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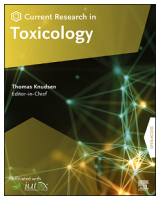

Mechanisms of neurotoxicity of fluoride or aluminum: implications for neurodegenerative disease risk

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ABSTRACT

Fluoride and aluminum are two naturally abundant elements with widespread industrial uses. Fluoride is also added to community water supplies as a public health intervention for dental cavity prevention. However, findings from animal studies show potential links of fluoride and aluminum exposure with neurodegenerative disease risk, particularly at high exposure levels. This review uniquely examines neurochemical and neurobiological impacts of fluoride and aluminum exposure as well as whether these processes may increase the risk of common and rare neurodegenerative diseases, including dementia, Parkinson's Disease, and motor neuron disease.

Fluoride and aluminum can cross the blood–brain barrier and accumulate in neural tissue, where they can interact to produce neurotoxic effects. Chronic exposure to fluoride and aluminum can cause oxidative stress, mitochondrial dysfunction, brain inflammation, and disruption of essential ions. These effects can contribute to impaired nerve signaling, cell damage, and protein aggregation—key factors in neurodegeneration. Co-exposure to aluminum–fluoride complexes may worsen these effects by increasing amyloid buildup and causing nerve cell death, although more research on aluminum-fluoride interactions is needed.

Additionally, many animal studies include relatively high fluoride or aluminum exposure levels, and epidemiological human data are scarce, particularly for less common neurodegenerative diseases. Moreover, these studies often rely on ecological or occupational exposure measures rather than individual biomarkers. Findings of this narrative review underscore the need for methodologically rigorous longitudinal human studies on fluoride, aluminum and neurodegenerative disease risk, particularly given the mechanistic basis for these potential associations.

1. Introduction

1.1. Fluoride exposure and public health

Fluoride naturally occurs in rock and soil and can leach into the drinking water via these media (Ozsvath, 2009). Fluoride can also be produced industrially as a biproduct of phosphate fertilizer or aluminum manufacturing. The addition of fluoride to salt, milk, or water has been used as a public health intervention since the 1940s to prevent dental caries, a major cause of global disease burden (ten Cate and Buzalaf, 2019; Pontigo-Loyola et al., 2024; Duchon, 2020). However, excess environmental fluoride exposure may also be a potential source of harm to animals, plants, and the public (Aguirre-Sierra et al., 2013; Banerjee et al., 2021; Taylor et al., 2025a). Industrial exposure to fluoride is also possible given that fluoride is used in the aluminum, petroleum, and plastics industries. Therefore, workers in these industries may be exposed to higher levels of fluoride than the general population (Choubisa and Choubisa, 2016).

According to the CDC and other major health organizations, community water fluoridation is a safe and cost-effective public health intervention that significantly reduces the prevalence of dental caries across all age groups (*JAMA*, 2000). As such, in 2022, more than 60% of the U.S. population had access to fluorinated community water systems for dental caries prevention with a targeted concentration of 0.7 mg/L (CDC, 2025; My Water's Fluoride, 2026; U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation, 2015). Furthermore, the CDC lists community fluoridation as one of the 10 greatest public health achievements of the 20th century due to its

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role in improving dental health equity (*JAMA*, 1999). However, concerns about potential risks of fluoride exposure to the brain, particularly during early development, as well as findings from a recent Cochrane review showing a weak benefit of fluoridation for dental caries prevention, have called this into question in recent years (Taylor et al., 2025b; Iheozor-Ejiofor et al., 2024).

The National Sanitation Foundation (NSF) approves three chemical additives for community fluoridation. These include hydrofluorosilic acid, sodium fluoride and sodium hexafluorisilicate (Duchon, 2020; National Sanitation Foundation, 2025). While the primary ingredient of these additives is fluoride, they can also contain other metals, including barium, lead, and aluminum, with aluminum levels being particularly high (Mullenix, 2014).

1.2. Aluminum exposure and bioavailability

Aluminum (Al) is one of the most abundant metals in the Earth's crust. It is widely present in the environment through soil erosion, volcanic eruptions, and manufacturing processes (Kuroda, 2000). Al ingestion can occur through certain foods, water, pharmaceuticals, cookware, vaccines, cosmetic products, and some industrially processed foods contaminated with Al (Greger, 1992; Pennington, 1988). Pine nuts, cocoa powder, and baking mixes are foods that can all have a high aluminum content (Stahl et al., 2017). While cookware is a main source of aluminum exposure, aluminum is poorly absorbed via the gastrointestinal tract but is more bioavailable when exposure is intramuscular or intravenous rather than oral (Soni et al., 2001). Skin absorption plays a secondary role and has been associated with an increased risk of breast cancer through aluminum-containing deodorants in some studies (Darbre, 2005) but not others (Mousavi and Vaghar, 2021; Namer et al., 2008). Long-term workers in the aluminum industry are also at an increased likelihood of aluminum exposure via inhalation from the aluminum-containing dust (Kraus et al., 2006).

The bioavailability of aluminum depends on the aluminum compound (ATSDR). Aluminum bound to a ligand is more soluble by forming a stable complex. For example, aluminum-citrate, the most soluble form, enhances gastrointestinal absorption and renal excretion due to its high solubility and small molecular size (Priest, 2004; Yokel, 2001). Whereas the absorption of aluminum also depends on the solution chemistry of the $Al3^{+}$ ions in the gastrointestinal fluid and the gastrointestinal pH (Berthon, 1996). In addition, the massive hydration of $Al3^{+}$ ions allows them to cross the intestinal epithelium paracellularly by solvent dragging (Berthon, 1996). Finally, aluminum can interfere with normal physiological absorption by substituting for essential elements or combining with them along shared pathways (Birch, 1995). While there is currently no enforceable maximum contaminant level (MCL) for aluminum in drinking water (i.e., a health-based standard set by the U.S. Environmental Protection Agency (EPA)), a Secondary Maximum Contaminant Level (SMCL) guideline of 0.05–0.2 mg/L has been established. SMCLs are non-enforceable guidelines that address aesthetic qualities such as taste, color, or odor rather than direct health risks (Public health service Agency for Toxic Substances and Disease Registry, 2008).

1.3. Health effects of excess fluoride and aluminum exposure

Excess fluoride and aluminum intake have been associated with adverse health effects. Both high and population-relevant levels of fluoride exposure have been associated with dental fluorosis, suppression of thyroid gland activity, and alterations in kidney and liver function parameters (Lin et al., 2023; Malin et al., 2018; Malin et al., 2019; Dong et al., 2021). In addition, several epidemiological studies have observed associations between higher prenatal, infant or childhood fluoride exposure and poorer child neurodevelopment outcomes, including reduced IQ, attention deficits, and behavior changes – even at fluoride concentrations near 0.7 mg/L found in fluoridated communities (Taylor et al., 2025a; Cantoral et al., 2021; Green et al., 2019; Malin et al., 2024; Bashash et al., 2018). These findings have raised concern about fetal and infant vulnerability during sensitive windows of brain development. However, the clinical and public health significance of these findings remains a subject of scientific debate (Taylor et al., 2025a). Moreover, there are few studies examining exposure to fluoride and neurocognitive outcomes in adults (Taylor et al., 2025a). Similarly, high levels of Al exposure have been shown to accumulate and cause functional damage to the nervous system, blood, bone, as well as respiratory, and immune systems (Willhite et al., 2012). High levels of aluminum have also been associated with neurocognitive changes in aluminum workers along with neurodegeneration; however, there are few studies on low-level aluminum exposure in relation to neurocognitive outcomes (Zeng et al., 2021).

Fluoride and aluminum frequently co-occur in environmental and occupational settings, including drinking water systems and industrial exposures. Despite this, most existing studies have examined their neurotoxic effects independently rather than jointly. Animal studies show that fluoride and aluminum exposure may contribute to neurodegeneration via similar molecular mechanisms. Moreover, there is evidence that their potential neurodegenerative impacts may interact through overlapping or complementary biological pathways (Varner et al., 1998; Russ et al., 2020). However, the extent to which co-exposure contributes to neurodegenerative processes in humans remains poorly understood and represents and import gap in the literature.

The following provides a comprehensive narrative review of the literature on potential neurodegenerative impacts of fluoride and aluminum exposure, as well as whether they are associated with neurodegenerative diseases. This narrative review was conducted by searching PubMed and Google Scholar for studies examining fluoride and aluminum exposure in relation to neurodegenerative diseases, including dementia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and prion diseases, as well as related neurobiological mechanisms. Search terms included combinations of “fluoride,” “aluminum,” “neurodegeneration,” “dementia,” “Parkinson's disease,” “ALS,” “prion disease,” “neurodegeneration,” and “neuroinflammation.” Both experimental and epidemiological studies were considered. No formal systematic review protocol was applied. Notably, no studies were identified examining fluoride or aluminum exposure in relation to prion diseases (See Table 1).

2. Neurodegeneration

2.1. Epidemiology of neurodegenerative diseases

Neurodegenerative diseases gradually damage and destroy parts of the central and/or peripheral nervous system. They often develop slowly, and symptoms begin to emerge in late adulthood. These diseases include dementia (including Alzheimer's disease), Parkinson's Disease, Motor Neuron Diseases (MND) such as Amyotrophic Lateral Sclerosis (ALS), and Prion Disease (e.g. Creutzfeldt-Jakob Disease). As of 2021, 57 million people worldwide were diagnosed with dementia, with nearly 10 million new cases per year (Dementia, 2026). Furthermore, it is estimated that 6.7 million older adults in the United States (US) currently suffer from Alzheimer's disease and the number is expected to reach 14 million by 2060 (CDC, 2024; Alzheimer, Association, 2024). In 2015, the total global social cost of dementia was estimated to be $818 billion (Wimo et al., 2017). Additionally, Parkinson's disease was estimated to affect approximately 6.1 million people worldwide as of 2016 (Feigin et al., 2019). It is expected to be the fastest-growing neurological disease in the world with a total annual US cost burden exceeding $50 billion by 2040 (Findley, 2007; Bloem et al., 2021). Conversely, MND and prion diseases are less common. As of 2024, Creutzfeldt-Jakob disease was estimated to affect 1–2 per million people globally annually, and as of 2019 MND was estimated to affect approximately 270,000

Table 1
Summary of studies on potential impacts of fluoride and/or aluminum exposure on neurodegenerative disease risk.

Title	Year	Author	Design/ participants	Disease	Main findings
1.) Exposure to Fluoride Aggravates the Impairment in Learning and Memory and Neuropathological Lesions in Mice Carrying the APP/PS1 double-transgenic Mutation	2019	Cao et al.	Animal (Mice) $N = 60$	Alzheimer's disease	• Untreated amyloid precursor protein (APP/PS1) mice showed reduced learning and memory abilities after 12 weeks of 0.3 mL fluoride treatment (1 mg/mL). • APP/PS1 mice treated with low or high doses of fluoride exhibited reduced learning and memory abilities after 4 or 8 weeks. • Fluoride exposure exacerbated the reduction of synaptic protein levels in the hippocampus. • Fluoride exposure increased oxidative stress in the hippocampus of APP mice.
2.) Neurotoxicity of Fluoride: Neurodegeneration in Hippocampus of Female Mice	2002	Bhatnagar et al.	Animal (Mice) $N = 20$	Neurodegeneration	• Light microscopy of hippocampal subregions showed numerous degenerated neuronal cell bodies in the CA3, CA4, and dentate gyrus (Dg) regions of adult female mice treated with sodium fluoride (30, 60, 120 ppm, in drinking water for 30 days). • Ultrastructural analysis revealed neurodegenerative features such as: Cell membrane degradation, Mitochondrial swelling, and clumping of chromatin material in neuronal cell bodies of CA3, CA4, and Dg regions. • Fluoride-exposed animals exhibited poor performance in motor coordination and maze tests. • Higher fluoride concentrations in drinking water were associated with worse behavioral performance.
3.) Aluminum exposure induces Alzheimer's disease-like histopathological alterations in mouse brain	2008	Rodella et al.	Animal (Mice) $N = 40$	Alzheimer's disease	• Mice received 2.5% aluminum sulfate in drinking water for 2–12 months. • Chronic aluminum exposure induced vascular β-amyloid deposition in the cerebral cortex, particularly after 12 months. • β-amyloid deposition occurred predominantly around cortical blood vessel bifurcations, resembling congophilic amyloid angiopathy. • Aluminum exposure reduced neuronal GRP78 expression, indicating impaired endoplasmic reticulum stress responses. • Neuropathological changes resembled cerebral amyloid angiopathy and Alzheimer's disease-like pathology.
4.) Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice	2002	Praticò et al.	Animal (Mice) $N = 12$	Alzheimer's disease	• APP transgenic mice received dietary aluminum supplementation (1 mg Al/g diet). • Aluminum exposure increased cerebral β-amyloid deposition and accelerated amyloid pathology. • Increased brain oxidative stress was observed following aluminum exposure.
5.) Neuroprotective Effects of Phytochemicals against Aluminum Chloride-Induced Alzheimer's Disease through ApoE4/LRP1, Wnt3/β-Catenin/GSK3β, and TLR4/NLRP3 Pathways with Physical and Mental Activities in a Rat Model	2022	Hamdan et al.	Animal (Rats) $N = 80$	Alzheimer's disease	• Rats received $AlCl_3$ (70 mg/kg/day) for 5 weeks to induce an Alzheimer's disease-like model. • Aluminum exposure dysregulated the ApoE4/LRP1 pathway, which involved in β-amyloid transport and clearance. • Aluminum exposure increased β-amyloid accumulation and was associated with cognitive impairment. • Results suggest that ApoE-mediated pathways may contribute to aluminum-induced Alzheimer's disease pathology.
6.) Interaction between aluminum exposure and ApoEε4 gene on cognitive function of in-service workers	2023	Wang et al.	Human (Occupational) $N = 1121$ aluminum factory workers	Cognitive impairment	• Plasma aluminum concentrations were positively associated with cognitive impairment. • ApoE ε4 carriers exhibited greater cognitive impairment than non-carriers. • A significant interaction was observed between plasma aluminum concentration and ApoE ε4 status. • Approximately 44.2% of the increased risk was attributable to the interaction between aluminum exposure and ApoE ε4.

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Table 1 (*continued*)

Title	Year	Author	Design/ participants	Disease	Main findings
7.) Chronic aluminum fluoride administration: I. Behavioral observations	1994	Varner et al.	Animal (Rats) N = 40	Neurobehavioral dysfunction	• No dysfunctions were detected in open-field, walking pattern, or balance beam tests. • In the first balance beam trial, AlF_3-treated (0.5, 5, 50 ppm, 45 weeks) animals performed better than controls. • No significant group differences were observed in spontaneous alternation or modified Morris water maze tests. • In the olfactory preference test, AlF_3-treated animals did not show normal odor preferences, suggesting impaired sense of smell. • Aluminum concentration in the brains of AlF_3-treated rats was nearly twice that of control animals.
8.) Relation between Aluminum Concentrations in Drinking Water and Alzheimer's Disease: An 8-year Follow-up Study	2000	Rondeau et al.,	Human *N* = 3777	Alzheimer's Disease	• Participants exposed to aluminum concentrations above 0.1 mg/L had approximately twice the relative risk of dementia and Alzheimer's disease compared to those exposed to lower concentrations (<0.1 mg/L). • No clear dose–response relationship was observed between aluminum exposure and dementia risk. • Participants exposed to higher silica levels (≥11.25 mg/L) had a lower adjusted relative risk of dementia.
9.) Aluminum and fluoride in drinking water in relation to later dementia risk	2020	Russ et al.	Human *N* = 6990	Dementia	• Dementia risk increased with higher water aluminum levels in both men and women. • Water fluoride levels were associated with dementia in both sexes. • No interaction was observed between aluminum and fluoride in relation to dementia risk.
10.) Occupational exposures to solvents and aluminum and estimated risk of Alzheimer's disease	1998	Graves et al.	Human *N* = 178	Alzheimer's disease	• Alzheimer's risk increased with longer duration of solvent exposure. • Aluminum exposure was not associated with Alzheimer's risk • However, high intensity solvent exposure was inversely associated with Alzheimer's disease risk.
11.) Occupational risk factors for Alzheimer disease: a case-control study	1997	Gun et al.	Human *N* = 340	Alzheimer Disease	• No statistically significant associations were observed between occupational exposures, including aluminium and Alzheimer's disease risk. • This null finding held for both the overall study population and participants with a family history of AD.
12.) Long-term effects of aluminum dust inhalation	2013	Peters et al.	Human *N* = 1894	Alzheimer Disease	• No significant association was observed between aluminum dust exposure and Alzheimer's disease mortality. • Prolonged inhalation of aluminum dust was associated with a higher risk of cardiovascular disease.
13.) A case-control study of Alzheimer's Disease and aluminum Occupation	2018	Salib & Hillier	Human *N* = 538	Alzheimer Disease	• Aluminum workers directly exposed to aluminum dust and fumes were not at greater risk than unexposed workers in the same plant
14.) Effects of fluoride on oxidative DNA damage, nitricoxide level, lipid peroxidation and cholinesterase enzyme activity in a rotenone-induced experimental Parkinson's model	2023	Kocak et al.	Animal (Rats) *N* = 72	Parkinson's Disease	• Rats treated with rotenone (ROT) and NaF showed significant increases in serum and brain MDA and NO levels. • GSH levels were decreased following combined ROT and NaF exposure. • Combined exposure also triggered DNA oxidative damage. • Elevated AChE and BChE activity and neuronal cell loss were observed after co-exposure.
15.) Aluminum exposure leads to neurodegeneration and alters the expression of marker genes involved to parkinsonism in zebrafish brain	2022	Capriello et al.	Animal (Zebrafish) *N* = 44	Parkinson's Disease	• Adult zebrafish were exposed to aluminum at 11 mg/L for 10, 15, and 20 days.

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Table 1 (*continued*)

Title	Year	Author	Design/ participants	Disease	Main findings
					• Aluminum concentration in the brains of treated fish increased exponentially, peaking at 15 days. • Aluminum-exposed brain tissues showed cellular disorders, diffuse edema, and neuronal degeneration. • Aluminum exposure altered the expression of **SYNB**, **SYNB2**, and **SNCGB** genes, which have been implicated in Parkinsonism.
16.) Iron and Aluminum Increase in the Substantia Nigra of Patients with Parkinson's Disease: An X-ray Microanalysis	1991	Hirsch et al.	Human	Parkinson's Disease	• In Parkinson's disease patients, iron content in the substantia nigra was increased in regions lacking neuromelanin and decreased in neuromelanin aggregates. • Iron levels in the central gray matter remained unchanged. • Lewy bodies in the substantia nigra showed high iron content and detectable aluminum. • Elevated iron and aluminum levels were not solely due to neuronal degeneration.
17.) Neuromelanin-containing neurons of the substantia nigra accumulate iron and aluminum in Parkinson's disease: a LAMMA study	1992	Good, Olanow & Perl	Human N = 6	Parkinson's Disease	• Iron content in neuromelanin granules was significantly elevated in Parkinson's disease (PD) patients. • Aluminum content in neuromelanin granules increased in 2 of 3 PD cases but was absent in controls.
18.) Metallomic Profiling and Linkage Map Analysis of Early Parkinson's Disease: A New Insight to Aluminum Marker for the Possible Diagnosis	2010	Ahmed & Santosh	Human *N* = 87	Parkinson's Disease	• Targeted metallomics analysis identified significant differences in 19 elements between Parkinson's disease (PD) patients and healthy controls. • Key altered elements included aluminum, copper, iron, manganese, and zinc.
19.) Intraneuronal Aluminum Accumulation in Amyotrophic Lateral Sclerosis and Parkinsonim-Demetia of Guam	1982	Perl et al.	Human (the Chamorro population) N = 8	Parkinson's Disease; Amyotrophic Lateral Sclerosis	• Aluminum accumulates significantly in both the nuclear and perinuclear cytoplasmic regions of hippocampal neurons containing neurofibrillary tangles (NFTs). • Intraneuronal aluminum accumulation may contribute to neurodegeneration in this population.
20.) Alpha particle excited X-ray fluorescence analysis for trace elements in cervical spinal cords of amyotrophic lateral sclerosis	1980	Mizumoto et al.	Human N = 12	Amyotrophic Lateral Sclerosis	• Trace element levels in the cervical spinal cord were measured using α-particle–excited X-ray fluorescence analysis. • ALS cases had higher contents of Al, Si, P, Ca, Ti, V, Mn, and Fe compared to controls. • Levels of S, Cl, K, Cu, and Zn were similar between ALS patients and controls within the standard deviation.
21.) The Pathogenetic Role of Metals in Motor Neuron Disease – The participation of Aluminum	1987	Yase	Human *N* = 16	Amyotrophic Lateral Sclerosis	• Neutron activation analysis (NAA) showed higher aluminum levels in all central nervous system regions of ALS cases compared to controls. • • Positive correlations were observed between calcium and aluminum levels, and/or between calcium and manganese levels in ALS cases.
22.) Aluminum deposition and Ca-hydroxyapatite formation in frontal cortex tissue of amyotrophic lateral sclerosis	1989	Yoshida	Human N = 20	Amyotrophic Lateral Sclerosis	• ALS patients showed significantly increased aluminum (Al) and calcium (Ca) levels in frontal cortex tissue. • Higher calcium/phosphorus ratios and calcium hydroxyapatite (Ca-HAp) levels were observed in ALS patients. • Aluminum content was significantly negatively correlated with both age of onset and age of death. • Ca-HAp (<3 ppm) was undetectable in control frontal cortex samples, but markedly elevated in ALS patients (111 ppm in patients < 60 years old and 168 ppm in patients ≥60 years old).
23.) Aluminum, calcium, and iron in the spinal cord of patients with sporadic amyotrophic lateral sclerosis using laser microprobe mass spectroscopy: a preliminary study	1995	Kasarskis	Human *N* = 10	Amyotrophic Lateral Sclerosis	• Aluminum (Al) concentrations were unchanged across all regions in ALS samples. • Iron (Fe) and calcium (Ca) levels increased 1.5- to 2-fold in the nuclei and cytoplasm of ALS neurons. • No corresponding increases were observed in capillaries or neuropil regions.

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Table 1 (*continued*)

Title	Year	Author	Design/ participants	Disease	Main findings
24.) Vanadium, aluminum, magnesium and manganese are not elevated in hair samples in amyotrophic lateral sclerosis	2009	Royce-Nagel et al.	Human $N = 200$	Amyotrophic Lateral Sclerosis	• No significant differences were found between ALS patients and healthy controls in vanadium, aluminum, magnesium, or manganese levels. • Participants with ALS were more likely to report occupational gasoline exposure (OR = 2.93, $p = 0.005$).

people worldwide with prevalence decreasing since the 1990s (Heinrich et al., 2023; Uttley et al., 2018). Although these diseases do not contribute to the global social burdens that dementia and Parkinson's disease do, they still have serious burdens on patients and their families, including high medical costs and declining quality of life (Heinrich et al., 2023).

2.2. Neurochemical and neurobiological impacts of fluoride and aluminum

2.2.1. Oxidative stress

Oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and the ability of biological systems to detoxify reactive intermediates or repair the resulting damage (Ozougwu, 2016; Bhattacharya, 2015). Experimental studies have demonstrated that chronic fluoride exposure can reach the central nervous system, disrupt blood-brain or blood-spinal-cord barriers, and increase markers of oxidative stress in neural tissue (Żwierełło et al., 2023; Qing-Feng et al., 2019; Dec et al., 2017; Shafi Bhat et al., 2021; Bhat et al., 2024a). Specifically, fluoride has been shown to elevate levels of superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and lipid peroxidation products, while reducing the activity of key antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, with additional evidence indicating disruption of glutathione-related pathways and detoxification systems (Dec et al., 2017; Shafi Bhat et al., 2021; Bhat et al., 2024b). Consequently, this oxidative burden can lead to lipid peroxidation, protein oxidation, and DNA damage, resulting in neuronal damage and cell death (Ansari and Scheff, 2010; Markesbery and Lovell, 1998; Valko et al., 2007). The brain is highly susceptible to oxidative damage because of its elevated oxygen consumption rate, abundant lipid content, and relatively low levels of antioxidant defenses (Shadfar et al., 2022). Given that neurons are non-dividing cells with limited regenerative capacity, oxidative stress can contribute to irreversible neuronal damage (Bondy, 2016). Emerging evidence also suggests that fluoride-induced oxidative stress may activate downstream signaling pathways involved in apoptosis and neuroinflammation, including nuclear factor kappa B (NF-κB) and other redox-sensitive transcription factors, which have been implicated in fluoride-related neurotoxicity (Bhat et al., 2024b; Morgan and Liu, 2011; Johnstone et al., 1999). These pathways may contribute to sustained neuronal damage and may interact with the glial activation process.

As with fluoride, aluminum can contribute to neural oxidative stress. Aluminum directly increases the production of ROS, including O_2^-, H_2O_2, and hydroxyl radical (OH) (Sharma and Dubey, 2007). These reactive molecules can wreak havoc on essential biomolecules (i.e., lipids, proteins, and nucleic acids), and disrupt cellular integrity and function. Lipid peroxidation driven by ROS can also impair cellular membrane integrity and enzyme activity (Valko et al., 2007). Furthermore, experimental studies show that aluminum exposure depletes antioxidant defenses such as glutathione (GSH), SOD, and catalase, diminishing their activity (Yamamoto et al., 2002; Rahimzadeh et al., 2022; N et al., 2011; Khanna and Nehru, 2007). Therefore, the extent of aluminum-induced oxidative stress depends on the degree of imbalance between production of ROS and the ability of cells to neutralize them. Weakened antioxidant defenses exacerbate neuronal vulnerability to oxidative stress, setting the stage for the cellular and molecular cascades that lead to neurodegeneration (Gao et al., 2011). The exacerbation of oxidative damage by aluminum is closely related to its ability to disrupt iron homeostasis. Aluminum catalyzes the redox activity of trace amounts of iron, leading to increased iron accumulation in the brain, thereby promoting the fenton transformations to produce more free radicals; such redox flux leads to the production of more reactive oxygen species (Becaria et al., 2006; Alexandrov et al., 2005). Furthermore, the circulation created by these reactive species amplifies the oxidative stress induced by aluminum, exacerbating its ability to disrupt the balance of metal ions in the brain (Viezeliene, 2022).

In addition to a direct chemical reaction, experimental studies indicate that fluoride-induced oxidative stress may be amplified under co-exposure to aluminum. For example, combined exposure has been shown to enhance oxidative stress and glial activation beyond levels observed with individual exposures, suggesting that co-exposure may amplify oxidative damage through shared and interacting biological pathways (Kaur et al., 2009).

2.2.2. Mitochondrial dysfunction

Mitochondria, the powerhouses of cells, serve as the primary source of reactive oxygen species and play a crucial role in cell energy production, which is also a key target for oxidative damage (Venditti and Di Meo, 2020). The vulnerability of the brain to oxidative stress and damage from fluoride exposure may be further exacerbated by its ability to disrupt mitochondrial function (Zhao et al., 2022a). In experimental studies, rats receiving sodium fluoride at concentrations of approximately 1–5 ppm in drinking water exhibited marked mitochondrial damage, including swelling, vacuolation, and disrupted cristae structure (Zhao et al., 2022a). These fluoride exposure levels are reported to be comparable to typical environmental exposure levels for North America because rats have been shown to need 5–10 times the fluoride exposure level to achieve the same serum fluoride levels as humans (National Research Council (NRC), 2006). When mitochondria are damaged, they are unable to slow down ROS, leading to a cascade of cellular damage and death (Zorov et al., 2014). For example, feeding high levels of sodium fluoride to three experimental groups of rats (20, 60, and 100 ppm), contributed to vacuolated swollen mitochondria in the neocortex, hippocampus, and cerebellum, in addition to the deposition of fluoride in these regions (Reddy et al., 2021). Although these exposure levels are sometimes described as environmentally relevant in animal models, it is important to note that such experimental dosing conditions may not fully reflect typical human exposure scenarios and may instead approximate higher-end or overexposed populations.

Aluminum exposure can also contribute to mitochondrial dysfunction, whereby it impairs the electron transport chain, reduces ATP production, and enhances mitochondrial ROS release (Reddam et al., 2022). This contributes to heightened oxidative stress and interferes with energy consumption of neuronal cells. This process may trigger apoptotic pathways, leading to neurodegeneration (Zhao et al., 2022a; Visioli et al., 2022; Guan et al., 1998).

2.2.3. Neuroinflammation and blood-brain barrier disruption

Evidence from animal models shows that fluoride can impair neuronal structure by altering membrane composition. Guan et al. (1998) exposed rats to 30 and 70 ppm of sodium fluoride (NaF) in

drinking water for 7 months and observed notable structural brain changes, including disruption of phospholipid bilayers, mitochondrial swelling, and neuronal degeneration in the hippocampus and cortex (Guan et al., 1998). Zhu et al. (2011) similarly reported that rats given a 30 mg/L NaF solution and distilled water for 9 months exhibited significant alterations in brain phospholipid composition and fatty acid profiles, which are essential for maintaining membrane integrity (Zhu et al., 2011). Both studies demonstrate that high levels of fluoride exposure can disrupt phospholipid metabolism and precipitate neuronal degradation. These concentrations substantially exceed typical fluoride levels in community water supplies and are more representative of endemic fluorosis regions or experimental toxicology conditions.

Fluoride exposure has also been shown to contribute to neuroinflammation that can compromise the integrity and functionality of the BBB (Strunecka et al., 2016; Lopes et al., 2020). The BBB serves as a pivotal checkpoint for maintaining homeostasis within the central nervous system by regulating the influx of substances from the bloodstream into the brain. Impairment of this barrier by inflammatory mediators related to fluoride exposure has been suggested as a potential mechanism by which peripheral immune cell infiltration may be facilitated, thereby exacerbating neuroinflammation (Bhat et al., 2024b). For example, exposure to sodium fluoride at 20–80 mg/L for 24 h in primary cultured rat hippocampal neurons caused significant DNA damage, S-phase cell-cycle arrest at 40 and 80 mg/L, and a dose-dependent increase in NF-κB expression (Zhang et al., 2008). However, these concentrations are higher than typical human environmental exposure levels and should therefore be interpreted cautiously when considering translational relevance. In another study of chickens, all high doses of sodium fluoride (500, 1000, 2000 mg/kg) triggered brain ferroptosis and neutrophil extracellular trap formation, while a particularly high fluoride concentration (2000 mg/kg) significantly damaged neurons, collectively exacerbating brain inflammation, and neuronal injury (Wang et al., 2023a). Again, these exposure conditions likely represent severe toxicological or overexposure scenarios rather than typical environmental exposure conditions in human populations.

The interplay between oxidative stress and neuroinflammation is particularly insidious due to the reciprocal amplification of these mechanisms. ROS generated during oxidative stress can activate transcription factors, such as NF-κB, thereby upregulating the expression of genes related to inflammatory responses (Morgan and Liu, 2011; Johnstone et al., 1999). Furthermore, cytokines and chemokines released during neuroinflammation can produce ROS in microglia and astrocytes, which are both involved in the brain's immune response (Dec et al., 2017). Glial cells play a vital role in maintaining central nervous system homeostasis by forming the cytoskeleton, regulating neuronal survival and differentiation, myelinating axons for rapid signal conduction, and balancing ion and neurotransmitter levels and may be disrupted by environmental toxicants such as fluoride (Dec et al., 2017; Jessen, 2004; Hanisch, 2002). Fluoride has been shown to activate astrocytes and microglia, which is a response to neuronal damage and a contributor to neuroinflammatory processes. Activated glial cells release inflammatory mediators, including cytokines and chemokines that may exacerbate neuronal damage (Dec et al., 2017; Thameem Dheen et al., 2007; Chen et al., 2016). This detrimental cycle of oxidative stress can also contribute to the pathogenesis of a wide range of neurodegenerative diseases, including Alzheimer's Disease, Parkinson's Disease, and ALS (Voet et al., 2019; Yuan et al., 2019; Zhang et al., 2017; Forlenza et al., 2014).

Likewise, aluminum exposure can trigger and sustain neuroinflammation. Chronic aluminum exposure activates glial cells and upregulates pro-inflammatory markers, increasing the production of cytokines, chemokines, and other mediators. This process can disrupt BBB integrity and exacerbate neuroinflammation (Bondy, 2016; Becaria et al., 2006; Alexandrov et al., 2005).

2.2.4. Disruption of metal ion homeostasis and electrolyte balance

Fluoride exposure has also been shown to contribute to the acidification of cells and electrolyte imbalance. Prolonged exposure to high fluoride concentrations can result in declines in plasma calcium and magnesium coupled with excess potassium (Johnston and Strobel, 2020; Dalamaga et al., 2008). This effect may be due to downstream stress signaling or binding of fluoride to these metals (Giachini and Pierleoni, 2004; Boink et al., 1994). In addition, electrolyte imbalance caused by fluoride exposure has been shown to disrupt cellular signaling and homeostasis (Johnston and Strobel, 2020; Boink et al., 1994). A cross-sectional study in India found that high fluoride intake from drinking water was associated with lower serum calcium ion concentrations in fluorosis patients while sodium ion concentrations were higher (Bhardwaj and Shashi, 2012). Interestingly, certain neurodegenerative conditions have been hypothesized to be associated with chronic nutritional deficiencies in essential minerals such as calcium and magnesium, along with excess levels of metallic trace elements including aluminum and manganese. However, causal mechanisms remain unclear (Mehri, 2020). Furthermore, long-term calcium and magnesium deficiencies can lead to secondary hyperparathyroidism, increased aluminum absorption, and metal deposition within the central nervous system (CNS) (Mehri, 2020).

2.2.5. Impaired cellular metabolism and neurotransmission

Fluoride exposure can also disrupt neuro cellular metabolic balance necessary for healthy neuronal function and glial support as well as interfere with key enzyme activities and neurotransmitter systems. Further, chronic exposure to high fluoride levels has been shown to alter phospholipid metabolism in rats (Guan et al., 1998). Phospholipids not only provide structural integrity to cells but also play a key role in signal transduction processes. By damaging these molecules, high fluoride exposures impair neuronal communication and integrity, reducing neuronal viability and altering synaptic activity. Furthermore, fluoride exposure has been shown to alter neurotransmitter metabolism, particularly glutamatergic neurotransmission. This can disrupt the delicate balance of excitatory and inhibitory signaling in the brain (Chen et al., 2023; Platt, 2007). Glutamate is the most abundant excitatory neurotransmitter in the central nervous system and is critical for synaptic plasticity, learning, and memory (Reis et al., 2009; Looser et al., 2024). Therefore, if fluoride exposure interferes with glutamate metabolism, this can result in excitotoxicity. As such, excessive glutamate levels can lead to neuronal damage and death, further exacerbating neurodegenerative processes (Chen et al., 2023; Ocharán-Mercado et al., 2025). Lastly, an animal study found that fluoride can also contribute to metabolic disruption by impairing the function of the glucose transporter GLUT1 (Jiang et al., 2014). Glucose transporters are critical for supplying neurons and glial cells with the glucose needed for energy production (Szablewski, 2017). Reduced activity of GLUT1 leads to reduced glucose uptake, energy deficits, and subsequent neuronal dysfunction (Dienel, 2019). Given the brain's high demand for glucose as its primary energy source, any disruption in glucose metabolism can affect neuronal survival and function (Dienel, 2019).

Aluminum exposure can also interfere with neurotransmission and synaptic activity (Abd El-Rahman, 2003). Specifically, high levels can affect the synthesis, release, and uptake of acetylcholine, glutamate, and dopamine. This can lead to neurochemical imbalances which may contribute to cognitive deficits and behavioral changes (Bielarczyk et al., 1998; Savory et al., 2006; Beal et al., 1989). Aluminum may affect the cholinergic system by inhibiting acetylcholinesterase activity, an enzyme important for cognitive function and memory processes. For example, Beal et al. (1989) reported that rabbits administered 100 μL of 1% aluminum chloride via an intraventricular route developed extensive neurofibrillary degeneration accompanied by significant reductions in choline acetyltransferase activity in the entorhinal cortex and hippocampus, as well as reductions in serotonin and norepinephrine concentrations (Beal et al., 1989). This process is also directly linked to

symptoms observed in neurodegenerative diseases such as Alzheimer's disease (Miu and Benga, 2006; Dey and Singh, 2022). Like fluoride, interference of glutamatergic neurotransmission from aluminum can promote excitotoxicity through excessive activation of NMDA receptors. This may lead to increased intracellular calcium and neuronal death, further exacerbating the neurodegenerative cascade (Platt, 2007). Moreover, exposure to Al complexes, such as Fluoroaluminate (AlF_x) may cause more severe disruptions of neuron metabolism than aluminum alone (Abd El-Rahman, 2003).

2.2.6. *Programmed neural cell death: apoptosis, autophagy dysregulation, pyroptosis, and necroptosis*

Programmed cell death plays an essential role in maintaining tissue homeostasis by eliminating damaged or dysfunctional cells. However, excessive activation of these pathways can contribute to neuronal loss and neurodegeneration (Goyal et al., 2024; Elmore, 2007). Evidence from experimental animal and cell culture studies suggests that both high fluoride and aluminum exposure can influence multiple forms of programmed neural cell death, including apoptosis, autophagy dysregulation, pyroptosis, and necroptosis (Xia et al., 2025; Chen et al., 2017; Lou et al., 2014; Kumar and Gill, 2014; Skalny et al., 2021).

Several experimental studies have shown that fluoride can induce neuronal apoptosis through oxidative stress-mediated mitochondrial dysfunction (Lou et al., 2014; Lou et al., 2013). For example, Lou et al. (2014) reported that chronic exposure to fluoride in drinking water (10 or 50 mg/L for 6 months) resulted in a dose-dependent increase in cortical neuronal apoptosis and altered Bcl-2/Bax expression in rats, indicating activation of intrinsic apoptotic pathways (Lou et al., 2014). Because mitochondria play a key role in regulating cell survival, fluoride-induced mitochondrial dysfunction may further amplify apoptoic signaling and neuronal loss. Fluoride exposure has also been associated with activation of inflammatory signaling pathways that may contribute to pyroptotic cell death and exacerbate neuroinflammation (Chen et al., 2017; Shuhua et al., 2012). For example, Wang et al. (2023) reported that high-dose sodium fluoride exposure (500–2000 mg/kg) induced ferroptosis and neutrophil extracellular trap formation in chicken brain tissue, accompanied by neuronal damage and increased inflammatory responses (Wang et al., 2023a). Although these exposure levels substantially exceed typical environmental exposures, they highlight biological processes that could be involved in fluoride-induced neuronal injury.

Aluminum exposure has also been linked to neuronal injury through several programmed cell death pathways (Johnson et al., 2005). Johnson et al. (2005) reported that exposure of Neuro-2a cells to aluminum maltolate (62.5–500 μM) induced apoptosis and necrosis in a concentration-dependent manner and was associated with activation of p53-mediated signaling, increased Bax expression, reduced Bcl-2 expression and caspase-3 activation (Johnson et al., 2005). These findings suggest activation of intrinsic apoptotic pathways following aluminum exposure. Aluminum has also been shown to disrupt autophagic processes responsible for removing damaged proteins and organelles, potentially increasing neuronal vulnerability to injury. For example, Tao et al. (2025) found that pharmacological activation of autophagy with rapamycin mitigated fluoride- and aluminum-induced neurotoxicity in hippocampal neurons and NG185–15 cells through the AMPK/mTOR/ULK1 pathways, suggesting that disruption of normal autophagic processes may contribute to neuronal damage following exposure (Tao et al., 2025). Other studies have reported increased apoptotic markers, mitochondrial damage, and neuronal loss following aluminum exposure, and further supporting a potential role of apoptosis in aluminum-induced neurotoxicity (Kumar and Gill, 2014; Johnson et al., 2005; Prakash and Kumar, 2013).

2.2.7. *Cellular epigenetic regulation*

Epigenetic mechanisms regulate gene expression without altering the underlying DNA sequence and play important roles in neuronal development, synaptic plasticity, and responses to environmental stressors (Day and Sweatt, 2011). There is evidence that both fluoride and aluminum can influence epigenetic processes, including DNA methylation, histone modification, and non-coding RNA expression, potentially contributing to long-term alterations in neural function (Fu et al., 2014; Raghunath et al., 2016; Zhao et al., 2024; Gao et al., 2024; Crapper et al., 1980; Ikram et al., 2021).

Several animal studies have reported epigenetic changes following fluoride exposure. Fu et al. (2014) demonstrated that sodium fluoride exposure (20–120 mg/L) altered DNA methylation and histone methylation patterns in mouse oocytes and early embryos, resulting in impaired embryonic development and reduced blastocyst formation (Fu et al., 2014). These findings suggest that fluoride may interfere with epigenetic regulation during critical developmental periods. In addition, Raghunath et al. (2016) found that fluoride exposure was associated with altered microRNA expression profiles, which may influence signaling pathways involved in oxidative stress, apoptosis, and cellular survival (Raghunath et al., 2016). More recently, Zhao et al. (2024) demonstrated that fluoride induced neuronal injury was mediated in part through dysregulation of miR-708-3p, which directly targets SIRT1 and contributes to mitochondrial dysfunction and apoptosis (Zhao et al., 2024). Cai et al. (2025) further reported that prenatal sodium fluoride exposure (100 mg/L) reduced expression of TET1, a key regulator of DNA hydroxymethylation, and was accompanied by impaired cognition and altered synaptic protein expression in mouse offspring (Cai et al., 2025). Therefore, high levels of fluoride exposure may influence multiple epigenetic pathways, including DNA methylation, histone modification, microRNA regulation and DNA hydroxmethylation. Evidence from human populations remains limited, however, a recent epigenome-wide association study among U.S. children reported associations between fluoride exposure during early adolescence and differential DNA methylation at multiple CpG sites, including loci involved in neurodevelopmental and cellular signaling pathways (Ruehlmann et al., 2024). These findings suggest that epigenetic alterations observed in experimental models may also occur in human populations; however, no human studies have examined epigenetic changes in relation to neurodegeneration specifically.

In terms of aluminum-induced epigenetic changes, experimental studies have reported that high levels of aluminum exposure can alter DNA methylation patterns, histone modifications, and non-coding RNA expression in neural tissues (Aschner et al., 2024; Gao et al., 2023). For example, Gao et al. (2023) reported that sub-chronic exposure of rats to aluminum chloride (2–8 g/L in drinking water for 12 weeks) impaired learning and memory and altered hippocampal expression of histone acetyltransferase 1 (HAT1) and histone deacetylase 2 (HDAC2), resulting in reduced histone H4 acetylation (Gao et al., 2023). These findings suggest that aluminum-induced cognitive dysfunction may be mediated, in part, through disruption of histone acetylation pathways. Additional studies have also reported aluminum-associated alterations in microRNAs involved in inflammatory signaling, amyloid processing, and neuronal survival, suggesting that epigenetic dysregulation may contribute to the long-term biological effects of aluminum exposure (Aschner et al., 2024).

2.2.8. *Protein Misfolding, cytoskeletal disruption, and synaptic loss from aluminum exposure*

Aluminum exposure may affect the structure and function of nucleic acids and proteins. Aluminum can bind to DNA and RNA phosphate groups, affect gene expression and regulation, and increase the risk of errors during transcription and translation (Zhao et al., 2022b). In a post-mortem observational study comparing post-autopsy brains from chronic renal dialysis patients and controls, Morris et al. (1989) found that transferrin receptor density colocalized with aluminum accumulation in the cortex and hippocampus. This suggests a potential role for aluminum transport in dialysis encephalopathy and Alzheimer's disease, given that this interaction can lead to protein misfolding, and the

formation of toxic aggregates (Morris et al., 1989). This mechanism is of particular concern in the context of neurodegenerative diseases, as it may contribute to the accumulation of pathological protein assemblies, such as amyloid plaques and tau tangles in Alzheimer's disease (Savory et al., 2006; Praticò et al., 2002).

Aluminum can also impact modulation of synaptic plasticity, which is integral for learning and memory (Walton, 2012). By impairing Long-term Potentiation (LTP) and Long-term Depression (LTD) processes, aluminum can alter synaptic strength and lead to declines in cognitive function. This is further exacerbated by aluminum-induced structural and functional changes in synaptic proteins and receptors, disrupting synaptic assembly and neurotransmitter receptor expression (Díaz-Nido and Avila, 1990). The cumulative impact of these disruptions is a significant impairment in neuronal connections, contributing to the pathophysiology of neurodegeneration.

Another pathway by which aluminum may contribute to neurodegenerative processes is by impacting cytoskeletal integrity and neuronal connectivity. The cytoskeleton is a complex network of microtubules, nerve filaments, and actin filaments that play a key role in maintaining cell shape, enabling intracellular transport, and facilitating synaptic connections (Díaz-Nido and Avila, 1990). The interaction of aluminum with cytoskeletal components can disrupt these essential cellular functions, resulting in altered neuron morphology, impaired axon transport, and synaptic dysfunction (Nixon et al., 1990; Karlik et al., 1980). Positively charged Al may bind to the electrophosphoic backbone of DNA and impact the DNA helix conformation, which can affect gene expression, replication, stability, and binding of other proteins (Matsumoto and Morimura, 1980; Parhad et al., 1989; Bizzi et al., 1984). In addition, elevated aluminum exposure may contribute to a neurodegenerative cascade by altering the structural integrity and elasticity of neurons, affecting their ability to withstand mechanical stress and maintain the appropriate axon diameter to achieve electrical conductivity (Shea et al., 1997; Hewitt et al., 1991). Aluminum exposure can also contribute to the accumulation of neurofilament aggregates. These aggregates impede intracellular communication and nutrient distribution, thereby exacerbating neuronal dysfunction (Shea et al., 1997; Kandimalla et al., 2016; Muma and Singer, 1996). Moreover, aluminum alters actin filament dynamics and affects dendritic spine morphology and synaptic stability, which can impair synaptic efficacy and neuronal connections (Díaz-Nido and Avila, 1990). These cytoskeletal disruptions, combined with aluminum-induced oxidative stress and mitochondrial dysfunction, can create a vicious cycle of neurodegeneration in which damaged neuronal connections and loss of synapses may translate into cognitive deficits and behavioral changes associated with neurodegenerative diseases.

Importantly, these mechanisms may not act independently. Co-exposure to fluoride and aluminum may amplify oxidative stress, neuroinflammation, and neuronal dysfunction through shared and interacting biological pathways. For example, in cultured hippocampal neurons, fluoride has been shown to enhance aluminum-induced disruption of neuronal interconnections, suggesting that co-exposure may potentiate neurotoxic effects through interacting biological mechanisms (Varner et al., 1998; Akinrinade et al., 2015). A schematic diagram of proposed mechanisms linking fluoride, aluminum exposure, and their co-exposure, to neurodegenerative processes is presented in Fig. 1 Proposed mechanisms of neurotoxicity of fluoride and aluminum exposure. Created in BioRender. Prabhu, S. (2026) https://BioRender.com/1ffohde.

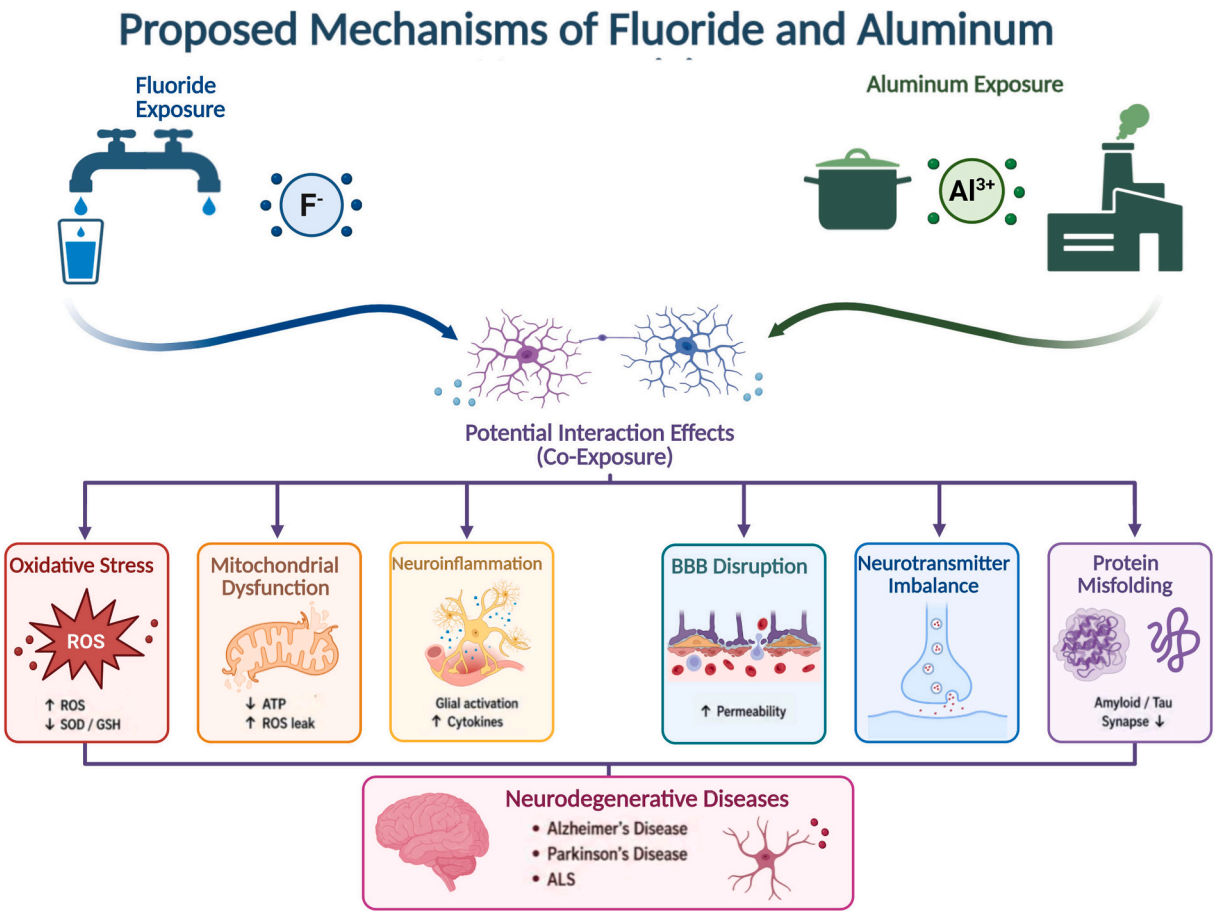

Fig. 1. Proposed mechanisms of neurotoxicity of fluoride and aluminum exposure. Created in BioRender. Prabhu, S. (2026) https://BioRender.com/1ffohde

3. Fluoride, aluminum and neurodegenerative disease risk

3.1. Dementia-type diseases

3.1.1. Animal studies

Dementia is a common neurodegenerative and progressive disease that primarily affects older adults. Globally, more than 55 million people have been diagnosed with dementia, of which Alzheimer's disease is the most common form, accounting for 60% - 70% of dementia cases (Dementia, 2026). Several animal studies have examined the impact of fluoride and aluminum exposure on neurocognition and dementia, especially Alzheimer's disease. For example, in one animal study, mice administered 0.3 mL of sodium fluoride solution by gavage daily exhibited learning and memory deficits as well as neuropathological damage (Cao et al., 2019). This was manifested as a significant increase in the number of extracellular amyloid plaques and intracellular Aβ accumulation in brain tissue, as well as an increase in the number of senile plaques in the hippocampus (Cao et al., 2019). Similar neuropathological changes have also been reported following aluminum exposure. For example, Rodella et al. (2008) found that mice exposed to aluminum sulfate (500 mg/L in drinking water) for 12 months developed cortical β-amyloid deposition resembling congophilic amyloid angiopathy and exhibited histopathological alterations consistent with Alzheimer's disease (Rodella et al., 2008). Likewise, Praticò et al. (2002) reported that dietary aluminum supplementation (1 mg Al/g diet) accelerated amyloid pathology and increased cerebral β-amyloid accumulation in APP transgenic mice (Praticò et al., 2002).

Emerging evidence also suggests that apolipoprotein E (ApoE), a major genetic risk factor for Alzheimer's disease, may modify the neurotoxic effects of aluminum exposure (Liu et al., 2013; Corder et al., 1993). In an $AlCl_3$-induced Alzheimer's disease rat model, animals exposed to a relatively high dose of aluminum chloride (70 mg/kg/day, intraperitoneally, for 5 weeks) exhibited dysregulation of the ApoE4/LRP1 pathway, which plays an important role in β-amyloid transport and clearance (Hamdan et al., 2022). These findings suggest a potential mechanism through which levels of aluminum exposure may promote β-amyloid accumulation and neurodegeneration. Evidence from human studies is more limited. However, among 1121 workers in an aluminum factory, Wang et al. (2023) reported a dose-response relationship between plasma aluminum concentrations and cognitive impairment. They also found that the ApoE ε4 allele interacted with aluminum exposure to further increase the risk of cognitive impairment (Wang et al., 2023b). Approximately 44.2% of the increased risk observed among individuals with both elevated plasma aluminum concentrations and the ApoE ε4 allele was attributable to the interaction effect (Wang et al., 2023b). Furthermore, in animal models and human cell studies, aluminum has been shown to alter kinase and phosphatase activity, leading to abnormal hyperphosphorylation of Tau, another key pathological feature of Alzheimer's Disease. Importantly, the presence of the ApoE ε4 allele appears to exacerbate Tau accumulation in addition to the accumulation of β-amyloid (Kandimalla et al., 2016; Wang et al., 2021). Those findings reflect that individuals carrying the ApoE ε4 allele may be more susceptible to the adverse neurological effects of aluminum exposure.

Similarly, other study have found that mice exposed to high concentrations of fluoride have reduced spatial learning and memory ability (Raghunath et al., 2016). Furthermore, mice treated with sodium fluoride have exhibited reduced brain mass, and neurodegeneration in the hippocampus, including cell membrane degeneration and mitochondrial swelling (Ge et al., 2018; Varner et al., 1994). For example, Varner et al. (1994) found that mice consuming water containing monofluoroaluminum complexes (A_1F_3), exhibited olfactory impairment but no learning and memory impairment (Varner et al., 1994). However, their subsequent research, found that compared with the control group, rats that ingested AlF_3 or NaF had higher immunoreactivity between β-amyloid and amyloid A on the dorsal side of the thalamus (Varner et al., 1998). In addition, the AlF_3 group had a larger range of moderate damage, more abnormal cells, and lower neuronal density in the right hippocampal region, which was also worse than the rats in the NaF group (Varner et al., 1998). Furthermore, a study of rabbits with aluminum exposure (200 μ mol Al/Kg, 400 mol μ Al/Kg) at different life stages, found that adult and elderly rabbits exhibited classical conditioning (eyeblink reflex) deficits in aluminum-induced response learning (Yokel et al., 1994).

3.1.2. Human studies

Few human studies have examined associations between fluoride exposure and dementia. Interestingly, a cross-sectional study in South Carolina published in the 1980s found that counties with the highest levels of fluoride in their drinking water had the lowest rates of dementia (Still and Kelley, 1980). However, a recent Scottish cohort study of 6990 participants found that higher fluoride and aluminum in drinking water were associated with increased risk of dementia (Russ et al., 2020). Moreover, the findings showed a dose-response relationship between average fluoride levels in drinking water and dementia risk among females (Russ et al., 2020). However, both studies relied on ecological water measurements rather than individual exposure assessment. Interestingly, an eight-year follow-up study of 3777 adults over 65 years of age in France found that participants who were exposed to aluminum concentrations in drinking water above 0.1 mg/L were approximately twice as likely to develop dementia or Alzheimer's disease than those who were exposed to aluminum concentrations less than 0.1 mg/L (Rondeau et al., 2000). While this study included longitudinal follow-up, the authors did not consider potential confounding by comorbidities such as hypertension or renal dysfunction, which can both influence aluminum retention and dementia risk. Additionally, other studies of occupational aluminum exposure have not found associations with dementia (Gun et al., 1997; Peters et al., 2013; Salib and Hillier, 1996; Graves et al., 1998). These null findings may reflect healthy worker bias, differences in cognitive assessment tools, or a small sample size.

3.2. Parkinsonism-type diseases

Parkinson's disease (PD) is another common neurodegenerative disease that affects motor function. Symptoms include difficulty moving and tremors, along with cognitive difficulties, co-occurring psychological disorders, and co-occurring dementia (World Health Organization, 2023). Animal studies have demonstrated a potential link between fluoride exposure and PD symptoms. For example, among rotenone (ROT)-induced experimental PD models in albino rats, rotenone (2 mg/kg SC for 28 days) and sodium fluoride (25, 50, or 100 μg/mL orally for 4 weeks) acted synergistically to cause oxidative DNA damage (Kocak et al., 2023). This suggests that exposure to high concentrations of fluoride, along with exposure to certain pesticides, may increase the risk of PD. Animal and human studies have also found a potential role of aluminum in the development of PD via its impacts on the substantia nigra. Capriello et al. (2022) found that aluminum exposure in adult zebrafish (3.6 mg/L of aluminum chloride ($AlCl_3$) continuously in their water for up to 20 days) induced glial activation, and altered expression of Parkinsonism-related genes, with the most pronounced effects observed at 10 and 15 days. Although partial recovery was noted by the 20th day, findings of this study still support a potential role of aluminum exposure in Parkinson's-like neurotoxicity (Capriello et al., 2022). In human studies, Hirsch et al. (1991) found that participants with PD had high levels of iron and aluminum in their substantia nigra (Hirsch et al., 1991). In subsequent case studies, two of three PD cases exhibited a significant increase in aluminum content in their neuromelanin granules, reflecting the deposition of aluminum in the substantia nigra (Good et al., 1992). Furthermore, in a serum test experiment involving 42 healthy controls and 45 treatment-naive PD patients, those with PD exhibited significant variations in 19 elements compared to the healthy

groups, particularly in aluminum, copper, iron, manganese, and zinc (Ahmed and Santosh, 2010). Moreover, aluminum was found to be a key element triggering differences in phosphorus concentrations and contributing to serum homeostasis imbalance in PD patients. (Ahmed and Santosh, 2010)

However, there are some limitations in this research in that pharmacologically induced animal models used for many PD studies, such as rotenone exposure, may not fully represent the multifactorial etiology of Parkinson's disease in humans. Additionally, co-exposure to multiple toxicants in experimental designs makes it difficult to isolate the independent effects of fluoride or aluminum. Human studies are also limited by relatively small sample sizes, cross-sectional designs, and dependence on post-mortem tissue analyses, which cannot establish temporal relationships or causality.

3.3. Motor neuron diseases (amyotrophic lateral sclerosis)

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease. As of 2017, there were 31,843 ALS patients in the US (Centers of Disease Control and Prevention, 2024). ALS interferes with nerve cell communication and contributes to nerve cell death, resulting in muscle weakness and paralysis. Environmental factors, including possible aluminum accumulation, have been explored as potential contributors to ALS, though causality remains unconfirmed. For example, a study of patients with ALS in Guam, found that aluminum accumulated significantly in their hippocampal region and perinuclear cytoplasm (Perl et al., 1979). The deposition of aluminum in neurons of ALS patients has also been confirmed in subsequent studies (Mizumoto et al., 1980; Yase, 1987; Yoshida et al., 1989). However, another preliminary study published in 1995 did not detect differences in aluminum, calcium, and iron concentrations in the spinal cord of ALS patients compared to healthy controls, nor did a study that examined hair samples from patients with ALS (Kasarskis et al., 1995; Royce-Nagel et al., 2010). There are no studies on fluoride exposure and ALS.

However, since ALS is a rare disease, studies exploring potential environmental contributors often include small sample sizes among limited populations. As a result, statistical power and generalizability are restricted. Furthermore, cross-sectional post-mortem analyses cannot determine whether metal buildup is a cause or a secondary effect of neurodegeneration. Lastly, these studies tend to lack detailed data on other environmental exposures, occupational history, dietary intake, and other potential confounding factors.

4. Discussion

Fluoride and aluminum have complex effects on neurochemical and structural mechanisms implicated in neurodegeneration yet are inconsistently associated with neurodegenerative diseases in epidemiological studies. At high levels, both can contribute to neurodegenerative processes by increasing oxidative stress and neuroinflammation, and contributing to programmed neural cell death, which are common pathways in the pathogenesis of diseases such as Alzheimer's and Parkinson's diseases. Specifically, oxidative stress can lead to neuronal damage characterized by lipid peroxidation, protein oxidation, and DNA damage, all of which play a role in neurodegeneration. In addition, the interaction of these processes within brain tissue may further disrupt cellular and molecular processes, including neurotransmitter function and cytoskeletal integrity (in the case of aluminum), which are essential for maintaining neuronal health. This disruption can initiate and propagate pathological processes in various neurodegenerative diseases, clinically manifested by cognitive decline, memory impairment, and other dementia-related symptoms. Although relatively few studies have directly examined fluoride and aluminum co-exposure, emerging experimental evidence suggests that these ions may interact to exacerbate neurotoxic effects. However, it is not yet clear whether these effects are synergistic, additive, or context-dependent. Future research is needed to evaluate combined exposures using both experimental and epidemiological approaches to better reflect real-world environmental conditions.

Additionally, numerous animal studies have found that exposure to high concentrations, and in some cases low concentrations, of fluoride and aluminum impairs cognitive function and enhances risk factors associated with neurodegenerative diseases; however, human research is scarce and presents a more heterogeneous picture. Some epidemiological studies have observed associations between higher levels of aluminum and fluoride in drinking water and an increased risk of dementia, while other studies have not. Furthermore, there is a lack of epidemiological studies on fluoride and aluminum exposure in relation to less common diseases like Parkinson's disease and ALS.

4.1. Limitations of studies on fluoride, aluminum, and neurodegeneration

There are important limitations in the studies on fluoride, aluminum and neurodegenerative disease risk that warrant consideration. First, many experimental studies depend on animal models exposed to relatively high fluoride or aluminum concentrations that may exceed levels typically observed in general human populations. These exposure levels may be more representative of highly exposed groups, such as individuals living in regions with endemic fluorosis, including parts of India and China, where naturally elevated fluoride concentrations in groundwater can substantially exceed levels observed in most community water systems (Choubisa and Choubisa, 2016; Wang et al., 2019). Second, human epidemiologic studies often rely on ecological or occupational exposure measures rather than individual biomarkers, which may lead to exposure misclassification and difficulties with determining generalizability of the findings. Additionally, several of the animal and human studies reporting significant associations have small sample sizes. Lastly, some studies lack sufficient adjustment for potential confounding factors such as socioeconomic status, comorbidities, or renal function. These methodological challenges emphasize the need for future prospective studies with large sample sizes that incorporate individual-level exposure assessment and standardized cognitive outcome measures.

5. Conclusions

Fluoride and aluminum are ubiquitous environmental exposures that can co-occur and are linked with neurodegenerative processes at high exposure levels in animal models. However, relatively few studies have examined neurodegenerative processes or disease risk in humans or at low exposure levels, particularly for rare diseases. Given the global aging population and the rising prevalence of neurodegenerative diseases, it is critical to understand the potential contribution of environmental factors. Findings of this narrative review underscore the need for methodologically rigorous longitudinal human studies on fluoride, aluminum and neurodegenerative disease risk.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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