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REVIEW ARTICLE

Chromium and Nickel Toxicity in Sheep: Pathophysiology and Management Approaches

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ABSTRACT

Nickel and chromium toxicity has become a major concern, mainly in sheep. These metals have various disadvantages: disabling the functionality of organs, disturbing physiological mechanisms, and causing oxidative stress, reproductive dysfunction, and immune suppression. Exposure to nickel affects the pulmonary, renal, and hepatic tissues, which leads to severe respiratory distress, nephrotoxicity, and hepatotoxicity. On the other hand, long exposure to chromium, especially hexavalent chromium, produces oxidative stress, DNA damage, and carcinogenic effects in the lungs, liver, and kidneys. The pathophysiology of chromium and nickel include oxidative impairments, obstruction with functionality of enzymes, inflammation, and infertility. Regular examination of feed and water sources, antioxidants in diet, and utilization of detoxifying agents control the toxic effects of these metals. Further, probiotics, chelators, and phytoremediation give promising solutions in lowering the accumulation of these heavy metals. This review discusses the mechanism of action of chromium and nickel toxicity in sheep, their effect on the physiological system. It also discusses potential mitigation approaches to ensure better animal health and livestock production.

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INTRODUCTION

Small ruminants, especially sheep, have a significant importance in the livestock industry and play an important role in the livelihood of farmers (Ahmad *et al*., 2024). Sheep are also a vital source of meat and contribute significantly to human nutrition by providing an array of essential nutrients (Ponnampalam *et al*., 2024). However, they may also act as reservoirs for various toxic substances, posing potential health risks (Nogara *et al*., 2024). Although the concentration of heavy metals and other toxic substances in the blood of sheep is typically minimal (Pereira *et al*., 2021). They accumulate in the muscles and milk of the sheep as chemical residues and pose a significant threat to public health (Fechete *et al*., 2024). These heavy metals are referred to as trace elements due to their minute concentrations, often measured in milligrams and micrograms per kilogram (Hossain *et al*., 2023).

Most heavy metals are non-biodegradable and are extracted from their mineral ores (Khalef *et al*., 2022; Jadaa and Mohammed, 2023). They are capable of circulating through global ecological cycles (Chen *et al*., 2021). After ingestion, the toxicity of these metals is due to the formation of complexes and ligands with organic compounds (Priyadarshanee *et al*., 2022). After combining with cellular components, they may cause modifications in biological molecules and alter the energy metabolism, resulting in cellular malfunctions or even death (Mishra *et al*., 2022). Furthermore, these metals can interact with common atoms such as oxygen, sulfur, and nitrogen, forming insoluble ligands that can inactivate crucial enzymes and disrupt protein structure (Kabogo *et al*., 2024). These ligands are involved in the inactivation of crucial enzymes and disrupt the protein structure. On combination of toxic metals with these atoms may inactivate the crucial enzyme systems or disrupt protein structure (Renu *et al*., 2021; Costa, 2023). Almost all heavy metals cause toxicity to the cells when they cross a specific threshold level. Various studies have identified the presence of heavy metals within the muscles, hepatic tissues, kidneys, blood, brain, and reproductive organs (Gupta *et al*., 2021; Ungureanu and Mustatea, 2022; Khalaf *et al*., 2024).

In recent years, the significance of nickel (Ni) and Chromium (Cr) has gained considerable attention. Ni is a very important trace element for small ruminants, especially sheep and goats (Pereira *et al*., 2021; Durak *et al*., 2024). The presence of Ni metal is very important to sheep because it is involved in the absorption of iron to improve hemoglobin concentration for better oxygenation of tissues (Asadi *et al*., 2022). It is also involved in the absorption of calcium into the bones to strengthen the skeleton (Nieboer *et al*., 2024). Furthermore, Ni acts as a cofactor for various enzymes necessary for cellular reactions and energy metabolism. It also acts as a signaling agent for the regulation of different and critical physiological processes, including blood pressure, sodium and potassium metabolism, and organ health (Zhong *et al*., 2024). Similarly, Cr is a very important trace element for the growth and health of animals and humans (Herrada *et al*., 2024). Cr is present in trivalent Cr (Cr3+) and hexavalent Cr (Cr6+) forms, but most of the supplements come in Cr3+ form (Monga *et al*., 2022). The most important Cr3+ supplements include chromium picolinate, chromium histidine, and niacin-bound chromium (Haider *et al*., 2023). Some studies suggest that Cr3+ supplementation enhances insulin function, promotes weight gain, and supports muscle anabolism (Tarrahi *et al*., 2021).

Ni and Cr, along with other transition metals, are indispensable for the synthesis of metalloenzymes while exhibiting toxicity even at relatively low concentrations (Zafar *et al*., 2023). The disruptions of biological processes by Ni and Cr have been documented, with their interference leading to a range of severe and hazardous effects (Sharma *et al*., 2022). Ni and Cr interact with other critical biological components necessary for the proper functioning of diverse metabolic pathways (Haidar *et al*., 2023). Given the widespread use of Ni and Cr containing compounds in industrial applications, the release of Ni and Cr into the environment is inevitable, posing a significant threat to the health of humans and animals (Verma *et al*., 2023). Both these metals are critical for sheep, where they play a crucial role in their physiological functions. But the elevated level of both metals causes skin eruptions, prolonged gestation periods, decreased hemoglobin levels, anemia, low hematocrit values, and impaired enzyme activities (Das *et al*., 2019). Various studies confirmed the presence of these metals in meat and other edible organs of sheep like liver, kidney, heart, lungs, and brain (Raeeszadeh *et al*., 2022). The increased level of these metals causes hepatotoxicity, cardiovascular disorders, hypertension, and nephrotoxicity (Renu *et al*., 2021; Chakraborty *et al*., 2022; Sharma *et al*., 2023). Many researchers have also reported the cytotoxicity and genotoxicity induced by both Ni and Cr (Sawicka *et al*., 2021; Mo *et al*., 2024). The elevated level of Ni causes oxidative damage to the kidneys and liver by causing granular degeneration and necrosis of liver cells (Ali *et al*., 2021). Similarly, the increased concentration of Cr in blood may also cause DNA damage along with oxidative damage to renal and liver cells (Chakraborty *et al*., 2022). Other signs and symptoms associated with increased levels of these metals include vomiting, cough, salivation, headache, salivation, malaise, fever, and depression (Gupta *et al*., 2021).

No doubt, extensive research related to these heavy metal toxicities has been conducted, but a critical gap remains related to the organ-specific effects and molecular mechanisms of Ni and Cr. Previous studies discussed the general toxicological effects, and few of them have compared their toxic mode of action, oxidative stress pathway, and their toxic effects on vital organs. Various reports lack an in-depth analysis of histological and pathological changes that limit their applicability in environmental and biomedical contexts. To overcome these deficiencies, this review article explores how Ni and Cr affect organs like the liver, kidneys, and reproductive organs, which lead to organ damage, anemia, reproductive issues, stunted growth, and reduced productivity. It also highlights the wide-ranging health impacts, including neurological and skin-related problems caused by prolonged exposure. To address these challenges, the article discusses strategies for managing toxicity, such as using detoxifying agents and antioxidants, monitoring feed and water quality, improving farming practices, and reducing environmental contamination from industrial sources. These measures aim to protect sheep health, enhance productivity, and prevent significant economic losses in the sheep industry.

Exposure to small ruminants and geographical distribution of Ni and Cr: Small ruminants, especially sheep and goat, are exposed to Ni and Cr through various environmental and dietary sources, including contaminated feed and water, soil ingestion during grazing, atmospheric deposition, fertilizers and pesticides, dirty slaughterhouses, and industrial effluents (Rehman *et al*., 2018; Masindi *et al*., 2021). Among all fodder is the primary and major source of toxicity in sheep (Waghorn, 2008), and a big source of its contamination is industrial water, soil, and a polluted environment that contains heavy metals (Nachana’a Timothy, 2019). Ni and Cr persist in the soil for long periods, entering the food chain through plants and animals and posing serious risks to consumers (Angon *et al*., 2024). This contamination is concerning because it compromises the safety and quality of animal products, undermining the goal of animal production, which is to supply healthy food to increasingly health-conscious consumers. The growing level of heavy metal (Ni and Cr) pollution, driven by industrialization and urbanization, is leading to environmental degradation, which further exacerbates the problem by contaminating soil, water, and air (Shrestha *et al*., 2021). Various sources of Ni and Cr are shown in Fig. 1.

Ni is a critical metal with a diverse geographical distribution, primarily concentrated in regions characterized by specific geological formations. According to recent studies, the largest Ni reserves are found in lateritic deposits and sulfide ores, with significant concentrations in Southeast Asia, Oceania, and parts of Eurasia (Soh Tamehe *et al*., 2024). Indonesia and the Philippines dominate global Ni production, accounting for nearly half of the world’s supply, as highlighted in a 2023 review on mineral resources (Mubarok *et al*., 2024). Indonesia’s lateritic Ni deposits, particularly in Sulawesi and Halmahera, are linked to extensive weathering of ultramafic rocks in tropical climates (Van der Ent *et al*., 2013). Australia’s Ni resources are distributed across Western Australia, notably the sulfide deposits of the Kambalda and Forrestania belts, while lateritic deposits are found in Queensland (Huston *et al*., 2021). Canada’s Sudbury Basin in Ontario, a meteorite impact structure, remains a historic and active source of sulfide Ni (Hashmi

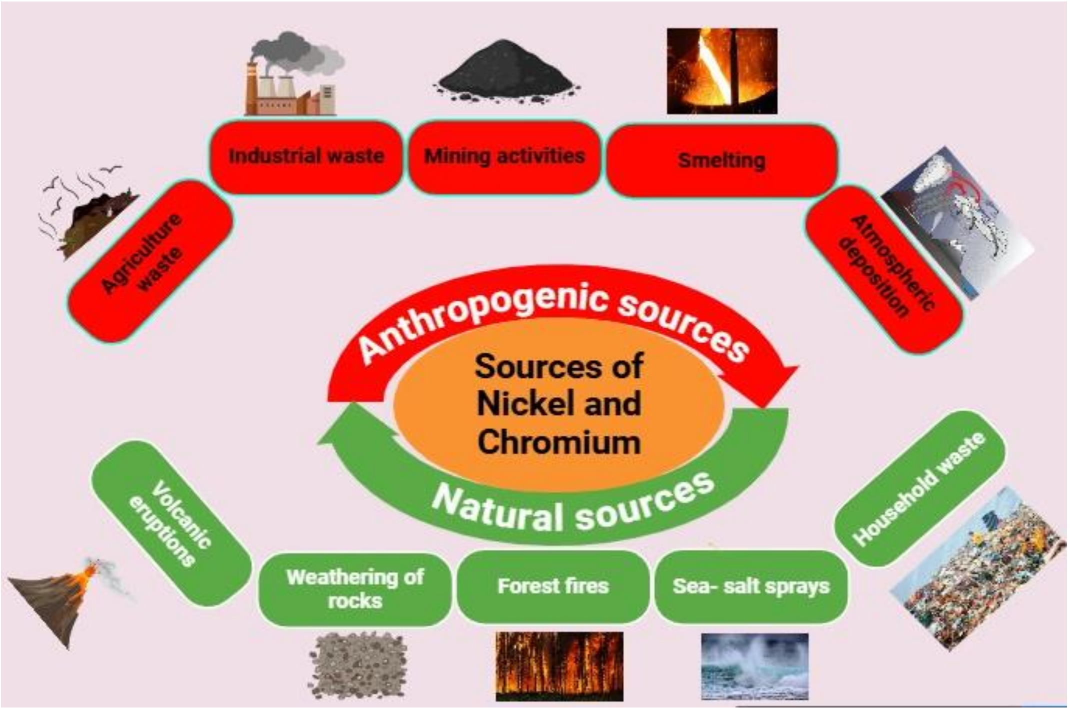

Fig. 1: Sources of nickel and chromium (www.biorender.com).

et al., 2021). New Caledonia, a French territory in the Pacific, possesses vast lateritic nickel reserves, estimated at 20-25% of global resources, concentrated in the southern Grande Terre region (Herring, 2003).

Similarly, Cr is predominantly found in chromite ore, with global distribution concentrated in specific regions. South Africa holds the largest reserves, accounting for approximately 70% of the world's chromite resources, primarily in the Bushveld Igneous Complex (Latypov *et al*., 2024). Kazakhstan ranks second, contributing nearly 12% of global production, with major deposits in the Kempirsai massif (Chen *et al*., 2024). India, particularly the Sukinda Valley in Odisha, contains around 18% of global reserves but faces environmental challenges due to intensive mining (Dutta, 2017). Other significant reserves exist in Turkey (Guleman district), Finland (Kemi mine), and Brazil (Bahia and Minas Gerais states), though these contribute smaller shares (Nriagu and Nieboer, 1988). The widespread geographical distribution of Ni and Cr, particularly in regions with intensive mining and industrial activities, highlights the potential for significant exposure risks to sheep through contaminated environments. The geographical distribution of these metals, their toxic effects on sheep, and environmental impacts are given in Table 1 below.

Mechanism of toxicity induced by Ni and Cr: The exact mechanism of Ni and Cr toxicity is now well understood, and several studies have highlighted its potential effect. In one of the studies, it is determined that it acts on calcium channels and disrupts calcium metabolism by blocking them (Arun *et al*., 2021). Another study confirmed that high concentrations of Ni interfere with iron absorption and assimilation (Piskin *et al*., 2022). Ni is also involved in the suppression of thrombospondin I (TSPI), which in turn promotes tumor angiogenesis and increases tumor growth (Roy, 2021). Furthermore, Ni also increased the level of the transcription factor hypoxia-inducible factor 1 (HIF-1) (Aschner *et al*., 2023). Elevated level of Ni and Cr also induces inflammation by activating transcription factors like NF-kB and lead to allergic reactions and hypersensitivity of the skin (Zhao *et al*., 2009). Both these metals also cause DNA methylation, histone deacetylation, and mutation in the p53 genes, which lead to impairment of DNA repair, inactivation of tumor suppressor genes, and regulation of cellular proliferation and apoptosis, respectively (Desaulniers *et al*., 2021; Zhao *et al*., 2022; Ghaedi *et al*., 2023). Moreover, both these metals are also responsible for the induction of oxidative stress that damages lipids, proteins, and DNA (Paithankar *et al*., 2021; Nowicka, 2022). Ni and Cr both cause various effects, which include genotoxicity, carcinogenicity, hepatotoxicity, nephrotoxicity, and reproductive toxicity. These all toxicities are discussed below.

Genotoxicity: Ni and Cr induce genetic abnormalities. Due to its reactive nature, Ni induces genetic abnormalities, including breakage of DNA strands, cause DNA methylation, and breakage of protein cross-links. It can also damage the nucleotide excision repair system, thus causing gene mutations and stimulating epigenetic gene silencing (Kasprzak, 2023; Yılmaz *et al*., 2023). Ni toxicity is also associated with chromosomal crossovers, micronuclear abnormalities, variations in nucleic acid concentration, and cellular modifications (Yaseen, 2021).

Genotoxicity is also associated with proteins present inside the nucleus and cytoplasm. Ni binds with the proteins and enhances the intracellular hydrogen peroxide level, which then increases the level of reactive oxygen species (Sun *et al*., 2022). Inside the nucleus, Ni causes epigenetic modifications by blocking enzymes that are important for DNA replication, transcription, translation, and recombination of DNA (Zhao *et al*., 2022). Similarly,

Table 1: Geographical distribution of Nickel and Chromium with potential role in causing toxicity in sheep.

Element	Country	Region	Sources	Affected area	Environmental impact	Toxic effects on sheep	References
Chromium	China	Hunan Province	Mining and smelting activities	Farmlands near mining sites	Soil contamination, reduced crop yield, bioaccumulation in plants	Kidney damage, osteomalacia, and reduced growth rates in sheep	(Liu *et al.*, 2023)
Nickel	India	Sukinda Valley	Chromite mining and industrial waste	Farmlands and grazing areas	Soil and water contamination, reduced vegetation, and bioaccumulation in plants	Respiratory distress, reduced weight gain, and liver damage in sheep	(Mushtaq *et al.*, 2024)
Nickel	Russia	Norilsk	Nickel smelting and industrial emissions	Surrounding tundra and grasslands	Soil acidification, reduced biodiversity, and air pollution	Neurological disorders, reduced fertility, and high mortality in sheep	(Alekseenko, 2021)
Chromium	Pakistan	Kasur District	Tannery waste and industrial effluents	Agricultural lands and water bodies	Soil and water contamination, reduced crop yield, and bioaccumulation in plants	Kidney damage, reduced milk production, and high mortality in sheep	(Bin-Jumah *et al.*, 2020)
Chromium	South Africa	Bushveld Igneous Complex	Chromite mining and smelting	Grazing lands and water sources	Soil contamination, reduced vegetation, and water pollution	Liver and kidney damage, reduced wool growth, and reproductive failure in sheep	(Phoon *et al.*, 2012)
Nickel	China	Shaanxi Province	Industrial emissions and wastewater	Farmlands near industrial zones	Soil contamination, reduced crop yield, and bioaccumulation in plants	Reduced weight gain, liver damage, and respiratory issues in sheep	(Acheampong, 2023)
Nickel	Canada	Sudbury Basin	Nickel mining and smelting	Grazing lands and water bodies	Soil acidification, reduced vegetation, and water pollution	Neurological disorders, reduced fertility, and high mortality in sheep	(Pilarczyk *et al.*, 2019)
Chromium	Italy	Piedmont Region	Tanneries and industrial effluents	Agricultural lands and rivers	Soil and water contamination, reduced biodiversity, and bioaccumulation in plants	Kidney damage, reduced milk production, and reproductive failure in sheep	(Apostoli and Catalani, 2015)
Chromium	Bangladesh	Dhaka Division	Tannery waste and industrial runoff	Farmlands and water bodies	Soil and water contamination, reduced crop yield, and bioaccumulation in plants	Liver and kidney damage, reduced wool growth, and high mortality in sheep	(Samad, 2021)

Cr mainly exists as trivalent Cr and hexavalent Cr forms, and its elevated level can cause toxicity (Monga *et al.*, 2022). The ionic resemblance of the oxyanion form (CrO_4) of hexavalent Cr with sulfate ions (SO_4) makes it easy to penetrate the cell. Upon entering the cell, it is reduced by ascorbic acid and biological thiols, including glutathione and cysteine, into trivalent Cr (Azeez *et al.*, 2021).

The reduction of hexavalent Cr generates ROS like hydrogen peroxide which is involved in the generation of oxidative stress and causes damage to cellular lipids, proteins, and DNA (Singh *et al.*, 2022). Notably, the presence of ascorbic acid reduces oxidative stress but leads to DNA double-strand break because of the production of trivalent Cr. These adducts are very difficult to repair cause permanent cellular damage and sometimes may lead to malignant formation (Wuri *et al.*, 2023). The mechanism of genotoxicity and related changes due to Ni and Cr accumulation are shown in Fig. 2.

Carcinogenicity: Ni and hexavalent Cr are associated with increased tumor development. Industries such as refineries, mining, smelting, and stainless-steel production are the major sources of Ni exposure to workers and nearby farm animals (Begum *et al.*, 2022). The research study revealed that divalent Ni is a potent carcinogen capable of producing tumors in both animals and humans (Kasprzak, 2023). Studies also revealed that Ni and Ni-derived compounds, such as Ni oxide, Ni chlorides, and Ni sulfates, have significant carcinogenic effects (Bellouard *et al.*, 2022; Patra *et al.*, 2024). In one of the studies, it was confirmed that high concentrations of various metals, including Ni @1.7mg/kg/day in the diet of sheep, increased the chances of tumors of the lungs, liver, kidneys, and upper gastrointestinal tract (Raeeszadeh *et al.*, 2022). Another study conducted by Khan *et al.* (2024) confirmed the cause of carcinogenicity in buffalo and sheep. Both species used *Zea mays* fodder, which has a high concentration of Ni due to soil contamination. Similarly, a study on rodents also showed that prolonged exposure to Ni oxide led to lung tumors, including adenomas, adenocarcinomas, squamous cell carcinoma, and fibrosarcomas (Cohen *et al.*, 2023). These studies suggest that the carcinogenic effect of Ni is due to genetic, epigenetic factors and oxidative stress.

Moreover, some Ni compounds have been shown to induce cell proliferation, which converts minor DNA damage into severe mutations. These mutations will ultimately lead to tumor development (Guo *et al.*, 2021). Similarly, the research studies revealed that hexavalent Cr is also mutagenic to both animals and humans. Studies on occupational exposure and chronic diseases in animals suggest that hexavalent Cr is associated with the production of free radicals that cause disruption of cell signals and play a critical role in its carcinogenic mechanism (Wang *et al.*, 2017; Hossini *et al.*, 2022). Similarly, trivalent Cr can make complexes with the proteins and DNA, which lead to protein DNA crosslinks, DNA deterioration, and blockage of cell signaling pathways, hence causing cancer growth (Georgaki *et al.*, 2023).

Cr toxicity is also associated with changes in protein signaling and genomic instability (Langie *et al.*, 2015). Long-term exposure to hexavalent Cr has been shown to cause chromosomal aberrations, which lead to lung cancer in animals (Meaza *et al.*, 2024). Research studies also revealed that hexavalent Cr blocks the DNA repair proteins by inhibiting transcription factors. Another research study conducted by Emurotu *et al.* (2024) confirmed the carcinogenicity of Ni and Cr, along with other heavy metals in the offal of sheep and cows. The study confirmed that higher concentrations of these metals in the liver, kidneys, and muscles of these animals can be carcinogenic, and offal is not appropriate for eating.

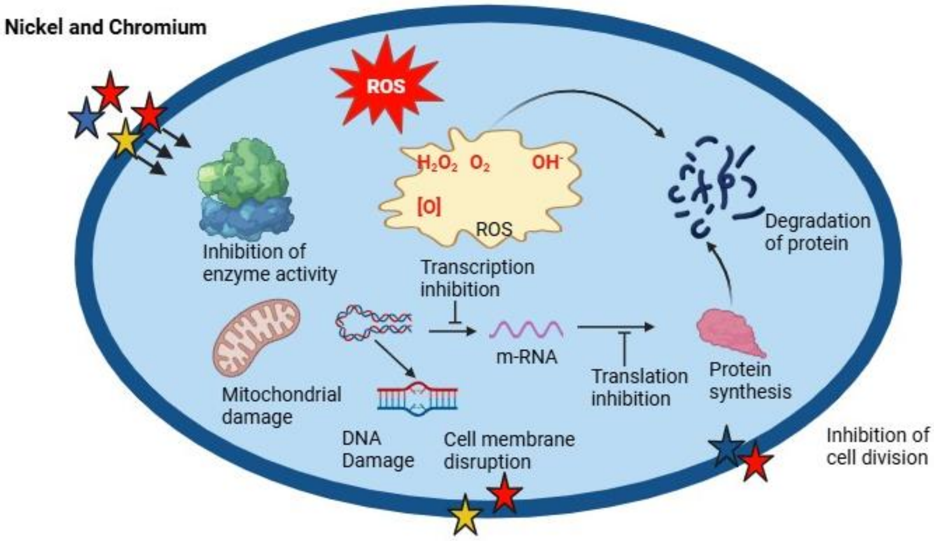

Fig. 2: Genotoxicity induced by nickel and chromium. The source of the diagram is www.biorender.com

Cr compounds such as zinc chromate in the combined form are less soluble in water and actively penetrate the cell membrane for active interaction with macromolecules such as proteins and nucleic acids. This combination causes alterations in the cellular organelles, and the chances of tumor growth are increased (Poljsak *et al*., 2010). Generally, the carcinogenicity of Cr and Ni depends upon various factors, including species, dose, duration of exposure, and potential interaction with other elements and individual health conditions. The mechanism of carcinogenicity is described in Fig. 3.

Hepatotoxicity: Ni and Cr both cause hepatotoxicity by producing oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, and disruption of cellular homeostasis (Cao *et al*., 2024). Both metals, when ingested through fodder or inhaled through contaminated air, accumulate in the liver and trigger a cascade of cellular events that cause liver damage. Ni causes liver damage by producing ROS through Fenton-like reactions (Teschke, 2022), while Cr produces ROS when its hexavalent form is reduced to a trivalent form (Saha *et al*., 2011). The ROS produced include superoxide anions, hydrogen peroxide, and hydroxyl radicals that disturb the antioxidant defenses of the liver, such as super oxidase mutase and catalase (Ahamed *et al*., 2013). The oxidative stress thus produced leads to lipid peroxidation, damages the cell membrane of hepatocytes, causes leakage of cellular contents, and disrupts the integrity of cellular integrity (Valko *et al*., 2005).

Both these metals accumulate in the mitochondria, interfere with the electron transport chain, and interrupt ATP production (Du *et al*., 2024). These are also involved in the disfunctioning of mitochondrial enzymes such as ubiquinone oxidoreductase, succinate dehydrogenase, cytochrome bc1 complex, cytochrome oxidase C, and citrate synthase (Sun *et al*., 2022; Alur *et al*., 2024). The impairment of these enzymes causes energy depletion and leads to the inhibition of essential metabolic functions. These events contribute to cellular dysfunction and death, either through apoptosis or necrosis, depending upon the severity of the damage (Zuo *et al*., 2024).

Ni and Cr are also involved in DNA damage directly or indirectly. These metals bind directly with DNA and cause base substitution and DNA cross-linking of hepatocytes. Ni may also interfere with phosphate groups in nucleotides and cause structural instability (Yang *et al*., 2022). They are also involved in the alteration of methylation patterns, leading to gene silencing of tumor suppressor genes and activation of oncogenes (Ahmed *et al*., 2010). Continuous exposure to Ni and Cr activates the liver's immune response, exacerbating tissue damage. They stimulate the Kupffer cells, also called liver macrophages, and stimulate the release of cytokines, tumor necrosis factor-alpha (TNF-α), interleukins (IL-6), and IL-1β. These pro-inflammatory cytokines aggravate oxidative stress and cause tissue injury (Casalegno *et al*., 2015). All these changes are involved in the production of tumors in liver cells.

Nephrotoxicity: Ni and Cr, after gaining entry into the body, are carried by the blood to different tissues of the body, including the kidneys (Lentini *et al*., 2017). The majority of the Ni and Cr is excreted through urine, but continuous exposure may lead to accumulation, which causes the production of ROS in the nephron. Production of ROS may lead to lipid peroxidation and oxidation of DNA and proteins resulting in cell apoptosis and nephrotoxicity (Sabolić, 2006; Reyes *et al*., 2013). These changes cause a high rise of albumin levels in the urine. In a research study conducted at livestock farms, it was confirmed that Ni and Cr cause damage to renal tubules at the corticomedullary junction, resulting in decreased urine levels and increased kidney weight (Mushtaq *et al*., 2024). Various other studies also confirmed the nephron toxic effects of heavy metals, including Ni and Cr, on livestock animals (Raikwar *et al*., 2008; Tahir and Alkheraije, 2023).

Reproductive toxicity: The toxic effect of heavy metals on the physiological system of animals has been extensively documented (Shahjahan *et al*., 2022). Ni and Cr, when accumulated in the body, have negative influences on reproductive tissues (Rzymski *et al*., 2015).

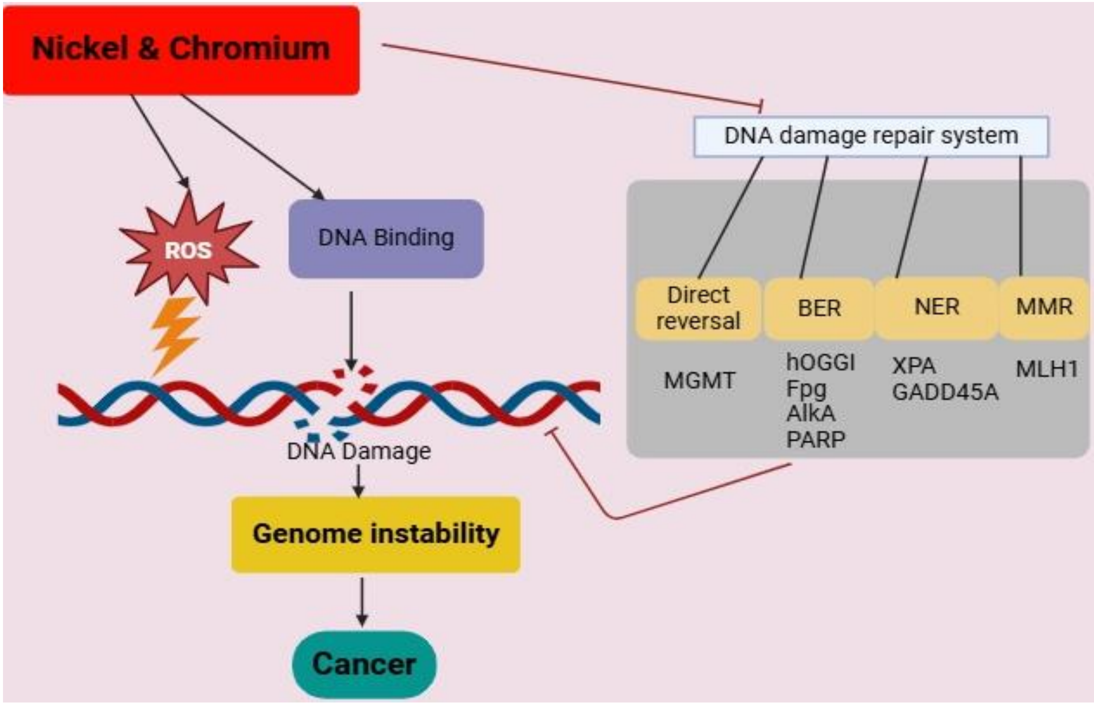

Fig. 3: Carcinogenicity induced by nickel and chromium. The source of the diagram is www.biorender.com

The bioaccumulation of these metals is correlated with the rising incidence of testicular dysgenesis across various species (Forgacs *et al*., 2012). Due to their hazardous effects, various reports of mortalities have also been reported in large and small ruminants (Mukherjee *et al*., 2022). These toxicants have also been linked with developmental decay and compromised reproductive potential, as well as disruption in testosterone-related genes (Ommati and Heidari, 2021). Furthermore, exposure to these metals causes severe testicular morphological alterations, dysregulation of cellular interactions, and perturbations in the integrity of tight and gap junctions (Dolati *et al*., 2020; Ilieva *et al*., 2020). Chronic exposure is also involved in the decrease of sperm count and a concurrent increase in the frequency of morphologically aberrant spermatozoa.

Additionally, these metals have also been linked to testicular degeneration and impaired testicular growth. One of the studies conducted by Heidari *et al*. (2021b) concluded that prolonged exposure to Ni and Cr, along with other heavy metals, has negatively impacted the reproductive health of Kermani rams as compared to those rams that were not exposed to Ni and Cr. Another study conducted by Heidari *et al*. (2021a) confirmed that heavy metal exposure causes detrimental effects on health and reproduction in Kermani sheep reared near a copper smelter.

The exposure of heavy metals like lead (Pb), copper (Cu), Cr, and Ni caused alterations in testicular gene expression, including HSD17B3 and CYP11A1. A significant decrease in reproductive hormones such as FSH, LH, and testosterone was also observed. These findings indicate disrupted hypothalamic-hypophyseal-testicular functions due to prolonged exposure to these metals and emphasize the need to further investigate Ni and Cr toxicities and their wider ecological impacts. Furthermore, the chronic exposure of Ni can also cause abnormalities in the newborn fetus. These metals pass through the placenta and accumulate in the fetal tissues, which leads to abnormalities of various tissues (McDermott *et al*., 2012). The toxic effects of these metals are shown in Fig. 4.

Management approaches: The management of Ni and Cr toxicity in livestock animals, particularly sheep, is very necessary to protect their health, productivity, and overall well-being (Kumar *et al*., 2017). The higher concentrations of these heavy metals pose severe toxic effects, including anemia, organ damage, neurological disorders, and reproductive failures, as discussed above (Fadlalla, 2022; Hussain *et al*., 2024). Chronic exposure to these metals can result in increased mortality at domestic and farm levels and cause economic losses to farmers. The presence of these metals in sheep products like meat and milk poses a serious threat to food items and public health, making their management very important for maintaining livestock sustainability and human health (Ziarati *et al*., 2018). Implementation of preventive strategies such as grazing management, soil and water testing, and better diet can significantly reduce the exposure (Peng *et al*., 2018). Furthermore, detoxification therapies, mineral supplementation, and supportive treatments may help to lessen the toxic effects in already affected animals (Oves *et al*., 2016). Some of the managemental strategies are described below and also mentioned in Fig. 5.

Chelation therapy and mineral supplementation: Chelation therapy is one of the important and effective methods to remove toxic metals like Ni and Cr from sheep bodies (Kim *et al*., 2019). Various chelating agents such as ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA), and dimercaptopropane sulfonate (DMPS) have been used that have ability to bind with Ni and Cr in the blood stream (Sears, 2013). The

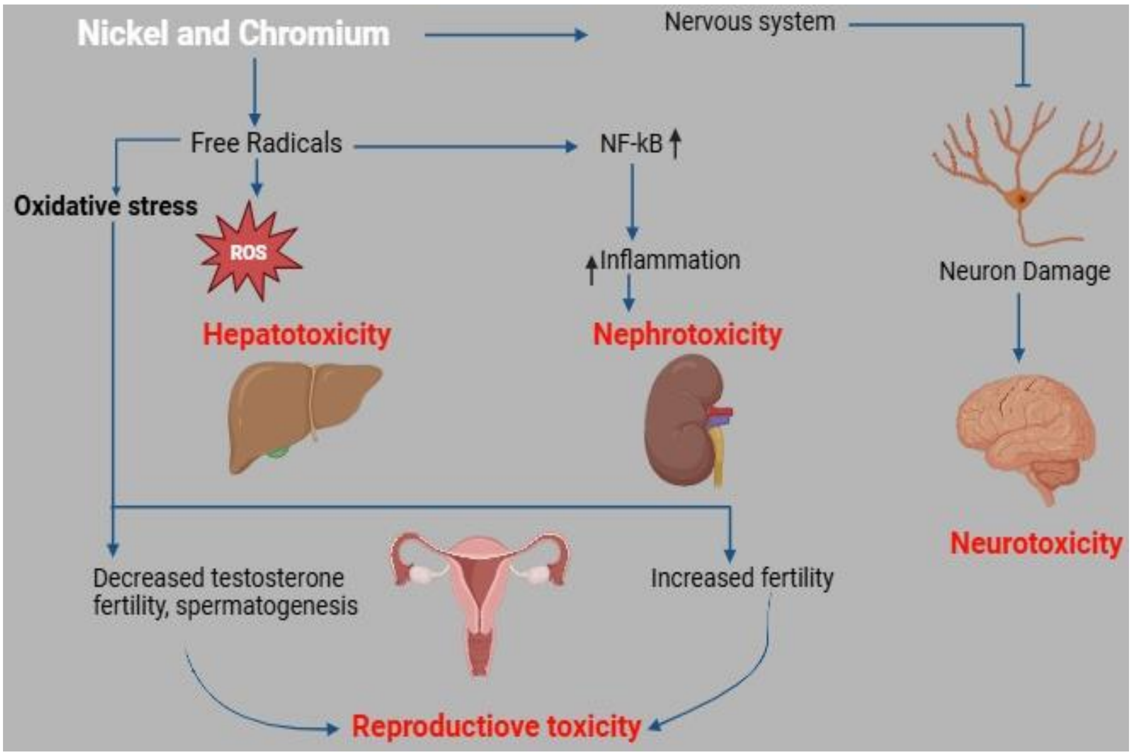

Fig. 4: Toxicities of different organs caused by the accumulation of nickel and chromium, the source of the diagram is www.biorender.com

binding of these chelates with the metals forms stable complexes that are then excreted through urine (Flora and Pachauri, 2010). Excretion of toxic metals from the body reduces their accumulation in the liver, kidneys, brain, and reproductive organs. This therapy is mostly used in acute poisoning where Ni and Cr cause severe oxidative stress, neurological impairments, and metabolic disturbances (Andersen and Aaseth, 2016).

On the other hand, chelation therapy must be done with caution in livestock, especially in sheep, because it can also deplete essential minerals like calcium, magnesium, and zinc leading to potential deficiencies (J Baran, 2010). So, chelation therapy should be properly dosed and monitored to remove toxic metals from the animal's body. Besides chelation therapy, mineral supplementation such as selenium, zinc, and iron play an important role in counteracting heavy metal toxicity (Reis *et al*., 2010). These minerals compete with Ni and Cr at the absorption site in the intestine and reduce their bioavailability and toxic effects (Zhai *et al*., 2018). These minerals are the key components of various enzymatic systems that help to neutralize the oxidative stress. For example, selenium is a key component of the glutathione peroxidase enzyme that is involved in the reduction of ROS and decreases oxidative stress (Shen *et al*., 2022).

Probiotics and Antioxidants: *Lactobacilli-based* probiotics and antioxidants can be used as an effective alternative to significantly reduce the toxic effects of Ni and Cr in dairy animals (Ansari *et al*., 2024). Probiotics obtained from Lactobacillus and Bifidobacterium play an important role in binding with heavy metals in the gut and preventing their absorption into the bloodstream, hence reducing the metal burden in the body and minimizing the systematic toxicity (Singh *et al*., 2024). Furthermore, these beneficial microbes enhance gut health, nutrient absorption and strengthen immune functions that are severely disturbed by the accumulation of heavy metals (Moawad *et al*., 2024). Moreover, these probiotics reduced the ROS, thus reducing metal-induced oxidative stress and inflammation (Abdel-Megeed, 2021).

Various antioxidants, such as Vitamin C, vitamin E, and glutathione, further help in combating oxidative damage caused by Ni and Cr (Hashem *et al*., 2021). Vitamin C enhances the immune response and facilitates the excretion of metals by forming soluble complexes, while vitamin E protects cell membranes from oxidative stress and preserves cellular integrity (Poli *et al*., 2022; Elgharib *et al*., 2023). Additionally, glutathione, a potent intracellular antioxidant has the ability to bind with heavy metals (Ni and Cr) and promote detoxification and restore normal metabolic functions (Averill-Bates, 2023). Antioxidants in combination with probiotics support overall health and increase the resilience of sheep against environmental metal contamination, making it a valuable approach for managing heavy metal toxicity.

Anti-inflammatory therapy: The harmful effects of Ni and Cr, including inflammation and oxidative stress, can be mitigated by providing non-steroidal anti-inflammatory drugs (NSAIDs) (Mucha *et al*., 2021). NSAIDs such as flunixin meglumine and meloxicam can be used to reduce inflammation, reduce pain, and minimize oxidative damage (Sohail *et al*., 2023). These drugs help by inhibiting the production of inflammatory mediators like prostaglandins and provide relief from the systematic effects of heavy metal exposure (Machado *et al*., 2021). NSAIDs with antioxidant supplementation play a crucial role in neutralizing free radicals generated by Ni and Cr toxicity (Fuller, 2022). However, the careful use of NSAIDS is very necessary because prolonged use or excessive administration can lead to gastrointestinal

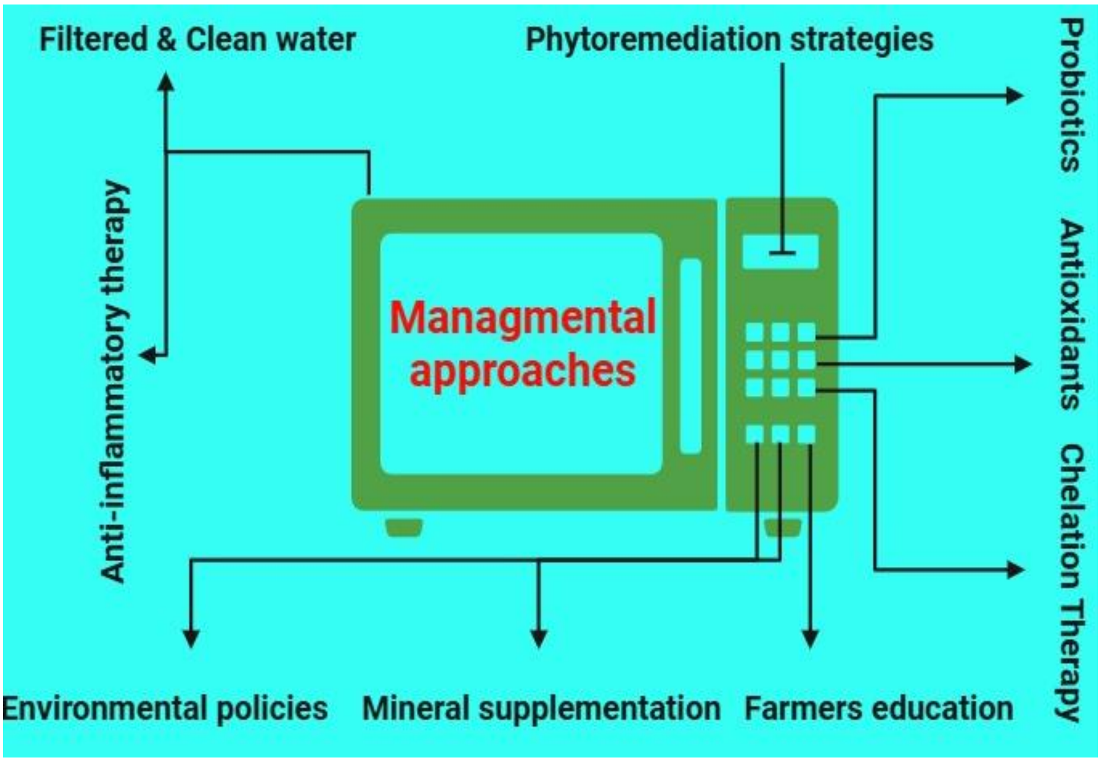

Fig. 5: Managemental approaches to tackle Nickel and chromium toxicities in sheep. The source of the diagram is www.biorender.com

disturbance, kidney damage, and other associated adverse effects (Sohail *et al*., 2023). Therefore, a balanced anti-inflammatory treatment with antioxidant support is recommended to manage heavy metal toxicity in small ruminants.

Other management approaches: Filtered and uncontaminated water also plays an important role in preventing metal toxicity (Saravanan *et al*., 2022). Water released from industries can pollute the water of ponds, canals, wells, and rivers, and it should be tested to check the Ni and Cr levels. The water for deep bore wells at the farm level and for domestic purposes should be utilized. Livestock watering troughs should be regularly cleaned and maintained to prevent the bioaccumulation of toxins from sediment and algae. Furthermore, better supplementation of activated charcoal and zeolites can significantly reduce the absorption of Ni and Cr from contaminated forages (Głąb *et al*., 2021).

Another effective and long-term solution for mitigating Ni and Cr toxicity in sheep is the remediation of contaminated grazing lands (Abdel-Rahman, 2022). Researchers have confirmed that phytoremediation strategies, such as growing of hyper-accumulator plants like Helianthus annuus (sunflower) and Chrysopogon zizanioides (vetiver grass) when grown near pasture, absorb and store heavy metals from the soil (Li *et al*., 2023; Yohannes *et al*., 2024). Additionally, soil amendments such as biochar, organic compost, and lime can help immobilize heavy metals, preventing their uptake by plants and animals (Qiu *et al*., 2021). As mentioned above about the industrial activities of mining, smelting, electroplating, and tannery operation are the major sources of Ni and Cr contamination in agricultural land and water sources. To avoid it strict environmental policies should be applied to regulate the industrial waste disposal. There should be a mandate for proper water treatment, controlled emissions, and regular monitoring of effluents before they discharge into the water and environment. There is a dire need to make buffer zones between industrial areas and grazing lands to minimize the contamination risks. At the end there is also a need to educate the farmers about the risks of heavy metal toxicity, early clinical signs in sheep, and proper management practices to prevent widespread toxicity. Awareness programs should focus on identifying contaminated areas, choosing safe grazing lands, and implementing dietary and medical interventions. Extension services and workshops can help farmers adopt preventive strategies, ensuring the health and productivity of their livestock while minimizing economic losses.

Conclusions: As Ni and Cr metals are accumulated from environmental exposure, polluted water and feed therefore, these are mainly concerns. These metals can cause oxidative stress, organ dysfunction, immune suppression, infertility, liver and kidney failure, and metabolic disturbances. In control strategies utilization of detoxifying agents, administer antioxidants with diet, regular examination of metal levels in feed and water are included. More research is required in order to understand the detoxification mechanism of action so that livestock productivity can be enhanced after controlling the toxic effects of these metals. To further increase the impact of these findings, adopting an integrated approach, integrating environmental monitoring, nutritional interventions, and clinical management can offer a holistic strategy to safeguard animal production and health. Proper management of these metals is necessary in order to obtain better health and production of sheep.

REFERENCES

Abdel-Megeed RM, 2021. Probiotics: a promising generation of heavy metal detoxification. Biol Trace Elem Res 199:2406-2413.

Abdel-Rahman GN-E, 2022. Heavy metals, definition, sources of food contamination, incidence, impacts and remediation: A literature review with recent updates. Egypt J Chem 65:419-437.

Acheampong S, 2023. Heavy metals' poisoning in farm animals, In: Heavy Metals-Recent Advances. IntechOpen.

Ahamed M, Ali D, Alhadlaq HA, *et al.*, 2013. Nickel oxide nanoparticles exert cytotoxicity via oxidative stress and induce apoptotic response in human liver cells (HepG2). Chemosphere 93:2514-2522.

Ahmad N, Yuan H, Zhu Z, *et al.*, 2024. Pakistan sheep industry its constrains and future trends. Trop Anim Health Prod 56:399.

Ahmed MH, El-Mahdy NM, El-Dessouky NA, *et al.*, 2010. Mechanism of nickel and chromium-induced immunotoxicity and oxidative stress: A comparative study. Med J Cairo Univ 78:413-426.

Alekseenko S, 2021. Meeting of the Russian Society for Trace Elements in Medicine (RUSTEM). J Trace Elem 38:134-160.

Ali AAM, Mansour AB and Attia SA, 2021. The potential protective role of apigenin against oxidative damage induced by nickel oxide nanoparticles in liver and kidney of male Wistar rat, *Rattus norvegicus*. Environ Sci Pollut Res 28:27577-27592.

Alur A, Phillips J, Xu D, *et al.*, 2024. Effects of hexavalent chromium on mitochondria and their implications in carcinogenesis. J Environ Sci Health, Part C 42:109-125.

Andersen O and Aaseth J, 2016. A review of pitfalls and progress in chelation treatment of metal poisonings. J Trace Elem Med Biol 38:74-80.

Angon PB, Islam MS, Kc S, *et al.*, 2024. Sources, effects and present perspectives of heavy metals contamination: Soil, plants and human food chain. Heliyon 10:28357

Ansari F, Lee CC, Rashidimehr A, *et al.*, 2024. The role of probiotics in improving food safety; detoxification of heavy metals and chemicals. Toxin Rev 43:63-91.

Apostoli P and Catalani S, 2015. Effects of metallic elements on reproduction and development, In: Handbook on the Toxicology of Metals. Elsevier, pp:399-423.

Arun KB, Madhavan A, Sindhu R, *et al.*, 2021. Probiotics and gut microbiome− Prospects and challenges in remediating heavy metal toxicity. J Hazard Mater 420:126676.

Asadi M, Toghdory A, Hatami M, *et al.*, 2022. Milk supplemented with organic iron improves performance, blood hematology, iron metabolism parameters, and biochemical and immunological parameters in suckling Dalagh lambs. Animals 12:510.

Aschner M, Skalny AV, Lu R, *et al.*, 2023. The role of hypoxia-inducible factor 1 alpha (HIF-1α) modulation in heavy metal toxicity. Arch Toxicol 97:1299-1318.

Averill-Bates DA, 2023. The antioxidant glutathione, In: Vitamins and hormones. Elsevier, pp:109-141.

Azeez NA, Dash SS, Gummadi SN, *et al.*, 2021. Nano-remediation of toxic heavy metal contamination: hexavalent chromium [Cr (VI)]. Chemosphere 266:129204.

Begum W, Rai S, Banerjee S, *et al.*, 2022. A comprehensive review on the sources, essentiality and toxicological profile of nickel. Royal Soc Chem Adv 12:9139-9153.

Bellouard M, Gasser M, Lenglet S, *et al.*, 2022. Toxicity and metabolomic impact of cobalt, chromium, and nickel exposure on HepaRG hepatocytes. Chem Res Toxicol 35:807-816.

Bin-Jumah M, Abd El-Hack ME, Abdelnour SA, *et al.*, 2020. Potential use of chromium to combat thermal stress in animals: A review. Sci Total Environ 707:135996.

Cao X, Zheng S, Zeng Y, *et al.*, 2024. Effects of chronic Cr and Ni co-exposure on liver inflammation and autophagy in mice by regulating the TLR4/mTOR pathway. Sci Total Environ 926:171921.

Casalegno C, Schifanella O, Zennaro E, *et al.*, 2015. Collate literature data on toxicity of Chromium (Cr) and Nickel (Ni) in experimental animals and humans. EFSA Supporting Publications 12:478E.

Chakraborty R, Renu K, Eladl MA, *et al.*, 2022. Mechanism of chromium-induced toxicity in lungs, liver, and kidney and their ameliorative agents. Biomed Pharmacother 151:113119.

Chen XF, Wang G, Mei YX, *et al.*, 2024. Mineral resources of Asia continent: Resource endowment, mining industry pattern, and contributions to the world economy. China Geology 7:1-24.

Chen YG, Huang JH, Luo R, *et al.*, 2021. Impacts of heavy metals and medicinal crops on ecological systems, environmental pollution, cultivation and production processes in China. Ecotoxicol Environ Saf 219:112336.

Cohen MD, Bowser DH, Costa M, *et al.*, 2023. Carcinogenicity and genotoxicity of lead, beryllium, and other metals, In: Toxicology of Metals, Volume I. CRC Press, pp:253-284.

Costa M, 2023. Mechanisms of nickel genotoxicity and carcinogenicity, In: Toxicology of Metals, Volume I. CRC press, pp:245-251.

Das KK, Reddy RC, Bagoji IB, *et al.*, 2019. Primary concept of nickel toxicity–an overview. J Basic Clin Physiol Pharmacol 30:141-152.

Desaulniers D, Vasseur P, Jacobs A, *et al.*, 2021. Integration of epigenetic mechanisms into non-genotoxic carcinogenicity hazard assessment: Focus on DNA methylation and histone modifications. Int J Mol Sci 22:10969.

Dolati P, Khodabandeh Z, Zamiri MJ, *et al.*, 2020. The effect of lead acetate and quercetin on the tight and gap junctions in the mouse testis. Biol Trace Elem Res 198:535-543.

Du J, Li Z, Cao X, *et al.*, 2024. Mechanism of mitochondrial kinetic imbalance and Nrf2 signaling pathway-mediated oxidative stress in nickel and/or chromium-induced kidney injury in mice. Antioxidants 13:980.

Durak MH, Gursel FE, Akis I, *et al.*, 2024. Investigation of serum trace element levels in sheep in diyarbakir province and districts. Indian J Anim Res 58:61-65.

Dutta K, 2017. Environmental Panorama of Sukinda Valley–a critical study. Indian J Anim Res 5:34-37.

Elgharib IM, Abdelhamid FM, E Elshopakey G, *et al.*, 2023. The ameliorative effect of vitamin C against hematological, biochemical, oxidative, and immunosuppressive effect of cadmium chloride in rats. Egyptian J Vet Sci 54:379-394.

Emurotu JE, Olawale O, Dallatu EM, *et al.*, 2024. Carcinogenic and non-carcinogenic health risk assessment of heavy metals in the offal of animals from Felele Abattoir, Lokoja, Nigeria. Toxicol Rep 13: 101701.

Fadlalla IMT, 2022. The interactions of some minerals elements in health and reproductive performance of dairy cows. In: New Advances in the Dairy Industry. IntechOpen.

Fechete FI, Popescu M, Mârza SM, *et al.*, 2024. Spatial and bioaccumulation of heavy metals in a sheep-based food system: implications for human health. Toxics 12:752.

Flora SJS and Pachauri V, 2010. Chelation in metal intoxication. Int J Environ Res Public Health 7(7):2745-2788.

Forgacs Z, Massányi P, Lukac N, *et al.*, 2012. Reproductive toxicology of nickel–review. J Environ Sci Health, Part A 47:1249-1260.

Fuller BB, 2022. Antioxidants and Anti-inflammatories. In: Cosmetic Dermatology: Products and Procedures. Wiley online Library, pp: 366-387.

Georgaki MN, Charalambous M, Kazakis N, *et al.*, 2023. Chromium in water and carcinogenic human health risk. Environments 10(2):33.

Ghaedi E, Esfahani SA, Keshavarz-Fathi M, *et al.*, 2023. Molecular mechanisms of metal-induced carcinogenesis. In: Cancer Research: An Interdisciplinary Approach. Springer, pp:295-360.

Głąb T, Gondek K, Mierzwa–Hersztek M, *et al.*, 2021. Biological effects of biochar and zeolite used for remediation of soil contaminated with toxic heavy metals. Sci Rep 11:6998.

Guo H, Deng H, Liu H, *et al.*, 2021. Nickel carcinogenesis mechanism: cell cycle dysregulation. Environ Sci Pollut Res 28 28:4893-4901.

Gupta AR, Bandyopadhyay S, Sultana F, *et al.*, 2021. Heavy metal poisoning and its impact on livestock health and production system. Indian J Anim Health 60(2):1-23

Haidar Z, Fatema K, Shoily SS, *et al.*, 2023. Disease-associated metabolic pathways affected by heavy metals and metalloid. Toxicol Rep 10: 554-570.

Haider AM, Ali A, Saleh EAM, *et al.*, 2023. The role of chromium supplementation in cardiovascular risk factors; a comprehensive reviews of putative molecular mechanisms. Heliyon 9:19826

Hashem MA, Abd El Hamied SS, Ahmed EMA, *et al.*, 2021. Alleviating effects of vitamins C and E supplementation on oxidative stress, hematobiochemical, and histopathological alterations caused by copper toxicity in broiler chickens. Animals 11:1739.

Hashmi S, Leybourne MI, Layton-Matthews D, *et al.*, 2021. Surficial geochemical and mineralogical signatures of Ni-Cu-PGE deposits in glaciated terrain: Examples from the South Range of the Sudbury Igneous Complex, Ontario, Canada. Ore Geol Rev 137:104301.

Heidari AH, Zamiri MJ, Ansari-Pirsaraei Z, *et al.*, 2021a. Physiological disturbances in rams chronically exposed to the chimney emissions of a copper smelter. Small Rumin Res 201:106450.

Heidari AH, Zamiri MJ, Nazem MN, *et al*., 2021b. Detrimental effects of long-term exposure to heavy metals on histology, size and trace elements of testes and sperm parameters in Kermani sheep. Ecotoxicol Environ Saf 207:111563.

Herrada A, Bariod L, Saïd S, *et al*., 2024. Minor and trace element concentrations in roe deer hair: A non-invasive method to define reference values in wildlife. Ecol Indic 159:111720.

Herring J, 2003. Globalization and its effects on forest diversity: A case study of New Caledonia. University of Ottawa (Canada). Pp: 1-11.

Hossain E, Nesha M, Chowdhury MAZ, *et al*., 2023. Human health risk assessment of edible body parts of chicken through heavy metals and trace elements quantitative analysis. PLoS One 18:e0279043.

Hossini H, Shafie B, Niri AD, *et al*., 2022. A comprehensive review on human health effects of chromium: Insights on induced toxicity. Environ Sci Pollut Res 29:0686-70705.

Hussain MI, Khan ZI, Ahmad K, *et al*., 2024. Toxicity and bioassimilation of lead and nickel in farm ruminants fed on diversified forage crops grown on contaminated soil. Ecotoxicol Environ Saf 283: 116812.

Huston DL, Doublier M, Downes P, *et al*., 2021. Geological Setting, Age and Endowment of Major Australian Mineral Deposits: A Compilation. Geoscience Australia pp:1-80

Ilieva I, Sainova I, Yosifcheva K, *et al*., 2020. Toxic effects of heavy metals (lead and cadmium) on sperm quality and male fertility. Acta Morphol Anthropol 27:63-75.

J Baran E, 2010. Chelation therapies: a chemical and biochemical perspective. Curr Med Chem 17:3658-3672.

Jadaa W and Mohammed H, 2023. Heavy metals–definition, natural and anthropogenic sources of releasing into ecosystems, toxicity, and removal methods–an overview study. Ecol Eng 24:249-271.

Kabogo IT, Nyamato GS, Ogunah J, *et al*., 2024. Extraction of heavy metals from water using chelating agents: a comprehensive review. Int J Environ Sci Technol 21:8749–8792.

Kasprzak KS, 2023. Oxidative DNA damage in metal-induced carcinogenesis. In: Toxicology of Metals. CRC press pp: 299-320.

Khalaf EM, Taherian M, Almalki SG, *et al*., 2024. Relationship between exposure to heavy metals on the increased health risk and carcinogenicity of urinary tract (kidney and bladder). Rev Environ Health 39:539-549.

Khalef RN, Hassan AI, Saleh HM, *et al*., 2022. Heavy metal's environmental impact, In: Environmental Impact and Remediation of Heavy Metals. IntechOpen.

Khan ZI, Muhammad FG, Ahmad K, *et al*., 2024. Nickel toxicology testing in alternative specimen from farm ruminants in a urban polluted environment. J King Saud Univ Sci 36: 103520.

Kim JJ, Kim YS, Kumar V, *et al*., 2019. Heavy metal toxicity: An update of chelating therapeutic strategies. J Trace Elem Med Biol 54:226-231.

Kumar A, Balouch A, Pathan AA, *et al*., 2017. Remediation techniques applied for aqueous system contaminated by toxic chromium and nickel ion. Geol Ecol Landsc 1:143-153.

Langie SAS, Koppen G, Desaulniers D, *et al*., 2015. Causes of genome instability: the effect of low dose chemical exposures in modern society. Carcinogenesis 36:S61-S88.

Latypov R, Chistyakova SY, Letsoele C, *et al*., 2024. Massive chromitites of the Bushveld Complex, South Africa: A critical review of existing hypotheses. Earth Sci Rev 256:104858.

Lentini P, Zanoli L, Granata A, *et al*., 2017. Kidney and heavy metals-The role of environmental exposure. Mol Med Rep 15:3413-3419.

Li Y, Rahman SU, Qiu Z, *et al*., 2023. Toxic effects of cadmium on the physiological and biochemical attributes of plants, and phytore-mediation strategies: A review. Environ Pollut 325:121433.

Liu Y, Huo B, Chen Z, *et al*., 2023. Effects of organic chromium yeast on performance, meat quality, and serum parameters of grow-finish pigs. Biol Trace Elem Res 201:1188-1196.

Machado GC, Abdel-Shaheed C, Underwood M, *et al*., 2021. Non-steroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal pain. BMJ 29:372.

Masindi V, Mkhonza P, Tekere M, *et al*., 2021. Sources of heavy metals pollution. In: Inamuddin, Ahamed, M.I., Lichtfouse, E., Altalhi, T. (eds) Remediation of Heavy Metals. Environmental Chemistry for a Sustainable World, vol 70. Springer, Cham. pp:419-454

McDermott S, Bao W, Aelion CM, *et al*., 2012. When are fetuses and young children most susceptible to soil metal concentrations of arsenic, lead and mercury? Spat Spatio-temporal Epidemiol 3:265-272.

Meaza I, Williams AR, Wise SS, *et al*., 2024. Carcinogenic mechanisms of hexavalent chromium: from dna breaks to chromosome instability and neoplastic transformation. Curr Environ Health Rep 11:484–546

Mishra M, Nichols L, Dave AA, *et al*., 2022. Molecular mechanisms of cellular injury and role of toxic heavy metals in chronic kidney disease. Int J Mol Sci 23:11105.

Mo Y, Zhang Y, Zhang Q, *et al*., 2024. The pulmonary effects of nickel-containing nanoparticles: cytotoxicity, genotoxicity, carcinogenicity, and their underlying mechanisms. Environ Sci Nano 11:1817-1846.

Moawad R, Osman A, Hassanein K, *et al*., 2024. Assessment of sweet whey fortified with *Bifidobacteria* and selenium on reduction of pesticide liver toxicity in albino rats. Ital J Food Saf 36:275.

Monga A, Fulke AB, Dasgupta D, *et al*., 2022. Recent developments in essentiality of trivalent chromium and toxicity of hexavalent chromium: implications on human health and remediation strategies. J Hazard Mater 7:100113.

Mubarok M, Syafi'ul W, Kartini E, *et al*., 2024. Nickel diplomacy: Strengthening Indonesia's role in the global battery and electric vehicles supply chain. In: AIP Conf Proc 3213(1):020003

Mucha P, Skoczyńska A, Małecka M, *et al*., 2021. Overview of the antioxidant and anti-inflammatory activities of selected plant compounds and their metal ions complexes. Mol 26:4886.

Mukherjee AG, Wanjari UR, Renu K, *et al*., 2022. Heavy metal and metalloid-induced reproductive toxicity. Environ Toxicol Pharmacol 92:103859.

Mushtaq A, Sajjad A, Ismail T, *et al*., 2024. Heavy metals accumulation in the meat, kidney and liver of cattle, broilers and goats sold in Quetta, Northwestern city of Balochistan, Pakistan. Br Poult Sci 65:740-750.

Nachana'a Timothy ETW, 2019. Environmental pollution by heavy metal: an overview. Chem 3:72-82.

Nieboer E, Tom RT, Sanford WBE, *et al*., 2024. Nickel metabolism in man and animals, In: Metal ions in biological systems. CRC Press, pp:91-121.

Nogara KF, Tavares QG, Palmeira M, *et al*., 2024. Effect of metals (Hg, Cd, Pb, Zn, Cr and Cu) on ruminants. In: Toxicology of Essential and Xenobiotic Metals. CRC Press, pp:59-78.

Nowicka B, 2022. Heavy metal–induced stress in eukaryotic algae-mechanisms of heavy metal toxicity and tolerance with particular emphasis on oxidative stress in exposed cells and the role of antioxidant response. Environ Sci Pollut Res 29:16860-16911.

Nriagu JO and Nieboer E, 1988. Production and uses of chromium. In: Chromium in the Natural and Human Environments. Wiley Publishers, New York, USA, pp:81-104.

Ommati MM and Heidari R, 2021. Amino acids ameliorate heavy metals-induced oxidative stress in male/female reproductive tissue, In: Toxicology. Elsevier, pp:371-386.

Oves M, Saghir Khan M, Huda Qari A, *et al*., 2016. Heavy metals: biological importance and detoxification strategies. J Bioremediat Biodegrad 7:1-15.

Paithankar JG, Saini S, Dwivedi S, *et al*., 2021. Heavy metal associated health hazards: An interplay of oxidative stress and signal transduction. Chemosphere 262:128350.

Patra A, Khatun N, Mandal T, *et al*., 2024. Occurrence and speciation of ni in the environment and the health risk to living organisms. In: Lithium and Nickel Contamination in Plants and the Environment. World Scientific connect. pp:231-262.

Peng WX, Marchal JLM, Van der Poel AFB, *et al*., 2018. Strategies to prevent and reduce mycotoxins for compound feed manufacturing. Anim Feed Sci Technol 237:129-153.

Pereira V, Miranda M, Sierra J, *et al*., 2021. Toxic and essential trace element concentrations in different tissues of extensively reared sheep in northern Spain. J Food Compos Anal 96:103709.

Phoon X, Ander EL, Plant JA, *et al*., 2012. Essential and beneficial trace elements. In: Pollutants, Human Health and the Environment. Wiley Online Library. pp:53-86.

Pilarczyk B, Tomza-Marciniak A, Pilarczyk R, *et al*., *et al*., 2019. Selenium, Se. mammals and birds as bioindicators of trace element contaminations in terrestrial environments: In: An Eco toxicological Assessment of the Northern Hemisphere. Springer Cham. pp:301-362.

Piskin E, Cianciosi D, Gulec S, *et al*., 2022. Iron absorption: factors, limitations, and improvement methods. ACS Omega 7:20441-20456.

Poli V, Aparna Y, Madduru R, *et al*., 2022. Protective effect of Vitamin C and E on enzymatic and antioxidant system in liver and kidney toxicity of Cadmium in rats. Appl Food Res 2:100098.

Poljsak B, Pócsi I, Raspor P, *et al.*, 2010. Interference of chromium with biological systems in yeasts and fungi: a review. J Basic Microbiol 50:21-36.

Ponnampalam EN, Priyashantha H, Vidanarachchi JK, *et al.*, 2024. Effects of nutritional factors on fat content, fatty acid composition, and sensorial properties of meat and milk from domesticated ruminants: an overview. Animals 14:840.

Priyadarshanee M, Mahto U, Das S, *et al.*, 2022. Mechanism of toxicity and adverse health effects of environmental pollutants, In: Microbial biodegradation and bioremediation. Elsevier, pp:33-53.

Qiu B, Tao X, Wang H, *et al.*, 2021. Biochar as a low-cost adsorbent for aqueous heavy metal removal: A review. J Anal Appl Pyrolysis 155: 105081.

Raeeszadeh M, Gravandi H, Akbari A, *et al.*, 2022. Determination of some heavy metal levels in the meat of animal species (sheep, beef, turkey, and ostrich) and carcinogenic health risk assessment in Kurdistan province in the west of Iran. Environ Sci Pollut Res 29: 62248-62258.

Raikwar MK, Kumar P, Singh M, *et al.*, 2008. Toxic effect of heavy metals in livestock health. Vet World 1:28-30.

Rehman K, Fatima F, Waheed I, *et al.*, 2018. Prevalence of exposure to heavy metals and their impact on health consequences. J Cell Biochem 119:157-184.

Reis LSLdS, Pardo PE, Camargos AS, *et al.*, 2010. Mineral element and heavy metal poisoning in animals. J Med Med Sci 1(2):560-579.

Renu K, Chakraborty R, Myakala H, *et al.*, 2021. Molecular mechanism of heavy metals (lead, chromium, arsenic, mercury, nickel and cadmium)-induced hepatotoxicity–A review. Chemosphere 271: 129735.

Reyes JL, Molina-Jijón E, Rodríguez-Muñoz R, *et al.*, 2013. Tight junction proteins and oxidative stress in heavy metals-induced nephrotoxicity. Biomed Res Int 2013:730789.

Roy RN, 2021. Nickel essentiality, toxicity and the mechanism of toxicity in animal. Pollut Res 40: 121-128.

Rzymski P, Tomczy K, Rzymski P, *et al.*, 2015. Impact of heavy metals on the female reproductive system. Ann Agric Environ Med 22:259-264.

Sabolić I, 2006. Common mechanisms in nephropathy induced by toxic metals. Nephron Physiol 104:107-114.

Saha R, Nandi R, Saha B, *et al.*, 2011. Sources and toxicity of hexavalent chromium. J Coord Chem 64:1782-1806.

Samad M, 2021. A five-decade systematic review of research progress on production and management of small ruminants in Bangladesh. J Vet Med One Health Res 3:1-91.

Saravanan A, Kumar PS, Hemavathy RV, *et al.*, 2022. A comprehensive review on sources, analysis and toxicity of environmental pollutants and its removal methods from water environment. Sci Total Environ 812:152456.

Sawicka E, Jurkowska K, Piwowar A, *et al.*, 2021. Chromium (III) and chromium (VI) as important players in the induction of genotoxicity-current view. Ann Agric Environ Med 28:1-10.

Sears ME, 2013. Chelation: harnessing and enhancing heavy metal detoxification—a review. Sci World J 2013:219840.

Shahjahan M, Taslima K, Rahman MS, *et al.*, 2022. Effects of heavy metals on fish physiology. A review. Chemosphere 300:134519.

Sharma M, Khan FH, Mahmood R, *et al.*, 2023. Nickel chloride generates cytotoxic ROS that cause oxidative damage in human erythrocytes. J Trace Elem Med Biol 80:127272.

Sharma P, Singh SP, Parakh SK, *et al.*, 2022. Health hazards of hexavalent chromium (Cr (VI)) and its microbial reduction. Bioengineered 13:4923-4938.

Shen Y, Huang H, Wang Y, *et al.*, 2022. Antioxidant effects of Se-glutathione peroxidase in alcoholic liver disease. J Trace Elem Med Biol 74:127048.

Shrestha R, Ban S, Devkota S, *et al.*, 2021. Technological trends in heavy metals removal from industrial wastewater: A review. J Environ Chem Eng 9:105688.

Singh B, Mal G, Kalra RS, *et al.*, 2024. Probiotics as chemical decontamination candidates, In: Probiotics as Live Biotherapeutics for Veterinary and Human Health, Volume 1: Functional Feed and Industrial Applications. Springer. pp:451-477.

Singh V, Singh N, Verma M, *et al.*, 2022. Hexavalent-chromium-induced oxidative stress and the protective role of antioxidants against cellular toxicity. Antioxidants 11:2375.

Soh Tamehe L, Zhao Y, Xu W, *et al.*, 2024. Ni (Co) Laterite Deposits of Southeast Asia: A Review and Perspective. Minerals 14:134.

Sohail R, Mathew M, Patel KK, *et al.*, 2023. Effects of non-steroidal anti-inflammatory drugs (NSAIDs) and gastroprotective NSAIDs on the gastrointestinal tract: a narrative review. Cureus 15:7080

Sun Q, Li Y, Shi L, *et al.*, 2022. Heavy metals induced mitochondrial dysfunction in animals: Molecular mechanism of toxicity. Toxicology 469:153136.

Tahir I and Alkheraije KA, 2023. A review of important heavy metals toxicity with special emphasis on nephrotoxicity and its management in cattle. Front Vet Sci 10:1149720.

Tarrahi MJ, Tarrahi MA, Rafiee M, *et al.*, 2021. The effects of chromium supplementation on lipid profile in humans: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 164:105308.

Teschke R, 2022. Aluminum, arsenic, beryllium, cadmium, chromium, cobalt, copper, iron, lead, mercury, molybdenum, nickel, platinum, thallium, titanium, vanadium, and zinc: molecular aspects in experimental liver injury. Int J Mol Sci 23:12213.

Ungureanu EL and Mustatea G, 2022. Toxicity of heavy metals, In: Environmental Impact and Remediation of Heavy Metals. IntechOpen.

Valko M, Morris H, Cronin MTD, *et al.*, 2005. Metals, toxicity and oxidative stress. Curr Med Chem 12: 1161-1208.

Van der Ent A, Baker A, Van Balgooy M, *et al.*, 2013. Ultramafic nickel laterites in Indonesia (Sulawesi, Halmahera): mining, nickel hyperaccumulators and opportunities for phytomining. J Geochem Explor 128:72-79.

Verma N, Rachamalla M, Kumar PS, *et al.*, 2023. Assessment and impact of metal toxicity on wildlife and human health, In: Metals in water. Elsevier, pp:93-110.

Waghorn G, 2008. Beneficial and detrimental effects of dietary condensed tannins for sustainable sheep and goat production-Progress and challenges. Anim Feed Sci Technol 147: 116-139.

Wang Y, Su H, Gu Y, *et al.*, 2017. Carcinogenicity of chromium and chemoprevention: a brief update. Onco Targets Ther 10:4065-4079.

Wuri L, Burghardt RC, Arosh JA, *et al.*, 2023. Hexavalent chromium disrupts oocyte development in rats by elevating oxidative stress, DNA double-strand breaks, microtubule disruption, and aberrant segregation of chromosomes. Int J Mol Sci 24:10003.

Yang Q, Han B, Li S, *et al.*, 2022. The link between deacetylation and hepatotoxicity induced by exposure to hexavalent chromium. J Adv Res 35:129-140.

Yaseen ZM, 2021. An insight into machine learning models era in simulating soil, water bodies and adsorption heavy metals: Review, challenges and solutions. Chemosphere 277:130126.

Yılmaz H, Kalefetoğlu Macar T, Macar O, *et al.*, 2023. DNA fragmentation, chromosomal aberrations, and multi-toxic effects induced by nickel and the modulation of Ni-induced damage by pomegranate seed extract in Allium cepa L. Environ Sci Pollut Res 30:110826-110840.

Yohannes SB, Mihret DU, Asamire AG, *et al.*, 2024. Use of Vetevera Grass (*Chrysopogon zizanioides*) in a Constructed Wetland to Remove Heavy Metals from Kege Wet Coffee Processing Plant, Dale Woreda, Sidama Regional State, Ethiopia. J Appl Sci Envir Manag 28:1083-1095.

Zafar W, Ashfaq M, Sumrra SH, *et al.*, 2023. A review on the antimicrobial assessment of triazole-azomethine functionalized frameworks incorporating transition metals. J Mol Struct 1288: 135744.

Zhai Q, Yang L, Zhao J, *et al.*, 2018. Protective effects of dietary supplements containing probiotics, micronutrients, and plant extracts against lead toxicity in mice. Front Microbiol 9:2134.

Zhao J, Shi X, Castranova V, *et al.*, 2009. Occupational toxicology of nickel and nickel compounds. J Environ Pathol Toxicol Oncol 28:177-208

Zhao L, Islam R, Wang Y, *et al.*, 2022. Epigenetic regulation in chromium-, nickel-and cadmium-induced carcinogenesis. Cancers 14:5768.

Zhong H, Li J, Cheng JH, *et al.*, 2024. Targeting different signaling pathways for food allergy regulation and potential therapy: A review. Crit Rev Food Sci Nutr 64:12860-12877.

Ziarati P, Shirkhan F, Mostafidi M, *et al.*, 2018. An overview of the heavy metal contamination in milk and dairy products. Acta Sci Pharma Sci 2:1-14.

Zuo M, Ye M, Lin H, *et al.*, 2024. Mitochondrial dysfunction in environmental toxicology: mechanisms, impacts, and health implications. Chem Res Toxicol 37:1794-1806.