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Review

Is the commonly used UV filter benzophenone-3 a risk factor for the nervous system?

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Benzophenone-3 (2-hydroxy-4-methoxybenzophenone, oxybenzone, or BP-3) is one of the most frequently used UV radiation absorbents, which are commonly referred to as sunscreen filters. Its widespread use in industrial applications provides protection against the photodegradation of a wide range of products but at the same time creates the risk of human exposure to benzophenone-3 unbeknownst to the individuals exposed. Topically applied benzophenone-3 penetrates individual skin layers, enters the bloodstream, and is excreted in the urine. In addition, benzophenone-3 easily crosses the placental barrier, which creates the risk of exposure to this substance in the prenatal period. Despite the widespread use and occurrence of benzophenone-3 in the human environment, little knowledge of the mechanisms underlying the effect of benzophenone-3 on the nervous system was available until recently. Only the most recent research, including studies by our group, has enabled the identification of new molecular mechanisms through which benzophenone-3 affects embryonic neuronal cells and the developing mammalian brain. Benzophenone-3 has been shown to induce neurotoxicity and apoptotic processes and inhibit autophagy in embryonic neuronal cells. Benzophenone-3 also alters expression and impairs function of receptors necessary for the proper development and function of the nervous system. The most worrying finding seems to be that benzophenone-3 contributes to an increased risk of developmental abnormalities and/or epigenetically based degeneration of neuronal cells by changing the epigenetic status of neuronal cells.

Keywords: benzophenone-3, chemical UV filter, nervous system, endocrine disrupting chemicals, neurotoxicity

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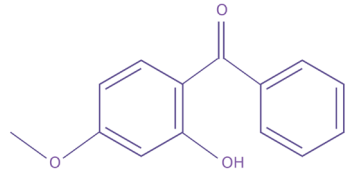
Abbreviations: BP-3, benzophenone-3; ER alpha/ESR1, estrogen receptor alpha; ER beta/ESR2, estrogen receptor beta; GPR30/GPER1, estrogen receptor associated with G protein; PPAR gamma, peroxisome proliferator-activated receptor gamma; RXR, retinoid X receptor; UV, ultraviolet

INDUSTRIAL PRODUCTION AND WIDESPREAD USE OF BENZOPHENONE-3

We have all heard about creams with a UV filter, and many people use them regularly. The use of cosmetics with UV filters has been the basis for the prevention of melanoma and other types of skin cancer for decades. However, are ultraviolet blockers always beneficial for our health? Is the commonly used UV filter benzophenone-3 a risk factor for the nervous system?

Benzophenone-3, also known as 2-hydroxy-4-methoxybenzophenone, oxybenzone or BP-3, is a lipophilic organic chemical compound with a molecular weight of 228.25 g/mol (Scheme 1). It is one of the most commonly used UV radiation absorbents in the industry, commonly known as sunscreen or sunblock. However, its use is not limited to sunscreen alone. Benzophenone-3 is a common ingredient in most daily cosmetics, including color cosmetic products, bath lotions, shampoos, perfumes, and face creams. Moreover, benzophenone-3 is also a component of artificial materials, such as plastic, textiles and paints. Its widespread use in industry provides protection against the photodegradation of a wide range of products but at the same time creates a risk of unknown exposure to benzophenone-3 in humans. This substance is very common in our life. For example, in Europe, the annual production of benzophenone-3 reaches 1000 tons (ECHA Report, 2020). The numbers speak for themselves.



Scheme 1. The chemical structure of benzophenone-3. Created with BioRender.com

EXPOSURE ROUTES OF THE HUMAN BODY TO BENZOPHENONE-3

Topical application of benzophenone-3 easily penetrates the skin layers, enters the bloodstream, and is then excreted mainly in the urine. However, the process of excretion of benzophenone-3 from the body is prolonged. Forty-eight hours after a single application of sunscreen cream, less than 0.5% of the dose applied is removed from the body, while benzophenone-3 is detected in the urine even 96 hours after initial exposure (Gustavsson *et al.,* 2002; Janjua *et al.,* 2008). More importantly, benzophenone-3 is a highly lipophilic substance that easily accumulates in the adipose tissue. This result has been proven by examining the adipose tissue of people from New York; the 32-year-old record holder had accumulated as much as ~5 mg of benzophenone-3 per kg of body fat (Wang *et al.,* 2015). Moreover, a study conducted by a U.S. government agency, the CDC (Centers for Disease Control and

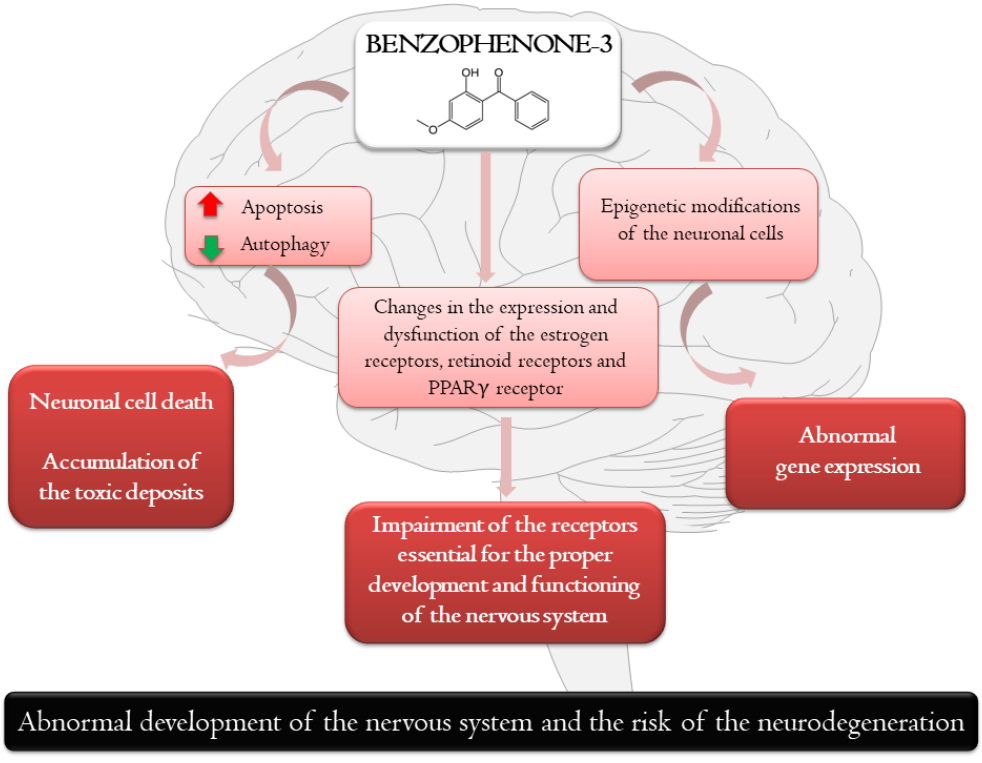
Prevention), found that nearly the entire global human population is exposed to benzophenone-3 (CDC Fourth Report, 2019). Under European legislation, the permissible concentration of benzophenone-3 as a UV filter could account for up to 10% of all cosmetic products, until recently. In view of the increasing reports of the negative effects of benzophenone-3 on human health and the environment, the European Commission has limited the use of benzophenone-3 since September 2017. Currently, its content in sunscreen products must not exceed 6%, and in other cosmetics, its content can reach up to 0.5% (Commission Regulation 2017/238). However, benzophenone-3 is still widely used as a UV filter in many other consumer products and in other noncosmetic industries, which potentially explains why, despite the restrictions, the benzophenone-3 content measured in urine samples from different populations is still not reduced (Frederiksen *et al.,* 2020).

An additional route of exposure to benzophenone-3 is via the gastrointestinal tract and respiratory system. Benzophenones (including benzophenone-3) occur naturally in bullocks heart, cherimoya, grape, mountain papaya, passion fruit, soursop, tea and vanilla. Contamination with benzophenone-3 has also been demonstrated in drinking-water as well as in food as a consequence of its migration from food packaging and its addition to food as flavoring (IARC Working Group, 2013). Moreover, benzophenone-3 is taken into the body along with the inhaled air since the dust ingestion is thought to be one of major sources of BP-3 exposure (Wan *et al.,* 2015). Nevertheless, personal care products are considered the main source of human benzophenone-3 exposure.

In addition to penetration through the skin, benzophenone-3 easily crosses the placental barrier, which creates a risk of exposure of the body to this substance during the prenatal period. Population studies have shown the presence of benzophenone-3 in amniotic fluid, placental tissue, and cord and fetal blood (Vela-Soria *et al.,* 2011; Phillippat *et al.,* 2013; Krause *et al.,* 2018; Song *et al.,* 2020). Moreover, benzophenone-3 has been detected in samples of breast milk, which confirms the possibility of exposure of the body to this substance during early postnatal development (Schlumpf *et al.,* 2010; Molins-Delgado *et al.,* 2018). A strong correlation between prenatal exposure to benzophenone-3 and an increased risk of fetal malformations has been reported, namely the Hirschprung's disease (Huo *et al.,* 2016). The basis for the development of Hirschprung's disease is caused by failed neural crest cells migration into the distal colon occurring from the 5th to 12th week of the embryogenesis, resulting in a lack of innervation in this region. This finding has been confirmed by Wang and others (Wang *et al.,* 2021), who demonstrated that exposure to benzophenone-3 induced a reduction in the number of enteric neurons and abnormal gastrointestinal physiology in zebrafish. In addition, benzophenone-3 has been shown to reduce the duration of pregnancy and increase the birth weight of newborns (Wolff *et al.,* 2008; Tang *et al.,* 2013; Philippat *et al.,* 2014; Ferguson *et al.,* 2018; Zhong *et al.,* 2020). When comparing the different stages of development of the human body in the presence of benzophenone-3, exogenous substances often achieve much higher concentrations in newborns and children, mainly due to the lower activity of enzymes metabolizing harmful substances than in adults.

EFFECTS OF BENZOPHENONE-3 ON THE SKIN AND CARCINOGENICITY

Due to the widespread use of benzophenone-3 to protect the skin, one should ask whether benzophenone-3 is safe for the skin? In 2014, the American Contact Dermatitis Society nominated benzophenone-3 as the 2014 Allergen of the Year since it causes both allergy and



Scheme 2. Benzophenone-3 action in the nervous system. Created with BioRender.com

photoallergy (Heurung *et al.,* 2014). Benzophenone-3 also induced phototoxicity in normal human keratinocytes by upregulating the expression of pro-inflammatory factors (e.g. COX-2, TNFα, and IL-8), and inhibited the development of the epidermal permeability barrier (Kim *et al.,* 2018). Moreover, acute exposures to environmentally relevant concentrations of benzophenone-3 induced genotoxicity and mutagenesis in *Poecilia reticulata* by inducing DNA damages and nuclear abnormalities in the erythrocytes (Almeida *et al.,* 2019). There is no information about the benzophenone-3 on promotion/progression of the skin cancer, but lately benzophenone-3 has been found to promote mammary tumorigenesis and to increase metastasis in lung cancer cells via epithelial to mesenchymal transition (Phiboonchaiyanan *et al.,* 2017; Kariagina *et al.,* 2020).

EFFECTS OF BENZOPHENONE-3 ON THE ENDOCRINE SYSTEMS

Substances that disrupt the hormonal balance by affecting the synthesis, transport or binding of hormones present in the body are widespread in the environment. Studies conducted in recent years have suggested that benzophenone-3 is partially responsible for an increase in the number of disorders in the functioning of the reproductive system, both in the male and female populations. Benzophenone-3 has been shown to inhibit the development of ovaries in an *in vitro* model, and its concentration in the female body is inversely correlated with the levels of gonadotropic hormones (FSH and LH) and the levels of sex hormone binding protein (SHBG) (Aker *et al.,* 2016; Pollack *et al.,* 2018; Santamaría *et al.,* 2019). Benzophenone-3 also impairs the hormonal balance in men by significantly lowering testosterone levels (Scinicariello & Buser, 2016). Moreover, benzophenone-3 causes long-term changes in the morphology and function of the mammary gland and delays breast development by 5-6 months in young women (Wolff *et al.,* 2015; LaPlante *et al.,* 2018). Additionally, benzophenone-3 has been identified as a potential breast cancer risk factor since it increases tumor cell proliferation and vascularity and decreases tumor cell apoptosis (Kariagina *et al.,* 2020). According to recent data, benzophenone-3 is associated with a higher risk of endometriosis in women (Peinado *et al.,* 2021).

Benzophenone-3 is a lipophilic substance whose chemical structure is similar to that of steroid receptor ligands (Schlecht *et al.,* 2004). To date, the estrogenic effects of benzophenone-3 in *in vitro* models have been indicated using the MCF-7 and MELN breast cancer cell lines, HELN cervical cancer cells, HEK293 embryonic human kidney cells and recombinant yeast strains (Schlumpf *et al.,* 2001; Gomez *et al.,* 2005; Schreurs *et al.,* 2005; Suzuki *et al.,* 2005; Kunz & Fent, 2006; Molina-Molina *et al.,* 2008). Benzophenone-3 has also been shown to increase uterine weight in ovariectomized rat females (Schlumpf *et al.,* 2001; Schlecht *et al.,* 2004; Suzuki *et al.,* 2005). The effect of benzophenone-3 on steroid hormones is not limited to direct effects on hormones but also involves damage to DNA fragments through a mechanism dependent on ERα estrogen receptors (Almeida *et al.,* 2019; Majhi *et al.,* 2020). The latest data from zebrafish show that benzophenone-3 affects estradiol biosynthesis, sex differentiation and gonadotropin-releasing hormone levels. Moreover, benzophenone-3 upregulates the expression of cytochrome P450 genes and glutathione metabolism-related genes (Meng *et al.,* 2020). Presumably, benzophenone-3 is also partially responsible for a significant decrease in the levels of the hormones fT3, fT4 and T4, which results in thyroid dysfunction in both men and women (Aker *et al.,* 2016; Kim *et al.,* 2017).

EFFECT OF BENZOPHENONE-3 ON THE NERVOUS SYSTEM

Benzophenone-3 induces neurotoxicity, induces apoptotic processes and inhibits autophagy

Despite the widespread use and occurrence of benzophenone-3 in the human environment, research on the effects of benzophenone-3 on the mammalian nervous system is scarce. The first studies examining the effect of benzophenone-3 on the nervous system were conducted on ovariectomized females. In this study, benzophenone-3 was found to reduce the gene expression of estrogen receptor α – *Era*, also known as *Esr1*, in the pituitary (Schlecht *et al.,* 2004). Moreover, the neurotoxic effects of benzophenone-3 were first observed in primary cultures of rat neocortical cells by Fediuk and others (Fediuk *et al.,* 2010). SH-SY5Y human neuroma cells are also sensitive to the toxic effects of this substance (Broniowska *et al.,* 2016). Only 4 years ago, researchers proved that the blood-brain barrier is not an obstacle to benzophenone-3, as it was identified in the brains of adults in a postmortem analysis (Van Der Meer *et al.,* 2017).

Based on these facts, knowledge of the mechanism underlying the effect of benzophenone-3 on the nervous system, especially in the early stages of development, was still negligible until recently. The latest research conducted by Wnuk and others (Wnuk *et al.,* 2018a; Wnuk *et al.,* 2018b; Wnuk *et al.,* 2018c; Wnuk *et al.,* 2019) allowed to identify the molecular mechanisms by which benzophenone-3 affects embryonic neuronal cells and the developing mammalian brain. According to these studies, the administration of benzophenone-3 to an *in vitro* model, *i.e.,* added to the culture of mouse primary neuronal cells, or an *in vivo* model, *i.e.,* administered to pregnant female mice (prenatal exposure), induces neurotoxicity and apoptosis while inhibiting the autophagy process. Natural processes of apoptosis and autophagy determine the normal development of the nervous system and participate in the response of neuronal cells to various types of stress factors. During neurogenesis, a large number of neurons is formed in the developing brain, and the excess neurons are eliminated at a later stage of development through apoptosis, which affects up to 50% of newly formed neurons (Rudin *et al.,* 1997). Autophagy, on the other hand, is responsible for removing malformed proteins and damaged organelles from cells. Disordered apoptosis and autophagy processes promote the formation of neurodevelopmental defects, including autism and schizophrenia, as well as various types of neurodegeneration (Margolis *et al.,* 1994; Rudin *et al.,* 1997; Jarskog *et al.,* 2005; Dong *et al.,* 2018).

Benzophenone-3 causes substantial apoptosis while inhibiting the autophagy process in mammalian neuronal cells. Through this mechanism, benzophenone-3 may lead to a loss of homeostasis between apoptosis and autophagy processes and consequently to an impairment of the nervous system development and neurodegeneration. According to Wnuk and others (Wnuk *et al.,* 2018a; Wnuk *et al.,* 2018b; Wnuk *et al.,* 2018c) benzophenone-3 added to an *in vitro* model or administered to pregnant females as a form of prenatal exposure causes

apoptosis in neuronal cells of the mouse brain. A similar conclusion was reported by Krzyżanowska and others (Krzyżanowska *et al.,* 2018), who observed apoptosis in the brains of rats after epidermal exposure to benzophenone-3. The same group also showed that epidermal exposure to benzophenone-3 damages neurons, which is associated with increase in the extracellular glutamate levels and lipid peroxidation (Pomierny *et al.,* 2019; Skórkowska *et al.,* 2020). Benzophenone-3 has also been shown to interfere with the nervous system by regulating the calcium signaling pathway (Meng *et al.,* 2020). An article by Philippat and others (Philippat *et al.,* 2017) confirms the neurodevelopmental dysfunction caused by benzophenone-3, since boys aged 3 and 5 were shown to exhibit behavioral disorders in response to prenatal exposure to this UV filter. Moreover, Guo and others (Guo *et al.,* 2020) showed a correlation between maternal and childhood urinary benzophenone-3 concentrations and poorer prosocial behaviors at 10 years of age. The observed associations were stronger in boys than in girls.

Benzophenone-3 changes the epigenetic status of neuronal cells

Exposure of the body at an early stage of development to environmental factors may contribute to epigenetic-related diseases. Epigenetic mechanisms, *i.e.,* biochemical modifications of DNA and histone proteins, which are the structural basis for chromatin stability, are thought to be involved in the etiology of autism or schizophrenia (Akbarian, 2014; Maloney & Lahiri, 2016; Siu & Weksberg, 2017). Benzophenone-3 also alters the epigenetic status of neuronal cells, as evidenced by decreased global DNA methylation levels and inhibited activity of the enzymes associated with DNA methylation and histone acetylation, *i.e.,* DNMT, HAT and HDAC (Wnuk *et al.,* 2018b; Wnuk *et al.,* 2018c; Wnuk *et al.,* 2019). Moreover, benzophenone-3 alters the expression of genes associated with neurogenesis and neurotransmitters, as well as numerous miRNAs involved in pathological conditions of the nervous system, especially schizophrenia and the Alzheimer's disease (Wnuk *et al.,* 2019). This suggests that the risk of developmental abnormalities and/or degeneration of neuronal cells is associated with benzophenone-3-related changes in the epigenetic status. The paper by Almstrup and others (Almstrup *et al.,* 2020) confirmed the results of our studies, where benzophenone-3 was associated with changes in the peripubertal epigenome, e.g., lower TRIP6 promoter methylation in the blood of children.

Benzophenone-3 changes the expression and impairs the functions of receptors crucial for the proper development and functioning of the nervous system

Numerous reports indicate the important role of estrogen receptors in the response to environmental factors such as endocrine disrupting chemicals, also known as endocrine disruptors. In addition to participating in the response to xenobiotics (which function as false hormones in the body), estrogen receptors determine the proper development and functioning of the brain. Therefore, impaired function of estrogen receptors can cause disorders observed both during ontogenesis and during diseases of the nervous system. For example, the brains of people suffering from schizophrenia or Alzheimer's disease show deficits in ERα estrogen receptors (also known as ESR1), particularly in the hippocampus and frontal cortex (Perlman *et al.,* 2005; Kelly *et al.,* 2008). In contrast, ERβ receptor (or ESR2)-deficient mice exhibit impaired synaptic plasticity and neurogenesis (Long *et al.,* 2012; Fan *et al.,* 2006). A deficiency in estrogen receptors associated with G protein, *i.e.,* GPR30 (also known as GPER1), leads to insulin resistance and dyslipidemia and causes inflammation (Sharma *et al.,* 2013).

Similar to estrogen receptors, retinoid type X receptors (RXRs) and peroxisome proliferator-activated receptor gamma (PPARγ) are also involved in neuronal cell responses to various types of exogenous substances and participate in the development of the nervous system. RXR and PPARγ receptors are mainly expressed in neuronal stem cells and regulate their proliferation, migration and differentiation (Defect *et al.,* 2006; Heneka *et al.,* 2011; Stergiopoulos & Politis, 2013). Mice lacking RXRα and RXRβ exhibit multiorgan defects (Krezel *et al.,* 1996). Dysregulation of RXR signaling pathways impairs brain development, learning and memory functions, and leads to neurodegeneration (Huang *et al.,* 2011; Nomoto *et al.,* 2012; Goodman 1998; Wysowski *et al.,* 2001; McCaffery *et al.,* 2006; van Neerven *et al.,* 2008). Altered PPARγ expression and/or abnormal activity are associated with neurodegenerative diseases and brain tumors (Chen *et al.,* 2012; Gupta *et al.,* 2018). The molecular mechanism of action of benzophenone-3 in neuronal cells and mammalian brains has been described by Wnuk and others (Wnuk *et al.,* 2018a; Wnuk *et al.,* 2018b; Wnuk *et al.,* 2019c Wnuk *et al.,* 2019). Based on these original data, the chemical UV filter benzophenone-3 changes the expression and disrupts the functions of estrogen receptors (ESR1, ESR2, and GPER1), retinoid X receptors (RXRα, RXRβ, and RXRγ) and PPARγ, which are crucial receptors for the proper development and functioning of the nervous system. The latest data from zebrafish confirmed that benzophenone-3 induced developmental neurotoxicity, such as delayed axonal growth, and altered cell proliferation and cell apoptosis, through a mechanism mediated by the RXRβ receptor (Tao *et al.,* 2020). The aforementioned effects of benzophenone-3 are consistent with our observations that benzophenone-3 impairs the expression of genes associated with neurogenesis and neurotransmitters, for which the abovementioned receptors may be partially responsible.

MODERN UV FILTERS – OUR FUTURE?

Scientists are still working to improve the chemical structure and function of UV filters. Benzophenone-3 derivatives such as BP-3-phenylamine and BP-3-methoxyphenylamine show much greater photostability than the original compound (González *et al.,* 2017). Polymeric nanoparticles and encapsulation, on the other hand, are another strategy for preventing benzophenone-3 from penetrating the skin (Martins *et al.,* 2014; Li *et al.,* 2015; Gilbert *et al.,* 2016; Barbosa *et al.,* 2019). Using more stable benzophenone-3 derivatives or their encapsulated forms will probably fundamentally inhibit the penetration of benzophenone-3 through the skin, placental barrier and blood-brain barrier, which will subsequently reduce the harmful effects of this substance on the human nervous system. As a result of these actions, a modern UV filter will no longer pose a threat to the nervous system.

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