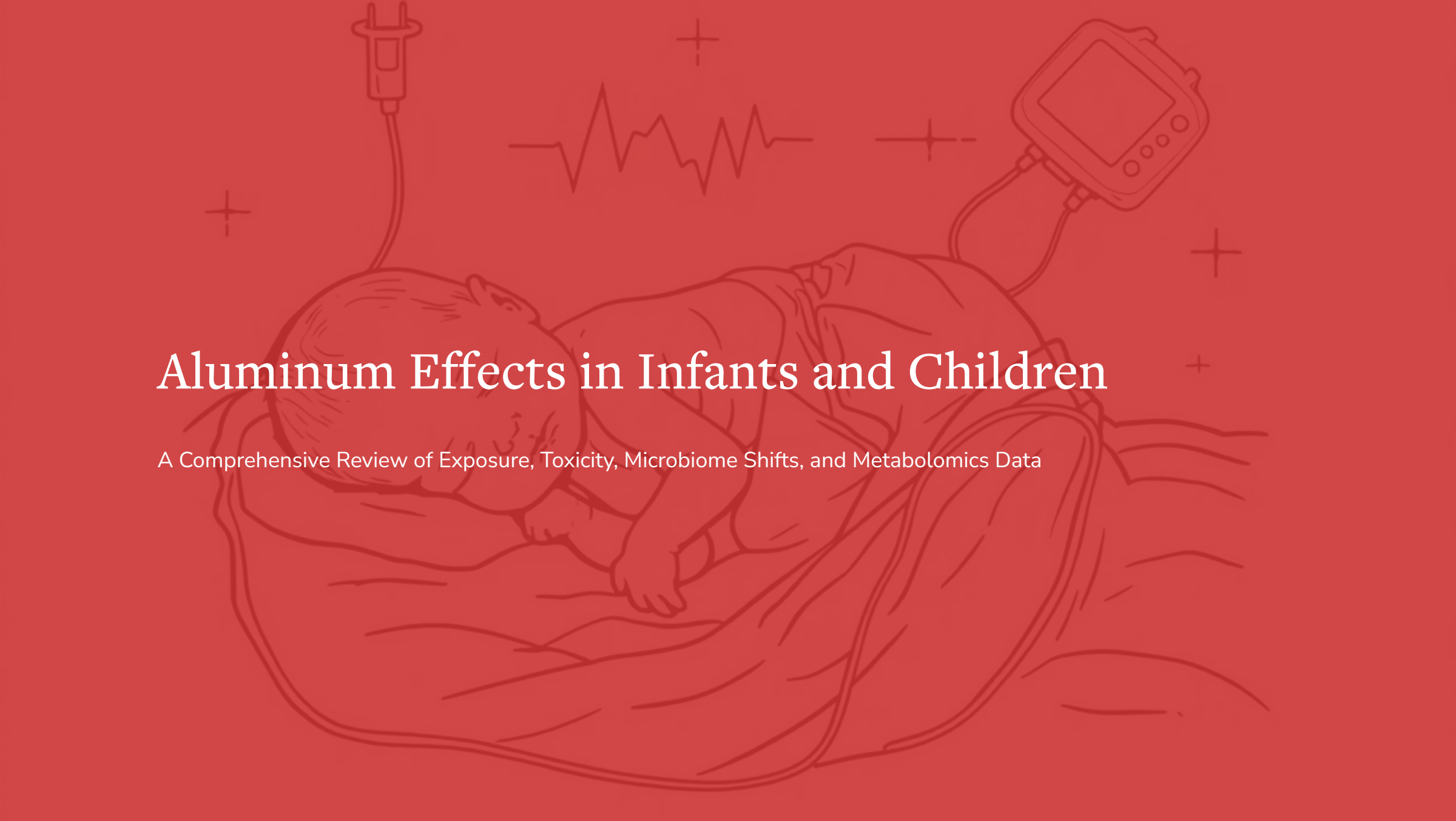


Aluminum Effects in Infants and Children

A Comprehensive Review of Exposure, Toxicity, Microbiome Shifts, and Metabolomics Data

Aluminum Exposure Sources and Pathways in Early Life

Aluminum is one of the most abundant elements in the earth's crust and is ubiquitously present in the environment, making exposure inevitable for infants and young children [1]. However, aluminum has no known biological function and is considered a contaminant in most foods and medications [1]. The primary routes of aluminum exposure in infants differ significantly from those in older children and adults, with parenteral nutrition representing the most clinically significant source in premature and medically fragile infants.

Parenteral Nutrition

Most problematic source in hospitalized infants

Dietary Sources

Infant formulas and complementary foods

Drinking Water

Environmental contamination

Vaccine Adjuvants

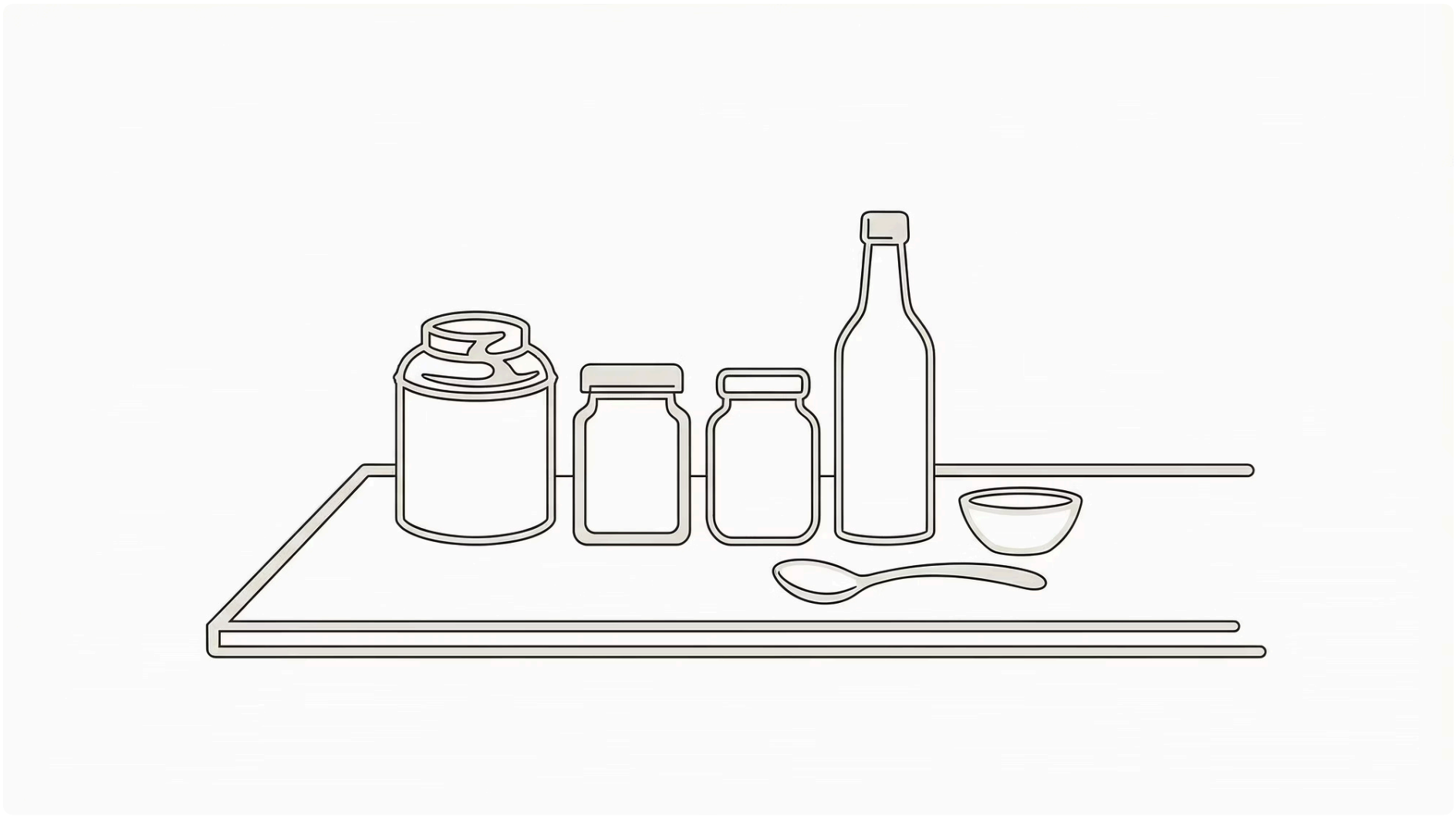
Pharmaceutical preparations

Total Parenteral Nutrition (TPN)

Total parenteral nutrition (TPN) has historically been the most problematic source of aluminum exposure in hospitalized infants. A prospective study on premature infants receiving TPN found that aluminum levels increased significantly from cord blood (3.35 ± 1.73 μg/L) to day 14 of life (4.79 ± 3.54 μg/L), representing a statistically significant increase [2]. The increase was particularly associated with the duration of parenteral feeding, with infants receiving parenteral nutrition for more than 10 days showing significantly higher serum aluminum levels [2]. This concern has been documented extensively, with aluminum contamination in large-volume and small-volume parenterals, including calcium phosphate salts, albumin, and heparin, identified as major contributors to total aluminum burden [3].

Dietary Exposure Through Infant Formulas and Foods

Dietary exposure through infant formulas and complementary foods represents another significant exposure pathway. A risk assessment study from Lebanon analyzing 41 infant formula samples and 76 baby food products found average daily aluminum intake of 0.01–0.0104 mg/kg body weight per day for infants aged 0–23 months [4]. While individual food items contained aluminum below the limit of detection in many cases, the hazard quotient exceeded 1 for some male and female infants, suggesting potential health risks from cumulative dietary exposure [4].



A comprehensive Monte Carlo simulation approach for Iranian infant formulas and complementary foods revealed that aluminum concentrations significantly exceeded FAO/WHO standards in 80 formula milk and 27 baby food samples, with non-cancer hazard indices exceeding the safety threshold of 1.0 for all age groups [5].

Additional Exposure Pathways

Drinking water and environmental contamination contribute additional exposure pathways. While aluminum levels in drinking water are variable globally, the chemistry and bioavailability of aluminum are highly dependent on water pH and the specific chemical form present [6]. Children engaging in certain behaviors such as geophagy (soil ingestion) may receive substantially higher aluminum exposure, though this remains an underappreciated route of exposure in many populations.

Vaccine adjuvants containing aluminum have been the subject of considerable debate regarding pediatric safety. Aluminum salts serve as widely-used adjuvants in preventive vaccines and allergy immunotherapy preparations [7]. However, the clinical significance of this exposure route in relation to total aluminum burden remains controversial, though multiple studies have documented that the benefits of vaccination substantially outweigh potential aluminum adjuvant concerns [11].

Toxicokinetics and Bioaccumulation in Infants

The unique physiological characteristics of infants and young children render them particularly vulnerable to aluminum accumulation and toxicity. Unlike in older children and adults, the immature renal system of infants is unable to efficiently excrete absorbed aluminum, leading to preferential bioaccumulation in vulnerable tissues.

01

Absorption and Distribution

Approximately 95% of circulating aluminum becomes bound to plasma proteins, chiefly transferrin

02

Renal Bottleneck

Glomerular filtration rates in preterm infants do not reach maturity until 34 weeks of gestation

03

Tissue Accumulation

Preterm infants have additional burden to excrete aluminum load, often exceeding renal capacity

Aluminum Absorption and Tissue Distribution

Aluminum absorption and tissue distribution patterns in infants differ markedly from adults. Preterm infants receiving parenteral aluminum face particular risk because the aluminum bypasses the gastrointestinal barrier entirely, and approximately 95% of circulating aluminum becomes bound to plasma proteins, chiefly transferrin [3]. However, approximately 5% remains ultrafilterable and is available for renal excretion. The developmental immaturity of the neonatal kidney presents a critical bottleneck, as glomerular filtration rates in preterm infants do not reach maturity until 34 weeks of gestation [3]. This physiological vulnerability means preterm infants have an additional burden to excrete the aluminum load they receive, which in many cases exceeds their renal capacity.

Metalomics Assessment of Infant Aluminum Status

A comprehensive metalomics study examining 77 infant-mother pairs found remarkable disparities in metal burden between infants and their mothers. The geometric mean concentrations of lead, cadmium, and aluminum in infants were approximately **three times higher** than in their mothers ($p < 0.0001$), with some individuals showing burden levels several tens of times higher than their mothers [8]. This finding underscores the exceptional capacity of the infant body to accumulate these toxic metals relative to maternal exposure.

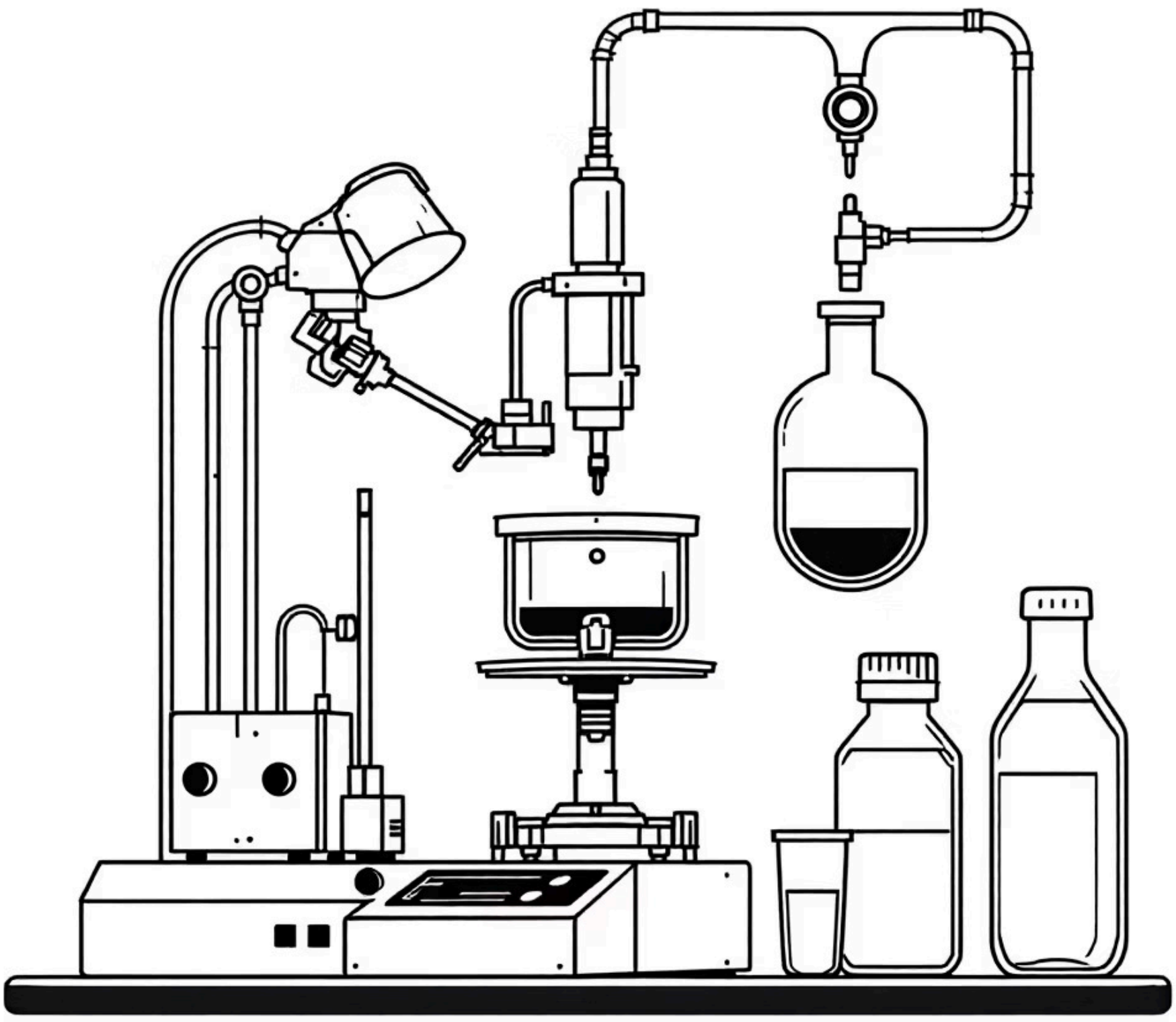
Toxic Metal Burden

- Lead, cadmium, and aluminum ~3x higher in infants
- Some individuals showed burden levels tens of times higher
- Exceptional capacity for accumulation in infant body

Essential Metal Deficiency

- Zinc, magnesium, and calcium significantly lower in infants
- 37.7% of child subjects estimated to be zinc-deficient
- Inverse correlations between essential and toxic metals

Interestingly, the same study found that essential metal levels such as zinc, magnesium, and calcium in infants were significantly lower than in mothers, with 37.7% of child subjects estimated to be zinc-deficient [8]. Significant inverse correlations were observed between zinc and lead ($r = 0.267$, $p = 0.019$), and between magnesium and arsenic ($r = 0.514$, $p < 0.0001$), suggesting potential competitive absorption or transport mechanisms [8].



Clinical evidence of aluminum's renal handling in infants comes from a notable case where an infant receiving high-aluminum parenteral solutions developed hypocalcemia when deferoxamine (an iron chelator with some aluminum-binding capability) was administered [3]. This case demonstrated the presumed sequence of events wherein aluminum interfered with calcium uptake in bone, resulting in osteopenia that took up the slack at the expense of serum calcium, a situation analogous to the "hungry bone syndrome" observed in primary hyperparathyroidism [3].

The metalomics field has enabled more sophisticated assessment of trace metal burden in infants. Recent work emphasizes that early assessment and intervention are crucial, as the toxic metal burden levels in infants and children warrant serious concern from the perspective of their harmful effects on normal growth and development [8]. The relationships between maternal and infant metal burdens vary by element, with aluminum showing a less intimate correlation with maternal exposure ($r = 0.451$) compared to mercury ($r = 0.539$), suggesting distinct absorption and retention mechanisms [8].

Neurotoxicological Effects and Developmental Outcomes

Aluminum's neurotoxic properties represent one of the most clinically significant concerns in infant and child health. The developing brain undergoes critical periods of cell proliferation, migration, differentiation, and myelination during infancy and early childhood, making this period particularly vulnerable to neurotoxic insults.

Prenatal and Early Postnatal Aluminum Exposure

Prenatal and early postnatal aluminum exposure has been associated with impaired neurodevelopment assessed via standardized developmental indices. A prospective cohort study examining prenatal metal exposure in the Wuhan Healthy Baby Cohort (N=1,088) found that higher maternal urinary levels of aluminum were significantly associated with lower Mental Development Index (MDI) scores in 2-year-old children [9]. The weighted quantile sum index of the metal mixture showed a significant inverse association with both MDI and psychomotor development index (PDI) scores, with **aluminum contributing the most to the associations** [9].

Interestingly, histidine, beta-alanine, purine, and pyrimidine metabolism significantly mediated these associations, suggesting that disturbances in amino acid, neurotransmitter, and neuroendocrine metabolism may be important mediators in contributing to impaired neurodevelopment of children [9].

Landmark Clinical Trial on Aluminum Neurotoxicity

The landmark clinical trial demonstrating aluminum's neurotoxic effects involved preterm infants who received parenteral solutions containing high aluminum concentrations (45 µg/kg per day) compared to age-matched controls receiving low-aluminum solutions (4-5 µg/kg per day) [3].

92	102	38%	17%
High Aluminum Group	Low Aluminum Group	High Aluminum >10 Days	Low Aluminum >10 Days
Bayley Mental Development Index score (± 20 SD) at 18 months	Bayley Mental Development Index score (± 17 SD) at 18 months	Fraction with MDI values below 85 points	Fraction with MDI values below 85 points (p = 0.03)

The infants receiving high aluminum had significantly lower Bayley Mental Development Index scores at 18 months (92 ± 20 standard deviation) compared to those receiving low aluminum (102 ± 17). Among 157 infants without neuromotor impairment, exposure longer than 10 days resulted in a higher fraction of high-aluminum group having mental development index values below 85 points (38% versus 17%, p = 0.03) [3].

Mechanisms of Aluminum Neurotoxicity

The mechanisms of aluminum neurotoxicity involve multiple pathways including oxidative stress, alterations in neurotransmitter systems, and disruption of calcium signaling. Aluminum is known to have neurotoxic properties that may induce clinical symptoms through oxidative stress and pro-inflammatory effects [2]. The element has been implicated in amyloidogenesis and other pathological processes relevant to neurodegenerative disease, though the specific mechanisms in developing versus mature brains remain incompletely understood [10].

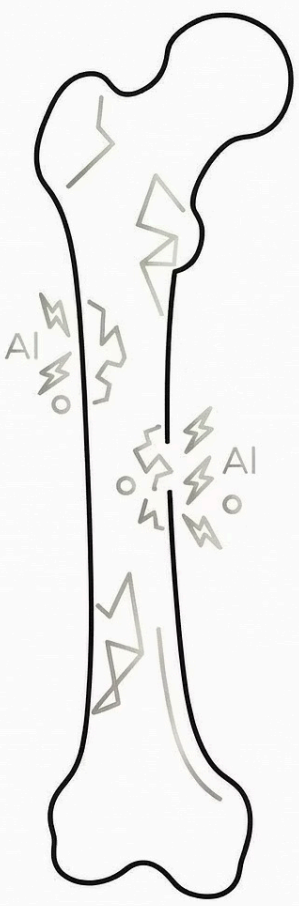
Developmental vulnerability as a modifying factor in aluminum-related neurologic effects requires particular consideration. A comprehensive review examining exposure to mercury and aluminum in early life emphasized that the safety levels of these substances have never been properly determined for fetuses, newborns, infants, and children, despite their long use as active agents in medicines and fungicides [11]. The review concluded that neurobehavioral effects of aluminum-containing adjuvants are not extraordinary and are easily detected in both high and low-income countries, particularly when co-exposure to other neurotoxicants occurs [11].

Bone and Metabolic Effects

Beyond neurotoxicity, aluminum's effects on bone and mineral metabolism represent critical toxicological concerns in growing children. Aluminum-induced osteomalacia and bone disease were first recognized in uremic patients on dialysis but have subsequently been documented in non-uremic children receiving high-dose aluminum exposure through parenteral nutrition or other sources.

Aluminum-Induced Osteomalacia and Bone Disease

The characteristic bone pathology associated with chronic aluminum exposure includes defective mineralization at the bone-forming surface, where aluminum accumulates [3]. Histochemical staining in biopsy specimens reveals aluminum deposition at the mineralization front, identical to the site where new bone forms. Dynamic histomorphometric analyses of biopsies from patients receiving long-term aluminum-containing TPN produced a striking finding: the quantitative concentration of aluminum at the mineralization front inversely correlated with the rate of bone formation [3]. Substitution of deionized water for dialysate use and the introduction of non-aluminum-containing phosphate-binding gels and crystalline amino acids led to gradual resolution of bone pain and improved bone formation [3].



Vitamin D-Resistant Osteomalacia

Deranged membranous bone formation, accumulation of osteoid matrix, reduced mineralization, decreased numbers of osteoblasts and osteoclasts, and decreased lamellar bands with elevated aluminum concentrations [6]

Stress Fractures

Disease can progress to stress fractures of the ribs, femur, vertebrae, humerus, and metatarsals

Diagnostic Threshold

Serum aluminum concentrations exceeding 100 µg/L have been reported with 75-88% positive predictive value for aluminum bone disease [6]

Hematopoietic and Central Nervous System Effects

Chronic aluminum exposure also manifests through hematopoietic effects, including an erythropoietin-resistant microcytic hypochromic anemia [6]. This anemia likely reflects aluminum's interference with iron metabolism and heme synthesis pathways. The metalomics study mentioned previously documented that essential metal levels such as zinc, magnesium, and calcium in infants were significantly lower than in mothers [8], suggesting that aluminum may competitively interfere with the absorption or retention of essential minerals critical for normal growth, bone development, and hematopoiesis.

Hematopoietic Manifestations

- Erythropoietin-resistant microcytic hypochromic anemia
- Interference with iron metabolism
- Disruption of heme synthesis pathways
- Competitive interference with essential minerals

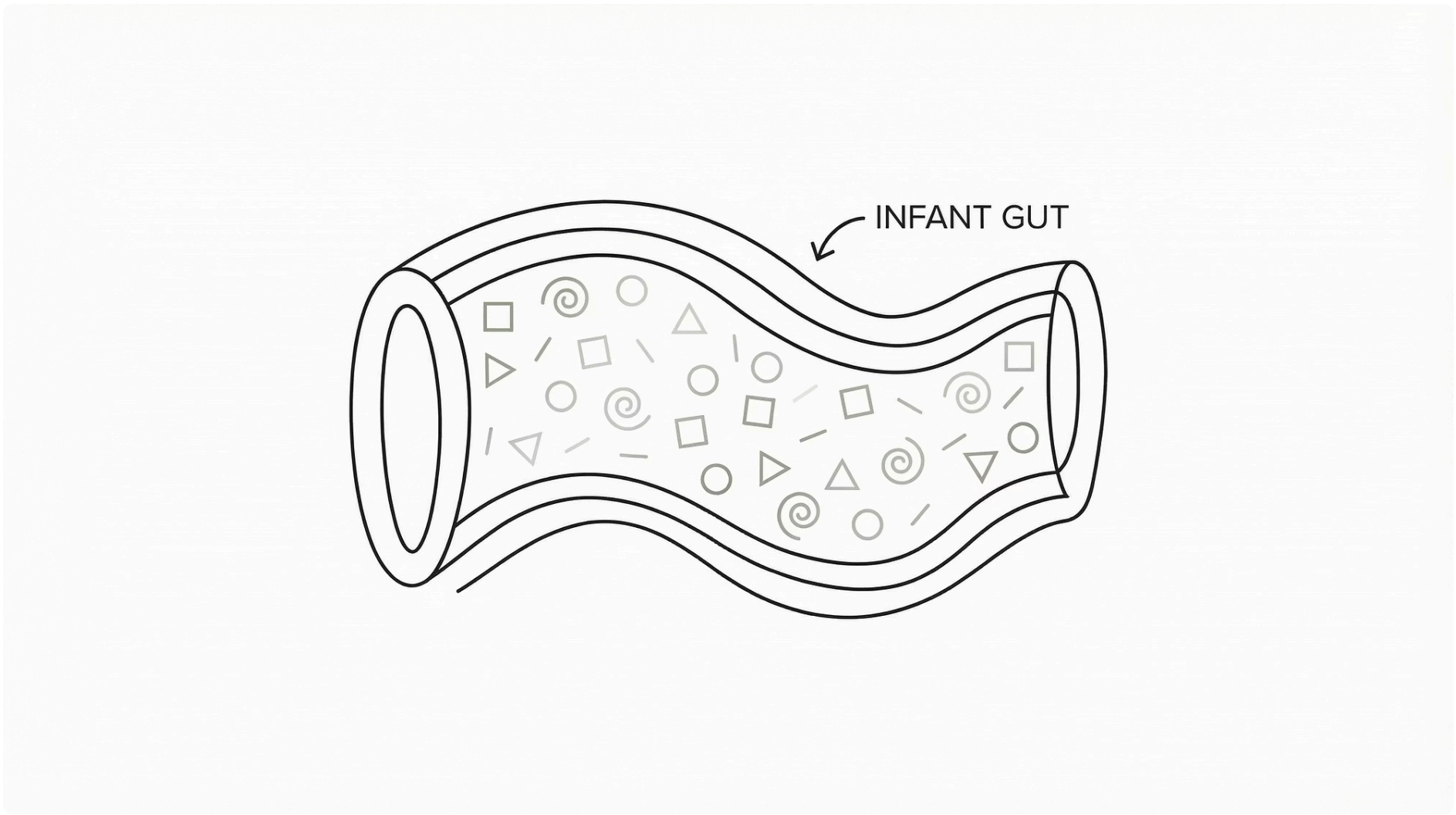
Central Nervous System Manifestations

- Speech difficulty and mutism
- Facial grimacing
- Multifocal seizures
- Dyspraxia
- Progression to frank encephalopathy in severe cases

Central nervous system manifestations of chronic aluminum exposure include speech difficulty, mutism, facial grimacing, multifocal seizures, and dyspraxia, related to aluminum accumulation in the brain [6]. These neurologic manifestations may progress to frank encephalopathy in severe cases, emphasizing the multisystem nature of aluminum toxicity.

Microbiome Shifts and Microbial Metalomics in Aluminum Exposure

The emerging field of microbial metalomics has revealed previously unrecognized interactions between aluminum exposure and the developing infant microbiome. These interactions occur during a critical window of microbiome colonization and maturation and may have long-term consequences for immune development and metabolic health.



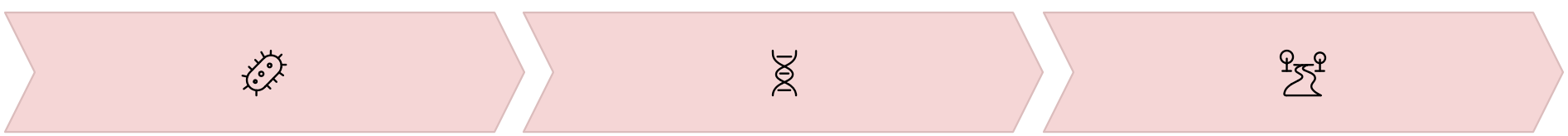
Multi-Omics Study of Mother-Infant Pairs

A landmark multi-omics study examining 146 mother-infant pairs found that prenatal trace element exposure, including aluminum, significantly impacts the developing infant gut microbiome [12]. The study measured trace elements in maternal hair samples and collected stool samples from infants at 3, 6, and 12 months after delivery for amplicon sequencing, metagenomics, and metabolomics. Results demonstrated that relative abundance of *Bifidobacterium*—a keystone genus associated with healthy infant development—increases under high exposure to aluminum and manganese [12].

During the first year of life, infants and their paired mothers had distinct microbial diversity and composition, with their bacterial community structures gradually approaching each other over time [12]. The study identified 56 differential metabolites between the first and second visit and **515 differential metabolites between the second and third visit**, indicating substantial metabolome remodeling associated with prenatal metal exposure [12].

Element-Specific Effects on Infant Microbiota

The differential impact of specific trace elements on infant microbiota composition was precisely quantified. Shannon diversity in 3-month-old infants was correlated positively with selenium and negatively with copper, demonstrating element-specific effects on microbial diversity [12]. Importantly, the study revealed that high levels of copper and arsenic exposure may induce the enrichment of antibiotic resistance genes (ARGs) in the infant gut, a finding with potential long-term implications for antimicrobial resistance [12].



Microbial Diversity Changes

Shannon diversity correlated positively with selenium and negatively with copper

Antibiotic Resistance Genes

High copper and arsenic exposure enriches ARGs in infant gut

Metabolome Remodeling

515 differential metabolites identified between visits

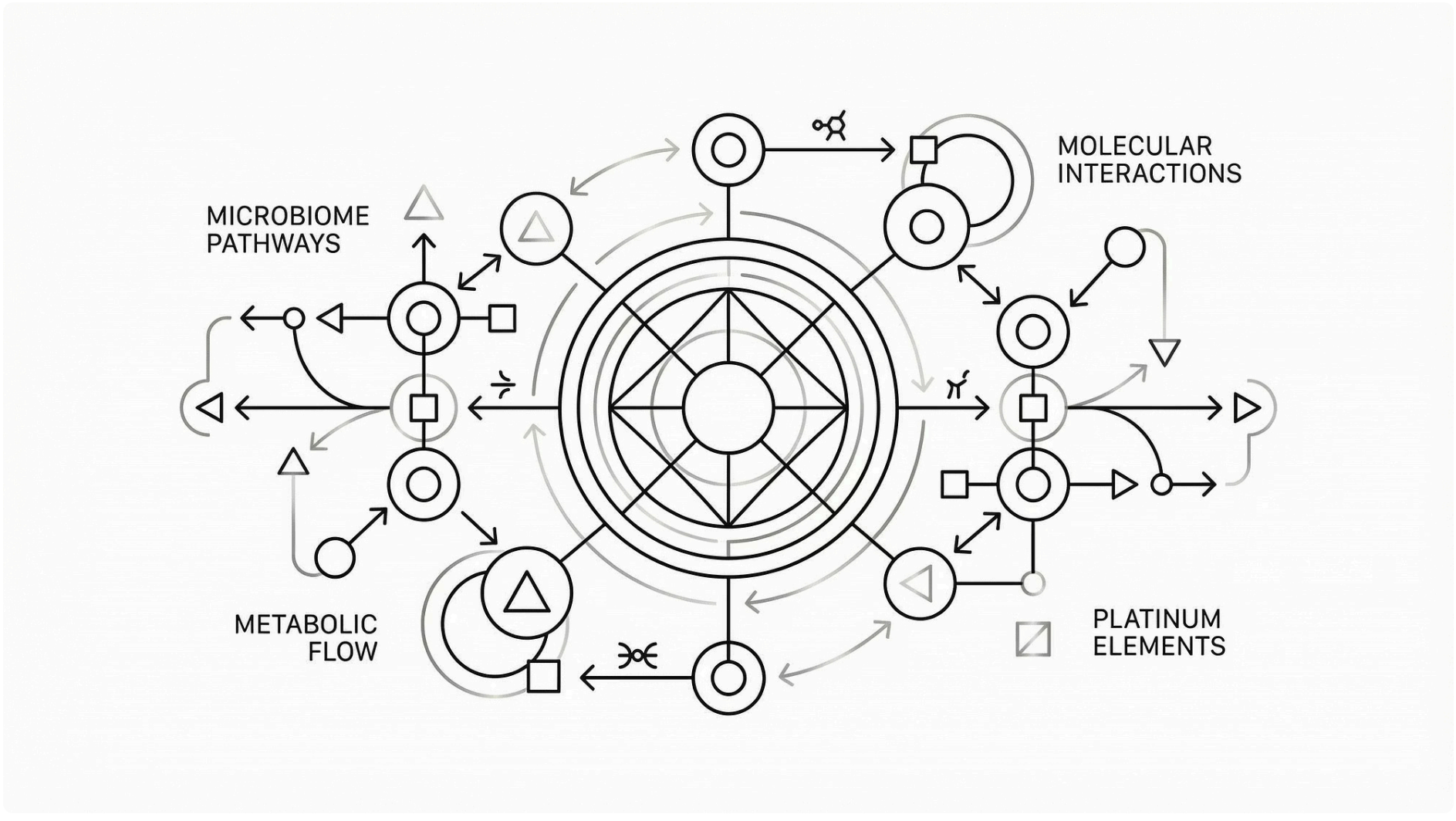
Aluminum-Tolerant Microbial Populations

Microbial metabolomics analysis has identified aluminum-tolerant microbial populations that colonize infant-associated microbiota. An innovative artificial intelligence-assisted Raman-activated cell sorting (AI-RACS) system was used to identify and characterize aluminum-tolerant microbes from environmental samples, validating the capacity of this technology to segregate microbial cells from intricate environmental samples and investigate their functional attributes [13]. This technological advance has enabled identification of specific bacterial strains capable of thriving under aluminum stress conditions, an important consideration for understanding the adaptive responses of infant microbiota.

The mechanisms by which microorganisms tolerate and respond to aluminum exposure involve sophisticated metalloproteins and regulatory systems. Heavy metal tolerance in bacteria includes the formation of biofilms, efflux systems, and enzymatic detoxification pathways that allow communities to adapt and survive in contaminated environments [14]. These adaptations are enhanced by mutations in genes and horizontal gene transfer, enabling microbial species to survive stress while simultaneously contributing to nutrient cycling and decomposition of organic matter [14]. Plant growth-promoting rhizobacteria such as *Rhizobium* and *Bacillus* are known contributors to phytoremediation processes and have demonstrated metal-binding capabilities and biosorption applications [14].

Metabolomics Alterations in Aluminum-Exposed Microbiota

The metabolomics alterations observed in aluminum-exposed infant microbiota reflect the metabolic burden imposed by metal stress. Beyond simple compositional shifts, aluminum exposure triggers coordinated changes in microbial metabolite production, including differential expression of metabolic pathways involved in stress responses. The identification of 515 differential metabolites between sequential visits in aluminum-exposed infants suggests substantial rewiring of metabolic networks, potentially affecting nutrient bioavailability, immune stimulation, and neurodevelopmental pathways that depend on bacterial metabolite production [12].



Microbial metabolomics assessment in infants has utilized mass spectrometry-based approaches to characterize metallophore production—specialized metal-chelating compounds produced by pathogenic and commensal microorganisms during infection and colonization stress [15]. These metallophores represent sensitive, noninvasive biomarkers of microbial metabolic state and may indicate shifts in microbiota composition and function in response to aluminum and other metal stress [15].

Regulatory Standards and Safety Considerations

Recognition of aluminum's toxicological potential in infants and children has led to regulatory interventions, though the adequacy and implementation of these standards remain subjects of ongoing refinement.

FDA Regulations and Proposed Standards

The United States Food and Drug Administration has been investigating aluminum contamination in parenteral solutions since 1986, ultimately proposing regulations to limit aluminum contamination and require labeling of products containing aluminum [3]. The regulatory response specifically addressed the concern that continuous delivery of high aluminum loads could confer cumulative toxicity, particularly in neonates receiving large infusions of aluminum-containing solutions.

Large-Volume Parenterals

FDA proposed upper limit of 25 µg/L for sodium chloride, dextrose, and water solutions

Small-Volume Components

Applicants must submit approval with validated assay methods and state aluminum content at expiry date

Labeling Requirements

Aluminum content must be stated on immediate container labels and pharmacy bulk packages

The FDA proposed amending regulations to add labeling requirements concerning aluminum and to specify an upper limit of 25 µg/L for certain large-volume parenteral solutions such as sodium chloride, dextrose, and water [3]. For small-volume components and biologicals, the FDA required applicants to submit approval with validated assay methods and to state the product's aluminum content and its concentration at the expiry date on immediate container labels and pharmacy bulk packages [3].

Despite these regulatory efforts, total aluminum concentration from some components continues to exceed the recommended final concentration in parenteral solutions [1]. The North American Society for Pediatric Gastroenterology and Nutrition responded to the FDA proposed rule by strongly endorsing interest in safety and encouraging expanded activity in restricting aluminum in biological agents, particularly albumin and other colloidal volume expanders [3]. The organization emphasized the need for specific definitions that would closely guide compounds administered to infants, given that no universally accepted safe daily aluminum dose has been established [3].

Clinical Management and Prevention Strategies

Dietary standards for aluminum have been established by international organizations. The provisional tolerable weekly intake (PTWI) set by JECFA is less than 6-7% of total complementary intake for both female and male infants aged 0-23 months, based on a tolerable intake of 2 mg/kg body weight per week [4]. However, in some populations consuming aluminum-contaminated water or foods, the hazard quotient has been estimated to exceed 1, indicating potential non-cancer health risks [4].

Clinical Management Approaches

The clinical management of aluminum toxicity in infants and children remains challenging. Chelation therapy using deferoxamine has been attempted in some cases but carries its own risks and is not routinely recommended for pediatric aluminum toxicity unless there is evidence of serious organ involvement. Instead, the primary focus remains on prevention through reduction of exposure, particularly in vulnerable populations such as preterm infants receiving parenteral nutrition, infants in regions with high-aluminum drinking water, and those consuming contaminated complementary foods.

Clinical Settings

- Substitute deionized water for dialysate use
- Implement non-aluminum-containing phosphate-binding gels
- Use crystalline amino acids instead of casein hydrolysate
- Adhere to validated manufacturing standards

Home Settings

- Awareness of aluminum contamination in drinking water
- Monitor food sources for aluminum content
- Select infant formulas with quality control measures
- Minimize exposure from environmental sources

Prevention strategies and exposure reduction represent the most practical approach. In clinical settings, measures to reduce aluminum exposure include substituting deionized water for dialysate use, implementing non-aluminum-containing phosphate-binding gels when necessary, using crystalline amino acids instead of casein hydrolysate in parenteral solutions, and adhering to validated manufacturing standards for large- and small-volume parenterals [3]. For infants and young children in home settings, awareness of potential aluminum contamination in drinking water and food sources, along with selection of infant formulas from manufacturers implementing quality control measures to minimize aluminum content, represents important preventive strategies.

The concerns about aluminum in infant formulas and antiperspirants have not been substantiated by robust evidence, though they warrant continued research [1]. In contrast, the evidence linking long-term, high-concentration aluminum exposure to neurodevelopmental impairment, bone disease, and microbiome alterations is substantial and warrants serious attention from healthcare providers and public health authorities.

Future Research Needs and Recommendations

Future research needs include larger epidemiological and intervention studies to clarify the thresholds for developmental toxicity in diverse populations, longitudinal assessments of microbiome recovery following cessation of high aluminum exposure, mechanistic studies of aluminum-microbiota interactions and their long-term health consequences, and development of biomarkers that can identify infants at greatest risk of aluminum-related adverse effects.

Epidemiological Studies

Larger studies to clarify thresholds for developmental toxicity in diverse populations

Microbiome Recovery

Longitudinal assessments following cessation of high aluminum exposure

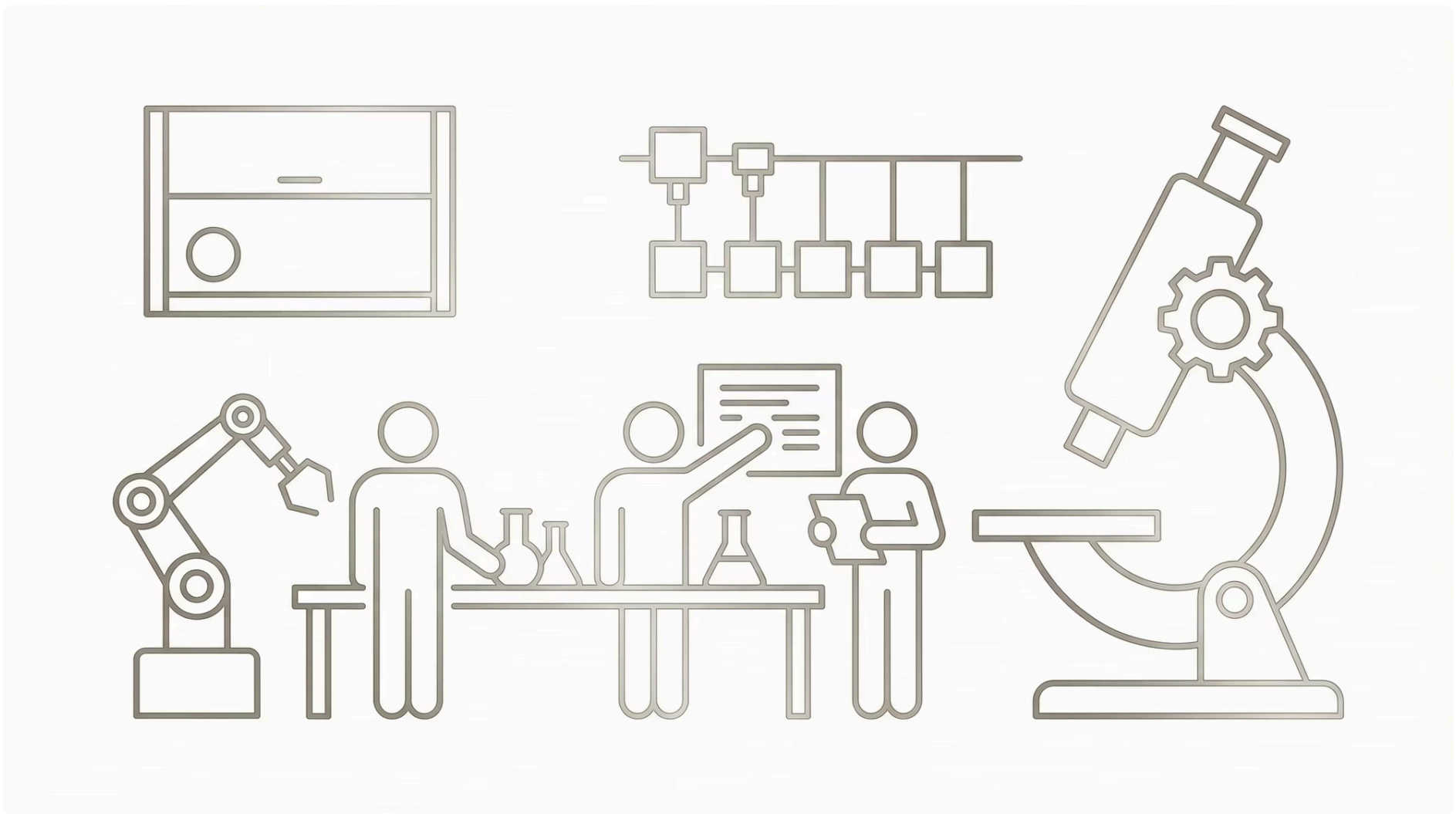
Mechanistic Studies

Aluminum-microbiota interactions and long-term health consequences

Biomarker Development

Identify infants at greatest risk of aluminum-related adverse effects

The integration of metabolomics, microbiomics, and metabolomics approaches—termed "multi-omics"—offers particular promise for understanding the complex interactions between aluminum exposure, microbiota composition, and developmental health outcomes [12].



The unique vulnerability of infants and young children to aluminum toxicity demands continued vigilance and scientifically-informed public health measures. As the field advances, understanding the mechanisms linking aluminum exposure, microbiome dysbiosis, and developmental impairment may lead to novel preventive and therapeutic interventions protecting the health of the world's most vulnerable populations.

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