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1 Pesticides at brain borders: impact on the blood-brain barrier,
2 neuroinflammation, and neurological risk trajectories.

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43 **Abstract**

44

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

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

70

71 The brain is evolutionarily shielded, physically and biologically, to ensure a
72 continuous fine-tuning of brain homeostasis and dependable synaptic transmission.
73 Three borders exist, namely the blood-brain barrier (BBB), the blood-to-cerebral
74 spinal fluid (B-CSF) barrier **formed by tight junctions between adjacent choroid plexus**
75 **(CP) epithelial cells, and the meninges where the CSF is filtered from peripheral**
76 **blood** (Figure 1; see ¹⁻⁷ for comprehensive reviews). These structures are the
77 sentinels of brain stability and immunity, surveilling and enabling exact
78 spatiotemporal synchronizations of neuronal networks that equate to physiological or
79 normal behaviors, correct memory, executive functions, development, and **aging** ^{5,8,9}.
80 In health, these biological structures strictly control the passage of xenobiotics,
81 exogenous compounds, toxins, and immune cells from the peripheral blood
82 circulation into the brain parenchyma ^{1,4,5,7}. Brain barriers, or borders, represent
83 sensitive sites where the presence and continuous accumulation of environmental
84 contaminants could have a negative impact and, in turn, promote a harmful sequel to
85 the brain ^{3,5,8,10-12}. Here, we focus on the BBB as the primary interface between
86 peripheral blood and the brain parenchyma. The BBB is a complex network of
87 capillaries, with each microvessel anatomically and functionally connected to distinct
88 groups of neurons, hence the terms neuro-glio-vascular unit (NGVU) and metabolic
89 neurovascular coupling ^{1,5}. The anatomical reach and the protection afforded by the
90 BBB are vast; the human brain contains 20-25 m² of capillaries, illustrating the
91 granular exchange to all brain regions and neuronal networks. The BBB is a multi-
92 cellular structure formed by endothelial cells, astrocytes, and pericytes,

93 communicating with one another, assembled in basement laminae, surrounded by
94 microglial cells and neurons within tens of micrometers distances (Figure 2). The
95 BBB endothelium is highly impermeable due to the expression of specific inter-
96 cellular tight-junctions¹. ATP (Adenosine triphosphate)-dependent transporter
97 proteins (and p450 metabolic enzymes^{13,14}) expressed at the endothelium are
98 instrumental in guaranteeing a highly selective exchange of molecules between the
99 peripheral blood and the brain. Transcytosis and endocytosis (e.g., caveolins) also
100 regulate BBB permeability⁵.

101
102 BBB damage participates in CNS diseases^{2,3,5,8,12} because it intersects with
103 neuroinflammation and dysregulates the homeostatic control (e.g., via glial buffering)
104 of ions, ATP, and neurotransmitter levels necessary for the maintenance of resting
105 potentials and synaptic transmission^{2,15}. These events are detailed in two reviews
106^{15,16}. BBB damage and neuroinflammation are ictogenic and can promote seizures⁶⁻
107^{8,15,17-19}. BBB damage accelerates neurodegeneration^{20,21}, is implicated in the
108 etiology of encephalopathies and psychiatric conditions, and represents a converging
109 risk factor for pathological aging²⁰, neurological and neuroimmunological disorders
110²². The BBB protects the brain from extra-physiological elements or toxins that could
111 pathologically interfere with the programmed developmental trajectories⁷.
112 Collectively, this literature illustrates the neurological dangers associated with
113 increased BBB permeability and neuroinflammatory changes; it underlines the
114 necessity of investigating the impact of environmental contaminants on brain barriers
115 to define elements of vulnerability pertinent to brain health. Within this framework, we
116 review experimental and clinical evidence for specific classes of pesticides currently
117 under scrutiny as they may pose exposome threats. We performed a Pubmed and

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

128

129 *2) Pesticides: from environmental omnipresence to brain access.*

130

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

141

142 These diversified exposure pathways are associated with detecting pesticides,
143 or their metabolites, in human body fluids such as breast milk ^{46,47}, urine ^{48,49}, blood
144 ^{50,51}, cerebrospinal fluid ⁵², amniotic fluid ^{53,54}, umbilical cord serum ⁵⁵, saliva ⁵⁶ and
145 seminal plasma ^{27,57}. The main entry routes of pesticides to the human body include
146 i) dermal absorption for occupational exposure, ii) oral exposure through the food
147 chain, accidental or intentional ingestion, and iii) inhalation ^{26,58}. These entry routes
148 converge into the blood circulation, reaching the brain via specific borders (Figure 2)
149 where two scenarios are possible: i) a lipophilic and low molecular weight (e.g.,
150 <400Da) molecule penetrates the BBB through the intact endothelium, reaching the
151 brain parenchyma; ii) a molecule enters the brain after having damaged the BBB
152 (e.g., increased permeability). In both circumstances, an extra-physiological molecule
153 enters the brain and could exert neuroglial toxicity. Importantly, at the BBB, a battery
154 of ATP-dependent drug transporter proteins represents the first line of defense from
155 exogenous compounds ^{13,14,59,60}. Efflux transporters pump lipophilic molecules back
156 into the peripheral blood from the apical endothelial cell, preventing their entry into
157 the brain. This ATP-binding cassette (ABC) superfamily includes the efflux
158 transporter P-glycoprotein (Pgp), which expression levels and activity govern the
159 exclusion of neurotoxicants from the brain ^{61,62}, together with the multidrug
160 resistance-associated proteins (MRPs) and the breast cancer resistance protein
161 (BCRP). A second family is a solute carrier (SLC) bidirectional transporter (export
162 and import). Members of the SLC family are described in ^{63,64}. Table 1 provides
163 archetypical examples of pesticides transported by ABCs or SLCs superfamilies. This
164 evidence is comprehensively reviewed in ⁶⁵⁻⁶⁷, along with relevant in vitro and in vivo
165 models commonly employed for screening experiments.

166

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

171

172 *In vitro* models are used to examine the impact of pesticides on BBB
173 permeability and NGVU cells^{68,69 70}. Table 2 presents a list of existing evidence for
174 each cell type while, in the text, we focus on particular examples. The cellular toxicity
175 of the organophosphate (OPs) malathion and malaoxon was tested using an *in vitro*
176 BBB model (endothelial cells BMEC or RBE4) and neuroblastoma cells (SH-SY5Y).
177 Cell viability was reduced with a significant permeability of malathion and malaoxon
178 across the BBB. Malathion decreased the expression of endothelial cells tight
179 junctions (occludins, claudin 5, Zonula occludens (ZO) 1, and ZO2). Paraoxon
180 affected the BBB *in vitro* by reducing cell viability and junctional mRNA and protein
181 expression^{69,71}. Paraoxon negatively impacted occludin and claudin structures in
182 human-derived endothelial cells⁷⁰.

183

184 With endothelial cells, astrocytes are a key component of BBB stability and a
185 neuroinflammatory regulator (Table 2). Astrocyte reactivity directly contributes to BBB
186 damage. They are sensitive to low-dose OPs. Malathion increased intracellular Ca⁺⁺
187 concentration and induced cytotoxicity via reactive oxidative species (ROS)
188 production⁷²⁻⁷⁴. Chlorpyrifos and parathion on human primary astrocytes caused glial
189 fibrillary acidic protein (GFAP) astrogliosis^{75,76}. The pyrethroid cyfluthrin elicited
190 inflammatory activations in primary human astrocytes⁷⁵. Lambda-cyhalotrin caused

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

195 We next examine microglia, the principal resident immune brain cells reacting
196 to pesticide exposure and impacting BBB permeability (Table 2). **Low chlorpyrifos**
197 **levels (0.3-300 μM)** triggered oxidative stress and pro-inflammatory states.
198 Chlorpyrifos promoted BV-2 microglial activation, proliferation, increased DNA
199 damage, generation of oxidative markers, and overexpression of pro-inflammatory
200 markers ⁷⁸. An increase in nitric oxide (NO) levels occurred 24 h after dichlorvos
201 exposure (10 μM), associated with up-regulation of inducible nitric oxide synthase
202 (iNOS) and pro-inflammatory cytokines like nitric oxide, TNF-α, and IL-1β ⁷⁹. At
203 concentrations of 25 μM or higher, deltamethrin and permethrin significantly
204 decreased microglial cell viability in a concentration- and time-dependent manner.
205 Permethrin- and deltamethrin stimulated microglia morphological transformation
206 (retraction of cell processes and an amoeboid shape) ⁸⁰. In the conditioned medium,
207 cypermethrin increased PKC-δ and iNOS in primary microglia, Tumor Necrosis
208 Factor-alpha (TNF-α), and interleukin (IL)-1β. Conditioned media from cypermethrin-
209 treated microglia induced toxicity in primary rat neurons ⁸¹. Exposure to ranging
210 concentrations (10–100 μM) of bifenthrin for 24 h decreased microglia viability with
211 maximal effects at 100 μM. No significant cell death occurred at lower concentrations
212 (0.1, 1, and 5 μM) ⁸².

213

214 In addition to NGVU cells, we here discuss the possible influence of pesticides
215 on circulating leukocytes (Table 2), critical cells interacting with the BBB to promote
216 neuroinflammatory changes and vascular damage. Lymphocyte exposure to OPs,
217 glyphosate, methyl parathion, malathion, and chlorpyrifos led to a significant viability
218 reduction and DNA damage, including DNA single-strand breaks (SSBs) and DNA
219 double-strand breaks (DSBs) as well as DNA protein cross-links (DPC) formation⁸³⁻
220⁸⁶. Monocytes or macrophage-like cells (RAW 264.7) exposed to β -Cypermethrin (24
221 h) showed cytotoxic effects, with decreased cell viability (35% and 79% with 50 μ M
222 and 100 μ M, respectively), phagocytosis, activation of intrinsic apoptotic pathway and
223 inhibition of the expressions of pro-inflammatory cytokines. ROS production and
224 oxidative stress were increased following this exposure⁸⁶. Overall, the immune
225 system could be a target for the toxic effects of pesticides⁸⁷; however, available
226 experimental and epidemiological data are insufficient to draw firm conclusions on
227 the immune-toxic risk associated with environmental contaminants. Comprehensive
228 studies are needed to unveil how pesticides promote cellular-level modifications with
229 specificity to peripheral and neuro-immune cross-talk.

230

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

232

233 Pesticide exposure during prenatal or juvenile stages represents a risk factor
234 for negative neurodevelopmental trajectories, including a decline in cognition,
235 hyperactivity, and autism spectrum disorders⁸⁸⁻⁹¹. Consistent with human
236 epidemiological studies, experimental data have strengthened the adverse
237 association between pesticides and neurological outcomes, also introducing a

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

242

243

244

245 4.1) Evidence from rodent models.

246

247 Pyrethroids are insecticides produced as synthetic derivatives of the pyrethrin
248 extracted from *Chrysanthemum cinerariaefolium* ⁹⁵. Their insecticidal properties are
249 based on altering the voltage-gated Na⁺ channels in insect neuronal membranes,
250 disrupting the Na⁺ current in the CNS ⁹⁶. The effects of pyrethroids extend to the
251 voltage-gated-calcium and potassium channels, glutamate, and acetylcholine
252 receptors ⁹⁷. Mice exposed to low concentrations of permethrin (0.3 ppm) during
253 prenatal and postnatal periods showed impairments in the formation of the neural
254 circuits, indicated by immature neuron marker (doublecortin) and decreased number
255 of astrocytes ⁹⁸. BBB integrity was not affected in rats exposed to permethrin (0.013,
256 0.13, 1.3 mg/kg/d) for 60 days ⁶⁸ (topical application). A follow-up study reported
257 neuronal cell death and neuronal cytoskeletal abnormalities ⁶⁸. Another synthetic
258 pyrethroid, bifenthrin, administered to adult rats for 60 days (0.6 and 2.1 mg/kg/d),
259 increased the expression of TNF α , IL-1b, IL-6, nuclear factor erythroid-2 (Nrf2),
260 cyclooxygenase-2 (cox-2), nuclear factor kappa-light-chain-enhancer of activated B
261 cells (NF-kB), and prostaglandin E2 (PGE2) in the hippocampus, with enhanced
262 oxidative stress markers (i.e. malondialdehyde (MDA), protein carbonyls (PCO), NO)

263 and reduced antioxidant defense (i.e. catalase (CAT), superoxide dismutase (SOD),
264 glutathione peroxidase GPx)^{82,99}. These inflammatory events can negatively impact
265 BBB integrity⁵. Similar results were obtained when cypermethrin was orally
266 administered to adult rats (1 mg/kg/day) or from gestational day (GD) 7 to post-natal
267 day (PND) 21 (1.5 mg/kg/d)^{100,101}. Microglia activation was triggered by cypermethrin
268 (1.5 mg/kg twice a week) intraperitoneally injected postnatally in rats⁹⁷; cypermethrin
269 crossed the BBB, leading to oxidative stress¹⁰². Allethrin, a pyrethroid-based
270 mosquito repellent, induced BBB permeability in the developing rat (inhalation)¹⁰³.

271

272 OPs irreversibly bind and inhibit acetylcholinesterase (AChE), preventing
273 acetylcholine breakdown, leading to its accumulation and the hyperstimulation of
274 cholinergic receptors^{104,105}. OPs are the most studied pesticides in experimental
275 models, with evidence supporting their etiological role in neurodegeneration (Table 3)
276¹⁰⁰. OPs permeate the BBB¹⁰⁶. Acute and chronic OPs exposure in rodents induces
277 neuroinflammation, activating glial cells and releasing pro-inflammatory cytokines,
278 prostaglandins, and chemokines^{107,108}. Acute exposure to
279 diisopropylfluorophosphate resulted in neuronal injury, neurodegeneration, and
280 neuroinflammation, with the activation of microglia and astrocytes, accompanied by
281 seizures^{109,110}. Chlorpyrifos is gaining attention due to its extensive use and non-
282 target species effects. It triggers neuroinflammation¹¹¹. Mice exposed to chlorpyrifos
283 (i.p., 5 mg/kg) for ten days showed no morphological changes in pyramidal neuronal
284 cells¹¹². When similar chlorpyrifos concentration was administered orally in rats for
285 one month, histopathological alterations of pyramidal neurons occurred¹¹³.
286 Chlorpyrifos impaired neurogenesis and synaptic integrity (synaptophysin
287 immunoreactivity). Thus, chlorpyrifos can cross the BBB¹¹² detected in the CNS of

288 exposed rodents ¹¹⁴. Chlorpyrifos dermally applied in adult mice increased GFAP
289 reactivity ¹¹⁵, affecting oxidative stress and antioxidant defense ^{102,113,114}. Signs of
290 neuroinflammation were reported when female mice were exposed to high
291 concentrations of glyphosate-based herbicides during pregnancy and lactation.
292 Glyphosate activates microglia and astrocytes and affects synaptic plasticity in the
293 pup hippocampus ¹¹⁶; it decreases anti-oxidant enzyme activities in the mouse brain
294 ¹¹⁷.

295 OCs, such as DDT, hexachlorocyclohexane (HCH), aldrin, or dieldrin, are
296 used in certain countries because of their low cost and effectiveness in controlling
297 insect-borne diseases (e.g., malaria) ^{118,119}, with long persistence and
298 bioaccumulation. OCs trigger neurotoxicity, blocking subunits of the GABA-A
299 receptors. Orally administered endosulfan (28 days, 5 mg/kg/d) to adult rats elicited
300 oxidative stress and deregulated the levels of neurotransmitters. Endosulfan can
301 negatively affect the developing brain by altering dopamine ^{120 121}. Endosulfan
302 administered to pregnant rats led to cerebellar and hippocampal inflammatory
303 pathways in the offspring ^{97,122}. Selective loss of dopaminergic neurons and
304 disruption of dopamine transport occurred when heptachlor was intraperitoneally
305 injected in adult mice (7 mg/kg twice a week for 8 weeks) or orally administered to
306 pregnant mice throughout gestation and lactation (3 mg/kg every 3 days for 2 weeks).
307 Heptachlor activates astrocytes and microglial cells in specific brain regions, such as
308 the ventral midbrain area, with dopaminergic system susceptibility to further damage
309 ^{123,124}. Methoxychlor injected i.p. for 20 days into adult mice decreased dopamine
310 levels and disrupted dopamine metabolism and transport, with a link to oxidative
311 stress at the mitochondrial level. GFAP immunoreactivity was increased ¹²⁵.

312

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

329

330 Paraquat is a well-known neurotoxicant that crosses the BBB ¹³⁸, causing
331 dopaminergic neuronal damage. Paraquat administered to adult mice (i.p, 5 – 80
332 mg/kg twice a week for 4 weeks) induced neuroinflammation with ROS production in
333 the substantia nigra, frontal cortex, and hippocampus, with activation of microglia
334 cells, increased expression of TNF α and IL1 β , and dopaminergic neurotoxicity. The
335 release of pro-inflammatory cytokines from the activated microglia may disrupt the
336 BBB endothelium ¹³⁹. Paraquat (i.p, 1 and 5 mg/kg every 2 days) administered for
337 several weeks in adult mice augmented BBB permeability. It activated microglia,

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

342

343 Rotenone is a natural lipophilic insecticide that interferes with the electron
344 transport chain. Rotenone can cross the BBB due to its lipophilicity. Two and 3-
345 weeks of rotenone exposure (i.p) in adult rodents diminished the expression of
346 endothelial tight junction proteins. Signs of toxicity were reported, such as microglia
347 and astrocyte activation, neuronal apoptosis, and progressive loss of dopaminergic
348 neurons. The activation of glial cells was associated with releasing cytokines and
349 chemokines ^{143,144}. Atrazine is an herbicide frequently detected in the environment.
350 Rodents exposed to atrazine via inhalation (25 mg for 28 days) or oral gavage (50 –
351 200 mg/kg 5 days a week for 45 days) showed neuroinflammation and neurotoxicity,
352 such as ROS levels and oxidative stress, production of pro-inflammatory cytokines,
353 microglia activation, and dopaminergic neurons degeneration ^{145,146}. Other pesticides,
354 such as ivermectin, a potent insecticide and anthelmintic, were also reported to cross
355 the BBB ¹⁴⁷.

356

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

363 permeability, but when it was tested with N,N-diethyl-meta-toluamide (DEET), a
364 decrease of BBB permeability in the cortex occurred⁶⁸. When orally administered to
365 rats, a mixture of chlorpyrifos and cypermethrin induced oxidative stress¹⁰². On the
366 other hand, when chlorpyrifos, methyl parathion, and malathion were administered in
367 rats, they did not show potentiation of toxicity¹⁵⁰.

368

369

370

371

372 4.2) Evidence from aquatic models.

373

374 The function of the BBB is conserved across different taxa^{151,152}. As in
375 mammals, fishes have brain endothelial cells, perivascular glia, and pericytes¹⁵²,
376 affording CNS protection¹⁵². In harmonization with the rodent data previously
377 presented, we review the impact of selected compounds (Table 3).

378

379 Pyrethroids can cross the BBB and trigger neurotoxic sequelae in aquatic
380 animals⁹⁵. Grass carp (*Ctenopharyngodon idella*) exposed to cypermethrin (0.65
381 µg/L) for 42 days displayed histopathological alterations at the cerebellar level, with
382 damaged myelin sheath layers and decreased synapses. The genes coding for BBB
383 tight junction proteins (claudins, occludin, ZO) were downregulated¹⁵³. Common carp
384 (*Cyprinus carpio*) exposed to deltamethrin (0.04 and 0.08 µM) for 96h showed
385 degenerative and necrotic neurons at the optic lobe with upregulation of apoptotic
386 markers as caspase (CAS) 3 and 8. Oxidative stress and inflammatory markers, such
387 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 μ g/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 μ g/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 μ g/L, 15 and 30 μ M) showed alterations for oxidative stress markers in

413 the brain, along with the upregulation of genes coding for pro-inflammatory cytokines
414 (e.g., *tnfa*, *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

438 (0.19 – 2.85 mg/L), with increased serotonin and norepinephrine levels ^{177,178}. Next,
439 avermectins are a group of natural substances generated from the fermented
440 products of *Streptomyces avermitilis*. Specifically, in invertebrates, avermectins **alter**
441 electrical transmission by enhancing the effects of glutamate at the glutamate-gated
442 chloride channel. Goldfish (*Carassius auratus*) exposed for 24h to avermectin (0.039
443 mg/L) showed upregulated mRNA levels of GABA_A receptors in the brain ¹⁷⁹.
444 Ivermectin can accumulate in the brain of gilthead sea bream (*Sparus aurata*) and
445 rainbow trout, with the risk of GABA_A extra-physiological activation ^{180,181}.
446 Furthermore, fipronil, from the group of pyrazoles, has an opposite modality of action
447 than avermectins. Fipronil blocks the insect GABA-a channels favoring
448 hyperexcitability. Insect GABA receptors are structurally similar to vertebrates;
449 zebrafish exposed to fipronil during early development (0.0003 to 5 mg/L) or
450 adulthood (100 – 2000 ppb) showed signs of oxidative stress and inflammation
451 (TNF α , NF- κ B, and brain-derived neurotrophic factor, BDNF) in the brain ^{182,183}.
452 Similar results were obtained in zebrafish embryos exposed for 96 hours to
453 glufosinate (0.5 – 5 ppm) ¹⁸⁴.

454

455 Another example is rotenone, a rapidly absorbed lipophilic insecticide that
456 interferes with the mitochondrial electron transport chain ¹⁸⁵. In zebrafish, rotenone
457 crosses the BBB, inhibits the respiratory chain, induces oxidative stress, and evokes
458 neuroinflammation ¹⁸⁶. Zebrafish exposed to a low concentration of rotenone for four
459 weeks displayed an increase in NO and LPO in the brain. SOD and GST antioxidant
460 activities were depleted in the brain; genes coding for the pro-inflammatory
461 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 (GABA_A
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 -cyhalothrin, 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.

487

488 *5. Pesticide exposure and CNS diseases.*

489

490 We review the experimental and clinical evidence tracing a link between
491 pesticide exposure and risk for neuropathological trajectories. Continuous or
492 repeated exposure to low levels of single pesticides or mixture during susceptible
493 periods (e.g., pregnancy and childhood) is a matter of high clinical significance
494 ^{42,193,194}. We focus on brain pathologies where pesticide exposure is a reported risk
495 factor and for which BBB damage and neuroinflammation play key roles.

496

497

498 *5.1) Neurodegeneration.*

499

500 Exposure to pesticides is a risk factor for adverse neurodegenerative
501 trajectories (see Table 3), including Parkinson's disease (PD) ¹⁹⁵, Alzheimer's
502 disease (AD) ¹⁹⁶, and amyotrophic lateral sclerosis (ALS) ¹⁹⁷ or multiple sclerosis
503 (MS) ¹⁹⁸. As an archetype example, the neurotoxic metabolite (MPP) of 1-methyl-
504 4phenyl-1,2,3,6-tetrahydropyridine (MPTP) was reported to cause PD in humans ¹⁹⁹.
505 An environmental risk for PD was suggested because MPP and the herbicide
506 paraquat are chemically analogous ²⁰⁰. Experimental and epidemiological studies
507 reinforced the association between paraquat exposure and risk for developing PD ¹⁹⁵,
508 the latter considered an occupational disease in farmers ²⁰¹. Experimentally, neonatal
509 exposure to the OP chlorpyrifos reduced dopaminergic neurons in rats, significantly
510 increasing microglia and astrocyte reactivity in the substantia nigra ²⁰². The OP
511 cypermethrin induced loss of dopaminergic neurons associated with microglia

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

521

522

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

534

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

545

546

547

548 *5.2) Neurodevelopmental and neuropsychiatric disorders.*

549

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

559 elevated levels of pyrethroids 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 children²²⁵. A pilot study on 40 patients presenting glyphosate or glufosinate
570 intoxication indicated that S100B might be a biomarker for predicting neurologic
571 complications²²⁶; its levels in biological fluids indicate BBB cells damage²²⁷⁻²²⁹.
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 S100B²³⁰. 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 exposure²³¹.

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

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

597

598

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

600

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

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

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

637

638 *7. Conclusions: pesticides and brain vulnerability.*

639

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

658

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

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

684 glyphosate in zebrafish larvae, although in the absence of visible brain malformations
685 or behavioral defects, supporting the notion of subtle and lingering vulnerability
686 conditions²⁵⁷.

687

688 Environmental exposures' ethical and social implications on brain health and well-
689 being are significant. An emerging neuroethics framework in environmental sciences
690 seeks possible threats from the continuous interaction between humans and the
691 environment²⁵⁸. The neuro-exposome, from contact with natural matrices to air
692 pollution, is a principal risk factor for cognitive impairment in young individuals and
693 abnormal or even accelerated aging trajectories. The finding summarized in this
694 review support the importance of environmental neuroethics as a contemporary field
695 of study to identify vulnerability factors that could shape brain health at the population
696 level or depending on geographic location.

697

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

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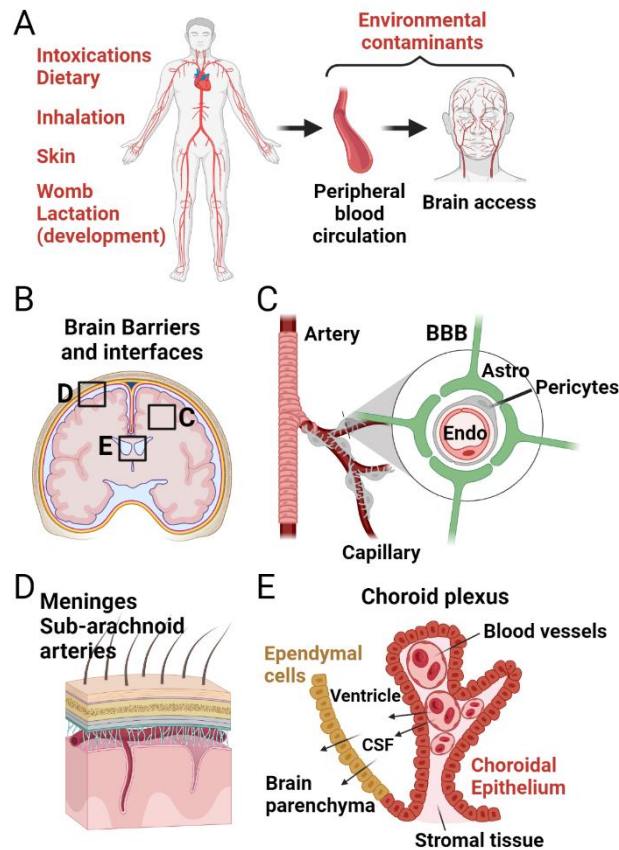
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Figure 1. Environmental contaminants reach brain borders and barriers. A) From external matrices, pesticides enter the body, reaching the peripheral blood circulation and the brain. **B-E)** Critical interfaces are the blood-brain barrier (BBB), the 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.

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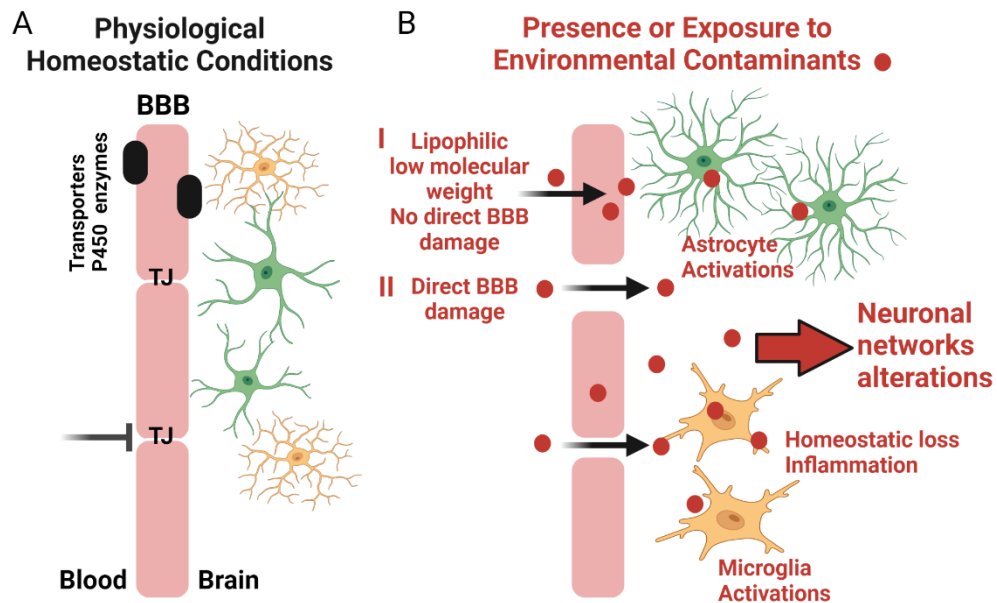
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Figure 2. Environmental contaminants, brain-barrier damage, neuroinflammation, and neurological alterations. **A)** The BBB is highly impermeable due to tight junctions (TJ), with specific drug transporters regulating the brain entry of specific nutrients. **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.

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

TRANSPORTE RS	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, resmethrin (pyrethroids) 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

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790 **Table 2.** Environmental pesticides at the BBB and intersections with
791 neuroinflammation: in vitro studies.
792

PESTICIDE GROUP	COMPOUND	MODEL	DOSE	DURATION	OUTCOMES	PATHWAYS	REF
BBB integrity							
OP	Chlorpyrifos	Neurovascular unit Endothelial cells	NVU: 0, 1, 3, 10, 30, 100 μ M / Endothelial cells: 0, 10, 30, 100, 300 μ M	2 h to 24 h	Chlorpyrifos treatment resulted in morphological changes to more circular-shaped cells. The highest exposure tested (300 μ M) 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 μ M	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							
Dipyrids	Paraquat	Human brain microvascular endothelial cells	1, 10, 100 μ M	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 μ M	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 μ M	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 μ M to 25 μ M	20 min	In GHA but not DI TNC1 and DBTRG-05MG cells, malathion induced Ca ²⁺ release from the endoplasmic reticulum and caused PKC-regulated Ca ²⁺ influx via 2-APB	Ca ²⁺ release from the endoplasmic reticulum and Ca ²⁺ entry via PKC-sensitive store-operated Ca ²⁺ 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 μ M	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 astrogloma (C6 cells)	40, 80, 160 μ M	3, 24 h	Decreased cellular viability and mitochondrial respiratory chain activities	Cell viability and mitochondria	270
OP	Chlorpyrifos	Astrocyte-neuron co cultures	10 μ M to 30 μ M	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 μ M	24 h	50% decrease in the length of the longest neurite in hippocampal neurons cultured with astrocytes previously treated with 10 μ M diazinon	Oxidative stress	272

		neuron co-cultures.					
OP/PYR	Chlorpyrifos/cyflutrin	Human primary astrocytes	1, 5, 25 μ M	7, 14 days.	Upregulation of pro-inflammatory targets	Astrocytes reactivity	75
PYR	Cypermethrin	Astrocytes culture	0–200 μ M	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 μ M	24 h	Cytotoxicity after 24 h treatment and increased [Ca ²⁺] by inducing Ca ²⁺ entry via store-operated Ca ²⁺ channels and Ca ²⁺ release from the endoplasmic reticulum.	Ca ²⁺ 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 μ M	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 μ M	48 h	Cypermethrin increases the level of PKC- δ and iNOS in primary microglia and TNF- α and IL-1 β 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 μ M	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 μ M	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 μ M	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	Lymphocyte s 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/m acrophage- 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

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821 **Table 3.** Environmental pesticides, BBB damage, inflammation, and time-dependent
822 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- α M-positive) cells.	203
Parkinson's disease	Phenylpyrazole	Fipronil	Male Sprague Dawley rats, 3 months	15 or 25 μ g/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

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

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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