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Review

Use of Cosmetics in Pregnancy and Neurotoxicity: Increased Risk of Congenital Enteric Neuropathies

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Abstract: Pregnancy is a specific vulnerable period for the growing fetus when exposure, especially in the early phases to toxic agents can decisively harm embryo development and compromise the future health of the newborn. The inclusion of various chemical substances in personal care products (PCPs) and cosmetic formulations can be associated with disruption and damage to the nervous system. Microplastics, benzophenones, parabens, phthalates and metals are among the most common chemical substances found in cosmetics that have been shown to induce neurotoxic mechanisms. Although cosmetic neurotoxin exposure is believed to be minimal, different exposure scenarios of cosmetics suggest that these neurotoxins remain a threat. Special attention should be paid to early exposure in the first gestation weeks, when critical processes, like the migration and proliferation of the neural crest derived cells start to form the ENS. Importantly, cosmetic's neurotoxins can cross the placenta barrier and so affect the future embryo, but are also secreted in the breast milk, so that babies remain exposed for longer periods, even after birth. In this review we explore how neurotoxins contained in cosmetic and PCPs may have a role in the pathogenesis of various neurodevelopment disorders and neurodegenerative diseases, and therefore also in congenital enteric aganglionosis as well as in postnatal motility disorders. Understanding the mechanisms of these chemicals used in cosmetic formulations and their role in neurotoxicity is crucial to determining the safety of use for cosmetic products during pregnancy.

Keywords: hirschsprung disease (HSCR); Congenital enteric neuropathies; enteric nervous system (ENS); pregnancy; neurotoxins

1. Introduction

1.1. Cosmetics Contain Neurotoxins

Cosmetics have been used on human bodies around the world since as early as 3000 B.C.E to cleanse, alter appearances, and enhance beauty [1]. In the modern cosmetic industry, the formulations of cosmetic products include an increasing number of chemical substances to improve product quality and effectiveness. However, many of these substances included can be characterized as neurotoxicants that have capabilities of damaging and disrupting cellular activity in the brain and nervous system.

The diversity of toxic substances included in cosmetics is impressive: paraformaldehyde, benzalkonium chloride, micro/nanoplastics, benzophenones, parabens derivates, phthalates and trace heavy metals among many others. These common compounds have shown a variety of mechanisms that have potential to induce cytotoxicity, genotoxicity and importantly here, neurotoxicity [2] (see Table 1).

While regulatory agencies have already banned certain substances from cosmetic formulations, the presence of the neurotoxins can still be present in detectable amounts due to contamination and different country regulations [3]. The extent of these various cosmetic substances and their exposure and concentration impact is not entirely understood, however there is correlation between the substance mechanisms and their neurotoxic effects.

Table 1. Most common neurotoxic components in Cosmetics and Personal Care Products.

Compound	Types	Found in*	Mechanisms	References
Microplastics Nanoplastics	Polyethene (PE) Polypropylene (PP) Polyvinylchloride (PVC) Polystyrene (PS) Polylactic (PLA)	Exfoliating Mosturizes Toothpaste Lipsticks Nail polish Packages	Inflammation Neurotransmitters disruption ↑Oxidative stress AChE Inhibition Cellular toxicity Lipid peroxidation Endocrine disruptors	[4] [4–6] [4–8] [4] [4,9] [5] [6]
Parabenes	Methylparaben (MtP) Butylparaben (BuP) Ethylparaben (EtP) Propyl paraben (PrP)	Shower gel Body cream Hair products Deodorant Fragances	Endocrine disruption Neurotoxicity ↑Oxidative stress Microbiote alterations	[9,10] [10–13] [13] [14]
Benzophenones	BP-1 BP-2 Oxybenzone-3/BP-3 BP-4	Sun blockers Fragances	Neuronal migration MAPK/ERK signaling AChE Inhibition Neurotransmitters disruption	[15] [16] [17] [18]
Phthalates	Di-ethyl-phthalate (DEP) Di-n-butyl phthalate (DBP) Dimethyl-phthalate (DMP)	Eyeshadows Fragances Nail polish Moisturizers Hair products	Endocrine disruption ↑Oxidative stress AChE Inhibition Microbiote alterations Cellular apoptosis	[19–21] [4] [4] [22] [20,23]
Metals Trace metals	Lead (Ld) Aluminium (Al) Cadmium (Cd) Nickel (Ni) Arsenic (As) Mercury (Hg) Manganese (Mn) Titanium dioxide (TiO2) Chromium (Cr) Iron (Fe) Copper (Cu) Cobalt (Co)	Lipsticks Eyeshadows Lotions Powders Additives Mascaras Foundations Sun blockers Toothpaste Eye products Additives	↑Oxidative stress AChE Inhibition Autophagia Apoptosis Microbiota alterations Blocking Ca2+/K+ channels Neurotransmitters disruption Endocrine disruption	[4,24–26] [4,27] [24,28] [29,30] [22] [31] [32] [33]

* (list of mainly products containing them, among many others).

Prior to the 1960s, the harmful effects of cosmetics were unknown. It was believed that cosmetics would remain on the surface of the body and exposure to the chemical compounds from the formulations was limited due to the protective barrier function of skin [34]. However, given the multiple exposure scenarios of cosmetics, systemic exposure of toxins following cosmetic application has been proven possible. Systemic exposure can happen through percutaneous penetration of products applied to the skin, inhalation of spray products, or ingestion of products applied around the oral cavity. The degree of systemic exposure is unclear and can depend on several factors including the concentration of the formulation, application area, amount and frequency of application, and duration of product use [33]. The complete formulation of the cosmetic is also important to consider as the inclusion of surfactants and co-solvents can help enhance skin penetration and dermal absorption of topically applied cosmetics [35]. These variety of factors make it difficult to determine the concentration extent in which humans may be exposed to the toxins.

Given that most cosmetic products are applied topically, dermal absorption is the most common route of exposure. Once the toxin passes through the epidermis it reaches the blood stream where it can then travel everywhere. Truly, toxins have been detected in human fluids and several tissues, which demonstrates their entirely dissemination through the human body [36].

1.2. Neurotoxins Pass the Placental Barrier and Accumulate in Breast Milk

Common neurotoxic ingredients in cosmetics have been detected in a variety of human tissues, including in maternal blood and urine, the placenta or even the umbilical cord (see Table 2).

First, neurotoxicity can damage the blood brain barrier (BBB) to the barrier structure or disruption of barrier regulatory functions [37]. In addition to crossing the blood brain barrier, many neurotoxins, such as parabens and ultraviolet filters [38], can cross placental barrier making prenatal exposure a concern. Prenatal exposure to toxins may be especially harmful given that the developing brain is a more susceptible target to toxicity as neurons proliferate, migrate and forge important synaptic connections to create an optimum adult brain structure [39].

Similarly, neurotoxic metal concentrations were measured in placenta tissue samples and demonstrated to affect birth outcome, where some metals adversely affected fetal growth [40]. Actually, metals were associated to derived neurodevelopmental and cognitive problems in children [41]. Benzophenone-3 and methylparaben exposure also correlated to lower birthweight in a large cohort analysis of American children [42].

Unfortunately, the toxicity of these chemicals is not limited to pregnancy: there is evidence on the presence and concentrations of bisphenols, parabens (PBs), and benzophenones (BPs) in human milk [43], which implies that the babies are exposed even after the gestational period.

Table 2. Detected mother/child transmission.

Detected in	Compound	References
Placenta barrier	Microplastics	[44–46]
	Parabens	[38]
	Benzophenones	[38]
	Metals	[40]
Breast milk	Microplastics	[43]
	Bisphenol	[43]
	Parabens	[43,47]
	Benzophenones	[43]
Maternal Urine/Blood	Benzophenones	[15,48]
	Parabens	[10]
Umbilical cord	Benzophenones	[48]
Intestine	Microplastics	[6,45,49,50]
	Parabens	[36]
	Phthalates	[22,36]
	Metals	[22]
Brain	Microplastics	[4,6,45]
	Parabens	[13]
	Benzophenones	[18]
	Phthalates	[22]

	Metals	[22]

2. Prenatal Exposure and Risk of Enteric Neuropathies

Maternal exposure to environmental toxics represents a major risk for the health of the newborn (see Table 3). Pregnant women are exposed daily (even unconsciously) to many toxicants through air, water, food, drugs, but also cosmetics. Smoking and alcohol are also well-known factors that compromise the development severely. The toxicity of some compounds is since years well-known by the society, thus it is easy to label them as negative and dangerous for pregnant women, for instance ethanol consumption [51]. Others are recognized as adverse, but not so easy to avoid, like the exposition to pesticides like glyphosate [52,53] or to microplastics [44,54]. However, the harmfulness of many compounds is not so obvious for the future mothers, although they are already related to neuronal damage, like commonly used drugs such as ibuprofen [55], anti-depressants [56,57], or cosmetics ingredients like oxybenzones (BP-3) [18,58].

Not only the consumption of cosmetics by pregnant women is quite frequent [59,60], but also a recent study collecting questionnaires from pregnant women reported that their risk perception seems to be low [61].

Aganglionar diseases, like Hirschsprung disease (HRSC, incidence 1/5,000), are congenital gastrointestinal disorders in which the intrinsic gastrointestinal innervation of the colon is absent or severely affected due to a failure of enteric neural crest cells migration during early embryogenesis (from 5 to 12 weeks) [62]. The regulation of this process is critical, and many different genes and proteins are involved in both migratory and colonization processes [63]. Currently, the only treatment is primarily surgical removal of the aganglionic bowel. Nevertheless, patients suffer complications such as the toxic megacolon and enterocolitis, leading to poor long-term outcome [64].

Although some genes have been identified, the condition is not fully explained by the genetic load [65,66] and many non-genetic factors also affect the development of the enteric nervous system (ENS) and so, impact the risk [62,67]. Altogether, these point out to an enviromental factor as a disease co-cause or trigger, suggesting that some cases of HSCR might be preventable [68].

While HSCR is a severe disease with huge impact on life quality, there might also be minor impacts on the ENS development, that are not leading to obvious damages, but rather to mild clinical symptoms such as continuous obstipation or else.

Consequently, the maternal exposure during early pregnancy is critical for developing congenital aganglionosis, or in milder cases, for the development of less severe motility disorders in children.

Cosmetic toxicants have been pointed as disruptors of the gut microbiota, namely to gastrointestinal dysbiosis, which can later cause neurotoxicity [36]. Indeed, alterations in the gut microbiome in combination with the individual genetics can transform the Enteric Nervous System (ENS), central nervous system and the immune system, impair barrier function, and contribute to various disorders such as irritable bowel syndrome, inflammatory bowel disease or neurodegeneration and mental issues [22,69].

Table 3. Neurotoxic compounds and associated embryo/development complications.

Compound	Impairment	Complications	References
Microplastics	Endocrine Disruption Neurotoxicity Inflammation Oxidative stress	Neurodevelopment	[6,50,70–72]
		Cognitive	[6,50,70–72]
		Behavioral	[6]
		Microbiota dysbiosis	[50,70–72]
		PLD	[6]
Benzophenones	Cellular migration	HSCR	[73]
	Neurotoxicity	Cognitive	[74]
Parabenes	Endocrine Disruption	Children overweight	[10]
	Oxidative stress	ASD	[75]
	Mitochondrial dysfunction	Cognitive	[76,77]

	Neuroinflammation		
Phthalates	Endocrine disruption Apoptosis Oxidative stress Microbiota dysbiosis	ADHD behavioral profile	[78]
		Anxiety	[79]
		Mental disorders	[22]
Metals	Autophagia Apoptosis Oxidative stress Microbiota dysbiosis	Memory, motor skills	[24]
		PD, AD	[24,80]
		Cognitive impairment	[33,81]
		ALS	[25,82,83]
		Mental disorders	[22]

* Parkinson-like Disease (PLD), Hirschsprung Disease (HSCR), Autism Spectrum Disorders (ASDs), Attention-deficit Hyperactivity Disorder (ADHD), Parkinson Disease (PD), Alzheimer Disease (AD), Amyotrophic Lateral Sclerosis (ALS).

3. Overview of Main Neurotoxins Contained in Cosmetics and PCPs

3.1. Microplastics and Nanoparticles

Microplastics (5 mm at 0.1 µm) and nanoplastics (<0.1 µm) had been extensively used as ingredients in personal care products (PCPs) and cosmetics [9,84,85]. Furthermore, microplastics have emerged as new huge and ubiquitous health and environmental problem all over the world [45]. They also pass into the food chain from the food packages, the cooking pots and the plastic bottles almost inevitably [49,86]. As a result, we are eating and drinking them every day and they accumulate in our intestines and organs [49,50,86].

Harmful effects of microplastic can be even worse, because they act as carriers of other dangerous chemicals such us heavy metals (Al, Cd, Co, Cr, Cu, Hg, Mn and Pb), polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), pesticides and persistent organic pollutants (POPs). All these can bioaccumulate and impair oxidative stress and cellular toxicity [9].

Still, microplastics have been reported to induce cross the BBB, induce inflammation and oxidative stress, disrupt neurotransmitters and so, lead to neurotoxicity, brain damage and impaired neuronal development in different animal models [4–8]. Moreover, microplastics effects can contribute to the development of other diseases such as central nervous system inflammation and Parkinson 's-like neurodegenerative disorders [6]. In addition, microplastics have been found to accumulate in the digestive system, where they damage the gut barrier and cause intestinal problems like inflammation and microbiota dysbiosis [50,70–72], which can induce neurotoxicity and neurodegeneration [22,69].

Besides, maternal exposure to microplastics like polystyrene have already been proved to cause metabolic disorders in the offspring [54], and microplastic nanoparticles are able to cross the placenta barrier and also to accumulate into it [44–46].

Altogether, microplastics can nave neurotoxic activity, affect the nervous system and reach the fetus, so they are good candidates to be disruptors of the development of the enteric nervous system and the intestinal innervation during fetal development.

3.2. Parabens

Parabens (PBs) are commonly used in the cosmetic industry as preservatives. Mainly, PBs are already reported to be important hormonal disruptors and to interact with estrogen, androgen and thyroid receptors [9].

Regarding this, we should not forget that pregnancy is a particularly vulnerable period to the potential risks of the endocrine disruptors. In a study that linked maternal parabens exposure to children obesity, parabens have been detected in maternal urine samples at 34th week of gestation, contained detectable paraben concentrations. Of notice, mothers that used paraben-containing cosmetic leave-on products on a daily basis had significantly higher urinary paraben concentrations [10]. However, exposition to PBs continues immediately after birth: PBs can also be found in

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breastmilk [43] and in processed infant food products, like milk-based infant formula and cereal-based complementary food [47].

Several works have reported PBs neurotoxicity. For instance, by interacting with the estrogen receptor, butylparaben (BuP) can drive apoptosis in primary cortical neurons in vitro, and so, was appointed as potential contributor to neurodegeneration in the brain [87]. In rat models, BuP displayed several neurotoxic activities, such as increased oxidative stress, decreased reduced glutathione levels and elevated oxidised glutathione, mitochondrial dysfunction, and neuroinflammation, among others [75]. Other studies using zebrafish embryos demonstrated the neurotoxicity of methyl- (MtP), ethyl- (EtP), and propyl-parabens (PrP) [88]. Also, MtP and BuP produced neurobehavioral toxicity in adult samples of zebrafish [11,12]. In animal models, prolonged exposure to PBs provokes microbiota alterations [22], which can cause ENS toxicity [69].

Concerning children, PBs are associated to attention and neurocognitive problems in small children [76,77] and were also linked to sensorineural hearing loss [89]. In addition, parabens have been related to autism spectrum disorders (ASDs) [75].

Hence, endocrine disruptors like PBs can be detected in high concentrations in expecting mothers, are neurotoxic and can induce neurodevelopmental problems in children.

3.3. Benzophenones

In the recent years, benzophenones, mainly ingredients of sunscreen cosmetics, have also been reported as neurotoxicants. Of them, Benzophenone-3 (also known as Oxybenzone 3, BP-3) is one of the most widely used UV filters, showing weak estrogen and strong anti-androgenic effects [15]. Also, it is small enough to pass through skin and placenta barriers, and it has been detected in the urine/blood of pregnant women as well as in fetal and umbilical cord blood [48]. Besides, BP-3 has good permeability through the BBB [18].

Studies using zebrafish models have shown that BP-3 exposure drives to altered enzymatic activity (Glutathione S-transferase -GST, catalase -CAT, and acetylcholinesterase -AChE), neurotoxicity and behavioral alterations [17]. Notably, BP-3 treatment in zebrafish resulted in enteric neurons loss and impairment of the ENS development by inhibiting MAPK/ERK signaling pathway [16]. Also, prenatal exposure to BP-3 dysregulates expression of neurogenesis- and neurotransmitter-related genes in the offspring [18]. In pregnant mice, exposure to BP-3 concerned placental function and morphology [90].

Regarding benzophenones exposition and consequences to human health, prenatal exposition to benzophenones has been related to neurocognitive problems in children [77].

Furthermore, BP-3 was proved to disrupt neuronal migration in in vitro neuronal cultures [15]. Maternal exposure to BP-3 was also epidemiologically associated to a higher Hirschsprung disease incidence in children, as higher urine concentrations correlated with higher HSCR [15]. Aside from that, under normal conditions BP-3 can travel to maternal blood reaching the fetus at high enough levels to inhibit migration of neural crest cells during critical embryonic development [15,48].

Therefore, the use of benzophenones during pregnancy does increase the risk of enteric aganglionosis in children.

Box 1. Sunscreen cosmetics show increasing risk of neurotoxicity

As many metals are used as UV filters, there is has been found to be an increasing risk in the toxicity when reacting with UV rays. Titanium dioxide, commonly used in sunscreen, exposure to UV causes the formation of hydroxyl radicals and leads to oxidation damage to DNA. This increases the risk for induced neurotoxicity if it absorbed through the skin [98]. In the context of sunburn, it should also be recognized that damaged sunburnt skin may be more susceptible to chemical absorption [99]**.** In conjunction with both factors, nanometals have also became incorporated into cosmetic formulations, specifically like TiO_2 in sunscreen, to achieve higher quality products. This poses a further threat to induce neurotoxicity. While there are unknowns about the impact of nanoparticles have on the body, the small size of these substances suggest that it allows for deeper skin penetration [100]**.** In addition, oxybenzones like BP-3, usually present in sunblockers, have been already associated to congenital enteropathies like Hirschsrpung disease [15,48]. Given these factors together, it is important that the neurotoxic effects of sunscreen products should be considered more closely in the future.

3.4. Phthalates

Phthalates are a family of chemicals used as plasticizers and solvents in various cosmetic products including eyeshadows, perfume, nail polish, moisturizers, and more [91]. Specifically, low molecular weight phthalates, Di-ethyl-phthalate (DEP), Di-n-butyl phthalate (DBP), and Dimethyl-phthalate (DMP) have a history of being used in cosmetic formulas [92]. There are several neurotoxic mechanisms of action that have been associated with phthalates including endocrine disruption, oxidative stress and cellular apoptosis.

Thyroid hormone regulation plays a crucial in brain development, and it can be disrupted by phthalate exposure. DBP exposure can lead to thyroid receptor T3 inhibition and thyroid hormone disruption [93,94]. DBP may also disrupt estrogen receptor signaling [95]. Like thyroid hormone signaling, estrogen also has effects on brain neurogenesis and neuroplasticity [95].

In addition to hormone signaling disruptions, phthalates have also been shown to increase oxidative stress by different mechanisms. DBP has been proved to increase ROS levels in vivo [19] and in vitro [20], as well as to increase of malondialdehyde (MDA) and nitric oxide (NO) levels in rats [21].

Induced apoptosis is another supported neurotoxic mechanism of phthalates [20]. In a rat model, prenatal DBP exposure resulted in caspase-3 activation as well as hippocampal neuron loss and structural alteration [29].

Numerous studies have linked phthalate exposure to human neurodevelopment disorders, being microbiota dysbiosis the probable nexus in-between [22]. For instance, attention-deficit hyperactivity disorder (ADHD) behaviors such as inattention and impulsivity have shown to have a positive correlation with DBP phthalate metabolite concentration found in urine of school-age (8-11 years) human subjects [96]. In addition, Engel et al. evaluated various parent-rated behavior differences of children ages 4 to 9 in relation to prenatal phthalates metabolite concentration in urine. They found mothers with higher metabolite concentrations had children with poorer scores associated with aggression, conduct, attention, externalizing problems, and overall, all behavior symptoms index summary score. These are results are also suggestive of the ADHD behavioral profile [97]. Animal behavior models have also agreed with these findings showing increases spontaneous motor activity in rats following DBP exposure, indicating the hyper-activity behavior that is common in ADHD [78]. Anxiety like behaviors have also been demonstrated to increase following DBP exposure in mice using an elevated plus maze and open-field test [79]. While these studies have agreed with the implications that phthalate neurotoxic mechanisms may lead to developmental disorders, there are other developmental disorders such as autism spectrum disorder that have shown contradicting results in association with phthalates exposure [23].

Given that phthalates are verified neurotoxicants with proved neuronal impairment consequences, they are good reasons to analyze their neurotoxic effects during ENS development.

3.5. Metals

Another dangerous neurotoxic component included in cosmetic formulation are metals including both heavy metals like lead (Pb), cadmium (Cd), nickel (Ni), arsenic (As), mercury (Hg), and manganese (Mn) and trace metals like chromium (Cr), iron (Fe), copper (Cu), and cobalt (Co). These are found in different cosmetics at various concentrations often used for pigmentation in makeup products or as UV filters in sunscreen [3]. Human exposure to metals has been shown to induce neurotoxicity through different mechanisms such as autophagy, synaptic transmission and oxidative stress. Autophagy occurring in the brain is a mechanism of neurodegenerative disorders such as Parkinson's disease, and Alzheimer's disease (AD). In a rat model, intrastriatal injection of manganese showed compensatory activation of autophagy in the short term [24]. Similarly, an overload of iron metal increased autophagic activity in in vitro neuronal cultures [28].

Metals may also induce neurotoxicity through disruption in synaptic transmission between neurons, as they highly involved in ion channels, neurotransmitter release and neurotransmitter receptors. For example, in hippocampal neuron culture, lead exposure has been shown to increase the release of both glutamate and GABA neurotransmitters independently of calcium. This indicates that a metal like lead have targets present at presynaptic terminals that can alter neurotransmitter release [32]. More importantly, lead has also been found to be capable of blocking both calcium channels and potassium channels that are critical in helping regulate neuron signaling [31]. In addition to signaling, metals may also affect neurotransmitter metabolism. Pohanka et al. showed that copper, aluminum, iron and calcium inhibit acetylcholinesterase (AChE), an enzyme that hydrolyzes acetylcholine, which leads to an effect in in cholinergic neurotransmission [27].

Like phthalates, oxidative stress is a well-known mechanism of metal toxicity. This is due to the fact that metals are redox-active, accepting or donating electrons, and can undergo redox cycling reactions creating ROS and RNS to result in oxidative stress [26]. Most ROS production has been found to be generated by the reaction of oxygen with copper and iron [25]. Metal production of ROS can play a key role in the coordination of signaling, as shown by Hidalgo et al. who demonstrated iron can generate calcium signals with ROS-mediated stimulation. However, in the presence of too much iron, calcium signaling may become excessive leading to neuronal cell death [30].

Overall, increased exposure to metals may result in a defective metal homeostasis which can contribute to neurodegenerative diseases. In the pathology of amyotrophic lateral sclerosis (ALS) it is hypothesized that increased copper levels may result in defective redox chemistry and subsequent ROS generation in ALS patients [82]. This is supported by studies that have shown copper chelators can inhibit the progression of ALS in mouse models [25].

Box 2. Oxidative stress plays a key role in cosmetic induced neurotoxicity and may contribute to neurodegenerative diseases.

In both phthalates and metals oxidative stress appears in many models as a key player of induced neurotoxicity in cosmetics. Oxidative stress is characterized as defective redox homeostasis due to the accumulation of oxygen reactive species (ROS) and reactive nitrogen species (RNS) or a decrease in antioxidant enzymes [101]. Oxidative stress is involved with other effects that could induce neurotoxicity including, DNA damage, oxidizing proteins, induced lipid peroxidation, and cell apoptosis [102]. Given the high consumption of oxygen in the central nervous system, the brain is vulnerable to oxidative stress injury [103,104]. In addition, the brain has been shown to have lower antioxidant defense capabilities than other tissues [21].

Oxidative stress is known to have an effect in neurogenerative diseases such as Alzheimer's disease (AD) Parkinson's disease (PD) and amyotrophic later sclerosis (ALS). It is unclear whether oxidative stress is an initiator of the disease pathologies or simply a consequence of brain degeneration. However, it is hypothesized that accumulative oxidative damage over time accounts for late life onset of these diseases.

These presences of metal exposure in humans have been correlated to the presence of neurogenerative disorders. ALS, Alzheimer's and Parkinson's patients all showed increased levels of copper and zinc. However, it is unclear whether these metals play a role in the onset of the disease or its' progression [80]. In addition, one ALS study has found there to be higher metal concentrations of metals in the CSF than corresponding blood plasma values, indicating mechanisms of inward transport of metals [83].

In addition to neurodegenerative diseases, metals also may influence neurodevelopment. Dual exposure of lead and mercury during late pregnancy have shown to have negative effects on the mental development index evaluating the problem solving, memory, classification and motor skills of infants at 6 months [81]. Like phthalates, heavy metals alter the gut microbiota, which ends inducing mental health problems [22].

All these toxicity mechanisms and associations to neuronal disorders and gastrointestinal dysbiosis, support metals neurotoxicity as probable disruptor of the enteric neuronal system development.

4. Conclusions

There are many cosmetic products containing toxic components like microplastics, parabens, benzophenones, phthalates and metals that are used in daily around the world life and impose neurotoxic threats to the human body. This may be associated with the fact that the extent of exposure is believed to be at too low of concentrations to have an effect, or because users care more about the quality of the product than its health effect. However, given the different use and exposure scenarios of cosmetics it is not clear what toxin concentrations are dangerous and their effect on the human body [81].

Despite literature that outlines the potential neurotoxic capabilities of these substances found in personal care products and cosmetics, they are continued to be used in formulations and ignored by consumers. Together, this means that there is work that needs to be done to understand a proper exposure model of cosmetic neurotoxins, as well as the direct causal relationships between mechanisms of the chemical and its neurotoxic effect.

However, especial attention should be paid to the consumption and composition of cosmetic and personal care products during pregnancy. Exposition to neurotoxins contained in these formulations during gestation could impair enteric neuronal development (and the complete neural colonization of the whole gut), as well as compromising the neuroimmunological interaction. Thus, it may cause congenital aganglionosis, as well as postnatal motility disorders as a consequence. Here we would like to inspire a more intense investigation concerning the specific effects of the above mentioned compounds to elaborate a catalogue of potential harmful substances for the ENS.

Finally, the urgent need for eradicating these neurotoxins compounds from all formulations is emerging.

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