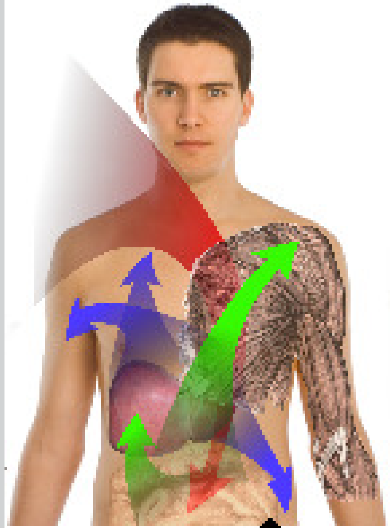
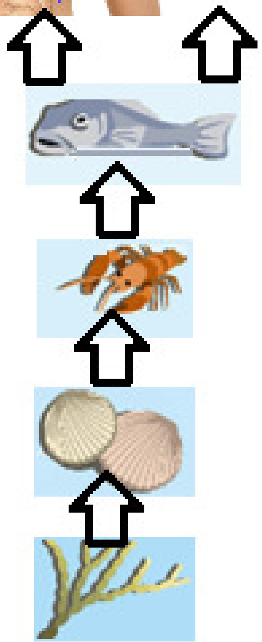
BfR
Risiken erkennen – Gesundheit schützen



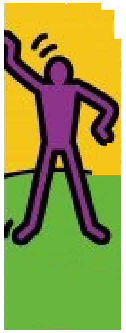


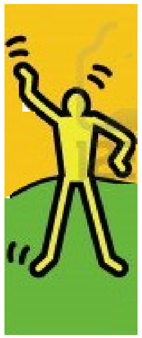
Modelling the bioavailability of trace elements

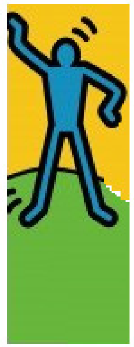
Dr. Jorge Numata

Federal Institute for Risk Assessment (BfR)
Unit 33: Epidemiology, Biostatistics and Mathematical Modelling

Why use modelling?

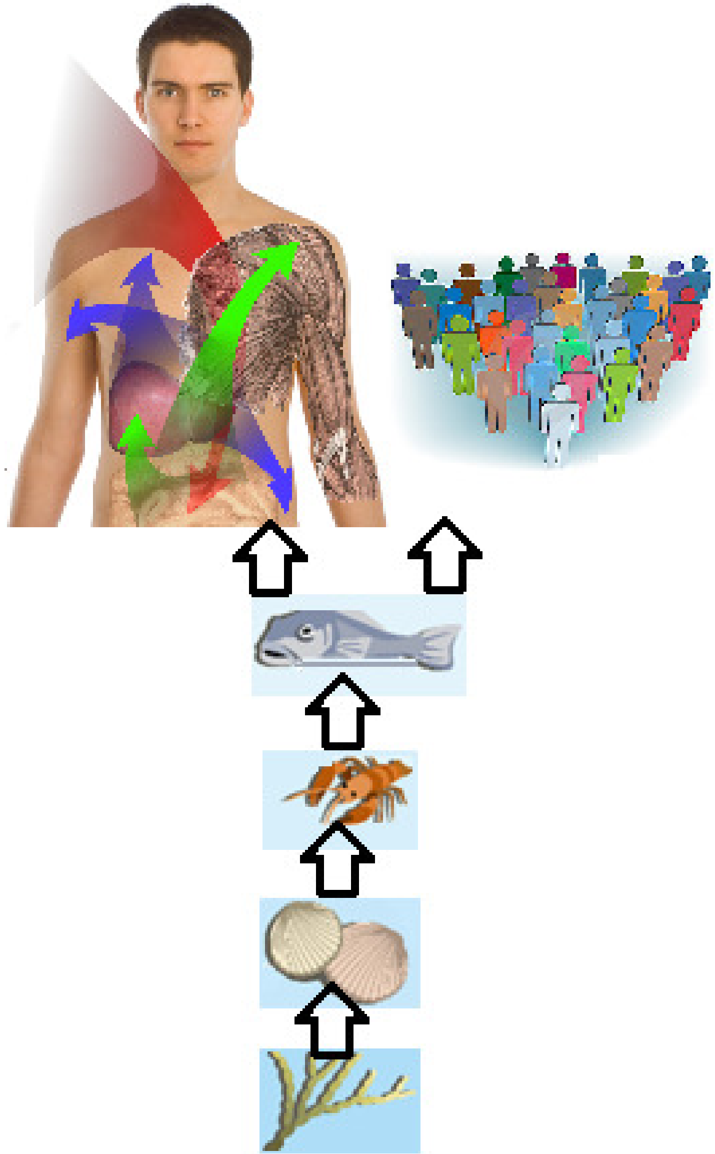





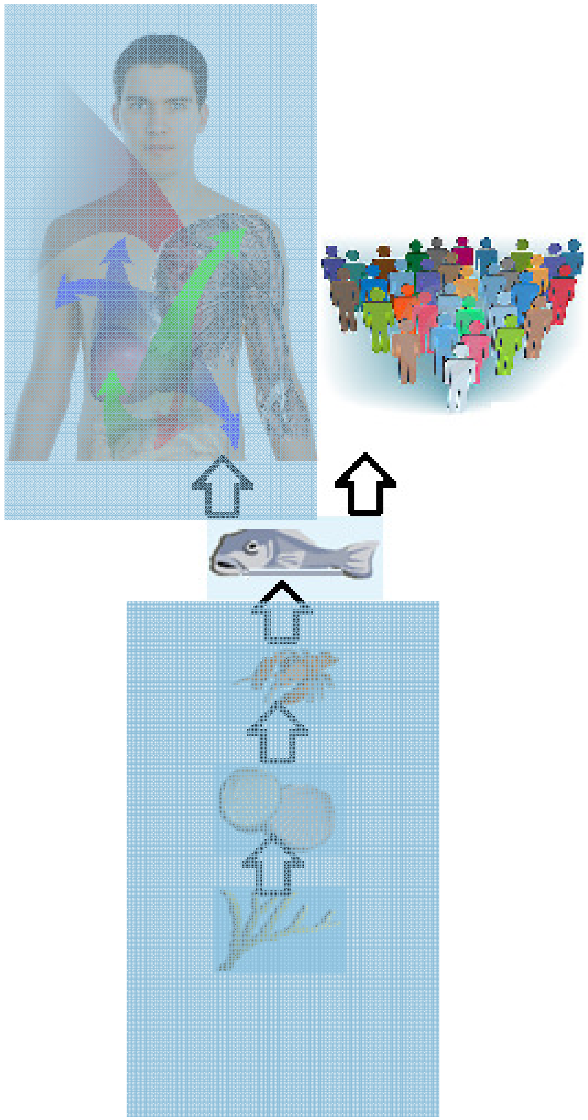


Why use modelling?

Bioavailability models for trace elements



Simulation of population absorption



Data:
Trace element chemical species
Popular co-ingested foods
Nutritional status of population

Prediction:
Estimate of actual amounts absorbed
Aid in quantifying fortification strategies
Risk assessment for under/overdosing

Simulation of Zn and Fe biofortification in Mexico

Data: Amounts of maize, wheat, beans and rice eaten, coingested foods, trace mineral contents, body reserves.

Model:

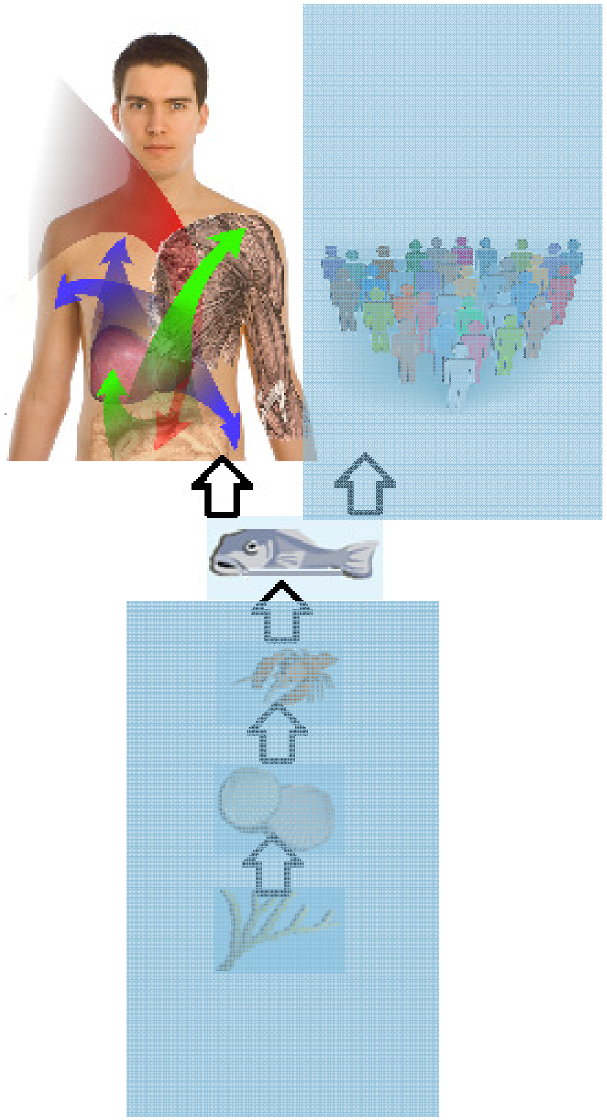
Zn: International Zinc Nutrition Consultative Group equation; total daily zinc intake and the phytate: zinc molar ratio

Fe: Bhargava Iron algorithm: promoters (vitamin C and meat), inhibitors (phytate)

Prediction: Biofortify maize with Zn to reduce ca. 50% of inadequacies. Fe inadequacy cannot be solved by biofortification.

Study: E Denova-Gutiérrez, A García-Guerra, M Flores-Aldana, S Rodríguez-Ramírez, C Hotz, Simulation model of the impact of biofortification on the absorption of adequate amounts of zinc and iron among Mexican women and preschool children, Food Nutr Bull, 29(3), p203-212, 2008

Models of **ADME** kinetics (compartment models)



Data:

Trace element chemical variants

Concentration in food and blood

Prediction:

Quantification of

Absorption, **D**istribution,

Metabolism (speciation) and **E**xcretion

Physiological pathways by inference

ADME kinetics: Bioavailability of calcium ascorbate > calcium acetate

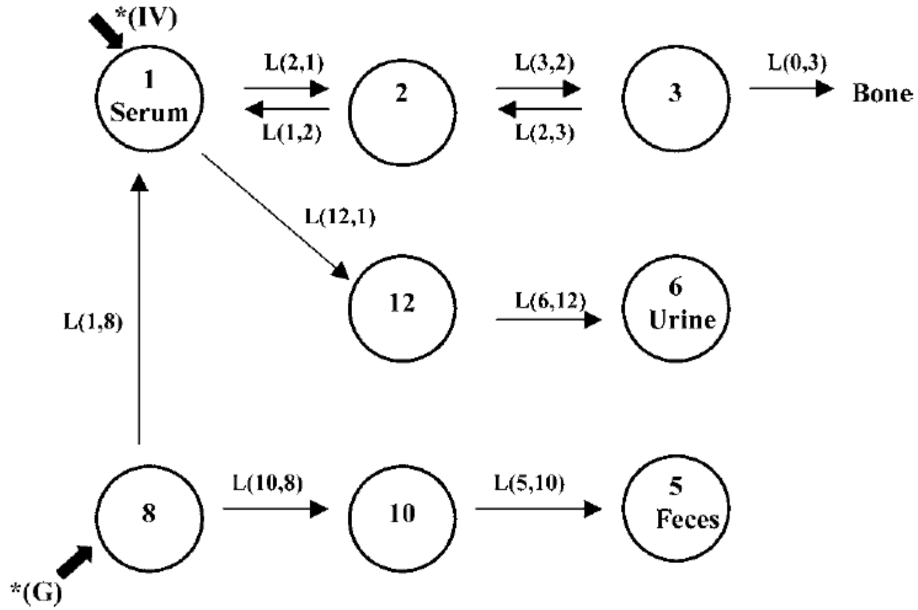
Experiment in rats with labeled ^{45}Ca ascorbate and acetate

Data: Intake, urine, femur, fecal concentrations

Prediction:

Kinetic parameters

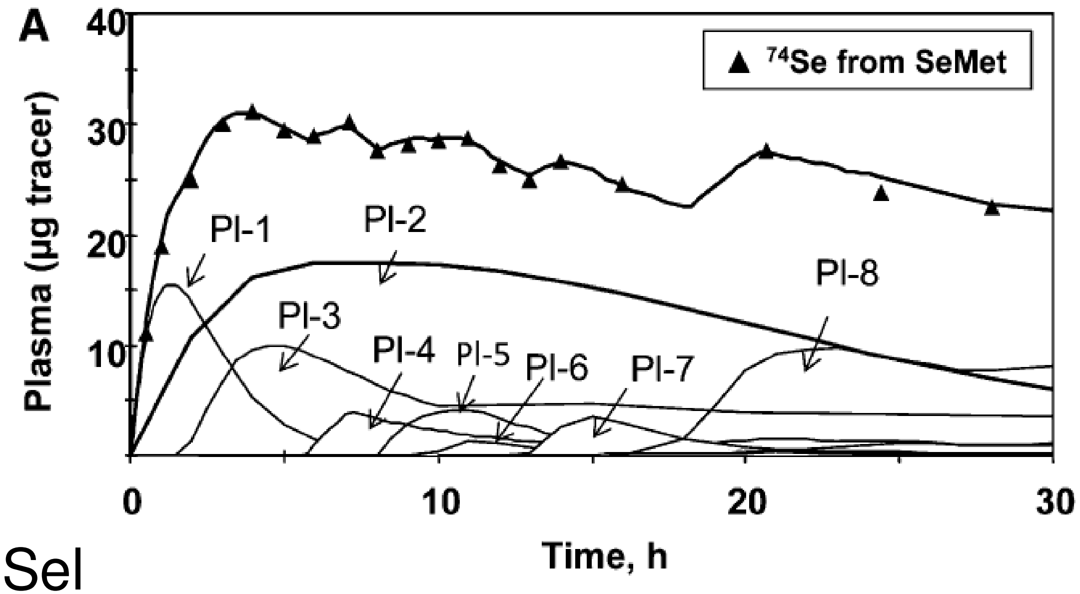
Ascorbate has faster uptake kinetics in 1 of 2 pathways



Study: J Cai, Q Zhang, ME Wastney, CM Weaver, Calcium Bioavailability and Kinetics of Calcium Ascorbate and Calcium Acetate in Rats, Exper Biol Med, 229, p40-45, 2004

Inorganic Selenite (^{76}Sel) vs Selenomethionine (^{74}SelMet) bioavailability human model

Data: 31 humans, 4 months
feces, urine, red blood cells
and plasma conc.
Separate isotope tracers

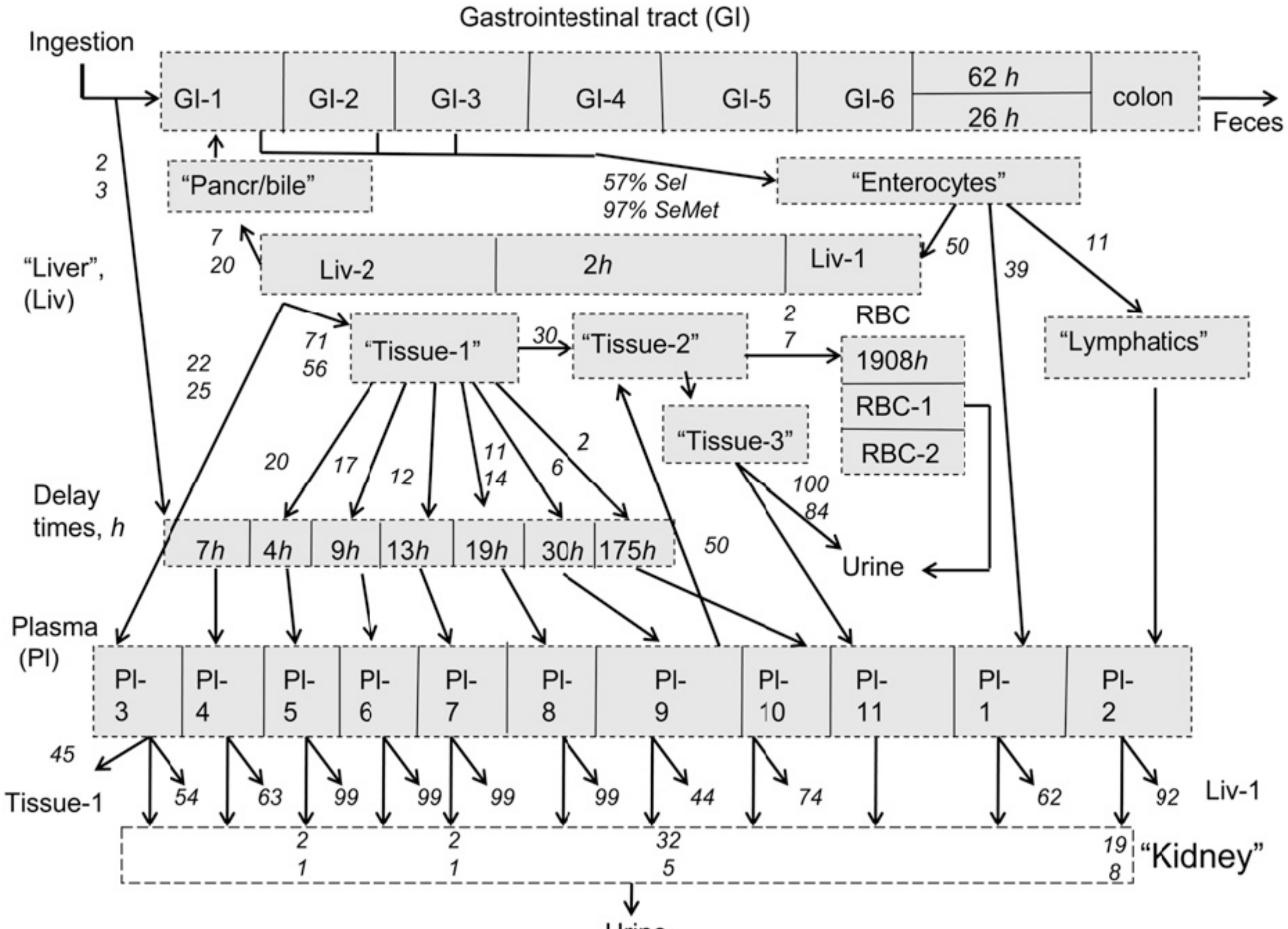


Prediction:
SelMet 70% higher absorption than Sel
Experimental multiple peaks → several plasma pools
Sel turnover 213 d, SelMet turnover 430 d
50% of absorbed Se uptaken by liver for Sel & SelMet

Study: ME Wastney ME, GF Combs Jr, WK Canfield, PR Taylor, KY Patterson, AD Hill, JE Moler, BH Patterson, A human model of selenium that integrates metabolism from selenite and selenomethionine, J Nutr, 141(4) p708-17, 2011

Inorganic Selenite (^{76}Sel) vs Selenomethionine (^{74}SelMet) bioavailability human model

Model:



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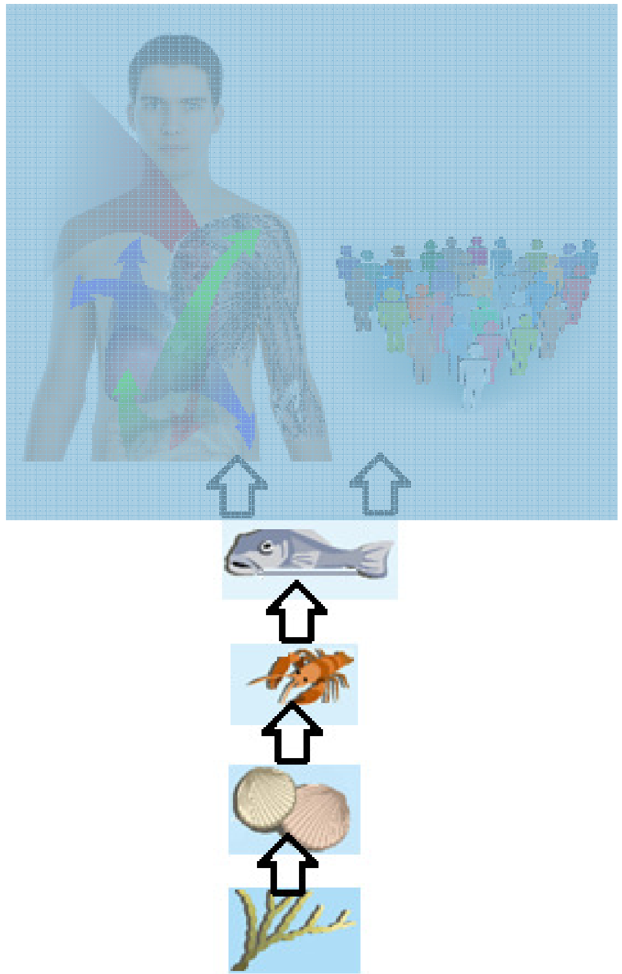
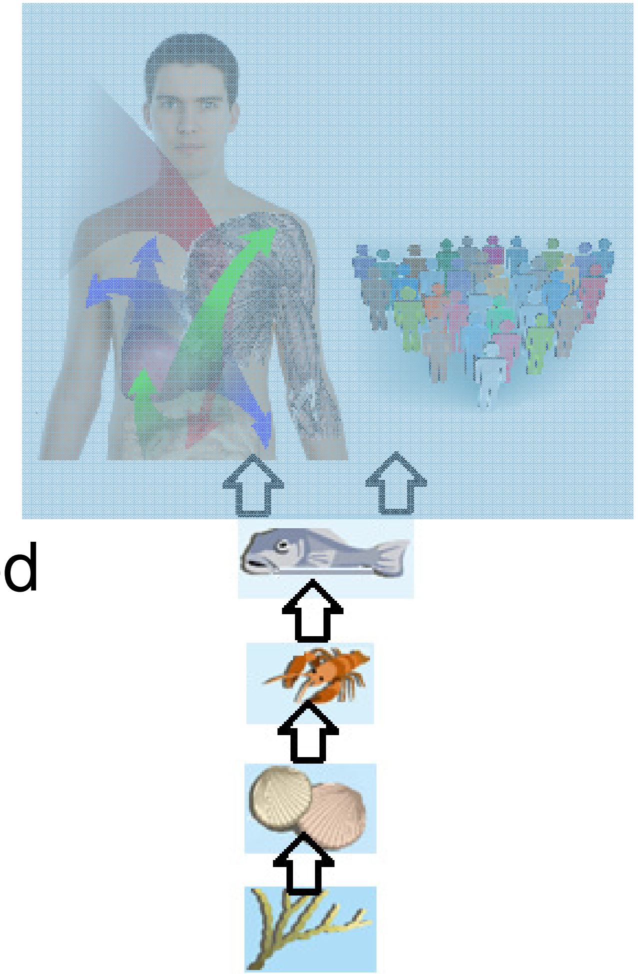
Kinetics of trace elements: trophic transfer

Data: Kinetic parameters for individual organisms´ ADME.

Model prediction: Estimation of the capacity of each trace element to bioaccumulate.



Kinetics of trace elements: trophic transfer



Risk assessment for biomagnification.

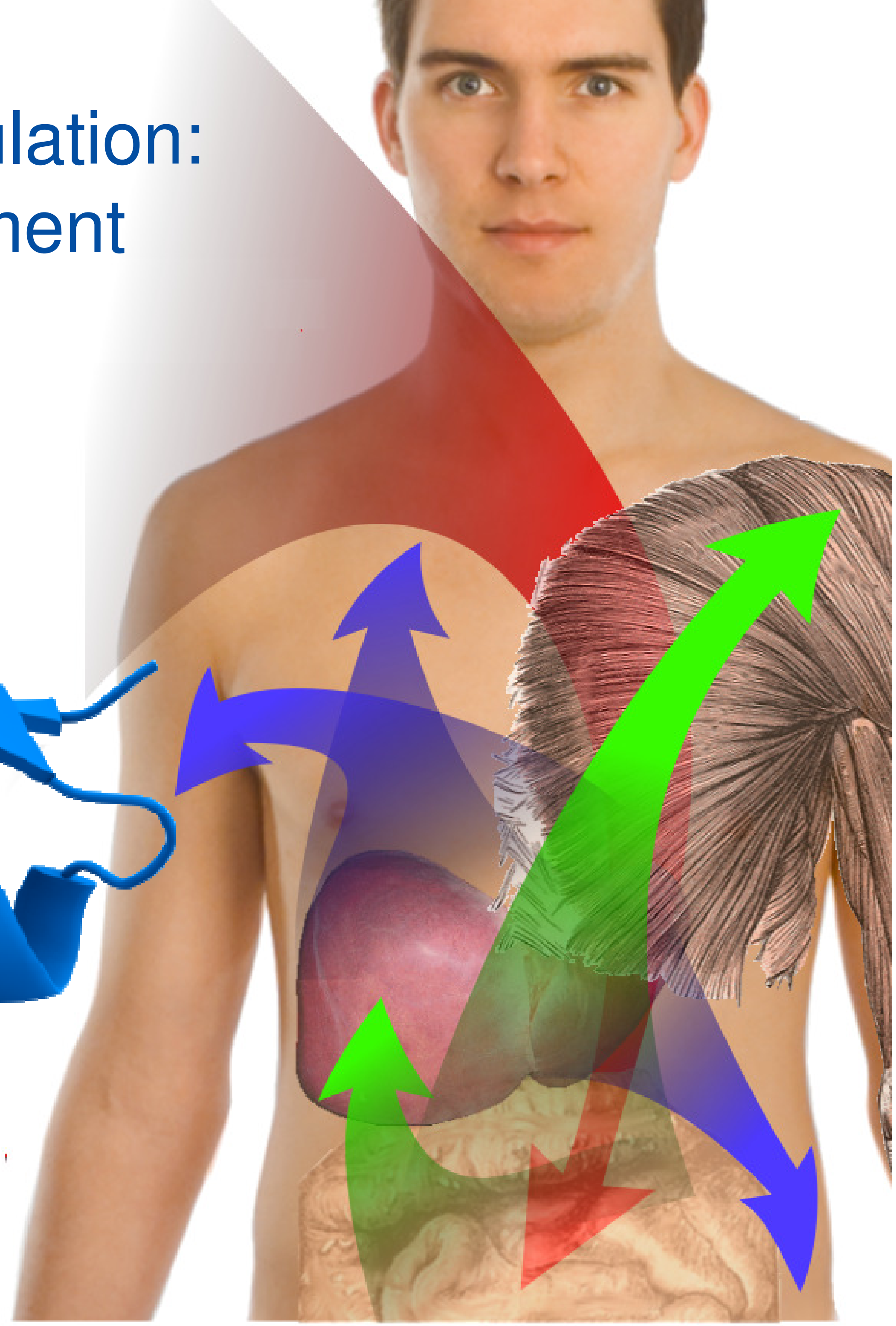
Non-elemental Se biomagnification is predicted and observed for most organisms.

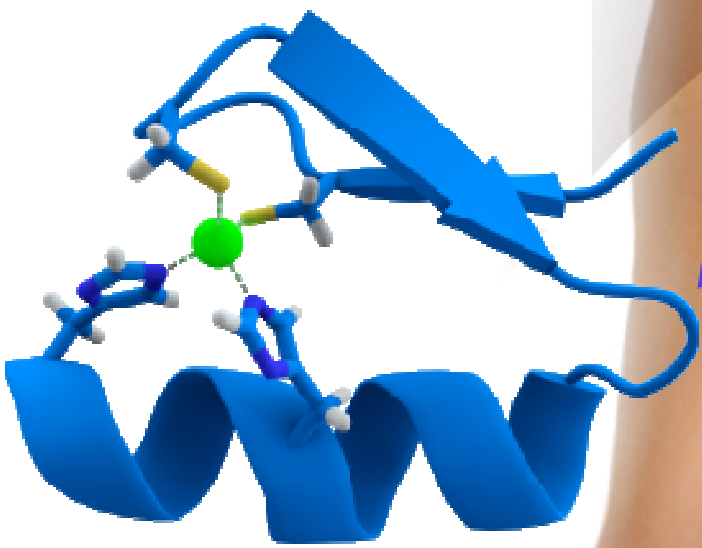
Cd biomagnification is only predicted for filter feeders.

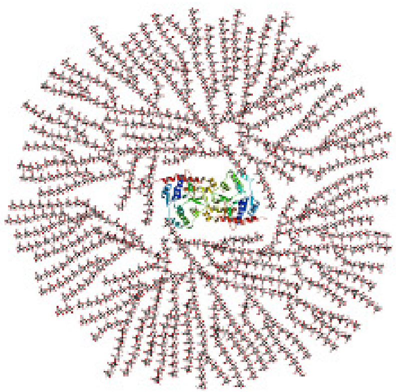
Cr is never expected to biomagnify.

Study: JR Reinfelder, NS Fisher, SN Luoma, JW Nichols, WX Wang, Trace element trophic transfer in aquatic organisms: A critique of the kinetic model approach, Sci Total Env, 219, p117-35, 1998

Molecular dynamics simulation: Understanding trace element binding to biomolecules







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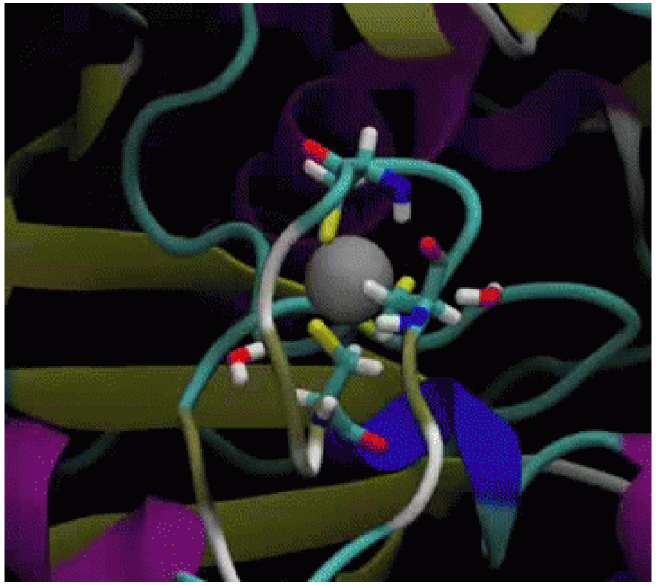
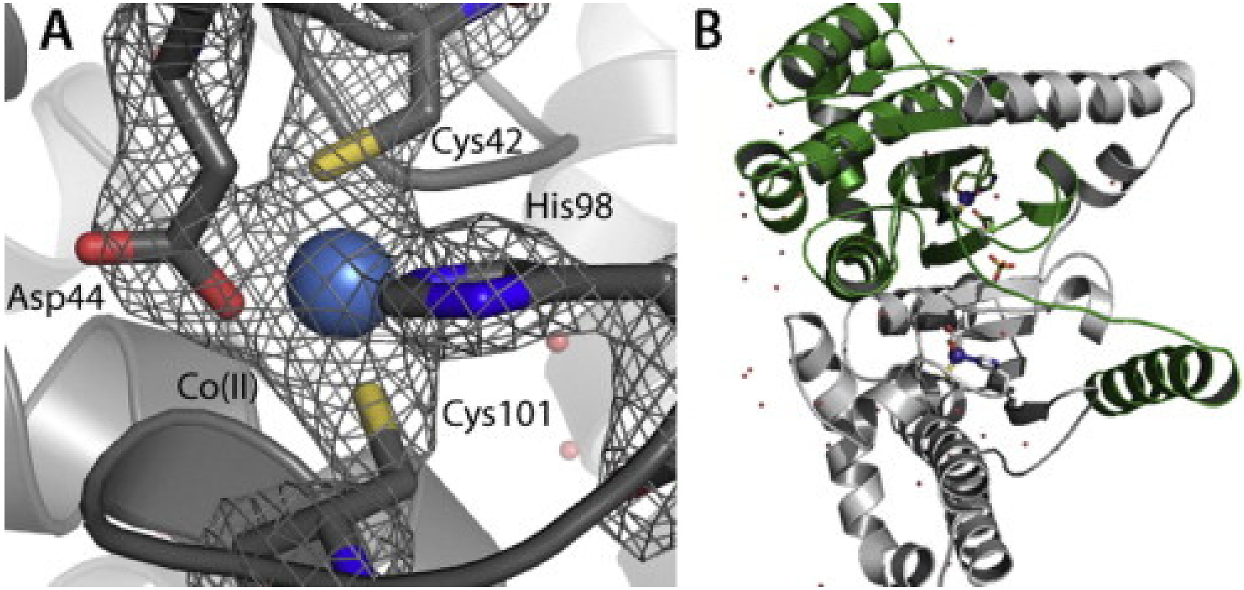
CP Molecular dynamics simulation: probing speciation of Co and Zn bound to biomolecules





Study: C Bresson, C Lamouroux, C Sandre, C Moulin et al., An interdisciplinary approach to investigate the impact of cobalt in a human keratinocyte cell line, Biochimie, 88(11), p1619-29, 2006

Video: Cysteine coordinating Zinc, http://youtu.be/o5-a39tbT9w

Image: KM Hoffmann, D Samardzic, K van den Heever, RS Rowlett, Arch Biochem Biophys, 511, p80-87, 2011

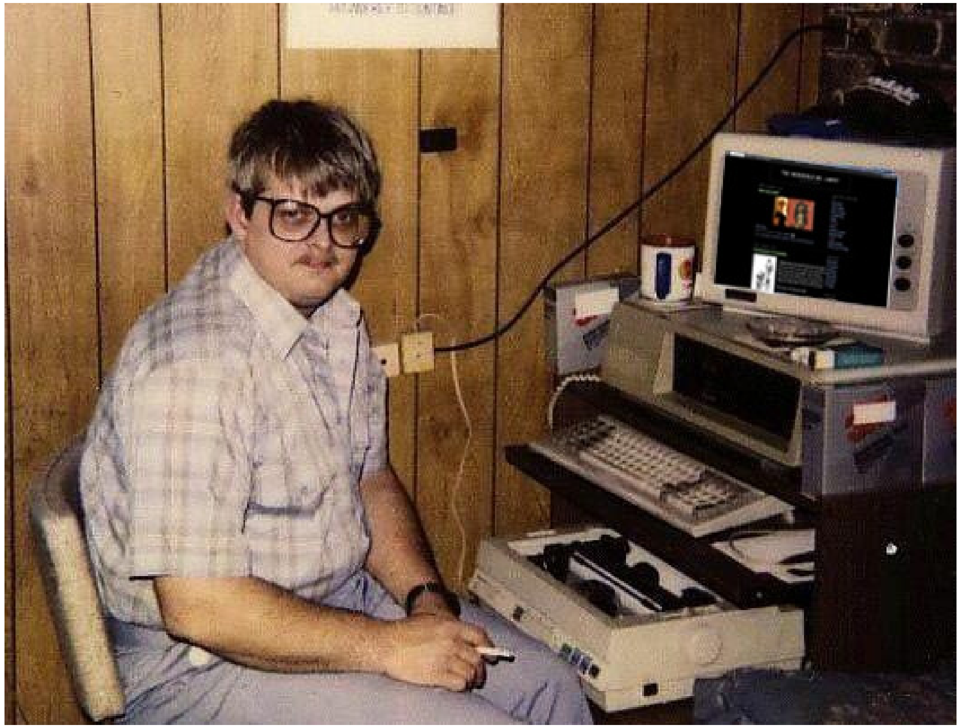
Modeling Software

WinSAAM: Kinetic compartmental modeling software

WinNonLin: Pharmacokinetics software

Charmm and **NAMD**: Molecular dynamics simulation

Matlab / **Octave**: General purpose numerical math, many scripts available



Models of Bioavailability

A model animates a mechanism with mathematics

Bioavailability is based on a mechanism

Bioavailability models deliver more than
a “single number”

Dream: couple models of
trophic transfer+animal feed+human metabolism

Risiken erkennen – Gesundheit schützen

FEDERAL INSTITUTE FOR RISK ASSESSMENT

Thank you for your attention

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