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Review

Adverse outcome pathway for the neurotoxicity of Per- and polyfluoroalkyl substances: A systematic review

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are endocrine disruptors with unambiguous neurotoxic effects. However, due to variability in experimental models, population characteristics, and molecular endpoints, the elucidation of mechanisms underlying PFAS-induced neurotoxicity remains incomplete. In this review, we utilized the adverse outcome pathway (AOP) framework, a comprehensive tool for evaluating toxicity across multiple biological levels (molecular, cellular, tissue and organ, individual, and population), to elucidate the mechanisms of neurotoxicity induced by PFAS. Based on 271 studies, the reactive oxygen species (ROS) generation emerged as the molecular initiating event 1 (MIE1). Subsequent key events (KEs) at the cellular level include oxidative stress, neuroinflammation, apoptosis, altered Ca^{2+} signal transduction, glutamate and dopamine signaling dyshomeostasis, and reduction of cholinergic and serotonin. These KEs culminate in synaptic dysfunction at organ and tissue levels. Further insights were offered into MIE2 and upstream KEs associated with altered thyroid hormone levels, contributing to synaptic dysfunction and hypomyelination at the organ and tissue levels. The inhibition of Na^+/I^- symporter (NIS) was identified as the MIE2, initiating a cascade of KEs at the cellular level, including altered thyroid hormone synthesis, thyroid hormone transporters, thyroid hormone metabolism, and binding with thyroid hormone receptors. All KEs ultimately result in adverse outcomes (AOs), including cognition and memory impairment, autism spectrum disorders, attention deficit hyperactivity disorders, and neuromotor development impairment. To our knowledge, this review represents the first comprehensive and systematic AOP analysis delineating the intricate mechanisms responsible for PFAS-induced neurotoxic effects, providing valuable insights for risk assessments and mitigation strategies against PFAS-related health hazards.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS), a class of organic compounds characterized by fire resistance, high stability, and non-biodegradability, have been employed in the production of fire extinguishers, textiles, and pesticides, etc. [1]. The widespread use of PFAS has led to serious pollution in the global environment over the past 70 years [2]. Certain PFAS have been listed in the List of Key Controlled New Pollutants in China (https://www.gov.cn/zhengce/2022-12/30/content_5734728.htm). Despite the implementation of effective control measures, high concentrations of PFAS continue to be detected in human and wildlife tissues, such as the brain, serum, milk, thyroid, placenta, follicular fluid, etc. [3–6]. Due to the high bioaccumulation potential and prolonged half-life of PFAS, such as hydrophobic F-53B, which can have a half-life of up to 49 years, they pose a significant threat to human health [7].

PFAS have been demonstrated to accumulate in the brain after undergoing complex blood circulation, leading to neurological damage. Increasing epidemiological studies have shown an association between PFAS and both neuropsychological and neuromotor deficits, particularly

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in children, as opposed to older adults [8–10]. However, findings have shown inconsistency due to variability in environmental or biological samples (e.g., drinking water, blood, breast milk, etc.) [11–14], study methodologies (e.g., cross-sectional, case-control, and prospective cohort, etc.) [15–17], and neurological assessment tools [18–20]. *In vivo* studies consistently reveal that PFAS exposure can cause aberrant neurobehavioral outcomes in animals, including impaired cognitive function, memory, and motor skills [21–23]. However, variations of toxicological endpoint (e.g., synapse, cholinergic, dopaminergic, etc.) [24–26] may differ based on the selected brain regions (e.g., hippocampus, cortex, cerebellum, etc.) [27–29], modes of PFAS exposure (e.g., oral gavage, ingestion of contaminated water, intraperitoneal injection, etc.) [30–32], and animal models used (e.g., zebrafish, mice, rats, etc.) [33–35]. At the cellular level, mechanisms involving oxidative stress, apoptosis, and Ca^{2+} signaling disorder have been investigated [36–38], yet establishing a direct association with detrimental neurological effects in humans or animals remains challenging. Consequently, a framework that connects molecular and cellular processes to adverse neurotoxic outcomes in animals, individuals, or populations is urgently needed to offer a comprehensive evaluation of PFAS-induced neurotoxicity.

Adverse outcome pathway (AOP) is a toxicological knowledge framework endorsed by the Organisation for Economic Co-operation and Development (OECD) and developed within the AOP-wiki. Its purpose is to streamline the assessment of safety and risk in response to exposures to environmental chemicals [39]. AOP succinctly delineates the relationship between Molecular Initiating Events (MIEs) and Adverse Outcomes (AOs) through Key Events (KEs), which are interconnected by Key Event Relationships (KERs) [40]. MIEs are a type of KE that occurs at the initiation point of the AOP. They represent the first point of contact where the chemical exerts its influence, triggering a series of downstream biological processes. KEs are measurable biological changes at various organizational levels (e.g., molecular, cellular, tissue, organ, organism, population) that follow from MIEs to AOs. KERs describe the causal links between KEs, providing the mechanistic and biological context connecting one KEs to another, and showing how an initial event leads to subsequent events and ultimately results in AOs. The European Food Safety Agency has emphasized the importance of AOP in systematizing toxicological evidence surrounding PFAS [41]. Presently, four reviews focusing on PFAS have elucidated toxic mechanisms associated with reproductive toxicity, low birth weight, and metabolic diseases through the lens of AOP [42–45]. To the best of our knowledge, no established or emerging AOPs currently exist that summarize the neurotoxic effects of PFAS.

In this review, we summarized current epidemiological, *in vivo*, and *in vitro* studies and established an AOP framework to provide a comprehensive overview of the mechanisms underlying PFAS-induced neurotoxicity. This study offers evidence in favor of the early risk assessment of PFAS exposure and clues to the identification and mitigation of negative consequences induced by PFAS.

2. Methods

The flow chart that illustrates the process of study selection is depicted in Fig. 1. Initially, a search yielding 304 studies was conducted in databases including "Web of Science" and "PubMed", using keywords involving "Per- and polyfluoroalkyl substances", "Neuro", "Neurotoxicity", and "Neurodevelopment". Subsequently, we summarized the neurobehavioral AOs associated with PFAS neurotoxicity from the aforementioned studies. A second search was conducted using the identified AOs ("Memory", "Cognition", "ADHD", "ASD") as keywords to ensure all relevant studies were included. Following the exclusion of systematic reviews, meta-analyses, studies on chemicals other than PFAS, investigations focusing on effects beyond neurotoxicity, and duplicate studies, a total of 163 studies were incorporated into the analysis. Among these, 64 were classified as epidemiological studies, 58 as *in vivo* studies, and 41 as *in vitro* studies. Human and animal studies were utilized to further validate the neurobehavioral AOs previously established. In both *in vivo* and *in vitro* studies, we selected all measurable biological events induced by PFAS in the included studies and defined them as KEs. Notably, among the included studies, seven specifically address the influence of thyroid hormones on the relationship between PFAS and neurotoxicity [46–52]. However, the majority of the 163 included studies focused on animal brain tissue, neural cells, human blood, and neurobehavioral assessments, making it challenging to identify thyroid hormones-related KEs and MIEs. To integrate these crucial KEs into the AOP framework and provide a more comprehensive understanding of PFAS neurotoxicity mechanisms, a third systematic search was conducted using the keywords "Per- and polyfluoroalkyl substances" and

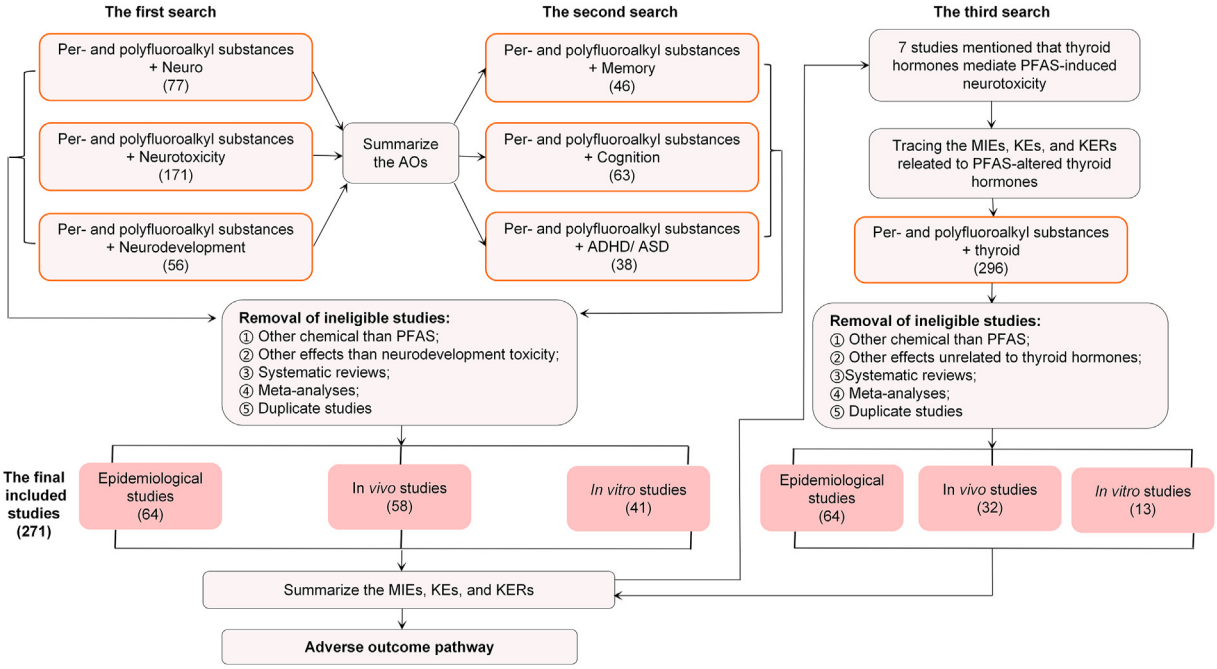

Fig. 1. Flow chart of study selection. Cutoff date: December 31, 2023.

"thyroid" to track thyroid hormone-related MIEs and upstream/downstream KEs influenced by PFAS. From this third search, 109 studies were included, comprising 64 epidemiological studies, 32 *in vivo* studies, and 13 *in vitro* studies.

Subsequently, the upstream and downstream relationships between KEs and AOs were synthesized based on the existing experimental evidence and information from AOP-wiki (https://www.aopwiki.org/). AOP-wiki serves as a repository for more than 400 AOP frameworks, providing a robust resource for identifying established pathways and connections. The KERs underwent evaluation through a confidence analysis based on the weight of evidence methodology, adhering to OECD guidelines and the Bradford Hill criteria [53]. These criteria encompass biological plausibility, essentiality, and empirical support, ensuring strong credibility and reliability, which are used to determine if there is a mechanistic relationship between upstream KEs and downstream KEs consistent with established biological knowledge [53]. Specifically, Does an upstream KE inhibit the downstream KEs and/or AOs if blocked? Do the upstream KEs occur at lower doses and earlier time points than the downstream KEs? Is the incidence of the upstream KEs greater than that of the downstream KEs? Is the empirical support for the AOP's expected pattern consistent across different taxa, species, and stressors? The confidence of the KERs was rated as strong, moderate, or weak.

Next, we identified the MIEs from the KEs based on the Bradford Hill criteria, as well as corroborative evidence from AOP-Wiki. This step involved scrutinizing the regulatory mechanisms to ensure that the identified MIEs could feasibly trigger the subsequent KEs. Finally, we conducted a comprehensive evaluation of the identified MIEs, KEs, KERs, and AOs, and constructed the AOP framework for PFAS neurotoxicity. This evaluation included a thorough review of the existing literature to confirm the validity of the proposed events and their relationships. We also integrated findings from epidemiological, *in vivo*, and *in vitro* studies to reinforce the robustness of the AOP framework. This integrative approach ensured that the framework was well-supported by empirical evidence, enhancing its applicability for assessing the neurotoxic effects of PFAS.

3. Results

Table 1 summarizes the selected PFAS compounds identified as having neurotoxic effects in all included studies. It primarily includes traditional PFAS (PFOS, PFOA, PFHxS, PFNA, PFOSA, PFDoA, PFTrDA, PFDA, and PFUnDA) and emerging PFAS (PFBS, F-53B, OBS, GenX, ADONA, PFHxA, HFPO-TA, 8:8 PFPiA, PFECA, and PFPeA). Except for PFOSA, all are ionizable PFAS. These functional groups contribute to their persistence, bioaccumulation, and biological activity, which may enhance their mobility within biological systems and potentially affect various tissues, including the brain.

The summary of MIEs, KEs, and AOs is shown in Fig. 2. Reactive oxygen species (ROS) generation was identified as MIE1, initiating subsequent KEs at the cellular level, including oxidative stress, neuroinflammation, apoptosis, altered Ca^{2+} signal transduction, glutamate and dopamine signaling dyshomeostasis, and reduction of cholinergic and serotonin. These events eventually culminate in synaptic dysfunction at the organ or tissue level. Additionally, the inhibition of Na^{+}/I^{-} symporter (NIS) is considered the MIE2 for the neuroendocrine effects. This is followed by the KEs of altered thyroid hormone synthesis, thyroid hormone transporters, thyroid hormone metabolism, and binding with thyroid hormone receptors at the cellular level, leading to altered thyroid hormone levels at the organ and tissue levels. Altered thyroid hormone levels contribute to synaptic dysfunction and hypomyelination. These upstream KEs ultimately lead to cognition and memory impairment, neuromotor development disorder, autism spectrum disorders, and attention deficit hyperactivity disorders. The assessment of the KERs is detailed in Table 2. "Strong" indicates substantial literature support, direct experimental evidence, and consistent findings across various

Table 1
Classification and characteristics of selected PFAS with neurotoxic effects.

Compound	Abbreviation	Carbon Chain Length	Functional Group	Traditional or Emerging	Chemical Structure	Additional Notes
Perfluorooctane sulfonate	PFOS	Long (C8)	Ionic Sulfonates	Traditional	$C_8F_{17}SO_3H$	Fire-fighting foams, stain repellents, surfactants
Perfluorooctanoic acid	PFOA	Long (C8)	Ionic Carboxylates	Traditional	$C_7F_{15}COOH$	Non-stick cookware, water repellents, industrial surfactants
Perfluorohexane sulfonate	PFHxS	Medium (C6)	Ionic Sulfonates	Traditional	$C_6F_{13}SO_3H$	Textiles, leather treatments, fire-fighting foams
Perfluorononanoic acid	PFNA	Long (C9)	Ionic Carboxylates	Traditional	$C_8F_{17}COOH$	Electronics, surfactants, and as processing aids
Perfluorooctane sulfonamide	PFOSA	Long (C8)	Neutral Sulfonamides	Traditional	$C_8F_{17}SO_2NH_2$	Insecticides, surfactants, and as a precursor to PFOS
Perfluorobutane sulfonate	PFBS	Short (C4)	Ionic Sulfonates	Traditional	$C_4F_9SO_3H$	Fire-fighting foams, industrial cleaners, Replacement for PFOS
Hexafluoropropylene oxide trimer acids	HFPO-TA	Long (C9)	Ionic Carboxylates	Traditional	$C_8F_{17}O_2COOH$	Manufacturing of non-stick coatings, similar to GenX
Pentacosafluorotridecanoic acid	PFTrDA	Long (C13)	Ionic Carboxylates	Traditional	$C_{12}F_{25}COOH$	Surfactants, anti-fouling coatings and treatments, electronics manufacturing, firefighting foams, specialty chemicals
Perfluorodecanoic acid	PFDA	Long (C10)	Ionic Carboxylates	Traditional	$C_9F_{19}COOH$	Production of fluoropolymers
Perfluorododecanoic Acid	PFDoA	Long (C12)	Ionic Carboxylates	Traditional	$C_{11}F_{23}COOH$	Production of fluoropolymers
Perfluoroundecanoic acid	PFUnDA	Long (C11)	Ionic Carboxylates	Traditional	$C_{10}F_{21}COOH$	Industrial applications
Chlorinated polyfluoroalkyl ether sulfonate	F-53B	Complex	Ionic Sulfonates	Emerging	$CF_3(CF_2)_nOCF(CF_2Cl)SO_3K$	Metal plating, alternative to PFOS
Sodium p-perfluorous nonenoxybenzene sulfonate	OBS	Complex	Ionic Sulfonates	Emerging	$C_6F_{13}C_6H_4SO_3Na$	Chromium electroplating, alternative to PFOA
Hexafluoropropylene oxide dimer acid	GenX	Medium (C6)	Ionic Carboxylates	Emerging	$C_5F_{11}OCOOH$	Manufacturing of fluoropolymers, Replacement for PFOA
Ammonium 4,8-dioxa-3H-perfluorononanoate	ADONA	Medium (C7)	Ionic Carboxylates	Emerging	$C_4F_9OC_2H_4COONH_4$	Fluoropolymer production, Substitute for PFOA
Perfluorohexanoic acid	PFHxA	Medium (C6)	Ionic Carboxylates	Emerging	$C_5F_{11}COOH$	Replacement for PFOA
Perfluorododecanoic acid	PFDoA	Long (C12)	Ionic Carboxylates	Emerging	$C_{11}F_{23}COOH$	Longer chain, potentially more bioaccumulative and persistent
8:8 Perfluoroalkyl phosphinic acid	8:8 PFPiA	Long (C8)	Ionic Phosphinates	Emerging	$C_8F_{17}P(O)(OH)_2$	Replacement for Long Chain PFAS
Perfluoro-4-isopropoxybutanoic acid	PFECA	Medium (C7)	Ionic Carboxylates	Emerging	$C_6F_{13}OCOOH$	Replacement for PFOA
Perfluoropentanoic acid	PFPeA	Short (C5)	Ionic Carboxylates	Emerging	C_4F_9COOH	Replacement for PFOA
Perfluoroheptanesulfonic acid	PFHpS	Medium (C7)	Ionic Sulfonates	Emerging	$C_7F_{15}SO_3H$	Substitute for PFOS

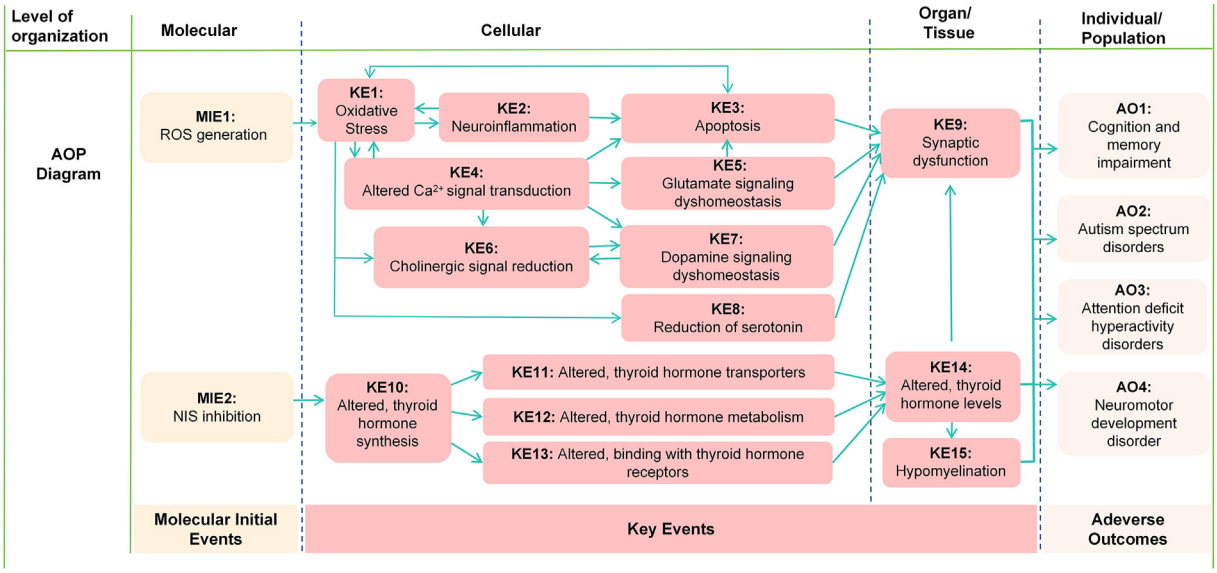

Fig. 2. Adverse Outcome Pathway diagram related to PFAS-associated neurotoxicity beginning with ROS generation and NIS inhibition. Beige cuboid: Molecular Initial Events (MIEs); Pink cuboid: Key Events (KEs); Pale orange cuboid: Adverse Outcomes (AOs).

Table 2
Summary and evaluation of KERs from the AOP.

Upstream Event	Relationship Type	Downstream Event	Weight of Evidence		
			Biological Plausibility	Essentiality	Empirical Evidence
ROS generation	adjacent	Oxidative Stress	Strong	Strong	Strong
Oxidative Stress	adjacent	Apoptosis	Strong	Strong	Strong
Oxidative Stress	adjacent	Neuroinflammation	Strong	Weak	Moderate
Neuroinflammation	adjacent	Apoptosis	Strong	Strong	Moderate
Altered Ca^{2+} signal transduction	adjacent	Apoptosis	Strong	Strong	Moderate
Glutamate signaling dyshomeostasis	adjacent	Apoptosis	Strong	Strong	Moderate
Apoptosis	adjacent	Synaptic dysfunction	Strong	Strong	Strong
Oxidative Stress	adjacent	Altered Ca^{2+} signal transduction	Strong	Weak	Moderate
Altered Ca^{2+} signal transduction	adjacent	Glutamate signaling dyshomeostasis	Strong	Strong	Moderate
Glutamate signaling dyshomeostasis	adjacent	Synaptic dysfunction	Strong	Weak	Moderate
Altered Ca^{2+} signal transduction	adjacent	Cholinergic signal reduction	Strong	Weak	Moderate
Cholinergic signal reduction	adjacent	Dopamine signaling dyshomeostasis	Strong	Weak	Moderate
Dopamine signaling dyshomeostasis	adjacent	Synaptic dysfunction	Strong	Weak	Strong
Oxidative Stress	adjacent	Reduction of serotonin	Strong	Strong	Strong
Reduction of serotonin	adjacent	Synaptic dysfunction	Strong	Weak	Moderate
NIS inhibition	adjacent	Altered, thyroid hormone synthesis	Strong	Strong	Strong
Altered, thyroid hormone synthesis	adjacent	Altered, thyroid hormone transporters	Strong	Weak	Moderate
Altered, thyroid hormone synthesis	adjacent	Altered, thyroid hormone metabolism	Strong	Weak	Moderate
Altered, thyroid hormone synthesis	adjacent	Altered, binding with thyroid hormone receptors	Strong	Weak	Moderate
Altered, thyroid hormone transporters	adjacent	Altered, thyroid hormone levels	Strong	Strong	Strong
Altered, thyroid hormone metabolism	adjacent	Altered, thyroid hormone levels	Strong	Strong	Strong
Altered, binding with thyroid hormone receptors	adjacent	Altered, thyroid hormone levels	Strong	Strong	Strong
Altered, thyroid hormone levels	adjacent	Hypomyelination	Strong	Strong	Strong
Altered, thyroid hormone levels	adjacent	Synaptic dysfunction	Strong	Strong	Moderate
Altered, thyroid hormone levels	adjacent	Impairment on neuromotor development	Strong	Strong	Strong
Altered, thyroid hormone levels	adjacent	Attention deficit hyperactivity disorders	Strong	Weak	Moderate
Synaptic dysfunction	adjacent	Impairment on learning and memory	Strong	Weak	Strong
Synaptic dysfunction	adjacent	Autism spectrum disorders	Strong	Weak	Strong
Synaptic dysfunction	adjacent	Attention deficit hyperactivity disorders	Strong	Weak	Strong
Synaptic dysfunction	adjacent	Impairment on neuromotor development	Strong	Weak	Strong
Hypomyelination	adjacent	Impairment on learning and memory	Strong	Weak	Strong
Hypomyelination	adjacent	Autism spectrum disorders	Strong	Weak	Strong
Hypomyelination	adjacent	Attention deficit hyperactivity disorders	Strong	Weak	Strong
Hypomyelination	adjacent	Impairment on neuromotor development	Strong	Weak	Strong

stressors. "Moderate" reflects partial understanding, indirect experimental evidence, and evidence from a limited number of specific stressors, with room for improvement. "Weak" denotes empirical evidence with unclear structural or functional relationships and insufficient or conflicting evidence. A total of 271 evidence-based studies informing the development of the AOP framework are meticulously documented in Supplementary Table S1-S21.

4. Discussions

4.1. MIE1: Reactive oxygen species (ROS) generation

ROS are the result of an imbalance between active metabolites and free radicals. PFAS can directly interfere with cellular redox balance, significantly increasing the frequency and rate at which molecular

oxygen (O_2) is erroneously oxidized to ROS rather than water. This interference leads to an overproduction of ROS, causing oxidative stress and subsequent cellular damage. Elevated levels of ROS have been detected in neuronal cells exposed to PFOS, PFOA, and PFHxS at concentrations below 400 μmol/L [37,38,54–65].

PFAS-increased ROS can initiate apoptosis and dysfunction in neurocytes through mitochondrial damage. Mitochondria represent the primary sites for excessive ROS-induced damage. Disruption of mitochondrial transmembrane potential and uncoupling of electron transport chains lead to the upregulation of Caspase and proapoptotic proteins, resulting in mitochondrial membrane rupture and apoptosis [60]. I*n vitro* studies have demonstrated that ROS generated by PFOS or PFOA disrupts mitochondrial transmembrane potential and oxidative respiration, leading to mitochondrial nuclear translocation and abnormal morphology [38,55,56,62]. I*n vivo* studies have shown that PFOS below 100 ppm disrupts redox balance and damages dopaminergic neurons via inhibition of mitochondrial superoxide dismutase in 72-h exposed *Caenorhabditis elegans* [61]. Furthermore, PFOS and PFOA (at concentrations below 300 μmol/L and exposure times of ≤12 h) can promote the release of toxic nitric oxide in a time-dependent manner in nerve cells through inducible nitric oxide synthase and intracellular calcium signaling triggered by ROS, ultimately leading to cell apoptosis [60,66].

ROS-stimulated stress response signaling pathways play a role in neurological dysfunction. Research has shown that PFOS or PFHxS elevates ROS levels and promotes mitochondrial dysfunction via the ERK/JNK/MAPK and Nrf2 signaling pathways in nerve cells in a dose-dependent manner, exacerbating neurocyte apoptosis [37,55,56,60,64]. An ERK inhibitor has been found to alleviate apoptosis in neuronal cells treated with PFOS or PFHxS [60,64,67]. Similarly, taurine, acting as an antioxidant, reduces ROS-related damage in PC12 cells after 24-h PFOS exposure [54]. Furthermore, N-acetylcysteine (NAC), another antioxidant, directly reduces ROS levels and maintains the redox balance within cells. By mitigating the oxidative damage induced by PFOS, PFOA, and PFHxS through the p53, Nrf2, JNK, and PKC signaling pathways, NAC protects cells from PFAS-induced oxidative stress and subsequent apoptosis [37,55,57,60,62,64,68]. Despite the robust evidence from animal and cellular studies, there are currently no epidemiological studies directly investigating the relationship between PFAS exposure and ROS generation in human populations.

We reviewed 163 papers from the first and second searches and found that ROS generation is the earliest measurable molecular event induced by PFAS exposure. Substantial evidence fulfilling the Bradford Hill criteria indicates that this disruption induces downstream oxidative stress and other key events. AOP 488 (https://www.aopwiki.org/aops/488) aligns with our collected experimental evidence, showing how ROS production leads to oxidative stress and apoptosis, ultimately resulting in neurotoxic AOs. Furthermore, integrating ROS as an MIE in AOPs is supported by another study [40], providing robust evidence for the pathways and mechanisms through which PFAS exert their neurotoxic effects.

4.1.1. KE1: Oxidative stress

Oxidative stress, which is characterized by an imbalance between oxidation and antioxidant processes within the organism, encompasses protein oxidation, lipid peroxidation, and DNA damage [69]. The accumulation of ROS, induced by PFAS, promotes oxidative DNA damage, which leads to reduced DNA synthesis and content, and increased nucleosomal DNA fragmentation, thereby ultimately impeding neuronal regeneration. This detrimental effect can potentially be mitigated by antioxidants [68,70–72]. An epidemiological study has revealed a significant increase in the DNA oxidative stress biomarker (8-hydroxy-2′-deoxyguanosine, 8-OHG) in urine among adults with elevated levels of serum PFOS [73]. However, the association between increased 8-OHG levels and adverse neurological effects in humans remains unproven.

More studies have demonstrated that PFAS impair the antioxidant activity within the nervous system. Epidemiological investigations have shown that higher concentrations of PFOS and PFOA are associated with elevated levels of serum bilirubin and albumin in humans, suggesting heightened lipid pro-oxidant activity and antioxidant properties [74,75]. Furthermore, serum PFAS levels in the second trimester have been linked to a significant increase in the marker of lipid peroxidation (8-iso-prostane-prostaglandin-F2α), potentially impacting fetal development through oxygen exchange with maternal blood [76]. I*n vitro*, PFOS, PFOA, PFNA, PFOSA, and PFBS have demonstrated a significant increase in the expression of malondialdehyde (MDA) in neurocytes [58,59,72,77]. MDA, a byproduct of lipid peroxide breakdown, impacts mitochondrial respiratory chain function and key enzyme activity.

Excessive peroxide accumulation is mitigated by antioxidant enzymes. Specifically, superoxide dismutase (SOD) converts superoxide anion radicals into oxygen and hydrogen peroxide (H_2O_2) in mitochondria, whereas catalase (CAT) breaks down H_2O_2 into harmless oxygen and water. Additionally, glutathione peroxidase (GPx) transforms toxic glutathione (GSH) into non-toxic Glutathione disulfide (GSSG) [78]. Short-term, low-concentration exposure might stimulate a compensatory increase in antioxidant enzymes as a mechanism to counteract initial oxidative stress. Studies have demonstrated that PFOS (below 100 ppm), PFBS (1 μmol/L), PFH_XA (1 μmol/L), PFOA (below 500 μg/L), GenX (below 500 μg/L), and HFPO-TA (below 500 μg/L) enhance the activity of SOD, GSH, and GPx in nematodes (72-h exposure), microglial cells (24-h exposure), and zebrafish (2–12 post-fertilization exposure), leading to effective clearance of ROS [58,61,63,79]. Conversely, decreased levels of SOD, GPx, CAT, GSH, and GSSG in PFAS-exposed mouse brain, astrocytes, and SH-SY5Y cells at concentrations greater than 100 μmol/L indicate a diminished antioxidant capacity and subsequent nerve damage [37,58,59,77,80].

Prenatal exposure to PFAS has been shown to be linked to offspring damage through the induction of oxidative stress. Numerous pathways associated with oxidative stress have been identified in PFOS-exposed zebrafish embryos and earthworms, which further impair neurological function [81,82]. The disruption of α-tubulin stability and the onset of brain necrosis in zebrafish embryos exposed to PFOS have been associated with dysregulated oxidative stress, mediated specifically by peroxiredoxin 2, essential biomarkers for axon growth and peroxide detoxification [83]. Additionally, ROS-triggered oxidative stress resulting from PFAS exposure has been found to adversely affect sperm motility, apoptosis of mouse oocytes, and zebrafish embryo development and cause alterations in calcium signaling and synaptic transmission pathways in the mouse cortex [84–87].

Extensive research across human, animal, and cellular studies supports oxidative stress as a critical KE in PFAS-induced neurotoxicity. Both *in vivo* and *in vitro* experimental evidence, supported by previously established AOP frameworks, robustly affirm its role as a downstream KE of ROS generation, capable of initiating a cascade of subsequent KEs.

4.1.2. KE2: Neuroinflammation

The elevation of oxygen free radicals and active oxidative substances leads to the release of inflammatory cytokines. *In vivo* studies have found that exposure to PFOS at concentrations below 2.0 mg/(kg·d) during pregnancy and lactation in rats leads to a significant upregulation of inflammatory factors in the hippocampus and cortex, including tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β), nuclear transcription factor-κB (NF-κB) [88]. Similarly, exposure to PFOS at concentrations ranging from 100 to 1000 μg/L in zebrafish from 24 to 96 post-fertilization (hpf) results in increased expression of IL-1β, TNF-α, NF-κB, and Interleukin 6 (IL-6) in the brain. *In vitro* studies by Chen et al. demonstrated that exposing astrocytes, SH-SY5Y cells, and C6 glioma cells to PFOS (<0.1–100 nM) for 12 and 24 h enhances the expression of IL-1β, p65, and TNF-α [89,90]. Yang et al. also exposed SH-SY5Y cells to PFOS (0.1–200 μmol/L) for less than 12 h, observing similar results [91]. Heightened levels of TNF-α are regulated by the JAK2/STAT3, Ca^{2+}, and protein kinase C (PKC) signaling pathways in PFOS-exposed astrocytes and microglia [90,91]. Inhibition of the AKT signaling pathway

effectively mitigated the PFOS-induced secretion of IL-1β, as well as the phosphorylation and degradation of IκBα, and the translocation of NF-κB and p65 from the cytoplasm to the nucleus in glioma cells [89]. Severe neuroinflammation can exacerbate PFAS-induced cellular apoptosis, neuronal loss, synaptic injury, and the decrease of spontaneous movement frequency and touch-evoked response, which are downstream KEs [88,90–92].

However, current research on the neuroinflammatory effects of PFOS has notable limitations. Most studies have focused exclusively on PFOS, neglecting other PFAS compounds that may have similar or differing neuroinflammatory profiles. Additionally, the doses used in *in vivo* studies are often significantly higher than the levels typically found in human exposure. For instance, the concentration of PFOS used in many animal studies, such as up to 1000 μg/L [92], far exceeds the PFOS levels commonly observed in human serum, which are generally below 100 ng/mL [93]. This discrepancy raises concerns about the relevance and applicability of these findings to human health, as the effects observed at such high concentrations may not accurately reflect the potential risks associated with real-world exposure levels. Further research is needed to explore the neuroinflammatory effects of PFOS at environmentally relevant concentrations and to investigate the impacts of other PFAS compounds on neuroinflammation.

4.1.3. KE3: Apoptosis

Apoptosis is a highly regulated process of programmed cell death that occurs in response to external stimuli. The families of anti-apoptotic intracellular proteins (Bcl-2) and pro-apoptotic proteins (Bax) modulate mitochondrial membrane permeability, transmembrane potential loss, and the activation of the caspase pathway to initiate apoptosis [94]. Caspase-3 and Caspase-7 are effector enzymes of apoptosis. They execute the final stages of apoptosis by cleaving specific substrates within the cell, leading to DNA fragmentation and disassembly of the cytoskeleton. Studies have detected a high apoptosis rate in SH-SY5Y cells [58], PC12 cells [64,95], microglial cells [57,60,68], and the hippocampus and cortex of mice [21] exposed to PFOS and PFH_XS. Up-regulation of Bax, Caspase-3, and Caspase-7, along with down-regulation of Bcl-2, has been observed in neurocytes and the hippocampus of mice following exposure to PFOS [37,54–56,59,67,95,96], PFOA [37,62], and PFNA [77], PFH_XS [64]. Bcl-2 typically acts to prevent apoptosis by maintaining mitochondrial membrane integrity and inhibiting the release of apoptogenic factors. PFAS exposure reduces the expression of Bcl-2, compromising the cell's ability to prevent apoptosis [97]. Bax promotes apoptosis by increasing the permeability of the mitochondrial membrane, leading to the release of cytochrome c and other pro-apoptotic factors into the cytosol. PFAS exposure increases Bax expression, which accelerates the apoptotic process.

PFAS induce cell apoptosis through the activation of multiple signaling pathways. The Ca^{2+}-dependent PKC-NF-κB signaling pathway plays a role in PFOS-induced cell apoptosis, and this effect can be reversed by PKC inhibitors [91]. Furthermore, miRNA-22 and miRNA-16 are shown to promote chromatin and nuclear condensation and fragmentation in SH-SY5Y cells exposed to PFOS through the ERK signaling pathway [98]. Inhibition of ERK is found to block caspase-3 activation in cerebellar granule cells exposed to PFOS [67,68] and PFH_XS [64,65]. Neurons are particularly susceptible to apoptosis due to their reliance on complex synaptic networks. Caspase activity disrupts synaptic structure by cleaving cytoskeletal proteins and impairing synaptic transmission. This loss of synapses and neuronal death disrupts neural circuits essential for behavior and cognition, manifesting as abnormalities like decreased touch-evoked response due to impaired sensory processing [88,92].

4.1.4. KE4: Altered Ca^{2+} signal transduction

ROS can oxidize and damage calcium channels on the membranes of the endoplasmic reticulum (ER) and mitochondria, leading to increased Ca^{2+} release. When a cell experiences stress or receives a signal stimulus, Ca^{2+} is released from the ER or mitochondria into the cytoplasm [99]. Ca^{2+} signaling plays a critical role in synaptic plasticity and the initiation and propagation of neuronal action potentials, primarily facilitated by the influx of extracellular Ca^{2+} and its release from the endoplasmic reticulum.

Observations indicate that brain and neuronal cells exposed to PFOS [91,97,100–102], GenX [36], and PFNA [77] exhibit elevated intracellular calcium levels, a phenomenon that can be mitigated by Ca^{2+} inhibitors such as nifedipine. Additionally, antagonists of peroxisome proliferator-activated receptor γ were found to reduce PFOS-induced Ca^{2+} accumulation and differentiation in embryonic neural stem cells [100]. Oxidative stress can also affect the function of calcium channels through oxidative modifications, such as those on ryanodine receptors (RyR) and inositol trisphosphate receptors (IP3R), increasing their permeability and further enhancing calcium release. Observations indicate that IP3R and RYR are implicated in Ca^{2+} release in hippocampal neurons induced by PFOS or PFOA, with IP3Rs playing a predominant role [66]. The activation of RYR, crucial for the PFAS-induced accumulation of Ca^{2+} within the endoplasmic reticulum, results in postsynaptic calcium signals and subsequent hyperactivity in zebrafish [81,103]. Additionally, increased Ca^{2+} levels activated downstream Ca^{2+}-dependent pathways, including the PI3K/AKT signaling pathway, which then regulated the NF-κB pathway and induced inflammation in astrocytes treated with PFOS [89,91]. PFOS and alternatives like F-53B or OBS were found to obstruct the cascade of Ca^{2+} signal transduction, affecting endoplasmic reticulum membrane proteins and neuromuscular pathways linked by Ca^{2+}, leading to nervous system damage and abnormal locomotion, including slow and restricted locomotion and lower swimming speed [24,26,81].

The cAMP/PKA/CREB signaling pathway serves as a crucial downstream pathway that is modulated by PFAS-induced Ca^{2+} signaling. This pathway involves Ca^{2+} signaling-mediated activation of adenylate cyclase, which leads to the production of cyclic AMP (cAMP), subsequently activating protein kinase A (PKA) within the nucleus. Additionally, calmodulin and Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) are activated during this process [104]. Subsequently, cAMP, PKA, and CaMKs translocate to the nucleus, where they phosphorylate cAMP response element-binding protein (CREB), thereby initiating gene transcription [104]. Furthermore, CaMKII, activated by PFAS-induced Ca^{2+} overload in nerve cells or the hippocampus of rats, plays a role in regulating cell proliferation and apoptosis [77,105,106]. Upregulation of the cAMP/PKA pathway-mediated CREB phosphorylation was observed in the hippocampus and cortex of Wistar rats exposed to PFOS from PND1 to PND35, and in SD rats exposed to PFOS for 91 days [105,106].

Existing studies have revealed multiple effects of PFAS on neural cells through calcium signaling pathways, but several key issues remain unresolved. Firstly, although PFAS has been shown to induce changes in calcium signaling pathways in various models, the specific mechanisms in humans are not yet clear. Secondly, there is a lack of direct evidence regarding the nuclear translocation of PKA, which necessitates further research to verify this process. Additionally, the potential effects of long-term exposure require more attention, especially the chronic effects of low-dose prolonged exposure.

4.1.5. KE5: Glutamate signaling dyshomeostasis

Glutamate is the primary excitatory neurotransmitter in the central nervous system. It transmits signals in the synaptic cleft by activating specific receptors, including N-methyl-D-aspartate receptors (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), metabotropic glutamate receptors (mGluRs), and ionic glutamate receptors (iGluRs). When glutamate binds to NMDA receptors and the membrane potential is sufficiently depolarized, NMDAR channels open, allowing the passage of Ca^{2+}. This process further regulates gene expression and structural changes in postsynaptic neurons.

Numerous studies have observed changes in molecular markers responsible for glutamate signal homeostasis. Rats exposed to PFOS from GD10 to GD20 exhibited decreased levels of mGluR2 and elevated

intracellular Ca^{2+} levels, resulting in heightened susceptibility to glutamate [107]. Changes in mGluR1 expression were associated with long-term depression and impaired learning in mice exposed to PFOS from PND1 to PND14 [28]. Furthermore, studies have shown upregulation of NMDAR and NR2B subunits, subtypes of ionotropic glutamate receptors, in the nervous systems of embryos or neonatal animals exposed to PFOS during prenatal and early postnatal periods [87,106]. Astrocyte-derived D-serine has been implicated in the pathogenesis of PFOS-induced neurotoxicity through increased NMDAR subunit expression [101]. An NMDAR antagonist has been shown to attenuate PFHxS-induced apoptosis in dopaminergic neurons [64]. In cerebellar granule neurons, both Ca^{2+} and NMDAR-dependent pathways operate in the presence of glutamate. However, in the absence of glutamate, the Ca^{2+} signal is attenuated, underscoring glutamate's significance as an excitatory neurotransmitter in neuronal communication [102].

The impact of PFAS on glutamate activity varies, with decreased glutamate levels observed in PFOS-treated rats and frogs [108,109] and increased levels noted in mice [28,96,110]. Similarly, elevated levels of glutamate were detected in astroglia and mice treated with PFOA [111,112], whereas lower levels were observed in male mice [113]. Nonetheless, altered glutamate activity due to PFAS exposure resulted in both neuronal and synaptic dysfunction. PFOS can decrease glutamate-activated currents in hippocampal neurons and disrupt glutamate–glutamine cycles in astrocytes [59,114]. Additionally, a decrease in presynaptic glutamate release, potentially attenuated by PKA inhibitors, led to reduced NMDAR-dependent long-term potentiation (LTP) induction in PFOA-exposed mice, culminating in anxiety-like behavior [111].

Glutamate serves as a precursor to γ-aminobutyric acid (GABA), a critical inhibitory neurotransmitter. Studies have demonstrated that PFNA and PFOS lead to alterations in GABA expression, aberrant swimming patterns, and epilepsy-like behaviors in zebrafish [34,115]. Reduction in GABA expression by PFOS and PFOA further caused oxidative DNA damage and neuromorphological abnormalities in the planarian *Dugesia japonica*, including impaired regeneration of ear and eye structures [70,71]. A significant correlation has been observed between altered GABA levels and impaired learning and memory in offspring exposed to PFOS-contaminated breast milk from PND1 to PND14 [33]. Exposure to PFAS levels below those typically encountered in occupational settings inhibited GABA-induced currents in human-induced pluripotent stem cells (hiPSC) [116]. Furthermore, PFOS has been shown to increase hypothalamic GABA concentrations and dopaminergic neuron activity in the pituitary gland, inhibiting prolactin secretion [31]. Meanwhile, thyroid-stimulating hormone-releasing hormone (TRH) has been identified as a prolactin-releasing factor, suggesting a role for neuroendocrine mechanisms in the neurotoxic effects of PFOS.

4.1.6. KE6: Cholinergic signal reduction

The increased intracellular calcium ion concentration promotes the fusion of synaptic vesicles with the presynaptic membrane. These synaptic vesicles contain acetylcholine, and the action of calcium ions enables acetylcholine to cross the synaptic cleft and bind to receptors on the postsynaptic membrane, such as nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). Acetylcholine is synthesized from choline and acetyl CoA by choline acetyltransferase (ChAT) and transferred into vesicles to form acetylcholine vesicle transporters. It then binds to nAChRs and mAChRs, inducing excitatory responses in synaptic clefts. Acetylcholinesterase (AChE) breaks down acetylcholine, terminating the neurotransmitter's excitatory effects on the postsynaptic membrane [117]. PFAS concentrations showed a negative association with levels of mAChRs and AChE in polar bear brains [118]. Decreased levels of nAChRs, AChE, and choline were observed in PFBS-exposed teleosts and PFOS-treated cortex of mice at PND10 [119,120]. A decrease in AChE activity in planarians induced by PFOA could potentially be mitigated by antioxidants [70]. Reduced levels of mAChRs, AChE, and ChAT, induced by PFAS, impact the synthesis and degradation of acetylcholine, influencing cortical neuron structure and potentially leading to synaptic or neuronal development damage [109,115,121].

4.1.7. KE7: Dopamine signaling dyshomeostasis

Alterations in Ca^{2+} signaling activity induced by PFOS [61,71,96,122], PFOA [122], including its substitutes F-53B and OBS, have the potential to disrupt dopamine formation and degradation, resulting in decreased dopamine activity in mice [96,123], zebrafish [24,26,115], nematodes [61], cod [30], polar bear [118], and planarians *D. japonica* [70,71]. Initially, tyrosine is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) via the catalytic action of tyrosine hydroxylase, facilitated by Ca^{2+} channel activation. Subsequently, L-DOPA is metabolized into dopamine by DOPA decarboxylase (DDC). Excess dopamine in synaptic vesicles is reabsorbed by the dopamine transporter (DAT) and metabolized by monoamine oxidase (MAO) into 3,4-dihydroxyphenylacetic acid (DOPAC), then converted to homovanillic acid (HVA) by catechol o-methyltransferase (COMT). PFOA and hexafluoropropylene-oxide-dimer-acid (GenX) decrease tyrosine hydroxylase and DAT levels during dopamine precursor and differentiation stages in hiPSC and SH-SY5Y cells [36,124]. Exposure to PFNA [115], PFOA [125], PFOS [24,34,92,126], F-53B [24,26,126], or OBS [24,126] in zebrafish elevated L-DOPA, tyrosine hydroxylase, and DAT levels, causing aberrant neurobehavioral patterns, including disrupted circadian rhythms and decreased swimming performance. Interestingly, a hierarchy of adverse effects on dopamine activity, determined by inhibited DNA synthesis and tyrosine hydroxylase expression, ranked as PFOSA > PFOS > PFBS ≈ PFOA [72]. Additionally, elevated concentrations of DOPAC and MAO have been observed in PFAS-exposed wild voles [127], mice [96], rats [27,31], and zebrafish [115], particularly in cod [30]. HVA, the terminal metabolite of dopamine, demonstrated reduced concentrations in the striatum and hippocampus after exposure to PFOS [27]. This indicates a potential disruption by PFAS in dopamine synthesis and metabolic pathways.

Dopamine diffuses to the postsynaptic membrane and binds to dopamine receptors (Drd1 and Drd2) on the postsynaptic neuron. Expression levels of Drd1 and Drd2 were observed to decrease in the striatum of rats, mice brains, and cod after PFAS exposure while being upregulated in zebrafish and the rat hippocampus [24,27,30]. Both Drd1 and Drd2 agonists have been demonstrated to amplify PFOS-induced spontaneous swimming behavior through the reduction of dopamine activity [128]. Furthermore, Drd1 has been shown to elevate cAMP levels via the guanine nucleotide-binding protein G(s), whereas Drd2 was observed to reduce cAMP levels through guanine nucleotide-binding protein G(i), indicating that inhibiting Drd1 or activating Drd2 could mitigate cAMP/PKA pathway activity [104]. Brain-derived neurotrophic factor (BDNF), c-fos, and Jun, essential downstream proteins in the cAMP/PKA pathway, are critical for neuronal development and synaptic plasticity. An epidemiological investigation demonstrated an association between PFHxS and BDNF levels in cord blood [129]. PFAS exposure has been linked to reduced BDNF concentration in neurocytes and weaned mice, enhanced methylation of the BDNF gene promoter, and consequent reduction in cell viability alongside increased apoptosis [32,98,130]. In summary, PFAS exposure has complex effects on dopamine signaling and its downstream pathways, impacting receptor expression, neuronal development, and synaptic plasticity, ultimately leading to altered behavior and increased neurotoxicity.

4.1.8. KE8: Reduction of serotonin

PFAS-induced dysregulation of dopamine activity correlates with decreased serotonin (5-HT) levels, a neurotransmitter crucial for mood, energy levels, memory, and the overall psychological state, modulated by Ca^{2+} signaling [47,61,70,71,115]. Reduced 5-HT levels, interacting with postsynaptic receptors, result in decreased neuronal activity and the onset of anxiety and depression in zebrafish [115], nematodes [61], and planarians Dugesia [70,71] following exposure to PFOS, PFOA, and

PFNA [131]. 3′-Triiodothyronine (T3) supplementation has demonstrated efficacy in counteracting the decreased 5-HT levels and related neurobehavioral effects due to F-53B exposure [47]. This study highlights that emerging PFAS may induce adverse neurological effects by disrupting thyroid hormone balance, thereby altering neurotransmitter expression. However, current research primarily demonstrates the mitigation or reversal of PFAS-induced neurological effects through thyroid hormone supplementation, reflecting the impact of PFAS on the neuroendocrine system. While these studies indicate the critical regulatory role of thyroid hormone in central nervous system health, direct evidence linking PFAS-induced thyroid hormone homeostasis disruption to neurotoxicity remains lacking. Further research is required to elucidate how PFAS affects thyroid hormone metabolism and its specific mechanisms in neurotoxicity, providing a theoretical basis for developing effective intervention strategies.

4.1.9. KE9: Synaptic dysfunction

Synapses are critical hubs in the central nervous system (CNS) where communication between neurons occurs. PFAS exposure can lead to significant disruptions in synaptic transmission through various detrimental effects on neurotransmitters and cellular processes. Dopamine reuptake by presynaptic neurons through DAT facilitates the fusion of synaptic vesicles with nerve endings or dendrites, aided by Ca^{2+} influx-induced action potentials. Several critical proteins integral to synaptic plasticity have been extensively investigated. An up-regulation of synaptophysin (Syp) and growth-associated protein-43 (GAP-43) has been observed in the hippocampus of newborn mice (PND 10) following exposure to single doses of PFOS and PFOA [132]. Moreover, enhanced expression levels of GAP-43, BDNF, and neural cell adhesion molecule 1 have been detected in neonatal rats (PND7), while reduced levels of these proteins were observed in rats (PND35) exposed to PFOS prior to weaning [29]. Additionally, reduced levels of synapsin and Syp, coupled with modifications in synaptic ultrastructure, have been noted in the hippocampus and cortex of rats exposed to PFOS during both intrauterine and lactational periods [88,133]. Critically, exposure to PFOS during prenatal and neonatal periods in rats has been linked to a significant reduction in transthyretin (TTR) levels and synaptic plasticity in the cortex, implying a pivotal disruption of the neuroendocrine system by PFOS in neurodevelopmental toxicity [87].

The blockade of voltage-gated Ca^{2+} channels, including L-type, T-type, N-type, and P/Q-type channels, in the presence of PFAS, has been shown to attenuate LTP, a crucial process underlying synaptic plasticity [134–136]. The administration of nifedipine, an L-type Ca^{2+} channel antagonist, was found to mitigate the enhancement of postsynaptic currents and field excitatory postsynaptic potentials (fEPSP) elicited by PFOS in hippocampal neurons, resulting in reduced neurite length [97]. In contrast, exposure to PFOS, F-53B, and PFOA was associated with a down-regulation of fEPSP and a lowered threshold for NMDAR-dependent LTP in rats, indicative of a postsynaptic mechanism compromising synaptic plasticity and eliciting anxiety-like behaviors [111,137]. Furthermore, research has illustrated that PKA inhibition eliminates LTP, whereas cAMP activation enhances LTP, highlighting the cAMP/PKA pathway's role in LTP modulation [138]. Evidence indicates that PFOS impairs synaptic structures through the cAMP/PKA pathway [88,133]. Additional research is required to elucidate the role of the cAMP/PKA pathway in mediating the effects of PFAS exposure on synaptic plasticity dysfunction.

4.2. MIE2: Na^+/I^- symporter (NIS) inhibition

NIS, a glycoprotein located on the membrane of thyroid follicular cells, plays a critical role in the uptake of iodide into the thyroid gland, marking the initial step in the biosynthesis of thyroid hormones. Thyroid hormones are essential for brain development and function, influencing neurogenesis, cell migration, myelination, and neuronal differentiation. In constructing the PFAS neurotoxicity framework, the inhibition of the NIS is recognized as a critical MIE. Numerous investigations have explored the inhibitory impacts of PFAS on NIS, employing high-throughput assays to measure radioactive iodide uptake and identifying PFOS and PFHxS as the predominant inhibitors [139–141]. *In vitro* studies have demonstrated that PFOS and PFOA inhibit NIS-mediated iodide uptake and thyrocyte proliferation in a dose-response relationship within 24 h [142,143], thereby reducing iodide accumulation [144], which may contribute to decreased intelligence quotient (IQ) scores in neonates owing to iodine deficiency [145]. Exposure to PFOA, GenX, and ADONA at concentrations below 1 μg/mL has been linked to diminished NIS levels in thyrocytes, a condition that may be alleviated through cAMP activation [142,143,146,147].

In vivo studies have shown that PFAS-induced NIS inhibition further compromises thyroid function and the growth of zebrafish larvae. PFHxA [148], PFDoA [149], HFPO-TA [79], PFOA [79], and GenX [79] have been identified to suppress NIS expression, induce thyroid cell apoptosis, and reduce locomotor activity in zebrafish. Maternal exposure to PFNA has been associated with changes in NIS expression in the F1 generation of zebrafish [150]. Additionally, exposure to F-53B at less than 6 mg/L for 4 weeks or 4 months has been implicated in substantial impairment of the hypothalamic-pituitary-thyroid (HPT) axis, attributed to the down-regulation of NIS, with effects persisting beyond the cessation of exposure [151,152].

The incorporation of NIS inhibition as a MIE is supported by substantial evidence within the AOP framework, as demonstrated in AOP 54 (https://www.aopwiki.org/aops/54), where NIS inhibition, by affecting molecular events related to thyroid hormone synthesis, ultimately leads to learning and memory impairment. Highlighting NIS as an MIE in our review underscores its critical role and is backed by extensive experimental evidence. In the context of PFAS-related studies, NIS inhibition often coincides with downstream thyroid hormone-related KEs. The evaluation of KERs between NIS inhibition and downstream KEs is notably robust, with outcomes being highly credible.

4.2.1. KE10: Altered, thyroid hormone synthesis

NIS facilitates the uptake of iodide, which is then oxidized and activated by thyroid peroxidase (TPO) within thyroid epithelial cells. Activated iodine is transported into the lumen of thyroid follicles, where it combines with tyrosine residues on thyroglobulin (TG), yielding iodinated tyrosines. Monoiodothyrosine (MIT) and diiodothyrosine (DIT) are further metabolized to produce thyroxine (T4) and triiodothyronine (T3) [153]. Simultaneously, the thyroid stimulating hormone receptor (TSHR) on the thyroid gland responds to thyroid stimulating hormone (TSH) from pituitary cells, stimulating T4 and T3 synthesis.

PFAS significantly alters the expression of molecules involved in the synthesis of T4 and T3. *In vitro* studies have shown that PFOS and PFOA reduce TPO, TG, TSHR levels, and N-glycosylation in rat FRTL-5 thyrocytes. These effects are reversible by a cAMP agonist [146,147]. *In vivo* studies indicate that exposure to PFOS [154], PFOA [155], PFDoA [149], and F-53B [151,152] lead to significant decreases in TPO and TG levels in zebrafish [149,152,154,155] or minnow [151]. Disruption of thyroid hormone synthesis in zebrafish exposed to F-53B was alleviated following depuration [152], an effect not observed in minnows [151]. Furthermore, compensatory upregulation of TPO, TG, and TSHR has been observed in SD rats or zebrafish exposed to PFOS [156], PFOA [79], F-53B [157], PFHxA [148], OBS [156], GenX [79], HFPO-TA [79], and PFTrDA [158], in response to persistent decreases in thyroid hormone levels.

Impaired thyroid function due to PFAS plays a crucial role in disrupting thyroid hormone synthesis. Thyroid abnormalities, such as lesions and cell apoptosis, identified in zebrafish and rats treated with PFOS [35,159] and alternatives F-53B [157], are characterized by reduced nuclear area in follicular epithelial cells and follicular hyperplasia. PFOS [152,160,161], PFOA [143,147], along with alternatives GenX [142,143] and ADONA [143], have been found to induce changes in gene expression associated with thyroid dysgenesis in both *in vivo* and

vitro studies. Notably, the disruptive impact on thyroid function by alternatives such as OBS and GenX was more pronounced than that observed with PFOS and PFOA [143,156]. Additionally, a recent case-control study indicated a potential association between PFAS concentrations and an increased risk of thyroid cancer [162]. Elevated levels of anti-thyroglobulin and thyroid microsomal antibodies, biomarkers for thyroid cancer, have been positively correlated with exposure to PFPeA and PFHxA [163], though this relationship awaits molecular validation. Current experimental studies predominantly focus on the expression of molecular biomarkers in animal or cell models, detecting changes in TPO, TG, and TSHR levels, along with compensatory mechanisms in response to PFAS exposure. However, there is a lack of experimental evidence involving inhibitors that could help evaluate the temporal effects between upstream and downstream KEs in the thyroid hormone synthesis pathway.

4.2.2. KE11: Altered, thyroid hormone transporters

The transport of thyroid hormones to various organs, including the fetal brain, is primarily mediated by thyroid-binding globulin (TBG) and TTR [164]. Epidemiological studies have shown that PFAS and T4 compete for binding sites on TTR in plasma and cerebrospinal fluid, resulting in decreased T4 levels [165]. Moreover, a negative association was observed between PFOS levels and TBG in Inuit adults [166]. In vivo studies on zebrafish have shown that PFOS [154,156], PFDoA [149], F-53B [151,152], and OBS [156] significantly decrease TTR levels, whereas PFOA [79], PFHxA [148], GenX [79], and HFPO-TA [79] significantly increase TTR levels [167]. PFAS characterized by higher degrees of perfluorination, extended carbon chains, and sulfonate groups show a preference for binding with TTR and TBG over alcoholic hydroxyl groups [168–170]. Furthermore, PFHxS exhibits the highest competitive binding activity for T4-TTR among PFAS, whereas F-53B demonstrates a greater affinity for TTR over TBG [171,172].

Once thyroid hormones are transported by thyroid hormone transport proteins to the neuronal cell nuclei, they initiate the activation of transcription elements, which subsequently activate the expression of genes necessary for synapse formation and other neural developmental processes. This gene activation is crucial for the development of related neural functions. However, when PFAS block or reduce the effectiveness of these transport proteins, the expression of neural genes dependent on thyroid hormones can be delayed, leading to developmental stalling. Despite this theoretical understanding, there has yet to be experimental research to observe this specific point in action. Further studies are needed to explore how PFAS-induced disruption in thyroid hormone transport affects gene expression and neurodevelopment, providing insights into the broader implications of PFAS exposure on brain development and function.

4.2.3. KE12: Altered, thyroid hormone metabolism

Deiodinase (Dio), an enzymatic catalyst crucial for deiodinating thyroid hormones and maintaining stable levels of T4 and T3, is vital for the development of organs, especially the fetal brain, which depends on thyroid hormones. The majority of circulating T3 is converted from T4 via the actions of Dio1/2/3, which have different but complementary roles in this process. Elevated levels of Dio1/2/3 have been observed in zebrafish and rats exposed to PFOS [154,173], PFDoA [149], PFTrDA [158], PFOA [174], and 8:8 PFPiA [48], whereas a down-regulation was observed in zebrafish exposed to substitute PFHxA [148,175] and F-53B [151,152,156]. Disruptions in deiodinase activity, manifesting as altered T3 and T4 ratios, have been correlated with PFHxA exposure in wildlife [176]. PFHxA has a six-carbon chain, shorter than PFOA's eight, resulting in lower bioaccumulation and different interactions with thyroid-related enzymes. F-53B, an alternative to PFOS, affects thyroid hormone pathways uniquely due to its sulfonate group and chlorine atom. This structure leads to distinct down-regulation of deiodinase enzymes, impacting hormone metabolism and causing disruption that differ from those caused by PFOS.

T3 and T4 undergo conjugation with glucuronic acid or sulfuric acid in the liver, followed by excretion into the intestine via bile for breakdown, culminating in elimination from the body through feces and urine. The expression of Uridine diphosphate glucosyltransferase (Ugt1a), crucial for thyroid hormone metabolism regulation, was down-regulated in zebrafish exposed to PFHxA [148], PFDoA [149], or F-53B [151,167], but up-regulated in rats' livers exposed to PFOS [177,178] and in zebrafish exposed to PFECA [179]. Further investigation into the underlying mechanisms is warranted beyond merely detecting changes in thyroid hormone metabolism-dependent gene expression induced by PFAS.

Both Dio and Ugt1a are crucial for regulating serum thyroid hormone levels. Dio enzymes convert T4 into the active T3, while Ugt1a-mediated conjugation and elimination processes maintain the balance by clearing excess hormones. Disruptions in these processes can lead to thyroid dysfunctions such as hypothyroidism or hyperthyroidism. PFAS-induced inhibition of NIS reduces iodine availability, impairing thyroid hormone synthesis. This reduction in T4 and T3 synthesis necessitates a compensatory increase in Dio activity to maintain thyroid hormone levels. However, if both Dio and Ugt1a functions are disrupted, as observed with PFAS exposure, the overall regulation of thyroid hormone homeostasis is further compromised, leading to significant endocrine disruptions.

4.2.4. KE13: Altered, binding with thyroid hormone receptors (TRs)

Thyroid hormones bind to TRs with high affinity within the nucleus, facilitating the formation of ligand-dependent transcription factors in the thyroid hormone response element region. This mechanism is crucial in mediating neuronal growth, differentiation, proliferation, and development [180]. Inadequate levels of thyroid hormones or TRs can lead to the suppression of transcription and hinder neurodevelopment [181]. TRs, encoded by TRα and TRβ genes, play distinct roles in various physiological processes. TRα, widely distributed in the brain, is essential for the maturation of Purkinje cells, GABAergic synapses, and differentiation of oligodendrocyte precursor cells. TRβ, specifically expressed in the hypothalamus and pituitary, is vital for the negative feedback regulation of the hypothalamic-pituitary-thyroid axis (HPT axis) [182–184].

Studies have shown that PFAS can activate TRs in cell-based Luciferase reporting assay [185]. Molecular docking studies have shown that F-53B and PFOS bind to the ligand-binding domains of TRα and TRβ with high affinity [152,171]. Elevated expression of TRα and TRβ was observed in zebrafish or Medaka exposed to PFOS [154,186], PFOA [79,174,186], PFHxA [148], GenX [79], and HFPO-TA [79], whereas F-53B [151,152,171] and PFDoA [149] suppressed TRα and TRβ expression. TRs knockout mice showed hypomyelination of oligodendrocytes and a diminished Purkinje cell response to T3, suggesting PFAS interference with TRs could impact neural development [183].

These mechanisms, critical for the regulation and compensation of thyroid hormones, ensure their stable circulation, which can be disrupted by PFAS and lead to significant alterations in thyroid hormone levels in serum and brain tissues.

4.2.5. KE14: Altered, thyroid hormone levels

Epidemiological studies have identified a significant association between PFAS and thyroid hormones. Numerous cohort studies have evidenced a positive relationship between T3 or TSH and PFOS or PFOA in adult or neonate serum across various populations, including those in the United States [187–189], China [10,190], and the Arctic Circle [191]. Additionally, similar associations have been observed in the blood of nestling peregrine falcons in Canada [176], as well as in drinking water in the United states [192,193]. PFNA and PFHxS have also shown a positive association with T4 and free thyroxine (FT4) among children, adolescents, and adults in cross-sectional cohorts, despite various confounding variables. These associations have been observed in studies conducted in China [194,195], the United states [188,189,192,196,197,199], Canada [198], France [200], and Spain [201]. Additionally, levels of F-53B have been significantly associated with decreased TSH and FT3

levels in Chinese adults [202], and have shown a positive association with FT3 and T3 in the cord blood of newborns in China [190,203]. Partial least-squares analysis identified F-53B as the primary factor influencing thyroid hormone levels in cord blood, with a stronger impact than PFOS and PFOA [190].

Prenatal exposure to PFAS can disrupt thyroid hormone levels in both the mothers and fetuses. Cohort studies conducted in China have observed that F-53B and long-chain perfluorocarboxylic acids significantly correlate with TSH, FT3, or FT4 levels in cord blood [203,204]. Pregnant women from China [10], Canada [205], the United states [187, 206,207], Japan [208], and France [200] with elevated levels of thyroid peroxidase antibody (TPOAb), a biomarker associated with hypothyroidism, have shown a significant inverse relationship between PFOA, PFDoA, PFHxS, PFOS, PFNA, or PFDA and levels of TSH or FT4. Elevated PFOS concentrations in cord blood or maternal serum have been associated with significantly higher TSH levels, particularly in male infants with TPOAb-negative mothers in China [209] and Japan [208]. In contrast, the association between PFOA and PFNA with TSH levels was more pronounced in cord blood from female infants in China [210]. Female infants in Korea, characterized by elevated levels of estrogen, PFOA, and PFPeA, exhibited higher T4 levels in cord blood [211], whereas male infants in France demonstrated lower T4 levels [212]. Furthermore, TBG production, which is stimulated by estrogen, was observed to increase T4 levels when interacting with PFAS in the fetus [213]. During the first trimester, elevated levels of human chorionic gonadotropin are known to stimulate the secretion of T4 and inhibit the production of TSH in the pituitary gland [214]. This period is pivotal for the development of the thyroid gland and nervous system. The association between PFOS and TSH was markedly pronounced in early pregnancy and diminished as pregnancy progressed [215]. Similarly, an inverse association was noted between PFOS and TSH, as well as between PFHxS and FT4 during early pregnancy, although this relationship shifted during mid-pregnancy [205–207,216–218]. Moreover, the association between PFAS and TSH was more pronounced in newborns delivered vaginally, while the association between PFAS and T3 was observed in infants born via cesarean section [210].

The variance in the relationship between PFAS and thyroid hormones was influenced by the methodology employed in analyzing blood samples. A consistent positive association was observed between PFOS and PFHxS with TSH in both maternal and cord serum samples [205, 207–209,212,215,216,219–223], and a comparable correlation was evident in the association between PFOA and FT4 [218,221,224]. However, a specific positive association between PFOS and FT3, T3, or T4 was distinctly observed in cord blood samples [194,225]. PFNA exhibited a positive correlation with TSH, FT3, or FT4 in maternal serum [205,208,212,217,218,221,224], contrasted by an inverse correlation with TSH in cord blood [210,211,224,226]. In maternal serum, PFDoA demonstrated a negative association with FT4, FT3, T4, or T3 [225], whereas a positive correlation with FT3 was exclusively identified in cord blood [227].

The inconsistencies in the association between PFAS and thyroid hormones across different human studies may be attributed to factors such as sex, birth method, the stage of pregnancy during sample collection, and differences in plasma samples. These variables can influence hormone levels and the body's response to PFAS exposure. Future research should consider these factors to better understand the impact of PFAS on thyroid hormone disruption. Additionally, there is a need for standardized methodologies and more longitudinal studies to assess the long-term effects of prenatal PFAS exposure on thyroid function.

In vivo studies across diverse animal models, including zebrafish and rats, have uniformly demonstrated that PFAS exposure results in decreased levels of thyroid hormones after both acute and chronic exposure to PFOS, OBS, and PFDoA [6,149,156,161,177]. Lifelong exposure to PFAS has been found to decrease T3 in wildlife [175]. Both prenatal and postnatal exposure to PFAS can lead to hypothyroxinemia in offspring [173]. Maternal exposure to F-53B interferes with T3 levels in both pups and dams of zebrafish [167], an effect that persists even after depuration [152,157]. Exposure to PFOS, GenX, PFECA, or PFAS mixtures can result in decreased levels of T3 and T4 in the bloodstream of pregnant rats and rabbits, ultimately leading to increased mortality rates and swim bladder abnormalities in offspring [179,228,229]. T4 supplementation ameliorates PFOA-induced damage to gene expression in HPTs [174].

Maternal thyroid hormones are essential for the maintenance of fetal neural development, owing to the immaturity of the fetal thyroid. Extensive research has confirmed that disturbances in thyroid hormone homeostasis within both maternal and fetal systems adversely affect the cognitive development of fetuses and children [230,231]. A birth cohort study in Taiwan region initially provided indirect evidence of this phenomenon, showing a negative association between maternal PFAS concentrations in late pregnancy and IQ scores in children aged 5 and 8. It further revealed a negative association between prenatal exposure to PFNA, PFUnDA, PFDA, and PFDoA levels and fetal T3, T4, FT4 [223, 232]. Subsequent cohort studies have further substantiated the mediating role of thyroid hormones in the association between PFAS exposure and abnormal neurodevelopment. A cohort study conducted in Norway demonstrated that maternal thyroid hormones were responsible for mediating 11.9%, 10.5%, or 19.0% of the association between PFOS, PFOA, or PFNA and neurobehavioral problems [52]. In Japan, a cohort study observed that FT4 mediated 17.6% of the association between maternal serum PFUnDA levels during late pregnancy and hyperactivity in 8-year-old children [50]. The Chinese cohort study revealed that TSH and FT4 levels in cord blood were associated with 12.9% and 19.63% of the variance in poor gross motor skills induced by PFBS in 1-year-old children [46]. Furthermore, T3 and FT3 were identified as mediators for 53% and 34% of the relationship between PFOS and cognitive function in older adults [51]. Obviously, thyroid hormones are a pivotal factor in the relationships between PFAS and neural development.

4.2.6. KE15: Hypomyelination

Thyroid hormones are key hormones that promote fetal and neonatal brain development. The dendrites and axon lengths of Purkinje cells exposed to PFOS exhibit significant damage in the absence of thyroid hormones [233]. Proteomic analysis indicates that PFOS significantly disrupts pathways associated with myelin formation in the cerebellum of chicken embryos [234]. A reduced myelin index and impaired remyelination capacity are observed in the cerebellum of mice exposed to PFOS during late pregnancy and lactation [49], a condition that can be mitigated with exogenous supplementation of T3. Although the underlying mechanisms remain unclear, three experimental studies have shown that supplementation with thyroid hormone can alleviate PFAS-induced neurotoxicity. These findings highlight the potential therapeutic role of thyroid hormone supplementation in mitigating neurodevelopmental damage caused by PFAS. More mechanistic studies are necessary to elucidate the pathways through which PFAS disrupt thyroid hormone homeostasis and impact neural development. Investigating the potential for thyroid hormone supplementation as a therapeutic intervention also warrants further exploration. By addressing these research gaps, we can develop a more comprehensive understanding of how PFAS exposure impacts neurodevelopment and identify effective strategies to mitigate these effects.

4.3. Adverse outcomes

4.3.1. AO1: Cognition and memory impairment

The dual effects of PFAS on children's cognition and memory abilities have been documented in epidemiological studies. Higher levels of PFOS, PFOA, PFNA, PFHxS, and PFHpS in serum in 3-year-old children in Norway [8] and Spain [235] are associated with lower scores in nonverbal working memory. PFHxS and PFOA in maternal plasma show negative associations with language memory in boys [235]. Infants exposed to higher concentrations of PFOA, PFOS, PFHxS, PFNA, and PFUnDA in utero

face a significantly increased risk of lower intelligence quotient (IQ), verbal IQ, and performance IQ scores in 7- to 10-year-old children in China [232,236], the United States [237,238], Sweden [239], Canada [240]. Higher concentrations of PFOS, PFOA, PFHxS, and PFNA in maternal serum during the first or second trimester are linked to reduced language, vocabulary, and reading abilities in children from Britain [241], the United States [20,242], and Spain [235]. Birth cohort studies conducted in China [243], Japan [244,245], Canada [246,247], and the United states [20] have found that prenatal exposure to PFOA, PFHpA, and PFDoA may negatively affect mental and cognitive development in toddlers. Higher concentrations of PFOA and PFNA in 8-year-old children may be linked to an increased likelihood of metacognitive impairments [248]. However, an increase in working memory by 4.1 or 5.7 points has been observed in 8-year-old American children whose mothers were exposed to PFOA or PFNA in the second trimester [249]. Improved cognition and verbal working memory have been observed in female infants at ages 1 and 3 exposed to PFAS in utero [10,235,238]. Two separate cohorts indicated that elevated levels of PFOA and PFNA in children's serum may be associated with higher IQ scores [249,250]. These positive effects should be interpreted with caution due to the lack of molecular evidence supporting a direct link between PFAS exposure and enhanced neurodevelopmental outcomes. Existing research highlights that fish consumption is a significant confounding factor in studies of neurodevelopment due to its high omega-3 fatty acid content, which may enhance cognitive development in children. For example, studies adjusting for children's fish intake have shown that the positive association between mercury levels in hair and memory and cognitive outcomes diminishes substantially [251]. A Spanish mother-infant cohort study reported an average seafood intake of 79.8 ± 35.2 g/d among pregnant women [235]. However, this study did not adjust for fish consumption, which could impact the interpretation of the positive association between PFAS exposure and children's cognitive function observed in that study [235]. Moreover, while it has been proposed that PFAS might act as agonists of PPAR-α receptors [5], potentially offering neuroprotective effects through anti-oxidative and anti-inflammatory mechanisms, there is currently a lack of molecular evidence to support this hypothesis.

Numerous animal studies have provided both behavioral and molecular evidence to support the notion that PFAS can lead to deficits in learning and memory. Specifically, neonatal mice exposed to PFOS during lactation showed impaired object location and recognition abilities, along with difficulties in visual discrimination tasks, suggesting compromised learning capabilities. These impairments were attributed to disruptions in synaptic plasticity and glutamate homeostasis in the hippocampus and cerebellum [28,33]. Similarly, rats [29,252] and mice [32,253] exposed to PFOS and F-53B during pregnancy and lactation exhibited prolonged escape latency in the water maze experiment, with the observed decline in memory ability potentially being influenced by dopamine-dependent synaptic plasticity. Furthermore, mice exposed to PFOS for a period of 3–6 months were found to exhibit delayed performance in locating the water maze platform and demonstrated reduced interest in exploring novel objects, indicative of a potential decline in object recognition, learning, and spatial memory abilities [21,96]. However, the majority of studies have predominantly focused on a limited number of specific PFAS compounds, primarily PFOS and F-53B, thereby leaving the effects of other PFAS largely unexplored. Moreover, the behavioral tasks employed in animal models, such as the water maze, provide valuable insights into spatial memory and learning but may not encompass the full spectrum of cognitive functions impacted by PFAS exposure. Furthermore, the underlying molecular mechanisms, such as synaptic plasticity and neurotransmitter homeostasis, require more detailed investigation to comprehensively understand how PFAS disrupt cognitive processes.

4.3.2. AO2: Autism spectrum disorders (ASD)

ASD is an early neurodevelopmental disorder that manifests in early childhood and is distinguished by deficits in communication abilities, as well as restricted patterns of behavior and interests. Several case-control studies conducted in America have indicated that higher PFHxS, PFOS, PFOA, PFHpA, and PFNA in both maternal [16,93,254] and child serum [245] and drinking water [255] are associated with an increased likelihood of ASD diagnosis in children between the ages of 2 and 5. However, prenatal exposure to PFOS and PFOA was linked to a decreased risk of ASD in children aged 5 to 9 [256]. An observed non-linear dose-response relationship between PFOA concentrations in maternal serum in the early or middle stages of pregnancy and the risk of ASD highlights the complexity of these interactions [257,258]. Research revealed an inverse association between the levels of PFAS in amniotic fluid and the risk of ASD, likely due to the weak estrogenic and anti-androgenic activities [259]. This study had a sample size of only 75 cases, which is relatively small, and thus, the reliability and credibility of the findings are questionable [259].

Additionally, several cross-sectional studies have found a significant association between PFAS and ASD-related symptoms, including social skills, language, and communication. Elevated levels of PFHxS, PFOS, PFOA, PFNA, PFDA, or PFUnDA in maternal plasma have been associated with increased language and communication in children aged 38 months to 4 years in Canada [247], Britain [241], the United States [20], China [243], Sweden [14]. Similarly, higher concentrations of PFHxS in maternal plasma during the third trimester have been linked to a higher likelihood of children exhibiting low trajectories in communication and problem-solving abilities [10]. Increased levels of PFAS in children or cord serum were also correlated with poor communication abilities in 6-month-old and 7- or 9-year-old children [17,18,231]. Elevated PFAS levels have been linked to personal-social difficulties in children aged 4 years in China [260]. Additionally, cohort studies conducted in Denmark [17,52], the United States [19,248,261,262], China [15,260], Italy [263], and Sweden [14] have found that elevated levels of PFOA, PFNA, and PFDA during intrauterine or childhood phases have been linked to exacerbated sleep disturbances, behaviors, restricted interests, and challenges in behavior regulation.

Despite the current observational and epidemiological data being compelling, there is a lack of experimental studies confirming that PFAS can induce ASD-related neurodevelopmental outcomes, as well as the causal relationships needed to understand the pathways and mechanisms involved. This means that the weight of evidence for upstream KEs and the KERs of this AO in constructing an AOP framework is relatively weak. Future research must address these gaps through well-designed experimental studies that incorporate both *in vitro* and *in vivo* models.

4.3.3. AO3: Attention deficit hyperactivity disorders (ADHD)

ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity. Studies conducted in Denmark [258], Norway [257,264], and Japan [50] indicate an elevated risk of ADHD in children associated with increasing levels of maternal PFOS, PFUnDA, PFTrDA, PFDA, and PFHxS in serum and breast milk. Furthermore, higher in-utero levels of PFOS have been linked to a heightened risk of hyperactivity in children aged 5 to 9 in Northern Europe [231,265]. Adverse neurological effects associated with ADHD were noted in school-age children in the United States [265,266] and South Korea [267] who had elevated PFAS levels detected in serum. Exposure to PFNA, PFHxS, and PFOA during childhood and in utero was correlated with lower scores in child attention and activity in China [268], the United States [262], and Japan [50]. *In vivo* studies have found that PFOA, ADONA, PFESA, PFHxS, and GenX at concentrations below 80 μmol/L exacerbate hyperactivity in zebrafish (exposed from 0 to 5 dpf) and mice (exposed during pregnancy or lactation) [22,269,270]. Exposure to PFAS compounds with longer carbon chains led to increased hyperactivity in zebrafish, notably PFOS, which showed a greater effect than PFHpS and PFHxS [269]. Dysregulation of Ca^{2+} signaling and downstream pathways, especially via the activation of the RyR, has been identified as a critical mechanism underlying hyperactivity in PFOS-exposed zebrafish larvae [81,103]. Aberrant Ca^{2+} signals induced by PFOS are linked to dopaminergic

deficits and neuronal excitation, which contribute to seizure-like electrophysiological signals and hyperactivity in zebrafish [34,128].

We must acknowledge that although case-control studies can clearly establish a link between PFAS exposure and ADHD [257,264], other epidemiological studies and behavioral experiments in zebrafish primarily indicate associations between PFAS and ADHD-related symptoms (hyperactivity and inattention). These findings alone cannot definitively diagnose ADHD, as it is a complex disorder lacking specific molecular diagnostic markers. Future research should aim to delve deeper into the broader spectrum of ADHD symptoms and their association with PFAS exposure. It is crucial to develop more precise and comprehensive diagnostic tools that can capture the full complexity of ADHD. Similar to ASD, ADHD also lacks experimental evidence, and the regulatory relationships between ADHD and upstream KEs depend on the weight of evidence assessed in the included studies, which are relatively weak. There is a critical need for well-designed experimental studies that clarify the biological mechanisms underlying PFAS exposure and its impact on neurodevelopmental disorders such as ADHD.

4.3.4. AO4: Neuromotor development disorder

PFAS have been found to significantly alter motor development *in vivo* studies. Offspring of rats and mice exposed to PFOS during pregnancy and lactation demonstrated enhanced motor activity, particularly in conditions of reduced glutamate activity [35,271]. Similarly, zebrafish exposed to PFOA during 5–122 hpf exhibited increased motor ability and an enhanced diving response in subsequent developmental stages [272]. The enhanced swimming speed observed in zebrafish exposed to PFOS during 6–96 hpf was attributed to an imbalance between oxidative stress and dopaminergic activity [273]. These findings suggest that the increased motor activity induced by PFAS is predominantly observed following maternal transgenerational exposure or during critical embryonic stages.

However, additional studies have revealed that PFAS decrease neuromotor activity. Epidemiological studies have identified a significant inverse relationship between motor development in children aged 6–24 months and the concentrations of PFNA, PFUnDA, PFBS, and PFHxS in maternal serum [46,243,246,274]. The motor abilities discussed here refer more to fine motor skills and gross motor development in infants and toddlers, mostly under the age of 1. In contrast, studies on PFAS and ADHD often focus on older children, typically over 1 year old and sometimes up to around 9 years old [50,231,262,265]. *In vivo* studies showing decreased motor activity often involve longer exposure durations. Several studies have demonstrated that GenX, F-53B, 6:2-FTCA, PFOA, PFBS, PFNA, and PFOS can lead to decreased locomotor activity in zebrafish or rats exposed for more than 5 days [23,26,47,48,108,115,125,275]. Notably, PFAS containing perfluoroalkyl sulfonic acid groups exhibit more pronounced neurobehavioral effects compared to perfluoroalkyl carboxylic acids, resulting in reduced overall activity levels [275,276]. Unstable glutamic acid levels and altered cholinergic gene transcription in the hippocampus and cortex have been identified as significant contributors to the observed reduction in spontaneous motor activity in rats and mice following exposure to PFOS [108,119]. Disruptions in Ca^{2+} homeostasis and dopaminergic function are implicated in the impaired locomotion observed in zebrafish offspring whose parents were exposed to PFOS, PFOA, F-53B, and OBS [26,125,126]. PFOS has been demonstrated to impact heat response by diminishing dopamine secretion through interference with Ca^{2+} signaling transduction [24]. Neonatal treatment with PFOS has been found to modify spontaneous behavior, decreasing nAChR-β2 and AChE levels while increasing mAChR-5 expression [119]. Impaired presynaptic and postsynaptic plasticity have been associated with negative motor and learning deficits induced by PFOS in lactating mice [28]. Oxidative DNA damage induced by PFOA was observed to hinder neuronal regeneration, impair locomotion development, and affect the formation of eyespots and auricles [70]. Similarly, the decrease in locomotor speed attributed to 8:8 PFPiA may be attributed to DNA methylation and disruption of thyroid hormones [48]. Notably, T3 supplementation was able to partially restore the reduced locomotor activity caused by PFAS exposure [47]. Nevertheless, current research has primarily focused on the effects of PFAS on motor activity and neurodevelopmental outcomes. The underlying mechanisms involving neuroendocrine disruption remain elusive. PFAS have been shown to interfere with thyroid hormone regulation, which is crucial for brain development and function. Understanding these mechanisms is essential for comprehensively assessing the long-term neurodevelopmental risks associated with PFAS exposure.

5. Strengths and limitations

This systematic review is the first to use the AOP framework to elucidate the neurotoxic mechanisms of PFAS. The AOP framework provides a comprehensive understanding of PFAS-induced neurotoxicity across multiple biological levels, from molecular to population. This structured and coherent approach synthesizes existing knowledge, crucial for advancing the field and informing risk assessment and regulatory decisions. Moreover, our review encompasses all relevant studies on PFAS neurotoxicity published up to December 31, 2023. This includes epidemiological and experimental studies involving human populations, animal models, and *in vitro* cell systems. By systematically cataloging all studies related to PFAS neurotoxicity and presenting the main content of each study according to MIEs, KEs, and AOs in the supplementary materials, we offer a valuable resource for researchers and policymakers. The extensive collation and analysis of data across diverse study designs and endpoints contribute significantly to the current understanding of PFAS neurotoxicity, serving as a robust reference point for future research.

Despite its comprehensive nature, this review has several limitations. Firstly, we constructed a conventional AOP framework based solely on qualitative assessments of molecular and biological events documented in the literature and AOP-Wiki. Our determination of MIEs, KEs, and AOs relied on existing AOP constructs and the Bradford Hill criteria for confidence evaluation, but it lacked a quantitative analysis (qAOP). Conducting a qAOP analysis requires extensive and high-quality quantitative data, which was not uniformly available across the studies we reviewed. This limitation precluded us from performing qAOP analysis within this review. Given the current data gaps, we prioritized a qualitative synthesis to establish a foundational understanding of PFAS-induced neurotoxicity. Future research should focus on generating robust quantitative datasets to facilitate qAOP analysis, thereby providing a more detailed and predictive framework for understanding PFAS neurotoxicity.

6. Conclusion and future directions

In summary, this review establishes the AOP framework for the first time, offering an integrated perspective on the mechanisms underlying PFAS-induced neurotoxicity. The ROS generation and NIS inhibition triggered by PFAS are identified as crucial MIEs, leading to key molecular and cellular events, with subsequent effects at tissue and organ levels, including altered thyroid hormone levels, synaptic dysfunction, and hypomyelination. Ultimately, these result in AOs characterized by impairments in cognition, memory, and neuromotor development, alongside an increased risk of neurodevelopmental disorders, including ASD and ADHD, at individual or population levels. This review establishes a solid foundation for the risk assessment of PFAS and delineates promising directions for future research aimed at a more profound understanding of toxicity mechanisms.

From the 271 studies reviewed, most epidemiological studies on human populations are concentrated in affluent regions like Northern Europe, East Asia, and North America, with little research from other areas. This disparity likely stems from differences in research funding, infrastructure, and public health priorities. While there is strong evidence linking PFAS to neurodevelopmental impairments, there is a lack of experimental evidence directly connecting PFAS to specific

neurodevelopmental disorders like ASD and ADHD, resulting in weak evidence for KERs with these disorders. Mechanistically, most studies have only measured molecular biomarkers related to key events, lacking in-depth insights. Additionally, many experimental studies use PFAS exposure levels much higher than those typically found in humans, which may not accurately reflect real-world impacts and complicates risk assessment. Given human exposure to PFAS mixtures, it is crucial to investigate the combined effects of multiple PFAS and their substitutes at environmentally relevant concentrations on the nervous system in future studies.

CRediT authorship contribution statement

Shenpan Li: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Shuangjian Qin:** Methodology. **Huixian Zeng:** Writing – review & editing. **Weichun Chou:** Writing – review & editing. **Anna Oudin:** Writing – review & editing. **Katja M. Kanninen:** Writing – review & editing. **Pasi Jalava:** Writing – review & editing. **Guanghui Dong:** Supervision, Funding acquisition. **Xiaowen Zeng:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interests

The authors declare no competing financial interest.

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Appendix A. Supplementary data

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