Targets in TOXICOLOGY Research Training Group

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Toxicity of Metals

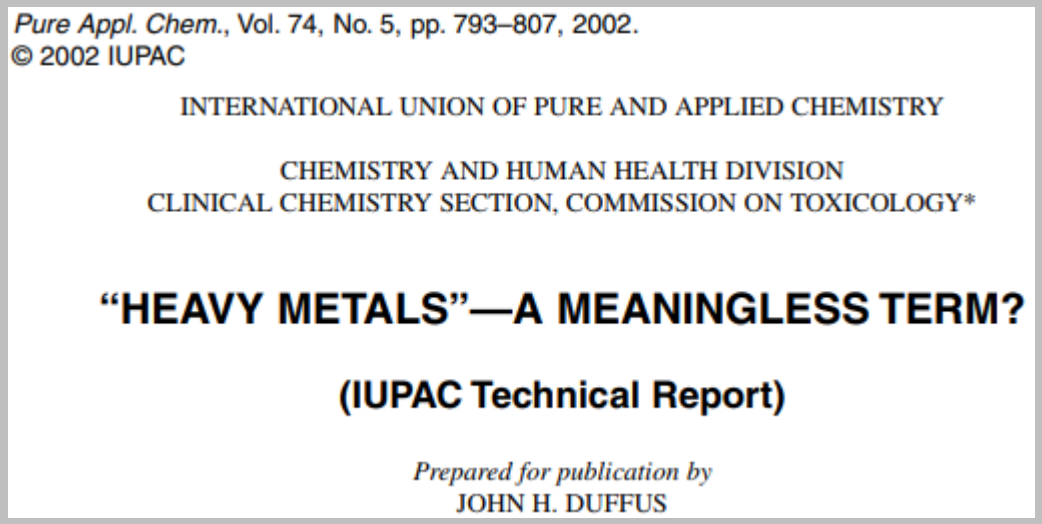
M1: Lung Basics and Principles of Toxicology
– Methods in Toxicology –

Jonas Tigges

14.03.2019

Heavy Metals - Definition

- No homogenous definition:



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

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

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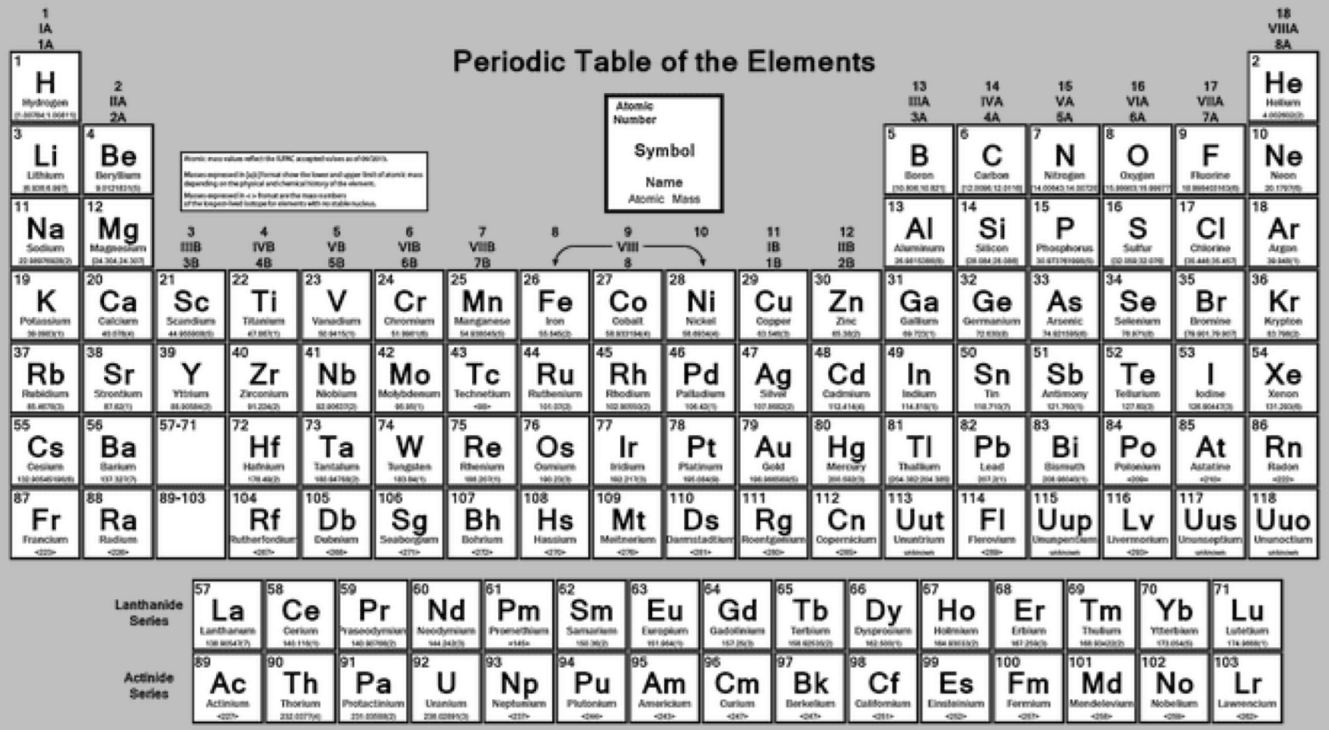

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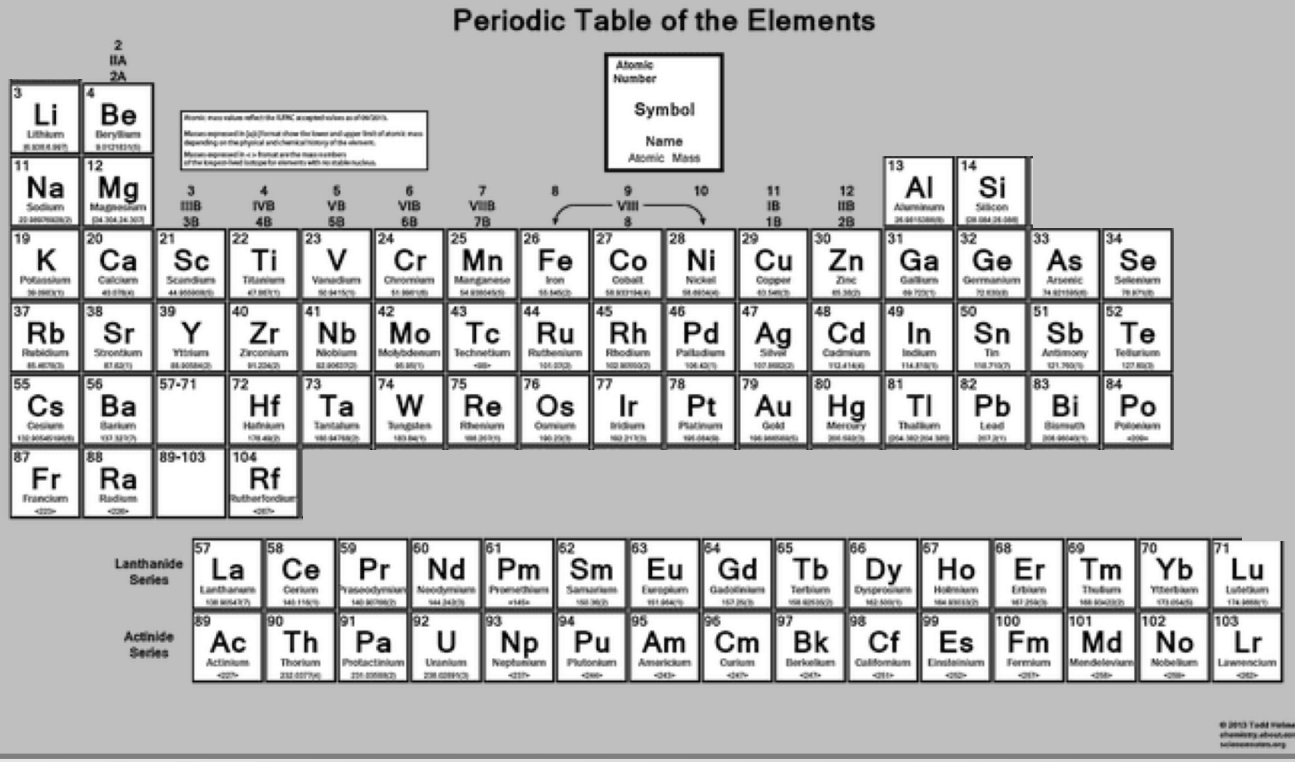

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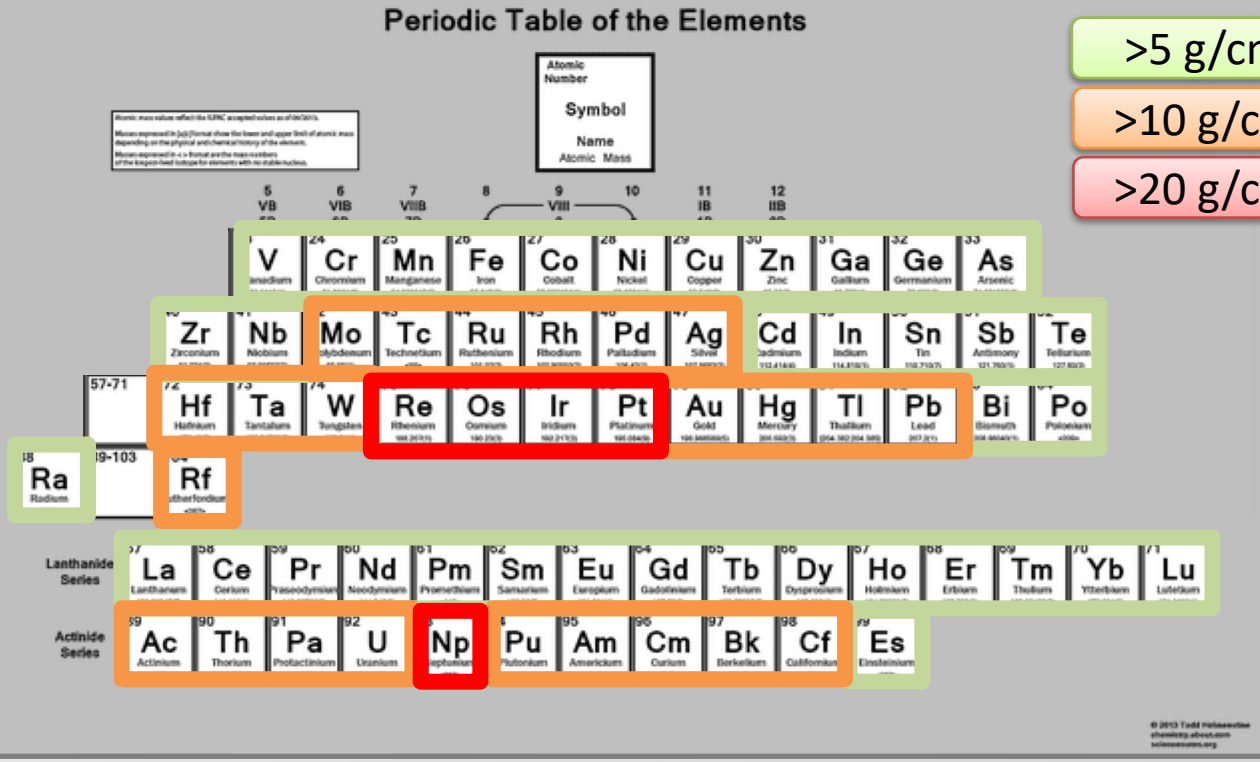

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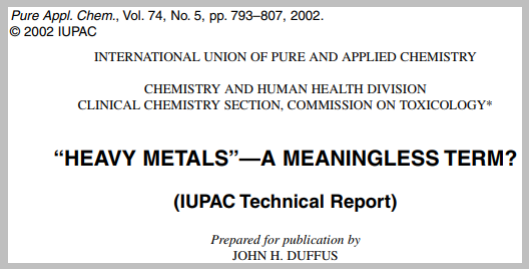
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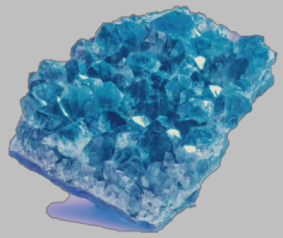
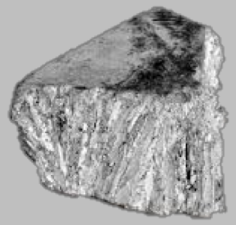
- No homogenous definition:

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

 Chromium	 Arsenic	 Lead
 Cadmium	 Cobalt	 Iron
 Nickel	 Mercury	 Zinc

Toxicity of metals

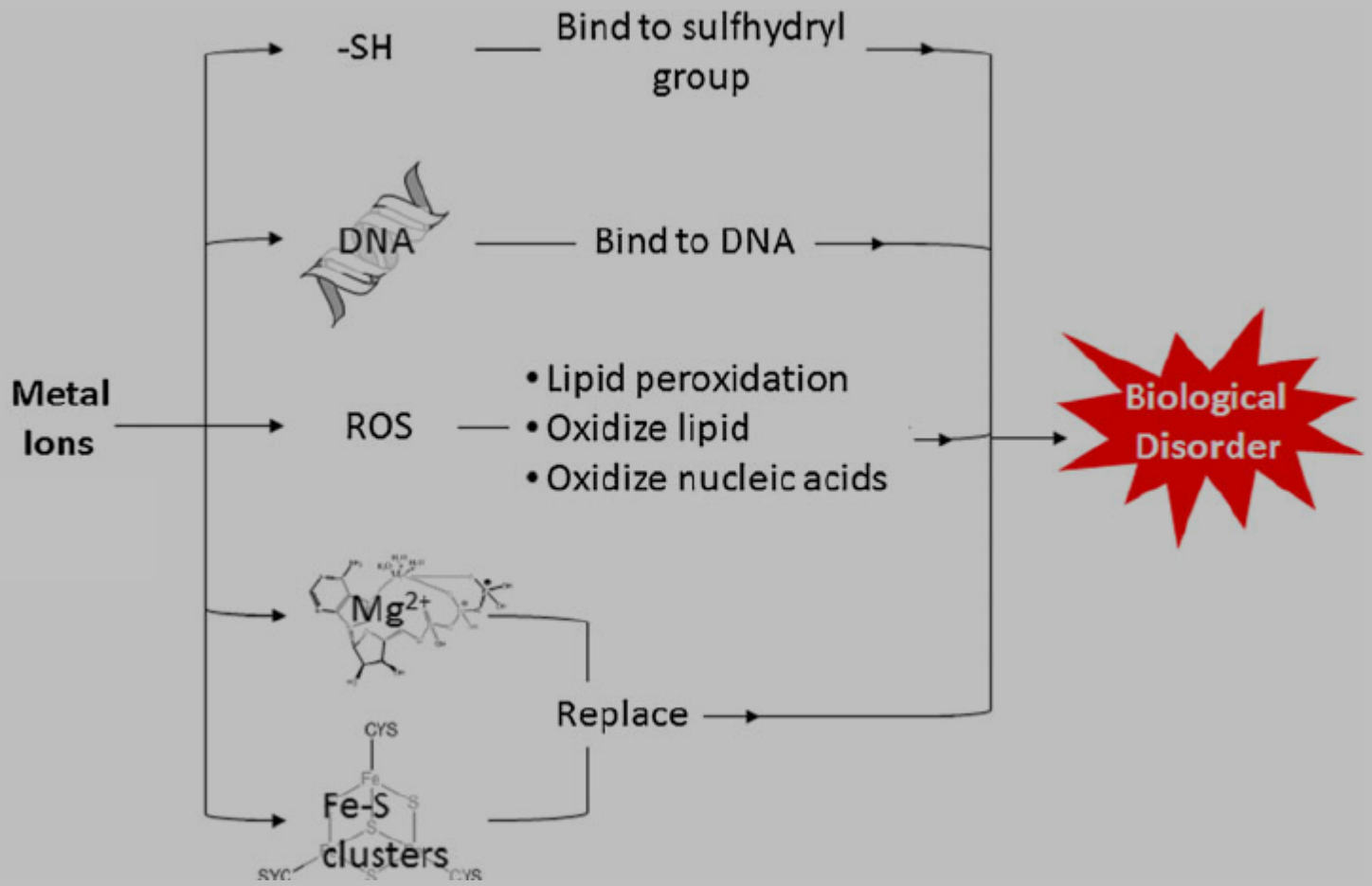
- Metals play an important role in many different body functions
- Transport and metabolism of oxygen
- Signal transduction
- DNA-binding of proteins
- Electron transfer

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

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

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

Mercury

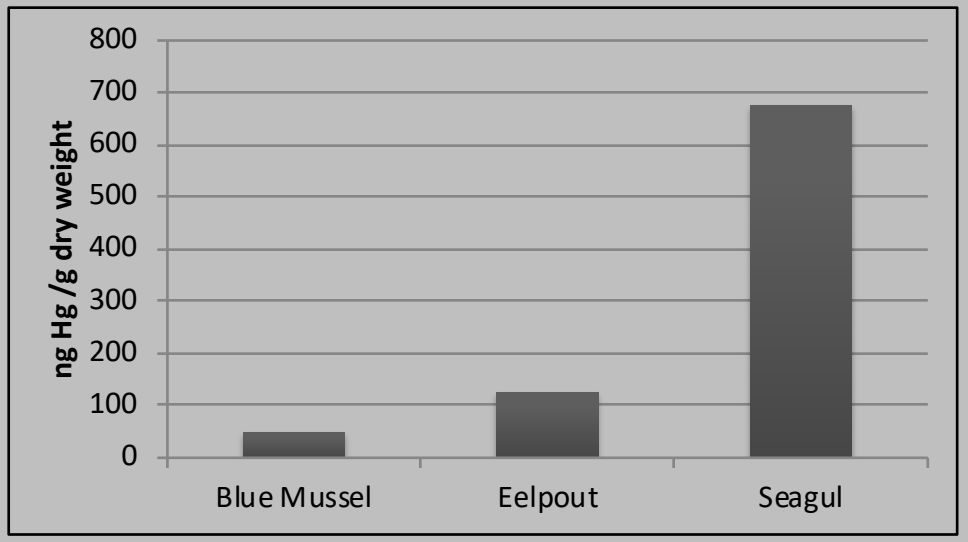
- **Occurrence/Exposition:**
  - Only metal that is in a liquid state at room temperature
  - Transformed by aquatic microorganisms to organic mercury compounds → bioaccumulation in the food chain
  - In amalgam-teeth-fillings and thermometer
  - Gold purification

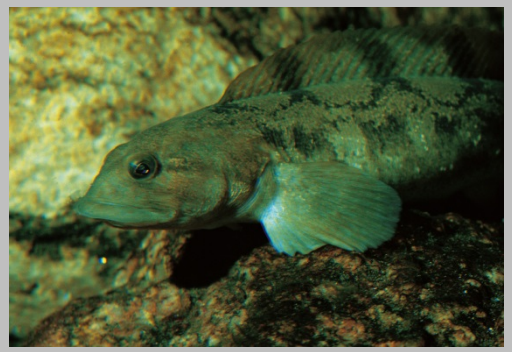
Thresholds (WHO/EPA):
Drinking Water: 1 µg/l
Food: 500 µg/kg Fish
PTWI: 1,6 µg/kg/w

LD_{50} :
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

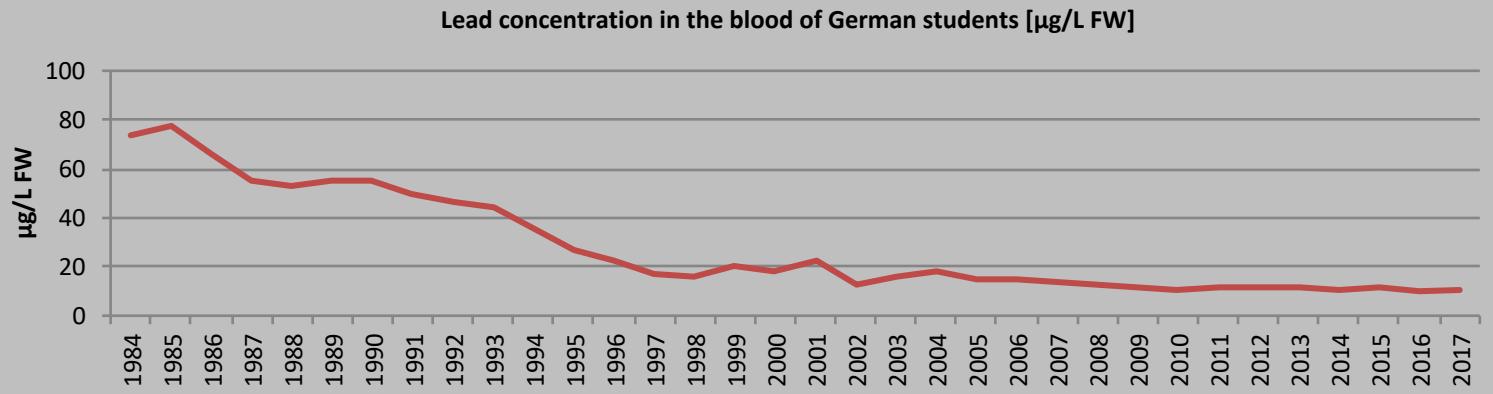
- 1956: uncontrolled waste disposal by the Chisso company (methyl-mercury-chloride)
- Accumulation in the Yatsushiro-Lake
- 17000 Inhabitants injured
- 3000 died

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 µg/kg

„First Munich fuel pump with lead-free fuel“



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-erstmals-bleifreies-benzin.html

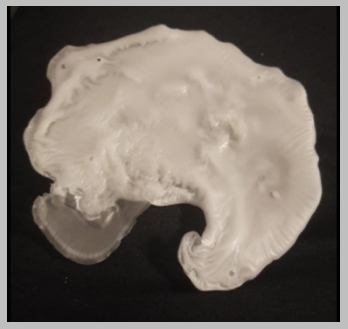
Lead

- **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

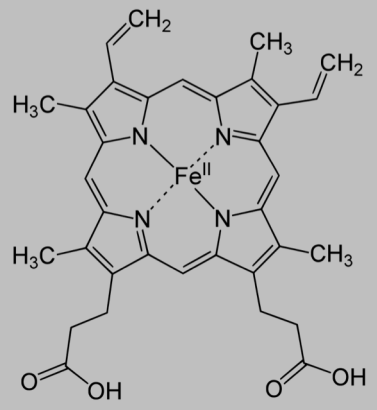


Thresholds (WHO): PTWI: 25 µg/kg bw; mussels: 1500 µg/kg; drinking water: 25 µg/L	LD_{50} : 630 mg/kg[1] (rat i.p.)

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



Heme b

https://de.wikipedia.org/wiki/H%C3%A4moglobin#/media/File:Heme_b.svg
https://pedclerk.bsd.uchicago.edu/page/iron-toxicity

Iron

- **Toxicity:**
  - Generation of reactive oxygen species via Fenton Reaction:

    Fenton Reaction

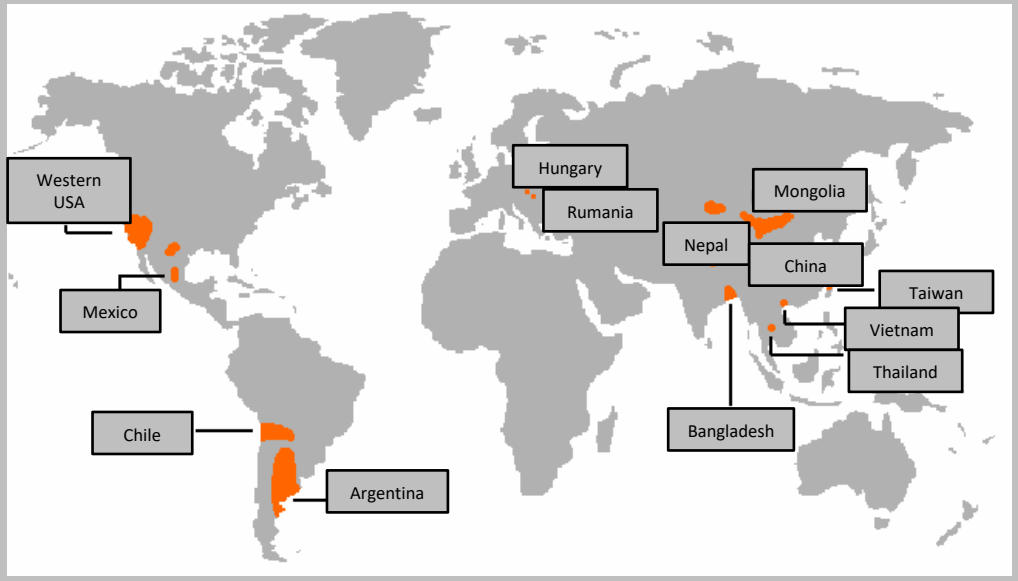
    $Fe(II) + H_2O_2 \longrightarrow Fe(III) + HO^- + HO^\bullet$

    → 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

Tresholds (WHO): PTWI: 0,8 mg/kg bw/day	LD_{50} : 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 µg/l
PTWI: 7 µg/kg/w

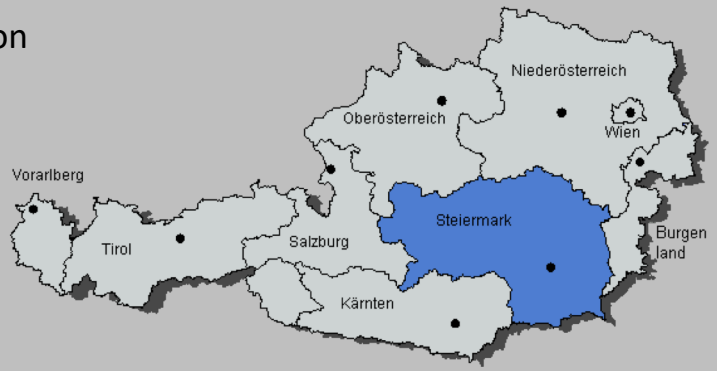
LD_{50} :
Arsenic: 763 mg/kg Rat, oral
Arsenic-(III)-oxide: 1,4 mg/kg

http://wilsonweb.physics.harvard.edu/arsenic/pictures/arsenic_project_pictures2.html

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)

Fig. 231. Arsenic-eaters of Styria.

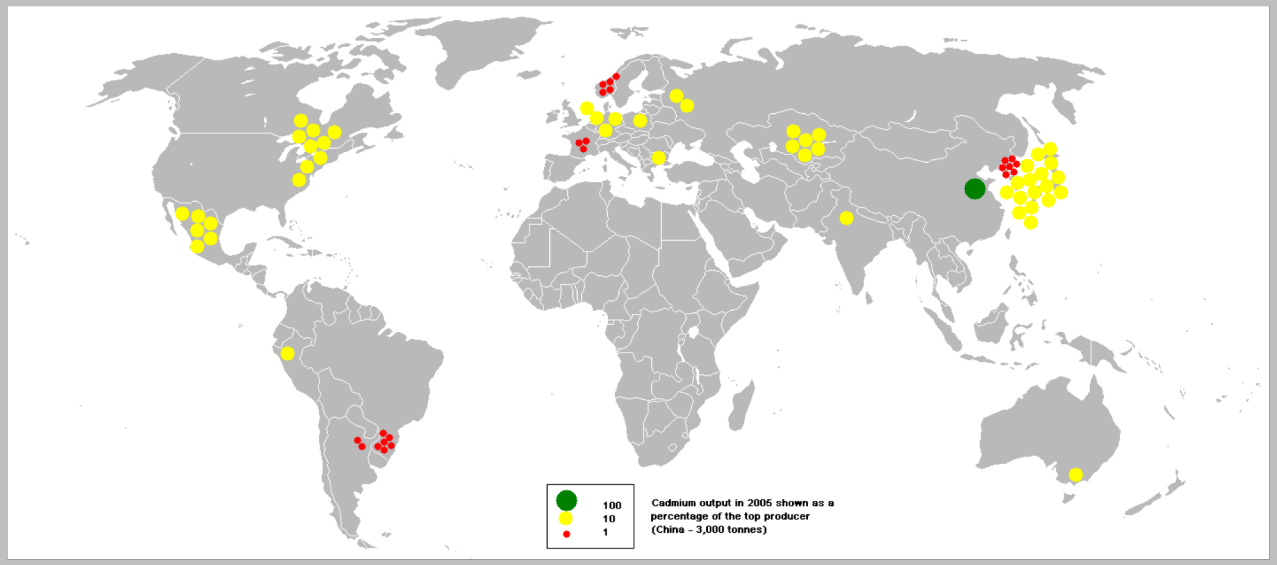


https://www.kleinezeitung.at/steiermark/suedostsued/4939072/Historische-Serie_Wie-der-Koenig-der-Gifte-fuer-Siechtum-sorgte

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

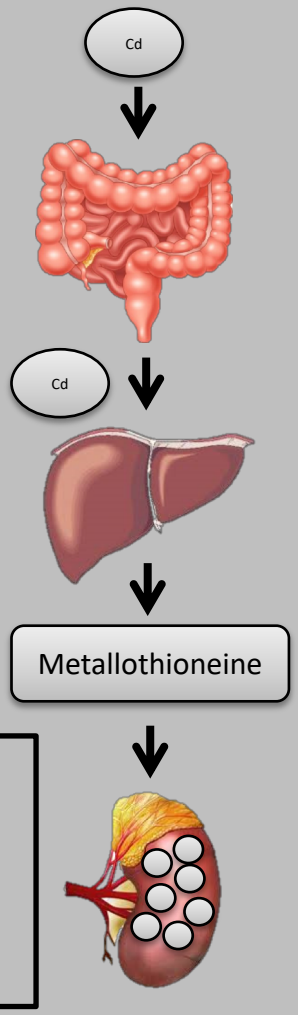


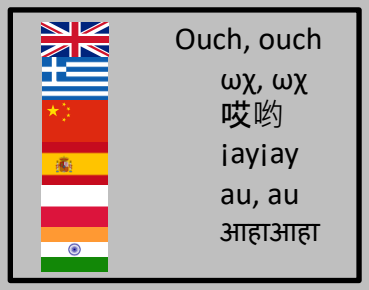
https://commons.wikimedia.org/wiki/File:2005cadmium.PNG

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)**



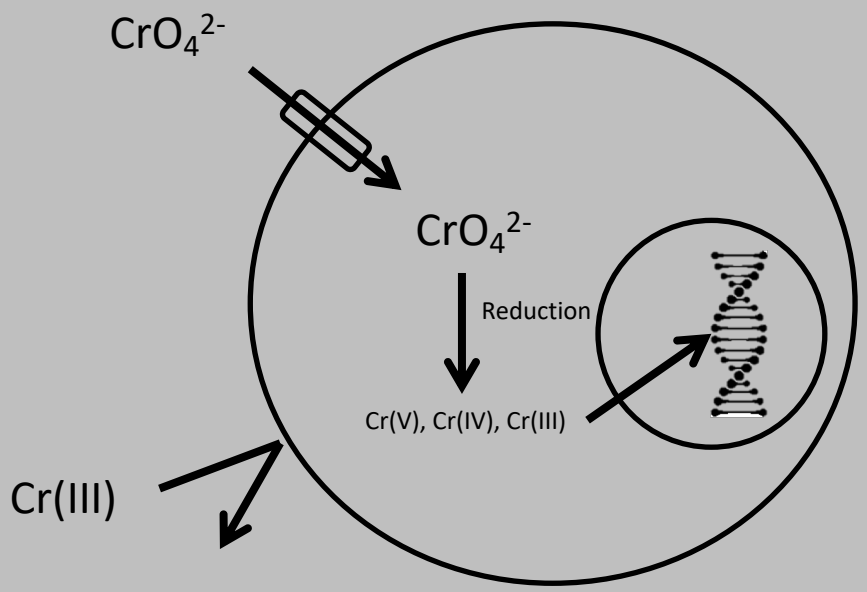


Thresholds:
• TWI: EFSA: 2,5 µg/kg bw; WHO: 25 µg/kg bw

LD_{50} :
• Cadmiumoxid: 72 mg/kg (rat oral)
• Cadmiumchloride: 88 mg/kg (rat oral)

Carcinogenicity of metals

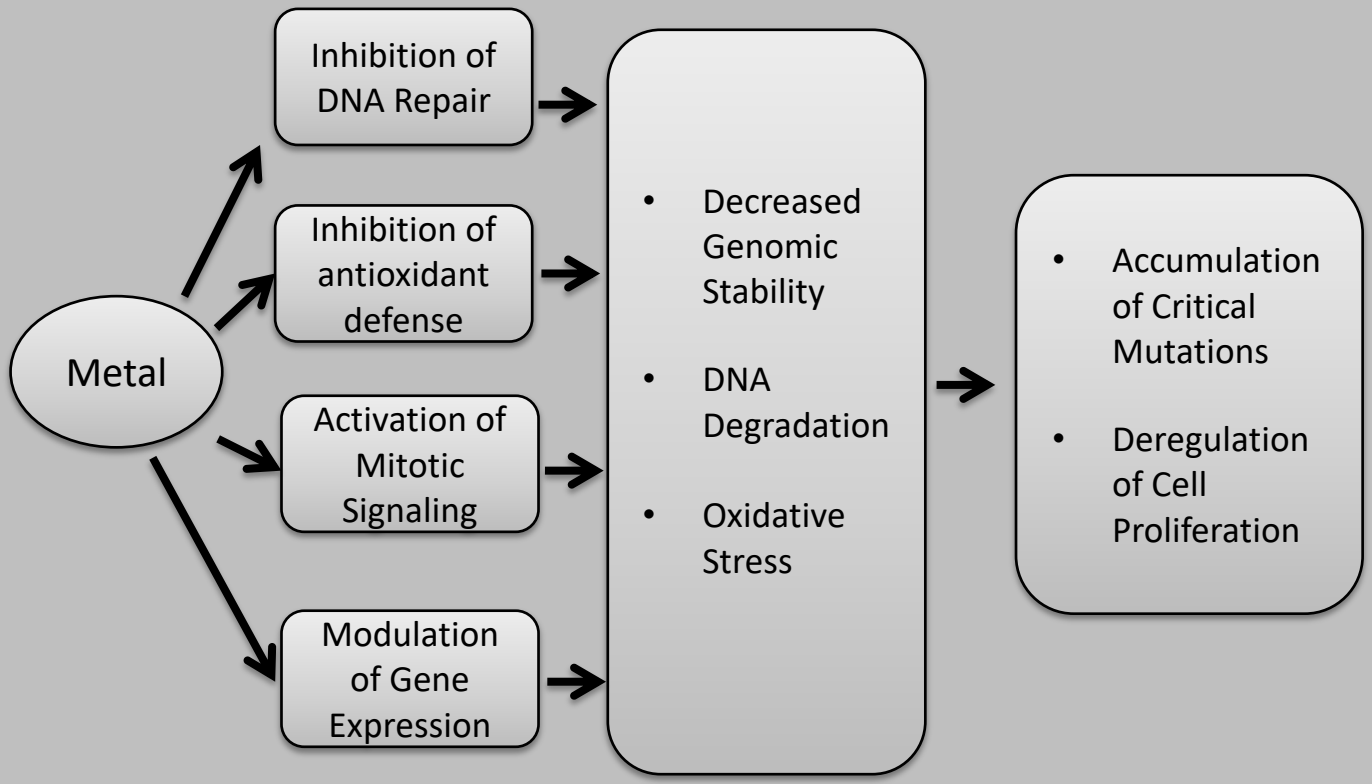
- Carcinogenic effects of metals are in most cases independent from direct interaction with DNA
- Exception: Chromate Anions CrO_4^{2-}



- 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)

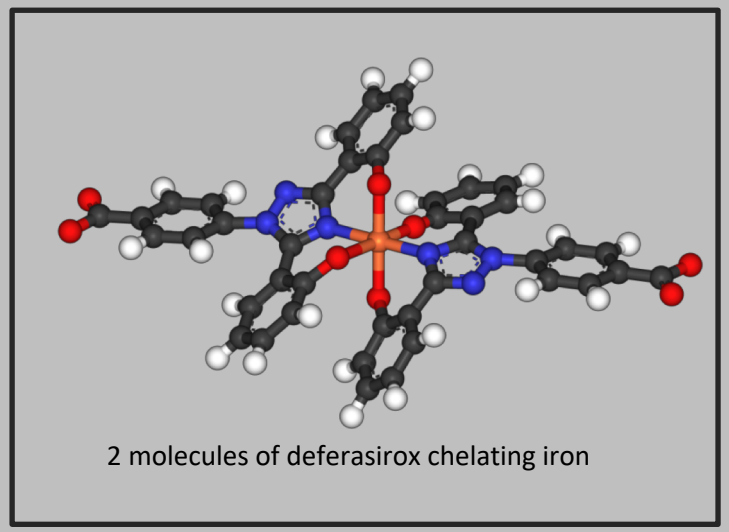
Carcinogenecity of metals



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 oraly) → 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

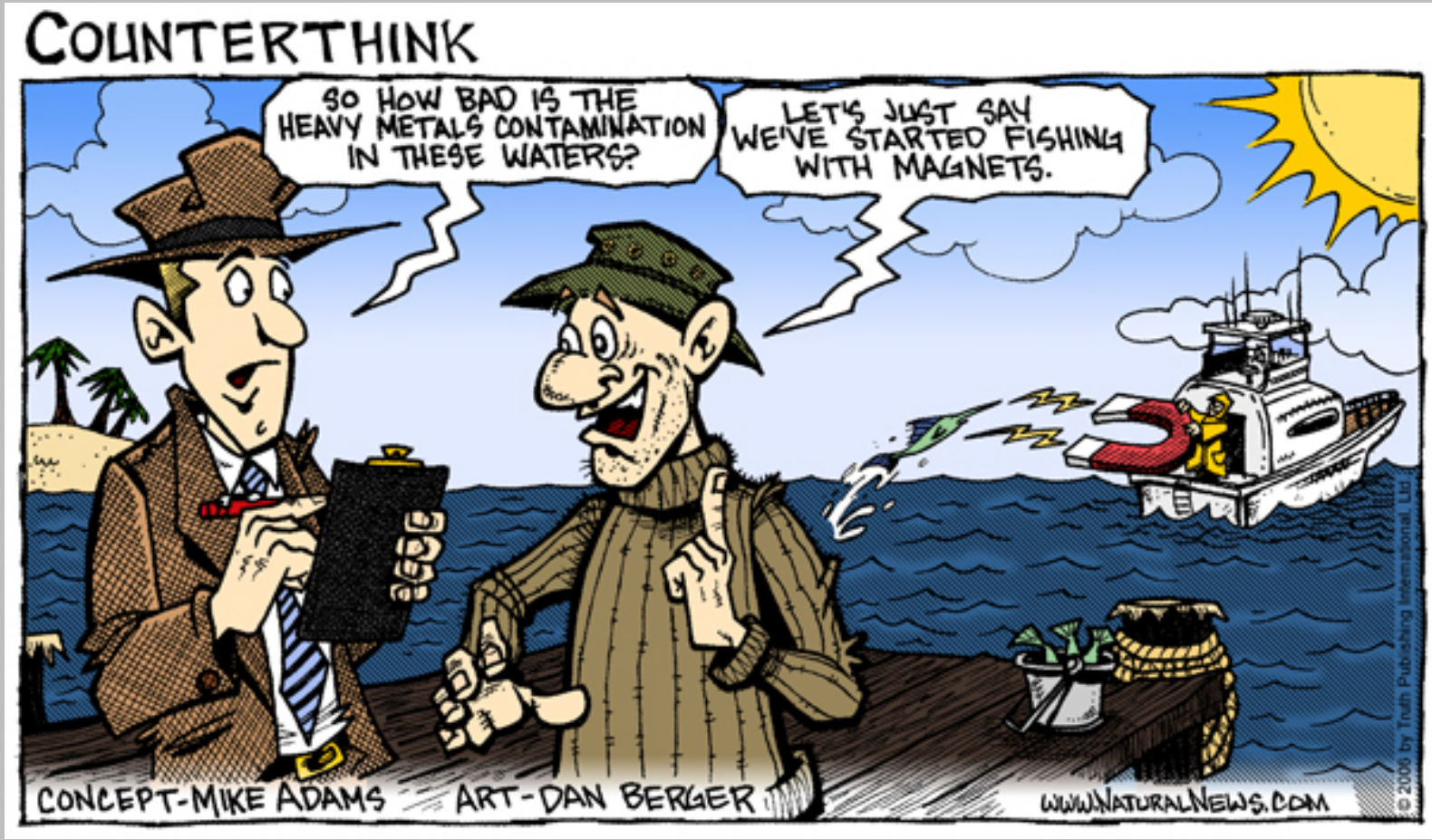


2 molecules of deferasirox chelating iron

https://en.wikipedia.org/wiki/Chelation_therapy#/media/File:Deferasirox%E2%80%93iron(III)_complex.png

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 sulfhydrate-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
SO HOW BAD IS THE HEAVY METALS CONTAMINATION IN THESE WATERS?
LET'S JUST SAY WE'VE STARTED FISHING WITH MAGNETS.
CONCEPT-MIKE ADAMS
ART-DAN BERGER
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