




A perspective on persistent toxicants in veterans and amyotrophic lateral sclerosis: identifying exposures determining higher ALS risk

Diane B. Re¹ · Beizhan Yan² · Lilian Calderón-Garcidueñas^{3,4} · Angeline S. Andrew⁵ · Maeve Tischbein⁵ · Elijah W. Stommel⁵ 

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Abstract

Multiple studies indicate that United States veterans have an increased risk of developing amyotrophic lateral sclerosis (ALS) compared to civilians. However, the responsible etiological factors are unknown. In the general population, specific occupational (e.g. truck drivers, airline pilots) and environmental exposures (e.g. metals, pesticides) are associated with an increased ALS risk. As such, the increased prevalence of ALS in veterans strongly suggests that there are exposures experienced by military personnel that are disproportionate to civilians. During service, veterans may encounter numerous neurotoxic exposures (e.g. burn pits, engine exhaust, firing ranges). So far, however, there is a paucity of studies investigating environmental factors contributing to ALS in veterans and even fewer assessing their exposure using biomarkers. Herein, we discuss ALS pathogenesis in relation to a series of persistent neurotoxicants (often emitted as mixtures) including: chemical elements, nanoparticles and lipophilic toxicants such as dioxins, polycyclic aromatic hydrocarbons and polychlorinated biphenyls. We propose these toxicants should be directly measured in veteran central nervous system tissue, where they may have accumulated for decades. Specific toxicants (or mixtures thereof) may accelerate ALS development following a multistep hypothesis or act synergistically with other service-linked exposures (e.g. head trauma/concussions). Such possibilities could explain the lower age of onset observed in veterans compared to civilians. Identifying high-risk exposures within vulnerable populations is key to understanding ALS etiopathogenesis and is urgently needed to act upon modifiable risk factors for military personnel who deserve enhanced protection during their years of service, not only for their short-term, but also long-term health.

Keywords Amyotrophic lateral sclerosis · Veterans · Etiology · Neurotoxicant · Persistent · Exposure

Introduction

Amyotrophic lateral sclerosis (ALS) is a predominantly sporadic, paralytic, and fatal condition caused by motor neuron degeneration [1]. Despite the identification of disease-causing mutations for ~10% of cases [2–4], the pathogenic mechanism(s) of ALS remain elusive, hampering the development of effective preventive or therapeutic strategies. It is thought there are likely as many types of toxic exposures leading to sporadic ALS as there are genetic variants causing familial or inherited ALS (> 25 causative genes) [4]. Interestingly, not all carriers of ALS-causing mutations develop ALS, even in old age. For instance, most mutations in TDP-43 exhibit a reduced penetrance [5]. There is also a large disparity at what age familial ALS presents. These observations suggest that, even in familial ALS, there are environmental influences. While sporadic ALS occasionally

✉ Elijah W. Stommel
Elijah.W.Stommel@hitchcock.org

¹ Department of Environmental Health Science, Center for Motor Neuron Biology and Disease, Columbia University, New York, NY, USA
² Department of Geochemistry, Lamont-Doherty Earth Observatory of Columbia University, Palisades, NY, USA
³ Department Biomedical Sciences, College of Health, University of Montana, Missoula, MT, USA
⁴ Universidad del Valle de México, Mexico City, Mexico
⁵ Department of Neurology, Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

results from oligogenic causes [6, 7], it is generally believed that most sporadic cases result from a combination of environmental factors and genetic susceptibilities. Currently, identifying rare genetic susceptibility factors that synergistically interact with a given environmental exposure requires a large case–control analysis, and often through the efforts of a global consortium.

The importance of environmental exposures in ALS etiology is supported by reports of high discordance of this disease in monozygotic twins [8, 9], conjugal ALS [10] and an increased risk of ALS for specific occupations [11], activities [12] and exposures (e.g. metals [13, 14], pesticides [15]). Relevant to veterans affected with ALS, disease risk increases, sometimes two-fold, with deployment [16] or total years of deployment [17]. Beard et al. also found ALS was positively associated with exposure to herbicides, pesticides, certain metals and burning agents [17]. Another study called genes and environmental exposures in veterans (GENEVA) used a retrospective exposure assessment to evaluate which industrial and occupational exposures, next to genetics, could drive the higher risk of ALS among military veterans [18]. They found that raters' confidence-modified exposure scores revealed potential higher exposure to hydrocarbon solvents, chlorinated solvents, and pesticides. Such evidence suggests that military personnel might be exposed to a variety of neurotoxicants and carcinogens whose adverse effects only emerge after sustained long-term exposure.

A recent study reported that the prevalence of El Escorial-defined 'definite' ALS cases is significantly higher among Air Force personnel, as well as among tactical operation officers and health care workers compared to other service branches and occupations [19]. These branch-specific differences are not reported by all studies [17, 20, 21]. Although a topic of debate, the suggested variation in rates among military branches may indicate that there are disproportionate exposures and/or factors experienced by certain military personnel. Despite such reports, there is no clear connection between a given environmental exposure and ALS veterans to date. One possible reason for this gap in understanding is that only a few studies (notably Fang et al., 2010 [22]) have evaluated biomarkers of physiological exposure to specific neurotoxicants, such as lead (Pb), in this population.

In this review, we assert that to reliably characterize the physiological burden of exposure in veterans, it is important to evaluate the potentially causal chemicals in disease-relevant tissues, such as the central nervous system (CNS). Importantly, the causative environmental exposure(s) likely occurred years prior to disease onset (e.g. 10+ years). Thus, due to changes of residence, retirement, etc., a given ALS patient is likely no longer actively exposed to the causal toxicants at the time of diagnosis. While epidemiological exposure assessments are therefore challenging, the direct measurement of persistent neurotoxicants from subject tissue

remains feasible and offers many advantages. For instance, toxic metals, such as Pb, accumulate in bones where they have a half-life of up to 30 years [23]. As a result of aging and decreased activity, metals like Pb can be mobilized from bones, thus internally extending potential exposures that may have initially occurred years ago. Similarly, the CNS is also known to accumulate such metals with a longer half-life than most soft organs [24] as well as lipophilic toxicants with stable chemical structures due to the high lipid content of CNS tissue [25]. Although this approach may not capture all toxicants that contribute to ALS (e.g. those that are not persistent), persistent and non-persistent toxicants are often co-emitted, and thus tracking the persistent ones presents a feasible mechanism for the identification of fundamental sources of exposure that will provide an overall more informed understanding of ALS environmental etiology as a whole.

Together, there are several questions that could greatly increase our understanding of the particular vulnerability of military veterans to ALS:

1. What toxic environmental exposures/toxicants are associated with ALS?
2. What concentrations and/or (sub)cellular accumulations of such toxicants are relevant to disease?
3. Are there synergistic patterns between associated toxicants and predisposing/lifestyle factors (e.g. prior head trauma, spinal cord injury, smoking, occupation etc.)?

Similarities in disease development between ALS and cancer

In 2014, a groundbreaking epidemiological study by Al-Chalabi et al. described the development of ALS as a multi-step process, similar to cancer [26]. The study was based on the premise that both ALS and cancer share characteristics such as the “onset being more common in later life, progression usually being rapid, the disease affecting a particular cell type, and showing complex inheritance” [26]. Using ALS registries from Ireland, the Netherlands, Italy, Scotland and England, Al-Chalabi and colleagues demonstrated a linear relationship between log incidence and log age in all five registries that was consistent with a six-step process [26], possibly derived from a combination of environmental exposures, genetic and other risk factors. Chiò et al. further demonstrated that patients with genetic mutations had fewer steps in their development of ALS, thereby supporting the idea of ALS as a multistep process [27]. Identifying exposures that serve as key steps or “hits” in ALS development will likely greatly increase our collective understanding of ALS etiology as well as the development of preventative and therapeutic strategies.

In this respect, military service members appear to represent a distinct subpopulation to which these principles could be applied. For instance, ALS incidence was found to be significantly higher during an approximate 10-year window following deployment for first Gulf War relative to those not deployed to the Gulf [28, 29]. Possibly following key exposures and/or interplay between toxicants and other risk factors, this defined window between service and disease onset provides a potential timeframe for the manifestation of ALS. Moreover, one study reports 85% of incident cases in Gulf War veterans within this window were <45 years of age [30]. This decreased age of onset (typical ALS onset is ≥ 60 years in the general population) may also suggest that the exposures experienced by military personnel were more frequent and/or intense than that of persons developing ALS in the general population. We posit that service-linked exposures may represent one step (or several) in the proposed multistep process of ALS development [26].

Military service and ALS

There are numerous reports suggesting an increased risk of ALS associated with military service [16, 31, 32]. A representative report by the United States National Academy of Medicine (US NAM, previously the Institute of Medicine) shows that, regardless of what war, ALS rates were generally increased and often doubled compared to rates in non-military individuals [16]. Although evidence based on such studies has often been deemed limited but suggestive (e.g. due to small samples sizes, given the rarity of disease), ALS is currently defined as a service-connected disease and the Department of Veterans Affairs (VA) has provided additional financial assistance to Gulf War veterans suffering from ALS [33]. As of 2010, more than 2 million service members have been deployed in support of Operation Enduring Freedom and Operation Iraqi Freedom [34]. ALS prevalence among US veterans deployed (2002–2015) was 19.7/100,000 [19]. Thus, understanding risk factors in the military setting could provide valuable insight and future mitigation strategies for current and future military service members.

The Gulf War serves as a notable case study when examining the connection between military service and ALS. In addition to a doubled incidence of disease compared to general population [28, 29], Haley observed that 8 years postwar, 85% of the incident cases in Gulf War veterans were <45 years of age [30]. The observed incidence in young veterans increased from 1 to 5 cases per year and was not explained by “a change in the interval from onset to diagnosis or by a change in the US population death rate of ALS in those aged <45 years” [30]. To this end, NAM have considered relationships between Gulf War illnesses in general (including ALS) and broad exposures to environmental

toxicants including insect repellents, such as *N,N*-diethyl-m-toluamide (DEET), oil well combustion products such as organic hydrocarbons (VOCs), diesel exhaust, and various polycyclic aromatic hydrocarbons (PAHs), or other substances likely to be encountered during service such as acid aerosols, hydrazines, mustard agents, sarin, pyridostigmine bromide, and depleted uranium [35]. However, NAM found insufficient evidence to demonstrate that subclinical exposures to these agents was associated with specific patterns of illness [36]. Previous studies probing this connection have been criticized in part for (1) a lack of evidence of a biologically credible environmental exposure that could result in such an increase in neurodegenerative illness (no reliable biomarker of CNS exposure) and (2) the statistical methodologies studies used [37–41]. In regards to the latter, however, subsequent investigations have confirmed the increased risk of ALS among deployed personnel using capture/recapture methodologies [42].

Although the etiology of ALS in veterans remains unclear, it is clear military service represents a unique circumstance that aggregates a special group of collective factors. For instance, military service members are exposed to multiple environmental hazards during deployment (e.g. pollutants from unregulated industry, particulate matter from desert environments, exhaust from military vehicles and aircraft, emissions from open-air burn pits and toxicants on military bases); among the myriad of toxicants present in these service-connected exposures, several were linked to diseases (e.g. lead, pesticides, dioxins, and even aerosolized cyanobacteria pertaining to Gulf Wars [43]). Soldiers also receive prophylactic treatment of cholinergic inhibitors, which have been linked with neurodegenerative disease and potentially ALS [17, 44], to protect them against nerve gas and insect pests. Beard et al. additionally identified numerous exposures associated with ALS and those with odds ratios > 3 included: treatment with nasopharyngeal radium, mixing or application of herbicides or burning agents as well as exposure to ground-level fumigation, nearby missile explosions, chemical agent-resistant compound paint or depleted uranium for munitions/armor [17]. Thus, while an effort has been made to link exposures to veteran service [32], no toxic exposures was demonstrated for its causal role in ALS.

In addition to environmental exposures, predisposing behavioral activities have also been considered in the context of military service and ALS. It has been postulated that the extreme physical exertion experienced by military personnel might also heighten ALS risk as well as smoking and alcohol consumption. However, variation in postwar ALS rates between military branches are not consistent with this idea. Altogether, previous attempts to establish a connection between military-linked environmental exposures and ALS based on historic records and questionnaires has proven

difficult. Thus, evaluating the physiological dose of potential neurotoxicants in target tissues using quantitative and advanced molecular techniques would allow for stronger and improved correlations to be made between persistent toxicants and ALS. Although certain environmental toxicants have short half-lives and would not be measurable in postmortem CNS tissue, selecting toxicants that are (1) likely to contribute to disease based on evidence from the literature (see below) and (2) would be measurable as much as a decade or more after exposure will likely yield robust information. Potential toxicants include chemical elements, nanoparticles (NPs) and persistent, lipophilic toxicants such as dioxins, polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs). These environmental toxicants and their sources are described in more detail below.

ALS-relevant and military-linked environmental exposure sources

Diesel exhaust

Certain occupational studies have found increased ALS risk among persons in occupations with high exposure to diesel exhaust [45], such as truck drivers [46, 47] and construction workers [48], machine operators [49] and bus drivers [49]. Thus, diesel exhaust represents a proposed common denominator for ALS. Diesel engines of comparable power produce between 2 and 10 or up to 40-fold more particulate emissions than gasoline engines without or with a catalytic converter, respectively [50]. Moreover, inhaled diesel exhaust particles are ‘biopersistent’ and may carry additional chemical compounds on their surface [51]. Thus, the importance of diesel engine emissions to human health is not only a reflection of the toxic chemicals produced, but also the ability of particulate matter to ‘trap’ additional chemicals, thereby potentially extending the duration of exposure [51]. As a result, this may allow for the prolonged contact of passenger chemicals with the respiratory epithelium and increase their chance of uptake and subsequent initiation of oxidative stress, systemic inflammation and de novo mutations from resultant genomic damage [51, 52]. Diesel exhaust also contain PAHs such as benzo(a)pyrene and as well as additional toxicants and carcinogens (acetaldehyde, acrolein, benzene, 1,3-butadiene, ethyl benzene, formaldehyde, n-hexane, naphthalene, styrene, toluene, and xylene) identified by the US Environmental Protection Agency (EPA) [53]. Accordingly, one must consider diesel exhaust-derived toxicants as potential risk factors for neurodegeneration and, more specifically, ALS.

Living in close proximity to heavy traffic and air pollution is associated with a higher incidence of dementia [54] and risk of neurodegeneration. For example, fine particulate air pollution (particulate matter < 2.5 microns; PM_{2.5}) has been

linked to Alzheimer’s disease (AD) and Parkinson’s disease (PD) [55]. Specific to ALS, one recent study found suggestive evidence of increased ALS risk due to long term, high-concentration exposures to particulate matter < 10 microns (PM₁₀) [56]. However, the statistical imprecision of the risk estimates due to the small sample size limited their capacity to definitively conclude an increase in risk [56]. In another study, Nunez et al. suggest that increased PM_{2.5} concentrations in New York state may contribute to the clinical aggravation of PD and ALS, especially for subjects > 70 years of age [57].

Jet exhaust

Detrimental health effects have been observed for those working or residing in close proximity to jet emissions, including certain cancers [58, 59]. As evidenced in vivo, exposure of mice to particles collected at two separate airports via intratracheal installation induced pulmonary acute phase response, inflammation and genotoxicity [60]. In connection with ALS, the literature suggests that civilian airline flight attendants, pilots and navigators likewise have higher rates of this disease [59, 61]. Given that ALS prevalence has been found higher for Air Force service members relative to other military branches by certain studies [19, 29], we speculate that exposure to jet exhaust may serve as a contributing factor.

Products from jet emissions include ultrafine combustion particles, lubrication oils (including organophosphate esters), PAHs, volatile organic compounds and chemical elements including: Pb, Copper (Cu), Chromium (Cr), Nickel (Ni), Iron (Fe), Zinc (Zn), and Aluminum (Al) among others [58]. Although we are aware of their production, the toxicity of aircraft emissions has not been extensively researched. Emitted particles are generally ultrafine (< 100 nm). Like particles derived from other combustion sources, they may deposit in respiratory airways when inhaled and potentially cause irreversible damage to lung tissue, as observed for NPs generally [62, 63]. Researchers have investigated the toxicity of NPs from the exhaust of a CFM56-7B turbofan, the most common aircraft turbine engine. Using an aerosol deposition chamber, Jonsdottir et al. observed varying amounts cell death and oxidative stress in cultured bronchial epithelial cells depending on the combination of turbine thrust level and fuel type [64]. This is of importance as different thrust settings and fuels (including jet propellant (JP)-8 jet fuel) reportedly emit varying particle amounts [65]. Similar to the commercial jet A-1 fuel, JP-8 is a kerosene-based fuel that is conventionally used in Air Force aircraft, military vehicles and generators, thus, is common chemical exposure for Air Force-associated personnel (e.g. flight and ground crew) [65, 66]. Although no direct connection has been made, it is of note that Pugh et al. identified a significant increase in

chronic obstructive pulmonary disease and asthma in veterans from the Iraq and Afghanistan Wars [67], which could possibly be associated with military-linked, environmental exposures. Exposure to jet fuel itself has been linked to hearing loss in both animal models [68] and humans [69]. Akin to urban pollution (described above), such auditory defects may also be potentially connected to NP-associated, brain-stem pathologies [70].

Together, current evidence suggests that exposure to toxicants derived from diesel and jet engine exhaust can cause detrimental health effects. However, there are differences between the two sources. One study found the size distribution of aircraft exhaust particles, including lead dibromide, is smaller than that produced by automobiles burning the same leaded fuel (13 vs. 35 nm mean diameter for all particle types, respectively) [71]. In a separate study, although 10–1000 nm particles were associated with both roadways and aircraft, a principle component analysis conducted by the authors revealed features that differentiated the two sources: larger particle size and higher black carbon concentrations were a feature of roadways, while smaller particles and lower amounts of black carbon were associated with aircraft [72]. Such differences may be relevant to our understanding of emission-linked exposures when considering their contribution to disease development, although it is possible the overall physiochemical properties of each are ultimately similar [60]. Overall, the neurotoxic mechanisms and potential for such environmental pollutants to drive the increased ALS risk observed in military service members, airline workers and truck drivers needs further study.

Brake and tire wear

In addition to the exhaust produced by combustion and other pollution sources associated with airports and air force bases, aircraft braking and tire wear can also lead to the release of potential toxicants through the abrasion and subsequent production of smoke and ultrafine dust from these mechanical systems [65, 73]. For instance, experimental data collected at a major European airport have also reported high levels metals including barium (Ba), Zn, molybdenum (Mo), Cu and antimony (Sb) from runway smoke [74] and separate study also observed the production of trace elements generated by aircraft landing [75]. Although data are limited, one study estimates that the rubber lost from tires on varying aircraft can vary from tens of grams to ~0.8 kg per landing [76].

Burn pits

Burn pits are open areas for burning solid waste that were widely used in combat zones before 2009. A report by the Institute of Medicine described burn pits in Iraq and

Afghanistan as burning waste that “consisted generally of 5–6% plastics, 6–7% wood, 3–4% miscellaneous noncombustibles, 1–2% metals, and 81–84% combustible materials” [77]. JP-8 was typically used as the accelerant and, although there are no official inventories, the refuse reportedly burned (i.e. plastics, metal cans, rubber, paints, solvents, petroleum, munitions and wood waste) produced hazardous emissions containing harmful particles and toxicants [77]. Unsurprisingly, exposure to burn pit emissions has been a cause for concern in relation to respiratory illness, cancer and neurological effects [77–79].

Pollutants investigated and detected during the evaluation of the Joint Base Balad burn pit included: dioxins, particulate matter (including metals), PAHs, volatile organic compounds [77]. Concentrations of polychlorinated dibenzo-p-dioxins and dibenzo-p-furans were overall low, but generally increased relative to urban environments. Additionally, a large contribution of the detected particulate matter, PAHs and volatile organic compounds were concluded to have likely originated from traffic and jet emissions as well as regional sources (e.g. normal human activity, dust storms, etc.). Thus, in combination with the presence of burn pits, such a nexus of exposures could potentially cause additive or synergetic health effects for those exposed. A public law mandated by Congress in 2013 required the VA to establish a registry for veterans with potential burn pit exposure in Iraq or Afghanistan through which participants can complete a questionnaire detailing their deployment/occupational, health and exposure history [80]. Together, these data could be used to epidemiologically investigate the link between burn pit exposure, in potential combination with other service-linked exposures, and ALS.

Neurotoxic effects of toxicants

PAHs

PAHs are by-products of combustion [81] and enter the human body from a variety of sources including: gasoline and diesel-fueled engines (e.g. jet fuel) [82], coal, solid waste, and oil burners [81], grilled and smoked meats [83], use of indoor fireplaces and stoves [84], and smoke from cigarettes [83, 85]. PAH residues are found frequently in suspended fine or ultrafine particulate matter in the air and inhalation is a major route of exposure [86]. They are lipophilic, are stored in fat tissues including those of the breast [87], and have been shown to cause mammary cancer in rodents [88]. In humans, autopsied samples revealed that the highest accumulation of PAHs occurred in abdominal fat and the brain [89]. At the toxicological level, some PAH compounds are able to bind the aryl hydrocarbon receptor (AHR), which regulates xenobiotic-metabolizing enzymes

including some of the cytochrome P450s, ultimately resulting in increased DNA mutations [90, 91]. PAHs also have been found to be directly genotoxic [92]. In the rodent brain, a gene expression analysis showed that exposure to PAHs in the form of diesel exhaust emissions activates several genes associated with antioxidant defenses and inflammation [93]. In addition, benzo[a]pyrene (B[a]P), an individual PAH compound, has been identified for its neurotoxic potential [94]. An *in vitro* study elegantly demonstrated that B[a]P is not directly toxic to neurons; it kills neurons via a non-cell autonomous mechanism by activating microglia [95], the resident immune cells of the brain that have been shown to play a key role in ALS [96]. Locomotor impairment after chronic exposure of B[a]P is significantly associated with development of neurodegenerative phenotypes typically affecting the dopaminergic system in zebrafish [97]. Histopathological observations in brain tissues showed a significant increase in pyknotic neuronal counts in the diencephalon and telencephalic region of zebrafish brain after B[a]P exposure and tyrosine hydroxylase, a marker of dopaminergic neurons, was reduced significantly in the exposure group. In addition to their neurotoxic effects, PAHs can be used to indicate exposure to incompletely combusted pollutants, such as soot. Soot particles can enter the brain and PAH compounds trapped inside the soot particles can be used to indicate the exposure from combustion [98].

Persistent organic pollutants (POPs): PCBs and dioxins

PCBs and dioxins are known as persistent organic pollutants (POPs) and have all been found at military bases and in conjunction with service-linked activities as previously described. In general, POPs are resistant to environmental degradation and can bioaccumulate, resulting in adverse impacts on human health such as an increased risk of ALS [99] and reduced ALS survival in association with increased plasma concentrations [100]. PCBs and dioxins are lipophilic and accumulate in fatty tissues [101], including the brain. Interestingly, accumulation of PCBs in the brain was clearly shown not to have any regionalization [102]. However, in adolescent and neonatal male rats, exposure to PCBs was shown to induce brain region-dependent exacerbation (e.g., in the hypothalamus) or silencing (e.g., the prefrontal cortex) of genes implicated in neuroimmune function such as those coding for factors of the nuclear factor kappa B (NF- κ B) complex [103, 104]. This suggests that despite homogeneous brain accumulation, PCBs can have brain area-specific neurotoxic effects probably based on regional gene–environment interaction. These two studies also indicate that neuroimmune dysregulation may be a prominent pathway of PCB neurotoxicity specifically in males. A similar sexual dimorphism is observed in ALS which preferentially affects men

with a male:female ratio that lessens (from ~2.5 to 1.4) with age [105]. PCB exposure has been associated with reduced cognition in older adults [106] and the specific PCB, PCB-151, has an increased odds ratio in relation to ALS [107]. It is of note that POPs, such as PCBs [108], are associated with multiple neurodegenerative diseases, such as PD [109–118]. Although diseases like ALS, PD and AD do not share the same neuropathology, it is possible that an overlapping, genetic susceptibility occurs through pleiotropy and lends to the existence of common environmental triggers [119–121].

Dioxins are another class of POPs and are a component of certain pesticides, such as Agent Orange, to which ALS has been positively associated [17]. Moreover, elevated levels of the dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has been detected in breast milk from mothers living near the Vietnam Bien Hoa Air Base [122]. Exposure to TCDD from Agent Orange is believed to be an immunotoxin and the probable cause of several types of cancer in Vietnam veterans based on its clear carcinogenicity in experimental animal models [123]. One key mechanism proposed for TCDD carcinogenicity is epigenetic remodeling [124]. Supporting this view, exposure to dioxins or dioxin-like compounds has been associated with CNS developmental abnormalities in zebrafish and epigenetic modifications are well known to be particularly important during neuronal development [125]. Dioxins may also alter the expression of genes related to neuroimmune function [126], neurotransmission [127, 128], neurodevelopment [129, 130] and cytotoxicity [131, 132]. Overall, the molecular cascade by which the neurodegeneration-linked, chemical toxicants described thus far (dioxins, PCBs, and PAHs) contribute to disease is unclear, although one possibility is neuroimmune changes implicating in particular microglial cells potentially via the activation of the AHR. *In vitro* studies report agonists of the AHR, which interestingly was shown to induce a robust DNA demethylation of the Cyp1a1 promoter upon dioxin exposure [133], may induce up to a threefold increase in the ALS-linked TDP-43 protein in BE-M17 (human neuronal cell line), motor neuron differentiated iPSCs and the murine brain [134]. Although further research remains, such observations suggest the possibility that TDP-43 could be a potential molecular link between exposure to dioxins and ALS.

Neurotoxic metals and elements

Specific metals have been linked to neurotoxicity and ALS [135–138]. In fact, exposure to certain metals was one of the earliest environmental risk factors proposed for ALS, although the jury is still out regarding their pathogenic role [139]. For instance, depending on the biospecimens used, there are discrepancies in the findings reported and peripheral measurements rarely reflect the CNS metal load [140, 141]. As described above, exposure to toxic metals is likely

a major concern in veterans and a number of metals including Pb, mercury (Hg), selenium (Se), Cu, manganese (Mn), Fe and arsenic (As) certainly deserve further investigation in ALS patient, CNS tissue. These metals were selected for their relevance to ALS in the literature and our own epidemiological studies [12, 142–144] and are described in more detail below:

- **Lead (Pb)** was the first metal found to be elevated in cerebrospinal fluid (CSF), blood, and tibia from ALS patients [22, 145, 146]. Systematic reviews and meta-analyses cite Pb as an exposure with ‘convincing evidence’ of a causal link to ALS [147, 148]. Animal studies demonstrate the transport of Pb^{2+} ions across the blood–brain barrier [149] and the accumulation of insoluble TDP-43 in the cortex of exposed mice [150]. Based on the analysis of blood samples from occupationally exposed humans, there is evidence to suggest Pb-induced oxidative damage [151]. Relevant to military exposures, shooting at firing ranges results in the discharge of Pb dust, and elevated blood Pb levels that are associated with a variety of adverse health outcomes including essential tremor, cardiovascular morbidities and mortality, and decreased renal function [152]. In Denmark, occupational Pb exposure 10 years prior to diagnosis was associated with increased ALS risk (odds ratio 1.33, 95% confidence interval 1.03–1.72) [153]. Our own prior work linked activities involving Pb (e.g. casting lead bullets, making stained glass with lead joints and casting or using lead fishing sinkers) to ALS risk [144]. Moreover, Pb exposures 20+ years prior to diagnosis had larger effect sizes compared to those occurring more recently [144]. A further Australian study also linked petrol Pb emissions to ALS death rates both temporally and spatially [154].
- **Mercury (Hg)** is potentially a risk factor for ALS [142, 143]. This metal was elevated in the brain of seven ALS patients compared to controls [155] and is associated with increased risk in several studies [139, 147, 156]. Case reports of Hg poisoning have shown convincing ALS-like, clinical symptoms and support a causal relationship [157–159]. Our own regional and nationwide US studies demonstrated higher toenail Hg levels in ALS patients compared to controls [142, 143]. In mutant SOD1 ALS mice, Hg accumulates in spinal neurons [160] and rats exposed to methylmercury (2 mg/kg/day) exhibited ALS-like neurological effects [161]. In vitro proteomics studies reveal that methylmercury exposure causes electron transport chain dysfunction, oxidative stress and ubiquitin proteasome system impairment [135], pathological mechanisms all linked to ALS. Methylmercury neurotoxicity may also involve glutamate dyshomeostasis and excitotoxicity [162], an ALS-linked
- mechanisms that could be of particular relevance to the multi-stage hypothesis of ALS [26].
- **Selenium (Se)** was also linked to ALS [163–166]. Embedded shrapnel from explosive devices and retained bullet fragments also can increase serum levels of toxic metals including Se [167]. Higher risk of ALS was found in naturally seleniferous US regions [168, 169]. Veterinary and experimental animal evidence suggests that motor neurons are particularly vulnerable to Se [139, 164]. Despite Se being elevated in the spinal cord of ALS patients [163, 170], studies measuring Se levels in ALS-patient CSF and blood found both negative and positive correlations with ALS status [13, 166, 171]. Some of the discrepancies in these studies may be due to interactions among elements. For example, although not yet conclusively shown in humans, Se may counteract the absorption of methylmercury [172, 173].
- **Copper (Cu)** has often been a focus of ALS research due to its role as a cofactor of SOD1 [174–176]. Moreover, the pesticide, copper sulfate can dissolve in blood after exposure and be carried throughout the body as well as transported across the blood brain barrier (BBB) as a free Cu ion [177]. Increased Cu levels were measured in the spinal cord of mutant TDP-43 ALS mice [175] and in the blood of veterans with ALS [13]. However, in various peripheral biospecimens, trends in Cu levels were inconsistent [141].
- Excessive **manganese (Mn)** exposure is known to cause manganism, a neurological disorder resembling PD [178]. Moreover, Mn can cause ALS-like symptoms (such as muscle weakness) and ALS-like lesions of the corticospinal tract were reported in Mn-exposed workers [179]. In agreement, increased ALS rates have been reported in Mn miners and smelters worldwide [180, 181]. Elevated Mn levels were detected in the spinal cord of ALS patients and animal models [175, 182], whereas in patient body fluids, both negative and positive findings were reported [13, 174, 183, 184]. Roos et al. observed CSF Mn to be significantly increased compared to CSF of controls [184]. Notably, CSF Mn concentrations were higher than those in the plasma concentrations, suggesting transport of this element into the CNS.
- **Iron (Fe)** accumulation in the CNS has been clearly demonstrated in ALS patients, animal models and in vitro cell models [185–187]. In contrast, most studies using peripheral biospecimens did not find sizable differences in Fe levels in blood, hair, nail, CSF, and urine of ALS patients and controls [140]. Yet, Fe likely has a role in ALS as chelation of this metal is beneficial in a SOD1 ALS mouse model [188].
- Lastly, **arsenic (As)** exposure was shown to cause ALS-like motor neuropathy [189–191] and was suggested as a risk factor for ALS in association with folate deficiency

[192]. A recent study reported lower As serum concentration in ALS patients, but As positively correlated with disease duration [136]. Prolonged As exposure in vitro triggers several features of ALS-linked TDP-43 pathology (e.g., mislocalization, aggregation) [193].

In addition to the ALS-linked elements described above, the following also possess evidence of an association with ALS: Using CSF ($n = 17$ cases, $n = 10$ controls), Roos et al. showed positive associations of ALS with Al, and cadmium (Cd), cobalt (Co), Zn, vanadium (V), and uranium (U) [137]. However, the Al finding was contradicted by a 1995 study of CSF that did not show elevation in ALS patients [185] as well as an additional study of temporal lobe tissue across neurological conditions did not find Al levels elevated in $n = 16$ ALS patients compared to age-matched controls [194]. Hozumi et al. found increased risk of ALS associated with Zn in the CSF ($n = 52$ cases, $n = 15$ controls). Zn was also elevated in CSF in a separate Greek cohort [195] as well as in the Roos 2013 CSF study [137], although this work was contradicted by Kapaki, who found no association with ALS and these elements in CSF ($n = 28$ cases, $n = 36$ controls) [196]. A further case study reported development of ALS in a battery worker exposed to high levels of Cd [197], although, elsewhere, Cd levels were lower in the CSF of ALS patients compared to controls [198]. Hozumi et al. found increased risk of ALS associated with elevated CSF magnesium (Mg) [183]. Using a cohort from the Danish National Patient Registry from 1982 to 2013 matched to controls, Dickerson et al. evaluated cumulative metal exposures estimated using job exposure matrices applied to occupational history. No statistically significant associations to ALS were discovered looking at Cr and Ni [199]. Lastly, based on studies of neurodegenerative illness in animals, Mo deficiency has been postulated to be a potential predisposing factor in ALS [200].

Several studies have directly assessed brain tissue for trace element levels. A review article of brain autopsy tissue sample measurements cites the detection of a large variety of the elements (see Table 3 of Grochowski et al. [201]), and provides quantitative reference levels for Cu, Zn, Mg, Fe, calcium (Ca), rubidium (Rb), Se, potassium (K), Mn, Al, silicon (Si), As, Ni, Pb, Cd, and Cr in various brain regions [201]. In studies of ALS, Cd and Zn were both significantly elevated in grey and white matter when Cd, Co, Cu, Fe, Mn, Rb, V, and Zn were measured in the brain tissue of $n = 8$ Guam ALS patients versus $n = 5$ controls [202]. By focusing on veterans, a population with increased ALS risk, and conducting a comprehensive assessment of elements in CNS tissue, one could potentially identify toxic elements that may not have been previously linked to ALS or examined in the general population. For example, uranium (U), Sb or tungsten (W; associated with munitions), rare earth and

platinum group elements have not typically been measured in brain tissue.

The mechanisms of toxicity by which metals contribute to neurodegeneration in ALS remain to be clarified. However, in other neurodegenerative diseases like AD, multiple studies have validated that exposure to metals disrupts critical, immune-related pathways leading to chronic neuroinflammation and neuronal loss [203]. Metals have often been studied separately in terms of immunotoxicity and neurotoxicity, but one elegant study demonstrates that Pb, for instance, induces the production of autoantibodies against neural proteins, including myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP) [204]. Therefore, Pb could contribute to the aggravation of neurodegenerative disease by exacerbating the immunogenicity of nervous system proteins. The consequences of metal dyshomeostasis in ALS has recently gained momentum and helped generate novel hypotheses, such as those linking mitochondrial dysfunction, intracellular calcium dyshomeostasis, pathological TDP-43 formation, pro-inflammatory microglia activation, and ultimately programmed neuronal cell death [205].

Nanoparticles (NPs)

NPs are particles ≤ 100 nm in all dimensions and exist in a variety of shapes, sizes and compositions (organic, inorganic and carbon based). The nanometer scale of these particles allows for their direct interaction with cells and/or passage through biological barriers. Molecules (including proteins) can coat the NP surface, forming a NP corona [206, 207] and effectively become particle passengers [208]. Leveraging this property, NPs have been used as a therapeutic delivery mechanism for a variety of chemotherapeutic compounds [209]. However, NP pharmacological characteristics are often quickly altered in vivo as NPs become coated with biological milieu following delivery. The interaction of NPs with cells is influenced by the proteins and other molecules attached to their surface, as demonstrated by one ex vivo study reporting that the binding specificity of targeted NPs can be lost in the presence of plasma proteins [210]. The complexity and diversity of protein interactions with NPs to form the corona has not been completely elucidated [207]. While NP size and ability to transport molecules contributes to their therapeutic promise, these same characteristics may also interfere with vital cellular processes, resulting in cellular toxicity as well as human health and environmental concerns [63, 209, 211, 212]. For instance, silver (Ag) NPs have been predominately used for the development of medicines, drug delivery systems and medical device coatings as a result of their antibacterial properties [213, 214], yet multiple studies have demonstrated the toxicity of Ag NPs in vitro and in vivo [209]. Thus, the soft duality of NP features may also pose a detriment to a number of organs

and highlights the need for a clearer understanding of these particles in biomedicine, manufacturing [215, 216] as well as general regulations for use [217].

As an environmental toxicant, NPs likely had a large impact in the days of Charcot when he first described ALS in the late 1860's (e.g. as product of combustion). Today, additional sources of NPs posing a potential health hazard are found in the form of powders, suspensions, or sprays, which are universally used in textiles, paints, cosmetics, water disinfectants, food packing and ubiquitous in polluted environments with combustion emissions [218, 219]. Given these sources for exposure, the respiratory and gastrointestinal tracts, mucosa and even skin represent entry routes for environmental NPs [220–223]. While large aerosolized particles tend to remain in the respiratory tract, NPs may cross the respiratory epithelium to enter blood vessels [224]. Once in the bloodstream, select NPs can directly cross the BBB and/or damage BBB integrity and increase its permeability [225–228]. Additionally, numerous studies demonstrate that NPs can also bypass the BBB entirely via the olfactory system (nasal olfactory epithelial → olfactory bulb → brain) [222, 229–232]. Furthermore, the substantia nigra and brainstem have been suggested as targets for NPs via access the gastrointestinal tract and neuroenteric system [221, 222, 224]. Although our understanding of NP entry routes and subsequent toxicity is evolving, toxic NPs typically appear to be inorganic in nature and water insoluble; toxicity also appears linked to dose and frequency [233–235].

Once NPs reach the brain, they can access neurons, oligodendrocytes and glia they may alter the structure or

activity of the nervous system and induce glial activation [236]. The primary neurotoxic mechanism of NPs is the generation of free radicals and induction of oxidative stress, which can damage biological macromolecules, inducing de novo mutations of DNA. In addition, NPs may directly or indirectly trigger apoptosis, autophagy, immune-responses, neuroinflammation and subsequent BBB damage [209, 237–247]. For instance, Xue et al. demonstrated SiO₂-, TiO₂-, and magnetite (Fe₃O₄)-NPs treatment caused microglial activation and cytokine secretion, resulting in PC12 toxicity and altered dopamine production [248]. Similarly, 10 and 30 nm Fe₃O₄-NPs were found to reduce dopamine rat brains as well [249]. Multiple factors may influence NP neurotoxicity including: size, shape, surface coatings, dissolution rates of metals, and interactions with specific cells and proteins [250]. Of particular, importance is size. In one study, Ag NPs (20 nm) exhibited increased cytotoxicity and pro-inflammatory response in cultured cells compared with larger particles (i.e. 80 nm) [251]. Similarly, a separate in vitro study indicated increased toxicity and oxidative stress from 20 vs 40 nm Ag NPs [252]. Ultimately, the exact neural damage and resultant neuropathology may depend on genetic susceptibility, individual NP characteristics and the differential access to target tissues achieved via their respective entry routes [253, 254] (Table 1).

Given the need to better understand the neurotoxic potential of NPs, one important question is: what is the threshold of NP exposure for neurodegeneration or neurodegenerative pathology? In study of Mexico City subjects, an autopsy study showed hyperphosphorylated tau in the brainstem of

Table 1 Examples of neurotoxic effects and mechanisms caused by environmental NPs

| Nanoparticle | Mechanism and relevance to neurodegeneration |
|--|---|
| Iron oxides: magnetite (Fe ₃ O ₄) iron oxide (Fe ₂ O ₃), | Axonal transport and bypass the BBB via the nasal olfactory epithelium [222, 255, 256] Daily exposure affects synaptic transmission and nerve conduction, causing neural inflammation, apoptosis, induced neural antioxidant responses, and immune cell infiltration [257] Disrupted Fe homeostasis [258, 259], release of free Fe ions to catalyze the production of reactive oxygen species (ROS) through the Fenton reaction [249, 260] as well as the promotion of amyloid-β toxicity, as shown in vitro [261] |
| Silicon dioxide (SiO ₂) | Increased oxidative stress and altered microglial function; deleterious effects on the striatum and dopaminergic neurons [262] Intranasal administration in a mouse model lead to cognitive dysfunction and impairment, synaptic changes as well as pathologies similar to neurodegeneration [263] Induction of neuron depolarization in a cell culture model; no detected change in gene expression [264] PD-like behavioral changes in SiO ₂ NP-exposed Zebrafish model [265] Dose-dependent cytotoxicity and AD-like pathology in vitro [266] |
| Titanium oxide (TiO ₂) | Absorption and translocation into the brain by any portal of entry. Can further cross the placental barrier and accumulate in the fetal brain, causing impairments in the fetal brain development [267] Damage to BBB and induction of inflammatory response [268, 269] Exposure precipitates the development of neuropathological findings of early PD, AD and ALS, some of which appear to be manifested symptomatically [221, 253, 270, 271] |
| Nickel (Ni) | Ni NPs increased (Aβ)40 and Aβ42 levels in murine brains [272] |

an 11-month-old baby, who was found to have to 20 $\mu\text{g}/\text{m}^3$ cumulative $\text{PM}_{2.5}$ (calculated for age at death + pregnancy time), a fraction of the 2522 $\mu\text{g}/\text{m}^3$ calculated for a 39 year old subject with AD neurofibrillary tangle advanced stages V-VI [270]. Calderón-Garcidueñas et al. additionally observed extensive structural organelle abnormalities in the substantia nigra involving mitochondria, endoplasmic reticulum and neuromelanin that were co-associated with the abundant presence of exogenous, Fe-, Al- and Ti-rich NPs in a population of young residents [221]. They also identified hyperphosphorylated tau, α -synuclein and TDP-43 in the brainstem of 182 Mexico City 27.29 \pm 11.8y old Metropolitan Mexico City residents [221]. The co-existence of markers for two common neurodegenerative diseases (sporadic AD and PD), as well as the less common ALS/frontotemporal degeneration (FTD), suggests a common etiological denominator. Thus, NPs may act as catalysts for reactive oxygen species formation, altered cell signaling, protein misfolding, aggregation and fibril formation [221], hence, the co-clustering of such diseases (ALS, PD, dementia) in select geographical pockets [273]. Similarly, Fe-rich and TiO_2 -NPs may (even at low concentrations) may accelerate α -synuclein fibrillization [274], thereby representing a possible a pathomechanism that could potentially contribute to development of neurodegenerative-disease-linked pathology. Together, Calderón-Garcidueñas et al. have suggested that the properties of NPs, which result in cellular damage, potentially represent an additional pathomechanisms contributing to the development of neurodegeneration [221].

It is clear there is extensive and unregulated exposure to nanoparticles released in the environment and that emission sources are highly variable across military and civilian populations (Table 2). With the noteworthy progress of nanotechnology during the last decade, NP products will continue to be used increasingly in our everyday commercial products, industrial processes and medical applications. Thus, in addition to considering the courses of nanoparticle themselves, other variables such as high traffic locations, residential areas, indoor environments, personal exposures, smoker, non-smoker, wind, season, etc. must also be taken into account to fully understand their potential risk.

Conclusions

The pathogenic mechanisms of ALS remain elusive and has hampered the development of prevention strategies and effective therapeutics for this fatal disease. Although efforts have been made in the veteran population to understand the observed elevated ALS rates, no definitive factors have been implicated. Thus, measuring persistent toxicants of interest in ALS-patient CNS tissue and, particularly in evaluating potential pathogenic exposures in veteran cohorts,

is warranted. Such a research approach could provide the basis for environmental exposure associations that are not unique to ALS, but potentially other neurodegenerative diseases with shared pleiotropy and to which veterans are also at higher risk [119–121, 298, 299]. To address this major challenge in ALS research, the field needs to further develop brain banks. In the traditional line of the Armed Forces Examiner System and Institute of Pathology [300], the Veterans Affairs Biorepository established a Brain Bank (VABBB) which provides a collection of carefully characterized, prepared and preserved CNS samples [301]. Moreover, linking these specimens to comprehensive demographic, lifestyle, residential, occupational, and clinical data are critical for the identification of novel associations between ALS and environmental toxicants. The Veterans Affairs Cooperative Studies Program Epidemiology Center in Durham, North Carolina (CSPEC-Durham) has assembled such a repository including extensive research data, genomic data, and study specimens (e.g., DNA, blood) for different content areas including ALS [302].

In summary, it will be crucial to evaluate service-linked toxicants such as PCBs, PAHs, dioxins, metals and NPs in veteran CNS tissue, none of which have been adequately evaluated in relation to neurodegenerative disease risk. These toxicant exposures in veterans appear to be persistent and cumulative, thereby, potentially allowing one to assess the link between ALS and past exposures. Based on the literature reviewed here, we hypothesize that the concentrations and/or distribution of proposed neurotoxicants will be increased and/or in the CNS tissue of ALS compared to controls. Advanced statistical techniques could be applied to clarify the ALS multistep hypothesis, evaluate toxicant synergy as well as anatomical and/or (sub)cellular locations. Finally, as brain banks often also collect genetic variant data, an evaluation of gene and environmental interactions could also be undertaken [121], thus enabling individualized risk assessments and exposure prevention strategies for susceptible individuals.

During their years of service, military personnel voluntarily expose themselves to short-term, life-threatening risks. Moreover, they may also often and unknowingly expose themselves to environmental factors as part of their duties, which can have dramatic consequences for their long-term health and lifespan. It is our responsibility as environmental health scientists to devise the best research strategies to clearly identify such factors, link them to disease and alert competent governmental agencies. The risk(s) associated with adverse exposures are certainly modifiable by prevention and mitigation strategies (e.g. personal protective equipment, exhaust emission control and reduction systems), which could be enabled by military authorities at lower costs than those associated with highly debilitating chronic diseases such as ALS (e.g., average total disease duration cost

Table 2 Veteran-relevant NP characteristics, Industrial Associations and/or Properties

| Expected NP detection profile | Shape and size | Expected cellular/anatomical location and properties in vitro and in vivo |
|---|--|--|
| <p>Elements from fuel combustion (gasoline, diesel, alternative mixed biofuels) and industrial sources (e-waste, lubricating oils) [275–282]: Fe, Pb, Ni, Cu, Cd, Hg, Al, Bismuth (Bi), Titanium (Ti)</p> <p>Technology-critical elements [283]: Gallium (Ga), Germanium (Ge), Indium (In), Tellurium (Te), Niobium (Nb), Tantalum (Ta), Thallium (Tl)</p> <p>Platinum Group Elements: Platinum (Pt), Palladium (Pd), Rhodium (Rh), Osmium (Os), Iridium (Ir), Ruthenium (Ru)</p> <p>Rare Earth Elements: Yttrium (Y), Lanthanum (La), Cerium (Ce), Praseodymium (Pr), Neodymium (Nd), Samarium (Sm), Europium (Eu), Gadolinium (Gd), Terbium (Tb), Dysprosium (Dy), Holmium (Ho), Erbium (Er), Ytterbium (Yb), Lutetium (Lu) [205, 282, 284–287]</p> <p>Detection of metalloid, Si [290], which may be of relevance in the veterans from the Gulf Wars where desert dust (e.g. SiO₂) and particulate matter are prevalent [291]</p> <p>Detection of Ti nanorods (versus spherical shape) to determine its industrial origin</p> | <p>Shape and size determine NP toxicity and capacity to reach target cells</p> <p>Coexistence of multiple metal NPs alter the original toxicity of individual NP [285, 288]</p> <p>Si NPs 7 + nm evoke oxidative stress and mitochondrial dysfunction [292, 293]</p> <p>Ti nanorods are associated with e-waste, while spherical Ti NPs are associated with food sources [297]</p> | <p>Mitochondria, Golgi apparatus, lysosomes, phagosomes, and nuclei [221]</p> <p>Need to define localization of NPs in the neurovascular unit, including the BBB at endothelial level (integrity of tight junctions) [221, 289]</p> <p>Within neurons, microglia, oligodendrocytes, astrocytes. Greater vulnerability of astrocytes expected [294]</p> <p>Subcellular accumulation in: Mitochondria, axons [295] and Autophagosomes [221, 296]</p> <p>Storage in autophagosomes [221]</p> <p>Membrane damage, cell cycle interference, reactive oxygen species formation [296]</p> |

per patient for care and service in the U.S. is \$1,433,992, excluding societal cost and family support cost [303]). We are hopeful that further research will address the urgent need to act upon modifiable risk factors for military personnel who deserve enhanced protection during their years of service for both their short- and long-term health.

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References

- Rowland LP, Mitumoto H, Przedborski S (2010) Amyotrophic lateral sclerosis, progressive muscular atrophy, and primary lateral sclerosis. In: Rowland LP, Pedley TA (eds) *Merritt's neurology*. Williams & Wilkins, Lippincott, pp 802–808
- Mejzini R et al (2019) ALS genetics, mechanisms, and therapeutics: where are we now? *Front Neurosci* 13:1310
- Mathis S et al (2019) Genetics of amyotrophic lateral sclerosis: A review. *J Neurol Sci* 399:217–226
- Nguyen HP et al (2018) ALS genes in the genomic era and their implications for FTD. *Trends Genet* 34(6):404–423
- Harms MM et al (1993) TARDBP-related amyotrophic lateral sclerosis. In: Adam MP (eds) *GeneReviews* [Internet]. University of Washington, Seattle, WA
- Leblond CS et al (2014) Dissection of genetic factors associated with amyotrophic lateral sclerosis. *Exp Neurol* 262(Pt B):91–101
- Cady J et al (2015) Amyotrophic lateral sclerosis onset is influenced by the burden of rare variants in known amyotrophic lateral sclerosis genes. *Ann Neurol* 77(1):100–113
- Al-Chalabi A et al (2010) An estimate of amyotrophic lateral sclerosis heritability using twin data. *J Neurol Neurosurg Psychiatry* 81(12):1324–1326
- Meltz Steinberg K et al (2015) Whole genome analyses reveal no pathogenetic single nucleotide or structural differences between monozygotic twins discordant for amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 16(5–6):385–392
- Camu W et al (1994) Conjugal amyotrophic lateral sclerosis: a report on two couples from Southern France. *Neurology* 44(3 Pt 1):547–548
- Gunnarsson LG, Bodin L (2018) Amyotrophic lateral sclerosis and occupational exposures: a systematic literature review and meta-analyses. *Int J Environ Res Public Health* 15(11):2371
- Andrew AS et al (2017) Environmental and occupational exposures and amyotrophic lateral sclerosis in New England. *Neurodegener Dis* 17(2–3):110–116
- Peters TL et al (2016) Blood levels of trace metals and amyotrophic lateral sclerosis. *Neurotoxicology* 54:119–126
- Figueroa-Romero C et al (2020) Early life metal dysregulation in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol* 7(6):872–882
- Kang H et al (2014) Amyotrophic lateral sclerosis and agricultural environments: a systematic review. *J Korean Med Sci* 29(12):1610–1617
- Institute of Medicine (2006) *Amyotrophic lateral sclerosis in veterans: review of the scientific literature*. The National Academies Press, Washington, DC
- Beard JD et al (2016) Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology. *Environ Int* 91:104–115
- Bello A et al (2017) Retrospective assessment of occupational exposures for the GENEVA study of ALS among military veterans. *Ann Work Expo Health* 61(3):299–310
- Sagiraju HKR et al (2020) Amyotrophic lateral sclerosis among veterans deployed in support of Post-9/11 U.S. conflicts. *Mil Med* 185(3–4):e501–e509
- Seals RM et al (2016) Amyotrophic lateral sclerosis and the military: a population-based study in the Danish Registries. *Epidemiology* 27(2):188–193
- Weisskopf MG et al (2005) Prospective study of military service and mortality from ALS. *Neurology* 64(1):32–37
- Fang F et al (2010) Association between blood lead and the risk of amyotrophic lateral sclerosis. *Am J Epidemiol* 171(10):1126–1133
- Mason LH et al (2014) Pb neurotoxicity: neuropsychological effects of lead toxicity. *Biomed Res Int* 2014:840547–840547
- Zeliger HI (2013) Exposure to lipophilic chemicals as a cause of neurological impairments, neurodevelopmental disorders and neurodegenerative diseases. *Interdiscip Toxicol* 6(3):103–110
- Birnbaum LS (1985) The role of structure in the disposition of halogenated aromatic xenobiotics. *Environ Health Perspect* 61:11–20
- Al-Chalabi A et al (2014) Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. *Lancet Neurol* 13(11):1108–1113
- Chiò A et al (2018) The multistep hypothesis of ALS revisited: the role of genetic mutations. *Neurology* 91(7):e635–e642
- Horner RD et al (2008) Amyotrophic lateral sclerosis among 1991 Gulf War veterans: evidence for a time-limited outbreak. *Neuroepidemiology* 31(1):28–32

29. Horner RD et al (2003) Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742–749
30. Haley RW (2003) Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750–756
31. McKay KA et al (2021) Military service and related risk factors for amyotrophic lateral sclerosis. *Acta Neurol Scand* 143(1):39–50
32. Beard JD, Kamel F (2015) Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology and survival. *Epidemiol Rev* 37(1):55–70
33. Department of Veterans Affairs (2009) Presumption of service connection for amyotrophic lateral sclerosis. Final rule. *Federal Regist* 74(212):57072–57074
34. Committee on the Assessment of the Readjustment Needs of Military Personnel, V.T., Families Board on the Health of Select, Populations Institute of Medicine (2013) In: *Returning home from Iraq and Afghanistan: assessment of readjustment needs of veterans, service members, and their families*. National Academies Press, Washington, DC
35. Institute of Medicine (1995) *Health consequences of service during the Persian Gulf War: initial findings and recommendations for immediate action*. The National Academies Press, Washington, DC
36. Hyams KC et al (2005) Resolving disputes about toxicological risks during military conflict: the US Gulf War experience. *Toxicol Rev* 24(3):167–180
37. Hotopf M, Wessely S (2005) Can epidemiology clear the fog of war? Lessons from the 1990–91 Gulf War. *Int J Epidemiol* 34(4):791–800
38. Kang HK et al (2002) Mortality among US and UK veterans of the Persian Gulf War: a review. *Occup Environ Med* 59(12):794–799
39. Rose MR, Brix KA (2006) Neurological disorders in Gulf War veterans. *Philos Trans R Soc Lond B Biol Sci* 361(1468):605–618
40. Armon C (2004) Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 62(6):1027–1029
41. Armon C (2007) Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 68(13):1083–1083
42. Coffman CJ et al (2005) Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990–1991) veterans using capture-recapture methods. *Neuroepidemiology* 24(3):141–150
43. Cox PA et al (2009) Cyanobacteria and BMAA exposure from desert dust: a possible link to sporadic ALS among Gulf War veterans. *Amyotroph Lateral Scler* 10(Suppl 2):109–117
44. Merwin SJ et al (2017) Organophosphate neurotoxicity to the voluntary motor system on the trail of environment-caused amyotrophic lateral sclerosis: the known, the unknown, and the unknown. *Arch Toxicol* 91(8):2939–2952
45. Dickerson AS et al (2018) Amyotrophic lateral sclerosis and exposure to diesel exhaust in a Danish cohort. *Am J Epidemiol* 187(8):1613–1622
46. Kurtzke JF, Beebe GW (1980) Epidemiology of amyotrophic lateral sclerosis: 1. A case–control comparison based on ALS deaths. *Neurology* 30(5):453–462
47. Pamphlett R, Rikard-Bell A (2013) Different occupations associated with amyotrophic lateral sclerosis: is diesel exhaust the link? *PLoS ONE* 8(11):e80993
48. Fang F et al (2009) Workplace exposures and the risk of amyotrophic lateral sclerosis. *Environ Health Perspect* 117(9):1387–1392
49. Park RM et al (2005) Potential occupational risks for neurodegenerative diseases. *Am J Ind Med* 48(1):63–77
50. IARC (1989) Diesel and gasoline engine exhausts and some nitroarenes, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer, Lyon, France
51. Steiner S et al (2016) Diesel exhaust: current knowledge of adverse effects and underlying cellular mechanisms. *Arch Toxicol* 90(7):1541–1553
52. Ehsanifar M et al (2019) Exposure to nanoscale diesel exhaust particles: oxidative stress, neuroinflammation, anxiety and depression on adult male mice. *Ecotoxicol Environ Saf* 168:338–347
53. Korotney D (2002) A comprehensive analysis of biodiesel impacts on exhaust emissions. Draft report of the US Environmental Protection Agency, Washington, DC
54. Chen H et al (2017) Living near major roads and the incidence of dementia, Parkinson’s disease, and multiple sclerosis: a population-based cohort study. *Lancet* 389(10070):718–726
55. Shi L et al (2020) Long-term effects of PM(2.5) on neurological disorders in the American Medicare population: a longitudinal cohort study. *Lancet Planet Health* 4(12):e557–e565
56. Filippini T et al (2021) Risk of amyotrophic lateral sclerosis and exposure to particulate matter from vehicular traffic: a case–control study. *Int J Environ Res Public Health* 18(3):973
57. Nunez Y et al (2021) Fine particle exposure and clinical aggravation in neurodegenerative diseases in New York State. *Environ Health Perspect* 129(2):27003
58. Bendtsen KM et al (2021) A review of health effects associated with exposure to jet engine emissions in and around airports. *Environ Health* 20(1):10
59. Nicholas JS et al (1998) Mortality among US commercial pilots and navigators. *J Occup Environ Med* 40(11):980–985
60. Bendtsen KM et al (2019) Airport emission particles: exposure characterization and toxicity following intratracheal instillation in mice. *Part Fibre Toxicol* 16(1):23
61. Pinkerton LE et al (2016) Mortality from neurodegenerative diseases in a cohort of US flight attendants. *Am J Ind Med* 59(7):532–537
62. Bonner JC (2010) Nanoparticles as a potential cause of pleural and interstitial lung disease. *Proc Am Thorac Soc* 7(2):138–141
63. Lu X et al (2014) Right or left: the role of nanoparticles in pulmonary diseases. *Int J Mol Sci* 15(10):17577–17600
64. Jonsdottir HR et al (2019) Non-volatile particle emissions from aircraft turbine engines at ground-idle induce oxidative stress in bronchial cells. *Commun Biol* 2:90
65. Masiol M, Harrison RM (2014) Aircraft engine exhaust emissions and other airport-related contributions to ambient air pollution: a review. *Atmos Environ* 95:409–455
66. Pleil JD et al (2000) Personal exposure to JP-8 jet fuel vapors and exhaust at air force bases. *Environ Health Perspect* 108(3):183–192
67. Pugh MJ et al (2016) Increasing prevalence of chronic lung disease in veterans of the wars in Iraq and Afghanistan. *Mil Med* 181(5):476–481
68. Fechter LD et al (2012) Subchronic JP-8 jet fuel exposure enhances vulnerability to noise-induced hearing loss in rats. *J Toxicol Environ Health A* 75(5):299–317
69. Kaufman LR et al (2005) Effects of concurrent noise and jet fuel exposure on hearing loss. *J Occup Environ Med* 47(3):212–218
70. Calderón-Garcidueñas L et al (2019) Increased gain in the auditory pathway, Alzheimer’s Disease Continuum, and air pollution: peripheral and central auditory system dysfunction evolves across pediatric and adult urbanites. *J Alzheimers Dis* 70(4):1275–1286
71. Griffith JD (2020) Electron microscopic characterization of exhaust particles containing lead dibromide beads expelled from aircraft burning leaded gasoline. *Atmos Pollut Res* 11(9):1481–1486

72. Austin E et al (2021) Distinct ultrafine particle profiles associated with aircraft and roadway traffic. *Environ Sci Technol* 55(5):2847–2858
73. Pant P, Harrison RM (2013) Estimation of the contribution of road traffic emissions to particulate matter concentrations from field measurements: a review. *Atmos Environ* 77:78–97
74. Amato F et al (2010) Concentrations, sources and geochemistry of airborne particulate matter at a major European airport. *J Environ Monit* 12(4):854–862
75. Bennett M et al (2011) Composition of smoke generated by landing aircraft. *Environ Sci Technol* 45(8):3533–3538
76. Morris K (2006) An estimation of the tyre material erosion from measurements of aircraft. British Airways Environmental Affairs, British Airways Technical Documents Relating to the Aircraft Operations Supporting the Project for the Sustainable Development of Heathrow, Document 7
77. Consensus Study Report (2015) Long-term health consequences of exposure to burn pits in Iraq and Afghanistan. *Mil Med* 180(6):601–613
78. Sharkey JM et al (2016) Postdeployment respiratory health care encounters following deployment to Kabul, Afghanistan: a retrospective cohort study. *Mil Med* 181(3):265–271
79. Liu J et al (2016) Burn Pit emissions exposure and respiratory and cardiovascular conditions among airborne hazards and open burn pit registry participants. *J Occup Environ Med* 58(7):e249–e255
80. National Academies of Sciences E et al (2017) In: Butler DA et al (eds) Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry. National Academies Press, Washington, DC
81. IARC (1984) Polynuclear aromatic hydrocarbons. Part 3, Industrial exposures in aluminum production, coal gasification, coke production, and iron and steel founding. In: International Agency for Research on Cancer Monographs on the Carcinogenic Risk of Chemicals to Humans.
82. Miguel A et al (1998) On-road emissions of particulate polycyclic aromatic hydrocarbons and black carbon from gasoline and diesel vehicles. *Environ Sci Technol* 32(4):450–455
83. Phillips D (1999) Polycyclic aromatic hydrocarbons in the diet. *Mutation Res* 443(1–2):139–147
84. Pedersen M et al (2009) Increased micronuclei and bulky DNA adducts in cord blood after maternal exposures to traffic-related air pollution. *Environ Res* 109:1012–1020
85. Lorenz DR et al (2021) Acrolein and other toxicant exposures in relation to cardiovascular disease among marijuana and tobacco smokers in a longitudinal cohort of HIV-positive and negative adults. *EClinicalMedicine* 31:100697
86. Bonner M et al (2005) Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. *Cancer Epidemiol Biomarkers Prev* 14(1):53–60
87. Obana H et al (1981) Polycyclic aromatic hydrocarbons in human fat and liver. *Bull Environ Contam Toxicol* 27:23–27
88. Ambrosone C, Shields P (1997) Molecular epidemiology of breast cancer. In: Aldaz C, et al (eds) Etiology of breast and gynecological cancers. Progress in Clinical and Biologic Research. Wiley-Liss Inc, New York, pp 93–99
89. Pastor-Belda M et al (2019) Bioaccumulation of polycyclic aromatic hydrocarbons for forensic assessment using gas chromatography–mass spectrometry. *Chem Res Toxicol* 32(8):1680–1688
90. Santodonato J (1997) Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere* 34(4):835–848
91. Kemp M et al (2006) Induction of the transferrin receptor gene by benzo[a]pyrene in breast cancer MCF-7 cells: potential as a biomarker of PAH exposure. *Environ Mol Mutagen* 47(7):518–526
92. Ralston S et al (1997) Stereoselective activation of dibenzo[a, l]pyrene and its trans-11,12-dihydrodiol to fjord region 11,12-diol 13,14-epoxides in a human mammary carcinoma MCF-7 cell-mediated V79 cell mutation assay. *Chem Res Toxicol* 10:687–693
93. Valand R et al (2018) Gene expression changes in rat brain regions after 7- and 28 days inhalation exposure to exhaust emissions from 1st and 2nd generation biodiesel fuels—the Fuel-Health project. *Inhal Toxicol* 30(7–8):299–312
94. Saunders CR et al (2006) Benzo(a)pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. *J Appl Toxicol* 26(5):427–438
95. Dutta K et al (2010) A common carcinogen benzo[a]pyrene causes neuronal death in mouse via microglial activation. *PLoS ONE* 5(4):e9984
96. Phani S et al (2012) The role of the innate immune system in ALS. *Front Pharmacol* 3:150
97. Das SK et al (2020) Chronic waterborne exposure to benzo[a]pyrene induces locomotor dysfunction and development of neurodegenerative phenotypes in zebrafish. *Neurosci Lett* 716:134646
98. Ohura T et al (2004) Polycyclic aromatic hydrocarbons in indoor and outdoor environments and factors affecting their concentrations. *Environ Sci Technol* 38(1):77–83
99. Kamel F et al (2012) Pesticide exposure and amyotrophic lateral sclerosis. *Neurotoxicology* 33(3):457–462
100. Goutman SA et al (2019) High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 90(8):907–912
101. Srogi K (2008) Levels and congener distributions of PCDDs, PCDFs and dioxin-like PCBs in environmental and human samples: a review. *Environ Chem Lett* 6(1):1–28
102. Ness DK et al (1994) PCB congeners in the rat brain: selective accumulation and lack of regionalization. *J Toxicol Environ Health* 43(4):453–468
103. Liberman DA et al (2020) Sex-specific effects of developmental exposure to polychlorinated biphenyls on neuroimmune and dopaminergic endpoints in adolescent rats. *Neurotoxicol Teratol* 79:106880
104. Bell MR et al (2018) Sex differences in effects of gestational polychlorinated biphenyl exposure on hypothalamic neuroimmune and neuromodulator systems in neonatal rats. *Toxicol Appl Pharmacol* 353:55–66
105. Manjaly ZR et al (2010) The sex ratio in amyotrophic lateral sclerosis: a population based study. *Amyotroph Lateral Scler* 11(5):439–442
106. Bouchard MF et al (2014) Polychlorinated biphenyl exposures and cognition in older US adults: NHANES (1999–2002). *Environ Health Perspect* 122(1):73–78
107. Su FC et al (2016) Association of environmental toxins with amyotrophic lateral sclerosis. *JAMA Neurol* 73(7):803–811
108. Ruder AM et al (2014) Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: a ten-year update. *Int J Hyg Environ Health* 217(2–3):176–187
109. Hatcher JM et al (2008) Parkinson’s disease and pesticides: a toxicological perspective. *Trends Pharmacol Sci* 29(6):322–329
110. Weisskopf MG et al (2010) Persistent organochlorine pesticides in serum and risk of Parkinson disease. *Neurology* 74(13):1055–1061
111. Rhodes SL et al (2013) Pesticides that inhibit the ubiquitin-proteasome system: effect measure modification by genetic variation in SKP1 in Parkinson’s disease. *Environ Res* 126:1–8
112. Steenland K et al (2013) Occupational pesticide exposure and screening tests for neurodegenerative disease among an elderly population in Costa Rica. *Environ Res* 120:96–101

113. Richardson JR et al (2009) Elevated serum pesticide levels and risk of Parkinson disease. *Arch Neurol* 66(7):870–875
114. Richardson JR et al (2011) β -Hexachlorocyclohexane levels in serum and risk of Parkinson's disease. *Neurotoxicology* 32(5):640–645
115. Corrigan FM et al (1996) Organochlorine compounds in human brain. *Hum Exp Toxicol* 15(3):262–264
116. Corrigan FM et al (2000) Organochlorine insecticides in substantia nigra in Parkinson's disease. *J Toxicol Environ Health A* 59(4):229–234
117. Hatcher JM et al (2007) Dieldrin exposure induces oxidative damage in the mouse nigrostriatal dopamine system. *Exp Neurol* 204(2):619–630
118. Hatcher JM et al (2008) Disruption of dopamine transport by DDT and its metabolites. *Neurotoxicology* 29(4):682–690
119. Bellou E et al (2020) Polygenic risk and pleiotropy in neurodegenerative diseases. *Neurobiol Dis* 142:104953
120. Pang SY et al (2017) The role of gene variants in the pathogenesis of neurodegenerative disorders as revealed by next generation sequencing studies: a review. *Transl Neurodegener* 6:27
121. Bradley WG et al (2018) Gene–environment–time interactions in neurodegenerative diseases: hypotheses and research approaches. *Ann Neurosci* 25(4):261–267
122. Nghi TN et al (2015) Dioxins and Nonortho PCBs in breast milk of vietnamese mothers living in the largest hot spot of dioxin contamination. *Environ Sci Technol* 49(9):5732–5742
123. Khan K et al (2016) Wartime toxin exposure: recognising the silent killer. *BMJ Case Rep*. <https://doi.org/10.1136/bcr-2016-217438>
124. Humphrey KM et al (2019) Establishing a role for environmental toxicant exposure induced epigenetic remodeling in malignant transformation. *Semin Cancer Biol* 57:86–94
125. Hill A et al (2003) Neurodevelopmental defects in zebrafish (*Danio rerio*) at environmentally relevant dioxin (TCDD) concentrations. *Toxicol Sci* 76(2):392–399
126. Xu G et al (2013) 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced inflammatory activation is mediated by intracellular free calcium in microglial cells. *Toxicology* 308:158–167
127. Xie HQ et al (2013) AhR-mediated effects of dioxin on neuronal acetylcholinesterase expression in vitro. *Environ Health Perspect* 121(5):613–618
128. Del Pino Sans J et al (2016) Developmental exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin may alter LH release patterns by abolishing sex differences in GABA/glutamate cell number and modifying the transcriptome of the male anterodorsal periventricular nucleus. *Neuroscience* 329:239–253
129. Gohlke JM et al (2009) AhR-mediated gene expression in the developing mouse telencephalon. *Reprod Toxicol* 28(3):321–328
130. Kimura E et al (2016) In utero and lactational dioxin exposure induces Sema3b and Sema3g gene expression in the developing mouse brain. *Biochem Biophys Res Commun* 476(2):108–113
131. Li Y et al (2013) 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induces microglial nitric oxide production and subsequent rat primary cortical neuron apoptosis through p38/JNK MAPK pathway. *Toxicology* 312:132–141
132. Xu G et al (2014) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces expression of p27(kip¹) and FoxO3a in female rat cerebral cortex and PC12 cells. *Toxicol Lett* 226(3):294–302
133. Ameyya HZ et al (2016) Dioxin induces Ahr-dependent robust DNA demethylation of the Cyp1a1 promoter via Tdg in the mouse liver. *Sci Rep* 6:34989
134. Ash PEA et al (2017) Dioxins and related environmental contaminants increase TDP-43 levels. *Mol Neurodegener* 12(1):35
135. Karri V et al (2018) Differential protein expression of hippocampal cells associated with heavy metals (Pb, As, and MeHg) neurotoxicity: deepening into the molecular mechanism of neurodegenerative diseases. *J Proteomics* 187:106–125
136. De Benedetti S et al (2017) Blood trace metals in a sporadic amyotrophic lateral sclerosis geographical cluster. *Biometals* 30(3):355–365
137. Roos PM et al (2013) Metal concentrations in cerebrospinal fluid and blood plasma from patients with amyotrophic lateral sclerosis. *Biol Trace Elem Res* 151(2):159–170
138. Callaghan B et al (2011) The association of exposure to lead, mercury, and selenium and the development of amyotrophic lateral sclerosis and the epigenetic implications. *Neurodegener Dis* 8(1–2):1–8
139. Trojsi F et al (2013) Exposure to environmental toxicants and pathogenesis of amyotrophic lateral sclerosis: state of the art and research perspectives. *Int J Mol Sci* 14(8):15286–15311
140. Cicero CE et al (2017) Metals and neurodegenerative diseases. A systematic review. *Environ Res* 159:82–94
141. Oggiano R et al (2018) Trace elements in ALS patients and their relationships with clinical severity. *Chemosphere* 197:457–466
142. Andrew AS et al (2018) Toenail mercury levels are associated with amyotrophic lateral sclerosis risk. *Muscle Nerve*. <https://doi.org/10.1002/mus.26055>
143. Andrew AS et al (2020) Keratinous biomarker of mercury exposure associated with amyotrophic lateral sclerosis risk in a nationwide U.S. study. *Amyotroph Lateral Scler Frontotemporal* 21:421–427
144. Andrew AS et al (2021) Risk factors for amyotrophic lateral sclerosis: a regional United States case–control study. *Muscle Nerve* 63(1):52–59
145. Kamel F et al (2005) Lead exposure as a risk factor for amyotrophic lateral sclerosis. *Neurodegener Dis* 2(3–4):195–201
146. Ingre C et al (2015) Risk factors for amyotrophic lateral sclerosis. *Clin Epidemiol* 7:181–193
147. Wang MD et al (2017) Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. *Neurotoxicology* 61:101–130
148. Belbasis L et al (2016) Environmental risk factors and amyotrophic lateral sclerosis: an umbrella review and critical assessment of current evidence from systematic reviews and meta-analyses of observational studies. *Neuroepidemiology* 46(2):96–105
149. Neal AP, Guilarte TR (2013) Mechanisms of lead and manganese neurotoxicity. *Toxicol Res (Camb)* 2(2):99–114
150. Ash PEA et al (2019) Heavy metal neurotoxicants induce ALS-linked TDP-43 pathology. *Toxicol Sci* 167(1):105–115
151. Kasperczyk S et al (2015) The effect of occupational lead exposure on lipid peroxidation, protein carbonylation, and plasma viscosity. *Toxicol Ind Health* 31(12):1165–1171
152. Laidlaw MAS et al (2017) Lead exposure at firing ranges—a review. *Environ Health* 16(1):34–34
153. Dickerson AS et al (2019) Population-based study of amyotrophic lateral sclerosis and occupational lead exposure in Denmark. *Occup Environ Med* 76(4):208–214
154. Zahran S et al (2017) Motor neuron disease mortality and lifetime petrol lead exposure: evidence from national age-specific and state-level age-standardized death rates in Australia. *Environ Res* 153:181–190
155. Khare SS et al (1990) Trace element imbalances in amyotrophic lateral sclerosis. *Neurotoxicology* 11(3):521–532
156. Zufiría M et al (2016) ALS: A bucket of genes, environment, metabolism and unknown ingredients. *Prog Neurobiol* 142:104–129
157. Adams CR et al (1983) Mercury intoxication simulating amyotrophic lateral sclerosis. *JAMA* 250(5):642–643

158. Praline J et al (2007) ALS and mercury intoxication: a relationship? *Clin Neurol Neurosurg* 109(10):880–883
159. Mangelsdorf I et al (2017) Healing of amyotrophic lateral sclerosis: a case report. *Complement Med Res* 24(3):175–181
160. Arvidson B (1992) Accumulation of inorganic mercury in lower motoneurons of mice. *Neurotoxicology* 13(1):277–280
161. Chuu J-J et al (2007) Differential neurotoxic effects of methylmercury and mercuric sulfide in rats. *Toxicol Lett* 169(2):109–120
162. Farina M et al (2011) Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. *Life Sci* 89(15–16):555–563
163. Mitchell JD et al (1986) Trace elements in the spinal cord and other tissues in motor neuron disease. *J Neurol Neurosurg Psychiatry* 49(2):211–215
164. Estevez AO et al (2012) Selenium induces cholinergic motor neuron degeneration in *Caenorhabditis elegans*. *Neurotoxicology* 33(5):1021–1032
165. Vinceti M et al (2012) Are environmental exposures to selenium, heavy metals, and pesticides risk factors for amyotrophic lateral sclerosis? *Rev Environ Health* 27(1):19–41
166. Vinceti M et al (2013) Cerebrospinal fluid of newly diagnosed amyotrophic lateral sclerosis patients exhibits abnormal levels of selenium species including elevated selenite. *Neurotoxicology* 38:25–32
167. Bilen B et al (2018) Examination of metal mobilization from a gunshot by scanning acoustic microscopy, scanning electron microscopy, energy-dispersive X-ray spectroscopy, and inductively coupled plasma optical emission spectroscopy: a case report. *J Med Case Reports* 12(1):391
168. Kilness AW, Hichberg FH (1977) Amyotrophic lateral sclerosis in a high selenium environment. *JAMA* 237(26):2843–2844
169. Vinceti M et al (1996) Amyotrophic lateral sclerosis after long-term exposure to drinking water with high selenium content. *Epidemiology* 7(5):529–532
170. Markesbery WR et al (1995) Neutron activation analysis of trace elements in motor neuron disease spinal cord. *Neurodegeneration* 4(4):383–390
171. Moriwaka F et al (1993) Mercury and selenium contents in amyotrophic lateral sclerosis in Hokkaido, the northernmost island of Japan. *J Neurol Sci* 118(1):38–42
172. Gribble MO et al (2016) Mercury, selenium and fish oils in marine food webs and implications for human health. *J Mar Biol Assoc U K* 96(1):43–59
173. Ralston NV (2008) Selenium health benefit values as seafood safety criteria. *EcoHealth* 5(4):442–455
174. Bergomi M et al (2002) Environmental exposure to trace elements and risk of amyotrophic lateral sclerosis: a population-based case–control study. *Environ Res* 89(2):116–123
175. Dang TN et al (2014) Increased metal content in the TDP-43(A315T) transgenic mouse model of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Front Aging Neurosci* 6:15
176. Lovejoy DB, Guillemin GJ (2014) The potential for transition metal-mediated neurodegeneration in amyotrophic lateral sclerosis. *Front Aging Neurosci* 6:173
177. Choi BS, Zheng W (2009) Copper transport to the brain by the blood–brain barrier and blood–CSF barrier. *Brain Res* 1248:14–21
178. Guilarte TR (2010) Manganese and Parkinson’s disease: a critical review and new findings. *Environ Health Perspect* 118(8):1071–1080
179. Wiśniewska-Hejka Z et al (1978) Neurological examinations of workers with chronic exposure to manganese dioxide during the production of piles and batteries. *Neurol Neurochir Pol* 12(4):435–441
180. Voss H (1939) Progressive bulbar paralysis and amyotrophic lateral sclerosis following chronic manganese poisoning. *Arch Gewerbepath Gewerbehyg* 9:464–476
181. Yanagihara R (1982) Heavy metals and essential minerals in motor neuron disease. *Adv Neurol* 36:233–247
182. Miyata S et al (1983) Increased manganese level in spinal cords of amyotrophic lateral sclerosis determined by radiochemical neutron activation analysis. *J Neurol Sci* 61(2):283–293
183. Hozumi I et al (2011) Patterns of levels of biological metals in CSF differ among neurodegenerative diseases. *J Neurol Sci* 303(1–2):95–99
184. Roos PM et al (2012) Manganese in cerebrospinal fluid and blood plasma of patients with amyotrophic lateral sclerosis. *Exp Biol Med* (Maywood) 237(7):803–810
185. Kasarskis EJ et al (1995) Aluminum, calcium, and iron in the spinal cord of patients with sporadic amyotrophic lateral sclerosis using laser microprobe mass spectroscopy: a preliminary study. *J Neurol Sci* 130(2):203–208
186. Jeong SY et al (2009) Dysregulation of iron homeostasis in the CNS contributes to disease progression in a mouse model of amyotrophic lateral sclerosis. *J Neurosci* 29(3):610–619
187. Kwan JY et al (2012) Iron accumulation in deep cortical layers accounts for MRI signal abnormalities in ALS: correlating 7 tesla MRI and pathology. *PLoS ONE* 7(4):e35241
188. Wang Q et al (2011) Prevention of motor neuron degeneration by novel iron chelators in SOD1(G93A) transgenic mice of amyotrophic lateral sclerosis. *Neurodegener Dis* 8(5):310–321
189. Vahidnia A et al (2007) Arsenic neurotoxicity—a review. *Hum Exp Toxicol* 26(10):823–832
190. Mazumdar S et al (2010) Arsenicosis: unusual neurological presentation from West Bengal. *J Assoc Physicians India* 58:201–202
191. Tyler CR, Allan AM (2014) The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. *Curr Environ Health Rep* 1(2):132–147
192. Dubey M, Shea TB (2007) Potentiation of arsenic neurotoxicity by folate deprivation: protective role of S-adenosyl methionine. *Nutr Neurosci* 10(5–6):199–204
193. Goh CW et al (2018) Chronic oxidative stress promotes GADD34-mediated phosphorylation of the TAR DNA-binding protein TDP-43, a modification linked to neurodegeneration. *J Biol Chem* 293(1):163–176
194. Lukiw WJ et al (2019) Aluminum in neurological disease—a 36 year multicenter study. *J Alzheimers Dis Parkinsonism* 8(6):457
195. Kaniias GD, Kapaki E (1997) Trace elements, age, and sex in amyotrophic lateral sclerosis disease. *Biol Trace Elem Res* 56(2):187–201
196. Kapaki E et al (1989) Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders. *Acta Neurol Scand* 79(5):373–378
197. Bar-Sela S et al (2001) Amyotrophic lateral sclerosis in a battery-factory worker exposed to cadmium. *Int J Occup Environ Health* 7(2):109–112
198. Vinceti M et al (2017) Lead, cadmium and mercury in cerebrospinal fluid and risk of amyotrophic lateral sclerosis: a case–control study. *J Trace Elem Med Biol* 43:121–125
199. Dickerson AS et al (2020) Study of occupational chromium, iron, and nickel exposure and amyotrophic lateral sclerosis in Denmark. *Int J Environ Res Public Health* 17(21):8086
200. Bourke CA (2016) Molybdenum deficiency produces motor nervous effects that are consistent with amyotrophic lateral sclerosis. *Front Neurol* 7:28
201. Grochowski C et al (2019) Analysis of trace elements in human brain: its aim, methods, and concentration levels. *Front Chem* 7:115
202. Gellein K et al (2003) Concentrations of Cd Co, Cu, Fe, Mn, Rb, V, and Zn in formalin-fixed brain tissue in amyotrophic

- lateral sclerosis and Parkinsonism-dementia complex of Guam determined by High-resolution ICP-MS. *Biol Trace Elem Res* 96(1–3):39–60
203. Huat TJ et al (2019) Metal toxicity links to Alzheimer's disease and neuroinflammation. *J Mol Biol* 431(9):1843–1868
 204. Waterman SJ et al (1994) Lead alters the immunogenicity of two neural proteins: a potential mechanism for the progression of lead-induced neurotoxicity. *Environ Health Perspect* 102(12):1052–1056
 205. Nakagawa Y, Yamada S (2021) A novel hypothesis on metal dyshomeostasis and mitochondrial dysfunction in amyotrophic lateral sclerosis: potential pathogenetic mechanism and therapeutic implications. *Eur J Pharmacol* 892:173737
 206. Hadjidemetriou M, Kostarelos K (2017) Nanomedicine: evolution of the nanoparticle corona. *Nat Nanotechnol* 12(4):288–290
 207. Cedervall T et al (2007) Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc Natl Acad Sci USA* 104(7):2050–2055
 208. Shang L et al (2014) Engineered nanoparticles interacting with cells: size matters. *J Nanobiotechnology* 12:5
 209. Sawicki K et al (2019) Toxicity of metallic nanoparticles in the central nervous system. *Nanotechnol Rev* 8(1):175–200
 210. Salvati A et al (2013) Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. *Nat Nanotechnol* 8(2):137–143
 211. Gato MA et al (2014) Physicochemical properties of nanomaterials: implication in associated toxic manifestations. *BioMed Res Int*. <https://doi.org/10.1155/2014/498420>
 212. Aillon KL et al (2009) Effects of nanomaterial physicochemical properties on in vivo toxicity. *Adv Drug Deliv Rev* 61(6):457–466
 213. Chen X, Schluesener HJ (2008) Nanosilver: a nanoproduct in medical application. *Toxicol Lett* 176(1):1–12
 214. Ahamed M et al (2010) Silver nanoparticle applications and human health. *Clin Chim Acta* 411(23–24):1841–1848
 215. Singh AK (2015) Engineered nanoparticles: structure, properties and mechanisms of toxicity. Academic Press, New York
 216. Khan I et al (2019) Nanoparticles: properties, applications and toxicities. *Arab J Chem* 12(7):908–931
 217. Zhang XQ et al (2012) Interactions of nanomaterials and biological systems: implications to personalized nanomedicine. *Adv Drug Deliv Rev* 64(13):1363–1384
 218. Jeevanandam J et al (2018) Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. *Beilstein J Nanotechnol* 9:1050–1074
 219. Bundschuh M et al (2018) Nanoparticles in the environment: where do we come from, where do we go to? *Environ Sci Eur* 30(1):6–6
 220. Teleanu DM et al (2018) Impact of nanoparticles on brain health: an up to date overview. *J Clin Med* 7(12):490
 221. Calderón-Garcidueñas L et al (2020) Quadruple abnormal protein aggregates in brainstem pathology and exogenous metal-rich magnetic nanoparticles. The substantia nigrae is a very early target in young urbanites and the gastrointestinal tract likely a key brainstem portal. *Environ Res* 191:110139
 222. Oberdörster G et al (2004) Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol* 16(6–7):437–445
 223. Fröhlich E, Salar-Behzadi S (2014) Toxicological assessment of inhaled nanoparticles: role of in vivo, ex vivo, in vitro, and in silico studies. *Int J Mol Sci* 15(3):4795–4822
 224. De Matteis V (2017) Exposure to inorganic nanoparticles: routes of entry, immune response, biodistribution and in vitro/in vivo toxicity evaluation. *Toxics* 5(4):29
 225. Gao H (2016) Progress and perspectives on targeting nanoparticles for brain drug delivery. *Acta Pharm Sin B* 6(4):268–286
 226. Busquets MA et al (2015) Magnetic nanoparticles cross the blood-brain barrier: when physics rises to a challenge. *Nanomaterials (Basel)* 5(4):2231–2248
 227. Zhou Y et al (2018) Crossing the blood–brain barrier with nanoparticles. *J Control Release* 270:290–303
 228. Lombardo SM et al (2020) Key for crossing the BBB with nanoparticles: the rational design. *Beilstein J Nanotechnol* 11:866–883
 229. Garcia GJM et al (2015) Olfactory deposition of inhaled nanoparticles in humans. *Inhalation Toxicol* 27(8):394–403
 230. Pardeshi CV, Belgamwar VS (2013) Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting. *Expert Opin Drug Deliv* 10(7):957–972
 231. Elder A et al (2006) Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ Health Perspect* 114(8):1172–1178
 232. Sutunkova M et al (2019) Toxic effects of low-level long-term inhalation exposures of rats to nickel oxide nanoparticles. *Int J Mol Sci* 20:1778
 233. Riediker M et al (2019) Particle toxicology and health—where are we? *Part Fibre Toxicol* 16(1):19
 234. Lewinski N et al (2008) Cytotoxicity of nanoparticles. *Small* 4(1):26–49
 235. Zoroddu MA et al (2014) Toxicity of nanoparticles. *Curr Med Chem* 21(33):3837–3853
 236. Li J, Ju D (2017) Neurotoxicity of nanomaterials and nanomedicine. Academic Press, New York
 237. Kumar V et al (2018) Chapter 17—impact of nanoparticles on oxidative stress and responsive antioxidative defense in plants. In: Tripathi DK et al (eds) *Nanomaterials in plants, algae, and microorganisms*. Academic Press, New York, pp 393–406
 238. Zuberek M, Grzelak A (2018) Nanoparticles-caused oxidative imbalance. *Adv Exp Med Biol* 1048:85–98
 239. Mauricio MD et al (2018) Nanoparticles in medicine: a focus on vascular oxidative stress. *Oxid Med Cell Longev* 2018:6231482–6231482
 240. Ganguly R et al (2019) Chapter 3—nanoparticles as modulators of oxidative stress. In: Maurya PK, Singh S (eds) *Nanotechnology in modern animal biotechnology*. Elsevier, Amsterdam, pp 29–35
 241. Lovisolo D et al (2018) Nanoparticles and potential neurotoxicity: focus on molecular mechanisms. *AIMS Mol Sci* 5:1–13
 242. Grissa I et al (2016) The effect of titanium dioxide nanoparticles on neuroinflammation response in rat brain. *Environ Sci Pollut Res Int* 23(20):20205–20213
 243. Kim B-G et al (2020) Effects of nanoparticles on neuroinflammation in a mouse model of asthma. *Respir Physiol Neurobiol* 271:103292
 244. Liang H et al (2018) Neuroinflammation is induced by tongue-instilled ZnO nanoparticles via the Ca²⁺-dependent NF-κB and MAPK pathways. *Part Fibre Toxicol* 15(1):39
 245. Manickam V et al (2018) Iron oxide nanoparticles induces cell cycle-dependent neuronal apoptosis in mice. *J Mol Neurosci* 64(3):352–362
 246. Sheng L et al (2015) Mechanisms of TiO₂ nanoparticle-induced neuronal apoptosis in rat primary cultured hippocampal neurons. *J Biomed Mater Res A* 103(3):1141–1149
 247. Lebda MA et al (2018) Potential role of α-lipoic acid and Ginkgo biloba against silver nanoparticles-induced neuronal apoptosis and blood-brain barrier impairments in rats. *Life Sci* 212:251–260

248. Xue Y et al (2012) Four types of inorganic nanoparticles stimulate the inflammatory reaction in brain microglia and damage neurons in vitro. *Toxicol Lett* 214(2):91–98
249. Imam SZ et al (2015) Iron oxide nanoparticles induce dopaminergic damage: in vitro pathways and in vivo imaging reveals mechanism of neuronal damage. *Mol Neurobiol* 52(2):913–926
250. Elsaesser A, Howard CV (2012) Toxicology of nanoparticles. *Adv Drug Deliv Rev* 64(2):129–137
251. Trickler WJ et al (2010) Silver nanoparticle induced blood-brain barrier inflammation and increased permeability in primary rat brain microvessel endothelial cells. *Toxicol Sci* 118(1):160–170
252. Haase A et al (2012) Effects of silver nanoparticles on primary mixed neural cell cultures: uptake, oxidative stress and acute calcium responses. *Toxicol Sci* 126(2):457–468
253. Calderón-Garcidueñas L et al (2020) Alzheimer disease starts in childhood in polluted Metropolitan Mexico City. A major health crisis in progress. *Environ Res* 183:109137
254. Calderón-Garcidueñas L et al (2019) Combustion and friction-derived nanoparticles and industrial-sourced nanoparticles: the culprit of Alzheimer and Parkinson's diseases. *Environ Res* 176:108574
255. Hopkins LE et al (2018) Repeated iron-soot exposure and nose-to-brain transport of inhaled ultrafine particles. *Toxicol Pathol* 46(1):75–84
256. Maher BA et al (2016) Magnetite pollution nanoparticles in the human brain. *Proc Natl Acad Sci USA* 113(39):10797–10801
257. Valdiglesias V et al (2016) Are iron oxide nanoparticles safe? Current knowledge and future perspectives. *J Trace Elem Med Biol* 38:53–63
258. Castellani RJ et al (2007) Iron: the Redox-active center of oxidative stress in Alzheimer disease. *Neurochem Res* 32(10):1640–1645
259. Coccini T et al (2017) Cytotoxicity and proliferative capacity impairment induced on human brain cell cultures after short-and long-term exposure to magnetite nanoparticles. *J Appl Toxicol* 37(3):361–373
260. Yarjanli Z et al (2017) Iron oxide nanoparticles may damage to the neural tissue through iron accumulation, oxidative stress, and protein aggregation. *BMC Neurosci* 18(1):51
261. Teller S et al (2015) Magnetite-Amyloid- β deteriorates activity and functional organization in an in vitro model for Alzheimer's disease. *Sci Rep* 5:17261
262. Zhou M et al (2016) Implications for blood-brain-barrier permeability, in vitro oxidative stress and neurotoxicity potential induced by mesoporous silica nanoparticles: effects of surface modification. *RSC Adv* 6(4):2800–2809
263. You R et al (2018) Silica nanoparticles induce neurodegeneration-like changes in behavior, neuropathology, and affect synapse through MAPK activation. *Part Fibre Toxicol* 15(1):28
264. Distasi C et al (2018) SiO₂ nanoparticles modulate the electrical activity of neuroendocrine cells without exerting genomic effects. *Sci Rep* 8(1):2760
265. Li X et al (2014) SiO₂ nanoparticles change colour preference and cause Parkinson's-like behaviour in zebrafish. *Sci Rep* 4:3810
266. Yang X et al (2014) Uptake of silica nanoparticles: neurotoxicity and Alzheimer-like pathology in human SK-N-SH and mouse neuro2a neuroblastoma cells. *Toxicol Lett* 229(1):240–249
267. Song B et al (2016) Unraveling the neurotoxicity of titanium dioxide nanoparticles: focusing on molecular mechanisms. *Beilstein J Nanotechnol* 7:645–654
268. Wu T, Tang M (2018) The inflammatory response to silver and titanium dioxide nanoparticles in the central nervous system. *Nanomedicine* 13(2):233–249
269. Disdier C et al (2017) Brain inflammation, blood brain barrier dysfunction and neuronal synaptophysin decrease after inhalation exposure to titanium dioxide nano-aerosol in aging rats. *Sci Rep* 7(1):1–13
270. Calderón-Garcidueñas L et al (2018) Hallmarks of Alzheimer disease are evolving relentlessly in Metropolitan Mexico City infants, children and young adults. APOE4 carriers have higher suicide risk and higher odds of reaching NFT stage V at ≤ 40 years of age. *Environ Res* 164:475–487
271. Calderón-Garcidueñas L et al (2020) Gait and balance disturbances are common in young urbanites and associated with cognitive impairment. Air pollution and the historical development of Alzheimer's disease in the young. *Environ Res* 191:110087
272. Kim SH et al (2012) Rapid doubling of Alzheimer's amyloid- β 40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution. *F1000Res* 1:70
273. Purdey M (2004) Elevated levels of ferrimagnetic metals in foodchains supporting the Guam cluster of neurodegeneration: do metal nucleated crystal contaminants [corrected] evoke magnetic fields that initiate the progressive pathogenesis of neurodegeneration? *Med Hypotheses* 63(5):793–809
274. Afitska K et al (1867) (2019) α -Synuclein aggregation at low concentrations. *Biochim Biophys Acta Proteins Proteom* 7–8:701–709
275. Coufalík P et al (2019) Content of metals in emissions from gasoline, diesel, and alternative mixed biofuels. *Environ Sci Pollut Res Int* 26(28):29012–29019
276. Sonntag DB et al (2012) Contribution of lubricating oil to particulate matter emissions from light-duty gasoline vehicles in Kansas City. *Environ Sci Technol* 46(7):4191–4199
277. Casado JE et al (2017) Unctuous ZrO₂ nanoparticles with improved functional attributes as lubricant additives. *Nanotechnology* 28(49):495704
278. Yasar A et al (2021) A comparison of waste recycling facilities for their contribution of heavy metals and trace elements in ambient air. *Environ Sci Pollut Res Int* 28:1–9
279. Cenci MP et al (2020) Precious and critical metals from wasted LED lamps: characterization and evaluation. *Environ Technol* 10:1–12
280. Bhagat J et al (2021) Toxicological interactions of microplastics/nanoplastics and environmental contaminants: current knowledge and future perspectives. *J Hazard Mater* 405:123913
281. Okeme JO, Arrandale VH (2019) Electronic waste recycling: occupational exposures and work-related health effects. *Curr Environ Health Rep* 6(4):256–268
282. Ghoshdastidar AJ, Ariya PA (2019) The existence of airborne mercury nanoparticles. *Sci Rep* 9(1):10733
283. Cardoso CED et al (2019) Recovery of rare earth elements by carbon-based nanomaterials—a review. *Nanomaterials (Basel)* 9(6):814
284. Živančević K et al (2021) Elucidating the influence of environmentally relevant toxic metal mixture on molecular mechanisms involved in the development of neurodegenerative diseases: In silico toxicogenomic data-mining. *Environ Res* 194:110727
285. Hang BT, Anh TT (2021) Controlled synthesis of various Fe₂O₃ morphologies as energy storage materials. *Sci Rep* 11(1):5185
286. Oggiano R et al (2021) An overview on amyotrophic lateral sclerosis and cadmium. *Neurol Sci* 42(2):531–537
287. Roos E et al (2020) Amyotrophic lateral sclerosis after exposure to manganese from traditional medicine procedures in Kenya. *Biol Trace Elem Res* 199:3618–3624
288. Engin AB (2021) Combined toxicity of metal nanoparticles: comparison of individual and mixture particles effect. *Adv Exp Med Biol* 1275:165–193
289. Calderón-Garcidueñas L et al (2002) Air pollution and brain damage. *Toxicol Pathol* 30(3):373–389

290. Tesaro M et al (2021) Metal(loid)s role in the pathogenesis of amyotrophic lateral sclerosis: environmental, epidemiological, and genetic data. *Environ Res* 192:110292
291. National Research Council Committee for Review of the, D.s.E.P.M.S.P.R. (2010) In Review of the Department of Defense Enhanced Particulate Matter Surveillance Program Report, National Academies Press (US). Copyright 2010 by the National Academy of Sciences. All rights reserved
292. Olvera HA et al (2013) Ultrafine particle levels at an international port of entry between the US and Mexico: exposure implications for users, workers, and neighbors. *J Expo Sci Environ Epidemiol* 23(3):289–298
293. Guerrero-Beltrán CE et al (2017) Silica nanoparticles induce cardiotoxicity interfering with energetic status and Ca(2+) handling in adult rat cardiomyocytes. *Am J Physiol Heart Circ Physiol* 312(4):H645-h661
294. Limón-Pacheco JH et al (2020) Astrocytes are more vulnerable than neurons to silicon dioxide nanoparticle toxicity in vitro. *Toxics* 8(3):51
295. Wei J et al (2020) Low-dose exposure of silica nanoparticles induces neurotoxicity via neuroactive ligand-receptor interaction signaling pathway in Zebrafish embryos. *Int J Nanomedicine* 15:4407–4415
296. Lojk J et al (2020) Toxicity mechanisms of selected engineered nanoparticles on human neural cells in vitro. *Toxicology* 432:152364
297. Gulati K et al (2012) Nanoengineered drug-releasing Ti wires as an alternative for local delivery of chemotherapeutics in the brain. *Int J Nanomedicine* 7:2069–2076
298. Weiner MW et al (2013) Military risk factors for Alzheimer's disease. *Alzheimers Dement* 9(4):445–451
299. Heyburn L et al (2019) The role of TDP-43 in military-relevant TBI and chronic neurodegeneration. *Front Neurol* 10:680
300. Weedn VW (2020) Origins of the armed forces medical examiner system. *Acad Forensic Pathol* 10(1):16–34
301. Brady CB et al (2013) The Department of Veterans Affairs Biorepository Brain Bank: a national resource for amyotrophic lateral sclerosis research. *Amyotroph Lateral Scler Frontotemporal Degener* 14(7–8):591–597
302. O'Leary MC et al (2021) Development of a multi-study repository to support research on veteran health: the VA Cooperative Studies Program Epidemiology Center-Durham (CSPEC-Durham) Data and Specimen Repository. *Front Public Health* 9:612806
303. Obermann M, Lyon M (2015) Financial cost of amyotrophic lateral sclerosis: a case study. *Amyotroph Lateral Scler Frontotemporal Degener* 16(1–2):54–57