Isotopi stabili non tradizionali in biomedicina

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GOETHE UNIVERSITÄT FRANKFURT AM MAIN

MeGic METALLOMICS AND GEOCHEMISTRY RESEARCH

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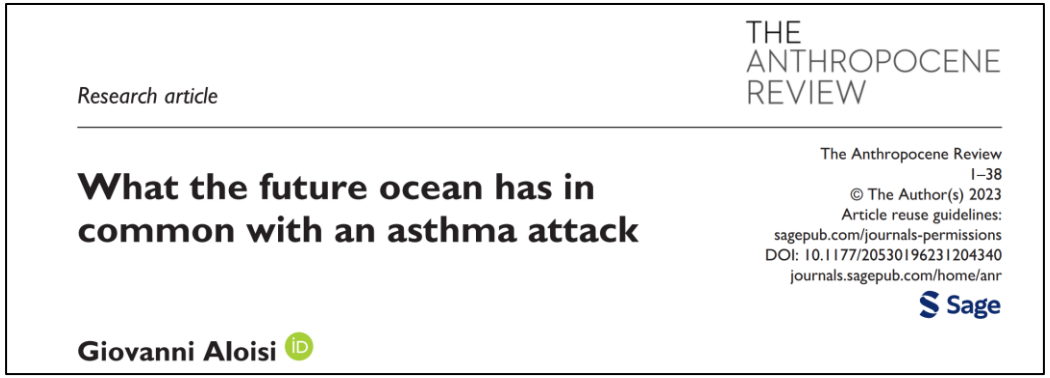
Stable isotopes

Unique tracers of biogeochemical processes

- Trace source and sink processes important for the inventories of major nutrients and chemical constituents.
- Record (past) changes in physical and biological processes affecting the Earth system.



Research article

THE ANTHROPOCENE REVIEW

What the future ocean has in common with an asthma attack

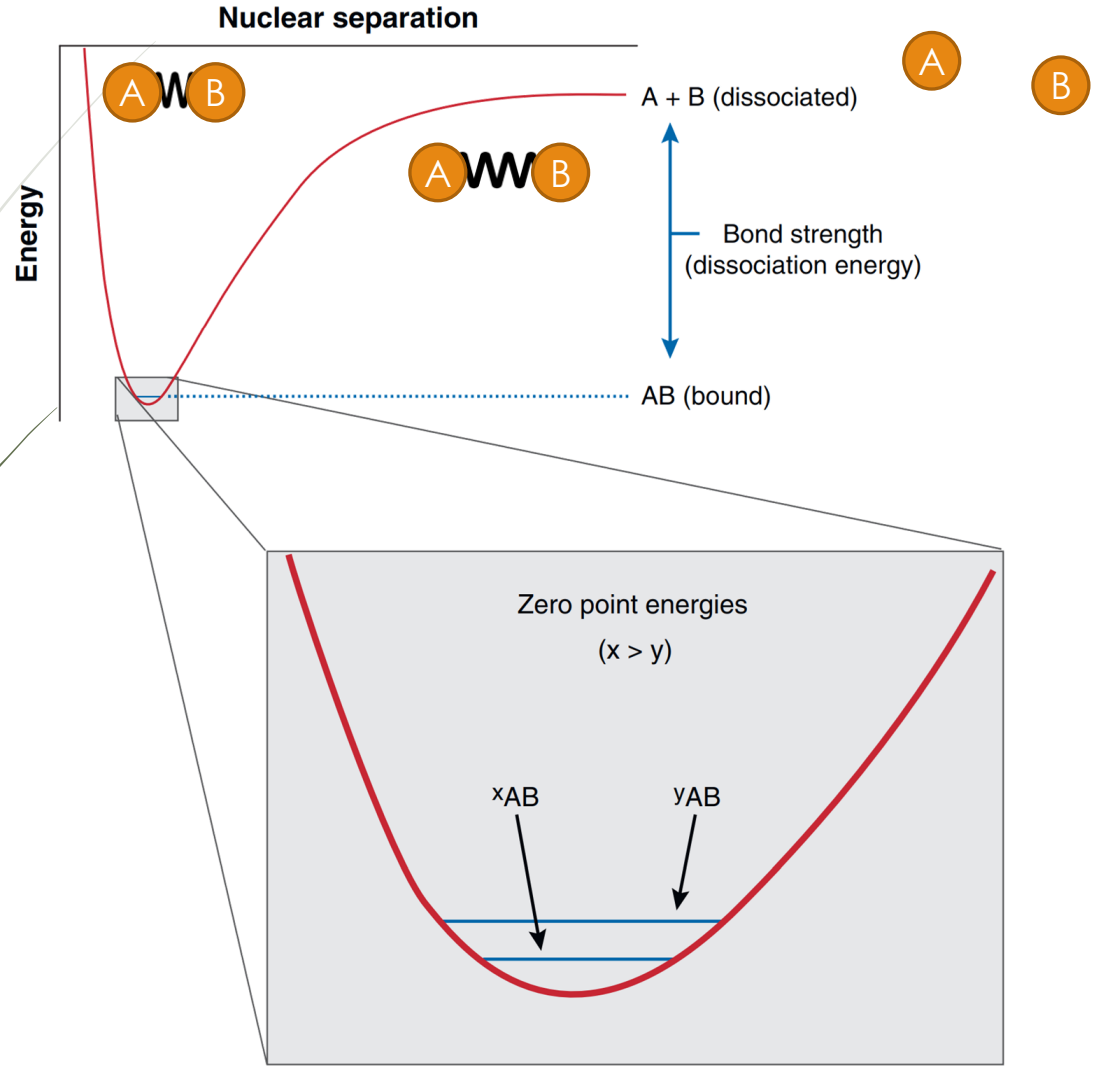
The Anthropocene Review
1–38

DOI: 10.1177/20530196231204340
journals.sagepub.com/home/anr
Sage

Giovanni Aloisi

Isotope fractionation

Mass dependent isotope fractionation…is a quantum process!



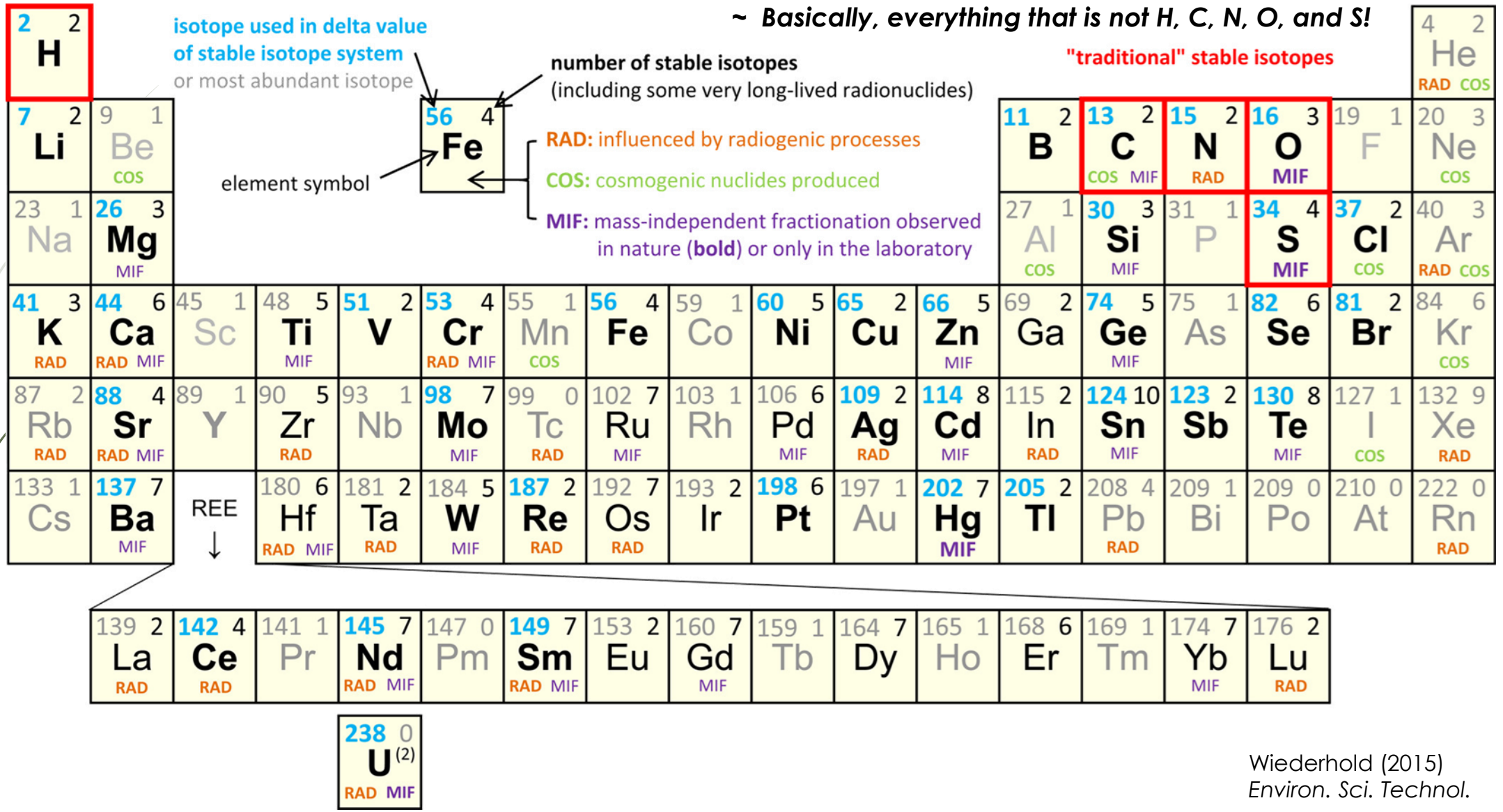
Chemical bonds of molecules with **heavy isotopes** have a **lower vibrational frequency** and therefore lower ZPE (zero-point energy).

The **binding energy** of molecules with **heavy isotopes is higher** than those with light isotopes.

Higher activation energy is required to break the bonds of molecules with **heavy isotopes**, which **favor phases with 'stronger' bonds**.

So: 'heavy' molecules → react slowly and favor phases with stronger bindings.

Non-traditional stable isotopes

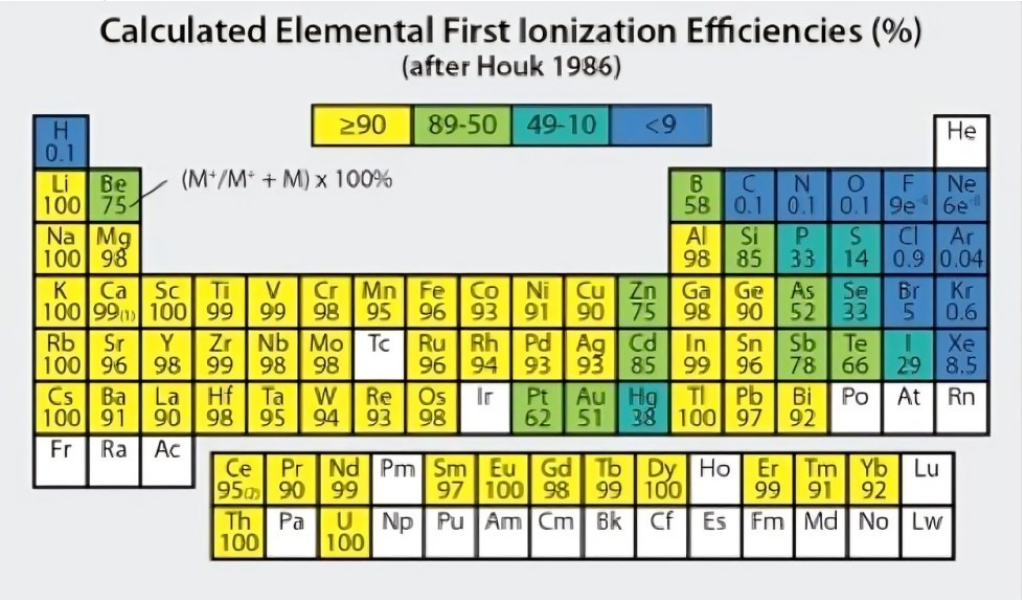


Wiederhold (2015)
Environ. Sci. Technol.

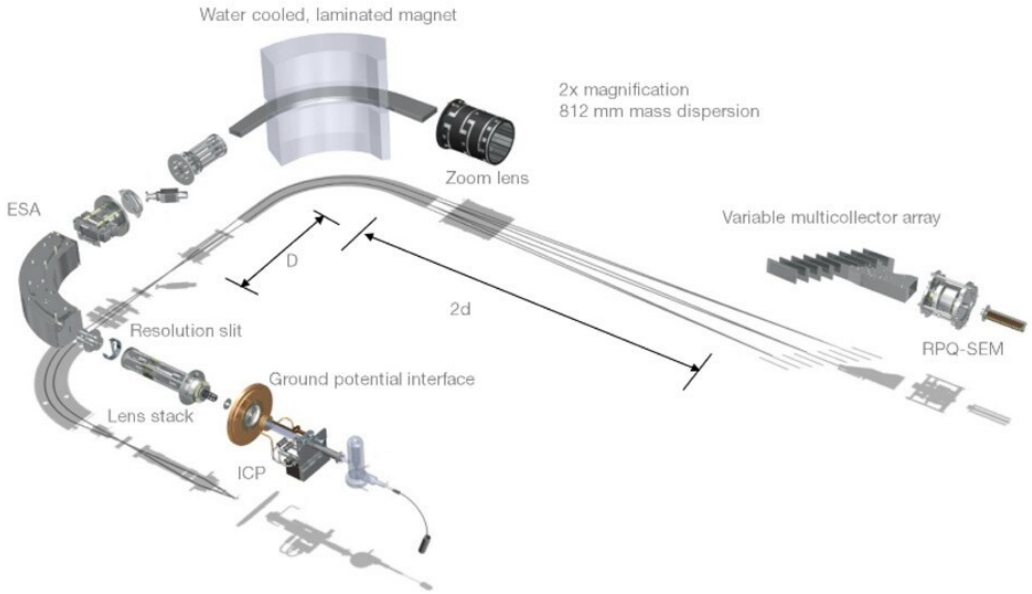
In **bold** are the elements for which a **high-precision analytical methodology** was developed.

Non-traditional stable isotopes

Multi-collector ICPMS



Balaram et al., 2022 *Geosyst. Geoenv.*



Neptune MC-ICPMS Thermo Scientific

1) ICP source → ionization efficiency
2) High sample throughput
3) Laser ablation systems coupling
4) Hyphenation (with e.g. LC o CG)
5) Collision/reaction cell (see Neoma and Sapphire)

Non-traditional stable isotopes

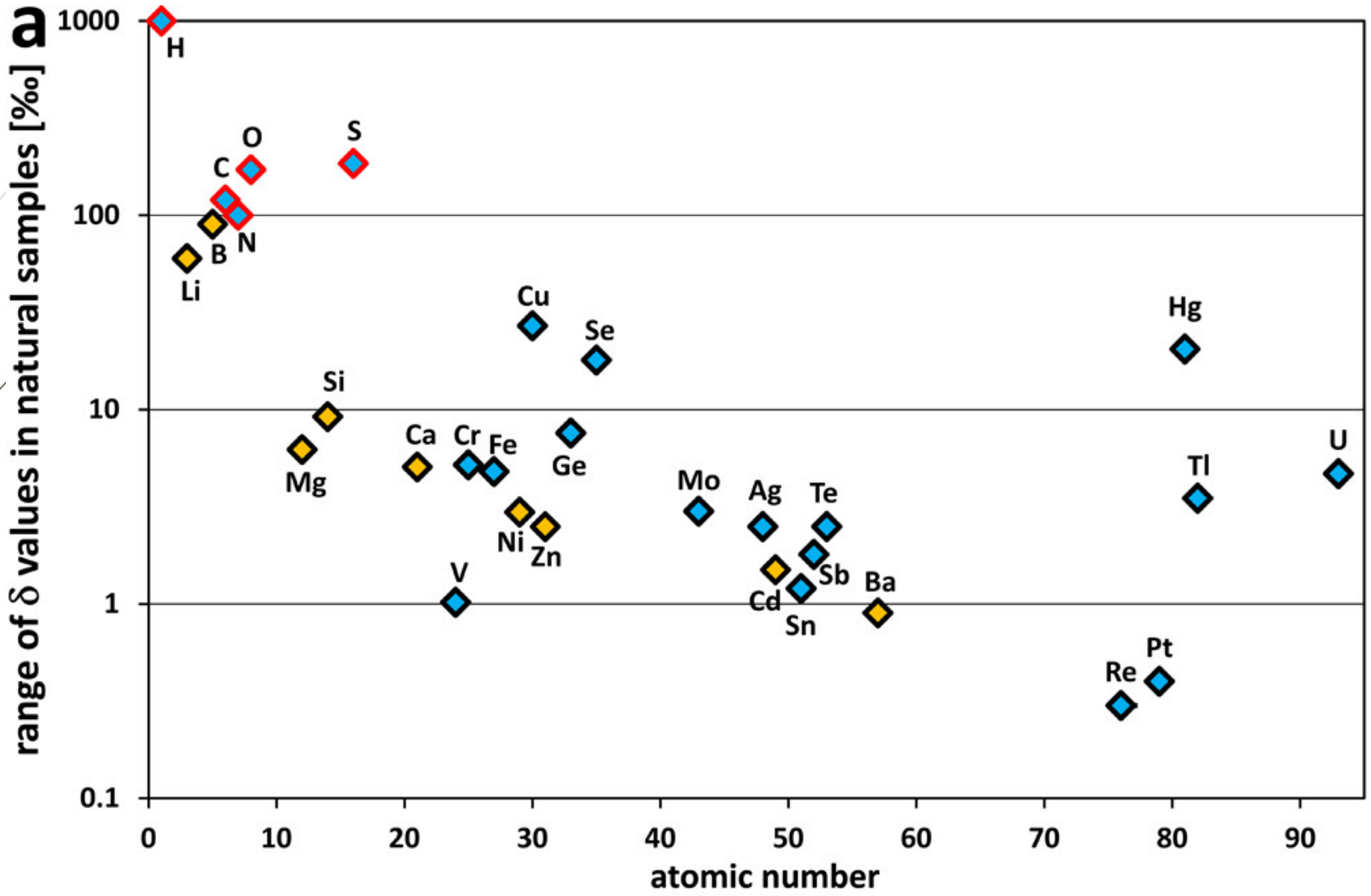
Figures of merit

1) Being mostly trace elements, their concentration varies from matrix to matrix.
2) From volatile(e.g. Zn and K) to refractory (e.g. Ca and Ti).
3) Redox-*sensitive*.
4) Various '*bonding partners*'.
5) Active in biological reactions.
6) High atomic number and more than two stable isotopes.

Susceptible to different types of fractionation, and thus crucial in tracing specific biogeological processes.

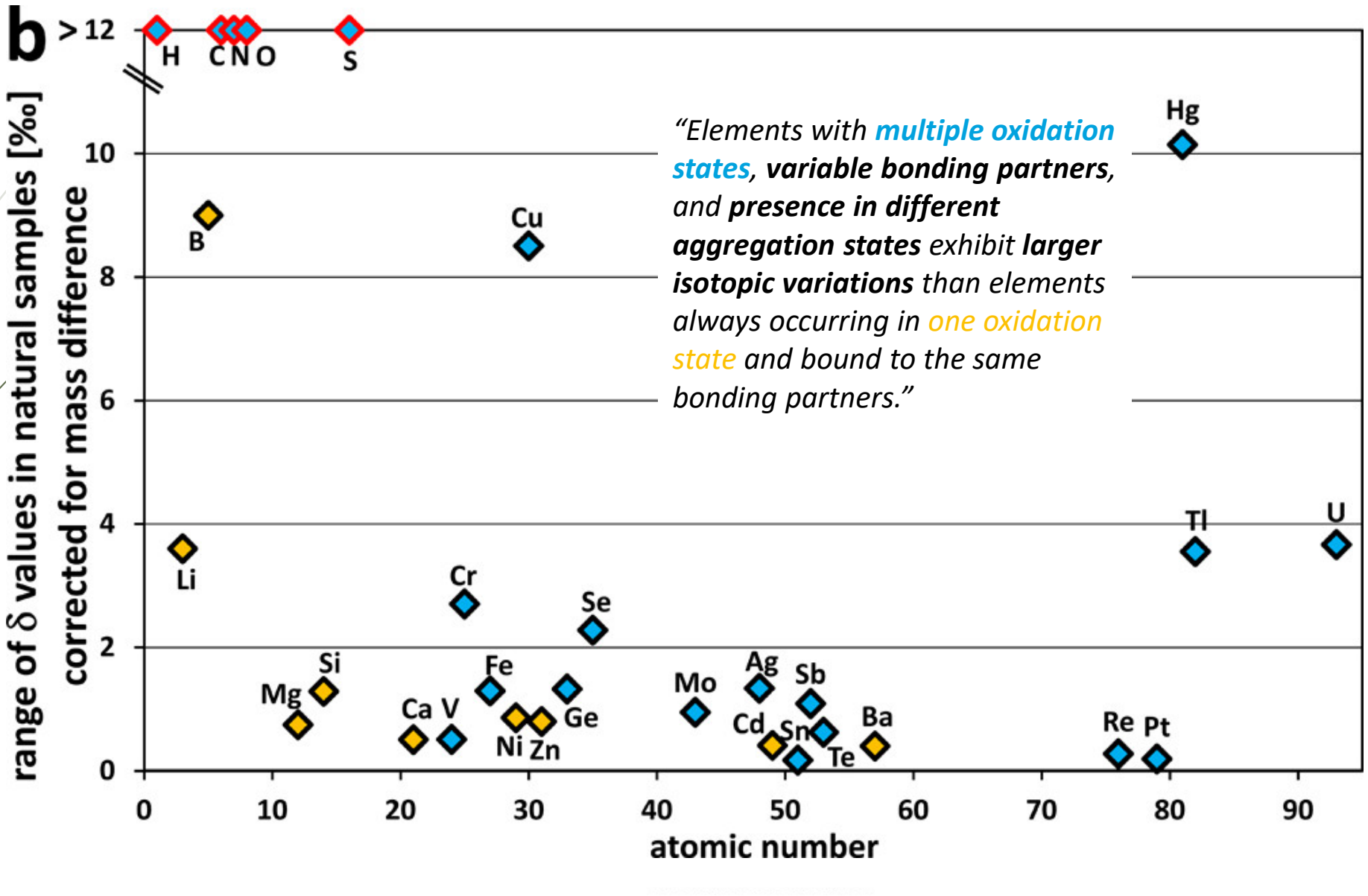
Non-traditional stable isotopes

Wiederhold (2015)
Environ. Sci. Technol.



Non-traditional stable isotopes

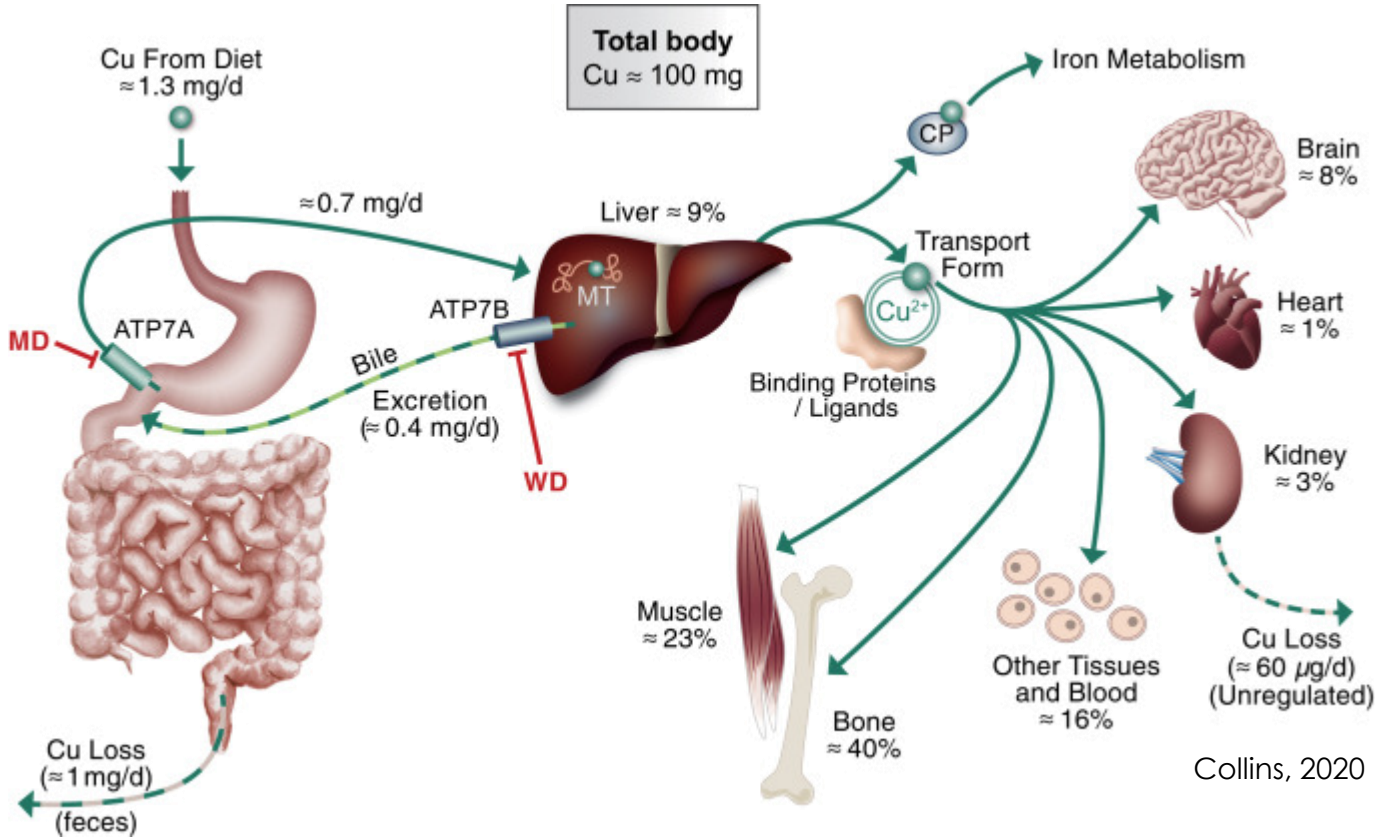
Wiederhold (2015)
Environ. Sci. Technol.



*"Elements with **multiple oxidation states**, **variable bonding partners**, and **presence in different aggregation states** exhibit **larger isotopic variations** than elements always occurring in one oxidation state and bound to the same bonding partners."*

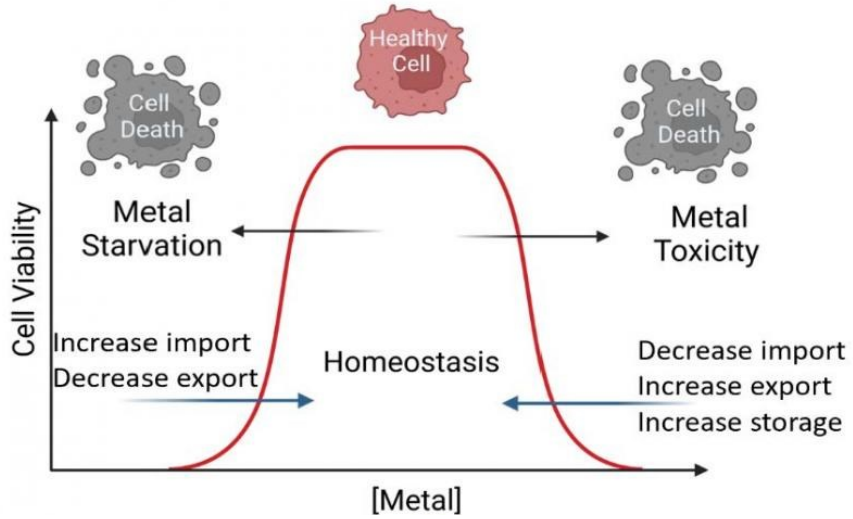
Metal homeostasis

Essential (trace) metals studied from an isotopic perspective:
K, Mg, Ca, Fe, Cu, Zn, Mo…



Collins, 2020

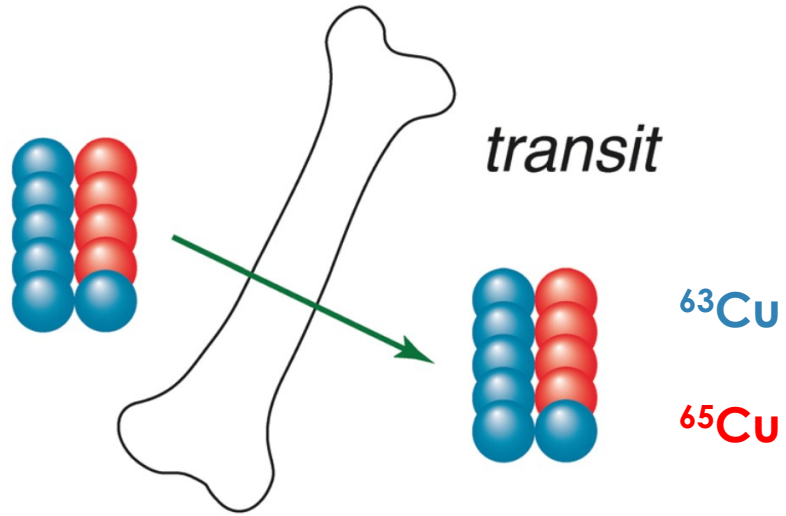
Copper cycle in the human body

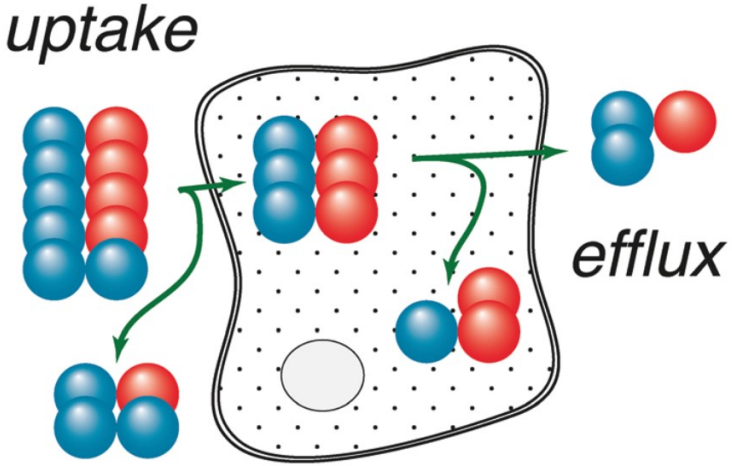


Homeostatic control of essential metals in the human body

Isotope effects in physiology

- At **steady-state** (i.e. the system is not growing) **no fractionation** is expected = isotope proportions in the system are unchanging (input and output balanced).
- When the **metal distributes itself between two coexisting channels**, such as the extracellular medium and cytosol, different pathways allocate a **different isotope abundance** to each channel.
- **Oxidation, biosynthesis, input, storage, and output** are expected to result in isotope fractionation.





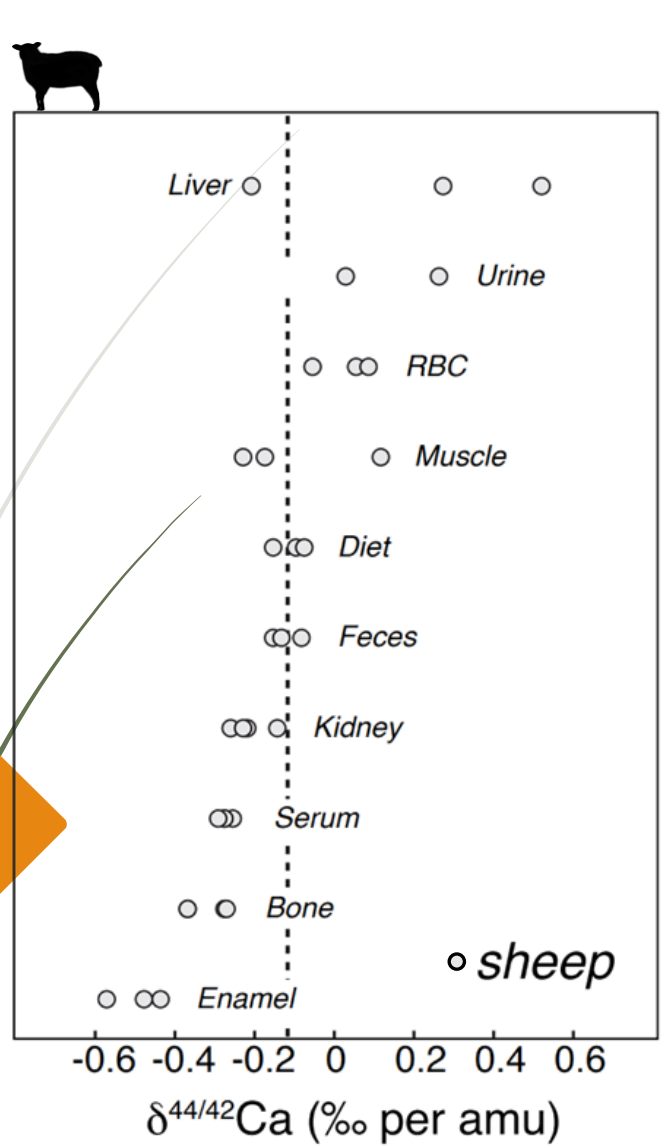
Albarede et al., 2016

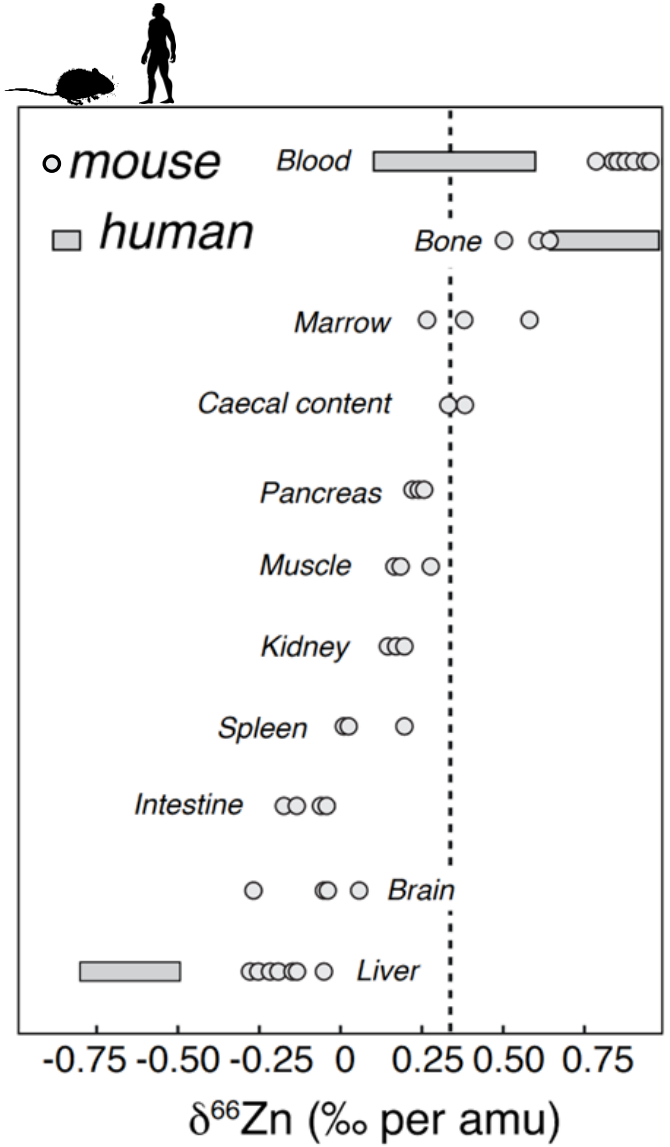
Isotope effects in physiology

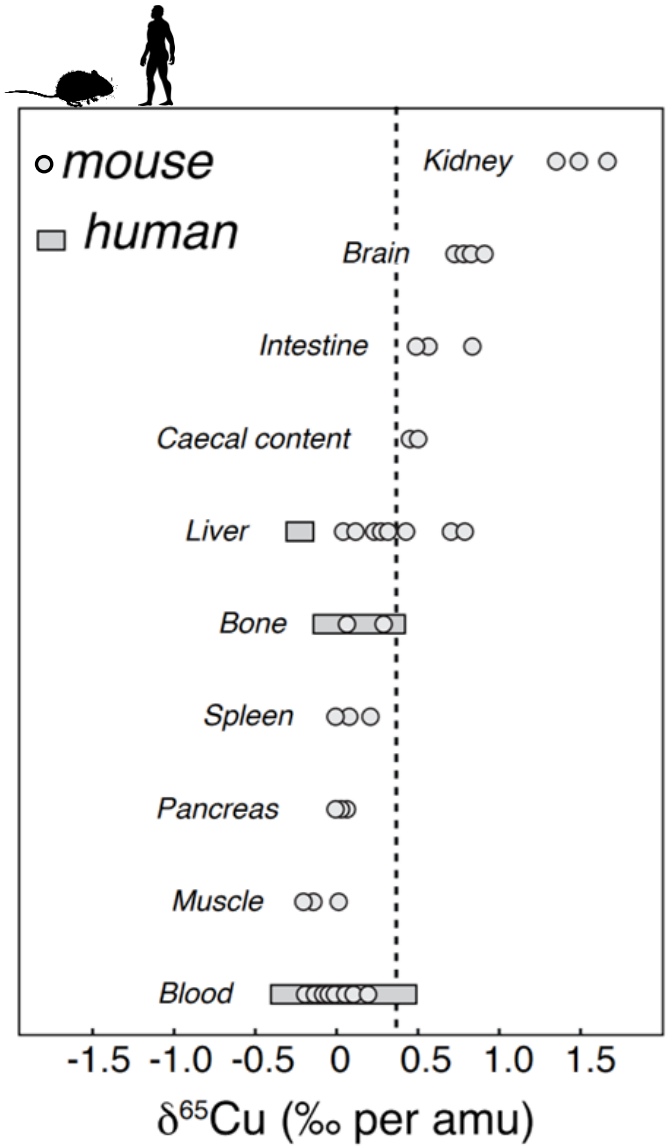
Heavy isotopes tend to concentrate in the **tight bonds**, in particular those involving the **oxidized form** (Cu^{2+} over Cu^{+} and Fe^{3+} over Fe^{2+}) and to bind preferentially with **ligands** with the **stronger electronegativity** (O > N > S).

Balter et al., 2013

Isotope effects in physiology







Albarede et al., 2016

Copper

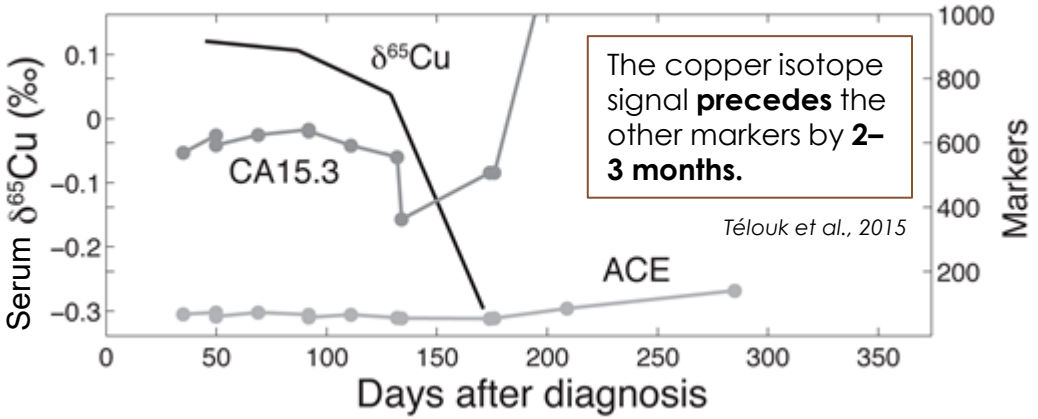
Overall, Cu(II) compounds are isotopically heavier than Cu(I) compounds.

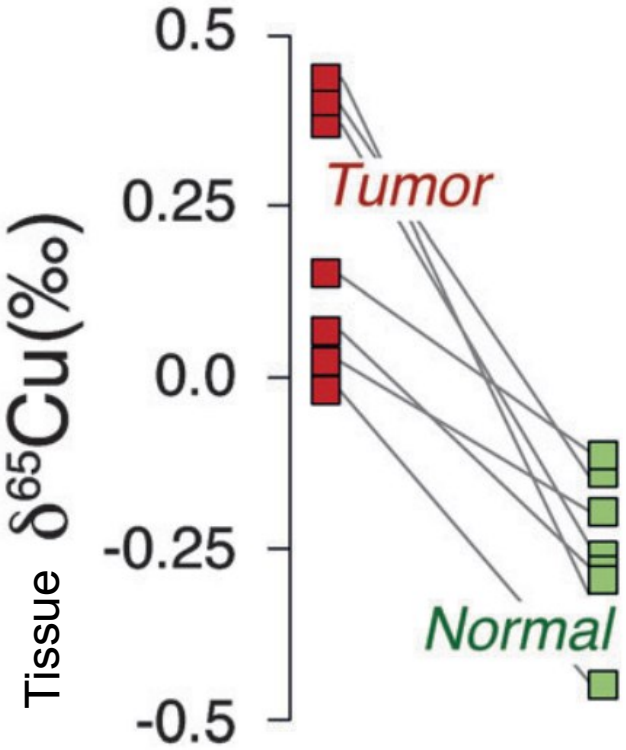
Copper (enzymes) is a tumor promoter and regulates the rapid proliferation cancer cells inside solid tumors.

1. Isotopically heavy Cu chelated by **lactate**, which cancer cells are known to produce massively, accumulates in the **cytoplasm** (*Télouk et al., 2015*).

2. Low $\delta^{65}Cu$ value of serum is due to the **release of intracellular copper from cysteine** clusters in metallothionein (*Balter et al., 2015*).

3. Low $\delta^{65}Cu$ values reveal the **hepatocellular and biosynthetic dysfunction of the liver**, synergistically with inflammation and water retention (*Costas-Rodrıguez et al., 2015*).



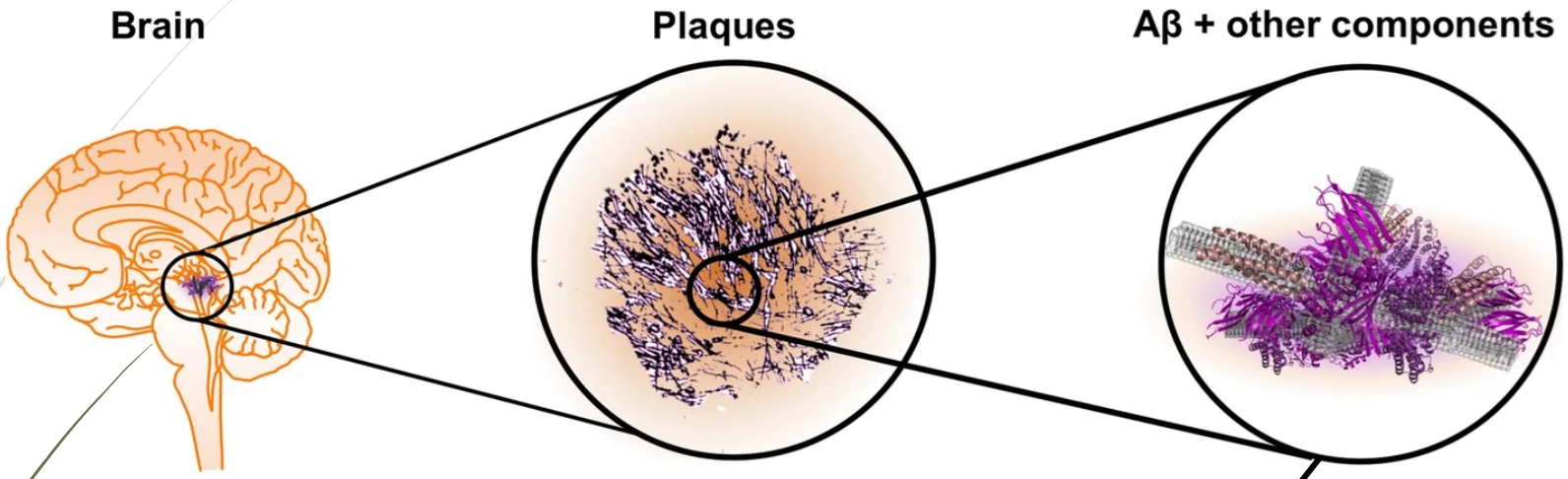


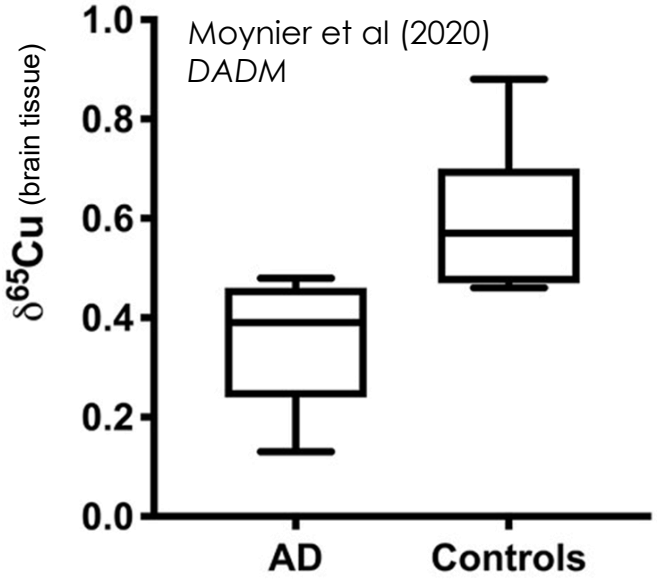
Albarede et al., 2016

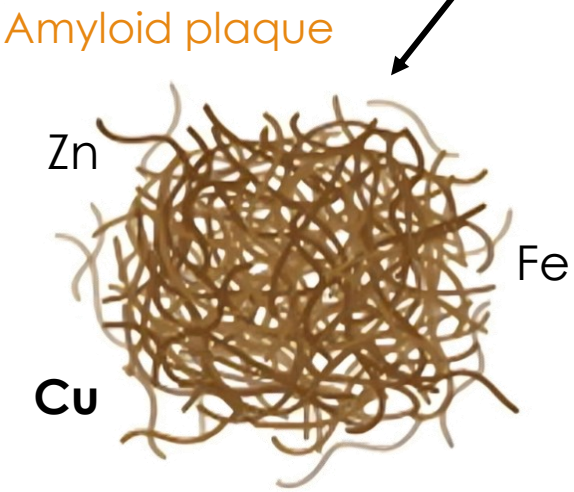
Copper

The Alzheimer geochemistry

Rahamn and Lendel (2021)
Mol. Neurodegener.







In a healthy brain, copper is bound to cysteine (amino acid) as Cu^{2+}.

In **amyloid plaques Aβ** is also **Cu^{+}** (reduced) → **isotopically lighter**.

- Early diagnosis (?)
- Understanding the pathophysiology – *dyshomeostasis.*

Calcium

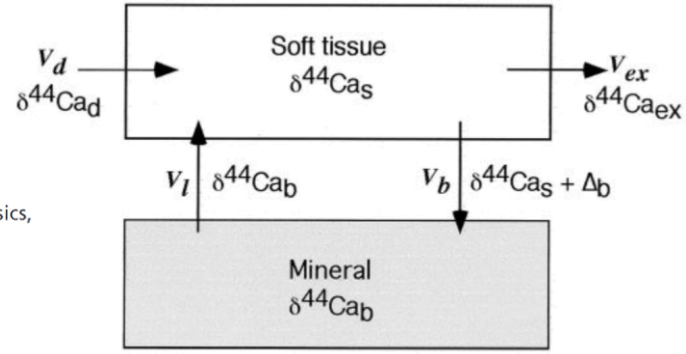
PNAS

Calcium isotope fractionation between soft and mineralized tissues as a monitor of calcium use in vertebrates

Joseph Skulan*†‡§ and Donald J. DePaolo‡¶

*Department of Geology and Geophysics, University of Wisconsin, Madison, WI 53706; Departments of †Integrative Biology, and ¶Geology and Geophysics, University of California, Berkeley, CA 94720; and ‡Berkeley Center for Isotope Geochemistry Earth Sciences Division, E. O. Lawrence Berkeley National Laboratory, Berkeley, CA 94720

Contributed by Donald J. DePaolo, September 21, 1999



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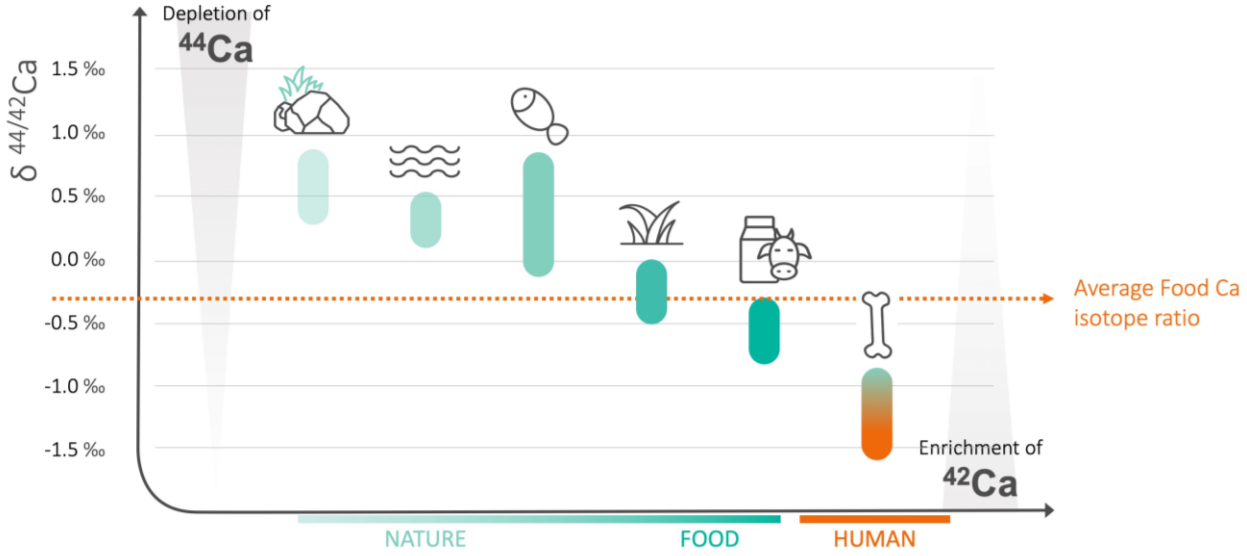
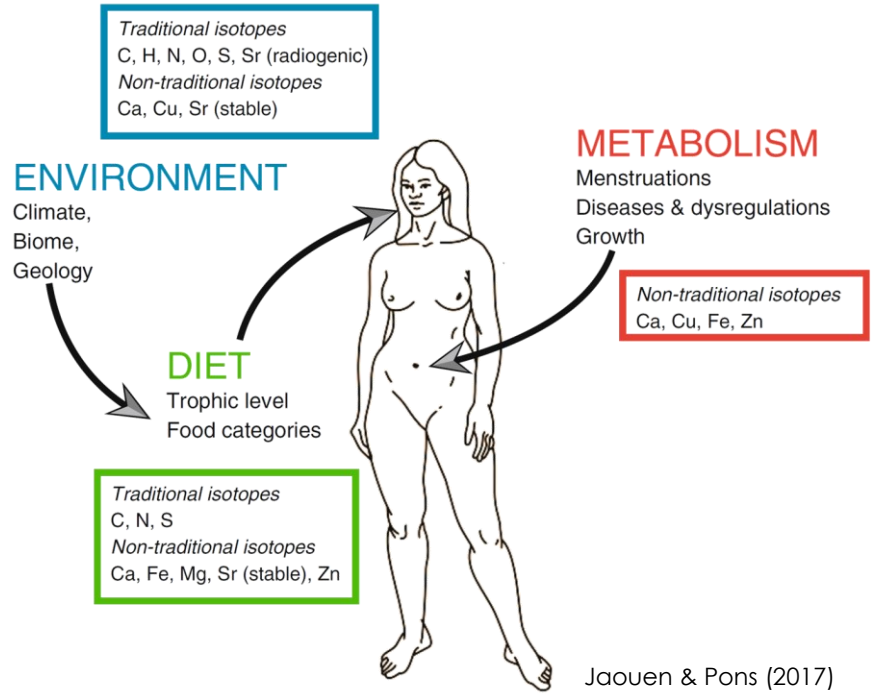
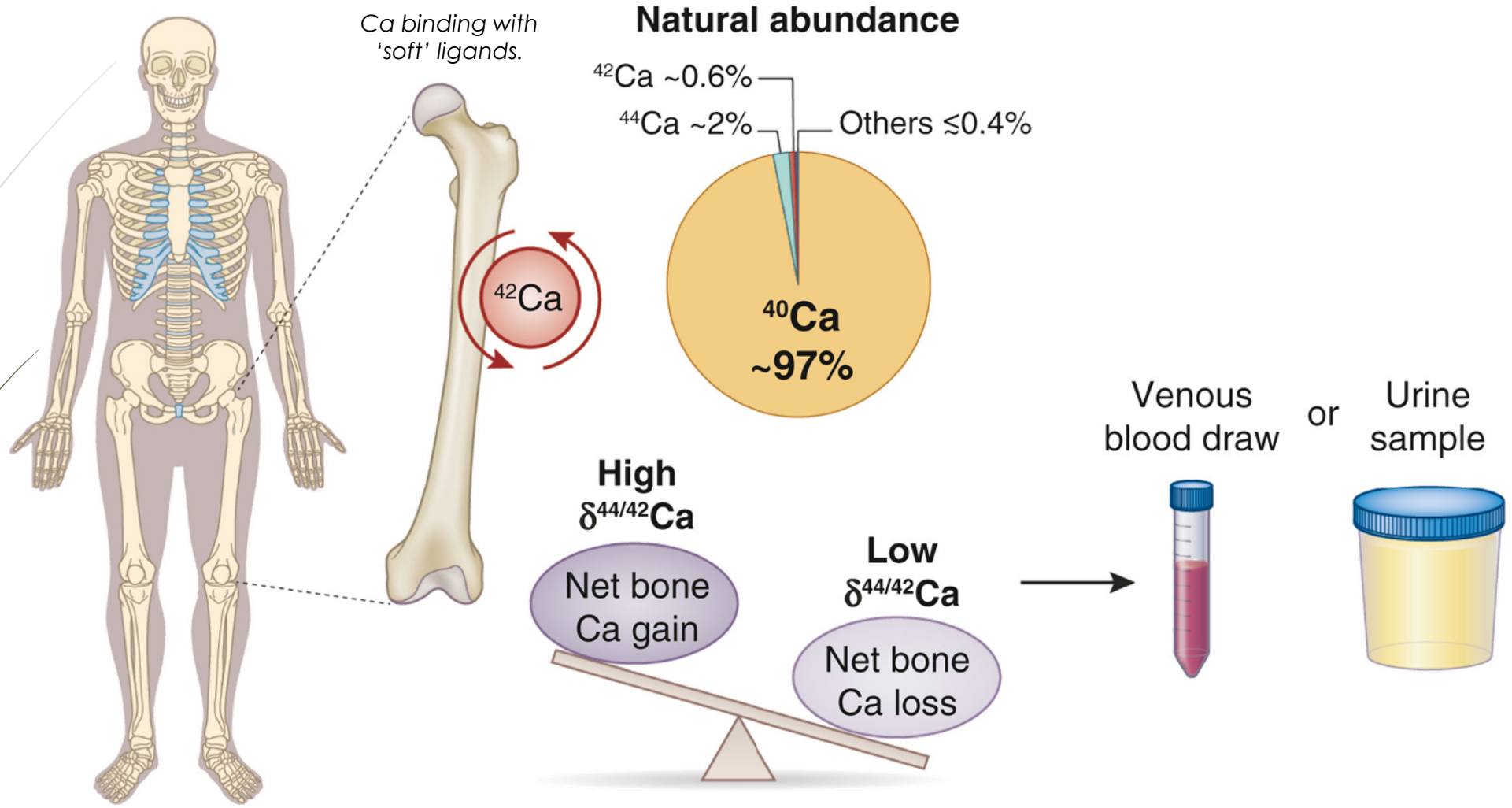




Eisenhauer 2006 – Chu et al., 2005 - osteolabs

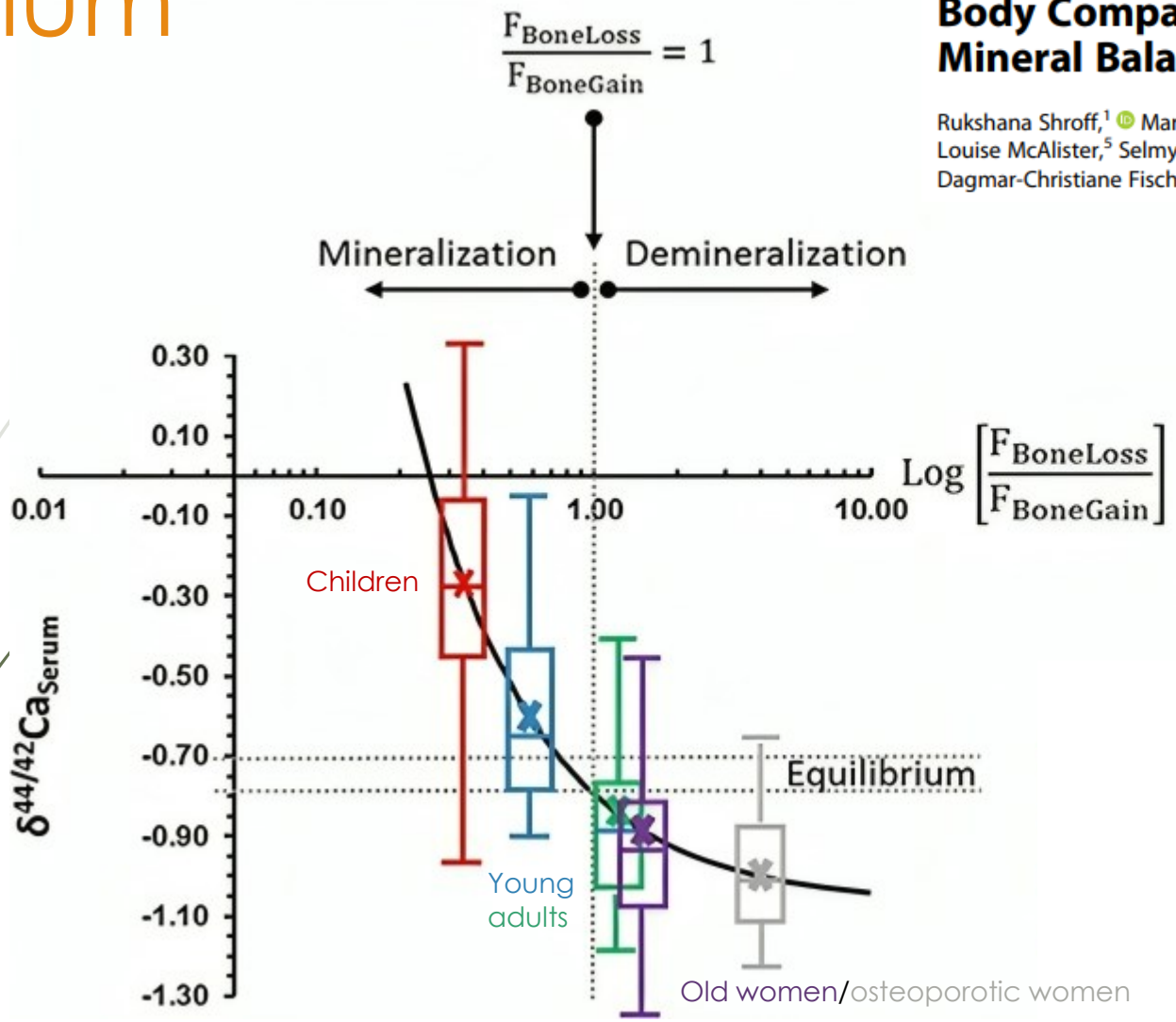
Jaouen & Pons (2017)

Calcium



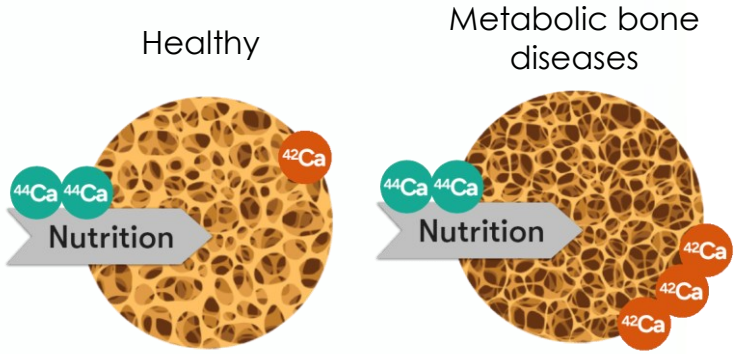
Gallant, Zheng (2022)

Calcium

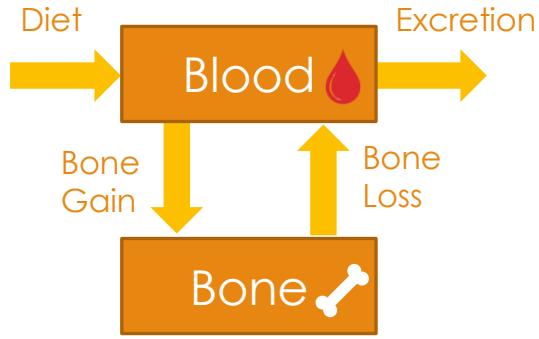


Naturally Occurring Stable Calcium Isotope Ratios in Body Compartments Provide a Novel Biomarker of Bone Mineral Balance in Children and Young Adults JBMR 2020

Rukshana Shroff,[1] Mary Fewtrell,[2,3] Alexander Heuser,[4] Ana Kolevica,[4] Alexander Lalayiannis,[1] Louise McAlister,[5] Selmy Silva,[1] Nadine Goodman,[1] Claus P Schmitt,[6] Lorenzo Biassoni,[2] Anja Rahn,[7] Dagmar-Christiane Fischer,[7] and Anton Eisenhauer[4]



*Isotopically **light Ca** is preferentially **enriched during chemical transport reactions** (for example, incorporation into **bone**), whereas the **heavy isotope** is preferentially **excreted** in urine and feces.*



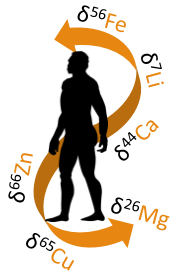
In older adults, bone resorption predominates. *This homeostatic balance between bone formation and resorption at different ages results in **changes in the bone mineral balance** throughout life.*

Take-home message(s)

- ✓ Isotope fractionation in the body can result from several physiological mechanisms, and can be a strong indicator for elemental **dyshomeostasis**.
- ✓ Non-traditional isotopes are strong tools to study the **interaction** between **metals and organic ligands** in the human body, metal chelation, trafficking and cycles.
- ✓ Meta-analyses and larger dataset will maybe allow to use **isotope ratios as routine clinical tools** to early detect key pathological conditions, such as cancer, neurodegenerative diseases, bone and kidney diseases.

EU COST Action: HIP

The Human Isotope Profile



cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

19

Geographic Distribution of Proposers

Country	ITC/ non ITC/ other	Number of institutions from that country	Number of researchers from that country	Percentage of the proposing network
Australia	other	2	2	3.51 %
Belgium	non ITC	3	3	5.26 %
Canada	other	1	1	1.75 %
Croatia	ITC	1	1	1.75 %
Czech Republic	ITC	2	3	5.26 %
France	non ITC	8	10	17.54 %
Germany	non ITC	6	8	14.04 %
Italy	non ITC	3	3	5.26 %
Japan	other	1	1	1.75 %
Lithuania	ITC	1	1	1.75 %
Poland	ITC	1	1	1.75 %
Portugal	ITC	1	1	1.75 %
Slovenia	ITC	3	3	5.26 %
Sweden	non ITC	2	2	3.51 %
Türkiye	ITC	1	2	3.51 %
United Kingdom	non ITC	3	5	8.77 %
United States	other	10	10	17.54 %

Born during the **Isotope Metallomics Workshop 2024**, ISMAR Venice

Core Expertise of Proposers: Distribution by Sub-Field of Science

50.9% Earth and related Environmental sciences
15.8% Chemical sciences
10.5% Clinical medicine
8.8% Biological sciences
7.0% Health Sciences
7.1% Other

UNIMORE: Anna Cipriani & Federico Lugli, secondary proposers

Main proposer: Dr. Giovanni Aloisi, IPGP, Paris