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Evaluation of the Histological Changes in the Liver of Mice Treated with Nickel Sulphate

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Abstract

Nickel sulphate ($NiSO_4$) is a common industrial substance employed in various applications such as electroplating, battery production, and metal coating. However, its continuous occupational and environmental exposure has elicited toxicological issues. This review is a critical assessment of the histopathological, biochemical and molecular alterations of the liver in mice exposed to nickel sulphate, correlating the findings from both animal and mechanistic tests. Studies evidently show that $NiSO_4$ leads to dose-related liver cell damage, necrosis, steatosis, inflammatory infiltration, and degeneration in animals, closely linked to the increase of serum transaminases and oxidative-stress biomarkers. From a mechanistic perspective, nickel exposure affects redox homeostasis, mitochondrial integrity, and lipid metabolism leading to ferroptosis, apoptosis, and endoplasmic reticulum stress signalling. Additionally, comparative data analysis between hepatic injuries induced by soluble and particulate nickel salts shows that the former is more fatal, highlighting the relevance of compound bioavailability and exposure pathway. The hepatoprotective effects of antioxidants and flavonoid supplements (e.g. selenium, silymamarin, hesperidin, etc.) against hepatic injury are seen in preclinical models. Cross-species researchers also show that there are conserved oxidative and inflammatory systems of damage, suggesting it may be applicable in human risk assessment. According to the review, early biomarkers, multi-omics, and mechanistically directed interventions are needed to enhance toxicological assessment. Overall, long-term exposure to nickel sulphate is a realistic risk for hepatic damage; therefore, increased occupational preventive and mechanistic research should be used to improve preventive and therapeutic strategies.

Keywords: Nickel sulphate ($NiSO_4$), Hepatotoxicity, Histopathology, Oxidative stress, Ferroptosis, Apoptosis, Mice model.

INTRODUCTION

Nickel is a natural transition metal found in the Earth's crust and is widely distributed both by natural and human activities. Nickel has become a widespread environmental pollutant in industrial applications (electroplating, alloy production, battery production), mining and smelting, and biodeposition by combustion (Mukherjee, 1998; Binkowski, 2019; Buxton *et al.,* 2019; Gates *et al.,* 2023). Nickel can occur in several different chemical forms (metallic nickel, oxides, sulfides and soluble salts); the soluble salts include nickel (II) sulfate (nickel sulphate, $NiSO_4$) a crucial industrial chemical in electroplating process and an intermediate in nickel chemistry (Das *et al*., 2010). The soluble salts of nickel have a higher bioavailability than the insoluble counterparts and, thus, are of particular concern when it comes to toxicological analysis (Gates *et al*., 2023). Exposure of nickel salts to animals and humans takes place in various ways. In the industrial facilities (mining, smelting, welding, electroplating), the main exposure routes are occupational inhalation and dermal contact (Cancer.gov 2022). General population exposure includes environmental pollution such as nickel in soil, dust and drinking water; another pathway is through dietary intake of nickel in plant-derived foods and materials that come in contact with food (WHO 2021; Kumar, 2021). Concisely, exposure occurs both in local high-intensity industrial sources and in the widespread low-intensity environmental and dietary sources.

Nickel compounds are a broad chemical group with variability in toxicology profiles with regard to speciation. Nickel sulphate (usually in the form of the hydrated hexahydrate $NiSO_4 \cdot 6H_2O$) is a water-soluble, readily dissociable source of Ni^{2+} ions and is commonly

found in electroplating baths, catalysts, and a precursor to other chemicals of nickel compounds (Sutherland and Costa, 2002; Prueitt and Goodman, 2015; Schaumlöffel, 2005). Nickel sulphate has a higher ability to enter the body system via oral, inhalational, or dermal exposure than more insoluble nickel compounds, which is why $NiSO_4$ is commonly used in toxicology and histopathology studies (NCBI, 2025). Exposure to nickel sulphate may be through inhalation of aerosols or dust (especially in the workplace), through ingestion of soluble, contaminated water or food and by dermal intake of soluble formulations (Hook, 2008; Hughson *et al.,* 2010; Gates *et al.,* 2023; Nieboer *et al.,* 2024). The proportion of the individual routes depends on the situation: inhalation is the most significant route in the case of environmental airborne exposures, ingestion plays a significant role in contaminating the environment and in the diet, and dermal exposures are relevant during handling of aqueous nickel solutions and nickel-containing consumer products (Gates *et al*., 2025).

When absorbed into the body, Ni^{2+} ions spread throughout it and accumulate in specific organs, including the liver and kidney, which are the primary locations of metal biotransformation and excretion (Sachan and Lal, 2017; Kumar 2021; Islam *et al.,* 2025; El-deeb *et al.,* 2025). Such organs are frequently the most tissue-loaded in comparison studies. Nickel sulphate is a soluble nickel salt with rapid systemic diffusion, which creates an issue of hepatic toxicity during acute and chronic exposures (Davies, 2005; Kumar, 2021). Liver is vital for xenobiotic metabolism - the enzymatic biotransformation, conjugation and biliary excretion to eliminate toxicants. Metabolic enzymes and antioxidant systems, which determine the fate and potential injury likelihood of metals, are hosted by hepatocytes and non-parenchymal cells (Teschke, 2022). This role frequently results in early biochemical and structural damage to the liver. Some critical evidence of cellular damage caused by nickel is provided by histopathology and helps to assess the risk in other species (Teschke *et al*., 2022).

The aim of this review is to gather and critically examine published evidence on histological alterations that occur in the liver of mice experimentally subjected to nickel sulphate. In particular, it will (1) capture the nature of morphological changes that have been reported in the studies (acute exposures versus subchronic/chronic regimens), (2) integrate histopathological with biochemical and mechanistic data (oxidative stress, mitochondrial injury, inflammatory signaling, cell-death pathways), and (3) reveal gaps in the methodologies and future research priorities, such as refined dosing paradigm, strain-specific responses, and integration of modern omics and imaging methodologies. Eventually, the review aims to explain the informative role of experimental histology on human health risk on nickel sulphate exposure and to propose areas where additional specific research is required. The recent experimental and mechanistic investigations into nickel-induced liver damage and protective measures (e.g., antioxidant mitigants) will be taken into consideration to put histopathology into the framework of toxicology (Zhou *et al*., 2023).

METHODOLOGY

Study design

A structured literature-based review was adopted in this review to synthesise existing data on the histopathological and mechanistic impact of nickel sulphate ($NiSO_4$) on the liver of mice. The sources of the retrieved and analysed published experimental/review articles were used to present a detailed perspective of the hepatic changes, the underlying toxicology, and methodological strategies that have been employed in nickel toxicity research.

Literature search strategy

The relevant studies were found in electronic databases such as PubMed, Scopus, ScienceDirect, Google Scholar, and ResearchGate and published within the years 2000 and 2025. The search terms covered both combinations of "*"nickel sulphate," "$NiSO_4$," "nickel hepatotoxicity," "liver histopathology," "mice," "oxidative stress,"* and *"apoptosis."*. Searches were refined using the Boolean operators (AND/OR). The reference lists of the retrieved articles were screened to get other relevant publications.

Inclusion and exclusion criteria

Inclusion criteria used in this review were that the studies had to use mice as their experimental animal, and nickel sulphate was applied either orally, intraperitoneally or inhaled. Also, only investigations reporting histopathological, biochemical, or molecular results concerning the hepatic functioning, and published in peer-reviewed journals in the English language were included. On the other hand, the studies were eliminated when they used other nickel compounds; for example, nickel chloride ($NiCl_2$), nickel oxide (NiO), or nickel nanoparticles (NiNPs) without direct comparison to nickel sulphate. Studies that were not documented with histological evidence or were only presented in the form of an abstract, conference proceedings or a document without peer review were also not considered.

Data extraction and synthesis

The data extracted per eligible study were: mouse strain, sex, age, route and duration of exposure to $NiSO_4$, administered dose, histological results, biochemical changes (ALT, AST, ALP, oxidative stress markers) and molecular endpoints (gene/protein expression associated with apoptosis, oxidative stress or ER stress). Qualitative synthesis and comparison of data were executed to uncover patterns of constant lesions, mechanistic relationships, and dose-response relationships.

Quality assessment

The rigor of the methods employed was assessed in accordance with the ARRIVE 2.0 requirements (Percie du Sert *et al*., 2020). Criteria include randomisation, the use of control groups, justification of sample size, ethical consent, blinding of histological analyses, and repeatability of staining/ scoring methods. The studies that do not present the essential methodological information were also mentioned but explained where necessary.

Ethical considerations

The review solely depended on already published animal research, which has received ethical approval from institutional committees. The authors did not conduct any new experiments on animals or humans.

Data analysis

Extracted data were categorized into mechanistic themes such as: oxidative stress and lipid peroxidation, mitochondrial dysfunction, DNA damage, inflammation, and apoptosis/necrosis. Comparative assessments were made across mouse strains, exposure pathways and exposure durations in attempts to explain differences in hepatic responses. Findings were explained against histopathological grading and biochemical indices found in the reviewed studies.

FINDINGS AND DISCUSSION

Nickel sulphate toxicokinetics

a) *Absorption, distribution, metabolism, and excretion (ADME):* Soluble nickel salts like nickel sulphate ($NiSO_4$) can dissociate and release Ni^{2+} ions which in turn permeate epithelial membranes effectively. Absorption in mammals primarily happens via the gastrointestinal tract, with consideration to nickel speciation, the dose, and competing ions targeting the intestinal absorption rate, with $NiSO_4$ being more bioavailable compared to insoluble forms (Begum *et al*. 2022). Absorption through the skin is negligible except when a barrier to the skin is impaired (Ozougwu, 2016; Latvala *et al.,* 2016). There is a high probability for $NiSO_4$ vapours in the atmosphere to be inhaled into the respiratory tract. This allows uptake into the system (Hsieh *et al.,* 1999; Miller *et al.,* 2001; Patra *et al.,* 2024). Ni^{2+} ions uptake and storage occur heavily in the liver because it has one of the most active sites for perfusion and detoxification processes. Dose-dependent accumulation of nickel in the liver is evident in rodent studies following exposure to soluble nickel salts (Qaisar *et al*., 2016). The voltammetry and atomic absorption findings in rats and mice reveal that Ni is deposited in the liver, kidney and spleen (Pereira *et al*. 1998). The excretion of nickel moves quickly, 80-90 per cent in one day in mice and a half-life of 2-3 days in rats (Brucka-Jastrzewska and Protasowicki, 2004; Kermanizadeh *et al*., 2015; Melo *et al*., 2017). The clearance was not significantly decreased by repeated dosing (Goodman *et al*., 2011; Teschke, 2022). However, chronic or high-dose exposures can break this equilibrium, resulting in an accumulation of nickel in proteins or intracellular pools and long-term hepatic effects despite systemic clearance.

b) *Biochemical Interactions in Hepatic Tissue:* In hepatocytes, Ni^{2+} ions react with sulfhydryl (-SH), histidine, and carboxylate amino acids of proteins and enzymes, changing their structure and blocking their activity (Ozougwu, 2016; Latvala et al., 2016; Zhao *et al.,* 2019; Guo *et al*. 2019). Nickel can substitute critical cofactors, including Zn^{2+} or Fe^{2+}, disrupting the work of metalloproteins and depleting glutathione, leading to redox imbalance (Jarrahi *et al*., 2020). These interactions may block the DNA repair and replication mechanism (Guo *et al*., 2019). One of the significant toxic effects of nickel is the development of oxidative stress, through redox cycling and Fenton-like reactions, which produce reactive oxygen species (ROS) of superoxide, hydrogen peroxide, and hydroxyl radicals (Latvala *et al*., 2016). Additional disruption of the electron transport in the mitochondria also encourages the production of ROS, and the inhibition of the endogenous antioxidants, such as superoxide dismutase and catalase, increases the oxidative stress (Ozougwu, 2016; Latvala *et al.,* 2016; Zhao *et al.,* 2019;). This accumulates oxidative stress, leading to lipid peroxidation, protein oxidation, and the breakage of DNA strands, which is observed by increased malondialdehyde and 8-hydroxydeoxyguanosine (Guo *et al*. 2019; Liu *et al*. 2015). $NiSO_4$ also induces ROS-mediated apoptosis through mitochondrial and ER stress in a non-hepatic system (Zou *et al*. 2017). Likewise, hepatic ROS excess production triggers MAPK/JNK, inflammation, and apoptosis, which have a histological appearance of centrilobular necrosis, ballooning of hepatocytes, and inflammatory infiltrates.

Mechanisms of Nickel Sulphate–Induced Hepatotoxicity

a) ***Oxidative Stress and Lipid Peroxidation Iron:***

Lipid peroxidation is one of the most important mechanisms of nickel-induced liver injury, which is shown by high levels of lipid peroxidation products, including malondialdehyde (MDA), and low levels of antioxidant enzymes, such as SOD, CAT, and GSH (Zhou 2023; Chen *et al*. 2024). Rodent experiments associate elevated MDA and decreased antioxidants with degeneration of the hepatocytes (Li *et al.,* 2015; Oz *et al.,* 2005; Koyu *et al.,* 2006; Renugadevi and Prabu, 2010; Zhou *et al.,* 2023). Hesperidin or plant extracts are examples of antioxidant co-treatments, which reinstate the activity of enzymes, as well as lowering pathology (Chen *et al*. 2024; Razzak 2025). Ni^{2+}, when used mechanically, causes redox imbalance and mitochondrial perturbation that results in the production

of ROS, lipid peroxidation, membrane damage, inflammation, and necrosis (Zhou *et al.,* 2023; Latvala *et al*. 2016).

b) *Mitochondrial Dysfunction:*

Mitochondria are another important target of nickel toxicity, as it has been reported that nickel-containing substances impair mitochondrial biogenesis, lower the membrane potential, and disrupt the electron transport chain (ETC), causing reduced ATP production (Guo *et al*. 2023; Zhou 2023). Ineffective ETC activity increases the production of ROS, which favours oxidative stress and mitochondrial permeability transition, leading to necrosis and apoptosis. Nanoparticles and nickel chloride reduce the ATP, modify PGC-1α in the expression and mitophagy processes, which connects the damage to mitochondria to energy loss and cell death (Guo *et al.,* 2023; Zhou *et al.,* 2023). As a result, focal degeneration and architectural loss resulting from hepatocyte mitochondrial dysfunction occur in centrilobular areas, particularly in metabolically active areas.

c) *DNA Damage and Genotoxicity:*

Nickel causes indirect and direct damage to the DNA, including strand breaks, oxidative lesions (8-OHdG), chromosomal aberrations, and inhibited DNA repair (Guo *et al.,* 2019; Krawic *et al*. 2023). Ni^{2+} compromises DNA through the production of ROS and the interaction with the chromatin and repairing proteins. Micronuclei formation, DNA cleavage, and disrupted cell-cycle signalling are found in rodent and cell studies (Dumala *et al*. 2017; Guo *et al.,* 2019). Such genotoxic stress causes apoptosis or senescence in hepatocytes, and chronic DNA damage can result in regenerative nodularity, atypia and fibrosis associated with nickel carcinogenicity.

d) *Inflammatory Pathways:*

Nickel exposure triggers pro-inflammatory signalling pathways in various cell types; NF-κB and MAPKs are the canonical pathways, and cytokines, including TNF-α and IL-6 are subsequently upregulated (Guo *et al.,* 2019; Chen *et al*. 2024). The increased production of cytokines in hepatic tissue promotes inflammatory cell (neutrophils, macrophages), oxidative and proteolytic damage. A number of in vivo experiments report hepatic inflammatory infiltration in parallel with biochemical markers of inflammation and increased transcription or protein levels of TNF-α, IL-6 and iNOS after nickel treatment (Guo *et al.,* 2019; Chen *et al*. 2024). The inflammatory environment enhances the death of the hepatocytes, the activation of the stellate cell, and may facilitate collagen deposition under chronic exposure in models of protracted exposure, when it is chronic in nature. Histological responses that also involve portal and lobular inflammation, interface activity and initial fibrotic alterations can also develop from chronic exposure.

e) *Apoptosis and Necrosis:*

Hepatocytes exposed to nickel are found to undergo apoptosis as well as necrosis as a result of exposure parameters. The mitochondrial cytochrome c release, caspase-9/3 activation, BAX/BCL-2 imbalance, and DNA fragmentation are involved in the process of apoptosis (Zou *et al*. 2017; Guo *et al.,* 2023). Accumulation of oxidative stress and mitochondrial failure causes necrosis, accompanied by membrane discontinuity and inflammation. Histologically, apoptosis is represented by nuclear condensation or apoptotic bodies, whereas necrosis is represented by confluent loss of cells and sinusoidal congestion. Apoptotic repair and necrotic injury interplay define tissue healing or fibrosis, as chronic necrosis facilitates fibrosis (Zhou *et al.,* 2023; Dumala *et al*. 2017).

Histopathological changes in the liver of mice treated with nickel sulphate

a) Gross Morphological Observations:

There are experimental reports of consistent levels of gross changes in the liver following moderate- to high exposures to nickel compounds. Animals with diseases often have smaller liver mass or liver index in relation to body weight, a pale or mottled hue and softer or friable texture, which is explained by the presence of hepatocellular degeneration, steatosis and congestion that is seen under the microscope. These gross signs have been reported with soluble nickel salts (e.g., $NiCl_2$/$NiSO_4$) as well as nickel nanoparticle preparations, and they tend to be similar to rises in circulating levels of hepatic enzymes (Cullen and Stalker, 2016; Father, 2017).

b) Microscopic Changes:

Microscopic findings show reversible hepatocyte injuries following nickel exposure, which include vacuolar change, cytoplasmic ballooning and lipid droplet accumulation, which show steatosis (Zhou *et al*., 2023). The use of oil Red O staining and ultrastructural data supports the evidence of increased lipogenesis, whereas $NiCl_2$ and NiNP models display apoptotic and necrotic characteristics, including chromatin fragmentation and apoptotic bodies (Akerlund, 2018; Mohammadinejad *et al.,* 2019; Geng, 2020). Hepatic injury is accompanied by vascular congestion, sinusoidal dilation, and cytokine-induced inflammatory infiltrates (TNF-α, IL-1β, CCL2) (Zhou *et al*., 2023). The chronic exposure causes the deposition of collagen, fibrosis, and accumulation of extracellular matrix (Wei *et al*., 2022).

c) Dose-Dependent and Time-Dependent Effects:

Acute/high dose nickel exposure leads to hepatocellular degeneration characterised by hydropic change, centrilobular necrosis, vascular congestion and acute inflammation, making the liver to become pale and soft. Subchronic or chronic exposure has a progressive lesion characterised by steatosis, chronic inflammation, mitochondrial damage, lobular distortion, and early

fibrosis. According to experimental research, there is a distinct dose-response relationship as increasing doses and exposure time led to the development of necrosis, steatosis, and apoptosis. Therefore, dose and duration determine the response of hepatic lesions reversibility or fibrosis (Zhou *et al*., 2023).

d) Correlation with Biochemical and Molecular Findings:

Nickel histopathological liver hepatocyte damage correlates with biochemical liver injury. In vivo investigations demonstrate high levels of serum ALT and AST, which are indicative of hepatocellular necrosis and membrane disruption, with necrosis, apoptosis and steatosis. Changes of ALP are dynamic and increase with cholestatic involvement. Oxidative stress, as indicated by the increase in MDA and decrease in SOD, CAT and GSH, is similar to the vacuolar degeneration and necrosis. TUNEL-positive hepatocytes are in line with apoptosis and ER stress pathways (PERK, IRE1, ATF6, caspases). Steatosis is due to upregulation of Srebp-1c, Fasn and Scd1. Invariably, the interaction of histological, biochemical, and molecular studies can explain the mechanisms of hepatic injury caused by nickel (Zhou *et al*., 2023).

Experimental Models and Methodological Considerations

a) Animal models (mice strains and age):

Nickel (Ni)-induced hepatotoxicity in most modern research employs the use of standard laboratory mouse strains (the most commonly used mouse strain is C57BL/6 (commonly referenced as C57BL/6J or C57/BL6) due to the well-characterised immune and metabolic history of this mouse strain) (Zhou *et al.,* 2023). Outbred Swiss albino or inbred BALB/c lines are other lines used by other investigators based on their availability and desired study purpose (to maximise generalisation or to investigate immune-biased responses). Ages were reported as in the range of young adults (6-10 weeks) or weight-matched adults, as age and developmental stage have a strong impact on the basal liver metabolism, antioxidant defences and exposure to xenobiotic damage; thus, authors should provide actual age (weeks) and weights to facilitate the reproducibility.

b) Routes and doses of nickel sulphate administration:

Nickel (Ni) exposure in mice is simulated in different routes based on the different pharmacokinetic characteristics. Rapid systemic delivery and precise dosing (1040 mg/kg/day 728 days in C57BL/6 mice) using intraperitoneal (i.p.) injections which can transmit nickel nanoparticles or soluble salts. This avoids intestinal absorption and first-pass metabolism (Zhou *et al*., 2023). Oral gavage mimics dietary or environmental intake of $NiSO_4$, and doses of 3-10 mg/kg are used over 14-28 days, and gastrointestinal absorption and hepatic metabolism are assessed (Massanyi *et al*., 2007; Ajdari and Ziaee-Ghahnavieh, 2014; El-Habit and Abdel Moneim, 2014). Exposures by other routes, such as topical, inhalation, and subcutaneous, are modelled specifically (Camarena *et al*., 2025). Researchers should also rationalise and describe dose selection, the form of salt, and parameters of administration.

c) Histological methods:

The tissues from observed hepatic lesions caused by nickel exposure need to be properly handled, fixed, stained and analysed using a microscope. Liver tissues are fixed in 10% neutral buffered formalin of the desired thickness to guarantee the consistency of the penetration after which they are paraffin-embedded and sectioned at the desired height of 46 µm to be observed under the light microscope (Gurina *et al*., 2023). Hematoxylin and eosin staining are still necessary in measuring architecture, hepatocyte degeneration, necrosis, congestion, and inflammation. Picrosirius Red, Oil Red O, Sudan, and PAS special stains depict fibrosis, lipid accumulation, and glycogen changes. To conduct oxidative or apoptotic research, IHC of cleaved caspase-3, 4-HNE, CHOP, and TUNEL tests are carried out (Krishna *et al*., 2013). The blinded scoring systems or the quantification of the digital images determines the possibility of repetition (Gurina *et al*., 2023).

d) Ethical and experimental controls:

Intense ethical management and suitable choice of controls play a crucial role in the study of nickel toxicity. Experiments must be institutionally ethically approved (IACUC or equivalent), and must be conducted in compliance with national and international welfare standards and also should be conducted in accordance with the 3Rs principles- Replacement, Reduction and Refinement. Reporting should be based upon the ARRIVE 2.0 requirements, whether it is randomised, blinded, justified by its sample size, humane endpoint, and alternative analgesia or anaesthesia usage. The information about housing, enrichment, fasting, and euthanasia is critical as it influences hepatic physiology (Percie du Sert *et al*., 2020). Experiments must be properly controlled by the use of the vehicle, pair-fed, and mechanistic positive controls of the research and both sexes should be taken into account or substantiated. Histologic scoring performed blindly and an independent review of the pathology also helps to guarantee the reliability of the data and its impartial interpretation (Rinwa *et al*., 2024).

e) Limitations and study variability:

Reports of hepatic histopathological changes of $NiSO_4$ display significant heterogeneity due to: strain and sex differences, exposure age, route and form of chemical (ionic salt vs. nanoparticle), dose and exposure duration, inconsistent tissue processing and staining methods, and inconsistent use of either blinded scoring or quantitative image analysis (Lippmann and Chen, 2009; Ryberg *et al.,* You, 2021; Sun *et al.,* 2021). Most of the older reports do not fully comply with the ARRIVE reporting items, making meta-analysis

difficult. More rigorous work should be done to minimise variability with future work focusing on standardised reporting (exact strain, age, sex, housing, dosing, fixation/processing protocols), objective scoring or digital quantification of lesions, and incorporation of both biochemical and molecular endpoints to connect morphology to mechanism (Zhou *et al*., 2023).

Comparative Insights

a) ***Comparison to other nickel compounds:***

Lab mice show overlapping but different hepatic effects of different nickel compounds. Centrilobular vacuolar degeneration, focal necrosis, and inflammatory infiltration are mainly caused by soluble salts such as nickel chloride ($NiCl_2$) and nickel nitrate, along with the occurrence of increased ALT/AST and oxidative stress markers (Kehiosh and Al-fatlawi, 2017; Magrone *et al.,* 2020; Nieboer *et al,* 2024; Khan *et al.,* 2022). Conversely, more severe oxidative and nitrative stress, mitochondrial damage, and apoptosis are caused by the greater surface reactivity and tissue retention of the particulate forms of nickel oxide and nickel nanoparticles (Adiguzel, 2023; Iqbal, 2021). Comparative analysis reveals that Ni nanoparticles are likely to cause higher hepatocyte apoptosis, congestion, and inflammation than soluble salts when administered in equivalent doses. Further, the measures and exposure paths complicate comparisons (Guo *et al*., 2016). The effects are mitochondrial dysfunction, ER stress, and disturbance of lipid metabolism that results in steatosis (Zhou *et al*., 2023).

b) ***Inter-species comparison (rats, mice, fish, rabbits, humans):***

Cross-species analysis demonstrates a shared pattern of nickel-induced hepatic injury with progressive oxidative stress, necrosis, apoptosis, inflammatory, and fibrotic processes in the case of chronic exposure. Centrilobular degeneration and inflammatory infiltration are also found in both mice and rats; however, the severity of the lesions is affected by strain-specific differences in cytochrome P450 isoforms and glutathione levels. Mechanistic studies are frequently done using mouse models, such as C57BL/6, whereas rat prevails in research on chronic exposure, with more severe fibrosis (Zhou *et al*., 2023). Dissolved nickel exposure induces hepatocellular vacuolation, changes in the biliary apparatus, and glycogen depletion in fish, which is explained by absorption through the gills and a specific metabolic pattern (McCarty *et al*., 2011; de Lapuente *et al*., 2015; Coady *et al*., 2016). Degenerative changes in the hepatic changes are also reported in rabbit studies. There are high levels of human data, primarily of an occupational nature, showing an increase in transaminases but a paucity of histologic data. Therefore, animal models in combination with mechanistic biomarkers can augment human risk (Branco *et al*., 2025).

c) ***Protective agents and mitigation Studies:***

Several experimental studies have found agents that counter nickel-induced hepatic injury. They are primarily antioxidants, vitamins, minerals and flavonoids found in plants. N-acetylcysteine (NAC) and selenium prevent hepatocellular necrosis through the restoration of glutathione and the increase of antioxidant enzymes; the prediction of hepatic lesions significantly decreases and is pretreated by selenium (Singh *et al*., 2012). Potent hepatoprotective effects, including the scavenging of free radicals, membrane stabilisation, and the suppression of inflammation and fibrosis, are also demonstrated by silymarin, an extract of milk thistle, in chronic exposure models (Dhande *et al*., 2024). Vitamin E and C, whether used individually or in combination, suppress lipid peroxidation, steatosis and necrosis, whereas the activity of selenium in selenoproteins strengthens antioxidant defences (Stehbens, 2003; Brzoska *et al*., 2016). Hesperidin, naringin, curcumin, and Opuntia ficus-indica extracts are plant flavonoids that have a significant beneficial effect on hepatic histology and antioxidant status, which is explained by their antioxidative and anti-inflammatory effects (Chen, 2024).

Implications for human health and environmental safety

Nickel sulphate, which is popular in electroplating, battery manufacturing and metal finishing, is a serious health hazard to both occupational and environmental health. Breathing and skin exposures are the main factors in industrial exposure, and soluble nickel salts can cause systemic poisoning. Special regulatory agencies declare several nickel compounds as hazardous or potentially genotoxic, and therefor require exposure monitoring and control (Richardson-Boedler, 2007; Birkett *et al*., 2019; Fuller, 2019). Despite a deficiency of direct human histopathology, there exists evidence of liver damage due to chronic elevated exposure of animals, biomarkers, and biomonitoring. There is centrilobular degeneration, steatosis, inflammation, apoptosis and fibrosis, increased transaminases and oxidative stress, shown using rodent models. Liver is thus discovered to be a target organ of systemic nickel toxicity, and cross-species oxidative and inflammatory processes support human applicability (McElroy, 2021).

The measures to prevent occupational health effects of exposure to nickel should include complete monitoring, which includes air and biological control, engineering control, personal protective equipment, and medical surveillance, including liver-function tests in cases of high exposure. Nickel is to remain on the list of possible causes of liver abnormalities before being diagnosed as the main cause, this requires careful evaluation of exposures to other risk factors such as alcohol consumption, and hepatitis virus (Zhao *et al*., 2009; Genchi *et al*., 2020; Begum *et al*., 2022). Industrial effluents, mining drainage and wastewater irrigation

increase the amount of nickel in soil and water, and the accumulation of this substance in the plant and aquatic organisms. This contamination affects the health of microorganisms and plants negatively and introduces the risk of chronic dietary exposure to nickel. These risks can be alleviated by integrated remediation approaches, soil testing, phytoremediation, wastewater controls, and regulatory limits of residues, but hotspots of residues are still of a major concern in the area (Rizwan *et al*., 2024).

Overall interpretation and recommendations

The awareness towards nickel exposure is necessary because although there is little or no human histological information, yet reliable evidence from animal and mechanistic data has established the fact that long-term and high-level exposure to bioavailable nickel compounds, especially nickel sulphate, can lead to hepatic injury (Janz *et al*., 2010; Lee *et al*., 2011). The preventive strategies must focus on control of exposures based on engineering, personal protective gear and workplace hygiene. It is also essential that medical surveillance, such as regular liver function tests of persons who have been exposed to a large dose, is conducted. To protect communities, environmental nickel emissions and food-chain contamination in high-risk areas should be monitored by the agencies of public health (Genchi *et al*., 2020; Begum *et al*., 2022; Nieboer *et al*., 2024). Research priorities integrating nickel biomarkers and liver outcomes, modelling environmental transfer into the food sources and testing of mitigation strategies as well as mechanistic and translational studies will prove vital to enhancing human risk assessment and evidence-based regulatory decisions (Zhou *et al*., 2025).

Future Research Directions

The following are guidelines to inform further research on the histological and mechanistic assessment of nickel sulphate ($NiSO_4$)-induced hepatic injury in mice. In every subsection, specific, empirically testable suggestions are promoted and connected with the current experimental or review evidence.

a) ***Early detection molecular biomarkers:***

Past histological studies show that lesions indicate late damage; hence, in future research, it is necessary to determine early biomarkers of hepatocellular stress before it is too late. Suggestive candidates are serum ALT/AST, oxidative stress (MDA, GSH/ GSSG ratio) and iron/ferroptotic proteins (ferritin, transferrin receptor, GPX4) and liver-specific microRNAs, including miR-122. The kinetics of the lesion can be correlated with biomarker kinetics by longitudinal studies of graded $NiSO_4$ exposure with serial blood and liver sampling. Ferroptosis and iron dysregulation have also been shown to have a connection with nickel toxicity, and thus GPX4 and lipid peroxidation adducts are some of the initial indicators (Wei *et al*., 2022; Yang *et al*., 2023). It is suggested that to come up with clinically translatable thresholds, controlled dose-response studies should be conducted with a standardised biomarker-histology correlate.

b) ***Long-term toxicity and recovery experiments:***

Mechanistic signatures and biomarkers that are missed by single-analyte measurements can be identified in an unbiased manner using omics techniques. Transcriptomic analyses of rodents indicate that nickel stress has effects disrupting lipid metabolism, oxidative balance, and inflammation, and proteomics demonstrates post-translational processes that drive steatosis, ER stress, and cell death (Zhang *et al*., 2024; Quintás *et al*., 2023). Combining bulk sequencing of RNA, LC-MS/MS/proteomics, and specific lipidomics of the same animals gives a multidimensional perspective of hepatic transcriptional and metabolic disturbances. Cellular or spatial RNA-seq makes it possible to map cell-type-specific responses in hepatocytes, Kupffer and stellate cells. Targeting Therapy NRF2, NF-KB, and UPR pathways analyses can be used to help guide therapy. Combining transcriptomic, proteomic and histological data complements the mechanistic knowledge of hepatotoxicity caused by nickel (Thiel *et al*., 2024; Zhang *et al*., 2024).

c) ***Formulation of therapeutic interventions:***

Mechanistic evidence has been provided about several intervention methods to nickel-induced hepatotoxicity: antioxidants and Nrf2 activators to stabilise redox homeostasis, iron chelators to prevent ferroptosis, and ferroptosis inhibitors to prevent lipid peroxidation. Natural extracts (hesperidin and Opuntia) lower Ni-induced hepatic damage, which contributes to the translation of the research (Chen *et al*., 2024; Razzak *et al*., 2025). Since the role of ferroptosis is increasingly being demonstrated (Yang *et al*., 2023; Scarpellini *et al*., 2023), a designed preclinical platform is suggested, consisting of mechanism-directed candidate screening (Nrf2 activators, GPX4 stabilisers, iron chelators), and preclinical testing of dose and mechanism using in vitro hepatocyte-Kupffer co-culture. Effectiveness and safety using $NiSO_4$ as exposure models should be confirmed via randomised in vivo mouse trials with endpoints of histology, serum, and omics (Chen *et al*., 2024; Scarpellini *et al*., 2023).

CONCLUSION

Exposure to nickel sulphate causes severe hepatic changes in mice, such as vacuolar degeneration, necrosis, steatosis, and inflammation and increased serum transaminases and oxidative stress biomarkers. The lesions indicate the disturbance of the redox balance, mitochondrial activity, and lipid metabolism, and ferroptosis and apoptosis are the most critical mechanisms of harm. The liver is one of the main target organs in nickel toxicity, as supported by evidence from animal studies, which supports its application in the assessment of the human health risk. Antioxidants, flavonoids and Nrf2 activators have promising hepatoprotective effects as preventive agents. It is

necessary to continue the studies which combine molecular biomarkers and omics technologies to develop effective mitigation measures and enhance the environmental and occupational safety in the case of nickel-induced hepatotoxicity.

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