shown in pre-pubescent female rats that exposure to BP reduces ovary weight while increasing growth of mammary glands. However, no evidence of this pro-carcinogenic effect has been detected in humans and methylparaben, and ethylparaben have been deemed safe for human health when used as preservatives in cosmetics at the maximum allowable concentrations (0.4% for an ester or 0.8% for combined use).

Aluminium

Antiperspirants, lipsticks and toothpastes are the main sources of systemic exposure to aluminium from cosmetics. It is generally accepted that the aluminium hydrochloride contained in antiperspirants forms insoluble aluminium hydroxide polymer gel plugs in the sweat ducts, thus preventing sweat from reaching the skin surface. Aluminium ion (Al^{3+}) can be absorbed in high quantities via abraded skin. *In vitro,* aluminium increases the proliferation of certain breast cancer cells, but through proliferation stress rather than via any mutagenic effect [10].

Mineral oils

Mineral oils and waxes are composed of saturated hydrocarbons made up of linear, branched chains and cyclical structures (Table 2). The main carbon chain consists of at least 15 carbon atoms, but it can contain over 90 carbons [11]. MOSH (Mineral Oil Saturated Hydrocarbons) is the term used to refer to a small fraction of mineral oil compounds. To date, no toxicological studies have demonstrated any significant potential toxicity of MOSH. MOAH (Mineral Oil Alkylated Hydrocarbons) form another minority fraction of trace aromatic compounds found in mineral oils, including those used in cosmetics. Lip care products contain only small traces of MOAH mineral oils and apparently pose no risk to consumers, as was confirmed in 2015 by the Canadian health authorities.

Recently, in Germany, the Federal Institute for Risk Assessment concluded that consumers should have no fears for their health even if mineral oils found in cosmetics penetrate the skin. Manufacturers use only pharmaceutical-grade mineral oils. Eight authors in charge of toxicovigilance in cosmetic companies conducted a comprehensive review of published studies on the penetration of mineral oils and waxes. None of the thirteen studies analysed in this publication found any evidence of resorption of these products or of systemic

diffusion. In both humans and hairless mice, there is an epidermal swelling effect caused by an increase in water content within the *stratum corneum* due to the occlusive effect of these substances. However, following short applications lasting a few hours, these substances do not diffuse beyond the corneal layer [11].

On the other hand, several carcinogenicity studies, available from the European Chemicals Agency (ECHA), confirm that pharmaceutical-grade mineral oils used in cosmetics (which contain very small traces of MOAH) have no carcinogenic effect. The European Union thus employs the risk phrase R45, "May cause cancer", together with Note N for Vaseline, which reads: "the classification as a carcinogen need not apply if the full refining history is known and it can be shown that the substance from which it is produced is not a carcinogen".

Overall, to date, there are no scientific arguments supporting the hypothesis that mineral oils in cosmetics induce cancer. This fear stems from a confusion between refined and unrefined petroleum jelly, with the notion of carcinogenic risk associated with hydrocarbon residues. In addition, the large family of highly purified hydrocarbons is one of the few instances of irritation and a results in a very small number of cases of allergy. However, on environmental grounds, there is a desire to eradicate all petroleum products.

Major classes of ingredients

Preservatives

Water-rich cosmetics require preservatives to prevent the development of bacteria, viruses and moulds [12]. Because of their mechanisms of action and their ability to bind to proteins, preservatives are necessarily toxic and most often allergenic. In addition, some are suspected of being EDs (certain parabens), exerting neurotoxic or hepatotoxic effects (glycol ethers,

including phenoxyethanol), worsening asthma (triclosan), or disrupting the balance of the skin microbiome.

Parabens

Abbasi et al. warned that by inhibiting the growth of *Roseomonas mucosa (R. mucosa*) to a greater extent than that of *Staphylococcus aureus,* parabens and quaternium-15 promoted selection in the skin microbiome of harmful strains rather than healthy strains [13]. Use of these preservatives in infants, especially in young children with atopic dermatitis (AD), apparently promotes a definitive imbalance within the microbiome. However, the effects on the microbiome require some qualification. Indeed, comparison of a group of 12 children at atopic risk and not receiving an emollient with another group of 11 children treated with moisturizer showed that emollients caused a decrease in pH and an increase in *Staphylococcus salivarius,* as well as improvement in AD [14].

In Europe, the United States and Canada, paraben concentrations may not exceed 0.4% for a paraben alone and 0.8% for a mixture of parabens. Resorption of parabens through the skin can occur. Braun et al. showed in 177 pregnant women that urinary levels of phthalates and parabens (butyl-paraben BP, methyl-paraben MP, propyl-paraben PP, mono-n-butyl phthalate MBP, and monoethyl phthalate MEP) were higher in women indicating in a questionnaire that they had used cosmetics, lotions and perfumes or colognes [15].

Parabens may be found in cord blood, maternal plasma and amniotic fluid. However, it is difficult to determine whether this is related to transcutaneous resorption or oral absorption [16]. In 215 Spanish students aged 18 to 23, there was no link between paraben levels and male fertility [17]. Parabens have been found in the coastal waters off Florida, where methylparaben causes increased vitellogenin levels in fish [18].

A recent review shows that parabens interfere with the normal functioning of endocrine hormones [19]. They can bind to nuclear receptors for androgens, oestrogens,

progesterone and glucocorticoids as well as peroxisome proliferator-activated receptors (PPAR). Further, they modulate the activity of enzymes that metabolize natural hormones such as aromatase and oestrogen sulphotransferase. However, certain of the effects observed in animal models have not been found in humans. In animals, the doses tested were very often high, leading some authors to conclude that such results could not be extrapolated to humans, since the latter were exposed to far lower concentrations in cosmetics.

According to the Scientific Committee on Consumer Safety (SCCS), methylparaben and ethylparaben used as preservatives in cosmetic products at the maximum allowed concentrations (0.4% for an ester or 0.8% for combined use) may be considered safe for human health [20]. Propylparaben and butylparaben are safe provided the sum of their individual concentrations does not exceed 0.19% [21].

Parabens are relatively non-allergenic. Following talk of their toxicity, they were replaced by preservatives that caused successive waves of contact allergy through delayed hypersensitivity. First came the mixture of methylchloroisothiazolinone and methylisothiazolinone (MCI/MI or "Kathon CG®"), which was superseded by Euxyl K400®. The latter is a mixture of methyldibromo glutaronitrile (or 1,2-dibromo-2,4-dicyanobutane), which is highly allergenic, and phenoxyethanol, which, like any glycol ether, is suspected of neurological, haematological and hepatic toxicity [22,23]. Phenoxyethanol is nevertheless often present in wipes.

After the 1990s, there was a return of parabens, but controversy over their toxicity again saw them banned from formulations. Use of formaldehyde liberators has decreased due to the notion of their toxicity following non-cosmetic exposure as well as their allergenicity. Then came the unfortunate re-discovery of high-dose methylisothiazolinone (MIT) which, in the 2010s, led to a widespread "epidemic" of contact allergy, with more than 10% of patients

tested in Europe, Australia or North America being sensitized [24-27]. Europe then responded by banning MIT in unrinsed products and limiting its concentration in rinsed products. However, one might well wonder what the next allergen will be; possibly iodopropynyl butylcarbamate, for which cases of contact allergy have already been reported [28].

Triclosan

Triclosan, which is used in antiseptic soaps, toothpastes, toothbrushes and body cleansing solutions, is absorbed and is found in urine. Its antiseptic potency has also been called into question. Animal studies have suggested a possible ED effect, but nothing has been demonstrated in humans. It is suspected of inducing bronchial hyperreactivity and asthma exacerbations [29]. European regulations have restricted its concentration to between 0.15% and 0.2% for mouthwashes and to 0.3% for nail cleansing products.

Alternatives

All chemical preservatives have varying degrees of sensitizing potency. What alternatives exist? Water/oil emulsions require fewer preservatives than oil/water, but it is not possible to change all formulations, since oil/water formulations are far more common and pleasant to use. Airless presentations can be offered for only a limited number of cosmetics since such bottles are expensive, possibly rich in plasticizers and unsuitable for lip balms for example. Replacement with essential oils (EO) is not a viable solution since the latter lose their antiseptic activity if they are diluted, evaporate due to their volatility, and have action dependent on pH and lipophilia, as well as possessing an odour and being allergenic.

Plastics

Bisphenols

Initially in the 1930s, bisphenol A (BPA) was clinically tested as a synthetic oestrogen. However, its destiny was somewhat different since it became a monomer extremely widely used in the production of polycarbonate plastics and as an additive for plastic materials. It is also found in epoxy resins. It leaches readily from plastic materials.

BPA, which crosses the placental barrier, reduces egg maturation, increases the risk of pre-term birth and of modification of anthropometric measurements at birth [30]. Later in life, BPA appears to cause increased adiposity and glucose metabolism abnormalities. In 2012, the Food and Drug Administration banned BPA in bottle teats and cups, and then in all product coatings intended for children. Europe banned BPA in teats in 2011. The BPA-free plastic label is insufficient since the replacement bisphenols used are also potent EDs, namely bisphenols S (BPS), F (BPF) and AF (BPAF).

To date, the alert concerns avoidance of mouth contact with plastics containing bisphenol. There are no warnings about cosmetic packaging. Bisphenols have never been determined in cosmetics.

Phthalates

Phthalates were often used in cosmetics in the past and their use is closely monitored. High molecular weight phthalates, such as di-2-ethylhexyl phthalate (DEHP) and diisononyl phthalate (DiNP), are used mainly in the manufacture of vinyl polychloride items for food packaging, building materials and medical devices. Low molecular weight phthalates, such as diethyl phthalate (DEP) and benzyl butyl phthalate, have been used in the manufacture of perfumes, ethanol denaturants and nail polish [31,32].

Phthalates are semi-volatile organic pollutants that are widespread in the environment of urban areas, as well as in homes and vehicle interiors. They show bioaccumulation and their limited biodegradation occurs through aerobic or anaerobic microorganisms. They are more easily biodegraded if they are of low molar mass. They can be stored in body fats in various ways depending on the lipid content of the organisms in question.

According to Wallner et al., the phthalates having the most potent oestrogen ED effect are mono-phthalate (2-ethylhexyl), benzyl butyl phthalate and di-n-butyl phthalate (DnBP) [33]. In humans, exposure to phthalates may be responsible for low birth weight and subsequent childhood obesity, but study results are contradictory. Kim and Park collated the results of several studies, mainly in American cohorts. Urinary levels of different phthalate metabolites were positively associated in men or women with waist size, body mass index (BMI) and obesity. There only appeared to be an aggravating effect on weight in children who were already overweight [34]. The influence of monoethyl phthalate (MEP) and monoethyl hexyl phthalate (MEHP) on liver function and cardiometabolic risk factors has been studied [33,34]. A statistically significant increase in serum transaminase levels and body mass index (BMI) was correlated with phthalate exposure. Urinary phthalate levels are thought to be correlated with increased triglycerides and decreased serum HDL cholesterol [33,34].

In vitro, DBP has a proliferative and pro-invasive action on breast and ovarian cancer cell lines [10]. Classified as CMR (carcinogenic, mutagenic, reprotoxic), many phthalates were banned in Europe in 2013. Use of DEP in cosmetics is allowed at limited concentrations (Table 3).

Leaching of phthalates from PVC and plastics occurs continuously, resulting in contamination of indoor air, house dust and food [31]. This may have an aggravating role in allergy or asthma [32]. Their presence in a cosmetic may be secondary to transfer from the plastic container to its contents, but also to transfer from another plastic surface with which

the cosmetic was in contact during manufacture or storage. According to Konieki et al., DEP, dimethyl phthalate (DMP), but also DiBP, DnBP and DEHP, have been found in cosmetics [32]. DEHP was prohibited in Canada, where this study was conducted. The authors believe that this contamination may have occurred via packaging. The most commonly found phthalate was DEP, with the highest concentrations being seen in perfumes, lotions and deodorants.

Given their omnipresence in the environment, can cosmetic phthalates be involved in systemic effects? Following assay of phthalate levels in urine samples collected from 50 Austrian mothers and their children with a mean age of 8 years, the levels were compared to answers on a questionnaire evaluating use of cosmetics. Significant correlations were found between urinary levels of MEP and terephthalates and use of hair foam, hair dye and makeup, but these women also used chewing gum and polyethylene bottles [35]. Braun et al. showed in 177 pregnant women that urinary levels of phthalates, parabens [butyl-parabens (BP), methyl-paraben (MP), propyl-paraben (PP), mono-n-butyl phthalate (MBP) and MEP] were higher in women who indicated in a questionnaire that they used cosmetics, lotions, perfumes and colognes [36].

In vitro, 35% of phthalates are absorbed through the skin in the rat. In humans, absorption is low, being estimated at 5% of the applied dose for DEP, 4% for DMP and 0.5% for DnBP [33]. For nail polish, Koniecki et al. have suggested subungual penetration of 0.6% over 24 hours [32]. The authors stress that these substances have a high risk of resorption if they are present in baby-care products.

The presence of phthalates in cosmetic products currently stems from container-content interactions, first during the storage of raw materials and then, naturally, in the manufacture and packaging of the finished product. It is important to ensure that legislation

on the eradication of most phthalates is respected. Studies of leaching from container to contents would be of value. A reduction in phthalates and bisphenols is desirable in packaging. The use of bulk cosmetics does not solve the problem of leaching from container to contents. Whatever the packaging used it must be inert in order to preserve the cosmetics as far as possible from contact with external microorganisms.

Phthalate and alkylphenol mixtures

In both *in vitro* and animal models, phthalates and alkylphenols interfere with the biosynthesis of sex steroids (androgens, oestrogens and progestin), their receptors, and the expression of enzymes involved in steroidogenesis [37]. There are conflicting results regarding extrapolation from these models to humans.

Silicones, dimethicones, cyclomethicones and simethicones

Silicones are derivatives of organic silica or silane; their INCI names end in "one," "conol," or "siloxane." Silicones are now among the most widely used materials in consumer and industrial applications. Hundreds of studies have been conducted by manufacturers of silicone products to assess their safety with regard to workers, consumers, the environment and manufacturing processes [38,39]. In cosmetic care, silicones provide a notable sensory effect when applied and their optical properties help mask imperfections. Silicone oils used in cosmetics are divided into two large families: volatile and non-volatile. Silicones are generally not biodegradable, but non-volatile polydimethylsiloxanes are degradable in soil and volatile silicones such as cyclopentasiloxane dimethicone and their derivatives, such as alkyl dimethicone and hydroxypropyl dimethicone, are degradable in air [40]. These types of silicone are therefore considered safe. They are used in cosmetic, medical and pharmaceutical formulations [41]. Some silicone elastomers are used in medical devices, for example in

extra-corporeal circulation and pacemakers, attesting to their excellent biocompatibility. Silicones are characterized by their very low chemical reactivity, low surface tension and especially marked hydrophobia, hence their wide use as excipients in pharmacy products and wound care [42].

Two volatile silicones pose a problem: octamethylcyclotetrasiloxane (D4 or cyclotetrasiloxane) and decamethylcyclopentasiloxane (D5 or cyclopentasiloxane) are considered safe for humans but have shown toxicity in rats and even an ED effect in mice [6]. Due to their possible bioaccumulation, since they are poorly biodegradable or non-biodegradable, in order to minimize their release into the environment, regulation of these volatile silicones has recently been amended (EU Regulation 2018/35 10/01/2018). Thus, since 31 January 2020, no rinsed cosmetic products containing more than 0.1% D4 or D5 may be put on the market. While regulations to reduce the use of D4 and D5 silicones are a welcome development, there is a lot of discussion about the use of these substances in cosmetics. Criticism concerns the fact that they are not natural and their accumulation in the environment. Since they are very poorly bio-degradable, little assimilation occurs in the organisms by which they are ingested. Removing all silicones, however, is difficult. Their texture to the touch, their "peach skin" effect and the sensory properties they lend to cosmetic products play an essential role in consumer choice, making them difficult to replace. While certain fatty acid esters are candidates for substitution, their use in formulations remains complex (Table 4).

Polyethylene glycols (PEGs) and their derivatives

These substances are widely used in different fields and especially in cosmetics. PEGs are used as solvents, humectants and solubilizers. PEG derivatives are surfactants. PEGs are of concern due to their toxic impurities and poor biodegradability. In addition to their carcinogenic risk, they are charged with inducing skin allergies. Finally, the

manufacturing process used to produce them remains highly pollutant, with permanent contamination of the environment.

The polymerization reaction employed in their manufacture leads to accumulation of by-products, some of which may be present in the finished product in a state of impurity. These include notably 1,4 dioxane. The latter is classified as "possibly carcinogenic to humans" (group 2B carcinogen). Other polymerization residues are produced such as residual ethylene oxide, antioxidants, oxidation products (peroxides, aldehydes), oligomers and metals. Ethylene oxide is neurotoxic and irritating to the respiratory system, skin and eyes. Its maximum allowable concentration in the air is 1 ppm for an 8-hour exposure period and 5 ppm for a 15-minute exposure period. It is toxic to microorganisms and fish. However, in running water, its concentration decreases rapidly as a result of evaporation, hydrolysis and biodegradation. PEGs are absorbed by the gastrointestinal tract and eliminated chiefly in urine. They do not easily penetrate healthy skin but can penetrate damaged skin, and in this case, as in burn victims, their renal toxicity is proven [43,44]. They can also facilitate the penetration of other compounds found in cosmetic products such as certain surfactants, stearates 2 and 20, and laureth-9.

Toxicity studies of PEGs in animals have revealed a low toxic profile with low acute oral and dermal toxicity, low chronic toxicity, no mutagenic potential, and no reproductive risk. In humans, alkyl PEG ethers are irritants.

However, the Cosmetic Ingredient Review took into account cases of toxicity resulting from contact in people who were burned and then treated with an antiseptic cream containing PEGs. Indeed, in 1982, nine burns patients undergoing prolonged treatment with a cream containing 99.8% polyethylene glycol (63% PEG-300, 32% PEG-4000 and 5% PEG-1000), 0.01% ethylene glycol, and 0.2% nitrofurazone developed kidney failure. Three died and toxic acute renal tubular necrosis was found in one of them. Deaths from kidney failure

have been attributed to the presence of PEGs and their metabolites in the circulation [44]. Significant amounts of di-acid metabolites and hydroxyl acids from PEG were found in the serum and urine of the three deceased patients. PEG metabolites produce renal destruction comparable to that induced by ethylene glycol.

In conclusion, PEGs have no demonstrated toxicity when used on healthy skin but should not be used on injured skin. They are prohibited in "organic" formulations.

Sulphates

The term "sulphates" refers to a family of anionic surfactants. They are deemed to be irritants. Surfactants are amphiphilic substances capable of binding on the one hand to a hydrophilic or watery environment and on the other hand to a lipophilic or oily environment. This structure gives them wetting, dispersant/solubilizing, emulsifying, foaming, bactericidal and detergent properties. Anionic surfactants, and in particular sulphates, are characterized by their detergent properties. Widely used in washing products because of their low cost, sulphates eliminate mostly lipophilic dirt and therefore all fatty substances on the skin, including surface lipids. It is this property that makes them irritant. Ethoxylation reactions reduce this irritant effect but also reduce their foaming capacity. They must be used with caution in formulations. On reactive skin, irritated skin or an inflammatory scalp, the more irritant lauryl sulphates should be excluded in favour of laureth sulphates, which are better tolerated.

Exfoliants

Plastic microbeads are solid plastic particles intentionally added to cosmetics. Their diameter is in all cases less than 5 mm and is usually between 0.15 and 0.55 mm. They are insoluble in water, used for exfoliation and/or cleansing, and are contained only in rinsed

products. After rinsing, they spread into the environment and pass through sewage treatment plants, polluting rivers and marine environments. While treatment plants retain up to 99% of such particles, given their high numbers they remain extensively present in the oceans [45-47]. These are non-biodegradable polymers that can take hundreds of years to decompose through oxidation or photodegradation pathways. Plastic microbeads are ingested by animals, pass through the food chain and are ecotoxic for aquatic and marine species. In addition, they appear to act as carriers for Persistent Organic Pollutants (POPs) in the environment.

Polyethylene plastic microbeads have been banned from exfoliants because of the toxicity of microplastics to marine wildlife. In 2015, before their ban, Gouin et al. estimated that 4073 tonnes of microbeads were used in Europe annually, which, when added to the output of Switzerland and Norway, gives an average daily figure of 17.5 mg per inhabitant [48].

Cosmetics are a minor source of microplastics; according to several studies they represent only around 0.1% of the total [48-50]. Use of rinsed exfoliating products varies from country to country in Europe. The Spanish are the biggest users in shower gels, the French in facial exfoliators, while the British and Irish are the biggest consumers in terms of abrasive hand cleaners [48].

The Non-Governmental Organization (NGO) "Beat the Microbead" and its application have worked to achieve the eradication of polyethylene microbeads. In May 2018, Cosmetics Europe announced that 97.6% of plastic microbeads had been removed [51]. A European ban on these microplastics as additives in cosmetics is envisaged in 2020. Similarly, the use of plastic powders (e.g. nylon) to provide silky or slippery effects in formulations may also be restricted or regulated.

Depending on the level of abrasiveness sought, cellulose or microcrystalline cellulose can be used as a replacement for microplastic beads. The advantages of these materials are

numerous: whiteness, durability and biodegradability. Cellulose is the most abundant polymer on earth, and cellulose beads pass through sewage treatment plants but have no impact on the oceans. Other alternatives such as silica and pumice (or pumice stone) exist but they are not biodegradable. Mineral or diatom powders allow exfoliation without environmental toxicity.

Derivatives of fruit kernels such as walnuts or apricot kernels, less regular in size and sometimes angular should be avoided on irritable or atopic skin. In addition, some are not white in colour and thus require a degree of irradiation that may interfere with their claims to be a natural product. Exfoliating gloves and hair gloves are very effective and non-pollutant.

Metals

The compounds of certain metals are used in the cosmetic industry, mainly as ultraviolet filters (titanium), in facial and body care products, and as pigments in coloured cosmetics. Metals may also be present in derivatives of mineral oils, paraffins, silicones and aliphatic hydrocarbons used in the production of numerous cosmetic preparations [52].

The European Union authorises the use of various pigments in cosmetics, in a wide range of colours: white (aluminium, barium sulphate, bismuth chloride oxide, calcium carbonate, calcium sulphate, magnesium carbonate, silver nitrate at 4% - and, solely for colouring eyelashes and eyebrows, titanium dioxide and zinc oxide); green (chromium oxide (III), chromium hydroxide (III), cobalt and aluminium oxide); brown (copper, gold); orange, red, yellow and black (iron oxides). Metal-based pigments are shown in lists of ingredients as the letters "CI" (Colour Index) followed by a number. Eyeshadows are the products most affected since they may contain significant concentrations of metallic salts in their compositions.

Avoidance of contact may be recommended in patients with proven contact allergy to a given metal, although there is no evidence that patients allergic to metals do not tolerate

these products [52]. To our knowledge, there are no cases of nickel sensitisation due to any cosmetic other than coloured make-up. Thyssen et al. showed that women allergic to nickel presented no more palpebral eczema when using mascara or blush than those who were not sensitised to the metal [53]. The lowest concentrations at which nickel-sensitised patients react are 0.59 ppm, or about 10 mmol/l [54]. Although this is an estimate, Thyssen et al. state that the maximum rate of nickel release from a cosmetic is 10 ppm and possibly lower [53].

To conclude, the role of metals in eyeshadows as inducers of contact eczema has not been proven. Patients with a strong reaction to a metal should be informed of the name under which the metal appears in the INCI code on the eye-shadow packaging in order to ascertain, in the event of a blush-related eczema, whether it contains the offending metal. In nickel-allergic individuals, attention should be focused instead on any metal brush or eyelash-curling devices that might induce eczema.

Aluminium

Aluminium salts present in antiperspirants disperse in the sweat, leaving a thin film of gel on the surface of the sweat glands. This mechanism limits the flow of perspiration without preventing the skin from breathing. This film is removed as the skin peels off or during cleansing. It should be noted that a concentration of 20% aluminium chloride corresponds to a value of 5% aluminium. Aluminium is also found in toothpastes and lipsticks. Aluminium is a metallo-oestrogen with neurotoxic potential on systemic administration. *In vitro,* aluminium can inhibit human acetylcholinesterase, an enzyme involved in cholinergic neurotransmission. There is controversy over exposure to aluminium and the risk of developing neurological diseases, particularly Alzheimer's disease.

Aluminium has been detected in healthy breast tissue and malignant lesions. It has been suggested that there is a link between the use of antiperspirants, the presence of

aluminium in the mammary gland and breast cancer. *In vitro,* aluminium chloride induces the growth of MCF-10A cells from human breast tumour cells. It is not mutagenic but induces a proliferation of stress and DNA deterioration [10]. To date, there is no *in vivo* evidence that aluminium exerts a carcinogenic function. Its presence in tumour lesions does not demonstrate that it is responsible for the development of cancer. There are many sources of aluminium exposure, particularly in vaccines; it is therefore difficult to determine the degree of liability of antiperspirants in the systemic diffusion of aluminium.

Alum stone is offered as an alternative to aluminium salts, even though it contains aluminium salts. There are two types. Natural alum stone extracted from rocks is a double salt of potassium and aluminium and is called potassium alun in the INCI (International Nomenclature of Cosmetic Ingredients). The other type is synthetic alum stone, made from ammonium and aluminium salts, and is called ammonium alum in the INCI. Used since antiquity, it forms an insoluble compound on the surface of the skin, making it astringent and enabling it to combat odours.

The French National Agency for Drug Safety (ANSM) has recommended the use of aluminium in low doses (0.6%). The risk to the consumer is less than the usual concentration, which is around 5% (20% of the mixture). The problem is that at 0.6%, the anti-perspirant effect no longer exists, thereby rendering such antiperspirants ineffective.

However, controversies about aluminium persist. Resorption of aluminium should be limited and in particular, it should not be applied to damaged skin. It would appear difficult to remove aluminium from antiperspirants, but the use of mineral powders should be evaluated.

Finished products

Essential oils and fragrant blends

In a great exodus back towards natural products, essential oils (EO) have made a remarkable entrance into the therapeutic and cosmetic arenas.

EO are complex mixtures of active, fragrant and reactive substances of plant origin. They have three main types of components: 1) the volatile terpenes, which are the first constituents of EO. When exposed to air, they quickly yield allergenic degradation (oxidation) products (limonene, linalool, etc.); 2) aromatic compounds derived from phenylpropane (coumarin, estragole, cinnamic alcohol); 3) compounds of various origins: carbides, aldehydes, esters resulting from distillation, pesticides used during growing.

Composition varies from one EO to another. In case of allergy, it is always necessary to test the EO used by the patient. It may contain pesticide residues (use of organic EO is recommended).

Distillation products, lavender and tea tree oils

Most EO are produced by distillation in a still. Heated water turns into steam and this water vapour passes through the plants and distils the multiple components of the plants before being discharged through a pipe called a swan neck. To cool the steam containing the extracted essence, the swan neck extends through a coiled pipe immersed in cold water. The liquid is collected in a container called a Florentine vase or *essencier* (essential oil separator). During decanting, the oil is lighter than the water, referred to as hydrolat, and floats, enabling it to be collected. Hydrolat is sometimes used (rose water or orange blossom water for example). EO can be obtained from flowers, leaves or the whole plant (flower, stem, leaves). For example, between 250 and 300 kg of geranium branches and leaves are needed to produce 500 g of EO.

All EOs can cause allergies but those most commonly involved are tea tree oil *(Melaleuca alternifolia oil)*, which causes eczema or polymorphic pseudo-erythema, and lavender EO, which can cause occupational eczema in masseurs and physiotherapists [56].

Melaleuca alternifolia EO is used in the treatment of many dermatoses, as well as for oral hygiene. Awareness of *Melaleuca alternifolia* is not exceptional. Of the 140 patients who responded to one or more of the five EO tested by the North American Contact Dermatitis Group, none had a positive test patch with the fragrance mix but 45% had positive patch tests for *Melaleuca alternifolia.* Half of these reactions were strong, and clinical ties were certain or probable in more than half of the cases [57]. This EO is composed of monoterpenes (35 to 50%), monoterpenols (30 to 50%), sesquiterpenes (5 to 8%), and cineole (3 to 15%). Its main allergen is ascaridole [58].

Use of essential oils does not guarantee prevention of ED effects. Indeed, essential oils of lavender and tea tree appear to exert *in vitro* oestrogen-like and anti-androgenic (anti-testosterone) ED effects. In 2007, Henley et al. reported gynaecomastia in three boys aged 4 to 10, one of whom who used cosmetics with lavender and tea tree EO, while the other two used lavender EO alone [59]. In two cases that were followed up, discontinuation of EO use was accompanied by the disappearance of gynaecomastia. In the third case which was not followed up, the authors reported that the homozygote twin who had the same environment but did not use products with lavender did not present gynaecomastia. The estrogenic and anti-androgenic properties of these two EO were subsequently demonstrated *in vitro* [60].

In 2018, Ramsay et al. orally reported the results of a study of the ED effect of eight components of the two EOs suspected as being EDs [61]. *In vitro*, on cells, the ED properties of four components common to both EOs (eucalyptol, 4-terpineol, dipentene/limonene and alpha-terpineol) and four others specific to one or the other (linalyl acetate, linalool, alpha-terpene and gamma-terpenine) were analysed. Many of these substances exert ED effects but

the abstract does not specify which ones and the study has not been published. It should be noted that the eight substances studied are found in 65 other EOs.

Produits of enfleurage

Other methods are used to extract scented products. Enfleurage relies on the power of fats to absorb odours naturally. When carried out hot, it allows a fragrant alcoholic extract to be produced. Use of the cold method, which involves placing flowers on the surface of fat to enable the fat to absorb perfume, is becoming less and less frequent in industry. It allows fragrant ointments to be obtained, as well as absolutes after processing with alcohol followed by evaporation.

Solvent extraction

Extraction using volatile solvents currently allows concretes and absolutes to be obtained. Plants are placed in vats called extractors and undergo successive washes with solvents that take up their fragrance. After decanting and filtering, the solvent is evaporated. A highly fragrant paste is obtained that is called concrete for flowers and resinoid for dry plants such as roots or mosses (e.g. oak moss). The concrete can then be washed with alcohol, resulting in a pure essence called the absolute [62].

Extraction by other processes, olive oil, oil of sweet almond, argan, neem, nigella, and so on

The term "cold" is used only for hesperids (e.g. oranges, lemons, bergamot). The zest is scraped and the resulting material is centrifuged, filtered and concentrated [62]. Some vegetable oils are obtained by pressing, such as olive oil, evening primrose oil, sweet almond oil. In fairly rare cases, certain of them, such as argan oil, neem oil or *Melia azadirachta* seed oil, may cause allergies [63-65].

On the other hand, nigella oil, obtained from a member of the Renonculus family *(Nigella sativa),* also called black cumin oil, El Baraka oil or the prophet's oil, causes acute eczema and polymorphic pseudo-erythema. Prized for its anti-infective and anti-inflammatory therapeutic

properties on skin, this EO, whose main active component is thymoquinone, is also used as an ingredient in homemade cosmetics. Besides thymoquinone, its other active ingredients are nigellicine, nigellidine, dithymoquinone, thymol, and carvacrol, as well as minor lipid constituents [66]. It is used in soaps, shampoos and hair masks because it seemingly improves hair sheen, texture and volume. It is also used in body relaxation creams [67]. Severe contact allergies have been reported with pure nigella EO following application to skin [68]. The agent responsible is thymoquinone [69]. Contact eczema may on occasion be systemically reactivated with polymorphic pseudo-erythema requiring hospitalization [70,71]. Sites selling cosmetics to make at home stipulate that only a few drops of EO or vegetable oil must be added to the base cream and that the customer alone is liable for any harmful effects following failure to heed the formula. However, the consumer and "amateur formulator" is not clearly aware of the risk of acute eczema or polymorphic pseudo-erythema following application to the skin of high concentrations of EO.

Conclusion

In conclusion, EOs and vegetable oils are allergenic, and sometimes cause intense polymorphic pseudo-erythema. In addition, lavender and tea tree EO have ED potential. These products must therefore be handled with care and expert advice is needed, which is not the case at present. Cosmetics made at home expose users to repeated handling of excessive concentrations of EO. In addition, when they do not contain preservatives, they should be used very quickly after manufacture to avoid risk of contamination with fungal agents or bacteria (*Staphylococcus aureus, Pseudomonas aeruginosa*).

Sunscreens

Sunscreens and ED effects

Some chemical screens have proven ED potency and exert harmful effects on the environment. Molecules having ED potency are shown in Table 1. The main agents are benzophenones, cinnamates and benzylidene camphor. The following sunscreens appear to have no ED effects: isoamyl p-methoxycinnamate, ecamsule (terephthalylidene dicamphor sulphonic acid), diethylamino hydroxybenzoyl hexyl benzoate, ethylhexyl triazone, polysilicone-15 and methyl anthranilate [6.7] (Table 5). Tinosorb M (methylene bis-benzotriazolyl tetramethylbutylphenol) and Tinosorb S (bis-ethylhexyloxyphenol methoxyphenyl triazine, bemotrizinol) do not appear to exert any ED action but their safety requires confirmation through further studies [6]. Avobenzone (butyl methoxydibenzoylmethane) appears devoid of any ED effects. Data on trolamine salicylate are insufficient to rule out an ED role, but its safety appears satisfactory [6].

Mineral screens

The ED potency of mineral screens is much debated and is non-existent as far as the U.S. Food and Drug Administration is concerned [72]. The toxic effects of mineral screens have been assessed in models exposed to high doses of these substances via the gastrointestinal and intra-peritoneal routes, which are far removed from the modes of exposure arising from use of sunscreens (Table 1).

To avoid the "white clown" effect of mineral sunscreens, their use as nanoparticles is now common in sun-care products. The safety of nanoparticles in these products is debated because human cells and enzymes are unable to degrade them. Fortunately, their diameter does not allow their resorption by healthy skin. Their fate on excoriated skin is unknown and as a precaution it seems reasonable to avoid their application in such cases.

Photoallergy

In addition to these ED effects, several sun protectants are actually photo-allergens. Fifteen of them are also part of the recommended battery in Europe to perform patch tests in patients with contact photo-allergy [73]. Photo-allergy to benzophenone-3 (oxybenzone, BP-3) exposes subjects to cross-reactions with other substances such as ketoprofen

Environmental toxicity of sun-care products

The photo-protective ingredients of sunscreens and cosmetics are released into the aquatic environment by swimmers coated with photo-protectors, by wastewater from coastal cities and boats, and by runoff.

At least 25% of the amount of sunscreen applied is found in bathing water, which represents a potential release of 4,000 to 6,000 tons per year liable to be deposited on coral beds. Danovaro et al. consider that 10% of the world's coral reefs are potentially at risk of bleaching caused or aggravated by sunscreen [74]. In 2008, sales of sun-care products were worth about half a billion dollars and annual production of UV filters totalled 10,000 tonnes. Over the past 20 years, massive bleaching of corals has been observed, corresponding to a loss of symbiosis between living organisms, zooxanthellae, and their hosts, stony corals or *Scleractinia*.

In addition to global warming, excessive UV irradiation, pollution, pesticides and bacteria, sunscreens have a negative impact on the survival of coral. Danovaro et al. have shown that sunscreens can induce a lytic viral cycle in symbiotic zooxanthellae and destroy them through viral reactivation [74].

A study was conducted on the Japanese island of Okinawa, where certain beaches are frequented by Japanese tourists and others by American soldiers with different habits in terms of sunscreen use [75]. The photo-protective substances found in the waters of the beaches were a reflection of the components of sunscreens used by visitors to these beaches. While the

maximum concentration of photo-protectors is observed in July and August in the coastal waters, it is just as high on the coral reef in June and September. The concentrations found remain lower than those that are lethal for coral, but the authors point to the long-term risk of chronic exposure of coral to these substances.

Sunscreens also have an impact on marine bacterioplankton. These lipophilic substances accumulate in aquatic animals and their effects on coral growth have been studied on planula, the larval forms of coral zooxanthellae.

In vitro, zooxanthellae are damaged by 4-ter-butyl-4'-methoxydibenzoylmethane, benzophenone-3, 4-methylbenzylildene camphor, octocrylene, ethylhexyl methoxycinnamate, and butyl parabens, but not by ethylhexyl salicylate. Butyl parabens, ethylhexyl methoxycinnamate, benzophenone-3 and 4-methylbenzylidene camphor cause complete bleaching even at very low concentrations (10 l/L). These results suggest that sun-care products containing butyl paraben, ethylhexyl methoxycinnamate (cinoxate), ethylhexyl methoxycinnamate (and possibly other cinnamates), benzophenone and 4-methylbenzylidene camphor are toxic to coral [74].

The effects of BP-3 on the planula of *Stylophora pistillata* coral, as well as its in *vitro* toxicity on coral cells of this species and six other coral species, have been studied [76]. BP-3 is a phototoxic agent and its side effects are exacerbated by light. Whether in darkness or light, BP-3 transforms planula from a moving state to a sessile (fixed), ossified and deformed state, enclosing the entire planula in its own skeleton. BP-3 is genotoxic, causing DNA damage, and it is also an ED. After exposure to light, the median lethal concentration (LC50) of BP-3 at 8 hours and 24 hours are 3100 g/L and 139 g/L, respectively. Even without light, toxicity persists with LC50s of 16800 g/L and 779 g/L. BP-3 contamination of coral reefs in the U.S. Virgin Islands ranged from 75 to 1400 g/L, while Hawaiian sites were contaminated between at 0.8 and 19.2 g/L. BP-3 therefore poses a real danger to coral reef conservation and

threatens the resilience of coral reefs to climate change. Downs et al. also reported the toxic effects of benzophenone-2 on corals with or without light [76]. All of these observations led Hawaii to ban the use of sun-care products containing BP-3 or ethylhexyl methoxycinnamate (cinoxate) on its beaches.

Although organic filters dominate the sun-care product market, the combined use of inorganic compounds, such as zinc oxide (ZnO) and titanium dioxide ($TiO_{2)}$, is constantly increasing due to the broad UV protective spectrum and their limited penetration into the skin [77]. The study by Corinaldesi et al. indicates that raw ZnO nanoparticles cause complete and potentially irreversible coral bleaching causing rapid and widespread mortality of zooxanthellae within stony corals [78]. Although the use of modified titanium dioxide in sunscreens is not completely free of potential negative effects, the results of the study by Corinaldesi et al. indicate that when used alone (i.e. as the sole ingredient), it has a limited impact on tropical stony corals [78,79]. A similar study conducted on *Montastraea faveolata* in the Caribbean Sea shows that titanium dioxide causes significant expulsion of zooxanthellae from all colonies, without mortality, suggesting possible acclimatization of coral to this stress [80]. The constituents of cosmetics harmful to corals are shown in Table 6.

Nano titanium dioxide (nano-TiO_2) acts on algae. The nano-TiO_2 contained in consumer products (toothpastes, sunscreens) are more toxic than industrial TiO_2 and inhibit growth of the diatom algae *Thalassiosira pseudonana*. This inhibition appears proportional to the time of exposure and to the concentrations of nano-TiO_2 in cosmetics [81]. In another study, the combined effects of nano-TiO_2 and phosphorus on *Chlorella ellipsoides* microalgae were evaluated. Optical density, total chlorophyll levels and antioxidant enzyme activities were significantly impaired, indicating that the mixture of the two compounds was harmful to microalgae in a freshwater ecosystem [82].

Is it possible to manufacture non-ED and environmentally friendly sunscreens?

The formulation of a sunscreen is very complex: it must allow protection against UVB with a minimum sun protection factor (SPF) of 6 and present a UVB/UVA protection ratio of 3 or less in "persistent pigment darkening" (PPD) at a critical wavelength of 370 nm [83].

To make and select a filter mixture, one or more of the photo-protectors authorized by the regulatory bodies must be used, i.e. formulation of a mixture of filters or powders based on the protection and photo-stability sought. Three essential points must be respected: the photo-protector must be safe and effective throughout the life of the product, the finished product must be effective, and the user must be observant about regular application of the product. To meet the criteria for a sunscreen, a cosmetic must consist of approximately 60-80% water and 10-20% broad-spectrum anti-UVA and UVB sunscreens. It contains emollients often associated with antioxidants (tocopherol, flavonoids). Emulsifiers and emollients are variable and allow the right texture to be created suitable for repeated use. They are gelifying agents, hydrophilic or lipophilic thickening filmogenic agents. Waxes, polymeric thickeners confer variable viscosity in cream, stick or aerosol formulations. Lasting adherence to skin is generally provided by cationic polymers and silicone oils ensure that the product is water-resistant [84]. It is necessary to ensure the removal of proven MEPs, even if this complicates the task of the formulator.

Manufacturers must ensure effective screens with a UVB/UVA protection ratio of 3 or less, and which remain stable at up to 40°C. Proven ED substances must be banned from screens and any new sunscreens should be studied for their ED action through work of the kind done in 2008 by Danovaro et al. [74] The ecological impact of sunscreens must also be taken into account and their toxicity to corals checked. Finally, it is necessary to take into consideration the ecological impact of mineral screens in the form of nanoparticles, which are more harmful than mineral screens without nanoparticles. It is not possible to propose

sunscreens to be applied only after swimming since most products are evaluated on dry skin and their photoprotective power is not determined for application on wet skin. However, a few commercial sunscreens have been tested after application on wet skin.

Haircare products

We will not examine all the side effects of haircare products. It should be remembered that some are allergenic to users, especially paraphenylenediamine (PPD), but also persulphate, ammonium thioglycolate and resorcinol [85].

PPD commonly causes contact eczema of the scalp combined with marked facial oedema that is particularly intense on all four eyelids. 2-methoxy-methyl-p-phenylenediamine appears to be less sensitizing than PPD, and seemingly reduces the risk of developing sensitisation. It is chemically close to PPD and para-toluenediamine and may lead to cross-reaction contact eczema in subjects already sensitized to PPD or para-toluenediamine [86]. Subjects with PPD allergies have a definitive contraindication to hair colouring agents containing PPD, but also to those containing substances that cause cross-reactions with PPD. The term “natural colouring” does not guarantee that the mixture does not contain PPD or any chemical substances causing cross allergies with PPD. However, purely plant colours exist that may be used by people allergic to PPD. Since they contain no chemical dyes, they provide "permanent" colouring and are capable of covering 100% of white hair. The product takes a long time to act, requiring from 1.5 to 2.5 hours to obtain a dark colour. The mixtures of pigments involved, their handling and the duration of the application require additional training of the hairdresser/colourist working with them.

Although the fad for "all natural" reigns supreme, it is surprising to see the use of blue, green and pink hair dyes. The composition of these products is poorly understood, but in

a published case of allergy to blue dye, the patient was allergic to Disperse blue 106, azo dye used with synthetic textiles [87].

A publication raises the issue of the risk of estrogenic ED-induced breast cancer in hair-growth stimulation products. The cosmetic constituents of haircare products do not contain oestrogen. We feel that use of oestrogenic solutions is a medical rather than a cosmetic topic because their active ingredient is a drug [88].

Labels and labelling

Labeling and risks

In terms of benefit-risk ratio, a cosmetic must present a risk to the health of the consumer close to zero. Labelling of cosmetics is mandatory in the "ingredients" section of the packaging. The first instruction in order to adopt a sensible attitude is thus to avoid cosmetics for which no information on the ingredients present is given under their INCI name, classified in descending order of weight. The list of ingredients appears on the package or is obtained from the retailer. The wording "does not contain" with regard to a particular class of ingredient, or "0%," which were purely marketing ploys that contributed to the spread of misconceptions, have been banned since 1 July 2019.

Since 2005, 26 perfumery substances have been recognized as potentially allergenic and must be included in this list if they are present above a defined threshold (10 ppm for unrinsed products and 100 ppm for rinsed products). In addition, use of the word "hypoallergenic" is now very limited in cosmetics. It was a claim by manufacturers that was not based on any European regulations or criteria. If a patient is allergic to a given substance, the latter should be sought in the list of ingredients

There is currently no application available in France to help people who are allergic to one or more ingredients in choosing a cosmetic that is suitable for them. The word "sensitive skin" also has no scientific definition. We will come back to labels that give an impression of safety. We will see that their main purpose is commendable environmental protection but that they are not intended to inform users whether or not the cosmetic contains sensitizing substances.

"Organic" and "natural" cosmetics

In recent years, there has been a huge increase in the number of "natural" or "organic" cosmetics reaching the market. How do you find your way around and what is the real quality of these products? A prerequisite exists: all cosmetic products must comply with Cosmetic Regulation 1223/2009 and thus follow all obligations related to cosmetic products. In particular, any cosmetics on which the INCI code does not appear in the composition must be banned.

As we wait and hope for a harmonized definition, a "natural" and "organic" cosmetic product may be defined as meeting the characteristics in one of the national or private biological/ecological reference works. To put it simply, all reference works on organic products suggest compliance with the following constraints:

- Regarding formulation: X% of substances are of natural origin, with Y% derived from organic farming
- Regarding manufacturing: the process must have been controlled.

According to REACH Regulation (EC Regulation 1907/2006 of 18 December 2006), natural products are "substances present in nature": "*a natural substance, in its natural state, untreated or treated only by manual, mechanical or gravitational means, by dissolution in water, by flotation, by extraction by water, by steam distillation or by heating only to*

remove water, or that is extracted from the air by some means." The term "*natural*" is thus not synonymous with "*of plant origin*" or "*harmless*".

An "*organic*" ingredient comes from organic farming. A natural ingredient is a plant, animal or mineral product directly derived from agricultural production, harvesting or work, unprocessed or else processed using methods covered in REACH.

A product of natural origin is a plant, animal or mineral product, processed using physical processes authorized in recognized specifications (e.g. clay, algae, plant extracts, honey, etc.).

ISO 16128 (published at the end of 2017) is the first harmonization text for biological ingredients, known as "*organic*" or "*natural*", substance by substance. Its purpose is to harmonize natural products and related language [89]. This standard does not rule on product claims, does not define a label, does not specify the conditions under which a product may be classified as natural or organic, and does not specify whether ingredients will be allowed or prohibited in a product labelled natural or organic. Part 1 of the standard (ISO 16128-1) distinguishes four types of ingredients: organic, organic derivatives, natural and natural derivatives. By using this standard, cosmetic ingredient manufacturers can already specify the category to which the ingredients they market belong. Part 2 of the standard (ISO 16128-2) calculates the indices associated with the different categories of organic and natural ingredients, i.e. the natural or biological portion of the finished products.

A label indicates specifications together with certification and a logo. Each label corresponds to a certifying body, a specification or a reference document. A reference document is a technical document defining the characteristics of an industrial product or service and the terms and conditions for monitoring compliance with these characteristics. The logo, name and main criteria of European labels are set out in Appendix 1. There are many labels, many of which are focused on the "*organic*" quality of ingredients while some also involve the notion of environmental protection, short production and consumption

channels which, while very important to the planet, do not allow assessment of the cosmetic quality of the product in question.

A single harmonized European label for natural and organic cosmetics seems essential. Some labels have been grouped together in a harmonized Cosmos - COSMetics Organic Standard - label that offers an international standard of natural and organic cosmetics, and which harmonizes among other things the BDIH, Cosmébio, Ecocert, ICEA and Soil Association standards.

Regardless of the actual label, the common fundamental principles respect the following principles: authorized and listed ingredients and manufacturing processes, very restricted use of synthetic ingredients, and of prohibited and listed ingredients and manufacturing processes. The main prohibitions are: no testing in animals (as with all European cosmetics); must not contain synthetic perfume or dye; must contain absolutely no synthetic preservatives such as parabens or phenoxyethanol; must not contain any ingredients from petrochemical processing (paraffins, silicone, PEG), GMOs, or substances treated with ionizing radiation or nanoparticles.

The certifiable part of an organic label must contain at least 95% of ingredients that are natural or of natural origin and at least 95% of organic plant ingredients, and at least 10% of all ingredients must have been produced by organic agriculture. It should be remembered that cosmetic products often contain 50 to 80% water, which is by definition non-certifiable.

The certifiable part of an Eco label must contain at least 95% ingredients that are natural or of natural origin, at least 50% of plant ingredients that are from organic farming and at least 5% of all ingredients that are obtained from organic farming.

The official European Ecolabel concerns soaps, shampoos and conditioners that are formulated from natural ingredients but without the obligation to use organic ingredients. This

Ecolabel guarantees that in relation to conventional products, labelled products contain fewer substances dangerous to the environment and to health, and that they have a lower impact on the aquatic environment, meet high biodegradability standards and use less packaging. Some ingredients are not allowed, such as alkylphenol ethoxylates and other alkylphenol derivatives, boric acid, borates and perborates, nitro musk, polycyclic musk and nitrilotriacetic acid. However, they may contain chemical preservatives.

With the implementation of the Sustainable Development Goals, the logos attributed to natural and organic cosmetics will develop further. Indeed, new generations of environmental labels are emerging. Some of them call for an environmental and ethical approach to the collection and processing of ingredients as manifest in the following for example: Organic Fair Trade, ESR, "*Main dans la main*" (Hand in hand), or an environmental approach focused on biodiversity, as is the case with "*Forest Garden Product*."

Soon in France, the carbon footprint of each product will be clearly labelled. The purpose of such labels, which should ideally be harmonized quickly, is first and foremost is to ensure environmental protection regarding the production and use of ingredients for cosmetics. It seems desirable that all these harmonization initiatives quickly enable easier understanding of labels for the consumer while allowing companies to defend and promote "laudable" eco-responsible cosmetics.

Conclusion. It is necessary to ask cosmetics manufacturers to quickly limit and remove ingredients that proven EDs or harmful for the environment, primarily in the formulation of sunscreens. At the end of 2019, the European Commission asked manufacturers to demonstrate as a priority the lack of harmfulness of the following 14 ingredients: kojic acid, benzophenone, benzophenone-3, benzyl salicylate, butylhydroxytoluene, homosalate, two soy isoflavones (genistein and daidzein), 4-methylbenzylidene camphor, octocrylene, propylparaben, resorcinol, triclocarban and triclosan. The Commission has also requested

safety studies on 14 other substances on a secondary list: benzophenone-1/BP-1, benzophenone-2/BP-2, benzophenone-4/BP-4, benzophenone-5/BP-5, butylated hydroxyanisole/BHA, tert-butylhydroxyanisole (BHT), butylparaben, butylphenyl methylpropianol/BMHCA, and cyclomethicone, cyclopentasiloxane/decamethylcyclopentasiloxane/D5, deltamethrin, ethylhexyl methoxycinnamate (EHMC), methylparaben, octyl methoxycinnamate (OMC)/octinoxate, salicylic acid, and triphenyl phosphate.

Determining the ED power of a cosmetic involves evaluating it in a cosmetic that that has remained in its packaging for several weeks (container-content interactions). It is necessary to know what blame is being attached to each ingredient incriminated and to adapt one's reasoning to the risks of toxicity to humans and to the environment, to skin type and to the exposed area (with inflammation, with or without corneal layer disorders), the site of application, the age of the user, and whether the cosmetic is left on the skin or rinsed off.

Buying "organic" cosmetics is primarily an eco-citizen gesture but does not mean that there is no risk of allergy or exposure to an ED effect. "Organic" cosmetics deserve to benefit quickly from the harmonization of labels to help guide consumers in their choices. Work is required on their formulation to ensure efficacy comparable to that of traditional cosmetics, and preservation remains their weak point.

Benefit/risk ratio analysis must be conducted cosmetic by cosmetic and we regret that some applications or blogs based on a personal list of "good" or "bad" products give a simplistic and alarmist answer to real questions concerning the safety of cosmetics. Some patients need to use cosmetics to avoid flare-ups of their dermatitis for example in atopic dermatitis, and anti-cosmetic scare campaigns, without scientific basis, are very harmful to these patients and to other consumers. Thus, dermatologists must now demand commitment from firms whose products they prescribe concerning the limitation or removal of substances

with ED effects that have been proven, even if only *in vitro,* and they must exercise constant environmental concern regarding the ingredients they recommend. They must also demand the removal from packaging of all claims devoid of any scientific basis, while reminding their patients that in case of allergy, switching to "organic" cosmetics is not the solution and that only allergic testing will identify the substance not tolerated. It will then be necessary to identify the offending substance in the list of ingredients, in the full knowledge that many of these substances are found in the formulas of "organic" and "non-organic" cosmetics alike. An application that provides the composition of a very large number of cosmetics would be of great help in assisting patients allergic to certain ingredients.

An eco-responsible approach, a little more science and fewer undocumented blogs would be a very welcome development for all consumers.

Conflicts of interest:

Annick Barbaud :

Novartis : Intervention lors de symposium, board pour études, protocoles

Sanofi : aide pour participation à des congrès

La Roche Posay : participation à un board, seulement en 2017, rédaction d'un livret de conseil en 2019

*Christine Lafforgue :

SVR : conseil scientifique

Filorga : conseil scientifique

Eau de Jonzac : communication scientifique

Mustela : communication scientifique

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	Oestrogens *in vitro*	Oestrogens *in vivo*	Progesterone *in vitro*	Androgens *in vitro*	Reproductive organs	Thyroid	CNS	Allergenicity	Other toxicity
PHOTOPROTECTANTS									
Benzophenones									
Benzophenone 3 (oxybenzone, BP3)	Oestrogen disruptor	Uterine size in rats (discordances) Anti-oestrogen effect in zebra fish ↑vitellogenin in rice fish	Antagonist	Antagonist	Rats: ↓ spermatogenesis (discordances) ↓ uterine weight			EU photoallergen (cross-reactions with ketoprofen)	↓ appetite and weight in girls if used by mother Detected in breast milk.
Benzophenone 2 (BP2)	Oestrogen disruptor	Mice: hypospadias Fish: affects gonads, secondary sexual characteristics, fertility (7)	Antagonist (3)	Antagonist		In vitro ↓ thyroid peroxidase Rats: ↑TSH but no disruption of TPO			
Benzophenone 1 (BP1)	Oestrogen disruptor	↑ vitellogenin	Antagonist	Antagonist (discordances)					Links with endometriosis posited
Other benzophenones			BP4: oestrogenic in zebra fish BP8: oestrogenic in rats					Benzophenone 4: EU photoallergen	
Benzylidene camphor									
3-Benzylidene camphor	Oestrogen disruptor	Rats: uterotrophic Rainbow trout and fat-head minnow: ↑ vitellogenin Action on molluscs [7] Affects gonads and results in feminization of male fish. Disrupts weight in offspring of exposed rats and fat-head minnow	Antagonist	Antagonist	In first generation descendants of exposed rats: Delayed puberty in males Cyclical and uterus-size abnormalities		Sexual behaviour disorders		
3-(4-methyl-benzylidene)-camphor or (4-MBC)	Anti-oestrogen	Rats: uterotrophic ↑ vitellogenin in fat-head minnow ↑ vitellogenin in rice fish liver Zebra fish: no effect	Antagonist	Antagonist	Rats: exposed, dams, with prostate changes and testicular enlargement in males, and uterotrophy in females	↓ Iodine uptake in 1st and 2nd generation offspring: ↑ TSH and T3	Sexual behaviour disorders in descendants	EU photoallergen	
Homosalate (HMS)	Oestrogen disruptor ↑ MCF-7 cell proliferation		Antagonist	Antagonist (discordances)					

2 ethylhexyl-4-methoxycinnamate = OMC = cinoxate	Oestrogen disruptor ↑ MCF-7 cell proliferation	Immature rats: uterotrophic, weight loss [6] Fish: ↑ vitellogenin in fat-headed minnow but no effect on zebra fish	Antagonist		Rats: disturbance in descendants: testosterone, sperm, uterotrophy	↓ Iodine uptake, discordance in TSH variations and ↓ T4 In rats: thyroid disturbances		EU photoallergen	Non-ED activity on reproductive organs Passage into breast milk and infants fed it
2-ethylhexyl 4-dimethylaminobenzoate (OD-PABA)	Oestrogen disruptor Endocrine effect on *Chironomus riparius* ↑ MCF-7 cell proliferation	Rats: no effect Fish: oestrogenic effect		Antagonist (discordances)					
4-aminobenzoic acid (PABA)	Oestrogen disruptor							EU photoallergen	
Octocrylene	Oestrogen disruptor	No		Antagonist				EU photoallergen	
Titanium dioxide		Ongoing discussion concerning TiO2 nanoparticles Male mice: high intraperitoneal doses - Reproductive inhibition in *Daphnia magna* (a freshwater invertebrate) ↓ egg production in zebra fish ↓ cocoon production in earthworms							
Zinc oxide		Ongoing discussion If administered orally: Hormonal problems in rats and chickens Toxic for sea urchin embryos Embryo malformation in zebra fish ↓ cocoon production in earthworms							
PLASTICIZERS									
PHTALATES (7) In fragrances, cosmetics and plastic packaging DEP, DBP, DEHP, MEHP In fragrances, less and less in cosmetics, possible leaching from plastic packaging DEP, DBP, DEHP, MEHP		Rats: DHEP ↓ oestradiol, inhibits ovulation In descendants. Abnormalities of reproductive organs and ↓ sperm production DHEP and DOP	Antagonist	Rats: DHEP and others: antagonist					Discussion ongoing about effects on weight, waist circumference, obesity. Demonstrated effects after ingestion. Impact in cosmetics under discussion: weight, waist

		disrupt sperm mobility							circumference, obesity, cardiovascular risk. Bioaccumulation occurs
Bisphenols **No warnings on cosmetics packaging**	**Bisphenol A (BPA): Synthetic oestrogen** Clinically tested in the 1930s like oestrogen. Banned in teats since 2011 **BPS and BPF** not banned in teats, despite same potency for ED		Interaction with progesterone receptors						Oral administration: Acts on glucocorticoid receptors BPA crosses the placental barrier, reduces egg maturation, affects birth weight, increases adiposity and disrupts glucose metabolism.
DIMETHICONES "silicones" Octamethylcyclotetrasiloxane (D4) Decamethylyclotetrasiloxane (D5) Dodecacyclotetrasiloxane (D6) Often in a mixture, called CYCLOMETHICONE (polydimethylsiloxanes) If associated with silica, simethicone		D4 in rats: Oestrogenic disruptor of cycle and fertility							
Other ingredients that could cause ED									
Parabens	*In vitro* oestrogenic effects of propyl, butyl, methyl and ethyl parabens	Mice: ↓ testosterone Rats: Butyl paraben, on descendants↓ amount and mobility of sperm. No effect on exposed rats ↑ vitellogenin in zebra fish larvae (*Danio rerio*)		Antagonist (28)	Parabens	*In vitro* oestrogenic effects of propyl, butyl, methyl and ethyl parabens		Weak contact allergens	
EDTA disodium								Weak contact allergen	Disruption of binding of intestinal vasoactive peptide to macrophages
Triethanolamine									Respiratory irritant for aquatic organisms
Triclosan	Ongoing discussion on oestrogen disruption			Ongoing discussion on androgen disruption	Ongoing discussion on thyroid disruption				May worsen asthma and increase bronchial hyper-reactivity in humans. In view of its potential toxicity, European regulations have limited the use of triclosan to between 0.15% and 0.2% in mouthwashes,

									and to 0.3% in nail cleansing products.
Essential oils of lavender and tea tree (82)		Oestrogenic ED (oestrogen-like)		Anti-androgenic (anti-testosterone) effect					
BHA Discussion regarding food, no warnings for cosmetics	Little effect on oestrogen receptors but increased oestrogen synthesis [69,70]	Increased oestrogen secretion in zebra fish [70]							Embryonic toxicity on zebra fish larvae Interference by synthetic phenolic derivatives (SPA) on the hypothalamic-pituitary-thyroid axis in larva Harmful effect on aquatic organisms, especially fish.

Table 1: endocrine disruption effects of cosmetic ingredients or packaging [5-7]

EU photoallergen: photoallergen included in the European photoallergen battery

INCI name	CAS No.	Chemical definition
C18-70 Isoparaffin	246538-80-7	Iso-alkanes containing 18-70 carbons. Branched chains
Microcrystalline wax	63231-60-7/ 64742-42-3	Mixture of paraffin wax and microcrystalline hydrocarbons. Obtained by solvent crystallization. Consists mainly of linear and branched hydrocarbon chains with > 35 carbons.
Ceresin	8001-75-0	A mixture of hydrocarbons obtained by purifying ozokerite with sulphuric acid followed by filtration.
Hydrogenated microcrystalline wax	64742-60-5 /92045-76-6	Hydrogenated wax
Hydrogenated microcrystalline wax	92045-76-6	Microcrystalline wax hydrogenated the presence of a catalyst
Microcrystalline wax	63231-60-7	Petroleum-derived wax. Consists of high molecular weight linear hydrocarbons. Characterized by small crystals.
Ozokerite	64742-33-2	Petroleum-derived and chemically neutralized hydrocarbon wax. Treated to remove any acids present. Consists mainly of saturated linear chain hydrocarbons ranging with 20 to 50 carbons.
Paraffin	8002-74-2/64742-51-4	Liquid or solid mineral dispersion of long-saturated and purified hydrocarbons obtained from crude oil.
Liquid paraffin	8012-95-1 / 8042-47-5	Highly refined white mineral oil derived from petroleum. Obtained by reacting a fraction of oil with sulphuric acid, or by hydrogenation, or by a combination of hydrogenation and acid treatment. Consists of saturated hydrocarbon chains ranging with 15 to 50 carbons.
Petroleum jelly	8009-03-8	Petroleum-derived hydrocarbon complex obtained in the form of semi-solid dispersion of crystalline and liquid hydrocarbons. Made up of saturated chains and containing > 25 carbons.
Synthetic wax	8002-74-2/ 68527-08-2	Oil wax obtained by the Fischer-Tropsch process or by ethylene polymerisation

Table 2: Composition of mineral oils.
C: carbon

Acronym	Name	Examples of use	**Regulations** (former uses)
DEHP = DOP	Di-ethylhexyl phthalate	Plastic objects, shower curtains, gloves, catheters	Banned (perfumes)
BBP	Butyl benzyl phthalate	Perfumes, adhesives, glue, etc.	Banned (perfumes)
DBP	Dibutyl phthalate	PVC, adhesives,	Banned since 2004 (nail varnish)
DINP	Diisononyl phthalate	PVC, adhesives, lacquers, etc.	
DIDP	Diisodecyl phthalate	PVC, anti-corrosives, textiles, inks	
DNOP	Di-n-octyl phthalate	Medical tubing, adhesives	
DIBP	Diisobutyl phthalate	Substitute for DBP	Banned (nail varnish)
DEP	Diethyl phthalate	Perfumes, deodorants	Perfume solvent allowed up to a maximum concentration of 50% or as a denaturing additive for ethanol up to a maximum concentration of 1% (denatured alcohol) [47]

Table 3: Phthalates - names, uses and current state of regulations governing their use in 2019

Substance	CAS No.	Alternative to	Alternative in	Price vs. Silicones
Isodecyl neopentanoate	60209-82-7	Cyclomethicone	Conditioners and shampoos	About twice as expensive
Glycol distearate	627-83-8	Cyclomethicone and dimethicone	Soaps, creams	About half the price
Dicapryl carbonate	1680-31-5	Cyclomethicone and dimethicone	Creams, lotions	Similar price
Diethylhexyl carbonate	14858-73-2	D5	Lotions, emulsions	Slightly cheaper
Hydrogenated polydecene	68037-01-4	Cyclomethicone	Non-rinse products, make-up	Slightly more expensive

Table 4: Possible substitutes for silicones

Sunscreen	INCI	Maximum concentration allowed
No ED effects		
Neo Heliopan® E 1000 (amiloxate)	isoamyl p-methoxycinnamate	10%
Mexoryl® SX (ecamsule)	terephtalylidene dicamphor sulfonic acid	10%
Uvinul® A Plus	diethylamino hydroxybenzoyl hexyl benzoate	10%
Uvinul® T 150 (octyl triazone)	ethylhexyl triazone	5%
Parsol® SLX (dimethicodiethyl benzalmalonate)	polysilicone-15	10%
Meradimate	menthyl anthranilate	Not in Appendix VI of the European regulations
Neo Heliopan® E 1000 (amiloxate)	isoamyl p-methoxycinnamate	
No apparent ED effects		
Tinosorb® M *(bisoctrizole*)	methylene bis-benzotriazolyl tetramethylbutylphenol	
Tinosorb® S (*bemotrizinol*)	bis-ethylhexyloxyphenol methoxyphenyl triazine	
Avobenzone	butyl-methoxy dibenzoyl methane	
No apparent ED effects but requiring further confirmation studies		
Trolamine salicylate (triethanolamine salicylate)		

Table 5: Sunscreens with no demonstrated endocrine-disrupting (ED) activity to date [6,7]

Sunscreens	Benzophenone-3 Benzophenone 2 4-tert-butyl-4-methoxydibenzoylmethane, 4-methylbenzylidene camphor, octocrylene, Ethylhexyl methoxycinnamate (and possibly other cinnamates) Zinc oxide in the form of raw **nanoparticles**
Other substances	Butylparaben

Table 6: Cosmetic ingredients harmful to coral