



Review

Trace Metals in Modern Technology and Human Health: A Microbiota Perspective on Cobalt, Lithium, and Nickel

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Abstract: The human microbiota plays a crucial role in maintaining host health through its considerable influence on immune function, nutrient metabolism, and overall homeostasis. While trace metals such as cobalt, lithium, and nickel are essential micronutrients at low concentrations, their increasing environmental accumulation presents emerging risks for microbial dysbiosis and related systemic health effects. This review examines the dual role of these trace metals as both beneficial nutrients and potential disruptors of microbial balance. Specifically, cobalt supports microbial diversity through its role in vitamin B12 synthesis, but excessive exposure can lead to dysbiosis. Lithium, beneficial at therapeutic concentrations by enhancing beneficial microbial populations, adversely affects gut barrier integrity by promoting inflammation and epithelial damage at higher concentrations. Similarly, nickel participates in essential enzymatic activities but promotes dysbiosis and inflammatory responses at elevated exposures. Furthermore, the growing environmental contamination by these metals poses risks to food systems and various microbial communities in the environment. Highlighting these environmental concerns, this review calls for sustainable management and multidisciplinary research to mitigate health risks to mitigate health risks associated with trace metal exposure.

Keywords: gut microbiota; cobalt; lithium; nickel; dysbiosis; environmental



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1. Introduction

With the rapid advancement of modern technologies, particularly battery development for electric vehicles, renewable energy storage, and portable electronics, the demand for metals such as cobalt, nickel, and lithium has surged. Nevertheless, their extraction, refinement, and recycling processes pose significant risks of environmental contamination [1]. These metals may infiltrate agricultural systems via contaminated irrigation water, soil, or livestock feed, subsequently accumulating within the food chain. Although trace amounts are essential for biological processes, elevated concentrations can disrupt gut microbial balance, adversely impacting both animal and human health [2,3].

Historically, cobalt, lithium, and nickel had limited applications, and their environmental and biological impacts were relatively minor. However, in recent years, their extraction, processing, and disposal have contributed to growing environmental contamination, raising concerns about their effects on human health. Though essential in trace amounts, these metals can disrupt microbial ecosystems when exposure exceeds physiological thresholds, whether via diet, pollution, or industry (Figure 1).

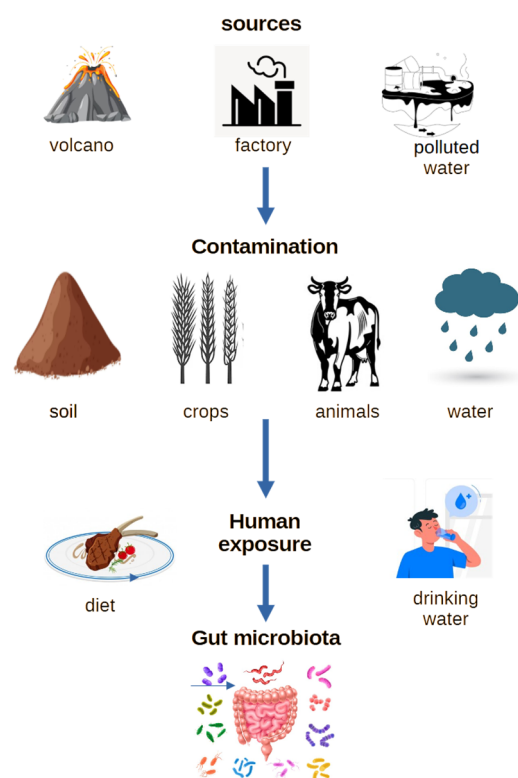


Figure 1. Pathways of human exposure to cobalt, lithium, and nickel and their impact on the gut microbiota. Natural and industrial sources, including volcanic activity, mining, manufacturing, and animal production, release cobalt, lithium, and nickel into the environment. These elements contaminate soil, crops, animals, and water supplies. Human exposure occurs through dietary intake and drinking water. Once ingested, these metals can influence the gut microbiota, potentially altering microbial composition and affecting host health.

The human microbiota, comprising trillions of bacteria, fungi, and viruses, inhabits diverse niches such as the oral cavity, skin, and gastrointestinal tract [4]. These microbial communities are crucial for host health, influencing immune regulation, nutrient metabolism, and overall homeostasis. Among these microbial ecosystems, the gut microbiota is particularly important due to its complex interactions with both the host and the external environment [5]. It plays pivotal roles in digestion, vitamin synthesis, immune modulation, and the gut–brain axis [6].

This review explores the dual roles of cobalt, lithium, and nickel as both essential nutrients and potential disruptors of microbial balance, with a particular focus on their interactions with gut microbiota and implications for systemic health. This document is a narrative review, which does not follow the formal methodology of a systematic review (e.g., PRISMA). We conducted a non-systematic, comprehensive search of the scientific literature using the following databases: PubMed, Web of Science, Scopus, and Google Scholar [7]. The search included publications in English, published between 2000 and 2024, using combinations of keywords such as “cobalt”, “lithium”, “nickel”, “gut microbiota”, “intestinal microbiome”, and “trace metals”. Articles were selected based on their scientific relevance, originality, and contribution to the understanding of the interactions between trace metals and the gut microbiota. Additional references were identified through snowballing [8]. By examining how these metals influence microbial dynamics, this review underscores the need for further research into their broader health effects, emphasizes the importance of developing regulatory measures to mitigate associated risks, and identifies opportunities for therapeutic interventions aimed at addressing environmental and health concerns.

2. The Gut Microbiota: A Dynamic Ecosystem Shaping Health and Disease

The gut microbiota plays a crucial role in human health by influencing digestion, immune regulation, and metabolic processes. This complex ecosystem comprises bacteria, archaea, fungi, and viruses that interact with the host through intricate signaling networks [9]. These interactions are essential for immune system maturation, nutrient metabolism, and overall homeostasis. Dysregulation of the microbiota, known as dysbiosis, has been associated with diseases such as inflammatory bowel disease [10], obesity [11], and neurological disorders [6].

Environmental and lifestyle factors, including diet, medication, and exposure to trace metals such as cobalt, lithium, and nickel, shape the composition and functionality of the microbiota. Trace metals, traditionally viewed primarily as nutrients, are increasingly recognized as modulators of microbial dynamics that influence immune signaling and systemic homeostasis.

A major function of the gut microbiota is the fermentation of complex carbohydrates, producing short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate. These SCFAs serve as energy sources for colonocytes and play key roles in regulating immune responses and maintaining gut barrier integrity [12]. The microbiota also contributes to host metabolism by facilitating nutrient absorption and generating bioactive metabolites that influence systemic inflammation and metabolic pathways [13].

The relationship between the host and its microbiota is dynamic and bidirectional. While microbiota impacts health, factors such as diet, genetics, and environmental exposure shape its composition. For example, a high-fat diet promotes pro-inflammatory bacteria, whereas a fiber-rich diet fosters SCFA-producing bacteria that enhance immune tolerance and gut health [14]. Emerging evidence suggests that these trace metals can similarly influence microbial composition, highlighting their role as both nutrients and potential disruptors.

The gut microbiota is dominated by the phyla Firmicutes, Bacteroidetes, and Actinobacteria, performing essential functions such as carbohydrate fermentation, SCFA production [15], and immune regulation [16]. Dysbiosis, characterized by microbial imbalance, has been implicated in a range of health disorders, including obesity, metabolic syndrome, and neurodegenerative diseases [17]. Understanding the mechanisms by which microbiota and host interact, particularly under the influence of environmental factors like trace metals, is essential.

3. Cobalt, Lithium, and Nickel: Emerging Concerns

The rising demand for cobalt, lithium, and nickel in high-tech industries, along with their potential for environmental contamination, underscores an urgent need for stricter regulatory measures and careful monitoring of their entry into food systems [18]. Due to the potential adverse effects of these metals on human and animal health, understanding their pathways into the food chain and implementing strategies to minimize contamination is crucial [19].

Cobalt is an essential trace element involved in the synthesis of vitamin B12, playing critical roles in red blood cell formation, neurological function, and energy metabolism. A deficiency in cobalt can lead to vitamin B12 deficiency, which negatively impacts gut microbiota diversity and function [20]. Studies in ruminants, such as cattle and lambs, show that cobalt supplementation can restore microbial balance, enhance immune responses, and reduce parasitic burdens associated with dysbiosis [19]. However, the origin and chemical form of cobalt significantly influence its biological effects [21]. While adequate levels are beneficial, elevated cobalt concentrations can disrupt microbial homeostasis.

Animal studies have shown that excessive cobalt intake alters microbial diversity and may induce oxidative stress and pro-inflammatory responses in the gut [22] (Figure 2).

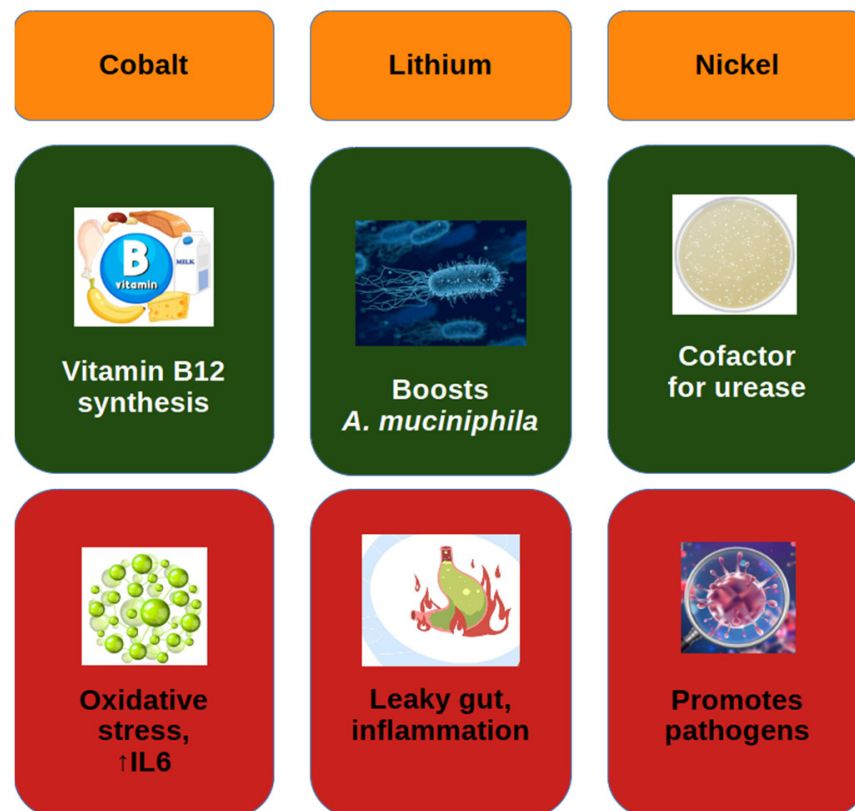


Figure 2. Dual effects of cobalt, lithium, and nickel on gut microbial function and host health. Each of these trace metals exerts both essential and harmful effects depending on concentration and context. Cobalt supports vitamin B12 synthesis but may induce oxidative stress and elevate pro-inflammatory cytokines (e.g., IL-6) at high levels. Lithium can enhance populations of beneficial bacteria, such as *Akkermansia muciniphila*, yet excessive intake is associated with increased gut permeability and inflammation. Nickel serves as a cofactor for microbial enzymes like urease but disrupts microbial balance by promoting pathogenic taxa such as *Escherichia coli*.

4. Cobalt, Lithium, and Nickel: Modulators of Microbial Diversity and Health

4.1. Cobalt's Influence on Microbiota

Cobalt is an essential trace element crucial for vitamin B12 synthesis, playing key roles in red blood cell formation, neurological function, and energy metabolism. Cobalt deficiency often leads to vitamin B12 deficiency, impairing gut microbiota diversity and function. Studies in ruminants, such as cattle and lambs, demonstrate that cobalt supplementation can restore microbial balance, enhance immune responses, and reduce parasitic burdens associated with dysbiosis [23]. The origin and chemical form of cobalt significantly influence its biological effects [24].

Elevated cobalt levels disrupt microbial balance, promoting dysbiosis. Animal studies reveal that excessive cobalt alters microbial diversity and may lead to oxidative stress and pro-inflammatory responses in the gut [25]. High cobalt levels perturb gut microbial balance and promote inflammatory pathways. These dual effects highlight cobalt's complex role in microbiota health, necessitating careful regulation of its environmental and dietary exposure (Figure 3).

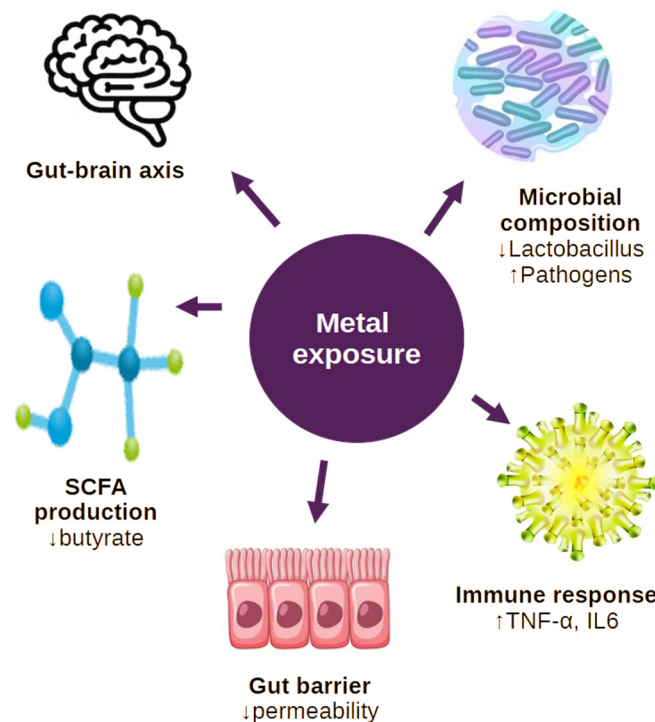


Figure 3. Mechanisms by which trace metal exposure alters gut microbial health. Exposure to trace metals can influence gut microbiota and host physiology through multiple interconnected pathways. Metal exposure alters microbial composition by reducing beneficial taxa such as *Lactobacillus* and promoting pathogenic species. It disrupts the intestinal barrier by increasing permeability, impairs the production of key short-chain fatty acids (SCFAs) like acetate and butyrate, and modulates immune responses by elevating pro-inflammatory cytokines such as TNF- α and IL-6. In the figure, the upward arrow ($\uparrow$) indicates an increase in the parameter (e.g., $\uparrow$ Pathogens, $\uparrow$ TNF- α , IL6), while the downward arrow ($\downarrow$) indicates a decrease (e.g., $\downarrow$ Lactobacillus, $\downarrow$ butyrate, $\downarrow$ permeability).

As previously mentioned, cobalt plays a dual role in gut microbiota dynamics, serving as both an essential nutrient and a potential disruptor. A key function of cobalt is its role in the synthesis of vitamin B12 (cobalamin) by specific gut bacteria such as *Lactobacillus reuteri* and *Bacteroides* [26]. Vitamin B12-dependent enzymes, such as methionine synthase, are crucial for bacterial metabolism and DNA synthesis, making cobalt essential for microbial diversity and metabolic activity. However, cobalt deficiency reduces microbial diversity and impairs microbial metabolic functions, as observed in studies on ruminants, where supplementation restored microbial balance and metabolic activity [27,28].

Excessive cobalt exposure, however, can disrupt gut microbial homeostasis through the generation of reactive oxygen species (ROS), leading to oxidative stress and cellular damage [29]. This oxidative stress damages microbial membranes and proteins, impairing microbial diversity. Furthermore, cobalt nanoparticles have antimicrobial effects [30]. Cobalt also competes with other essential metals, such as iron and zinc, for transporter systems and enzyme cofactors, further disrupting microbial metabolism. Additionally, cobalt exposure alters gut epithelial signaling, influencing cytokine production (e.g., IL-6), which can modulate immune responses and indirectly affect microbial populations both in mouse and human [31,32].

4.2. Lithium's Influence on Microbiota

Lithium, widely utilized both as a mood stabilizer and in battery technologies, exerts diverse effects on the gut microbiota, depending on its concentration [33]. Environmental

lithium contamination, primarily from battery waste, poses additional risks to microbial ecosystems, with potential implications for agriculture and public health (Figure 3).

High doses of lithium activate gut macrophages, triggering the release of pro-inflammatory cytokines such as TNF- α and IL-1 β , thereby impairing intestinal homeostasis and exacerbating inflammation [28], altering microbial composition, and impairing intestinal integrity [34]. This compromised gut integrity alters microbial metabolic pathways, notably reducing the production of short-chain fatty acids (SCFAs), which play essential roles in colonocyte energy metabolism and immune regulation [35]. Lithium's interactions with the gut-brain axis are another important mechanism, as changes in microbial composition influence the production of neuroactive metabolites, such as serotonin precursors, linking gut health to psychiatric outcomes [34].

These findings emphasize the need for sustainable lithium management and further research into its microbiota-modulating effects [36].

4.3. Nickel's Influence on Microbiota

Nickel plays a dual role in gut microbiota, functioning as both a nutrient and a potential disruptor [37]. Nickel serves as a cofactor for microbial enzymes, such as urease, which is essential for certain gut bacteria like *Helicobacter pylori* and plays a key role in microbial nitrogen and carbon metabolism [38]. However, its benefits are largely limited to microbial processes rather than direct host nutritional needs [39]. Beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* [40] are inhibited by high nickel levels, while pathogenic species like *Escherichia coli* thrive [41], contributing to inflammation and metabolic dysfunctions [42]. These imbalances contribute to dysbiosis, inflammation, and conditions like systemic nickel allergy syndrome (SNAS) [43].

Nickel contamination stems from industrial emissions, electroplating waste, polluted water sources, and dietary intake via contaminated crops and seafood. Sustainable practices in nickel extraction and recycling are vital for minimizing its health and environmental risks [18] (Figure 3).

5. Future Directions

5.1. Understand Involved Mechanisms

Interactions between heavy metals and the gut microbiota have been studied over the past decades, with a few reviews available on the topic [44,45]. However, most of these provide broad overviews without focusing on specific metals or their dual effects. In contrast, the present review offers a focused analysis of cobalt, lithium, and nickel, exploring both their toxicological and potential therapeutic impacts on the gut and oral microbiota.

Future research should prioritize detailed mechanistic studies to uncover the specific molecular and cellular pathways through which cobalt, lithium, and nickel influence gut microbiota. This includes understanding the role of oxidative stress in microbial membrane damage, the modulation of SCFA production, and the immune signaling pathways triggered by these metals, such as cytokine production and their downstream effects. Establishing dose-response relationships is crucial for identifying the exposure thresholds at which cobalt, lithium, and nickel transition from essential nutrients to microbial and systemic health disruptors. Such research would enable the development of safe exposure guidelines and inform therapeutic applications.

Given lithium's role in psychiatric treatments [46], future research should explore how its microbiota-modulating effects influence neuroinflammation, neurotransmitter synthesis, and psychiatric outcomes.

Long-term studies on chronic low-dose exposure to cobalt, lithium, and nickel are essential to assess their cumulative impacts on gut microbiota and systemic health. These

studies are particularly relevant given the widespread environmental contamination resulting from industrial activities. Moreover, future work should explore how host-specific factors, such as genetics, diet, and pre-existing health conditions, influence the effects of these metals on gut microbiota. This would pave the way for personalized exposure recommendations tailored to individual health profiles.

5.2. Gut–Brain Axis

Another promising avenue of research lies in the exploration of the gut–brain axis and neuroinflammation, especially in the context of lithium. Lithium’s potential to modulate neuroactive metabolite production through gut microbiota and its impact on neuroinflammation should be investigated to better understand its role in psychiatric treatments [35]. Similarly, cobalt’s role in vitamin B12 synthesis and its therapeutic potential for addressing microbial deficiencies in specific populations warrant further exploration. Additionally, nickel-based interventions to counteract dysbiosis in nickel-sensitive individuals, perhaps through probiotics or dietary adjustments, should be examined.

5.3. Environmental Applications

Understanding the impact of cobalt, lithium, and nickel on microbial ecosystems is crucial for developing innovative environmental applications. For instance, bioremediation strategies [47,48] can leverage microbes capable of tolerating or metabolizing these metals to clean up contaminated environments. Nickel-resistant bacteria, for example, could be employed to restore polluted agricultural soils or water systems [49], mitigating the adverse effects of metal contamination.

Insights into the interactions between these metals and soil or plant-associated microbiota could also inform sustainable agricultural practices. Such research could enhance crop health and productivity while reducing environmental risks associated with metal contamination. These efforts must prioritize both environmental sustainability and the preservation of microbial diversity, which is essential for maintaining ecosystem resilience [50].

Environmental studies should focus on assessing the pathways through which cobalt, lithium, and nickel contaminate ecosystems. This includes evaluating their bioavailability in soil and water systems and understanding their impact on microbial communities in agricultural and aquatic environments. Additionally, advancements in bioremediation techniques, such as employing metal-tolerant microbes, and the development of efficient recycling technologies to recover these metals from electronic waste, have the potential to significantly reduce their environmental footprint. These approaches will be vital for addressing the ecological challenges posed by the increasing use of these trace metals.

5.4. Beyond Scientific Investigation

Ethical and socioeconomic implications of trace metal mining require attention, particularly in regions heavily impacted by cobalt and lithium extraction. Research should aim to strike a balance between industrial demands and the need for environmental preservation and public health protection (Figure 4). The development of biomarkers or microbiota-based diagnostics to monitor exposure levels and their effects on microbial and systemic health could provide valuable tools for both research and clinical practice [51].

Finally, collaboration with policymakers is crucial to translating scientific findings into actionable guidelines for regulating environmental exposure to these metals and promoting sustainable industrial practices. By integrating mechanistic research, therapeutic innovation, and environmental sustainability, future studies can address the dual challenges of harnessing the benefits of cobalt, lithium, and nickel while mitigating their risks to human health and ecosystems.

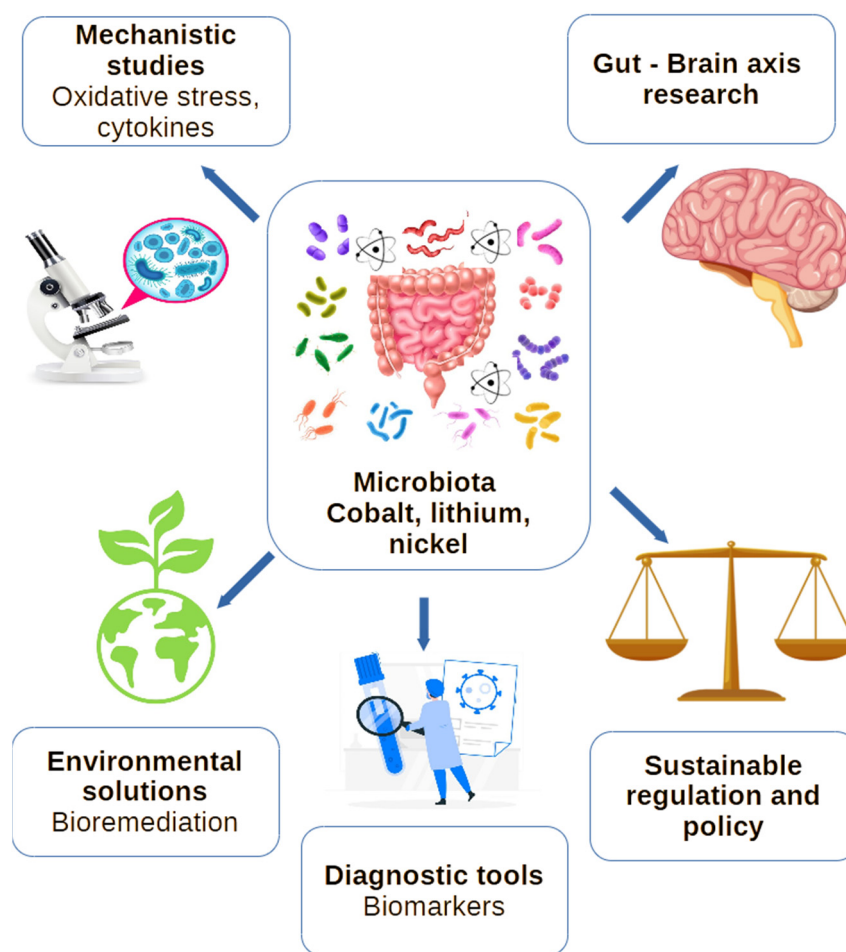


Figure 4. Future perspectives on trace metals and microbiota. This radial diagram illustrates the main future research and application pathways related to the impact of cobalt, lithium, and nickel on the gut microbiota and human health. Each node represents a key area of development: Mechanistic studies focused on deciphering molecular pathways, such as oxidative stress, cytokine signaling, and metal-induced shifts in microbial metabolism. Gut–brain axis research investigating how trace metal-induced microbiota changes influence neuroinflammation, neurotransmitter synthesis, and psychiatric outcomes. Environmental solutions, including microbial bioremediation strategies to remove or neutralize metal contaminants in soils, water, and agricultural systems. Diagnostic tools: development of biomarkers and microbiota-based diagnostics to monitor exposure and predict individual susceptibility to metal-induced dysbiosis. Sustainable regulation and policy: strategies for balancing industrial metal demand with public health protection and environmental sustainability through evidence-based policy-making.

6. Conclusions

Although cobalt, lithium, and nickel are not classified as highly toxic, their increasing industrial use raises significant concerns regarding environmental contamination and long-term health risks.

The rising demand for these three elements in modern technologies necessitates urgent attention to their environmental and health implications, requiring advanced research into metal–microbiota interactions, including dose–response dynamics and long-term impacts, alongside the exploration of innovative therapeutic applications, such as microbiota-targeted interventions using trace metals. Equally crucial is prioritizing sustainable practices in metal extraction, recycling, and waste management to reduce environmental contamination. Addressing these challenges demands a multidisciplinary approach integrating microbiome science, environmental sustainability, and precision medicine,

enabling us to balance the therapeutic potential of these metals with their environmental risks and foster improved human health and ecological stability in an era of rapid technological advancement.

A deeper understanding of microbiota–metal interactions will be crucial in mitigating potential health risks and developing microbiota-targeted interventions for individuals exposed to high levels of these metals.

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Abbreviations

The following abbreviations are used in this manuscript:

SCFA	Short-Chain Fatty Acids
ROS	Reactive Oxygen Species
IL6	Interleukin 6
SNAS	Systemic Nickel Allergy Syndrome

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