Comprehensive Literature Review: Chromium Effects in Infants and Children

This comprehensive literature review examines the critical issue of chromium contamination in infant and child nutrition, exploring the complex interplay between chemical speciation, toxicity mechanisms, exposure pathways, and regulatory frameworks that govern the safety of our youngest and most vulnerable populations.

Introduction: Chromium Speciation and Its Dual Nature in Early Life

Chromium exists as a ubiquitous environmental contaminant with a fundamentally important characteristic: its toxicity is entirely dependent on its oxidation state [1]. The two stable oxidation states of chromium encountered in natural environments and in food systems are trivalent chromium, Cr(III), and hexavalent chromium, Cr(VI), each presenting markedly different biological and toxicological profiles [2]. While Cr(III) has been postulated as an essential trace element necessary for glucose and lipid metabolism, Cr(VI) represents a documented human carcinogen with extensive occupational and environmental health concerns [3]. This speciation-dependent hazard profile creates a unique regulatory challenge, particularly when considering early-life populations, where the compressed margins of safety and high relative intake per kilogram of body weight elevate chromium contamination from a simple nutritional issue to an important indicator of process and contact-material integrity [1].

The European Food Safety Authority (EFSA) CONTAM Panel has established a tolerable daily intake (TDI) for Cr(III) of 300 µg/kg body weight per day, based on a no observed adverse effect level (NOAEL) derived from rat studies with an applied uncertainty factor of 1000 [1]. This assessment acknowledges the substantial uncertainty in available data concerning developmental and reproductive toxicity in early life populations. Notably, the Panel applied an additional tenfold uncertainty factor beyond the standard human extrapolation uncertainties to account for these developmental sensitivities [1]. In contrast, regulatory guidance for Cr(VI) remains more conservative, with drinking water standards typically set at 0.1 mg/L by the World Health Organization, reflecting the recognized carcinogenic potential of the hexavalent form [4].

The speciation-dependent nature of chromium toxicity is not merely academic; it has profound practical implications for food safety assessment, particularly in products consumed by infants and young children. In infant formula and complementary foods, both forms of chromium can be present depending on the water source, processing conditions, and materials used in food preparation and storage [5]. The identification of chromium contamination should thus trigger not only quantitative risk assessment but also speciation analysis to properly characterize the actual hazard posed to vulnerable populations.

Dietary Sources and Food Contamination in Early Life

Infants and young children experience markedly different exposure scenarios to chromium compared to the general adult population, primarily due to their dietary composition and consumption patterns. The reliance on liquid foods, such as infant formula and milk-based products, combined with high consumption of acidic foods and beverages, creates specific vulnerability pathways [5]. Median dietary chromium intakes reported by EFSA differ substantially across age groups, with toddlers (1 to <3 years) consuming 28.6-44.0 µg/day, other children (3 to <10 years) consuming 55.4-76.2 µg/day, and adolescents consuming progressively higher absolute amounts [1]. Critically, when normalized per kilogram of body weight, toddlers experience substantially higher relative intakes, creating a margin of safety that is approximately 80-300 times lower than the TDI in the best-case scenarios [1].

Infant Formula

Average concentrations significantly exceeded FAO/WHO standards across all seasons in Iranian market samples [5]

Baby Food Products

All calculated hazard indices (HI) values exceeded the safety threshold of 1 [5]

Cereal-Based Foods

Cumulative hazard indices exceeded unity when considering all detected elements [6]

A comprehensive risk assessment study examining infant formula and complementary foods from the Iranian market identified that the average concentrations of chromium in infant formula and baby food samples significantly exceeded FAO/WHO standards across all seasons [5]. All calculated hazard indices (HI) values exceeded the safety threshold of 1, indicating that infants and toddlers faced potential carcinogenic and non-carcinogenic risks even from commercially available products [5]. Similarly, analysis of cereal-based complementary foods in Brazil found that while total chromium levels were below detection limits in most products, the cumulative hazard indices when considering all detected elements exceeded unity, highlighting the importance of multi-element consideration in early-life risk assessment [6].

Drinking Water as a Chromium Source

Drinking water represents a critical but often underappreciated source of chromium exposure, particularly for infants whose fluid intake is proportionally higher than adults and who may consume formula reconstituted with tap water. The EFSA assessment noted that chromium in drinking water occurs predominantly as Cr(VI), while in food chromium exists mainly as Cr(III) [1]. Seasonal variations in chromium contamination have been documented in groundwater sources, with significant differences between summer and winter months in some regions [7]. For children, the hazard quotient (HQ) values associated with chromium from drinking water remain below established safety thresholds in most well-regulated water systems, yet in mining-affected areas or regions with naturally high chromium concentrations, non-carcinogenic risks specifically related to chromium exposure have been identified as concerning [8].

Well-Regulated Systems

Hazard quotient (HQ) values remain below safety thresholds in most well-regulated water systems

Seasonal monitoring shows variations between summer and winter months [7]

High-Risk Areas

Mining-affected areas show concerning non-carcinogenic risks [8]

Regions with naturally high chromium concentrations require enhanced monitoring

Process and Contact-Material Integrity

A particularly important but often overlooked aspect of chromium in infant and child nutrition is its role as an indicator of process and contact-material integrity. The presence of chromium contamination in foods intended for infants—beyond naturally occurring levels—frequently signals potential contamination from equipment corrosion, stainless steel contact surfaces, or insufficiently treated water used in food processing and reconstitution [5]. The pH-dependent nature of chromium solubility means that the acidic environment of many infant foods (such as fruit-based purees, juice blends, and fermented products) enhances chromium leaching from contact materials [5]. Thus, elevated chromium levels in these products may reflect broader concerns about manufacturing hygiene, water treatment adequacy, or equipment maintenance rather than representing a primary nutritional exposure route. This indicator function of chromium becomes particularly valuable in resource-limited settings where comprehensive food safety monitoring infrastructure is limited.

Equipment Corrosion

Stainless steel surfaces in processing equipment

Water Treatment

Insufficiently treated water used in processing

Acidic Foods

Enhanced leaching in fruit purees and fermented products

EFSA-Derived TDI Values and Application in Pediatric Populations

The EFSA CONTAM Panel's derivation of a TDI of 300 µg Cr(III)/kg body weight per day represents the foundation for current regulatory assessment [1]. The derivation process merits careful examination, as it directly impacts risk characterization in infants. The NOAEL of 300 µg/kg body weight per day was derived from repeated-dose animal toxicity studies, where general toxicity endpoints consistently showed no adverse effects even at the highest doses tested [1]. From this NOAEL, the Panel applied an uncertainty factor of 1000: a standard 100-fold factor for extrapolation from rodents to humans and for human variability, coupled with an additional 10-fold factor to account for uncertainty in developmental and reproductive toxicity data [1]. This multiplicative approach represents a cautious risk assessment strategy, reflecting acknowledgment of data gaps in early-life toxicity.

300	1000	9x
TDI (µg/kg/day)	Uncertainty Factor	Safety Margin
Tolerable daily intake for Cr(III) established by EFSA	Applied to account for developmental sensitivities	Even at 95th percentile intake in toddlers

When comparing actual dietary intakes to the TDI, the estimated margins of safety in the Norwegian assessment—which aligns with EFSA intake data—revealed that even at the 95th percentile intake in toddlers (the most highly exposed group), chromium exposure remains approximately nine times lower than the TDI [1]. However, this finding should not be interpreted as indicating absolute safety; rather, it demonstrates that under current exposure scenarios in well-regulated food supply systems, the safety margin is maintained. The same assessment noted that if maximum limits for chromium in food supplements were set at 300 µg per daily dose, and combined with median dietary intake plus the 95th percentile supplemental intake, the total exposure would remain 16-48 times lower than the TDI across all age groups [1].

Compressed Margins of Safety and Age-Related Vulnerability

The concept of "compressed margins of safety" in infants and young children reflects several biological realities specific to early-life development. First, per-kilogram body weight intake of chromium is substantially higher in toddlers than in older children or adults due to their relatively high food consumption-to-body-weight ratio [1]. Second, the developing organs of infants and very young children may exhibit enhanced sensitivity to toxic effects, as reflected in the additional 10-fold uncertainty factor applied by EFSA [1]. Third, the immature detoxification capacity of infant hepatic systems may reduce the efficiency of chromium metabolism and excretion.

01

Higher Relative Intake

Per-kilogram body weight intake substantially higher in toddlers due to food consumption-to-body-weight ratio

02

Enhanced Sensitivity

Developing organs exhibit enhanced sensitivity to toxic effects during early life

03

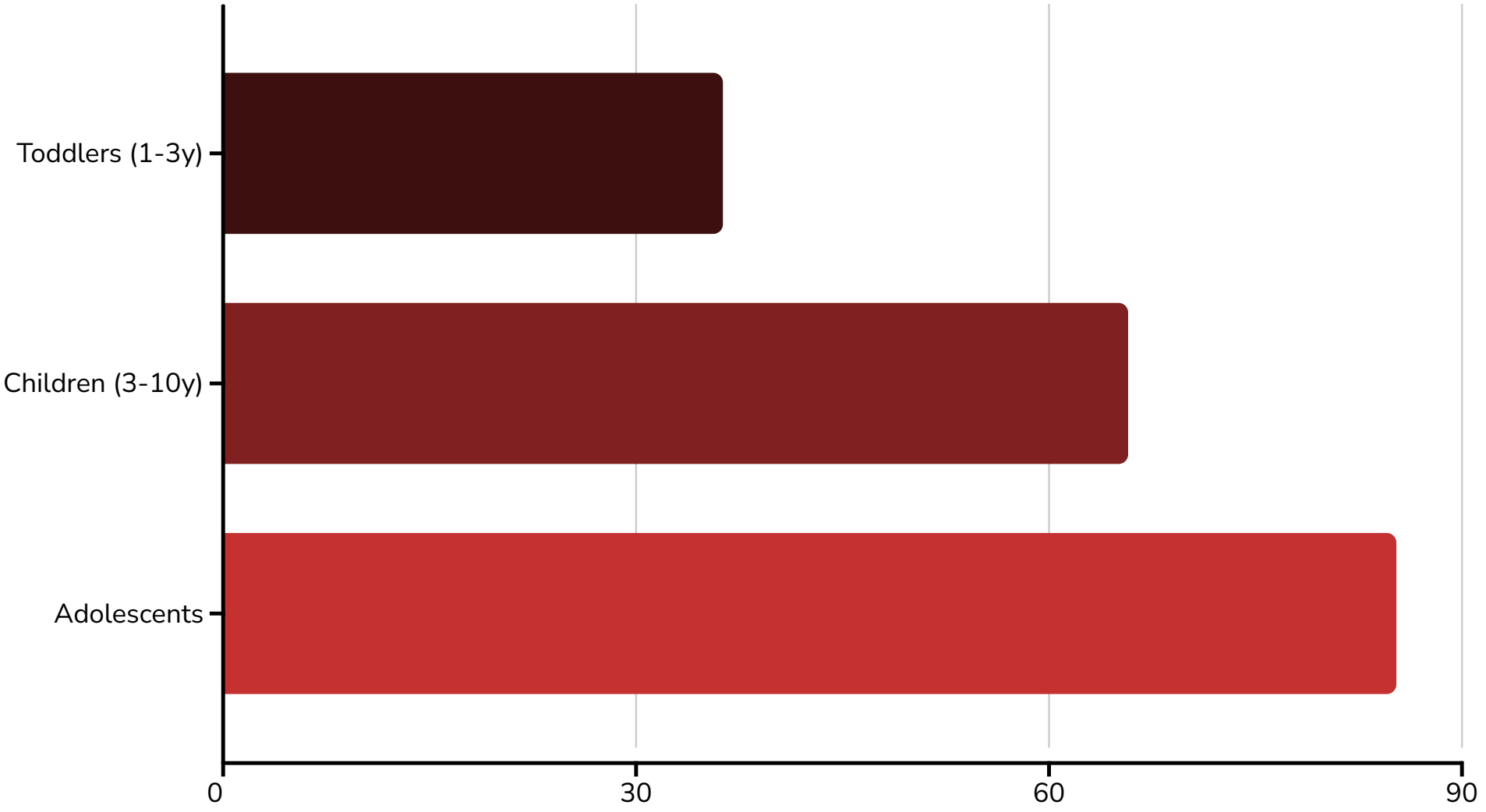
Immature Detoxification

Infant hepatic systems have reduced efficiency of chromium metabolism and excretion

An integrated safety assessment framework for food additives in early life suggested that the acceptability of daily intake (ADI) derived for general populations may not be appropriately applied to pre-weaned infants and young children without specific reassessment [9]. The framework proposed that for vulnerable early-life populations, combined with an in-depth review of existing toxicological and nutritional data, targeted juvenile toxicity studies should be considered to investigate safe use levels in food products [9]. This principle applies directly to chromium, where the margin between the TDI and typical early-life exposures, while currently adequate, requires continuous vigilance.

Comparative Hazard Assessment Across Age Groups

Risk characterization studies employing hazard quotient (HQ) and margin of exposure (MOE) calculations have consistently identified infants and toddlers as the most vulnerable age groups [5]. In the Iranian infant formula study, cancer risk estimates ranged from 9.55×10^{-6} to 3.57×10^{-5}, with the highest risks observed in the youngest age groups [5]. While these risks remain within internationally accepted thresholds for regulatory action (typically 1×10^{-6}), the proximity of some estimates to this threshold warrants ongoing surveillance.



An important observation from multiple risk assessments is that non-carcinogenic hazard indices frequently exceeded unity in infant and toddler populations even when individual element exposures appeared acceptable [5]. This finding suggests a potential for cumulative toxicity when multiple trace elements are considered simultaneously—a scenario frequently encountered in real dietary exposures. The chromium contribution to overall hazard indices, while not always the highest among contaminants, nevertheless represents a meaningful component of total non-carcinogenic risk in some food products.

Cr(III): Bioavailability, Essentiality Claims, and Toxicity

Trivalent chromium exhibits fundamentally different biological behavior than its hexavalent counterpart. The absorption of Cr(III) from food sources is remarkably poor, ranging from 0.4 to 2.5% depending on the chemical form and presence of other dietary components, while supplemental Cr(III) absorption ranges from 0.1 to 5.2% [1]. This low bioavailability reflects the chemical properties of Cr(III) that limit its cellular uptake; the trivalent form exists primarily as a highly charged cation that does not readily penetrate cell membranes [2].

Toxicity Profile

The oral route of Cr(III) exposure results in very low toxicity, with hardly any well-documented observations of toxicity after oral ingestion in humans [1]

In animal repeat-dose toxicity studies, the NOAEL consistently corresponded to the highest dose tested [1]

Genotoxicity

Results from in vitro bacterial mutagenicity assays have been consistently negative [10]

At extremely high concentrations in vitro, certain Cr(III) compounds cause chromosomal damage, but these far exceed relevant exposure levels [10]

The scientific controversy surrounding the essentiality of chromium persists despite decades of research. While chromium has been postulated as necessary for the efficacy of insulin in regulating carbohydrate, lipid, and protein metabolism, no definitive mechanisms for these roles have been identified [1]. The lack of clearly demonstrated biochemical functions led regulatory authorities to reclassify chromium from an essential element to a nutritional supplement status, reflecting the insufficient evidence for dietary requirement recommendations [1].

Cr(VI): Carcinogenicity, Genotoxicity, and Toxicity Mechanisms

Hexavalent chromium presents a toxicological profile fundamentally different from Cr(III). Cr(VI) is classified as a Class A carcinogen and a known human lung carcinogen [2], [3]. The mechanisms of Cr(VI) toxicity involve multiple pathways, with particular emphasis on its generation of reactive oxygen species (ROS) and subsequent oxidative stress [11]. Upon cellular entry, Cr(VI) undergoes intracellular reduction, generating reactive intermediates including Cr(V) and Cr(IV) species that participate in redox cycling and DNA damage [12].

DNA Damage

Altered expression of genes related to DNA damage signaling and oxidative stress response [13]

Epigenetic Changes

Changes to DNA methylation patterns, histone modifications, and microRNA expression [2]

Neurotoxicity

Behavioral effects including alterations in locomotion, memory, and object recognition [15]

Genotoxic effects of Cr(VI) have been demonstrated across multiple model systems, including altered expression of genes related to DNA damage signaling, oxidative stress response, inflammation, and cell death pathways [13]. The molecular mechanisms underlying Cr(VI) carcinogenicity involve epigenetic modifications including changes to DNA methylation patterns, histone tail modifications, and alterations in microRNA expression [2]. Recent investigations have identified circulating exosomal microRNAs as potential mediators of Cr(VI)-induced genotoxicity and immunosuppression, with specific miRNAs (particularly miR-4467, miR-345-5p, miR-144-3p, and miR-206) showing capacity to discriminate between individuals with high genetic damage burden [14].

The neurotoxic potential of Cr(VI) extends beyond its well-characterized carcinogenic effects. Studies in guinea pigs, which uniquely cannot endogenously synthesize vitamin C and therefore represent better translational models for human Cr(VI) sensitivity, demonstrated behavioral effects following occupationally relevant inhalation exposures [15]. Observable effects included alterations in open field locomotion, elevated plus maze performance, Y-maze spatial memory, and novel object recognition, with associated hippocampal chromium accumulation and essential metal dyshomeostasis [15].

Speciation-Dependent Cellular Uptake and Detection Methods

The fundamental difference between Cr(III) and Cr(VI) toxicity profiles reflects their different abilities to cross cellular membranes and generate reactive intermediates. Cr(VI) enters cells through anion transporters that normally transport sulfate and other essential anions, exploiting normal cellular machinery to deliver a toxic payload [13]. In contrast, Cr(III), being a highly charged cation, penetrates cell membranes poorly, explaining its generally low toxicity despite higher total chromium exposure [13]. However, when Cr(III) is presented as particulate material or in certain complex forms, enhanced cellular uptake and toxicity can occur, indicating that chemical form influences bioavailability even within the trivalent state [13].

Diphenylcarbazide Method

Classical spectrophotometric approach, relatively simple and low-cost [16]

1

HPLC-ICP-MS

Sophisticated hyphenated technique providing molecular and elemental information [18]

2

Electrochemical Detection

Specialized methods for sensitive chromium speciation [19]

3

A critical finding emerged from studies examining Cr_2O_3 particles: while most Cr(III) particles showed low toxicity comparable to soluble Cr(III), one particle type released considerable amounts of Cr(VI), exhibiting toxicity profiles matching soluble Cr(VI) [13]. This observation underscores that even materials nominally described as "Cr(III)" may contain oxidized chromium species due to incomplete control of oxidation state during manufacturing, highlighting the importance of stringent chemical characterization in products intended for infants.

Accurate determination of chromium speciation represents a technical challenge critical to proper risk assessment, particularly for infant foods where speciation directly impacts hazard characterization. Multiple analytical approaches have been developed for chromium speciation, including spectrophotometric methods utilizing diphenylcarbazide (DPC) [16], [17], high-performance liquid chromatography coupled with inductively coupled plasma mass spectrometry (HPLC-ICP-MS) [18], and specialized electrochemical detection methods [19].

Chromium in Microbial Pathogenesis and Microbiome Dynamics

The presence of chromium in environmental and biological systems exerts selective pressure on microbial communities, driving the emergence and enrichment of chromium-resistant taxa. Comprehensive analysis of soil microbial communities exposed to both Cr(III) and Cr(VI) revealed speciation-dependent patterns of microbial sensitivity and resistance [20]. Notably, Cr(VI) demonstrated greater toxicity to bacterial communities than Cr(III), with significant reductions in Shannon-Wiener diversity indices in soils exposed to hexavalent chromium [20]. This differential toxicity reflects the greater bioavailability and reactivity of Cr(VI) in driving oxidative stress within microbial cells.

Actinobacteria

Chromium-resistant bacteria showing increased relative abundance in contaminated environments [20]

Bacillus subtilis

Demonstrated remarkable capacity for Cr(VI) reduction, converting 75% to less toxic Cr(III) within 72 hours [21]

Phytoremediation

Plant growth-promoting traits including IAA production and phosphate solubilization [21]

The taxonomic composition of chromium-exposed soil communities showed clear adaptive responses, with relative abundance of chromium-resistant bacteria of the phylum Actinobacteria increasing substantially, while chromium-sensitive groups including Acidobacteriota and Proteobacteriota became depleted [20]. Specific bacterial genera including *Phycisoccus* and *Arthrobacter* showed selective enrichment in Cr(III)-contaminated soils, while *Mycoplana* and *Cellulosimicrobium* species increased in Cr(VI)-affected environments [20]. These shifts demonstrate that microbial resistance mechanisms are profoundly influenced by chromium speciation.

While research specifically examining chromium effects on the human microbiota remains limited, emerging evidence suggests that chromium contamination induces dysbiotic shifts analogous to those observed with other heavy metals. The broader literature on metal effects on gut microbiota demonstrates that heavy metal exposure can damage intestinal epithelial barrier integrity, cause loss of microbial and immune homeostasis, and promote dysbiosis associated with gastrointestinal inflammation [22]. Given chromium's capacity to generate reactive oxygen species and oxidative stress, the mechanisms by which chromium may alter microbiota composition likely involve both direct antimicrobial effects on susceptible taxa and indirect effects mediated through intestinal epithelial barrier dysfunction.

Microbial Chromium Redox Transformation and Metallomics

At the microbiota level, chromium redox transformation represents a critical process influencing chemical speciation and bioavailability. Microbial reduction of Cr(VI) to Cr(III) occurs through multiple enzymatic mechanisms, primarily involving chromate reductase enzymes that catalyze the reduction using electrons from organic or inorganic donors [11]. This transformation is particularly significant for environmental fate and transport, as Cr(III) exhibits lower mobility and bioavailability compared to Cr(VI) [24].

Studies examining chromium behavior in soil under alternating wet-dry cycles—simulating natural rainfall patterns—revealed that microbial processes contribute substantially to Cr(VI) reduction in soil environments [24]. During wet-dry cycling, Cr(VI) concentrations in soil decreased while residual and oxidizable chromium fractions increased, reflecting internal reduction reactions mediated by microbial activity and coupled redox processes [24]. The involvement of microorganisms in consuming organic matter during these cycles further influenced chromium speciation dynamics [24].

Conversely, in certain soil conditions, microbial oxidation of Cr(III) can occur. Manganese oxide minerals, when present in soil, catalyze oxidation of Cr(III) to Cr(VI), potentially with microbial mediation [25]. Investigation of acid birnessite and cryptomelane—two manganese oxide minerals—demonstrated their capacity to oxidize Cr(III) during flooded soil conditions, with Cr(VI) concentrations increasing 2.4-fold in amended soils compared to controls [25]. This phenomenon highlights the complexity of chromium speciation dynamics in natural environments and the potential for microbial-mineral interactions to shift chromium chemistry.

Metallomics—the comprehensive study of metal and metalloid species and their interactions within biological systems—remains an underdeveloped area specifically for chromium and human microbiota. However, emerging metallomics approaches reveal intricate relationships between metal availability and microbial community composition [26]. Studies on zinc, a metal sharing similar uptake mechanisms and biological roles with chromium in some contexts, demonstrate that excessive metal bioavailability alters aquatic and soil microbial diversity, affecting absorption and metabolic processes [26]. Gram-positive bacteria including *Bacillus* and *Staphylococcus* species, as well as Gram-negative organisms such as *Pseudomonas* and *Klebsiella*, have emerged as promising agents for bioremediation of metal-contaminated environments through biosorption and enzymatic reduction mechanisms [26].

Chromium as an Indicator and Risk Mitigation Strategies

An often-overlooked but critical function of chromium monitoring in infant and child nutrition is its role as a sentinel indicator of food processing adequacy and contact-material integrity. The presence of chromium contamination in products not naturally containing significant chromium levels frequently signals upstream processing concerns rather than primary contamination events. Stainless steel equipment, which constitutes the majority of food processing machinery and contains 18-30% chromium by weight, represents a potential source of chromium leaching during food preparation, storage, and reconstitution [5].

1	**Source Level Control** Stringent control of water treatment in facilities producing infant formula and complementary foods
2	**Processing Level Control** Material selection minimizing stainless steel contact with acidic foods, or using coating technologies to reduce chromium leaching
3	**Product Level Control** Speciation-based testing to distinguish Cr(III) from Cr(VI) and assess actual hazard
4	**Population Level Control** Dietary diversification to reduce reliance on any single potential contamination source

The pH dependence of chromium solubility amplifies this concern in infant nutrition products. Acidic foods and beverages—categories that include fruit-based complementary foods, juice-containing products, and fermented foods—exhibit substantially higher chromium leaching from stainless steel surfaces compared to neutral or alkaline products [5]. The combination of high surface-area-to-volume ratios characteristic of infant food preparation (blending, straining, sieving) with prolonged contact times (storage) and acidic conditions creates an environment particularly conducive to chromium mobilization.

Current regulatory frameworks for chromium in infant and child nutrition products require harmonization and strengthening across jurisdictions. The EFSA approach, which acknowledges developmental sensitivity through application of an additional 10-fold uncertainty factor, provides a scientifically defensible foundation [1]. However, regulatory implementation across different jurisdictions remains inconsistent. Some regions have established maximum contaminant levels for specific foods, while others rely solely on general food standards without age-specific considerations [5].

Regulatory authorities should consider implementing age-adjusted risk assessments that explicitly account for the compressed margins of safety in infants and toddlers. This approach would involve: (1) lowering acceptable contaminant levels for infant-targeted products compared to general population standards; (2) requiring mandatory speciation analysis for chromium in products where contamination is detected; (3) establishing monitoring programs that track chromium levels in the most vulnerable subpopulation; and (4) implementing traceability systems that enable rapid identification of contamination sources when elevated levels are detected.

Research Gaps, Future Directions, and Conclusions

Significant research gaps persist in several critical areas. First, longitudinal studies examining the relationship between early-life chromium exposure and long-term developmental outcomes remain absent. While the EFSA assessment identified developmental toxicity as a key uncertainty warranting additional safety factors, direct human evidence from exposed populations remains limited. Prospective cohort studies following infants from birth through childhood, with detailed dietary exposure assessment and developmental milestone monitoring, would provide valuable data for refining risk assessments.

Mechanistic Studies

Examining chromium speciation changes during digestion and intestinal passage in human infant gut

Metallomics Research

Characterizing how chromium bioavailability influences human microbiota composition and function

Analytical Methods

Standardized methods for chromium speciation in infant foods with international harmonization

Material Science

Mechanisms of chromium release from stainless steel under various conditions to inform engineering solutions

The future of chromium risk assessment in infant nutrition depends critically on integration of speciation information into regulatory frameworks. Current regulations typically address "total chromium" without distinguishing between Cr(III) and Cr(VI), despite the fundamentally different hazard profiles of these species. This approach likely overestimates risk when products contain predominantly Cr(III) and underestimates risk when Cr(VI) predominates.

An evidence-based regulatory framework would: (1) establish separate maximum residue levels for Cr(III) and Cr(VI) in products intended for infants and young children; (2) require speciation analysis when total chromium exceeds a defined threshold; (3) apply different uncertainty factors during risk characterization based on the specific species present; and (4) establish enhanced monitoring for products with known risk factors (e.g., acidic formulations, high surface-area-to-volume ratios, extended storage periods).

> **Summary and Conclusions:** Chromium presents a complex toxicological challenge in infant and child nutrition, primarily because its hazard profile is entirely dependent on chemical speciation. While Cr(III) exhibits relatively low toxicity via the oral route, Cr(VI) represents a recognized human carcinogen with potential for adverse developmental and neurological effects. Infants and young children face compressed margins of safety due to their high relative dietary intake per kilogram of body weight and reliance on liquid, frequently acidic foods. The EFSA-derived TDI of 300 µg Cr(III)/kg body weight per day provides a defensible scientific foundation for risk assessment, incorporating appropriate uncertainty factors to account for developmental sensitivities.

Chromium's presence in infant foods and water often reflects inadequate process control or contact-material integrity rather than primary contamination, positioning it as a valuable quality control indicator. The emerging understanding of chromium's effects on microbial pathogenesis and microbiota composition suggests that chronic low-level exposure may influence gut microbiota structure and immune development, though this area remains understudied. Future advancement of chromium risk assessment in early life requires integration of speciation data, longitudinal developmental studies, comprehensive metallomics approaches, and harmonized international regulatory frameworks that appropriately account for the heightened vulnerability of the youngest population segments.

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