

Essential for humans  
 Suggested to be essential for humans  
 Nonessential for humans

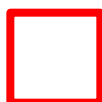
1	1																	18	
1	<b>H</b>	2																	<b>He</b>
2	3	4												5	6	7	8	9	10
	<b>Li</b>	<b>Be</b>												<b>B</b>	<b>C</b>	<b>N</b>	<b>O</b>	<b>F</b>	<b>Ne</b>
3	11	12												13	14	15	16	17	18
	<b>Na</b>	<b>Mg</b>												<b>Al</b>	<b>Si</b>	<b>P</b>	<b>S</b>	<b>Cl</b>	<b>Ar</b>
4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	
	<b>K</b>	<b>Ca</b>	<b>Sc</b>	<b>Ti</b>	<b>V</b>	<b>Cr</b>	<b>Mn</b>	<b>Fe</b>	<b>Co</b>	<b>Ni</b>	<b>Cu</b>	<b>Zn</b>	<b>Ga</b>	<b>Ge</b>	<b>As</b>	<b>Se</b>	<b>Br</b>	<b>Kr</b>	
5	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	
	<b>Rb</b>	<b>Sr</b>	<b>Y</b>	<b>Zr</b>	<b>Nb</b>	<b>Mo</b>	<b>Tc</b>	<b>Ru</b>	<b>Rh</b>	<b>Pd</b>	<b>Ag</b>	<b>Cd</b>	<b>In</b>	<b>Sn</b>	<b>Sb</b>	<b>Te</b>	<b>I</b>	<b>Xe</b>	
6	55	56	57	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	
	<b>Cs</b>	<b>Ba</b>	<b>La</b>	<b>Hf</b>	<b>Ta</b>	<b>W</b>	<b>Re</b>	<b>Os</b>	<b>Ir</b>	<b>Pt</b>	<b>Au</b>	<b>Hg</b>	<b>Tl</b>	<b>Pb</b>	<b>Bi</b>	<b>Po</b>	<b>At</b>	<b>Rn</b>	
7	87	88	89	104	105	106	107	108	109	110	111	112	113	114	115				
	<b>Fr</b>	<b>Ra</b>	<b>Ac</b>	<b>Rf</b>	<b>Db</b>	<b>Sg</b>	<b>Bh</b>	<b>Hs</b>	<b>Mt</b>	<b>Ds</b>	<b>Rg</b>	<b>Uub</b>	<b>Uut</b>	<b>Uuq</b>	<b>Uup</b>				

s-block elements

d-block elements

p-block elements

s-block elements		d-block elements										p-block elements					
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9	Group 10	Group 11	Group 12	Group 13	Group 14	Group 15	Group 16	Group 17	Group 18
1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57-71 La-Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89-103 Ac-Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Uub						



Bulk Metals



Trace



Ultra-trace

f-block elements

Lanthanoids	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
Actinoids	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

Metal	g/75 kg
Na	70 – 120
K	160 – 200
Ca	1100
Mg	25
Fe	4 – 5
Zn	2 – 3
Cu	$80 - 120 \times 10^{-3}$
V	$15 \times 10^{-3}$
Mn	$1 \times 10^{-2}$
Co	$1.2 \times 10^{-3}$
Mo	$10 \times 10^{-3}$
Ni	?

Average  
intracellular  
concentration

$$[\text{Fe}]_{\text{total}} = 0.5 \text{ mM}$$

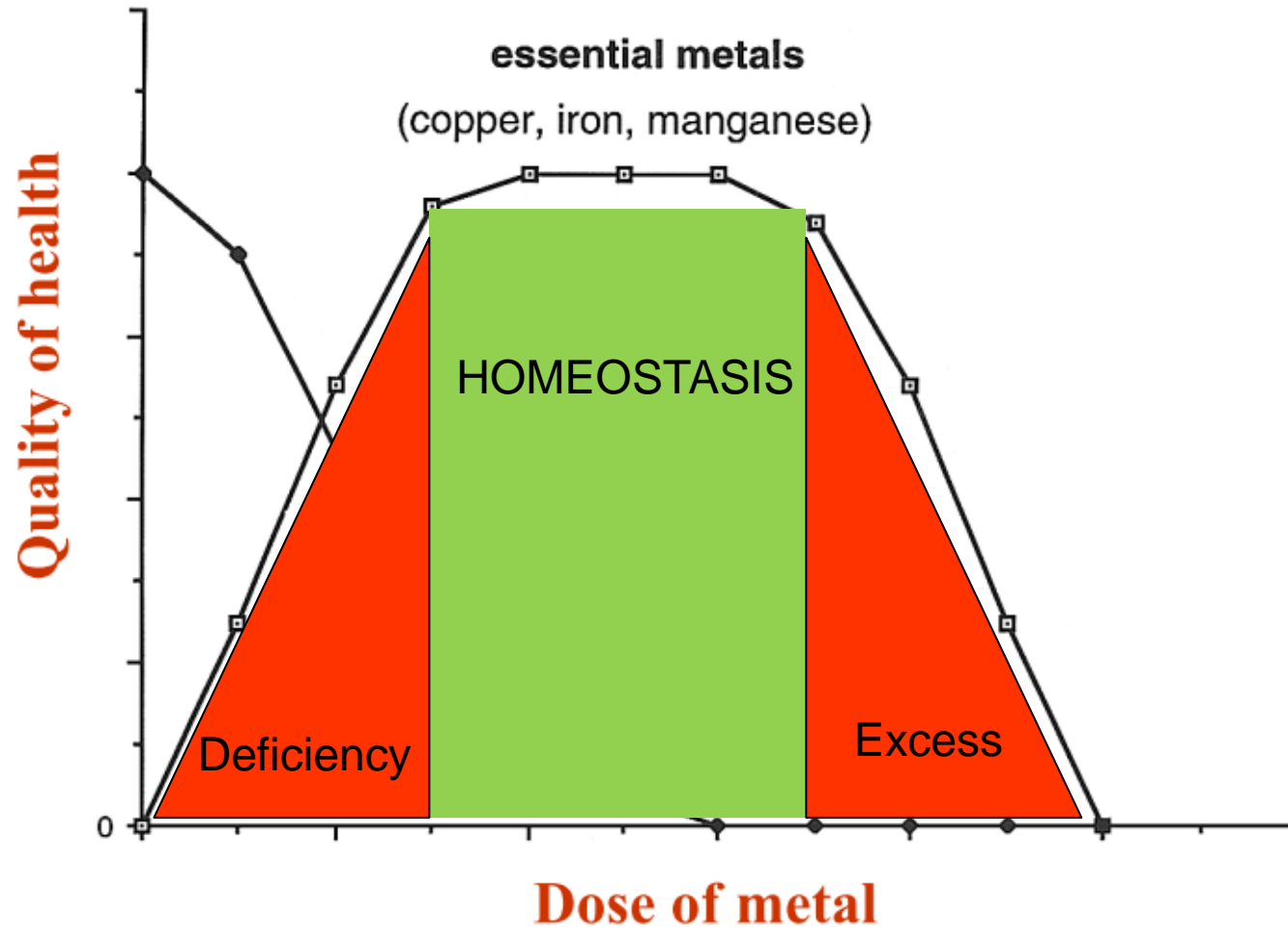
$$[\text{Zn}]_{\text{total}} = 0.5 \text{ mM}$$

$$[\text{Cu}]_{\text{total}} = 50 \text{ } \mu\text{M}$$

Ion	Intracellular (mM)	Extracellular (mM)
Na <sup>+</sup>	10	150
K <sup>+</sup>	100	5
Mg <sup>2+</sup>	2.5	1.5
Ca <sup>2+</sup>	0.1 <sup>a</sup>	2.5
Cl <sup>-</sup>	4	100

<sup>a</sup>0.1 μM in the cytoplasm of resting cells

# Dose-response curve



Genome  
Proteome  
**Metallome**

The entirety of metals contained in each type of cell of a species, each with its specific **amount, speciation and localization**

# HSAB Principle

## Ligands (Lewis bases)

Hard; class (a)	$F^-$ , $Cl^-$ , $H_2O$ , $ROH$ , $R_2O$ , $[OH]^-$ , $[RO]^-$ , $[RCO_2]^-$ , $[CO_3]^{2-}$ , $[NO_3]^-$ , $[PO_4]^{3-}$ , $[SO_4]^{2-}$ , $[ClO_4]^-$ , $[ox]^{2-}$ , $NH_3$ , $RNH_2$
Soft; class (b)	$I^-$ , $H^-$ , $R^-$ , $[CN]^-$ ( <i>C</i> -bound), $CO$ ( <i>C</i> -bound), $RNC$ , $RSH$ , $R_2S$ , $[RS]^-$ , $[SCN]^-$ ( <i>S</i> -bound), $R_3P$ , $R_3As$ , $R_3Sb$ , alkenes, arenes
Intermediate	$Br^-$ , $[N_3]^-$ , $py$ , $[SCN]^-$ ( <i>N</i> -bound), $ArNH_2$ , $[NO_2]^-$ , $[SO_3]^{2-}$

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# HSAB Principle

## Metal centres (Lewis acids)

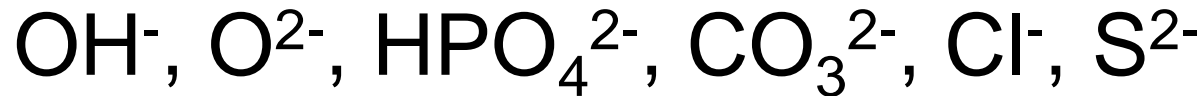
Hard; class (a)	$\text{Li}^+$ , $\text{Na}^+$ , $\text{K}^+$ , $\text{Rb}^+$ , $\text{Be}^{2+}$ , $\text{Mg}^{2+}$ , $\text{Ca}^{2+}$ , $\text{Sr}^{2+}$ , $\text{Sn}^{2+}$ , $\text{Mn}^{2+}$ , $\text{Zn}^{2+}$ , $\text{Al}^{3+}$ , $\text{Ga}^{3+}$ , $\text{In}^{3+}$ , $\text{Sc}^{3+}$ , $\text{Cr}^{3+}$ , $\text{Fe}^{3+}$ , $\text{Co}^{3+}$ , $\text{Y}^{3+}$ , $\text{Th}^{4+}$ , $\text{Pu}^{4+}$ , $\text{Ti}^{4+}$ , $\text{Zr}^{4+}$ , $[\text{VO}]^{2+}$ , $[\text{VO}_2]^+$
Soft; class (b)	Zero oxidation state metal centres, $\text{Tl}^+$ , $\text{Cu}^+$ , $\text{Ag}^+$ , $\text{Au}^+$ , $[\text{Hg}_2]^{2+}$ , $\text{Hg}^{2+}$ , $\text{Cd}^{2+}$ , $\text{Pd}^{2+}$ , $\text{Pt}^{2+}$ , $\text{Tl}^{3+}$
Intermediate	$\text{Pb}^{2+}$ , $\text{Fe}^{2+}$ , $\text{Co}^{2+}$ , $\text{Ni}^{2+}$ , $\text{Cu}^{2+}$ , $\text{Os}^{2+}$ , $\text{Ru}^{3+}$ , $\text{Rh}^{3+}$ , $\text{Ir}^{3+}$

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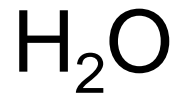


# Biological ligands

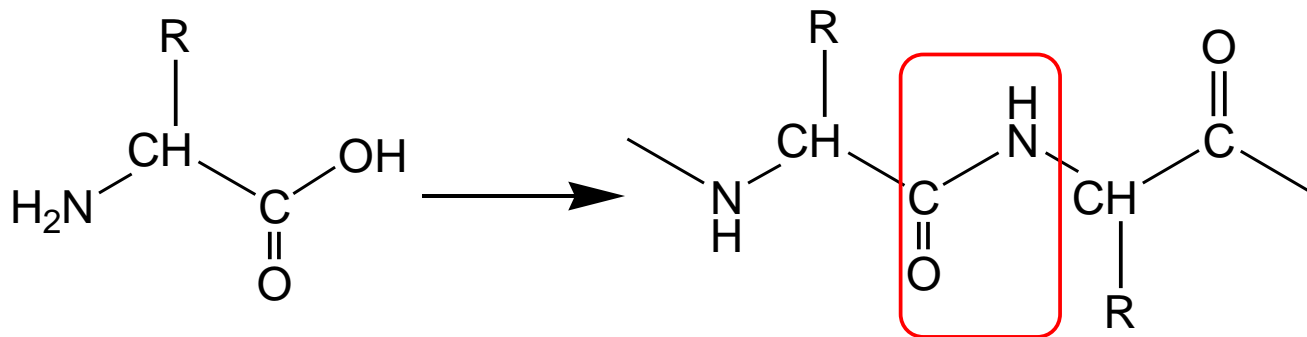
## Anions



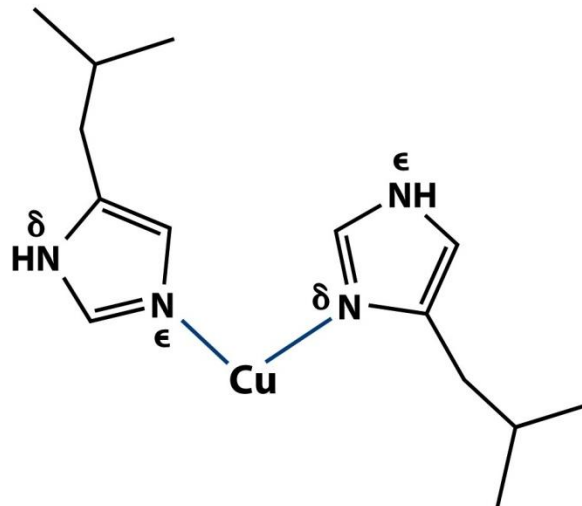
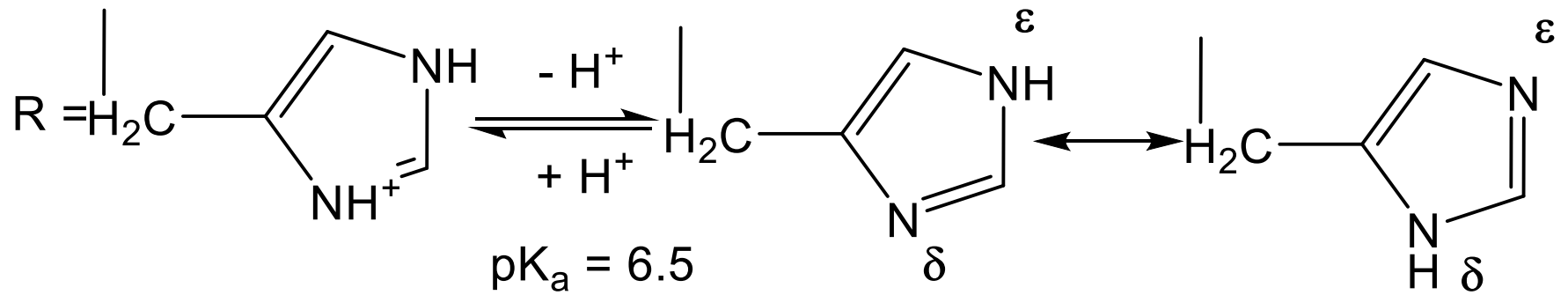
## Water



## Aminoacid side-chains



# Histidine

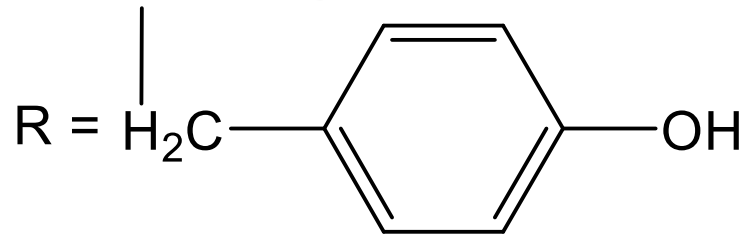


## Cysteine and Methionine



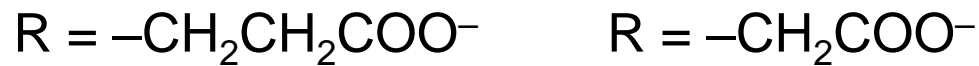
$$\text{pK}_a = 8.5$$

## Tyrosine



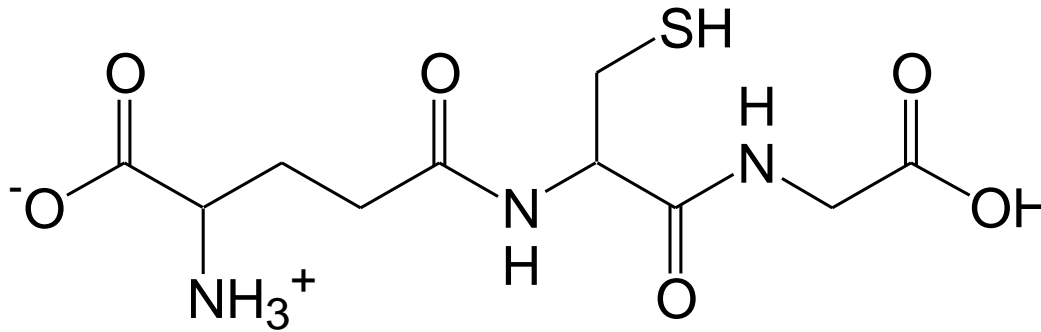
$$\text{pK}_a = 10$$

## Glutamate and Aspartate



$$\text{pK}_a = 4.5$$

# GLUTATHIONE

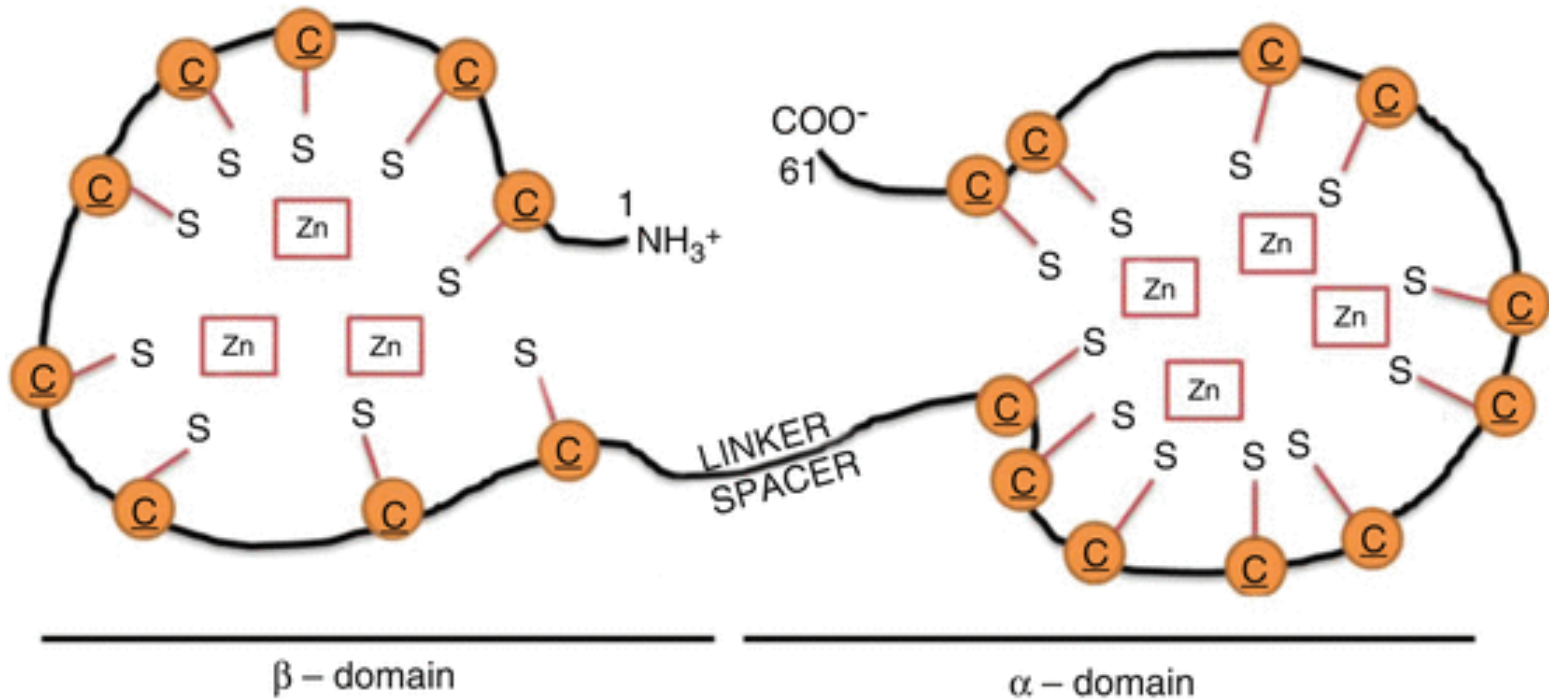


GSH

Glu-Cys-Gly

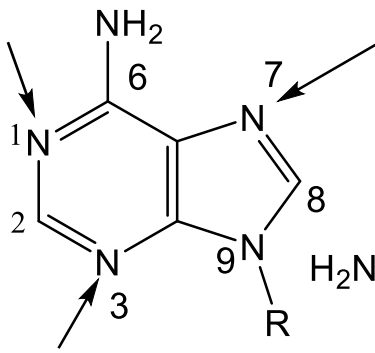
0.5 – 10 mM intracellular

# Metallotioneine

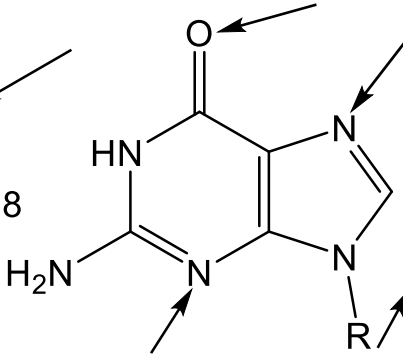


6 kDa,  
ca. 60 a.a.  
fino 30% cys

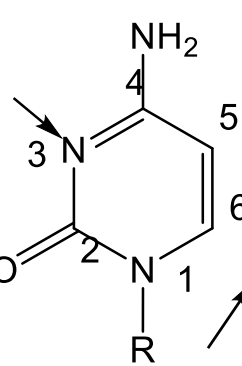
# Nucleobasi



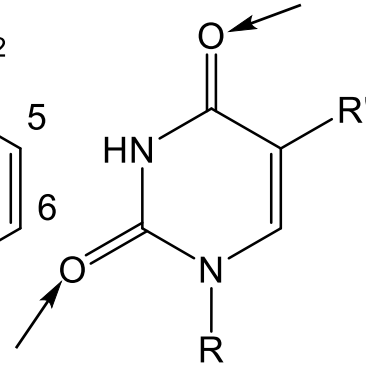
Adenine



Guanine

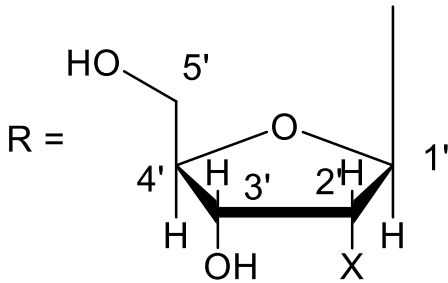


Cytosine



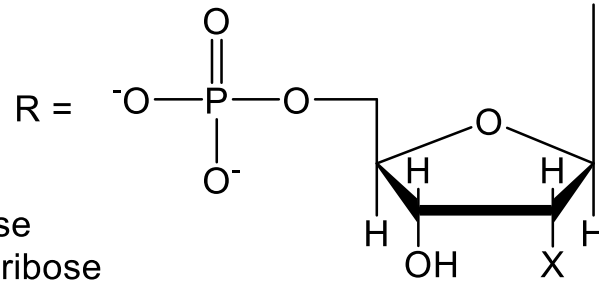
R' = H = Uracil  
R' = CH<sub>3</sub> = Thymine

R = H **Nucleobase**

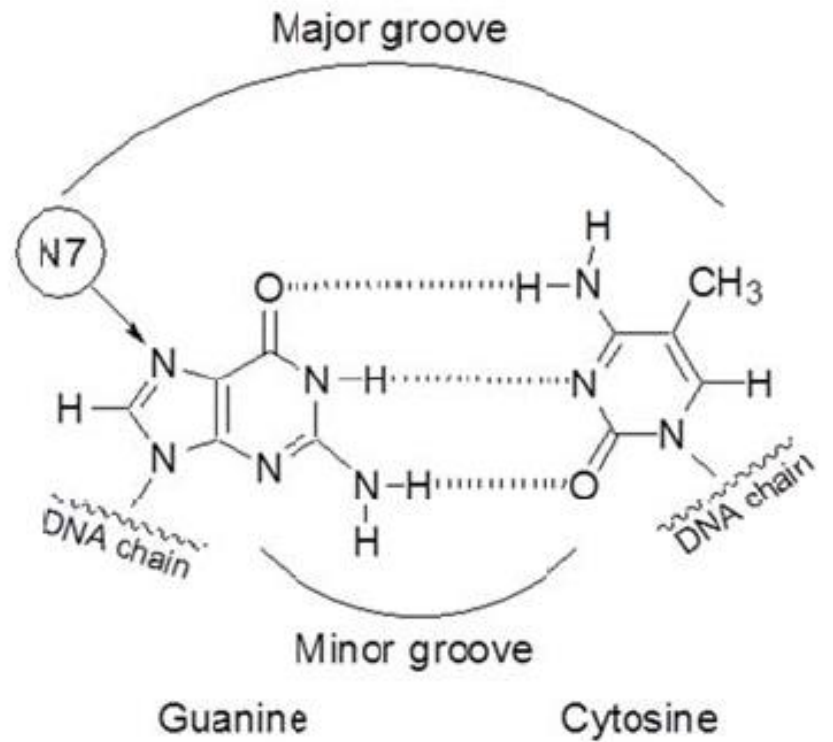
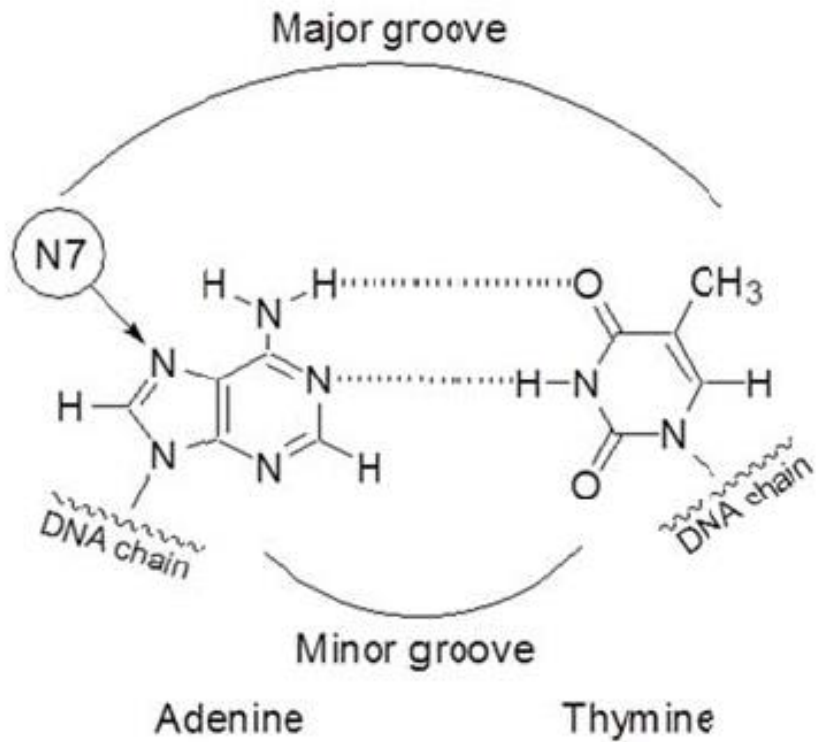


**Nucleoside**

X = OH ribose  
X = H deoxyribose



**Nucleotide**



# Endogenous reducing agents

Electron transfer enzymes

Ascorbic acid: 11–79  $\mu\text{M}$  in the blood

Glutathione: 0.5 – 10 mM intracellular

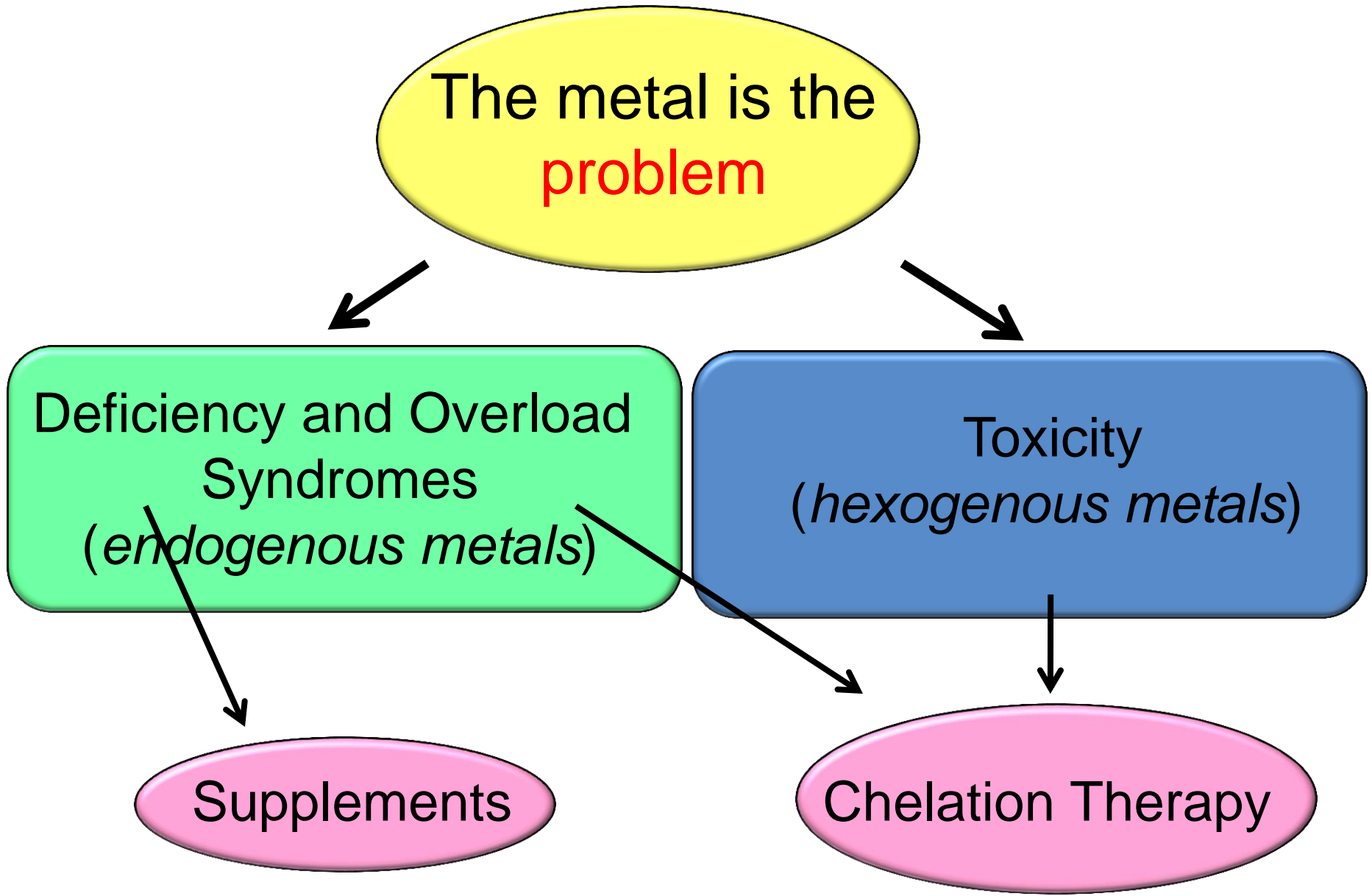


Medicinal  
Inorganic  
Chemistry

```
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*)

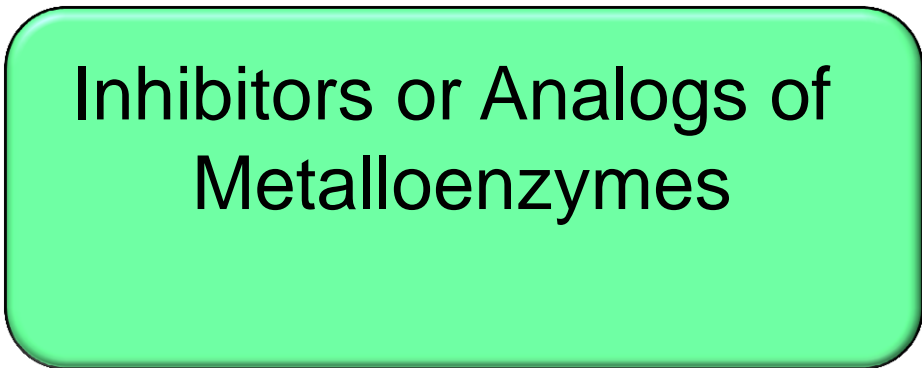
Supplements

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*

Cd

Martedì 17 Settembre 2019 (0)

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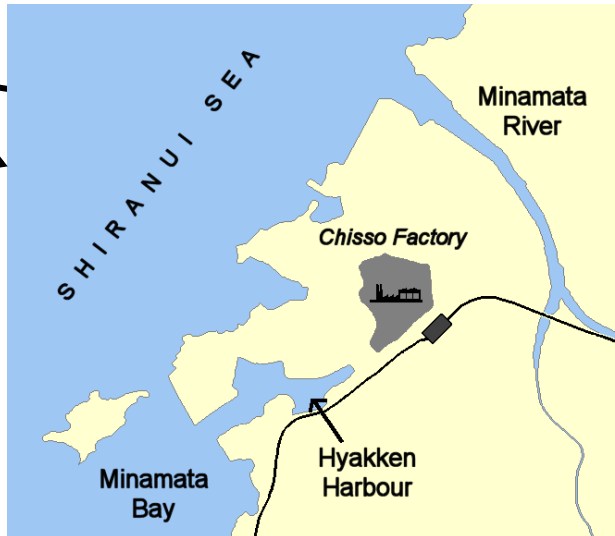
Tl

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

As

*Minamata Disease*

Hg



Be

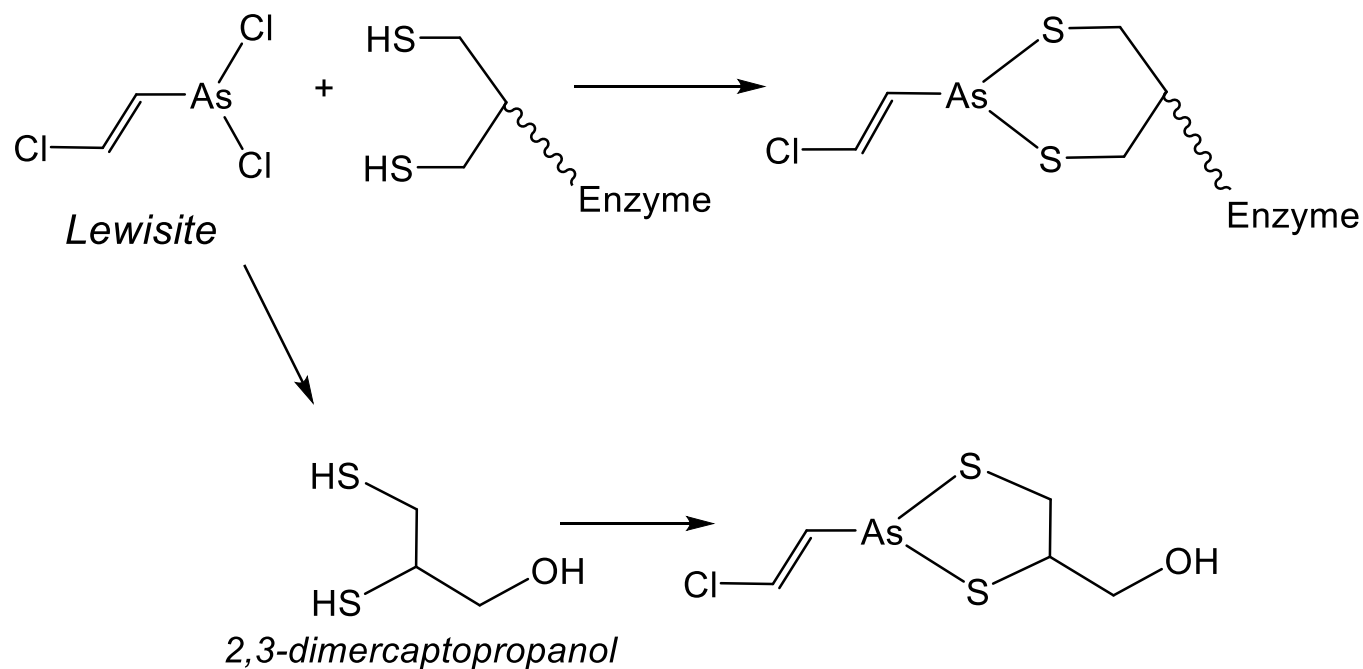
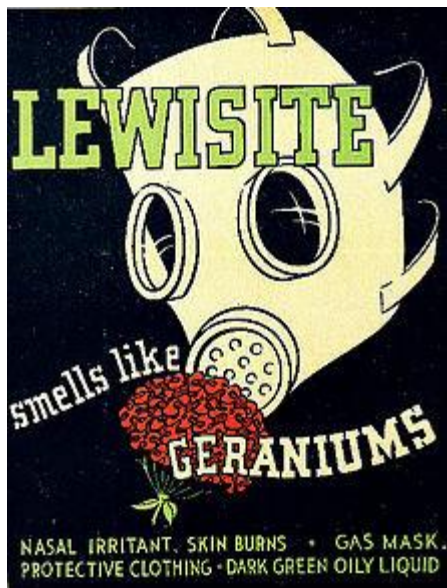
Cr



F

Se

# Chelation Therapy

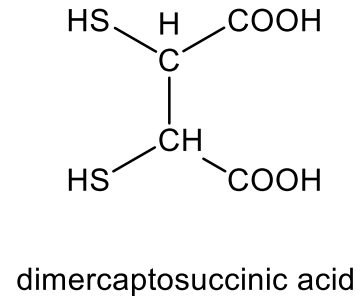
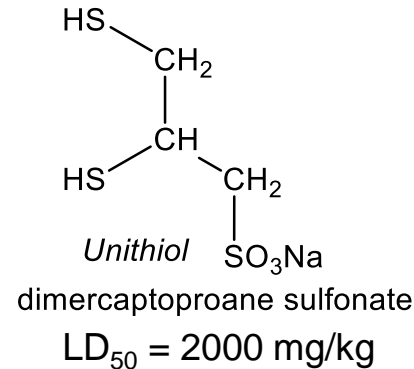
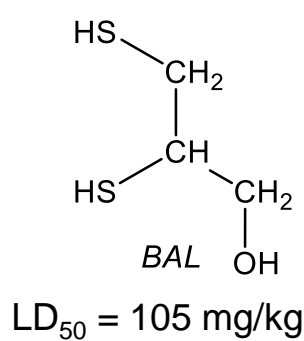


**BAL = *British Anti-Lewisite***

# Chelation Therapy

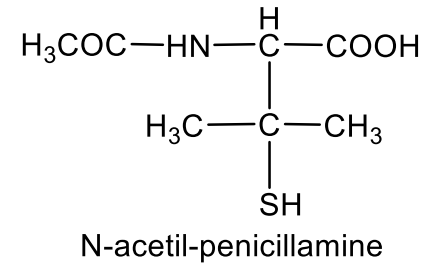
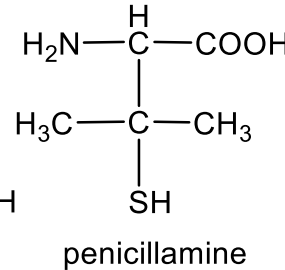
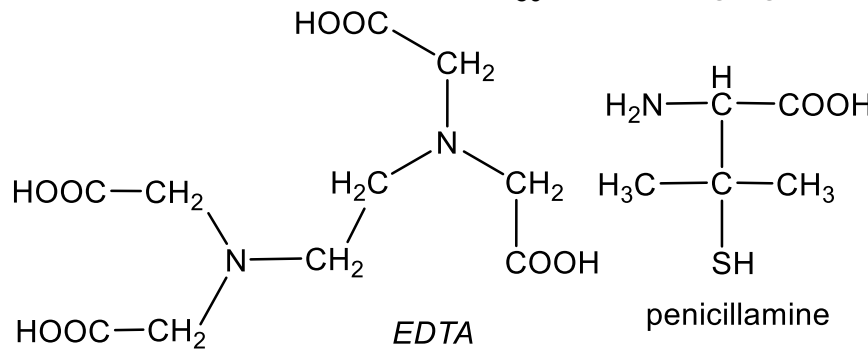
## Agent:

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



## Adducts:

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

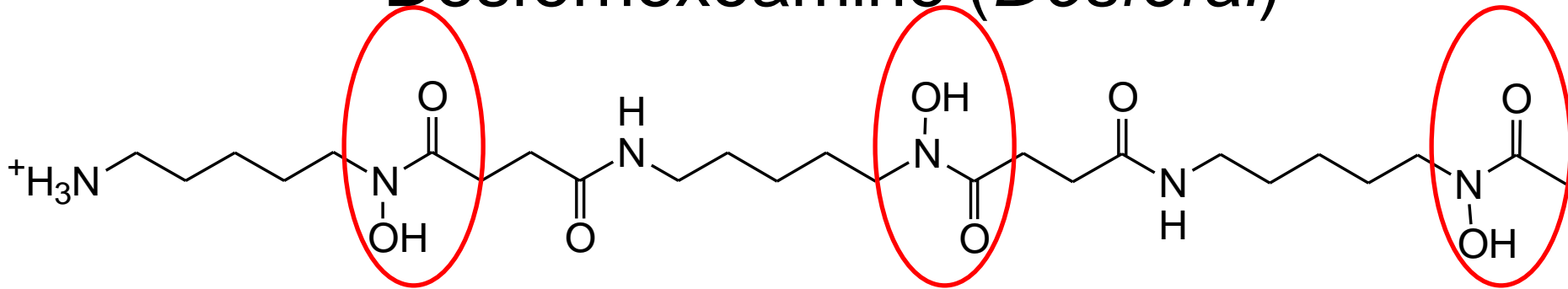


# Iron chelation therapy

- 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*)

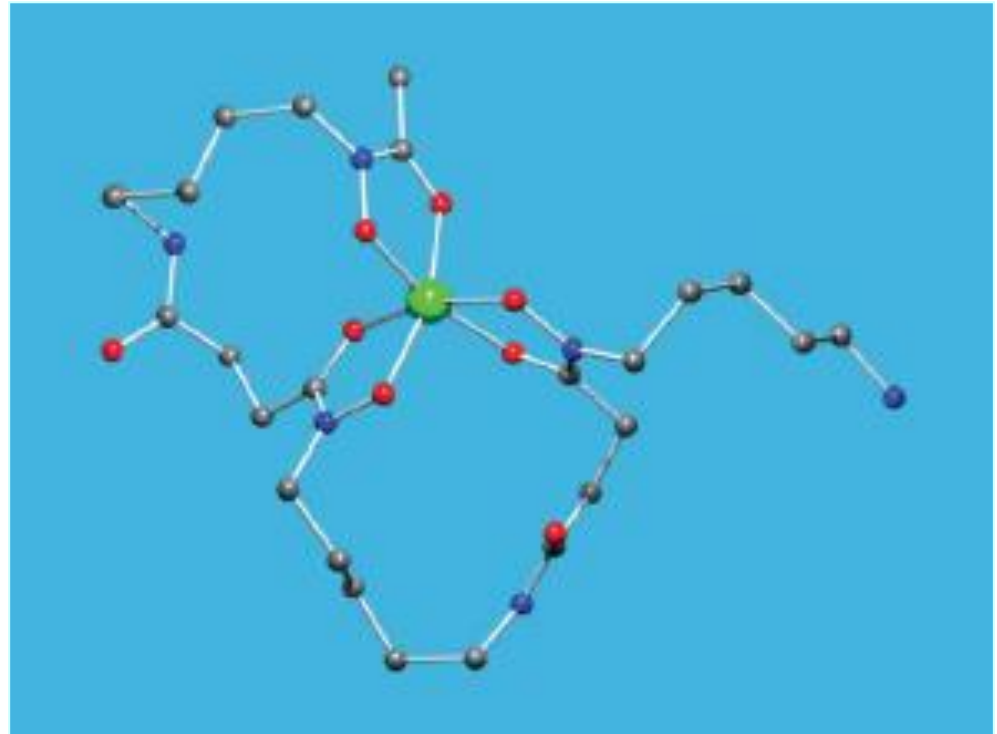
Natural siderophore from *Streptomyces pilosus*

FDA approval: 1968

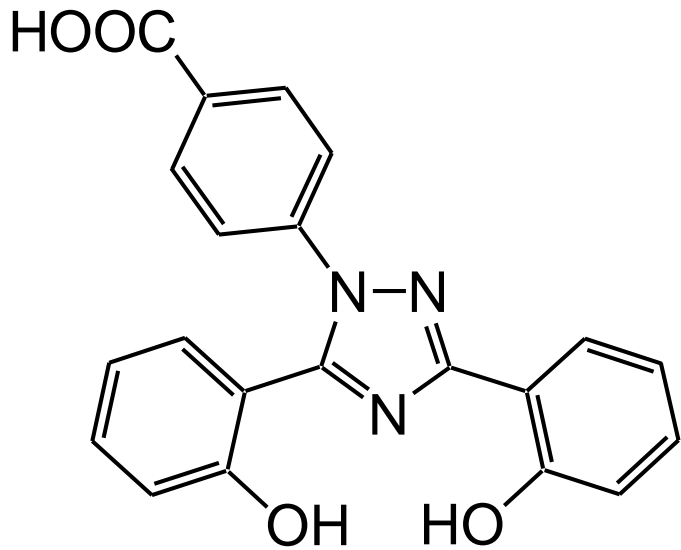
pFe = 26.6

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

Drawback: very long  
infusion time: 8 – 12 h



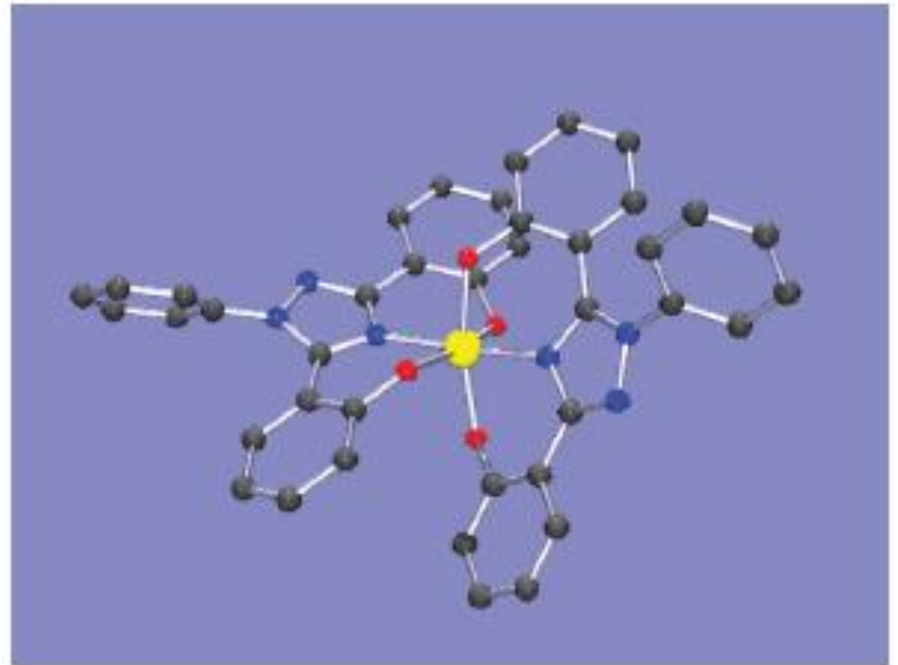
# *Deferasirox*: Orally active



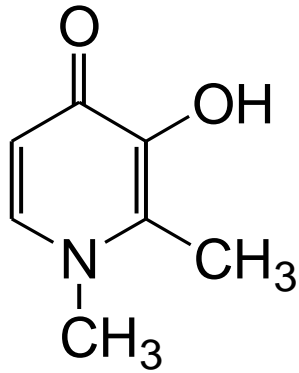
bis-hydroxyphenyl-triazole  
*deferasirox*

pFe = 20

FDA approval: 2005



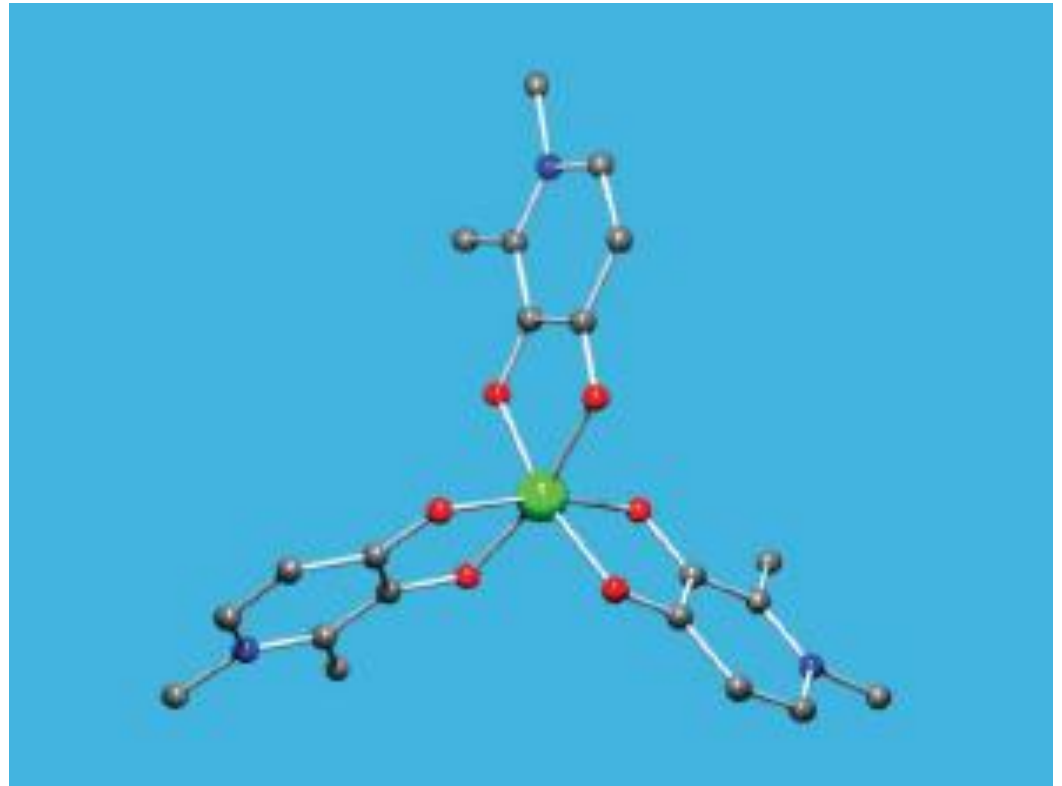
# *Deferiprone*: Orally active

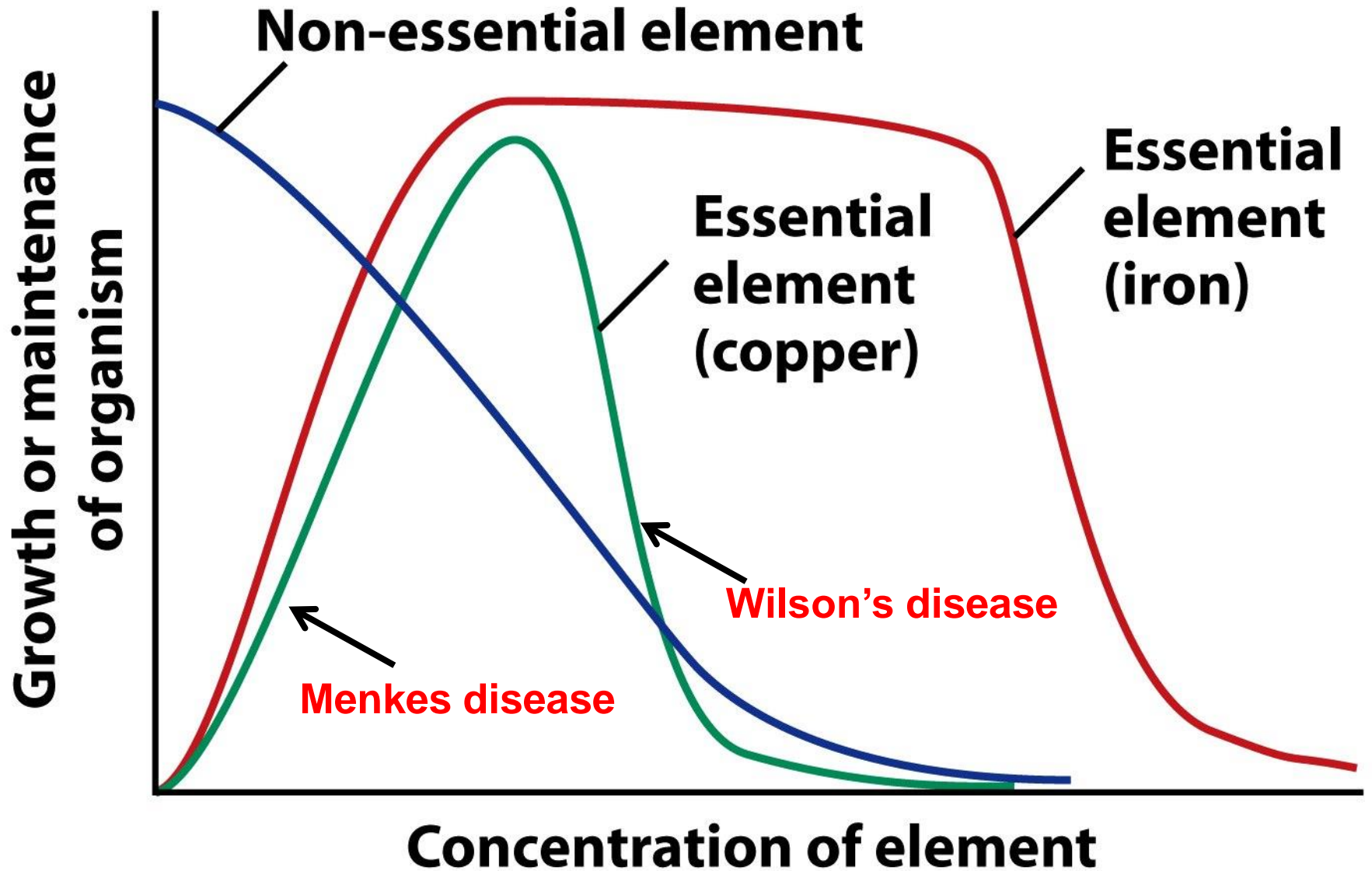


3,4-dihydroxypyridinone  
*deferiprone*

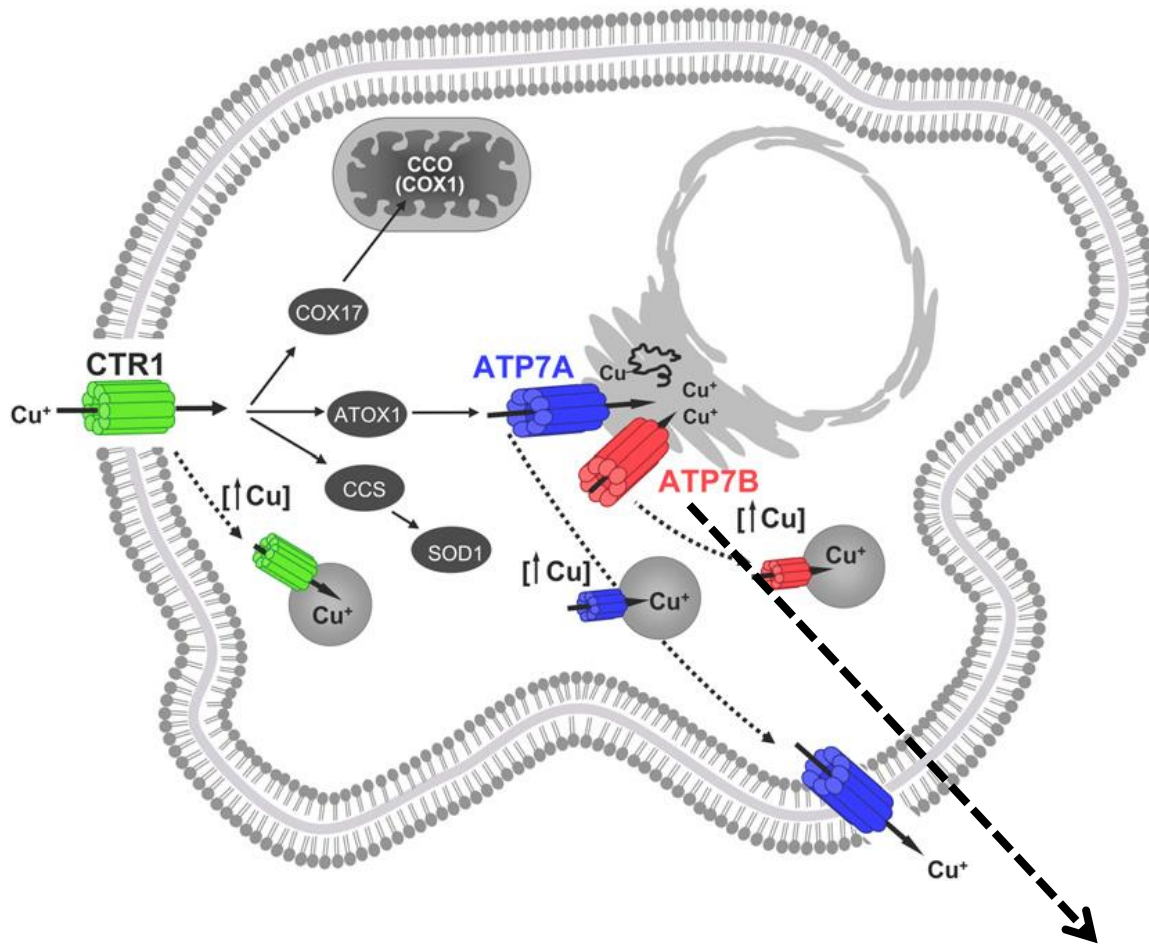
pFe = 20

2011 FDA approval as  
second-line oral drug



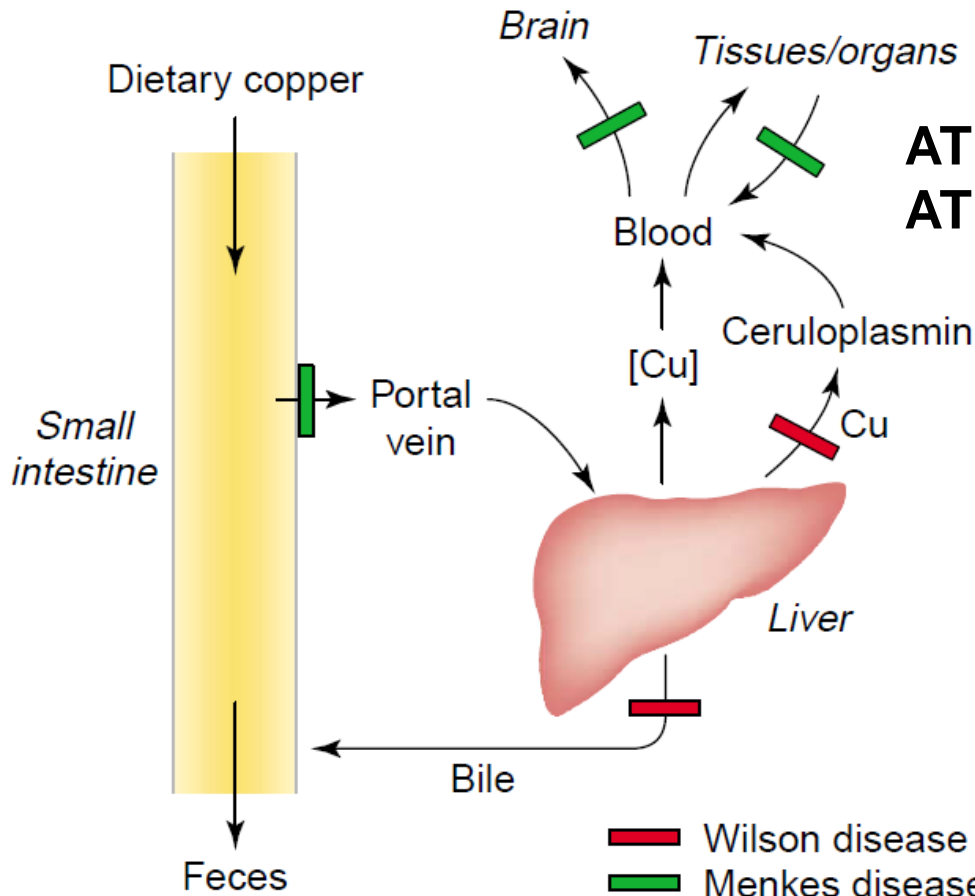


# Copper homeostasis



**ATP7A**: ubiquitous

**ATP7B**: liver, kidneys, brain

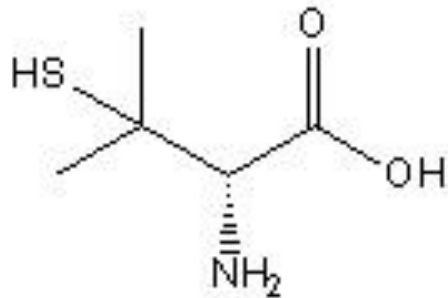


**ATP7A:** Menkes disease, Cu deficiency  
**ATP7B:** Wilson's disease, Cu overload

█ Wilson disease  
█ Menkes disease     $\rightarrow$   $\text{Cu(II)(His)}_2$

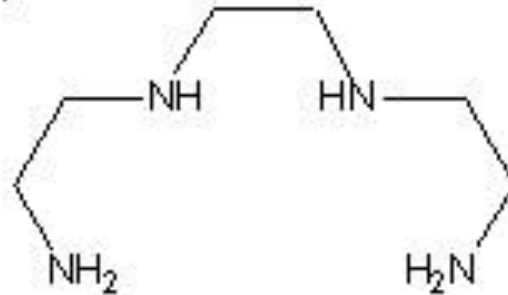
# Chelanti per la Sindrome di Wilson (rimozione Cu)

a)



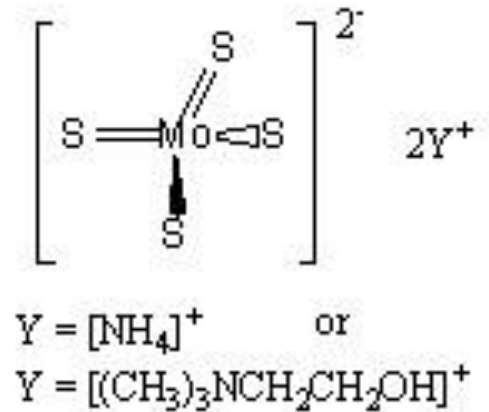
D-penicillamina

b)

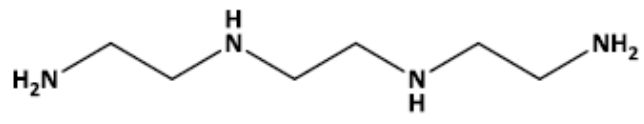


Trien (o *Trientina*)  
(tris-etilenetetrammina)

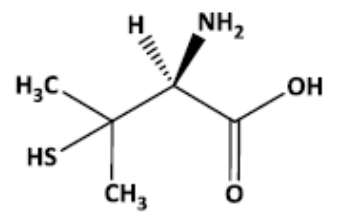
c)



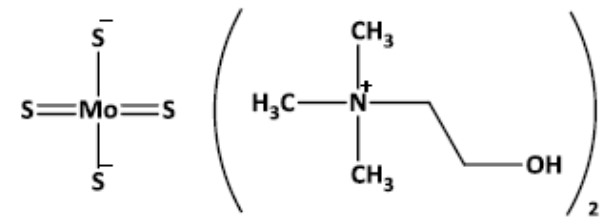
Tetratiomolibdato



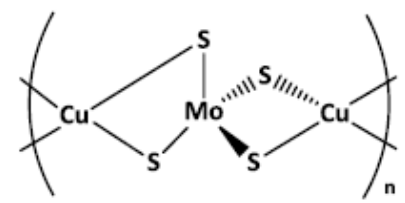
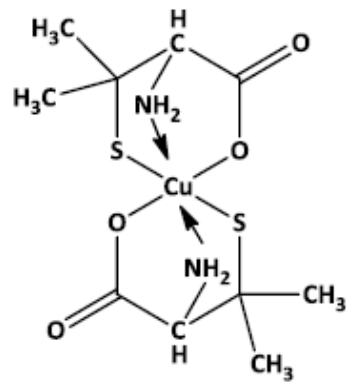
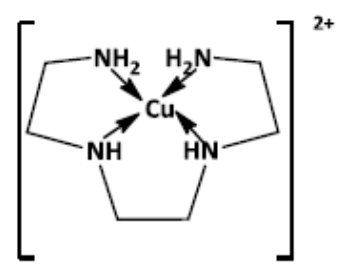
a



b



c





**Table 2. Agents for the Treatment of Wilson Disease**

agent	mechanism of action	daily adult dosage
D-penicillamine <sup>a</sup>	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 <sup>b</sup>	blocking the intestinal absorption of copper and a copper chelator	Up to 2 mg/kg orally in divided doses

<sup>a</sup> Administered with supplementation of 25 mg of pyridoxine orally daily. <sup>b</sup> Experimental.