Ecosphère Continentale et Côtière

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Stable Metal Isotopes in Medical Innovation:

State of the Art and a Future Application to Podoconiosis

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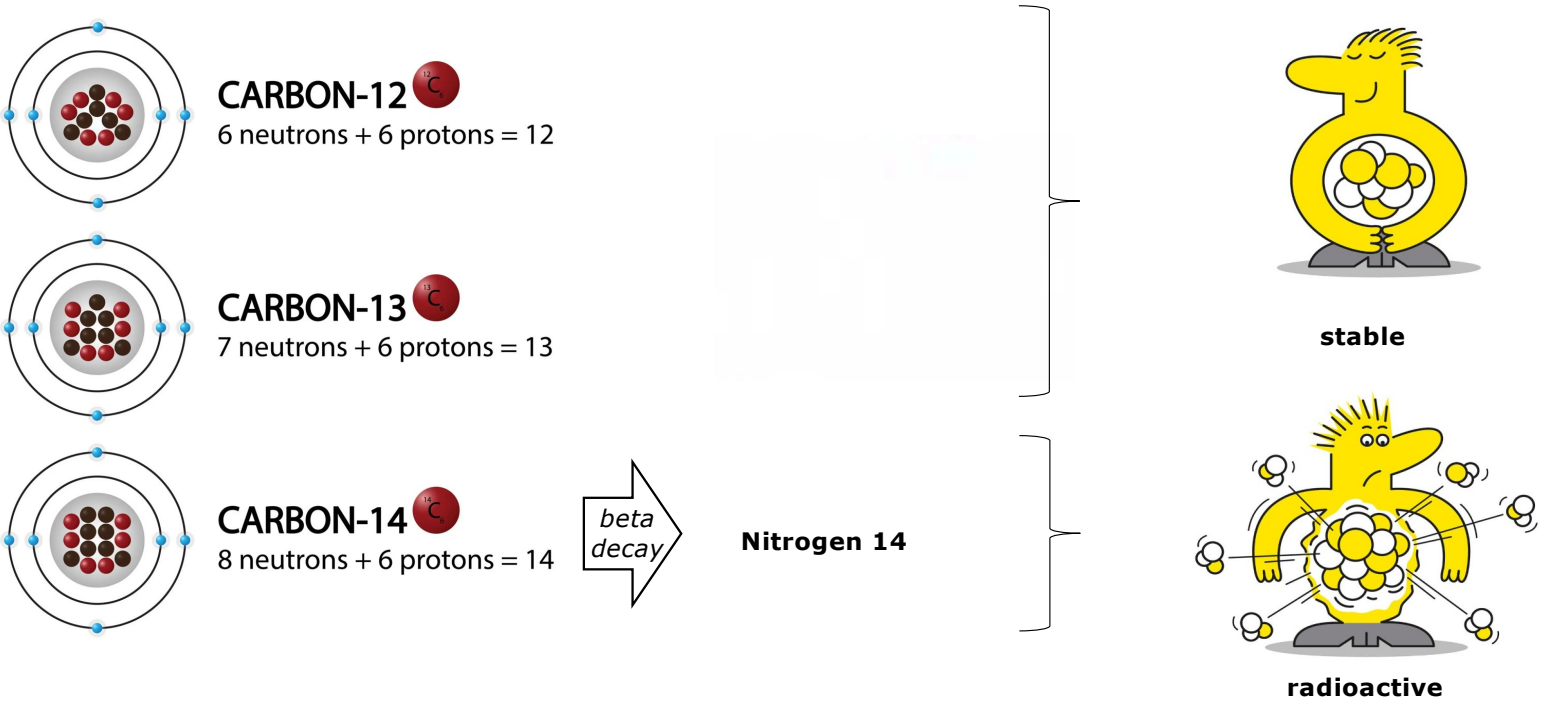
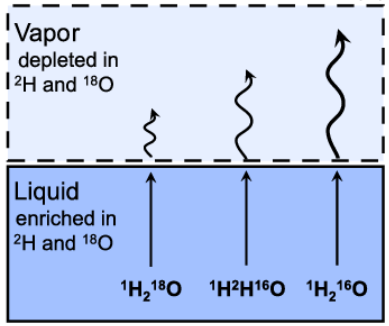
What Are Isotopes?

- Isotopes are atoms of the same element with the same number of protons but different numbers of neutrons.

- Example: C

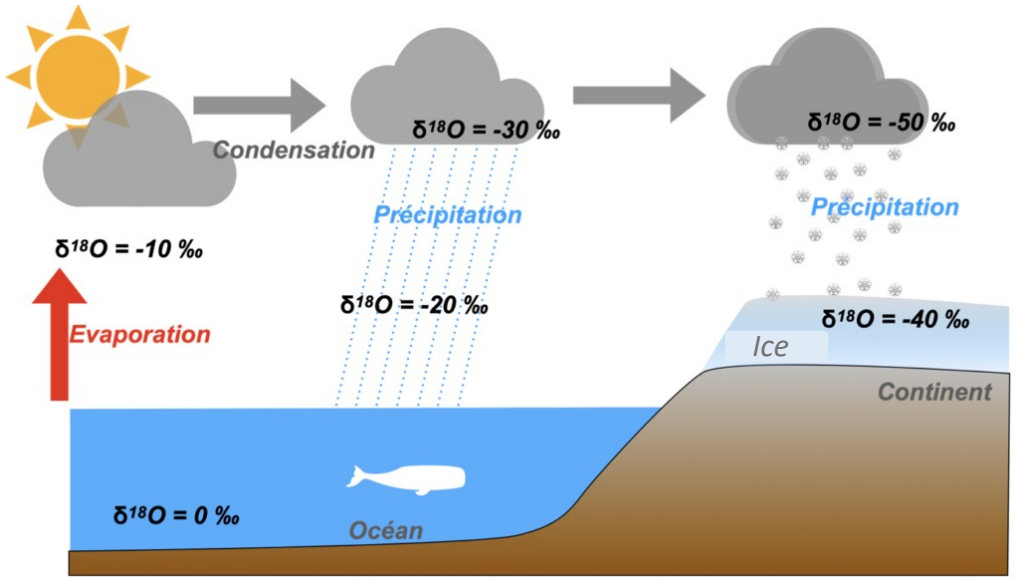


Isotope variation – fractionation processes

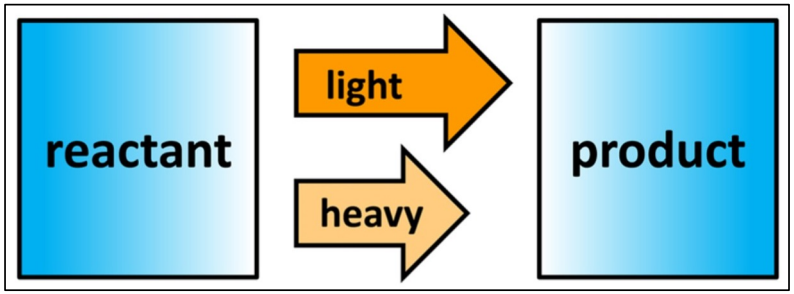


$$\delta^{18}O = \left(\frac{\left(\frac{^{18}O}{^{16}O}\right)_{sample}}{\left(\frac{^{18}O}{^{16}O}\right)_{standard}} - 1 \right) \times 1000$$

$\delta^{18}O_{cloud} < \delta^{18}O_{ocean}$

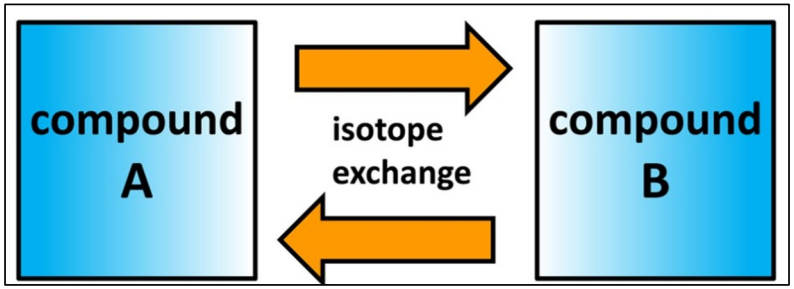


KINETIC ISOTOPE FRACTIONATION



e.g., **biological processes**

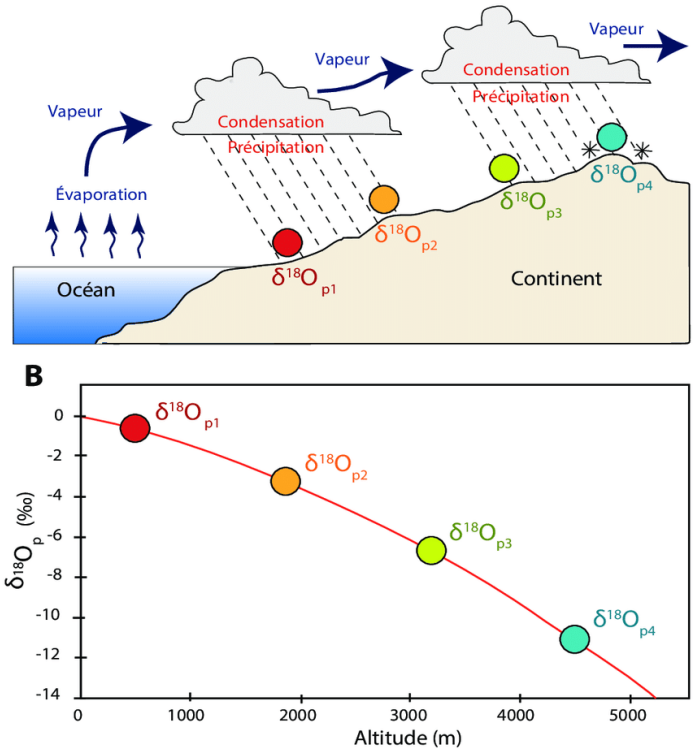
EQUILIBRIUM ISOTOPE FRACTIONATION



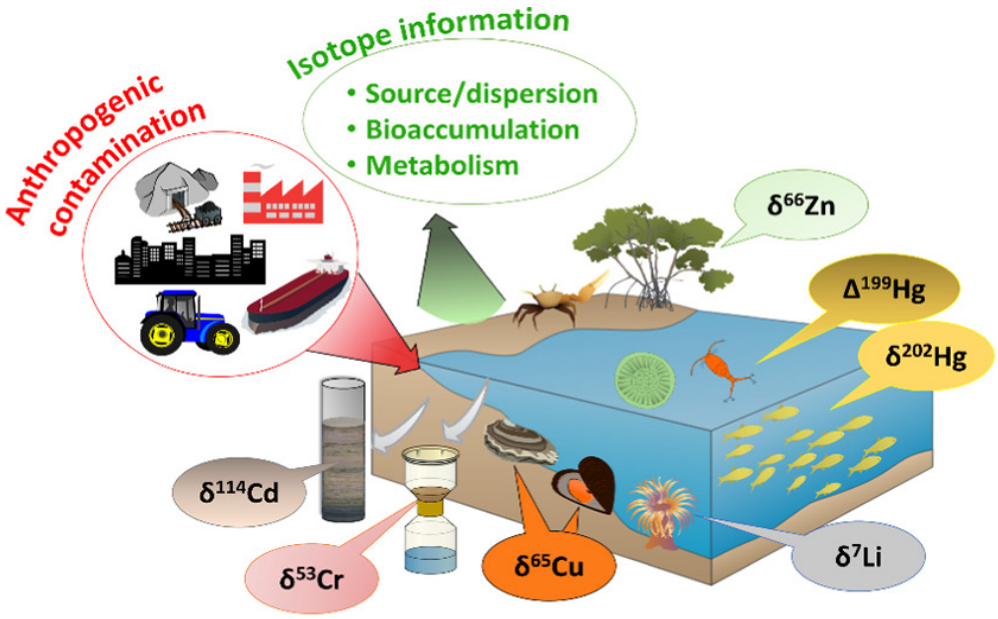
e.g., redox state

Why Measure Isotopes?

- To trace natural processes (e.g., water cycle, pollution, biological activity)



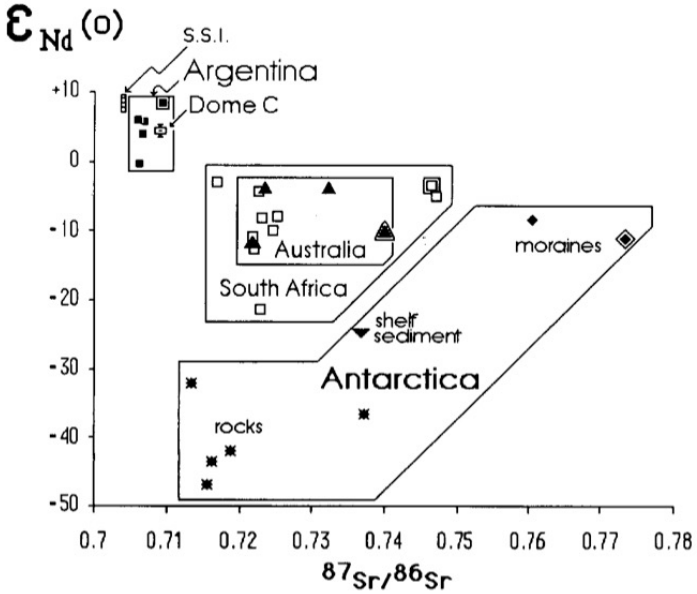
Botsyun et al. (2020)



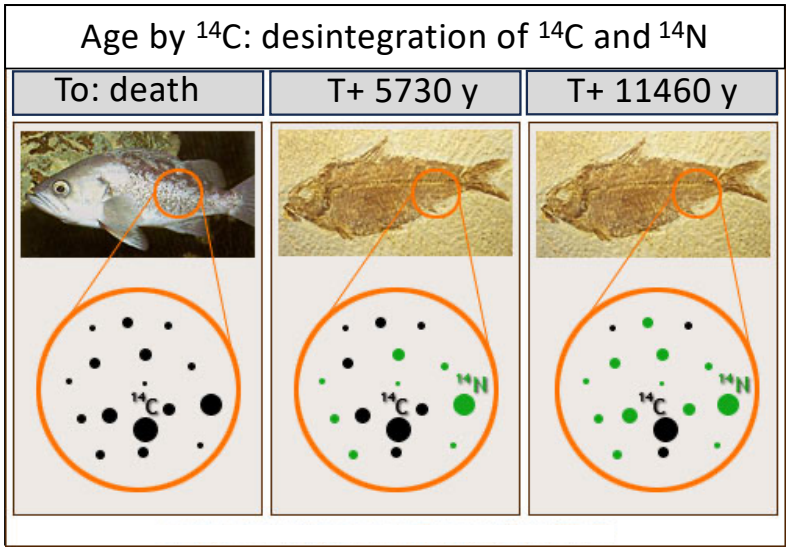
Araujo et al. (2022)

Why Measure Isotopes?

- To trace natural processes (e.g., water cycle, pollution, biological activity)
- To determine the origin or age of samples (e.g., fossils, ice cores, food)



Grousset et al. (1991)



Hominides.com

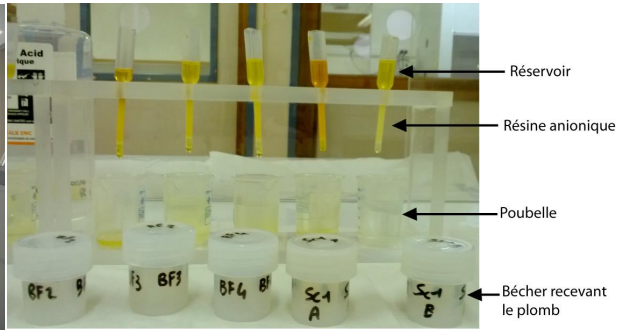
Why Measure Isotopes?

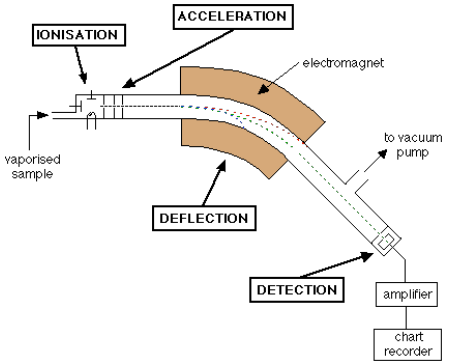
- To trace natural processes (e.g., water cycle, pollution, biological activity)
- To determine the origin or age of samples (e.g., fossils, ice cores, food)
- Recent analytical development allowing to assess very small isotopic variations of traditional stables (N, C) and non-traditional isotopes (Cu, Zn, Fe)

  => application in archaeology & medicine

How Are Isotopes Measured?

- Attack of the samples with acid
- Separation of different elements on ion exchange columns in a clean laboratory
- Use of mass spectrometry
  - Ionize the sample
  - Separate isotopes based on **(m/z)**
  - Measure isotope abundances

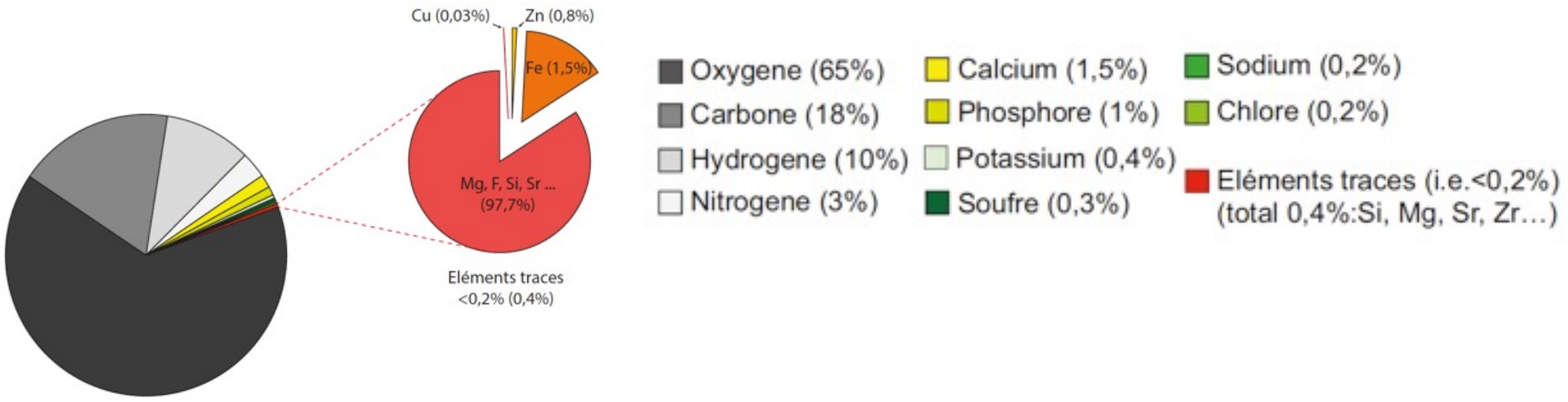




$$\partial^{65}Cu = \left[\frac{\left(^{65}Cu/^{63}Cu\right) \text{ sample} - \left(^{65}Cu/^{63}Cu\right) \text{ ref}}{\left(^{65}Cu/^{63}Cu\right) \text{ ref}} \right] \text{x}10^{3}$$

Application of isotope geochemistry methods to health

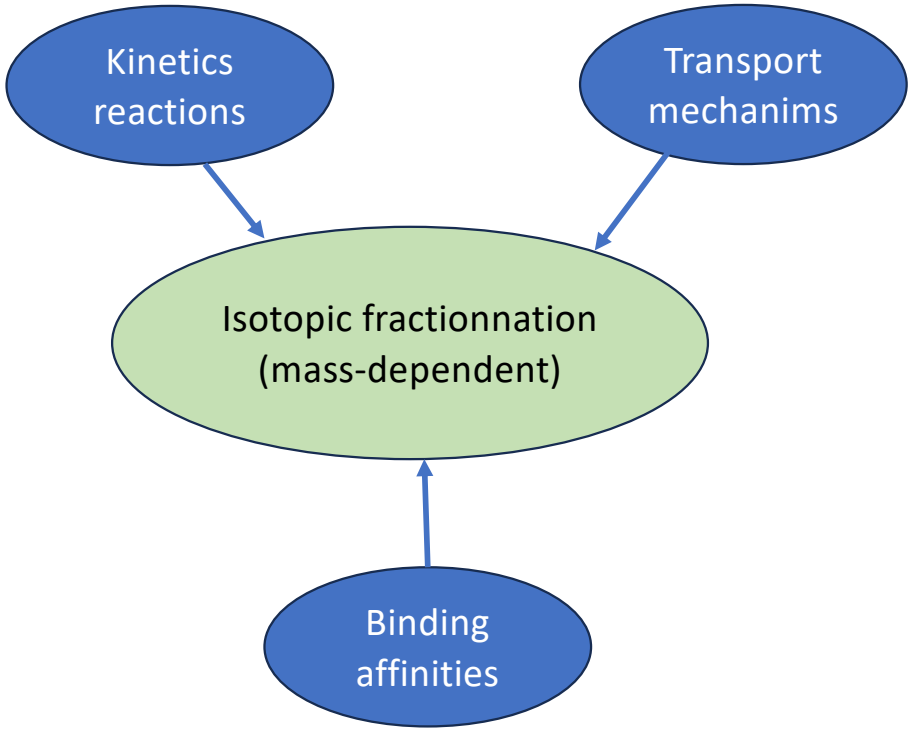
- Alkaline earth metals & transition metals promising as medical diagnostic tools
  => specific in biological functions, short turnover rate

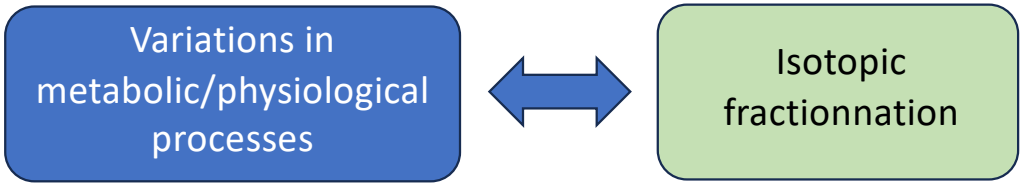


Schematic representation of the percentage of different chemical elements present in the human body

Lucie et al. (2018)

- Stable isotopes are effective natural tracers of metabolism and nutrient pathways

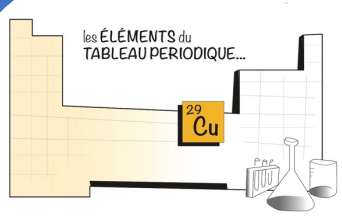




Reliable biomarkers for pathological conditions

Why are Cu isotopes a useful marker ?

- Micronutrient involved in many physiological processes and in key mechanisms of carcinogenesis and tumor progression



Copper
[Ar] $3d^{10}\,4s^{1}$

- Redox reactions
  - Mitochondrial electron transport
    - Cytochrome c oxidase
- Electron transport
- Enzyme catalysis
  - Protection from oxidative stress
    - Superoxide dismutase

Faster turnover rate **< 6 weeks**

↓

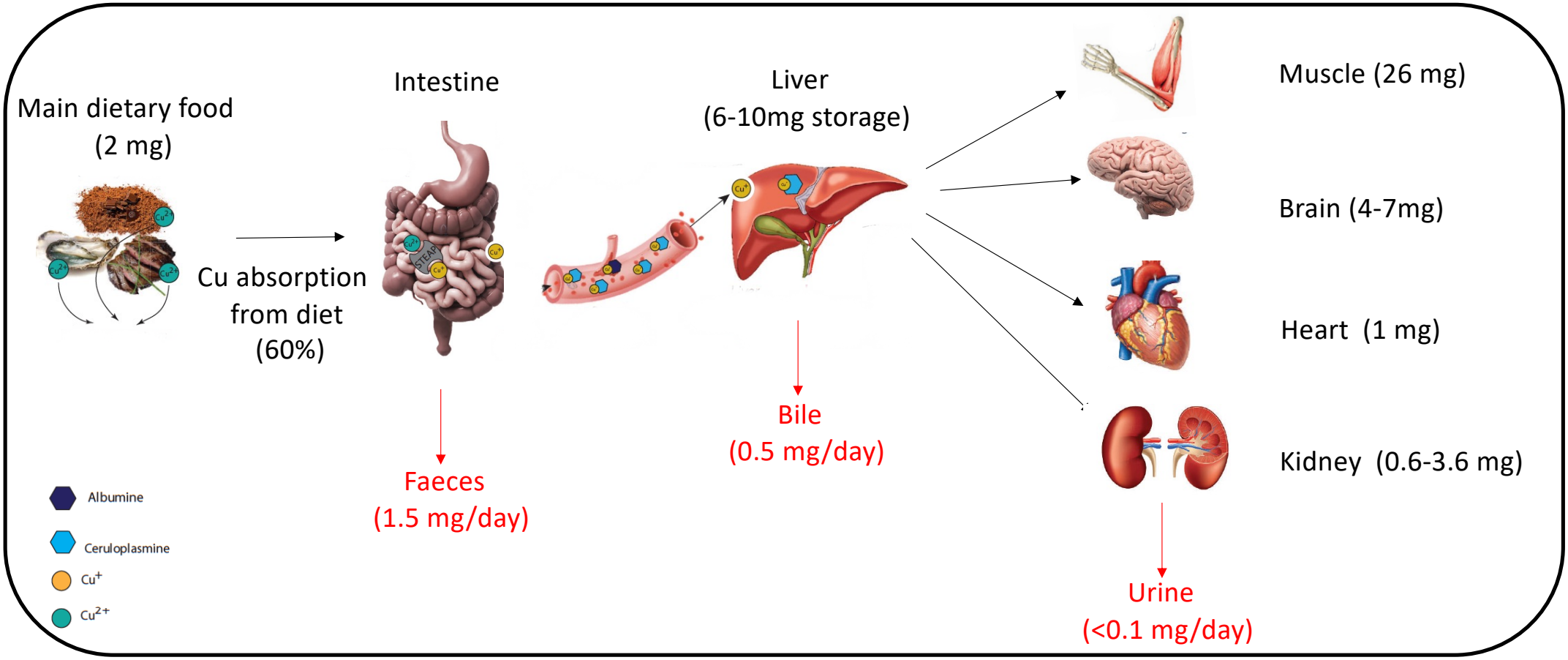
Shorter /proportionate to the evolution of the pathology and treatments

Two isotopes ^{65}Cu and ^{63}Cu

$$\partial^{65}Cu = \left[\frac{\left(^{65}Cu/^{63}Cu\right)\text{ sample} - \left(^{65}Cu/^{63}Cu\right)\text{ ref}}{\left(^{65}Cu/^{63}Cu\right)\text{ ref}}\right] \times 10^{3}$$

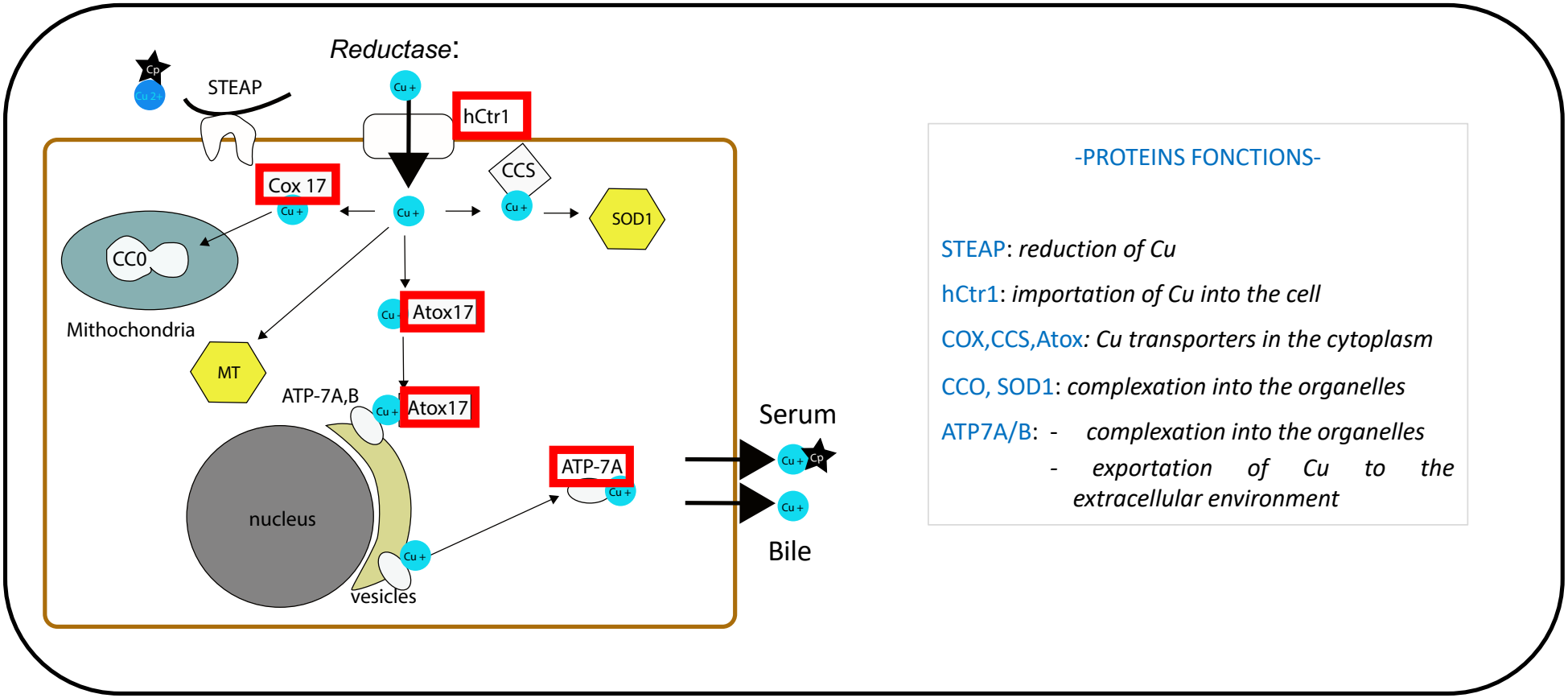
Tracking Rapid Disease Evolution

Copper metabolism in human bodys at the organism scale



Modified from Lucie et al. (2018)

Copper metabolism in human bodys at cell scale



-PROTEINS FONCTIONS-

STEAP: *reduction of Cu*

hCtr1: *importation of Cu into the cell*

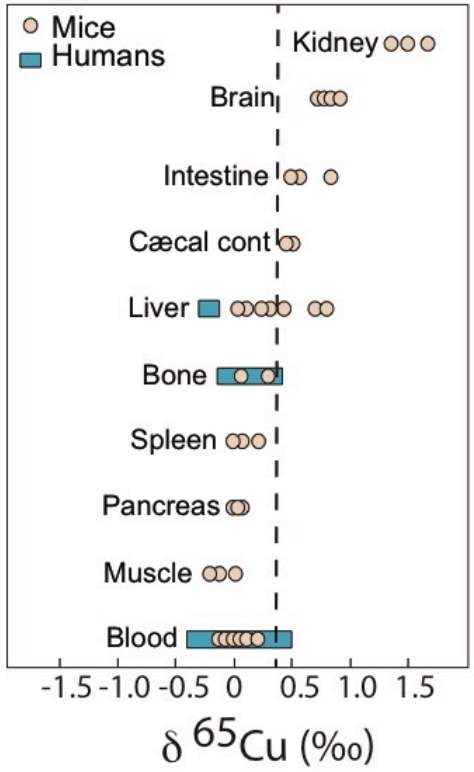
COX,CCS,Atox: *Cu transporters in the cytoplasm*

CCO, SOD1: *complexation into the organelles*

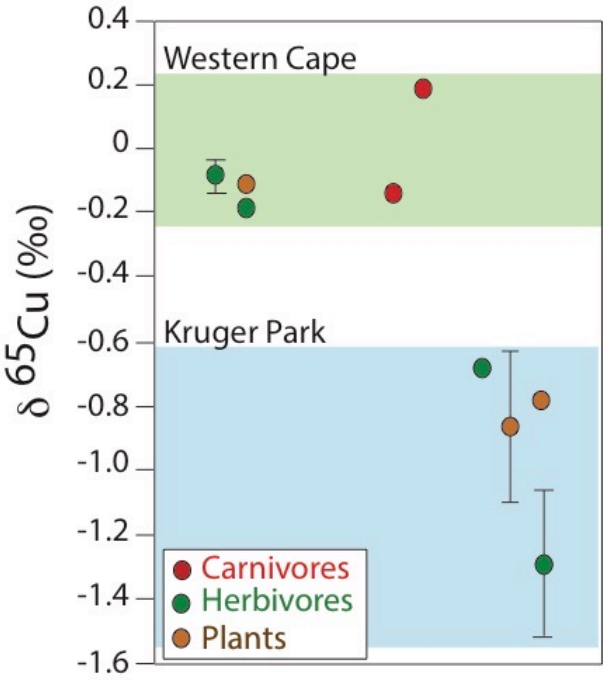
ATP7A/B: - *complexation into the organelles*
- *exportation of Cu to the extracellular environment*

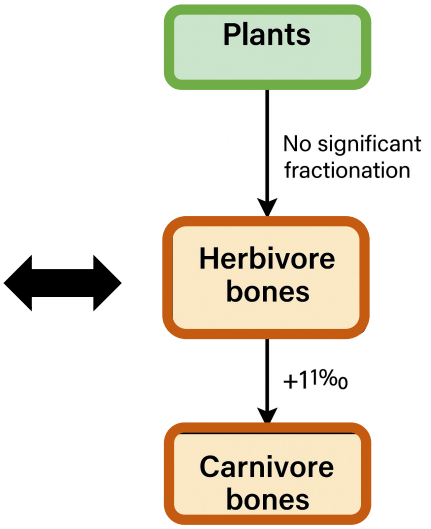
Modified from Albarède et al. (2016)

Cu isotopic composition of healthy heterotrophic organisms



Balter et al. (2013)



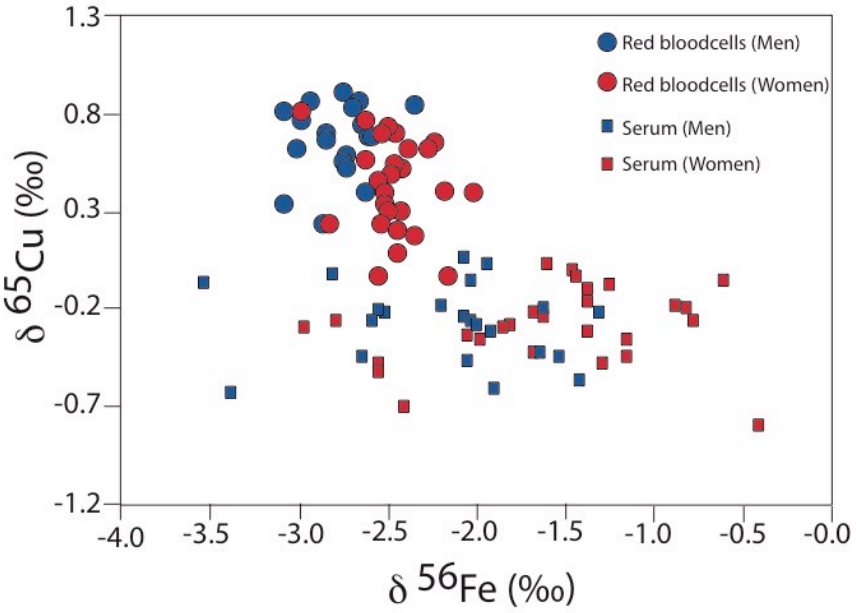


Jaouen et al. (2013)

Copper stable isotopes are naturally fractionated in biological systems

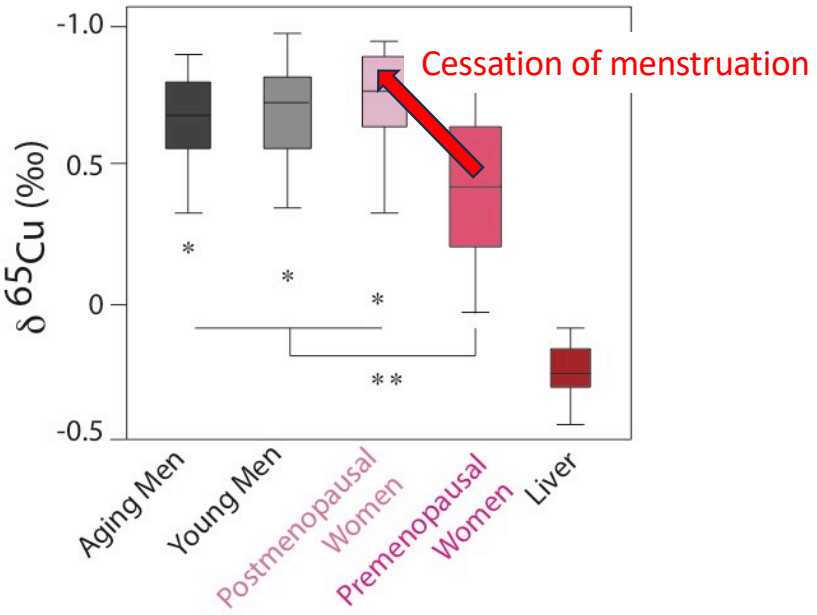
Variations related to differential intestinal absorption of metals

Cu isotopic composition of healthy heterotrophic organisms



Albarede et al. (2011)

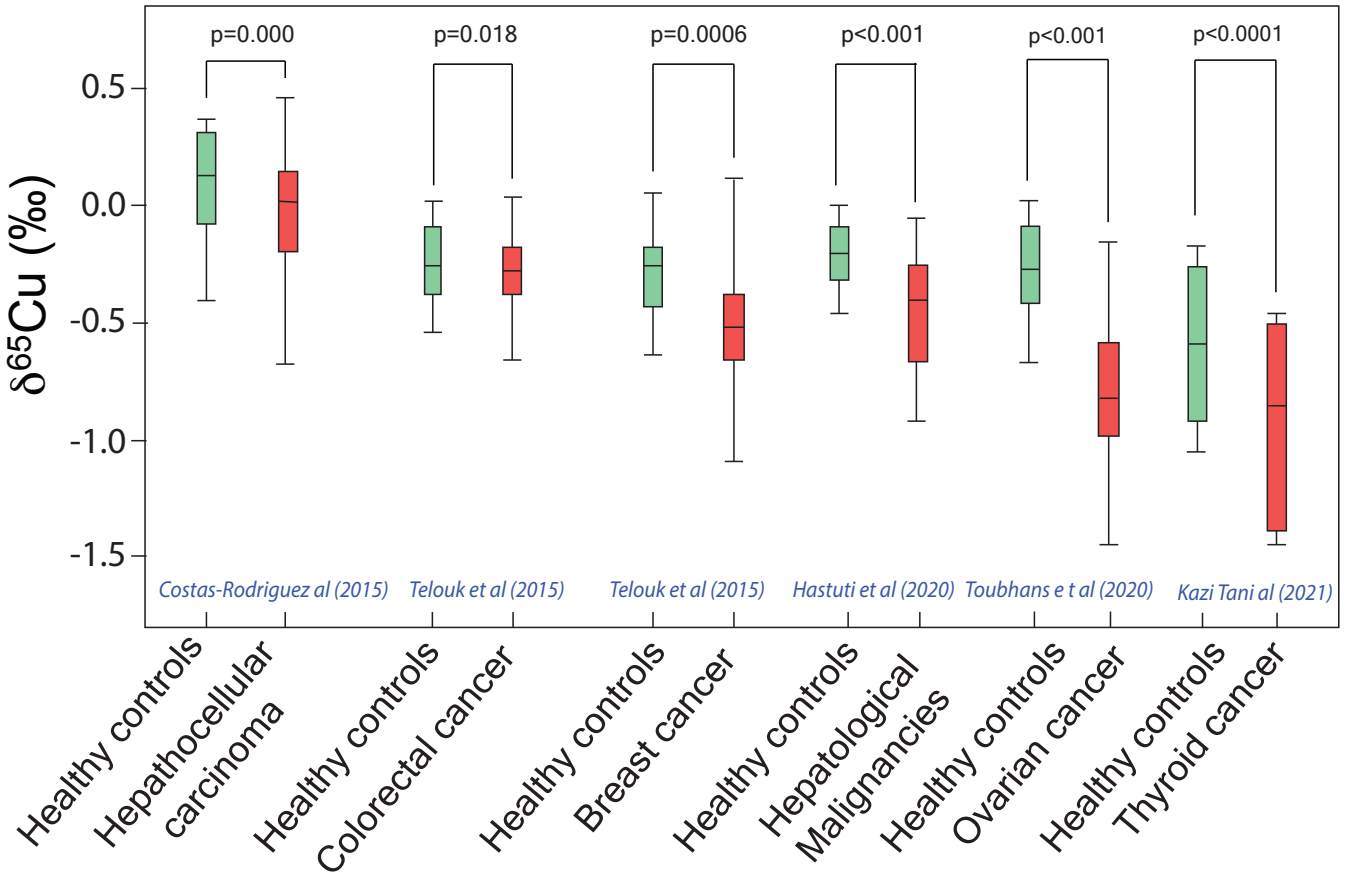
Red blood cells enriched in ^{65}Cu compared to serum



Jaouen and Balter (2013)

Postmenopausal women isotopically heavier than premenopausal women

- Cu isotopic composition of serum cancer patients -



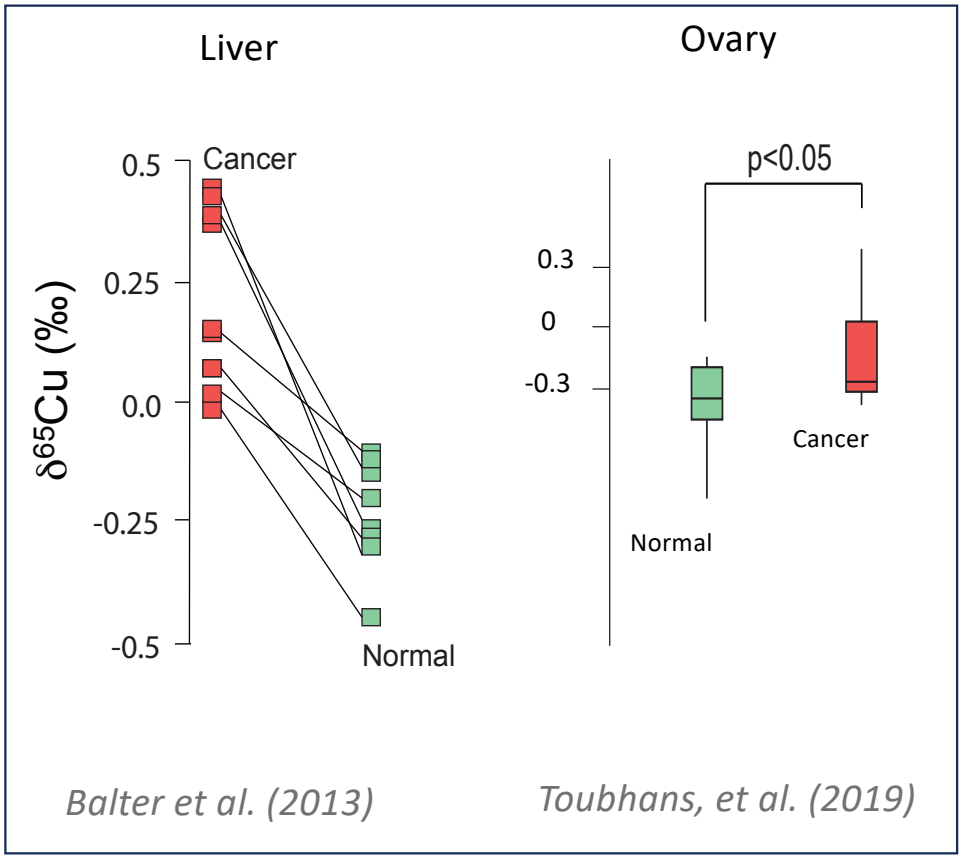
healthy

cancer & inflammatory diseases

- Cu isotopic composition of organs cancer patients: mirror effect -

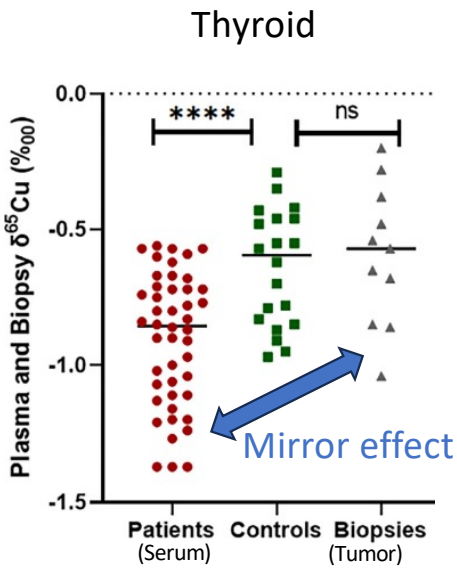
cancer & inflammatory diseases

healthy



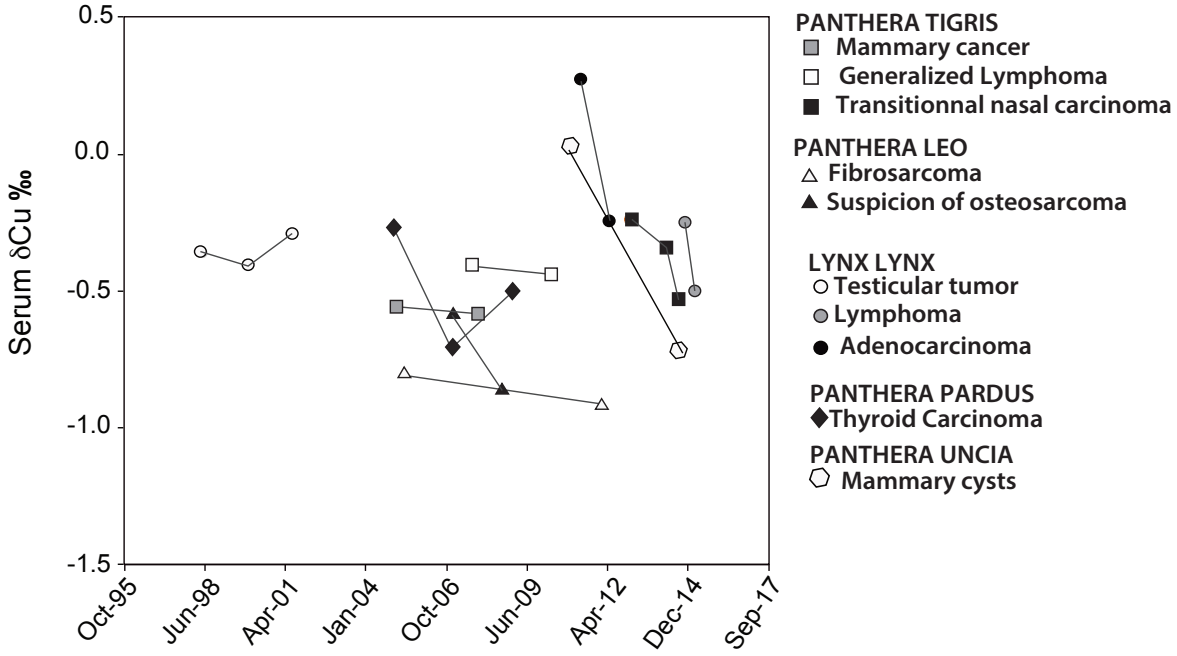
Balter et al. (2013)

Toubhans, et al. (2019)

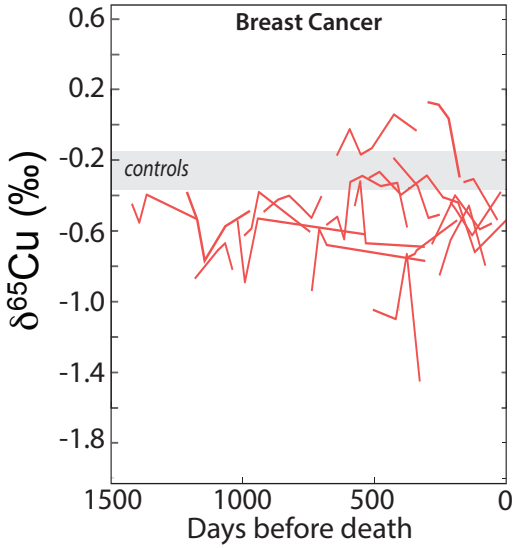


Kazi Tani et al. (2021)

Monitoring felines diagnosed with cancer

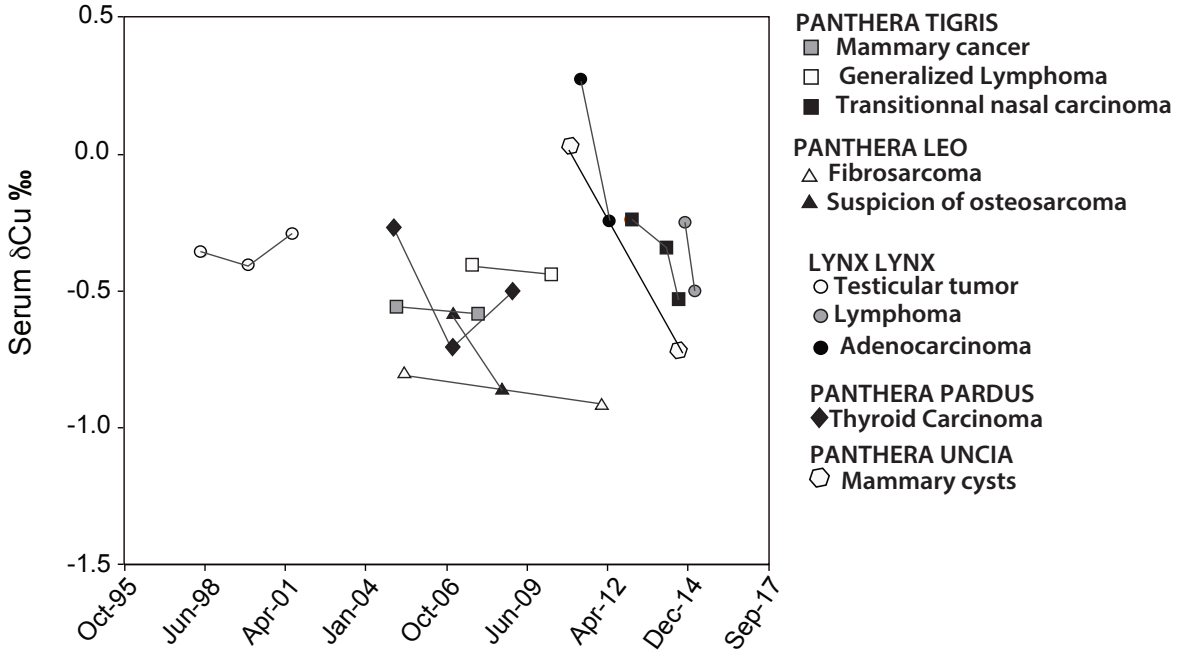


Gourlan et al. (2019)



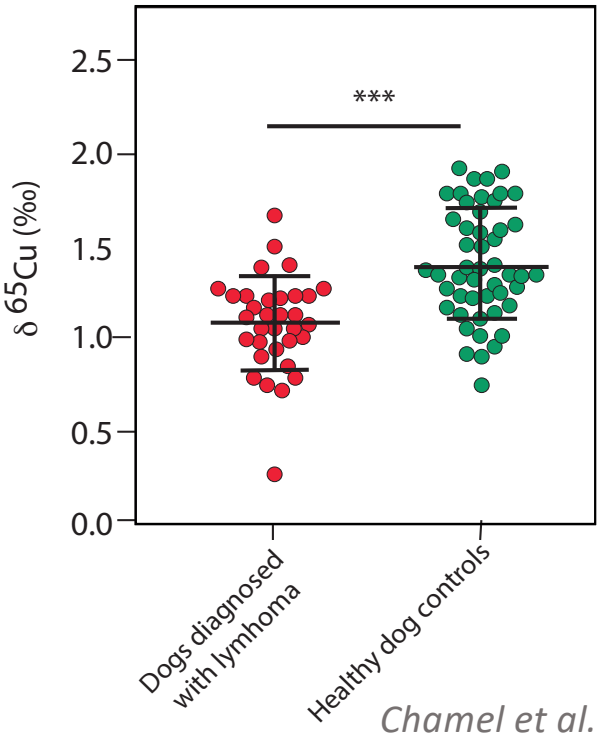
Telouk et al. (2015)

Monitoring felines diagnosed with cancer



Gourlan et al. (2019)

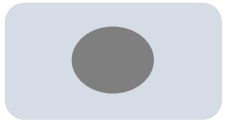
Dogs diagnosed with lymphoma



Chamel et al. (2017)

As for human patients, a negative shift in Cu isotope compositions ($\delta^{65}Cu$) is systematically observed for dogs and felines diagnosed with cancer.

Cu isotopic fractionation



Cancer cell

Preferential chelation of ^{65}Cu

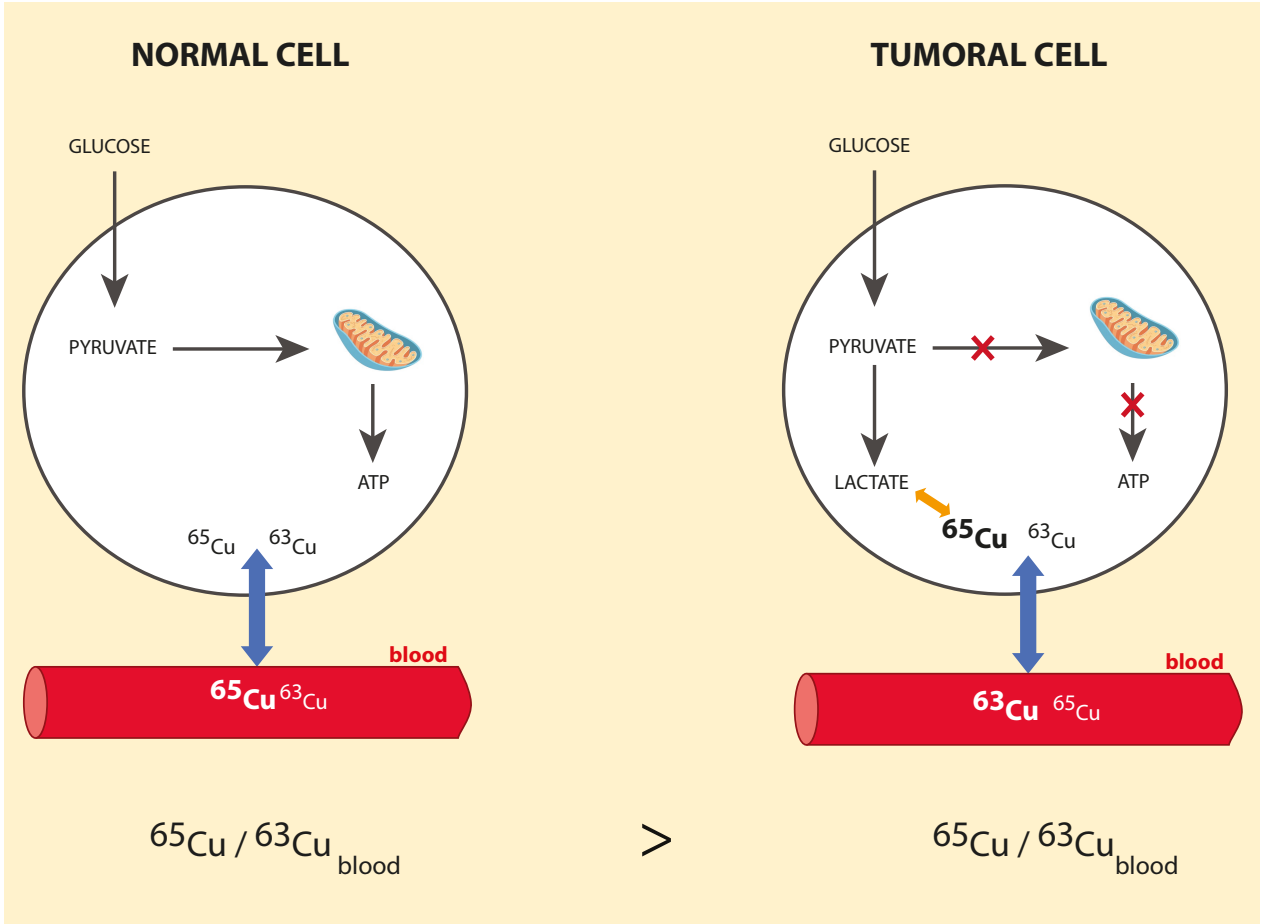
Isotopic fractionation

Role of lactate

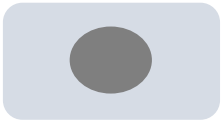
Telouk et al. (2015)

Cu isotopic fractionation

Role of lactate
Telouk et al. (2015)



Cu isotopic fractionation

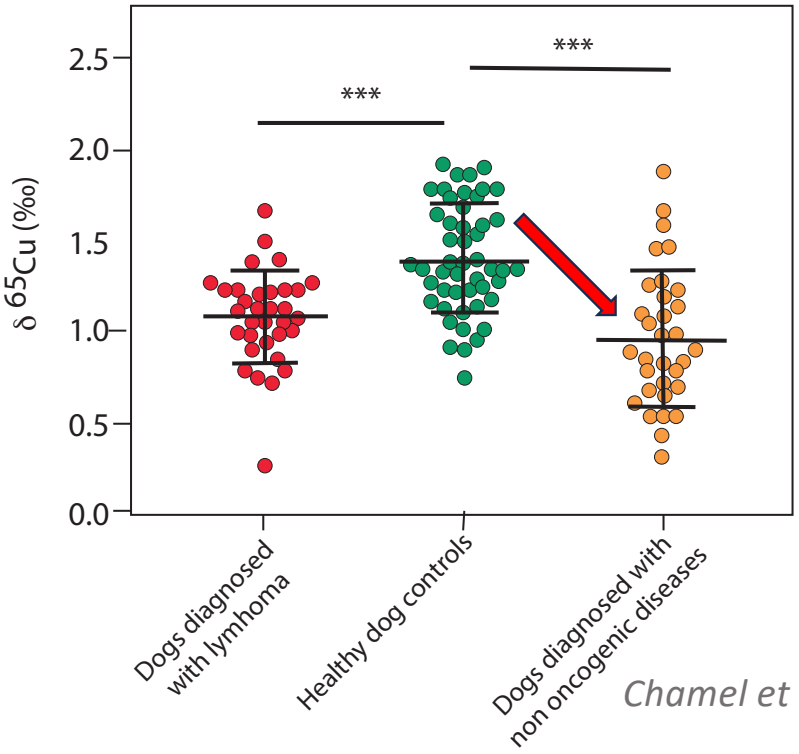


Cancer cell

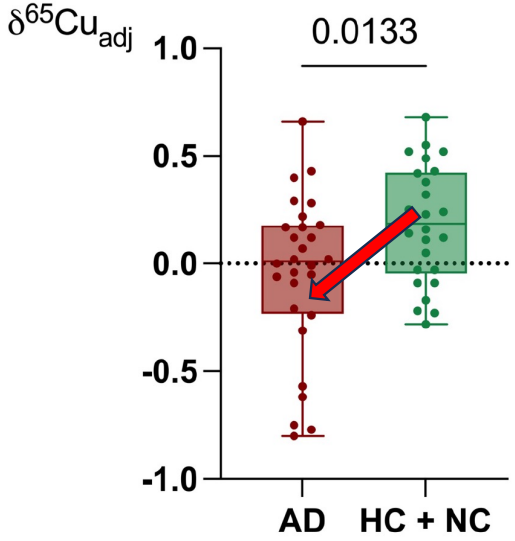
Preferential chelation of ^{65}Cu

Isotopic fractionation

- Role of lactate/Cells in bone marrow or lymph nodes
  Telouk et al. (2015)
  Hastuti et al. (2020)
- Metallothioneins
  Balter et al. (2015)
- Tumor cell Environement
  Bondanese et al. (2016)
- Copper transporters
  Cadiou et al. (2017)
  Toubhans et al. (2019)



Chamel et al. (2017)



Lahoud pers.comm

AD: Alzheimer's Disease

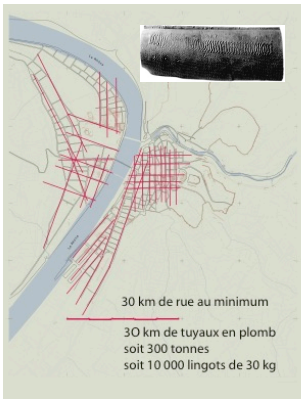
HC: Healthy Controls

NC: Neurological Controls

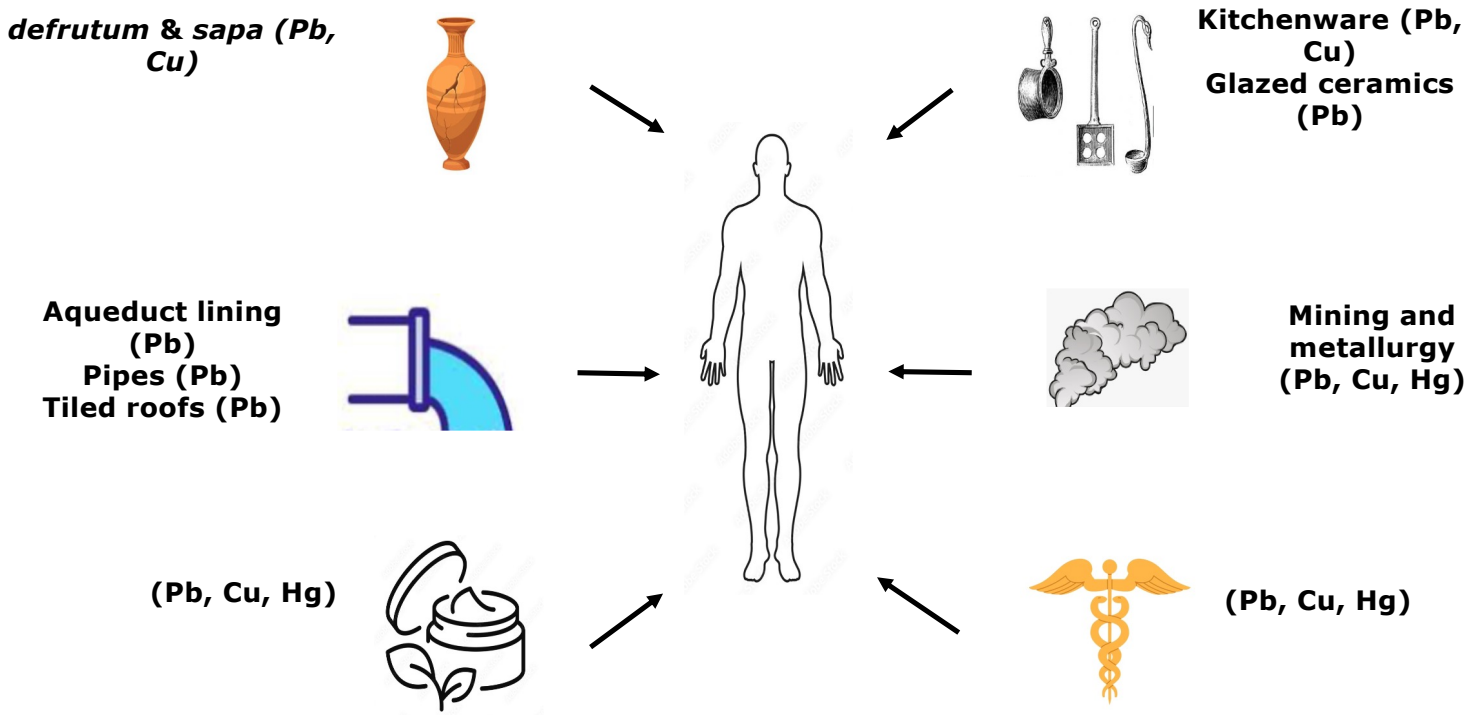
Modification of Cu homeostasis by inflammation

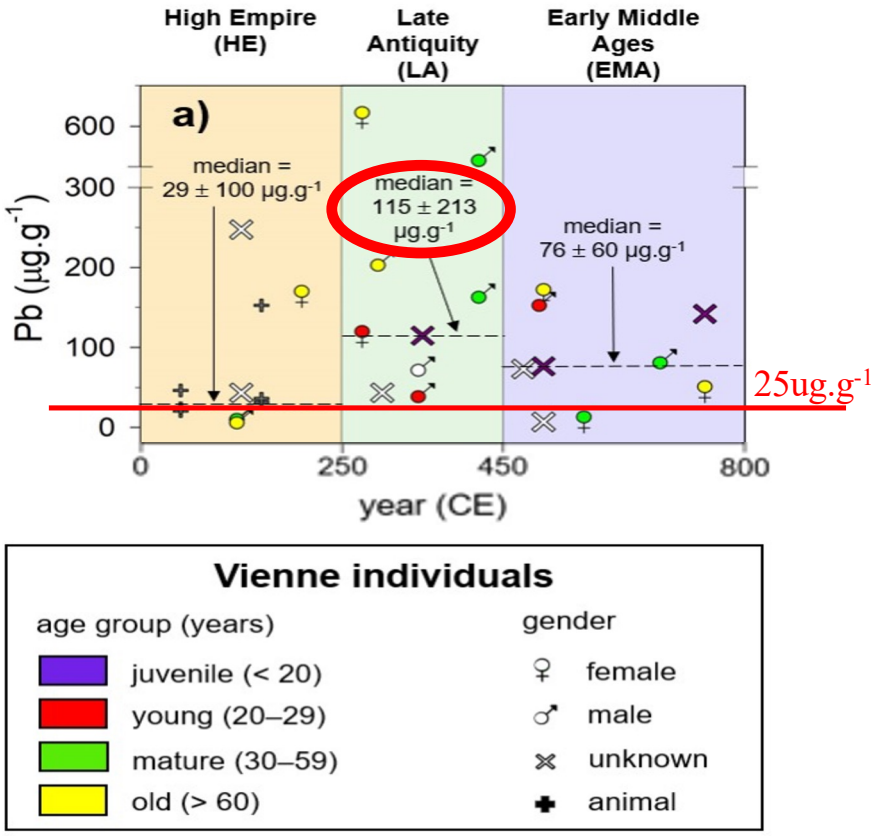
=>δ^{65}Cu good tool for tracking health status

Human exposure and impact of mining on health



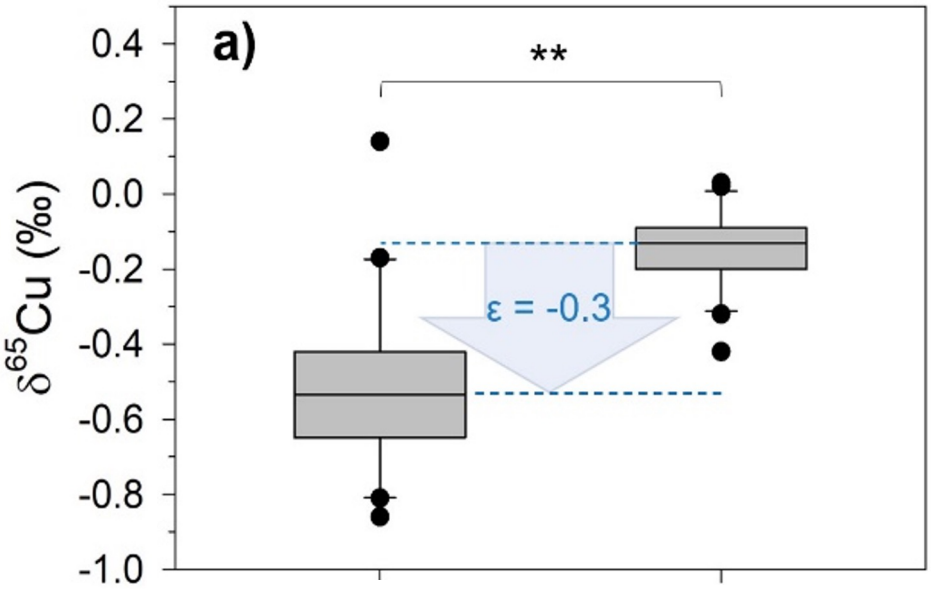
Burdy & Coche (1992)





Heredia thesis (2024)

Human exposure to Pb was widespread throughout the entire city



Heredia thesis (2024)

Jaouen et al. 2012. JAS.

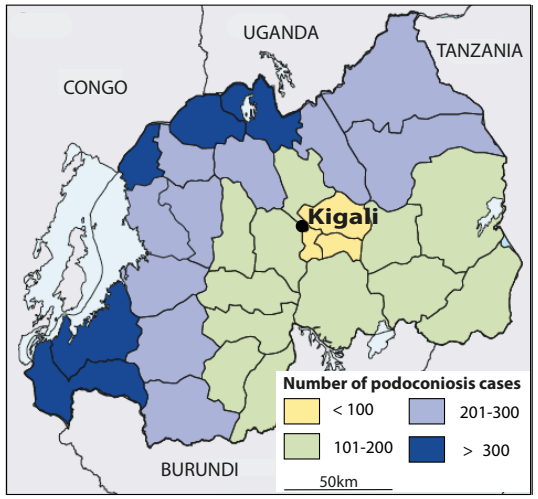
Health deterioration due to the negative physiological consequences of human exposure to Pb

General Context

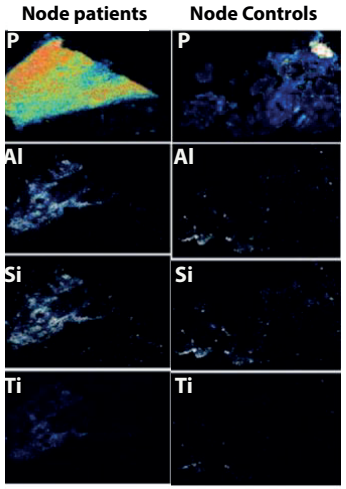
- Non-parasitic tropical disease *(Price et Henderson 1978)*
- 4 million people affected
- High-risk zones: high-altitude, fertile volcanic soils (e.g., Rwanda)

Origin

- No infectious agent identified
- Caused by barefoot exposure to irritant soils
- Key particles: allophane, halloysite, imogolite
- Climate change → migration to fertile risk zones



Deribe et al.(2019)



Busser et al.(2018)

Aggravating factors

- Increasing demographic pressure

=>High prevalence: 1.5 per 1,000 in NW/W Rwanda

Biological and human Impact

- Accumulation of Si, Al, P, Zr in lymph nodes
- Exaggerated T-cell immune response

=> Pain, disability, loss of productivity (up to 45%)

=> Stigmatization: social, educational, religious exclusion

Challenging and research

- No curative treatment currently available
- Unidentified exact cause → prevention remains difficult
- Ongoing research on epigenetic and immune mechanisms

MGIMNT Project

Ecosphère Continentale et Côtière

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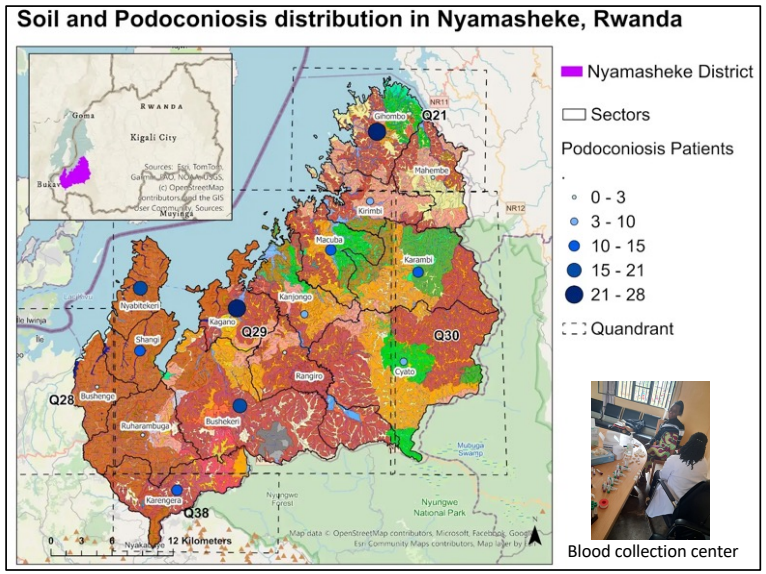
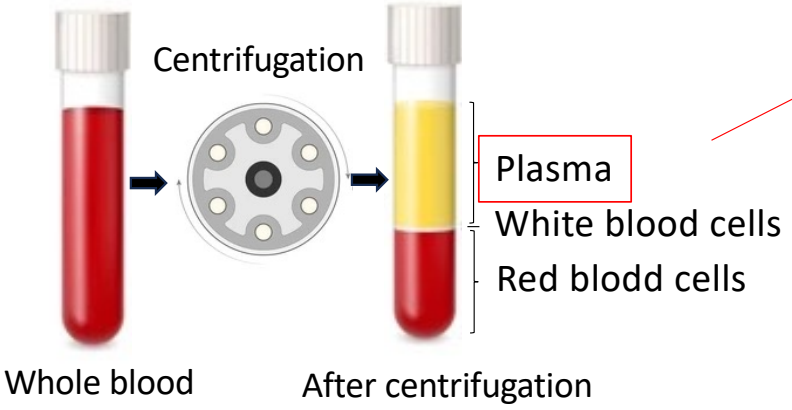
As part of the broad, multidisciplinary project *"One Health and Podoconiosis"*

Goals of this project

Conduct an integrated geo-medical study by:

- Performing **isotopic analysis (blood)** to support the development of **early detection tools** for the disease





δ^{65}Cu patients
δ^{65}Cu controls

To evaluate δ^{65}Cu as a diagnostic biomarker

Rwanda ethics agreement for blood and skin sampling obtained in june 2025

Goals of this project

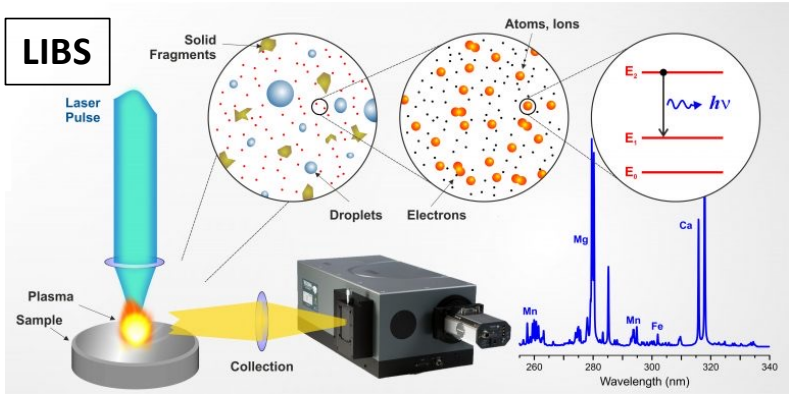
Conduct an integrated geo-medical study by:

- Identifying **particles responsible for podoconiosis/ location of elements on feet**

Soil

+

Biopsies



Take home message

- Isotopic geochemistry dedicated to Earth Sciences (paleoreconstitution, datation, pollution..)
- 
  
  Recent analytical development allowing very small isotopic variations of traditional stables (C, N) and non-traditional (Cu, Zn ,Fe) isotopes
- Interest on isotopic variations of **Cu** on biological samples (animal/human) to access pathological/paleopathological conditions since 2000
- Podoconiosis is a non-parasitic tropical disease caused by irritant particles
  => Evaluation of $\delta^{65}Cu$ as an Early Detection Biomarker of Podoconiosis
  => Identifying irritant particles and their location in the feet

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THANK YOU FOR YOUR ATTENTION

We welcome your questions and comments

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