



National Institute of Environmental Health Sciences
Your Environment. Your Health.

Concept Clearance: Mechanistic Toxicology of METALS: Metal Exposure, Transport, Action, Localization, and Susceptibility NAEHS Council

September 10, 2026

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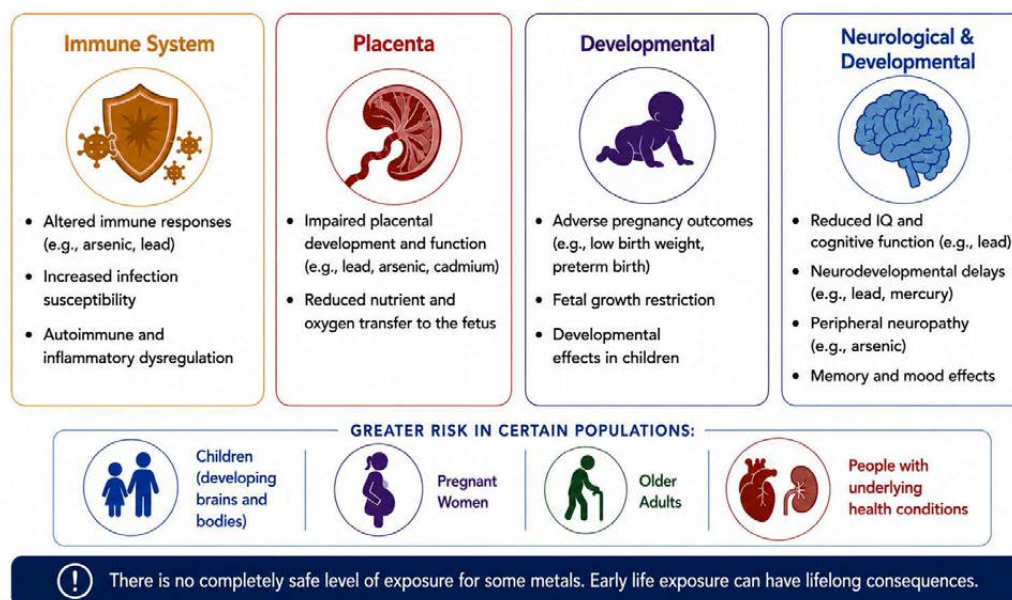
1																	2
H																	He
3	4											5	6	7	8	9	10
Li	Be											B	C	N	O	F	Ne
11	12											13	14	15	16	17	18
Na	Mg											Al	Si	P	S	Cl	Ar
19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
55	56	57-71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
87	88	89-103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118
Fr	Ra		Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og
57	58	59	60	61	62	63	64	65	66	67	68	69	70	71			
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu			
89	90	91	92	93	94	95	96	97	98	99	100	101	102	103			
Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr			

The Initiative: Examine mechanistic pathways linked with a functional outcome

Metal exposure → internal/target-tissue dose → molecular target → key biological events → functional outcome

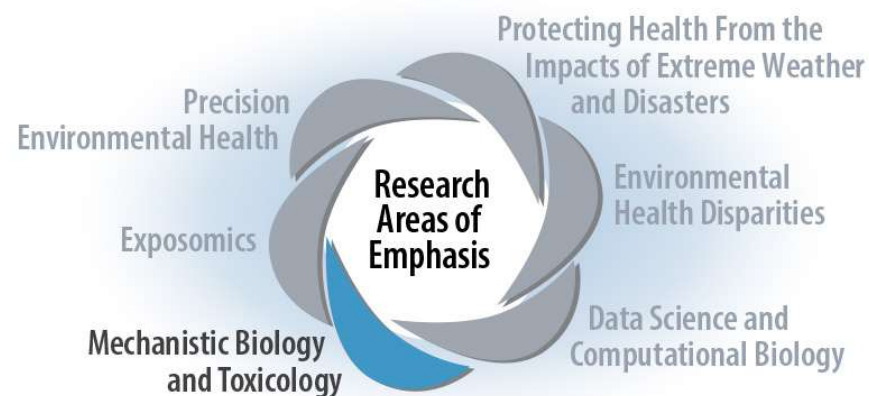
Main Health Effects Associated with Environmental Metal Exposure

Metals can affect multiple body systems across the life course.



The Initiative: Examine mechanistic pathways linked with a functional outcome

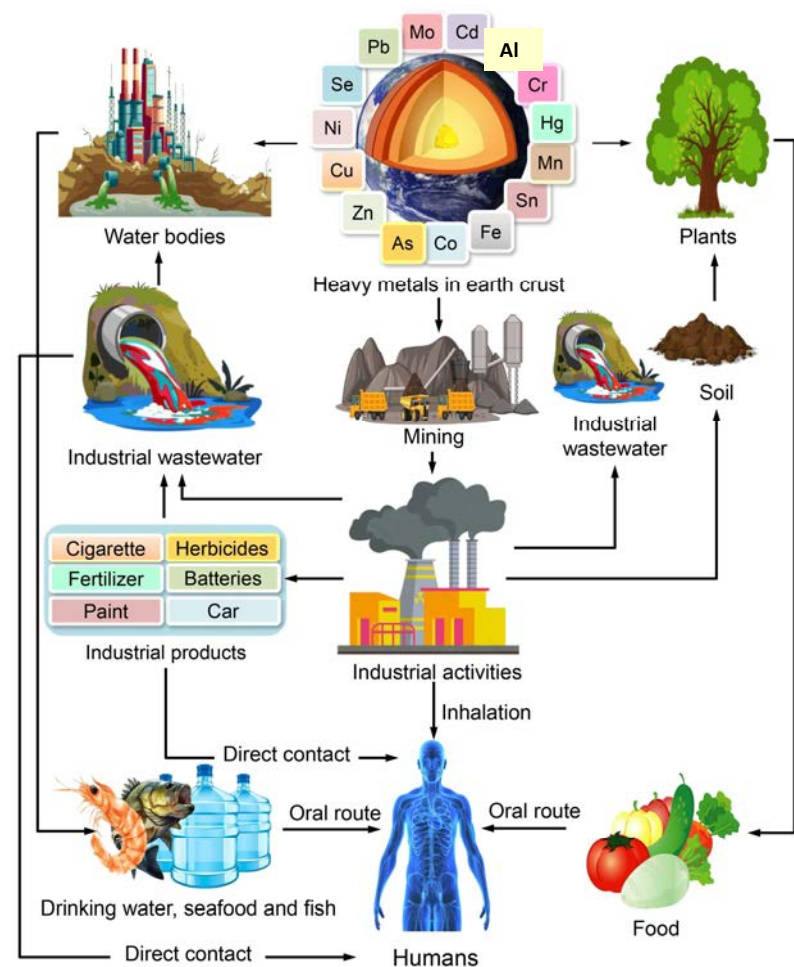
- Across dose ranges, chemical forms, exposure routes, exposure timing, developmental stages, susceptibility factors, and physiology
- Advance mechanistic understanding of understudied metal exposures (e.g., aluminum or lithium) resulting in adverse to beneficial outcomes
- Improve hazard identification, risk assessment, and understanding of susceptibility to metals across the life course



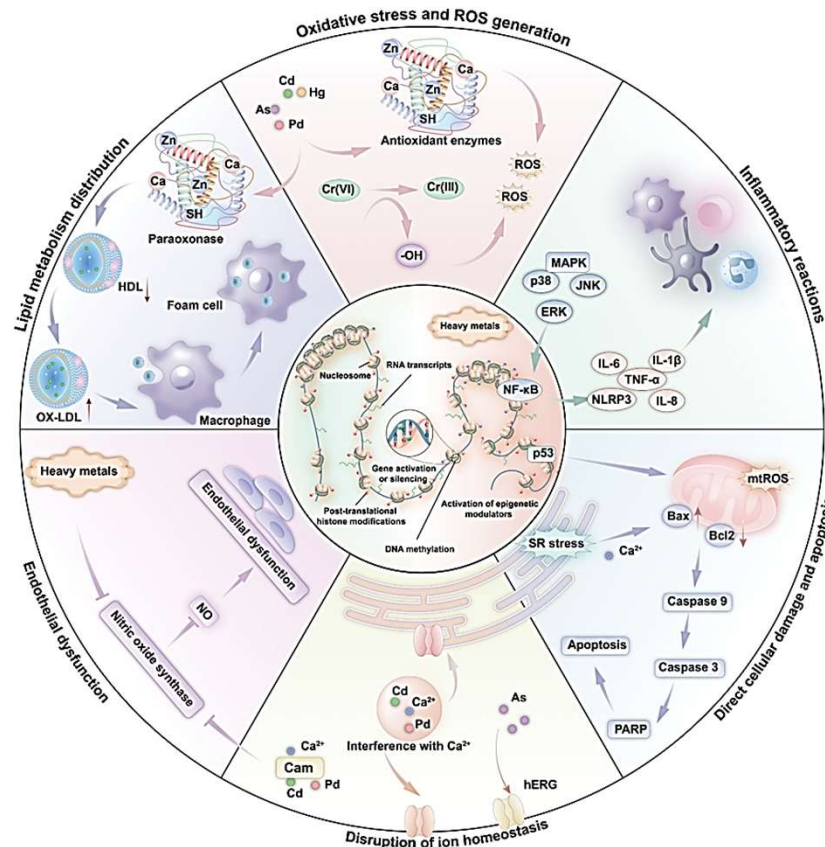
From NIEHS's 2025-2029 Strategic Plan

Background

- Exposures to metals may arise from natural and anthropogenic sources
- Essential to biological function (e.g., Mg, Mn, Fe, Cu, Zn, Co, etc.)
- May produce toxicity/health effects depending on
 - Chemical form (e.g., oxidation state, solubility, particle characteristics, formulation)
 - Dose
 - Exposure route
 - Receptor binding
 - Tissue/cellular compartment/target
 - Duration of exposure
 - Developmental stage
 - Physiology
 - Pre-existing conditions



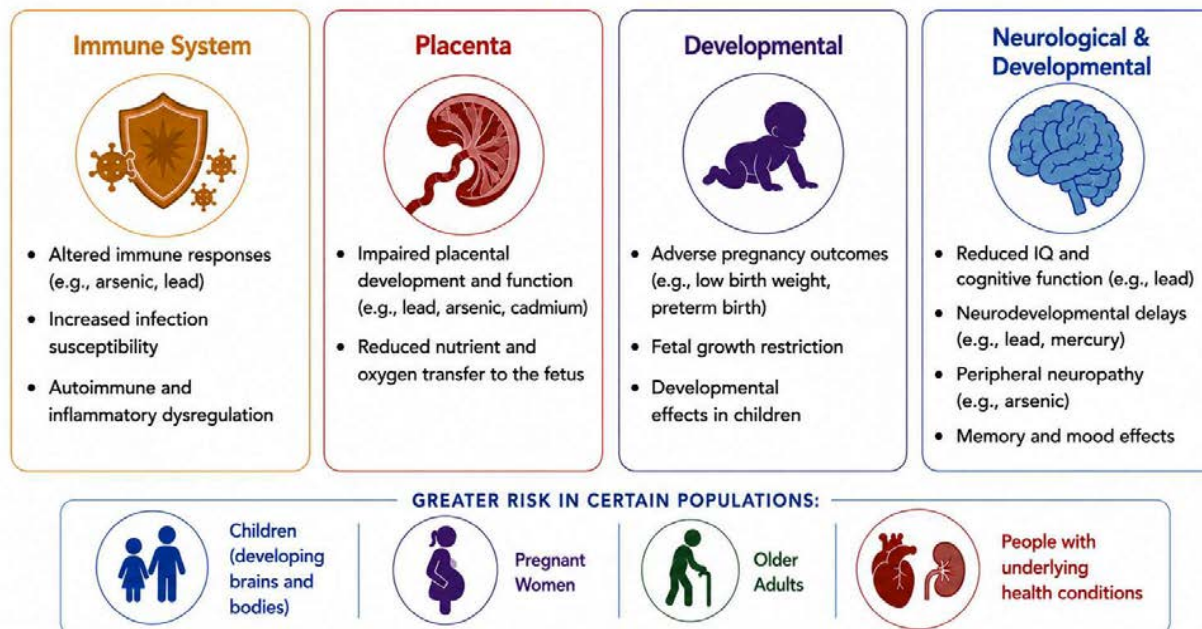
Some General Mechanisms of Metals Toxicity



Initiative Areas of Focus

Main Health Effects Associated with Environmental Metal Exposure

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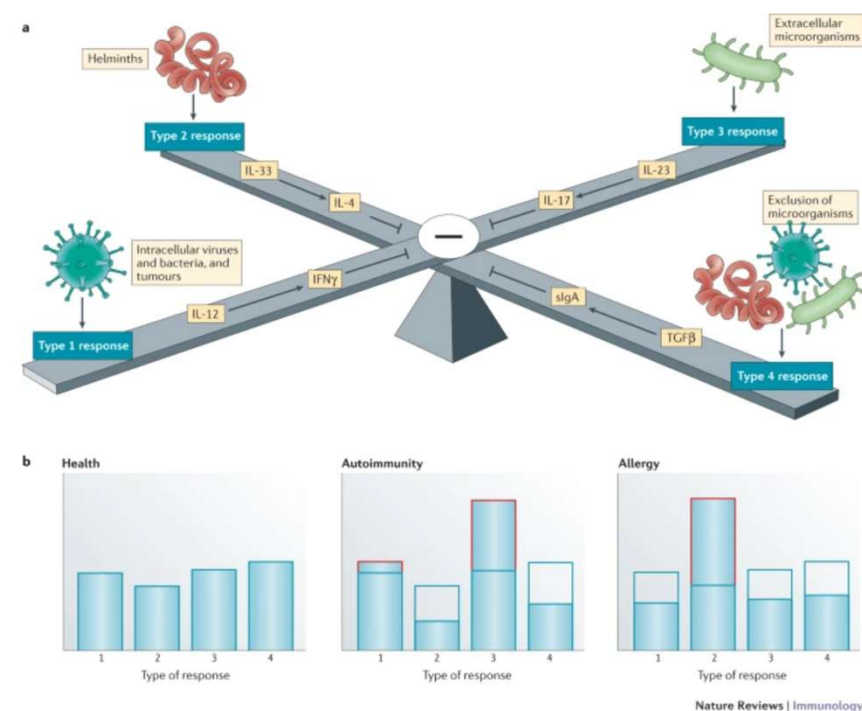
There is no completely safe level of exposure for some metals. Early life exposure can have lifelong consequences.

Immune Homeostasis and Immunotoxicology

Immune homeostasis is the immune system's ability to stay balanced:

- strong enough to fight infection
- controlled enough to avoid attacking your own tissues or overreacting to harmless antigens.

If that balance slips, the consequence is chronic inflammation, allergy, or autoimmunity.



<https://fiveable.me/immunobiology/key-terms/immune-homeostasis>

Eberl, G. *Nat Rev Immunol* **16**, 524–532 (2016). <https://doi.org/10.1038/nri.2016.75>

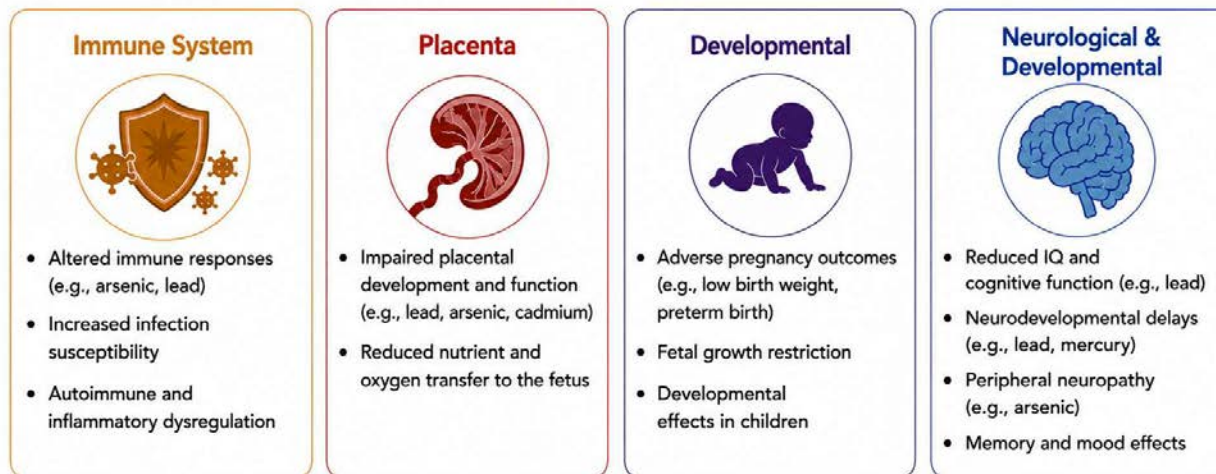
Immune Homeostasis and Immunotoxicology

- A major objective of this initiative is to identify mechanisms through which metals influence immune homeostasis.
- Relevant research could address:
 - Innate or adaptive immune-cell activation
 - Differentiation
 - Trafficking
 - Tolerance
 - Memory
 - Inflammatory signaling
 - Resolution
 - Immunometabolism
 - Redox-sensitive signaling
 - Innate sensing pathways
 - Communication among immune and nonimmune cells

Metals Exposure – Placental and Developmental Effects

Main Health Effects Associated with Environmental Metal Exposure

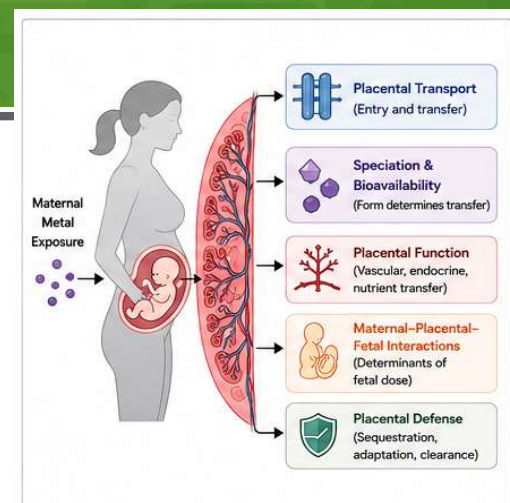
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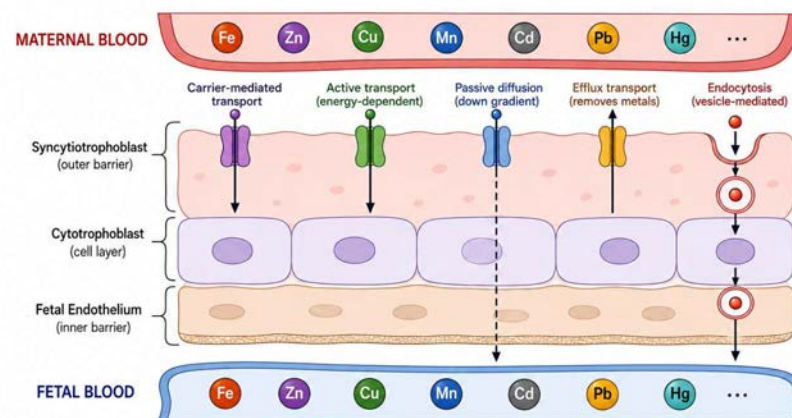
Placental Exposures

- **Placental transport** — mechanisms controlling fetal metal exposure
- **Speciation & bioavailability** — which metal forms reach the fetal compartment
- **Placental function** — effects on vascular, endocrine, and nutrient-transfer pathways
- **Maternal-placental-fetal interactions** — determinants of fetal dose and response
- **Placental defense mechanisms** — sequestration, adaptation, and clearance



Metal Transport Across the Maternal-Fetal Barrier

Metals move from maternal blood to fetal blood through trophoblast and endothelial layers

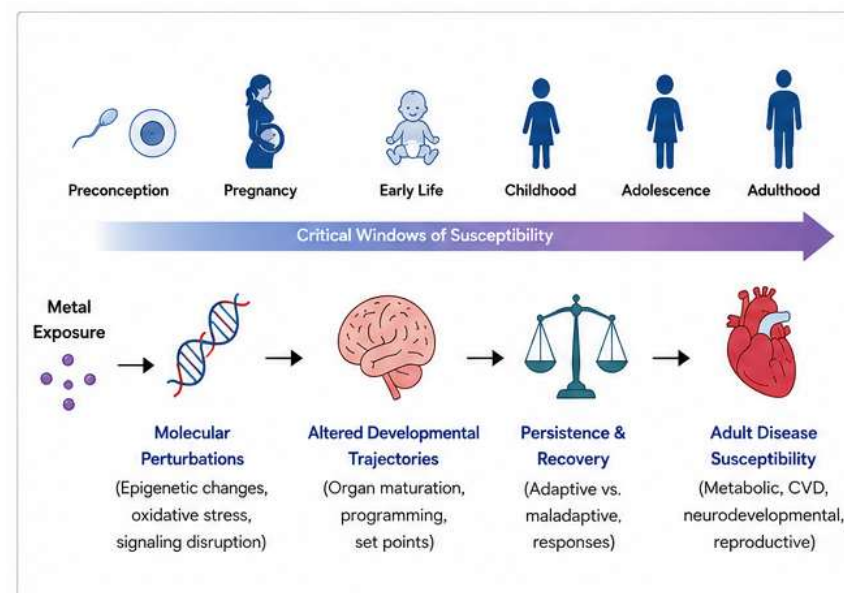


The placenta selectively transports metals.

Transporters, diffusion, and endocytosis regulate metal uptake, efflux, and detoxification at the maternal-fetal interface.

Developmental Origins of Health and Disease

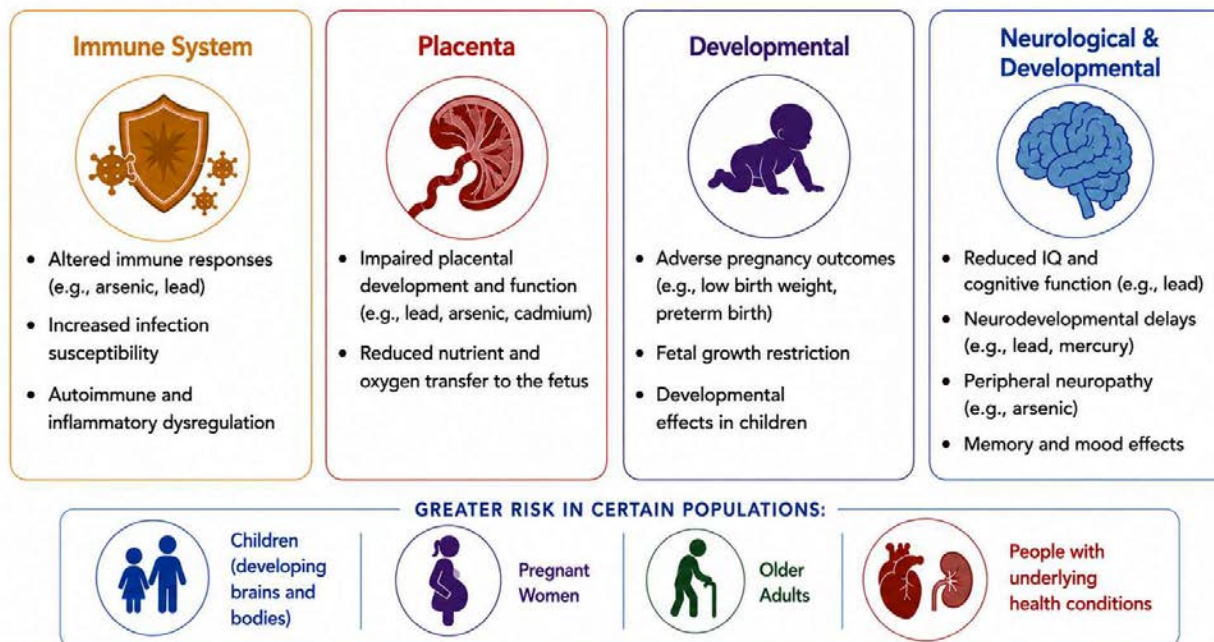
- **Critical exposure windows** — when metal exposures have lasting consequences
- **Developmental programming** — mechanisms establishing long-term disease susceptibility
- **Persistence & recovery** — why some early-life effects resolve while others persist
- **Altered developmental trajectories** — organ maturation, biological set points, and function
- **Early exposure → adult disease** — mechanistic links to later-life health outcomes



Metals Exposure – Neurological Effects

Main Health Effects Associated with Environmental Metal Exposure

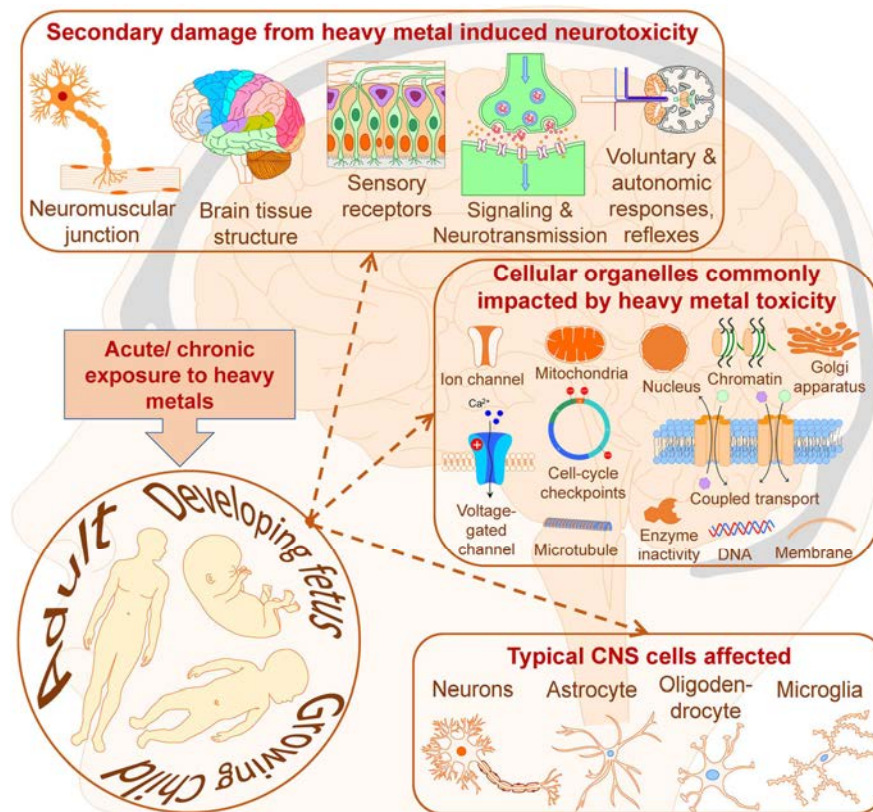
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Mechanistic Basis of Metal Neurotoxicity

- Many metals cross the blood-brain barrier
 - Specialized transport systems (Cu, Zn, Mn, Mg, Fe)
 - Leverage related transport (Cd²⁺ using Zn²⁺ transporters)
- Damage to BBB (Pb disruption of calcium signaling)
- Sequestration and saturation of transport mechanisms and intercellular trafficking
- Oxidation of macromolecules generates free radicals and reactive oxidative species
 - Perturbs signaling cascades throughout and initiation of apoptotic pathways
- Metals that maintain homeostasis (e.g., Mn) and a narrow optimal window to support endogenous functions

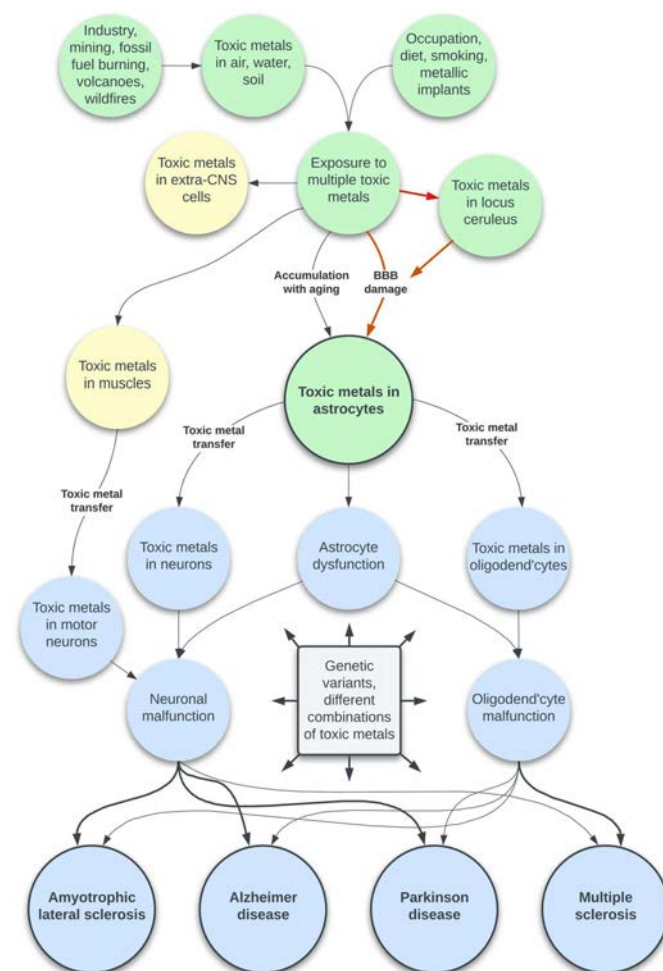


Kothapalli C. *Current Opinion in Toxicology* **2021**, 26, 33; <https://doi.org/10.1016/j.cotox.2021.04.003>

Handbook on the Toxicology of Metals 4E <http://dx.doi.org/10.1016/B978-0-444-59453-2.00015-9>

Neurological Outcomes from Metal Exposure

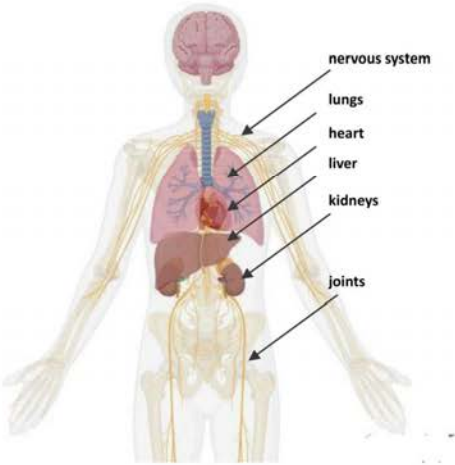
- Overt clinical manifestations from acute, high-dose exposure to many metals (poisoning)
- Longer duration, lower dose exposure can lead to sustained dysregulation
- Some metals lead to localized damage (Mn and dopaminergic neurons), some broad (Pb)
- Specific effects of exposure depends on the developmental window – what stage of nervous system development (e.g., MeHg exposure produces more severe effects if prenatal than postnatal)
- Phenotypic presentation depends on perturbed pathways, selective targeting of central or peripheral nervous system functions, and overall mode of toxicity



Metal Neurotoxicity Data Gaps

- Evaluating the role of extracellular vesicles (EVs) in metal cargo and as biomarkers of environmental toxicity and disease progression
- Assessing the impact of metal exposures on neuroactive metabolites (including neurotransmitters) produced from gut microbiota that affect brain function
- Discerning vulnerable exposure windows for exposure to metals in neurological disease progression
- Elucidating impact of metals on neuroimmune pathways

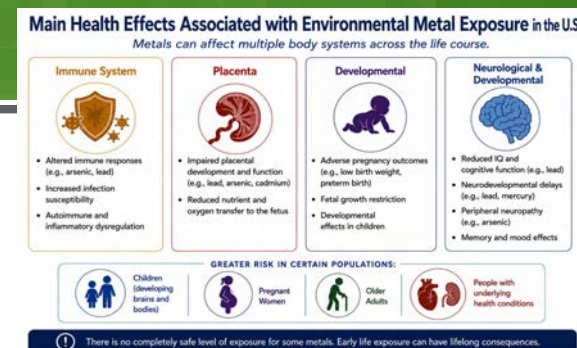
Neuroimmune effects from metals exposures

Metal	Main sources	Main mechanisms	Connections to autoimmune diseases	Major organs susceptible to metal accumulation
Mercury	dental amalgams, fish consumption, occupational exposure	oxidative stress stimulation of proinflammatory cytokines release of self-antigens	multiple sclerosis	
Lead	contaminated water, industrial exposure, old paint	oxidative stress binding to proteins mitochondrial dysfunction	systemic lupus erythematosus	
Cadmium	industrial processes, batteries, paints, cosmetics	oxidative stress mitochondrial dysfunction	rheumatoid arthritis	
Aluminum	cookware, food packaging, antacids	oxidative stress stimulation of proinflammatory cytokines amyloid beta aggregation, activation of immune cells	neurological disorders	
Nickel	jewelry, coins, cell phones, diet, occupational exposure	functioning as a hapten oxidative stress activation of immune cells	contact dermatitis, potential association with multiple sclerosis	
Palladium	dental restorations, jewelry	oxidative stress hypersensitivity delayed-type hypersensitivity	potential hypersensitivity	
Gold and Silver	dental restorations, jewelry, occupational exposure	oxidative stress modulation of mast cell function	rheumatoid arthritis, potential triggering of autoimmune response	

Autoimmune hallmarks perturbed by metals: hapten formation, ROS generation, cytokine production, blood-brain barrier disruption, neuroinflammation, immune cell activation and migration, gut-brain axis disruption

Overall Knowledge Gaps to be Addressed by Initiative

- Total metal concentration alone may be insufficient to explain biological activity in settings where speciation, oxidation state, physicochemical form, or cellular localization influences mechanism.
- Distribution of metals to susceptible tissues and cellular compartments, adaptation, recovery, and persistence.
- For essential metals, optimal ranges of exposure or internal concentration:
 - May differ by developmental stage, nutritional or physiological state, chemical form, target tissue, role in homeostatic regulation, developmental susceptibility, and competition for endogenous transport pathways.
- For some metals (e.g., aluminum, lithium), uncertainties remain on biological distribution, receptor-binding, dose-response relationships, and potential short- or long-term biological effects.



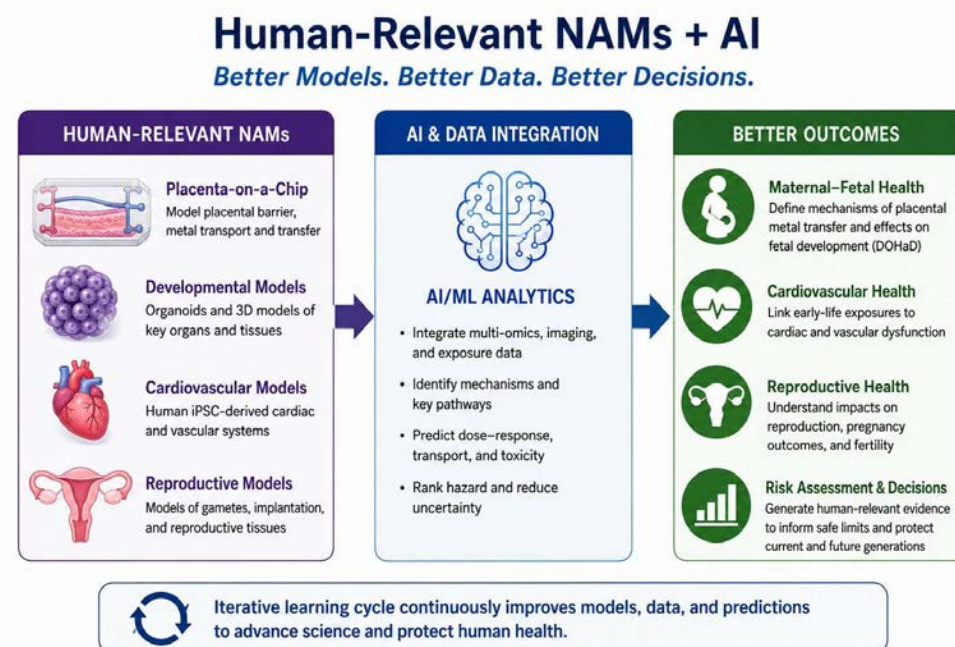


Several Outcomes from Initiative

- Supports a high priority area to HHS and MAHA's focus on "Reducing Americans' Exposure to Harmful Chemicals"
- Moves beyond exposure-health outcome associations to experimental and integrative understanding of mechanisms that determine biological responses to metals
- Supports NIEHS's area of emphasis of "Mechanistic Toxicology" and will provides a rich set of research questions to further develop innovative new approach methodologies.
- Provides enhanced coordination of the NIEHS metals portfolio (something that we have not been able to do for unsolicited research)
- Adds novel area of research (e.g., neuroimmune effects)
- Brings together research under a defined initiative to foster and accelerate coordination and collaboration among metals researchers

New Approach Methodologies

- **Human-relevant models** — organoids, organ-on-chip, and primary cell systems for metal toxicology
- **Mechanistic dose–response** — NAMs that bridge environmental exposure to target-tissue dose and response
- **Metal disposition in vitro** — models incorporating uptake, speciation, trafficking, sequestration, and clearance
- **Advanced mechanistic endpoints** — single-cell, spatial, imaging, and multi-omic approaches to identify key events
- **Translation & validation** — integrate NAMs with human biospecimens and computational models to improve human relevance

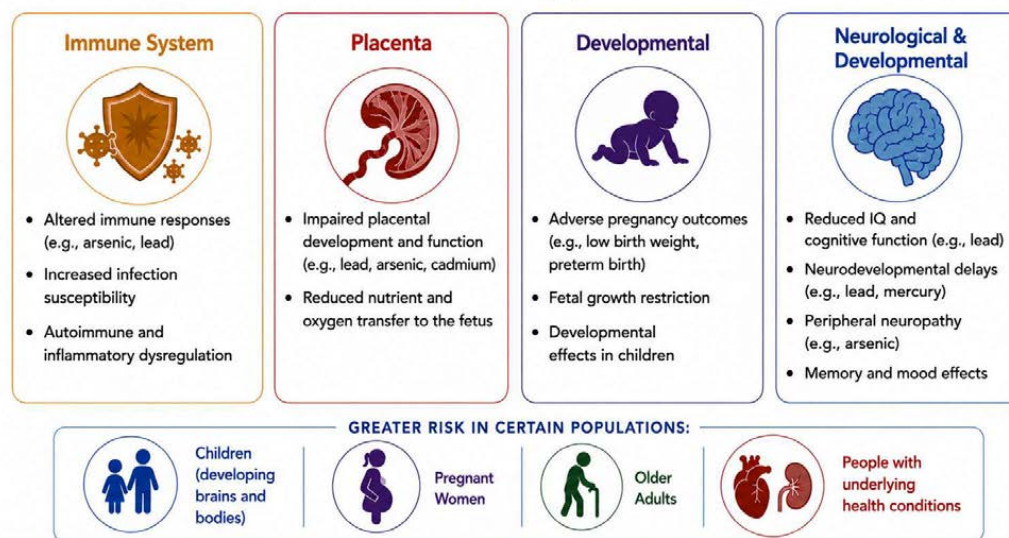


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Thank you!

- Council Discussion

