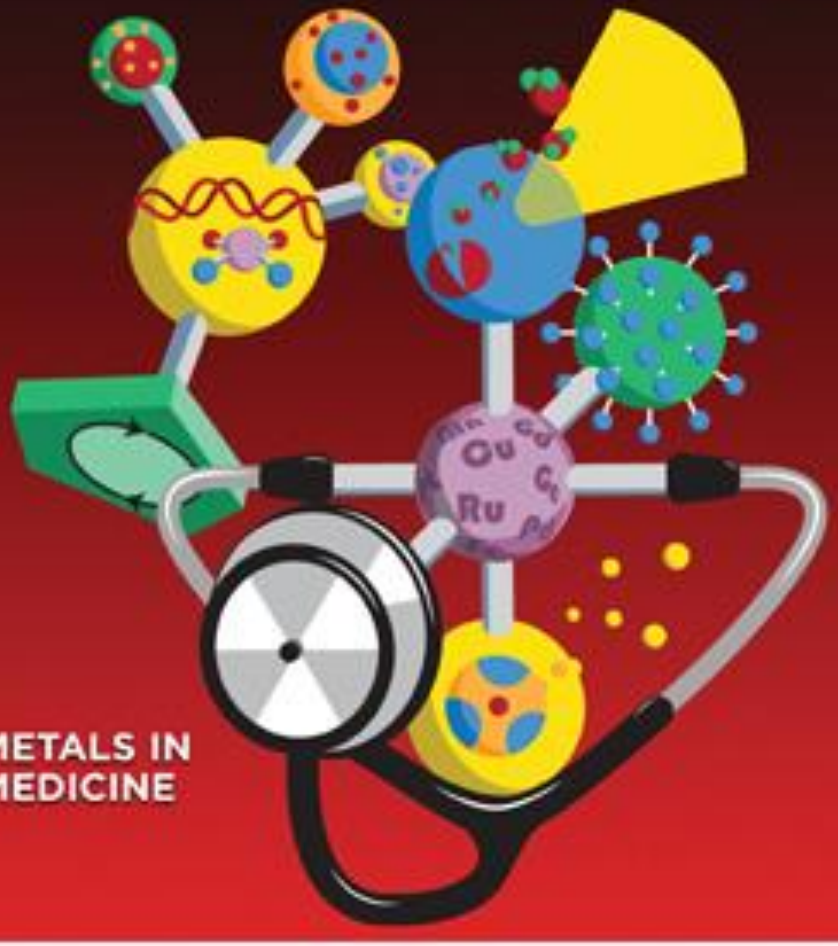
JANUARY 23, 2019
VOLUME 119
NUMBER 2

pubs.acs.org/CR

CHEMICAL REVIEWS

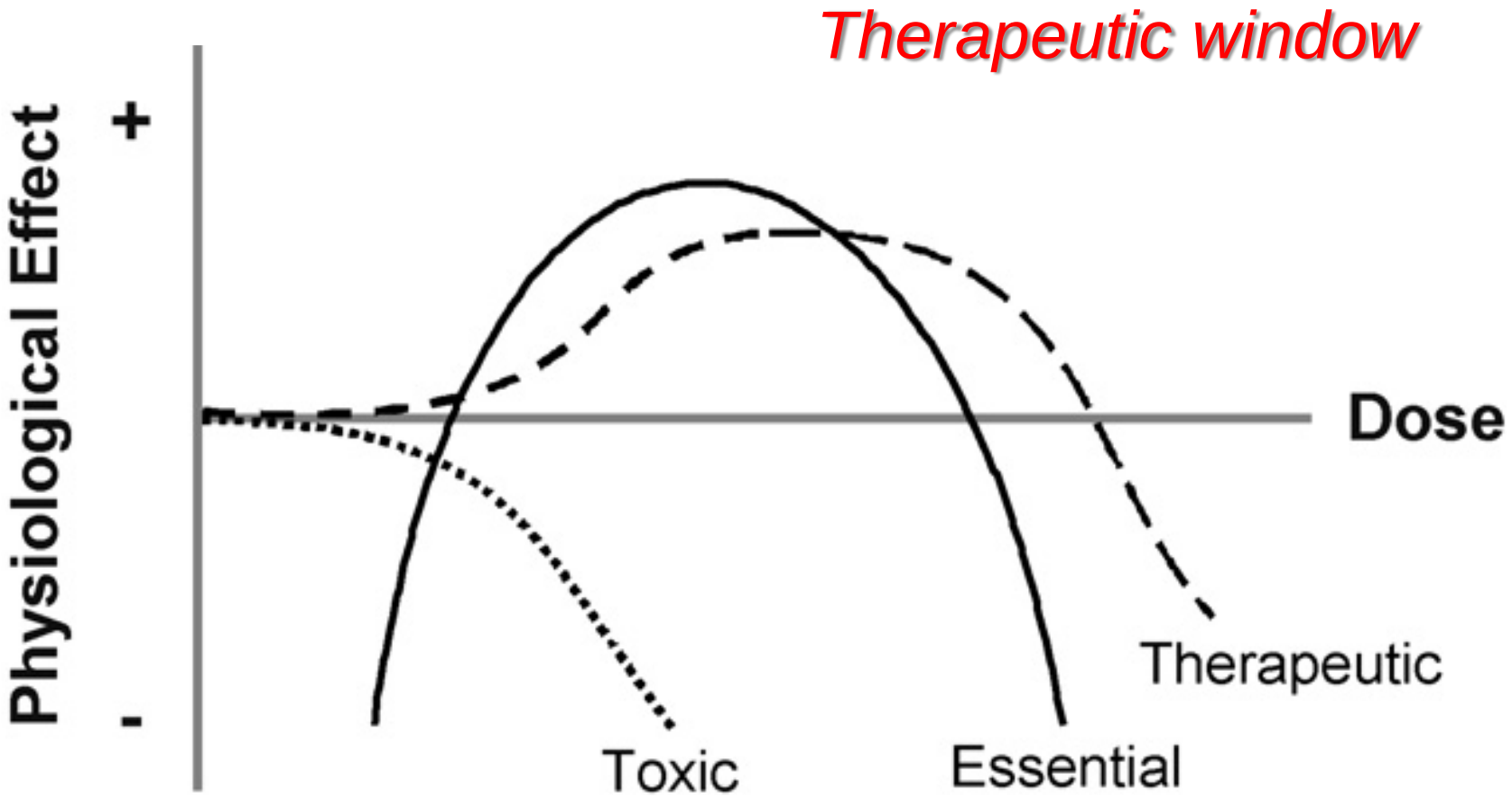


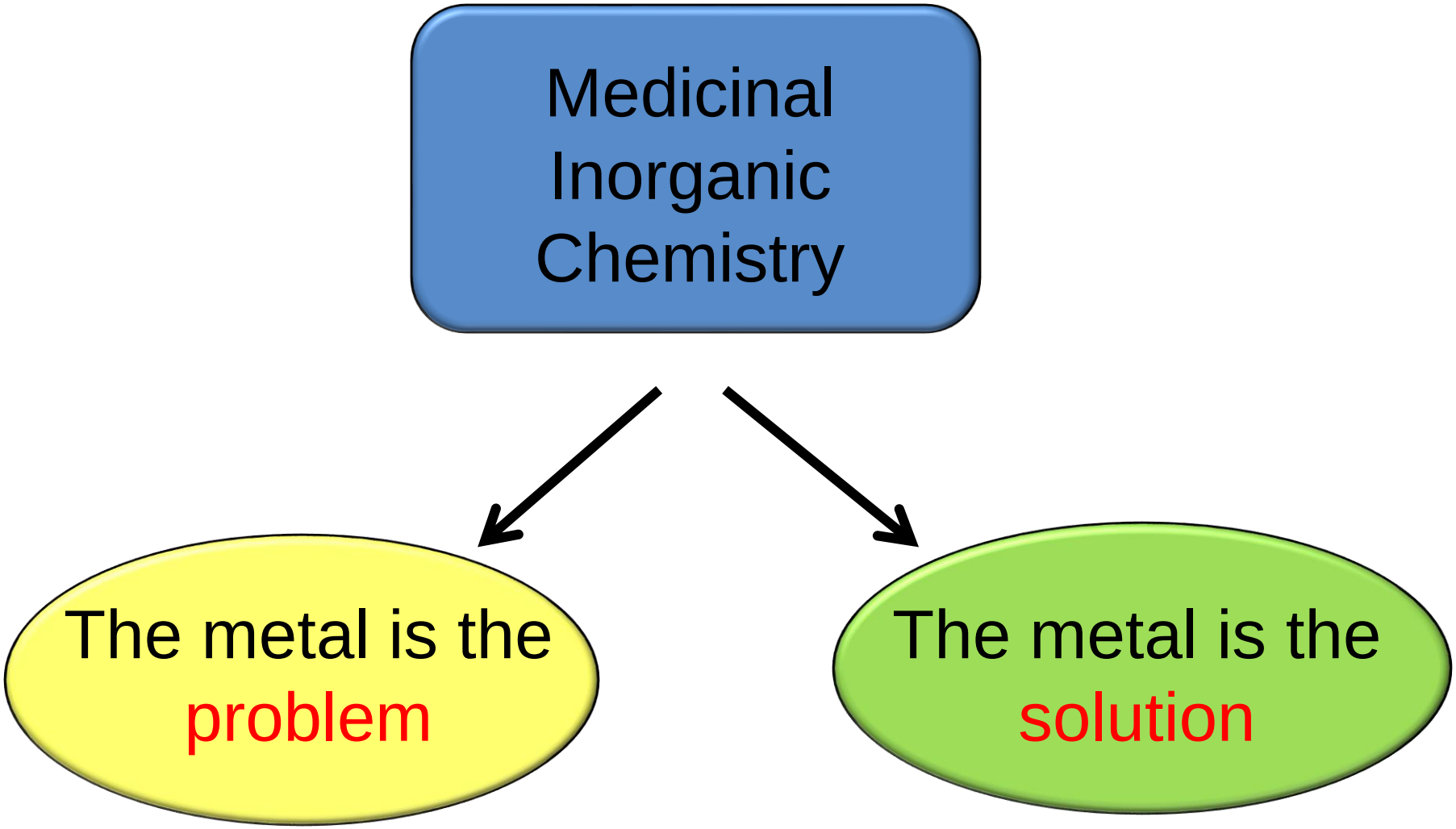
METALS IN MEDICINE

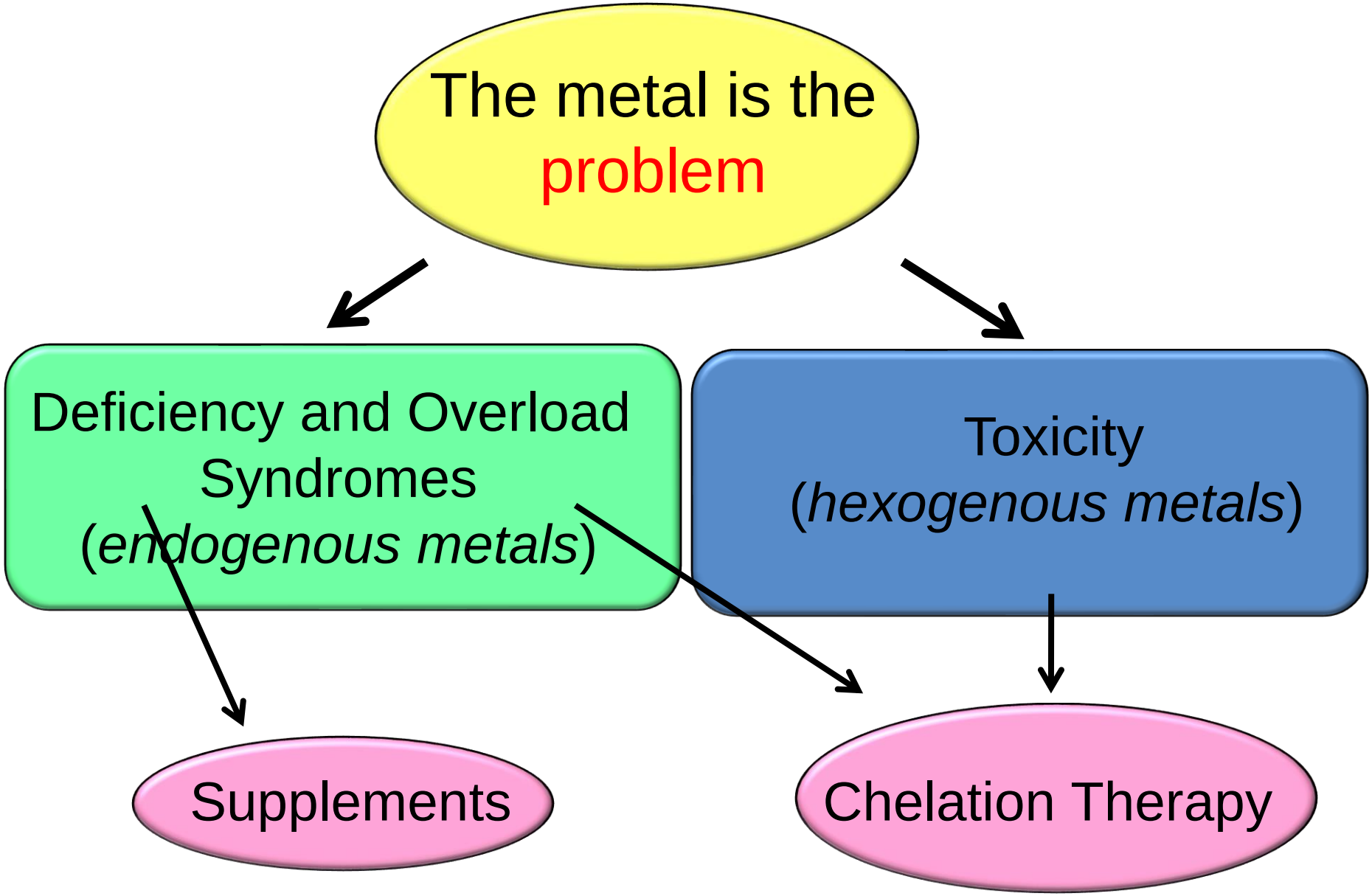
ACS Publications
Most Trusted. Most Cited. Most Read.

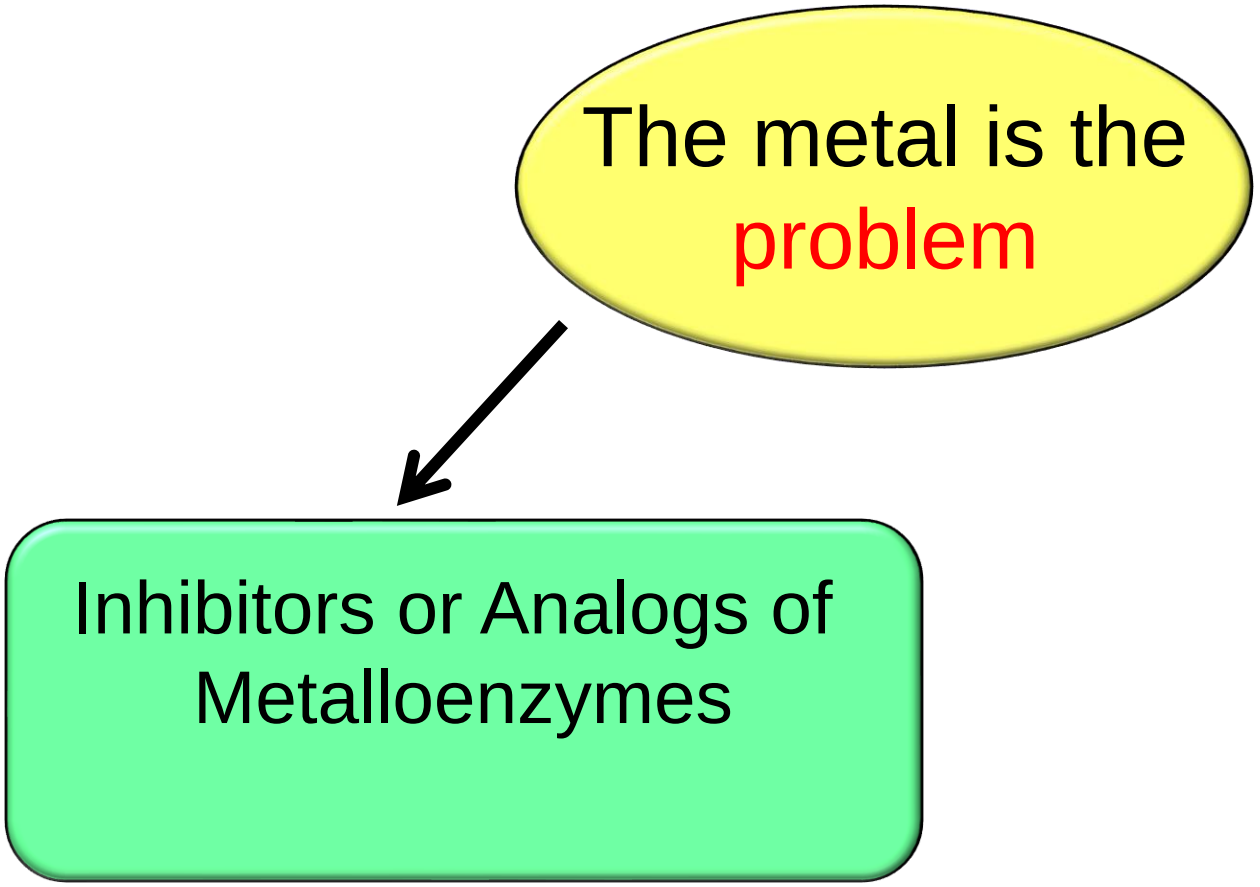
www.acs.org

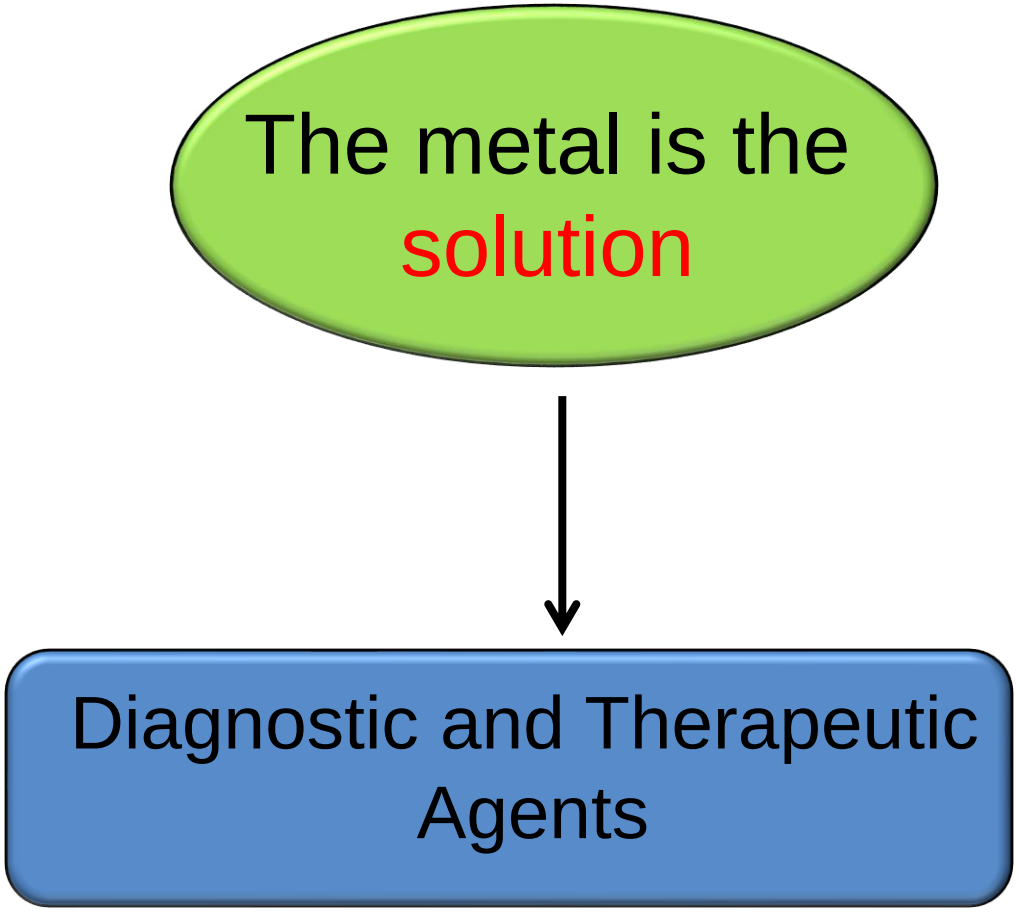
Diagramma di Bertrand




Medicinal Inorganic Chemistry
The metal is the problem
The metal is the solution


The metal is the problem
Deficiency and Overload Syndromes (*endogenous metals*)
Toxicity (*hexogenous metals*)
Supplements
Chelation Therapy


The metal is the problem
Inhibitors or Analogs of Metalloenzymes


The metal is the
solution
Diagnostic and Therapeutic
Agents

Tossicità di metalli esogeni e altri elementi

Pb

Cd

Tl

Hg

Be

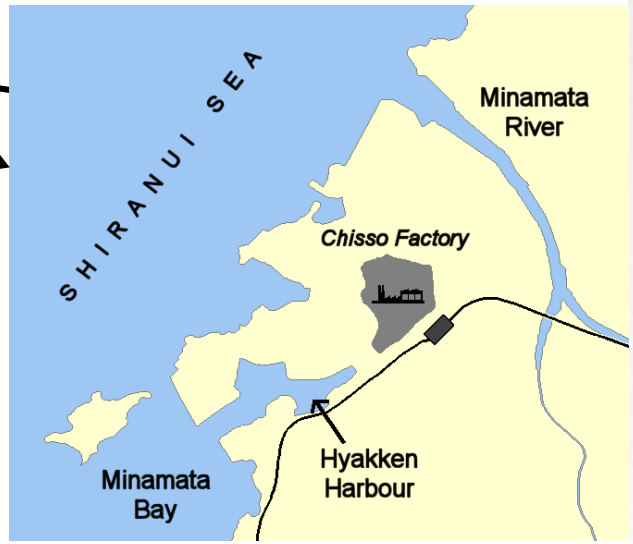
Cr

Itai Itai Disease

Martedì 17 Settembre 2019 (0) Facebook Twitt

Processo d'appello per il killer del tallio: la procura chiede l'ergastolo

Minamata Disease

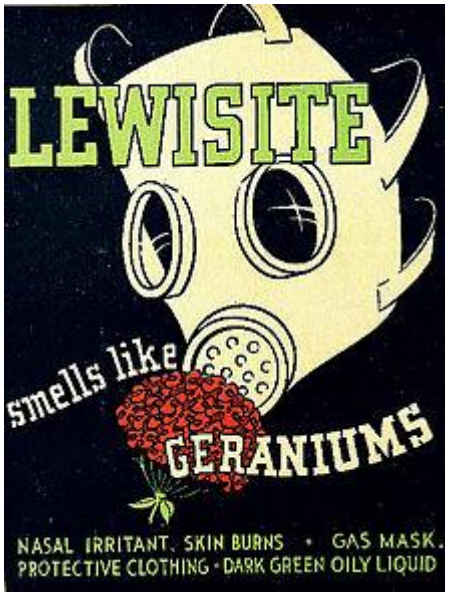


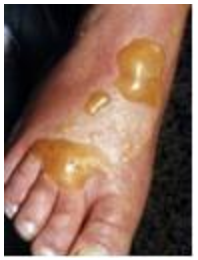
As

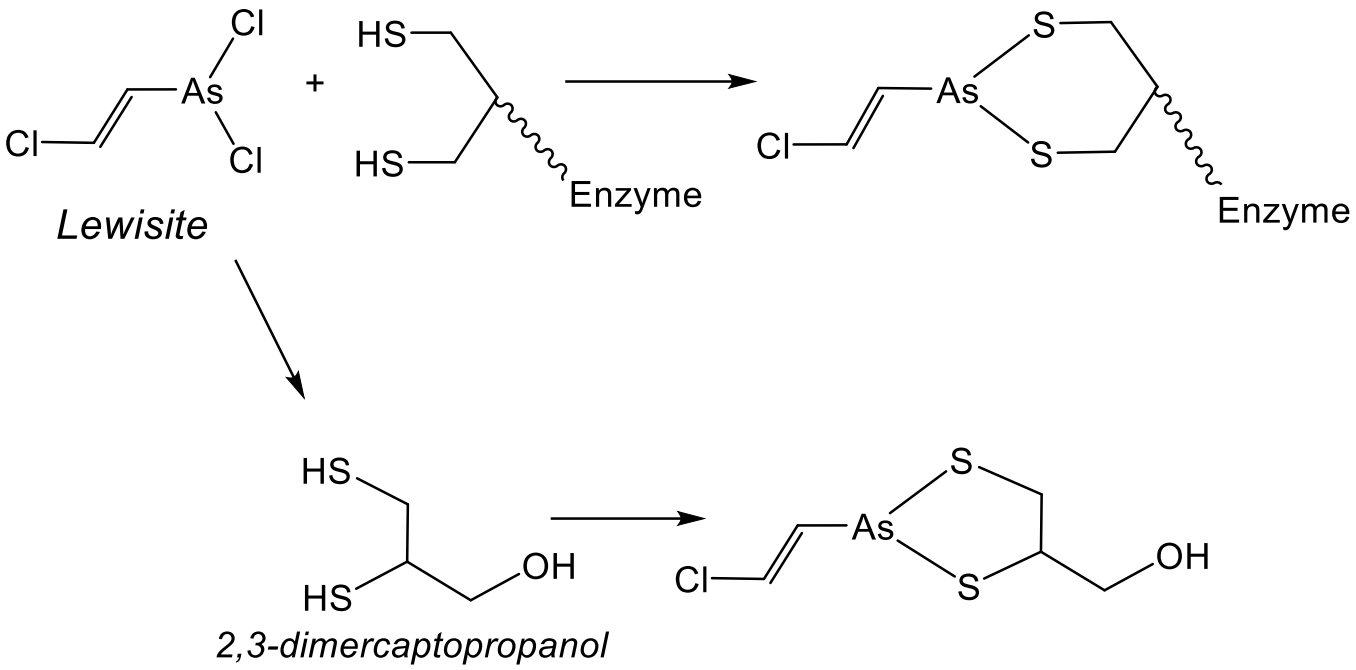
F

Se

Chelation Therapy





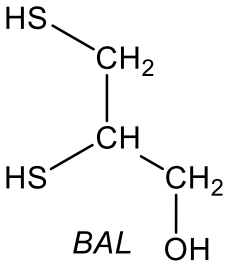


BAL = *British Anti-Lewisite*

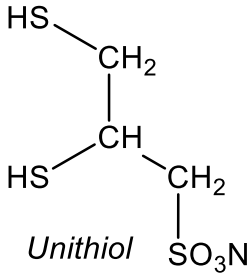
Chelation Therapy

Agent:

- Effective (i.e. match the binding preferences of the ion)
- Selective
- Non toxic
- Resistant to metabolism
- Unexpensive

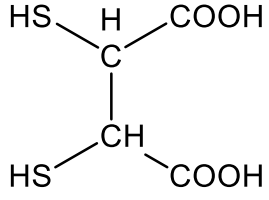


LD_{50} = 105 mg/kg



dimercaptoproane sulfonate

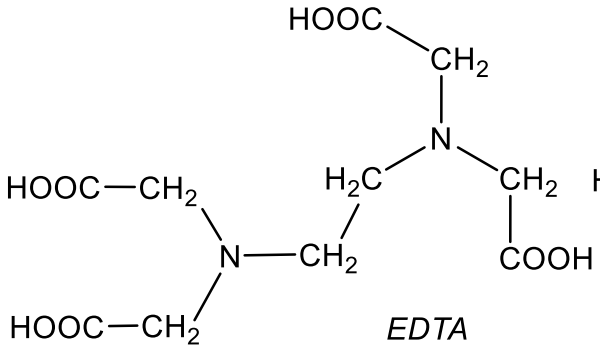
LD_{50} = 2000 mg/kg



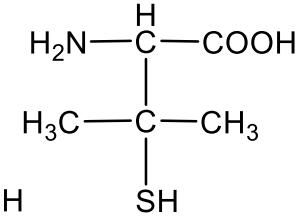
dimercaptosuccinic acid

Adducts:

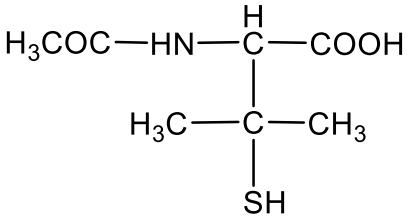
- Stable
- Non toxic
- Highly soluble in water (rapid clearance)
- Resistant to metabolism



EDTA



penicillamine



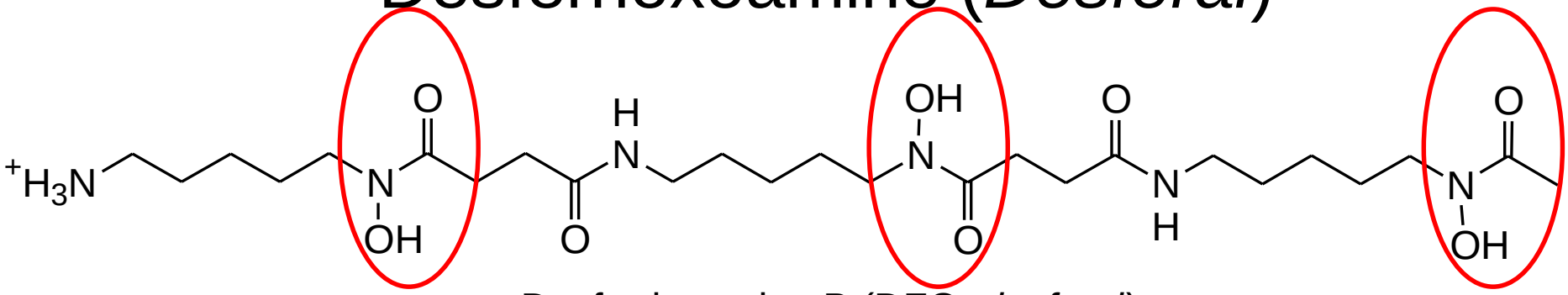
N-acetil-penicillamine

Iron chelation therapy

- Mammals are unable to regulate the export of Fe
- Patients affected by severe forms of anemia (e.g. thalassemia) need frequent blood transfusions
- Transfusions lead to iron overload
- Iron overload, if untreated, leads to premature death
  Fenton chemistry: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$
- Chelation therapy is essential

1. Efficacia del chelante
2. Tossicità
3. Costo
4. Modo di somministrazione (*compliance*)

Desferrioxoamine (*Desferal*)



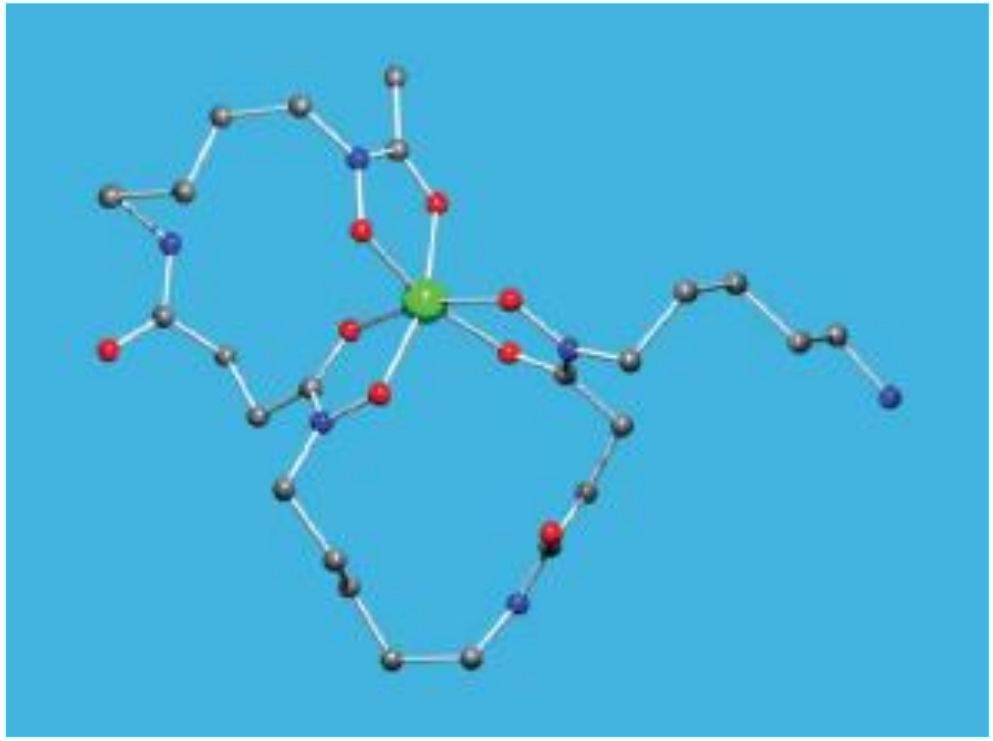
Desferrioxamine B (DFO, *desferal)*

Natural siderophore from *Streptomyces pilosus*

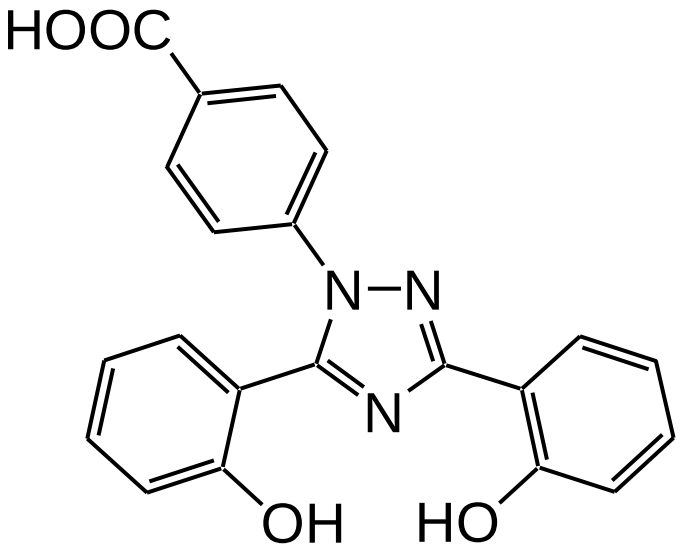
FDA approval: 1968

pFe = 26.6
pFe = -log[Fe^{n+}]

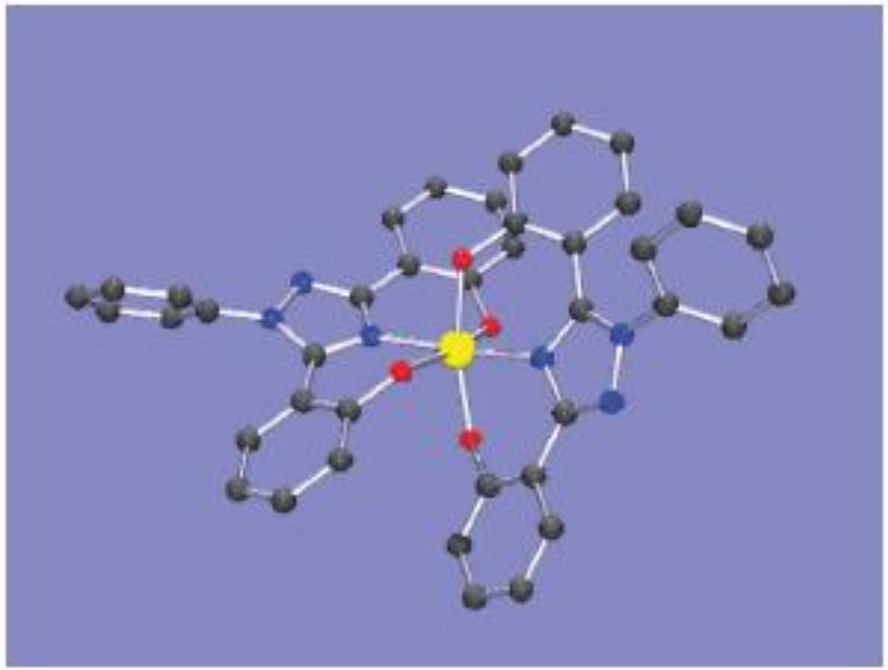
Drawback: very long infusion time: 8 – 12 h



Deferasirox: Orally active



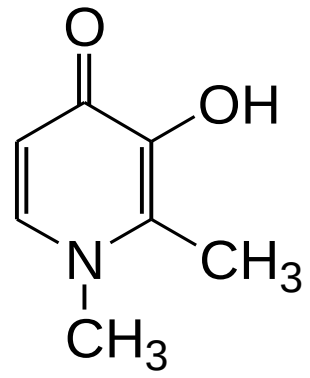
bis-hydroxyphenyl-triazole
deferasirox



pFe = 20

FDA approval: 2005

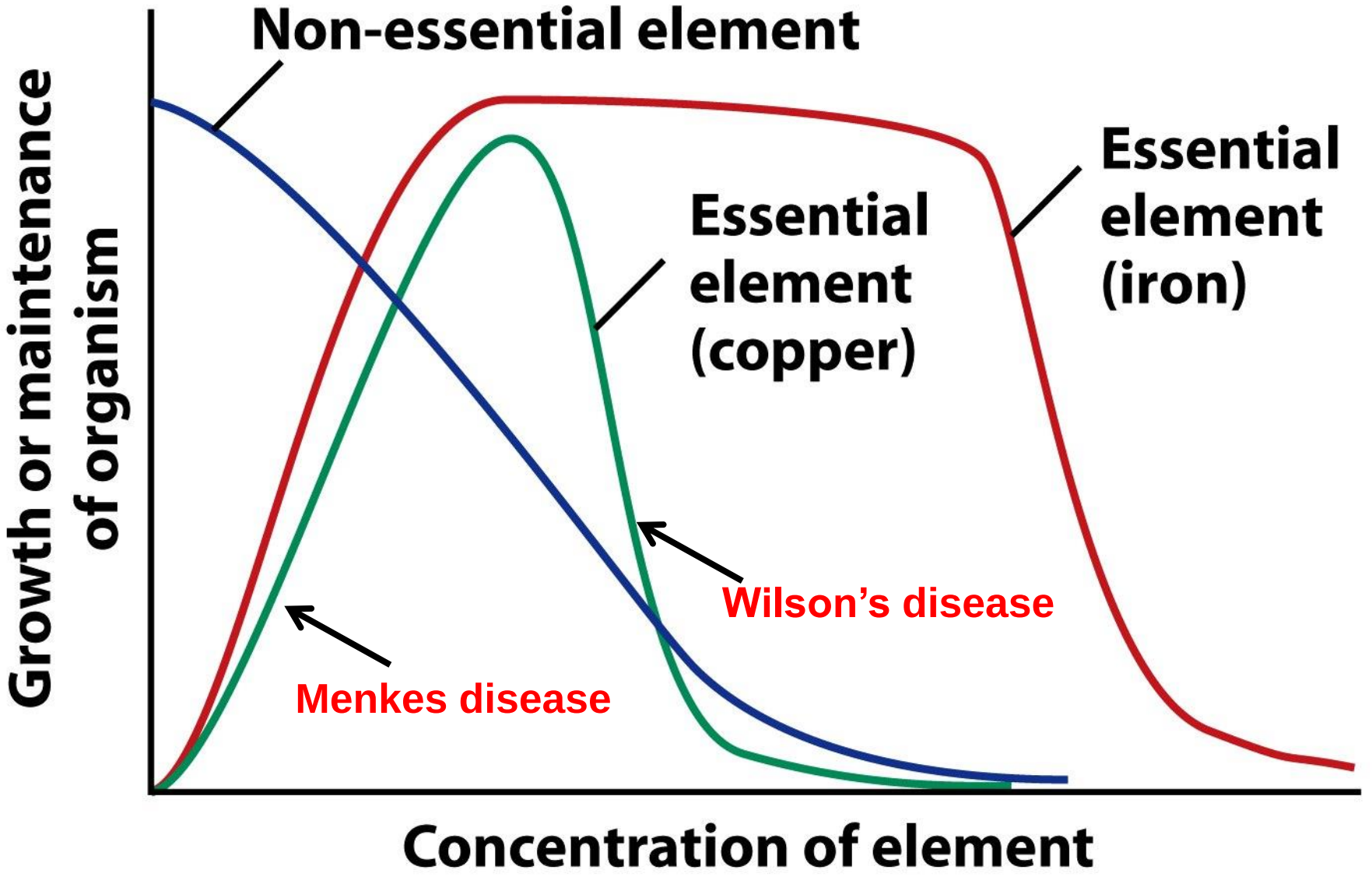
Deferiprone: Orally active



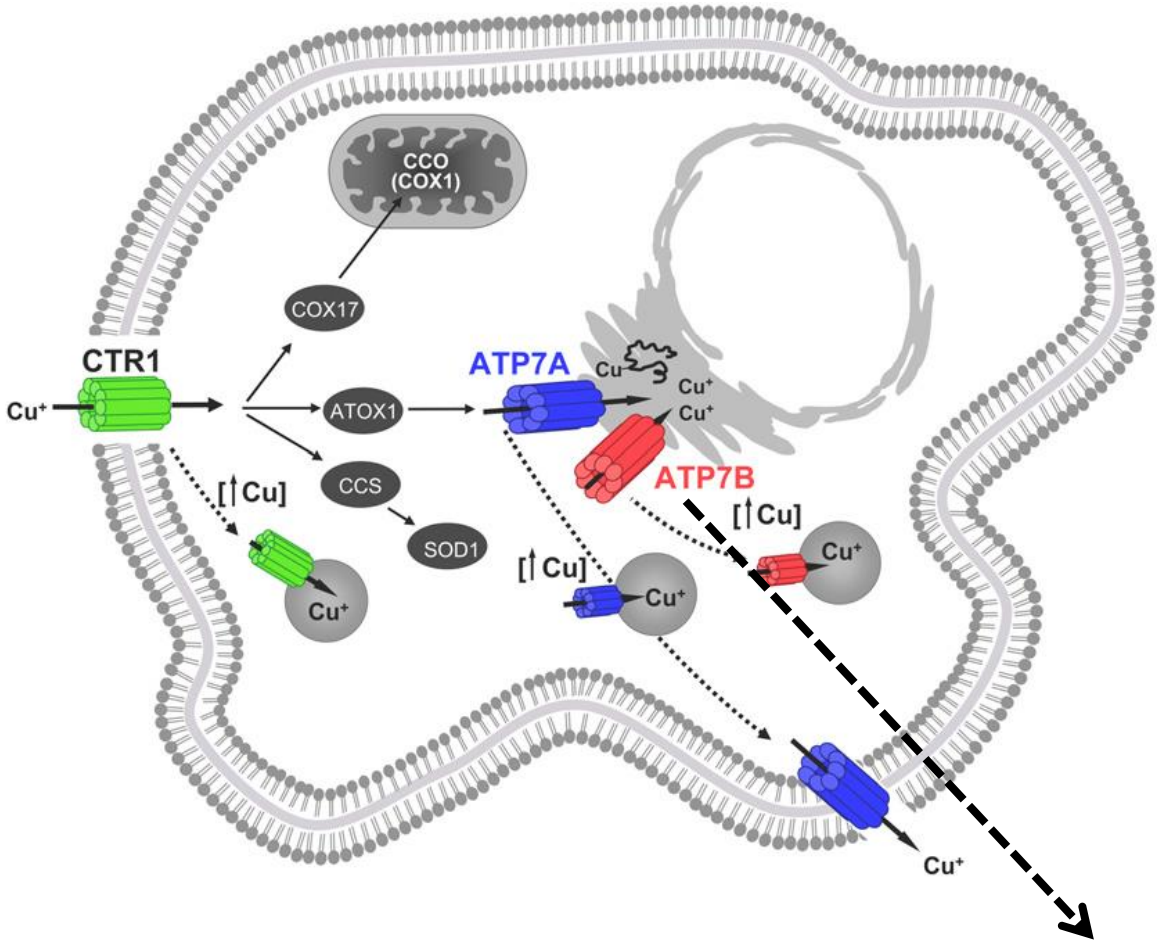
3,4-dihydroxypyridinone
deferiprone

pFe = 20

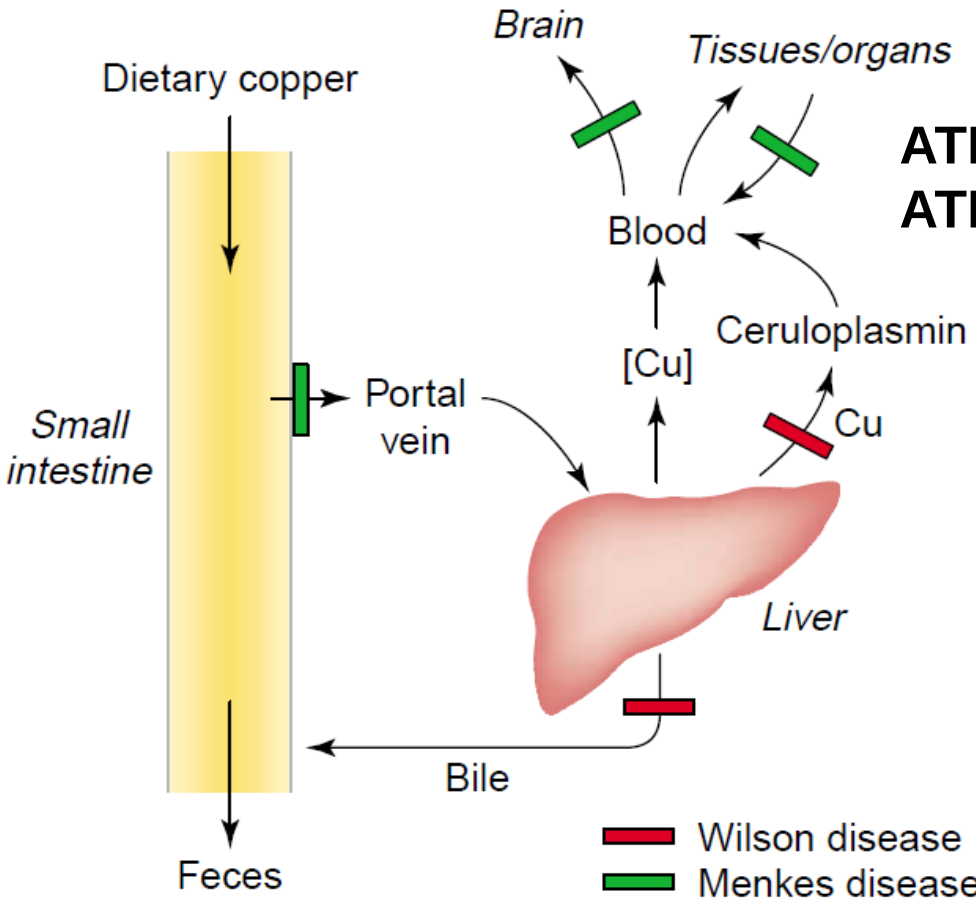
2011 FDA approval as <u>second-line</u> oral drug


Non-essential element
Essential element (iron)
Essential element (copper)
Wilson's disease
Menkes disease
Growth or maintenance of organism
Concentration of element

Copper homeostasis



ATP7A: ubiquitous
ATP7B: liver, kidneys, brain

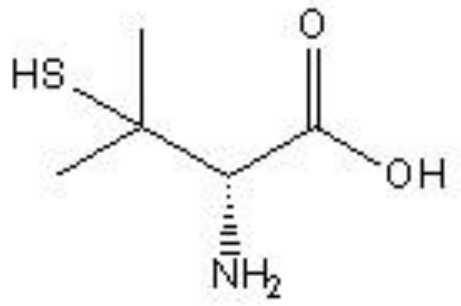


ATP7A: Menkes disease, Cu deficency
ATP7B: Wilson's disease, Cu overload

→ $Cu(II)(His)_2$

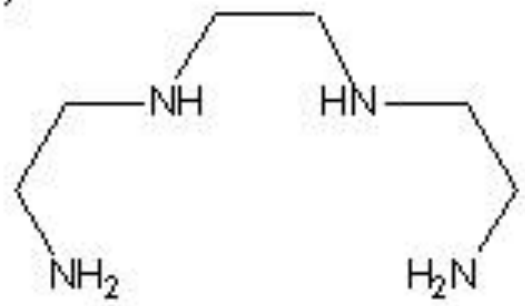
Chelanti per la Sindrome di Wilson (rimozione Cu)

a)



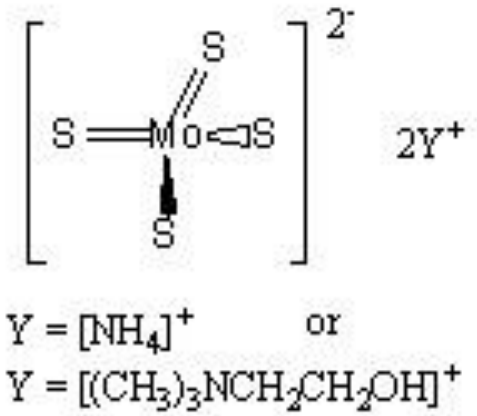
D-penicillamina

b)

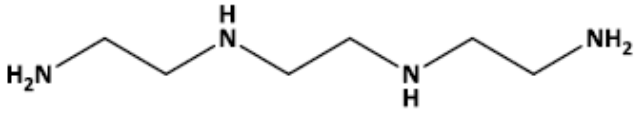


Trien *(*o *Trientina*)
(tris-etilenetetrammina)

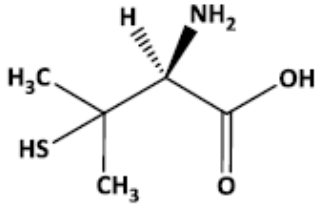
c)



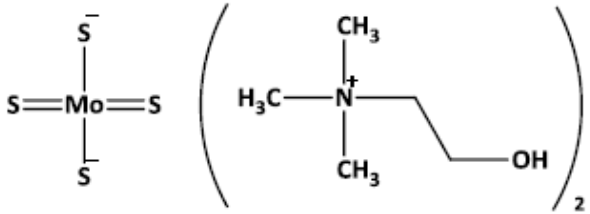
Tetratiomolibdato


H
N
H2N
NH2
N
H

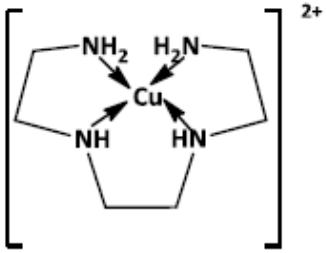
a

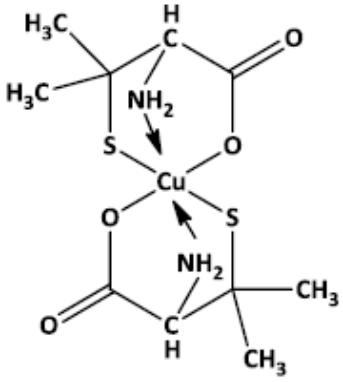

H
NH2
H3C
OH
HS
CH3
O

b


S
S
Mo
S
S
CH3
H3C
N
CH3
OH
2

c


NH2
H2N
Cu
NH
HN
2+


H3C
H
C
O
H3C
NH2
S
O
Cu
O
S
NH2
CH3
O
C
H
CH3

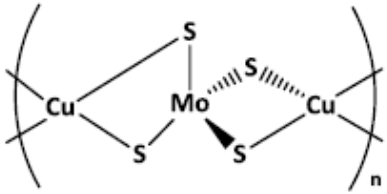

S
Cu
Mo
S
Cu
S
S
n

Table 2. Agents for the Treatment of Wilson Disease

agent	mechanism of action	daily adult dosage
D-penicillamine[a]	reduction and chelation of copper; urinary excretion of copper by mobilizing copper from organs	1−2 g orally in divided doses
triethylenetetramine (Trien)	copper chelator and urinary excretion	0.75−1.5 g orally in divided doses
zinc salts	inhibits intestinal absorption of copper by induction of intestinal cell metallothionein; may also induce hepatic metallothionein	150−200 mg orally in divided doses
british anti-Lewisite (BAL)	copper chelator	3 mL of 10% BAL in peanut oil im
tetrathiomolybdate[b]	blocking the intestinal absorption of copper and a copper chelator	Up to 2 mg/kg orally in divided doses

[a] Administered with supplementation of 25 mg of pyridoxine orally daily. [b] Experimental.