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Role of Environmental Contaminants in the Etiology of Alzheimer's Disease: A Review

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Abstract

Alzheimer's dis ease (AD) is a leading cause of mortality in the developed world with 70% risk attributable to genetics. The remaining 30% of AD risk is hypothesized to include environmental factors and human lifestyle patterns. Environmental factors possibly include inorganic and organic hazards, exposure to toxic metals (aluminium, copper), pesticides (organochlorine and organophosphate insecticides), industrial chemicals (flame retardants) and air pollutants (particulate matter). Long term exposures to these environmental contaminants together with bioaccumulation over an individual's life-time are speculated to induce neuroinflammation and neuropathology paving the way for developing AD. Epidemiologic associations between environmental contaminant exposures and AD are still limited. However, many *in vitro* and animal studies have identified toxic effects of environmental contaminants at the cellular level, revealing alterations of pathways and metabolisms associated with AD that warrant further investigations. This review provides an overview of *in vitro*, animal and epidemiological studies on the etiology of AD, highlighting available data supportive of the long hypothesized link between toxic environmental exposures and development of AD pathology.

Keywords: Adult-onset disease, Alzheimer's disease, endocrine disruptors, environmental contaminants, metals, neuropathology, Parkinson's disease, pesticides, synergistic effects, toxins

BACKGROUND

Today, aging human populations around the globe are facing an epidemic of Alzheimer's disease (AD), with the number of cases estimated to rise to nearly 106 million by 2050 [1]. Now representing the sixth leading cause of death in the United States (Fig. **1**) [2, 3], AD accounts for 60 to 80 percent of

reported cases of dementia [4] and 400,000 deaths in the U.S. alone in 2010 [4]. Human AD pathology is characterized by a progressive decline of cognitive function, memory, and intellectual ability [5] leading to irreversible neurodegenerative impairment. Although being diagnosed mostly as a late-onset disease [6], early onset (at age 40-50 years) AD has been observed in more than 200,000 people in the U.S. [7]. The key mediator of AD pathology is the brain amyloid-β protein that forms dimers and oligomers, leading to protein aggregation visible in the post-mortem brains as plaques. Plaques are accompanied by aggregates of phosphorylated tau protein called neurofibrillary tangles. Together these lesions are thought to cause synaptic loss and neuronal cell death, resulting in cognitive dysfunction [8, 9].

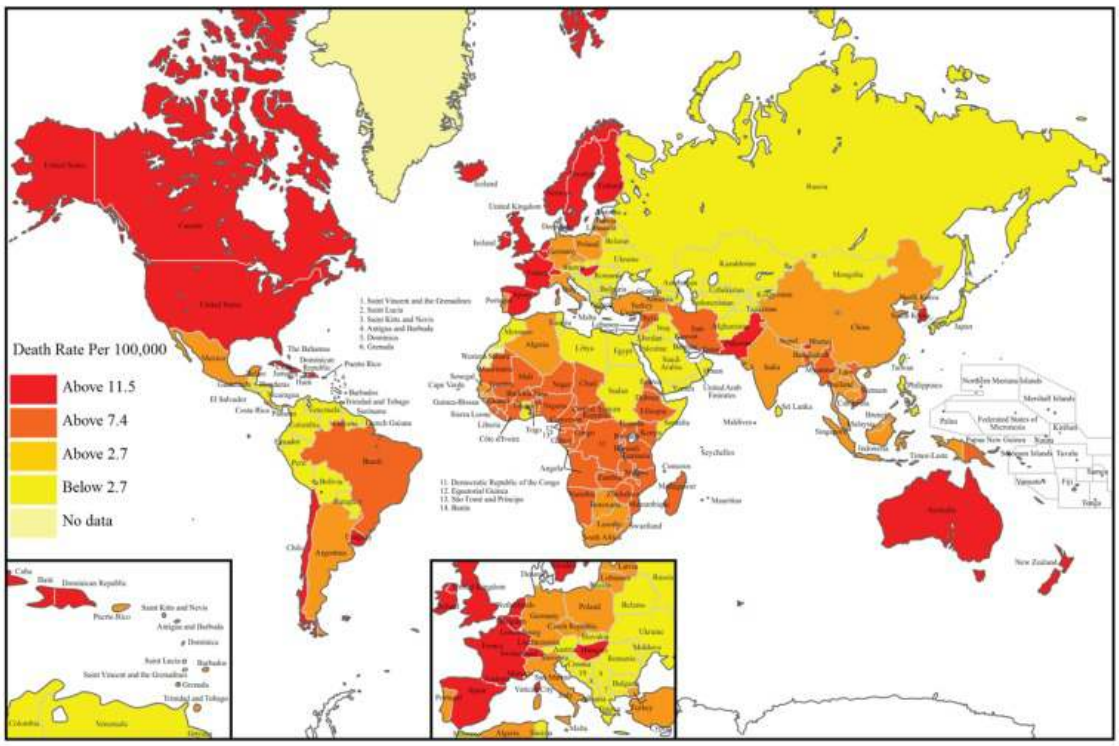

Fig. (1)

World map illustrating the global distribution of deaths caused due to Alzheimer's Disease/Dementia using WHO data from 2011. Image courtesy: Image recreated from http://www.worldlifeexpectancy.com/cause-of-death/alzheimers-dementia/by-country/.

Multiple factors have been reported to contribute to the etiology of AD including, but not limited to, aging, genetics [10], head injury [11], and exposure to certain chemicals and compounds [12]. The genetic component of AD risk is well established as being associated mostly with the *APOE-E4*

allele [10] and with less common autosomal dominant forms of AD. In contrast, the role of environmental exposures and their mechanisms contributing to the pathogenesis of sporadic AD continues to be a subject of discussion. This is partly because of the presumably extended time lapse between exposure and onset of the disease. Scientists have proposed the LEARn (Latent Early–life Associated Regulation) model with an underlying "two-hit" theory, which combines genetic and environmental risk factors in an epigenetic pathway, suggesting that AD risk is established during early

life [13, 14]. The progression of AD takes place over 1-3 decades and the estimated time between triggering events and onset of the disease ranges from several years to several decades, making it difficult to pinpoint particular causative factors. Of all risk factors associated with AD, genetic predisposition is believed to account for about 70% of the overall risk, with the remaining 30% thought to be due to obesity, smoking, lack of exercise, mid-life hypertension, diabetes and exposure during life to environmental agents [15, 16]. Recent research on AD has pinpointed the involvement of aggregated amyloid beta-protein and tau protein [17] while some studies emphasize the role of the LEARn pathway [18]. However, few studies have been directed towards the role of environmental toxins in the development of AD, and more laboratory and epidemiological studies are needed to identify possible associations. Importantly, while not all contaminants and toxins have been tested in research studies showing impact on the central nervous system (CNS), the risks of developing AD and Parkinson's disease (PD) in elderly persons as a result of neurologic impairments caused by environmental toxins is established [19].

In this article, we review the five categories of environmental agents, including (*i*) toxic metals, (*ii*) insecticides/pesticides, (*iii*) industrial/commercial pollutants, (*iv*) antimicrobials and (*v*) air pollutants, all known or hypothesized to induce or aggravate AD or AD-like progression *in vitro,* in animal models and in human research subjects (Figs. **2** and **3**; Table **1**). Toxic metals such as aluminium [20] and lead [21, 22] have been linked with numerous neurodegenerative diseases including AD, causing toxicity to multiple organs of the human body. Other elements such as copper and arsenic have been associated in experimental model systems with the disruption of homeostasis of brain amyloid-β protein [23, 24]. Chronic exposures to pesticides such as organophosphates [25], including occupational exposure especially in agriculture, have been shown to lead to cognitive and psychomotor impairment and possibly to the development of AD and Parkinson’s disease [19]. Murine neonates exposed to brominated flame retardants, which are readily absorbed by body fat, showed behavioural changes, while adult mice displayed impaired learning and memory [26]. Plasticizers (additives that soften plastic making it resilient and elastic) include bisphenol A and phthalates. These chemicals can cross the fetoplacental barrier, and were observed to result in growth retardation and neurological damage [27]. Broad spectrum antimicrobials, which are active ingredients of consumer products like soaps and toothpastes, are known to cause neurodevelopmental disturbances and behavioural changes; however, evidence directly linking these to AD is lacking [28, 29]. Studies utilizing animal models and epidemiological approaches have reported other evidence linking exposure to toxic metals [30, 31] and air pollutants [12] to neurological symptoms, including AD. Importantly, most of the implicated environmental toxins are endocrine disrupting chemicals featuring the potential to impair neurogenesis and cognitive function in the developing and aging brain, and affecting neurological function throughout the human lifespan [32].

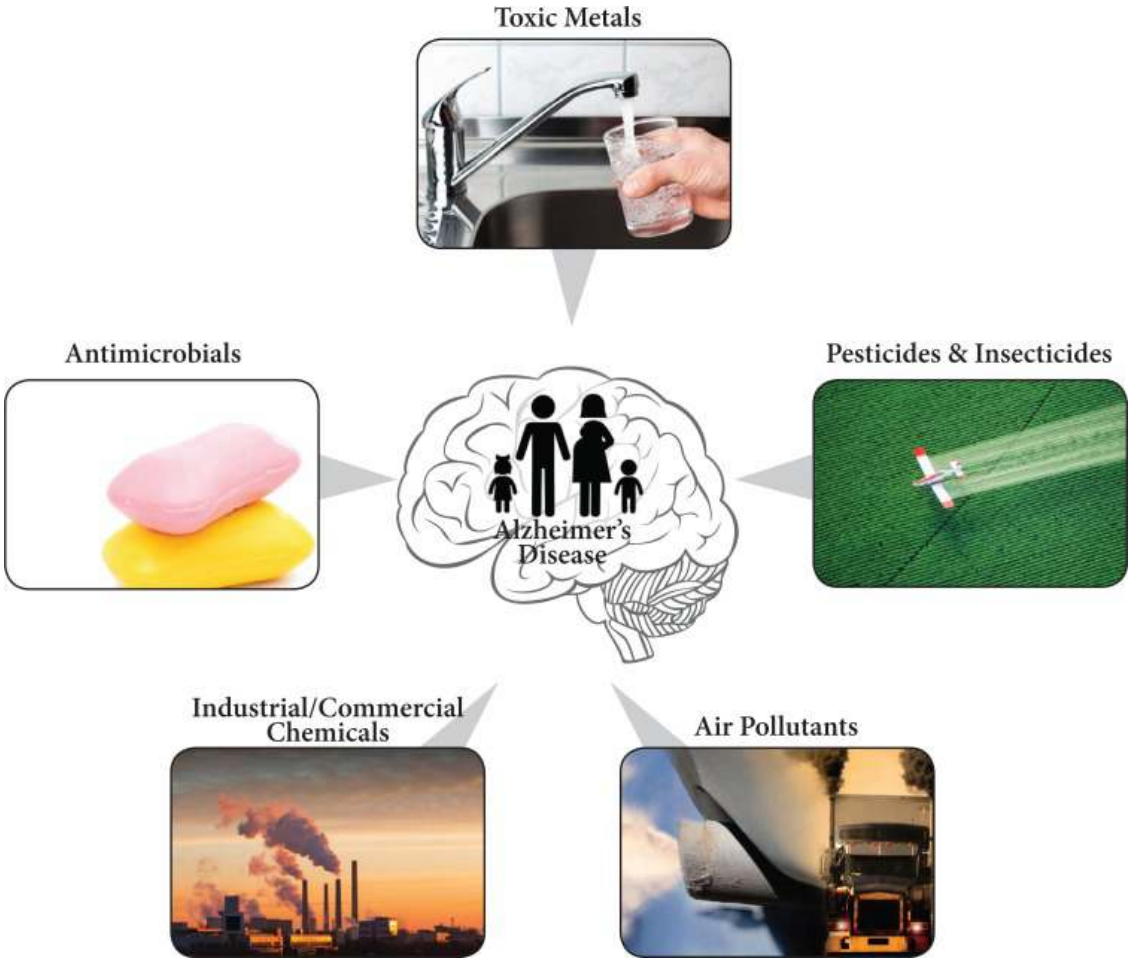

Fig. (2)

Environmental and man-made contaminants/toxins associated with AD include toxic metals, pesticides/insecticides, other industrial/ commerical chemicals, and air pollutants. Exposure occurring *in utero*, during child growth and development, in adult life causing an increased risk for AD and AD-like pathology later in life.

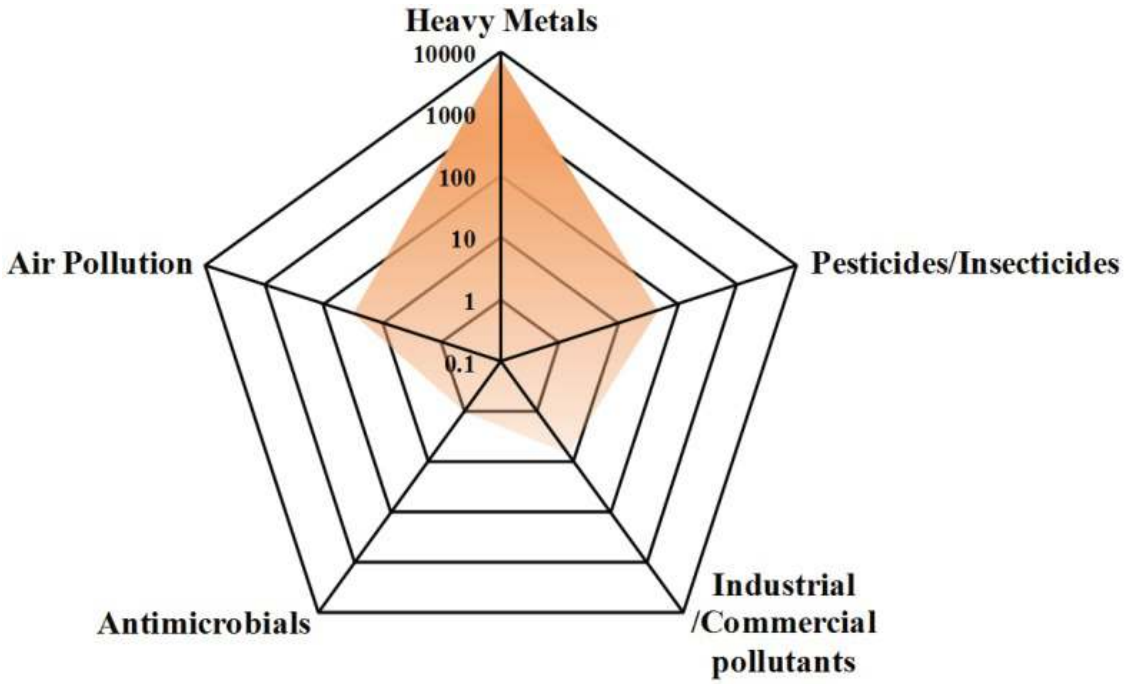

Fig. (3)

Radar graph representing studies published (8102 papers) on the five categories of environmental contaminants assocaited with AD or AD-like progression.

Table 1

Research studies reporting environmental factors known or suspected to be directly or indirectly associated with patho-genesis of Alzheimer's disease.

vironmental Factor	Dose Used in Experiment or Measured Levels	Reference	Human/ Animal/ *In vitro* Study	Summary
	The mean (SD) blood lead level was 3.5 (2.2) µg/dL and tibia lead level was 18.7 (11.2) µg/g.	[22]	991 sociodemographically diverse, community-dwelling adults	Age-related decrements in cognitive functio may be associate with early lead exposure
	The median baseline blood, patella, and tibia lead concentrations were 5 µg/dL (Interquartile ranges 3–6), 25 µg/g bone mineral (17–37), and 20 µg/g bone mineral (13–28), respectively.	[46]	Human longitudinal epidemiological, 1089 participants in the Normative Aging Study	Cumulative exposu to lead can adverse affect performance cognitive tests in t visuomotor domai
	Mean patella lead was 25.0 µg/g bone (SD = 20.7), and mean tibia lead was 19.2 (SD = 14.6)	[190]	Human longitudinal epidemiological, VA Normative Aging Study (NAS); 362 participants	Lead exposure is associated with impaired motor function
Manganese	Control animals 8.9 ± 1.1 µg/L and 109.9 ± 15.3 µg/L in Mn-exposed animals.	[55]	Seven adult male macaques, 5–6 years old received 330.28 ± 0.35 mg Mn/kg body weight (bw)	May initiate or accelerate a proces predisposing to A like pathology an cognitive dysfunct
	The mean ± SEM of frontal cortex Mn concentrations were:	[54, 73]	Macaques receiving 3.3-5.0 mg Mn/kg weekly for 10 months	Chronic mangane (Mn) exposure produces a

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It remains presently unknown whether a single agent or mixtures of environmental factors or contaminants contribute to AD onset and disease progression. Further research is underway to provide new insights into potential mechanisms, with the goal of identifying environmental risk factors and developing strategies for reducing harmful exposures contributing to AD pathology. The Centers for Disease Control and Prevention in conjunction with the Agency for Toxic Substances and Disease Registry have developed Minimum Risk Levels for some hazardous substances, as tabulated in (Table 2). Having provided above a brief synopsis of the knowledge base of AD etiology, we discuss in the following in greater detail the five categories of environmental agents implicated with AD pathology.

Table 2

Body burden (blood, urine, total body levels), minimum risk levels, and exposure limits for environmental contaminates in healthy individuals.

Environmental Contaminants	Name	Levels in Blood, Urine (Mean/ Range)	Total Body Level	Minimal Risk Levels (MRLs)
TOXIC METALS				
	Aluminum	Blood 1-3 µg/L Urine mean value 23.7 µg/L	For 70 kg adult 30–50 mg/ kg body weight	1 mg aluminum/kg/day for chronic oral exposure (≥365 days)
	Arsenic	≤ 1 ppm in nails ≤ 1 ppm in hair Blood < 1 µg/L in Urine 0.0-35 µg/L	Toxicity of arsenic depends upon exposure	0.005 mg As/kg/day for acute oral exposure (≤14 days) to inorganic arsenic; 0.0003 mg As/kg/day for chronic oral exposure (≥1 year) to inorganic arsenic
	Cadmium	Blood level 0.315 µg/L Urine level 0.193 µg/g creatinine (0.185 µg/L)	For 70 kg adult, 10-50 mg/ kg body weight	1 X 10-5 mg Cd/m3 has been derived for chronic inhalation exposure to cadmium (≥1 year). 3 X 10-5 mg Cd/m3 has been derived for acute-inhalation exposure to cadmium (≤14 days)

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TOXIC METALS

Human exposure to toxic metals is a common condition worldwide, resulting from multiple exposure pathways including inhalation of contaminated air, dermal absorption of metals contained for example in soil, and ingestion of contaminated water and foodstuff, such as agricultural crops, meat and seafood. Exposure to metals has been documented to cause acute and chronic toxicity, with outcomes including degenerative diseases and cancer [33-35]. Aggregation of amyloid-β protein on neuronal cells following exposure to aluminium, zinc, copper, iron and cadmium chloride salts indicates that

metal exposures may trigger AD-like pathologies [36]. Although some metals consumed in moderation are required for maintaining good human health, excessive or insufficient amounts are known to cause adverse health effects (Tables **1** and **2**).

A possible linkage of **aluminium (Al)** neurotoxicity with AD was discovered in cats and deceased human subjects [37]. Aluminium induced neuropathy includes neurofibrillary degeneration, oxidative stress and inflammatory response. Although Al may act as a cross-linker for *in vitro* amyloid-β oligomerization, whether or not Al plays a role in human AD pathogenesis is still uncertain and controversial [20, 36].

Trace amounts of **copper (Cu)** in the diet were found to induce amyloid-β plaques and learning deficits in an AD rabbit model, including structural changes in amyloid-β

protein with formation of plaques-like structures [30, 38]. Long term exposure of mice to high levels of Cu was shown to result in increased levels of brain amyloid-β protein and in neuroinflammation, two phenomena viewed as hallmarks of AD development [39]. Cu is physiologically complexed with essential enzymes such as superoxide dismutase, cytochrome c oxidase, and ceruloplasmin, and it has been posited that the decrease in Cu in brain regions severely affected by AD can be associated with a decreased abundance of these enzymes in the regions of the brain [40]. Human studies demonstrated altered Cu metabolism to be associated with oxidative pathology in AD [41].

Epidemiological studies have revealed high deposition of **iron (Fe)** from unknown sources in the hippocampus, amygdala and cerebral cortex regions of AD subjects [31, 40, 42]. *In vitro* studies have illustrated that iron together with aluminium is involved in the formation of aggregates of Aβ 42 to form amyloid fibrils with β-pleated sheet conformations [43]. A recent study employing magnetic resonance imaging reported increased iron levels and decreased tissue integrity in the hippocampus region of AD subjects [44].

Inorganic **lead (Pb)** is the current environmental hazard for humans as the organic forms of Pb have been phased out [45]. Early exposure to Pb is known to impact physiological development. This may possibly increase the susceptibility later in life to neurodegeneration and AD pathology; reported experimental effects of Pb exposure include an increased expression of amyloid precursor protein and increased production of amyloid-β protein [21]. A longitudinal cohort of men evaluated by magnetic resonance spectroscopy revealed hippocampal gliosis; it is known that the hippocampus is affected early and severely in AD [46]. Toxicological and population based research has implicated environmental Pb exposure as a cause of general neurotoxicity with decline in cognition in both children and adults [47].

Industrial exposure to **cobalt (Co)** was observed to cause an increase in the accumulation and concentration of this metal in humans, eliciting associated adverse effects on neuromuscular transmission [48] and neurological status [49]. Compared to age-matched controls, elevated levels of Co were observed in post-mortem AD brain tissue, especially in the nucleus basalis of Meynert, a region commonly affected in AD [31].

Elevated exposure to **cadmium (Cd)**, particularly in occupational settings has been linked to neurological symptoms and neurobehavioral problems involving loss of attention, psychomotor speed and memory [50]. Higher, and significantly different Cd contents were seen in hippocampal tissues and in the cerebral cortex of AD subjects, when compared to age-matched control subjects [42]. *In vitro* experiments have illustrated that Cd causes self-aggregation of the tau peptide R3, thereby potentially impacting AD pathogenesis [51] by mechanisms including astrocyte and neural cell toxicity [49].

Brain biopsy of a single human subject with high **manganese (Mn)** level revealed multiple neuritic plaques and neurofibrillary tangles, which are characteristic of AD [52]. However, the high level of Mn and its association for development of AD warrants further investigations in other AD patients. In a murine study, intranasally administered Mn was shown to cause toxicity in the CNS, targeting astrocytes and leading to an increased abundance of the glial fibrillary acidic protein [53]. Previously, chronic Mn exposure in non-human primates had been observed to cause cellular stress and neurodegenerative changes, including diffuse amyloid-β protein plaques in the frontal cortex [54]. More recently, AD-like pathology and cognitive dysfunction with impairment of visuospatial associative learning were observed to be associated with Mn exposure in macaques [55].

Mercury (Hg) is a well known neuro toxin and also has been reported to be a risk factor for the development of AD. Animal and *in vitro* studies have demonstrated that mercury causes tau protein hyperphosphorylation, and the increased formation of amyloid-β protein [56]. Hg ions disrupt membrane structural integrity of neurites and neuron growth cones [57] and also inhibit binding of guanosine triphosphate (GTP) to β-tubulin reducing the biological activity, causing abnormal partition and ultimately microtubule degeneration as shown in AD brain homogenates [58].

Arsenic (As) has been speculated to represent an essential trace element in human nutrition, but its toxicity at higher doses in people and animals is much more firmly established [59]. Geological and epidemiological data indicate that environmental arsenic concentrations in topsoils (7–18 ppm range) are positively correlated with the prevalence and mortality of AD and dementias in countries like Italy, Spain, Belgium, France, Norway and Switzerland [60]. In another study, rat cerebellar granule neurons exposed to arsenic illustrated neurotoxicity, apoptosis and activation of p38 and JNK3 MAP kinases in the signalling pathways [61]. Epidemiological data from 434 human participants found low-level arsenic exposure linked to poorer neuropsychological functioning [62]; however, another study indicated a positive correlation between serum arsenic and cognitive ability, suggesting that seafood consumption of arsenic in addition to docosahexaenoic acid plays a role in delaying AD [23]. Since, arsenic and its compounds are used in pesticides, insecticides and herbicides, exposure to contaminated food, water and air may induce brain neuronal apoptosis; however, there is no direct evidence linking As with AD [63]. Thus, there is an absence of verified cases of human morbidity or mortality resulting from exposure to low levels of arsenic in topsoils as well as its correlation to cognitive functioning.

Selenium (Se) is both an essential nutrient and, at elevated concentrations, an environmental toxicant [64]. Epidemiological studies have observed Se deficiency in AD patients when compared with an age matched control group as evidenced by Se levels measured in plasma, erythrocytes and nails [65]. However, there is a need for confirmatory studies correlating Se status and AD etiology. In contrast, a study in *Caenorhabditis elegans* has shown that high Se concentrations induce oxidative stress, with reduced cholinergic signalling and degeneration of cholinergic neurons by depleting glutathione [66]. The study also points out that the environmental toxicant Se induces general neurodegeneration. As direct experimental evidence is lacking for a link between Se intake, absorption and onset of AD, further studies and clinical interventions are needed [67, 68].

Zinc (Zn) is another essential trace mineral, playing a role in the metabolic activity of some 300 human enzymes and influencing physiologies as diverse as wound healing, cell division and synthesis of DNA and proteins [69]. Deficiency of Zn in blood serum has been associated with pathogenic AD mechanisms [23], affecting microtubule polymerization and microtubule networks [70]. However, further confirmatory studies are required to establish this possible relationship. Aberrant extracellular and intracellular zinc levels suggestive of dyshomeostasis in AD have been observed in several brain regions of individuals with normal levels of Zn in their diet [71]. These studies revealed that zinc in the brain may serve twin contrasting roles. Excess zinc in senile plaques and vascular amyloid deposits

may initiate amyloid deposition affecting polymerized microtubule stability; and at the same time it may also counter oxidative stress and neurotoxicity, thereby preventing neurodegeneration and cognitive impairment in a process of potential therapeutic use.

Metal mixtures also are believed to play a role in the development of neurodegenerative diseases, potentially acting synergistically rather than displaying simple, additive effects. Many studies have linked long term or short term toxic metal exposure to AD at low levels [42, 72] that point to the possibility of synergistic co-toxicity, possibly altering metabolism, oxidative stress response and neurotoxic potency. For example, one study showed significantly higher levels of Cu in the frontal cortex of macaque brains following Mn exposure [73], suggesting a synergistic effect between co-exposure to metals and metal dyshomeostasis.

INSECTICIDES AND PESTICIDES

Population growth and the increased demand in industrial food production have resulted in widespread use of synthetic pesticides, with exposure to some of which having been linked to AD [19, 74]. Increased use of pesticides in industrialized agriculture has polluted the natural and built environment, resulting in bioaccumulation of toxicants and affecting human health (Tables **1** and **2**). The use of insecticides/pesticides in household and agricultural areas has exponentially increased over the course of the past four decades [75]. Resultant environmental exposure to these insecticides and pesticides has also been linked to the development of neurodegenerative disorders like Parkinson's disease [76, 77]. Many pesticides target the nervous system of insect pests, and similarly are neurotoxic to humans by adversely affecting cell signaling, disturbing neurochemical processes, and causing neurotoxicity [78]. While the use of organophosphates, carbamates and pyrethroids has decreased over the years, the use of neonicotinoids and other compounds is still increasing [79]. Acute, chronic and long term exposures to pesticides have been associated with neurological disorders including AD [80]. Informative work includes a French cohort study called PAQUID (Personnes Agées QUID) that followed 3,777 individuals aged 65 years or older since 1988 until the present time; univariate analysis of data from follow-up exams spaced 5 and 10 years apart showed that AD and occupational pesticide exposure were significantly associated with increased risk (odds ratio of 2.9); this relationship remained significant even after adjusting for education and smoking status (relative risk = 2.4, 95% confidence interval [CI]=1.0-5.6) [19].

Certain pesticides may be harmless as a single exposure, but when mixed with other pesticides, they can be toxic and alter the body metabolism of animals as well as humans [81, 82]. Some pesticides are cholinesterase inhibitors or have similar effects on other molecular targets causing long-term, lasting toxic effects on the CNS [83].

Epidemiological studies illustrate that exposure to **organochlorines** (Hazard Ratio=1.49; 95% CI of 0.99–2.24) and **organophosphates** (Hazard Ratio=1.53; 95% CI of 1.05–2.23) are associated with an increased risk of dementia and AD later in life; this association was identified in *The Cache County Study* using the Cox proportional hazards model [84]. Among the organochlorine pesticides are hexachlorocyclohexane (HCH) and aldrin, two extremely persistent pesticides. When humans are exposed through food or drinking water to HCH isomers (α-HCH, β-HCH and γ-HCH) and aldrin, the slow metabolism and excretion of these pesticides together with their notable hydrophobicity promote bioaccumulation. A pilot study in a population of North Indians reported that increased blood levels of β-HCH and the organochlorine compound dieldrin were associated with significant increases in AD risk, independent of the genetic risk factor, with odds ratios of 2.78 (95% CI of 1.35–5.69) and 2.34, respectively [85]. Epidemiological studies and experimental studies showed that these pesticides induce oxidative stress and neurotoxicity [24]. Similarly, organophosphate insecticides like parathion

were shown to cause morphological changes and affect non-cholinesterase targets like motor proteins, neuronal cytoskeleton and axonal transport [86]. Organochlorine and organophosphate insecticides have been documented to affect glucose and lipid metabolism and the endocrine system [87]. Although, severe acute poisoning can be rectified [88], long term exposure can cause neurobehavioral effects [89] and, at the cellular level, can induce decreased cell viability due to lipid peroxidation and genotoxicity [90]; these adverse effects ultimately may increase the risk of developing AD.

Carbamates such as carbofuran, along with organophosphates, are a group of cholinesterase inhibiting pesticides. Mammalian laboratory experiments have demonstrated that neuronal nicotinic acetylcholinesterase receptors are susceptible to toxicity induced by carbamate pesticides and may contribute to long-term disruption of the nervous system [91]. Gestational and postnatal exposure of mice to **bipyridyles** (paraquat) in combination with carbamate showed reduced levels of dopamine and loss of nigral dopamine neurons [92]. Further, mice exposed to paraquat showed mitochondrial dysfunction in cerebral cortex, which in turn is known to promote impairment of cognition function with elevated levels of Aβ protein [93]. **Rotenone** is another pesticide that causes mitochondrial dysfunction; it is an inhibitor of mitochondrial complex I, destabilizes microtubules, and is strongly associated with Parkinson disease etiology [94]. The role of rotenone in the pathogenesis of AD has not been studied in depth, but the compound's ability to induce mitochondrial dysfunction may constitute a causative factor for AD [95].

Fipronil, a phenylpyrazole insecticide, is a neurological agent that selectively inhibits insect gamma-aminobutyric acid (GABA) receptors. Experiments in zebrafish embryos suggest that fipronil impairs spinal locomotor pathways and causes neurodegeneration [96]. In humans, exposure to fipronil causes an increased risk of mild, temporary health effects, including neurological symptoms [97]. Examination of the human AD brain showed functional remodeling of GABAergic neurotransmission similar to fipronil toxicity [98] suggesting that long term exposure to fipronil may be a predisposing factor for AD.

Pyrethroid pesticides commonly used in agriculture and urban settings are known neurotoxicants and can be transformed into neurotoxic degradates. These pesticides induce cognitive abnormalities, imbalanced tau phosphorylation and AD-like pathology in rats [99], pathological cell death and neurotrophic effects on neurons in human cell lines [100, 101]. A study in Ecuadorian children confirmed that maternal occupational exposure to pesticides like pyrethroids and organophosphates induces developmental neurotoxicity during pregnancy, which is an important risk factor for impaired neurobehavioral development in offspring [102]. Importantly, exposure to pesticides has been related to development of CNS disorders including AD [19]. However, the role of pyrethroid pesticides as agents directly causing AD is uncertain and requires further research. For example, a rat study showed neonatal exposure to permethrin or cypermethrin to induce long-lasting developmental effects, including behavioral changes, altered dopaminergic activity, and increased oxidative stress [103]. It has been established that *in utero* exposures to neurotoxic chemicals reduce the number of neurons in critical areas of the developing brain, causing altered dopamine levels with advancing age which are also associated with PD and AD [104]. These observations have spawned hypotheses that environmental pesticides may contribute to AD development.

Furthermore, in the 1990s, a new generation of pesticides called **neonicotinoids** were introduced which selectively bind to insect receptors for nicotinic acetylcholine. Neurotoxic insecticides that may bioaccumulate in the food chains were observed to cause changes in the mobility of lotic macroinvertebrates measured in continuous flow microcosms as downstream drift [105]. *In vitro* experiments with peripheral human blood lymphocytes showed neonicotinoid pesticides to cause cytotoxicity and genotoxicity [106]. Commonly used neonicotinoids like acetamiprid and imidacloprid

act in the same manner as nicotine, readily passing through the blood-brain barrier and causing adverse effects in neonatal rat cerebellar cultures, suggesting potential risks to developmental stages in humans [107].

OTHER INDUSTRIAL AND COMMERCIAL POLLUTANTS

Urbanization and industrialization certainly have contributed to increases in environmental contamination, causing multiple health hazards to humans and other organisms [108]. Whether naturally occurring or being of anthropogenic origin, contaminants in air, water, soil, and food as well as in drugs can potentially harm or cause adverse effects to humans. Many of these contaminants tend to bioaccumulate in living organisms where they may cause toxicity (Tables **1** and **2**). An overview of these contaminants and their potential role in the etiology of AD is presented in the following sections.

Brominated flame retardants (BFRs) are widely used in commerce with polybrominated diphenyl ethers (PBDEs) representing the historically most widely used compounds, found in electrical appliances, building materials, and textiles. Adult mice exposed to PBDEs showed altered spontaneous behavior, impaired learning and memory, and decreased hippocampal cholinergic receptors [26]. *In vitro* studies showed that PBDEs are neurotoxic and amyloidogenic specifically causing Ca^{2+}-ATPase inhibition, amyloid-β peptide release, and apoptosis a key neuro-degenerative pathology observed in AD [109]. Multiple health effects and permanent aberrations in spontaneous behavior have been reported in neonatal and adult animals after exposure to commercial PBDE mixtures causing developmental neurotoxicity [26, 110]. Over the years, biomonitoring of the level and effects of toxins and ensuing regulatory interventions have helped to curb the use and exposure to these BFRs; however, lingering large quantities of these compounds still render many populations vulnerable to toxic exposures and effects [111, 112]. Recent research on amniotic fluid contamination highlights the potential for fetal exposure, suggesting that younger generations are at risk of neurodevelopmental toxicity similar to that seen in animal studies [113]. Some commonly used BFRs have been reported to cause neuronal cell death leading to production of β-amyloid peptide a key feature of AD [109]. Based on these results, flame retardants are believed to potentially increase the risk of AD, but more studies are needed to explore their role and importance as AD risk factors. Meanwhile, multiple studies have highlighted the importance of early life exposure to environmental agents as a risk factor for programming and developing adult-onset disease [14, 114].

Alkylphenol polyethoxylates (APEOs) are found in the paper, paint, pesticides and textile industry. **Nonylphenol (NP) and octylphenol (OP)** are degradates and transformation products of detergents formulated from alkylphenol polyethoxylates. NP has been shown to cause long-term harmful effects on reproductive and developmental physiology, as it binds to estrogen receptors and exerts estrogenic actions in bovine oocytes [115]. Similarly, estrogenic effects were seen in OP exposed turtles together with increased expression of amyloid-like precursor protein-2 and amyloid precursor protein, accumulation of which causes neuronal degeneration in AD brains [116]. Deposition of alkylphenols in aquatic and terrestrial environments and subsequent bioaccumulation in animals and food crops increases the likelihood of human exposure as well as ensuing risks to human health especially through ingestion of certain fish species [117, 118]. Thus far, studies on the toxic effects of alkylphenols have focused mostly on animal models where endocrine-disrupting effects have been observed [119]. Alkylphenols together with other endocrine disrupting chemicals have been linked to a number of diseases including AD [120], with an important concern being the risk of programming diseases in adult life via early exposure during windows of susceptibility.

Dioxins are naturally occurring and unintentionally produced byproducts of chemical manufacturing comprised of various toxic congeners of polychlorinated di-benzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like chemicals, including certain congeners of polychlorinated biphenyls (PCBs). Together with similarly behaving but structurally distinct polycyclic aromatic hydrocarbons (PAHs), dioxins exhibit toxicity and biological effects mediated through their binding to the aryl hydrocarbon receptor (AhR) and signalling pathways [121, 122]. Dioxins are very stable, lipophilic organohalogen compounds and are known to alter neurotransmitter functions in the CNS, affect Ca^{2+} homeostatic processes, and induce oxidative stress [49]. The most potent dioxin congener, 2, 3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), was observed to increase in neuronal cells calcium levels and tau phosphorylation via up-regulation of phospho-glycogen synthase kinase-3 β. These *in vitro* changes are similar to the pathologies of post-mortem brain tissues of AD patients [123]. TCDD also was observed to impact gene expression in the developing brain [121], induce neurotoxicity and neuronal apoptosis in the rat brain cortex and in PC12 cell lines through down-regulation of the Wnt/β-catenin signalling pathway [124]; furthermore, it was shown to disrupt murine adult neurogenesis which potentially may affect memory processes [125] via toxicity to neuronal processes. Other widely used, dioxin-like chemicals are specific congeners of **polychlorinated biphenyls** (**PCBs)**. These mass-produced but now banned organochlorines are known to trigger health effects in humans following bioaccumulation in wildlife and food animals and other exposure routes [126]. An epidemiological study from Eastern Slovakia showed a significant association between exposure to dioxin-like PCBs and decreased cognitive development as well as decreased motor skills in children and their mothers. The study suggested that these effects, especially for children, may be the result of endocrine disruption, modification of neurotransmitter functions, or reduced thyroid hormones in the brain development *in utero* [127, 128] suggestive of early exposure leading to origins of diseases in later life which may be true for AD development as indicated by the LEARn model. Another study linked the presence of PCBs to decreased sperm motility in humans [129]. Case studies showed that exposure to PCBs produces certain clinical features consistent with AD type dementia [130] and cohort studies revealed that women occupationally exposed to PCBs are more susceptible to Parkinson's and AD than PCB-exposed men [131]. Although PCBs have been strongly associated with neuropathology observed in Parkinson's disease [132], the role of PCBs in adverse neurodevelopment and neurodegeneration relating to AD is not well understood and requires further research.

Bisphenol A (BPA) and **phthalates** are used in water bottles and food cans as plasticizers and plastic building blocks, which can migrate into water and food stuff [133] and may affect human health over time as they cause epigenetic modifications [134] and other effects [135]. BPA has been linked to developmental, reproductive impairments and changes in brain and behaviour in experimental animals [136]. Importantly, BPA has been shown to interfere with spine synapse formation in the prefrontal cortex and hippocampus, which may have clinical implications resembling the events in AD [137]. BPA can disrupt expression of the *Kcc2* gene through epigenetic mechanisms causing neurodevelopmental toxicity [138]. BPA mimics estrogenic activity and affects dopaminergic neurotransmission [139]. BPA exposure was shown to have an adverse effect on the brain of primates, causing spine synaptic remodeling suggestive of a critical impact on cognition and mood [140]. BPA is an endocrine disrupting compound and was shown to trigger decreased immune function in a study conducted on samples from the 2003-2006 National Health and Nutrition Examination Survey or NHANES [141]. A urinary maternal and childhood BPA cohort study revealed that gestational exposure to BPA causes anxious, depressive, and hyperactive behaviours in children and especially girls [142]. Similarly, prenatal phthalate exposure was associated with social impairment and poor cognition in children [143] with girls being more vulnerable to the neurotoxic effects of phthalates than boys [144]. Fish exposed to diethylhexyl phthalate (DEHP) showed reduced neurotransmitter activity and behavioral changes [145]. DEHP was shown to significantly inhibit acetylcholinesterase activity

and upregulate glial fibrillary acidic protein as well as myelin basic protein in zebrafish embryos [146]; it also was observed to cause cognitive dysfunction and increased phosphorylation of tau protein in aged rats prenatally exposed to DEHP [147]. Efforts are ongoing to reduce and replace the use of these chemicals, which also may reduce potential adverse impacts on human health of DEHP acting alone or in synergy with other common industrial compounds such as BPA. The use of BPA in baby bottles and phthalates in children's toys has been banned but several consumer goods still contain these chemicals with the magnitude of risk posed being subject to debate and discontent. Since humans are exposed to numerous chemicals, it is not surprising that their exposure might influence various metabolisms and functions in the body. For example, one study proposed synergistic toxicity of phthalates and PCBs as a potential cause of decreased sperm motility [129] but similar studies on the effect of mixtures of plasticizers and plastic components in the context of AD are lacking.

ANTIMICROBIALS

Antimicrobials including non-halogenated and polychlorinated organic compounds have been in widespread, high-volume use for more than five decades as preservatives and as active ingredients of antimicrobial consumer and personal care products. These compounds possess immunotoxic, neurotoxic and brain damaging properties and hence are of potential concern to the human health [148-150] especially with respect to AD etiology. Overuse of cleaning products can lead to hyper-hygienic conditions (known to be associated with low lymphocyte turnover), which in turn can lead to immune-dysregulation as seen in autoimmunity similar to the inflammation observed in AD. Countries with greater degree of sanitation and lower degree of pathogen prevalence have higher age-adjusted AD rates, suggesting that AD risk is inversely related to microorganism exposure [151]. Overuse of antimicrobials and disinfectants has been suggested to induce conditions which may lead to AD or AD-like pathology but definitive research studies on such associations are lacking. Listed in (Tables **1** & **2**) are animal and human studies identifying relevant body burdens of antimicrobial chemicals. Major antimicrobials are discussed in the following sections.

Hexachlorophene (HCP) is a polychlorinated binuclear aromatic compound historically used at high volume as a disinfectant and more recently exclusively as a preservative. In the 1970s it was established that HCP causes developmental, neurotoxic and brain damaging effects, triggering a ban of the compound in 1972 from high-volume uses as an antimicrobial [152]. Human exposure to HCP in the U.S. population peaked in the 1970s and has been much reduced since, with usage of the chemical as a preservative constituting the only documented remaining exposure route.

In vitro studies on the effects of HCP exposure on the murine brain showed decreased activity of brain succinate dehydrogenase [153]. Studies on sheep supported the finding that HCP causes changes in brain metabolism [154]. Since the use of HCP was prevalent prior to 1973, studies using premature infant brains and follow-up work in children showed vacuolar encephalopathy after intensive exposures of prematurely and newly born infants [155, 156] from repeated whole body bathing using formulations containing 3% HCP. In part due to limited epidemiological studies and data, researchers thus far have been unable to establish whether HCP and structurally related antimicrobials may play a role in the induction and pathology of AD or AD-like symptoms. Uses of HCP have since been replaced by the two antimicrobials, triclosan and triclocarban, that show structural similarity to HCP and share some of its human health concerns [152].

Triclocarban (TCC) and triclosan (TCS) are antimicrobial agents used in personal care products, primarily in liquid and bar soaps and some uses of TCS in toothpastes. *In vitro* assays illustrate that TCC and its analogs enhance hormone-dependent induction of estrogen and androgen-dependent gene expression, whereas TCS causes disruption of brain Ca^{2+} homeostasis by altering the ryanodine (Ry)

receptor type 1; this may contribute to neurotoxicity as well as altered neurodevelopment and neuroplasticity [148]. Anuran studies have revealed that TCS modulates thyroid hormone associated gene expression, causing alterations in transcript levels of the brain thyroid hormone receptor α in premetamorphic tadpoles and disrupting postembryonic development [29]. Similarly, murine studies demonstrated that TCC levels can disrupt hormone signalling pathways and that *in utero* exposure impairs neurogenesis and neurobehavioral development [157], affecting the survival rate in female rat neonates [158]. Increased aromatase and estrogens levels were seen in developing brains of zebrafish embryos with combined effects of BPA and TCC, although individual compound exposure did not show any effect [159]. While muscle function has been associated with mild cognitive impairment with AD [160], one study reported that TCS impairs excitation–contraction coupling in striated muscle dynamics of fish and mice [161] which may be of concern to both susceptible populations and environmental health. Human studies showed detectable urinary levels of TCC [162] and TCS [163], confirming ongoing continuous exposure of human populations to anthropogenic antimicrobials and potential chronic and acute health effects [152]. Previous research has reported levels of TCS and TCC in maternal urine and cord blood plasma in an US urban population [164]. The relevance of these exposures to the development of AD is still uncertain and deserves further study.

Parabens (methyl, benzyl, butyl, propyl, and ethyl) are antifungal and bactericidal chemicals widely used in personal care products including soaps, cosmetics and perfumes. Parabens are endocrine disruptors causing mitochondrial toxicity [165]. Recent reports suggest that paraben exposure may lead to diminished ovarian reserve in women [166] and induction of oxidative stress biomarkers such as 8-hydroxy-2-deoxyguanosine and malondialdehyde, both detectable in the urine of mothers and their newborns [167]. Whereas urinary concentrations can inform on the body burden in human populations [168, 169], such data by themselves are not suitable for revealing the relationship to neurotoxicity or neurodevelopmental disorders, and by extension, potential roles in AD. Animal studies on paraben exposure show bioaccumulation in fish brain, causing reduced neurotransmitter activity and leading to behavioral changes as a result of neurotoxicity and neurodevelopmental disturbances [28]. Rat offspring prenatally exposed to butyl paraben showed neurodevelopmental disorders [150], adversely affecting adult behavior with outcomes including anxiety and learning disabilities following exposure [170]. These results suggest that even small doses of parabens can cause changes in metabolism of animals and potentially of humans, increasing the risk of behavioral changes and neurological symptoms triggered in the wake of these exposures.

It has been suggested that exposure to environmental microorganisms is important for the regulation and proper functioning of the immune system, and that maintaining a hyper hygienic behaviour may increase the incidence of AD [151]. In addition, several researchers have indicated a possible role of endocrine disruptors in the progression of AD [32]. But again, more studies are needed to confirm or refute these working hypotheses.

AIR POLLUTANTS

Oxidative stress and free radicals are generated as a result of imbalances in metabolism caused by biological, physical or chemical exposures [171]. Free radicals may accumulate over an individual's lifetime and later induce neuroinflammation and neuropathology [172]. Recent studies have implicated **particulate matter** (PM, composed of particles measuring in diameter 2.5 μm or smaller and collectively termed $PM_{2.5}$) in the causation of AD and other neurodegenerative disorders. Researchers have examined whether toxic metals including nickel, vanadium, lead and certain gases such as CO, NO_x, and SO_2 present in polluted air may cause reactive oxygen species (ROS) production, oxidative stress, chronic neuroinflammation, cerebrovascular damage, Aβ peptide accumulation, and neuron damage/loss contributing to AD pathogenesis [173]. AD associated amyloid-β40 and amyloid-β42

levels were increased in mice brains of mice exposed to a nickel nanoparticle model of air pollution [174]. In Mexico City, children exposed to severely polluted environments demonstrated neuronal accumulation of misfolded proteins similar to the anatomy observed in the early stages of both AD and Parkinson's disease [12]. Another study by the same group revealed that 56% children had prefrontal white matter hyperintense lesions caused by PM-induced damage to the CNS by PM in early life, which may be a predisposing factor for the development of neuroinflammation and neurodegeneration later in life [175]. The authors suggest that particle exposure activates the pathogen sensors and reactive oxygen species, thereby generating brain inflammation [176]. Ozone is the main component of photochemical pollution and adult Wistar rats chronically exposed to ozone showed increases in ROS, memory deficiency, dysregulation of inflammatory processes, progressive neurodegeneration, as well as impaired brain repair in the hippocampus, an area heavily affected in AD brains [177]. Importantly, human and animal studies suggest that air pollution (PM, gases, organic compounds, and metals) may cause an increased expression of markers associated with neurodegenerative disease pathologies and also may cause developmental neurotoxicity contributing to the etiology of neurodevelopmental disorders [178]. Epidemiological, observational, clinical, and experimental studies have reported that air pollution causes diseases of the CNS including AD [179].

Laboratory animal experiments have shown that volatile organic compounds (VOCs) including volatile solvents like phenol, a simple aromatic alcohol contained in cleaning agents and fuels can cause morphologic changes in neurons and biochemical changes in synapses and neurotransmitters. A case-control study from 1995 showed that occupational exposure to VOCs can cause an imbalance in the neurotransmitter system thereby potentially influencing the onset of AD. Exposure to one or more VOCs (benzene and toluene; phenols and alcohols; ketones; other solvents) yielded an adjusted AD odds ratio of 2.3 (95% CI of 1.1–4.7); among men, the odds ratio was higher at 6.0 (95% CI of 2.1–17.2) [180]. Exposure to hydrocarbon fuels induces neurological symptoms including depression, frequent headaches, numbness, and dizziness [181]. A recent study using gas chromatography and mass spectrometry confirmed that AD patients have higher levels of VOCs than healthy controls [182].

CONCLUSION

Though environmental exposures are known to play a role in the development of AD, the specific agents and exposure thresholds remain an area of both investigation and speculation. A spectrum of organic and inorganic substances have been associated with AD risk but irrefutable evidence from human studies to date still remains elusive in many cases. Agents of established neurotoxicity deserve further study for their potential role in promoting the development of AD but, at the same time, only a small fraction of these neurotoxins ultimately may be associated with AD. Yet, the percentage of the population affected by AD cases is high and projected to increase further in the future. Multiple classes of environmental chemicals have been hypothesized to play a role in the etiology of AD. A substantial body of literature exists, identifying both inorganic and organic chemicals as possible risk factors for AD development. In contrast, only a few studies are available thus far exploring the role of exposure to environmental mixtures of chemicals on the etiology of AD. With future increases in human life expectancy projected, AD as a late-in-life onset disease is destined to rise, as shown here in a hypothetical schematic diagram (Fig. **4**). Efforts are under way to limit the production of and human exposure to neurotoxic and AD-risk posing chemicals contained in cosmetics and consumer products [152, 183, 184]. For example, several countries are phasing out the use of harmful chemicals including phthalates, BPA, TCS and TCC [152, 255]. However, environmental exposures to complex mixtures of organic and inorganic AD risk factors will continue into the future due to both the large spectrum of AD-related chemicals in commercial use and the essential services some of these chemicals provide to humanity. Adding to a delay in exposure reduction is the fact that most of the environmental

contaminants have been tested *in vitro* and in animal models only and sometimes at concentrations orders of magnitude higher than those experienced by the general population; thus, there remains considerable uncertainty and scepticism as to the relevance of single and composite exposures for adverse neurological effects observed in human populations. Moreover, the decade-long time delay between exposure and onset of disease render studies on AD etiology inherently challenging. Also, genetic susceptibility combined with the presence of environmental factors will modify the magnitude of any effects and complicate the analysis of population data. While many environmental contaminants are documented to contribute to toxic body burdens in human populations, pinpointing subtle and time-delayed effects through epidemiological studies and linking them to AD constitutes a supreme challenge. Very large, detailed epidemiological studies tracking lifetime exposure to environmental contaminants are needed to confirm the role of specific chemicals and chemical mixtures in AD etiology. These studies ideally should be flanked with laboratory studies concentrating on a determination of toxic body burdens in human tissue (e.g., fat, brain, and bone) of victims presumed to suffer from AD. Since misdiagnosis in AD patients is known to be rampant, neuropathologically diagnosed AD should be confirmed postmortem via brain autopsies. Careful analyses of autopsy confirmed AD cases, their corresponding laboratory determined toxic body burdens and their genetic risk factors will be essential for expanding the still limited knowledge of the role of environmental chemical agents in the etiology of AD. Finally, this review emphasises the need for adequate funding of future studies required to firmly establish associations between environmental causes and development of AD and other neurodegenrative disorders.

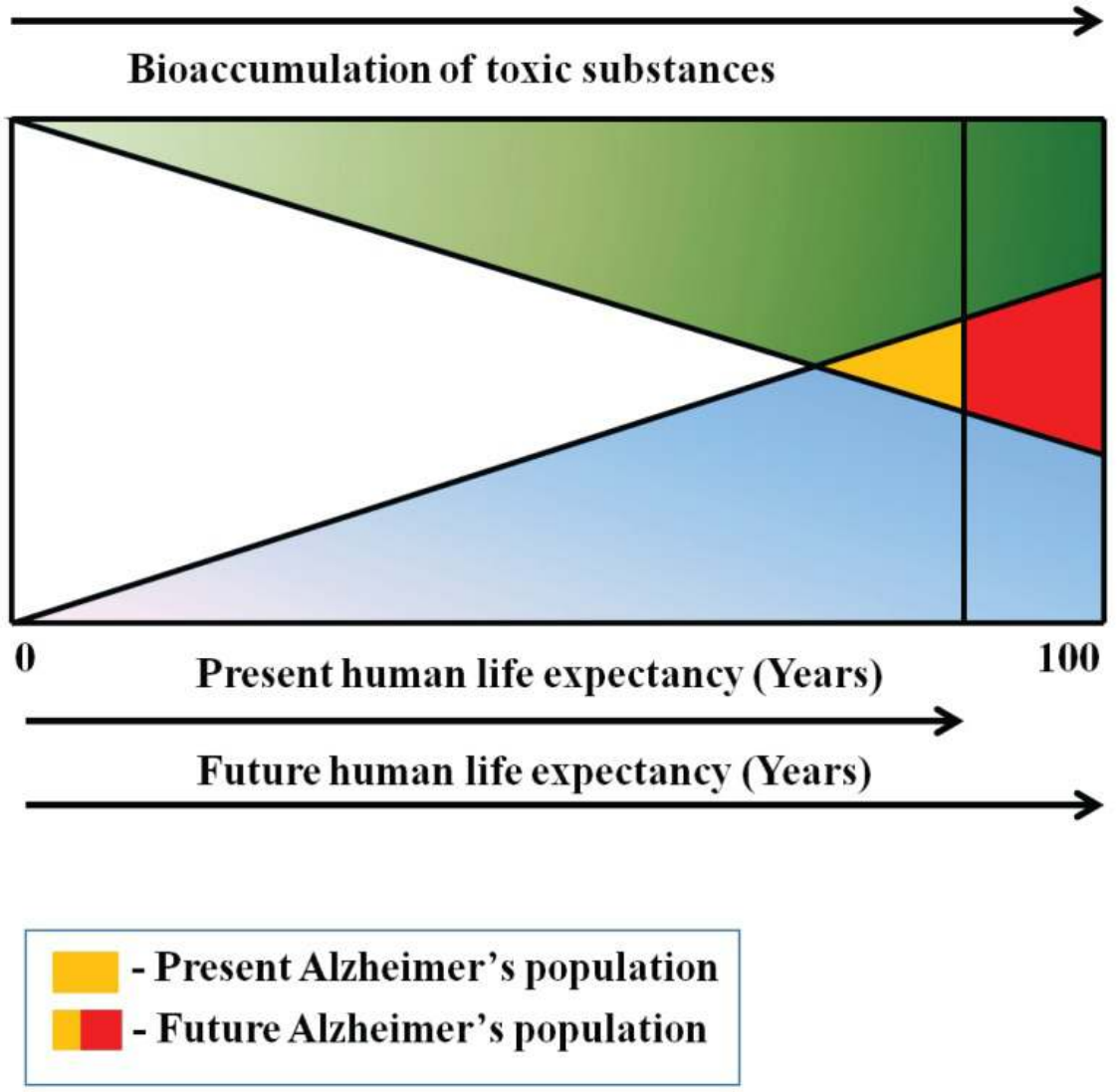

Fig. (4)

Hypothetical schematic diagram depicting the expected increasing incidence of Alzheimer's disease due to increased human life expec-tancy

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Glossary

ABBREVIATIONS

AhR = Aryl hydrocarbon receptor

ALS = Amyotrophic Lateral Sclerosis

APEOs = Alkylphenol polyethoxylates

BFRs = Brominated flame retardants

BPA = Bisphenol A

b.w. = body weight

CNS = central nervous system

MUFA = DEHP = Diethylhexyl phthalate

GABA = gamma-aminobutyric acid

GTP = guanosine triphosphate

HCH = hexachlorocyclohexane

HCP = Hexachlorophene

LEARn = Latent Early–life Associated Regulation

NHANES = National Health and Nutrition Examination Survey

NP = Nonylphenol

OP = Octylphenol

PAHs = Polycyclic aromatic hydrocarbons

PAQUID = Personnes Agées QUID

PBDEs = Polybrominated diphenyl ethers

PCBs = Polychlorinated biphenyls

PCDDs = Dibenzo-p-dioxins

OP = Octylphenol

PAHs = Polycyclic aromatic hydrocarbons

PCDDs = Dibenzo-p-dioxins

PCDDs = Polychlorinated dibenzofurans

PD = Parkinson's disease

PM = Particulate matter

ROS = Reactive oxygen species

TCC = Triclocarban

TCDD = 2, 3,7,8-tetrachlorodibenzo-p-dioxin

PCDDs = Dibenzo-p-dioxins

TCS = Triclosan

VOCs = Volatile organic compounds

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