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Review

Sun lotion chemicals as endocrine disruptors

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ABSTRACT

Ultraviolet solar radiation is a well-known environmental health risk factor and the use of sun lotions is encouraged to achieve protection mainly from skin cancer. Sun lotions are cosmetic commercial products that combine active and inactive ingredients and many of these are associated with health problems, including allergic reactions and endocrine disorders. This review focuses on their ability to cause endocrine and reproductive impairments, with emphasis laid on the active ingredients (common and less common UV filters). In vitro and in vivo studies have demonstrated their ability to show oestrogenic/anti-oestrogenic and androgenic/anti-androgenic activity. Many ingredients affect the oestrous cycle, spermatogenesis, sexual behaviour, fertility and other reproductive parameters in experimental animals. Their presence in aquatic environments may reveal a new emerging environmental hazard.

Key words: Active ingredients, Endocrine disruptors, Environmental hazard, Reproductive impairments, Sun creams, Sun lotions, Sunscreens, UV filters

1. INTRODUCTION

Ultraviolet (UV) solar radiation is one of the most studied environmental health risk factors. The Earth's atmosphere functions as a natural shield, but it cannot protect us completely from the UV radiation that reaches the surface.[1,2] Skin has its own protective mechanisms, such as tanning and stratum thickening, but the level of photoprotection is insufficient to prevent the harmful effects of UV radiation.[3,4]

To achieve a better level of protection, the use of sun lotions and creams, often with a high protection factor, is advised.[5] However, health issues associated with their ingredients exist and include, among others, allergic reactions[6-8] as well as endocrine and reproductive disorders.[9,10] Manufacturers of sun lotions constantly modify the composition of their products (active and inactive ingredients) to make them more effective and safer for consumers. Nevertheless, the safety of these products is relative and questionable.

Sun lotions have become popular commercial products. Furthermore, many cosmetic products (not only sun lotions and creams) are on the market containing

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some of the active ingredients.[11] Therefore, exposure to these UV filters does not occur only through traditional sun protection products. This review article focuses on the ability of UV filter chemicals to cause endocrine and/or reproductive impairments.

1.1. UV solar radiation

UV solar radiation is usually divided into three groups. The most energetic, known as UV-C (100-280 nm), is completely absorbed by atmospheric molecular oxygen and ozone and does not reach the Earth's surface. UV-B (280-315 nm) reaches the surface, its quantity being determined by stratospheric ozone concentration since ozone is a strong absorber at these wavelengths. UV-A (315-400 nm) reaches the surface without significant losses during its passage through the atmosphere. Cloudiness impedes both UV-A and UV-B.[1,12,13] As both UV-B and UV-A cause negative health effects,[3,14] protection from these forms of radiation is indicated.

To avoid a possible confusion with the spectral ranges mentioned above, it is useful to redefine them according to photobiology. Taking into consideration the biological effects, the spectrum between 200-290 nm is called UV-C and that between 290 and 320 nm UV-B, while UV-A covers the 320-400 nm range.[12]

Exposure to UV radiation causes, inter alia, sunburn, tanning, photoaging, melanoma and other malignancies, cataracts and immunosuppression.[3,14-16] Although UV-A penetrates more deeply into the skin,[17] UV-B is considered to cause more biological effects than UV-A.[3] Nevertheless, skin exposure to UV-B is necessary for the cutaneous synthesis of vitamin D.[18]

1.2. Sun lotions

Sun lotions are cosmetic products that protect from UV radiation after topical dermal application due to their active ingredients. These ingredients absorb or block UV irradiation by reflection and/or scattering.[19,20] Their properties protect their users from UV-B or both UV-B and UV-A, depending on their formulation.

Commercial sun lotions are grouped into three categories. The first includes those products whose UV filters are organic chemical absorbers.[19,21-23] The second group includes products which contain metal oxides (inorganic UV filters, e.g. titanium dioxide and/or zinc oxide).[19-24] The third group includes formulations which combine organic and inorganic agents.[21,24]

Manufacturers combine different UV filters (hereinafter referred to as "active ingredients") to increase the sun protection factor (SPF) of their lotions or creams.[21,25] Simply phrased, SPF is a numerical value indicating the protection level against sunburn.[21]

1.3. Endocrine disruptors and reproductive health

Endocrine disruptors are chemicals that alter the normal function of the endocrine system, leading to a variety of health problems, such as reproductive impairments and female and male cancers as well.[26-29]

Exposure to endocrine disruptors starts in utero and never ceases throughout life, since these chemicals are present in a variety of daily products, including food, bottled water and cosmetics.[30-35] Some of the ingredients of sun lotions show endocrine altering and disrupting properties.[9,36,37]

Possible reproductive impairments are crucial because they are associated with infertility.[26,27,38-41] The life of all living organisms is strongly connected with the environment and reproduction is the key factor for their survival.[42] Endocrine disruptors are omnipresent in ecosystems and some of their properties, including their bioaccumulation potential, should be taken seriously into account.[43]

1.4. Sun lotion chemicals and routes of exposure

Since sun lotions and creams are applied to the skin, the main route of exposure to them is dermal. The skin is the body's largest organ. It has its own defence mechanisms such as the formation of a protective barrier.[44] With regard to sun lotions, the effectiveness of the skin as a barrier against chemicals, biological agents and radiation depends on many factors such as the body site of application, the person's age, the health status of the skin, the frequency of the application, the duration of skin contact with the product and the possible presence of chemicals that enhance the penetration of other substances.[17,45-47]

Furthermore, exposure is also possible through inhalation. Apart from the fact that some sun lotions

are sprays,[48] many sun lotions contain fragrances made with endocrine disruptors.[49]

Finally, exposure through ingestion is also possible, especially as a result of hand-to-mouth habit.[50] Generally, this behaviour is a noteworthy risk factor for children.[51] Additionally, sunscreen lipsticks contribute to the exposure by ingestion.[52,53]

2. ORGANIC CHEMICAL ABSORBERS

Since the production of the first sun lotions and creams, many organic absorbents have been used as filters. The most common organic chemical absorbers include the chemicals discussed below.

2.1. Benzophenone compounds

2.1.1. Oxybenzone

Oxybenzone (or 2-hydroxy-4-methoxybenzophenone, benzophenone-3, BP3) is a benzophenone (BP) compound (commonly used as a UV filter) with known endocrine disrupting characteristics. In vitro studies (human oestrogen receptor alpha (hERα) and human androgen receptor (hAR) assays) indicate that BP3 displays oestrogenic, anti-oestrogenic and anti-androgenic activity.[9]

BP3 exhibits anti-oestrogenic and anti-androgenic activity in vivo in fish. In the brain of adult zebrafish males, BP3 down-regulates alpha oestrogen receptors and androgen receptors. The effects mainly occur at an aquatic concentration of 84 μg/l, but that concentration is much higher than the highest environmental level of 10 μg/l, as had been hypothesized by this study.[54] Fish exposure to oxybenzone also affects egg production and hatching. For instance, exposure of Japanese medaka to 620 μg/l of BP3 reduces egg production (temporarily) and the normally expected hatching percentage. However, effects on these parameters also occur at lower concentrations (132 μg/l, 16 μg/l). Significant vitellogenin induction occurs at high doses, e.g. 620 μg/l in the Japanese medaka (vitellogenin is a biomarker for oestrogenic results).[55,56]

Furthermore, oxybenzone increases the uterine weight of immature rats with a median effective dose (ED50) in the range of 1000 to 1500 mg/kg/day (dietary administration). A continuous breeding study revealed that the exposure of mice to high doses of BP3 reduces the number and the weight of offspring and increases the mortality of the lactating dams. The no observed adverse effect level (NOAEL) for reproductive toxicity was 1.25% in feed.[57] However, a dermal application of high doses (up to 400 mg/kg/day) to male mice does not affect reproductive organ weight or production and quality of sperm.[58]

In humans, a reduction of birth weight in girls and an increase in boys may also be associated with maternal exposure to oxybenzone,[59] which has also been detected in breast milk.[60]

2.1.2. Benzophenone-1

Benzophenone-1 (2,4-dihydroxybenzophenone, BP1) is a common metabolite of oxybenzone. BP1 binds to oestrogen receptors obtained from rats' uteri.[61] Its oestrogenic and anti-androgenic activities have been confirmed in vitro (hERα and hAR assays).[9] Its oestrogenic activity has also been confirmed in vivo in fishes (significant vitellogenin induction at 4.919 mg/l).[62] Ex vivo assays with testes from mice and rats revealed that BP1 inhibits testosterone synthesis.[63]

Moreover, BP1 affects the early life-stage development of the marine copepod *Acartia Tonsa*. Environmental conditions, such as salinity and temperature, influence the toxic effect. For instance, at 20°C, the median effective concentration (EC50) was 1.1 mg/l and at 15°C, 0.49 mg/l.[64]

Finally, endometriosis in women, which is an oestrogen-dependent disease, is associated with exposure to benzophenone compounds and especially with exposure to BP1.[65]

2.1.3 Other benzophenone compounds

Benzophenone-2 (2,2′,4,4′-tetrahydroxybenzophenone, BP-2) is another sun lotion component of the benzophenone group. In vitro assays revealed its ability to display oestrogenic, androgenic and anti-androgenic activity.[9] In addition, in utero exposure of male mice to BP-2 causes hypospadias.[66] Its oestrogenic activity has been confirmed in vivo in fishes.[62,67,68] Exposure of fishes to BP-2 affects the gonads, the secondary sex characteristics, spawning activity and fertility with a lowest observed effect concentration (LOEC) of 1.2 mg/l.[67,68]

Experiments with zebrafish showed that suliso-

benzone (Benzophenone-4, BP4) disrupts the normal endocrine function of the animals (oestrogenic activity) and induces alterations in the genes related to thyroid development. The lowest effect concentration (LEC) was found to be 30 µg/l.[69] Furthermore, BP4 shows oestrogenic/anti-oestrogenic and anti-androgenic properties in vitro.[9]

Dioxybenzone (Benzophenone-8, BP8), which is also a sun lotion benzophenone ingredient, shows oestrogenic activity in vitro.[70] 4-hydroxybenzophenone (or p-hydroxybenzophenone) is another benzophenone compound with endocrine disrupting properties in vitro.[71] What is more, 4-hydroxybenzophenone displays endocrine activity in juvenile female rats and increases the weight of their uterus after subcutaneous administration.[72]

2.2. Octyl methoxycinnamate

Octyl methoxycinnamate (ethylhexyl methoxycinnamate, octinoxate, OMC) is a commonly used UV filter with known endocrine disrupting properties.[9,36]

In rats, OMC causes various impairments, including the alteration of the normal release of the luteinizing hormone-releasing hormone (LHRH) and of the amino acid neurotransmitters from the hypothalamus.[73] This sunscreen filter can decrease the normal serum concentrations of the hormones: thyrotropin (thyroid-stimulating hormone, TSH), thyroxine (T4) and triiodothyronine (T3) in rats. This reveals a possible impact on the function of the hypothalamic-pituitary-thyroid axis.[74]

OMC exhibits anti-oestrogenic and androgenic/anti-androgenic activity but no oestrogenic activity in hERα and hAR assays.[9] Furthermore, a two-generation study with rats concluded that OMC has no oestrogenic effect in vivo either. A NOAEL of 450 mg/kg bw/day (dietary administration) for reproductive disorders was established and a dose of 1000 mg/kg bw/day was found to be able to delay the sexual maturation of the offspring for a few days.[75]

Exposure to OMC by gavage leads to a decrease of T4 concentration in female rats (dams) and affects the reproductive and the neurological development of their offspring. Exposure to 1000, 750 or 500 mg/kg bw/day from gestation day 7 to postnatal day 17 negatively affected the sperm counts of the male offspring.[76] OMC also increases the uterine weight of immature rats with an ED50 of 935 mg/kg/day (dietary administration).[36] Moreover, the exposure of the aquatic insect *Chironomus riparius* to OMC affects its normal endocrine function.[77]

Skin absorption of OMC is possible, which accounts for its presence in plasma, urine and human milk.[60,78] Its presence in human milk leads to neo-natal exposure, which is of particular concern.

2.3. 4-methylbenzylidene camphor

4-methylbenzylidene camphor (4-MBC, enzacamene) disrupts normal endocrine function in rats, fishes, aquatic molluscs and insects.[37,77,79,80]

In vitro assays (hERα and hAR) have revealed its anti-oestrogenic and anti-androgenic properties.[9] Exposure of rats to 4-MBC (dietary administration of F0 generation and F1 until adulthood) increases the uterine weight of the female offspring and the thyroid weight of both sexes in the two generations.[37] 4-MBC delays male puberty and disrupts the normal female sexual behaviour of the offspring (dietary administration of F0 generation and F1 until adulthood) with a NOAEL of 0.7 mg/kg/day and a lowest observed adverse effect level (LOAEL) of 7 mg/kg/day.[10] An ED50 of 309 mg/kg/day (dietary administration) was determined in immature rats for increasing uterine weight.[36]

2.4. 3-benzylidene camphor

The UV filter 3-benzylidene camphor (3-BC) exhibits endocrine disrupting activity (oestrogenic, anti-oestrogenic and anti-androgenic) as demonstrated using hERα and hAR assays.[9] 3-BC shows oestrogenic activity not only in vitro but also in vivo in fish and aquatic molluscs.[62,80]

3-BC delays male puberty and disrupts normal female sexual behaviour and the oestrous cycle of rat offspring (dietary administration as in the case of 4-MBC, NOAEL: 0.07 mg/kg/day and LOAEL: 0.24 mg/kg/day).[10] Additionally, less heavy rat uteri are associated with exposure to 3-BC.[37]

Exposure to 3-BC is also associated with disorders of the normal reproductive function of fish, produces feminization of male secondary sex characteristics and affects the gonads (male and female) and fertility with a LOEC of 3 µg/l.[68]

2.5. PABA, OD-PABA, Et-PABA

PABA (para-aminobenzoic acid, p-aminobenzoic acid, 4-aminobenzoic acid), OD-PABA (Padimate O, Octyl-dimethyl PABA, Ethylhexyl dimethyl PABA) and Et-PABA (Ethyl-4-aminobenzoate) are chemicals known for their ability to absorb UV radiation.

Regarding likely effects of PABA on the endocrine and/or the reproductive system, research until now is limited. A study has demonstrated anti-oestrogenic activity in a hERα assay,[9] but other experiments have not revealed a noteworthy connection or a negative effect. For instance, the exposure of pregnant rats to PABA at 50 mg/kg (intragastric administration) slightly affects the normal development of the body mass of rat foetuses, but this effect was characterized as "insignificant", as body mass development usually becomes normal after birth.[81]

OD-PABA displays oestrogen antagonistic activity in vitro[70] and shows an endocrine effect in the aquatic insect *Chironomus riparius*.[77] Et-PABA is also an endocrine disrupting agent. Oestrogenic activity in vitro and in vivo in fishes has been shown.[9] Both chemicals display anti-androgenic activity in vitro.[9]

2.6. Other organic filters

The organic UV filters octocrylene (OC), homosalate (HMS, homomethyl salicylate) and octisalate (octyl salicylate, OS or ethylhexyl salicytate, EHS) show anti-oestrogenic, androgenic and anti-androgenic activity in hERα and hAR assays.[9] The available data, e.g. for octocylene,[82] does not reveal reproductive risks.

Tinosorb M (methylene bis-benzotriazolyl tetramethylbutylphenol, bisoctrizole) and Tinosorb S (bis-ethylhexyloxyphenol methoxyphenyl triazine, bemotrizinol) are organic compounds used in sun lotions. None of these ingredients is expected to have an endocrine disrupting activity (in vitro assays and in vivo subcutaneous administration).[83] In any case, both chemicals are relatively new components and more research is needed on their possible effects on the endocrine and the reproductive systems.

Avobenzone (butyl-methoxydibenzoylmethane) is additionally an active compound, regarding which more investigation is indicated. Limited evidence suggests that it does not display oestrogenic activity.[36]

More investigation is also needed to determine a possible endocrine and reproductive disrupting role of 2-Ethoxyethyl p-methoxycinnamate (cinoxate), trolamine salicylate (or triethanolamine salicylate) and Mexoryl SX (Ecamsule). Lack of evidence as to endocrine disrupting properties and/or reproductive impairments characterizes the majority of the remaining and less common ingredients as well. These compounds include, among others, Amiloxate (Isoamyl p-Methoxycinnamate), Mexoryl SX (Ecamsule), Uvinul A Plus (diethylamino hydroxybenzoyl hexyl benzoate), octyl triazone (ethylhexyl triazone, Uvinul T 150), polysilicone-15 (Parsol SLX) and Methyl anthranilate (Meradimate).

3. METAL OXIDES

Titanium dioxide (TiO_2) and zinc oxide (ZnO) are two metal oxides traditionally known for their sunblocking properties.[20] Sun lotion manufacturers formerly used the bulk form of these materials, but nanotechnology advances have made possible the use of their nanoscale form. The new nanoscale ingredients are more aesthetic, as they do not produce the characteristic opaque film created by the largescale ones.[84]

Regarding their possible dermal penetration/absorption, there are studies that have shown that these nanoparticles do not penetrate the skin deeper than the stratum corneum in vitro or do not exhibit skin penetration in vivo.[85] However, Zn from ZnO nanoparticles can be absorbed by a healthy skin and can be detected in human urine and/or blood samples.[86] The parameter "healthy skin" is important because if the skin has e.g. a disrupted stratum corneum, the behaviour of these particles may be different.[84]

Nanoparticle forms of both metal oxides produce reactive oxygen species (ROS) in the presence of UV radiation.[84] In general, ZnO nanoparticles are considered more toxic than TiO_2 nanoparticles.[87]

3.1. Zinc oxide

Zinc is a necessary trace element for normal reproductive function, such as normal spermatogenesis and the oestrous cycle.[88] However, a study revealed that high doses of dietary zinc may cause apoptosis of reproductive tissues in hens.[89] Other experiments have shown that zinc in high doses causes hormonal problems in rats.[90]

In mice, ZnO nanoparticles accumulate in liver and cause oxidative stress, DNA damage and apoptosis in its cells two weeks after oral exposure to 300 mg/kg.[91] Furthermore, in *Cyprinus carpio* fishes, ZnO nanoparticles bioaccumulate more easily and cause more oxidative damage compared to its bulk counterparts.[92]

ZnO nanoparticles are toxic for white sea urchin embryos with an EC50 of 99.5 μg/l.[93] ZnO nanoparticle aggregates affect zebrafish and cause delayed embryo hatching (84 hours EC50 for this study: 23.06 mg/l) and likely malformations in embryos and larvae.[94] The aquatic toxicity of ZnO nanoparticles is attributed to Zn^{2+} ions (mainly), or to the nanoparticles themselves, or to a possible combination of both.[94-96]

Moreover, a study revealed that the nanoforms of ZnO can impede normal cocoon production (a reproductive parameter) of earthworms in artificial soil conditions, exhibiting greater toxicity attributed to the dissociation of Zn ions.[97]

3.2. Titanium dioxide

Nanoparticles of TiO_2 present a risk factor for the male mouse reproductive system, affecting the normal density and motility of the sperm at high doses of exposure (500 mg/kg, intraperitoneal injection every other day).[98] The intravenous injection of TiO_2 nanoparticles with a diameter of 35 nm disrupts normal pregnancy progression in already pregnant mice.[99] Chronic exposure (21 days) of the aquatic organism *Dapnia magna* to nanoparticles of TiO_2 (0.1, 0.5, 1, 5 mg/l) inhibits its reproduction.[100]

Chronic exposure (13 weeks) of zebrafish to 0.1 mg/l and 1 mg/l of TiO_2 nanoparticles negatively affects their reproductive system and reduces egg production.[101] Chronic exposure (21 days) to nanoparticles of TiO_2 (length: 50 nm, width: 10nm) coated with hydrated silica, dimethicone/methicone copolymer and aluminum hydroxide (T-Lite SF-S) affects the reproduction of *Daphnia magna* freshwater invertebrates in a negative way. A LOEC of 10 mg/l and a no observed effect concentration (NOEC) of 3 mg/l were defined. The concentration of 10 mg/l caused a two-day delay in the production of the first offspring. The EC50 for the reproductive outcomes was 26.6 mg/l.[102]

Another known effect related to reproductive toxicity issues is the decrease of cocoon production by earthworms in artificial soil due to exposure to nano TiO_2.[97] Furthermore, a possible endocrine role of TiO_2 nanoparticles can be deduced from the induction of insulin resistance in liver-derived cells.[103]

The use of nanoparticles raises safety issues. One of the most important is possible transport through the placental barrier leading to potential disruption of normal embryogenesis and to foetal exposure.[104] TiO_2 nanoparticles are detected in the male offspring after subcutaneous administration to pregnant mice and cause reproductive impairments leading to problematic spermatogenesis.[105]

4. SKIN PENETRATION ENHANCERS

Sun lotions can act as penetration enhancers by favouring the flux of hazardous chemicals through the skin.[106-108] A study had demonstrated that these products can increase the penetration of benzene through human skin in vitro, but it did not identify the culpable components.[106] However, a newer study showed that the active ingredients octyl methoxycinnamate, oxybenzone, sulisobenzone, OD-PABA, octisalate, homosalate and the insect repellent DEET can increase the penetration of 2,4-dichlorophenoxyacetic acid through hairless mouse skin in vitro. Only Octocrylene did not promote the uptake.[108]

Many of the chemicals that penetrate the skin more easily show endocrine disrupting activity and/or cause reproductive impairments. For instance, as mentioned above, some sun lotions can act as penetration enhancers for 2,4-dichlorophenoxyacetic acid.[107,108] This substance, known for its endocrine disrupting role,[109] is a widely used herbicide. 2,4-dichlorophenoxyacetic acid can affect normal development of the central nervous system of rats and their spermatogenesis.[110,111] It also disrupts normal rat maternal behaviour.[112] Farmers who are exposed to herbicides and daily spend many hours outside and use sunscreens to protect themselves from UV radiation face a higher risk for this kind of penetration.[107,108]

Therefore, possible endocrine disrupting activity and/or impairment of the reproductive system caused by increase of exposure to other chemicals can be an indirect effect of the use of UV filter chemicals.

5. INACTIVE INGREDIENTS

Sun lotions are formulated using inactive ingredients such as parabens (alkyl esters of p-hydroxybenzoic acid). Parabens are common preservatives of pharmaceutical and cosmetic products. Not all sun lotions contain parabens and many manufactures have replaced them with other substances. For instance, during this research, a brand was identified whose previous formulations contained three parabens (propylparaben, butylparaben and methylparaben), but its new ones are paraben-free. Other ingredients (both inactive and active) also changed, although it was commercialized as the same product with the same SPF. Other common inactive ingredients are dimethicones, phthalates, disodium ethylenediaminetetraacetate (EDTA), triethanolamine and water.

5.1. Parabens

Parabens show endocrine disrupting activity and are known to negatively affect the male reproductive system.[113] Below is a selection of examples that arouse concern among scientists about their use in cosmetics.

Male rats exposed to propylparaben at four concentrations (0.00% (control) and 0.01, 0.1 and 1.0%) in their diet revealed a dose-dependent decrease of the testosterone concentration in the serum.[114] Butylparaben shows the same effect in male mice and inhibits their spermatogenesis.[115] Maternal rat exposure to butylparaben affects the development of the reproductive system of the F1 male offspring after subcutaneous injections, leading to decreased sperm count and motility.[116]

Propylparaben, butylparaben, methylparaben and ethylparaben display oestrogenic activity in vitro. However, oral exposure of rats did not result in oestrogen activity. On the other hand, subcutaneous administration of butylparaben resulted in oestrogenic effects in vivo in rats.[117]

Parabens have the ability to display 17β-oestradiol-like effects and bind to the alpha and beta oestrogen receptors.[118] The beta oestrogen receptor (ERβ) may be engaged in the development of melanoma.[119] This is the basis for major concern regarding the binding of parabens with oestrogen receptors.[117,118] Exposure to parabens may also cause increased oestradiol concentrations in the skin as a result of their ability to inhibit the oestrogen sulfation mechanism.[120]

Therefore, the use of endocrine disruptors, such as parabens, in cosmetic products for cutaneous use (e.g. sun lotions) poses significant health risks.[113] Furthermore, it should be mentioned that methylbaraben enhances the negative effect of UV-B radiation on skin keratinocytes.[121]

5.2. Dimethicones

Siloxanes are inactive ingredients that are used in cosmetic products such as sun lotions and creams. The most commonly used are octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6). The mixtures containing mainly these siloxanes are known as "cyclomethicones". Sun lotion manufacturers use polydimethylsiloxane silicone (PDMS) formulations known as "dimethicones" in which D4 is present in their final formulation. A dimethicone can be combined with whatever/any form of silica to produce "simethicone", which is another inactive ingredient in sun lotions.[122-124]

D4 shows endocrine disrupting activity and causes reproductive disorders. More in particular, D4 exhibits weak oestrogenic and anti-oestrogenic activity in rats.[125] What is more, the daily exposure of rats to D4 vapour in a variety of concentrations provokes a longer oestrous cycle and decreases fertility indices. A NOAEL of 300 ppm for female reproductive toxicity has been determined, while the NOAEL for males is 700 ppm.[126]

5.3. Phthalates

Even though phthalates are not mentioned in the list of ingredients, they might be part of the formulation of the ingredient known as "fragrance", "perfume" and "parfum" (or other related terms). For manufacturers it is not compulsory to reveal the components of their fragrances because the composition of these products can be kept secret.[49,127] Exposure to phthalates might also result from their migration from the plastic packaging into the cosmetic product.[128]

Numerous papers have been published on the health effects of phthalates such as diethyl phthalate (DEP), di-n-butyl phthalate (DBP) and di(2-ethylhexyl phthalate (DEHP) and of their metabolites such as mono(2-ethylhexyl) phthalate (MEHP).[129-133] This overview is limited to a few characteristic aspects of

their effects on the endocrine and the reproductive system.[133,134]

Exposure of female rats to DEHP reduces oestradiol concentration in serum, prolongs the oestrous cycle and inhibits ovulation.[135] Further, DEHP shows anti-androgenic activity of DEHP in rats.[136] In utero and during lactation, DEHP causes abnormalities of the male reproductive tract in rats and reduces daily sperm production.[137] An in vitro experiment with human spermatozoa revealed that the previously mentioned phthalates and di-n-octyl phthalate (DOP) affect sperm motility.[138]

5.4. Other inactive ingredients

Disodium EDTA is commonly used in sun lotions. The disodium salt of EDTA disturbs the binding of the Vasoactive Intestinal Peptide (VIP) to the membranes of the macrophages with a Half-maximal Inhibitory Concentration (IC50) of 5.4 mM.[139]

Furthermore, there are other inactive ingredients which are not harmless. Triethanolamine irritates the upper respiratory tract of rats with a 90-day no observed adverse effect concentration (NOAEC) of 4.7 mg/m^3 and produces systemic toxicity at high doses.[140] Moreover, in aquatic organisms chronic effects cannot be excluded.[141] Many other ingredients induce health problems such as allergic reactions.[142-144]

Therefore, there are hidden dangers related to the inactive ingredients. Some of them show endocrine/reproductive impairments, but more research is required to identify and quantify these hazards.

6. SUN LOTIONS AND VITAMIN D

Vitamin D is necessary for the development and the maintenance of a healthy skeleton.[18] Ninety percent of the vitamin D essential for good health is produced cutaneously.[145] More specifically, UV solar radiation is necessary for the cutaneous synthesis of previtamin D3[18] and the wavelengths of the UV-B region are the most efficient for this synthesis.[18,146] The active ingredients in sun lotions reduce exposure to and absorption of UV-B radiation through the skin. Consequently, active ingredients inhibit the production of the vitamin.[147]

When the cutaneous synthesis is insufficient, additional intake through food or through supplements is recommended. Vitamin D deficiency has been associated with skeletal problems, such as rickets in children and osteomalacia in adults, as well as with a variety of cancers.[148]

Vitamin D deficiency impedes the secretion of insulin from isolated rat pancreas cells[149] and it causes reproductive and fertility deficiencies in both female and male rats.[150,151]

Vitamin D deficiency during human pregnancy is a significant risk factor for preeclampsia.[152] In addition, low vitamin D intake during pregnancy is associated with decreased birth weight.[153]

7. DISCUSSION

Many active ingredients of sun lotions pose health risks, while they also negatively affect environmental quality, and in particular aquatic life.

Commercial sun lotions and creams usually consist of more than one chemical filter to achieve the desirable level of protection.[21] Consequently, users are exposed to a cocktail of chemicals. Harmful cocktail effects might emerge even if the endocrine disrupting chemicals are present in concentrations lower than their individual NOEC.[154,155] Sun lotions are a typical cocktail example because they contain a variety of substances with documented endocrine disrupting activity (UV filter mixtures).[156]

An individual consumer applies a relatively small amount of a sun protection lotion, which is in the order of micrograms per cm^2,[157] but the total quantity used by all consumers together is thousands of tons. It has been estimated that annually 4000-6000 tons enter the aquatic environment in reef areas by washing off.[158]

Concentrations of organic filters found in natural waters are of the order of ng/l, while in contaminated waters they reach the order of μg/l.[68,159] Although the concentrations are still low, it should be noted that sun lotions and creams persist in the environment for up to a century and the currently widespread use of these commercial products may drastically increase their environmental levels. Nanoparticles such as TiO_2 (which are relatively new ingredients) are measured in waters in concentrations of μg/l.[162]

The fate and the properties of these chemicals and of their degradation products and their possible ability to produce combination effects determine their final impact. The current low concentrations in natural waters are no guarantee for the absence of negative effects. Furthermore, the properties of the by-products in swimming pool waters, where the concentration of UV filters can be of the order of μg/l,[163] may conceal significant threats. For instance, it has been shown that the chlorination process (chlorine is used to disinfect swimming pool waters) is able to produce mutagenic substances if octyl methoxycinnamate is present.[164]

Consumers use sun lotions to protect themselves from the harmful effects of solar UV radiation. However, a possible inadequate application combined with the ignorance of the real effects of UV radiation promotes a false sense of safety. What is more, many sun lotion ingredients are associated with health risks, including endocrine and reproductive impairments. Apart from personal use and subsequent exposure to these agents through skin contact, exposure also occurs through inhalation and ingestion, especially during swimming.[165] In crowded swimming areas, large amounts of sun lotion chemicals end up in the water and exposure becomes more complex.

The proper use of cosmetics, including sun lotions, is advantageous for health, but special emphasis should also be given to complementary protection measures, such as appropriate clothing and avoiding of exposure during the hours of highest sunlight intensity.[5,166]

Endocrine and reproductive impairments are known to be caused in aquatic organisms, such as zebrafish and *Dapnia magna*, by some sun lotion agents.[69,100] Amongst other effects, sun lotion chemicals also contribute to the bleaching of coral reefs.[158] Moreover, the "ubiquity" of these emerging pollutants in aquatic environments raises bioaccumulation and biomagnification issues.[167,168] Consequently, the danger for aquatic life cannot be ignored.

The increasing use of sun lotions, their continuous washing off from the surface of the human body in the water and indirect environmental contamination through waste water treatment plants necessitates an immediate and appropriate response to this new emerging hazard.[169]

There are knowledge gaps concerning the properties of sun lotion chemicals that should be addressed by future research. The issues that need special consideration include possible bioaccumulation, the effects that result from the combination of these chemicals and the effects of their metabolites and of their degradation compounds. Furthermore, the likely involvement of the ERβ in the development of melanoma and topical treatment with cosmetics containing substances with oestrogenic activity (e.g. UV filters, parabens) are two issues that require special attention.[113,119]

8. CONCLUSIONS

Are sun lotion chemicals endocrine disruptors? These ingredients do have endocrine disrupting properties and affect the reproductive system of experimental animals, revealing a potential danger for wildlife. The precise in vivo effects on humans are difficult to measure and the human data are limited. However, adverse health effects in humans cannot be excluded and the increasing use of sun lotions may be an unidentified threat for normal human endocrine and/or reproductive function.

Formulations of commercial sun lotions are mixtures of active and inactive ingredients both of which are related to health hazards. Different active (and inactive) ingredients are combined to offer a better level of UV protection. This makes their composition more complex, but also increases the possibility of combination effects. Due to the current widespread use of sun lotions and to the existing scientifically documented knowledge, the raising of awareness of the subject is more important than ever before. Aquatic toxicity issues require more investigation, and this new emerging environmental hazard should not be underestimated.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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