

Review:

UV-filter pollution: current concerns and future prospects

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Abstract

UV-filters are widely used in cosmetics and personal care products to protect users' skin from damage caused by ultraviolet (UV) radiation from the sun. Globally, an estimated 16,000 to 25,000 tonnes of products containing UV-filters were used in 2014 with modern consumption likely to be much higher. Beyond this use in cosmetics and personal care products, UV-filters are also widely used to provide UV-stability in industrial products such as paints and plastics. This review discusses the main routes by which UV-filters enter aquatic environments and summarises the conclusions of studies from the past 10 years that have investigated the effects of UV-filters on environmentally relevant species including corals, microalgae, fish and marine mammals. Safety data regarding the potential impact of UV-filters on human health are also discussed. Finally, we explore the challenges surrounding UV-filter removal and research on more environmentally friendly alternatives to current UV-filters.

Key words:

Ecotoxicology, endocrine-disrupting chemical, microplastics, oxybenzone, UV-filter.

Introduction

There is growing concern regarding the role of personal care products (PCPs) in the pollution of aquatic environments (e.g., Ebele, Abou-Elwafa Abdallah and Harrad 2017). This concern has, for example, influenced the use of microplastics (MPs) (Dauvergne 2018), plastic particles smaller than 5 mm in diameter (Lusher *et al.* 2015). MPs are either specifically manufactured for the cosmetic industry for use in products such as facial cleaners and toothpastes (primary MPs), or are produced by the degradation of larger pieces of plastic (secondary MPs) (Kalčíková *et al.*

2017). MPs have been found in many aquatic environments, and in the tissues of invertebrates, fish, and large aquatic mammals including whales and seals (Karlsson *et al.* 2017; Zhu *et al.* 2019; Donohue *et al.* 2019; Hernandez-Milian *et al.* 2019; Moore *et al.* 2020; Burkhardt-Holm and N'Guyen 2019). The prevalence of MPs, combined with their potentially toxic effects, has led to the re-evaluation of their use in cosmetics (Lam *et al.* 2018). For example, in 2018 concerns regarding PCPs resulted in the United Kingdom banning the use of primary MPs in any consumer products as part of their 25 Year Environment Plan (Kentin and Kaarto 2018). Other countries, including the United States, Canada and Australia, have now also limited or banned the use of primary MPs (Lam *et al.* 2018).

Another commonly used component of many cosmetics and PCPs are ultraviolet (UV) light filters (UV-filters) (Osterwalder, Sohn and Herzog 2014). UV-filters are commonly used as UV-stabilizers for products such as perfumes, or as UV-protection in products such as moisturisers, tanning and sun-protection products (Blüthgen, Zucchi and Fent 2012). UV-filters are also used worldwide in a large range of industrial products (Molins-Delgado *et al.* 2017). In these industrial situations they are used as additives to reduce the degradation rate of plastics and paints when they are exposed to the sun's ultra-violet rays (Fent, Zenker and Rapp 2010; Wojciechowski *et al.* 2015).

Generally, UV-filters can be categorized into two groups: organic and inorganic (Morlando *et al.* 2016). Organic UV-filters are chemicals that absorb the sun's UVA and/or UVB rays (Serpone, Dondi and Albini 2007), with the most commonly used organic UV-filters being oxybenzone (BP-3), octinoxate (ethylhexyl methoxycinnamate or EHMC), 4-methylbenzylidene camphor (4-MBC), octyl dimethyl p-aminobenzoate (OD-PABA), and octocrylene (OC) (Tsui *et al.* 2014).

Titanium dioxide (TiO₂) and zinc dioxide (ZnO) are the most common inorganic UV-filters (Morlando *et al.* 2016), with these functioning due to their ability to reflect or refract UVA and/or UVB (Serpone, Dondi and Albini 2007).

In 2014 it was estimated that between 16,000 and 25,000 tonnes of products containing either organic or inorganic UV-filters were being used worldwide (Díaz-Cruz and Barceló 2009; Osterwalder, Sohn and Herzog 2014; Wu *et al.* 2016). Although more recent global estimates are not available, usage of products containing UV-filters in the U.S. alone is now estimated to be between 9,000 and 32,000 tonnes annually (Narla and Lim 2020). This substantial growth is likely due to an increased public awareness of environmentally influenced conditions such as skin cancer and premature skin aging and the increased recommendations by dermatologists (Osterwalder, Sohn and Herzog 2014; Leiter, Keim and Garbe 2020).

Similar to the case of MPs, there are now growing concerns regarding the potential of UV-filters to act as pollutants (Schneider and Lim 2019a). However, in contrast to MPs, UV-filters are still widely available to consumers around the world. With this in mind, here we review the various types of UV-filters, their prevalence worldwide, and their eco-toxicological potential. Finally, we consider the improvements that could be made in the management of these pollutants and reflect on some future research priorities.

Organic UV-filters

The chemical properties of organic UV-filters make them especially suitable for their role as topical skin barriers. For example, many organic UV-filters are large molecules with aromatic moieties comprised of carbonyl-groups or methoxy-groups (Hopkins, Snowberger and Blaney

2017), and their molecular structure gives them a high UV-filtering potential over a range of UV wavelengths (280 nm to 400 nm) (Hopkins and Blaney 2016). It is also thought that these large aromatic moieties generally result in low levels of skin permeability (Zhang *et al.* 2017). For example, Hewitt *et al.* (2020) found that benzophenone had a skin permeability of $0.87 \mu\text{g}\cdot\text{cm}^{-2}$ after 24 hours, which is more than 10-fold lower than that of many other cosmetic components such as the fragrance Anisyl alcohol (skin permeability of $10.15 \mu\text{g}\cdot\text{cm}^{-2}$ after 24 hours). Despite this, some studies have suggested that, despite the low skin permeability, between 1-10% of benzophenone-3 (BP-3) is absorbed through the skin and excreted in urine (Gonzalez *et al.* 2006; Cozzi, Perugini and Gourion-Arsiquaud 2018; Souza and Maia Campos 2017). That said, the skin permeability of BP-3 and other UV-filters may be even higher than that detected in urine due to accumulation within cells resulting from their lipophilic properties and low water solubility (represented by a high Log-k_{ow} value, the octanol-water partition value that is used to assess the bio-accumulation factor of a chemical) (Gago-Ferrero, Díaz-Cruz and Barceló 2011; Badia-Fabregat *et al.* 2012; Nakata, Murata and Shinohara 2009). Specifically for BP-3, this type of bio-accumulation has been demonstrated, with a far higher concentration of BP-3 found in human adipose tissue ($>5 \mu\text{g}\cdot\text{L}^{-1}$) than that detected in urine samples ($>0.4 \mu\text{g}\cdot\text{L}^{-1}$) (Wang, Asimakopoulos and Kannan 2015).

Although it is uncertain exactly how much gets absorbed by the skin, the majority of UV-filters will, either directly or indirectly, enter our marine or freshwater environments through activities such as swimming or via showering and urination (Gonzalez *et al.* 2006). This has been evidenced by the sampling of surface water from large metropolitan areas (containing both commercial and industrial developments) around the world that found that UV-filter concentrations increased in line with population density and was higher in areas with poor

waste-water-treatment (WWT) strategies (Tsui *et al.* 2014). In combination, this suggests that a large proportion of the UV-filter pollution comes from the plumbing system. Further evidence for the entry of UV-filters into marine environments was provided by sampling of both surface water and column water from areas in France used for recreational swimming, with this showing higher concentrations of UV-filters in recreational areas than off-shore, and fluctuations in the concentration that tracked the number of beach-goers (Labille *et al.* 2020). Similarly, a seasonal increase of 27% in the total UV-filter concentration was detected in rivers and waste-water-treatment (WWT) plant effluents during the summer months (Ekpeghere *et al.* 2016).

Ineffective WWT methods themselves also play a considerable role in organic UV-filter pollution (Ekpeghere *et al.* 2016; Tsui *et al.* 2014). One commonly used WWT strategy is the use of activated sludge, where flocs of bacteria, protozoa, and other microorganisms are used to breakdown organic UV-filters. However, due to their high log- k_{ow} values, organic UV-filters tend to accumulate within the sludge making biodegradation ineffective (Badia-Fabregat *et al.* 2012). An example of this was seen in a study that investigated the effectiveness of activated sludge treatment, where it was found that only 28-51% of BP-3 was removed from the water (Vassalle *et al.* 2020). Physical WWT strategies such as UV-radiation treatment have also been shown to be ineffective in removing UV-filters; for example, Gago-Ferrero *et al.* (2012) found that both BP-3 and BP-1 were poorly degraded by UV exposure, with no decrease in BP-3 level observed after 24 hours of treatment.

Inorganic UV-filters

In contrast to the situation with organic UV-filters, it is believed that inorganic UV-filters have negligible skin permeability due to their large particle size and insoluble nature (Kim *et al.* 2017; Tang *et al.* 2018). Given their low skin absorption potential, it can be assumed that inorganic UV-filters also get washed off and enter water supplies in a similar manner to organic UV-filters (Gondikas *et al.* 2014). Unlike organic UV-filters however, inorganic UV-filters are more effectively removed in WWT plants; in fact it has been calculated that modern day WWT plants remove up to 90% of TiO₂ from influents (Mahlalela, Ngila and Dlamini 2017). Despite this, TiO₂ has been detected in post-treatment effluents of WWT plants around the world at measurable levels (between 0.5 and- 6.5 µg.L⁻¹ (Neal *et al.* 2011; Gondikas *et al.* 2014). The fact that TiO₂ is still detectable post- treatment has raised concern for the levels of TiO₂ in untreated waters as this could lead to pollution caused by WWT overflow spills. Wang *et al.* (2020) estimated that the levels of TiO₂ could reach as high 150 µg.L⁻¹ in untreated wastewater. Furthermore, TiO₂ has been shown to accumulate within the biosolids of sewage sludge as well as potentially in sediments polluted by untreated waters. Gottschalk *et al.* (2015) estimated that the amounts of TiO₂ in such areas could exceed 100 mg.kg⁻¹. The fact that sewage sludge from WWT plants is sometimes used as fertiliser also amplifies the risk that sediment-dwelling and soil-dwelling organisms could be exposed to high amounts of TiO₂. Given that TiO₂ is considered moderately toxic by the American Environmental Protection Agency (EPA) and has an EC₅₀ concentration (the concentration of a chemical at which a 50% reduction in tested endpoints is induced) of between 1 and 10 mg.L⁻¹ (Hu *et al.* 2020; Soler de la Vega *et al.* 2021; Gottschalk *et al.* 2015), this exposure could negatively affect such organisms.

UV-filter migration

Organic and inorganic UV-filters have been detected near WWT effluents, nearshore waters, and in recreational sites worldwide (Cadena-Aizaga *et al.* 2020). This is not surprising given how they are used and how they move into both marine and freshwater environments.

Unexpectedly, organic UV-filters do not however seem to be limited to these areas. For example, analysis of water from the rural Antarctic peninsula region identified varying levels of organic UV-filters in all samples (Dominguez-Moruco *et al.* 2021). Although some of this UV-filter pollution could be attributed to a small amount of wastewater runoff from the science stations, these data suggest that UV-filters from other, more inhabited, are traveling large distances.

The full extent of UV-filter migration remains unknown, but one possibility is that UV-filter migration is facilitated by MPs (O'Donovan *et al.* 2020). This is possible given that many plastic products already contain UV-filters as preservatives. Moreover, other plastics, such as the low-density polyethylene (LDPE) micro pellets used worldwide in the production of household items, reusable bags and food packaging, have been shown to absorb environmental BP-3 and later release it when consumed by an organism (Kyaw *et al.* 2012; Wu *et al.* 2016). O'Donovan *et al.* (2020) studied the effects of this on the marine clam, *Scrobicularia plana* and found that MPs containing BP-3 caused oxidative stress in the digestive system, an effect not seen in clams consuming virgin MPs. This study, and other similar work (e.g., Rainieri *et al.* 2018), argues that the toxic effects of MPs and chemical pollutants can be synergistic. Two hypotheses for this increase in toxicity are that (1) the amount of chemical pollutants released from MPs is higher compared to environmental pollution levels due to accumulation within the MPs (Bakir, Rowland and Thompson 2014), or that (2), contaminated MPs remain in the organism for

extended periods of time, therefore increasing the chemical pollutant exposure time (Rainieri *et al.* 2018).

The distribution of MPs has been widely researched (Khatmullina and Isachenko 2017; Iwasaki *et al.* 2017; Courtene-Jones *et al.* 2017); small plastic fragments for example, like those that can absorb UV-filters, have been shown float in the upper water column (<5 m) for extended period of time depending on the type and condition of the plastic (Khatmullina and Isachenko 2017). Floating MPs are subjected to strong surface currents and surface winds, resulting in a large horizontal migration (Reisser *et al.* 2015), this is evidenced by sampling studies reporting large-scale seasonal MP migration coinciding with periods of strong surface currents and surface winds (Iwasaki *et al.* 2017). Eventually MPs travel vertically through the water and settle within the deep sea sediment (Kowalski, Reichardt and Waniek 2016; Courtene-Jones *et al.* 2017). The nature of MPs horizontal and vertical travel within the water column, combined with their ability to absorb and release UV-filters could provide a reasoning for the unexpected travel of UV-filters to remote areas such as the Antarctic region.

Environmental breakdown

It is generally believed that environmental forces contribute heavily to the degradation of chemical pollutants (Ahmed *et al.* 2017), however, this may not be the case for some UV-filters (Rodil *et al.* 2009; Badia-Fabregat *et al.* 2012). For example, EHMC and OP-PADA are both heavily affected by UV-radiation, having half-lives of between 20 and 57 hours (Rodil *et al.* 2009; Badia-Fabregat *et al.* 2012), but BP-3 has shown only a 8% degradation after being exposed to artificial solar light for 20 days (Liu *et al.* 2011). Natural rivers and oceanic sediment also usually play large parts in the bio-degradation of pollutants, however, due to the high Log- k_{ow} value, this

process can be limited in the case of some UV-filters (Gago-Ferrero *et al.* 2012). Regardless of the method, the degradation of UV-filters can lead to the release of derivative chemicals due to hydrolysis (Vione *et al.* 2015); indeed, this is the case with EHMC UV-degradation, where the main derivative is 4-methoxybenzaldehyde (Vione *et al.* 2015).

Little is known regarding the environmental fate of inorganic UV-filters, largely due to the lack of qualitative data (Bundschuh *et al.* 2018). This is largely due to the fact that engineered nano-particles, such as those used as inorganic UV-filters, are often undistinguishable from naturally occurring ones and to the fact that environmental concentrations of these particles tend to be relatively low (Bundschuh *et al.* 2018; Schneider and Lim 2019a). Despite this, studies based on batch systems using model compounds and environmental forces suggest that inorganic UV-filters are heavily broken down in the environment due to factors such as water salinity, environmental pH and ionic forces (Bundschuh *et al.* 2018; Schaumann *et al.* 2015; Wong *et al.* 2010; Minetto *et al.* 2017). It is also believed that the environmental degradation of TiO₂ and ZnO nano-particles would lead to the release of Zn⁺ and OH⁻ free radicals, of which the effects on organisms remains largely unknown (Minetto *et al.* 2017; Haynes *et al.* 2017; Schneider and Lim 2019a).

Effects on the environment

Whilst it is clear that UV-filters are present in our environment at varying concentrations (Tsui *et al.* 2014), their biotic effects remain uncertain. Looking at the effect that UV-filters have on some key ecological species does however give insight into their ecotoxic potential. For example, it is estimated that 40% of coastal coral colonies worldwide are exposed to UV-filter pollution (Downs *et al.* 2016), with exposure to UV-filters linked to coral bleaching (Downs *et al.* 2014;

Corinaldesi *et al.* 2018). Studies have shown that when under the influence of UV-light, BP-3 causes oxidative stress to the thylakoid membrane in zooxanthellae (Downs *et al.* 2016), the dinoflagellates that live in symbiosis with corals, jellyfish and sea sponges, providing them with essential photosynthesis products (Ben-Zvi, Eyal and Loya 2015). The decrease of zooxanthellae within the coral matrix causes the lightening of the brown colour of the corals, a process often associated with the coral bleaching process (Downs *et al.* 2014; Corinaldesi *et al.* 2018). The oxidative stress caused by organic UV-filters when exposed to UV-light is believed to be due to the release of degradation products (Lai, Chen and Lin 2020; Rodil *et al.* 2009). Inorganic UV-filters can also cause damage in this manner, with, for example, the reactive oxygen species produced by the degradation of TiO₂ causing both damage to tissues and to DNA (Zhao *et al.* 2019; Zhang and Sun 2004; Haynes *et al.* 2017; Faria *et al.* 2014).

Microalgae are also a significant part of many aquatic food webs, and are often essential in maintaining ecosystem health (Nava and Leoni 2021). For this reason, studies have started focusing on how UV-filters affect some key algal species. Similar to the damage seen in corals, UV-filters can cause damage to photosynthetic pigment production in algae (Mao *et al.* 2017; Paredes *et al.* 2014). In a study conducted by Mao *et al.* (2017), several model microalgae species were used, including the microalgae *Chlamydomonas reinhardtii*, as bioassays to assess the ecotoxic potential of BP-3. It was concluded that at environmentally relevant concentrations (*i.e.*, 0.1 and 1 µg.L⁻¹) BP-3 was systematically absorbed by the algae and caused a decrease in chlorophyll *a* (chl-*a*) (Mao *et al.* 2017). At higher concentrations (>10 µg.L⁻¹) the decrease in chlorophyll-*a*, chlorophyll *b* and carotenoid content resulted in a reduction in photosynthetic pigment production which subsequently led to a decrease in growth

rate (Mao *et al.* 2017). Another study reported similar results for the micro-algae *Isochrysis galbana* with an EC₅₀ of 13.87 µg.L⁻¹ (Paredes *et al.* 2014).

As well as affecting the pillars of the aquatic ecosystems such as corals and algae, UV-filters have also been shown to directly affect fish (Zhang *et al.* 2016; Tapper *et al.* 2019; Alamer and Darbre 2018). For example, exposure to OCT has been shown to cause an increased vitellogenin (VTG) induction in the model fish species *Danio rerio*, while exposure to BP-3 has been shown to cause an increased VTG induction in rainbow trout (Tapper *et al.* 2019; Zhang *et al.* 2016). VTG is an egg-yolk precursor protein expressed in oviparous female fish as a response to oestrogen signalling within liver cells (Nagler *et al.* 2010). VTG expression in male fish is used as a classic biomarker for endocrine disrupting compounds (EDCs) as it only appears with external oestrogenic exposure (Yamamoto *et al.* 2017; Nagler *et al.* 2010). The presence of EDCs has been shown to be detrimental for both female and male fish fertility; a study in 2008 found that it caused endocrine imbalance, malformation of the gonads, altered social behaviours and a reduced spermatozoa count in males (Xu *et al.* 2008). Interestingly, work focussing on low level EDC exposure in flathead minnows found feminization of male fish and the near extinction of the population within the enclosed testing lake (Kidd *et al.* 2007). Further to this, prenatal 4MCB exposure has also been shown to cause spinal malformation and motility issues in *D. rerio*, with effects observed at exposure concentrations of 3.69 mg.L⁻¹ and above (Li *et al.* 2016). Although these levels of 4MCB are approximately 50 times higher than those that are routinely sampled in influents, the high log-K_{ow} value of 4MCB means that it could bio-accumulate within the fish (Balmer *et al.* 2005; Li *et al.* 2016).

UV-filters have also been detected in marine mammals (e.g., Gago-Ferrero *et al.* 2013) and, despite the scarcity of such studies, the maternal transfer of UV-filters has also been demonstrated in two dolphin species, *Pontoporia blainvillei* and *Sotalia guianensis* (Alonso *et al.* 2015). This work found EHMC in both placental and milk samples and in the case of the *P. blainvillei*, EHMC levels in foetal muscle tissue were found to be significantly higher than in the maternal tissue, suggesting efficient maternal transfer of the UV-filter (Alonso *et al.* 2015; da Silva *et al.* 2021).

It has been proven difficult to accurately predict which UV-filters pose a significant environmental threat. It has previously been suggested that environmental risk assessment is dependent on how long the pollutant remain within the environment. For example, EHMC is highly toxic to algae (EC50= 74.72 µg.L⁻¹), but due to its rapid breakdown in the environment it has been deemed to be a low environmental risk (Paredes *et al.* 2014). The hypothesis that environmentally unstable chemicals pose little threat to organisms regardless of toxicity due to limited exposure time, does not however concur with studies such as that of Alonso *et al.* (2015) where dolphins were found to have still accumulated these chemicals within their tissues. This highlights the need for more research in this area to better understand the bio-accumulation effect of UV-filters, and to be able to make more accurate environmental risk assessments.

Research in this area is however in its infancy; not only is the exact extent and mechanism of toxicity unknown for many UV-filters, the long-term effects on ecosystems at environmentally relevant concentrations are unknown. Despite this general pattern, BP-3 has been consistently highlighted as a particular concern because it remains stable within the environment, is toxic at

relatively low levels, and due to its lipophilic tendency, it also has the ability to accumulate within aquatic organisms (Paredes *et al.* 2014).

Effects on humans

Systematic disruption of neural function

As discussed above, between 1 and 10% of organic UV-filters are believed to penetrate human skin. This, in combination with other exposure routes such as contact with polluted waters, has led to many studies focusing on the potential adverse effects that BP-3 may have on the human body (Cozzi, Perugini and Gourion-Arsiquaud 2018; Souza and Maia Campos 2017). The fact that BP-3 has been detected at very high frequencies in urine (between 94% and 98% of samples taken in America and Denmark respectively), and that it has been found in human breast milk, suggests that most people are, or have been, exposed to BP-3 (Molins-Delgado *et al.* 2018; Calafat *et al.* 2008).

Worryingly, BP-3 has been shown to travel through the blood-brain barrier and can accumulate in the white matter of the brain, with concentrations of up to 0.32 ng.g^{-1} having been found in frozen human post-mortem samples (Van Der Meer *et al.* 2017; Wang, Asimakopoulos and Kannan 2015). Although, in humans, the effects of this are unknown, BP-3 has been shown to induce oxidative stress and apoptosis within the hippocampus and frontal cortex of rat models (Pomierny *et al.* 2019). Furthermore, BP-3 also increased the concentration of extracellular glutamine in the brain of mice (Pomierny *et al.* 2019), a change associated with hippocampal atrophy and diseases such as medication-resistant temporal lobe epilepsy, and in Alzheimer's, Parkinson's and Huntington's disease in humans (Cavus *et al.* 2008).

Oestrogenic disruption

Many studies have suggested that organic UV-filters cause disruption to the endocrine system and could potentially be classified as EDCs (Alamer and Darbre 2018; Wnuk *et al.* 2018; Krause *et al.* 2018; Huang *et al.* 2020). For example, assays using both human cancer cell lines and immature rats have demonstrated oestrogenic effects of the UV-filters 3-benzylidene camphor (3-BC) and 4-MBC (Schlumpf *et al.* 2004; Alamer and Darbre 2018). Here, uterine bioassays in immature rats showed a significant increase in uterine weight (Schlumpf *et al.* 2004). Similarly, the cancer cell work indicated that at concentrations similar to that sampled in human breast milk (Schlumpf *et al.* 2010), EHMC, 4-MBC, BP-3, and homosalate all caused an increase in invasiveness and cell migration of MCF-7 (Alamer and Darbre 2018), a breast cancer cell line with oestrogen, progesterone and glucocorticoid receptors.

Prenatal exposure

It has been shown that BP-3 can penetrate the placental cellular barrier and has been sampled in amniotic fluid, placental tissue and foetal blood, raising potential concerns about its impact on foetal health and development (Vela-Soria *et al.* 2011; Philippat *et al.* 2012; Krause *et al.* 2018; Wnuk *et al.* 2018; Tang *et al.* 2013; Song *et al.* 2020). A study conducted by Wnuk *et al.* (2018) for example, demonstrated that prenatal BP-3 exposure changes the expression of ESR1-ESR2 receptors (ESRs) and G-protein-coupled receptors (GPER1). ESR1 and ESR2 are the major oestrogen receptors responsible for many endocrine processes, but they also play an important role in the maintenance of neural health by inhibiting CASPASE-mediated neural cell death and by maintaining a neutral BCL2-BAX protein ratio (Wnuk *et al.* 2018; Wnuk and Kajta 2017; Zhou *et al.* 2018; Gingerich *et al.* 2010; Foot, Henshall and Kumar 2017). GPER1 receptor signalling

is also important in the maintenance of healthy brain function as it plays a major role in the regulation of intra- and intercellular communication and has been shown to provide neural protection by mediating 17β -oestradiol in hippocampal and cortical cells (Lu *et al.* 2016; Wnuk and Kajta 2017; Liu, Lou and Fu 2016). Disruption of either ESRs or of GRER1 signalling could lead to increased levels of neural apoptosis, which has been shown to have severe adverse effects on human development, resulting in anatomic abnormalities and potential mental disabilities (Roth and D'Sa 2001).

Another worrying effect caused by BP-3 was demonstrated by Wnuk *et al.* (2018), who reported that BP-3 inhibited global DNA methylation and decreased DNMT activity. An interruption in DNA methylation caused by an endocrine disruptor, such as BP-3, could induce a multigenerational epigenetic effect by impacting the germ line during the methylation process in a developing gonad (Anway and Skinner 2006; Wnuk *et al.* 2018). It has also been demonstrated that BP-3 can alter the germ line development in rat models; this proved to be detrimental to the rats' fertility, as the early follicle population and the number of mature oocytes was decreased (Santamaría *et al.* 2019).

Prenatal BP-3 exposure has also been shown to induce abnormal migration of the enteric neural crest cells 293T and SH-SY5Y cell lines (Huo *et al.* 2016; Justus *et al.* 2014). Incomplete migration of these cell lines has been shown to result in an absence of ganglia in the distal colon which can lead to the development of Hirschsprung's disease (Szyberg and Marszalek 2014; Meinds *et al.* 2019). This condition causes severe constipation and discomfort in humans and usually results in surgical intervention with many patients continuing to suffer throughout their lives (Meinds *et al.* 2019).

Finally, many studies have suggested that BP-3 affects the growth of human foetuses, although interestingly, here results are conflicting. Whilst some studies have reported an increase in the total foetal growth in both females and males (Philippat *et al.* 2012; Ferguson *et al.* 2018), others have reported a decrease in abdominal circumference in males (Ferguson *et al.* 2018), and the total foetal weight in females (Wolff *et al.* 2008), suggesting more research in this area is needed to clarify the situation.

Effects on puberty

Multiple UV-filters have also recently been linked to changes in the timing of puberty (Huang *et al.* 2020). In this study, almost 300 individuals were assessed using both the Tanner staging method, the medical standard for assessing puberty growth rates (Koopman-Verhoeff *et al.* 2020), and questionnaires in two separate years (2011 and in 2013). The participants also had urine samples taken at both sampling times to assess the prevalence and concentrations of 12 commonly used UV-filters. BP-3 was the most common UV-filter detected, and levels were found to be associated with reduced testicular growth rate, suggesting an anti-androgenic effect on males. Levels of EHMC, another commonly detected organic UV-filter, were also found to be associated with delayed male puberty, while OD-PABA was shown to accelerate female puberty (Huang *et al.* 2020). Whilst this is the first study to look at the epidemiologic effects that UV-filters had on human pubertal development, these results suggest that better understanding the true extent of these effects is a priority.

Current progress and future prospects

Alternatives

Considering the increasing demand for UV-protection products and our current understanding of UV-filter toxicity, many manufacturers and researchers have spent the last decade trying to develop alternative, safer and more environmentally friendly options. For example, BP-3 derivatives have been investigated as potential options, with BP-4 shown to be less toxic than BP-3 having a EC50 value near 10.000 $\mu\text{g.L}^{-1}$ (slightly toxic) in the algae *Isochrysis galbana*, the crustacean *Scorpaenopsella armata*, the sea-urchin *Paracentrotus lividus* and the bivalve *Mytilus galloprovincialis* (Paredes *et al.* 2014). Although it is believed that the additional sulfonic acid group in BP-4 plays a crucial role in this decreased observed toxicity, further toxicity data are needed to accurately assess its toxicity and suitability as a safe UV-filter (Du *et al.* 2017). Interestingly, toxicity tests such as these ruled out using BP-2, a derivative of BP-3. Originally suggested as a potentially environmentally friendly option, it was since been found that BP-2 is an even more potent EDC due to an increased ability to bind to oestrogenic receptors (Thia, Chou and Chen 2020).

Another possible approach is to develop novel synthetic UV-filters. Avobenzone (AVO) is one such option, with the FDA recently demonstrating a far lower skin absorption capability for AVO than for OXY, with the overall maximum plasma concentrations being 7.1 ng/mL and 258.1 ng/mL respectively (Matta *et al.* 2020; Zhong *et al.* 2020). Although a lower absorption capability is favourable as this reduces the amount of direct exposure to the user via the dermis, the absorption capability of both these chemicals were far above the FDA's threshold of 0.5 ng/mL, prompting the FDA to suggest further investigation. Given that these AVO levels resulted from a single application on 75% of the body, and that beachgoers using suntan lotion report reapplying

an average of 2.6 times a day (Labilie *et al.* 2020; Ahn *et al.* 2019), levels would be expected to be much higher in real world use.

Aside from the development of more classic UV-filters, as mentioned above, a promising approach to sustainable UV-filter development is to focus on using natural compounds derived from plants and algae. Several studies have identified such extracts showing promising UV-protecting capabilities as well as ROS reducing capabilities. A study by Almeida *et al.*, in 2015 for example found that *Castanea sativa* leaf extract at a concentration of 1 µg/mL was able to reduce the amount of UV-mediated DNA damage in a human keratinocyte cell line by 66.4%. However, despite these discoveries, there are currently no approved sun protection products containing plant extracts as active ingredients. This stems from a number of issues with currently known active ingredients. Firstly, as with organic UV-filters, some natural compounds can potentially have adverse effects on the user. For example, treatment with an extract of edible red seaweed *Eucheuma cottonii* was found to have an antioxidant effect on a human keratinocyte cell line, but caused cytotoxic effects at high concentrations (Lim *et al.* 2015). Secondly, the addition of natural compounds can also alter the stability of a formulation; for example the green *Coffea arabica* seed oil has been shown to have UV-protective capabilities however formulations containing this extract were highly viscosity, making the application of such a product difficult, likely resulting in an insufficient coating of the skin (Wagemaker *et al.* 2015).

WWT improvements

The removal of UV-filters through WWT plants has been shown to be flawed as traditional removal methods are not designed to remove emerging pollutants, resulting in a large amount of UV-filter remaining within the water supply (Tsui *et al.* 2014; Ekpeghere *et al.* 2016; Salthammer 2020). Improvements in the effectiveness of WWT methods could greatly reduce the amount of UV-filter pollution, resulting in a reduction of the environmental risk associated with UV-filter production and use (Vasilachi *et al.* 2021).

Currently, one of the main WWT methods is the use of active sludge. This method relies on flocs of microorganisms suspended freely within a wastewater system to breakdown organic chemicals (Sehar and Naz 2016). However, due to their large structure, lipophilic nature and high bio-accumulation factor, UV-filters are inefficiently broken down and accumulate within the bacterial sludge which then settles to the bottom of the system (Badia-Fabregat *et al.* 2012; Vasilachi *et al.* 2021; Sehar and Naz 2016). The bacterial sludge is then treated as waste and disposed of, potentially resulting in substantial pollution itself (Ji *et al.* 2020).

One suggested way to improve the efficiency of WWT plants is by the incorporation of specific micro-organisms that can metabolize UV-filters. Some novel studies have used the "reverse discovery" method to identify microorganisms that can break down these complex molecules (Suleiman *et al.* 2019). Here, biosolids that showed bio-degradation potential were identified and sampled, and individual microorganism strains within samples were identified and tested for efficiency (Suleiman *et al.* 2019). The fungus *Tinae versicolor* was found to efficiently break down 4-MBC (100% in 24 hours) (Badia-Fabregat *et al.* 2012), and recently, Fagervold *et al.* (2021) found that the bacteria *Sphingomonas wittichii* (strain BP14P) efficiently broke down BP-3 (>95% degradation after 4 days) by using it as a carbon source. The biodegradation of other

UV-filters has however been shown to be more difficult. Fagervold *et al.* (2021) found that with the addition of R2B media, *S. wittichii* also broke down 2-ethylhexyl salicylate (ES) and homosalate, but at low rates (28% and 18% within 14 days respectively). Suleiman *et al.*, (2019) also identified a bacterial species (*Mycobacterium agri*) that broke down 19% of OC within 10 days. Recently a study identified river sediment from China containing an unknown mix of microorganisms were shown to be able to reduce EHMC levels within seven days (Zhang *et al.* 2021).

The use of these effective bacterial and fungal strains could be implemented in WWT plants and tailored to the specific UV-filters that are commonly detected in the influents of that area, resulting in a great improvement in effectiveness of these WWT plants. This, alongside modern treatment strategies such as the implementation of bio-films, membrane filters and constructed wetlands within treatment systems, could provide a much higher degree of UV-filter removal and could partly mitigate the environmental risk some UV-filters pose (Khan *et al.* 2020; Sehar and Naz 2016; Chen *et al.* 2016; Vasilachi *et al.* 2021).

Regulations

Public interest on the effect of UV-filters on corals has led to some countries implementing regulations on the use and distribution of UV-filters. For example, in 2017 the EU reduced the maximum concentration of OXY allowed in PCPs from 10% to 6% (Commission regulation, 2017) . More significantly, in January 2020, the republic of Palau was the first country to ban the use of BP-3, EHMC, octocrylene and 4MBC in PCPs (Republic of Palau, 2018). The island of Aruba quickly followed suit and banned the use, distribution and import of BP-3 in July 2020 (Gobierno Aruba, 2020). Since then, a number of similar bills banning UV-filter use in PCPs

have been passed in Hawaii, Bonaire and in some areas of Mexico (Narla and Lim 2020). Although these bans protect areas from direct exposure to UV-filters, ocean currents play a role in the distribution of UV-filters, potentially undermining the effect of local rules. In the case of MPs for example, despite being protected, the Galapagos islands still experience high levels of MP pollution with the great majority believed to be brought in by currents from South America (Jones *et al.* 2021). To combat this effect, both local bans and global regulations would be necessary. Additionally, more studies, such as those performed to investigate MP pollution migration, could provide further insight as to where regulation of the use of UV-filters would best be implemented.

Conclusion

There is evidence to suggest that UV-filters pose an environmental risk due to their various exposure routes, their global prevalence, their high bio-accumulation potential and their known toxicity to environmentally crucial species. It has also been shown that some UV-filters may pose a direct threat to human health due to their ability to migrate through cellular barriers and cause endocrine disruption affecting both early embryonic, and pubertal, development. Beyond this, preliminary studies suggest that some UV-filters could also contribute to the development of degenerative neural diseases.

Although traditional WWT strategies are not designed to handle the pollution from PCPs, changes to the systems currently used may reduce the amount of circulating within our water supply. Such changes in combination with further regulations on the use and distribution of these products and the potential replacement of these with novel environmentally friendly UV-filters could together greatly reduce the amount of harmful UV-filters in our water supply, and

the amount reaching our marine and freshwater ecosystems. To achieve this goal however, more research must be performed to further understand the distribution and movement of UV-filters within the environment, and to accurately assess the toxicity of novel UV-filters.

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