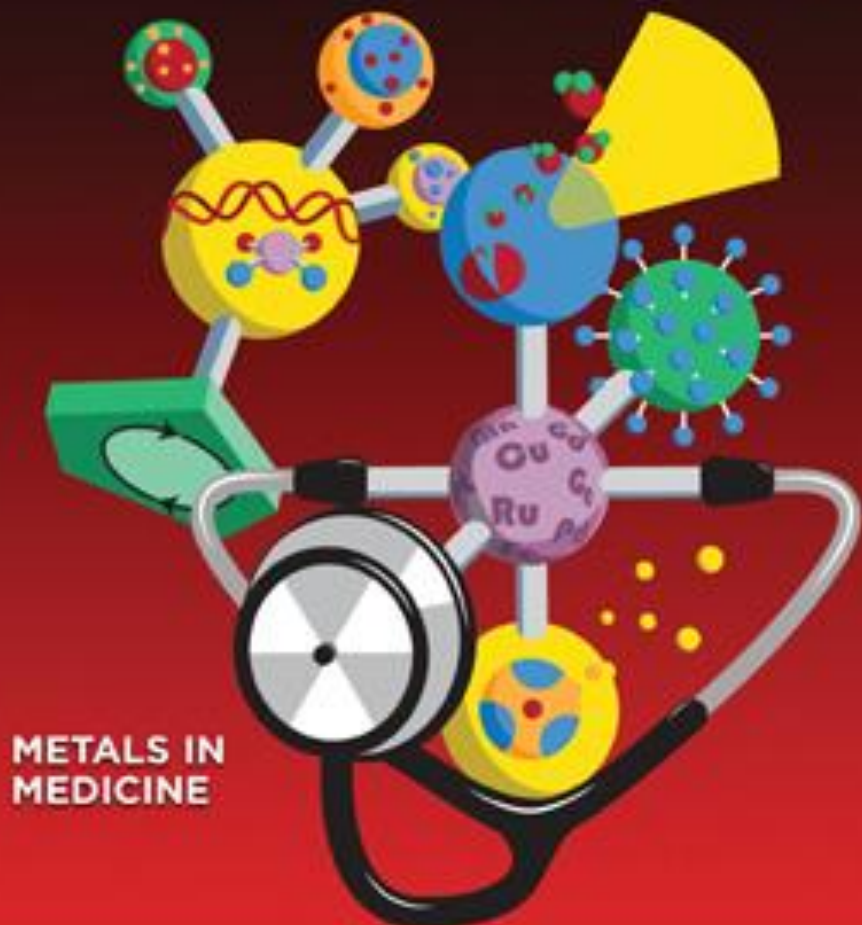


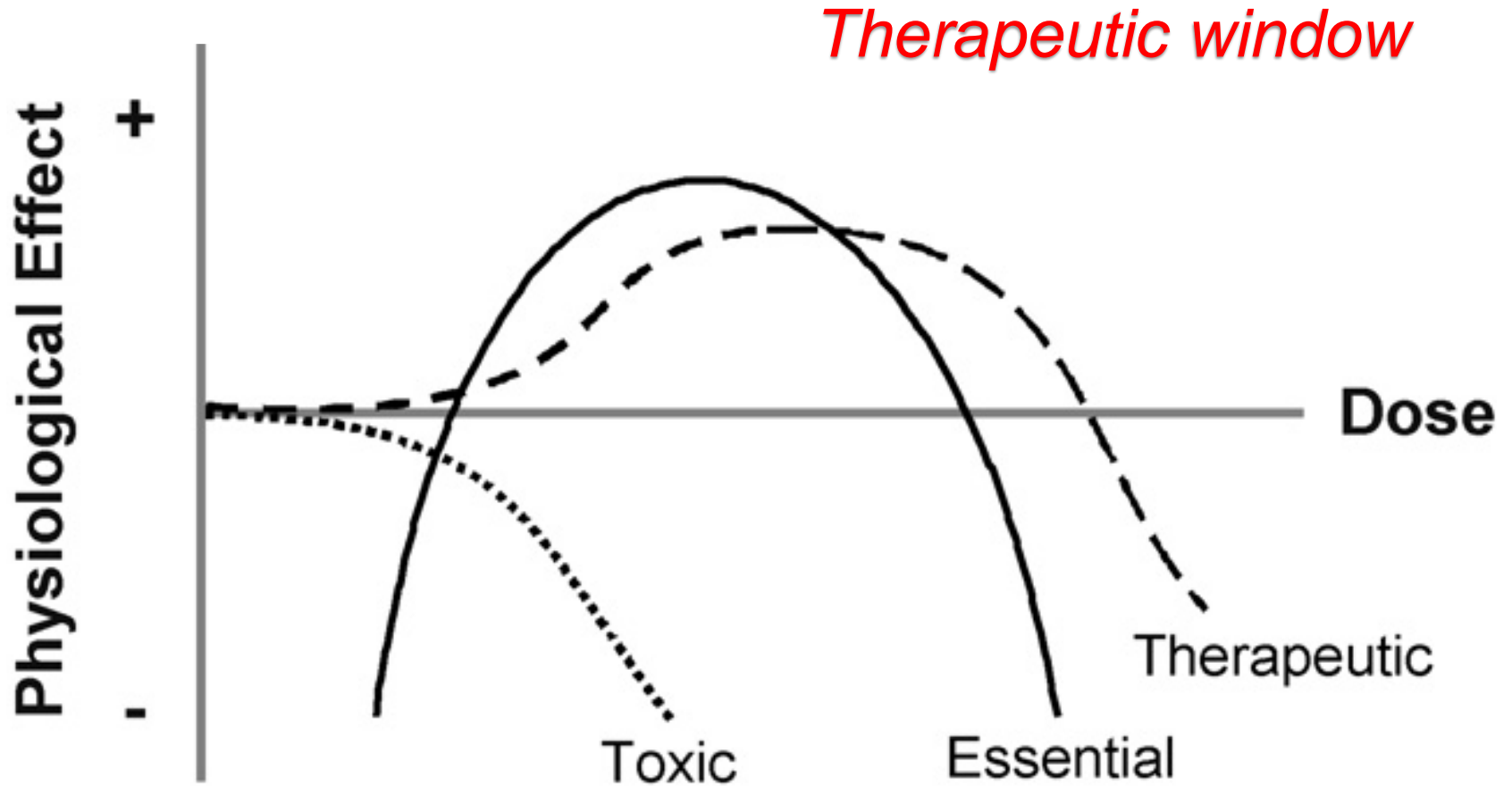
JANUARY 23, 2019
VOLUME 19
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CHEMICAL REVIEWS

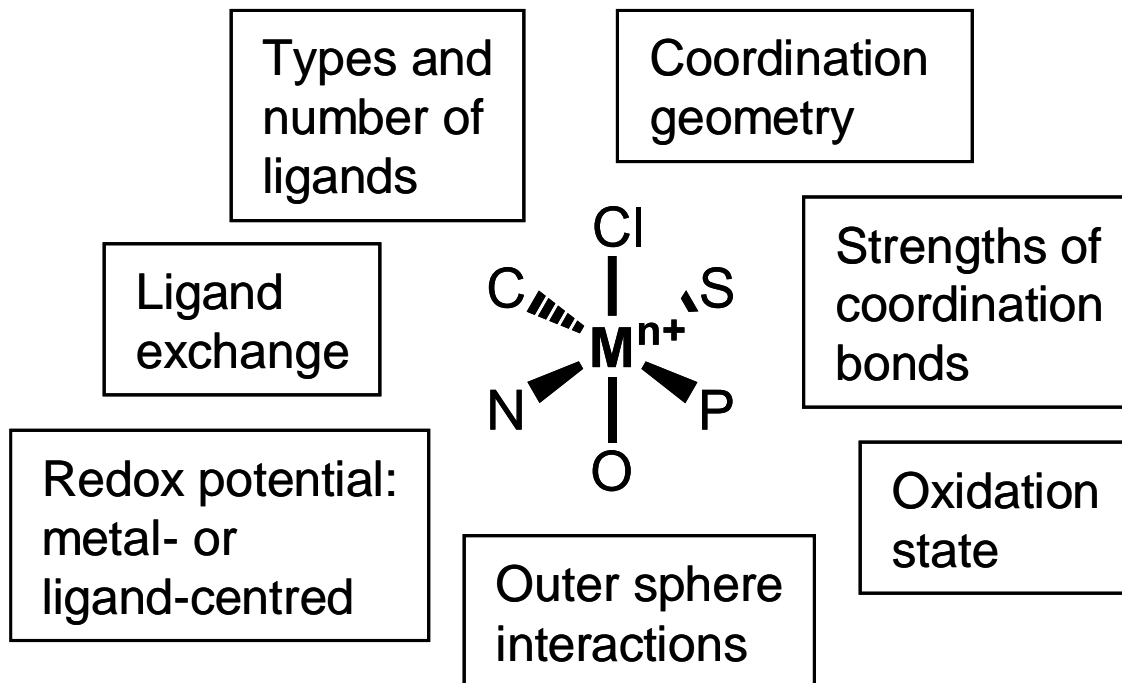


**METALS IN
MEDICINE**

Diagramma di Bertrand



Speciation



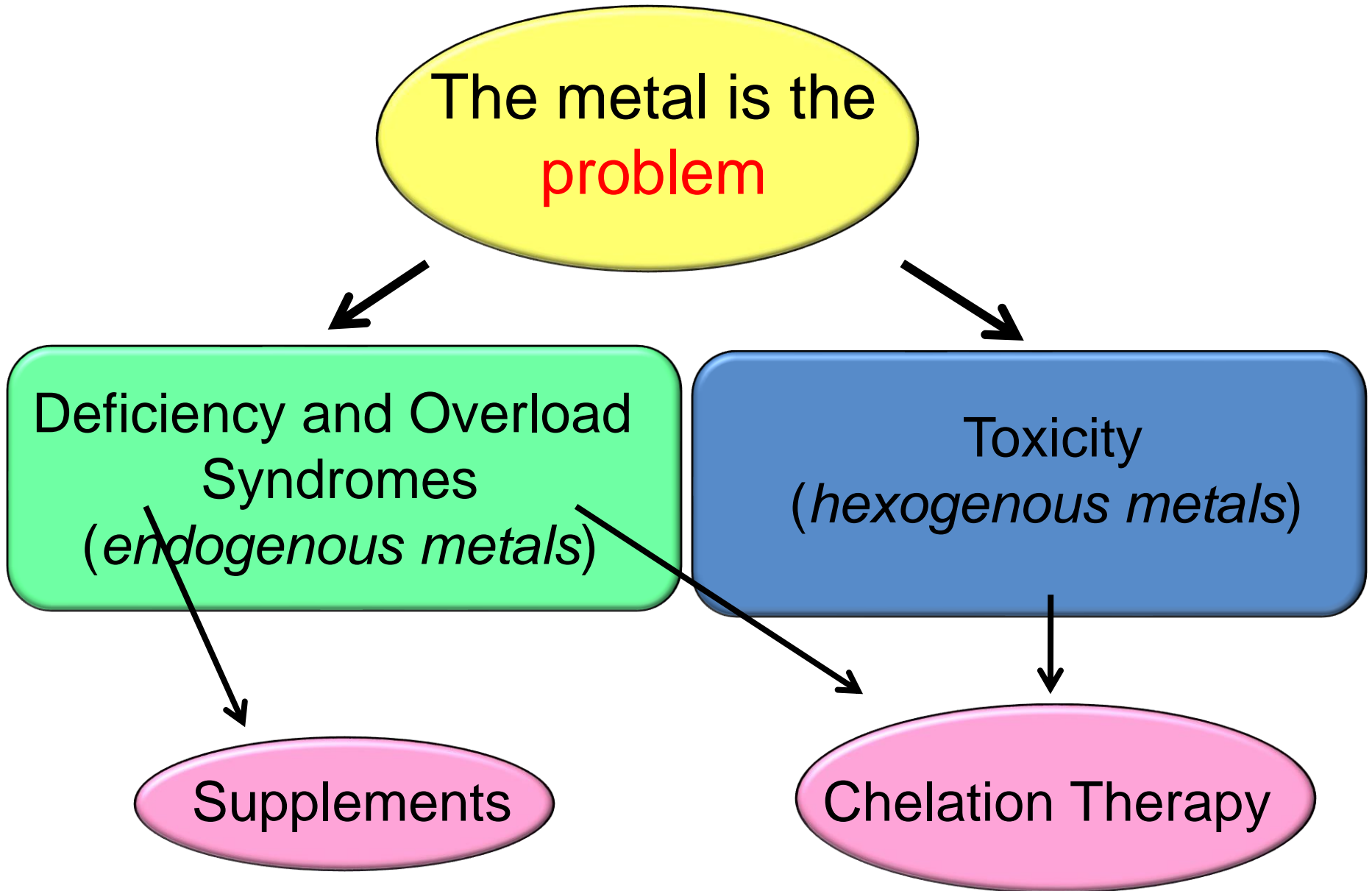
Proprietà	Commenti (esempi)
Numero di Coordinazione	Intero intervallo: 2 – 10; tipicamente da 4 a 6 per i metalli di transizione, può essere più variabile per i metalli dei gruppi principali (<i>e.g.</i> Bi) e più grande per i lantanidi (<i>e.g.</i> 9)
Geometria	Esempi: lineare (Au^{I}), planare-quadrata (Pt^{II}), tetraedrica (<i>e.g.</i> complessi ‘piano-stool’ Ru^{II}), bipiramidale trigonale, ottaedrica (Ti^{IV} , Ru^{III} , Pt^{IV}), possibile chiralità centrata sul metallo (Co^{III} , Rh^{III})
Stato di Ossidazione	Ampio intervallo (tipicamente 0 – 7 in ambiente biologico); i diversi stati di ossidazione favoriscono diversi numeri di coordinazione e velocità di scambio dei leganti (<i>e.g.</i> Pt^{IV} vs Pt^{II})
Tipo di Legante	Ampio numero di atomi donatori <i>e.g.</i> C, N, O, alogenuri, P, S, Se. Leganti chelanti; denticità <i>e.g.</i> (κ^2) 1,2-diamminoetano, (κ^6) EDTA; apticità <i>e.g.</i> legami di tipo η^6 e η^4 per il benzene
Stabilità Termodinamica	Ampio intervallo di forza del legame M–L (tipicamente 50–150 $\text{kJ}\cdot\text{mol}^{-1}$), molto più debole rispetto al tipico legame covalente, <i>e.g.</i> legame singolo C–C (250 – 500 $\text{kJ}\cdot\text{mol}^{-1}$)
Stabilità Cinetica	Il tempo di vita dei legami M–L copre un intervallo molto ampio (ns – anni). Dipende molto dallo stato di ossidazione del metallo e dagli altri leganti; può essere stereospecifico, <i>e.g.</i> effetto <i>trans</i> nel Pt^{II} .
Proprietà dei Leganti	Interazioni relative alla sfera esterna dei leganti, <i>e.g.</i> legame a idrogeno, interazioni idrofobiche (< 50 $\text{kJ}\cdot\text{mol}^{-1}$), possono servire al riconoscimento recettoriale (chiralità inclusa); possono subire trasformazioni <i>in vivo e.g.</i> di tipo redox, idrolisi, reazioni enzimatiche (<i>e.g.</i> ad opera del P450 nel fegato).
Stabilità Nucleare	Nuclei radioattivi possono essere usati per seguire il metabolismo dei composti <i>e.g.</i> $^{195\text{m}}\text{Pt}$ ($t_{1/2} = 4$ d) e $^{99\text{m}}\text{Tc}$ ($t_{1/2} = 6$ h). A seconda del nuclide variano il tipo di decadimento (α , β , γ) e il tempo di semi-vita.

Medicinal
Inorganic
Chemistry

```
graph TD; A[Medicinal Inorganic Chemistry] --> B([The metal is the problem]); A --> C([The metal is the solution]);
```

The metal is the
problem

The metal is the
solution



The metal is the
problem

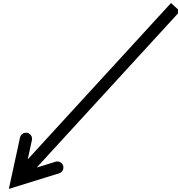
Deficiency and Overload
Syndromes
(*endogenous metals*)

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

Itai Itai Disease (Toyama, JP)

Cd

Martedì 17 Settembre 2019 (0)

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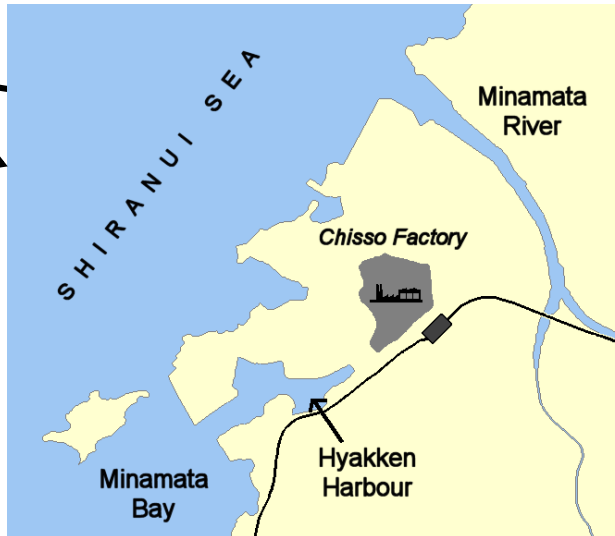
Tl

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

As

Minamata Disease (JP)

Hg



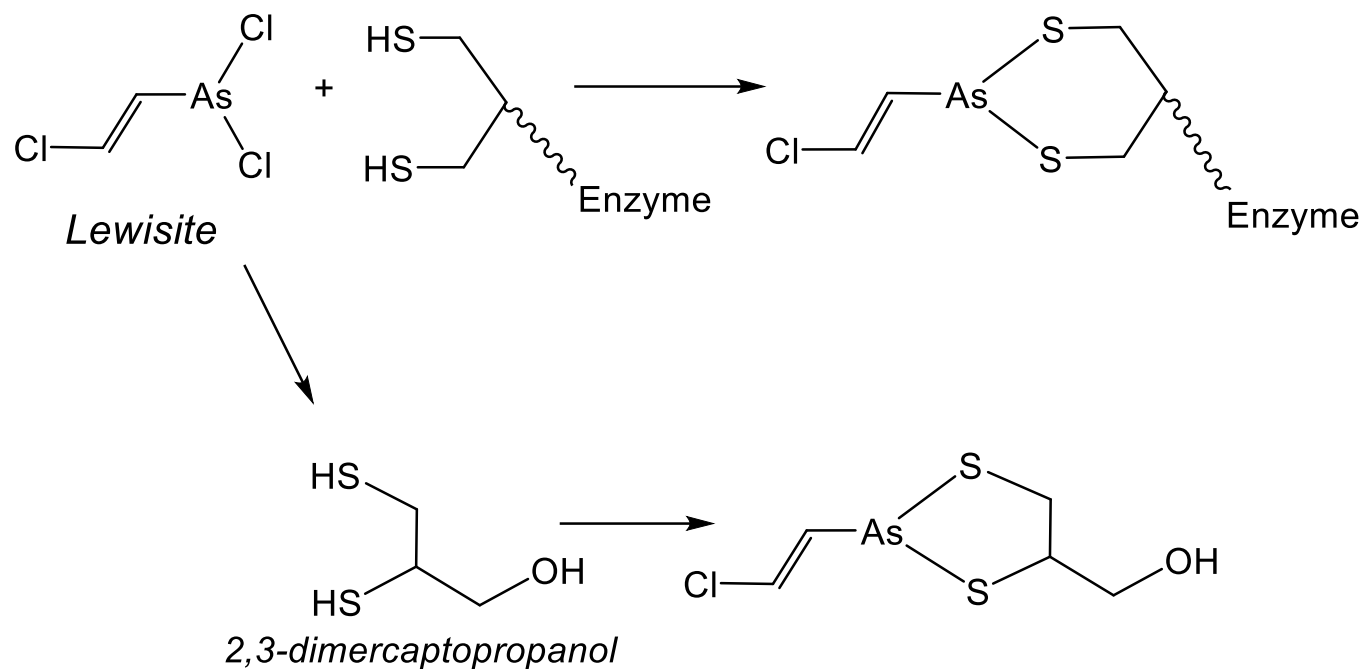
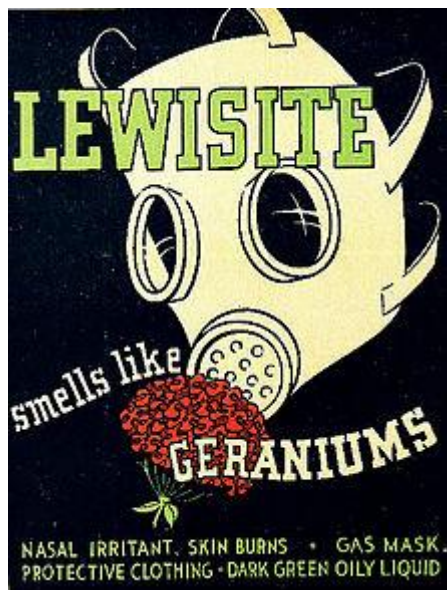
Be



Se

Cr

Chelation Therapy

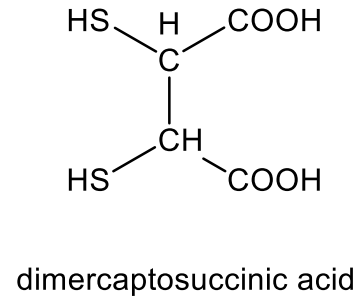
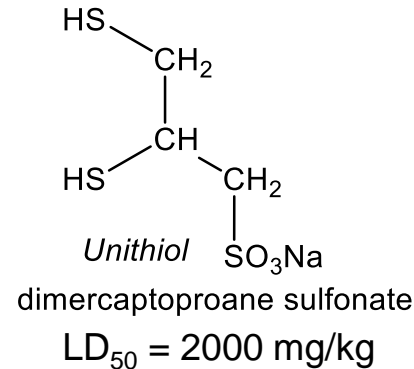
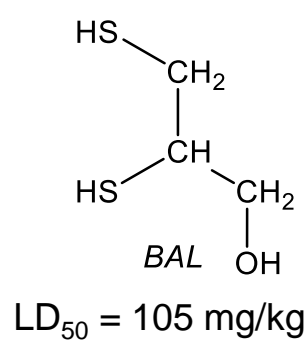


BAL = *British Anti-Lewisite*

Chelation Therapy

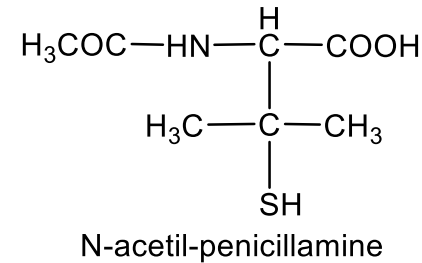
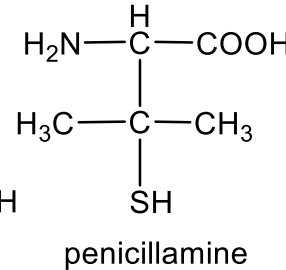
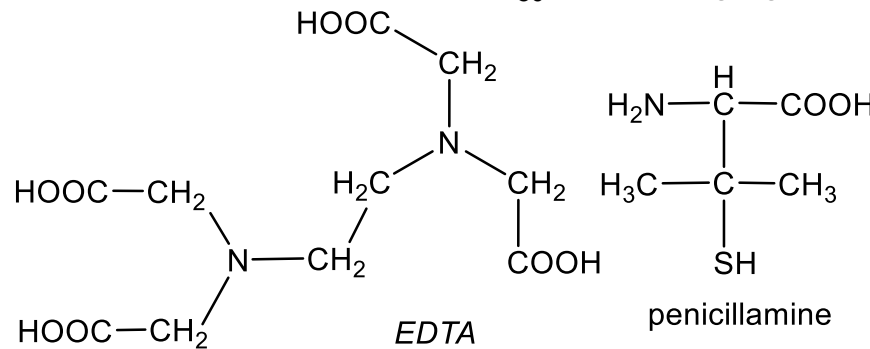
Agent:

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



Adducts:

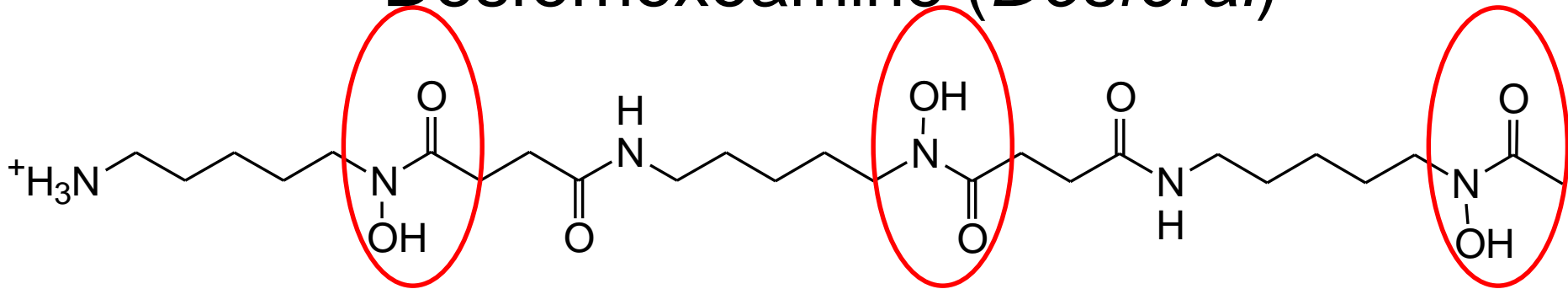
- Stable
- Non toxic
- Highly soluble in water (rapid clearance)
- Resistant to metabolism



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: $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}\cdot + \text{OH}^-$
- Chelation therapy is essential
 1. Efficacia del chelante
 2. Tossicità
 3. Costo
 4. Modo di somministrazione (*compliance*)

Desferrioxamine (*Desferal*)



Desferrioxamine B (DFO, *desferal*)

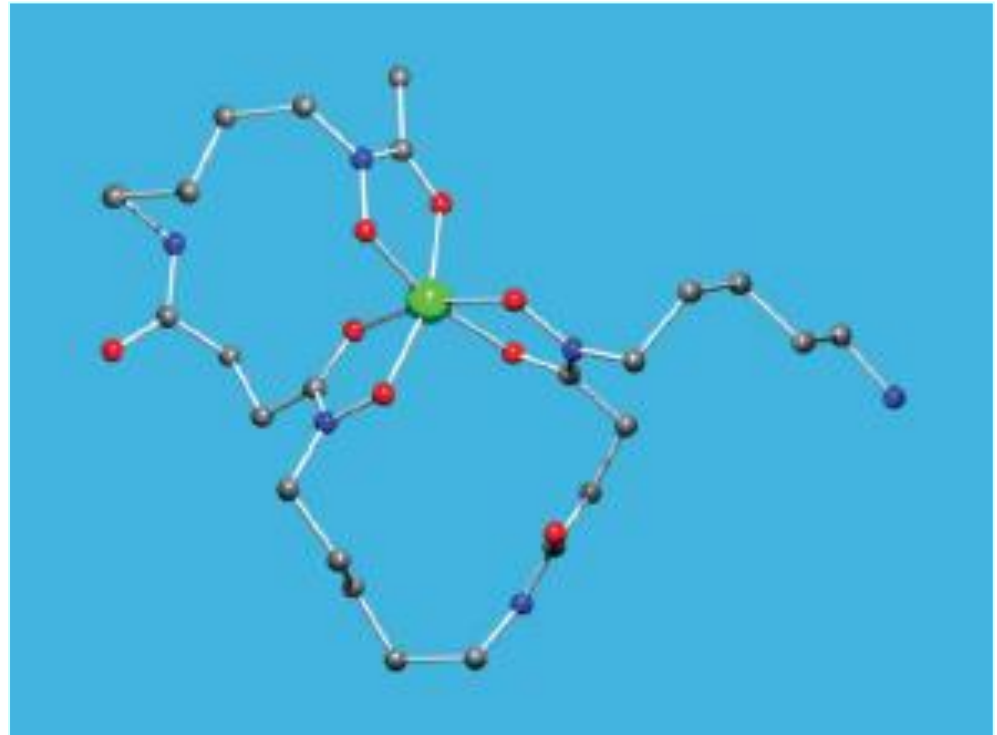
Natural siderophore from *Streptomyces pilosus*

FDA approval: 1968

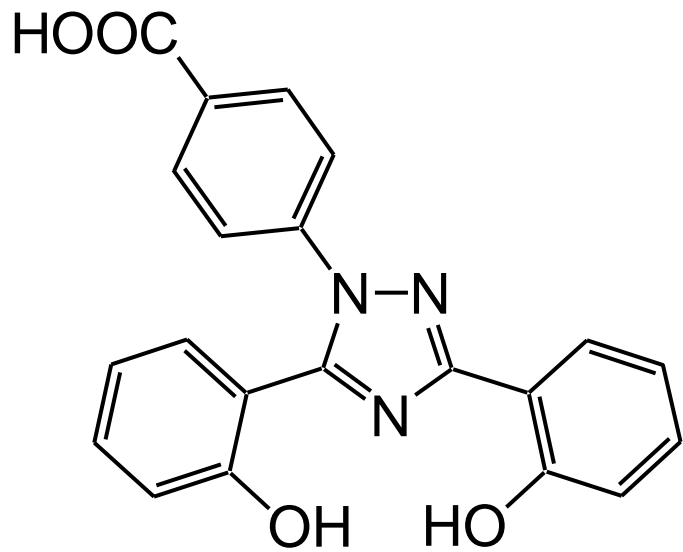
$pFe = 26.6$

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

Drawback: very long
infusion time: 8 – 12 h



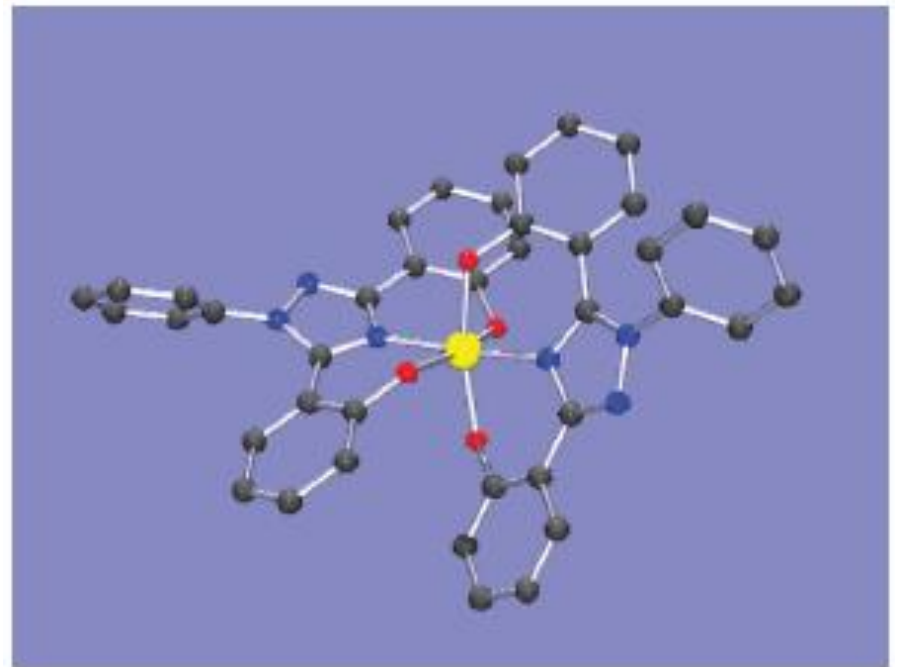
Deferasirox: Orally active



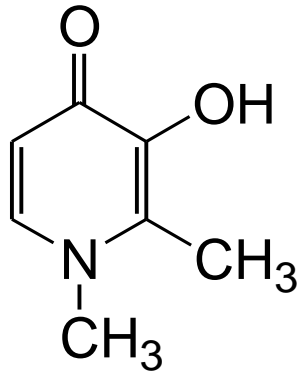
bis-hydroxyphenyl-triazole
deferasirox

pFe = 20

FDA approval: 2005



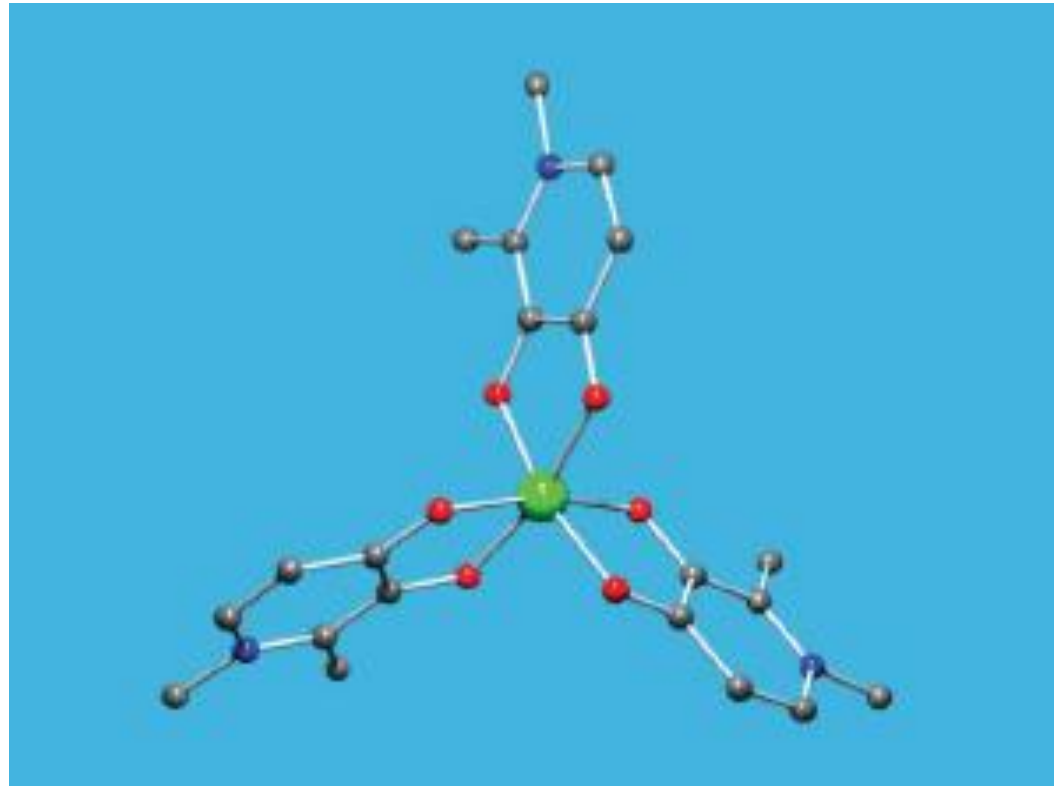
Deferiprone: Orally active

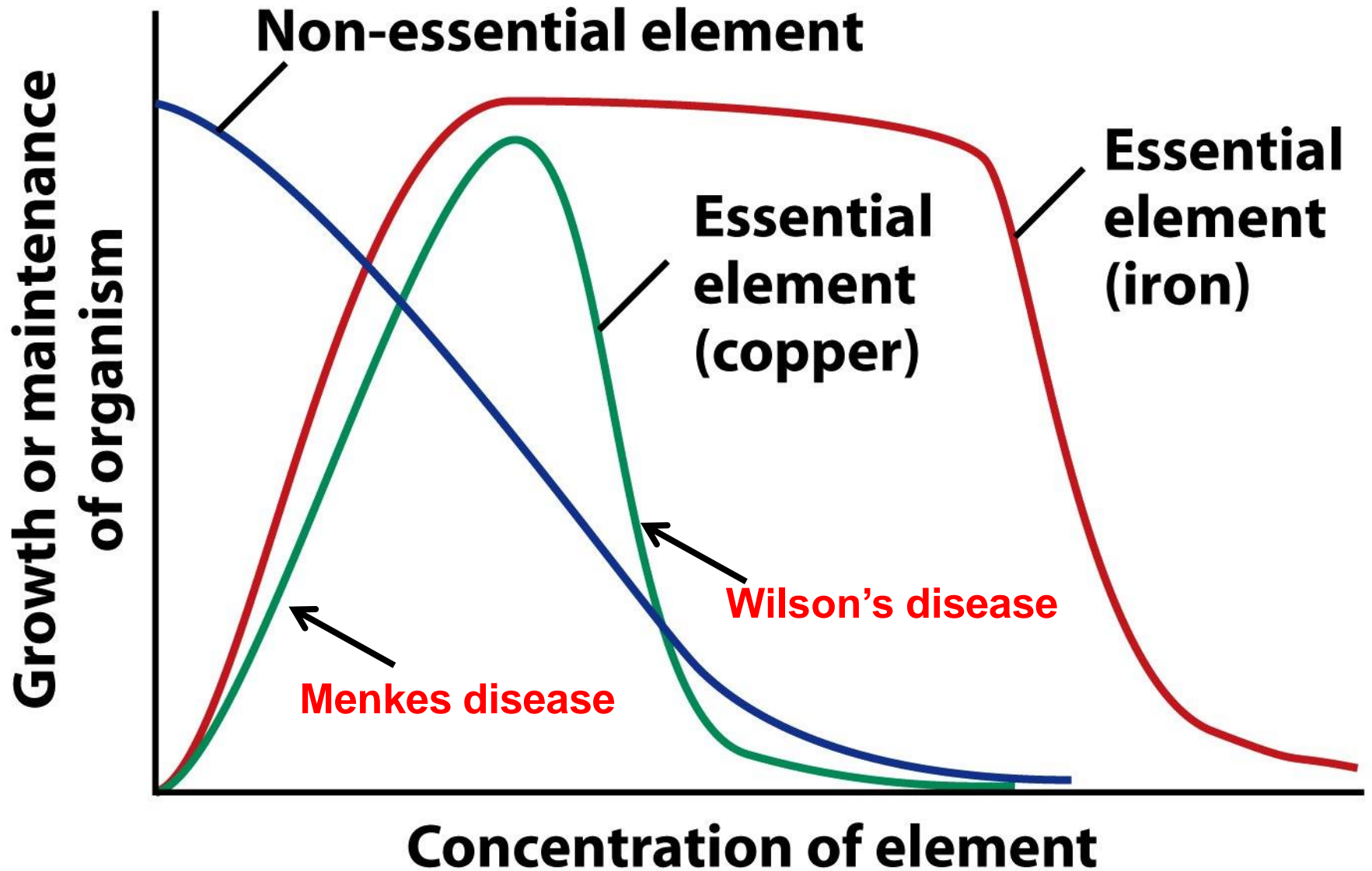


3,4-dihydroxypyridinone
deferiprone

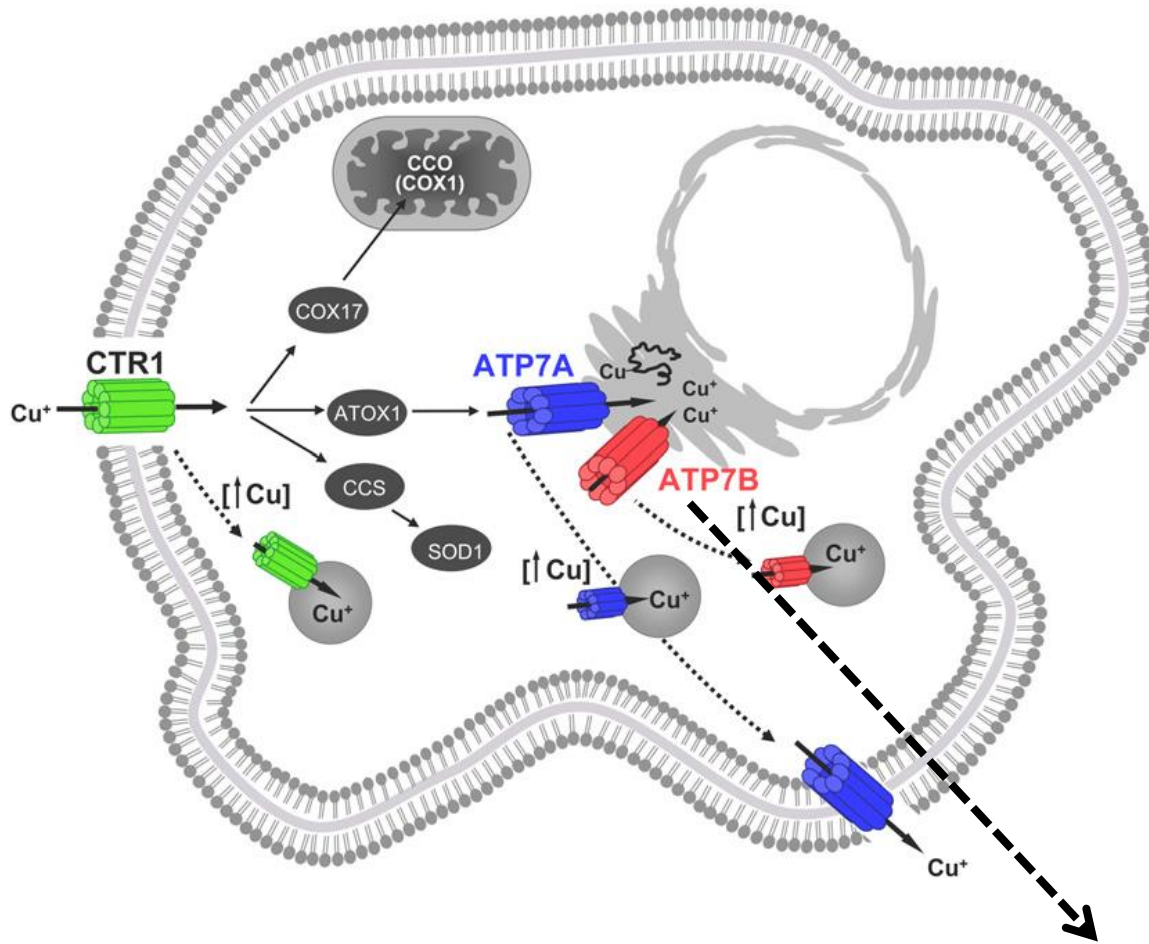
pFe = 20

2011 FDA approval as
second-line oral drug



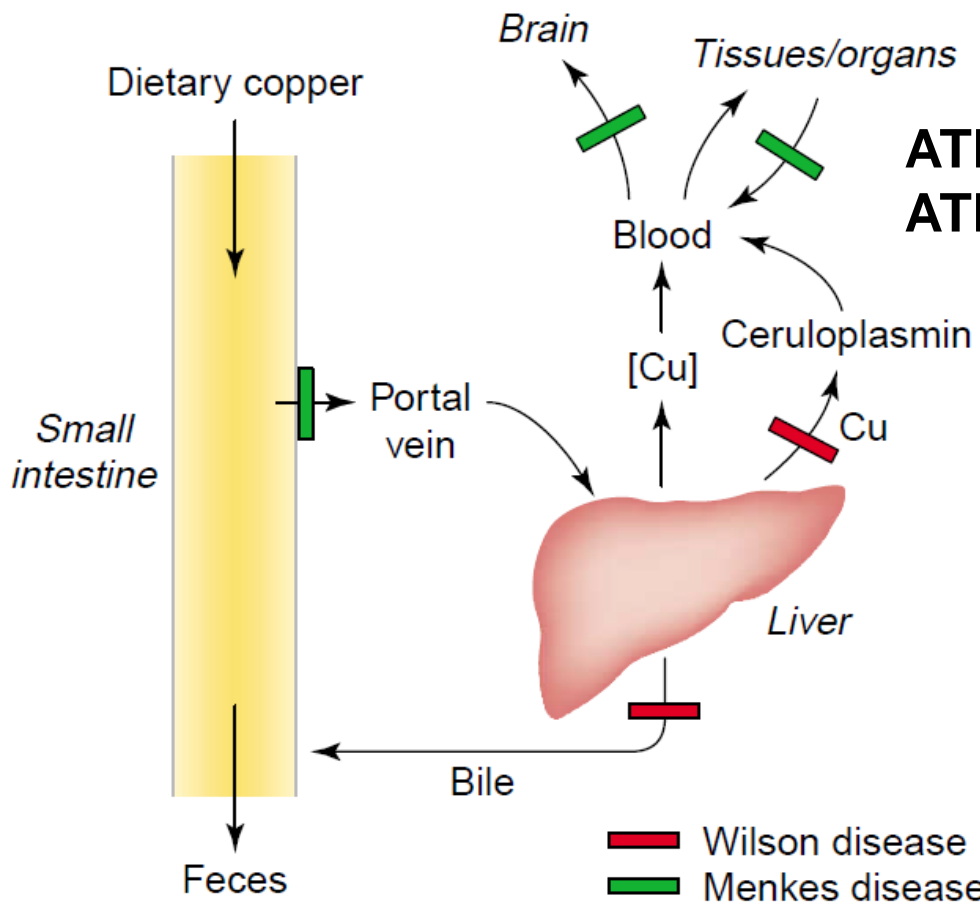


Copper homeostasis

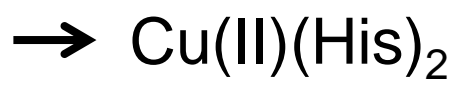


ATP7A: ubiquitous

ATP7B: liver, kidneys, brain

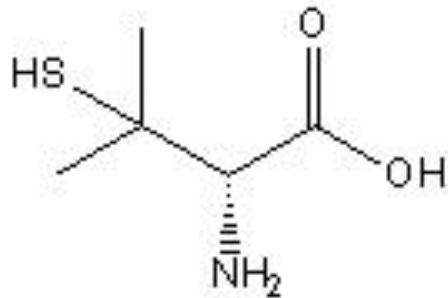


ATP7A: Menkes disease, Cu deficiency
ATP7B: Wilson's disease, Cu overload



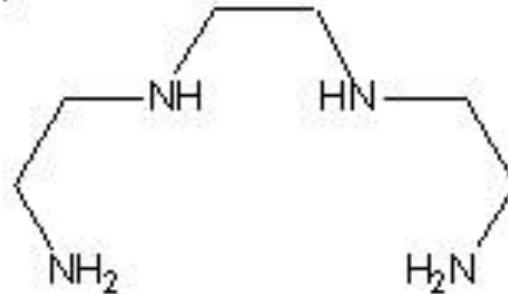
Chelanti per la Sindrome di Wilson (rimozione Cu)

a)



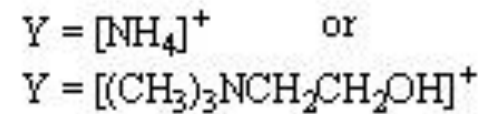
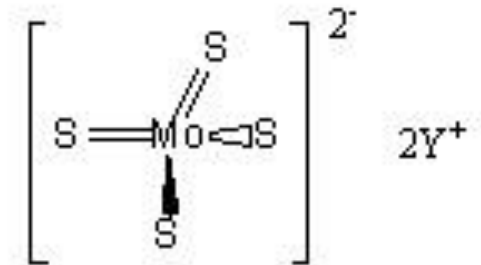
D-penicillamina

b)

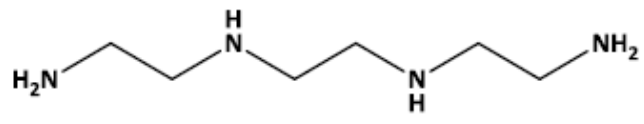


Trien (o *Trientina*)
(tris-etilenetetrammina)

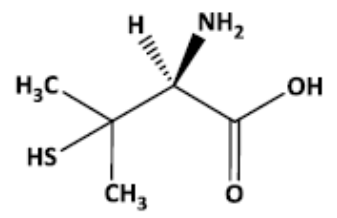
c)



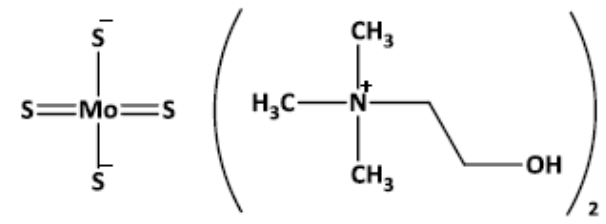
Tetratiomolibdato



a



b



c

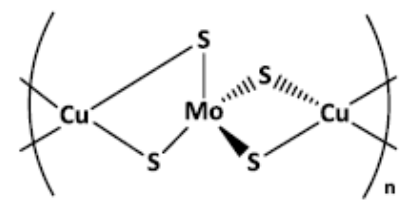
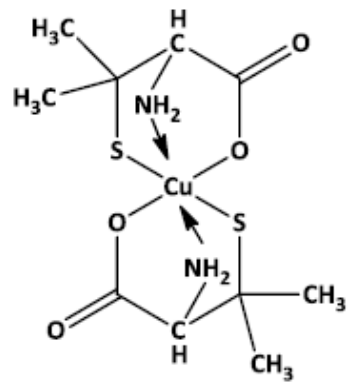
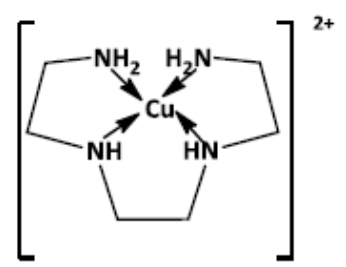


Table 2. Agents for the Treatment of Wilson Disease

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.