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Cerebral concentration and toxicity of endocrine disrupting chemicals: The implication of blood-brain interfaces

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Abstract:

Endocrine disrupting chemicals (EDCs) act on peripheral endocrine organs or interfere with general endocrine pathways. Several EDCs alter the central regulation of neuroendocrine pathways, and affect neurological functions, and as such can be classified as neurotoxic molecules. Environmental pollutants classified as EDCs and affecting the central nervous system include perfluoroalkanes, parabens, phthalates, organotins, bisphenols, benzophenones, polychlorinated biphenyls, and dioxins. In this review we provide a brief description of these families of EDCs. We report and compare the EDC concentrations measured in the brain of humans and wild animals naturally exposed to these molecules, as well as in the brain of laboratory animals experimentally exposed to EDCs. The importance of using sophisticated analytical tools to detect EDCs in the brain is pointed out. The ability of blood-brain interfaces to reduce the brain exposition to EDCs in adult and during development is discussed in relation with the specific morphological, transport and metabolic properties of these cellular layers. Finally, we review the evidence that blood-brain interfaces neuroprotective functions can be altered by EDCs, a process that may participate to the central toxic action of these molecules. Overall this analysis points to the implication of blood-brain interfaces in setting the extent of central EDCs toxicity, although most evidences are indirect. Therefore, more specific blood-brain interface-oriented studies are called for in this field of EDC neurotoxicology.

Key words: blood-brain barrier, choroid plexus, endocrine disrupting chemicals, transport, metabolism

highlights

- Perfluoroalkanes, parabens, phthalates, organotins, bisphenols, benzophenones, polychlorinated biphenyls, and dioxins are environmental endocrine disrupting chemicals (EDCs) that can be classified as neurotoxic molecules.
- Knowledge on EDC concentrations in brain stem from brain analysis in either wild animals and human naturally exposed to these chemicals, or laboratory animals experimentally exposed to EDC.
- brain concentration of EDCs is highly variable, and is influenced by the molecular structures and the half-lives of the compounds.
- Very few experimental studies attempt to correlate brain concentrations of EDCs with their effect on the central nervous system.
- blood-brain interfaces play a role in the cerebral bioavailability of EDCs. Most evidences however remain indirect. Barrier permeability to EDCs may be modified by efflux transporters and detoxifying enzymes.
- Blood brain barrier neuroprotective functions are altered by some EDCs, a process that may participate to the neurological dysfunctions attributed to these toxicants.

Introduction

Endocrine disrupting chemicals (EDCs) are defined as exogenous agents that disturb the normal endocrine functions, through affecting the synthesis, secretion, transport, binding and metabolism of hormones (Annamalai and Namasivayam, 2015). They can mimic a natural hormone and induce inappropriate body responses (e.g. inappropriate insulin production), block hormone-specific receptors and consequently the corresponding hormonal activity (e.g. growth hormone receptors), or else stimulate or inhibit endocrine pathways to cause overproduction or underproduction of specific hormones. As a result, various general functions and systems can be impacted, ranging from reproduction, development and metabolism, to immune system and liver functions, leading to, or worsening, pathologies such as hormone-related cancers, diabetes, obesity or infertility (De Coster and van Larebeke, 2012; Karthikeyan et al., 2019). EDCs are found at low levels in thousands of products, whether natural or man-made such as toys, furniture, medical devices and cosmetics, and form an important part of the pollutants found in the environment. Human and animals can be exposed to EDCs through different routes that include ingestion during consumption of food and water, skin absorption, inhalation, and also by transfer from mother to fetus across the placenta or from mother to infant via lactation (Gore et al., 2014). In this article, we focus on perfluoroalkanes, parabens, phthalates, organotins, bisphenols, benzophenones, polychlorinated biphenyls, and dioxins, which are environmental EDCs that have an impact on neurological functions (Table 1).

EDCs have an action on selected peripheral endocrine organs or interfere with global endocrine pathways. It is not obvious to delineate the specific action of each EDC because in an environmental context they are hardly ever isolated and the human body is often exposed to various EDCs simultaneously. A large panel of literature describes serious endocrine-related deleterious effects on human health and on wild life upon exposure to these pollutants, as illustrated by the following examples.

PCBs alter the circulating levels of thyroid hormones in human (Meeker et al., 2007). Prenatal exposure to PCB is also linked to unfavorable birth outcome. The effects differ with the

number of chlorine atoms on the molecules. For example, Low-chlorinated PCB congeners were negatively associated with the length of gestation in human (Tang et al., 2018).

Both estrogenic and antiestrogenic activity has also been reported for PCBs. These opposite actions depend on the structure of the molecules. PCB with an ortho substitution and non-coplanar PCB possess an estrogenic action, while di-ortho, multiple-Cl- substituted PCBs possess antagonistic activities towards the estrogen receptor functions. Several PCB congeners are pleiotropic. For instance, PCB 138 possess both receptor-mediated anti-estrogenic and anti-androgenic effects (Bonefeld-Jorgensen et al., 2001).

Exposure of adult men to **phthalates** induces a decline in sperm concentration, and is associated with decreased thyroid hormones in serum and altered semen quality (Minguez-Alarcon et al., 2018; Wang et al., 2018). The effect of phthalates on women reproductive system is also documented in *in vitro* and *in vivo* animal studies. In mouse the formation of phthalate metabolite is directly linked to ovary dysfunction, accelerating primordial follicle recruitment (Hannon et al., 2014; Hannon et al., 2015). Exposure of rats to Di-(2-ethylhexyl) phthalate before puberty also induce sexual precocity (Liu et al., 2018). Individual phthalates act on different receptors and hormonal pathways, with various potencies, hence the cumulative consequences of a simultaneous exposure to multiple phthalate are difficult to predict (Mankidy et al., 2013). **Bisphenols** seem to be negatively associated with reproductive/developmental functions, and to be especially connected with adult, adolescent and child obesity. The mechanism is not clearly elucidated, but may involve an interaction with thyroid hormone receptors, an activation of estrogen receptors, a dysregulation of adipocyte differentiation, an increased absorption of lipids, and an insulinotropic action (Boucher et al., 2014; Darbre, 2020; Koutaki et al., 2021). Exposure to **Dioxins** induces a defect in the reproductive function in many species, including decreased spermatogenesis and infertility, ovarian dysfunction, and fetal loss (Kogevinas, 2001). In addition, a demasculinization of male offspring and a feminization of sex behavior has been observed following pre-natal exposure to dioxin of male rats, suggesting that dioxins interfere with sexual differentiation (Hojo et al., 2006). **Perfluoroalkanes** have a damaging impact on metabolism, fertility, fetal growth, adiposity, and on the ability of the immune system to fight infections (Joensen et al., 2009; Stein et al., 2016; Braun et al., 2021). Exposure to **Organotins** induces developmental abnormalities. The endocrine-disruptive effects of Tributyltin are clearly seen in some marine organisms that develop ambiguous genitalia, such as imposex characterized by a

superimposition of male and female characters in mollusks (Mattiessen and Gibbs, 1998; Laranjeiro et al., 2016). This is mainly attributed to the inhibition of aromatase, the enzyme that converts androgen to estrogen (Sharan et al., 2013). Tributyltin is embryotoxic for several aquatic organisms such as sea urchins, clams and fish (Roepke et al., 2005; Inoue et al., 2006; Hano et al., 2007). In mammals, Dibutyltin induces malformations and apoptotic fetal resorption (Furukawa et al., 2017). Tributyltin has obesogenic activity (Grun, 2014), and in fetuses induces Multipotent Stem Cells to Become Adipocytes (Kirchner et al., 2010). **Parabens** disturb the concentration of female steroid sex hormones in serum, which in human results in a decreased estradiol/progesterone ratio. *In vitro and in vivo* experimental studies conducted in young female mice revealed a significant increase in adipocytes number and in white adipose tissue mass upon exposure to alkyl-paraben. These changes increased with the alkyl chain length and were linked to an activation of PPARs (Nowak et al., 2018; Elmore et al., 2020). **Benzophenones** affect reproductive organs in both sexes. In rodents this includes delay in male puberty, alterations in reproductive organs, and change of the estrogen cycle, in line with an estrogenic and antiandrogenic activity attributed to these compounds. Benzophenone derivatives also induce disturbance of hypothalamic–pituitary–thyroid axis. Dermal exposure to low dose of benzophenone-3 during early pregnancy in mice induces sex ratio alterations and modification in the growth curve of male mice (Schlumpf et al., 2004; Krause et al., 2012; Santamaria et al., 2020).

In some instances, EDCs alter the central regulation of neuroendocrine pathways, and as such can be classified as neurotoxic molecules. The following examples illustrate some of the central effects induced by exposure to these molecules.

Exposure to **PCB** is linked to morphological changes in neurons and to altered neurological development. For example, exposure to PCBs has been associated with an altered methylation of genes involved in autism spectrum disorder, and with developmental defects of the nervous system, behavioral changes, learning deficits, reduced attention and impulsivity (Klinefelter et al., 2018; Dickerson et al., 2019). **Paraben** intoxication in rats shows similarities with the autistic-like rat model with respect to changes in oxidative and inflammatory stress markers in brain, suggesting that, to some extent, paraben may cause or contribute to this brain pathology (Hegazy et al., 2015). In mice perinatal exposure to n-butyl paraben induces an overweight in offspring, that could be mediated by a modification of an epigenetic enhancer

leading to an altered expression of pro-opiomelanocortin, and by a defective food intake neuronal regulation (Leppert et al., 2020). **Benzophenones** may interfere with the hypothalamic–pituitary–thyroid axis (Broniowska et al., 2019). Dermal exposure to benzophenone 3 in rats causes neuronal damages which may be related to an increased concentration of extracellular glutamate in brain and to an induction of apoptosis. It leads to an impaired spatial memory (Pomierny et al., 2019). Perinatal exposure to **dioxin** enhances the expression of AhR target genes in brain, and alters the neuro-morphology of the brain in mice. It also affects a variety of cognitive and neurobehavioral functions in humans which could also be explained by the expression of the transcription factor AhR in neurons, the latter being a main receptor for dioxin (Kimura et al., 2021). The neurotoxicity of **Organotins** is described in multiple reports, and is linked to the generation of an oxidative stress, to an astrocyte activation, or to an overexpression of inflammatory molecules. This neurotoxicity translates to demyelination and edema. Developmental exposure leads to a reduction of endogenous neurogenesis and influences synaptic plasticity. Exposure to organotins leads ultimately to neurodevelopmental abnormalities, loss of vigilance, disorientation, and memory deficits (Toesca et al., 2016; Ferraz da Silva et al., 2017). **Phthalates** can induce several neurological dysfunctions, such as an impairment of cognition and psychomotor skills in children. A correlation between phthalate exposure and attention-deficit or hyperactivity disorders has been reported in human. Following fetal exposure, phthalates induce brain development disorders that contribute to an impairment of spatial learning and memory. Phthalate neurotoxicity may derive from reactive oxygen species production and from hippocampal down-regulation of brain-derived neurotrophic factor, a key player in dendrite outgrowth and synaptic plasticity associated to cognitive and learning functions. Studies specifically conducted on phthalates neurotoxicity remains however scarce (Kavlock et al., 2006; Lin et al., 2015; Giuliani et al., 2020). **Bisphenol A** affects hippocampal neurogenesis, induces hippocampal neuron apoptosis, and causes behavioral, learning and memory deficits. It also modifies neuronal pathways and/or centers involved in nociception and pain (Khadrawy et al., 2016). Bisphenol A also impairs hypothalamic gliogenesis during postnatal development, and this alters sexual maturation by preventing GnRH neurons which produce gonadotropin-releasing hormone to function in an optimal glial environment (Pellegrino et al., 2021). Experimental evidences that developmental exposure to **perfluorosulfonates** induce neuroendocrine disturbances and neurodevelopmental delays have been reported (Austin et

al., 2003; Lau et al., 2003). Exposure to these molecules lead to spontaneous hyperactivity in zebrafish, disrupt hippocampal cells in mice, and alter the hypothalamic-pituitary-adrenal axis in rats (Long et al., 2013; Spulber et al., 2014; Salgado-Freiria et al., 2018). In human, recent epidemiological data showed that high levels of perfluoroalkyl acids is associated with behavioral difficulties in 7-year old children (Oulhote et al., 2016).

To produce these central deleterious effects, endocrine disruptors need to accumulate into the brain parenchyma to a toxicologically significant extent. The brain is functioning in a secure environment provided by blood-brain interfaces (BBIs) and the cerebrospinal fluid circulation. The BBIs comprise the blood-brain barrier located at the endothelium of the brain vasculature, and the blood-CSF barriers located at the epithelium of the choroid plexuses and at the arachnoid membrane, upstream and downstream of the CSF circulation, respectively. The CSF, mainly produced by the choroid plexuses, circulates in the ventricles of the brain, and then in the subarachnoid and cisternal spaces. It drains the brain before being resorbed either through the venous blood or by drainage into the lymphatic system. Collectively, the BBIs, coupled to the CSF production, circulation and resorption, prevent the accumulation of numerous potentially deleterious compounds of systemic origin into the brain, maintain the cerebral interstitial fluid inorganic ion homeostasis necessary for brain function, and allow an optimal supply of nutriment and micronutrients to the brain. The cerebral vascular network and the choroid plexuses also play an important role in brain development and in the control of neuroimmune interactions (Hladky and Barrand, 2016; Ghersi-Egea et al., 2018b; Liebner et al., 2018).

The cerebral bioavailability of EDCs should therefore be limited to some extent by the BBIs, as a result of 1) the presence of tight junctions that seal the barrier cells together and prevent the paracellular diffusion of blood-borne molecules into the brain interstitial fluid and CSF, 2) the activity of efflux transporters that decrease the transcellular blood-brain influx of many lipophilic compounds and increase the efflux from brain of unwanted metabolites, and 3) the activity of drug metabolizing enzymes, mainly located at the choroidal epithelium, that detoxify exogenous toxic compounds (Strazielle and Ghersi-Egea, 2013). An increasing amount of data points to BBIs dysfunctions as important factors of toxicant-induced neurological disorders (Zheng and Ghersi-Egea, 2020), in line with BBIs playing a key role in the maintenance of cerebral homeostasis. The cerebral bioavailability of EDCs, the influence of

brain interfaces on the entry of EDCs into the central nervous system (CNS), and the impact of EDCs on brain interfaces functions are discussed below.

1 Evidence for the presence of endocrine disruptor chemicals in the brain, mechanism of brain penetration

While a large number of papers describe the central effect of EDCs, few papers actually report actual EDCs concentrations in the brain. Information can be obtained from two types of studies. The first one relates to “wildlife” studies, in which the brain of animals or humans living in polluted areas have been analyzed. The second type relate to experimental studies, in which various animal species were artificially exposed to pollutants, in order to mimic an environmental exposure or an acute toxicity.

1.1 Analysis of brains from species naturally exposed to endocrine disruptor chemicals

Several studies have been conducted on brains from human sampled post-mortem, or from wild-type animals such as birds or fishes. These studies are summarized in Table 2.

Bisphenols is found in brain tissue, with concentration usually higher in animals than in human brain. While Renz et al. find little bisphenol A in the brain of wild fishes (Renz et al., 2013), other laboratories report concentration ranging from 30 ng/g up to 50 ng/g in the brain of this species (Ros et al., 2016). In goose brain, concentrations reach up to 37 ng/g of bisphenol A, and up to 340 ng/g of 4-ter-octylphenol (Bodziach et al., 2021). In comparison, in human, detected concentrations for phenol derivatives do not exceed 3,2 ng/g (Geens et al., 2012; van der Meer et al., 2017; Charisiadis et al., 2018). Both bisphenol A and bisphenol F concentrations were similar in the hypothalamus and the white matter (van der Meer et al., 2017; Charisiadis et al., 2018). The cerebral concentrations depend on the structure of the bisphenols. Chlorobisphenol and Bisphenol-F accumulate more than bisphenol A, the latter being more hydrophilic (Charisiadis et al., 2018). Very few data on **Benzophenones** are available. One study realized postmortem on human brain report that Benzophenone-3 was not detected in the hypothalamus and was detected at concentration up to 0,32g/g in white matter (van der Meer et al., 2017). Numerous **perfluoroalcanes** were found in brains from both human and wild life animals. the concentrations in post mortem samples of human brains are higher, reaching 350 ng/g (Perez et al., 2013), than those measured in the brain of whales (86,6 ng/g) (Dassuncao et al., 2019) and in the brain of polar bears (31,4 ng/g) (Greaves

et al., 2013). **PCBs** are among the most documented EDCs with respect to their accumulation into the brain of animal species naturally exposed to environmental pollutants, and a few studies also report concentrations in human brain. PCBs are declined in numerous congeners (Table 1). In human, the values measured in postmortem brain samples are consistent from one study to another. In one study the sum of 24 PCB concentrations amounts to 11,8 ng/g of tissue and the maximal concentration for the most abundant PCB is 3,1 ng/g of tissue (Chu et al., 2003). In another study performed on 12 selected PCB congeners, the concentration of the most abundant individual PCB congener is 12 ng/g of lipid, which approximately translates to 1,9 ng/g of tissue, based on a lipid content in the wet brain of 16%, and the sum of all 8 measured PCB is equivalent to 8 ng/g of tissue (Mitchell et al., 2012). In a third study the total and individual maximal concentrations is equivalent to 45 ng/g and 24 ng/g, respectively (Bachour et al., 1998). In animals, PCB concentrations measured in brain are more variable. In seals, the total PCB concentration is 9,6 ng/g (Wang et al., 2010). In polar bear that feed on seals, PCBs accumulate in liver and fat to levels 33 and 7,5 higher than in seal, respectively, while the cerebral concentration remains low and equivalent between the two species, which could suggest efficient blood-brain interfaces to limit the penetration of PCB in the mammalian brain (Letcher et al., 2009). In fish brain the total PCB concentration is variable between studies, ranging from 40 ng/g tissue (sum of 12 congeners) (Bachour et al., 1998) to 19,9 µg/g of lipids (approximately 3 µg/g of tissue) (Brazova et al., 2012). In Birds the total cerebral concentration of 7 PCB was found to be 13 ng/g in cormorants and up to 428 ng/g wet weight in sparrow hawks (Naert et al., 2007). Whether the variability in brain concentrations observed in non-mammals species is due to differential exposure to PCB or to differences in blood-brain interfaces efficiency to reduce brain exposure to PCBs is unknown.

Paraben concentration in the brain varies according to species and to the geographic area of study. Concentrations of methyl Paraben and its main metabolite p.hydroxybenzoic acid were found to be respectively 25,4 and 370 ng/g in common dolphins brains, which was lower than those measured in other organs. (Jeong et al., 2019). Another study performed on fishes provides different results. A total of 58 brain fishes was analyzed for methyl, ethyl, propyl and butyl parabens and none was detected (Renz et al., 2013). In human, parabens were detected at concentrations up to 1.16 ng/g in hypothalamus and 0,26 ng/g in white-matter tissue (van der Meer et al., 2017). **Dioxins** has also been detected in brain with TCDD levels ranging from 0,11 pg/g in fishes to 0,4 –3,3 pg/g in seabirds. The brain was the organ were TCDDs were

detected at the lowest level (Wu et al., 2000; Wan et al., 2006). The brains of three infants that died from Sudden infant death syndrome were analyzed for dioxin. The levels were very low, revealing an absence of dioxin accumulation in this tissue (Beck et al., 1994). Data on **Organotins** concentrations in the brain are very scarce, with only one study reporting butyltin and phenyltin to be present in brains of fishes at concentrations of 0,2 mg/g and 0,1 mg/g, respectively. These concentrations are similar to those measured in other organs (Harino et al., 2000). No data seems available concerning **phthalates**.

In conclusion, the limited data available in brain concentrations of species naturally exposed to environmental pollutants suggest that, with the exception of perfluoroalkanes, cerebral levels of EDCs are higher in animals than in human. We can hypothetically conclude that wild life animals live in a higher EDCs-contaminated environment than human. It may also be possible that mammals and especially primate brains are better protected from EDCS accumulation than other species by blood-brain interfaces.

1.2 Experimental evidence for the accumulation of endocrine disruptor chemicals in the brain

Prediction of EDCs accumulation into the brain also comes from experimental studies in which laboratory animals are exposed to these chemicals. This raises the question of the toxicological relevance of these approaches, in which the doses and route of administration sometimes mimics more an acute intoxication than an environmental exposure. These studies provide however mechanistic information relative to the brain penetration and accumulation of EDCs. Surprisingly, to our knowledge no experimental data are available concerning paraben penetration into the brain, while numerous studies measured brain concentration in in wild animals (see above). Examples of experimental data obtained from the other EDCs families are shown in Table 3. They generated the following information.

A. Influence of the exposure scheme. The concentrations found into the brain is strongly dependent on the type of exposure (single dose versus chronic treatment), doses, and administration routes which can include oral gavage, exposition through drinking water, intravenous or intraperitoneal injection, or dermal exposure). For example, in adult male rats, tributyltin given at a dose of 30 mg/Kg by gavage leads 3 days later to tin brain concentrations ranging from 3 to 15 ng/g depending of brain areas, (~15-80 ng/g of tributyltin) (Mitra et al., 2015). When given a lower tributyltin-equivalent dose of 1 mg/kg by gavage, brain Tin

concentrations were ~20 ng/brain (15 ng/g) 24 hours later (Rodriguez-Gonzalez et al., 2005). In contrast intraperitoneal exposure to 2,5 or 4 mg/kg of tributyltin led to tributyltin brain concentration reaching 1,5 µg/g after 16 hours (Doctor et al., 1983), and to an olfactory bulb concentration of 1 µg/g after 3 days (Tomiyama et al., 2010). As another example, in rat an intravenous infusion of benzyl butyl phthalate at 5 mg/kg/hour for 18 hours led to a brain concentration of 68 ng/g (Kim et al., 2015), while the ingestion by gavage of a 50 mg/kg Di-(2-ethylhexyl)phthalate dose, or ingestion of dibutylphthalate for four weeks through feed at dosed at 1g/kg, led only to traces of the phthalates in the brain (Williams and Blanchfield, 1975; Ikeda et al., 1978).

In developing animals, an additional degree of complexification is reached as the routes of EDCs delivery to the brain involves access to the fetus across the placenta, and after birth feeding on contaminated milk. Bisphenol A given to pregnant dams at a single dose of 100 µg/kg, was not detected in fetuses when the route of administration was by gavage, while it readily accumulated in the fetal brain when administered intravenously. This indicates that the route of administration changes the systemic bioavailability of the EDC and that to some extent the placental barrier restricts the access of the molecule to the fetus. (Doerge et al., 2011). When dams were treated orally with dioxin at a dose of 10 µg/kg at gestational day 15, the mother brain contained 0,42 ng/g of dioxin 24 hours later and 0,35 ng/g 5 days later. The time course of dioxin concentration in fetal brains was inverted, from 0,193 ng/g 24 hours after treatment to 0,298 ng/g 5 days later (Ishida et al., 2010), again indicating the placental influence on the kinetic of dioxin accumulation in the fetal brain. Another study based on rat dam exposure to organotins by oral gavage from gestational day 8 onwards, showed that the fetal brains accumulated the compounds, and that pups brain retained organotin for several days after birth. Transfer of both tributyltin and dibutyltin to pups through lactation appeared to be minimal, and the origin of organotins found in the brain postnatally was mainly the initial gestational exposure (Cooke et al., 2008).

B. Influence of endocrine disruptor chemical half-lives. EDC biological half-life is highly dependent on chemical family to which they belong, and can range from hours, to days or even years. The serum half-lives of parabens, phthalates, benzophenones and bisphenol are relatively short in human, ranging from <1hours for the first two families, to 7-9 hours, and 6-20 hours, for benzophenones and bisphenols, respectively. The metabolites of these EDCs are often eliminated more slowly. Organotin half-lives are in the month range, and

perfluoroalkanes, dioxins and PCBs present much longer half-lives, respectively of 3-8 years, 6-11 years and 4-41 years (Table 1). This may in part explain the lack of experimental studies investigating brain concentration of parabens, as their pharmacokinetic complicates the experimental setting allowing to measure the brain penetration of these compounds. The short half-lives of phthalates may also in part contribute to the limited amount of the native molecules found in the brain, as they are rapidly metabolized (table 3). The influence of the biological half-life on EDC brain penetration depends on the nature of peripheral tissue in which EDCs are stored within the body, which will impact the actual concentration of EDC circulating in the plasma, i.e. available for delivery to the brain. If the brain itself is a storage tissue for EDC, long half-lives are obviously a key factor setting cerebral concentrations. Differences between animal species need to be considered when extrapolating data from animals to human. For instance, mice and humans display similar bisphenol A half-lives that are close to 12 hours, while other species such as horses, sheeps and dogs display shorter half-lives that range from 0.6 to 5 hours (Table 1). The half-life of benzophenone-3 appears also higher in human than in rodent.

C. Variability between endocrine disruptor families. The different families of EDCs have very different abilities to penetrate into the brain. For example, considering an identical route of exposure, and very long half-lives for both families, the brain concentration-to-administered dose ratio is 20 times higher for perfluoroalkanes than for Dioxin, and the brain-to-plasma concentration ratio at the time of brain sampling is 4.5 times higher for the perfluoroalcanes than for dioxin (Ishida et al., 2010; Kawabata et al., 2017). These comparisons between studies however suffer from different limitations such as the differences in the doses used between EDC families, or experimental protocols that are not always described in sufficient details to warrant a correct comparison. Formal comparisons of EDC cerebral bioavailability within a same study in which EDCs plasma concentrations are monitored over time are crucially lacking.

D. Variability within endocrine disruptor families. Within an EDCs family, brain levels of EDCs that belong to a same family also vary according to the number and position of substituents on the molecules. For instance, when comparing tri, di or monobutyltin cerebral levels following identical dosing, tributyltin was found to be the most abundant species in brain. This is likely explained by its higher lipophilicity (Rodriguez-Gonzalez et al., 2005). When

benzophenone 2 and 3 were administered through dermal exposure at a dose of 100mg/kg twice a day for 22 days, Benzopheneone 3 was found in different brain regions at concentrations ranging from 40 to 50 ng/g (Pomierny et al., 2019), while benzophenone 2 levels were of 5 to 20 ng/g only following a four week-treatment (Broniowska et al., 2019). The administration of three perfluoro acids, perfluorooctanoic acid, perfluorodecanoic acid and perfluorododecanoic acid, given as a single oral dose of 50mg/kg- to rats, led to brain concentration after 10 days that were not detectable, 4.7 µg/g and 44 µg/g, respectively. This shows the strong influence of the number of fluorinated carbons on brain distribution of perfluorinated compounds (Kawabata et al., 2017). Perfluorododecanoic acid, whose brain/serum ratio reached 1.8, caused more cognitive deficits than the other two perfluoro acids (Kawabata et al., 2017). The cerebral availability of different PCB congeners has also been studied. In rats, following inhalation exposure to congeners with ortho-substitution ranging from mono- to pentachlorobiphenyls (aroclor 1242), highest PCB concentrations in brain were found for PCB 20 and PCB 28 (trichlorinated PCB) both with one ortho chloro substitution (Hu et al., 2010). In another study four PCBs have been given by intramuscular injection to pregnant sheep. One of them PCB 169, which bear no ortho substitution, was found at low level in adult sheep brain by comparison to blood circulating levels, but surprisingly strongly accumulated in the lamb brain. This was not observed to the same extent with the other compounds (Jan et al., 1999). These data show that PCBs have different abilities to penetrate into the brain, the underlying mechanisms being for now understood.

1.3 Role of blood-brain interfaces in controlling the cerebral penetration of endocrine disruptor chemicals

The extent to which brain barriers contribute to the differences in brain accumulation observed between EDCs has not been thoroughly investigated. Tight junctions prevent paracellular diffusion of molecules across brain interfaces. This strongly restrict blood-to-brain permeability of most hydrophilic compounds, and likely explains the strong difference in cerebral levels, and in blood-to-brain concentration ratio, observed between different organotin species with varying lipophilicity (Rodriguez-Gonzalez et al., 2005). It may also in part explain the differential cerebral bioavailability of PCB congeners (Ness et al., 1994; Jan et al., 1999) and the low concentration of benzophenone-2 in brain despite its high serum and adipose tissue levels (Broniowska et al., 2019). However, these studies and most other studies

describing brain bioaccumulation of EDCs are not designed to specifically evaluate EDCs blood-brain permeability. For instance, whether experiments are performed at blood-to-brain steady state concentration ratio is not controlled, or area-under-the-curve of blood concentration time function is not measured, preventing accurate permeability coefficients to be determined. True influx constant measurements, which can be achieved both in adult and in developing rodents, (Gherzi-Egea et al., 2015) would shed more light on the efficiency of brain barriers to limit the penetration of EDCs into the CNS. Plasma protein binding and accumulation in cerebral cells over long period of time are other factors that set brain concentration levels in addition to the intrinsic blood-brain interfaces permeability to EDCs. To distinguish high blood-brain permeability from long-term retention in neural cell membranes, EDCs concentration can be measured in the brain interstitial fluid (ISF) and in the CSF. This can be done by direct CSF sampling or by microdialysis of ISF. To our knowledge only one study used this approach coupled to HPLC-mass spectrometry, to show in monkey that a bolus intravenous injection of 100 µg/kg bisphenol A led to a hypothalamic ISF concentration of the compound that was 5 times lower than the plasma concentration (Kurian et al., 2015). Besides tight junctions which limit the penetration of polar xenobiotics into the brain, efflux transporters can limit the cerebral accumulation of amphiphilic and lipophilic compounds. At the BBB the main efflux transporters are ABCB1 (p-glycoprotein), ABCG2 (Breast Cancer Resistant protein), and selected organic anion and cation transporters such as SLC22A8 (OAT3). At the BCSFB, efflux transporters include, but are not restricted to, ABCC1 and ABCC4, SLC22A8, and in rodent *oatp3* and *oatp2* (Strazielle and Gherzi-Egea, 2013). The recognition of EDCs as substrates for efflux transporters at the BBB and BCSFB has not been investigated, but studies conducted in carrier-expressing cells, peripheral organs, and whole organisms provide evidence that some EDCs are substrates for these efflux transporters. Experiments realized in urchin's embryo showed that Bisphenol A used at a 100 nM concentration is prevented from accumulating in embryonic cells by *Abcb1* (Bosnjak et al., 2014). Transcellular transport studies across Caco-2 epithelial cells monolayers in the presence of verapamil used as an ABCB1 inhibitor also indicate that bisphenol-A is an ABCB1 substrate (Yoshikawa et al., 2002). However, another study realized *in vitro* using transporter-expressing cells suggest that bisphenol A is substrate for human but not rat ABCG2, albeit with a probable high K_m (optimal concentration of 30 µM (Mazur et al., 2012). The measurement of bisphenol A accumulation by MDCK cells overexpressing human ABCG2 or ABCB1 transporters, following exposure to 40

nM of the compound, confirmed that this molecule is substrate for ABCG2 (Dankers et al., 2013). These differences in transporter recognition observed among studies may be explained by species-related transporter affinity differences for bisphenols, and/or by the limited specificity of the transporter inhibitors used in the studies. Experiments using SLC22A6 and SLC22A8 expressing embryonic human kidney cells exposed to 10 μ M perfluoroalkanes showed that several of these compounds, including perfluoro-octanoate, were transported by these organic anion carriers. This may be of special relevance to the blood-CSF barrier where CSF-to-blood organic anion efflux is highly active (Strazielle and Ghersi-Egea, 2013). perfluorooctanoic acid used at a 1 μ M concentration was also shown to be substrate for ABCG2, but not ABCB1, when these ABC proteins were overexpressed in MDCK cells (Dankers et al., 2013). Data concerning phthalates are controversial. One study suggests that neither Bis(2-ethylhexyl) phthalate, nor mono(2-ethylhexyl) phthalate, (1 to 100 μ M) interacts with ABCB1, ABCG2 and ABCC transporters (Dankers et al., 2013), while other studies suggest that the former can be substrate for ABCB1, albeit at high concentration (Yoshikawa et al., 2002; Kim et al., 2007). The use of engineered cell lines overexpressing mouse or human ABCB1, as well as of mice knockout for *Abcb1* showed that this efflux transporter did not transport PCBs and did not interfere with their diffusion into the brain. Data generated using tumor cells showed that Organotins appears not transported by ABCB1 either (Rocamora-Reverte et al., 2012; Bohacova et al., 2018). To our knowledge, no information concerning the ability of efflux carrier identified at the brain barriers other than those discussed above to transport EDCs is available, and no information relative to any efflux transporter is available concerning the transport of parabens, dioxins and benzophenone. Finally, as in an environmental setting the body is exposed simultaneously to multiple EDCs from the same families (e.g. PCBs, phthalates), or even to multiples EDCs from different families, potential interactions between EDCs for cerebral influx and efflux mechanisms would be worth investigating.

Drug metabolizing enzymes are associated with blood-brain interfaces and can impact the cerebral bioavailability of toxicant. This is especially true at the blood-CSF barrier, where several detoxifying enzymes, mainly of the phase II of drug metabolism, are highly expressed, sometimes reaching hepatic levels. They include glutathione-S-transferases (GSTs), UDP-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs) (Strazielle and Ghersi-Egea, 1999; Kratzer et al., 2013; Kratzer et al., 2018). No information is available concerning the efficiency of these enzymes to act as a metabolic barrier limiting EDCs concentration into the

CNS. However, some EDCs are conjugated in peripheral organs, suggesting that a similar metabolism could also occur at brain barriers. For instance, UGT1A1 is the main Phase II enzyme implicated in the direct detoxification of benzophenone 2 in hepatocytes (de Sousa et al., 2016). Bisphenol F and bisphenol A are bio-transformed into both glucuronide and sulfo-conjugates by the liver (Cabaton et al., 2008; Ousji et al., 2020). Tetrabromo-bisphenol A is also conjugated to glucuronic acid in the liver (Zalko et al., 2006). The uterine epithelial sac forms an enzymatic barrier restricting the access of bisphenol A to the embryo, through a conjugation of the compound by UGT followed by an extrusion of the metabolite into the maternal side (Matsumoto et al., 2007). This mechanism shows similarities with the coupled conjugation and efflux processes evidenced at the blood-CSF barrier for other toxicants in rat (Strazielle and Ghersi-Egea, 1999; Kratzer et al., 2018). Many paraben molecules are actively glucuronidated by the liver, in addition to being hydrolyzed (Abbas et al., 2010). Although PCB are mainly metabolized into hydroxylated metabolites, some, such as PCB11, are undergoing further extensive phase II metabolism, presumably by glucuronidation and sulfation in the liver (Hu et al., 2014). EDCs such as dioxins and organotin undergo a metabolic transformation limited to an oxidative (phase I), cytochrome P-450-dependent process.

Altogether this literature indicates that our knowledge on the capacity of brain barriers to reduce the cerebral bioavailability of different EDCs into the brain would benefit from studies evaluating the role of efflux transporters and metabolic enzymes located at blood-brain interfaces in this process.

The question of the cerebral regionalization of EDCs accumulation needs to be raised. The vascular network density varies from one brain area to another, with large differences between grey and white matter (Wei et al., 1993). A differential permeability between the BBB and the BCSFB can influence EDCs concentration in periventricular areas. Accumulation of EDCs by neural cells can differ from one area to another. Yet, few investigations of EDCs brain levels have been done at the regional level. In human, no obvious difference in bisphenol A and bisphenol F concentration was observed between the hypothalamus and the white matter (van der Meer et al., 2017; Charisiadis et al., 2018). Similarly, no gross variations on Bisphenol A concentration was observed between brain regions micro-dissected 48 hours after a 100 mg/kg oral dose of the EDC (Kim et al., 2004). In contrast, benzophenone 3 was detected in human white matter but not hypothalamus (van der Meer et al., 2017), and experimental studies from another group showed that while benzophenone 3 concentrations

were similar between the frontal cortex and the hippocampus in rat topically exposed to the drug (Pomierny et al., 2019), the concentration of benzophenone 2 was four times lower in hippocampus than in the cortical area (Broniowska et al., 2019). Autoradiography is a highly resolutive technique that has been used in the past to unravel changes in EDCs concentrations in small brain structures. For example, this allowed to demonstrate a preferential accumulation of di-(2-ethylhexyl)phthalate in the neuroepithelium of the mouse embryo that generate neural cell precursors, following exposure of the dam to the molecule (Lindgren et al., 1982). Unfortunately, the complication of the legislation with respect to the use of radioisotopes, and the autoradiographic technique itself which can be time consuming when low levels of radioactivity are expected, necessitating days or weeks of exposure to radiosensitive film/detectors, prevent its use in most laboratories.

Finally, the question of the blood-brain interfaces permeability towards EDCs during the embryonic and postnatal periods of development needs to be addressed. For a long time, the brain barriers have been considered more permissive during development than in adult, making the placenta the main barrier between the mother blood and fetal brain prior birth, and suggesting an easy cerebral penetration of toxicants during the postnatal period of development. Tight junctions that seal the barrier cells however are efficient very early during development, and choroidal enzymatic detoxifying systems are especially active during the perinatal period, when the liver is still immature. The developmental profile of efflux transporters varies from one protein to another (Strazielle and Ghersi-Egea, 2015). In this respect ABCB1 substrates may be more prone to reach the developing brain as the expression and activity of ABCB1 at the blood brain barrier reach adult levels only postnatally. The relative importance of the blood-CSF barrier as a gate of entry into the brain is higher during development than in adult. This results from the early appearance and maturation of the choroid plexuses, while the vascular network develops only gradually pre and postnatally (Ek et al., 2012; Ghersi-Egea et al., 2018a; Ghersi-Egea et al., 2018b). The mechanisms that set the blood-brain permeability of EDCs during fetal, postnatal and adult periods of life are therefore bound to be different, and need to be addressed by dedicated studies.

2. Analytical hurdles to the assessment of endocrine disruptor chemical concentrations in the brain

The amounts of EDCs in brain often range from 10 to 100 ng/g, or even below, yet these low concentrations remain toxicologically significant. Therefore, accurate techniques are required with high sensitivity and very low limit of quantification, to help interpret epidemiological studies on the central effect of exposure to EDCs, and mechanistic studies on EDC neurotoxicity. EDCs can enter the brain as a mixture of compounds, and metabolites of the mother molecules can be present. Precisely identifying the molecular species present in the brain, and measuring the concentration of multiple endocrine disruptors in a single analysis is therefore very important. Ultra or high-performance liquid chromatography tandem Mass spectroscopy, with triple quadrupole mass spectrometer detector is the technique of choice used for the quantification of most EDCs levels in brain (phthalates, Bisphenol, Perfluoroalkanes, paraben, benzophenone). For some specific molecules, more tailored techniques are needed. For example, gas chromatography analysis is more adapted to PCB or dioxin quantification. In the case of organotins, the accumulation of tin (Sn) in brain tissue can be measured by atomic emission spectroscopy (Cooke et al., 2008).

These different pieces of equipment needed to perform EDCs analyses are technologically advanced and often require specific expertise. It is important to note also that a sample preparation is necessary before the analysis is performed. The EDCs needs to be extracted from brain tissue, the samples cleaned up, and concentrated. Solid phase extraction, liquid-liquid extraction, chiral chromatography, filtration, and concentration, are techniques widely used for sample preparation, that also require expertise and can be time-consuming. For selected studies such as brain regionalization of EDC levels, additional analytical tools can be called for, such as autoradiography using radioactive compounds. Widely used in the 1980-2000 years, these techniques are not so commonly used nowadays and can be performed only in dedicated laboratories. These technological constraints likely explain the limited number of correlative analysis that combine measurement of EDCs concentration within the brain with studies assessing the neurological consequences of systemic exposure to EDCs. This is why the research field of neurotoxicology applied to EDCs will greatly benefit from multicentric programs associating laboratories with an analytical chemistry expertise, to laboratories specialized in neurobehavior, neurophysiology, cerebral cellular biology, and blood-brain barrier studies.

3. Evidences that blood-brain interfaces can be toxic targets for endocrine disruptor chemicals

In the recent years the dynamic regulation of brain interfaces functions, including the limitation of paracellular diffusion by tight junctions, influx and efflux transport processes, and neuroimmune interactions has been highlighted, and in some instances involves endocrine receptors. This prompted a regain of interest to investigate the brain barriers themselves as targets for EDC toxicity in the last 6 years. The data still remain scarce, and concern mostly the blood-brain barrier. Both historical and new studies are mostly restricted to overall barrier integrity assessment following exposure to organotins, phthalates and organohalogens. Efflux transporters and immune activation have also been investigated in the context of phenol derivatives and perfluoroalcanes exposure. Table 4 summaries the main literature that investigated the effects of environmental endocrine disruptors on blood-brain interfaces function *in vivo* or using isolated capillaries.

Studies realized with organotins where based on toxic exposure regimen mimicking acute intoxication. The observed effects on BBB integrity are controversial. For instance, tributyltin has been found to affect the barrier transiently (Hara et al., 1994), or in a more sustained fashion (Mitra et al., 2015). Triethyltin and trimethyltin have been reported to either increase barrier permeability (Joo et al., 1969; Ceccariglia et al., 2014), or have no effect (Hultstrom et al., 1984; Inoue et al., 1987; Little et al., 2002). These discrepancies appear not linked to the route of administration (Table 4). Exposure to phthalates, in a setting mimicking environmental human exposure, induce an increased BBB permeability, accompanied by a decrease in the expression of a tight junction accessory molecule and of a protein involved in caveolin formation (Ahmadpour et al., 2021). Among organohalogens, only PCBs have been studied for their effect on the blood-brain barrier, mainly by two laboratories. The first group reports decreased expression of Cldn5, and variable, sometimes contradictory (occludin) effects on other tight junction proteins in adult mice. Some of these studies are unclear with respect to the level of PCB exposure applied, but the administration scheme seems to reflect mostly acute intoxication with for example a reported oral dose of 50 mg/kg (150 μ mole/kg) (Seelbach et al., 2010; Eum et al., 2015). The group interestingly reports a potentiation of PCB effects on the BBB when the toxic molecule is bound to nanoparticles (Zhang et al., 2012; Zhang et al., 2013). The second group reports a downregulation of many tight junction-associated proteins following an intraperitoneal treatment of 2mg/kg Arochlor in rat (Selvakumar et al., 2018). Among perfluoroalcanes, perfluorooctane sulfonate was shown to induce tight junction protein downregulation and endothelial morphological alterations when given orally and chronically to

mice at doses relevant to human exposure (Yu et al., 2020). The limited information available for parabens, once used as adjuvant in radiopack administered to patients for imaging, suggests that, at least when used acutely, these molecules do not induce gross alteration of the barrier integrity (Craver et al., 1968; Strain et al., 1969). No information is to our knowledge available concerning benzophenone.

BBB alterations may be subtler than an overt barrier dysfunction linked to tight junction alteration and may concern only selected barrier functions, yet remaining toxicologically significant. This was observed mainly for phenol derivatives and perfluoroalcanes. Exposing isolated capillaries to bisphenol A induces a weak-to-sustained inhibition of ABCG2 expression and function depending on the concentration used, and a sex dependent change in ABCB1 function (Nickel and Mahringer, 2014; Cannon et al., 2019). These two efflux transporters are key elements of the BBB neuroprotective functions. A dysfunction of these two transporters has also been observed in live capillaries isolated from both male and female rats, upon *ex vivo* exposure to the perfluoroalkane GEN-X, or in capillaries isolated from GEN-X-treated rats (Cannon et al., 2020). Benzophenones have been identified as inhibitors of ABCB1, (Farman et al., 2020), Bisphenols as inhibitors of organic anion and cation transporters (Bruyere et al., 2017) in non-brain systems, but their interaction with brain-interface transporters has not been characterized.

Exposure to phenol derivatives such as bisphenol A also induces an increased immune cell accumulation in meningeal and perivascular spaces (Brinkmayer 2014) and an overall increased neuroinflammation (Brinkmeyer-Langford et al., 2014; Rogers et al., 2017) in responses to inflammatory challenges. Whether this involves a direct effect of bisphenol A on BBB-associated immune attributes such as adhesion molecules remain to be assessed.

Only one group investigated the effect of an endocrine disruptor on the choroid plexus functions. They showed that chronic exposure to PCB153 mimicking an environmentally relevant human exposure induces a decrease in the choroidal expression of tight junction proteins and also an alteration in the VEGF/VEGF receptor signaling that may impact the choroid plexus vasculature in the female sheep (Szczepkowska et al., 2013; Szczepkowska et al., 2016).

These few studies highlighting BBI-specific functional alterations upon endocrine disruptor exposure, clearly call for a more thorough investigation of specific transport pathways responsible for both influx and efflux at brain barriers, and involving all SLC proteins, ABC proteins, and receptors responsible for targeted transcytosis. They also call for the investigation of other BBI functions such as immune quiescence, neuroimmune regulation, and endocrine functions. It is surprising that the choroid plexuses did not deserve more attention as a potential

target for endocrine disruptors, since these structures are considered as being endocrine organs. They are both sources of, and targets for, various biologically active endogenous molecules and hormone carriers. The endocrine functions of the choroid plexuses play important role in brain development, and throughout life to maintain cerebral homeostasis (Gherzi-Egea et al., 2018b). An almost completely overlooked field of research is the effect of endocrine disruptors on the developmental profile of neuroprotective BBI attributes. The brain develop in a specific environment controlled by blood-brain interfaces whose properties evolve during pre- and postnatal development. The developmental characteristics of the BBB are partly under the prenatal influence of pericytes and postnatal influence of glial cells (Ek et al., 2012; Strazielle and Gherzi-Egea, 2015; Gherzi-Egea et al., 2018a). If altered, the developmental regulation of BBI functions can impact the establishment of neural networks, and brain maturation. Only one *in vitro* work showed that TCDD can interfere with glial-endothelial cell cross talk, leading to a decrease in the integrity of a cerebral endothelial cell monolayer (Miyazaki et al., 2016). Finally, TCDD binds to, and activate the Ah receptor, and this translate in the induction of ABCG2 and ABCB1 transporters expression, a mechanism shown to occur also at the blood-brain barrier (Wang et al., 2011; Campos et al., 2012; Halwachs et al., 2013). This property is shared by coplanar, dioxin-like” PCBs which in non-brain cell system induce ABCG2 (Manzini et al., 2017). As AhR activation can also lead to an upregulation of CYPs involved in deleterious metabolic activation processes, the meaning of these activation pathway needs to be further explored at the levels of the brain interfaces.

Conclusion.

EDCs are exogenous and persistent agents found at low doses in thousands of products. They disturb the normal endocrine functions in human and animals through different routes and can be transferred from mother to fetus. EDCs can have an action on selected peripheral endocrine organs, interfere with the general endocrine pathways, and in some instances alter the central regulation of neuroendocrine pathways. As such they can be classified as neurotoxic molecules. The mains exogenous molecules with such effects are perfluoroalcanes, parabens, phthalates, organotins, bisphenols, benzophenones, polychlorinated biphenyls, and dioxins. The present review of the literature reveals large family- and structure-dependent differences in the accumulation of EDCs in the brain. The data suggest that blood-brain interfaces limit the cerebral accumulation of some of the EDCs, although most evidences

are so far indirect. Measuring EDCs in the brain remains challenging, and call for sophisticated Analytical/ equipment, and dedicated expert scientists. The literature analysis also points to the brain interfaces as potential targets for EDCs. Functional alteration of these barriers, even subtle, will be a risk factor for further neurological impairment, as it will increase the susceptibility of the brain towards other deleterious, potentially neurotoxic compounds. Clearly more specific brain interface-oriented studies are called for in this field of neurotoxicology.

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References.

- Abbas S, Greige-Gerges H, Karam N, Piet MH, Netter P, Magdalou J (2010) Metabolism of parabens (4-hydroxybenzoic acid esters) by hepatic esterases and UDP-glucuronosyltransferases in man. *Drug Metab Pharmacokinet* 25:568-577.
- Ahmadpour D, Mhaouty-Kodja S, Grange-Messent V (2021) Disruption of the blood-brain barrier and its close environment following adult exposure to low doses of di(2-ethylhexyl)phthalate alone or in an environmental phthalate mixture in male mice. *Chemosphere* 282:131013.
- Annamalai J, Namasivayam V (2015) Endocrine disrupting chemicals in the atmosphere: Their effects on humans and wildlife. *Environ Int* 76:78-97.
- Austin ME, Kasturi BS, Barber M, Kannan K, MohanKumar PS, MohanKumar SM (2003) Neuroendocrine effects of perfluorooctane sulfonate in rats. *Environ Health Perspect* 111:1485-1489.
- Aylward LL, Collins JJ, Bodner KM, Wilken M, Bodnar CM (2013) Elimination rates of dioxin congeners in former chlorophenol workers from Midland, Michigan. *Environ Health Perspect* 121:39-45.
- Bachour G, Failing K, Georgii S, Elmadfa I, Brunn H (1998) Species and organ dependence of PCB contamination in fish, foxes, roe deer, and humans. *Arch Environ Contam Toxicol* 35:666-673.
- Beck H, Dross A, Mathar W (1994) PCDD and PCDF exposure and levels in humans in Germany. *Environ Health Perspect* 102 Suppl 1:173-185.
- Bodziach K, Staniszevska M, Falkowska L, Nehring I, Ozarowska A, Zaniewicz G, Meissner W (2021) Distribution paths of endocrine disrupting phenolic compounds in waterbirds (*Mergus merganser*, *Alca torda*, *Clangula hyemalis*) from the Southern Baltic. *Sci Total Environ* 793:148556.
- Bohacova V, Seres M, Pavlikova L, Kontar S, Cagala M, Bobal P, Otevrel J, Brtko J, Sulova Z, Breier A (2018) Triorganotin Derivatives Induce Cell Death Effects on L1210 Leukemia Cells at Submicromolar Concentrations Independently of P-glycoprotein Expression. *Molecules* 23.
- Bonefeld-Jorgensen EC, Andersen HR, Rasmussen TH, Vinggaard AM (2001) Effect of highly bioaccumulated polychlorinated biphenyl congeners on estrogen and androgen receptor activity. *Toxicology* 158:141-153.
- Bosnjak I, Borra M, Iamunno F, Benvenuto G, Ujevic I, Buselic I, Roje-Busatto R, Mladineo I (2014) Effect of bisphenol A on P-glycoprotein-mediated efflux and ultrastructure of the sea urchin embryo. *Aquat Toxicol* 156:21-29.
- Boucher JG, Boudreau A, Atlas E (2014) Bisphenol A induces differentiation of human preadipocytes in the absence of glucocorticoid and is inhibited by an estrogen-receptor antagonist. *Nutr Diabetes* 4:e102.
- Braun JM, Eliot M, Papandonatos GD, Buckley JP, Cecil KM, Kalkwarf HJ, Chen A, Eaton CB, Kelsey K, Lanphear BP, Yolton K (2021) Gestational perfluoroalkyl substance exposure and body mass index trajectories over the first 12 years of life. *Int J Obes (Lond)* 45:25-35.
- Brazova T, Hanzelova V, Miklisova D (2012) Bioaccumulation of six PCB indicator congeners in a heavily polluted water reservoir in Eastern Slovakia: tissue-specific distribution in fish and their parasites. *Parasitol Res* 111:779-786.
- Brinkmeyer-Langford C, Rodrigues A, Kochan KJ, Haney R, Rassu F, Steelman AJ, Young C, Riggs P, Storts R, Meagher MW, Welsh CJ (2014) Consequences of perinatal bisphenol A exposure in a mouse model of multiple sclerosis. *Autoimmunity* 47:57-66.

- Broniowska Z, Bystrowska B, Starek-Swiechowicz B, Pomierny B, Krzyzanowska W, Walczak M, Budziszewska B (2019) Benzophenone-2 Concentration and Its Effect on Oxidative Stress and Apoptosis Markers in Rat Brain. *Neurotox Res* 36:39-48.
- Brown RA, Nazario CM, de Tirado RS, Castrillon J, Agard ET (1977) A comparison of the half-life of inorganic and organic tin in the mouse. *Environ Res* 13:56-61.
- Bruyere A, Hubert C, Le Vee M, Chedik L, Sayyed K, Stieger B, Denizot C, Parmentier Y, Fardel O (2017) Inhibition of SLC drug transporter activities by environmental bisphenols. *Toxicol In Vitro* 40:34-44.
- Cabaton N, Zalko D, Rathahao E, Canlet C, Delous G, Chagnon MC, Cravedi JP, Perdu E (2008) Biotransformation of bisphenol F by human and rat liver subcellular fractions. *Toxicol In Vitro* 22:1697-1704.
- Campos CR, Schroter C, Wang X, Miller DS (2012) ABC transporter function and regulation at the blood-spinal cord barrier. *J Cereb Blood Flow Metab* 32:1559-1566.
- Cannon RE, Trexler AW, Knudsen GA, Evans RA, Birnbaum LS (2019) Tetrabromobisphenol A (TBBPA) Alters ABC Transport at the Blood-Brain Barrier. *Toxicol Sci* 169:475-484.
- Cannon RE, Richards AC, Trexler AW, Juberg CT, Sinha B, Knudsen GA, Birnbaum LS (2020) Effect of GenX on P-Glycoprotein, Breast Cancer Resistance Protein, and Multidrug Resistance-Associated Protein 2 at the Blood-Brain Barrier. *Environ Health Perspect* 128:37002.
- Ceccariglia S, D'Altocolle A, Del Fa A, Silvestrini A, Barba M, Pizzolante F, Repele A, Michetti F, Gangitano C (2014) Increased expression of Aquaporin 4 in the rat hippocampus and cortex during trimethyltin-induced neurodegeneration. *Neuroscience* 274:273-288.
- Charisiadis P, Andrianou XD, van der Meer TP, den Dunnen WFA, Swaab DF, Wolffenbuttel BHR, Makris KC, van Vliet-Ostapchouk JV (2018) Possible Obesogenic Effects of Bisphenols Accumulation in the Human Brain. *Sci Rep* 8:8186.
- Choi JJ, Choi YJ, Chen L, Zhang B, Eum SY, Abreu MT, Toborek M (2012) Lipopolysaccharide potentiates polychlorinated biphenyl-induced disruption of the blood-brain barrier via TLR4/IRF-3 signaling. *Toxicology* 302:212-220.
- Chu S, Covaci A, Schepens P (2003) Levels and chiral signatures of persistent organochlorine pollutants in human tissues from Belgium. *Environ Res* 93:167-176.
- Collet SH, Picard-Hagen N, Lacroix MZ, Puel S, Viguie C, Bousquet-Melou A, Toutain PL, Gayrard V (2015) Allometric scaling for predicting human clearance of bisphenol A. *Toxicol Appl Pharmacol* 284:323-329.
- Cooke GM, Forsyth DS, Bondy GS, Tachon R, Tague B, Coady L (2008) Organotin speciation and tissue distribution in rat dams, fetuses, and neonates following oral administration of tributyltin chloride. *J Toxicol Environ Health A* 71:384-395.
- Craver BN, Chinn C, Hess SM, Swoap JR (1968) Penetration through the blood-brain barriers of cats after intracarotid injections of 125-I sodium diatrizoate, methylglucamine diatrizoate, or methylglucamine diatrizoate plus parabens and the retention of 131-I methylglucamine diatrizoate in the blood of rats. *Radiology* 90:142-146.
- Dankers AC, Roelofs MJ, Piersma AH, Sweep FC, Russel FG, van den Berg M, van Duursen MB, Masereeuw R (2013) Endocrine disruptors differentially target ATP-binding cassette transporters in the blood-testis barrier and affect Leydig cell testosterone secretion in vitro. *Toxicol Sci* 136:382-391.
- Darbre PD (2020) Chemical components of plastics as endocrine disruptors: Overview and commentary. *Birth Defects Res* 112:1300-1307.

- Dassuncao C, Pickard H, Pfohl M, Tokranov AK, Li M, Mikkelsen B, Slitt A, Sunderland EM (2019) Phospholipid Levels Predict the Tissue Distribution of Poly- and Perfluoroalkyl Substances in a Marine Mammal. *Environ Sci Technol Lett* 6:119-125.
- De Coster S, van Larebeke N (2012) Endocrine-disrupting chemicals: associated disorders and mechanisms of action. *J Environ Public Health* 2012:713696.
- de Sousa G, Teng S, Salle-Siri R, Pery A, Rahmani R (2016) Prediction of the metabolic clearance of benzophenone-2, and its interaction with isoeugenol and coumarin using cryopreserved human hepatocytes in primary culture. *Food Chem Toxicol* 90:55-63.
- Dickerson AS, Ransome Y, Karlsson O (2019) Human prenatal exposure to polychlorinated biphenyls (PCBs) and risk behaviors in adolescence. *Environ Int* 129:247-255.
- Doctor SV, Sultatos LG, Murphy SD (1983) Distribution of trimethyltin in various tissues of the male mouse. *Toxicol Lett* 17:43-48.
- Doerge DR, Twaddle NC, Vanlandingham M, Brown RP, Fisher JW (2011) Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. *Toxicol Appl Pharmacol* 255:261-270.
- Ek CJ, Dziegielewska KM, Habgood MD, Saunders NR (2012) Barriers in the developing brain and Neurotoxicology. *Neurotoxicology* 33:586-604.
- Elmore SE, Cano-Sancho G, La Merrill MA (2020) Disruption of normal adipocyte development and function by methyl- and propyl- paraben exposure. *Toxicol Lett* 334:27-35.
- Eum SY, Jaraki D, Andras IE, Toborek M (2015) Lipid rafts regulate PCB153-induced disruption of occludin and brain endothelial barrier function through protein phosphatase 2A and matrix metalloproteinase-2. *Toxicol Appl Pharmacol* 287:258-266.
- Farman S, Javed A, Arshia, Khan KM, Nasir A, Khan AU, Lodhi MA, Gul H, Khan F, Asad M, Parveen Z (2020) Benzophenone Sulfonamide Derivatives as Interacting Partners and Inhibitors of Human P-glycoprotein. *Anticancer Agents Med Chem* 20:1739-1751.
- Ferraz da Silva I, Freitas-Lima LC, Graceli JB, Rodrigues LCM (2017) Organotins in Neuronal Damage, Brain Function, and Behavior: A Short Review. *Front Endocrinol (Lausanne)* 8:366.
- Furukawa S, Tsuji N, Kobayashi Y, Yamagishi Y, Hayashi S, Abe M, Kuroda Y, Kimura M, Hayakawa C, Sugiyama A (2017) Effect of dibutyltin on placental and fetal toxicity in rat. *J Toxicol Sci* 42:741-753.
- Geens T, Neels H, Covaci A (2012) Distribution of bisphenol-A, triclosan and n-nonylphenol in human adipose tissue, liver and brain. *Chemosphere* 87:796-802.
- Gherzi-Egea JF, Saudrais E, Strazielle N (2018a) Barriers to Drug Distribution into the Perinatal and Postnatal Brain. *Pharm Res* 35:84.
- Gherzi-Egea JF, Babikian A, Blondel S, Strazielle N (2015) Changes in the cerebrospinal fluid circulatory system of the developing rat: quantitative volumetric analysis and effect on blood-CSF permeability interpretation. *Fluids Barriers CNS* 12:8.
- Gherzi-Egea JF, Strazielle N, Catala M, Silva-Vargas V, Doetsch F, Engelhardt B (2018b) Molecular anatomy and functions of the choroidal blood-cerebrospinal fluid barrier in health and disease. *Acta Neuropathol* 135:337-361.
- Giuliani A, Zuccarini M, Cichelli A, Khan H, Reale M (2020) Critical Review on the Presence of Phthalates in Food and Evidence of Their Biological Impact. *Int J Environ Res Public Health* 17.
- Gore AC, Crews D, Doon LL, La Merrill M, Patisoil H, Zola A (2014) Introduction to endocrine disrupting chemicals (EDCs). A guide for public interest organizations and policy-makers. In: (Society E, ed): <https://www.endocrine.org/-/media/endosociety/files/advocacy-and-outreach/important-documents/introduction-to-endocrine-disrupting-chemicals.pdf>.

- Greaves AK, Letcher RJ, Sonne C, Dietz R (2013) Brain region distribution and patterns of bioaccumulative perfluoroalkyl carboxylates and sulfonates in east greenland polar bears (*Ursus maritimus*). *Environ Toxicol Chem* 32:713-722.
- Grun F (2014) The obesogen tributyltin. *Vitam Horm* 94:277-325.
- Halwachs S, Wassermann L, Lindner S, Zizzadoro C, Honscha W (2013) Fungicide prochloraz and environmental pollutant dioxin induce the ABCG2 transporter in bovine mammary epithelial cells by the arylhydrocarbon receptor signaling pathway. *Toxicol Sci* 131:491-501.
- Hannon PR, Peretz J, Flaws JA (2014) Daily exposure to Di(2-ethylhexyl) phthalate alters estrous cyclicity and accelerates primordial follicle recruitment potentially via dysregulation of the phosphatidylinositol 3-kinase signaling pathway in adult mice. *Biol Reprod* 90:136.
- Hannon PR, Brannick KE, Wang W, Flaws JA (2015) Mono(2-ethylhexyl) phthalate accelerates early folliculogenesis and inhibits steroidogenesis in cultured mouse whole ovaries and antral follicles. *Biol Reprod* 92:120.
- Hano T, Oshima Y, Kim SG, Satone H, Oba Y, Kitano T, Inoue S, Shimasaki Y, Honjo T (2007) Tributyltin causes abnormal development in embryos of medaka, *Oryzias latipes*. *Chemosphere* 69:927-933.
- Hara K, Yoshizuka M, Doi Y, Fujimoto S (1994) Effect of bis (tributyl tin) oxide on permeability of the blood-brain barrier: a transient increase. *Occup Environ Med* 51:735-738.
- Harino H, Fukushima M, Kawai S (2000) Accumulation of butyltin and phenyltin compounds in various fish species. *Arch Environ Contam Toxicol* 39:13-19.
- Hegazy HG, Ali EH, Elgoly AH (2015) Interplay between pro-inflammatory cytokines and brain oxidative stress biomarkers: evidence of parallels between butyl paraben intoxication and the valproic acid brain physiopathology in autism rat model. *Cytokine* 71:173-180.
- Hladky SB, Barrand MA (2016) Fluid and ion transfer across the blood-brain and blood-cerebrospinal fluid barriers; a comparative account of mechanisms and roles. *Fluids Barriers CNS* 13:19.
- Hojo R, Zareba G, Kai JW, Baggs RB, Weiss B (2006) Sex-specific alterations of cerebral cortical cell size in rats exposed prenatally to dioxin. *J Appl Toxicol* 26:25-34.
- Hu X, Adamcakova-Dodd A, Thorne PS (2014) The fate of inhaled (14)C-labeled PCB11 and its metabolites in vivo. *Environ Int* 63:92-100.
- Hu X, Adamcakova-Dodd A, Lehmler HJ, Hu D, Kania-Korwel I, Hornbuckle KC, Thorne PS (2010) Time course of congener uptake and elimination in rats after short-term inhalation exposure to an airborne polychlorinated biphenyl (PCB) mixture. *Environ Sci Technol* 44:6893-6900.
- Hultstrom D, Tengvar C, Forssen M, Olsson Y (1984) Distribution of exudated FITC-dextran in experimental vasogenic brain edema produced by a focal cryogenic injury. *Acta Neuropathol* 63:13-17.
- Ikeda GJ, Sapienza PP, Couvillion JL, Farber TM, Smith CP, Inskip PB, Marks EM, Cerra FE, van Loon EJ (1978) Distribution and excretion of two phthalate esters in rats, dogs and miniature pigs. *Food Cosmet Toxicol* 16:409-413.
- Inoue S, Oshima Y, Usuki H, Hamaguchi M, Hanamura Y, Kai N, Shimasaki Y, Honjo T (2006) Effects of tributyltin maternal and/or waterborne exposure on the embryonic development of the Manila clam, *Ruditapes philippinarum*. *Chemosphere* 63:881-888.
- Inoue T, Nagara H, Kondo A, Fukui M, Tateishi J (1987) Effects of intracarotid hyperosmolar mannitol in triethyl tin (TET)-induced rat brain edema--preservation of blood-brain barrier (BBB) in TET edema. *Brain Res* 414:309-313.

- Ishida T, Matsumoto Y, Takeda T, Koga T, Ishii Y, Yamada H (2010) Distribution of 14C-2,3,7,8-tetrachlorodibenzo-p-dioxin to the brain and peripheral tissues of fetal rats and its comparison with adults. *J Toxicol Sci* 35:563-569.
- Jan J, Vrecl M, Pogacnik A, Bavdek SV (1999) Tissue distribution of planar and non-planar chlorobiphenyls, 4,4'-DDE and hexachlorobenzene in sheep and lambs. *Chemosphere* 38:2607-2612.
- Jeon HK, Sarma SN, Kim YJ, Ryu JC (2008) Toxicokinetics and metabolisms of benzophenone-type UV filters in rats. *Toxicology* 248:89-95.
- Jeong Y, Xue J, Park KJ, Kannan K, Moon HB (2019) Tissue-Specific Accumulation and Body Burden of Parabens and Their Metabolites in Small Cetaceans. *Environ Sci Technol* 53:475-481.
- Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jorgensen N (2009) Do perfluoroalkyl compounds impair human semen quality? *Environ Health Perspect* 117:923-927.
- Joo F, Takacs O, Varga L, Domjan G, Borcsok E, Rott S, Rosta M, Zoltan OT, Csillik B, Foldi M (1969) Collapse of the blood-brain barrier in lymphostatic cerebral hemangiopathy and in triethyltin poisoning. *Med Exp Int J Exp Med* 19:342-350.
- Karthikeyan BS, Ravichandran J, Mohanraj K, Vivek-Ananth RP, Samal A (2019) A curated knowledgebase on endocrine disrupting chemicals and their biological systems-level perturbations. *Sci Total Environ* 692:281-296.
- Kavlock R, Barr D, Boekelheide K, Breslin W, Breyse P, Chapin R, Gaido K, Hodgson E, Marcus M, Shea K, Williams P (2006) NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of di(2-ethylhexyl) phthalate. *Reprod Toxicol* 22:291-399.
- Kawabata K, Matsuzaki H, Nukui S, Okazaki M, Sakai A, Kawashima Y, Kudo N (2017) Perfluorododecanoic Acid Induces Cognitive Deficit in Adult Rats. *Toxicol Sci* 157:421-428.
- Khadrawy YA, Noor NA, Mourad IM, Ezz HS (2016) Neurochemical impact of bisphenol A in the hippocampus and cortex of adult male albino rats. *Toxicol Ind Health* 32:1711-1719.
- Kim CS, Sapienza PP, Ross IA, Johnson W, Luu HM, Hutter JC (2004) Distribution of bisphenol A in the neuroendocrine organs of female rats. *Toxicol Ind Health* 20:41-50.
- Kim JH, Yun J, Sohng JK, Cha JM, Choi BC, Jeon HJ, Kim SH, Choi CH (2007) Di(2-ethylhexyl)phthalate leached from medical PVC devices serves as a substrate and inhibitor for the P-glycoprotein. *Environ Toxicol Pharmacol* 23:272-278.
- Kim MG, Kim TH, Shin BS, Lee YB, Lee JB, Choi HG, Lee Y, Yoo SD (2015) Sensitive liquid chromatography-tandem mass spectrometry method for the simultaneous determination of benzyl butyl phthalate and its metabolites, monobenzyl phthalate and monobutyl phthalate, in rat plasma, urine, and various tissues collected from a toxicokinetic study. *Anal Bioanal Chem* 407:7391-7400.
- Kimura E, Kohda M, Maekawa F, Fujii-Kuriyama Y, Tohyama C (2021) Neurons expressing the aryl hydrocarbon receptor in the locus coeruleus and island of Calleja major are novel targets of dioxin in the mouse brain. *Histochem Cell Biol* 156:147-163.
- Kirchner S, Kieu T, Chow C, Casey S, Blumberg B (2010) Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol Endocrinol* 24:526-539.
- Klinefelter K, Hooven MK, Bates C, Colter BT, Dailey A, Infante SK, Kania-Korwel I, Lehmler HJ, Lopez-Juarez A, Ludwig CP, Curran CP (2018) Genetic differences in the aryl hydrocarbon receptor and CYP1A2 affect sensitivity to developmental

- polychlorinated biphenyl exposure in mice: relevance to studies of human neurological disorders. *Mamm Genome* 29:112-127.
- Koch HM, Preuss R, Angerer J (2006) Di(2-ethylhexyl)phthalate (DEHP): human metabolism and internal exposure-- an update and latest results. *Int J Androl* 29:155-165; discussion 181-155.
- Kogevinas M (2001) Human health effects of dioxins: cancer, reproductive and endocrine system effects. *Hum Reprod Update* 7:331-339.
- Koutaki D, Paltoglou G, Vourdoumpa A, Charmandari E (2021) The Impact of Bisphenol A on Thyroid Function in Neonates and Children: A Systematic Review of the Literature. *Nutrients* 14.
- Kratzer I, Liddelow SA, Saunders NR, Dziegielewska KM, Strazielle N, Ghersi-Egea JF (2013) Developmental changes in the transcriptome of the rat choroid plexus in relation to neuroprotection. *Fluids Barriers CNS* 10:25.
- Kratzer I, Strazielle N, Saudrais E, Monkkonen K, Malleval C, Blondel S, Ghersi-Egea JF (2018) Glutathione Conjugation at the Blood-CSF Barrier Efficiently Prevents Exposure of the Developing Brain Fluid Environment to Blood-Borne Reactive Electrophilic Substances. *J Neurosci* 38:3466-3479.
- Krause M, Klit A, Blomberg Jensen M, Soeborg T, Frederiksen H, Schlumpf M, Lichtensteiger W, Skakkebaek NE, Drzewiecki KT (2012) Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. *Int J Androl* 35:424-436.
- Kurian JR, Keen KL, Kenealy BP, Garcia JP, Hedman CJ, Terasawa E (2015) Acute Influences of Bisphenol A Exposure on Hypothalamic Release of Gonadotropin-Releasing Hormone and Kisspeptin in Female Rhesus Monkeys. *Endocrinology* 156:2563-2570.
- Laranjeiro F, Sanchez-Marin P, Barros A, Galante-Oliveira S, Moscoso-Perez C, Fernandez-Gonzalez V, Barroso C (2016) Triphenyltin induces imposex in *Nucella lapillus* through an aphallic route. *Aquat Toxicol* 175:127-131.
- Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, Butenhoff JL, Stevenson LA (2003) Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci* 74:382-392.
- Lee S (2018) Pharmacokinetic features of benzophenone-3 after dermal application in humans. In: Department of Environmental Health Graduate School of Public Health. <https://s-space.snu.ac.kr/bitstream/10371/141945/1/000000149406.pdf>
- p46: Seoul National University.
- Leppert B et al. (2020) Maternal paraben exposure triggers childhood overweight development. *Nat Commun* 11:561.
- Letcher RJ, Gebbink WA, Sonne C, Born EW, McKinney MA, Dietz R (2009) Bioaccumulation and biotransformation of brominated and chlorinated contaminants and their metabolites in ringed seals (*Pusa hispida*) and polar bears (*Ursus maritimus*) from East Greenland. *Environ Int* 35:1118-1124.
- Liebner S, Dijkhuizen RM, Reiss Y, Plate KH, Agalliu D, Constantin G (2018) Functional morphology of the blood-brain barrier in health and disease. *Acta Neuropathol* 135:311-336.
- Lin H, Yuan K, Li L, Liu S, Li S, Hu G, Lian QQ, Ge RS (2015) In Utero Exposure to Diethylhexyl Phthalate Affects Rat Brain Development: A Behavioral and Genomic Approach. *Int J Environ Res Public Health* 12:13696-13710.
- Lindgren A, Lindquist NG, Lyden A, Olsson T, Ullberg S (1982) A whole body autoradiographic study on the distribution of ¹⁴C-labelled di-(2-ethylhexyl)phthalate in mice. *Toxicology* 23:149-158.
- Little AR, Benkovic SA, Miller DB, O'Callaghan JP (2002) Chemically induced neuronal damage and gliosis: enhanced expression of the proinflammatory chemokine, monocyte

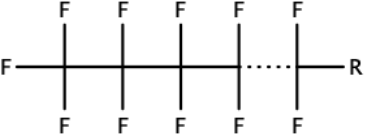




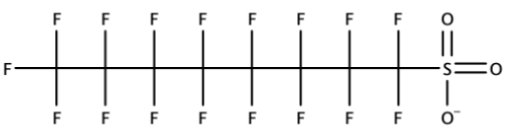
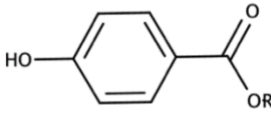
- chemoattractant protein (MCP)-1, without a corresponding increase in proinflammatory cytokines(1). *Neuroscience* 115:307-320.
- Liu T, Wang Y, Yang M, Shao P, Duan L, Li M, Zhu M, Yang J, Jiang J (2018) Di-(2-ethylhexyl) phthalate induces precocious puberty in adolescent female rats. *Iran J Basic Med Sci* 21:848-855.
- Long Y, Wang Y, Ji G, Yan L, Hu F, Gu A (2013) Neurotoxicity of perfluorooctane sulfonate to hippocampal cells in adult mice. *PLoS One* 8:e54176.
- Mankidy R, Wiseman S, Ma H, Giesy JP (2013) Biological impact of phthalates. *Toxicol Lett* 217:50-58.
- Manzini L, Halwachs S, Girolami F, Badino P, Honscha W, Nebbia C (2017) Interaction of mammary bovine ABCG2 with AFB1 and its metabolites and regulation by PCB 126 in a MDCKII in vitro model. *J Vet Pharmacol Ther* 40:591-598.
- Matsumoto J, Iwano H, Inoue H, Iwano N, Yamashiki N, Yokota H (2007) Metabolic barrier against bisphenol A in rat uterine endometrium. *Toxicol Sci* 99:118-125.
- Mattiessen P, Gibbs PE (1998) Critical appraisal of the evidence for tributyltin-mediated endocrine disruption in mollusks. *Environ Toxicol cChem* 17:37-43.
- Mazur CS, Marchitti SA, Dimova M, Kenneke JF, Lumen A, Fisher J (2012) Human and rat ABC transporter efflux of bisphenol a and bisphenol a glucuronide: interspecies comparison and implications for pharmacokinetic assessment. *Toxicol Sci* 128:317-325.
- Meeker JD, Altshul L, Hauser R (2007) Serum PCBs, p,p'-DDE and HCB predict thyroid hormone levels in men. *Environ Res* 104:296-304.
- Minguez-Alarcon L, Williams PL, Chiu YH, Gaskins AJ, Nassan FL, Dadd R, Petrozza J, Hauser R, Chavarro JE, Earth Study T (2018) Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: Identifying potential predictors. *Environ Int* 121:1297-1303.
- Mitchell MM, Woods R, Chi LH, Schmidt RJ, Pessah IN, Kostyniak PJ, LaSalle JM (2012) Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder. *Environ Mol Mutagen* 53:589-598.
- Mitra S, Siddiqui WA, Khandelwal S (2015) Differential susceptibility of brain regions to tributyltin chloride toxicity. *Environ Toxicol* 30:1393-1405.
- Mitra S, Gera R, Siddiqui WA, Khandelwal S (2013) Tributyltin induces oxidative damage, inflammation and apoptosis via disturbance in blood-brain barrier and metal homeostasis in cerebral cortex of rat brain: an in vivo and in vitro study. *Toxicology* 310:39-52.
- Miyazaki W, Fujiwara Y, Katoh T (2016) The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the development and function of the blood-brain barrier. *Neurotoxicology* 52:64-71.
- Naert C, Van Peteghem C, Kupper J, Jenni L, Naegeli H (2007) Distribution of polychlorinated biphenyls and polybrominated diphenyl ethers in birds of prey from Switzerland. *Chemosphere* 68:977-987.
- Ness DK, Schantz SL, Hansen LG (1994) PCB congeners in the rat brain: selective accumulation and lack of regionalization. *J Toxicol Environ Health* 43:453-468.
- Nickel S, Mahringer A (2014) The xenoestrogens ethinylestradiol and bisphenol A regulate BCRP at the blood-brain barrier of rats. *Xenobiotica* 44:1046-1054.
- Nowak K, Ratajczak-Wrona W, Gorska M, Jablonska E (2018) Parabens and their effects on the endocrine system. *Mol Cell Endocrinol* 474:238-251.
- Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, Zobel LR (2007) Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect* 115:1298-1305.

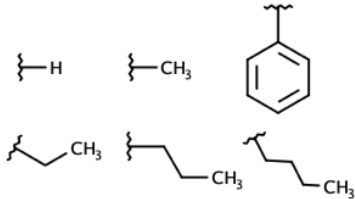
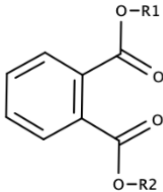
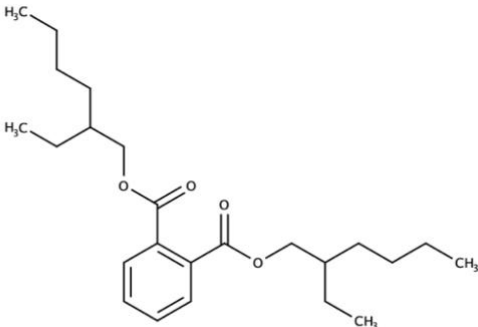
- Oulhote Y, Steuerwald U, Debes F, Weihe P, Grandjean P (2016) Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances. *Environ Int* 97:237-245.
- Ousji O, Ohlund L, Sleno L (2020) Comprehensive In Vitro Metabolism Study of Bisphenol A Using Liquid Chromatography-High Resolution Tandem Mass Spectrometry. *Chem Res Toxicol* 33:1468-1477.
- Pellegrino G et al. (2021) GnRH neurons recruit astrocytes in infancy to facilitate network integration and sexual maturation. *Nat Neurosci* 24:1660-1672.
- Perez F, Nadal M, Navarro-Ortega A, Fabrega F, Domingo JL, Barcelo D, Farre M (2013) Accumulation of perfluoroalkyl substances in human tissues. *Environ Int* 59:354-362.
- Pomierny B, Krzyzanowska W, Broniowska Z, Strach B, Bystrowska B, Starek-Swiechowicz B, Maciejaska A, Skorkowska A, Wesolowska J, Walczak M, Budziszewska B (2019) Benzophenone-3 passes through the blood-brain barrier, increases the level of extracellular glutamate and induces apoptotic processes in the hippocampus and frontal cortex of rats. *Toxicol Sci*.
- Renz L, Volz C, Michanowicz D, Ferrar K, Christian C, Lenzner D, El-Hefnawy T (2013) A study of parabens and bisphenol A in surface water and fish brain tissue from the Greater Pittsburgh Area. *Ecotoxicology* 22:632-641.
- Rocamora-Reverte L, Carrasco-Garcia E, Ceballos-Torres J, Prashar S, Kaluderovic GN, Ferragut JA, Gomez-Ruiz S (2012) Study of the anticancer properties of tin(IV) carboxylate complexes on a panel of human tumor cell lines. *ChemMedChem* 7:301-310.
- Rodriguez-Gonzalez P, Rodriguez-Cea A, Alonso JI, Sanz-Medel A (2005) Species-specific isotope dilution analysis and isotope pattern deconvolution for butyltin compounds metabolism investigations. *Anal Chem* 77:7724-7734.
- Roepke TA, Snyder MJ, Cherr GN (2005) Estradiol and endocrine disrupting compounds adversely affect development of sea urchin embryos at environmentally relevant concentrations. *Aquat Toxicol* 71:155-173.
- Rogers JA, Mishra MK, Hahn J, Greene CJ, Yates RM, Metz LM, Yong VW (2017) Gestational bisphenol-A exposure lowers the threshold for autoimmunity in a model of multiple sclerosis. *Proc Natl Acad Sci U S A* 114:4999-5004.
- Ros O, Vallejo A, Olivares M, Etxebarria N, Prieto A (2016) Determination of endocrine disrupting compounds in fish liver, brain, and muscle using focused ultrasound solid-liquid extraction and dispersive solid phase extraction as clean-up strategy. *Anal Bioanal Chem* 408:5689-5700.
- Salgado-Freiria R, Lopez-Doval S, Lafuente A (2018) Perfluorooctane sulfonate (PFOS) can alter the hypothalamic-pituitary-adrenal (HPA) axis activity by modifying CRF1 and glucocorticoid receptors. *Toxicol Lett* 295:1-9.
- Santamaria CG, Meyer N, Schumacher A, Zenclussen ML, Teglia CM, Culzoni MJ, Zenclussen AC, Rodriguez HA (2020) Dermal exposure to the UV filter benzophenone-3 during early pregnancy affects fetal growth and sex ratio of the progeny in mice. *Arch Toxicol* 94:2847-2859.
- Sasso AF, Pirow R, Andra SS, Church R, Nachman RM, Linke S, Kapraun DF, Schurman SH, Arora M, Thayer KA, Bucher JR, Birnbaum LS (2020) Pharmacokinetics of bisphenol A in humans following dermal administration. *Environ Int* 144:106031.
- Schlumpf M, Schmid P, Durrer S, Conscience M, Maerkel K, Henseler M, Gruetter M, Herzog I, Reolon S, Ceccatelli R, Faass O, Stutz E, Jarry H, Wuttke W, Lichtensteiger W (2004) Endocrine activity and developmental toxicity of cosmetic UV filters--an update. *Toxicology* 205:113-122.

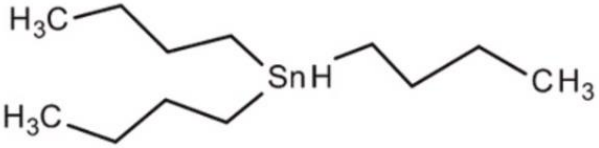
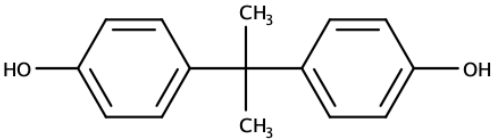
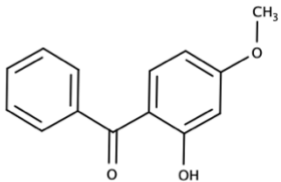
- Seelbach M, Chen L, Powell A, Choi YJ, Zhang B, Hennig B, Toborek M (2010) Polychlorinated biphenyls disrupt blood-brain barrier integrity and promote brain metastasis formation. *Environ Health Perspect* 118:479-484.
- Selvakumar K, Bavithra S, Krishnamoorthy G, Arunakaran J (2018) Impact of quercetin on tight junctional proteins and BDNF signaling molecules in hippocampus of PCBs-exposed rats. *Interdiscip Toxicol* 11:294-305.
- Selvakumar K, Prabha RL, Saranya K, Bavithra S, Krishnamoorthy G, Arunakaran J (2013) Polychlorinated biphenyls impair blood-brain barrier integrity via disruption of tight junction proteins in cerebrum, cerebellum and hippocampus of female Wistar rats: neuroprotective role of quercetin. *Hum Exp Toxicol* 32:706-720.
- Sharan S, Nikhil K, Roy P (2013) Effects of low dose treatment of tributyltin on the regulation of estrogen receptor functions in MCF-7 cells. *Toxicol Appl Pharmacol* 269:176-186.
- Shin MY, Shin C, Choi JW, Lee J, Lee S, Kim S (2019) Pharmacokinetic profile of propyl paraben in humans after oral administration. *Environ Int* 130:104917.
- Spulber S, Kilian P, Wan Ibrahim WN, Onishchenko N, Ulhaq M, Norrgren L, Negri S, Di Tuccio M, Ceccatelli S (2014) PFOS induces behavioral alterations, including spontaneous hyperactivity that is corrected by dexamfetamine in zebrafish larvae. *PLoS One* 9:e94227.
- Stein CR, McGovern KJ, Pajak AM, Maglione PJ, Wolff MS (2016) Perfluoroalkyl and polyfluoroalkyl substances and indicators of immune function in children aged 12-19 y: National Health and Nutrition Examination Survey. *Pediatr Res* 79:348-357.
- Strain WH, Rivers RJ, Jr., O'Reilly RJ, Danahy DT, Thomas MR, Wilson RM (1969) Effect of parabens on the permeability of the blood: brain barrier to water-soluble radiopaque media. *Am J Roentgenol Radium Ther Nucl Med* 105:404-410.
- Strazielle N, Gherzi-Egea JF (1999) Demonstration of a coupled metabolism-efflux process at the choroid plexus as a mechanism of brain protection toward xenobiotics. *J Neurosci* 19:6275-6289.
- Strazielle N, Gherzi-Egea JF (2013) Physiology of blood-brain interfaces in relation to brain disposition of small compounds and macromolecules. *Mol Pharm* 10:1473-1491.
- Strazielle N, Gherzi-Egea JF (2015) Efflux transporters in blood-brain interfaces of the developing brain. *Front Neurosci* 9:21.
- Szczepkowska A, Lagaraine C, Robert V, Dufourny L, Thiery JC, Skipor J (2013) Effect of a two-week treatment with a low dose of 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153) on tight junction protein expression in ovine choroid plexus during long and short photoperiods. *Neurotoxicol Teratol* 37:63-67.
- Szczepkowska A, Lagaraine C, Robert V, Mlynarczuk J, Dufourny L, Thiery JC, Skipor J (2016) PCB153 (2,2',4,4',5,5'-hexachlorobiphenyl) differentially affects the VEGF/VEGFR system depending on photoperiod in the ovine choroid plexus. *Ecotoxicol Environ Saf* 124:303-308.
- Tang M, Yin S, Zhang J, Chen K, Jin M, Liu W (2018) Prenatal exposure to polychlorinated biphenyl and umbilical cord hormones and birth outcomes in an island population. *Environ Pollut* 237:581-591.
- Toesca A, Geloso MC, Mongiovi AM, Furno A, Schiattarella A, Michetti F, Corvino V (2016) Trimethyltin Modulates Reelin Expression and Endogenous Neurogenesis in the Hippocampus of Developing Rats. *Neurochem Res* 41:1559-1569.
- Tomiyama K, Nakashima H, Arakawa Y, Kumagai H (2010) Mechanism underlying the olfactory disturbance induced by an intraperitoneal injection of tributyltin chloride in rats. *Toxicology* 276:110-114.
- van der Meer TP, Artacho-Cordon F, Swaab DF, Struik D, Makris KC, Wolffenbuttel BHR, Frederiksen H, van Vliet-Ostaptchouk JV (2017) Distribution of Non-Persistent

- Endocrine Disruptors in Two Different Regions of the Human Brain. *Int J Environ Res Public Health* 14.
- Wan Y, Hu J, An W, Zhang Z, An L, Hattori T, Itoh M, Masunaga S (2006) Congener-specific tissue distribution and hepatic sequestration of PCDD/Fs in wild herring gulls from Bohai Bay, North China: comparison to coplanar PCBs. *Environ Sci Technol* 40:1462-1468.
- Wang D, Shelver WL, Atkinson S, Mellish JA, Li QX (2010) Tissue distribution of polychlorinated biphenyls and organochlorine pesticides and potential toxicity to Alaskan northern fur seals assessed using PCBs congener specific mode of action schemes. *Arch Environ Contam Toxicol* 58:478-488.
- Wang X, Hawkins BT, Miller DS (2011) Activating PKC-beta1 at the blood-brain barrier reverses induction of P-glycoprotein activity by dioxin and restores drug delivery to the CNS. *J Cereb Blood Flow Metab* 31:1371-1375.
- Wang YX, Zhou B, Chen YJ, Liu C, Huang LL, Liao JQ, Hu XJ, Lu WQ, Zeng Q, Pan A (2018) Thyroid function, phthalate exposure and semen quality: Exploring associations and mediation effects in reproductive-aged men. *Environ Int* 116:278-285.
- Wei L, Otsuka T, Acuff V, Bereczki D, Pettigrew K, Patlak C, Fenstermacher J (1993) The velocities of red cell and plasma flows through parenchymal microvessels of rat brain are decreased by pentobarbital. *J Cereb Blood Flow Metab* 13:487-497.
- Williams DT, Blanchfield BJ (1975) The retention, distribution, excretion, and metabolism of dibutyl phthalate-7-14 C in the rat. *J Agric Food Chem* 23:854-858.
- Wimmerova S, Lancz K, Tihanyi J, Sovcikova E, Kocan A, Drobna B, Palkovicova L, Jureckova D, Fabisikova A, Conka K, Trnovec T (2011) Half-lives of serum PCB congener concentrations in environmentally exposed early adolescents. *Chemosphere* 82:687-691.
- Wu WZ, Zhang QH, Schramm KW, Xu Y, Kettrup A (2000) Distribution, transformation, and long-term accumulation of polychlorinated dibenzo-p-dioxins and dibenzofurans in different tissues of fish and piscivorous birds. *Ecotoxicol Environ Saf* 46:252-257.
- Yoshikawa Y, Hayashi A, Inai M, Matsushita A, Shibata N, Takada K (2002) Permeability characteristics of endocrine-disrupting chemicals using an in vitro cell culture model, Caco-2 cells. *Curr Drug Metab* 3:551-557.
- Yu Y, Wang C, Zhang X, Zhu J, Wang L, Ji M, Zhang Z, Ji XM, Wang SL (2020) Perfluorooctane sulfonate disrupts the blood brain barrier through the crosstalk between endothelial cells and astrocytes in mice. *Environ Pollut* 256:113429.
- Zalko D, Prouillac C, Riu A, Perdu E, Dolo L, Jouanin I, Canlet C, Debrauwer L, Cravedi JP (2006) Biotransformation of the flame retardant tetrabromo-bisphenol A by human and rat sub-cellular liver fractions. *Chemosphere* 64:318-327.
- Zhang B, Chen L, Choi JJ, Hennig B, Toborek M (2012) Cerebrovascular toxicity of PCB153 is enhanced by binding to silica nanoparticles. *J Neuroimmune Pharmacol* 7:991-1001.
- Zhang B, Choi JJ, Eum SY, Daunert S, Toborek M (2013) TLR4 signaling is involved in brain vascular toxicity of PCB153 bound to nanoparticles. *PLoS One* 8:e63159.
- Zheng W, Gherzi-Egea JF (2020) Brain Barrier Systems Play No Small Roles in Toxicant-induced Brain Disorders. *Toxicol Sci* 175:147-148

Table 1. Families of endocrine disruptors for which a central toxicity has been reported. As examples, the structure of molecules cited in the text are reported.

<p align="center">Pollutant family (Karthikeyan et al., 2019)</p>	<p align="center">Main use or origins Physico-chemical properties Half-lives information</p>
<p>PERFLUOROALKANES</p> <p>Organic substances in which all of the hydrogens of the hydrocarbons are substituted with fluorine atoms. The number of carbons varies from 5 to 15. Perfluorinated compounds can be perfluoro alkylcarboxylic acid, sulfonic acid, sulfonamide, phosphonic acid, phosphinic acid.</p> <p>Gen X is the next generation perfluorinated compound created to substitute short-chain Perfluoroalkanes. It is the trade name for the ammonium salt of hexafluoropropylene oxide–dimer acid.</p> <div style="text-align: center;">  </div> <p>R possible functions:</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  </div> <div style="text-align: center;">  </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;">  </div> <div style="text-align: center;">  </div> </div> <p>Example: Perfluorooctane sulfonate (PFOS)</p> <div style="text-align: center;">  </div>	<p>Fire retardants, detergents and surfactants, water repellents Used in pesticides, cosmetics, engine Oil</p> <p>Very high thermal and chemical stability due to the extremely stable Fluorine-carbon bonds. Anionic compound, present a hydrophilic head and a hydrophobic tail.</p> <p>Examples of serum half-lives (human) perfluorooctanesulfonate =5.4 years perfluorohexanesulfonate =8.5 years perfluorooctanoate = 3.8 years (Olsen et al., 2007)</p>
<p>PARABENS</p> <p>Para-hydroxybenzoic acid esters with different alkyl or aryl groups.</p> <div style="text-align: center;">  </div> <p>R possible functions:</p>	<p>Used as preservatives in cosmetics, food, drugs. Wide antimicrobial activity, particularly against Gram-positive bacteria and fungi. An increase in alkyl chain length improves antimicrobial effectiveness.</p> <p>Chemically stable. Limited solubility in water, easily soluble in acetone, ethanol, chloroform, glycerin and propylene glycol.</p> <p>Examples of plasma half-lives (human) Free propylparaben = 0,9 h</p>

	<p>Conjugated propylparaben = 2.9 h p-hydroxybenzoic acid = 2.4 h p-hydroxyhippuric acid = 1.3 h (Shin et al., 2019)</p>
<p>PHTHALATES</p> <p>Diesters of 1,2-benzenedicarboxylic acid (phthalic acid) containing a benzene ring with two ester functional groups, R1 and R2. These groups are commonly alkyl chain formed by 8 to 13 carbon atoms.</p>  <p>Example: Di(2-ethylhexyl) phthalate (DEHP)</p> 	<p>Used to increase the flexibility of plastics. Used in food packaging, plastic goods, toys, vinyl products, adhesives, detergents lubricating oils, fragrances, insecticides, inks, paints, cosmetics, pharmaceuticals.</p> <p>Soluble in most organic solvents and oils, high hydrophobicity, strong absorption of the high molecular weight phthalates to organic particle.</p> <p>Examples of biological half-lives (human) di(2-ethylhexyl)phthalate is rapidly metabolized. Primary metabolite: Mono(2-ethylhexyl)phthalate = 5 h Further oxidized metabolites = 10 to 24 h (Koch et al., 2006)</p>
<p>ORGANOTINS</p> <p>Formed by one to four organic chains attached to a tin atom via carbon-tin covalent bonds. The most frequently found organotins are monobutyltin (MBT), dibutyltin (DBT), tributyltin (TBT) and triphenyltin (TPT). When there are fewer than four carbon-tin bonds, the organotin cation can combine with an anion such as acetate, carbonate, chloride, fluoride, hydroxide, oxide, or sulfide. The toxicity of organotins generally increases with the number of organic chains from one to three and decreases with the incorporation of a fourth. Triorganotins are therefore more toxic than other forms. Their Toxicities are also related to the number of carbon atoms within the alkyl chain.</p>	<p>Preservatives (Fungicides, biocides, bactericides, insecticides). Thermal stabilizers of poly vinyl chloride. Found in plastic products, wood, textiles, paper, leather and electrical equipment, paint, etc.</p> <p>Relative low solubility in water between, 1.0 to 100 mg/liter.</p> <p>Example of biological half-life (mouse) trin-butyltin oxide = 29 days (Brown et al., 1977)</p>

<p>Tributyltin oxide (bis-[tri-n-butyltin]-oxide) consists in two molecules of Tributyltin linked to an Oxygen Example: Tributyltin (TBT)</p> 													
<p>BISPHENOLS Formed by two hydroxyphenyl groups in para position. The best-known bisphenol is bisphenol A. Other bisphenols such as bisphenol B, bisphenol F, bisphenol S, differ by the substituent chains on the central carbon, or by a substitution of the central carbon with sulfur. Example: Bisphenol A</p> 	<p>Constitutional monomer of polycarbonate plastic and epoxy resins production. Found in plastic of food and beverage containers, linings of tin cans, plastic bottles, baby bottles, etc.</p> <p>Bisphenol A is a moderately polar substance with good solubility in most organic solvents and moderate solubility in water (100 to 300 mg/L at 25°C).</p> <p>Examples of animal biological half-lives (h)</p> <table border="1" data-bbox="829 958 1380 1025"> <tr> <td>Horses</td> <td>Sheep</td> <td>Pigs</td> <td>Dogs</td> <td>Rats</td> <td>Mice</td> </tr> <tr> <td>0.94</td> <td>1.3</td> <td>0.97</td> <td>0.62</td> <td>5.6</td> <td>13.3</td> </tr> </table> <p>Examples of serum half-lives(human) Dermal route: Free BPA= 17,6 h total BPA=21.4 h Oral route: Free BPA=5.6 h total BPA= 6.4 h (Collet et al., 2015; Sasso et al., 2020)</p>	Horses	Sheep	Pigs	Dogs	Rats	Mice	0.94	1.3	0.97	0.62	5.6	13.3
Horses	Sheep	Pigs	Dogs	Rats	Mice								
0.94	1.3	0.97	0.62	5.6	13.3								
<p>BENZOPHENONES Benzophenone derivatives are benzophenone or diphenylmethanone with methoxy or hydroxy groups. Example: Benzophenone-3</p> 	<p>Chemical UV filter and fragrance enhancer. Found in sunscreen, hair dyes, cosmetics, perfumes, textiles, inks, and paints, food packaging.</p> <p>Lipophilic compounds. Very persistent in the environment.</p> <p>Example of biological half-life (rat) benzophenone-3 = 4.6 h Examples of serum half-lives (human) Free benzophenone-3 = 9 h total benzophenone-3 = 7 h (Jeon et al., 2008; Lee, 2018)</p>												
<p>POLYCHLORINATED BIPHENYLS (PCBs) Mixture of synthetic chemicals that are formed from the chlorination of biphenyl. The number of chlorine atoms is between 1 and 10. There are 209 different PCB molecules – or congeners – resulting from the</p>	<p>Coolants and lubricants. Used in inks, paints, electrical equipment, etc.</p> <p>Chemically stable. low biodegradability.</p> <p>Examples of PCB serum half-lives (human)</p>												

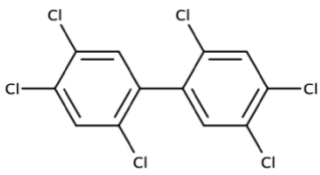
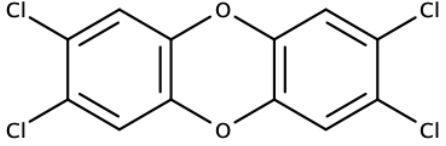
<p>number and placement of chlorine atoms on the aromatic rings. PCBs are generally found as mixture of congeners. The most common commercial mixtures are called Aroclors. The degree of chlorination is indicated by the last two digits in the Aroclor name. For example, Aroclor 1254 is a commercial mixture of PCBs with an average chlorine content of 54%.</p> <p>A greater toxicity is generally associated with a higher number of chlorine atoms on the PCBs. PCBs with non-ortho chloride substitution or mono-ortho chloride substitution are referred to as coplanar PCB congeners (e.g. PCB 77, 126) and have dioxin-like toxicologic effects.</p> <p>PCB with two or more, ortho-positions chloride substitutions are referred to as non-coplanar PCBs (e.g. PCB 118, 123, 138, 153 and 180), and do not express dioxin-like toxicity.</p> <p>Example: PCB 153</p> 	<p>Adult (in years) PCB-28 = 4.6 y / PCB-74 = 15.9 y / PCB-105 = 13.7 y / PCB-118 = 13.8 y / PCB-156 = 41.0 y</p> <p>Adolescent (in years) PCB- = 6 y / PCB-138 = 11 y / PCB-153 = 11 y / PCB-156 = 6 y / PCB-170 = 11.1 y / PCB-180 = 11 y (Wimmerova et al., 2011)</p>
<p>DIOXINS</p> <p>Dioxins is a generic name for polychlorinated dibenzo-p-dioxins The most toxic dioxin compound is 2,3,7,8-Tetrachlorodibenzo-p-dioxin, also referred to as TCDD or dioxin.</p> <p>Example : TCDD</p> 	<p>Formed as a byproduct of a number of human and natural activities, including incineration of wastes containing chlorine-based chemical compounds, forest fires, chlorine bleaching of pulp during paper fabrication, herbicide production, production of Polyvinyl Chloride (PVC) plastics. TCDD was the primary toxic component of the chemical weapon Orange Agent.</p> <p>bioaccumulates in in soils and sediments, and in food chain. More prevalent in animals with body fat. Insoluble in water, High lipophilicity, high stability.</p> <p>Examples of serum half-lives (human) TCDD = 6.1 to 11.3 years (Aylward et al., 2013)</p>

Table 2. Concentrations of endocrine disruptor chemicals in brain structures from wild animals and human environmentally exposed to these toxicants.

Unless specified otherwise, concentration data are expressed per gram of wet tissue. X: no information regarding correlations with neurophysiological/behavioral dysfunction reported

Exposition	Concentration	Brain structures	Species	reported central effects	references
Bisphenols					
bisphenol A	0 - 120 pg/g Mean = 16.4 pg/g	Whole brain	Wild fishes	X	(Renz et al., 2013)
bisphenol A	Mean = 40 ng/g	Whole brain	Wild fishes	X	(Ros et al., 2016)
bisphenol A 4-ter-octylphenol 4-nonylphenol	0.4 - 37 ng/g (depending on bird species) 2.6 - 340 ng/g (depending on bird species) 0 - 272 ng/g (depending on bird species)	Whole brain	Wild water birds	X	(Bodziach et al., 2021)
bisphenol A 4-nonylphenol	Mean = 0.91 ng/g undetected	Brain structure unspecified	Human	X	(Geens et al., 2012)
bisphenol A	0.3 - 26.3 ng/g Mean = 3.2 ng/g	Hypothalamus	Human	X	(van der Meer et al., 2017; Charisiadis et al., 2018)
	0.3-3.3 ng/g Mean = 1.2 ng/g	White matter			
bisphenol A	0.9-14.5 ng/g Mean = 2.52 ng/g	Hypothalamus	Human	X	(Charisiadis et al., 2018)
bisphenol A	0.9 – 5.7 ng/g Mean = 1.65 ng/g	White matter			
bisphenol F	1.7- 30.8 ng/g Mean = 3.95 ng/g	Hypothalamus			
bisphenol F	1.7 – 3.4 ng/ g Mean = 2.40 ng/g	White matter			
Benzophenones					
benzophenones 3	Not detected Mean = 0.32 ng/g	Hypothalamus White matter	Human	X	(van der Meer et al., 2017)
Perfluoroalcanes					

sum of 10 perfluoro acids (PFCAs) Examples: perfluorotridecanoic acid (C13)	Mean = 77 ng/g	Whole brain	Polar bear	X	(Greaves et al., 2013)
perfluorooctane sulfonate C8	Mean = 24.1 - 48.6 ng/g, depending on brain structures	Pons and medulla, Cerebellum, Cortices, Striatum, Thalamus, Hypothalamus			
perfluorosulfonates (C6 to -C10)	Mean = 30.5 – 58.8 ng/g, depending on brain structures	Whole brain			
perfluorosulfonates (C6 to -C10)	Mean = 1.30 - 35.2 ng/g, depending on chain length				
sum of 24 perfluoroalkyl substances	Median = 86.6 ng/g	Brain structure unspecified	Whale	X	(Dassuncao et al., 2019)
perfluorohexanoic acid	Mean = 180 ng/g	Brain structure unspecified	Human	X	(Perez et al., 2013)
perfluorohexyl ethanoic acid	Mean = 18.6 ng/g				
perfluorotetradecanoic acid	Mean = 24.8 ng/g				
perfluorooctane sulfonic acid	Mean = 4.9 ng/g				
PCBs					
sum of 24 PCBs	Mean = 11.8 ng/g	Brain structure unspecified	Human	X	(Chu et al., 2003)
most abundant: PCB 153 PCB 180	Mean = 3.10 ng/g Mean = 2.78 ng/g				
8 PCB studied	0 - 215 ng/g lipid (~0-32 ng/g) depending on PCB congeners	Cortex	Human	PCB found more frequently in the brain of patients suffering from autism with known	(Mitchell et al., 2012)
example: PCB 95	0 – 175 ng/g lipid (~0-26 ng/g) depending on PCB congeners	Cerebellum			
	3.7 ng/g lipid (~0.55 ng/g) in one case, not detected in 42 cases	Cortex and cerebellum	Control subject		

	59.3 ng/g lipid (~8.9 ng/g) in one case, not detected in 31 cases Mean of 32 cases: 10 ng/g lipid (~1.5 ng/g) (detected in 10 cases, undetected in 22 cases)	Cortex and cerebellum Cortex and cerebellum	Autism of unknown etiology Autism, with a known genetic basis	genetic basis	
8 PCB studied	Mean of the most abundant PCB = 100 ng/g lipid (~15 ng/g) Mean of the most abundant PCB = 10 ng/g lipid (~1.5 ng/g) Mean of the most abundant PCB = 100 ng/g lipid (~15 ng/g)	Brain structure unspecified Whole brain Whole brain	Human Deer; fox Fishes	X	(Bachour et al., 1998)
sum of 145 PCB	Mean = 9.6 ng/g	Whole brain	Seal	X	(Wang et al., 2010)
sum of 20 PCBs	Low cerebral concentrations Brain/fat ratio = 1/10 brain/liver ratio = 1/40	Brain structure unspecified	Polar bear	X	(Letcher et al., 2009)
sum of 6 PCBs	Mean = 19.9 µg/g lipids (~3 µg/g). Mean = 1.17- 7.96 µg/g lipids (~0.19 - 1.26 µg/g) depending on PCB congeners	Whole brain	Predator fishes	X	(Brazova et al., 2012)
sum of 7 PCBs	Median: 13 ng/g - 428 ng/g depending on bird species Median: Up to 30 ng/g (for PCB138 or PCB153)	Whole brain Whole brain	Different bird species Sparrow hawks	X	(Naert et al., 2007)
non ortho PCBs	Mean = 20.4 pg/g	Whole brain	Herring gulls	X	(Wan et al., 2006)
mono ortho PCBs	Mean = 494 pg/g				
coplanar PCBs	Mean = 507 pg/g				
Parabens					
methyl Paraben	Mean = 25.4 ng/g	Whole brain	Common dolphins	X	(Jeon et al., 2008)
p.hydroxybenzoic acid	Mean = 370 ng/g				
methyl, ethyl, propyl and butyl parabens	Non-detectable	Whole brain	Fishes	X	(Renz et al., 2013)

methyl Paraben	0.06 - 1.16 ng/g Mean = 0.2 ng/g 0.14 - 0.26 ng/g Mean = 0.18 ng/g	Hypothalamus White-matter tissue	Human	X	(van der Meer et al., 2017)
Dioxins					
Sum TCDDs	Mean = 0.11 pg/g Mean = 3.34 pg/g	Whole brain Whole brain	Common carp Piscivorous birds	X	(Wu et al., 2000)
2,3,7,8 TCDD	Mean = 0.41 pg/g	Whole brain	Herring gulls	X	(Wan et al., 2006)
Organotins					
butyltin	Mean = 0.2 mg/g	Whole brain	Fishes	X	(Harino et al., 2000)
phenyltin	Mean = 0.1 mg/g				

Table 3: Selected studies reporting concentrations of endocrine disruptor chemicals in brain structures from animals experimentally exposed to toxicants.

Unless specified otherwise, concentration data are expressed per gram of wet tissue. X: no information regarding correlations with neurophysiological/behavioral dysfunction are reported. abbreviation: GD: gestational day.

Exposition	Concentration	Brain Structure	Species, developmental stage	Effect on brain functions	references
Bisphenol A single dose 100 µg/kg oral gavage of dams	not detected	Fetus whole brain	Rat (Dams, fetuses and developing rats)	x	(Doerge et al., 2011)
single dose 100 µg/kg intravenous injection in dams	117 pmol/g on GD12 62 pmol/g on GD16 22 pmol/g on GD20	Fetus whole brain			
Oral gavage 100 µg/kg Neonatal rats of different ages	2H after gavage Postnatal day 3: 2.1 pmol/g Postnatal day 10: 0.94 pmol/g Postnatal day 21: 0.86 pmol/g	Pups whole brain Pups whole brain Pups whole brain			
benzophenone					
benzophenone 3 dermal exposure 100mg/kg twice daily to dams from the first to the last day of pregnancy, and to male rats whose mothers received Benzophenone, from 43 to 56 days of age	50.6 ng/g 46.7 ng/g	Frontal cortex Hippocampus	Rat (Dams and male adults)	Benzophenone 3 impairs spatial memory	(Pomierny et al., 2019)
benzophenone 2 dermal exposure 100mg/Kg twice	5 ng/g	Hippocampus	Rat (adults)	No sign of apoptosis and	(Broniowska et al., 2019)

daily during 4 weeks	20 ng/g 20 ng/g	Frontal cortex Cerebellum		oxidative stress	
Perfluoroalcano					
Perfluoroalcano single oral dose 50mg/kg	Measurement after 10 days:	Whole brain	Rats (adults)	Perfluorododecanoic acid causes anxiety, attention and memory deficits	(Kawabata et al., 2017)
perfluorooctanoic acid	not detectable				
perfluorodecanoic acid	4.7 µg/g				
perfluorododecanoic acid	44 µg/g				
PCB					
Aroclor 1242 exposure by inhalation, 10 days, (~1,4mg/day)	Concentration max ≈ 100 ng/g lipid (≈15ng/g) for PCB 20 + PCB 28	Whole brain	Rat (adults)	x	(Hu et al., 2010)
PCB mixture intramuscular injection of a single dose (1.3 mg PCB 54; 0.5 mg PCB 80; 1.4 mg PCB 155; 0.7 mg PCB 169)	Measurement 2 months after injection PCB 54: 1.1 ng/g fat (≈0.16ng/g) PCB 80: 1.1 ng/g fat (≈0.16ng/g) PCB 155: 46 ng/g fat (≈6.9ng/g) PCB 169: 11 ng/g fat (≈1.6ng/g) PCB 54: 1 ng/g fat (≈0.15ng/g) PCB 80: 1.1 ng/g fat (≈0.16ng/g) PCB 155: 15 ng/g fat (≈2.3ng/g)	Female whole brain Female whole brain Female whole brain Female whole brain Lamb whole brain Lamb whole brain Lamb whole brain	Sheep (lactating females and lambs)	x	(Jan et al., 1999)

	PCB 169: 470 ng/g fat (≈15ng/g)	Lamb whole brain			
Dioxin					
TCDD oral gavage, single dose of 10 µg/kg to dams at gestational day 15	0.42 ng/g one day after treatment 0.35 ng/g five days after treatment 0.193 ng/ at GD16 0.298 ng/g at GD20	Dam whole brain Dam whole brain Fetus whole brain Fetus whole brain	Rat (dams and fetuses)	x	(Ishida et al., 2010)
Organotin					
tributyltin or dibutyltin oral gavage daily 10 µg/kg from gestational 8 day up to birth tributyltin tributyltin dibutyltin dibutyltin	1800 ng/g at GD20 1750 ng/g at P6 350 ng/g at GD20 100 ng/g at P6 400 ng/g at GD20 500 ng/g at P6 180 ng/g at GD20 130 ng/g at P6	Whole brain Dam whole brain Pup whole brain Dam whole brain Pup whole brain	Rat (dams and pups)	x	(Cooke et al., 2008)
Tributyltin oral gavage single dose 30 mg/Kg	2-30 ng/g Sn depending on brain areas	Cerebellum, Hippocampus, hypothalamus, striatum	Rat (adults)	Central oxidative stress with elevated lipid peroxidation and protein carbonylation	(Mitra et al., 2015)
Mono-, di- or tri- butyltin single dose 2 µg Sn monobutyltin dibutyltin	Total amount 0.1 ng Sn 0.2 ng Sn	Whole brain	Rat (adults)	X	(Rodriguez- Gonzalez et al., 2005)

tributyltin single dose 20 µg Sn monobutyltin dibutyltin tributyltin	2 ng Sn 0.4 ng Sn 2.8 ng Sn 21 ng Sn				
tributyltin intraperitoneal injection, 4 mg/kg, single dose	1.5 µg/g after 16 hours	Whole brain	Mouse (adults)	x	(Doctor et al., 1983)
tributyltin intraperitoneal injection 2.5 mg/kg of body weight	1.5 µg/g after 24 h 0.75 µg/g after 96 h	Olfactory bulb	Rat (adults)	olfactory disturbance s	(Tomiyam a et al., 2010)
Phthalate					
benzyl butyl phthalate 5 mg/kg/hour for 18 hours of continuous intravenous infusion	68 ng/g Metabolites: Monobenzyl phthalate 37ng/g Monobutyl phthalate 87ng/g	Whole brain	Rat (adults)	X	(Kim et al., 2015)
dibutylphthalate 10 mg bolus per gavage or 1g/kg of feed for 12 weeks	Traces	Whole brain	Rat (juveniles to adults)	X	(Williams and Blanchfiel d, 1975; Ikeda et al., 1978)
Diisooctylphthalate or Butylglycolylbutyl oral administration, 50mg/kg/day for 21-28 day	Traces	Whole brain	Dog, Mini pig, Rat (adults)	x	(Ikeda et al., 1978)

Table 4. Examples of in vivo and ex-vivo studies investigating blood-brain interfaces as targets for environmentally-borne xenobiotic endocrine disruptors.

Abbreviation: BBB: blood-brain barrier; IP: intraperitoneal; IV: intravenous; ICA: intra carotid artery; WB: Western Blot

Endocrine diusruptors	Species	Developm ental stage at the time of treatment	Treatment and time of analyze	Brain areas investigated	Observed effects on BBB or BCSFB	References
Tributyltin	Male Wistar rats	4 weeks	10 to 30 mg/kg, gavage. Analyses: 3 and 7 days later	Striatum Cerebellum Hippocampus Hypothalamus Cerebral cortex	Increase in BBB permeability following 20&30 mg/kg dosing (Evans blue marker). Correlation with Sn accumulation in brain tissue. Variation from region to region.	(Mitra et al., 2015) (Mitra et al., 2013)
Tributyltin oxide	Male Wistar rats	Adult	58,5 mg/kg, gavage. Analyses: 0,5 to 24 hours later	Hypothalamus	Transient increase in BBB permeability at 2 hours (leakage of lanthanum observed by EM). Possibly related to Sn interference with Ca at tight junctions.	(Hara et al., 1994)
Triethyltin	Male Sprague-Dawley rats	Adult	10 mg/kg, IP. Analyses: 12-48 hours later	Multiple structures	No change in BBB permeability (evans blue marker), despite the occurrence of a brain edema resulting from the acute intoxication.	(Inoue et al., 1987)
Triethyltin	Male hamsters	Adult	5-10 mg/kg, IV. Analyses: 4-24 hours later	Multiple structures, including white matter	No or limited change in BBB permeability (dextran markers), despite the occurrence of a brain edema resulting from the acute intoxication.	(Hultstrom et al., 1984)

Triethyltin	Male and female R-Amsterdam albino rats	Adult	5&7,5 mg/kg IP. Analyses: 48hours later	Whole brain	Increased BBB permeability (evidenced by serum protein in brain).	(Joo et al., 1969)
Trimethyltin	Female Wistar Rats	Adult	8 mg/kg, IP. Analyses: 21-25 days later.	Cerebral cortex Hippocampus	Possible increase in BBB permeability (evidenced by IgG extravasation observed on histology). Possible link with VEGF/VEGFR signaling activation. Increase in AQP4 expression .	(Ceccariglia et al., 2014)
Trimethyltin	Male Long-Evans rats	6 weeks	8 mg/kg, IP. Analysis: 1,3,5,7 21 days later.	Hippocampus	No effect on BBB permeability (assessed by IgG extravasation), except a small increase in IgG evidenced by WB at day 21, when a strong hippocampal cell loss is observed.	(Little et al., 2002)
di(2-ethylhexyl)phthalate w/wo a mixture of other phthalates	Male C57BL/6J mice	Adult	5 to 50 µg/kg/day for 6 weeks, peros. Other phthalates: 0,25 to 0,5 µg/kg/day for 6 weeks, peros	Hippocampus, Medial preoptic area	increased BBB permeability (Evans blue marker, IgG extravasation). Decreased zona occludens-1 (WB) but not Cldn5 or occluding expression. Decreased caveolae protein Cav-1 (Immunolabelling and WB).	(Ahmadpour et al., 2021)
Bisphenol A	Male and female SJL mice submitted to virus-induced neuroinflammation	Pre and postnatal stages	10 µg/kg /day, gavage of dam, gestation and lactation period. Analysis: 20 weeks of life	Spinal cord	Increased meningeal and perivascular immune cell infiltration (indirect evidence of altered neuroimmune regulation at blood brain interfaces).	(Brinkmeyer-Langford et al., 2014)
Bisphenol A	Male Wistar rats	Adult	0.5 to 1µM, analysis: 6 hours later	Isolated viable capillaries	Weak inhibition (compared to Ethinyl-estradiol) of BCRP expression and function.	(Nickel and Mahringer, 2014)

Tetrabromo-bisphenol A	Male and female Sprague-Dawley rats	Adult	Isolated capillaries: 1-100 μ M, analysis: 6 hours later In vivo: 250 mg/kg, gavage. Analysis: 6 hours later	Isolated viable capillaries	Dose and time dependent decrease in BCRP function, increase in PGP (male), and ER- α -dependent decrease in PgP (female) functions.	(Cannon et al., 2019)
methyl and propyl para-hydroxybenzoates	Cats	Adult	2 x 4 mg, ICA. Analysis: 10 minutes later		No changes in radiopack penetration into the brain.	(Craver et al., 1968)
methyl and propyl para-hydroxybenzoates	Male and female Rhesus monkeys	Adult	2 x 4 mg, ICA Analysis: a few minutes later		No changes in radiopack penetration into the brain.	(Strain et al., 1969)
PCB 118	Male C57/B16 mice	Adult.	Unclear, possibly 67 μ moles/kg, or 206 pg/kg, ICA, Analysis: 24 hours later	Whole brain Isolated capillaries	Increased permeability (sodium fluorescein co-administered with LPS). Occludin down-expression (Immunolabelling and WB). Reproduced in a brain endothelial cell line.	(Choi et al., 2012)
PCB153	Male C57/B16 mice	Adult	5 μ g/kg, ICA Analysis: 24 hours later	Whole brain Isolated capillaries	PCB153 bound to nanoparticle, but not PCB alone increases BBB permeability to fluorescein and favors monocyte transmigration. PCB153 bound to nanoparticle, but not PCB alone decreases occludin and claudin 5 expression, possibly by interaction with TLR4 signaling	(Zhang et al., 2012) (Zhang et al., 2013)

					Free and nanoparticle-bound PCB153 induce a pro-inflammatory phenotype.	
PCB153	Male C57/B16 mice	Adult	150 µmoles/kg, gavage. Analysis: 48 hours later	Isolated viable capillaries	Decrease in occludin expression (immunolabelling). Effect reproduced in a brain endothelial cell line.	(Eum et al., 2015)
PCB126, 118 153	Male C57/B16 mice	Adult	150 µmoles/kg, gavage. Analysis: 48 hours later	Whole brain Isolated capillaries	Increased permeability of BBB to fluorescein. All PCB: Cldn5 downregulation (WB, immunosignal), No occludin expression change. PCB 118 and 153: increased ZO1 expression. (Enhanced susceptibility to melanoma cell invasion into the brain)	(Seelbach et al., 2010)
Arochlor 1254 (PCB mix)	Male Wistar Rat	Adult	2mg/kg, IP. Analysis: 24 hours later	Hippocampus Cerebrum Cerebellum	Occludin, Cldn5, JAM ZO1 ZO2 AF6 protein expression (WB) or mRNA level decreased.	(Selvakumar et al., 2018) (Selvakumar et al., 2013)
PCB153	Sheep (ewe)	Adult	0,33 mg/kg/day, 3 times a week, three weeks.	Lateral ventricle choroid plexuses	Decreased protein (but not mRNA) levels of Cldn1, ZO2, AF6. No change in Cldn5, Jam, other ZO protein expression (WB). Changes observed only when the treatment is applied during short days, when plasma PCB levels are highest.	(Szczepkowski et al., 2013)
PCB153	Sheep (ewe)	Adult	0,33 mg/kg/day, 3 times a week, three weeks.	Lateral ventricle choroid plexuses	Increase in VEGF164 mRNA and protein (WB), together with a decrease in VEGFR expression.	(Szczepkowski et al., 2016)

					Changes observed only when the treatment is applied during short days.	
GEN-X	Male and female Sprague-Dawley rats	Adult	Isolated capillaries: 0,1 to 1000 nM, Analysis: 1 to 4 hours later In vivo: 0.03 to 3 nmoles/kg, gavage. Analysis: 5 hours later	Isolated capillaries	Decreased ABCB1 (PPAR- γ dependent) and ABCG2 transport function following ex vivo exposure to 0,1-100 nM and 1-1000 nM GEN-X, respectively, or in vivo Gen-X exposure. No protein level changes.	(Cannon et al., 2020)
Perfluorooctane sulfonate (PFOS)	Male ICR mice	Adult	0,25-50 mg/kg/day, for 28 days, gavage	Cerebral cortex	Decreased Cldn5, ZO1, Occludin from 25 mg/kg dosing. Signs of altered endothelial cells by electron microscopy.	(Yu et al., 2020)
Dioxin (TCDD)	Rat isolated capillaries Rat vivo	Brain and SC	0,05 to 0,5 nM, measure 3 hours later 5 mg/kg, Then capillary isolation 48 h later		Increases Pgp and Bcrp transport activity via an AhR-dependent mechanism (3 h seems rapid). Increased PgP activity and protein level, increased BCRP protein level.	(Campos et al., 2012)