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, biostatisticians, 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?!