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Concept Clearance

Branch: HSRB

Council Period: 202610

Concept Title: METALs

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Introduction

Metals are ubiquitous components of the environment. They may influence biological function or produce toxicity depending on the identity and chemical form of the metal, dose, route and duration of exposure, developmental stage, physiological context, and interactions with endogenous biological systems. Human exposures may arise from natural and anthropogenic environmental sources, food, beverages (including water), dietary supplements, consumer products, occupational settings, and medically-relevant materials.

The biological deposition and activity of a metal may differ substantially among elemental, ionic, particulate, complexed, and organometallic forms. Biological effects may also depend on oxidation state, solubility, particle characteristics, molecular binding partners, formulation, and the biological compartment in which exposure occurs. Consequently, measurements of total metal concentration alone may be insufficient to explain biological activity in settings where speciation, physicochemical form, or cellular localization materially influences mechanism.

NIEHS investments have produced a substantial body of research and established adverse biological and health effects associated with exposure to metals such as lead, cadmium, and mercury. Important mechanistic questions nevertheless remain regarding the molecular and cellular events connecting exposure and internal dose with biological dysfunction; the processes determining distribution to susceptible tissues and cellular compartments; and the mechanisms distinguishing adaptation and recovery from persistent biological effects.

Additionally, optimal ranges of exposure or internal concentration of essential metals (e.g., magnesium) may differ by developmental stage, nutritional or physiological state, chemical form, and tissue context. However, a mechanistic understanding is lacking as to how essential metals are homeostatically regulated, affect developmental susceptibility, compete for endogenous transport pathways, and biological effects outside of homeostatically regulated ranges.

Research Goals and Scope

This initiative aims to support mechanistic research to understand how exposure to metals and metal-containing compounds alters biological processes relevant to human health. Of interest is elucidation of absorption, distribution, transport, cellular trafficking, biological interactions, mechanisms of action, and how metals may alter immune homeostasis, cross the placental barrier, or gain access to and affect the central nervous system. Studies may employ experimental models, new approach methodologies, computational approaches, or leverage human biospecimens to address defined mechanistic hypotheses.
Goals include:
• Advancing understanding of molecular, cellular, tissue, and physiological mechanisms through which metals, metal-containing compounds, and their mixtures influence biology and health.
• Defining mechanisms governing metal absorption, transport, biodistribution, cellular uptake, trafficking, transformation, retention, and clearance.
• Elucidating mechanisms through which metals affect immune homeostasis, immune development, placental function, nervous-system function, neurodevelopment, and

neuroimmune interactions.
• Improving understanding of metal-specific biological effects across dose ranges, chemical forms, exposure routes, developmental stages, and physiology.
• Advancing understanding of aluminum, including aluminum-containing compounds encountered through environmental, consumer-product, occupational, and medically relevant exposures.
• Addressing unresolved biological questions concerning low-level lithium exposure and its potentially adverse, neutral, or beneficial biological effects.
• Encouraging human-relevant mechanistic toxicology through use of human biospecimens, human-derived experimental systems, new approach methodologies, and computational approaches.
• Generating mechanistic knowledge capable of improving hazard identification, risk assessment, and understanding of susceptibility to metals across the life course.

Mechanism and Justification

The "Mechanistic Toxicology of METALS: Metal Exposure, Transport, Action, Localization, and Susceptibility" proposal recognizes the NIEHS has a long history of supporting research that has provided mechanistic insight and information on exposure-health outcome-associations resulting from exposures to metals. It aims to both build on this existing knowledge while addressing key information gaps with the goal of providing an integrative understanding of mechanisms that determine biological responses to metals. This initiative will also provide an environmental health sciences framework by anchoring experimental conditions in environmentally relevant exposure scenarios and explicitly defining how exposure context informs the interpretation of underlying biological mechanisms. In addition, this initiative is a high priority area to HHS, supports MAHA’s focus on “Reducing Americans’ Exposure to Harmful Chemicals”, and is well-aligned with the mechanistic toxicology focus area of the NIEHS Strategic Plan.