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Current Insights into Plausible Mechanisms of Chromium (VI) Neurotoxicity in the Brain and Future Perspectives

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Abstract

Background: Hexavalent chromium (Cr (VI)) is a known neurotoxin and environmental contaminant. Despite its recognition, the underlying mechanisms by which Cr (VI) induces neurological damage remain insufficiently explored. The complexities of the Central Nervous System (CNS), including the Blood Brain Barrier (BBB) and supporting brain cells, contribute to regions-specific susceptibility within the brain. Understanding Cr (VI) neurotoxicity is crucial for its potential role in neurodegenerative diseases.

Methods: A Systematic Review was conducted using international databases (PubMed, Medline, Scopus, and Web of Science) and Google Scholar. Only open-access, free full-text articles published in English between 2010 and 2025 were included. Following PRISMA 2020 guidelines, a total of 19 relevant studies were selected, comprising 12 animal-based and 7 human cohort studies.

Results: Animal studies investigated the effects of Cr (VI) via various administration methods and doses, revealed evidence of oxidative stress, inflammatory markers, and apoptotic changes in the brain. Interventional studies showed delayed toxicity when antioxidant agents were used prior to Cr (VI) exposure, including PDC (Potassium Dichromate), SA (Sodium Alginate), and TNG (Tangeretin). Human studies, including autopsies and cell culture analyses, demonstrated neurotoxic effects in conditions such as ALS (Amyotrophic Lateral Sclerosis), nAMD (Neovascular Age-Related Macular Degeneration).

Conclusion: Animal studies have clarified the role of oxidative stress in Cr (VI)-induced neurotoxicity. Human cohort studies have identified Cr (VI) as an environmental risk factor for both neurodegenerative and neurobehavioral disorders. Future research should focus on defining harmful levels of Cr (VI) and exploring potential antioxidant therapies.

Keywords: Chromium, Toxicity, Heavy metals, Neurodegenerative disorders, Oxidative stress, Neuroinflammation

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Introduction

Chromium (Cr) is a heavy metal that naturally occurs in two primary oxidation states: trivalent chromium [Cr(III)] and hexavalent chromium [Cr(VI)]. Cr(III) is considered less harmful and may even be beneficial in trace amounts, whereas Cr(VI) is well known for its carcinogenic properties and is recognized as a major environmental contaminant (1-5). Industrial activities such as coal and oil combustion, the use of oxidizing pigments, paint manufacturing, fertilizer production, oil well drilling, metal plating, and leather processing con-

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↑***What is "already known" in this topic:***
Hexavalent chromium (Cr (VI)) is widely recognized as a neurotoxin, that is associated with oxidative stress and neuronal damage. However, the mechanisms by which Cr (VI) induces neurotoxicity, particularly regarding its impact on the blood-brain barrier (BBB) and subsequent neurodegenerative diseases, remain underexplored.

→***What this article adds:***
This review consolidates the current understanding of Cr (VI) induced neurotoxicity, emphasizing experimental findings and human cohort studies. It highlights the role of Cr (VI) in oxidative stress, neuroinflammation, and neurodegenerative disorders, while also proposing future research directions and potential therapeutic approaches such as antioxidant interventions.

tribute substantially to environmental Cr(VI) pollution (6). Occupational exposure, primarily through inhalation, is strongly associated with an elevated risk of lung cancer, while ingestion of contaminated water has been linked to an increased risk of liver cancer. Once inside the body, Cr(VI) mimics sulfate and phosphate ions, allowing it to enter cells passively through ion channels (7). Within the cytoplasm, it is rapidly reduced to Cr(III), proceeding through intermediate oxidation states such as Cr(V) and Cr(IV) (8). This redox process generates reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide, and hydroxyl radicals, all of which contribute to cellular oxidative stress. Furthermore, Cr(VI) has been shown to induce genomic instability by disrupting DNA repair pathways and damaging mitochondria both key mechanisms in carcinogenesis (9). Hexavalent chromium [Cr(VI)] is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), confirming its carcinogenicity in humans (10). Despite this established toxicity, research into the neurological effects of Cr(VI) remains limited. The blood–brain barrier (BBB), which protects the brain from harmful substances, relies on the coordinated activity of astrocytes, microglia, pericytes, endothelial cells, and certain neurons, to maintain its structural integrity and selective permeability. This integrity is essential for preventing the entry of toxic agents such as heavy metals into the central nervous system (CNS) (11, 12). It remains unclear whether Cr(VI) can cross or damage the BBB. The detection of chromium in cerebrospinal fluid (CSF) from a hip transplant case in which it was identified as Cr(III) rather than Cr(VI)—suggests that chromium, in general, may have the potential to interact with or penetrate the CNS (13). An alternative route of entry into the brain could be through the olfactory bulb, which lies outside BBB protection (14).

Moreover, the hypothalamus and pituitary gland, which are involved in several homeostatic processes, maintain continuous contact with the blood stream and possess a weaker BBB (15). These regions could therefore represent potential entry points for Cr(VI). However, the mechanisms underlying Cr(VI)-induced neurotoxicity re main poorly understood. Although the toxic effects of Cr(VI) are well documented, there is limited occupational evidence linking chromium exposure to neurological or behavioral disorders (16). Animal studies have described the pathophysiolog ical basis of chromium-induced neurotoxicity and highlighted the potential therapeutic relevance of certain agents (17–19).

Understanding these mechanisms could provide important insights for human studies investigating the association between Cr(VI) exposure and neurodegenerative disorders such as Alzheimer's or Parkinson's disease.

Therefore, this systematic review examines the existing literature on Cr-(VI) toxicity and its adverse effects on the central and peripheral nervous systems. The specific objectives of this review are to:

1. Summarize experimental studies elucidating the possible mechanisms of nerve damage caused by Cr(VI) toxicity;
2. Summarize observational studies demonstrating the clinical implications of Cr-(VI) exposure;
3. And Identify research gaps and propose recommendations for future studies and guidelines.

Methods

Search Strategy

This systematic literature review was conducted in accordance with the PRISMA 2020 guidelines. A comprehensive search of relevant scientific literature was performed across major international databases, including PubMed, Scopus, Web of Science, and Embase, to ensure broad coverage of related studies. Additionally, Google Scholar was searched to capture freely available and gray literature. The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators (AND, OR), applying the following keywords: ("chromium" OR "Cr(VI)" OR "hexavalent chromium") AND ("brain" OR "central nervous system" OR "CNS") AND ("toxicity" OR "neurotoxicity" OR "oxidative stress" OR "inflammation" OR "apoptosis" OR "neurodegeneration"). The search covered studies published between January 2010 and March 2025, restricted to English-language, full-text, and open-access articles. To ensure completeness, the reference lists of relevant publications, as well as the "Cited By" and "Related Articles" sections of included studies, were also manually screened. A total of 14,264 records were initially identified across all databases. Of these, 13,902 were excluded through automated filtering and duplicate removal. After de-duplication, 38 articles were selected for eligibility assessment, of which 19 were retained for reporting and discussion. The remaining 18 articles were excluded for the following reasons: (1) Cr-(VI) was not discussed; (2) neuronal tissues were not assessed; (3) toxicity outcomes were not considered; and (4) the paper was a review articles. The details of this selection process are summarized in Figure 1.

Selection Criteria

Automated filters were applied during the search to narrow down relevant studies. The inclusion criteria were as follows: Studies published between 2010 and 2025; Full-text, open--access, original research articles; Published in the English language; and Investigating chromium (VI)-induced neurotoxicity in animal models, human subjects, or cell-based systems. The exclusion criteria were as follows: Review articles, editorials, or case reports; Studies not assessing neuronal tissues or brain regions; Studies not involving Cr(VI) exposure or focusing on non-neurological outcomes; and Reports involving mixed or confounding metal exposures (Pb, Hg, Cd, Ni) in which chromium-specific effects could not be clearly distinguished.

To minimize confounding, studies that involved co-exposure to other heavy metals such as lead (Pb), mercury (Hg), cadmium (Cd), or nickel (Ni) were carefully evaluated. Only those providing analytical distinction or reporting isolated Cr(VI)-specific findings were prioritized for inclusion, whereas studies lacking clear separation were excluded. After applying all filters, the number of articles

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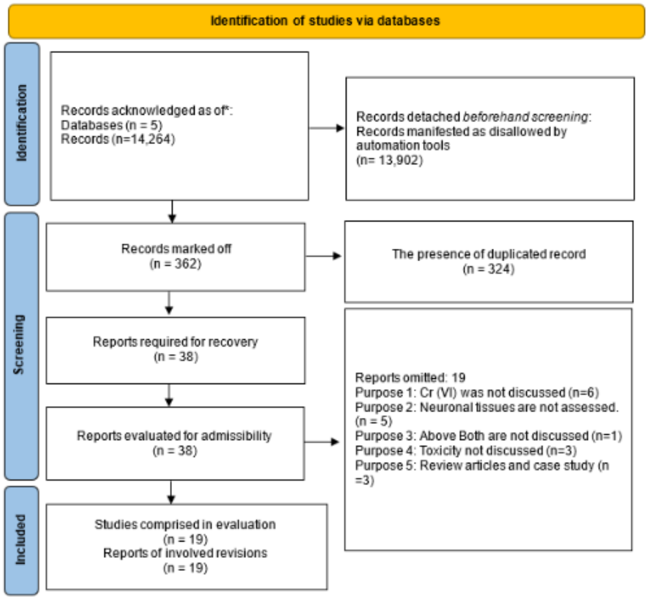

Figure 1. PRISMA Flow Diagram

was reduced to 362.

Data Extraction

Two independent reviewers conducted the screening and data extraction processes. Any discrepancies between reviewers were resolved through discussion and consensus to ensure accuracy and minimize selection bias. During data extraction, information on co-exposure to other metals and environmental contaminants was recorded to identify potential confounders, and studies isolating Cr(VI)-specific effects were highlighted for detailed review.

Quality Assessment

The methodological quality and risk of bias of the included studies were systematically evaluated. For animal studies, SYRCLE's Risk of Bias tool was applied to assess sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. For observational human studies, the Newcastle–Ottawa Scale (NOS) was used, evaluating selection, comparability, and outcome domains. Most animal studies demonstrated a low to moderate risk of bias, primarily due to limited reporting of randomization and blinding. Human cohort and case–control studies scored 7–8 out of 9 on the NOS, indicating good methodological quality with minor concerns related to exposure assessment and potential confounding by other metals. A summary of the quality assessment results for all included studies is presented in (Table 1).

Results

In this section, the authors briefly present the findings of the systematic literature review (SLR). The summarized results are provided separately in tabular form. Among the 19 studies included, 12 were animal--based and 7 were human cohort studies. The detailed results are presented in (Table 2).

Table 3 summarizes experimental and animal studies investigating the neurotoxic effects of hexavalent chromium [Cr(VI)]. The findings indicate that Cr(VI) can cross the blood–brain barrier, leading to oxidative stress, neuroinflammation, apoptosis, and mitochondrial dysfunction. Evidence from studies on rodents, fish, and neuronal cell cultures demonstrates neuronal injury and behavioral impairments, whereas antioxidants such as salicylic acid and —coenzyme Q10 have shown potential neuroprotective effects.

Table 4 summarizes human observational and epidemiological studies examining the association between chromium and mixed-metal exposure and neurological outcomes.

Table 1. Summary of Quality and Risk-of-Bias Assessment of Included Studies

Authors / Year	Assessment Tool	Score / Risk Level
Ding et al. 2024 (20)	SYRCLE	Moderate
Tang et al. 2024 (21)	SYRCLE	Moderate
Salama et al. 2016 (22)	SYRCLE	Moderate
Hegazy et al. 2021 (23)	SYRCLE	Low
Kumari et al. 2014 (24)	SYRCLE	Moderate
Hryntsova et al. 2022 (25)	SYRCLE	Moderate
Chan et al. 2012 (26)	SYRCLE	Moderate
Vielee et al. 2024 (27)	SYRCLE	Low
Saleh et al. 2022 (28)	SYRCLE	Low
Sedik et al. 2023 (29)	SYRCLE	Moderate
Tripathi et al. 2022 (30)	SYRCLE	Moderate
Zhu et al. 2019 (31)	SYRCLE	Low
Baj et al. 2022 (32)	NOS	8/9
Rechtman et al. 2020 (33)	NOS	7/9
Invernizzi et al. 2023 (34)	NOS	8/9
Viau et al. 2021 (35)	NOS	7/9
Heesterbeek et al. 2020 (36)	NOS	7/9
Parent et al. 2017 (37)	NOS	7/9
Figueroa-Romero et al. 2020 (38)	NOS	8/9

Table 2. Brief results of studies on neurological properties of Cr (VI)

No	Authors / Year	Type of study	Place of study	Relevance with current article
1	Ding et al. 2024 (20)	Investigational	Guizhou Medical University	Evidence of Cr (VI) crossing BBB
2	Tang et al. 2024 (21)	Investigational	Xiamen Medical College, China	Metabolic properties of Cr (VI) on Astrocytes
3	Salama et al. 2016 (22)	Investigational	National Research Centre, Egypt	Acute brain and lung injuries with intranasal exposure of Cr (VI)
4	Hegazy et al. 2021 (23)	Investigational	National Research Centre, Egypt	Behavioral and neurotoxicological defect after intra-nasal exposure
5	Kumari et al. 2014 (24)	Investigational	NEERI, Nagpur, India	Measurement of oxidative stress biomarker in Cr (VI) toxicity
6	Hryntsova et al. 2022 (25)	Investigational	Department of Morphology, Ukarain	Oxidative stress in induced Cr (VI) noxiousness measured in Pineal gland
7	Chan et al. 2012 (26)	Investigational	The University of Hong Kong	Cr enhanced MRI of retina
8	Vielee et al. 2024 (27)	Investigational	University of Louisville, Louisville	Selective accumulation of Cr (VI) in hippocampus
9	Saleh et al. 2022 (28)	Investigational Interventional	Ain Shams University, Egypt	SA attenuates the ROS production and protects against Cr (VI) toxicity
10	Sedik et al. 2023 (29)	Investigational Interventional	National Research Centre, Egypt	Neuroprotective effect of tangeretin (TNG)
11	Tripathi et al. 2022 (30)	Investigational Interventional	ICMR, Ahemdabad, India	Beneficial properties of CoenzymeQ10, Biochanin A and Phloretin
12	Zhu et al. 2019 (31)	Investigational Interventional	College of Xinjiang Uyghur Medicine, China	Protection by Aiweixin contrary to Cr (VI) toxicity
13	Baj et al. 2022 (32)	Retrospective cohort study	Medical University of Lublin, Poland	Pathomechanism of neurodegeneration after multi element exposure
14	Rechtman et al. 2020 (33)	Observational	School of Medicine at Mount Sinai,NY, USA	Multiple metal exposure and adolescents behavior
15	Invernizzi et al. 2023 (34)	Observational	Icahn School of Medicine at Mount Sinai, New York	Multi metal exposure and functioning of brain networks in adolescents
16	Viau et al. 2021 (35)	Observational	Defense, Health, Environment, Centre Léon, France	Delayed nucleoshuttling of DSB by ATM protein
17	Heesterbeek et al. 2020 (36)	Case control Observational	Radbound University, Netherlands	Association of trace elements with age related macular degeneration
18	Parent et al. 2017 (37)	Observational	INTERPHONE study (7 participating countries)	Association of glioma risk and occupational exposure of heavy metals
19	Figueroa-Romero et al. 2020 (38)	Case control retrospective	University of Michigan	Association of metal exposure and development of ALS

Chromium was frequently co-detected with lead, copper, nickel, or manganese. Elevated chromium levels were correlated with impaired cognition, altered brain connectivity, and increased oxidative stress markers. Postmortem analyses revealed neural metal accumulation, whereas cohort studies reported variable findings, emphasizing the need for larger, well-controlled longitudinal investigations.

Table 5 provides a comparative overview of the key neurotoxic mechanisms of chromium (VI) in relation to other major heavy metals, lead (Pb), mercury (Hg), and cadmium (Cd). While all induce oxidative stress and neuroinflammation, Cr(VI) uniquely crosses the blood–brain barrier via anion channels and preferentially accumulates in the hippocampus and hypothalamus. In contrast, Pb and Hg cause more pronounced disruptions in neuronal signaling and mitochondrial function, whereas Cd primarily interferes with DNA repair processes. The table also highlights distinct antioxidant- and chelation-based protective strategies relevant to each metal.

Discussion

This section elaborates and synthesizes the findings of the studies included in the final review. The discussion is organized into three subsections corresponding to the research objectives and emphasizes the mechanistic pathways of oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction underlying Cr(VI)-induced neurotoxicity.

The findings of Experimental studies - On animals

Collectively, animal studies identify oxidative stress as the primary mechanism by which Cr(VI) induces neurotoxicity, with inflammation, apoptosis, and mitochondrial dysfunction acting as interconnected pathways contributing to neuronal injury. Cr(VI) has been shown to cross the blood–brain barrier (BBB), accumulate in specific brain regions, and cause dose- and time-dependent oxidative damage. Experimental methods of Cr(VI) administration included intraperitoneal, intranasal, and oral routes, while assessment techniques such as immunohistochemistry, electron microscopy, and biochemical analysis. were used to evaluate neurotoxicity. Salma A. et al. reported that intranasal administration of potassium dichromate (PDC) in rats produced a dose-dependent increase in chromium accumulation in the brain, with up to 46% of the administered dose reaching the brain at 2 mg/kg. Intraperitoneal administration at 15 mg/kg resulted in 36%

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Table 3. Key Points of Animal Studies Examining Chromium (VI)-Induced Neurotoxicity and Protective Interventions

Authors / Year	Samples Population	Chromium doses	Tissue / Biomarkers studied	Key findings
Ding et al. 2024 (20)	57 mice	6 mg/kg (intraperitoneal) for 14 and 28 days	Several brain regions	Hypothalamus was identified as area of entry
Tang et al. 2024 (21)	Rat brain astrocyte culture	0–16 µM Cr(VI) for 24 h	Brain astrocytes	Mitochondrial disruption and apoptosis
Salama et al. 2016 (22)	30 male Wistar rats	0.5–2 mg/kg (intranasal) and 15 mg/kg (intraperitoneal)	Overall brain	42% of instilled dose intranasally was able to reach to the brain
Hegazy et al. 2021 (23)	32 male albino Wistar rats	0.125–0.5 mg/kg for 2–8 weeks	Astrocytes and Oligodendroglia	Major toxic effects have come on locomotor and cognitive functions
Kumari et al. 2014 (24)	Lbeo Rohita, freshwater fish	48.3 ppm Cr(VI) for up to 15 days	Liver, Muscle, Gills, and Brain Oxidative stress	Catalase. SOD, Glutathione Reductase activities increased
Hryntsova et al. 2022 (25)	24 white sexually mature male rats	0.1 mg/L $K_2Cr_2O_7$ in water (90 days)	Pineal gland extraction and GPX-1 estimation	Abnormal morphological changes in cells and elevated levels of GPX-1
Chan et al. 2012 (26)	36 Adult Sprague-Dawley rats	1–100 mM PDC (intravitreal)	CrMRI was accomplished at 1-day postinjection upto two weeks	The iris showed a posology-dependent growth in T1-abnormal high hyperintensity
Vielee et al. 2024 (27)	162 man and woman Sprague-Dawley scale of diverse age groups	0.05–0.1 mg/L Cr(VI) in drinking water for 90 days	Brain stem, cerebral cortex, cerebellum, hippocampus, hypothalamus, and striatum	Geriatric female hippocampus accumulates the largest amount of Cr (VI)
Saleh et al. 2022 (28)	40 Wistar male rats	10–200 mg/kg PDC ± SA	AchE, MAOA, Dopamine, 5-HT, NAD+, HSP70, caspase-3, protein reporting, DNA injury	SA significantly reduced the ROS production, DNA damage and neurotoxicity, increased S100B protein
Sedik et al. 2023 (29)	32 male adult Wistar rats	2 mg/kg PDC ± TNG 50–100 mg/kg	Bevioral changes, MDA, Nrf2 expression, TNF-α, IL-6, GSH, MDA	Reduced toxic effects with pre-exposure of TNG
Tripathi et al. 2022 (30)	40 Adult Swiss albino male mice	Cr(VI) 75 ppm ± antioxidants (CoQ10, BCA, PHL)	GSH, SOD , ACEs activity, head DNA %, Nrf2 expression,LPO	Oxidative stress was found, reduced significantly after antioxidants
Zhu et al. 2019 (31)	Nematodes	10 mM PDC ± 0.05–0.125 vol AWX	ROS manufacture	AWX had the time dependent protection against Cr (VI) toxicity

Note: Units standardized to mg/kg (animal doses), ppm (aquatic/cellular exposures), and µM (in-vitro concentrations) for consistency.

Table 4. Key Points of Human Observational Studies Investigating Chromium (VI) and Multi-Metal Exposure-Related Neurotoxicity

Authors / Year	Samples	Chromium or or metal exposure	Tissue / Biomarkers studied	Key findings
Baj et al. 2022 (32)	178 postmortem samples	51 elements incl. Cr (ICP-MS)	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	Cr was originated as the part of element cluster deposited on optic pathway
Rechtman et al. 2020 (33)	150 adolescents	Mn, Pb, Cu, Cr, Ni (ICP-MS)	Self-assessment scales for externalization behavior	Pb, Cr, and Cu contributed most to associations between metals and externalizing symptoms.
Invernizzi et al. 2023 (34)	193 young adults	Mn, Pb, Cr, Cu (ICP-MS)	Resting–state practical MRIscans for global and limited efficacy (global:GE; local:LE) in 111 brain areas	Substantial undesirable relations among the metal blend and GE and LE
Viau et al. 2021 (35)	Cell cultures	Al, Cu, Zn, Ni, Cd, Pb, Cr, Fe (≤100 µM)	Irradiation and Immunofluorescence	Metal Induced delay in the nucleo-shuttling of ATM proteins which, consequently delay DNA recognition and repair
Heesterbeek et al. 2020 (36)	236 nAMD patients, 236 controls	Trace metals via ICP-MS	Plasma concentrations of trace elements	Significant alterations in trace metal points amid the patients with nAMD and controls.
Parent et al. 2017 (37)	2054 glioma cases, 5160 controls	Occupational exposure to Pb, Cd, Ni, Cr, Fe	-	No exposure -outcome relationship found
Figueroa-Romero et al. 2020 (38)	36 ALS patients, 31 controls	Cr, Mn, Ni, Zn (ICP-MS)	Laser ablation-IC-PMS was managed to gain period sequence data of metal in teeth from autopsies or dental extractions	Metal levels were upraised in cases than in controls with early life exposure

Note: Observational studies revealed consistent associations between cumulative or mixed metal exposure and neuropsychiatric, neurodevelopmental, or neurodegenerative outcomes, underscoring Cr(VI) as a key component of the toxic metal burden.

brain distribution. Intranasally exposed rats exhibited reduced locomotor activity, elevated malondialdehyde (MDA), and decreased glutathione (GSH) and catalase levels, indicating oxidative stress (22). The study pro-

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Table 5. Comparative Overview of Neurotoxic Effects of Cr(VI) vs Other Heavy Metals

Mechanism	Chromium (VI)	Lead (Pb)	Mercury (Hg)	Cadmium (Cd)
Blood–Brain Barrier (BBB) Interaction	Crosses BBB via anion channels; accumulates in hippocampus & hypothalamus	Disrupts BBB integrity; alters endothelial tight junctions	Strong BBB permeability; binds thiols in endothelial cells	Weak BBB penetration; accumulates mainly in choroid plexus
Primary Mechanism of Toxicity	Oxidative stress, Cr(VI); Cr(III) reduction generating ROS	Interferes with calcium signaling, induces oxidative stress	Binds to sulfhydryl groups causing mitochondrial dysfunction	Promotes oxidative stress and inhibits DNA repair enzymes
Inflammatory Response	NF-κB activation, IL-1β, IL-6, TNF-α upregulation	Activates microglia and astrocytes	Induces pro-inflammatory cytokine release	Elevates TNF-α, IL-8, and metallothionein expression
Neuronal Effects	Apoptosis, mitochondrial injury, synaptic dysfunction	Axonal degeneration, cognitive impairment	Neuronal necrosis, tremors, visual and motor dysfunction	Synaptic loss, cognitive decline
Target Brain Regions	Hippocampus, hypothalamus, pineal gland	Cortex, hippocampus, cerebellum	Cerebellum, occipital cortex	Hippocampus, cerebellum
Protective Strategies	Antioxidants (CoQ10, TNG, SA, AWX) activate Nrf2 pathway	Chelation (EDTA), antioxidant support	Selenium, N-acetylcysteine	Zinc supplementation, antioxidants
Mechanism	Chromium (VI)	Lead (Pb)	Mercury (Hg)	Cadmium (Cd)

posed intranasal exposure as a suitable experimental model for simulating occupational Cr(VI) exposure in industries such as chromium plating and steel manufacturing. These findings support the hypothesis that oxidative imbalance initiates cellular damage, which is subsequently amplified by inflammatory cascades and apoptotic responses. Hegazy R. et al. examined repeated intranasal PDC administration in rats–(0.125–0.5 mg/kg/day, five days per week) and reported neuronal loss, astrocyte proliferation, and cognitive and locomotor impairments, further supporting occupational exposure relevance (23). Ding J. et al. and Tang H. et al. established a mechanistic sequence beginning with BBB disruption, followed by microglial activation, and culminating in mitochondrial dysfunction and neuronal apoptosis. These effects were mediated by increased expression of inflammatory markers (NF-κB, IL-1β, IL-6, TNF-α) and decreased antioxidant capacity (Nrf2, Nqo-1, Ho-1, 8-OHdG) (23).

Comparatively, studies such as those by Vielee S.T. et al. and Hryntsova N. et al. emphasized region-specific vulnerability, with the hippocampus, hypothalamus, and pineal gland being particularly susceptible due to their high metabolic activity and distinctive vascular characteristics (25, 27). These studies also reported sex- and age-dependent variations, with older female rats exhibiting greater Cr(VI) accumulation (27). Moreover, mitochondrial dysregulation, metal dyshomeostasis (Fe, Cu), and apoptosis consistently emerged as common patterns across different models, linking Cr(VI) exposure to neuronal degeneration and aging-like phenotypes. In one study, rats were exposed to Cr(VI) through drinking water for 90 days at doses of 0.05 and 0.1 mg/L, with the highest accumulation observed in geriatric females. Differences in gastric characteristics and Cr(VI) absorption related to age and sex were suggested as possible contributing factors. The study also demonstrated dyshomeostasis of essential metals (Fe, Cu, Se, Mn, Co, Mg), with gerontogenic effects observed in exposed young female rats (27). Dysregulation of essential elements such as iron (Fe) and copper (Cu) contributes to age-related neurological alterations. Excess Fe is associated with neurodegenerative diseases, whreas Cu imbalance–disrupts mitochondrial function and contributes to various disorders (39). Kumari et al. exposed Labeo rohita fish to Cr(VI), revealing increased oxidative stress markers in the liver, muscle, gills, and brain (24). Tang H. et al. analyzed Cr(VI)-treated rat astrocytes and found elevated ROS and 8-OHdG–levels, along with disrupted mitochondrial membranes, indicating oxidative stress and DNA damage. They also observed blood–brain barrier (BBB) disruption, altered sphingolipid metabolism, and abnormalities in the methionine–cysteine cycle, all associated with apoptosis and oxidative injury (21). Similarly, Hryntsova N. et al. reported oxidative stress in the pineal gland after 90 days of Cr(VI) exposure, accompanied by strong antioxidant protection (GPX-1). Morphological changes, including vascular damage and astrocyte activation, were evident; however, BBB disruption was not required due to the pineal gland's anatomical location (25). Additionally, Chan K.C. et al. demonstrated dose-dependent chromium toxicity via intravitreal potassium dichromate injections. Radiological imaging revealed increased retinal Cr contrast, while histological analysis showed altered lipid distribution. The reduction of Cr(VI) to Cr(III) generates reactive oxygen species, leading to disrupted lipid metabolism and impaired axonal transport (26). Interventional animal studies have highlighted the therapeutic potential of antioxidants. Coenzyme Q10, Biochanin A, Phloretin, Tangeretin (TNG), Aiweixin (AWX), and Sodium Alginate (SA) were shown to reduce ROS generation, restore antioxidant enzyme activity, and attenuate apoptosis (28–31). Collectively, these findings reveal a consistent mechanistic pattern: Cr(VI)-induced oxidative stress activates inflammatory and apoptotic pathways, leading to neuronal damage that can be mitigated through antioxidant modulation of the Nrf2/HO-1/NQO1 signaling axis. Further supporting evidence was provided by Tripathi S. et al., who investigated the neuroprotective effects of Coenzyme Q10, Biochanin A, and Phloretin in 40 mice exposed to arsenic and Cr(VI). Antioxidant treatment reduced metal accumulation, improved oxidative stress

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markers, and restored body weight in toxin-exposed groups (30). Similarly, Sedik et. al. demonstrated Tangeretin's (TNG) protective effects against Cr (VI)-induced brain injury by enhancing Nrf2 signaling and reducing inflammation and apoptosis in rats (29). Zhu B. et. al. showed that Aiweixin (AWX) decreased ROS production, with moderate doses providing significant protection without observable toxicity (31).

To investigate the neuroprotective action of Sodium Alginate (SA), Saleh E. M. et. al. examined its effects against Cr (VI) -induced neurotoxicity, focusing on oxidative stress, apoptosis, and neural damage. SA, known for its antifungal, antidiabetic, antioxidant, and anti-inflammatory properties, significantly reduced oxidative stress, apoptosis, and cellular injury in treated rats (28). Despite these promising findings, a knowledge gap persists due to several limitations in existing studies. One study based its conclusions on short-term Cr (VI) exposure, which may not accurately reflect the neurotoxicity resulting from chronic environmental exposure (23). Small sample sizes were also reported as a limitation (21). Moreover, most studies primarily focused on Cr (VI) accumulation and biomarker assessments, while functional evaluations—such as behavioral alterations and sensori-motor performance—were not addressed (20, 22). Furthermore, emerging research connects Cr(VI)-induced neurotoxicity to broader "toxic aging" concepts. Wise et al. (2024) introduced the "Toxic Aging Coin", illustrating how environmental toxicants, including metals, accelerate aging through oxidative stress, inflammation, and cellular senescence. This perspective supports the present review's findings that oxidative and inflammatory cascades mediate both neurotoxicity and premature neurodegeneration (40). In addition, Cao et al. (2020) demonstrated that taxifolin mitigates Cr(VI)-induced endothelial dysfunction and inflammation in HUVEC and THP-1 cells by suppressing MAPK and NF-κB activation, indicating therapeutic potential through antioxidant and anti-apoptotic mechanisms (41). Similarly, Dhande and Pansare (2024) reported that extracts of Tridax procumbens significantly reversed rotenone-induced oxidative and behavioral deficits in zebrafish and fruit fly models, supporting the neuroprotective relevance of plant-derived antioxidants (42). Furthermore, several studies have shown comparable neuroprotective and antinociceptive effects of both synthetic and natural compounds, such as thiazolidine derivatives, in diabetic neuropathic pain models, emphasizing antioxidant and anti-inflammatory mechanisms consistent with those observed in the Cr(VI)-induced neurotoxicity pathway (43–45).

The findings of Observational studies on humans

Human studies provide complementary yet less direct evidence, describing metal dyshomeostasis and mixed heavy metal exposures associated with neurotoxicity. Baj J. et al. reported increased Cr concentrations in the optic chiasma linked to neuropathological alterations (32), while Rechtman. et al. identified correlations between exposure to multiple metals (Mn, Pb, Cu, Cr, Ni) and behavioral abnormalities in adolescents (33). However, it must be explicitly acknowledged that Cr(VI) rarely occurs in isolation in human studies; most observations involve co-exposure with other metals. This substantially limits the ability to attribute the observed effects specifically to hexavalent chromium. In the context of environmental monitoring, Oralbekova et al. (2021) proposed a mathematical data assimilation model to optimize real-time monitoring of atmospheric heavy metals, including chromium, in urban environments such as Almaty City (46). Similarly, Zhartybayeva et al. (2023) applied ARIMA-based mathematical modeling to predict water pollution trends in Kazakhstan's Akmola region, emphasizing the ecological and public health implications of heavy metal contamination (47). These approaches highlight the critical role of mathematical modeling in the early detection and prevention of Cr(VI) exposure in human populations.

Invernizzi A. et al. reported that urinary Cr levels correlated with reduced brain network efficiency on fMRI, suggesting systemic neurotoxicity (34). Radiological studies have further highlighted the Radiation-Induced ATM Nucleo-Shuttling (RIANS) model, which links ATM protein translocation to radiation-induced cellular toxicity and genomic instability. Similarly, Viau M. et al. demonstrated that concurrent exposure to multiple metals (Al, Cu, Zn, Ni, Pd, Cd, Pb, Cr, Fe) delayed ATM nucleo-shuttling and impaired DNA repair, indicating that genotoxic stress arises primarily from cumulative metal burden rather than isolated Cr(VI) exposure (35). These findings underscore that direct evidence of Cr(VI)-specific effects in human studies remains limited, with most data derived from mixed-metal exposure scenarios.

In addition, Chen et al. (2019) provided molecular insights into Cr(VI)-induced carcinogenesis, identifying both genetic and epigenetic mechanisms —such as histone modification and miRNA dysregulation —that may also contribute to neural genomic instability. Moreover, Al-Hussaniy et al. (2022) demonstrated that Panax ginseng protects against chemotherapy-induced cardiotoxicity and oxidative stress through caspase-mediated apoptosis modulation, reinforcing the role of antioxidant phytocompounds in mitigating toxicant-induced organ injury, a mechanism relevant to Cr(VI)-associated neuroprotection (49). Singh et al. (2025) further confirmed the antioxidant potential of several traditional medicinal plants, emphasizing that phytochemical screening through antioxidant assays can guide future preclinical and clinical investigations in toxicology and neuroprotection (50). Heesterbeek T.J. et al. reported lower chromium concentrations in individuals with neovascular age-related macular degeneration (nAMD) compared with healthy controls, suggesting a potential protective effect of chromium against oxidative stress. The study also associated cadmium levels with smoking and barium levels with antihypertensive drug use (36). Regarding metal exposure and cancer risk, several metals are classified as carcinogenic to humans, while inorganic lead is categorized as a probable carcinogen. To assess whether occupational exposure to these metals increases glioma risk, Parent M.E. et al. conducted a case–control study including 2,054 glioma pa-

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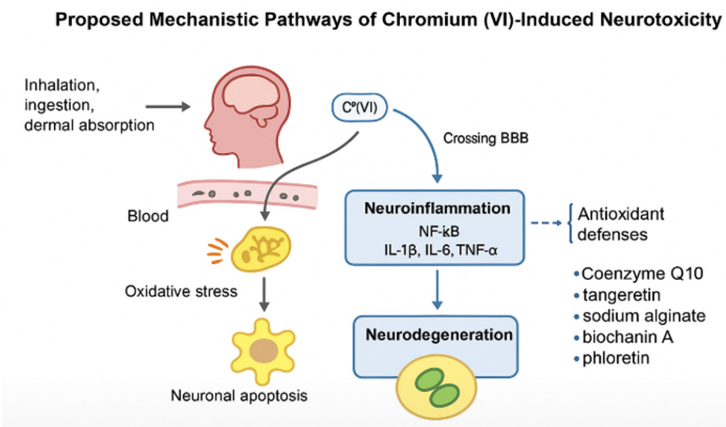

Figure 2. Proposed Mechanistic Pathways of Chromium (VI)-Induced Neurotoxicity

tients and 5,160 controls. No clear association was observed between exposure to lead, cadmium, nickel, chromium, or iron and glioma risk, despite exposure being assessed using the Finnish Job Exposure Matrix (FINJEM). The authors noted that a limited sample size reduced statistical power (37). Lee C. et.al. published a case report describing heavy metal toxicity in a parkinsonism patient with a metal--on--metal hip implant. MRI was used to visualize potential heavy metal (Cr and Co) deposition in the basal ganglia, which was associated with disease progression (51). These findings highlight the importance of careful decision--making when selecting prosthetic materials. However, larger case—control studies are needed to better elucidate the relationship between prosthetic-associated metal exposure and neurotoxicity. Identifying risk factors and developing radiological markers to assess Cr-(VI) toxicity represent key research priorities for human cohort studies. Limitations noted in previous investigations include small sample sizes (35), subjective bias in self-reported questionnaires (28), an exclusive focus on linear associations while neglecting non-linearity, and a lack of systematic measurement approaches (34). The scarcity of consistent Cr(VI)-specific data, combined with small cohorts and confounding co-exposures (Pb, Cd, Ni, Fe), further restricts causal inference. Nevertheless, these studies collectively support chromium's contribution to oxidative and inflammatory neurotoxicity in humans, aligning with mechanisms established in animal models. Additionally, Mazakova et al. (2024) emphasized the growing role of mathematical modeling in toxicological and pharmacological research, demonstrating that such approaches can optimize pharmacokinetic and pharmacodynamic models, improve dose prediction, and enhance understanding of complex biological interactions (52). Incorporating these modeling frameworks could strengthen future Cr(VI) neurotoxicity research by improving exposure quantification, mechanistic prediction, and therapeutic optimization. Figure 2 illustrates the plausible mechanisms underlying Cr(VI)-induced neurotoxicity in the brain. Following inhalation, ingestion, or dermal absorption, Cr(VI) enters systemic circulation and crosses the blood—brain barrier (BBB) via anion channels. Within neural cells, Cr(VI) undergoes stepwise intracellular reduction to Cr(V), Cr(IV), and Cr(III), generating excessive reactive oxygen species (ROS). Elevated ROS levels trigger oxidative stress, leading to lipid peroxidation, DNA damage, and mitochondrial dysfunction. Subsequent activation of NF-κB and associated inflammatory pathways promotes the release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), resulting in neuroinflammation and microglial activation. Persistent oxidative and inflammatory stress further induce neuronal apoptosis through caspase activation, contributing to neurodegeneration in vulnerable brain regions such as the hippocampus and hypothalamus. Protective mechanisms include the activation of endogenous antioxidant defense pathways, particularly the Nrf2/HO-1/NQO1 signaling cascade, as well as the administration of exogenous antioxidants such as Coenzyme Q10, tangeretin, sodium alginate, biochanin A, and phloretin, which collectively mitigate oxidative damage and neuronal loss.

Integrative synthesis and clinical implications

Synthesizing evidence from both animal and human studies, Cr(VI)-induced neurotoxicity follows a multifactorial cascade involving oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis. This interconnected mechanistic sequence disrupts neural homeostasis, particularly in brain regions such as the hippocampus and hypothalamus. Antioxidant-based interventions that enhance Nrf2 signaling and suppress ROS generation consistently demonstrate neuroprotecti ve effects, highlighting their potential translational relevance to clinical practice. Clinically, these findings emphasize the importance of proactive screening and preventive measures in chromium-exposed populations. Regular neurological assessments, monitoring of oxidative stress biomarkers, and dietary antioxidant supplementation may help mitigate early neurotoxic effects. Moreover, industrial and occupa-

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tional health protocols should prioritize exposure surveillance, worker education-, and safety compliance to minimize chromium-related risks. In summary, while animal studies provide well-defined mechanistic insights, human evidence remains constrained by co-exposure to multiple metals and methodological variability. Future longitudinal, exposure-controlled studies are essential to isolate Cr(VI)-specific effects and to evaluate targeted therapeutic strategies aimed at modulating oxidative and inflammatory pathways.

Limitations

This systematic review has several limitations. First, the small sample sizes of many included experimental and clinical studies limit the generalizability of the findings. Second, most data were derived from cross-sectional or short-term exposure studies, lacking longitudinal evaluation of cumulative effects. Third, only English-language and open-access studies were included, which may introduce selection and publication bias. Finally, variability in chromium measurement techniques and frequent co-exposure to other metals in human studies may confound the attribution of observed effects solely to Cr(VI).

Future Directions

Entry into the Brain

Future research should investigate the mechanisms by which Cr-(VI) enters the brain, either through the blood–brain barrier (BBB) or via regions outside it and how its entry route, mode of administration, and target brain region influence neurotoxicity.

Factors affecting Neurotoxicity

Age and sex appear to modulate Cr(VI) neurotoxicity, with early-life exposure potentially increasing susceptibility to neurodegenerative changes. Cr-(VI) may act as a gerontogen, disrupting metal homeostasis in a sex-dependent manner.

Sites of Neurotoxicity

Cr-(VI) tends to accumulate–in specific brain regions, particularly the hippocampus, where it affects multiple neuronal and glial cell types, leading to functional impairment.

Pathophysiological mechanisms

Cr-(VI) induces oxidative stress, apoptosis, and neuroinflammation. Future studies should further explore its epigenetic effects and mitochondrial dysfunction, as well as their contributions to the progression of neurodegenerative processes.

Conclusion

The literature indicates that heavy metal ions such as Cr (VI), released from various industrial processes, are recognized as significant environmental toxins. The current systematic review summarizes recent research on Cr-(VI)--induced oxidative stress and neuronal damage. Animal--based experimental studies primarily elucidate the pathophysiological mechanisms of Cr-(VI) toxicity in the brain and peripheral nervous system, whereas human cohort studies highlight associations and risk factors related to neurodegenerative and neurobehavioral disorders. Interventional studies predominantly conducted in animal models—have demonstrated the therapeutic potential of anti-oxidants in preventing and alleviating Cr (VI)-induced neurotoxicity. However, studies involving large cohorts of individuals with neurological disorders remain limited, representing a clear research gap in the existing literature. Future research should focus on population -based case –control models exploring the relationship between Cr(VI) exposure and diverse neurological conditions. Such investigations are essential to develop effective preventive strategies and to optimize therapeutic dosing for mitigating Cr (VI) related neurotoxicity

Authors' Contributions

MI: Conceptualization, project administration, funding acquisition, and supervision.

NA: Methodology, literature search (PubMed, Scopus, Web of Science), data extraction, and writing – original draft preparation.

SR: Data curation, quality assessment of included studies, and critical review of the manuscript.

YI: Formal analysis, methodology support, and validation of standardized units.

SS: Quality and risk-of-bias assessment using SYRCLE and NOS tools.

GS: Validation of results, visualization of mechanistic pathways, and final editing.

All authors have read and agreed to the published version of the manuscript.

Ethical Considerations

Not applicable.

Acknowledgment

Not applicable.

Conflict of Interests

The authors declare that they have no competing interests.

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