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1 Perspective

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

4

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22

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.

34

35 **Text**

36 With increasing longevity, age-related neurodegenerative diseases have become major causes of
37 disability and mortality^{1,2}. 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^{3,4}. Despite their diverse clinical manifestations,
46 neurodegenerative diseases share common mechanisms⁵. Misfolded protein aggregation in specific
47 brain areas (β -amyloid and tau in AD and α -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 mechanisms⁵. 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 factors⁶. 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 burden⁷⁻⁹. 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,¹ while the level of current evidence
62 with pesticide exposure is moderate¹⁰. 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^{2,10,11}. 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.¹² 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_{2.5}), 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 effects¹³.

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 chemicals¹⁴. 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 individuals¹⁵. Both US and
110 EU initiatives highlight disparities in human exposure due to geographical specificities or
111 socioeconomic factors^{14,15}. 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 lifetime¹⁶. 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^{10,17}. Hence, increased risk among pesticide users were estimated at 50% for AD
138 and >65% for PD¹⁷, 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 risk¹⁰. 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 studies¹⁸⁻²³. Progress in modelling ambient air exposure in the vicinity
144 of fields enabled pesticide-wide association studies in PD¹⁹. 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 controls²⁰, and twice more
148 Lewy pathology were reported in the presence of the organochlorine insecticide heptachlor epoxide
149 in brain tissue donors²¹.

150 Metals have been widely investigated through biomarkers, mostly in case-control studies^{24,25},
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^{24,25}. Solvent exposure was also suggested to play a role in PD and AD in
154 occupational settings²⁶⁻²⁹, 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^{11,19}.

159 Among ubiquitous pollutants in the general population, the strongest epidemiological evidence so far
160 has been obtained with PM_{2.5} level in ambient air³⁰⁻³². Each increase in PM_{2.5} air concentration of 10
161 µg/m³ (US EPA annual standard) may increase the risk of all-cause dementia, AD and PD by
162 approximately 30%, 65% and 15%, respectively³¹. 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 function³³⁻³⁶. 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 stressors³⁷. Human studies identified a potential role of
170 lead, PCBs and air pollution in attention-deficit hyperactivity disorder and autism in children³⁸.
171 Moreover, preclinical studies have shown that exposure to various chemical stressors during *in-utero*
172 and postnatal periods promote neurodegeneration in adulthood³⁹. 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 families⁴⁰. 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_{2.5}^{41,42}.
186 Research also suggests potential pleiotropic effects on multiple neurodegenerative pathways for

187 non-persistent insecticides such as organophosphate pesticides, pyrethroids and neonicotinoids⁴²,
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 foods⁴³. Furthermore, toxicology and
195 neuroepidemiology have investigated relatively few molecules, many of them being already
196 restricted⁴⁴, 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 species⁴⁵,
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 organisms⁴⁶. 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 organisms⁴⁵⁻⁴⁹. 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_{2.5}) in
213 neurodegenerative diseases³¹, less is known about smaller particles⁵⁰, 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 neurotoxicity⁵¹⁻⁵³. 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^{54,55}. 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 biotarget⁵⁶. 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 emerging⁵⁷. 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 life⁵⁸. 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 chlorpyrifos⁵⁹, desnitroimidacloprid and
242 imidacloprid⁶⁰. 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 health⁶¹. 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 individually⁶². In
270 humans, higher circulating polybrominated diphenyl ethers (PBDEs) were associated with impaired
271 memory only in adults with high serum PCBs levels⁶³, 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 modification⁶⁴. 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^{35,36,63,65}. 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 diseases⁶⁶.

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 microbiota⁶⁶. 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).⁶⁶

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^{67–69}. 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^{70–72}. 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 AD⁷⁰. 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 phthalates⁷¹. In
332 another study, an unknown halogen-containing compound was found increased in the plasma of AD
333 cases compared to controls⁷². 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 HRMS⁷³ 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.

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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 epidemiology¹⁶. **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)^{24,74}. **POP pesticides** (largely represented by organochlorine insecticides in the literature; purple square) affect a broad range of
416 pathways, including misfolded (amyloid- β) protein aggregation⁷⁵; yet most studied pathways attributed to these compounds include
417 disruption of neurotransmitter systems (norepinephrine, dopamine, GABA, glutamate) and oxidative stress⁷⁶. **Other insecticides** have also
418 been predominantly involved in the disruption of the cholinergic system, in particular organophosphates (to a lesser extent carbamates)⁷⁷
419 and neonicotinoids⁶⁰. 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)^{49,59} oxidative stress (for the pyrazole fipronil)⁷⁹, α -synuclein aggregation⁴⁷ and mitochondrial
422 dysfunction⁴⁸ (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 disruption⁸⁰ and mitochondrial dysfunction⁸¹
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 neurotoxicity⁸². **Combustion pollutants** (PM2.5,
427 cigarette smoke, PAHs, dioxins; grey squares) have been largely implicated in the promotion of neuroinflammation and oxidative stress⁴¹,
428 albeit specific chemicals may be involved in other specific pathways. **PM2.5** impair the lysosomal function and autophagic flux⁸³, **dioxins**
429 disrupt the permeability of the BBB⁸⁴ and the **PAH** benzo(a)pyrene and phenanthrene impact neurotransmitter systems (e.g.
430 acetylcholinesterase and dopamine)⁸⁵. **Cigarette smoke** displays contrasting effects on misfolded protein production and accumulation due
431 to the dual exposure to combustion pollutants and nicotine.^{86,87} 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 neurotransmission⁸⁸⁻⁹⁰, although
434 other mechanisms begin to be suggested (e.g. long-chain PFAS may penetrate and disrupt the BBB permeability⁹¹).

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.
Pesticides	Occupational	++	10,17	+	10,17
	Non-occupational	(+)	10,19,21	(+)	10,20,23
Metals	Occupational	+/-*	25	∅	24
	No distinction	+/-**	25,92	+/-***	24,93
Organic solvents	Occupational	+/-	26,27	+/-	28,29
	Non-occupational	∅	11	∅	
PM2.5		+	30,31	++	31,32
Gaseous air pollutants (e.g. NOx)		(+)	30	(+)	32
Second-hand cigarette smoke		(+)	94	(+)	94
Dioxins		∅	95	∅	95
PAHs		∅		∅	33
PCBs		∅	22,96	+/-	23,96
Flame retardants		∅		∅	63,97
Long-chain PFAS		∅	98	∅	34,98
Bisphenols		∅		∅	36
Phthalates		∅	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 needed⁶⁶. 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 throughput⁶⁶. 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 data⁹⁹. 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 development¹⁰⁰. 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

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- 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



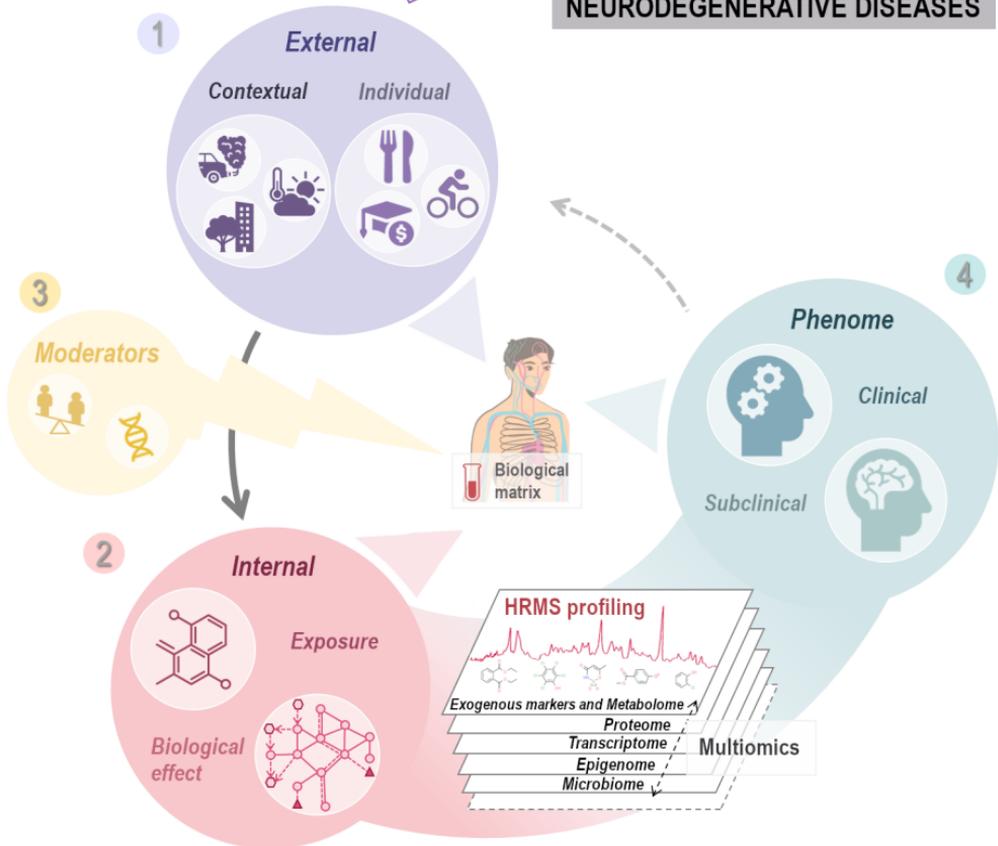
Bisphenols, phthalates

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

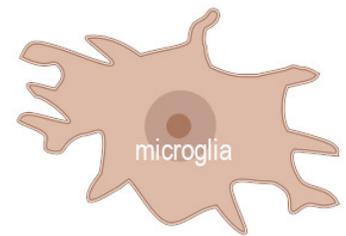
Mitochondrial dysfunction

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

neuron



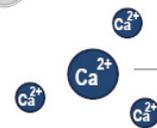
astrocyte



microglia

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



Ca²⁺ dyshomeostasis

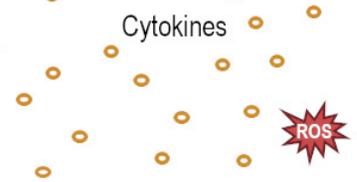
- Insecticides

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

**Glial cell activation
Neuroinflammation**

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



Cytokines

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