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Review

Potentially Toxic Elements in the Avian Nervous System: From Bioaccumulation to Neurotoxicity and Ecological Consequences

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Abstract

Environmental contamination by potentially toxic elements (PTEs) poses a persistent threat to wildlife, yet their accumulation and neurotoxic effects in the avian nervous system remain poorly understood. Although birds are widely recognised as valuable bioindicators of environmental pollution, most biomonitoring studies have focused on conventional tissues such as the liver, kidney, blood and feathers rather than on neural tissues, despite the high susceptibility of the nervous system to toxic injury. This review synthesises current knowledge on the bioaccumulation and neurotoxicity of PTEs in the avian nervous system, with emphasis on the brain, retina, optic pathways and spinal cord. Mercury remains the best-characterised avian neurotoxicant, whereas increasing evidence indicates that lead, cadmium and interactions with essential elements also contribute to neural dysfunction through distinct but partially overlapping mechanisms. Taken together, the available evidence indicates that neurotoxicity cannot be interpreted solely based on total elemental concentrations but also depends on chemical speciation, regional and cellular localisation, disruption of neural metal homeostasis and the intrinsic vulnerability of different neural tissues. Despite increasing evidence of PTE accumulation in neural tissues, important knowledge gaps remain regarding tissue-specific susceptibility and the links between neural damage, behavioural impairment and ecological performance. This review highlights the avian nervous system as an underexplored but biologically relevant target of environmental PTE exposure and highlights the need for more integrative approaches combining chemical, histopathological and functional assessments to improve avian biomonitoring and ecological risk assessment.

Keywords: potentially toxic elements; birds; avian nervous system; neurotoxicity; bioaccumulation; methylmercury; oxidative stress; ecotoxicology

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Academic Editor: Ana Luísa Patrício da Silva

Received: 8 July 2026
Revised: 9 August 2026
Accepted: 17 August 2026
Published: 20 August 2026

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1. Introduction

Environmental contamination by potentially toxic elements (PTEs) represents a persistent threat to ecosystem integrity, wildlife health and biodiversity. Anthropogenic activities, including industrialisation, mining, fossil-fuel combustion and agricultural intensification, have substantially increased the release of metallic and metalloid contaminants into terrestrial, freshwater and marine ecosystems, although natural processes such as volcanic activity, rock weathering and hydrothermal emissions also contribute to environmental inputs [1–6]. Because many PTEs persist in the environment and enter food webs, they

may bioaccumulate within organisms and biomagnify across trophic levels, increasing contaminant burdens in top predators [7]. Figure 1 illustrates the principal pathways through which PTEs are transferred across terrestrial and aquatic food webs and ultimately accumulate in birds.

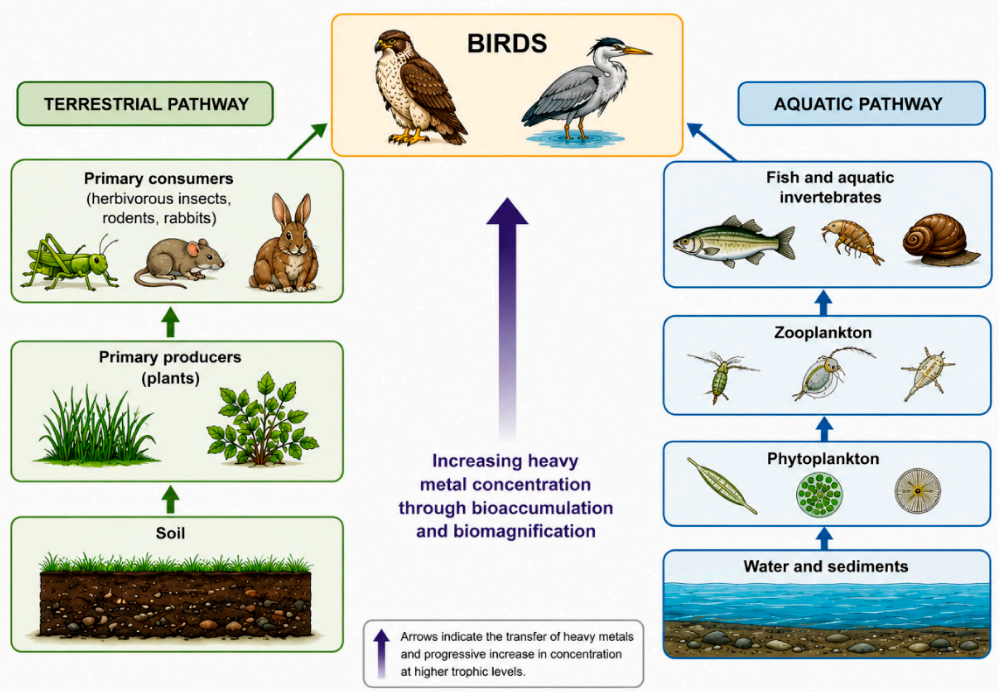


Figure 1. Simplified schematic representation of the terrestrial and aquatic pathways leading to the bioaccumulation and biomagnification of potentially toxic elements (PTEs) in birds. Arrows indicate the transfer of PTEs through food webs and their progressive increase in concentration at higher trophic levels. Conceptual illustration created by the authors with the assistance of ChatGPT 5.5 (OpenAI, San Francisco, CA, USA) and subsequently reviewed and edited by the authors.

Because these elements differ considerably in their biological roles and toxicological profiles, the term potentially toxic elements is increasingly preferred over heavy metals, as toxicity depends on concentration, chemical speciation, bioavailability and exposure conditions rather than on physical properties alone [8,9]. While elements such as Zn, Cu, Fe, Mn and Se are essential within physiological ranges, others, including Pb, Cd and Hg, have no known biological function and may induce toxic effects at relatively low concentrations [10].

Birds are widely recognised as valuable bioindicators of environmental contamination because of their broad ecological distribution, diverse trophic ecology and sensitivity to environmental change [11–13]. Numerous biological matrices, including feathers, blood, eggs and internal organs, have been used to assess avian exposure [13–18]. However, research has focused predominantly on the liver and kidney, whereas comparatively little attention has been paid to the nervous system, despite the ability of several PTEs to cross the blood–brain barrier and affect neural tissues [19,20].

Previous reviews have addressed different aspects of PTE exposure and toxicity, including environmental occurrence and toxicological effects in wildlife and humans [7], the use of avian matrices for contaminant biomonitoring [16,18,21], and the molecular mechanisms underlying metal-induced neurotoxicity [19,20,22]. However, these complementary perspectives have not specifically integrated the available evidence on PTE bioaccumulation and neurotoxic effects within the avian nervous system. This knowledge gap is particularly relevant because the nervous system is characterised by high metabolic activity, elevated oxygen consumption and complex ion-dependent signalling, features

that increase its susceptibility to oxidative, mitochondrial and excitotoxic damage [23,24]. Unlike conventional biomonitoring matrices, neural tissues not only reflect contaminant exposure but may also provide direct evidence of biologically relevant effects on sensory, cognitive and behavioural functions that are critical for survival and fitness. Moreover, birds possess highly specialised neural structures, including the hippocampus and an exceptionally developed visual system, which are essential for spatial navigation, migration, prey detection, predator avoidance and other complex behaviours [25–31].

Although the mechanisms of PTE neurotoxicity, including oxidative stress, mitochondrial dysfunction, impaired neurotransmission, disruption of ion homeostasis and neuronal or glial damage, are increasingly recognised [20,22], current knowledge in birds remains fragmented. Most studies are limited to measuring total elemental concentrations in brain tissue, whereas information on chemical speciation, regional distribution, histopathological alterations, neurochemical changes and functional consequences remains scarce. Likewise, neural structures such as the retina, optic pathways and spinal cord have received far less attention than the brain.

Moreover, the available evidence is characterised by important taxonomic, ecological and methodological biases. Most studies have focused on aquatic birds, seabirds and raptors and on mercury and lead, whereas terrestrial taxa, other potentially toxic elements and neural structures beyond the brain remain comparatively understudied [13–15,21]. These limitations hinder a comprehensive understanding of PTE neurotoxicity in birds and highlight the need for broader taxonomic coverage and more integrated assessments of the avian nervous system.

Accordingly, this review synthesises current knowledge on the bioaccumulation of potentially toxic elements in the avian nervous system, critically evaluates the evidence for their neurotoxic effects across different neural structures, and identifies the principal taxonomic, geographical and methodological gaps that should inform future research in avian neuroecotoxicology.

2. Factors Influencing PTE Accumulation in the Avian Nervous System

The accumulation of PTEs in the avian nervous system is governed by a complex interplay of ecological, biological and physicochemical factors that determine exposure, uptake, tissue distribution and biological effects (Figure 2). Although concentrations in the brain are generally lower than those reported for organs primarily involved in uptake, storage and detoxification, such as the liver and kidney [32–38], this does not necessarily imply a lower neurotoxic risk. The biological significance of neural accumulation depends not only on tissue concentration but also on chemical speciation, regional distribution within the nervous system, exposure history and the intrinsic susceptibility of different neural cell populations.

PTE accumulation varies considerably among species and populations and is strongly influenced by ecological traits, including habitat, diet and trophic position. Piscivorous, predatory and scavenging birds are generally more exposed because biomagnification increases contaminant burdens at higher trophic levels [39–41]. Biological variables such as age, sex and body condition, together with local environmental pressures, may further influence neural exposure and tissue distribution [34,35,42,43]. In addition, the selective permeability of the blood–brain barrier plays a key role in regulating the entry of different elements into neural tissues, although its effectiveness varies among elements and exposure scenarios.

Because neural tissues are often difficult to obtain, many studies have relied on surrogate matrices such as blood, liver, kidney or feathers to estimate internal exposure. While significant correlations between these matrices and brain concentrations have been

reported for some elements, these relationships are highly species-, element- and context-dependent and should therefore be interpreted with caution rather than assumed to be universally applicable [33,43–45].

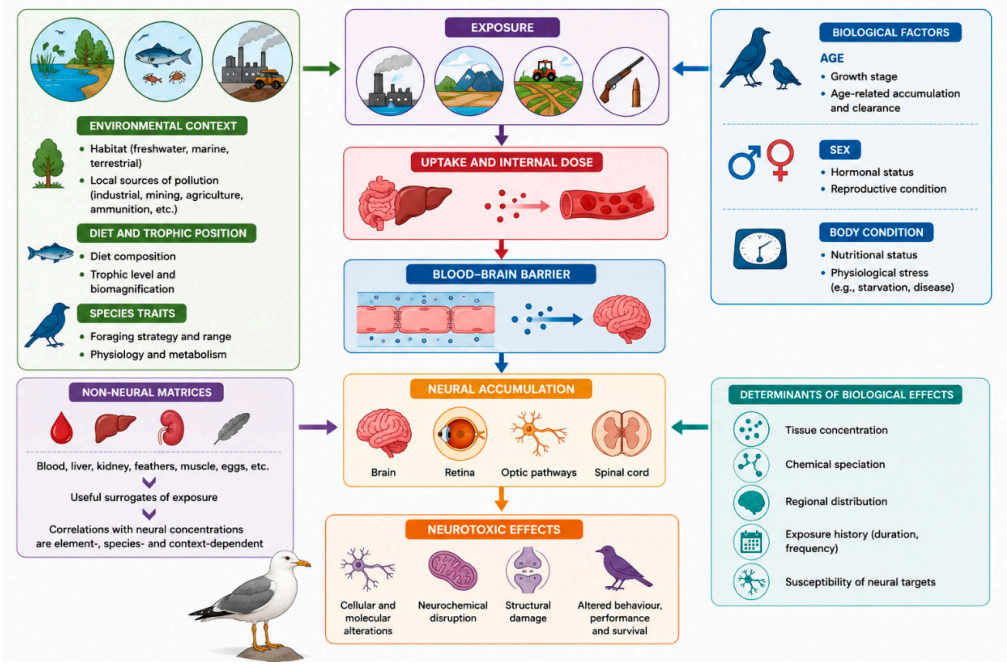


Figure 2. Conceptual framework illustrating the principal factors influencing the accumulation of potentially toxic elements (PTEs) in the avian nervous system. Neural exposure results from the interaction between environmental sources, ecological traits (habitat, diet and trophic position), biological characteristics (age, sex and body condition), and the selective permeability of the blood–brain barrier. The biological significance of neural accumulation depends not only on tissue concentration but also on chemical speciation, regional distribution, exposure history and the susceptibility of neural targets, ultimately determining the neurotoxic effects of individual PTEs. Conceptual illustration created by the authors with the assistance of ChatGPT 5.5 (OpenAI) and subsequently reviewed and edited by the authors.

Figure 2 summarises the principal factors influencing PTE accumulation in the avian nervous system, from environmental exposure to neural uptake and the biological determinants of neurotoxic effects.

Despite these common patterns, PTEs differ markedly in their environmental sources, toxicokinetics, capacity to accumulate in neural tissues and mechanisms of neurotoxicity. Therefore, each element must be considered individually to understand its biological significance. The following sections review the available evidence for the principal PTEs investigated in birds, beginning with mercury, the most extensively studied neurotoxic element in avian species.

3. Major Potentially Toxic Elements in the Avian Nervous System

3.1. Mercury

Mercury is the most extensively investigated PTE in avian neural tissues owing to its environmental persistence, microbial conversion into methylmercury (MeHg), biomagnification through aquatic food webs and well-established neurotoxicity [39,40,46]. Thus, piscivorous and predatory birds are particularly vulnerable because they accumulate Hg through contaminated prey. Across avian studies, MeHg consistently represents the predominant mercury species in the brain, accounting for more than 90% of total cerebral Hg in several species [45,47]. Experimental studies further demonstrate that Hg accumulates

in the developing brain, distributes across multiple cerebral regions and may persist in neural tissue for prolonged periods, indicating that brain concentrations integrate both recent and chronic exposure [48–50].

Mercury exposure has been associated with a broad spectrum of neurological alterations, including oxidative stress, disrupted neurotransmitter metabolism, impaired neural development and cognitive deficits. MeHg exposure has been associated with delayed cerebellar maturation, altered Purkinje cell organisation and impaired spatial learning despite limited gross anatomical changes [51,52]. However, neurochemical alterations are not consistently correlated with brain Hg concentrations, suggesting that tissue burden alone does not fully predict neurotoxicity [53,54]. Available experimental evidence suggests that these effects are largely mediated through disruption of thiol- and selenol-dependent proteins, leading to oxidative stress, mitochondrial dysfunction and impaired glutamate homeostasis. Although these mechanisms have been characterised mainly in mammalian and cellular models, they provide a plausible mechanistic framework for interpreting the oxidative, neurochemical and developmental alterations observed in birds [19,55–59].

Mercury neurotoxicity is further influenced by its interaction with selenium (Se), an essential element involved in antioxidant defence through selenoproteins. Co-accumulation of both elements has often been proposed to mitigate Hg neurotoxicity by promoting Hg–Se complex formation and preserving Se-dependent cellular functions [60,61]. However, evidence from avian studies indicates that this interaction is considerably more complex. In common loons and bald eagles, brain Se concentrations and Hg:Se molar ratios were not consistently associated with protection against neurochemical alterations, and Hg-related changes in glutamatergic markers were detected despite Se co-accumulation [54,62,63]. Accordingly, tissue Se concentrations or Hg:Se molar ratios should not be interpreted as reliable indicators of protection because they do not account for chemical speciation, intracellular distribution or Se bioavailability for selenoprotein synthesis.

Among the PTEs investigated to date, mercury is the element for which the most comprehensive evidence is available regarding neural accumulation and neurotoxicity in birds. This body of knowledge provides a valuable reference for interpreting the neural effects of the remaining PTEs discussed in the following sections.

3.2. Lead

Lead (Pb) is the second most extensively investigated PTE in avian neural tissues. Its continued relevance to avian health reflects its persistence in contaminated environments and the multiple exposure pathways affecting wild birds, including industrial emissions, polluted soils and sediments, contaminated prey and the ingestion of lead ammunition or ammunition fragments [64,65].

Available studies reveal considerable interspecific variability in cerebral Pb accumulation. Low brain concentrations have been reported in young common terns and experimentally exposed American kestrels, despite substantial dietary exposure [33,37]. By contrast, comparatively high cerebral Pb concentrations have been detected in waterfowl and gulls, and in several studies Pb was among the elements showing the greatest relative accumulation in brain tissue [14,15,66,67]. These findings indicate that cerebral Pb accumulation is influenced by species, exposure route, dose, duration of exposure, age and ecological context.

An important characteristic of Pb neurotoxicity is that its biological significance depends not only on total brain concentration but also on its regional distribution within the nervous system. Using laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS), Torimoto et al. (2021) demonstrated preferential Pb localisation in cerebellar Purkinje cells and the mesencephalon of experimentally exposed ducks and kites [68]. Pb

accumulation was also accompanied by altered cerebral copper (Cu) distribution, suggesting disruption of essential metal homeostasis in addition to direct neurotoxic effects. This localisation is biologically relevant because Purkinje neurons are essential for cerebellar output and motor coordination, whereas the avian mesencephalon contains major centres involved in visual processing and motor integration, notably the optic tectum [69].

The developing nervous system appears especially vulnerable to Pb exposure. Experimental exposure during chick embryogenesis produced cerebellar abnormalities and early impairments in motor behaviour [70]. Experimental evidence further indicates that Pb primarily exerts its neurotoxic effects by competing with Ca^{2+}, thereby disrupting calcium-dependent signalling, neurotransmitter release and synaptic organisation [71–73]. These alterations are accompanied by oxidative stress, mitochondrial dysfunction and activation of apoptotic pathways in avian neural tissues [74,75], suggesting that Pb neurotoxicity results from the combined disruption of neuronal signalling, energy metabolism and cell survival. Compared with mercury, the mechanisms underlying Pb neurotoxicity remain less extensively characterised in birds. However, the available evidence consistently indicates that Pb can accumulate in functionally important brain regions and interfere with key cellular processes involved in neural development, neurotransmission and motor function.

3.3. Cadmium

Cadmium (Cd) generally accumulates at lower concentrations in the avian brain than in the liver or kidney, although measurable cerebral accumulation and considerable interspecific variability have been reported [14,15,35,66,76,77]. Cerebral Cd concentrations may increase with age and prolonged exposure, indicating that even relatively low tissue levels may be biologically relevant under chronic exposure conditions. Experimental studies in chickens have demonstrated that Cd can induce neuronal degeneration, neuronal atrophy and cell death in the avian brain [78]. Compared with mercury and lead, evidence for Cd neurotoxicity in birds remains more limited. However, the available studies consistently indicate that disruption of essential metal homeostasis represents a central mechanism underlying Cd-induced neural injury. In particular, Cd interferes with the regulation of essential elements, especially zinc (Zn), iron (Fe), selenium (Se) and Cu, which are required for antioxidant defence, enzyme activity and normal neuronal function [22,79]. Chronic Cd exposure in chickens was associated with Cd and Cu accumulation, depletion of Se, Fe and Zn, and altered expression of genes involved in metal transport and metallothionein regulation, indicating a profound disturbance of cellular metal homeostasis [80]. Although Cd is not a redox-active metal, it promotes oxidative stress indirectly by impairing mitochondrial function, displacing essential metals and weakening antioxidant defences [79,81]. Experimental evidence further indicates that Cd neurotoxicity involves disruption of the MTF1–metallothionein regulatory axis [82] and impaired autophagic flux through the AMPK–ULK1 pathway in the cerebral cortex of chickens [78]. Together, these alterations compromise cellular defence mechanisms, favour the accumulation of damaged proteins and mitochondria, and ultimately promote neuronal degeneration and apoptosis.

4. Neural Metal Homeostasis: A Common Target of Potentially Toxic Elements

PTE neurotoxicity should not be interpreted solely as the direct consequence of the accumulation of an individual contaminant. Instead, increasing evidence indicates that exposure to toxic elements may reorganise the neural metal environment by altering the distribution, availability and biological functions of essential elements required for normal neuronal physiology. Consequently, the balance among essential and non-essential elements emerges as a key determinant of neural homeostasis and susceptibility to neurotoxic injury.

Essential elements such as Zn, Cu, Fe, Mn and Se play indispensable roles in the avian nervous system and should not be regarded simply as contaminants when detected in neural tissues. They participate in antioxidant defence, mitochondrial metabolism, neurotransmission, synaptic organisation and neuronal signalling, and their concentrations are therefore tightly regulated. For example, Zn is heterogeneously distributed within the avian brain and is particularly abundant in telencephalic regions involved in learning, memory, synaptic plasticity and song control [83,84].

Rather than acting independently, toxic and essential elements interact within this tightly regulated metal network. As discussed in the previous sections, Hg, Pb and Cd exposure has been associated with alterations in the distribution or availability of essential elements, including Se, Zn, Cu and Fe. Mercury may interfere with Se-dependent antioxidant systems, Pb has been associated with altered cerebral Cu distribution, and Cd disrupts the homeostasis of Zn, Fe, Se and Cu through changes in metal transport and metallothionein regulation [54,68,80]. These findings indicate that PTE neurotoxicity frequently involves disruption of physiological metal homeostasis in addition to the direct effects of the toxic element itself. It should also be recognised that the biological relevance of chemical speciation differs among PTEs. For mercury, toxicity is closely linked to its chemical form, particularly methylmercury, making speciation analysis essential for understanding its environmental behaviour and neurotoxic potential. In contrast, the neurotoxicity of Pb and Cd appears to depend more on their ability to compete with essential elements for biologically relevant metal-binding sites than on classical chemical speciation itself. Future studies should therefore investigate these competitive interactions as a complementary mechanism underlying the disruption of neural metal homeostasis.

Disturbances in essential metal homeostasis may have profound functional consequences because these elements regulate multiple processes required for neuronal viability. Competition between toxic metals and physiological ions, particularly Zn and Ca, may alter receptor organisation, synaptic stability and intracellular signalling, whereas changes in Se, Fe and Cu availability may compromise antioxidant capacity, mitochondrial metabolism and other metal-dependent cellular functions [20,22,79]. Therefore, neural dysfunction may arise not only from toxic metal accumulation but also from secondary disturbances affecting essential metal-dependent pathways.

Understanding PTE neurotoxicity therefore requires considering the neural metallome as an integrated regulatory network rather than evaluating individual elements in isolation. This integrative perspective provides a more comprehensive framework for interpreting the complex interactions that ultimately determine neural vulnerability in birds.

5. Beyond the Brain: The Retina, Optic Pathways and Spinal Cord as Vulnerable Neural Targets of PTE Exposure

Research on PTE accumulation in the avian nervous system has focused predominantly on the brain, while the retina, optic pathways and spinal cord have received comparatively little attention. Although these structures have been largely overlooked, they are integral components of the central nervous system and play essential roles in vision, sensorimotor integration and locomotion. This imbalance represents one of the clearest knowledge gaps in the current literature.

Despite the limited evidence available, existing studies indicate that elemental accumulation within the eye is region-specific. Eckhert (1983) described distinct distributions of Cu, Fe and Zn across the cornea, lens, retina, choroid and sclera, whereas Spalding et al. (2000) reported Hg and MeHg accumulation in avian eyes without resolving their localisation within the different retinal layers [36,85]. This knowledge gap is particularly important because the retina is not simply a sensory organ but a specialised extension of the central

nervous system. Birds depend heavily on high visual acuity, colour discrimination, motion detection and spatial orientation for essential behaviours such as foraging, predator avoidance, mate choice, migration and navigation [27,29,30,86]. These visual capabilities rely on a highly specialised retina characterised by multiple cone types, coloured oil droplets, high photoreceptor densities and, in many species, one or more foveae. As a result, the retina represents a functionally critical component of the nervous system and a plausible, yet largely overlooked, target of PTE-induced neurotoxicity.

Several retinal cell populations may be particularly susceptible to PTE exposure. The retinal pigment epithelium is of special interest because melanin can bind divalent metal ions, potentially promoting local metal retention and altering epithelial support of adjacent photoreceptors [31,87,88]. Photoreceptors constitute another likely target owing to their exceptionally high metabolic demands and strong dependence on mitochondrial function, making them especially vulnerable to oxidative and metabolic injury. Likewise, Müller glial cells regulate extracellular ion homeostasis and participate in glutamate and GABA metabolism [89]; disruption of these functions could promote secondary excitotoxic damage within the retina. Together, these characteristics suggest that the retina may be one of the most vulnerable neural tissues to PTE-induced dysfunction.

Evidence from non-avian vertebrates further supports the potential vulnerability of ocular tissues to toxic metals. Metal accumulation has been reported in the retinal pigment epithelium, choriocapillaris, retina, optic nerve and central nervous system glia [90,91]. Moreover, the ability of Hg to cross the blood–brain barrier and accumulate in neural tissue [19] suggests that similar mechanisms could operate in neurosensory structures. Although these findings cannot be directly extrapolated to birds, they identify potential cellular targets that warrant investigation in avian models and wild populations.

Knowledge of the optic pathways and spinal cord is even more limited. The optic tectum is the principal centre for visual processing in birds and is essential for integrating retinal information required for visually guided behaviours, whereas the spinal cord plays a central role in motor coordination, posture and locomotion. However, evidence for PTE accumulation in these structures is almost absent. Pass (1975) reported selective methylmercury accumulation in astrocytes throughout the brain and spinal cord, as well as in ependymal cells of the Mallard duck, whereas neuronal labelling was observed only at the highest exposure level [92]. Beyond this pioneering study, virtually no information is available regarding elemental distribution, cellular targets or functional consequences of PTE exposure in the avian spinal cord or optic pathways.

The scarcity of studies on ocular tissues and the spinal cord probably reflects, at least in part, technical challenges associated with the small amount of available tissue, the difficulty of isolating specific neural structures and the risk of cross-contamination during dissection. Nevertheless, recent advances in spatially resolved analytical techniques, including LA-ICP-MS and related imaging approaches, now enable trace-element analysis in small and anatomically complex neural tissues [68,93]. The current emphasis on whole-brain analyses is therefore likely to underestimate the functional consequences of PTE exposure in birds. Subtle alterations affecting specialised neural structures involved in vision or motor control may profoundly impair foraging efficiency, predator avoidance, migration and reproductive success, even in the absence of overt neuropathology. Integrating spatial elemental mapping with histopathology, cell-specific biomarkers and functional assessments of visual and motor performance will therefore be essential for achieving a more complete understanding of avian neuroecotoxicology.

To summarise the evidence base reviewed above, Table 1 provides an evidence-based synthesis of the main patterns of PTE accumulation and neurotoxic endpoints reported in avian neural tissues.

Table 1. Evidence-based synthesis of PTE accumulation and neurotoxic endpoints in avian neural tissues.

Synthesised Message	Evidence Reported in the Reviewed Studies	*n*	Taxa/Ecosystems	Support Within the Reviewed Studies	Supporting Studies
Cerebral burden is generally lower than in peripheral organs, but measurable or high cerebral concentrations occur in some contexts.	Comparative tissue studies reported lower metal concentrations in brain than in liver, kidney, muscle, bone, feathers or blood for several elements. Detectable or comparatively high cerebral burdens were nonetheless reported in some waterfowl and gull studies, particularly for Pb, Cr, Zn and Cd. Blood was found to be an unreliable predictor of cerebral Hg in one comparative study.	11	Anseriformes, Charadriiformes, Pelecaniformes, Galliformes, Suliformes and other orders; aquatic, marine and terrestrial systems	Broad support within the reviewed studies	[14,15,32–35,37,38,43,66,77]
Mercury neural exposure is shaped by chemical form, dose, developmental stage and retention over time.	Studies reporting Hg speciation found that MeHg predominated in brain tissue. Experimental work showed dose-related and developmentally progressive cerebral accumulation, prolonged and variable brain retention, and accumulation patterns related to dietary exposure and methylmercury form.	6	Galliformes, Passeriformes, Accipitriformes and Charadriiformes; experimental and field studies	Broad support within Hg-focused studies	[45,47–50,94]
Only a minority of studies link cerebral residues to biochemical, neurochemical, histological or functional endpoints.	Cerebral exposure was associated with oxidative-stress biomarkers, neurochemical changes, delayed cerebellar maturation, heterotopic Purkinje neurons, clinical neurological signs, ataxia and mortality at high Hg exposure. One herring-gull study found geographical variation in brain Hg without detectable neurochemical effects.	7	Passeriformes, Pelecaniformes, Charadriiformes and Accipitriformes; field and experimental studies	Limited; includes one negative neurochemical study	[36,44,51,53,54,95,96]
Where examined, neural exposure showed regional, cellular or ocular specificity.	Elemental distribution was reported in CNS glial and ependymal cells, Purkinje cells, the mesencephalon, telencephalic and song-control regions, and ocular tissues including retina and vitreous humour. One gull study additionally reported neurohistological alterations associated with environmental exposure.	6	Anseriformes, Passeriformes, Columbiformes, Charadriiformes and Accipitriformes; aquatic, marine and terrestrial systems	Consistent but mainly descriptive	[68,83–85,92,97]
Elemental relationships and biological condition complicate interpretation of neural exposure.	Inter-element relationships involving Pb, Cd, Cu and essential elements were reported in the brain, and body condition was associated with contaminant burden in one study. These findings caution against interpreting single-element brain concentrations in isolation.	3	Anseriformes and Charadriiformes; aquatic and marine systems	Limited	[42,67,76]

Note: This table synthesises only the findings reported in the reviewed studies and introduces no mechanisms, effects or references beyond that evidence base. Each study is assigned to a single primary message to avoid redundancy; *n* values sum to the full set of 33 studies. "Support within the reviewed studies" reflects the number and consistency of studies supporting each message and is not a formal risk-of-bias assessment. Speciation values and localisation findings describe processes relevant to neurotoxicity but do not by themselves demonstrate functional damage. Abbreviations: Cd, cadmium; CNS, central nervous system; Cr, chromium; Cu, copper; Hg, mercury; MeHg, methylmercury; Pb, lead; PTE, potentially toxic element; Zn, zinc.

6. Towards an Integrated Framework for Avian Neuroecotoxicology

The evidence reviewed here indicates that avian neuroecotoxicology is progressively shifting from descriptive biomonitoring towards a more mechanistic understanding of PTE-induced neural dysfunction. Although birds are widely used as bioindicators of environmental contamination, most studies have relied on conventional biomonitoring matrices such as the liver, kidney, blood and feathers, whereas direct assessment of the nervous system remains comparatively limited [11,13,21]. As discussed throughout this review, neurotoxicity cannot be explained solely by total elemental concentrations, but also depends on chemical speciation, regional and cellular localisation, interactions with essential elements and the biological context of exposure [45,47,68]. These observations highlight the need to move beyond descriptive measurements of tissue burdens towards a more integrated understanding of the mechanisms linking contaminant exposure with neural dysfunction.

One of the principal priorities for future research will be to expand investigations beyond whole-brain analyses towards spatially resolved studies of the avian nervous system. The retina, optic pathways and spinal cord remain among the least explored neural structures despite their central roles in vision, sensorimotor integration and locomotion [36,85,92]. Recent advances in spatially resolved analytical techniques, including LA-ICP-MS, together with histopathology, neuronal and glial markers and functional assessments, now provide unprecedented opportunities to identify tissue- and cell-specific targets of PTE exposure [68,93]. However, despite these important advantages, LA-ICP-MS should primarily be regarded as a spatial imaging technique rather than a fully quantitative analytical approach. In many applications, elemental images remain semi-quantitative, and accurate determination of PTE concentrations still requires complementary bulk analytical methods, such as conventional ICP-MS following acid digestion and appropriate calibration. Consequently, integrating both methodologies offers the most comprehensive strategy by combining precise elemental quantification with high-resolution spatial localisation within neural tissues. Such approaches will be essential to determine whether neural vulnerability differs among specialised cell populations and functionally distinct regions of the nervous system.

Future research should also investigate toxic elements within the broader context of neural metal homeostasis rather than as isolated contaminants. As discussed for Hg, Pb and Cd, interactions between toxic and essential elements—including Hg–Se, Pb-associated alterations in Cu distribution and Cd-induced disruption of Zn, Fe and Se homeostasis—demonstrate that neurotoxicity frequently results from perturbation of physiological metal networks rather than from the direct effects of a single element [22,54,68,80]. Adopting multi-element approaches that combine elemental quantification with chemical speciation, molecular markers of metal transport and antioxidant defence, and analyses of metal-dependent cellular pathways will therefore provide a more comprehensive understanding of the mechanisms underlying neural injury.

Finally, stronger integration between laboratory and field studies will be necessary to establish how neural alterations translate into behavioural and ecological consequences. Linking elemental accumulation with neurochemical, histopathological and behavioural endpoints will improve our understanding of how environmental contamination affects sensory performance, locomotion, predator avoidance, migration and ultimately the fitness of wild bird populations [27,29,30,46]. Such cross-disciplinary approaches will also facilitate the translation of mechanistic findings obtained under controlled laboratory conditions into ecologically realistic scenarios encountered by wild bird populations.

Advancing avian neuroecotoxicology will therefore require multidisciplinary frameworks that integrate exposure assessment, chemical speciation, spatial elemental mapping,

histopathology, molecular biomarkers and functional analyses across multiple levels of biological organisation. Such integrative approaches will provide a more complete understanding of how potentially toxic elements disrupt neural function and will strengthen the use of birds as bioindicators of environmental contamination and ecosystem health.

7. Conclusions

PTEs can accumulate in the avian nervous system and disrupt neural function through multiple, often interconnected mechanisms involving oxidative stress, mitochondrial dysfunction, impaired neurotransmission and disruption of metal homeostasis. Although mercury remains the best-characterised avian neurotoxicant, increasing evidence indicates that lead, cadmium and other PTEs also affect neural tissues through distinct, yet partially overlapping, mechanisms.

One of the principal conclusions emerging from this review is that neurotoxicity cannot be interpreted solely based on total elemental concentrations. Instead, chemical speciation, regional and cellular localisation, interactions between toxic and essential elements, and the intrinsic vulnerability of different neural tissues collectively determine biological outcomes. Consequently, the avian nervous system should be regarded as a complex and heterogeneous target rather than as a single anatomical compartment.

Ultimately, a comprehensive understanding of avian neuroecotoxicology will require not only quantifying elemental burdens but also determining where toxic elements accumulate, in which chemical forms they occur, how they interact with essential elements, and how these processes ultimately impair neural function, behaviour and ecological performance.

Author Contributions: Conceptualization, R.C., A.N.-S., M.G. and Y.S.; investigation, R.C., A.N.-S., N.O., M.G. and Y.S.; data curation, R.C., A.N.-S., M.G. and Y.S.; writing—original draft preparation, R.C., A.N.-S., N.O., M.G. and Y.S.; writing—review and editing, R.C., A.N.-S., M.G. and Y.S.; funding acquisition, A.N.-S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the University of Alicante, grant number GRE23-06A.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: During the preparation of this manuscript, the author(s) used ChatGPT (GPT-5.5, OpenAI) for the generation of figures. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AMPK	AMP-activated protein kinase
Ca^{2+}	Calcium ion
Cd	Cadmium
CNS	Central nervous system
Cr	Chromium
Cu	Copper
Fe	Iron
GAD	Glutamate decarboxylase
GenAI	Generative artificial intelligence
GS	Glutamine synthetase
Hg	Mercury
LA-ICP-MS	Laser ablation inductively coupled plasma mass spectrometry

MeHg	Methylmercury
Mn	Manganese
MTF1	Metal regulatory transcription factor 1
NMDA	N-methyl-D-aspartate
Pb	Lead
PTE	Potentially toxic element
Se	Selenium
TBARS	Thiobarbituric acid-reactive substances
ULK1	Unc-51-like autophagy-activating kinase 1
Zn	Zinc

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