Toxicology Reports 4 (2017) 245–259

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Neurotoxic effect of active ingredients in sunscreen products, a contemporary review

Joanna A. Ruszkiewicz[a,*], Adi Pinkas[a], Beatriz Ferrer[a], Tanara V. Peres[a], Aristides Tsatsakis[b], Michael Aschner[a]

[a] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, United States
[b] Department of Forensic Sciences and Toxicology, University of Crete, Heraklion, Crete, Greece

ARTICLE INFO

Keywords:
Neurotoxicity
Sunscreen
Zinc oxide
Titanium dioxide
Octyl methoxycinnamate
Benzophenone-3
4-Methylbenzylidene camphor
Octocrylene

ABSTRACT

Sunscreen application is the main strategy used to prevent the maladies inflicted by ultraviolet (UV) radiation. Despite the continuously increasing frequency of sunscreen use worldwide, the prevalence of certain sun exposure-related pathologies, mainly malignant melanoma, is also on the rise. In the past century, a variety of protective agents against UV exposure have been developed. Physical filters scatter and reflect UV rays and chemical filters absorb those rays. Alongside the evidence for increasing levels of these agents in the environment, which leads to indirect exposure of wildlife and humans, recent studies suggest a toxicological nature for some of these agents. Reviews on the role of these agents in developmental and endocrine impairments (both pathology and related mechanisms) are based on both animal and human studies, yet information regarding the potential neurotoxicity of these agents is scant. In this review, data regarding the neurotoxicity of several organic filters: octyl methoxycinnamate, benzophenone-3 and −4, 4-methylbenzylidene camphor, 3-benzylidene camphor and octocrylene, and two allowed inorganic filters: zinc oxide and titanium dioxide, is presented and discussed. Taken together, this review advocates revisiting the current safety and regulation of specific sunscreens and investing in alternative UV protection technologies.

1. Introduction

Sunscreen application is the main strategy used to prevent the maladies inflicted by the sun since the 1930s. Unfortunately, although global use of sunscreen is continuously on the rise, so is the prevalence of malignant melanoma − a cancer type which is mainly caused by sun exposure [1–4]. There are several types of electromagnetic radiation emitted by the sun. One type − ultraviolet (UV) radiation − is composed of three wavelengths: UVA rays, which range at 320–400 nm and are not absorbed by the ozone layer, UVB rays, which range 290–320 nm and are partially absorbed by the ozone layer, and UVC rays, which are stopped by the ozone layer. The detrimental effects of exposure to UVA and UVB rays, which can cross the epidermis, have been reviewed and it was concluded that such exposure leads to reactive oxygen species (ROS) generation, DNA/protein/lipid damage, activation of various signal transduction pathways, compromised skin defense systems, altered growth, differentiation, senescence and tissue degradation, to name a few [5–7]. Two kinds of UV filters are currently being used in sunscreens for minimization of these adverse effects: organic (chemical) filters, e.g. octyl methoxycinnamate (OMC), benzophenone-3 (BP-3) or octocrylene (Table 1), which absorb light in the UV range, and inorganic (physical) filters, zinc oxide (ZnO) and titanium dioxide (TiO_2), which scatter and reflect UV rays. Sunscreens are usually comprised of more than one of these UV filters: organic, inorganic or a mixture of both types, which gives broad-spectrum of protection. Beyond its debatable efficiency, questions regarding the main ingredients of different sunscreens are being raised in recent years, mainly about the prevalence of these ingredients in the environment and about their potential toxicity.

1.1. Human exposure and detrimental effects

Many factors might influence human exposure to UV filters: geographic location, season, lifestyle, gender or occupation, which means it can be highly individualized. For instance, a study in Australia showed 56% of people apply sunscreens at least 5 days per week, and 27% of

* Corresponding author.
E-mail addresses: joruszkiewicz@gmail.com, joanna.ruszkiewicz@einstein.yu.edu (J.A. Ruszkiewicz), adi.pinkas@gmail.com (A. Pinkas), beatriz.ferrervillahoz@einstein.yu.edu (B. Ferrer), Tanara.Peres-Vieira@einstein.yu.edu (T.V. Peres), aristsatsakis@gmail.com (A. Tsatsakis), michael.aschner@einstein.yu.edu (M. Aschner).

http://dx.doi.org/10.1016/j.toxrep.2017.05.006
Received 31 March 2017; Received in revised form 19 May 2017; Accepted 25 May 2017
Available online 27 May 2017

Table 1
Organic UV filters.

International nomenclature of cosmetic ingredients (INCI)	*United States adopted name (USAN)*	*Other names*
UVB filters		
4-methylbenzylidene camphor*	Enzacamene	
Homosalate	Homosalate	
Isoamyl-*p*-methoxycinnamate	Amiloxate	
Octyl dimethyl PABA	Padimate O	OD-PABA
Octyl methoxycinnamate	Octinoxate	2-ethylhexyl 4-methoxy cinnamate
Octyl salicylate	Octisalate	2-ethylhexyl salicylate
p-aminobenzoic acid	p-aminobenzoic acid	4-aminobenzoic acid, PABA
Triethanolamine	Trolamine salicylate	
UVA filters		
Disodium phenyl dibenzimidazole tetrasulfonate	Bisdisulizole disodium	
Butyl methoxydibenzoylmethane	Avobenzone	
Menthyl anthranilate	Meradimate	
Terephthalylidene dicamphor sulfonic acid	Ecamsule	Mexoryl SX
UVB-UVA filters		
Benzophenone-3	Oxybenzone	2-hydroxy-4-methoxybenzophenone
Benzophenone-4	Sulisobenzone	
Benzophenone-8	Dioxybenzone	
3-Benzylidene camphor[a]		Mexoryl SD
Bis-ethylhexyloxyphenol methoxyphenyl triazine[a]	Bemotrizinol	Tinosorb S
Cinoxate	Cinoxate	
Drometrizole trisiloxane[a]		Mexoryl XL
Methylene bis-benzotriazolyl Tetramethylbutylphenol[a]	Bisoctrizole	Tinosorb M
Octocrylene	Octocrylene	2-ethylhexyl 2-cyano-3,3-diphenylacrylate
Phenylbenzimidazole sulfonic acid	Ensulizole	

[a] Not approved by the Food and Drug Administration, used in other parts of the world.

people use it less frequently − 2 or fewer days per week [8] and a study in Denmark showed 65% of the sunbathers used one or more sunscreens [9].

Dermal exposure is the most relevant entry route of chemicals related to sunscreen use, however considering a common human behavior related to sunscreen application, e.g. eating and drinking with sunscreen applied on hands and lips, gastrointestinal or pulmonary exposure should also be considered [10–12]. The typically recommended mode of application (2 mg/cm^2) [13] implies a single dose of sunscreen product may be as large as 40 g, assuming application on the total body surface (2 m^2 for an average adult male), which for an average adult male weighting 78 kg and a typical concentration of about 10% of active ingredient in a commercial product, means maximum exposure around 50 mg/kg body weight (bw) [14]. Simple calculation suggests that with a maximum skin penetration up to 5% for some organic filters [15], the total amount of compound absorbed from a single application might be up to 200 mg, or 2.56 mg/kg bw, assuming an average bw of 78 kg for adult males. However, with application frequently thinner than recommended, partial body cover and different properties of compounds, these doses are usually much lower. For instance, a study on Australian population showed that the median daily amount of sunscreen applied was 1.5 g/day (range, 0–7.4 g/day) and the median quantity of sunscreen applied was 0.79 mg/cm^2 [8], whereas sunbather in Denmark applied on average 0.5 mg/cm^2 [9], in both cases it was less than half the amount needed to achieve the labeled sun protection factor.

Levels of UV filters found in human samples are usually low. In one epidemiological study, 2517 urine samples from United States (US) general population were analyzed for the presence of benzophenone-3 (BP-3), as part of the 2003–2004 National Health and Nutrition Examination Survey [16]; BP-3 was detected in 97% of the samples, with mean concentration of 22.9 ng/ml and 95th percentile concentration of 1040 ng/ml. In another study, investigating correlation between couples' presence of urinary benzophenone-type UV filters and sex ratio of their offspring, the mean concentrations of these compounds ranged from 0.05 ng/ml to 8.65 ng/ml, with BP-3 as the most predominant among the study population (samples collected between 2005 and 2009 in Michigan and Texas) [17]. Interestingly, about nine times higher than previously reported levels of BP-3 (up to 13000 ng/ml, average around 200 ng/ml) were found in urine samples collected in 2007–2009 from Californian females, which is probably a result of specific demographics [18].

The experimental studies confirm substantial absorption and distribution of organic filters, whereas inorganic filters seem to penetrate the human skin in a minimal degree. When adults applied a sunscreen formulation containing 10% of BP-3, 4-methylbenzylidene camphor (4-MBC) and octyl methoxycinnamate (OMC) on a daily basis (2 mg/cm^2) for a week, the mean urine concentrations for these ingredients were 60, 5, 5 ng/ml for females and 140, 7, 8 ng/ml for males, respectively [19]. At the same time, maximum plasma concentrations for these ingredients, reached 3–4 h after application, were 200, 20, 10 ng/ml for females and 300, 20, 20 ng/ml for males, respectively. Similar findings were reported following a 4-day exposure to these ingredients, which were detectable in the plasma of human males and females merely 2 h following application [20]. More data on human skin penetration and distribution of various UV filters, both organic and inorganic, can be found in recent reviews [21,22,15].

Of importance, some UV filters were also found in human milk samples. In a cohort study between 2004 and 2006, 54 human milk samples were analyzed; UV filters were detectable in 46 samples and levels were positively correlated with the reported usage of UV filter products [23]. Concentrations of ethylhexyl methoxy cinnamate (EHMC), octocrylene (OC), 4-MBC, homosalate (HMS) and BP-3 ranged 2.10–134.95 ng/g lipid, with EHMC and OC being most prevalent (42 and 36 positive samples, respectively) and an average of 7 positive samples for the other three [23]. In other study, levels of BP-3 in maternal urinary samples taken in gestational weeks 6–30 were positively correlated with the overall weight and head circumference of the baby [24]. These reports rise concerns about potential prenatal exposure and developmental toxicity of UV filters.

Besides intentional sunscreen application, additional routes might intensify human contact, namely occupational and environmental exposure. Workplace contact may be a source of substantial exposure to sunscreens, especially inorganic filters − nanoparticles (NPs) of ZnO

and TiO_2, which are frequently manufactured and stored as nanopowder. One study reported the presence of ZnO NPs in the work environment in an industrial scale plant in Japan. Electron microscopy analysis revealed the presence of a large number of submicron and micro-sized aggregated ZnO structures (concentrations not showed) [25]. Occupational exposures to TiO_2 NPs have been reported more frequently and was summarized in a recent review, demonstrating that the respirable TiO_2 concentration in the workers' breathing zone might reach 150 μg/m^3 [26]. Experimental studies suggest that with insufficient protection, inhalation of nanoparticles aerosol might result in pulmonary and systemic alterations. A single 10–30 min inhalation of a high dose (20–42 mg/m^3) of ZnO NPs aerosol increased levels of the inflammatory cytokines interleukin (IL)-6, IL-8, and tumor necrosis factor α (TNF-α) in bronchoalveolar lavage fluid within 3 h after exposure in humans Kuschner et al., 1997. However, chronic, low-concentration exposure is more likely in workplaces, its effects are poorly known. Occupational exposure to sunscreen NPs was discussed more extensively in [12].

Environmental exposure is another way UV filters reach humans. Swimming in or drinking contaminated water might increase the contact, and thus absorption (through dermal and oral route) of these compounds. Recent data reviews indicate that the highest UV filter concentrations were found in rivers, reaching 0.3 mg/l for the benzophenone derivatives (e.g. BP-3), whereas ng to μg/l range were detected in lake and sea water. Moreover, lower levels (few ng/l) of organic UV filters were found in tap and groundwater [27–29,31]. Organic UV filters accumulate in wastewater treatment plants (WWTPs) up to mg/l concentrations, and since conventional WWTPs are not able to remove them, they are consequently released into rivers, lakes and oceans Ramos et al., 2016. Swimming pools are sinks for UV filters and its chlorine byproducts, at the μg/l range, or higher. Analysis by Sharifan et al. suggested that small, urban swimming pools might contain significantly higher, than in natural waters, levels of UV filters: 2.85, 1.9, 1.78 and 0.95 g/l, respectively of EHMC, OC, 4-MBC and BP-3, which question their safety for using them people, especially children [30].

Due to the widespread application of these compounds in many daily-use products and growing awareness of the risk associated with the sun exposure, the market of UV filters increases every year. Thus, increasing usage, persistent input and accumulation in environment is becoming an issue of great concern because of threat to human health, but also to the environment. UV filters were found to be ubiquitous in many aquatic systems and aquatic biota. Occurrence and impact (including toxicity) of UV filters on environment have been reviewed extensively elsewhere [27–29,31]. Aquatic organisms are frequently studied and UV filters were found at ng/g range in many of them, especially in fish and mussels, but also crustacean, mammals and aquatic birds [28]. In a study of the presence of several UV filters in Swiss lakes and rivers (which receive input from waste water treatment plants and recreational activity), and the fish which live inside them, water concentrations of BP-3, 4-MBC, EHMC and OC ranged 2–35 ng/l, while lower limit of detection (LOD) in fish for those compounds was 3–60 ng/g, with concentrations reaching as high as 166 ng/g for 4-MBC [11]. Later study showed even higher levels of BP-3, 4-MBC and EHMC (range 6–68 ng/l) in Swiss river, moreover substantial amount of EHMC was found in fish (up to 337 ng/g) and in cormorants (up to 701 ng/g), suggesting food-chain accumulation [10]. Many ecotoxicological studies addressed the potential damage of sunscreens and their components and *in vitro* experiments suggested that UV filters might be toxic for some aquatic microorganisms. UV filters were detected in nearshore waters around Majorca Island at variable concentrations: 53.6–577.5 ng/l for BP-3, 51.4–113.4 ng/l for 4-MBC, 6.9–37.6 μg/l for Ti, 1.0–3.3 μg/l for Zn, and various popular sunscreen formulations were shown to affect negatively the growth of local phytoplankton *Chaetoceros gracilis*, however at concentrations much higher than those detected in natural waters (EC50: 45–218 mg/l after 72 h treatment) Tovar-Sanchez et al., 2013. This is a typical observation. For instance, EC50 values of selected organic filters (e.g. BP-3, BP-4, EHMC, 4-MBC) in standardized toxicity assays on three aquatic species, *Daphnia magna*, *Raphidocelis subcapitata* and *Vibrio fischeri*, were in the mg/l range for all the species, which suggest minimal risk for these organism in their natural ecosystems [32]. However, like many researchers suggest, toxic effects of chronic, low-dose exposures cannot be ruled out and require further investigations [32]. Moreover, with increased usage and lack of efficient removal, environmental contamination will probably increase in the future. Recent report on coral bleaching showed that environmental contamination with BP-3 already poses a hazard to coral reef. The levels of BP-3 detected in coral reefs in the U.S. Virgin Islands (75–1400 μg/l) and Hawaii (0.8–19.2 μg/l) might lead to death of several local coral species with LC50: 8–340 μg/l and LC20: 0.062–8 μg/l (4 h exposure) [33].

Therefore, while sunscreens have been effective in protecting against a variety of UV-related pathologies, such as sunburns, actinic keratoses, squamous cell carcinomas and melanomas [34], growing popularity and thus, possibility for exposure questions their safety in environment and human health. Available data imply, that sunscreen compounds might block vitamin D synthesis or act as endocrine disruptor and lead to developmental toxicity. The effects of sunscreen on cutaneous synthesis of vitamin D induced by sunlight have been a subject of debate for recent years, however the newest analysis suggests, that normal usage of sunscreen by adults do not decrease cutaneous synthesis of vitamin D [35]. The endocrine disruptive and developmental toxicity of many organic UV filters in experimental models is well established, these filters seem to be associated with altered estrogen, androgen and progesterone activity, reproductive and developmental toxicity and impaired functioning of the thyroid, liver or kidneys, reviewed elsewhere [36,37,1,38,29]. Since many of UV filters were shown to cross the blood-brain barrier (BBB), the risk for neurotoxicity also occurs. In this review, the potential neurotoxicological effects of exposure to sunscreen have been discussed, as literature regarding the neurotoxicity of both organic and inorganic UV filters is presented.

2. Organic filters

Organic or chemical filters are the most popular and widely used in sunscreens and other cosmetic products. Data from 2003 indicate that over 80% sunscreen products contained OMC, 60% contained BP-3, and 20% contained octocrylene (OC) or HMS, whereas inorganic filters were present in around 20% of products [39]. Organic filters can be classified by the type of ultraviolet (UV) radiation they absorb, namely UVB, UVA or UVB-UVA filters (Table 1). As mentioned previously, the main route of human exposure is dermal absorption, however other routes and environmental exposure should be also considered. The last is particularly true for organic filters, which, due to their high lipophilicity could bioaccumulate in aquatic organism and reach humans through the food chain. Thus, they also are emergent as an environmental pollutant [40]. Chemical UV filters are easily absorbed by the skin and reach the systemic circulation, and accumulate in various tissues, as adipose tissue, liver and the brain [41–44]. Their lipophilicity permits them to readily cross the BBB, nonetheless, the effect of organic UV filters in the central nervous system (CNS) has been yet to fully addressed. However, there is a wide range of *in vitro* and *in vivo* studies of the toxic effects of UV filters as endocrine disruptors. And since it is known that other chemicals classified as endocrine disruptors can impair neuronal transmission, synaptic plasticity and produce neurotoxic effects [45], chemical filters might potentially produce similar effect. The documented neurotoxic effects of organic UV filters have been described below and summarized in Table 2.

2.1. Octyl methoxycinnamate

Octyl methoxycinnamate (OMC) is a UVB filter also known as

Table 2
Neurotoxic effects of organic UV filters.

Compound	*Exposure model*	*Experimental design*	*Effect*	*Reference*
Octyl methoxycinnamate	Wistar rats	Oral (gavage) administration during gestation and lactation 500–1000 mg/kg/day	Decreased motor activity in female offspring, increased spatial learning in male offspring.	[46]
	Sprague-Dawley rats, female	Oral (gavage) administration for 5 days 10–1000 mg/kg/day	Non-estrogenic interference within the rodent HPT axis; no changes in pre-proTRH mRNA in mediobasal-hypothalamus.	[47]
	Wistar rats	*In vitro* incubation of hypothalamus isolated from adult rats, 60 min 0.263 μM	Decreased hypothalamic release of GnRH. Increased GABA release and decreased Glu production in males. Decreased Asp and Glu production in females.	[48]
	Wistar rats	*In vitro* incubation of hypothalamus isolated from immature rats, 60 min 0.263 μM	Decreased hypothalamic release of LHRH. Increased GABA release in males, decreased Asp and Glu levels in females.	[49]
	SH-SY5Y neuroblastoma cell line	72 h 10^{-8}–10^{-4} M	Decreased cell viability and increased caspase-3 activity.	[50]
Benzophenone-3	*Danio rerio*	Waterborne 14 days for adult 120 h for embryos 10–600 μg/l	Anti-androgenic activity: decreased expression of *esr1*, *ar* and *cyp19b* expression in the brain of males.	[51]
	Sprague-Dawley rats	Dermal application 30 days 5 mg/kg/day	No changes in behavioral tests (locomotor and motor coordination).	[42]
	Rat primary cortical astrocytes and neurons	1–7 days 1–10 μg/ml	Decreased cell viability of neurons but not of astrocytes.	[42]
	SH-SY5Y neuroblastoma cell line	72 h 10^{-8}–10^{-4} M	Decreased cell viability and increased caspase-3 activity.	[50]
Benzophenone-4	*Danio rerio*	Waterborne 14 days 30–3000 μg/l	Upregulated estrogenic-related genes: *vtg1*, *vtg3*, *cyp19b* in the brain of males.	[52]
4-methylbenzyli-dine camphor	Long Evans rats	Oral (in diet) administration during mating, pregnancy, lactation, until adulthood of offspring 7, 24, 47 mg/kg/day	Impaired female proceptive and receptive sexual behavior. Altered expression of oestrogen- related gens in a sex- and region −dependent manner.	[53–55]
	Wistar rats	Subcutaneous administration during pregnancy 20–500 mg/kg/day	Altered hypothalamic release of Glu and Asp in male offspring. Inhibited testicular axis in male offspring during the pre-pubertal stage and stimulated during peri-pubertal stage.	[56]
	Danio rerio	Embryos exposed in medium 68 h 1–50 μM	Inhibited AChE activity, impaired early muscular and neuronal development.	[57]
	Neuro-2a mouse neuroblastoma cell line	45 min 0.1–100 μM	Inhibited AChE activity.	[57]
	SH-SY5Y neuroblastoma cell line	72 h 10^{-8}–10^{-4} M	Decreased cell viability and increased caspase-3 activity.	[50]
3-benzylidene camphor	Long Evans rats	Oral (in food) administration during mating, pregnancy, lactation, until adulthood of offspring 0.24–7 mg/kg/day	Impaired proceptive and receptive sexual behavior and disturbed estrous cycles of female offspring. Altered expression of oestrogen- related gens in a sex- and region-dependent manner.	[55]
Octocrylene	*Danio rerio*	Waterborne 14 days 22–383 μg/l	Impaired expression of genes related with development and metabolism in the brain.	[58]

Abbreviations: AChE: acetylcholine esterase; ar: androgen receptor; Asp: aspartate; cyp19b: cytochrome P450 aromatase b; esr1: estrogen receptor; GABA: gamma amino butyric acid; Glu: glutamate; GnRH: gonadotrophin-releasing hormone; HPT: hypothalamo-pituitary-thyroid; pre-proTRH: pre-pro-thyrotrophin-releasing hormone; vtg1, vitellogin 1; vtg3: vitellogin 3.

octinoxate and 2-ethylhexyl 4-methoxy cinnamate. This compound is approved as a cosmetic ingredient in US and in European Union (EU) in concentrations of 7.5–10% [1].

Dermal penetration of OMC has been measured *in vitro*, with values ranged from 0.2% to 4.5% of the applied dose, depending on the experimental conditions, however systemic absorption seems to be much lower. In humans, when a cream containing 10% OMC was applied to the entire body (40 g), OMC was absorbed through the skin and is detectable in blood (maximum concentrations 10 ng/ml in females and 20 ng/ml in males) and in urine (5 ng/ml in females and 8 ng/ml in males). Taking the highest detectable concentration (20 ng/ml) and assuming 4.7 l of blood, the systemic absorption represents only 0.002% of the applied dose [19].

Several studies indicated that OMC acts as an endocrine disruptor due to the ability to interfere with endocrine system at different levels [47,59,60]. *In vitro* and *in vivo* studies in rodents have shown that OMC have estrogen activity [61,62]. In humans OMC exposure has minor, but statistically significant effects on the levels of testosterone and estradiol [19]. Moreover, some studies suggested that OMC can interact with the hypothalamo-pituitary-thyroid (HPT) axis [63]. Ovariectomized rats exposed to 57.5 mg/20 g body weight of OMC applied via food presented a decrease in thyroxine (T_4) levels without changes in triiodothyronine (T_3) or thyroid-stimulating hormone (TSH) levels [60].

OMC has also a non-estrogenic endocrine disrupting activity in the HPT axis absent altering the expression of pre-pro-thyrotrophin-releasing hormone (pre-proTRH) in the mediobasal hypothalamus, but affecting the axis in other points, when was administrated orally (10–1000 mg/kg/day) for 5 consecutive days [47]. Experiments with rats showed that OMC (0.263 μM) decreases the hypothalamic release of gonadotrophin-releasing hormone (GnRH) [48] and luteinizing hormone-releasing hormone (LHRH) [49] *in vitro*. Furthermore, *in vitro* experiments in hypothalamic cells from male and female adult rats showed that the same dose of OMC inhibited the release of

neurotransmitters aspartate (Asp) and glutamate (Glu), but not gamma-aminobutyric acid (GABA) in females, whereas in males decreased Glu and increased GABA release [48]. Similar results were found in hypothalamus isolated from immature rats (pre-pubertal and peri-pubertal males and females) [49]. These results indicate that OMC disrupts the normal neuroendocrine mechanism in a sex-dependent manner. Moreover, a study of offspring of dams treated with OMC (500–1000 mg/kg/day) showed sex-dependent behavioral changes, namely decreased motor activity in females, but not in males, and improved spatial learning in males, suggesting that OMC can affect neuronal development, however the doses used in these experiments were extremely high, not relevant to possible human exposure [46]. Corroborating these observations, recent studies in neuroblastoma cell line (SH-SY5Y) demonstrated that exposure to high concentrations of OMC (0.01–100 μM) decreased cell viability and increased apoptosis, however effective concentrations were not observed *in vivo* [50].

2.2. Benzophenone-3

Benzophenone-3 (BP-3, oxybenzone) is a common organic filter used in sunscreens and other personal care products (nail polish, lotions, lipsticks) in a maximum allowed concentration of 6% in US. It is used as broad-spectrum UV filter due to absorption of both UVB and short UVA rays [1].

BP-3 applied topically in human can cross the skin by direct penetration through the intercellular laminae of the stratum corneum (SC) or by passive diffusion by high-concentration gradient and then reach the blood [64]. When 25 volunteers applied a commercially available sunscreen containing 4% BP-3 for 5 days, their urine samples showed that approximately 4% of BP-3 is absorbed into the system [65]. BP-3 was detected in more than 80% of urine samples of healthy Danish children and adolescents (median concentration 0.92 ng/ml) [66]. Repeated (4 days) topical applications (2 mg/cm^2 of sunscreen formulation) of BP-3 resulted in urine levels up to 81 ng/ml and plasma levels up to 238 ng/ml [20]. Moreover, another concern relates to the fact that the simultaneous application of some insect repellents components such as *N, N*-diethyl-*m*-toulamide (DEET) and BP-3 can enhance skin penetration of each other when jointly applied [42]. Once BP-3 is in the systemic circulation, it is transported to different organs. BP-3 is a highly lipophilic, and in rats it has been detected in liver [41,42,44,43] and in brain (15.5–34.1 ng/g) [42]. High concentrations of BP-3 were also detected in adipose tissue after topical administration [41].

High, not environmentally relevant concentration of BP-3 (up to 1000 μg/l) were shown to disrupt the neuro-endocrine system in fish [67,68]. BP-3 (waterbone exposure 10–600 μg/l, where the lowest concentration represents the worst-case, environmentally relevant concentration) impaired the sexual behavior of *Danio rerio* zebrafish adult males by decreasing the expression of androgenic genes: estrogen receptor 1 (*esr1*), androgen receptor (*ar*) and cytochrome P450 aromatase B (*cyp19b*) in the brain at concentration 84 μg/l [51]. Whereas topical administration of BP-3, at dosage which mimics possible human exposure (5 mg/kg/day for 30 days) in male and female Sprague-Dawley rats did not affect locomotor activity and behavioral test, nor did it produce neurological deficits [42]. Moreover, no effect on rat primary cortical astrocyte cultures were detected when cells were incubated with low, physiological concentrations (0.1–10 μg/ml) of BP-3 for up to 7 days [42]. However, studies in rat primary cortical neuronal cultures [42] and SH-SY5Y neuroblastoma cell line [50] showed decreased cell viability after BP-3 treatment at moderate concentrations (e.g. 1–10 μg/ml).

2.3. Benzophenone-4

Benzophenone-4 (BP-4, sulisobenzone) is frequently used as UV absorber at concentration up to 10% [1].

BP-4 was found in human placenta (0.25–5.41 ng/g), suggesting efficient skin penetration and accumulation, which may lead to exposure of human embryos and fetuses [69]. BP-4, like BP-3 is a benzophenone derivative, yet its potency as an estrogenic disruptor has been not well defined.

In zebrafish, adult males exposed to high concentrations (3000 μg/l) of BP-4 for 14 days displayed estrogenic activity by up-regulation of estrogenic-related genes: vitellogin 1 (*vtg1*), vitellogin 3 (*vtg3*) and the *cyp19b* in the brain, however lower dosages did not induce changes. In contrast, in the liver, some of these genes (*vtg1*, *vtg3*) were down-regulated [52]. No other effects in the nervous system were reported.

2.4. 4-methylbenzylidene camphor

4-methylbenzylidene camphor (4-MBC) or enzacamene is an organic camphor derivative used as a UVB filter in sunscreen and other cosmetic products. Although the compound is not approved by the Food and Drug Administration (FDA), other countries allow it usage at maximum concentration of 4% [1].

4-MBC is a high lipophilic component which can be absorbed through the skin and was found in human tissues, including placenta [70]. Repeated (4 days) topical applications (2 mg/cm^2 of sunscreen formulation) of 4-MBC resulted in urine levels up to 4 ng/ml and plasma levels up to 18 ng/ml [20]. When orally administrated to rats, 4-MBC reaches the liver where is metabolized to 3-(4-carboxybenzylidene) camphor and 3-(4-carboxybenzylidene) hydroxycamphor [71]. 4-MBC exhibits a toxic activity as estrogenic endocrine disruptor [62,59,68]. Moreover, *in vivo* studies suggest that 4-MBC affected the thyroid axis [63].

Several studies described the effects of 4-MBC on developing neuroendocrine system. Rats exposed to 4-MBC (7–47 mg/kg) in diet before mating, during pregnancy and lactation, and in the offspring until adulthood, showed a region- and sex-dependent alteration in the oestrogenic genes in the brain [55,54,53]. For instance, the expression of progesterone receptor (PR) was decreased in the ventromedial hypothalamic area of 4-MBC-treated females, but not in males [55]. In addition, females showed impaired proceptive and a non-receptive sexual behavior after 4-MBC exposure [55]. Female sexual behavior was significantly impaired at the lowest doses studied 7 mg/kg/day, which resulted in rat milk concentration of 208.6 ng/g lipid, which is over 10 times higher than value (19 ng/g lipid) found in human milk [55]. Subcutaneous administration of high dosages (up to 500 mg/kg/day) during pregnancy and lactation altered the hypothalamic secretion of excitatory amino acids Glu and Asp in male offspring. These neurotransmitters play a role as stimulators of gonadal axis, thus the observed changes are consistent with alterations in sexual development of male offspring, affecting pre-pubertal stage, but stimulating the peri-pubertal stage [56]. In addition, 4-MBC has been reported to have an acetylcholinesterase (AChE) inhibitory activity. Zebrafish embryos exposed to 15 μM 4-MBC for 3 days showed abnormal axial curvature and exhibited impaired motility. 4-MBC also impaired muscle development and axon pathfinding [57]; however, the dose used in the study was significantly higher than those detected in environmental aquatic media. Inhibition of AChE activity was also observed in mammalian Neuro-2a cells exposed to 10 and 100 μM for 45 min, indicating a possible mechanism for the 4-MBC-induced muscular and neuronal defects [57]. 4-MBC (up to 100 μM) has been shown recently to decrease cell viability and induce apoptosis in neuroblastoma cell line (SH-SY5Y), suggesting possible neurotoxic effects, however again, effective concentrations were not observed *in vivo* [50].

2.5. 3-benzylidene camphor

3-benzylidene camphor (3-BC) is a lipophilic compound closely related to 4-MBC. It is used in sunscreen products in EU, at a maximal concentration of 2% [1].

After topical application to rats for 65 days (60–540 mg/kg/day) 3-

BC was detected in all analyzed tissues, including the brain (concentration 0.13–1.2 μg/g), suggesting that similar disposition and distribution may occur in humans [72]. Though not detectable in urine of Danish children [66], the compound was found in human placenta [70].

Analogous to 4-MBC, 3-BC has also been described as an estrogenic disruptor [59,73]. Moreover, it has been reported that 3-BC can affect the CNS. Rats pre- and postnatally treated with 3-BC (0.24–7 mg/kg/day) showed region- and sex-specific response in expression of genes involved in sexual behavior: PR, estrogen receptors (ERa, ERb), and steroid receptor coactivator-1 (SRC-1) in the brain [55].

2.6. Octocrylene

Octocrylene (OC) is an ester belonging to the cinnamates family and is present in sunscreen and daily care cosmetic products at a maximal concentration of 10%. It can absorb UVB and high energy components of UVA radiation [74]. To date there are few studies on its accumulation and toxicity, especially in aquatic organism [75–77].

Zebrafish embryos and adult male exposed to environmentally relevant concentrations of OC in water (22–925 μg/l) absorbed and accumulated this compound. Moreover, the microarray analysis from adult zebrafish male exposed to OC (383 μg/l) showed major impairment in the expression of 628 genes in the brain regulating mainly developmental processes and 136 genes in the liver, responsible mainly for metabolism [58].

3. Inorganic filters

Inorganic (physical) ingredients used in modern sunscreens include metal oxide particles, typically titanium dioxide (TiO_2) and zinc oxide (ZnO), which occurs typically at 5–10% concentration (maximum allowed is 25%). While chemical filters still dominate in sunscreen products, the usage of physical compounds is constantly growing. One of the reasons is that they have a higher spectrum of protection − TiO_2 is very effective in absorbing UVB, while ZnO absorbs mainly the UVA range, and the combination of both particles provides a broad UV protection. Other advantages of physical filters are lack of skin sensitization and limited skin penetration [78]. However, these mineral filters, when in normal pigment size range (200–400 nm for ZnO, 150–300 nm for TiO_2) have poor particle dispersion, which makes them difficult to apply; they also reflect and scatter light, which result in undesirable visible white film on the skin. With nanotechnology, these materials can be reduced to nanoparticles (NPs) (< 100 nm) which are easier to apply and are transparent on the skin [12]. Nevertheless, with micronization some properties are changed − they may be more bioreactive and easier penetrate the skin and other tissues, leading to concerns about their safety use. Moreover, part of the absorbed UV radiation can generate free radicals on the surface of metal oxides in the presence of water and this photocatalytic activity increases with decreasing NPs size. NP-induced cyto- and genotoxicity has been associated with increased photocatalytic activity, leading to increased production of free radicals [79]. Despite increased awareness of nanomaterials toxicity, the nanoneurotoxicity is a relatively new field with numerous data gaps awaiting improvements. One of the main reasons for this is the lack of reliable methods for NPs detection and quantification. Only estimates and predictions about NPs concentration in natural environments are available, and they suggest that TiO_2 might be present in the range 0.7–24.5 μg/l, whereas ZnO might reach higher levels, up to 76 μg/l [80]. Analogously, NPs accumulation and physiological concentrations are difficult to assess; thus, most studies report changes in Zn and Ti ion levels only. This also raises questions regarding the relevance of predominantly high-dose exposures used in toxicological studies. To date, most studies attesting to neurotoxic effect of NPs have been carried out in acutely high concentration exposure scenarios, and their relevance to “real-life” exposure scenarios needs to be further assessed.

3.1. Zinc oxide

Zinc oxide nanoparticles (ZnO NPs) are used not only in sunscreens, but also in pigments (UV-absorbers, paintings) and electronic equipment (thin film transistors, semi-conductors, liquid crystal displays, light-emitting diodes) due to their exceptional optoelectronic, piezoelectric, ferromagnetic and optical properties. Moreover, their antiseptic activity makes them potentially useful in treatment of bacteria-related infections or diseases [81]. As their commercial utilization has increased, wider application raises the potential risk of human exposure [82].

3.1.1. ZnO NPs absorption and transport across the BBB

Several *in vitro* and *in vivo* studies evaluated the fate and toxicity of ZnO NPs from different exposures: dermal, gastrointestinal or pulmonary. Dermal absorption is a major route of ZnO NPs exposure from sunscreen application. Most studies demonstrated that ZnO NPs did not penetrate into deeper layers of the skin (SC) [83,84,22,85,86]. However, some data indicated that ZnO NPs penetrated the skin to a limited extent. A small increase of zinc ions (Zn^{2+}) in the blood and urine was observed in humans exposed to ZnO NPs-containing sunscreen products for five constitutive days *via* healthy skin [87]. Human skin *in vitro* was shown to absorb 0.34% of ZnO NP after 72 h [88]. In general, penetration ability of NPs increases when the skin barrier is damaged, pursuant to sunburn, skin disease or physical damage. ZnO NPs were found to better penetrate tape-stripped, lesioned or wounded, rather than healthy human skin [85,89]. Moderate skin sunburn increased the penetration of ZnO NPs in pigs, however transdermal absorption was not detected [90]. *In vitro* studies reported similar findings, only a limited number of ZnO NPs were found on the outer surface of the SC, and no particles were observed in the deeper SC layers [83,84]. Generally, the risk of ZnO NPs exposure from dermal absorption is rather low, however, considering a common human behavior related to sunscreen application, e.g. eating and drinking with sunscreen applied on hands and lips, gastrointestinal or pulmonary exposure should also be considered, moreover, as mentioned previously, the occupational exposure might be of high concern for some people [12].

Inhalation might be specifically associated with increased brain exposure, since the olfactory nerves can directly transport particles into the brain. In fact, Kao et al. observed the translocation of ZnO NPs into the brain following nasal administration (6 h airborne exposure) in a Sprague Dawley rats [91]. In healthy human adults inhaling 500 $\mu g/m^3$ of ZnO NPs for 2 h, the results were below the threshold for acute systemic effects on the respiratory, hematologic, and cardiovascular endpoints [92]. Other studies have shown that various NPs can enter the brain across the BBB [81,93]; however, a limited number of studies address this issue for ZnO NPs. The BBB was found to be intact in rats after repeated oral administrations of ZnO NPs for 28 days (500 mg/kg) [94], however the presence of ZnO NPs in the rat brain was observed after oral administration for 21 days (500 mg/kg) [95]. Moreover, Yeh et al. (2012) showed increased ^{65}Zn accumulation in the mouse brain up to 10 days after single-dose (120 g) intravenous injection of small (10 nm) ^{65}ZnO NPs [96]. In adult mice, neuronal NPs localization was observed for several days after single oral (gavage) administration of 3 mg of fluorescent ZnO NP. Decreased fluorescent signal over time is consistent with biodegradation or elimination of NPs from the brain [97]. Additional studies are needed to investigate the brain penetration capacity of ZnO NPs.

Other reviews discuss absorption, distribution, metabolism and excretion of ZnO NPs in humans and experimental models more extensively [12,79,82]. To date, data available indicate that ZnO NPs can be absorbed *via* different routes and distributed to a range of organs, including the brain and placenta. Distribution depends on the size of ZnO NPs, the dose, time and route of exposure. The fate of ZnO NPs

Table 3
Neurotoxic effects of ZnO NPs.

Compound	*Exposure model*	*Experimental design*	*Effect*	*Reference*
ZnO NPs	Wistar rats	Intraperitoneal injection biweekly, 8 weeks 4 mg/kg	Attenuated spatial cognition capability, enhanced long-term potentiation.	[99]
	Wistar rats	Intravenous injection single dose 25 mg/kg	Increased brain Zn concentrations; no changes in neurotransmitter levels, locomotor activity, exploratory behavior or spatial working memory.	[100]
	Wistar rats, male	Intraperitoneal injection, 10 days 25 mg/kg/day	Decreased iron and calcium, but not Zn, sodium and potassium levels in rat brain homogenates; unchanged emotional behavior.	[101]
	Wistar rats, male	Oral (gavage) 7 days 600 mg/kg	Elevated TNF-α, IL-1β, IL-6, CRP, MDA, decreased GSH and SOD levels, CAT, and GPx activity.	[102]
	Sprague-Dawley rats	Oral 13 weeks 134.2, 268.4, 536.8 mg/kg/day	Increased Zn levels in the brain of male rats.	[103]
	C57BL/6J mice, male	Intraperitoneal injection 3 times per week, 4 weeks 5.6 mg/kg	Impaired learning and memory abilities, suppression of cAMP/CREB signaling pathway.	[104]
	Swiss albino mice, male	Intraperitoneal injection every other day, 8 times 5.6 mg/kg	Improved behavioral and cognitive impairment in mice with depressive-like behaviors.	[105]
	Swiss albino mice, male	Oral 21 days 500 mg/kg	Elevated ROS levels, altered antioxidant system, increased DA and NE levels, presence of ZnO NPs in neurons.	[95]
	ICR mice, pregnant female	Subcutaneous at GD 5, 8, 11, 14, 17 100 μg/day	Changed DA, 5-HT and their metabolites levels in a 6-week old offspring.	[106]
	Cyprinus carpio	Waterborne 1–14 days 0.5, 5, 50 mg/l	Changed CAT, SOD, GPx activity, GSH levels and lipid peroxidation.	[107]
	Prochilodus lineatus	Waterborne 5, 30 days 7, 70, 700 μg/l	Increased protein oxidative damage, decreased AChE activity.	[108]
	Apis mellifera carnica	Oral (food) 10 days 0.8 mg Zn/ml	Decreased brain weight and increased brain AChE and GST activity.	[109]
	Isolated rat neurons	1 mg/ml	Increased the opening number of sodium channels, delayed rectifier potassium channels, enhanced excitability of neurons.	[110]
	Rat primary neurons	24 h 1–100 μg/ml	Concntration-dependent cytotoxicity, disrupted cell membranes, DNA damage.	[111]
	Mouse neural stem cells	24 h 3–24 ppm	Concentration-dependent decrease in cell viability; apoptosis, necrosis, release of zinc ions.	[112]
	RCS96 rat Schwann cells	6–48 h 4–400 μg/ml	Concentration- and time-dependent decrease in cell viability; apoptosis and necrosis, G2/M phase cell cycle arrest, release of Zn ions.	[113]
	Human olfactory neurosphere-derived cells	2–24 h 10–80 μg/ml	Decreased cell viability, activation of numerous pathways associated with stress, inflammation and apoptosis.	[114]
	RCG-5 rat retinal ganglion cells	4–72 h 2.5–10 μg/ml	Concentration- and time-dependent decrease in cell proliferation; cell cycle arrest, ROS generation, increased caspase-12, decreased bcl-2 and caspase-9.	[115]
	RCG-5 rat retinal ganglion cells	6–72 h 2.5–10 μg/ml	Decreased mitochondrial membrane potential, increased ROS production, increased caspase-12.	[116]
	RCG-5 rat retinal ganglion cells	4–72 h 2.5–10 μg/ml	Decreased expression and activity of the plasma membrane calcium ATPase, disrupted intracellular calcium homeostasis, increased ROS production.	[117]
	PC12 rat pheochromocytoma and SH-SY5Y human neuroblastoma	24 h 10–10000 μM	Decreased cell viability, mitochondrial impairment, internalization of ZnO NPs in membrane-bound vesicles.	[91]
	SH-SY5Y human neuroblastoma	6, 12, 24 h 5–30 mg/ml	Concentration- and time-dependent decrease in cell viability; apoptosis via the PI3 K/Akt/caspase-3/7 pathway and necrosis by LOX-mediated ROS production.	[118]
	SH-SY5Y human neuroblastoma	3–48 h 10–80 μg/ml	Concentration- and time-dependent decrease of cell viability, apoptosis and cell cycle alterations, genotoxicity: micronuclei, H2AX phosphorylation, DNA damage.	[119]
	U87 human brain tumor	24 h 1–200 μg/ml	Concentration-dependent cytotoxicity e.g. increased formation of micronuclei.	[120]
	Rat primary astrocytes	6, 12, 24 h 4, 8, 12 μg/ml	Reduced cell viability, increased LDH release, stimulated ROS generation, caspase-3 activation, decreased MMP, phosphorylated JNK, ERK, p38 MAPK.	[121]
	C6 glia cells	3, 6, 24 h 5–80 μg/ml	Time- and concentration-dependent cytotoxicity, apoptosis and increased ROS production.	[122]
	A172, U87, LNZ308, LN18, LN229 glioma cell lines and normal human astrocytes	24 h 1, 5, 10 mmol/l	Cytotoxicity and ROS generation in glioma lines, but not in normal human astrocytes.	[123]
	N9 mouse microglial cell line	5–60 min; 1–24 h 1–100 μg/ml	Increased intracellular calcium and ROS levels, decreased intracellular ATP level, upregulated apoptosis markers.	[124]

(continued on next page)

Table 3 *(continued)*

Compound	*Exposure model*	*Experimental design*	*Effect*	*Reference*
	BV-2 mice microglia cell line	2–24 h 10 μg/ml	Increased cytotoxicity; activated PINK1/parkin-mediated mitophagy.	[125]

Abbreviations: 5-HT: 5-hydroxytriptamine; Akt: protein kinase B; cAMP: cyclic adenosine monophosphate; CAT: catalase; CREB: cAMP response element binding protein; CRP: c-reactive protein; DA: dopamine; ERK: extracellular signal-related kinase; GSH: glutathione; GPx: glutathione peroxidase; GST: glutathione-S-transferase; H2AX: H2A histone family member X; IL-1β: interleukin-1β; IL-6: interleukin-6; JNK: c-Jun N-terminal kinase; LDH: lactate dehydrogenase; LOX: lipoxygenase; MDA: malondialdehyde; MMP: mitochondrial membrane potential; NE: norepinephrine; NPs: nanoparticles; p38 MAPK: p38 mitogen-activated protein kinase; PINK1: PTEN-induced putative kinase 1; PI3 K: phosphoinositide 3-kinase; ROS: reactive oxygen species; SOD: superoxide dismutase; TNF-α: tumor necrosis factor α; Zn: zinc; ZnO: zinc oxide.

remains unclear; most data suggest that ZnO NPs decompose in medium or in cells and release Zn^{2+} which are responsible for toxic effects. However, this issue, together with the risk of long-term exposure and absorption *via* healthy *vs*. damaged skin remain to be established.

3.1.2. Neurotoxic effects in vivo

Although increasing number of studies aimed to investigate the potential toxicity of ZnO NPs in different cell types and animal systems [98,82,12], little is known about their neurotoxic effects (Table 3), especially *in vivo*. ZnO NPs exposure was shown to induce neurobehavioral changes in experimental animals. Impaired learning and memory abilities, and hippocampal pathological changes were demonstrated in old (18 months) mice following ZnO NPs exposure (intraperitoneally, i.p., 5.6 mg/kg, three times per week for four weeks) [104]. The spatial learning and memory ability was attenuated in ZnO NPs-treated (i.p. 4 mg/kg, biweekly for 8 weeks) Wistar rats. The exposed animals exhibited prolonged escape latency in the Morris water maze (MWM), and enhanced long-term potentiation (LTP), but not sufficient depotentiation in the dentate gyrus (DG) region of the hippocampus [99]. ZnO NPs administered i.p. for several days ameliorated the behavioral and cognitive impairment in young Swiss male mice with depressive-like behaviors, suggesting that they may affect neuronal synaptic plasticity [105]. Subcutaneous administration of ZnO NPs in pregnant ICR mice at gestation day (GD) 5, 8, 11, 14 and 17 (100 μg/day) affected dopamine (DA), 5-hydroxytriptamine (5-HT) and their metabolites' levels in a 6-week old offspring [106]. This observation questions the safety of ZnO NPs exposure during pregnancy, potential transfer through placenta and the effect on developing brain. In contrast, single intravenous injection of ZnO NPs (25 mg/kg) did not affect locomotor activity, exploratory behavior, spatial working memory or neurotransmitter: norepinephrine (NE), epinephrine (EPI), DA, and 5-HT levels in adult male Wistar rats 14 days after injection, despite the plasma and brain Zn^{2+} levels increased in treated group [100]. Sub-acute ZnO NPs treatment (25 mg/kg, 10 days) resulted in minimal effect on emotional behavior (e.g. unaffected anxious index), but showed alteration in trace elements homeostasis in rat brain homogenates: decreased levels of iron (Fe^{2+}) and calcium (Ca^{2+}), while Zn^{2+}, sodium (Na^{+}) and potassium (K^{+}) concentrations remained unchanged [101].

Disrupted ion homeostasis is an important pathomechanisms of neurotoxicity, and ZnO NPs might affect it. Long-term (13 weeks) oral ZnO NPs administration (134.2, 268.4, 536.8 mg/kg/day), resulted in detection of slightly, but significantly higher Zn^{2+} levels in the brain of male rats (but not in female) [103]. In isolated rat hippocampal CA3 pyramidal neurons the ZnO NPs solution (1 mg/ml) was shown to enhance the current amplitudes of I_{Na} and I_K by increasing the opening number of sodium channels, delaying rectifier potassium channels, and enhancing the excitability of neurons, leading to intracellular Na^{+} accumulation and K^{+} efflux. These might disturb the ionic homeostasis and the physiological functions of neurons [110].

Oxidative stress and disrupted antioxidant system is another effect observed in brains of ZnO NPs-treated animals. Oral ZnO NPs (500 mg/kg) administration for 21 consecutive days resulted in elevated ROS levels and altered antioxidants: glutathione (GSH) levels, superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione S-transferase activity (GST), in both the brain and liver of male Swiss albino mice [95]. Combined with increased DA and NE levels in the cerebral cortex, these results suggest a neurotoxic potential for ZnO NPs [95]. Changes in CAT, SOD, GPx activity, GSH levels and lipid peroxidation was also observed in the brain and other organs of juvenile carp (*Cyprinus carpio*) exposed to waterborne ZnO NPs (0.5, 5, 50 mg/l) for 1, 3, 7, 10 and 14 days [107]. Exposure to environmentally relevant concentrations of ZnO NPs (7, 70, 700 μg/l) for 5 and 30 days led to increased protein oxidative damage in the brain and gills, but not in the liver, and decreased AChE activity in the brain and muscle of *Prochilodus lineatus* juvenile fish [108]. Honey bees (*Apis mellifera carnica*) exposed to ZnO NPs (0.8 mg Zn/ml) in food for 10 days showed decreased brain weight and increased brain AChE and GST activity [109]. Week-long oral administration of ZnO NPs (600 mg/kg) to male Wistar rats resulted in decreased brain CAT, GPx, and GR activities, decreased GSH and SOD levels, but elevated malondialdehyde (MDA) level and inflammatory markers: TNF-α, IL-1β, IL-6, C-reactive protein (CRP). The neurotoxic effects were partially reversed by the antioxidant and anti-inflammatory compound, hesperidin [102]. The pro-oxidant and pro-inflammatory effect of ZnO NPs was also observed in the serum and the brain of mice injected with ZnO NPs (i.p., 5.6 mg/kg) three times per week for four weeks [104]. In this study the suppression of cAMP/CREB signaling pathway was also identified: the contents of hippocampal cyclic adenosine monophosphate (cAMP), cAMP response element binding protein (CREB), phosphorylated CREB and synapsin I, were decreased in ZnO NPs-treated mice in an age-dependent manner [104].

3.1.3. Neurotoxic effects in vitro

The neurotoxic effect of ZnO NPs *in vitro* has been also evaluated, demonstrating oxidative stress- and apoptosis-related cytotoxicity. Deng et al. [112] have demonstrated that ZnO NPs impaired viability of neural stem cells (NSCs) in a concentration-, but not size-dependent manner. Twenty-four-hour exposure of concentrations higher than 12 ppm induced apoptosis and necrosis in the NSCs. Authors suggested that observed changes might result from the Zn^{2+} dissolved in solution or intracellularly, rather than from NPs, since ZnO NPs were not detectable in apoptotic cells, and similar cytotoxicity was observed after treatment with $ZnCl_2$ [112]. In primary rat astrocytes ZnO NPs exposure (4, 8, 12 μg/ml for 6–24 h) was found to reduce cell viability, increase lactate dehydrogenase (LDH) release, stimulate ROS generation, and elicit caspase-3 activation in a concentration- and time-dependent manner [121]. Apoptosis was shown by nuclear condensation and poly(ADP-ribose) polymerase-1 (PARP) cleavage. ZnO NPs stimulated the phosphorylation of c-Jun N-terminal kinase (JNK), extracellular signal-related kinase (ERK), and p38 mitogen-activated protein kinase (p38 MAPK). A decrease in mitochondrial membrane potential (MMP) and increase in the expression of Bax/Bcl-2 ratio was also observed, suggesting mitochondria-mediated apoptosis [121]. ZnO NPs (1–100 μg/ml, 24 h) induced concentration-dependent cytotoxicity, disrupted cell membranes and DNA damage in rat primary neuronal cells, human fibroblasts and A549 cells, but not in HepG2 cells and human skin keratinocytes [111]. A time- and concentration-dependent cytotoxicity characterized by apoptosis and increased ROS production

was also observed in ZnO NPs-treated (5–80 μg/ml) C6 glial cells [122]. ZnO NPs exposure (1–100 μg/ml) resulted in increased intracellular Ca^{2+} and ROS levels, decreased intracellular ATP level and upregulated apoptosis markers in mouse microglial cell line [124]. ZnO NPs (1, 5, 10 mmol/l, 24 h) evoked cytotoxicity in the human glioma cell lines (A172, U87, LNZ308, LN18, LN229), but not in normal human astrocytes. Cytotoxicity observed in the glioma cells was related to increased ROS generation, and *N*-acetyl-L-cysteine (NAC) treatment decreased the cytotoxic effect of the ZnO NPs in these cells [123]. ZnO NP-induced cytotoxicity was also observed in microglia (BV-2 cells) exposed to 10 μg/ml ZnO NPs for 2–24 h [125]. ZnO NPs induced parkin protein translocation from the cytoplasm to the mitochondria, implying the involvement of mitophagy in ZnO NPs-induced toxicity [125].

The neurotoxicity of ZnO with four different hierarchical architecture: monodispersed spherical NPs (35 nm), hollow ZnO microspheres (2.7 mm), and larger, prism- and flower-like structures, was evaluated in RSC96 rat Schwann cells [113]. Cells were treated with ZnO at doses 4, 8, 40, 80, 400 μg/ml for 6, 12, 24, and 48 h. ZnO NPs and microspheres displayed significant cytotoxic effects on Schwann cells in concentration- and time-dependent manners, whereas no or low cytotoxic effect was observed when the cells were treated with the prism-like and flower-like ZnO. Cell apoptosis and G2/M cell cycle arrest were observed when RSC96 Schwann cells were exposed to ZnO nanoparticles and microspheres at a dose of 80 μg/ml for 12 h. The time-dependent increase of Zn^{2+} concentration in the culture media suggests that the cytotoxic effects were associated with the decomposition of ZnO hierarchical architecture and the subsequent release of Zn^{2+}, and not exclusively to the nanoparticulated fraction [113].

Neurotoxicity of ZnO NPs was examined in rat pheochromocytoma PC12 and human neuroblastoma SH-SY5Y cells, showing significant cell loss after 24 h treatment at concentration of 0.1 mM in PC12 cells and 1 mM in SH-SY5Y cells [91]. Moreover, when the PC12 cells were treated with 1 mM (81.4 μg/ml) ZnO NPs for 10 min, the endocytosis of ZnO NPs was observed and increased cellular Zn^{2+} levels indicated that ZnO NPs may be converted to Zn^{2+} in endosomes, and then be mobilized into the cytoplasm, leading to Zn^{2+} dyshomeostasis [91]. The cytotoxic and genotoxic effects of ZnO NPs in SHSY5Y cells under different exposure conditions were also investigated by Valdiglesias et al. [119]. Despite the results showed that ZnO NPs (10–80 μg/ml) do not enter the neuronal cells, their presence in the medium induced decrease in cell viability, apoptosis, cell cycle alterations, and genotoxicity, including micronuclei production, H2AX (H2A histone family, member X) phosphorylation and DNA damage (primary and oxidative) in a concentration- and time-dependent manner. Unlike in previously described studies, free Zn^{2+} released from the ZnO NPs was not responsible for the viability decrease [119]. Exposure of SH-SY5Y cells to ZnO NPs (10, 15, 20, 25, 30 mg/ml) resulted in neurotoxicity, as confirmed by LDH activity assay, mitochondria toxicity test (MTT) and Muse™ cell viability assay. Allopurinol, NAC and α-tocopherol protected from ZnO NP-induced cytotoxicity. Electron microscopy revealed typical necrotic characteristics, such as swelling or loss of cell organelles and rupture of the cytosolic or nuclear membrane at 12 h and 24 h after ZnO NPs exposure. Apoptotic changes (annexin V and caspase-3/7 activities) were evident at 12 h and 24 h, but not 6 h after exposure to 15 mg/ml ZnO NPs. PI3 kinase (PI3 K) and p-Akt/Akt (protein kinase B) activities induced by ZnO NPs were significantly decreased by esculetin (antioxidant) or LY294002 (PI3 K inhibitor). Esculetin reduced the production of ROS and the depletion of antioxidant enzymes induced by ZnO NPs. ZnO NPs induced apoptosis via the PI3 K/Akt/caspase-3/7 pathway and necrosis by lipoxygenase (LOX)-mediated ROS production [118]. Treatment with ZnO NPs (1–200 μg/ml) induced cytotoxicity (e.g. increased formation of micronuclei) in the human brain tumor U87 cells in a concentration-dependent manner, but did not affect normal human HEK cells [120]. Different types of ZnO NPs (coated < 200 nm and uncoated < 30 nm) (10–80 μg/ml, incubated for 2, 6 or 24 h) induced cytotoxicity in human olfactory neurosphere-derived (hONS) cells *via* mechanisms associated with cell stress, inflammation and apoptosis [114]. Changes in cytokines IL-6 and IL-8 secretion, increase in caspase-3/7 activity, and phosphorylation of key proteins involved in signaling pathways: MAPK/ERK (pMEK, pERK, pJNK, p-cJUN, p-p38), Akt (pAkt, pBAD) and NF-κB (pNF-κB, pI-κB) has been demonstrated. Microarray RNA analysis revealed that short-term (2 h) exposure to ZnO NPs activated pathways involved in cellular stress responses (e.g. upregulation of Nrf2-mediated oxidative stress response pathway), whereas longer (6 h) exposure affected pathways more related to cell injury and repair. Of note, the cellular response was dependent on NPs surface coatings [114]. ZnO NPs (2.5–10 μg/ml) induced cytotoxicity in rat retinal ganglion cells (RGC-5) and inhibited cell proliferation in a time- and concentration-dependent manner. Moreover, ZnO NPs treatment led to cell cycle arrest of S and G2/M phases, ROS production and increased level of caspase-12 and decreased levels of bcl-2 and caspase-9 [115]. Further, the same group showed that ZnO NPs decreased the MMP in RGC-5 cells [116], ZnO NPs (2.5–10 μg/ml) have been shown to decrease the expression and activity of the plasma membrane calcium ATPase, increase intracellular Ca^{2+} level and disrupt the intracellular calcium homeostasis which might trigger mitochondrial dysfunction, ROS production and cell death [117].

3.2. Titanium dioxide

Titanium dioxide (TiO_2) is widely used as a white pigment in paint, ink, plastic, and paper and as food additive, while the nanosized TiO_2 is also used for its photocatalytic activity in self-cleaning materials and for its UV absorption capacity in sunscreen. Moreover, TiO_2 is included in the list of inactive ingredients by the FDA, considering it safe to be used in dental paste, oral capsules, suspensions, tablets, dermal preparations and non-parenteral medicines. TiO_2 particles are believed to possess low toxicity and thus are widely used in biomedical applications for their excellent biocompatibility. The range of light that is scattered as well as other properties of TiO_2 depend on the particle size. It naturally exists in three crystal structures: anatase (tetragonal), rutile (tetragonal), and brookite (orthorhombic). Anatase and rutile TiO_2 both have a tetragonal structure, while the TiO_6 octahedron of anatase TiO_2 is distorted to be larger than that of the rutile phase [126]. When the size of TiO_2 is diminished to nanoscale (diameter < 100 nm), the bioactivity and physiochemical properties of nano-sized TiO_2 are significantly different from the properties of their bulk analogue [127,128]. Nanoparticles of TiO_2 (TiO_2 NPs) are allowed as sunscreen additives in concentrations of up to 25% [1]. The increased use of nanosized materials has led to an increased burden of TiO_2 NPs in aquatic environments. It is, however, unclear how high levels might occur in environment and if they are harmful to organisms [129]. Analogous to ZnO NPs, the increased demand for products containing TiO_2 is met by increased occupational exposure. Apart from the NIOSH 2011 current intelligence bulletin, to date, no occupational or environmental exposure limits for TiO_2 NPs have been set by any other regulatory agency. The number of workers currently exposed to TiO_2 dust is not available.

Often when a product is so attractive to industry, the understanding about its risk assessments is insufficient and lags behind their rapid advancement and widespread applications [130]. In the case of TiO_2 NPs, it is not yet clear how they are transported into or out of the brain, how they accumulate or what kind of behavioral or cognitive dysfunction they may cause, however the evidence summarized in this (Table 4) and other review articles [130,128,79,149–154] may indicate that their toxic potential remains to be fully elucidated

3.2.1. TiO_2 absorption and transport across the BBB

Dermal absorption is the most relevant entry route of chemicals related to sunscreen use. Several studies have analyzed TiO_2 penetrance into intact or damaged skin using different models. On the whole,

Table 4
Neurotoxic effects of TiO_2 NPs.

Compound	*Exposure model*	*Experimental design*	*Effect*	*Reference*
TiO_2 NPs	Mice	Intratracheal instillations once per week for 4 weeks 13.2 mg/kg	Inflammatory cell aggregation and neuron necrosis. Ti level in the brain 3 days after a single instillation was upregulated by 100%.	[131]
	Wistar rats, male	Intratracheal 0.1, 1.0, 10.0 mg/kg	Ti accumulation in the brain and dose-dependent injury. TiO_2 NPs with diameter of 200 nm did not cause significant alterations in the brain.	[132]
	BBB model based on rat primary endothelial cells (BECs) and astrocytes	Acute exposure: 24 h, 0–500 μg/ml Chronic exposure: 5 days, 0–100 μg/ml	Reduced expression of P-gp, claudin 5, caveolin-1, and caveolin-2 associated with BBB integrity.	[133]
	Fisher F344 rats, male	Intravenous single dose 1 mg/kg	Upregulation of tight junction proteins, modulation of P-gp mRNA expression and persistent brain inflammation markers: IL-1β, IP-10, GFAP and CXCL1. No Ti accumulation in the brain after 24	[134]
	Mice	Intranasal 90 days 2.5, 5.0, 10 mg/kg	Ti accumulation in the brain. Oxidative stress, high levels of lipid, protein, and DNA peroxidation, overproliferation of glial cells, tissue necrosis, hippocampal cell apoptosis. Microarray showed significant alterations of 249 genes expression.	[135]
	Mice, female	Intranasal instillation every other day for 2, 10, 20, 30 days 500 μg	Ti accumulation in hippocampus after 30 days of rutile exposure. Irregular arrangement and loss of neurons, morphological changes and oxidative damage in hippocampus. Increased TNF-α and IL-1β levels.	[136]
	Mice, female	Intranasal instillation every other day for 2, 10, 20, 30 days 500 μg	Imbalance of monoaminergic neurotransmitters, increased NE and 5-HT, while levels of DA, DOPAC, HVA and 5-HIAA were decreased.	[137]
	Wistar rats, male	Intragastrical 60 days 50, 100, 200 mg/kg	Downregulated AChE activity. Increased plasmatic and brain IL-6. Increased GFAP expression.	[138]
	Zebrafish embryos	96 hpf 0.1, 1, 10 μg/ml	Hatching time was decreased, with increase in malformation rate. Accumulation in brain with ROS and cell death in hypothalamus. Alterations in behavior and PD-related genes.	[139]
	Caenorhabditis elegans	24 h 7.7, 38.5 μg/ml	GC–MS-based metabolomics perturbations mainly occurred in TCA cycle, glyoxalate, tricarboxylate, inositol phosphate, Gly, Ser, Thr, Gln, and Glu metabolism.	[140]
	Caenorhabditis elegans	96 h under dark or light conditions 1–100 mg/l	Light exposure induced the production of ROS and increased toxicity from a median effect concentration of more than 100 mg/l to 53 mg/l.	[141]
	D384 glial cell line and SH-SY5Y human neuroblastoma	24 h 15, 31 μg/ml,	Concentration- and time-dependent alterations of mitochondrial function, cell membrane damage, inhibition of cell proliferation. Effects dependent on TiO_2 size. Neuronal cells were more sensitive than glial cells.	[142]
	U373 human glial cells and C6 rat glial cells	24–96 h 2.5–40 μg/cm^2	DNA fragmentation assessed in U373 cells, but not in C6 cells. Morphological changes associated with depolymerization of F-actin, apoptotic cell death.	[143]
	U373 human glial cells and C6 rat glial cells	2–24 h 20 μg/cm^2	Increased expression of antioxidant enzymes: GPx, CAT, SOD2, lipid peroxidation and mitochondrial depolarization.	[144]
	PC12 rat pheochromocytoma	6–48 h 1–100 μg/ml for	Apoptosis prevented by a ROS scavenger, N-MPG.	[145]
	Co-culture of PC12 cells with primary rat microglia	24–48 h 0.25–0.5 mg/ml	Supernatant from TiO_2 NPs treated microglia caused significant cytotoxicity in PC12 cells.	[146]
	PC12 cell line	24 h 1–125 μg/ml	Decreased cell viability, mitochondrial impairment and decreased DA levels.	[139]
	BV2 microgial cells	6, 18 h 2.5–120 ppm	Release of ROS, mitochondrial hyperpolarization	[147]
	BV2 microgial cells, N27 neurons, primary cultures of rat striatum	2, 6, 24, 48 h 2.5–120 ppm	Microglia generated ROS damages neurons in complex primary cultures. No cytotoxicity in isolated N27 neurons	[148]

Abbreviations: 5-HIAA: 5-hydroxyindole; 5-HT: 5-hydroxytriptamine; AchE: acetylcholine estarese; BBB: blood-brain barrier; CAT: catalase; CXCL1: chemokine C-X-C motif ligand 1; DA: dopamine; DOPAC: 3,4-dihydrophenylacetic acid; GC–MS: gas chromatography mass spectrometry; GFAP: glial fibrillary acidic protein; Gly: glycine; Gln: glutamine: Glu: glutamate; GPx: glutathione peroxidase; HVA: homovanillic acid; hpf: hours post fertilization; IL-1β: interleukin-1β; IL-6: interleukin-6; IP-10: interferon gamma-induced protein 10; NE: norepinephrine; N-MPG: *N*-(2-mercaptopropionyl)glycine; NPs: nanoparticles; PD: Parkinson's disease; P-gp: P-glycoprotein; ROS: reactive oxygen species; Ser: serine; SOD2: superoxide dismutase 2; TCA: tricarboxylic acid cycle; TNF-α: tumor necrosis factor α; Thr: threonine; Ti: titanium; TiO_2: titanium dioxide.

studies demonstrated that TiO_2 NPs cannot permeate intact and damaged skin and can be found only in the stratum corneum and epidermis, without reaching the brain or peripheral organs [155–158]. Furthermore, low cytotoxicity observed in human HaCaT keratinocytes, suggests a low toxic potential of these nano-compounds at the skin level. These results can be explained by the great stability and low ionizing capacity of these particles and are in accordance with several studies in the literature [159–161]. However, studies simulating real-world scenarios on sunburned skin, with UV exposure in long-term chronic exposure conditions need to be conducted to assure the safety of TiO_2 in sunscreen.

Long-term intake of TiO_2 NPs at low doses was assayed in rats. Animals received 1 or 2 mg/kg TiO_2 suspension per day for 5 consecutive days. On the sixth day their gut tissue was analyzed for TiO_2 content and possible adverse effects. A sex-specific effect on villus cells proliferation was observed in male rats, indicating a potential role for the endocrine system in this process. Oxidative stress in intestinal cells was transient and decreased after 24 h [162].

NPs have the ability to cross the BBB. While this may be desirable for drug-delivery systems [163], it can also pose a risk of unwanted accumulation of potentially harmful chemicals in the brain. In an *in vivo* study by Li et al. (2010), mice were chronically exposed to TiO_2 NPs of

3 nm diameter (4 mg/kg) *via* intratracheal instillations. After 4 weeks, inflammatory cell aggregation and neuron necrosis were present. The amount of Ti in the brain was measured by inductively coupled plasma mass spectrometry (ICP-MS) 3 days after a single instillation of 4 mg/kg TiO_2 and found to be upregulated by 100% (120 ng/g Ti in controls, compared to 240 ng/g in treated animals) [131].

3.1.2. TiO_2 neurotoxic effects in vivo

The diameter of TiO_2 NPs seems to be important for its carriage. Rats were treated with TiO_2 NPs (0.1, 1, 10 mg/kg) suspension of different diameters (10, 20, and 200 nm) through intratracheal treatment. Seventy-two hours later, TiO_2 NPs with diameters of 10 and 20 nm were both transported into the brain, inducing dose-dependent alteration in pro-inflammatory markers (TNF-α, IL-1β and IL-10). However, TiO_2 NPs with diameter of 200 nm did not cause significant alterations in the brain [132]. In a BBB model based on rat primary endothelial cells (BECs) and astrocytes, TiO_2 NPs (acute exposure for 24 h with 0–500 μg/ml or chronic exposure for 5 days with 0–100 μg/ml) could not only pass through the BBB but also disrupt its integrity by reducing the expression of P-glycoprotein (P-gp), claudin 5, caveolin-1, and caveolin-2, which are associated with the BBB integrity [133].

The effects of TiO_2 NPs on the brain may not occur by a direct interaction between the chemical and the BBB. [134] described the *in vivo* uptake and clearance of TiO_2 NPs by BECs and demonstrated a Ti burden in the liver, spleen and lungs up to a year after intravenous (i.v.) administration of TiO_2 NPs (1 mg/kg) to rats, with a very low clearance rate. At this dose, the authors did not observe Ti accumulation in the brain, however upregulation of tight junction proteins, modulation of P-gp mRNA expression and persistent brain inflammation markers such as IL-1β, IP-10 (interferon gamma-induced protein 10), GFAP (glial fibrillary acidic protein) and CXCL1 (chemokine C-X-C motif ligand 1) were observed. The authors suggested that TiO_2 NPs can exert an indirect effect on the CNS that seems dependent on circulating biomarkers potentially released by organs accumulating Ti [134].

Brain levels of 0.05–0.15 μg/ml were detected after intranasal administration of 2.5–10 mg/kg TiO_2 NPs for 90 consecutive days in association with oxidative stress, high levels of lipid, protein, and DNA peroxidation, overproliferation of glial cells, tissue necrosis, hippocampal cell apoptosis in mice. Microarray showed significant alterations of 249 genes expression involved in oxidative stress, apoptosis, memory and learning, brain development, lipid metabolism, DNA repair, signal transduction, immune response and response to stimulus in the brain-injured mice. Some of these genes may be potential biomarkers of brain toxicity caused by TiO_2 NPs exposure [135].

Female mice were intranasally instilled with 500 μg of two types of well-characterized TiO_2 NPs (i.e. 80 nm, rutile or 155 nm, anatase) every other day for 2, 10, 20 or 30 days. High Ti accumulation (ranging from 0.13 to 0.3 μg/ml) was more pronounced in hippocampus after 30 days of rutile exposure, compared to other brain regions (cerebellum, olfactory bulb or cortex). Histological analysis revealed irregular arrangement and loss of neurons, morphological changes and oxidative damage in the hippocampus. Increased TNF-α and IL-1β levels were also observed [136]. Translocated TiO_2 NPs (500 μg) caused imbalance of monoaminergic neurotransmitters, with significantly increased NE and 5-HT levels, while levels of DA, 3,4-dihydrophenylacetic acid (DOPAC), homovanillic (HVA), and 5-hydroxyindole acetic acid (5-HIAA) were decreased [137].

Acetylcholinesterase activity was evaluated in plasma and brain of rats after 60 days intragastric treatment with anatase TiO_2 NPs (50, 100, 200 mg/kg). Plasmatic AChE activity was decreased with the increasing TiO_2 NPs doses. The higher doses of TiO_2 NPS caused a significant decrease in the AChE activity in the brain. These effects were accompanied by IL-6 increase in the brain and plasma and increased levels of GFAP in cerebral cortex, suggesting neuroinflammation [138]. Cognitive function may have also been compromised in this model, but behavioral experiments are lacking. Studies that describe the specific proteins that carry TiO_2 to and/or from the brain are lacking.

In zebrafish larvae exposed to environmentally relevant concentrations (1–10 μg/ml) of TiO_2 NPs induced Parkinson's disease (PD)-like symptoms, with locomotor alteration, reduced DA, Lewy bodies formation and alterations in mRNA levels of *pink1, parkin* and *α-syn,* that were significantly increased in a dose-dependent manner. The authors observed TiO_2 accumulation in brain and oxidative stress, with cell death in hypothalamus. To further investigate TiO_2 effects on DAergic cells, the authors exposed PC12 cells to 1–125 μg/ ml TiO_2 NPs for 24 h. Cell viability was decreased at the higher dose and similarly to zebrafish, DA levels were decreased. This study suggests a role for TiO_2 exposure in the development of PD [139].

Caenorhabditis elegans (*C. elegans*) is an excellent biological model organism for environmental risk assessment. Gas chromatography mass spectrometry (GC–MS)-based metabolomics approach was used to understand the toxicity of sub-lethal concentrations (7.7 and 38.5 μg/ml) of TiO_2 NPs (< 25 nm). Most of the significant perturbations occurred in organic acids (citric, lactic, fumaric, succinic and malic acids) and amino acids. Differential marker metabolites identified from the metabolomic analysis suggested that the disturbances, mainly occurred in metabolism of: glyoxalate, inositol phosphate, tricarboxylate, glycine (Gly), serine (Ser) threonine (Thr) glutamine (Gln) and Glu [140]. Toxicity of bulk-scale (~160 nm) and nanoscale (21 nm) TiO_2 was tested under dark and light conditions. Light exposure induced the production of ROS by nanoscale TiO_2 and increased toxicity of the nanomaterial from a median effect concentration of more than 100 mg/l to 53 mg/l. The observation that light increased the toxicity of the highly photoactive nanoscale TiO_2 suggests that ROS play a role in the photoactivated toxicity of the nanomaterial. No evidence of intracellular oxidative stress was found. Because TiO_2 accumulated in worm intestines, as observed by microscopy, the authors suggested that ROS were formed extracellularly in the apical surface of the worms' intestinal cells [141].

3.2.3. TiO_2 neurotoxic effects in vitro

In vitro human cell models may represent a valid instrument to investigate TiO_2 NPs effects on CNS and to determine their underlying mechanistic processes, providing information about doses of exposure. [142] demonstrated concentration- and time-dependent alterations of the mitochondrial function on D384 (glial cell line) and SH-SY5Y (neuronal cell line) cells starting at the dose of 31 and 15 μg/ml TiO_2 (15–69 nm in diameter, anatase isoform), respectively, after 24 h exposure. Neuronal cells were more sensitive than glial cells. These effects were more pronounced in cells exposed to NPs compared to TiO_2 bulk, where with the latter effects appeared only at the highest doses (125 and 250 μg/ml) after 24 and 48 h, similarly in both cerebral cell lines. Cell membrane damage was present in both cell lines starting at 125 μg/ml after 24 h exposure and also dependent on TiO_2 size. TiO_2 NPs were potent inhibitors of cell proliferation in human CNS cells after prolonged exposure (up to 10 days) at doses ranging from 0.1 to 1.5 μg/ml [142].

TiO_2 NPs induced apoptosis in both human (U373) and rat (C6) glial cells at 96 h of treatment, evidenced by active caspase-3 starting at 5 $\mu g/cm^2$. At this concentration, DNA fragmentation assessed with the TUNEL assay was observed in U373 cells, but not in C6 cells. Morphological changes associated with depolymerization of F-actin were found, accompanied by apoptotic cell death [143]. In a similar protocol of exposure, TiO_2 NPs induced oxidative stress in U373 and C6 glial cells, mediating changes in the cellular redox state, which was correlated with increase in antioxidant enzyme expression (GPx, catalase and SOD2) and lipoperoxidation. Mitochondrial depolarization was also observed. These effects occurred within 24 h exposure to 20 $\mu g/cm^2$ TiO_2 NPs [144]. Oxidative stress was also present in rat PC12 cells exposed to TiO_2 NPs 50 μg/ml for 24 h (P25 type, 21 nm in average size) and *N*-(2-mercaptopropionyl)-glycine (N-MPG), a kind of ROS scavenger, prevented apoptosis in this model [145], indicating that

oxidative stress is an important factor in TiO_2 NPs-induced neurotoxicity.

P25 (an uncoated photo-active, largely anatase form of nanosize TiO_2, not used in sunscreen) stimulates ROS in BV2 microglia at 2.5–120 ppm, starting at 5 min exposure [147] and was later found to be nontoxic to isolated N27 neurons. However, P25 rapidly damages neurons at low concentrations (5 ppm, 6 h) in complex brain cultures of striatal cells, suggesting that microglial generated ROS damages neurons [148]. Ability of activated microglia to induce death of target cells was studied by Xue et al. (2012) in co-culture with PC12 cells. Supernatant from TiO_2 NPs-treated (0.25–0.5 mg/ml) microglia caused significant cytotoxicity in PC12 cells. The authors suggested that TiO_2 NPs stimulated microglia produced inflammatory factors, which caused PC12 cells cytotoxicity [146].

Recent studies report endoplasmic reticulum stress (ER stress) as a common response to NPs related toxicity. The ER stress also known as unfolded protein response (UPR) refers to an important cellular self-protection mechanism, which can be activated to counteract the cell situation of stress (overloading proteins or direct ER damage). ER stress was observed in human epidermal keratinocytes (HEKn) and human umbilical vein endothelial cells (HUVEC) exposed to up to 20 $\mu g/cm^2$ for 16–24 h [164], [165]. Analogous to neural cells, oxidative stress was also observed in different cell types, demonstrating that TiO_2 can affect a wide range of tissues. For example, the lung is a primary target of NPs exposure, especially in occupational settings. In the case of TiO_2 inhalation, nanoscale particles may deposit in the lung interstitium and cause inflammation [166]. Several excellent reports are available on TiO_2 effects on peripheral tissues, such as skin [167], kidney [168], liver [169], lung [170] and vascular endothelial cells [171].

4. Conclusions and future perspectives

Although some UV-related pathologies could be prevented by applying sunscreen, the efficiency and safety of these products is questionable. As the use of sunscreen is continuously increasing worldwide, so do the levels of environmental accumulation and human, and wildlife exposure. Whether concentration resulted from daily use and/or environmental contact possesses a realistic hazard to humans and other organisms is still unknown. Numerous studies raised concerns about the association between exposure to substances commonly found in sunscreens and endocrine and developmental impairments. In this review, the potential neurotoxicity of such substances is presented and the question of cost-benefit is raised regarding large scale use of sunscreen in its current composition. Although most studies reviewed in this paper reported adverse neurotoxic effects of UV filters at concentrations substantially higher that those observed in environment and human tissues, these studies should not be disregarded, as they afford potential pathomechanisms which might occur in other conditions or sensitive populations. It is noteworthy, that gene x environment interactions *vis-à-vis* toxicity of sunscreen components has yet to be studied. Unfortunately, the effects of repeated, long-term and low-dose exposures to single compounds and mixtures of various UV filters is also poorly studied. More studies are needed to evaluate the realistic hazard of contemporary sunscreens. Furthermore, it is also timely and meritorious to advance studies on alternative, safer and more efficient UV filters.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgment

This work has been supported by the National Institutes of Health [grant numbers NIEHS R01ES07331, NIEHS R01ES10563 and NIEHS R01ES020852].

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