Metals in tissues: notes for discussion

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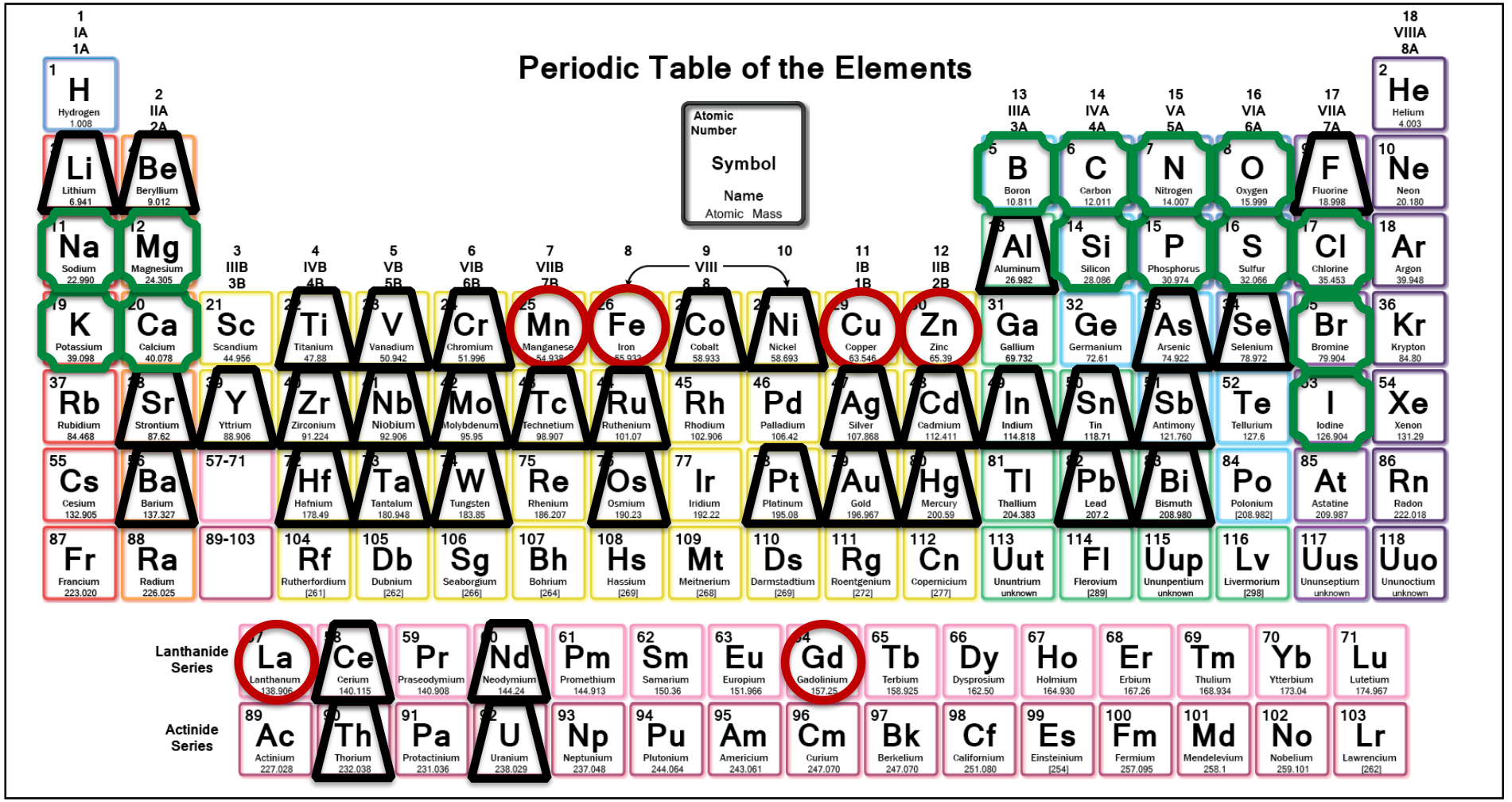
- Many metals found in tissues in **insoluble** particulate form => evidence of prior exposure
  - **Recognized limitations**: processed tissues lose soluble materials; particulate deposits need to be large enough to resolve in EM; concentration of element(s) need to be high enough to detect in individual particulates [SEM/EDS is NOT a bulk analytical technique]; consequently, semi-quantitative results may not fully correlate with quantitative results (such as ICP-MS)
  - Different (micro)analytical methods each have various limitations
- Toxicity evaluations are complex, involving animal and *in vitro* studies as well as epidemiologic and morphologic/ analytical human studies
- Periodic table shows the elements detected in tissues over 40+ yrs in our lab [using mostly SEM/EDS but also SIMS, raman spectroscopy and sXRF]
- Exposure > Retention > Detection
- How are short and long term effects defined? … Detected?
- Interdisciplinary teams required for functional tests and evaluations; e.g., neurotoxicologists, psychologists, psychiatrists, physiologists, pathologists, bio-statisticians, epidemiologists, radiologists, etc.

Conflicts of Interest

Previously served as an expert in litigation regarding Gd and NSF, and currently involved in a research project on Gd in brain tissues funded by Guerbet Pharmaceuticals.

Elements detected in tissues as insoluble deposits (particles) over 40 + years in our lab

Red = of special interest re Gd studies; Black = other metals; Green = others



Further Points to consider re Metals

- Speciation of detected elements:
  - SEM/EDS does provide multi-element analysis of individual particulate materials, showing associations (such as Gd with Ca, P, Na, Fe)
    - Detection of same particles in fresh frozen tissues rules out artefact from tissue fixation process
  - Other methods (EXAFS) can show atomic structure of such deposits (Gd phosphate).
- Long term storage (e.g., in bones) and later release has been shown for Pb and La
- Voluminous literature exists on toxic effects of many metals in CNS and other systems have been described in humans, other animals, and cells, but gaps needing further study remain
    - E.g., dissociation of Gd from chelate may result in unknown number of intermediate metabolites/compounds, the toxicology of which of course has not been evaluated
    - Could there be any resultant organo-metallic compounds formed? Cf Toxicity of organo -Sn, -Pb , -Hg
- Mechanisms: Calcium competition/channel blockers, phosphate binding, hypersensitivity reactions, inflammation, fibrosis, cognitive impairment, Parkinson's (e.g., welding)
- Need models: what conc of Gd deposits of what diameter(s) result in a certain observed MRI signal? – assuming surface of 'particles' can interact with water molecules [Note: many of observed deposits are in the ***nanoparticle*** size range]
- IMPORTANT not to rush to use alternatives/substitutes for Gd without adequate pre-clinical testing, e.g. in renal failure, liver failure models
- Would anyone have thought to use chelated Pb as hypothetical contrast agent? !