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Perspective

Assessing the contribution of the chemical exposome to neurodegenerative disease

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Abstract

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

Text

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

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

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

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

Our chemical environment in the Anthropocene

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

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

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

The exposome concept

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

Chemical stressors and neurodegenerative diseases

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

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

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

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

Vulnerability of neurodegeneration-related mechanisms to chemical toxicity. The brain is highly vulnerable to the toxicity of environmental stressors[37]. Human studies identified a potential role of lead, PCBs and air pollution in attention-deficit hyperactivity disorder and autism in children[38]. Moreover, preclinical studies have shown that exposure to various chemical stressors during *in-utero* and postnatal periods promote neurodegeneration in adulthood[39]. However, brain vulnerability to chemicals is not limited to the developmental period and aging increases vulnerability to chemical neurotoxicity, owing to the multiple age-related alterations at play in the brain (e.g., atrophy, decrease in blood flow and metabolism, BBB leakage), which increase its sensitivity to xenobiotics and reduce its capacity to compensate for impairment. Furthermore, experimental studies have documented the impact of chemical stressors on main neurodegenerative pathways (**Figure 2**), with large heterogeneity in the amount of literature across chemical families[40]. Metals, pesticides, organic solvents, and combustion pollutants have been most extensively studied, while research on synthetic additive chemicals such as FRs and plastic-related endocrine-disrupting compounds is only emerging. In all chemical classes, general neurotoxic pathways such as oxidative stress, mitochondrial dysfunction, and disruption of neurotransmission have been the most investigated so far. Yet the impact of certain pollutants on pathways specific of neurodegenerative diseases (misfolded protein aggregation) and on key associated mechanisms is also emerging in the literature, especially neuroinflammation which appears affected by widespread pollutants such as airborne PM2.5[41,42]. Research also suggests potential pleiotropic effects on multiple neurodegenerative pathways for

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non-persistent insecticides such as organophosphate pesticides, pyrethroids and neonicotinoids[42], thus raising increasing concern in the scientific community.

Gaps in science and unmet challenges to study the impact of chemicals on neurodegenerative diseases

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

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

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

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

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

Refining predictive neurotoxicology. The toxicological impact of chemicals depends on various factors, which together determine the kinetics, dynamics and metabolism of compounds. As with other diseases, an incomplete understanding of chemical toxicokinetics clearly impedes our ability to decipher the impact of chemicals on neurodegenerative diseases. Physiologically based pharmacokinetic (PBPK) tools allow to model the distribution of pollutants within an organism by compartmentalizing it (liver, muscle, brain). The overarching aim is to determine exposure levels at which a given chemical which penetrates the body is likely to reach the brain and exert adverse effects – along with deciphering the factors which determine these toxicokinetic and toxicodynamic parameters. This is particularly challenging in neurosciences since the permeability of the BBB is selective and variable according to chemicals.
In addition to PBPK, the development of Adverse Outcome Pathways (AOPs) is expected to strongly support predictive toxicology (https://aopwiki.org/). An AOP describes a sequence of molecular, cellular and organ-level events named key events (KE) which ultimately lead to an adverse outcome such as a neurodegenerative disease. The robustness of an AOP depends on strong experimental and human evidence which validate the sequence of events. If an AOP is robust enough, then it may allow to predict an adverse outcome when a KE is modulated by a chemical. For example, an AOP leading to PD is described at https://aopwiki.org/aops/3. Unfortunately, very few AOPs related to neurodegenerative diseases have been developed so far.

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

Profiling the internal chemical exposome through high-throughput molecular approaches

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

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

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

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

Conclusion

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

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Figures, Tables and Boxes

Figure legend

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

Figure 1A. Chemicals in modern life

Figure 1B. The exposome of neurodegenerative diseases

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

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

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

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

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

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Table 1. Overview of the epidemiological literature on chemical exposures and neurodegenerative 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]	Ø	[24]
	No distinction	+/-**	[25,92]	+/-***	[24,93]
Organic solvents	Occupational	+/-	[26,27]	+/-	[28,29]
	Non-occupational	Ø	[11]	Ø	
PM2.5		+	[30,31]	++	[31,32]
Gaseous air pollutants (e.g. NOx)		(+)	[30]	(+)	[32]
Second-hand cigarette smoke		(+)	[94]	(+)	[94]
Dioxins		Ø	[95]	Ø	[95]
PAHs		Ø		Ø	[33]
PCBs		Ø	[22,96]	+/-	[23,96]
Flame retardants		Ø		Ø	[63,97]
Long-chain PFAS		Ø	[98]	Ø	[34,98]
Bisphenols		Ø		Ø	[36]
Phthalates		Ø	[65]	Ø	[35]

All associations are in the direction of an increased risk of neurodegenerative disease with increased chemical exposure, except for second-hand smoke and Parkinson's Disease (inverse association).
++: high evidence supported by many consistent studies,
+: moderate evidence supported by several consistent studies,
(+): emerging evidence supported by few but consistent studies
+/-: low evidence supported by several inconsistent studies
Ø: insufficient evidence due to very limited number of available studies
*For occupational Mn exposure (i.e., the most convincing occupational metal exposure associated with PD)
**For Pb exposure (i.e., the most convincing metal exposure associated with PD)
***For Pb, Hg, Al and Cu exposures (i.e., the most convincing metal exposures associated with AD)

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

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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[66]. 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[66]. 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[99]. 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[100]. 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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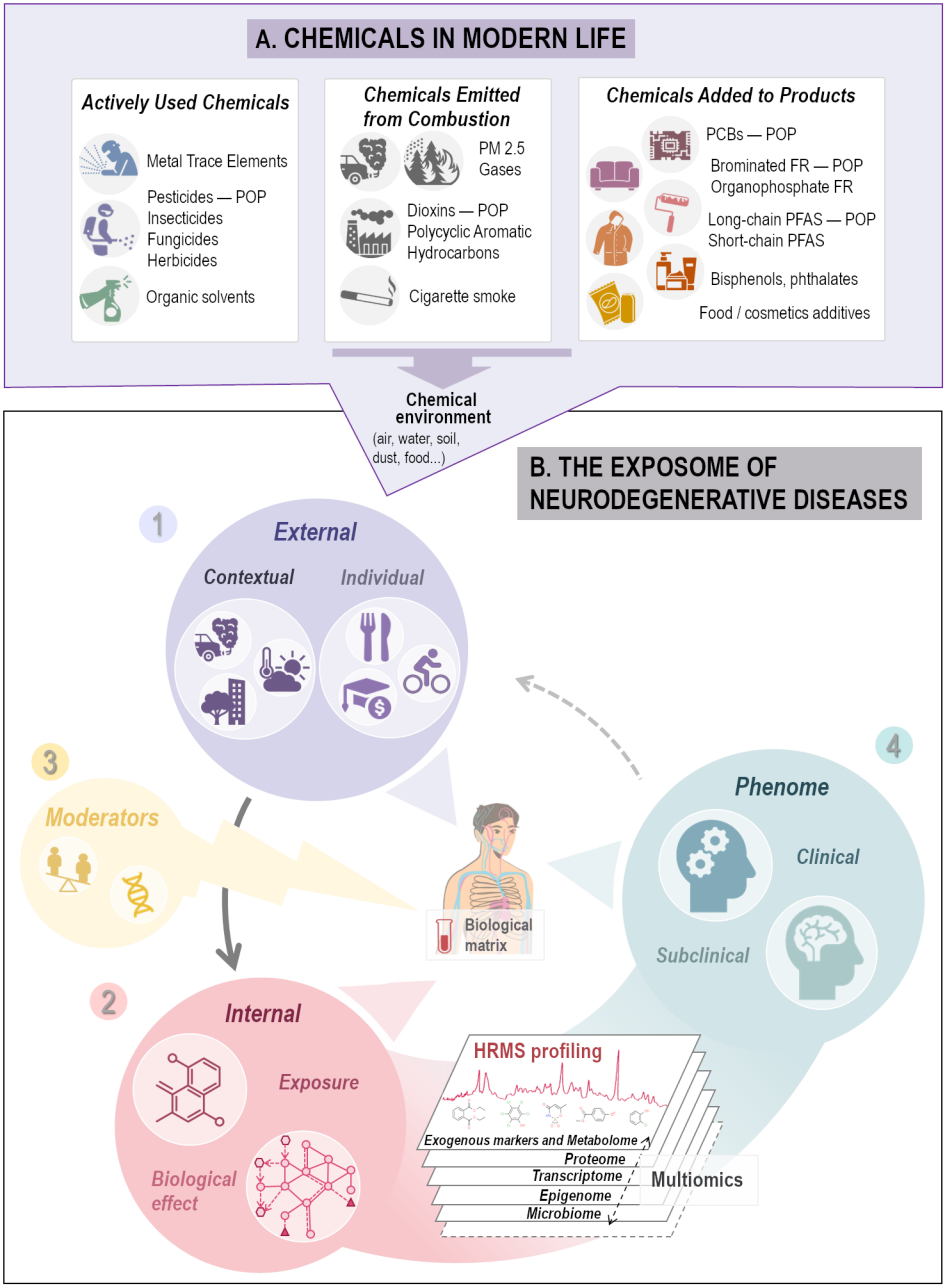
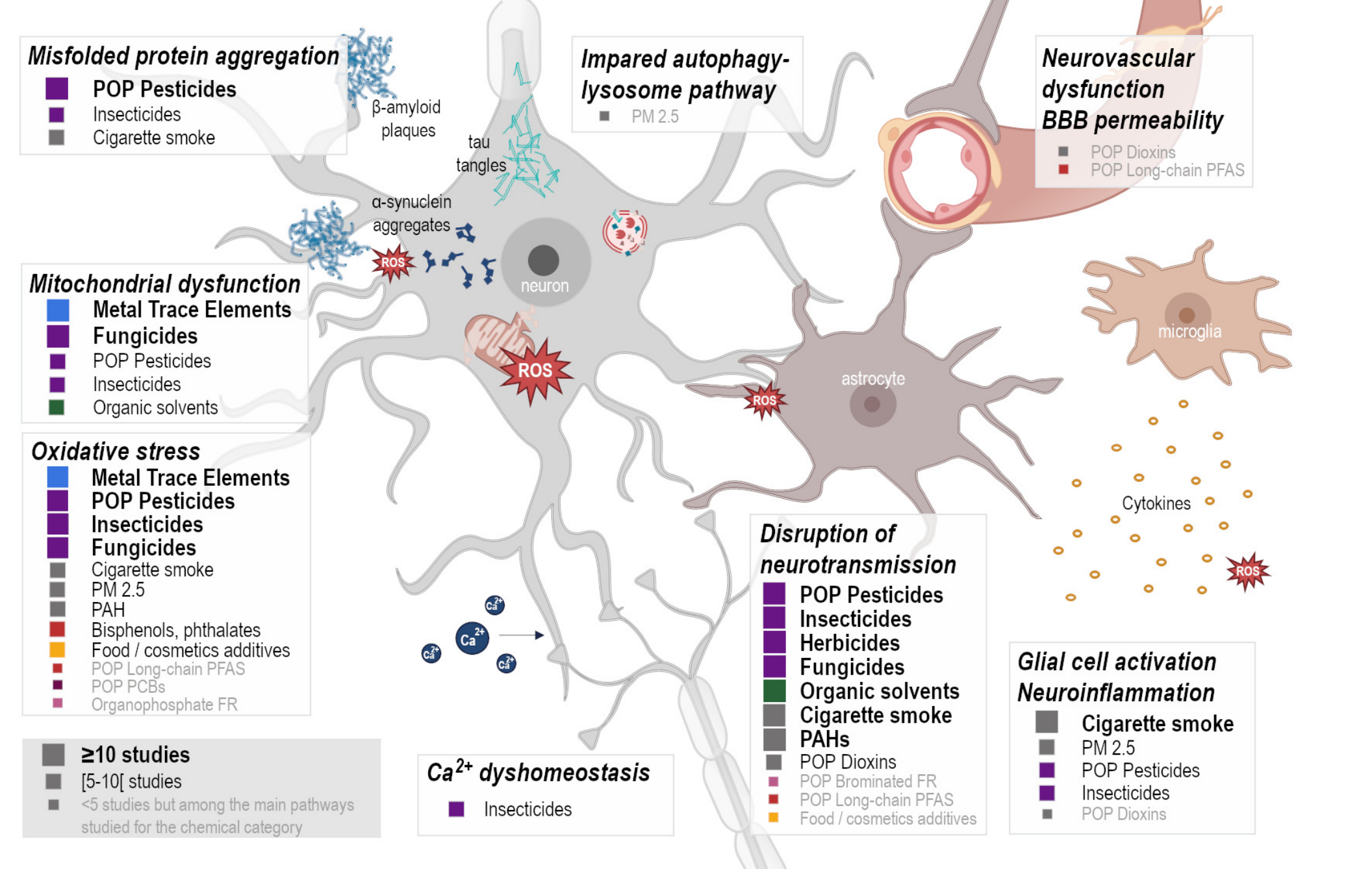

A. CHEMICALS IN MODERN LIFE
Actively Used Chemicals
Metal Trace Elements
Pesticides — POP
Insecticides
Fungicides
Herbicides
Organic solvents
Chemicals Emitted from Combustion
PM 2.5
Gases
Dioxins — POP
Polycyclic Aromatic Hydrocarbons
Cigarette smoke
Chemicals Added to Products
PCBs — POP
Brominated 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
1
External
Contextual
Individual
3
Moderators
Biological matrix
4
Phenome
Clinical
Subclinical
2
Internal
Exposure
Biological effect
HRMS profiling
Exogenous markers and Metabolome
Proteome
Transcriptome
Epigenome
Microbiome
Multiomics


Misfolded protein aggregation
POP Pesticides
Insecticides
Cigarette smoke
β-amyloid plaques
tau tangles
α-synuclein aggregates
Impared autophagy-lysosome pathway
PM 2.5
Neurovascular dysfunction BBB permeability
POP Dioxins
POP Long-chain PFAS
ROS
neuron
Mitochondrial dysfunction
Metal Trace Elements
Fungicides
POP Pesticides
Insecticides
Organic solvents
astrocyte
microglia
Cytokines
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
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
≥10 studies
[5-10[studies
<5 studies but among the main pathways studied for the chemical category
Ca2+ dyshomeostasis
Insecticides