Pesticides at brain borders: Impact on the blood-brain barrier, neuroinflammation, and neurological risk trajectories

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Abstract

Pesticides are omnipresent, and they pose significant environmental and health risks. Translational studies indicate that acute exposure to high pesticide levels is detrimental, and prolonged interaction with low-level pesticides, as single and cocktail, could represent a risk factor for multi-organ pathophysiology, including the brain. Within this research template, we focus on pesticides' impact on the blood-brain barrier (BBB) and neuroinflammation, physical and immunological borders for the homeostatic control of the central nervous system (CNS) neuronal networks. We examine the evidence supporting a link between pre- and postnatal pesticide exposure, neuroinflammatory responses, and time-depend vulnerability footprints in the brain. Because of the pathological role of BBB damage and inflammation on neuronal transmission from early development, varying exposures to pesticides could represent a danger, perhaps accelerating adverse neurological trajectories during aging. Refining our understanding of how pesticides influence brain barriers and borders could enable the implementation of pesticide-specific regulatory measures directly relevant to environmental neuroethics, the exposome, and one-health frameworks.

1) Brain borders: the blood-brain barrier is a port of entry into the CNS.

The brain is evolutionarily shielded, physically and biologically, to ensure a continuous fine-tuning of brain homeostasis and dependable synaptic transmission. Three borders exist, namely the blood-brain barrier (BBB), the blood-to-cerebral spinal fluid (B-CSF) barrier formed by tight junctions between adjacent choroid plexus (CP) epithelial cells, and the meninges where the CSF is filtered from peripheral blood (Figure 1; see [1-7] for comprehensive reviews). These structures are the sentinels of brain stability and immunity, surveilling and enabling exact spatiotemporal synchronizations of neuronal networks that equate to physiological or normal behaviors, correct memory, executive functions, development, and aging [5,8,9]. In health, these biological structures strictly control the passage of xenobiotics, exogenous compounds, toxins, and immune cells from the peripheral blood circulation into the brain parenchyma [1,4,5,7]. Brain barriers, or borders, represent sensitive sites where the presence and continuous accumulation of environmental contaminants could have a negative impact and, in turn, promote a harmful sequel to the brain [3,5,8,10-12]. Here, we focus on the BBB as the primary interface between peripheral blood and the brain parenchyma. The BBB is a complex network of capillaries, with each microvessel anatomically and functionally connected to distinct groups of neurons, hence the terms neuro-glio-vascular unit (NGVU) and metabolic neurovascular coupling [1,5]. The anatomical reach and the protection afforded by the BBB are vast; the human brain contains 20-25 m^2 of capillaries, illustrating the granular exchange to all brain regions and neuronal networks. The BBB is a multi-cellular structure formed by endothelial cells, astrocytes, and pericytes,

communicating with one another, assembled in basement laminae, surrounded by microglial cells and neurons within tens of micrometers distances (Figure 2). The BBB endothelium is highly impermeable due to the expression of specific inter-cellular tight-junctions [1]. ATP (Adenosine triphosphate)-dependent transporter proteins (and p450 metabolic enzymes [13,14]) expressed at the endothelium are instrumental in guaranteeing a highly selective exchange of molecules between the peripheral blood and the brain. Transcytosis and endocytosis (e.g., caveolins) also regulate BBB permeability [5].

BBB damage participates in CNS diseases [2,3,5,8,12] because it intersects with neuroinflammation and dysregulates the homeostatic control (e.g., via glial buffering) of ions, ATP, and neurotransmitter levels necessary for the maintenance of resting potentials and synaptic transmission [2,15]. These events are detailed in two reviews [15,16]. BBB damage and neuroinflammation are ictogenic and can promote seizures [6-8,15,17-19]. BBB damage accelerates neurodegeneration [20,21], is implicated in the etiology of encephalopathies and psychiatric conditions, and represents a converging risk factor for pathological aging [20], neurological and neuroimmunological disorders [22]. The BBB protects the brain from extra-physiological elements or toxins that could pathologically interfere with the programmed developmental trajectories [7]. Collectively, this literature illustrates the neurological dangers associated with increased BBB permeability and neuroinflammatory changes; it underlines the necessity of investigating the impact of environmental contaminants on brain barriers to define elements of vulnerability pertinent to brain health. Within this framework, we review experimental and clinical evidence for specific classes of pesticides currently under scrutiny as they may pose exposome threats. We performed a Pubmed and

Google Scholar search for the period 2010 to 2022, using combinations of two or more keywords: pesticides, neurotoxicology, zebrafish, rodent models, blood-brain barrier, neurovascular unit, tight junctions, neuroinflammation, astrocytes, microglial cells, neurodegeneration, seizures, psychiatric disorders, and brain development. Including only two databases and a primary focus on a ten years period are potential research strategy flaws. We provide a general overview of pesticides at the brain interfaces and summarize data obtained using *in vitro* and *in vivo* models showing the impact of pesticides at the NGVU. We examine how pesticides constitute risk factors for adverse neurological trajectories, focusing on pathological conditions where BBB damage and neuroinflammation are implicated.

2) Pesticides: from environmental omnipresence to brain access.

With more than 1700 product formulations and increasing amounts applied in cropland areas [23] (https://www.fao.org/faostat/en/#data/EP/visualize), pesticides raise environmental and health alarms [24-26]. Pesticides are present in matrices, such as water bodies [23,24,27-29], ice [30], rainwater [31], coastal areas [32], soil and sediment [29,31,33]. Pesticide residues are found in wildlife species [34-36].[26]. They can be present in spaces other than agriculture, including schools, playgrounds, households, recreational water, or urban green areas [25,26]. Occupational exposure is particularly relevant for agricultural workers or pesticide manufacturers, with potential exposure to high concentrations [37,38]. Non-occupational exposures can be significant for residents near crop fields or pesticide facilities [39-43 44,45].

These diversified exposure pathways are associated with detecting pesticides, or their metabolites, in human body fluids such as breast milk [46,47], urine [48,49], blood [50,51], cerebrospinal fluid [52], amniotic fluid [53,54], umbilical cord serum [55], saliva [56] and seminal plasma [27,57]. The main entry routes of pesticides to the human body include i) dermal absorption for occupational exposure, ii) oral exposure through the food chain, accidental or intentional ingestion, and iii) inhalation [26,58]. These entry routes converge into the blood circulation, reaching the brain via specific borders (Figure 2) where two scenarios are possible: i) a lipophilic and low molecular weight (e.g., <400Da) molecule penetrates the BBB through the intact endothelium, reaching the brain parenchyma; ii) a molecule enters the brain after having damaged the BBB (e.g., increased permeability). In both circumstances, an extra-physiological molecule enters the brain and could exert neuroglial toxicity. Importantly, at the BBB, a battery of ATP-dependent drug transporter proteins represents the first line of defense from exogenous compounds [13,14,59,60]. Efflux transporters pump lipophilic molecules back into the peripheral blood from the apical endothelial cell, preventing their entry into the brain. This ATP-binding cassette (ABC) superfamily includes the efflux transporter P-glycoprotein (Pgp), which expression levels and activity govern the exclusion of neurotoxicants from the brain [61,62], together with the multidrug resistance-associated proteins (MRPs) and the breast cancer resistance protein (BCRP). A second family is a solute carrier (SLC) bidirectional transporter (export and import). Members of the SLC family are described in [63,64]. Table 1 provides archetypical examples of pesticides transported by ABCs or SLCs superfamilies. This evidence is comprehensively reviewed in [65-67], along with relevant in vitro and in vivo models commonly employed for screening experiments.

3) Pesticides at the neuro-glio-vascular unit: in vitro studies.

In vitro models are used to examine the impact of pesticides on BBB permeability and NGVU cells [68,69] [70]. Table 2 presents a list of existing evidence for each cell type while, in the text, we focus on particular examples. The cellular toxicity of the organophosphate (OPs) malathion and malaoxon was tested using an *in vitro* BBB model (endothelial cells BMEC or RBE4) and neuroblastoma cells (SH-SY5Y). Cell viability was reduced with a significant permeability of malathion and malaoxon across the BBB. Malathion decreased the expression of endothelial cells tight junctions (occludins, claudin 5, Zonula occludens (ZO) 1, and ZO2). Paraoxon affected the BBB *in vitro* by reducing cell viability and junctional mRNA and protein expression [69,71]. Paraoxon negatively impacted occludin and claudin structures in human-derived endothelial cells [70].

With endothelial cells, astrocytes are a key component of BBB stability and a neuroinflammatory regulator (Table 2). Astrocyte reactivity directly contributes to BBB damage. They are sensitive to low-dose OPs. Malathion increased intracellular Ca^{++} concentration and induced cytotoxicity via reactive oxidative species (ROS) production [72-74]. Chlorpyrifos and parathion on human primary astrocytes caused glial fibrillary acidic protein (GFAP) astrogliosis [75,76]. The pyrethroid cyflutrin elicited inflammatory activations in primary human astrocytes [75]. Lambda-cyhalotrin caused

cytotoxicity (24 h exposure) by inducing Ca2+ entry via store-operated Ca2+ channels and Ca2+ release from the endoplasmic reticulum [72]. Cypermethrin on rat astrocytes led to apoptosis by disrupting the autocrine/paracrine mode of HB-EGF-EGFR signaling [77].

We next examine microglia, the principal resident immune brain cells reacting to pesticide exposure and impacting BBB permeability (Table 2). Low chlorpyrifos levels (0.3-300 µM) triggered oxidative stress and pro-inflammatory states. Chlorpyrifos promoted BV-2 microglial activation, proliferation, increased DNA damage, generation of oxidative markers, and overexpression of pro-inflammatory markers [78]. An increase in nitric oxide (NO) levels occurred 24 h after dichlorvos exposure (10 µM), associated with up-regulation of inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines like nitric oxide, TNF-α, and IL-1β [79]. At concentrations of 25 µM or higher, deltamethrin and permethrin significantly decreased microglial cell viability in a concentration- and time-dependent manner. Permethrin- and deltamethrin stimulated microglia morphological transformation (retraction of cell processes and an amoeboid shape) [80]. In the conditioned medium, cypermethrin increased PKC-δ and iNOS in primary microglia, Tumor Necrosis Factor-alpha (TNF-α), and interleukin (IL)-1β. Conditioned media from cypermethrin-treated microglia induced toxicity in primary rat neurons [81]. Exposure to ranging concentrations (10–100 µM) of bifenthrin for 24 h decreased microglia viability with maximal effects at 100 µM. No significant cell death occurred at lower concentrations (0.1, 1, and 5 µM) [82].

In addition to NGVU cells, we here discuss the possible influence of pesticides on circulating leukocytes (Table 2), critical cells interacting with the BBB to promote neuroinflammatory changes and vascular damage. Lymphocyte exposure to OPs, glyphosate, methyl parathion, malathion, and chlorpyrifos led to a significant viability reduction and DNA damage, including DNA single-strand breaks (SSBs) and DNA double-strand breaks (DSBs) as well as DNA protein cross-links (DPC) formation [83-86]. Monocytes or macrophage-like cells (RAW 264.7) exposed to β-Cypermethrin (24 h) showed cytotoxic effects, with decreased cell viability (35% and 79% with 50 μM and 100 μM, respectively), phagocytosis, activation of intrinsic apoptotic pathway and inhibition of the expressions of pro-inflammatory cytokines. ROS production and oxidative stress were increased following this exposure [86]. Overall, the immune system could be a target for the toxic effects of pesticides [87]; however, available experimental and epidemiological data are insufficient to draw firm conclusions on the immune-toxic risk associated with environmental contaminants. Comprehensive studies are needed to unveil how pesticides promote cellular-level modifications with specificity to peripheral and neuro-immune cross-talk.

4) Pesticides at the neuro-glio-vascular unit: in vivo studies.

Pesticide exposure during prenatal or juvenile stages represents a risk factor for negative neurodevelopmental trajectories, including a decline in cognition, hyperactivity, and autism spectrum disorders [88-91]. Consistent with human epidemiological studies, experimental data have strengthened the adverse association between pesticides and neurological outcomes, also introducing a

pathological impact on the BBB [92-94]. Table 3 and the text below review data obtained using rodent and aquatic models. We examine the effects of pesticides (pyrethroids, OPs, organochlorines (OCs), neonicotinoids, and other agents and mixtures) at the BBB and the intersection with neuroinflammation.

4.1) Evidence from rodent models.

Pyrethroids are insecticides produced as synthetic derivatives of the pyrethrin extracted from *Chrysanthemum cinerariaefolium* [95]. Their insecticidal properties are based on altering the voltage-gated Na+ channels in insect neuronal membranes, disrupting the Na+ current in the CNS [96]. The effects of pyrethroids extend to the voltage-gated-calcium and potassium channels, glutamate, and acetylcholine receptors [97]. Mice exposed to low concentrations of permethrin (0.3 ppm) during prenatal and postnatal periods showed impairments in the formation of the neural circuits, indicated by immature neuron marker (doublecortin) and decreased number of astrocytes [98]. BBB integrity was not affected in rats exposed to permethrin (0.013, 0.13, 1.3 mg/kg/d) for 60 days [68] (topical application). A follow-up study reported neuronal cell death and neuronal cytoskeletal abnormalities [68]. Another synthetic pyrethroid, bifenthrin, administered to adult rats for 60 days (0.6 and 2.1 mg/kg/d), increased the expression of TNFa, IL-1b, IL-6, nuclear factor erythroid-2 (Nrf2), cyclooxygenase-2 (cox-2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and prostaglandin E2 (PGE2) in the hippocampus, with enhanced oxidative stress markers (i.e. malondialdehyde (MDA), protein carbonyls (PCO), NO)

and reduced antioxidant defense (i.e. catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase GPx) [82,99]. These inflammatory events can negatively impact BBB integrity [5]. Similar results were obtained when cypermethrin was orally administered to adult rats (1 mg/kg/day) or from gestational day (GD) 7 to post-natal day (PND) 21 (1.5 mg/kg/d) [100,101]. Microglia activation was triggered by cypermethrin (1.5 mg/kg twice a week) intraperitoneally injected postnatally in rats [97]; cypermethrin crossed the BBB, leading to oxidative stress [102]. Allethrin, a pyrethroid-based mosquito repellent, induced BBB permeability in the developing rat (inhalation) [103].

OPs irreversibly bind and inhibit acetylcholinesterase (AChE), preventing acetylcholine breakdown, leading to its accumulation and the hyperstimulation of cholinergic receptors [104,105]. OPs are the most studied pesticides in experimental models, with evidence supporting their etiological role in neurodegeneration (Table 3) [100]. OPs permeate the BBB [106]. Acute and chronic OPs exposure in rodents induces neuroinflammation, activating glial cells and releasing pro-inflammatory cytokines, prostaglandins, and chemokines [107,108]. Acute exposure to diisopropylfluorophosphate resulted in neuronal injury, neurodegeneration, and neuroinflammation, with the activation of microglia and astrocytes, accompanied by seizures [109,110]. Chlorpyrifos is gaining attention due to its extensive use and non-target species effects. It triggers neuroinflammation [111]. Mice exposed to chlorpyrifos (i.p., 5 mg/kg) for ten days showed no morphological changes in pyramidal neuronal cells [112]. When similar chlorpyrifos concentration was administered orally in rats for one month, histopathological alterations of pyramidal neurons occurred [113]. Chlorpyrifos impaired neurogenesis and synaptic integrity (synaptophysin immunoreactivity). Thus, chlorpyrifos can cross the BBB [112] detected in the CNS of

exposed rodents [114]. Chlorpyrifos dermally applied in adult mice increased GFAP reactivity [115], affecting oxidative stress and antioxidant defense [102,113,114]. Signs of neuroinflammation were reported when female mice were exposed to high concentrations of glyphosate-based herbicides during pregnancy and lactation. Glyphosate activates microglia and astrocytes and affects synaptic plasticity in the pup hippocampus [116]; it decreases anti-oxidant enzyme activities in the mouse brain [117].

OCs, such as DDT, hexachlorocyclohexane (HCH), aldrin, or dieldrin, are used in certain countries because of their low cost and effectiveness in controlling insect-borne diseases (e.g., malaria) [118,119], with long persistence and bioaccumulation. OCs trigger neurotoxicity, blocking subunits of the GABA-A receptors. Orally administered endosulfan (28 days, 5 mg/kg/d) to adult rats elicited oxidative stress and deregulated the levels of neurotransmitters. Endosulfan can negatively affect the developing brain by altering dopamine [120] [121]. Endosulfan administered to pregnant rats led to cerebellar and hippocampal inflammatory pathways in the offspring [97,122]. Selective loss of dopaminergic neurons and disruption of dopamine transport occurred when heptachlor was intraperitoneally injected in adult mice (7 mg/kg twice a week for 8 weeks) or orally administered to pregnant mice throughout gestation and lactation (3 mg/kg every 3 days for 2 weeks). Heptachlor activates astrocytes and microglial cells in specific brain regions, such as the ventral midbrain area, with dopaminergic system susceptibility to further damage [123,124]. Methoxychlor injected i.p. for 20 days into adult mice decreased dopamine levels and disrupted dopamine metabolism and transport, with a link to oxidative stress at the mitochondrial level. GFAP immunoreactivity was increased [125].

Neonicotinoids are nicotinic acetylcholine receptor (nAChR) agonists due to their structural similarities with nicotine [126], evoking excitatory responses in the insect central nervous system. Because of their effects on pollinator populations, some neonicotinoids (clothianidin, thiamethoxam, imidacloprid) are banned in the EU. Neonicotinoids were reported to penetrate the BBB poorly, with exceptions in the brain of mice and zebrafish [127 128]. Neonicotinoids and their metabolites can affect neurodevelopment and neurotransmission and induce oxidative stress and neuroinflammation in rodent models [129,130]. Acetamiprid accumulates into the brain upon a few days of oral ingestion in adult mice, affecting the expression levels of nAChR without causing gross histomorphological brain changes [131]. Exposure to acetamiprid and imidacloprid (5 mg/kg day) in postnatal mice reduced neurogenesis in the hippocampal dentate gyrus and increased the number of activated microglia. Both neonicotinoids can permeate the BBB [132]; accordingly, imidacloprid and its metabolites were reported to cross the BBB upon oral exposure to gestational mice [133], causing oxidative stress and inflammation [134]. Importantly, ROS production exerts a key role in neonicotinoid-associated neurotoxicity [130 135-137].

Paraquat is a well-known neurotoxicant that crosses the BBB [138], causing dopaminergic neuronal damage. Paraquat administered to adult mice (i.p, 5 – 80 mg/kg twice a week for 4 weeks) induced neuroinflammation with ROS production in the substantia nigra, frontal cortex, and hippocampus, with activation of microglia cells, increased expression of TNFa and IL1b, and dopaminergic neurotoxicity. The release of pro-inflammatory cytokines from the activated microglia may disrupt the BBB endothelium [139]. Paraquat (i.p, 1 and 5 mg/kg every 2 days) administered for several weeks in adult mice augmented BBB permeability. It activated microglia,

which release pro-inflammatory cytokines, such as IL-1b, in the dentate gyrus [140]. When pregnant mice were exposed to paraquat (aerosol), the offspring showed microglia activation [141]. However, one study did not report neuropathological alterations in male mice exposed to the maximum tolerated doses of paraquat [142].

Rotenone is a natural lipophilic insecticide that interferes with the electron transport chain. Rotenone can cross the BBB due to its lipophilicity. Two and 3-weeks of rotenone exposure (i.p) in adult rodents diminished the expression of endothelial tight junction proteins. Signs of toxicity were reported, such as microglia and astrocyte activation, neuronal apoptosis, and progressive loss of dopaminergic neurons. The activation of glial cells was associated with releasing cytokines and chemokines [143,144]. Atrazine is an herbicide frequently detected in the environment. Rodents exposed to atrazine via inhalation (25 mg for 28 days) or oral gavage (50 – 200 mg/kg 5 days a week for 45 days) showed neuroinflammation and neurotoxicity, such as ROS levels and oxidative stress, production of pro-inflammatory cytokines, microglia activation, and dopaminergic neurons degeneration [145,146]. Other pesticides, such as ivermectin, a potent insecticide and anthelmintic, were also reported to cross the BBB [147].

Lastly, assessing the effects of a mixture is necessary and a complex task because the impact of each combination might vary according to the compound and the doses [148]. We here provide a few examples. Endosulfan and cypermethrin in a mixture or single components showed dissimilar effects on neuroinflammatory markers in the hippocampus [97]. Pesticides unable to cross the BBB when used as a single may quickly enter the CNS when mixed [149]. Permethrin does not alter BBB

permeability, but when it was tested with N,N-diethyl-meta-toluamide (DEET), a decrease of BBB permeability in the cortex occurred [68]. When orally administered to rats, a mixture of chlorpyrifos and cypermethrin induced oxidative stress [102]. On the other hand, when chlorpyrifos, methyl parathion, and malathion were administered in rats, they did not show potentiation of toxicity [150].

4.2) Evidence from aquatic models.

The function of the BBB is conserved across different taxa [151,152]. As in mammals, fishes have brain endothelial cells, perivascular glia, and pericytes [152], affording CNS protection [152]. In harmonization with the rodent data previously presented, we review the impact of selected compounds (Table 3).

Pyrethroids can cross the BBB and trigger neurotoxic sequelae in aquatic animals [95]. Grass carp (*Ctenopharyngodon idella*) exposed to cypermethrin (0.65 µg/L) for 42 days displayed histopathological alterations at the cerebellar level, with damaged myelin sheath layers and decreased synapses. The genes coding for BBB tight junction proteins (claudins, occludin, ZO) were downregulated [153]. Common carp (*Cyprinus carpio*) exposed to deltamethrin (0.04 and 0.08 µM) for 96h showed degenerative and necrotic neurons at the optic lobe with upregulation of apoptotic markers as caspase (CAS) 3 and 8. Oxidative stress and inflammatory markers, such as 8-hydroxy-2' -deoxyguanosine (8-OHdG), iNOS, glutathione S-transferase (GST),

388 and DNA damage were detected in neurons and glial cells of cypermethrin-exposed
389 carps and rainbow trouts [154-156]; similar results were obtained in neotropical fish
390 *Prochilodus lineatus* exposed to ng/L levels of λ-cyhalothrin [136,137]. In common carp,
391 NO vasodilation negatively impacts cerebrovascular structures [152]. Adult and embryo
392 zebrafish exposed to low concentrations of deltamethrin (0.25 – 2 µg/L) showed
393 persistent alterations in dopaminergic-related gene expression and locomotor activity
394 [157,158] [159]. Chinook salmon (*Oncorhynchus tshawytscha*) exposed for 96 hours to
395 environmentally relevant concentrations (0.15 and 1.50 µg/L) of bifenthrin presented
396 neuronal metabolic dysfunction linked to axonal development, as well as apoptotic
397 and inflammatory activations [160].
398
399 OPs are studied in aquatic models. Chlorpyrifos is associated with brain
400 histopathological lesions, neuronal degeneration or death in common carp [161,162], and
401 alteration of monoaminergic neurotransmitters in zebrafish embryos [163]. Existing
402 studies report increased 8-OHdg, CAS3, iNOS immunoreactivity in common carp [161];
403 gene transcription for markers associated with neuronal dysfunctions and
404 neuroinflammatory mechanisms in Atlantic salmon (*Salmo salar*) and common carp
405 [162,164]; deregulation of the antioxidative system, such as SOD, GST, glutathione
406 reductase (GS) or catalase (CAT) activities and elevated lipid peroxidation (LPO) and
407 MDA, a secondary LPO product, in guppy fish brain (*Poecilia reticulata*) and common
408 carp [162]. Deregulated ROS activities occur with trichlorfon and parathion exposures in
409 catfish (*Rhamdia quelen*) and common carp [162,165]. After pesticide exposure,
410 excessive ROS formation negatively impacts cerebrovascular tight junctions [165].
411 Zebrafish embryos exposed to a ranging concentration of chlorpyrifos or bifenthrin
412 (100 – 300 µg/L, 15 and 30 µM) showed alterations for oxidative stress markers in

413 the brain, along with the upregulation of genes coding for pro-inflammatory cytokines
414 (e.g., *tnfα*, *il-1β*, *cox2b*). Bifenthrin downregulates pro-angiogenic BBB genes [166-168].
415 Nile tilapia (*Oreochromis niloticus*) exposed to bifenthrin presented oxidative stress
416 and neuroinflammation markers in the brain [168].
417
418 Next, OCs such as dichlorodiphenyltrichloroethanes (p,p'-DEE, p,p′-DDD, p,p′-
419 DDT), drins (dieldrin, aldrin, endrin), hexachlorocyclohexanes (HCHs) and
420 endosulfan can cross the BBB and are detected in brain tissues of wild fish, e.g.,
421 from Lake Apopka (FL, USA) and a soybean growing area in Argentina [169,170]. In the
422 hypothalamus of zebrafish and largemouth bass (*Micropterus salmoides*), dieldrin
423 (0.03 – 1.8 µg/g and 2.29 mg/kg dry weight feed/d) interferes with the mRNA and
424 protein levels of T-cell receptors, interleukins, oxidative stress, and cell viability [171,172].
425 Similar results were obtained in zebrafish embryos exposed to clethodim (10 – 500
426 µg/L) [173].
427
428 Neonicotinoids are studied in freshwater species. Imidacloprid (0.001 -10
429 mg/L) elicited DNA damage and oxidative stress in brain tissue [136,137,174]. Rainbow
430 trout exposed to environmentally relevant concentrations of clothianidin (3, 15, 30
431 µg/L) for 21 days displayed signs of cell damage in the brain and histopathological
432 lesions such as neuron and glial cell damage in the cerebral cortex [175]. Thifluzamide,
433 an organofluorine compound from the thiazoles group, was tested in aquatic models.
434 The environmental impact is significant, as fluoro-containing agrochemicals
435 decompose into inorganic fluorides, negatively influencing wildlife and contaminating
436 soil or water [176]. Thifluzamide exhibits adverse effects (oxidative damage, cell
437 apoptosis, and inflammation) on non-target organisms such as zebrafish embryos

(0.19 – 2.85 mg/L), with increased serotonin and norepinephrine levels [177,178]. Next, avermectins are a group of natural substances generated from the fermented products of *Streptomyces avermitilis*. Specifically, in invertebrates, avermectins alter electrical transmission by enhancing the effects of glutamate at the glutamate-gated chloride channel. Goldfish (*Carassius auratus*) exposed for 24h to avermectin (0.039 mg/L) showed upregulated mRNA levels of GABAa receptors in the brain [179]. Ivermectin can accumulate in the brain of gilthead sea bream (*Sparus aurata*) and rainbow trout, with the risk of GABAa extra-physiological activation [180,181]. Furthermore, fipronil, from the group of pyrazoles, has an opposite modality of action than avermectins. Fipronil blocks the insect GABA-a channels favoring hyperexcitability. Insect GABA receptors are structurally similar to vertebrates; zebrafish exposed to fipronil during early development (0.0003 to 5 mg/L) or adulthood (100 – 2000 ppb) showed signs of oxidative stress and inflammation (TNFa, NF-kB, and brain-derived neurotrophic factor, BDNF) in the brain [182,183]. Similar results were obtained in zebrafish embryos exposed for 96 hours to glufosinate (0.5 – 5 ppm) [184].

Another example is rotenone, a rapidly absorbed lipophilic insecticide that interferes with the mitochondrial electron transport chain [185]. In zebrafish, rotenone crosses the BBB, inhibits the respiratory chain, induces oxidative stress, and evokes neuroinflammation [186]. Zebrafish exposed to a low concentration of rotenone for four weeks displayed an increase in NO and LPO in the brain. SOD and GST antioxidant activities were depleted in the brain; genes coding for the pro-inflammatory interleukins were upregulated [187]. Rotenone also impaired the dopamine system in

462 zebrafish [186]. Ziram, another toxic pesticide from the dithiocarbamate family, showed
463 similar effects [187].
464
465 Finally, we address the case of pesticide mixtures [188]. When zebrafish
466 embryos were exposed to 6 pesticides (boscalid, chlorpyrifos, ziram, thiophanate,
467 thiacloprid, captan) or their mixture during development, the impact was molecule- or
468 cocktail-specific [189]. In another study, zebrafish embryos were exposed for 96h to a
469 pesticide mixture, from low to high levels, based on the environmental concentrations
470 for each compound. The pesticides chosen were: Abamectin (modulation glutamate-
471 gated chloride channel), carbaryl and chlorpyrifos (AChE inhibition), fipronil (GABAa
472 antagonist), imidacloprid (nicotinic Ach receptor), methoxychlor (Na channel
473 modulator). Differentially expressed genes were related to neurogenesis and synaptic
474 plasticity, e.g., forebrain development (*npas4a*), nerve cell growth and differentiation,
475 synaptic plasticity, and memory (e.g., *egr1, vgf*) [190]. Zebrafish exposed to iprodione
476 (dixarboximide), pyrimethanil (anilinopyrimidine), pyraclostrobin (strobilurin), and
477 acetamiprid (neonicotinioid), alone or in combination during embryonal development
478 showed deregulated expressions for genes coding for cell apoptosis (*cas8, cas9,*
479 *p53, bax*), oxidative stress (*cat, CuSod, MnSod)* and cytokines (*il, tnfa*). Expression
480 of *P53* and *tnf* was primarily modified during exposure to pesticide combinations
481 compared to individual exposures [191]. The avermectin abamectin, the triazole
482 difenoconazole, the pyrethroid λ-cyhalotrhin, and the neonicotinoid imidacloprid
483 provoked synergistic or antagonist toxicity when their mixtures were tested in
484 zebrafish and *Prochilodus lineatus* [137,192]. This emerging evidence underscores the
485 importance of studying complex mixtures of pesticides, cross-comparing to the effect
486 of single molecules to unravel synergistic neurotoxic effects.

5. Pesticide exposure and CNS diseases.

We review the experimental and clinical evidence tracing a link between pesticide exposure and risk for neuropathological trajectories. Continuous or repeated exposure to low levels of single pesticides or mixture during susceptible periods (e.g., pregnancy and childhood) is a matter of high clinical significance [42,193,194]. We focus on brain pathologies where pesticide exposure is a reported risk factor and for which BBB damage and neuroinflammation play key roles.

5.1) Neurodegeneration.

Exposure to pesticides is a risk factor for adverse neurodegenerative trajectories (see Table 3), including Parkinson's disease (PD) [195], Alzheimer's disease (AD) [196], and amyotrophic lateral sclerosis (ALS) [197] or multiple sclerosis (MS) [198]. As an archetype example, the neurotoxic metabolite (MPP) of 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP) was reported to cause PD in humans [199]. An environmental risk for PD was suggested because MPP and the herbicide paraquat are chemically analogous [200]. Experimental and epidemiological studies reinforced the association between paraquat exposure and risk for developing PD [195], the latter considered an occupational disease in farmers [201]. Experimentally, neonatal exposure to the OP chlorpyrifos reduced dopaminergic neurons in rats, significantly increasing microglia and astrocyte reactivity in the substantia nigra [202]. The OP cypermethrin induced loss of dopaminergic neurons associated with microglia

activation [203,204]. However, it remains unclear whether inflammation is a cause or consequence of cypermethrin-associated PD. Hydrophobic OCs can bind to a partially folded a-synuclein conformation, accelerating the fibril deposit process, a primary biomarker of PD. Other studies demonstrated that OCs lead to oxidative stress in dopaminergic cells, and a-synuclein aggregation, highlighting the importance of these pesticides in PD pathogenesis. Analyses of a cohort of subjects affected by PD, and living in rural areas with suspected environment pesticides, showed high level of dichlorodiphenyldichloroethylene (DDE) as compared to a control population [205].

Existing meta-analyses suggest pesticide exposure could represent a risk factor for AD [196]. Notably, the pathological role of inflammation and BBB permeability in AD was proposed, including plaque-associated microglia exhibiting a reactive phenotype and passage of serum components into the brain across the damaged BBB [206]. Chlorpyrifos exposure caused chronic microglial dysregulations and accelerated neurodegeneration [207]. Cypermethrin elicits upregulation in both Aβ and (p)-tau in adolescent rats by stimulating a typical pro-amyloidogenic processing of amyloid precursor protein (APP) through beta-site APP cleaving enzyme 1 (BACE) and presenilin-1 (PS) [208]. Cypermethrin exposure promoted oxidative stress and microglial activation [209]. An increased level of Aβ was reported in an AD model after exposure to chlorpyrifos [210].

Environmental factors, including metals, organic solvents, and pesticides, may contribute to ALS and MS [211]. The increased occupational risk of ALS and MS in farmers and gardeners could be linked to exposure to glyphosate-based herbicides [198]. However, the underlying mechanisms remain unclear, with a possible influence of epigenetics mechanisms. Pesticides can induce different epigenetic alterations in the expression levels of miRNAs and the modulation of DNA methylation [212-214]. In this specific field of research, PD is the most documented [215,216]. For example, 20 miRNAs were significantly altered by pesticide exposure. Among these miRNAs, the hsa-miR-210-3p is particularly interesting as it has been associated with developing PD [213].

5.2) Neurodevelopmental and neuropsychiatric disorders.

In the developing brain, the forming BBB is vulnerable to toxins. Quinalphos (OP), cypermethrin (pyrethroid), and lindane (OC) were tested on developing rats, concluding that oral exposure at critical periods of development could lead to neurological dysfunction (Table 3), with effects emerging later in life [217]. Pesticides passing the placental barrier enables this brain vulnerability during pregnancy (Table 4). Immature rats exposed to pyrethroid-based mosquito repellent display similar pathological patterns impacting BBB permeability [103]. Although the permeability of the BBB to pyrethroids is limited, the permeability of the immature BBB allows pyrethroid in the brain resulting in neurologic effects during early development [218]. In turn,

559 elevated levels of pyrethyroids in the immature rat brain favor BBB damage because
560 of neuroinflammation [219,220].
561
562 Pre- and postnatal exposure to pesticides are associated with a risk for
563 depressive behavior, mental retardation, and attention deficit or hyperactivity
564 disorder. The Chamacos study showed a relationship between the urine levels of OP
565 biomarkers in women and the prevalence of attention deficit hyperactivity disorder in
566 their children [221 222]**.** Two studies evaluating chlorpyrifos cord blood levels found that
567 maternal exposure to this OP was associated with decreased working memory and
568 full-scale IQ [223,224]. Prenatal exposure to malathion was linked with abnormal reflexes
569 in children [225]. A pilot study on 40 patients presenting glyphosate or glufosinate
570 intoxication indicated that S100B might be a biomarker for predicting neurologic
571 complications [226]; its levels in biological fluids indicate BBB cells damage [227-229].
572 Experimentally, subchronic exposure to glyphosate (from GD 5 until PND 60) leads to
573 glutamate excitotoxicity, oxidative damage, and depressive-like behavior associated
574 with a decreased serum level of S100B [230]. In rodents, prenatal exposure to
575 deltamethrin increased anxiety; deltamethrin altered cellular adhesion and
576 vasculature development in Chd8V986*/+ mice with autism spectrum disorder-like
577 phenotypes; the disease phenotype was exacerbated in the mutant mice following
578 deltamethrin exposure [231].
579
580 *5.3) Seizures and Epilepsy.*
581
582 The societal impact of epilepsy varies worldwide [232,233,234]. A study examined
583 the prevalence and risk of developing epilepsy in areas of high vs. low pesticide

exposure based on agronomic data [235]. The study population consisted of 4007 subjects diagnosed with epilepsy and 580,077 control subjects adjusted for age, sex, and geographical area. Epilepsy prevalence was significantly higher in areas associated with elevated pesticide use [235]. Significantly, seizures and epilepsy are associated with increased BBB permeability [236]; this could facilitate access to pesticides in the epileptic brain, perhaps accelerating the pathology (Table 3). Importantly, OPs, acting as potent irreversible cholinesterase inhibitors, can activate brain cholinergic receptors due to acetylcholine accumulation, initiating a seizure [237]. Exposure to Paraoxon leads to status epilepticus associated with neuronal damage [238-240]. The integrity of the BBB is a safeguard against neurotoxic molecules, such as pesticides, which critically influence its stability. This notion extends to adult life stages when exposure to environmental pesticides can impact the integrity of the BBB, influencing or accelerating neurodegeneration.

6. In search of pathological mechanisms: the example of glyphosate.

The molecular mechanisms by which pesticides promote neuro-glio-vascular toxicity remain elusive because of the high chemical heterogeneity of these molecules. If we focus on glyphosate, the most utilized herbicide in agriculture, several avenues have been explored. Biological effect in humans and other mammals includes oxidative stress and mitochondrial dysfunction, which could trigger genetic damage, cytotoxicity, biochemical changes, inflammation or immunosuppression, endocrine disruption, and gut microbiome changes, resulting in health damage, including neurologic disorders and behavioral and cognitive changes.

These impacts of glyphosate have been recently reviewed in [241,242]. Glyphosate could indirectly interfere with brain function by impacting the microbiota composition. Glyphosate performs as an inhibitor of 5-enolpyruvylshikimate-3-phosphate synthase (EPSP synthase), not only in plants but also in bacteria. An inhibiting effect on EPSP synthase from intestinal microbiota has been reported, affecting mainly beneficial bacteria. Glyphosate-induced intestinal dysbiosis impacts the CNS, triggering emotional, neurological, and neurodegenerative disorders [243]. Glyphosate exposure has been reported to significantly alter brain monoaminergic neurotransmitters levels (dopamine, serotonin, norepinephrine), in a brain regional- and dose-dependent manner, in rat [244] and fish [245]; these effects may contribute to its overall spectrum of neurotoxicity. Eventually, the described effect of pesticides on the permeability of the BBB may support a direct consequence of glyphosate and its metabolites on molecular targets of CNS cells, which are not yet well known. For example, acute glyphosate exposure of rat hippocampal slices (but also chronic exposure *in vivo*) reduced glutamate uptake and metabolism within glial cells, which is associated with increased release of this neurotransmitter in the synaptic cleft. Consequently, the excess of glutamate increases Ca^{2+} influx in neurons by activating NMDA receptors and voltage-dependent Ca^{2+} channels, leading to oxidative stress and neural cell death [246]. Importantly, glyphosate and its major metabolite, aminomethylphosphonic acid (AMPA), have structural similarities to glutamate and glycine. Glutamate is the major excitatory neurotransmitter in the brain, and glycine is the co-agonist required with glutamate to activate the NMDA type of glutamate receptors. Hence, glyphosate may also bind directly to the glycine or glutamate binding pocket of NMDA receptors and affect learning and memory processes driven by this receptor. The case of glyphosate can be generalized to other compounds when multiple molecular and

cellular actions could underlie the toxic effects on the brain. More targeted studies are required, mainly because the concentrations of environmental contaminants tested are somehow excessive compared to the daily exposure levels.

7. Conclusions: pesticides and brain vulnerability.

The proposed evidence illustrates how exposure to environmental contaminants, particularly pesticides, can represent an ecotoxicological and brain health risk factor. We here offer a few final remarks: first, the duration of exposure matters. Accumulating evidence shows how pre-clinical studies should re-center on real-life risk simulation (long-term, life-long exposure modalities) to mimic adequately environmental and health-relevant scenarios [247,248]; this experimental paradigm will enable the discovery of risk factors pertinent to human pathological adaptations or susceptibility conditions, especially during aging. This consideration leads to our second remark: levels of exposure matter. While a bulk of past studies focused on the effect of high-level exposures, recent research is redirecting toward testing the impact of low levels, from NOAEL (non-observable adverse effect level) to ADI (acceptable daily intake) established by regulatory agencies. Because most studied positions within intoxication paradigms, the significance of experimental data to global human health needs continuous refinements, with difficult cross-comparisons between experimental and human studies. Key factors include the route of body entry, levels (with appropriate dose scaling across species), frequency, duration of contact, specific toxicity, kinetics, metabolism rate, the system's sensitivity, and the number and types of pesticides tested simultaneously.

Again, one archetypical example is glyphosate; exposure in rodents negatively influences neuronal transmission and behavior, although at levels higher than the ADI [230,249] . Maternal exposure to high levels of glyphosate promotes autistic-like behavioral deficiencies in murine male offspring [250]. However, current data indicate that levels of glyphosate in humans are commonly low, although high-exposure episodes can occur [251,252]. Epidemiological indication supports a link between glyphosate exposure and neurodevelopmental disorders [253]. Within this framework, the permeability and the distribution of pesticides at the placental barrier (Table 4) represent critical elements that will shape the developmental trajectory of the womb. However, results remain highly debated [254]. Exposure to glyphosate during prenatal or newborn periods was associated with a risk for attention deficit and hyperactivity disorders in children with parents previously exposed to glyphosate [255]. However, these data were insufficient to support public concern for developmental risks [255]. Importantly, children living in farmworker communities are particularly exposed to pesticides, such as pyrethroids, OCs, and OPs. In these environments, children could be at risk (reviewed in [256]).

Lastly, the modalities of experimental investigation matter. From molecular to cellular and physiological levels, it is fundamental to unravel apparent phenotypes and explain existing discrepancies between studies, experimentally and clinically. Low exposure levels require sensitive analytical techniques to capture physiological adaptations. Spatial tissue transcriptomic and single-cell analyses could deliver the resolution and depth needed to recognize pathway activations with temporal and regional precisions. The latter could provide a signature corresponding or not to behavioral phenotypes. For instance, extra-physiological transcript and cellular-level (e.g., BBB cells) fingerprints were found in response to exposure to low levels of

glyphosate in zebrafish larvae, although in the absence of visible brain malformations or behavioral defects, supporting the notion of subtle and lingering vulnerability conditions [257].

Environmental exposures' ethical and social implications on brain health and well-being are significant. An emerging neuroethics framework in environmental sciences seeks possible threats from the continuous interaction between humans and the environment [258]. The neuro-exposome, from contact with natural matrices to air pollution, is a principal risk factor for cognitive impairment in young individuals and abnormal or even accelerated aging trajectories. The finding summarized in this review support the importance of environmental neuroethics as a contemporary field of study to identify vulnerability factors that could shape brain health at the population level or depending on geographic location.

In summary, refining our knowledge of how environmental pesticides interact with brain barriers and borders could disclose disease mechanisms inherent to the exposome, with time- and age-dependent pathological trajectories and susceptibility elements representing objective risk factors for neurological diseases.

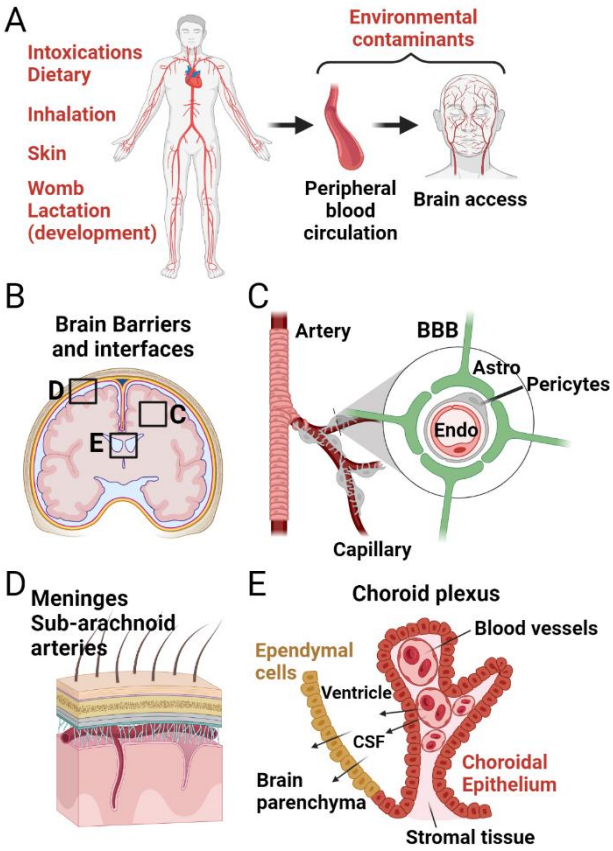

Figure 1. Environmental contaminants reach brain borders and barriers. A) From external matrices, pesticides enter the body, reaching the peripheral blood circulation and the brain. **B-E)** Critical interfaces are the blood-brain barrier (BBB), the meninges with subarachnoid arteries, and the choroid plexus for the production of cerebral spinal fluid (CSF). Specifically, the BBB is a network of capillaries in the brain parenchyma, constituted by a multi-cellular assembly of endothelium, astrocytes, and pericytes. The BBB and adjacent neurons form the neuro-glio-vascular unit.

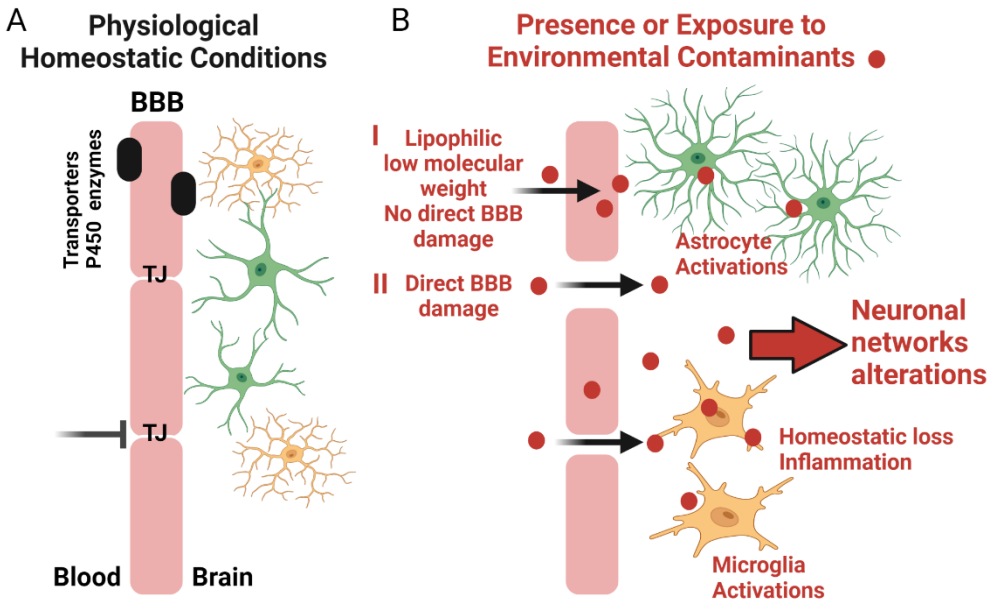

Figure 2. Environmental contaminants, brain-barrier damage, neuroinflammation, and neurological alterations. A) The BBB is highly impermeable due to tight junctions (TJ), with specific drug transporters regulating the brain entry of specific nutrients. **B)** From the peripheral blood, I) lipophilic and low molecular weight pesticides could pass through the BBB endothelial cells. Once in the brain, they could affect neuroglia cells enabling inflammation and secondary BBB permeability; II) on the other hand, blood pesticides could directly damage the BBB endothelium (e.g., disrupting TJ), increasing capillary permeability and triggering neuroinflammation. Both scenarios result in pesticide entry into the brain, modifying the parenchymal homeostatic control and altering synaptic transmission in networks.

Table 1. Relevant interactions between pesticides and drug transporters at the BBB.

TRANSPORTERS	PESTICIDES	REF
ABCs		
Pgp	Diazinon, 1-methyl-4-phenyl-4-phenylpyridinium ion (MPP+), rotenone Methylparathion, endosulfan, cypermethrin, fenvalerate DDT, endosulfan Dibrom, Profenofos	62 259 260
BCRP	DDT, endosulfan Allethrin, tetramethrin, permethrin, resmetrhin (phyrethroids) Phosmet, Profenofos	261 260 262
MRP	Allethrin,tetramethrin Profenofos	260 261 262
SLCs		
Amino acid transporters (LATs)	Glyphosate	263
Monocarboxylate transporters (MCTs)	2,4-dichlorophenoxyacetate (2,4-D) Triclopyr	264 265
Organic anion transporters (OATs)	Allethrin, tetramethrin Fenamiphos, malathion, metasystox, profenofos	266 262
Organic anion-transporting polypeptides (OATPs)	Allethrin, tetramethrin Fenamiphos, malathion, parathion, phosmet, profenofos, temephos	64 262
Organic cation transporters (OCTs)	Allethrin, tetramethrin Fenamiphos, fenitrothion, malathion, methyl-parathion, parathion, phosmet, profenofos, propetamphos	64 262
Multidrug and toxin extrusion (MATE)	Allethrin,tetramethrin Fenamiphos, phosmet, propetamphos	64 262

Table 2. Environmental pesticides at the BBB and intersections with neuroinflammation: in vitro studies.

PESTICIDE GROUP	COMPOUND	MODEL	DOSE	DURATION	OUTCOMES	PATHWAYS	REF
BBB integrity							
OP	Chlorpyrifos	Neurovascular unit Endothelial cells	NVU: 0, 1, 3, 10, 30, 100 µM / Endothelial cells: 0, 10, 30, 100, 300 µM	2 h to 24 h	Chlorpyrifos treatment resulted in morphological changes to more circular-shaped cells. The highest exposure tested (300 µM) resulted in most cells displaying punctate cell morphology or clumping, indicating cell death. The treatments caused significant disruption of acetylcholine metabolism.	Cell morphology	267
OP	Malathion/oxon	In vitro BBB model (rats' astrocytes, endothelial cells (RBE4 or BMEC), and neuroblastoma cells SH-SY5Y	1 mM, 100, 10, 1, 0.1, 0.01 µM	24 h	Significant decay in cell viability. Malathion and Malaoxon permeability through the barrier (leakage was assessed by measuring the inhibition of AChE enzyme in SH-SY5Y cells in a barrier system)	Cell viability	71
	Malathion Malaoxon	In vitro BBB model (endothelial cells, RBE4 or BMEC)	Malathion 10^{-5} M, malaoxon 10^{-6} M	2, 4, 8, 16, 24 h	Malathion decreases the proteins associated with tight junction formation	Tight junction proteins occludin, claudin 5, and scaffold ZO1 and ZO2	69
Endothelial cells							
Dipyridyls	Paraquat	Human brain microvascular endothelial cells	1, 10, 100 µM	24 h	Altered pathways linked to complex I of mitochondrial respiration and significantly decreased mitochondrial function. Modulation of the cholesterol biosynthesis pathway	Mitochondrial function/cholesterol biosynthesis	268

		(HBMECs)					
PYR	Pyrethroid	Microvascular Endothelial Cells	10 µM	24 h	No effect on viability; ROS production; Thiobarbituric acid-reactive substances; Protein carbonyl; oxidative stress	Cell viability and ROS production	269
OP	Paraoxon	Human CD34+ derived ECs and bovine brain pericytes	100, 300, 600, 900, 1200 µM	24 h	Paraoxon directly affects the BBB in vitro by attenuating viability, integrity, and junctional mRNA and protein expression	Tight junction proteins occludin, claudin 5, and scaffold proteins ZO1 and ZO2 in endothelial cell	70
Astrocytes / Oligo							
OP	Malathion	Gibco®Human Astrocytes (GHA cells), DI TNC1 normal rat astrocytes, BTRG-05MG human glioblastoma cells	20 µM to 25 µM	20 min	In GHA but not DI TNC1 and DBTRG-05MG cells, malathion induced Ca2+ release from the endoplasmic reticulum and caused PKC-regulated Ca2+ influx via 2-APB	Ca2+ release from the endoplasmic reticulum and Ca2+ entry via PKC-sensitive store-operated Ca2+ channels	72
OP	Malathion	Human induced pluripotent stem cell (iPSC)-derived neurons and astrocytes in 3D-matrix	10^{-1}, 10^{-3}, and 10^{-5} M	24 h	A higher astrocyte-to-neuron ratio promotes viability following acute malathion exposure	Cell viability	73
OP	Malathion	Gibco® Human Astrocytes (GHA cells)	0, 5, 10, 15, 20, 25 µM	24 h	Cell morphological changes include cell shrinkage, a decrease in cell number, and loss of cell-to-cell contact.	Cell cycle alterations and ROS production	74
OP	Parathion / Chlorpyrifos	Mixed-cell aggregate cultures from fetal rat telencephalon	Parathion: 10^{-9} to 10^{-5} M Chlorpyrifos: 10^{-7} to 10^{-5} M	10 d	Increase in GFAP expression and astrogliosis	Astrocytes reactivity	76
OP	Glyphosate	Rat astroglioma (C6 cells)	40, 80, 160 µM	3, 24 h	Decreased cellular viability and mitochondrial respiratory chain activities	Cell viability and mitochondria	270
OP	Chlorpyrifos	Astrocyte-neuron co cultures	10 µM to 30 µM	48 h	Astrocytes reduce the toxic effect induced by Chlorpyrifos exposure on neurons	Cell viability	271
OP	Diazinon/ Diazoxon	Primary cultures of cortical astrocytes Astrocyte–	0, 0.1, 1, 10 µM	24 h	50% decrease in the length of the longest neurite in hippocampal neurons cultured with astrocytes previously treated with 10 µM diazinon	Oxidative stress	272

		neuron co-cultures.					
OP/PYR	Chlorpyrifos/ cyflutrin	Human primary astrocytes	1, 5, 25 µM	7, 14 days.	Upregulation of pro-inflammatory targets	Astrocytes reactivity	75
PYR	Cypermethrin	Astrocytes culture	0–200 µM	0, 24,48 h	Cypermethrin inhibits Epithelial Growth Factor Receptor (EGFR) signaling, reduces EGFR activation-dependent Heparin-Binding-EGF synthesis, attenuates HB-EGF-dependent EGFR expression, promotes apoptosis through the EGFR inactivation in rat astrocytes	Autocrine/paracrine mode of HB-EGF-EGFR signaling at two levels	77
PYR	Lambda-cyhalotrin	Gibco®Human Astrocytes	5-25 µM	24 h	Cytotoxicity after 24 h treatment and increased [Ca2+] by inducing Ca2+ entry via store-operated Ca2+ channels and Ca2+ release from the endoplasmic reticulum.	Ca2+ release	273
Microglia							
PYR	Permethrin and deltamethrin	Immortalized mouse (C57Bl/6) microglial cells, BV2 and primary microglia	0, 0.5, 1, 5, 10, 25, 50, 100 µM	24, 48 h	Higher concentrations of permethrin and deltamethrin significantly decrease cell viability and activate microglia cells.	Cell viability and microglia morphology	80
PYR	Cypermethrin	Primary microglia and neuronal culture	0.125 µM	48 h	Cypermethrin increases the level of PKC-δ and iNOS in primary microglia and TNF-α and IL-1β in the conditioned medium. The conditioned media of Cypermethrin-treated microglia induce toxicity in the rat primary neurons.	Pro- and anti-inflammatory cytokines	81
PYR	Bifenthrin	Primary microglia culture and organotypic hippocampal slice (OHSCs)	0,1, 1, 5, 10, 20, 40, 100 µM	24 h	Bifenthrin induced a significant decrease in cell viability with higher doses. Bifenthrin does not cause cell death in microglia and astrocytes	Oxidative stress	82
OP	Chlorpyrifos	Immortalized mouse (C57Bl/6) microglial cells, BV2	0.3, 1, 3, 10, 30, 100, 300 µM	96 h	Chlorpyrifos triggered oxidative stress and pro-inflammatory states in microglial cells, promoted BV-2 cell activation and proliferation, and increased DNA damage and generation of oxidative markers.	Oxidative stress	79
OP	Dichlorvos	Rat primary microglial cultures	0 to 60 µM	24, 36, 48 h	Significant increase in iNOS and NO associated with inflammatory cytokines	Oxidative stress	78
White blood cells							
OP	Malathion	Lymphocytes	1/4 to 1/20 LC_{50} (5.2	2, 4, 8, 12 h	Malathion significantly reduced lymphocyte viability and caused	Cell and DNA viability	84

		suspension (Wistar rats)	mg/L)		DNA damage.		
OP	Glyphosate	Human peripheral whole blood (HMWB)	0.1, 1, 10, 100, 1000, 10000 µM	4, 20 h	Glyphosate alone could not considerably decrease the viability of HMWB cells	Cell viability	[85]
OP	Methyl parathion/ Chlorpyrifos	Lymphocytes suspension extracted (Wistar rats)	1/4 to 1/20 LC_{50} (0.135 mg/L)	2, 4, 8, 12 h	Malathion significantly reduced rat lymphocyte viability and caused DNA damage.	Cell and DNA viability	[84]
PYR	β-Cypermethrin	Monocyte/macrophage-like cells (RAW 264.7 cells)	50 - 100 µM	24 to 48 h	Exposure to β-Cypermethrin reduced cell viability and increased ROS production	Cell viability and ROS production	[86]

Table 3. Environmental pesticides, BBB damage, inflammation, and time-dependent neuropathophysiology: in vivo studies.

DISEASE	PESTICIDE GROUP	COMPOUND	MODEL AND AGE	DOSE, ROUTE	EXPOSURE DURATION	OUTCOMES	REF
Neurodegenerative diseases							
Alzheimer disease	OP	Chlorpyrifos	Female wild-type (WT) and TgF344-AD rats	10 mg/kg bw/d, subcutaneous injections	Daily for 21 d	Chlorpyrifos induced cognitive impairment associated with the dysregulation of microglia	207
Parkinson's disease	OP	Chlorpyrifos	Sprague-Dawley rats, PND 11 (both sexes)	5 mg/kg bw/d, subcutaneous injection	Daily from PND 11 – 14	Chlorpyrifos induced a significant reduction of dopaminergic neurons and significant activations of microglia and astrocytes in the substantia nigra	202
Parkinson's disease	OP	Cypermethrin	Male Wistar rat pups, PND 5	1.5 mg/kg bw/d, Intra-peritoneal injection	Twice a week from 5-19	Cypermethrin increased the number of macrophages or microglia cells (integrin-Alpha M-positive cells) associated with a reduction of Tyrosine-Hydroxylase-positive cells leading to significant impairment in motor activities	204
Parkinson's disease	OP	Cypermethrin	Male Wistar rat pups, PND 5	1.5 mg/kg bw/d, Intra-peritoneal injection	Twice a week from 5-19, and the rats were re-challenged with 15 mg/kg bw/ twice a week for 12 weeks	Cypermethrin altered motor functions, favored the loss of dopaminergic (TH-positive) neurons, with activated microglial (integrin-αM-positive) cells.	203
Parkinson's disease	Phenylpyrazole	Fipronil	Male Sprague Dawley rats, 3 months	15 or 25 µg/kg bw/d, microinjections into the substantia nigra	From 7 d to 16 d post-injection	Fipronil exerted a neurotoxic effect on nigrostriatal dopaminergic neurons	274
Neuropsychiatry Conditions							
Depressive disorder	OP	Glyphosate	Adult male Wistar rats	Drinking water, 70 mg/kg bw/d	Maternal exposure from GD 5 to PND 15 or PND 60	Glyphosate induced a depressive-like behavior profile and altered the serum levels of the astrocytic protein S100B.	230
Autism	PYR	Deltamethrin	Chd8V986*/+ male mice crossed with C57BL/6J females	3 mg/kg bw/every 3 days mixed into peanut butter	From E0 (maternal exposure to deltamethrin) to PND22	Prenatal exposure to deltamethrin led to increased anxiety along with altered cellular adhesion and vasculature development in Chd8V986*/+ mice evaluated at 6 and 12 months of age	231
Attention-deficit/hyperactivity disorder	PYR	Deltamethrin	Adult male and female C57BL/6 mice	0.5 mg/kg bw/d mixed into peanut butter	3 groups: maternal exposure from gestational day (GD) 0 to 5 or GD 6 to 15 and GD 16 to birth	Expression levels of NMDA receptor subunits were decreased in the hippocampus and cerebral cortex of male mice.	275

Epilepsy							
	OP	Paraoxon	Adult male Sprague-Dawley rats	2 mg/kg, one sub-cutaneous administration	Acute treatment, analysis 1h to 1 month and 3 to 6 months	Paraoxon-exposed rats undergo a rapid transition to status epilepticus	240
	OP	Paraoxon	Adult male Sprague-Dawley rats	2 routes: 200 nM to 300 nM intrahippocampal infusions or intra-peritoneal route at 0.35 mg/kg	Acute treatment	Direct injection of 200 nmol paraoxon into the hippocampus caused self-sustaining seizures.	239
	OP	Paraoxon	Adult male Sprague-Dawley rats	450 µg/kg bw/d, one sub-cutaneous administration	Acute treatment, analysis from 2 to 6 weeks after the poisoning	Animals developed generalized tonic-clonic convulsions	276
	OP	Paraoxon	Adult male Sprague-Dawley rats	0.45 mg/kg, intra-muscular injections	Acute treatment, analysis 24 h after poisoning	Paraoxon-treated rats resulted in generalized tonic-clonic convulsions and electrographic evidence of status epilepticus	238

847
848 **Table 4.** Examples of placental transfer in humans, mice, and rats. Detection of
849 pesticides (and their metabolites) in fetal tissues for rodents and placenta/umbilical
850 cord blood for humans.
851

SPECIE	COMPOUND	TISSUE	REF
MOUSE	Clothianidin (Neonicotinoid)	Fetal tissue	277
	Permethrin, α-cypermethrin (Pyrethroids)	Placenta, fetal body, and amniotic fluid	278
	Azoxystrobin (Strobilurin)	Embryo's brain and placenta	279
RAT	Atrazine, simazine and propazine (Triazines)	Fetal brain and liver	280
	Atrazine (Triazine)	Fetal tissue	281,282
	Permethrin (Pyrethroid)	Fetal liver, brain and blood, and placenta	283
	Fenvalerate (Pyrethroid)	Placenta, fetal liver and testis	284
	Fipronil (Phenyl-pyrazole)	Placenta, amniotic fluid and fetus	285
	Bitertanol (Triazole), propiconazole (Triazole), cypermethrin (Pyrethroid), terbuthylazine (Triazine), malathion (OP)	Amniotic fluid	286
HUMAN	Dichlorodiphenyltrichloroethane (DDTs), hexachlorocyclohexanes (HCHs), and hexachlorobenzene (HCB) (OCs)	Umbilical cord blood and/or placenta	55,287,288
	DDT and/or HCH (OCs)	Umbilical cord blood and/or placental tissue	289,290,291,292,293,294,295,296,297
	DDT, chlordane (CHL), HCH (OCs)	Placental tissue or umbilical cord blood	298,299
	DDT, HCH, aldrin, heptachlor (OCs)	Placental tissue	300
	DDT, HCH, Heptachlor, Endosulfan, Chlordane, Aldrin, Dieldrin, Endrin, Methoxychlor (OCs)	Umbilical cord blood	301
	Aldrin ad Dieldrin (OCs)	Umbilical cord blood	302
	Glyphosate	Umbilical cord blood	303
	2,4-dichloroacetic acid (Phenoxy), prometryn (Triazine), simazine (Triazine), and captan (Phthalimide)	Umbilical cord blood	304
	Bendiocarb (Carbamate)	Umbilical cord blood	305

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