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## Assessing the contribution of the chemical exposome to neurodegenerative disease

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1 Perspective

2 **Assessing the contribution of the chemical exposome to neurodegenerative**  
3 **disease**

4

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23 **Abstract**

24 Over the past few decades, numerous environmental chemicals from solvents to pesticides have  
25 been suggested to be involved in the development and progression of neurodegenerative diseases.  
26 Most of the evidence has accumulated from occupational or cohort studies in humans or laboratory  
27 research in animal models, with a range of chemicals being implicated. What has been missing is a  
28 systematic approach analogous to genome-wide association studies that have identified dozens of  
29 genes involved in Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases.  
30 Fortunately, it is now possible to study hundreds to thousands of chemical features under the  
31 exposome framework. This commentary explores how advances in mass spectrometry make it  
32 possible to generate exposomic data to complement genomic data to better understand  
33 neurodegenerative diseases.

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35 **Text**

36 With increasing longevity, age-related neurodegenerative diseases have become major causes of  
37 disability and mortality<sup>1,2</sup>. The two most common neurodegenerative diseases, Alzheimer's disease  
38 (AD) and Parkinson's disease (PD), affect more than 45 million and 6 million persons worldwide,

39 respectively. AD manifests clinically by progressive impairment in memory, learning and executive  
40 functions. PD is characterized by motor symptoms, including bradykinesia, tremor, and postural  
41 instability, as well as a range of non-motor symptoms. Both AD and PD include long preclinical and  
42 prodromal periods during which pathophysiological processes evolve silently over years before  
43 leading to progressive symptoms in later ages. Drugs and/or surgery are available for symptom relief,  
44 and novel therapies are emerging to slow disease progression in AD but thus far no intervention can  
45 substantially alter the course of the disease processes<sup>3,4</sup>. Despite their diverse clinical manifestations,  
46 neurodegenerative diseases share common mechanisms<sup>5</sup>. Misfolded protein aggregation in specific  
47 brain areas ( $\beta$ -amyloid and tau in AD and  $\alpha$ -synuclein in PD, although some overlap in the aggregated  
48 proteins has been reported) is considered a neuropathological hallmark of these diseases. Moreover,  
49 in both pathologies, proteinopathy is accompanied by a disruption of multiple molecular pathways  
50 affecting neurons and non-neuron cells, including: protein degradation systems, mitochondrial  
51 function, blood brain barrier (BBB) permeability, glial cell-mediated neuroinflammatory processes as  
52 well as basic neurophysiology mechanisms<sup>5</sup>. All these processes contribute to neurodegeneration  
53 and lead to neuronal death.

54 Such commonalities in pathogenesis suggest there may be some common causes in  
55 neurodegenerative diseases, although no common etiological factor, beyond age, has been  
56 identified. Both PD and AD (in their sporadic forms, which represent the vast majority of cases) are  
57 multifactorial diseases resulting from a combination of genetic and environmental risk factors<sup>6</sup>. The  
58 multiple susceptibility loci identified so far are specific to each disease (e.g. *APOE4* for AD, *SNCA* and  
59 *LRRK2* for PD) and only explain a portion of the disease burden<sup>7-9</sup>. Established non-genetic risk  
60 factors for AD include female sex, lifestyle (e.g. physical inactivity, ~~unhealthy~~ Western-style diets),  
61 cardiometabolic health, psychosocial factors and air pollution,<sup>1</sup> while the level of current evidence  
62 with pesticide exposure is moderate<sup>10</sup>. In PD, males are at higher risk and there is evidence that  
63 exposure to pesticides in occupational populations (e.g., farmers) and to solvents such as  
64 trichloroethylene contribute to disease development, while nicotine and caffeine are potential  
65 protective factors<sup>2,10,11</sup>. However, compared to lifestyle or metabolic factors, there has been little  
66 study of the wide array of potentially neurotoxic chemicals originating from agricultural, industrial, or  
67 household sources.

68 Here we survey epidemiological and experimental evidence relating the chemical component of  
69 exposome (i.e., chemicals individuals are exposed to from various environmental sources) to  
70 neurodegenerative diseases. We focus on pollutants that mostly result from anthropogenic activities  
71 and have been involved in toxicology pathways. We identify gaps and pitfalls in existing research and  
72 we formulate a roadmap for next-generation studies in order to push forward exposome research in  
73 neurosciences and the methodological innovations that have accompanied this conceptual  
74 revolution.

## 75 **Our chemical environment in the Anthropocene**

76 Chemicals are ubiquitous in modern life. More than 100,000 chemicals are currently used worldwide,  
77 and the production continues to increase.<sup>12</sup> Some chemicals are directly used, either alone or as  
78 mixtures, in agricultural, industrial and household activities including pesticides, solvents or metals  
79 (**Figure 1A**). Other contaminants are emitted into the air from natural or anthropogenic combustion  
80 processes, including fine particulate matter of less than 2.5 microns of diameter (PM<sub>2.5</sub>), gases, and  
81 organic compounds (e.g. dioxins). Some synthetic chemicals are added by the industry to consumer  
82 products for their technological properties. These include polychlorinated biphenyls (PCBs), flame  
83 retardants (FRs), per-fluorinated compounds (PFAS), plasticizers including recognized endocrine  
84 disruptors (bisphenols, phthalates), and other cosmetic and food additives. Many of these chemicals  
85 have half-lives of several years and are persistent in the environment including the food chain,  
86 resulting in chronic exposures for human populations, even after their use has been banned or  
87 restricted. Several of these compounds have been listed as Persistent Organic Pollutants (POPs)  
88 under the Stockholm convention because of their high lipophilicity, their resistance to xenobiotic

89 metabolism, and their recognized persistence in the environment. Recognized POPs include  
90 organochlorine pesticides, first generation brominated flame retardants (BFRs), dioxins, PCBs, and  
91 some long-chain PFAS; additional substances are continuously included. POPs have been  
92 progressively prohibited in most countries and replaced by novel compounds (although their long-  
93 term safety is unknown), but human populations remain continuously exposed (e.g., food  
94 contamination). Moreover, alternative molecules have also raised concerns for the environment and  
95 health. For example, from the 1940s until now, organochlorine pesticides were progressively  
96 replaced by organophosphates, carbamates and pyrethroids, as well as neonicotinoids and pyrazoles.  
97 Likewise, organophosphorus flame retardants (OPFRs) and short-chain PFAS have emerged as  
98 alternatives to first generation brominated FRs and PFAS species. Many of these novel less persistent  
99 substances activate toxicity pathways, e.g. oxidative stress, and because exposure is sustained, they  
100 may exert long term effects<sup>13</sup>.

101 With increasing concern about this pollution, some large research programs on biomonitoring (i.e.  
102 measuring exogenous chemicals and their transformation products in the human body, usually blood  
103 or urine) have started mapping the exposure of humans to environmental contaminants. Hence, the  
104 US National Health and Nutrition Evaluation Survey demonstrated that the general US population is  
105 commonly exposed to metals, POPs, solvents and non-persistent chemicals<sup>14</sup>. More recently, the  
106 large-scale European Human Biomonitoring Initiative measured actual exposure to multiple  
107 contaminants found at concentrations that, in some cases, exceeded available human guidance  
108 values (i.e. internal levels below which there is no appreciable health risk). Certain exposure  
109 biomarkers of non-persistent substances were detected in almost 100% of individuals<sup>15</sup>. Both US and  
110 EU initiatives highlight disparities in human exposure due to geographical specificities or  
111 socioeconomic factors<sup>14,15</sup>. However, while these current initiatives help rank these substances  
112 (several hundreds) as priority toxic substances, the vast majority of our multi-chemical world remains  
113 so far uncharacterized. Furthermore, the agencies responsible for regulation of these compounds,  
114 the European Food Safety Authority (EFSA) and European Chemical Agency (ECHA) in the EU and the  
115 Environmental Protection Agency (EPA) in the U.S. operate in most cases under a model that  
116 examines one chemical at a time, which limits the ability to evaluate formulations and complex  
117 multiple exposures.

## 118 **The exposome concept**

119 Capturing all the environmental exposures faced by an individual represents a major challenge due to  
120 geographical specificities or socioeconomic factors which also vary during the lifetime. To address  
121 these unmet challenges, a novel holistic concept has been envisioned that provides a systematic and  
122 comprehensive analysis of the environmental factors an individual is exposed to during their  
123 lifetime<sup>16</sup>. The *exposome* integrates, in a single framework: external exposures that arise from the  
124 outside milieu (**Figure 1B panel 1**); biological fingerprints of these exposures in biofluids (**Fig. 1B.2**);  
125 susceptibility factors which modulate biological responses to the environment (**Fig. 1B.3**); and the  
126 biological alterations resulting from the cumulative toxicity of those exposures (**Fig. 1B.4**). The  
127 temporal dimension of the exposome is key to the development of chronic diseases particularly for  
128 diseases such as AD and PD which develop silently over years. There may be critical time-windows for  
129 exposures; for example, the development of a healthy brain is critical for the constitution of a  
130 cognitive reserve and is a central component of resilience mechanisms in AD. Thus, child exposure to  
131 chemicals could affect neurodevelopment and lead to neurodegenerative diseases in adulthood,  
132 underlining the importance of geographical exposomes over the life-course of an individual.

## 133 **Chemical stressors and neurodegenerative diseases**

134 Epidemiology of chemical exposures and neurodegenerative diseases. A majority of research has  
135 focused on pesticides, metals, solvents and fine particulate matters (**Table 1**). The most consistent  
136 associations have been found between occupational exposure to pesticides and the risk of PD, and

137 AD to a lesser extent<sup>10,17</sup>. Hence, increased risk among pesticide users were estimated at 50% for AD  
138 and >65% for PD<sup>17</sup>, and PD is now recognized as an occupational disease for French farmers and for  
139 US veterans exposed to the Agent Orange. However, specific substances have remained difficult to  
140 incriminate so far, although there is evidence that some herbicides (e.g. paraquat) and insecticides  
141 (e.g. organochlorine) might increase PD risk<sup>10</sup>. In both AD and PD, research in the general population  
142 which can be exposed to lower levels of pesticides has been more limited, with, at best, emerging  
143 evidence supported by a few studies<sup>18-23</sup>. Progress in modelling ambient air exposure in the vicinity  
144 of fields enabled pesticide-wide association studies in PD<sup>19</sup>. Recent biomarker-based studies  
145 demonstrated that low-grade exposure resulted in quantifiable circulating levels and increased  
146 disease risk. For example, nearly 4-fold higher serum levels of the organochlorine insecticide  
147 dichlorodiphenyldichloroethylene (DDE) was found in AD cases versus controls<sup>20</sup>, and twice more  
148 Lewy pathology were reported in the presence of the organochlorine insecticide heptachlor epoxide  
149 in brain tissue donors<sup>21</sup>.

150 Metals have been widely investigated through biomarkers, mostly in case-control studies<sup>24,25</sup>,  
151 although the weight of evidence was low overall. Evidence with metals in both occupational and non-  
152 occupational populations have been generally insufficient except for occupational manganese  
153 exposure and PD<sup>24,25</sup>. Solvent exposure was also suggested to play a role in PD and AD in  
154 occupational settings<sup>26-29</sup>, but similarly to metals, prospective studies have been very limited and the  
155 weight of evidence is low overall. Moreover, studies are lacking on exposures in the general  
156 population, i.e., solvent use in domestic activities or exposure from food or ambient air, although  
157 research in this field is emerging, such as recent studies linking trichloroethylene in contaminated  
158 water and ambient hydrocarbon solvents (e.g. xylene) with higher risk of PD<sup>11,19</sup>.

159 Among ubiquitous pollutants in the general population, the strongest epidemiological evidence so far  
160 has been obtained with PM<sub>2.5</sub> level in ambient air<sup>30-32</sup>. Each increase in PM<sub>2.5</sub> air concentration of 10  
161 µg/m<sup>3</sup> (US EPA annual standard) may increase the risk of all-cause dementia, AD and PD by  
162 approximately 30%, 65% and 15%, respectively<sup>31</sup>. In contrast, most synthetic additive chemicals (e.g.  
163 FRs, PFAS, preservatives) have received little attention and there is insufficient evidence in exiting  
164 epidemiological literature to date, except from studies using biomarkers of the U.S. NHANES in  
165 relation with cognitive function<sup>33-36</sup>. Overall, although the use of biomarkers in general populations  
166 have started developing, research linking large-scale exposure assessment to specific health  
167 outcomes is only in its infancy.

168 **Vulnerability of neurodegeneration-related mechanisms to chemical toxicity.** The brain is highly  
169 vulnerable to the toxicity of environmental stressors<sup>37</sup>. Human studies identified a potential role of  
170 lead, PCBs and air pollution in attention-deficit hyperactivity disorder and autism in children<sup>38</sup>.  
171 Moreover, preclinical studies have shown that exposure to various chemical stressors during *in-utero*  
172 and postnatal periods promote neurodegeneration in adulthood<sup>39</sup>. However, brain vulnerability to  
173 chemicals is not limited to the developmental period and aging increases vulnerability to chemical  
174 neurotoxicity, owing to the multiple age-related alterations at play in the brain (e.g., atrophy,  
175 decrease in blood flow and metabolism, BBB leakage), which increase its sensitivity to xenobiotics  
176 and reduce its capacity to compensate for impairment. Furthermore, experimental studies have  
177 documented the impact of chemical stressors on main neurodegenerative pathways (**Figure 2**), with  
178 large heterogeneity in the amount of literature across chemical families<sup>40</sup>. Metals, pesticides, organic  
179 solvents, and combustion pollutants have been most extensively studied, while research on synthetic  
180 additive chemicals such as FRs and plastic-related endocrine-disrupting compounds is only emerging.  
181 In all chemical classes, general neurotoxic pathways such as oxidative stress, mitochondrial  
182 dysfunction, and disruption of neurotransmission have been the most investigated so far. Yet the  
183 impact of certain pollutants on pathways specific of neurodegenerative diseases (misfolded protein  
184 aggregation) and on key associated mechanisms is also emerging in the literature, especially  
185 neuroinflammation which appears affected by widespread pollutants such as airborne PM<sub>2.5</sub><sup>41,42</sup>.  
186 Research also suggests potential pleiotropic effects on multiple neurodegenerative pathways for

187 non-persistent insecticides such as organophosphate pesticides, pyrethroids and neonicotinoids<sup>42</sup>,  
188 thus raising increasing concern in the scientific community.

## 189 **Gaps in science and unmet challenges to study the impact of chemicals on** 190 **neurodegenerative diseases**

191 Integrating all routes of exposures and widening the list of chemicals of emerging concern. Routes of  
192 exposure for a given contaminant have been rarely characterized exhaustively. In neurosciences,  
193 exposure to pesticides in the general population is often studied through ambient air pollution  
194 models, ignoring intake through contaminated foods<sup>43</sup>. Furthermore, toxicology and  
195 neuroepidemiology have investigated relatively few molecules, many of them being already  
196 restricted<sup>44</sup>, and have ignored most recent exposures of potential concern. Biomonitoring has only  
197 recently been used to link internal exposure to neurological impacts.

198 Non-persistent pesticides such as neonicotinoids and pyrethroids remain poorly studied, in spite of  
199 emerging concern for their neurotoxicity. Compared with older non-persistent insecticides, like  
200 organophosphates, neonicotinoids act selectively on insect nicotinic acetylcholine receptors and  
201 have low affinity for vertebrate receptors, which reduces toxic risk in those non-target species<sup>45</sup>,  
202 although this theory has been challenged by experimental data showing a wide range of toxic effects  
203 in various animal species, including mammals. Pyrethroids target the nervous system of insects  
204 primarily by inhibiting voltage-gated sodium channels, but due to similarities in neural function, they  
205 also have neurotoxic properties in non-target organisms<sup>46</sup>. The gradual increase in neonicotinoids  
206 and pyrethroids in the environments raises the risk of toxicity to human populations, while there is  
207 currently limited knowledge on their long-term effects on organisms<sup>45-49</sup>. Likewise, many ubiquitous  
208 chemicals in modern life (e.g., FRs, fluorosurfactants, plasticizers, food, and cosmetic additives) have  
209 been overlooked, in spite sometimes of their structural or chemical proximity with banned  
210 compounds. For example, many of these contaminants contain halogen groups (fluorine, chlorine,  
211 bromine) that are fat-soluble and may thus penetrate the brain easily and exert direct neurotoxicity  
212 effects. Besides, while the literature supports a role of large particle pollution (PM<sub>2.5</sub>) in  
213 neurodegenerative diseases<sup>31</sup>, less is known about smaller particles<sup>50</sup>, especially micro- and  
214 nanoplastics (released from the breakdown of plastic wastes) and engineering nanoparticles  
215 (synthesized by the chemical industry for their technological properties). Due to their small size,  
216 nanomaterials can sorb various pollutants on their surface (e.g. metals), cross biological barriers and  
217 reach the brain and exert neurotoxicity<sup>51-53</sup>. Finally, besides xenobiotics, there are many natural  
218 chemical compounds in the chemical exposome, such as microbial-derived compounds that are  
219 known to regulate multiple aspects of brain health. Hence, associations of, e.g., bile acids,  
220 neurotransmitters and short-chain fatty acids produced by microbial fermentation of certain dietary  
221 fibers, with neurodegenerative diseases have been reported<sup>54,55</sup>. As the gut microbiota contributes to  
222 the metabolisms of certain xenobiotics (e.g. polyphenols), interactions between both xenobiotic  
223 chemicals and microbial metabolites are also likely, but they have been underexplored.

224 In addition, some molecular pathways have been less investigated than others. For instance, while  
225 approximately half of the experimental studies mentioned oxidative stress in our scoping review,  
226 neurovascular dysfunction (a strong risk factor for neurodegeneration) was considered in less than  
227 5% of them, despite the interest in the BBB as a toxicology biotarget<sup>56</sup>. Studies have been centered  
228 on neurons and less on non-neuronal populations such as glial cells in spite of their central role in  
229 brain functions. Similarly, the impact of pollutants on intercellular communication remains poorly  
230 understood, with novel mechanisms implicating extracellular vesicles, currently emerging<sup>57</sup>. Thus, a  
231 significant portion of the chemical exposome of neurodegenerative diseases remains to be  
232 deciphered.

233 Extrapolating preclinical models to human health. Experimental studies are limited by constraints,  
234 such as the use of systemic routes of administration for animal models (e.g., intraperitoneal  
235 injections) which are not representative of real life<sup>58</sup>. Also, the internal exposure characterized by a  
236 slow release of POPs from adipose tissue (or potentially the myelin sheath), remains relatively

237 unexplored. Similarly with *in vitro/ex vivo* experimental studies, exposing cells or tissues to a given  
238 chemical does not accurately reflect real-life exposure patterns, which include exposure to the  
239 parent compound as well as its metabolites formed within the live body sometimes by other tissues.  
240 This is of particular importance since various metabolites were demonstrated to be more neurotoxic  
241 than their parent compound, such as chlorpyrifos-oxon and chlorpyrifos<sup>59</sup>, desnitroimidacloprid and  
242 imidacloprid<sup>60</sup>. New *in vitro* models could partially overcome these deficiencies, for example brain  
243 organoids, *in vitro* models of brain blood barriers or organs-on-chip models.

244 **Refining predictive neurotoxicology.** The toxicological impact of chemicals depends on various  
245 factors, which together determine the kinetics, dynamics and metabolism of compounds. As with  
246 other diseases, an incomplete understanding of chemical toxicokinetics clearly impedes our ability to  
247 decipher the impact of chemicals on neurodegenerative diseases. Physiologically based  
248 pharmacokinetic (PBPK) tools allow to model the distribution of pollutants within an organism by  
249 compartmentalizing it (liver, muscle, brain). The overarching aim is to determine exposure levels at  
250 which a given chemical which penetrates the body is likely to reach the brain and exert adverse  
251 effects – along with deciphering the factors which determine these toxicokinetic and toxicodynamic  
252 parameters. This is particularly challenging in neurosciences since the permeability of the BBB is  
253 selective and variable according to chemicals.

254 In addition to PBPK, the development of Adverse Outcome Pathways (AOPs) is expected to strongly  
255 support predictive toxicology (<https://aopwiki.org/>). An AOP describes a sequence of molecular,  
256 cellular and organ-level events named key events (KE) which ultimately lead to an adverse outcome  
257 such as a neurodegenerative disease. The robustness of an AOP depends on strong experimental and  
258 human evidence which validate the sequence of events. If an AOP is robust enough, then it may  
259 allow to predict an adverse outcome when a KE is modulated by a chemical. For example, an AOP  
260 leading to PD is described at <https://aopwiki.org/aops/3>. Unfortunately, very few AOPs related to  
261 neurodegenerative diseases have been developed so far.

262 **Deciphering mixture effects.** Single exposure assessment has prevailed in research for practical  
263 reasons, although it does not reflect the multiplicity of co-exposures in real life and fails to capture  
264 the potential additive or synergistic effects of chemicals that likely underlie the impact of the  
265 chemical exposome on health<sup>61</sup>. There is biological rationale in joint investigation of compounds with  
266 close chemical structure or common biotargets, as they may have additive effects or potentiate each  
267 other regarding toxicological hazard (e.g. activating the same KE). Hence, for example, exposure to a  
268 mixture of As, Cd, and Pb at environmentally-relevant concentrations in rats increases the content of  
269 cerebral amyloid beta at higher levels than the sum of effects of each metal tested individually<sup>62</sup>. In  
270 humans, higher circulating polybrominated diphenyl ethers (PBDEs) were associated with impaired  
271 memory only in adults with high serum PCBs levels<sup>63</sup>, suggesting potential synergy between these  
272 compounds. Alternatively, co-exposure may be defined based on the co-persistence of compounds in  
273 the environment, such as with Cd and chlorpyrifos which both accumulate in food chains and may be  
274 more likely to exert joint effects in biological systems. This was demonstrated in rats, in which low  
275 dose exposures of a mixture of Cd and chlorpyrifos induced brain oxidative stress, while individual  
276 treatments did not result in any observable modification<sup>64</sup>. The proof of concept of mixture effects  
277 on health with moderate to low levels of exposures has been provided by some emerging  
278 epidemiological science exploring co-exposures to multiple pollutants, interactions or mixture  
279 effects<sup>35,36,63,65</sup>. However, mixture studies have been seldom applied to neurodegenerative diseases.  
280 Exposome studies can explore and map agnostically the entire chemical exposome in populations  
281 exposed to very different environments and identify novel potentially harmful combinations that  
282 would deserve deep experimental investigations.

283  
284  
285 **Profiling the internal chemical exposome through high-throughput molecular approaches**

286 Measuring with accuracy all the components of the exposome represents a tremendous challenge  
287 which has been only very partly met so far, although new technologies have recently developed. For  
288 example, assessment of the external components of the exposome no longer relies on indirect tools  
289 (such as questionnaires coupled with job-exposure matrices to evaluate occupational exposures or  
290 Geographical Information System and spatial modeling to monitor ambient air exposures) but is also  
291 aided by technologies for direct measurement of exposures in real time, such as wearable sensors.  
292 The development of omics-based molecular approaches has allowed simultaneous analysis of  
293 thousands of biological entities at a large scale – a technological revolution which has enabled the  
294 development of exposomics. High-resolution mass spectrometry (HRMS)-based methods applied to  
295 various matrices, allows to uncover unknown elements of the internal chemical exposome associated  
296 with neurodegenerative diseases<sup>66</sup>.

297 Exposomics and HRMS to look beyond the streetlamp. Omics allow the analysis of thousands of  
298 components within different molecular layers underlying biological mechanisms. In addition to  
299 conventional tandem mass spectrometry that can now provide robust exposure data for a selected  
300 list of contaminants, the advancements of HRMS (in particular, sensitivity) combined with  
301 bioinformatics developments, has allowed emergence of new generation, large-scale exposomics  
302 studies. Among all omics-based approaches, HRMS is unique in that it enables to measure  
303 simultaneously thousands of small molecules (generally 50–1200 Da) present in biospecimen,  
304 encompassing endogenous metabolites, exogenous chemicals and their transformation products as  
305 well as the small molecules from the microbiota<sup>66</sup>. In addition to identification of hundreds of  
306 molecules, HRMS captures thousands of unidentified chemical features in need of characterization.  
307 When applied to well-phenotyped cohorts, with ideally multiple biospecimen collection time points  
308 to handle intraindividual variability in metabolite concentrations, these methods provide a unique  
309 opportunity to identify chemical mixtures associated with neurodegenerative diseases. Robust  
310 targeted methods that provide quantitative data can then validate the new chemical markers  
311 identified (**Box 1**). However, implementation of exposomic studies faces numerous challenges since  
312 the chemical space is highly variable (>100,000 chemicals are currently used), diverse in nature (with  
313 wide ranges of physicochemical properties), heterogeneous in concentration levels from one  
314 substance to another (ultra-trace substances being difficult to detect), and dynamic (in particular for  
315 non-persistent chemicals with very short half-lives).<sup>66</sup>

316 Exposomics and neurodegenerative diseases. Since the first advocacy on the need for data-driven  
317 exposome-wide association studies based on blood HRMS chemical profiling, the application of these  
318 promising methodologies has been very limited in the neurodegenerative disease field. Some studies  
319 have successfully identified blood biomarkers (for AD) implicated for instance in hypoxia, oxidative  
320 stress, as well fatty acid, phospholipid and acylcarnitines metabolism<sup>67–69</sup>. Most of blood-based  
321 biomarkers identified will then require validation; nevertheless, all these proof-of concept studies  
322 support the applicability of HRMS-based to identify biomarkers that could facilitate, for instance,  
323 early diagnosis. Moreover, the continuous increase of sensitivity of HRMS instruments as well as the  
324 recent launch of large EU and US initiatives aiming to push forward these exposomics-based methods  
325 at large scales mean that the time is ripe for this change of paradigm in neurodegenerative diseases.  
326 Emerging HRMS-based pilot studies (with generally less than 50 participants) have begun identifying  
327 chemicals associated with AD or PD<sup>70–72</sup>. For example, a commonly used plasticizer (bis(2-ethylhexyl)  
328 phthalate) was detected in greater abundance in the cerebrospinal fluid of patients with Lewy bodies  
329 compared with patients with AD<sup>70</sup>. Another HRMS-based exploratory study analysed the chemical  
330 exposome and metabolome in the hair of AD patients versus controls and reported differences in  
331 dietary long-chain unsaturated fatty acids, gut-derived indole metabolites and phthalates<sup>71</sup>. In  
332 another study, an unknown halogen-containing compound was found increased in the plasma of AD  
333 cases compared to controls<sup>72</sup>. The identity of this novel molecule might be unveiled in the future as  
334 annotation workflows and HRMS databases progress. **Although some initial HRMS-based studies  
335 have not identified the association between pesticides and PD or AD reported in experimental or**



336 epidemiological data, research on neurodegenerative diseases is currently too limited in the  
337 emerging HRMS field, with populations or instruments not diverse or sensitive enough to draw any  
338 conclusion. However, pesticides have been recently detected in large-scale biomonitoring studies in  
339 the general population using HRMS<sup>73</sup> so we are confident that the research effort on  
340 neurodegenerative diseases using HRMS will soon be able to provide the relevant pesticide data.  
341 There is an acute need to push towards future application of HRMS-based methodologies in large-  
342 scale population-based prospective studies that could provide some breakthrough results in the  
343 upcoming years regarding the identification of chemical signatures associated with  
344 neurodegenerative diseases. Initiatives underway at the National Institutes of Aging in the U.S.  
345 appear poised to capitalize on these new technologies.

## 346 **Conclusion**

347 The past 25 years have witnessed a genomic revolution in neurodegeneration. Dozens of gene  
348 variants have been implicated across the disease spectrum. Yet, we know from inheritance studies  
349 that there are limits to genomic discovery. Once geneticists have identified the missing heritability  
350 the overwhelming reality is that the environment and gene-environment interactions represent the  
351 missing everything else. Compared to other fields, there has been a lag in exposome research on the  
352 neurodegeneration front, maybe because those diseases pose very specific challenges: one of the  
353 biggest research challenges is certainly the long disease development lag; while neurodevelopmental  
354 diseases occur early in life, the search window between exposures and diagnosis is relatively small,  
355 whereas neurodegenerative diseases take decades to develop, making prospective studies in  
356 diseases of aging so much longer and difficult to implement. Although the focus here has been on the  
357 chemical component of the exposome, it is important to note that social and behavioral factors also  
358 play a key role in neurodegeneration. Fortunately, advances in geospatial technologies and HRMS  
359 make it possible to link such variables to the underlying biology and chemistry. This creates  
360 unprecedented opportunities for merging genetics with the environment in a comprehensive  
361 manner. Future advances in neurodegeneration will necessitate integrating across many omic layers.  
362 Exposomics provides the comprehensive environmental omic layer that will help extract the maximal  
363 information from ongoing efforts in genomics, proteomics, and imaging.

364  
365

366 **Figures, Tables and Boxes**

367

368 **Figure legend**

369

370

371 **Figure 1. The chemical exposome of neurodegenerative diseases: from epidemiological concept to**  
372 **implementation**

373

374 Figure 1A. Chemicals in modern life

375

376 Figure 1B. The exposome of neurodegenerative diseases

377

378 **Panel A** depicts primary sources of chemical exposures in everyday life in our modern societies. Some chemicals are **used** by humans either  
379 alone or as mixtures, for agricultural, industrial and domestic activities (**panel A, left**) and contaminate populations from occupational use  
380 but also potentially through consumption of contaminated products. These include metal trace elements, pesticides (including insecticides,  
381 fungicides and herbicides) and solvents. Other chemicals are **emitted** in the environment from natural or anthropogenic combustion  
382 processes (**panel A, middle**) and expose populations living in contaminated areas breathing or consuming contaminated air/products. These  
383 chemicals include PM2.5, gaseous pollutants (e.g., carbon monoxide, nitrogen oxides and ozone), organic compounds (dioxins and polycyclic  
384 aromatic hydrocarbons), and cigarette smoke for passive smokers. Finally, some chemicals are directly **added** to consumer products to  
385 improve their technological properties (PCBs; brominated and organophosphate FRs; long-chain and short-chain per-fluorinated compounds  
386 [PFAS]; plastic-related compounds including bisphenols and phthalates; cosmetic and food preservatives/additives). These contaminants are  
387 ubiquitous in our modern life and populations are exposed by using or consuming these products. Many of these chemicals are persistent in  
388 the environmental media (air, water, soil, dust and food) resulting in constant sources of human exposure. Some have been classified as  
389 POPs under the Stockholm convention due to their recognized persistence in the environment, wide distribution, bioaccumulation in  
390 organisms through the food chain, and toxicity (POPs refer to Persistent Organic Pollutants; see supplementary material for more details on  
391 each chemical class). These environmental chemical exposures feed part of the **exposome concept** as first conceptualized by C. Wild in the  
392 context of cancer epidemiology<sup>16</sup>. **Panel B** presents the epidemiological concept underlying the chemical exposome of neurodegenerative  
393 diseases, linking **external (B1)** and **internal (B2)** components of the exposome, with potential intervention of **moderators**, also referred to  
394 as **susceptibility factors**, which modulate biological responses to the environment, such as sex, individual genomic background and social  
395 inequalities (**B3**); up to the **phenome (B4)** which materializes the impact of the exposome on neurodegenerative diseases. In this view, the  
396 external component encompasses contextual (or “general external”) factors such as general environmental contamination, characteristics  
397 of the built environment and social inequalities, as well as individual (or “specific external”) factors including experiences, behaviors and  
398 lifestyle, and various pollutant exposures resulting from individual behaviors/choices; while the internal component of the exposome  
399 comprises all exogenous chemicals and their transformation products, as well as markers of the associated biological responses. In direct  
400 continuity, the phenome encompasses subclinical alterations ascertained by change in diverse biomarkers (e.g., neuroimaging or fluid-based  
401 biomarkers) in the preclinical phase of neurodegenerative diseases when cognitive (and motor) function is intact, followed by clinical  
402 symptoms (mild cognitive impairment in AD, motor dysfunction in PD) and eventually disease diagnosis. Yet, deciphering the depth and  
403 complex links of that chemical exposome remains extremely challenging and necessitates to be explored within an exposomic framework,  
404 where characterization of the internal component of the exposome (primarily markers of exogenous exposures) through complementary  
405 HRMS approaches have become a central player, together with the integration of biological effects and endogenous processes at various  
406 omics levels (i.e. epigenome, transcriptome, proteome, metabolome, microbiome...).

407 *Abbreviations: FR: flame retardants; HRMS: high resolution mass spectrometry; PCBs: polychlorinated biphenyls; PFAS: per-fluorinated*  
408 *compounds; PM2.5: particulate matter; POP: persistent organic pollutants.*

409

410 **Figure 2. Cellular and molecular pathways affected by chemical pollutants in Alzheimer's and**  
411 **Parkinson's neurodegenerative diseases.**

412 Multiple chemical families have been involved in neurodegenerative disease pathways. **Metal Trace Elements** (blue square), including non-  
413 essential toxic metals (e.g. Cd, Hg, Pb, Al, As) and essential metals with imbalanced status (Fe, Zn, Cu, Mn), have been extensively implicated  
414 in mitochondrial dysfunction and oxidative stress (directly through ROS production and/or indirectly through the depletion of antioxidants  
415 species)<sup>24,74</sup>. **POP pesticides** (largely represented by organochlorine insecticides in the literature; purple square) affect a broad range of  
416 pathways, including misfolded (amyloid- $\beta$ ) protein aggregation<sup>75</sup>; yet most studied pathways attributed to these compounds include  
417 disruption of neurotransmitter systems (norepinephrine, dopamine, GABA, glutamate) and oxidative stress<sup>76</sup>. **Other insecticides** have also  
418 been predominantly involved in the disruption of the cholinergic system, in particular organophosphates (to a lesser extent carbamates)<sup>77</sup>  
419 and neonicotinoids<sup>60</sup>. This is in agreement with their mode of action, i.e., inhibition of the acetylcholinesterase enzyme and binding to  
420 nicotinic acetylcholine receptors, respectively; however, they also impact multiple other pathways including calcium dyshomeostasis (for  
421 organophosphate and neonicotinoids)<sup>49,59</sup> oxidative stress (for the pyrazole fipronil)<sup>79</sup>,  $\alpha$ -synuclein aggregation<sup>47</sup> and mitochondrial  
422 dysfunction<sup>48</sup> (for, e.g. pyrethroid insecticides). In contrast to POP and non-POP insecticides that have been involved in multiple mechanisms,  
423 **herbicides** and **fungicides** have been primarily involved in neurotransmitter (dopamine) system disruption<sup>80</sup> and mitochondrial dysfunction<sup>81</sup>  
424 respectively (although research is emerging on pathways specific of neurodegenerative diseases, such as misfolded protein aggregation).  
425 **Organic solvents** (green square) have received less attention than pesticides or metals, but dysfunctions in mitochondria and  
426 neurotransmitter systems are suspected to be central components of solvent-related neurotoxicity<sup>82</sup>. **Combustion pollutants** (PM2.5,  
427 cigarette smoke, PAHs, dioxins; grey squares) have been largely implicated in the promotion of neuroinflammation and oxidative stress<sup>41</sup>,  
428 albeit specific chemicals may be involved in other specific pathways. **PM2.5** impair the lysosomal function and autophagic flux<sup>83</sup>, **dioxins**  
429 disrupt the permeability of the BBB<sup>84</sup> and the **PAH** benzo(a)pyrene and phenanthrene impact neurotransmitter systems (e.g.  
430 acetylcholinesterase and dopamine)<sup>85</sup>. **Cigarette smoke** displays contrasting effects on misfolded protein production and accumulation due  
431 to the dual exposure to combustion pollutants and nicotine.<sup>86,87</sup> Experimental research on synthetic additive chemicals (**PCBs**, **FR**, **PFAS**,  
432 **bisphenols**, **phthalates** and **food/cosmetic additives**; red and orange squares) and neurodegenerative disease-related pathways is only  
433 emerging, and have so far focused on general neurotoxic pathways such as oxidative stress and disruption of neurotransmission<sup>88-90</sup>, although  
434 other mechanisms begin to be suggested (e.g. long-chain PFAS may penetrate and disrupt the BBB permeability<sup>91</sup>).

435 *Abbreviations: BBB: blood brain barrier; FR: flame retardants; PAH: polycyclic aromatic hydrocarbons; PCBs: polychlorinated biphenyls; PFAS:*  
436 *per-fluorinated compounds; PM2.5: fine particulate matter; POP: persistent organic pollutant; ROS: reactive oxygen species*

437

438 **Table 1. Overview of the epidemiological literature on chemical exposures and neurodegenerative**  
 439 **diseases**

Chemical exposures		Parkinson's Disease / Motor Impairment		Alzheimer's Disease / Cognitive Impairment	
Substance	Source	Evidence	Selected ref.	Evidence	Selected ref.
<b>Pesticides</b>	Occupational	++	10,17	+	10,17
	Non-occupational	(+)	10,19,21	(+)	10,20,23
<b>Metals</b>	Occupational	+/-*	25	∅	24
	No distinction	+/-**	25,92	+/-***	24,93
<b>Organic solvents</b>	Occupational	+/-	26,27	+/-	28,29
	Non-occupational	∅	11	∅	
<b>PM2.5</b>		+	30,31	++	31,32
<b>Gaseous air pollutants (e.g. NOx)</b>		(+)	30	(+)	32
<b>Second-hand cigarette smoke</b>		(+)	94	(+)	94
<b>Dioxins</b>		∅	95	∅	95
<b>PAHs</b>		∅		∅	33
<b>PCBs</b>		∅	22,96	+/-	23,96
<b>Flame retardants</b>		∅		∅	63,97
<b>Long-chain PFAS</b>		∅	98	∅	34,98
<b>Bisphenols</b>		∅		∅	36
<b>Phthalates</b>		∅	65	∅	35

440 All associations are in the direction of an increased risk of neurodegenerative disease with increased chemical exposure, except for second-  
 441 hand smoke and Parkinson's Disease (inverse association).

442 ++: high evidence supported by many consistent studies,

443 +: moderate evidence supported by several consistent studies,

444 (+): emerging evidence supported by few but consistent studies

445 +/-: low evidence supported by several inconsistent studies

446 ∅: insufficient evidence due to very limited number of available studies

447 \*For occupational Mn exposure (i.e., the most convincing occupational metal exposure associated with PD)

448 \*\*For Pb exposure (i.e., the most convincing metal exposure associated with PD)

449 \*\*\*For Pb, Hg, Al and Cu exposures (i.e., the most convincing metal exposures associated with AD)

450  
 451 *Abbreviations: PAHs: polycyclic aromatic hydrocarbons, PCBs: polychlorinated biphenyls; PFAS: per-fluorinated compounds; PM2.5: fine*  
 452 *particulate*  
 453

**Box 1. Using HRMS to measure exogenous and endogenous chemicals in human samples: challenges to overcome.** HRMS-based methods enable agnostic Exposome-Wide Association Studies (ExWAS) to examine environmental chemical factors associated with neurodegenerative diseases. Although HRMS-based methods can already reproducibly profile hundreds to thousands of exogenous chemicals and their transformation products in human biological samples (plasma, CSF), improvements are needed<sup>66</sup>. The first limitations are purely technical and lie in the bounded versatility of HRMS technologies, limiting the diversity of chemicals that can be analysed within a given platform. In addition, analytical sensitivity must be enhanced to improve the detection of low-abundant exogenous chemicals (and metabolites). The development of large mass spectrometry facilities equipped with a wide range of HRMS-based instruments should improve coverage of the chemical space and increase throughput<sup>66</sup>. There is also a need to establish a strong collaboration and harmonisation of relevant laboratories/analytical facilities to support concerted large-scale research efforts. A major bottleneck of HRMS-based methods is the complexity of the annotation process (i.e., assigning a putative identity to feature from HRMS datasets), meaning that the vast majority of information collected by HRMS-based methods remains, to date, unannotated (usually less than 10% of all features generated in HRMS are successfully identified). Identification of features is a tedious process involving many steps and typically relies on having a reference standard to confirm the structure of a putative feature. New computational strategies are emerging to help with the structural elucidation of unknown structures. For instance, fragmentation trees with structural elucidation provide a combined and coherent assessment of molecular structures from MS/MS data<sup>99</sup>. Although still at the proof-of-principle stage, the use of molecular networking also has great potential to aid both MS-based disease diagnostics and drug development<sup>100</sup>. Other innovations based on *in silico* bioinformatics tools help to provide information about the potential structures of chemicals undergoing biological transformation (e.g., phase I/II metabolites). Other critical efforts needed in this field include the development of a coordinated approach between experts working with both targeted and HRMS-based approaches, and the synthesis of novel standards by manufacturers for individual chemicals and their metabolites in order to provide accurate and robust measurements of the newly identified chemicals at the population level.

*Abbreviations: CSF: cerebrospinal fluid; HRMS: high resolution mass spectrometry; MS/MS: tandem mass spectrometry.*

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466

467 **References**

- 468 1. Livingston, G. *et al.* Dementia prevention, intervention, and care: 2020 report of the Lancet  
469 Commission. *The Lancet* **396**, 413–446 (2020).
- 470 2. Ascherio, A. & Schwarzschild, M. A. The epidemiology of Parkinson’s disease: risk factors and  
471 prevention. *Lancet Neurol* **15**, 1257–1272 (2016).
- 472 3. Schneider, L. A resurrection of aducanumab for Alzheimer’s disease. *The Lancet Neurology* **19**,  
473 111–112 (2020).
- 474 4. van Dyck, C. H. *et al.* Lecanemab in Early Alzheimer’s Disease. *New England Journal of Medicine*  
475 **388**, 9–21 (2023).
- 476 5. Gan, L., Cookson, M. R., Petrucelli, L. & La Spada, A. R. Converging pathways in  
477 neurodegeneration, from genetics to mechanisms. *Nat Neurosci* **21**, 1300–1309 (2018).
- 478 6. Nussbaum, R. L. & Ellis, C. E. Alzheimer’s Disease and Parkinson’s Disease. *New England Journal*  
479 *of Medicine* **348**, 1356–1364 (2003).
- 480 7. Kunkle, B. W. *et al.* Genetic meta-analysis of diagnosed Alzheimer’s disease identifies new risk  
481 loci and implicates A $\beta$ , tau, immunity and lipid processing. *Nature Genetics* **51**, 414 (2019).
- 482 8. Keller, M. F. *et al.* Using genome-wide complex trait analysis to quantify ‘missing heritability’ in  
483 Parkinson’s disease. *Human Molecular Genetics* **21**, 4996–5009 (2012).
- 484 9. Rappaport, S. M. Genetic Factors Are Not the Major Causes of Chronic Diseases. *PLOS ONE* **11**,  
485 e0154387 (2016).
- 486 10. *Effects of Pesticides on Health – New Data.* (INSERM, EDP Sciences, 2022). doi:10.1051/978-2-  
487 7598-2721-3.
- 488 11. Goldman, S. M. *et al.* Risk of Parkinson Disease Among Service Members at Marine Corps Base  
489 Camp Lejeune. *JAMA Neurology* (2023) doi:10.1001/jamaneurol.2023.1168.
- 490 12. Landrigan, P. J. *et al.* The Lancet Commission on pollution and health. *The Lancet* **391**, 462–512  
491 (2018).
- 492 13. Jokanović, M., Oleksak, P. & Kuca, K. Multiple neurological effects associated with exposure to  
493 organophosphorus pesticides in man. *Toxicology* **484**, 153407 (2023).
- 494 14. Woodruff, T. J., Zota, A. R. & Schwartz, J. M. Environmental chemicals in pregnant women in the  
495 United States: NHANES 2003-2004. *Environ Health Perspect* **119**, 878–885 (2011).
- 496 15. Govarts, E. *et al.* Harmonized human biomonitoring in European children, teenagers and adults:  
497 EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies  
498 (2014–2021). *International Journal of Hygiene and Environmental Health* **249**, 114119 (2023).
- 499 16. Wild, C. P. Complementing the Genome with an “Exposome”: The Outstanding Challenge of  
500 Environmental Exposure Measurement in Molecular Epidemiology. *Cancer Epidemiol Biomarkers*  
501 *Prev* **14**, 1847–1850 (2005).
- 502 17. Gunnarsson, L.-G. & Bodin, L. Occupational Exposures and Neurodegenerative Diseases-A  
503 Systematic Literature Review and Meta-Analyses. *Int J Environ Res Public Health* **16**, E337 (2019).
- 504 18. Brouwer, M. *et al.* Environmental exposure to pesticides and the risk of Parkinson’s disease in  
505 the Netherlands. *Environment International* **107**, 100–110 (2017).
- 506 19. Paul, K. C. *et al.* A pesticide and iPSC dopaminergic neuron screen identifies and classifies  
507 Parkinson-relevant pesticides. *Nat Commun* **14**, 2803 (2023).
- 508 20. Richardson, J. R. *et al.* Elevated Serum Pesticide Levels and Risk for Alzheimer Disease. *JAMA*  
509 *Neurology* **71**, 284–290 (2014).
- 510 21. Ross, G. W. *et al.* Association of brain heptachlor epoxide and other organochlorine compounds  
511 with lewy pathology. *Movement Disorders* **34**, 228–235 (2019).
- 512 22. Weisskopf, M. G. *et al.* Persistent organochlorine pesticides in serum and risk of Parkinson  
513 disease. *Neurology* **74**, 1055–1061 (2010).
- 514 23. Medehouenou, T. C. M. *et al.* Exposure to polychlorinated biphenyls and organochlorine  
515 pesticides and risk of dementia, Alzheimer’s disease and cognitive decline in an older population:  
516 a prospective analysis from the Canadian Study of Health and Aging. *Environmental Health* **18**, 57  
517 (2019).

- 518 24. Cicero, C. E. *et al.* Metals and neurodegenerative diseases. A systematic review. *Environmental*  
519 *Research* **159**, 82–94 (2017).
- 520 25. Zhao, Y., Ray, A., Portengen, L., Vermeulen, R. & Peters, S. Metal exposure and risk of Parkinson's  
521 disease: a systematic review and meta-analysis. *Am J Epidemiol* kwad082 (2023)  
522 doi:10.1093/aje/kwad082.
- 523 26. Goldman, S. M. *et al.* Solvent exposures and Parkinson disease risk in twins. *Ann Neurol* **71**, 776–  
524 784 (2012).
- 525 27. Nielsen, S. S. *et al.* Solvent exposed occupations and risk of Parkinson disease in Finland. *Clin*  
526 *Park Relat Disord* **4**, 100092 (2021).
- 527 28. Koeman, T. *et al.* Occupational exposures and risk of dementia-related mortality in the  
528 prospective Netherlands Cohort Study. *American Journal of Industrial Medicine* **58**, 625–635  
529 (2015).
- 530 29. Letellier, N. *et al.* Association between occupational solvent exposure and cognitive performance  
531 in the French CONSTANCES study. *Occup Environ Med* **77**, 223–230 (2020).
- 532 30. Hu, C.-Y. *et al.* Association between ambient air pollution and Parkinson's disease: Systematic  
533 review and meta-analysis. *Environ Res* **168**, 448–459 (2019).
- 534 31. Gong, Y. *et al.* Global ambient particulate matter pollution and neurodegenerative disorders: a  
535 systematic review of literature and meta-analysis. *Environ Sci Pollut Res* **30**, 39418–39430 (2023).
- 536 32. Weuve, J. *et al.* Exposure to Air Pollution in Relation to Risk of Dementia and Related Outcomes:  
537 An Updated Systematic Review of the Epidemiological Literature. *Environmental Health*  
538 *Perspectives* **129**, 096001 (2021).
- 539 33. Best, E. A., Juarez-Colunga, E., James, K., LeBlanc, W. G. & Serdar, B. Biomarkers of Exposure to  
540 Polycyclic Aromatic Hydrocarbons and Cognitive Function among Elderly in the United States  
541 (National Health and Nutrition Examination Survey: 2001–2002). *PLOS ONE* **11**, e0147632 (2016).
- 542 34. Park, S. K., Ding, N. & Han, D. Perfluoroalkyl substances and cognitive function in older adults:  
543 Should we consider non-monotonic dose-responses and chronic kidney disease? *Environ Res*  
544 **192**, 110346 (2021).
- 545 35. Weng, X. *et al.* Association between mixed exposure of phthalates and cognitive function among  
546 the U.S. elderly from NHANES 2011–2014: Three statistical models. *Science of The Total*  
547 *Environment* **828**, 154362 (2022).
- 548 36. Shi, Y. *et al.* Association between exposure to phenols and parabens and cognitive function in  
549 older adults in the United States: A cross-sectional study. *Science of The Total Environment* **858**,  
550 160129 (2023).
- 551 37. Rock, K. D. & Patisaul, H. B. Environmental Mechanisms of Neurodevelopmental Toxicity. *Curr*  
552 *Environ Health Rep* **5**, 145–157 (2018).
- 553 38. Vrijheid, M., Casas, M., Gascon, M., Valvi, D. & Nieuwenhuijsen, M. Environmental pollutants and  
554 child health—A review of recent concerns. *International Journal of Hygiene and Environmental*  
555 *Health* **219**, 331–342 (2016).
- 556 39. Modgil, S., Lahiri, D. K., Sharma, V. L. & Anand, A. Role of early life exposure and environment on  
557 neurodegeneration: implications on brain disorders. *Transl Neurodegener* **3**, 9 (2014).
- 558 40. Tanner, C. M., Goldman, S. M., Ross, G. W. & Grate, S. J. The disease intersection of susceptibility  
559 and exposure: chemical exposures and neurodegenerative disease risk. *Alzheimers Dement* **10**,  
560 S213–225 (2014).
- 561 41. Shi, J.-Q. *et al.* NLRP3 Inflammasome: A Potential Therapeutic Target in Fine Particulate Matter-  
562 Induced Neuroinflammation in Alzheimer's Disease. *J Alzheimers Dis* **77**, 923–934 (2020).
- 563 42. Cresto, N. *et al.* Pesticides at brain borders: Impact on the blood-brain barrier,  
564 neuroinflammation, and neurological risk trajectories. *Chemosphere* **324**, 138251 (2023).
- 565 43. Nougadère, A. *et al.* Total diet study on pesticide residues in France: Levels in food as consumed  
566 and chronic dietary risk to consumers. *Environment International* **45**, 135–150 (2012).
- 567 44. Turusov, V., Rakitsky, V. & Tomatis, L. Dichlorodiphenyltrichloroethane (DDT): ubiquity,  
568 persistence, and risks. *Environmental Health Perspectives* **110**, 125–128 (2002).



- 569 45. Costas-Ferreira, C. & Faro, L. R. F. Neurotoxic Effects of Neonicotinoids on Mammals: What Is  
570 There beyond the Activation of Nicotinic Acetylcholine Receptors?—A Systematic Review.  
571 *International Journal of Molecular Sciences* **22**, 8413 (2021).
- 572 46. Andersen, H. R. *et al.* Pyrethroids and developmental neurotoxicity - A critical review of  
573 epidemiological studies and supporting mechanistic evidence. *Environmental Research* **214**,  
574 113935 (2022).
- 575 47. Wan, F. *et al.* The pyrethroids metabolite 3-phenoxybenzoic acid induces dopaminergic  
576 degeneration. *Sci Total Environ* **838**, 156027 (2022).
- 577 48. Jiao, Z., Wu, Y. & Qu, S. Fenpropathrin induces degeneration of dopaminergic neurons via  
578 disruption of the mitochondrial quality control system. *Cell Death Discov* **6**, 78 (2020).
- 579 49. Loser, D. *et al.* Functional alterations by a subgroup of neonicotinoid pesticides in human  
580 dopaminergic neurons. *Arch Toxicol* **95**, 2081–2107 (2021).
- 581 50. Gan, W., Manning, K. J., Cleary, E. G., Fortinsky, R. H. & Brugge, D. Exposure to ultrafine particles  
582 and cognitive decline among older people in the United States. *Environ Res* **227**, 115768 (2023).
- 583 51. Oberdörster, G., Elder, A. & Rinderknecht, A. Nanoparticles and the Brain: Cause for Concern? *J*  
584 *Nanosci Nanotechnol* **9**, 4996–5007 (2009).
- 585 52. Prüst, M., Meijer, J. & Westerink, R. H. S. The plastic brain: neurotoxicity of micro- and  
586 nanoplastics. *Part Fibre Toxicol* **17**, 24 (2020).
- 587 53. Shan, S., Zhang, Y., Zhao, H., Zeng, T. & Zhao, X. Polystyrene nanoplastics penetrate across the  
588 blood-brain barrier and induce activation of microglia in the brain of mice. *Chemosphere* **298**,  
589 134261 (2022).
- 590 54. Cryan, J. F., O’Riordan, K. J., Sandhu, K., Peterson, V. & Dinan, T. G. The gut microbiome in  
591 neurological disorders. *Lancet Neurol* **19**, 179–194 (2020).
- 592 55. Connell, E. *et al.* Microbial-derived metabolites as a risk factor of age-related cognitive decline  
593 and dementia. *Molecular Neurodegeneration* **17**, 43 (2022).
- 594 56. Kelly, G. C., Watase, C. K. & Ho, D. H. Blood-Brain Barrier Function as a Biomarker in Toxicology:  
595 Impact of Environmental Toxicants. in *Biomarkers in Toxicology* (eds. Patel, V. B., Preedy, V. R. &  
596 Rajendram, R.) 1–25 (Springer International Publishing, Cham, 2022). doi:10.1007/978-3-030-  
597 87225-0\_36-1.
- 598 57. Nicholson, S., Baccarelli, A. & Prada, D. Role of brain extracellular vesicles in air pollution-related  
599 cognitive impairment and neurodegeneration. *Environmental Research* **204**, 112316 (2022).
- 600 58. Ardeshir, R. A., Zolgharnein, H., Movahedinia, A., Salamat, N. & Zabihi, E. Comparison of  
601 waterborne and intraperitoneal exposure to fipronil in the Caspian white fish (*Rutilus frisii*) on  
602 acute toxicity and histopathology. *Toxicology Reports* **4**, 348–357 (2017).
- 603 59. Meijer, M., Hamers, T. & Westerink, R. H. S. Acute disturbance of calcium homeostasis in PC12  
604 cells as a novel mechanism of action for (sub)micromolar concentrations of organophosphate  
605 insecticides. *Neurotoxicology* **43**, 110–116 (2014).
- 606 60. Loser, D. *et al.* Acute effects of the imidacloprid metabolite desnitro-imidacloprid on human  
607 nACh receptors relevant for neuronal signaling. *Arch Toxicol* **95**, 3695–3716 (2021).
- 608 61. OECD. *Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals*.  
609 (OECD, 2018). doi:10.1787/ceca15a9-en.
- 610 62. Ashok, A., Rai, N. K., Tripathi, S. & Bandyopadhyay, S. Exposure to As-, Cd-, and Pb-mixture  
611 induces A $\beta$ , amyloidogenic APP processing and cognitive impairments via oxidative stress-  
612 dependent neuroinflammation in young rats. *Toxicol Sci* **143**, 64–80 (2015).
- 613 63. Fitzgerald, E. F. *et al.* Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs)  
614 and neuropsychological status among older adults in New York. *Neurotoxicology* **33**, 8–15 (2012).
- 615 64. Xu, M.-Y., Wang, P., Sun, Y.-J., Yang, L. & Wu, Y.-J. Joint toxicity of chlorpyrifos and cadmium on  
616 the oxidative stress and mitochondrial damage in neuronal cells. *Food Chem Toxicol* **103**, 246–  
617 252 (2017).
- 618 65. Yoon, J. *et al.* Urinary Phthalate Metabolites and Slow Walking Speed in the Korean Elderly  
619 Environmental Panel II Study. *Environ Health Perspect* **131**, 47005 (2023).

- 620 66. David, A. *et al.* Towards a comprehensive characterisation of the human internal chemical  
621 exposome: Challenges and perspectives. *Environment International* **156**, 106630 (2021).
- 622 67. Orešič, M. *et al.* Metabolome in progression to Alzheimer's disease. *Translational Psychiatry* **1**,  
623 tp201155 (2011).
- 624 68. Varma, V. R. *et al.* Brain and blood metabolite signatures of pathology and progression in  
625 Alzheimer disease: A targeted metabolomics study. *PLoS Med.* **15**, e1002482 (2018).
- 626 69. Arnold, M. *et al.* Sex and APOE  $\epsilon$ 4 genotype modify the Alzheimer's disease serum metabolome.  
627 *Nat Commun* **11**, 1148 (2020).
- 628 70. Agin, A. *et al.* Environmental exposure to phthalates and dementia with Lewy bodies:  
629 contribution of metabolomics. *J Neurol Neurosurg Psychiatry* **91**, 968–974 (2020).
- 630 71. Chang, C.-W. *et al.* Monitoring long-term chemical exposome by characterizing the hair  
631 metabolome using a high-resolution mass spectrometry-based suspect screening approach.  
632 *Chemosphere* **332**, 138864 (2023).
- 633 72. Niedzwiecki, M. M. *et al.* High-resolution metabolomic profiling of Alzheimer's disease in plasma.  
634 *Annals of Clinical and Translational Neurology* **7**, 36–45 (2020).
- 635 73. Huber, C. *et al.* A large scale multi-laboratory suspect screening of pesticide metabolites in  
636 human biomonitoring: From tentative annotations to verified occurrences. *Environment*  
637 *International* **168**, 107452 (2022).
- 638 74. Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M. R. & Sadeghi, M. Toxic Mechanisms of  
639 Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Frontiers in Pharmacology*  
640 **12**, (2021).
- 641 75. Eid, A. *et al.* Effects of DDT on Amyloid Precursor Protein Levels and Amyloid Beta Pathology:  
642 Mechanistic Links to Alzheimer's Disease Risk. *Environ Health Perspect* **130**, 87005 (2022).
- 643 76. Oyovwi, M. O. *et al.* Repeated endosulfan exposure induces changes in neurochemicals,  
644 decreases ATPase transmembrane ionic-pumps, and increased oxidative/nitrosative stress in the  
645 brains of rats: Reversal by quercetin. *Pestic Biochem Physiol* **175**, 104833 (2021).
- 646 77. Fernandes, L. S. *et al.* In vitro study of the neuropathic potential of the organophosphorus  
647 compounds trichlorfon and acephate. *Toxicol In Vitro* **29**, 522–528 (2015).
- 648 78. Taillebois, E., Cartereau, A., Jones, A. K. & Thany, S. H. Neonicotinoid insecticides mode of action  
649 on insect nicotinic acetylcholine receptors using binding studies. *Pesticide Biochemistry and*  
650 *Physiology* **151**, 59–66 (2018).
- 651 79. Farder-Gomes, C. F. *et al.* Harmful effects of fipronil exposure on the behavior and brain of the  
652 stingless bee *Partamona helleri* Friese (Hymenoptera: Meliponini). *Science of The Total*  
653 *Environment* **794**, 148678 (2021).
- 654 80. Hernández-Plata, I., Giordano, M., Díaz-Muñoz, M. & Rodríguez, V. M. The herbicide glyphosate  
655 causes behavioral changes and alterations in dopaminergic markers in male Sprague-Dawley rat.  
656 *Neurotoxicology* **46**, 79–91 (2015).
- 657 81. Liu, C. *et al.* Exposure to the environmentally toxic pesticide maneb induces Parkinson's disease-  
658 like neurotoxicity in mice: A combined proteomic and metabolomic analysis. *Chemosphere* **308**,  
659 136344 (2022).
- 660 82. Soares, M. V. *et al.* Neurotoxicity induced by toluene: In silico and in vivo evidences of  
661 mitochondrial dysfunction and dopaminergic neurodegeneration. *Environ Pollut* **298**, 118856  
662 (2022).
- 663 83. Wang, Y. *et al.* Exposure to PM2.5 aggravates Parkinson's disease via inhibition of autophagy and  
664 mitophagy pathway. *Toxicology* **456**, 152770 (2021).
- 665 84. Miyazaki, W., Fujiwara, Y. & Katoh, T. The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the  
666 development and function of the blood–brain barrier. *NeuroToxicology* **52**, 64–71 (2016).
- 667 85. Xia, Y. *et al.* Effects of subchronic exposure to benzo[a]pyrene (B[a]P) on learning and memory,  
668 and neurotransmitters in male Sprague–Dawley rat. *NeuroToxicology* **32**, 188–198 (2011).
- 669 86. Park, E.-J. *et al.* Whole Cigarette Smoke Condensates Induce Accumulation of Amyloid Beta  
670 Precursor Protein with Oxidative Stress in Murine Astrocytes. *Toxics* **9**, 150 (2021).

- 671 87. Ono, K., Hasegawa, K., Yamada, M. & Naiki, H. Nicotine breaks down preformed Alzheimer's  
672 beta-amyloid fibrils in vitro. *Biol Psychiatry* **52**, 880–886 (2002).
- 673 88. Costa, L. G., Pellacani, C., Dao, K., Kavanagh, T. J. & Roque, P. J. The brominated flame retardant  
674 BDE-47 causes oxidative stress and apoptotic cell death in vitro and in vivo in mice.  
675 *Neurotoxicology* **48**, 68–76 (2015).
- 676 89. Moyano, P. *et al.* Bisphenol A single and repeated treatment increases HDAC2, leading to  
677 cholinergic neurotransmission dysfunction and SN56 cholinergic apoptotic cell death through  
678 AChE variants overexpression and NGF/TrkA/P75NTR signaling disruption. *Food Chem Toxicol*  
679 **157**, 112614 (2021).
- 680 90. Huang, W. *et al.* Effects of di-(2-ethylhexyl) phthalate (DEHP) on behavior and dopamine  
681 signaling in zebrafish (*Danio rerio*). *Environ Toxicol Pharmacol* **93**, 103885 (2022).
- 682 91. Yu, Y. *et al.* Perfluorooctane sulfonate disrupts the blood brain barrier through the crosstalk  
683 between endothelial cells and astrocytes in mice. *Environmental Pollution* **256**, 113429 (2020).
- 684 92. Paul, K. C., Horvath, S., Del Rosario, I., Bronstein, J. M. & Ritz, B. DNA methylation biomarker for  
685 cumulative lead exposure is associated with Parkinson's disease. *Clin Epigenetics* **13**, 59 (2021).
- 686 93. Farooqui, Z. *et al.* Associations of cumulative Pb exposure and longitudinal changes in Mini-  
687 Mental Status Exam scores, global cognition and domains of cognition: The VA Normative Aging  
688 Study. *Environmental Research* **152**, 102–108 (2017).
- 689 94. Liu, W., Wang, B., Xiao, Y., Wang, D. & Chen, W. Secondhand smoking and neurological disease: a  
690 meta-analysis of cohort studies. *Reviews on Environmental Health* **36**, 271–277 (2021).
- 691 95. Ames, J. *et al.* Neurocognitive and physical functioning in the Seveso Women's Health Study.  
692 *Environ Res* **162**, 55–62 (2018).
- 693 96. Raffetti, E. *et al.* Polychlorinated biphenyls (PCBs) and risk of dementia and Parkinson disease: A  
694 population-based cohort study in a North Italian highly polluted area. *Chemosphere* **261**, 127522  
695 (2020).
- 696 97. Zhao, Y. *et al.* Association between organophosphorus flame retardants exposure and cognitive  
697 impairment among elderly population in southern China. *Sci Total Environ* 157763 (2022)  
698 doi:10.1016/j.scitotenv.2022.157763.
- 699 98. Mastrantonio, M. *et al.* Drinking water contamination from perfluoroalkyl substances (PFAS): an  
700 ecological mortality study in the Veneto Region, Italy. *Eur J Public Health* **28**, 180–185 (2018).
- 701 99. Dührkop, K. *et al.* SIRIUS 4: a rapid tool for turning tandem mass spectra into metabolite  
702 structure information. *Nat Methods* **16**, 299–302 (2019).
- 703 100. Quinn, R. A. *et al.* Molecular Networking As a Drug Discovery, Drug Metabolism, and  
704 Precision Medicine Strategy. *Trends Pharmacol Sci* **38**, 143–154 (2017).
- 705  
706

# A. CHEMICALS IN MODERN LIFE

## Actively Used Chemicals



Metal Trace Elements



Pesticides — POP



Insecticides



Fungicides



Herbicides



Organic solvents

## Chemicals Emitted from Combustion



PM 2.5  
Gases



Dioxins — POP  
Polycyclic Aromatic  
Hydrocarbons



Cigarette smoke

## Chemicals Added to Products



PCBs — POP

Brominated FR — POP  
Organophosphate FR



Long-chain PFAS — POP  
Short-chain PFAS



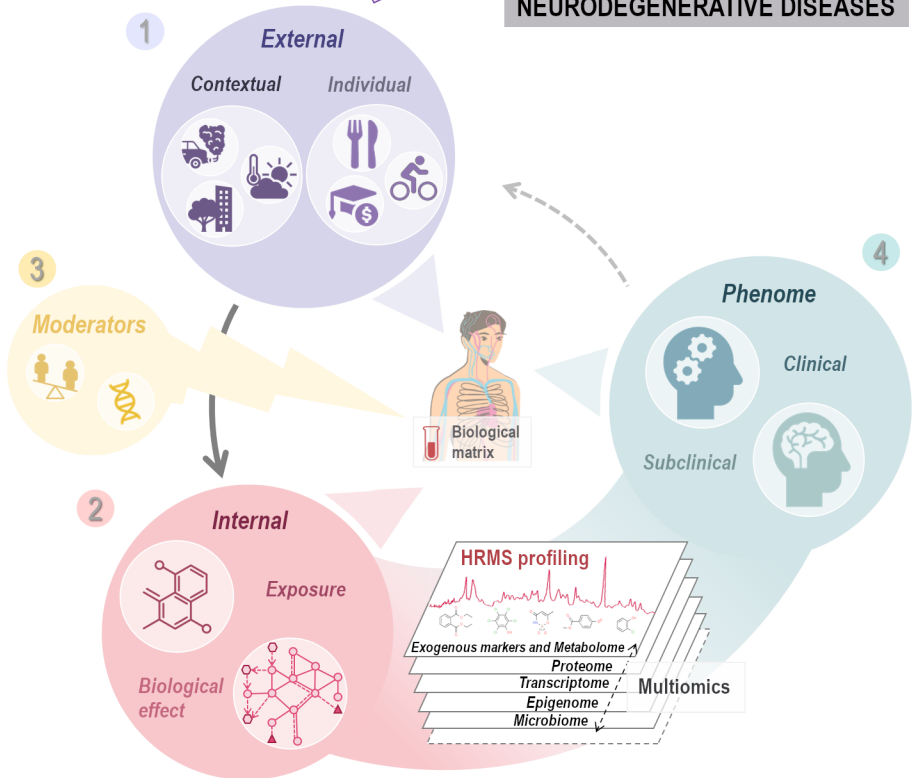
Bisphenols, phthalates

Food / cosmetics additives

## Chemical environment

(air, water, soil,  
dust, food...)

# B. THE EXPOSOME OF NEURODEGENERATIVE DISEASES



**Misfolded protein aggregation**

- POP Pesticides
- Insecticides
- Cigarette smoke

β-amyloid plaques

tau tangles

α-synuclein aggregates

**Impaired autophagy-lysosome pathway**

- PM 2.5

**Neurovascular dysfunction  
BBB permeability**

- POP Dioxins
- POP Long-chain PFAS

**Mitochondrial dysfunction**

- Metal Trace Elements
- Fungicides
- POP Pesticides
- Insecticides
- Organic solvents

neuron

ROS

astrocyte

ROS

**Oxidative stress**

- Metal Trace Elements
- POP Pesticides
- Insecticides
- Fungicides
- Cigarette smoke
- PM 2.5
- PAH
- Bisphenols, phthalates
- Food / cosmetics additives
- POP Long-chain PFAS
- POP PCBs
- Organophosphate FR

Ca<sup>2+</sup>

**Ca<sup>2+</sup> dyshomeostasis**

- Insecticides

**Disruption of neurotransmission**

- POP Pesticides
- Insecticides
- Herbicides
- Fungicides
- Organic solvents
- Cigarette smoke
- PAHs
- POP Dioxins
- POP Brominated FR
- POP Long-chain PFAS
- Food / cosmetics additives

microglia

Cytokines

ROS

**Glial cell activation  
Neuroinflammation**

- Cigarette smoke
- PM 2.5
- POP Pesticides
- Insecticides
- POP Dioxins

- ≥10 studies
- [5-10] studies
- <5 studies but among the main pathways studied for the chemical category