

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, 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

Periodic Table of the Elements

1 IA 1A		2 IIA 2A		3-10										13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A
1 H Hydrogen 1.008	2 He Helium 4.003	3 Li Lithium 6.941	4 Be Beryllium 9.012	5 B Boron 10.811	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180	11 Na Sodium 22.990	12 Mg Magnesium 24.305	13 Al Aluminum 26.982	14 Si Silicon 28.086	15 P Phosphorus 30.974	16 S Sulfur 32.066	17 Cl Chlorine 35.453	18 Ar Argon 39.948		
19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.88	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.833	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.39	31 Ga Gallium 69.723	32 Ge Germanium 72.61	33 As Arsenic 74.922	34 Se Selenium 78.972	35 Br Bromine 79.904	36 Kr Krypton 84.80		
37 Rb Rubidium 84.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868	48 Cd Cadmium 112.411	49 In Indium 114.818	50 Sn Tin 118.71	51 Sb Antimony 121.760	52 Te Tellurium 127.6	53 I Iodine 126.904	54 Xe Xenon 131.29		
55 Cs Cesium 132.905	56 Ba Barium 137.327	57-71	72 Hf Hafnium 178.49	73 Ta Tantalum 180.948	74 W Tungsten 183.85	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.967	80 Hg Mercury 200.59	81 Tl Thallium 204.383	82 Pb Lead 207.2	83 Bi Bismuth 208.980	84 Po Polonium [208.982]	85 At Astatine 209.987	86 Rn Radon 222.018		
87 Fr Francium 223.020	88 Ra Radium 226.025	89-103	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [266]	107 Bh Bohrium [264]	108 Hs Hassium [269]	109 Mt Meitnerium [268]	110 Ds Darmstadtium [269]	111 Rg Roentgenium [272]	112 Cn Copernicium [277]	113 Uut Ununtrium unknown	114 Fl Flerovium [289]	115 Uup Ununpentium unknown	116 Lv Livermorium [293]	117 Uus Ununseptium unknown	118 Uuo Ununoctium unknown		
Lanthanide Series		57 La Lanthanum 138.905	58 Ce Cerium 140.115	59 Pr Praseodymium 140.908	60 Nd Neodymium 144.24	61 Pm Promethium 144.913	62 Sm Samarium 150.36	63 Eu Europium 151.966	64 Gd Gadolinium 157.25	65 Tb Terbium 158.925	66 Dy Dysprosium 162.50	67 Ho Holmium 164.930	68 Er Erbium 167.26	69 Tm Thulium 168.934	70 Yb Ytterbium 173.04	71 Lu Lutetium 174.967			
Actinide Series		89 Ac Actinium 227.028	90 Th Thorium 232.038	91 Pa Protactinium 231.036	92 U Uranium 238.029	93 Np Neptunium 237.048	94 Pu Plutonium 244.064	95 Am Americium 243.061	96 Cm Curium 247.070	97 Bk Berkelium 247.070	98 Cf Californium 251.080	99 Es Einsteinium [254]	100 Fm Fermium 257.095	101 Md Mendelevium 258.1	102 No Nobelium 259.101	103 Lr Lawrencium [262]			

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? !