



Toxicity of Metals

M1: Lung Basics and Principles of Toxicology
– Methods in Toxicology –

Jonas Tigges

14.03.2019

Heavy Metals - Definition

- No homogenous definition:

Pure Appl. Chem., Vol. 74, No. 5, pp. 793–807, 2002.

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INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

CHEMISTRY AND HUMAN HEALTH DIVISION

CLINICAL CHEMISTRY SECTION, COMMISSION ON TOXICOLOGY*

“HEAVY METALS”—A MEANINGLESS TERM?

(IUPAC Technical Report)

Prepared for publication by

JOHN H. DUFFUS

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1. Definition in terms of density

Periodic Table of the Elements

Atomic Number
Symbol
Name
Atomic Mass

Atomic mass values reflect the IUPAC accepted values as of 2002/01/01.
Masses reported in bold/italic show the lower and upper limit of atomic mass depending on the physical and chemical history of the element.
Masses expressed in \pm format are the mass numbers of the longest-lived isotopes for elements with no stable nucleus.

1 1A 1A 1 H Hydrogen (1.00784 u, 1.00811 u)	2 2A 2A 4 He Helium (4.002602 u)																	18 VIIIA 8A 2 He Helium (4.002602 u)																													
3 1A 1A 3 Li Lithium (6.941 u, 6.991 u)	4 2A 2A 4 Be Beryllium (9.012182 u)																	5 3A 3A 5 B Boron (10.811 u, 10.821 u)	6 4A 4A 6 C Carbon (12.0107 u, 12.011 u)	7 5A 5A 7 N Nitrogen (14.00643 u, 14.00748 u)	8 6A 6A 8 O Oxygen (15.99903 u, 15.99978 u)	9 7A 7A 9 F Fluorine (18.9984032 u)	10 8A 8A 10 Ne Neon (20.1797 u)																								
11 1A 1A 11 Na Sodium (22.98976928 u)	12 2A 2A 12 Mg Magnesium (24.304 u, 24.305 u)	3 3B 3B 3 Sc Scandium (44.955912 u)	4 4B 4B 4 Ti Titanium (47.88 u)	5 5B 5B 5 V Vanadium (50.9415 u)	6 6B 6B 6 Cr Chromium (51.9961 u)	7 7B 7B 7 Mn Manganese (54.938045 u)	8 8 8 8 Fe Iron (55.845 u)	9 VIII VIII 9 Co Cobalt (58.933194 u)	10 VIII VIII 10 Ni Nickel (58.6934 u)	11 9B 9B 11 Cu Copper (63.546 u)	12 10B 10B 12 Zn Zinc (65.38 u)	13 3A 3A 13 Al Aluminum (26.9815385 u)	14 4A 4A 14 Si Silicon (28.0855 u, 28.086 u)	15 5A 5A 15 P Phosphorus (30.973761998 u)	16 6A 6A 16 S Sulfur (32.059 u, 32.07 u)	17 7A 7A 17 Cl Chlorine (35.4464 u, 35.453 u)	18 8A 8A 18 Ar Argon (39.948 u)																														
19 1A 1A 19 K Potassium (39.0983 u)	20 2A 2A 20 Ca Calcium (40.078 u)	21 3B 3B 21 Sc Scandium (44.955912 u)	22 4B 4B 22 Ti Titanium (47.88 u)	23 5B 5B 23 V Vanadium (50.9415 u)	24 6B 6B 24 Cr Chromium (51.9961 u)	25 7B 7B 25 Mn Manganese (54.938045 u)	26 8 8 26 Fe Iron (55.845 u)	27 VIII VIII 27 Co Cobalt (58.933194 u)	28 VIII VIII 28 Ni Nickel (58.6934 u)	29 9B 9B 29 Cu Copper (63.546 u)	30 10B 10B 30 Zn Zinc (65.38 u)	31 3A 3A 31 Ga Gallium (69.723 u)	32 4A 4A 32 Ge Germanium (72.6305 u)	33 5A 5A 33 As Arsenic (74.921595 u)	34 6A 6A 34 Se Selenium (78.9718 u)	35 7A 7A 35 Br Bromine (79.904 u, 79.907 u)	36 8A 8A 36 Kr Krypton (83.798 u)																														
37 1A 1A 37 Rb Rubidium (85.4678 u)	38 2A 2A 38 Sr Strontium (87.62 u)	39 3B 3B 39 Y Yttrium (88.90584 u)	40 4B 4B 40 Zr Zirconium (91.224 u)	41 5B 5B 41 Nb Niobium (92.90638 u)	42 6B 6B 42 Mo Molybdenum (95.94 u)	43 7B 7B 43 Tc Technetium <20>	44 8 8 44 Ru Ruthenium (101.07 u)	45 VIII VIII 45 Rh Rhodium (102.90550 u)	46 VIII VIII 46 Pd Palladium (106.42 u)	47 9B 9B 47 Ag Silver (107.8682 u)	48 10B 10B 48 Cd Cadmium (112.414 u)	49 3A 3A 49 In Indium (114.818 u)	50 4A 4A 50 Sn Tin (118.710 u)	51 5A 5A 51 Sb Antimony (121.757 u)	52 6A 6A 52 Te Tellurium (127.603 u)	53 7A 7A 53 I Iodine (126.90447 u)	54 8A 8A 54 Xe Xenon (131.29 u)																														
55 1A 1A 55 Cs Cesium (132.90545196 u)	56 2A 2A 56 Ba Barium (137.327 u)	57-71 3B 3B 57-71 La-Lu Lanthanide Series	72 4B 4B 72 Hf Hafnium (178.49 u)	73 5B 5B 73 Ta Tantalum (180.94788 u)	74 6B 6B 74 W Tungsten (183.84 u)	75 7B 7B 75 Re Rhenium (186.207 u)	76 8 8 76 Os Osmium (190.23 u)	77 VIII VIII 77 Ir Iridium (192.222 u)	78 VIII VIII 78 Pt Platinum (195.084 u)	79 9B 9B 79 Au Gold (196.966569 u)	80 10B 10B 80 Hg Mercury (200.59 u)	81 3A 3A 81 Tl Thallium (204.3833 u, 204.384 u)	82 4A 4A 82 Pb Lead (207.2 u)	83 5A 5A 83 Bi Bismuth (208.9804 u)	84 6A 6A 84 Po Polonium <209>	85 7A 7A 85 At Astatine <209>	86 8A 8A 86 Rn Radon <222>																														
87 1A 1A 87 Fr Francium <223>	88 2A 2A 88 Ra Radium <226>	89-103 3B 3B 89-103 La-Lu Actinide Series	104 4B 4B 104 Rf Rutherfordium <261>	105 5B 5B 105 Db Dubnium <262>	106 6B 6B 106 Sg Seaborgium <263>	107 7B 7B 107 Bh Bohrium <264>	108 8 8 108 Hs Hassium <277>	109 VIII VIII 109 Mt Meitnerium <268>	110 VIII VIII 110 Ds Darmstadtium <271>	111 9B 9B 111 Rg Roentgenium <272>	112 10B 10B 112 Cn Copernicium <285>	113 3A 3A 113 Uut Ununtrium <288>	114 4A 4A 114 Fl Flerovium <289>	115 5A 5A 115 Uup Ununpentium <290>	116 6A 6A 116 Lv Livermorium <293>	117 7A 7A 117 Uus Ununseptium <294>	118 8A 8A 118 Uuo Ununoctium <294>																														
																		57 3B 3B 57 La Lanthanum (138.90471 u)	58 4B 4B 58 Ce Cerium (140.12 u)	59 5B 5B 59 Pr Praseodymium (140.90765 u)	60 6B 6B 60 Nd Neodymium (144.242 u)	61 7B 7B 61 Pm Promethium <145>	62 8 8 62 Sm Samarium (150.36 u)	63 9B 9B 63 Eu Europium (151.964 u)	64 10B 10B 64 Gd Gadolinium (157.25 u)	65 3B 3B 65 Tb Terbium (158.92535 u)	66 4B 4B 66 Dy Dysprosium (162.50 u)	67 5B 5B 67 Ho Holmium (164.93032 u)	68 6B 6B 68 Er Erbium (167.259 u)	69 7B 7B 69 Tm Thulium (168.93032 u)	70 8 8 70 Yb Ytterbium (173.045 u)	71 9B 9B 71 Lu Lutetium (174.967 u)	89 3B 3B 89 Ac Actinium <227>	90 4B 4B 90 Th Thorium (232.0377 u)	91 5B 5B 91 Pa Protactinium (231.03688 u)	92 6B 6B 92 U Uranium (238.02891 u)	93 7B 7B 93 Np Neptunium <237>	94 8 8 94 Pu Plutonium <244>	95 9B 9B 95 Am Americium <243>	96 10B 10B 96 Cm Curium <247>	97 3B 3B 97 Bk Berkelium <247>	98 4B 4B 98 Cf Californium <251>	99 5B 5B 99 Es Einsteinium <252>	100 6B 6B 100 Fm Fermium <257>	101 7B 7B 101 Md Mendelevium <258>	102 8 8 102 No Nobelium <259>	103 9B 9B 103 Lr Lawrencium <260>

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2 IIA 2A												13	14		
3	4											11	12	13	14
Li	Be											IB	IIIB	Al	Si
11	12	3	4	5	6	7	8	9	10	11	12	13	14		
Na	Mg	IIIB	IVB	VB	VIB	VIIIB	VIII	VIII	VIII	IB	IIIB	Al	Si		
19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se
37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te
55	56	57-71	72	73	74	75	76	77	78	79	80	81	82	83	84
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po
87	88	89-103													
Fr	Ra		Rf												

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
Lanthanide Series														

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
Actinide Series														

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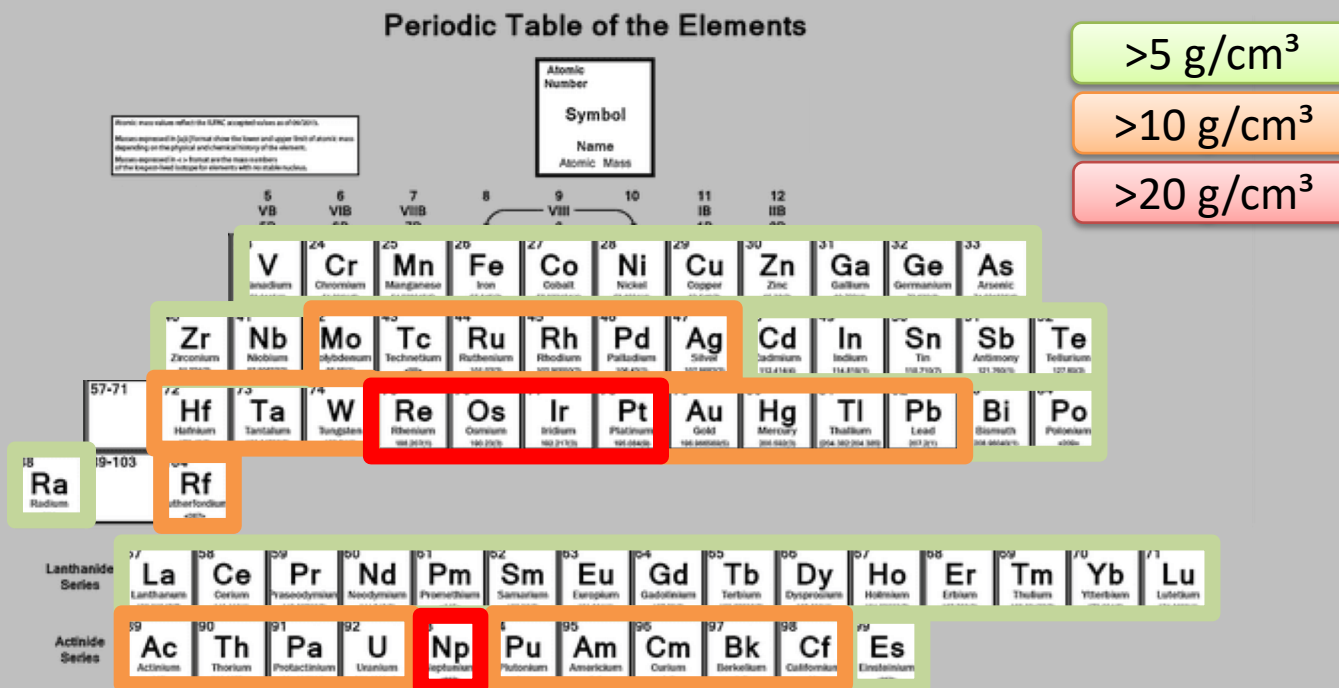
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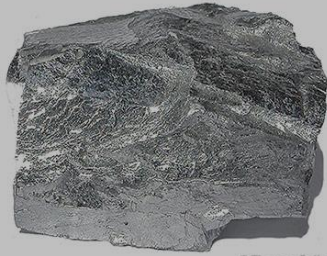
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 1. Definition in terms of density
 2. Definition in terms of atomic weight (relative atomic mass)
 1. „Metal with a high atomic mass“
 2. „Metal of atomic weight greater than sodium“
 3. ...
 3. Definition in terms of atomic number
 1. „Any metal with an atomic number beyond calcium“
 2. „Any element with an atomic number greater than 20“
 4. Definitions via toxicity
 1. „Element commonly used in industry and **generically toxic to animals and to aerobic and anaerobic processes**, but not every one is dense or entirely metallic. Includes As, Cd, Cr, Pb, Hg, Ni, Se, Zn“
 2. „Outdated generic term referring to lead, cadmium, mercury, and some other elements **which generally are relatively toxic** in nature“

Heavy Metals - Definition



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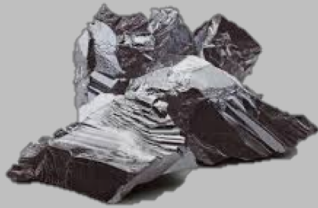
Chromium



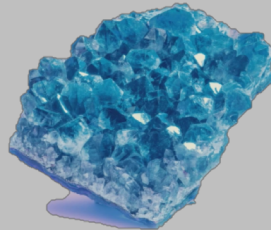
Arsenic



Lead



Cadmium



Cobalt



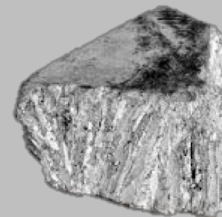
Iron



Nickel



Mercury



Zinc

Toxicity of metals

- Metals play an important role in many different body functions
- Transport and metabolism of oxygen
- Signal transduction
- DNA-binding of proteins
- Electron transfer

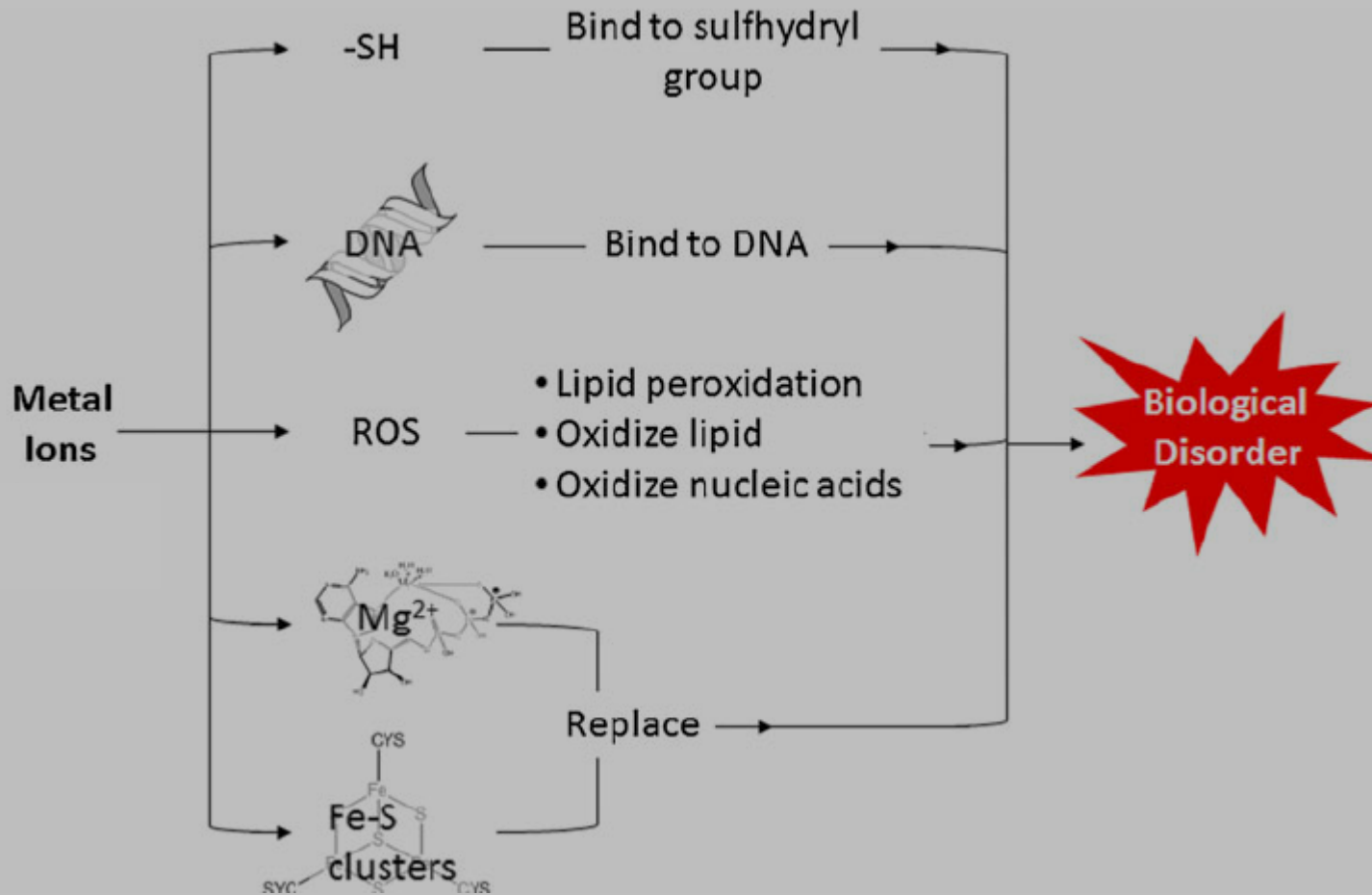
Metal	Essential	Toxic
Chromium	✓	✓
Arsenic		✓
Lead		✓
Cadmium		✓
Cobalt	✓	
Iron	✓	✓
Nickel	✓	
Mercury		✓
Zinc	✓	✓



Paracelsus (1493-1541) : „All things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison.”

Modified from Toxikologie: Band 2: Toxikologie der Stoffe; Wiley-VCH Verlag GmbH & Co. KGaA; Auflage: 1. (17. Februar 2010)

Toxicity of metals



Han, Sung & Auger, Christopher & Castonguay, Zachary & P. Appanna, Varun & Thomas, Sean & Appanna, Vasu. (2012). The unravelling of metabolic dysfunctions linked to metal-associated diseases by blue native polyacrylamide gel electrophoresis. *Analytical and Bioanalytical Chemistry*. 405. 1-11. 10.1007/s00216-012-6413-9.

Toxicity of metals

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Germany

German who poisoned colleagues' sandwiches receives life sentence

Victims of 'Klaus O' suffered serious damage to health from ingesting mercury and lead

AP in Berlin

Thu 7 Mar 2019 22:42 GMT



586



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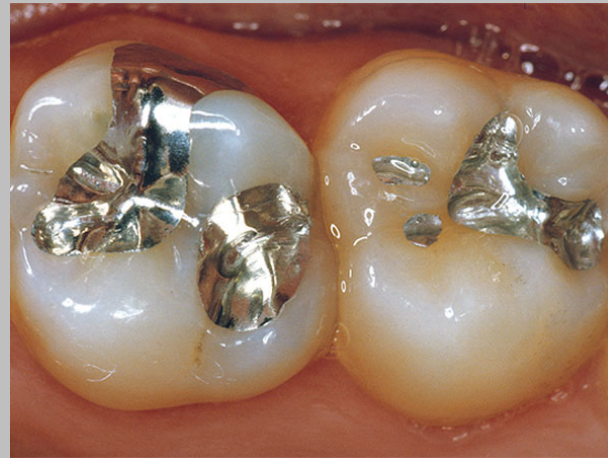


<https://www.theguardian.com/world/2019/mar/07/german-who-poisoned-co-workers-sandwiches-receives-life-sentence> (08.03.2019, 12:49)

Mercury

- **Occurrence/Exposition:**

- Only metal that is in a liquid state at room temperature
- Transformed by aquatic microorganisms to organic mercury compounds → bioaccumulation in the food chain
- In amalgam-teeth-fillings and thermometer
- Gold purification

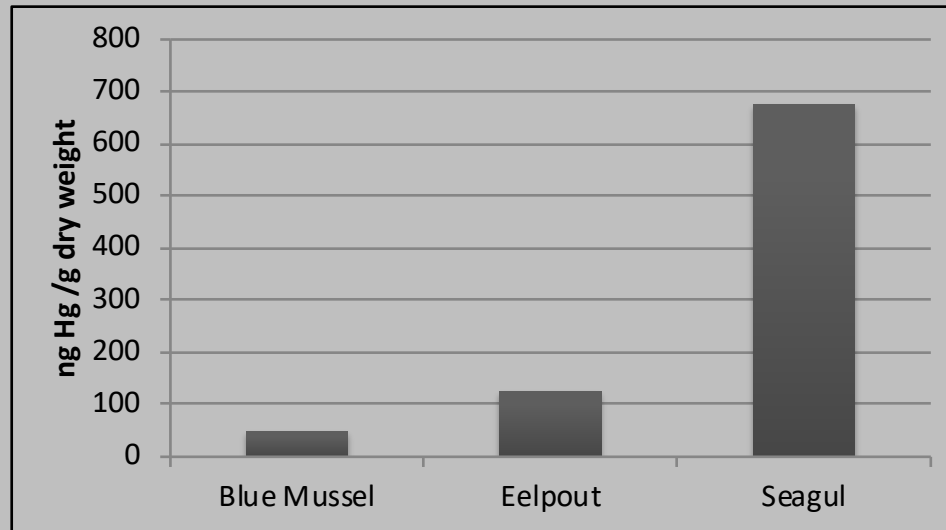


Thresholds (WHO/EPA):
Drinking Water: 1 µg/l
Food: 500 µg/kg Fish
PTWI: 1,6 µg/kg/w

LD₅₀ :
Mercury(II)acetat: 24 mg/kg bm (mouse)
Methyl-mercury: 53 mg/kg bm (mouse)

<https://www.zm-online.de/archiv/2018/13/titel/die-neuen-regelungen-zu-amalgam/>

Samples from Baltic Sea (2017)



https://www.umweltprobenbank.de/de/documents/investigations/analytes?analytes=10003&specimen_types=10002

Mercury

- **Toxicity:**

- Reactivity with free Sulfhydryl-groups of Proteins → Damaging of neuronal microtubule → Paralysis, Ataxia
- Inhibition of antioxidative enzymes → oxidative damage (especially in the brain)
- Inorganic Mercury-salts: corrosive, acidic burn of the esophagus and GIT; necrosis of renal tubule cells in the kidneys → kidney failure
- Malformations in newborn

Minamata Disease

- 1956: uncontrolled waste disposal by the Chisso company (methyl-mercury-chloride)
- Accumulation in the Yatsushiro-Lake
- 17000 Inhabitants injured
- 3000 died



W. Eugene Smith (1972): „Tomoko in Her Bath, Minamata, Japan”

Lead

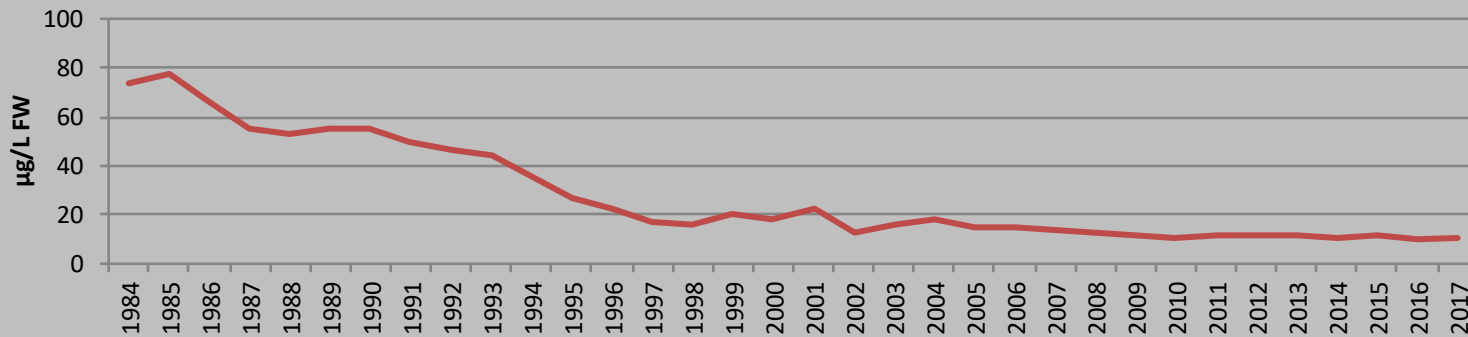
- **Occurrence/Exposition:**

- Batteries and colors
- Tetramethyl-lead as additive in fuel until 1988
- Concentrations in food: 10 – 200 $\mu\text{g}/\text{kg}$



„First Munich fuel pump with lead-free fuel“

Lead concentration in the blood of German students [$\mu\text{g}/\text{L FW}$]



https://www.umweltprobenbank.de/de/documents/investigations/analytes?analytes=10003&specimen_types=10002
https://www.t-online.de/auto/technik/id_66375236/benzinpreise-vor-30-jahren-gab-es-erstmal-bleifreies-benzin.html

Lead

- **Toxicity**

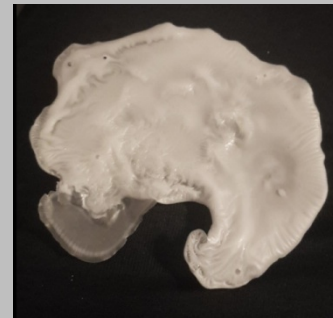
Acute exposure:

- Poisoning only at high concentrations

Chronic exposure:

- Absorption in GIT
- Accumulation in the bones (half life time 10-30 years)
- CNS development impaired
- Reduced kidney function
- High blood pressure
- Possibly carcinogenic

→ German tradition of pouring lead at new years eve was prohibited in 2018



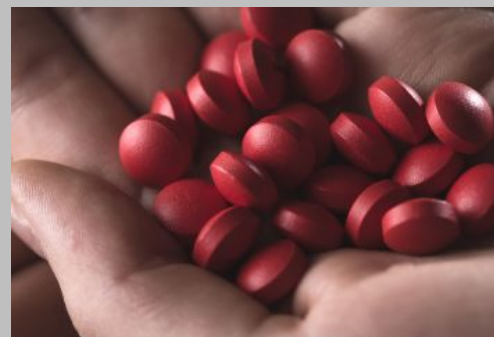
Thresholds (WHO):
PTWI: 25 $\mu\text{g}/\text{kg}$ bw; mussels: 1500 $\mu\text{g}/\text{kg}$;
drinking water: 25 $\mu\text{g}/\text{L}$

LD_{50} :
630 mg/kg^1 (rat i.p.)

Iron

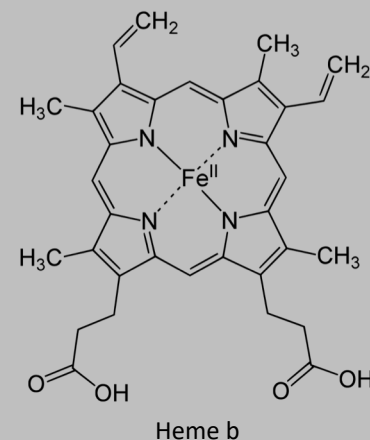
- **Occurrence/Exposition:**

- Exposure via food: liver and beef (Heme-iron, good bioavailability), apples
- Food coloring
- Pigments in paint



- **Essential needs:**

- Most important: Iron(II) and Iron(III)
- Involved in
 - Oxygen transport: Hemoglobin
 - Oxygen diffusion into muscles: Myoglobin
 - Electron transport in the respiratory chain: Cytochrome



Iron

- **Toxicity:**

- Generation of reactive oxygen species via Fenton Reaction:

Fenton Reaction



- Damaging of proteins, nucleic acids, lipids and biological membranes
- **Acute toxic effects:** 20-60 mg/kg bw → direct caustic injury to the gastrointestinal mucosa
- **Chronic toxic effects:** 150-1200 mg/day → Iron concentrates in mitochondria → cell death
- Increased risk of oxidative DNA damage and tumor development

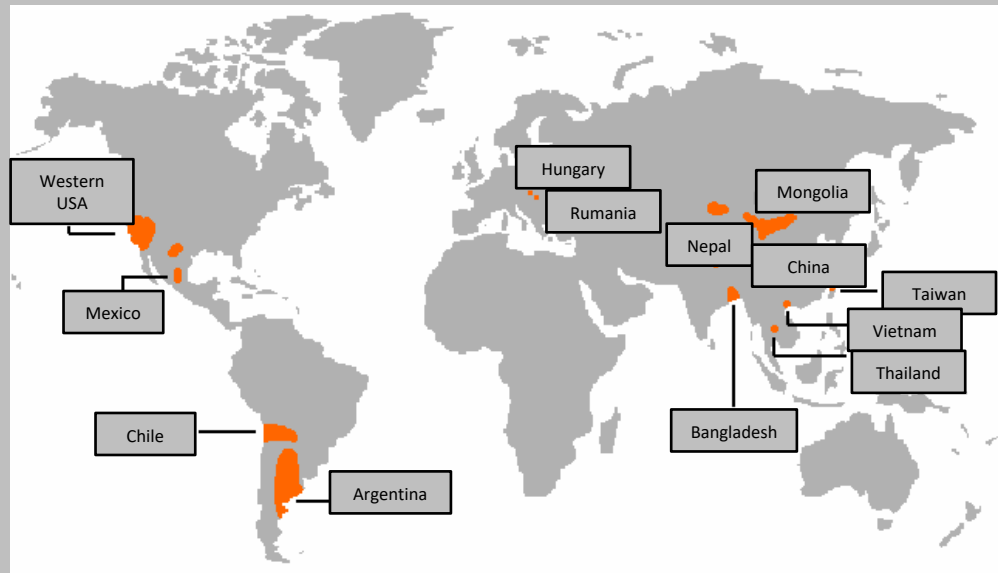
Thresholds (WHO):
PTWI: 0,8 mg/kg bw/day

LD₅₀ :
30 g/kg oral (rat)

Arsenic

- **Occurrence/Exposition:**

- Drinking water
- Fish (Arsenobetain)
- Rice (20-900 µg/kg)
- In semiconductor manufacturing, wood protection agents, glass-industry



https://upload.wikimedia.org/wikipedia/commons/2/2b/Weltkarte_arsenrisikogebiete.gif

Arsenic

- **Toxicity:**

- Decoupling of the respiratory chain through substitution of phosphate at ATP → Dying of cells
- Acute exposure: spasms, nausea, inner bleedings
- Chronic exposure: impairment of CNS, respiratory tract, skin, liver, peripheral blood vessels → Black Foot Disease



Black foot disease

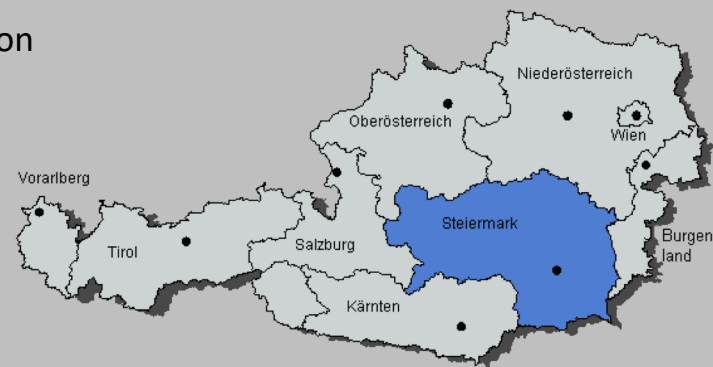
Thresholds (WHO/EPA):
Drinking Water: 10 $\mu\text{g/l}$
PTWI: 7 $\mu\text{g/kg/w}$

LD₅₀ :
Arsenic: 763 mg/kg Rat, oral
Arsenic-(III)-oxide: 1,4 mg/kg

Arsenic-(III)-oxide-Eater

- **Arsenic as psychoactive substance (Arsenic-Eater)**

- 19th century especially in Austria
- „The cocaine of the styrian farmers“
- <2 mg: Increase of appetite and general well-being
- warm feeling in the stomach (through irritation of the gastric mucosa)



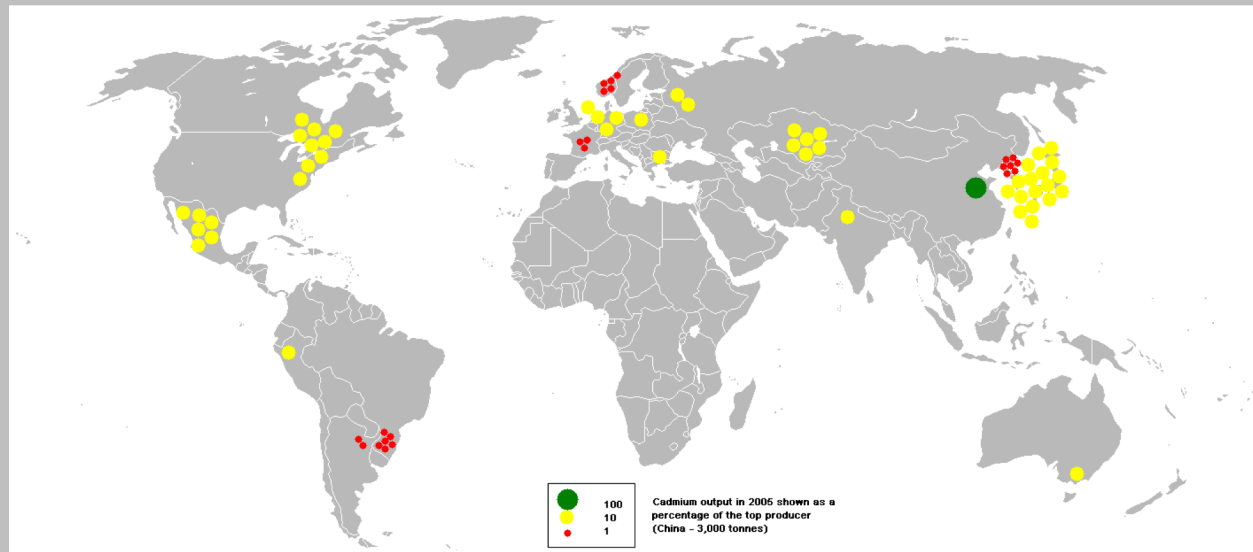
https://www.kleinezeitung.at/steiermark/suedostsued/4939072/Historische-Serie_Wie-der-Koenig-der-Gifte-fuer-Siechtum-sorgte

Cadmium

- **Occurrence/Exposition:**

- Naturally occurring as Cadmium oxide, Cadmium chloride, Cadmium sulfate, Cadmium sulfite
- Usage in solders, pigments, as stabilizer in PVC and batteries
- Food: Accumulation in soil and plants → Nuts, seeds, cacao, tobacco and linseed (maximum daily intake: 20g)

→ Accumulation in liver and kidney

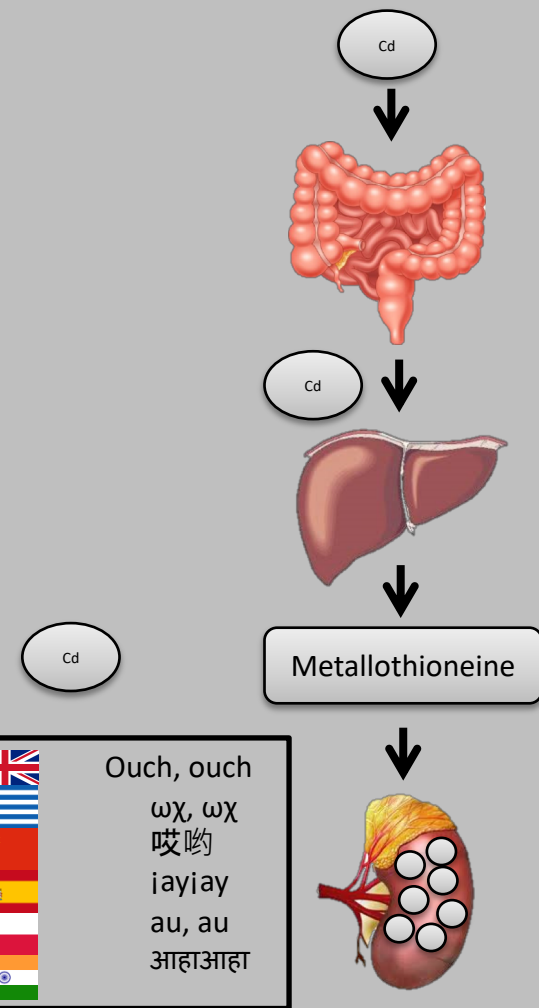


<https://commons.wikimedia.org/wiki/File:2005cadmium.PNG>

Cadmium

- **Toxicity:**

- Uptake through food and resorption in the GIT
- Transport to the liver → Induction of Metallothioneine synthesis
- Cadmium/Metallothioneine complex formation
- Transport to the kidneys → filtration → reabsorption by the renal tubule cells
- Accumulation in the kidneys → Kidney damage and Proteinuria
- Inhibition of Ca uptake in the GIT → Bone damage
- „Itai Itai Disease“ (Aua Aua Disease)



Thresholds:

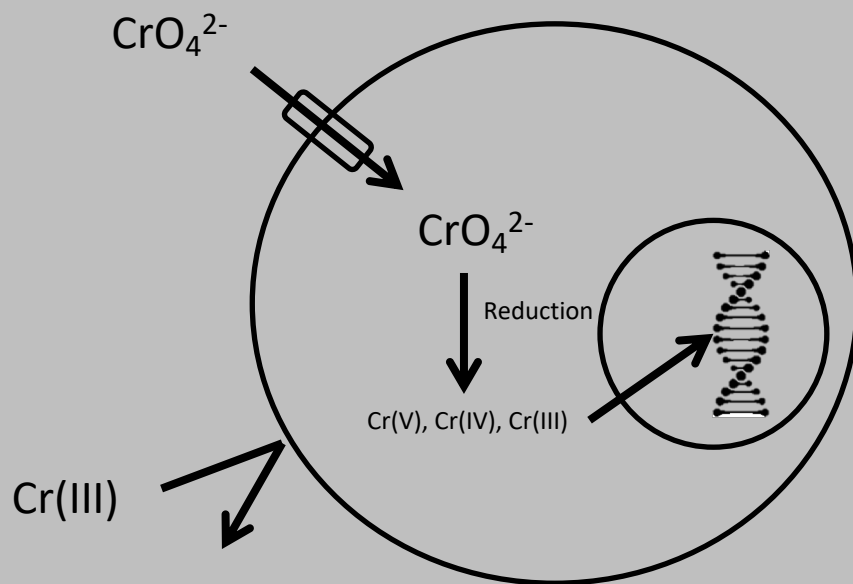
- TWI: EFSA: 2,5 $\mu\text{g}/\text{kg bw}$; WHO: 25 $\mu\text{g}/\text{kg bw}$

LD₅₀ :

- Cadmiumoxid: 72 mg/kg (rat oral)
- Cadmiumchloride: 88 mg/kg (rat oral)

Carcinogenicity of metals

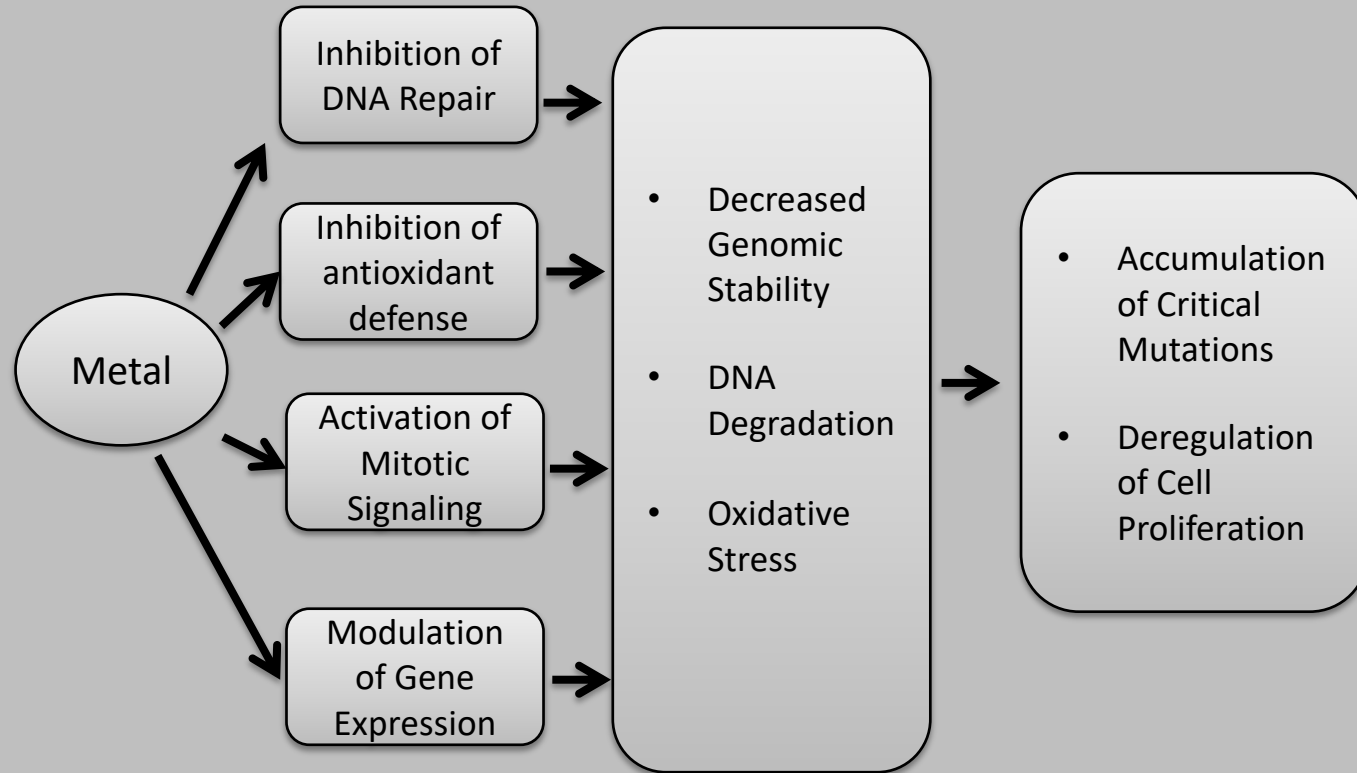
- Carcinogenic effects of metals are in most cases independent from direct interaction with DNA
- Exception: Chromate Anions CrO_4^{2-}



- Ternary chrome DNA-Adducts
- DNA-protein connections
- Oxidative DNA damage
- Chromosome damage
- Mutations

Modified from Toxikologie: Band 2: Toxikologie der Stoffe; Wiley-VCH Verlag GmbH & Co. KGaA; Auflage: 1. (17. Februar 2010)

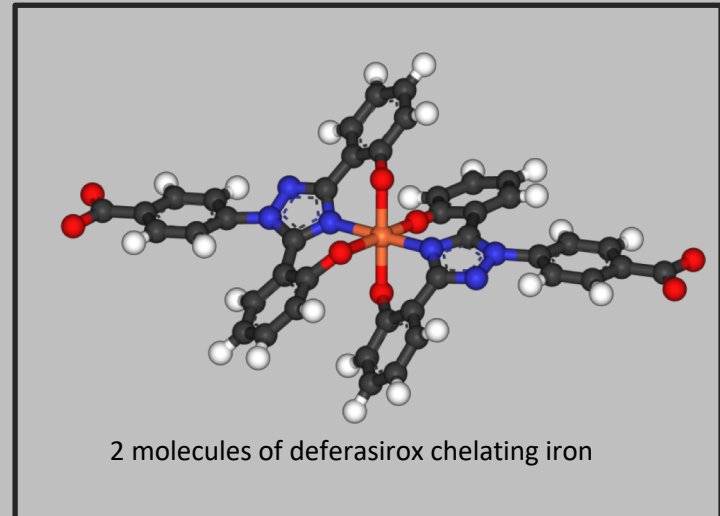
Carcinogenicity of metals



Review on Some Emerging Endpoints of Chromium (VI) and Lead Phytotoxicity - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Major-mechanism-of-Pb-genotoxicity-Adapted-from-Beyersmann-and-Hartwig-2008_fig3_221929148 [accessed 13 Feb, 2019]

Chelation-Therapy

- Administration of chelating agents (i.v.; i.m. or orally) → provision of multiple electron-donating groups → formation of stable metal complexes
- Complexes are dissolved in the blood and eliminated in urine
- Suitable for arsenic, mercury, lead, copper, gold or iron, depending on the chelator used
- Side effects: dehydration, low blood calcium, kidney damage, allergic reactions, lowered levels of dietary elements



Conclusions

- Heavy metals can be defined by density, atomic weight, atomic number or toxicity
- Many metals are essential for mammalian body functions, but can also cause harmful effects, if the concentrations are too high
- Examples for toxic metals are mercury, lead, cadmium, arsenic and iron
- Toxic mechanisms of metals include binding to sulfhydryl-groups, ROS generation and replacement of essential metals
- Carcinogenicity of metals is caused by inhibition of DNA repair, inhibition of antioxidant defense, activation of mitotic signaling or modulation of gene expression. Direct DNA modifications are rare

COUNTERTHINK

