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

Agnieszka Wnuk and Małgorzata Kajta

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

Received: 14 June, 2021; revised: 23 June, 2021; accepted: 30 June, 2021; available on-line: 05 August, 2021

Acknowledgments of Financial Support: This study was financially supported by the statutory fund of the Maj Institute of Pharmacology, Polish Academy of Sciences in Krakow, Poland.

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](https://doi.org/10.18388/abp.2020_5741)

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, 2017).
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; Philippat 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
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 P. 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 (Phiboonchayanan et al., 2017; Kariagina et al., 2020).

**EFFECTS OF BENZOPHENOONE-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 gonadotrophic hormones (FSH and LH) and the levels of sex hormone binding protein (SHBG) (Aker et al., 2016; Pollack et al., 2018; Santamaria 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 vascularization 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 ERx 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 BENZOPHENOONE-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 – Esr1, 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 neurooma 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; Jarlskog 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 (Akkarian, 2014; Maloney & Lahiri, 2016; Siu & Wexberg, 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 periventricular 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; Stengs-Poulos & 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 (RXRs, RXRγ, and RXRβ) 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.

Acknowledgements

The manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English
speaking editors at American Journal Experts – CBDC-4C5E-241E-18F9-C927.

REFERENCES

Abdalian S (2014) Epigenetic mechanisms in schizophrenia. Dialogues Clin Neurale 16: 405–417.

Aker AM, Watkins DJ, Johns LE, Ferguson KK, Soldin OP, Anzalota Del Toro LV, Abshawabeke AN, Cordero JP, Meeker JD. (2016) Phenols and phthalates in relation to reproductive and thyroid hormones in pregnant women. Environ Res 151: 30–37. https://doi.org/10.1016/j.envres.2016.07.002

Almeida SDS, Rocha TL, Qualhato G, Oliveira LR, Amaral CLD, Conceição PR, Saaboo Monte S, BuUlio EFCL. (2016) Exposure to environmentally relevant concentrations of benzophenone-3 induced genotoxicity in P. reticulata. Aquat Toxicol 216: 105293. https://doi.org/10.1016/j.aquatox.2016.10.029

Almstrum K, Frederiksen H, Andersson AM, Juul A (2020) Levels of endocrine-disrupting chemicals are associated with changes in the peri-pubertal epithome. Endocr Connect 9: 845–857. https://doi.org/10.1530/EC-20-0286.

Barbosa TC, Nascimento LED, Bani C, Almeida T, Nery M, Santos RS, Menezes LRO, Zelitskia A, Fernandes AR, Cardoso JC, Jäger A, Jäger F, Sanchez-Lopez E, Nalone I, Souto EB, Sevirino P (2019) Development, cytotoxicity and eye irritation profile of a new sunscreen formulation based on benzophenone-3-poly(caprolactone) nanoparticles. Toxicol 7: 51. https://doi.org/10.3390/toxics4004051

Broniowska Ż, Pomierny B, Smaga I, Filip M, Budziszewska B (2016) Oxybenzone alters mammary gland morphology in mice exposed to environmentally relevant concentrations of benzophenone-3, a common component of topically applied sunscreens. Clin Exp Dermatol 27: 691–694. https://doi.org/10.1111/ced.12205.

Gustavsson Gonzalez H, Farbrot A, Lärkó O. (2002) Percutaneous absorption of benzophenone-3, a common component of topical sunscreen. J Dermatol Sci 29, 109–116. https://doi.org/10.1016/S0923-3609(02)00195-X.

Heneka MT, Reyes-Irisarri E, Hill M, Kummer MP. (2011) Impact and therapeutic potential of PPARs in Alzheimer’s disease. Curr Neuropharmacol 9: 643–650. https://doi.org/10.2174/1567205117951978376325.

Heuring AR, Raju SJ, Warsaw EM. (2014) Benzophenones. Dermatitis 25: 3–10. https://doi.org/10.1097/DER.0b013e3182800025. Erratum in: Dermatitis 25, 2014 Mar-Apr: 925–926. https://doi.org/10.4318/dermatitis.2014.03.019

Huang JK, Jarjour AA, Nait Oumesmar B, Kermoin C, Williams A, Krezel W, Kagechika H, Bauer J, Zhao C, Baron-Van Evercooren A, Champron P, Fritch-Fenster-Constant G, Franklin RJM. (2011) Retinoid X receptor gamma signaling accelerates CNS remyelination. Nat Neurosci 14: 45–53. https://doi.org/10.1038/nm.2702

Huo W, Cai P, Chen M, Li H, Tang J, Xu C, Zhe W, Tang W, Xia Y (2016) The relationship between prenatal exposure to BP-3 and Hirschsprung’s disease. Chemosphere 144: 1091–1097. https://doi.org/10.1016/j.chemosphere.2015.09.019.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. (2013) Some Chemicals in Personal and Consumer Products: Food and Drinking-Water. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 101. BENZOPHENONE-3. https://www.ncbi.nlm.nih.gov/books/NBK373188/

Januja NR, Kongshoj B, Andersson AM, Wolff HC. (2008) Sunscreens in human plasma and urine after repeated whole-body topical application. J Eur Acad Dermatol Vener 22: 456–461. https://doi.org/10.1111/j.1468-3033.2007.02492.x

Jansske LF, Glantz GA, Lifmore JH, Lieberman JA (2005) Apoptotic mechanisms in the pathophysiology of schizophrenia. Png Nppbpharmacol Biol Psychiatry 29: 846–858. https://doi.org/10.1016/j.jnpb.2005.03.010.

Kariagina A, Morozova E, Hoshary R, Appar Deep MD, Borin MA, Haslam SZ, Schwarz RC. (2020) Benzophenone-3 promotion of mammalian tumorigenesis is diet-dependent. Oncotarget 11: 4465–4478. https://doi.org/10.18632/oncotarget.27831

Kelly JF, Biens JH, Shah A, Mekea KA, Schneider JA, Soriano E, Bennett DA. (2008) Levels of estrogen receptors alpha and beta in frontal cortex of patients with Alzheimer’s disease: relationship to Mini-Mental State Examination scores. Curr Alzheimer Res 5: 45–51. https://doi.org/10.2174/156720508783884611

Kim HJ, Lee E, Lee M, Ahn S, Kim J, Liu J, Jin SH, Ha J, Bae H, Lee R, Noh M. (2018) Peroxisome proliferator-activated receptor gamma 3 plays a role in benzophenone-3-induced phototoxicity in normal human keratinocytes. Tocod Appl Pharm 338: 174–181. https://doi.org/10.1016/j. taap.2017.11.021

Kim HJ, Kim S, Won S, Choi K. (2017) Considering common sources of exposure in association studies – urinary benzophenone-3 and DEHP metabolites are associated with altered thyroid hormone balance in the NHANES 2007–2008. Environ Int 107: 25–32. https://doi.org/10.1016/j.envint.2017.03.013

Krause M, Frederiksen H, Sundberg K, Jorgensen FS, Jensen LN, Norgaard P, Jorgensen C, Erthberg P, Juul A, Drzewiecki KT, Skakkebaek NE, Andersson AM. (2018) Presence of benzophenones commonly used as UV filters and absorbers in paired maternal and fetal samples. Environ Int 110: 51–60. https://doi.org/10.1016/j.envint.2017.10.005

Kwok W, Dupe V, Mark M, Dieich A, Kastner P, Champron P (1996) RXR gamma null mice are apparently normal and compound RXR alpha +/-/RXR beta -/-/RXR gamma -/- mutant mice are viable. Proc Natl Acad Sci U S A 93: 9010–9014. https://doi.org/10.1073/pnas.93.19.9010.

Kwiatowska W, Pomierny B, Starcz-Świechowiez B, Broniwowska Z, Strach B, Budziszewska B. (2018) The effects of benzophenone-3 on apoptosis and the expression of sex hormone receptors in the frontal cortex and hippocampus of rats. Toxicol Lett 296: 63–72. https://doi.org/10.1016/j.toxlet.2018.08.006.

Kunz PY, Fent K (2006) Multiple hormonal activities of UV filters and comparison of in vivo and in vitro estrogenic activity of ethyl-4-aminobenzoate in fish. Aquat Toxicol 79: 305–324. https://doi.org/10.1016/j.aquatox.2006.06.016

LaPlante CD, Bansal R, Dunphy KA, Jerry DJ, Vanderbend LN. (2018) Oxybenzone alters maternal mammary morphology in mice exposed during pregnancy and lactation. J Endocr Soc 2: 903–921. https://doi.org/10.1210/jensc.2018-00052.

Li CC, Lin YT, Chen SY, Sie SF, Chen-Yang YW. (2015) Improvement in UV protection retention capability and reduction in skin damage due to the absorption of benzophenone-3. Z. Physiol. Chem. 396: 1203–1213.
penetration of benzophenone-3 with mesoporous silica as drug carrier by encapsulation. *J Photochem Photobiol B* 148: 277–283. https://doi.org/10.1016/j.jphotobiol.2015.04.027

Long J, He P, Shen Y, Li R (2012) New evidence of mitochondrial dysfunction in the female Alzheimer’s disease brain: deficiency of estrogen receptor-β. *J Alzheimer Dis* 30: 545–558. https://doi.org/10.3233/JAD-12-120828

Majhi PD, Sharma A, Roberts AL, Daniele E, Majewski AR, Chuong MC, Long J, He P, Shen Y, Li R (2020) Effects of benzophenone-3 and propylparaben on estrogen receptor-dependent t-loops and DNA damage in breast epithelial cells and mice. *Environ Health Perspect* 128: 17002. https://doi.org/10.1289/EHP3113

Maloney B, Lahiri DK (2016) Epigenetics of dementia: understanding disease and clinical relevance of programmed cell death. *Annu Rev Med* 67: 267–281. https://doi.org/10.1146/annurev-med-041813-133707

Santamaria CG, Abad JE, Porpora MM, Meyer N, Zelenchuk AG, Kaas L, Rodríguez-HA (2007) The UV filter benzophenone-3 on the early follicular assembly in rat whole ovary cultures. *Annu Lett* 303: 48–54. https://doi.org/10.1016/j.annaled.2018.12.016

Schlecht C, Klammer H, Jarry H, Wuttke W (2004) Effects of estra diol, benzophenone-2 and benzophenone-3 on the regulation of the estrogen receptors (ER) alpha and beta, the estrogen receptor-related receptor 1 (ERR1) and the aryl hydrocarbon receptor (AhR) in adult ovario-ovarian tissues. *Toxicol* 205: 123–130. https://doi.org/10.1016/j.tox.2004.06.044

Schlumpf M, Cotton B, Consience M, Haller V, Steinmann B, Lichtensteiner W (2001) In vitro and in vivo estrogenticity of UV. *Environ Health Perspect* 109: 239–244. https://doi.org/10.1289/ehp.01109239

Schlumpf M, Ypské W, Wittassek M, Angerer J, Mascher H, Mascher B, Voik C, Birchler M, Lichtensteiner W (2010) Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlorine pesticides, PBDEs, and PCBs in human milk: correlation of UV filters with use of cosmetics. *Chronobiol Int* 27: 1173–1183. https://doi.org/10.1080/074205209.2010.514177

Sharma G, Hu C, Brigan JI, Zhu G, Hathaway HJ, Prossnitz ER (2013) GPER deficiency in male mice results in insulin resistance, dyslipidemia, and a proinflammatory state. *Endocrinology* 154: 4136–4145. https://doi.org/10.1210/en.2013-1357

Siut MT, Welsberg R (2017) Epigenetics of autism spectrum disorder. *Adv Exp Med Biol* 978: 63–90. https://doi.org/10.1007/978-3-319-53889-4_4

Skórzyńska A, Maciejska A, Pomierny B, Krzyżanowska W, Starzek-Szwecikowsz B, Bystrowska B, Broniowska Ż, Kazez G, Budzińska B (2020) Effect of combined prenatal and adult benzo phenone-3 dermal exposure on factors regulating neurodegenerative processes, blood hormone levels, and motoric parameters in male rats. *Neurotoxicology* 37: 683–701. https://doi.org/10.1016/j.neuro.2017.04.047

Suzuki T, Kitamura S, Khota R, Sugihara K, Fujimoto N, Ohta S (2006) Estrogenic and antiandrogenic activities of 17 benzophenone derivatives using fish and human estrogen receptor-specific binding assays. *Toxicol Appl Pharmacol* 232: 384–395. https://doi.org/10.1016/j.taap.2007.10.071

van Neerven S, Kampmann E, Mey J (2008) RAR/RXR and PPAR/ RXR signaling in neurological and psychiatric diseases. *Prog Neurobiol* 85: 433–451. https://doi.org/10.1016/j.pneurobio.2008.04.008

Vela-Soria F, Jiménez-Díaz I, Rodríguez-HA, R. Zafra-Gómez A, Ballesteros O, Navañon A, Vílchez JL, Fernández MF, Olea N (2011) Determination of benzophenones in human placental tissue.
Is the commonly used UV filter benzophenone-3 a risk factor for the nervous system?

Wada K, Nakajima A, Katayama K, Kudo C, Shibuya A, Kubota N, Teranishi Y, Tachibana M, Miyoshi H, Kamisaki Y, Mayumi T, Kadokawa T, Blumberg RS (2006) Peroxisome proliferator-activated receptor gamma-mediated regulation of neural stem cell proliferation and differentiation. J Biol Chem 281: 12673–12681. https://doi.org/10.1074/jbc.M513786200

Wan Y, Xue J, Kannan K (2015) Occurrence of benzophenone-3 in indoor air from Albany, New York, USA, and its implications for inhalation exposure. Sci Total Environ 537: 304–308. https://doi.org/10.1016/j.scitotenv.2015.08.020.

Wang L, Asimakopoulos AG, Kannan K (2015) Accumulation of 19 environmental phenolic and xenobiotic heterocyclic aromatic compounds in human adipose tissue. Environ Sci 78: 45–50. https://doi.org/10.1016/j.envsci.2015.02.015

Wang J, Meng X, Feng C, Xiao J, Zhao X, Xiong B, Feng J (2021) Benzophenone-3 induced abnormal development of enteric nervous system in zebrafish through MAPK/ERK signaling pathway. Chemosphere 280: 130670. https://doi.org/10.1016/j.chemosphere.2021.130670.

Wnuk A, Rzemieniec J, Lason W, Krzepkowski W, Kajta M (2018a) Apoptosis induced by the UV filter benzophenone-3 in mouse neuronal cells is mediated via attenuation of Erα/Pparγ and stimulation of Erβ/Gpr30 signaling. Mol Neurobiol 55: 2362–2383. https://doi.org/10.1007/s12035-017-0480-z

Wnuk A, Rzemieniec J, Lason W, Krzepkowski W, Kajta M (2018b) Benzophenone-3 impairs autophagy, alters epigenetic status, and disrupts retinoid X Receptor signaling in apoptotic neuronal cells. Mol Neurobiol 55: 5059–5074. https://doi.org/10.1007/s12035-017-0704-2

Wnuk A, Rzemieniec J, Liwia E, Lasoni W, Kajta M (2018c) Prenatal exposure to benzophenone-3 (BP-3) induces apoptosis, disrupts estrogen receptor expression and alters the epigenetic status of mouse neurons. J Steroid Biochem Mol Biol 182: 106–118. https://doi.org/10.1016/j.jsbmb.2018.04.016

Wnuk A, Rzemieniec J, Staroń J, Liwia E, Lasoni W, Bojarski A, Kajta M (2019) Prenatal exposure to benzophenone-3 impairs autophagy, disrupts RXRs/PPARγ signaling, and alters epigenetic and post-translational statuses in brain neurons. Mol Neurobiol 56: 4820–4837. https://doi.org/10.1007/s12035-018-1401-5.

Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, Wetmar J, Calafat AM (2008) Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect 116: 1092–1097. https://doi.org/10.1289/ehp.11007.

Wolff MS, Teitelbaum SL, McGovern K, Pinney SM, Windham GC, Galvez M, Pajak A, Rybak M, Calafat AM, Kushi LH, Biro FM; Breast Cancer and Environment Research Program (2015) Environmental phenols and pubertal development in girls. Environ Int 84: 174–180. https://doi.org/10.1016/j.envint.2015.08.008

Wysowski DK, Pitts M, Beitz J (2001) An analysis of reports of depression and suicide in patients treated with isotretinoin. J Am Acad Dermatol 45: 515–519. https://doi.org/10.1067/mjd.2001.117730

Zhong Q, Peng M, He J, Yang W, Huang F (2020) Association of prenatal exposure to phenols and parabens with birth size: A systematic review and meta-analysis. Sci Total Environ 703: 134720. https://doi.org/10.1016/j.scitotenv.2019.134720.