

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

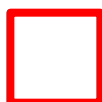
1	1																	18
1	H	2																He
2	3	4										5	6	7	8	9	10	
	Li	Be										B	C	N	O	F	Ne	
3	11	12										13	14	15	16	17	18	
	Na	Mg										Al	Si	P	S	Cl	Ar	
4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	37	38	39	40	41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

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	15×10^{-3}
Mn	1×10^{-2}
Co	1.2×10^{-3}
Mo	10×10^{-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 ⁺	10	150
K ⁺	100	5
Mg ²⁺	2.5	1.5
Ca ²⁺	0.1 ^a	2.5
Cl ⁻	4	100

^a0.1 μM in the cytoplasm of resting cells

Dose-response curve

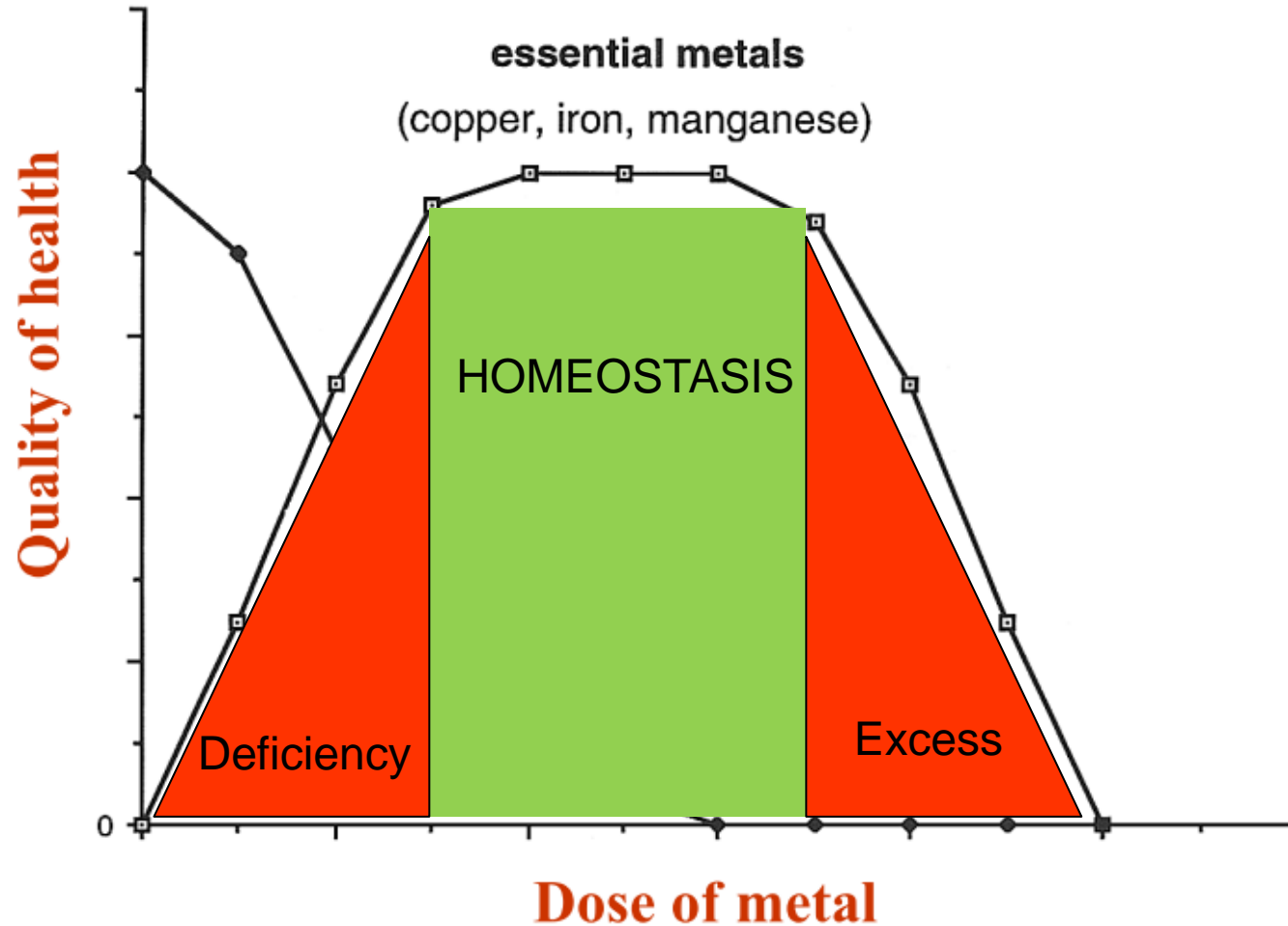
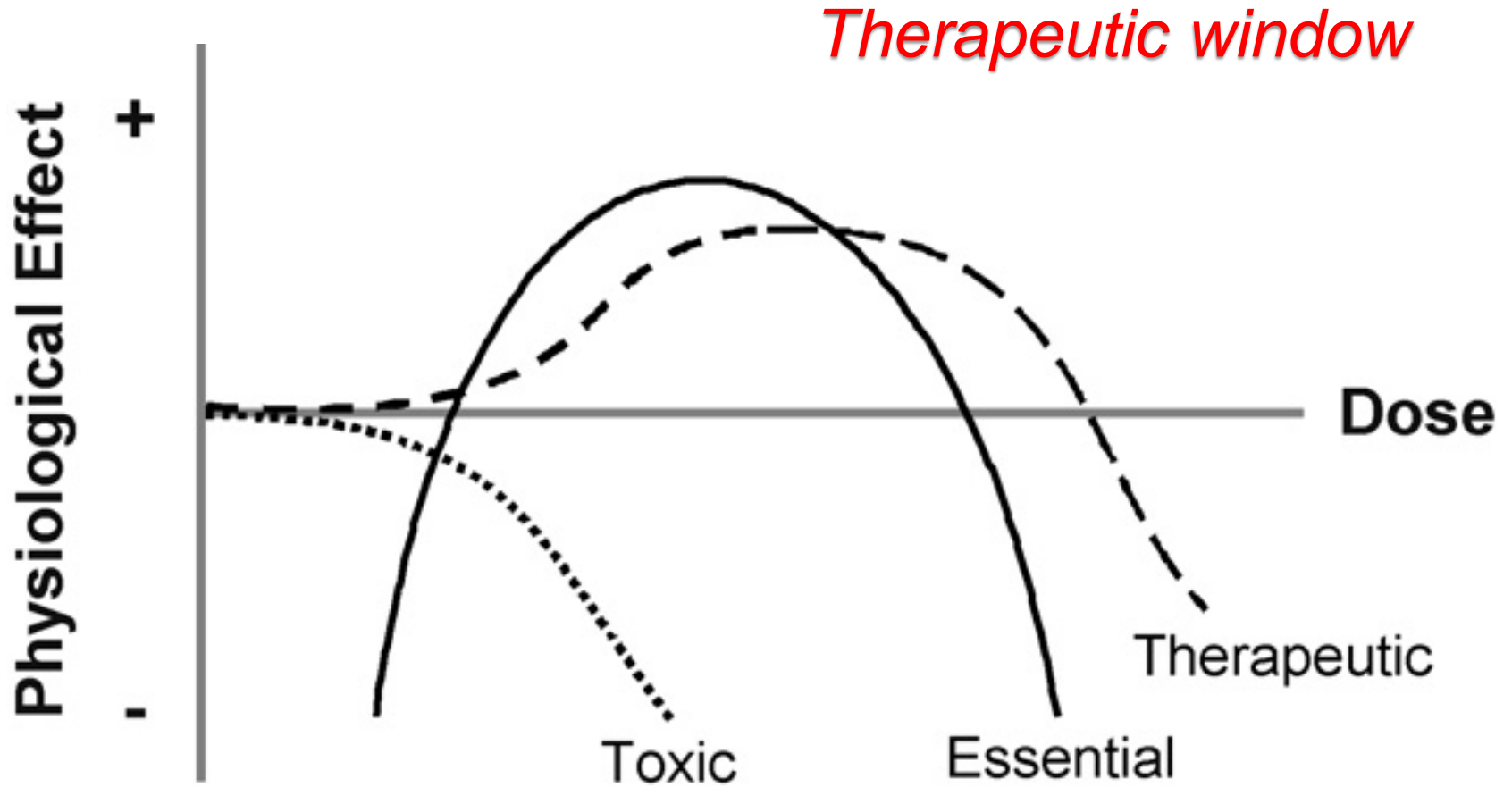


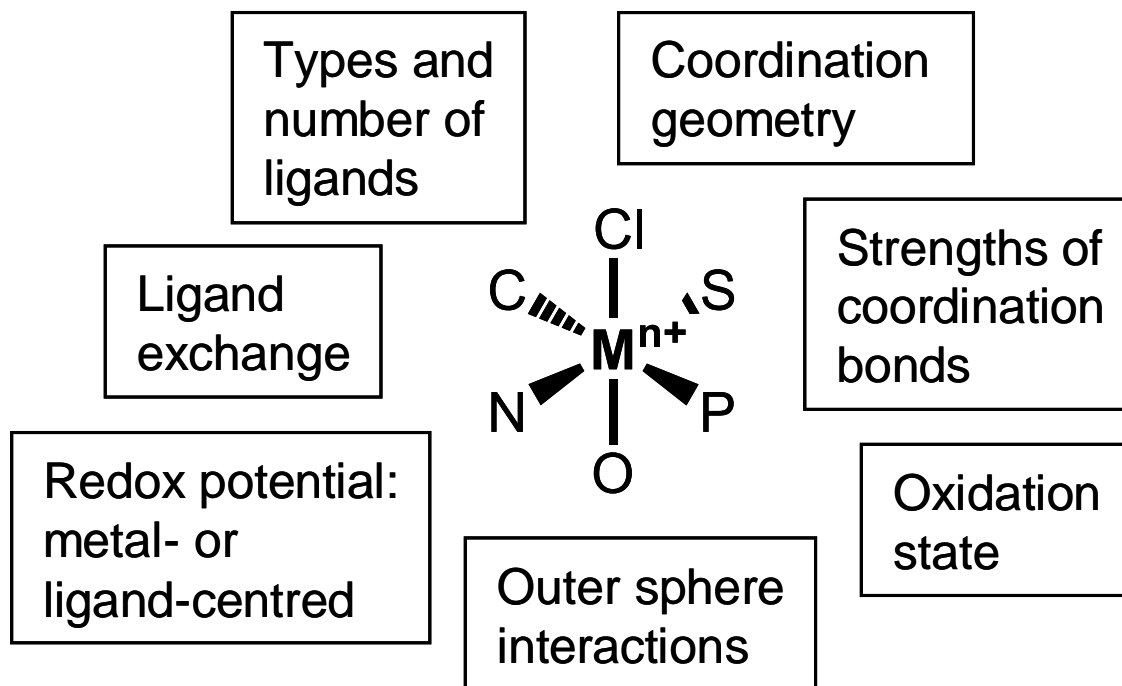
Diagramma di Bertrand



Genome
Proteome
Metallome

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

Speciazione



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), $ArNH_2$, $[NO_2]^-$, $[SO_3]^{2-}$

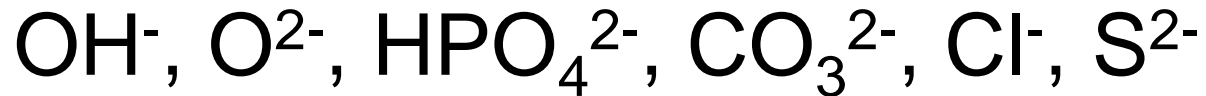
HSAB Principle

Metal centres (Lewis acids)

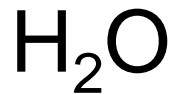
Hard; class (a)	Li^+ , Na^+ , K^+ , Rb^+ , Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+} , Sn^{2+} , Mn^{2+} , Zn^{2+} , Al^{3+} , Ga^{3+} , In^{3+} , Sc^{3+} , Cr^{3+} , Fe^{3+} , Co^{3+} , Y^{3+} , Th^{4+} , Pu^{4+} , Ti^{4+} , Zr^{4+} , $[\text{VO}]^{2+}$, $[\text{VO}_2]^+$
Soft; class (b)	Zero oxidation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

Biological ligands

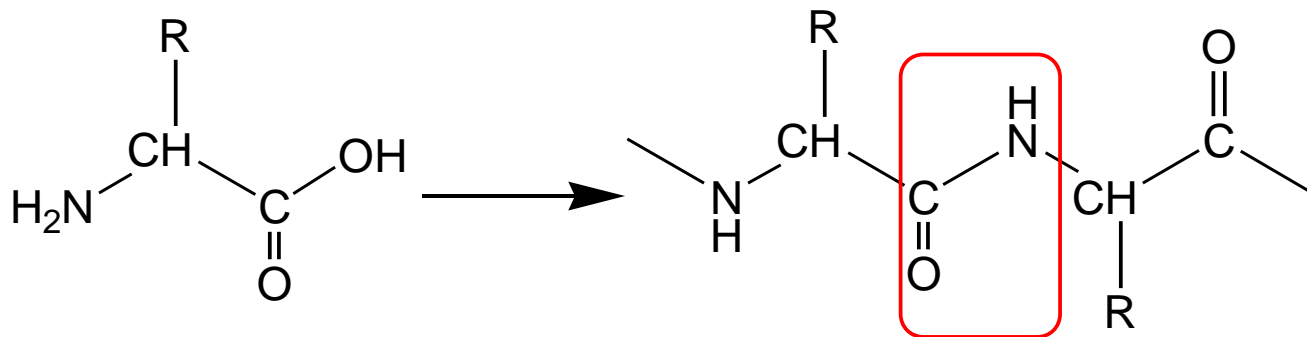
Anions



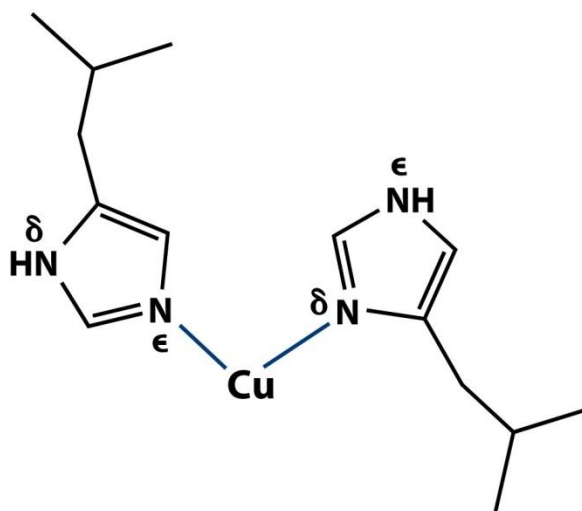
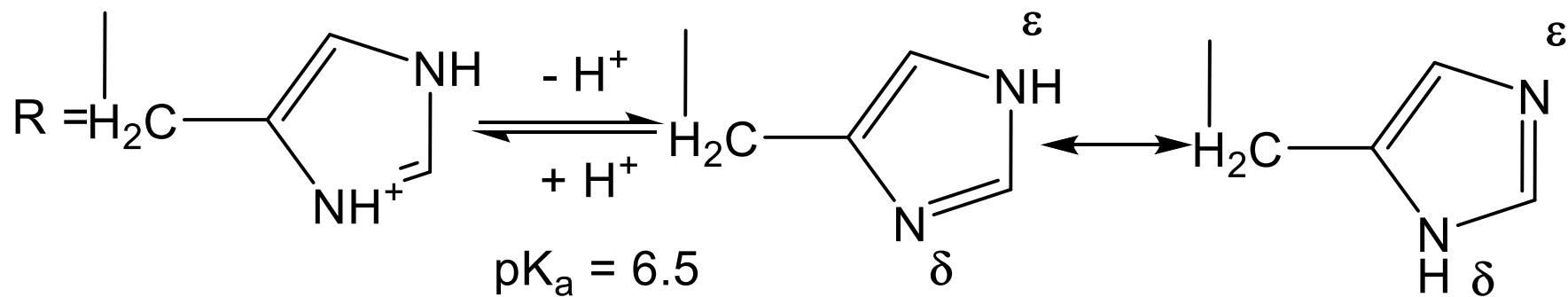
Water



Aminoacid side-chains



Histidine

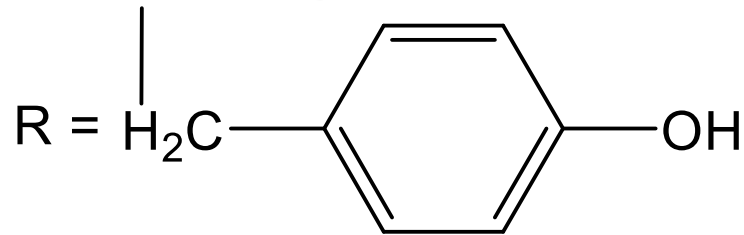


Cysteine and Methionine



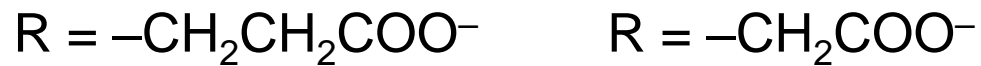
$$\text{pK}_a = 8.5$$

Tyrosine



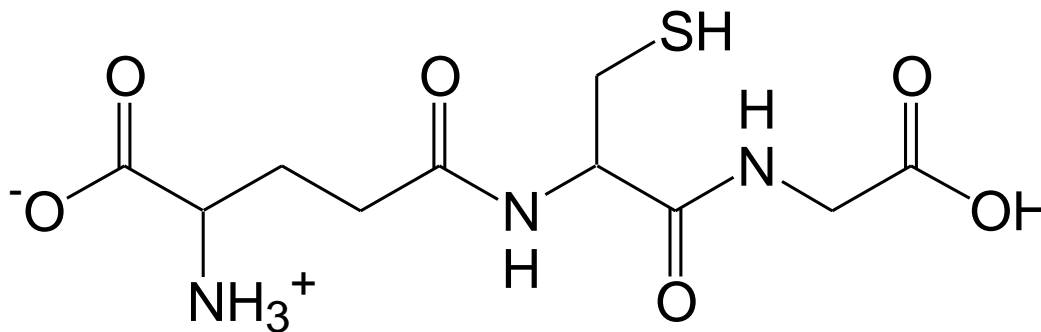
$$\text{pK}_a = 10$$

Glutamate and Aspartate



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

GLUTATHIONE

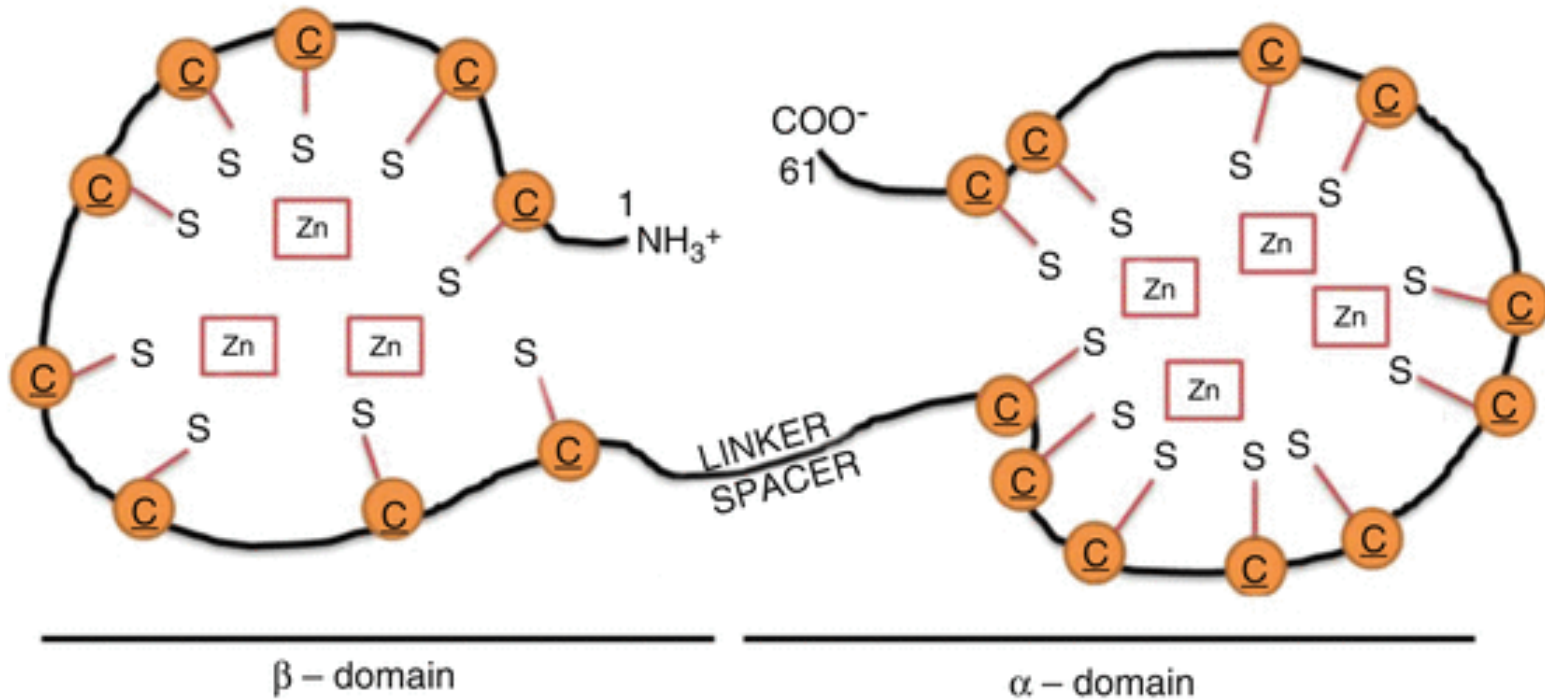


GSH

Glu-Cys-Gly

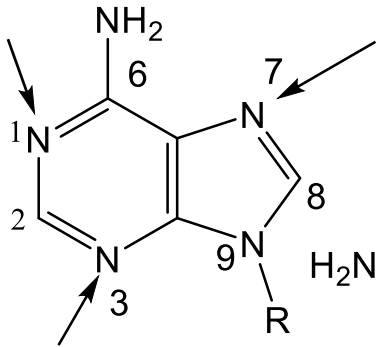
0.5 – 10 mM intracellular

Metallotioneine

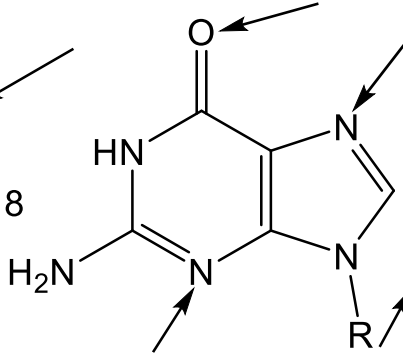


6 kDa,
ca. 60 a.a.
fino 30% cys

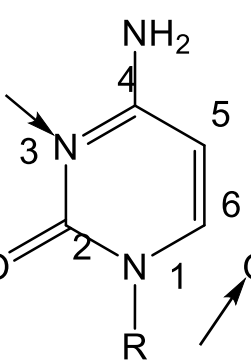
Nucleobasi



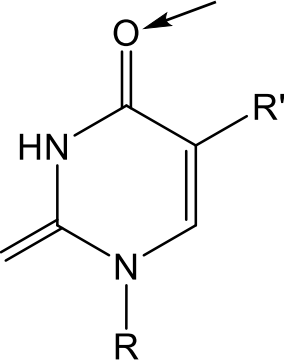
Adenine



Guanine

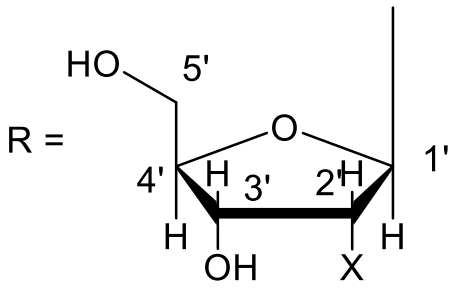


Cytosine



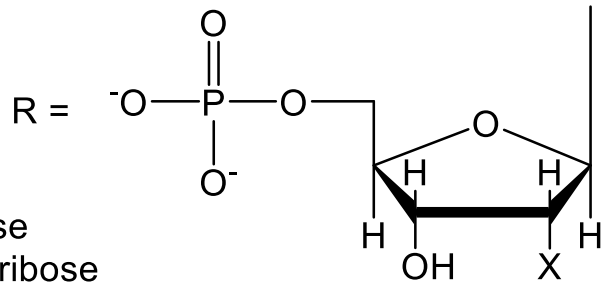
R' = H = Uracil
R' = CH₃ = Thymine

R = H **Nucleobase**

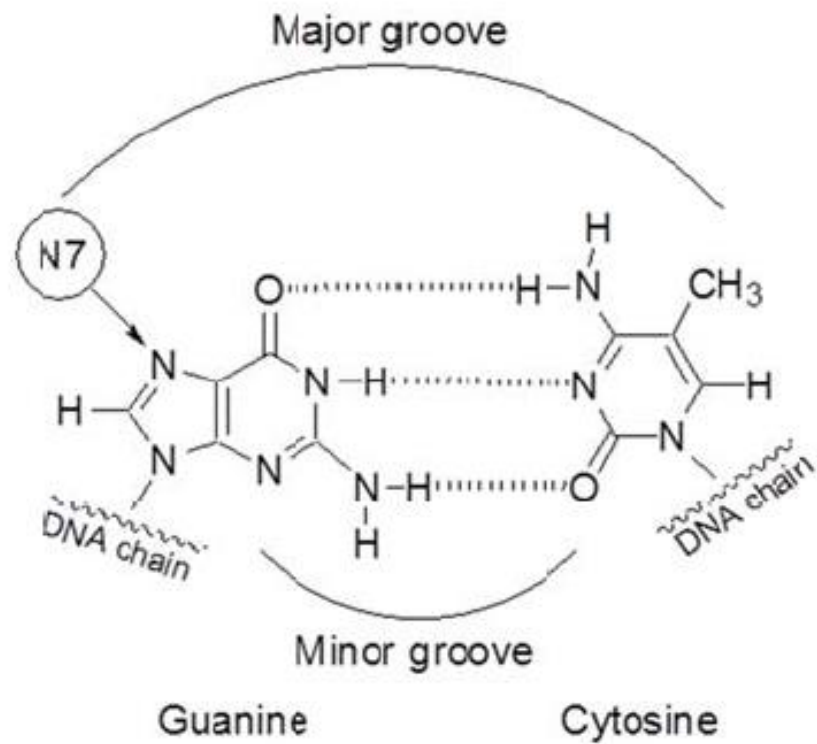
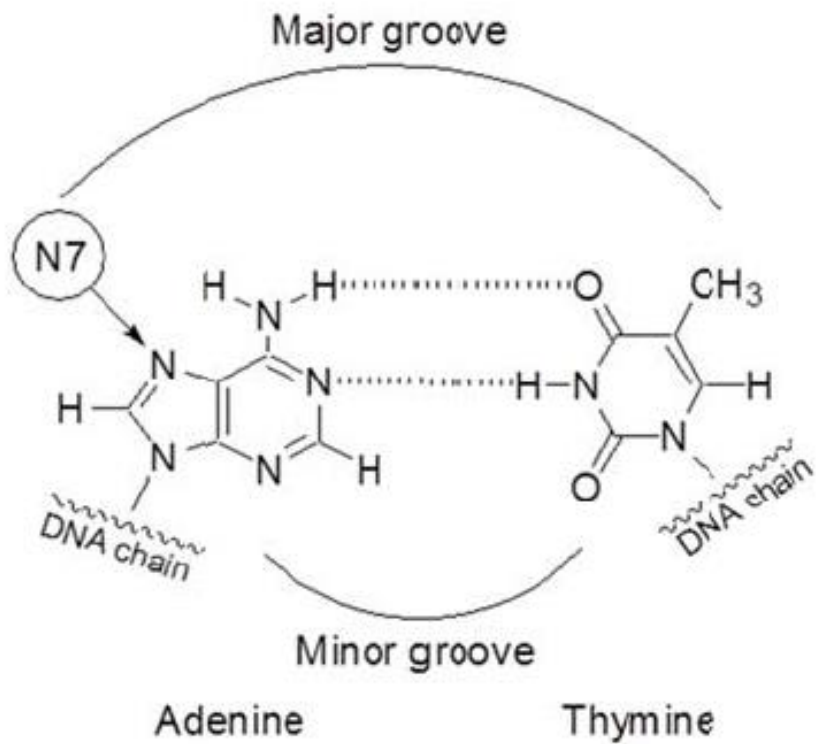


Nucleoside

X = OH ribose
X = H deoxyribose



Nucleotide



Endogenous reducing agents

Electron transfer enzymes

Ascorbic acid: 11–79 μM in the blood

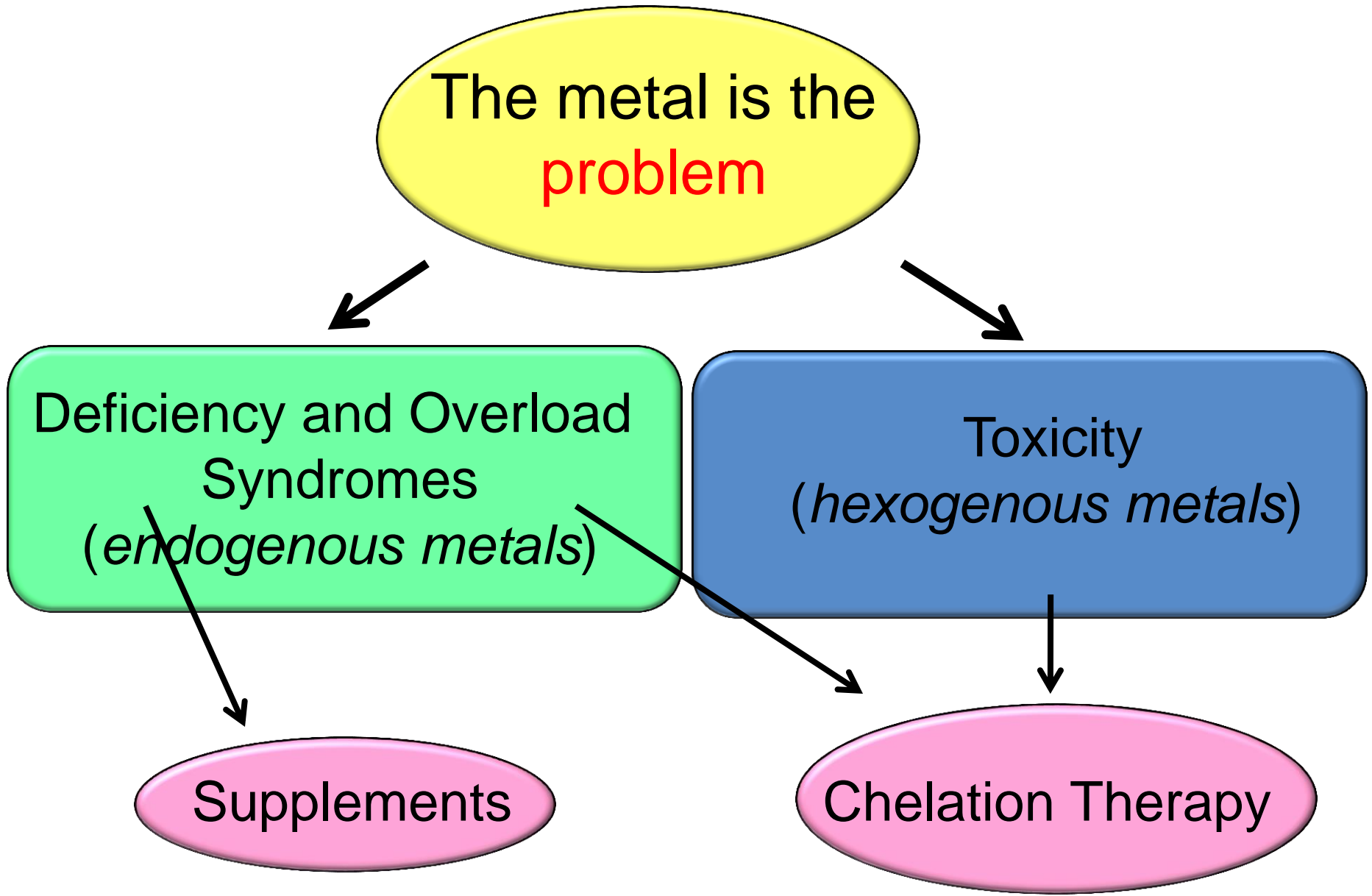
Glutathione: 0.5 – 10 mM intracellular

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

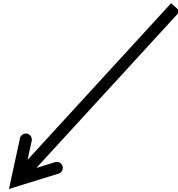
Deficiency and Overload
Syndromes
(*endogenous metals*)

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

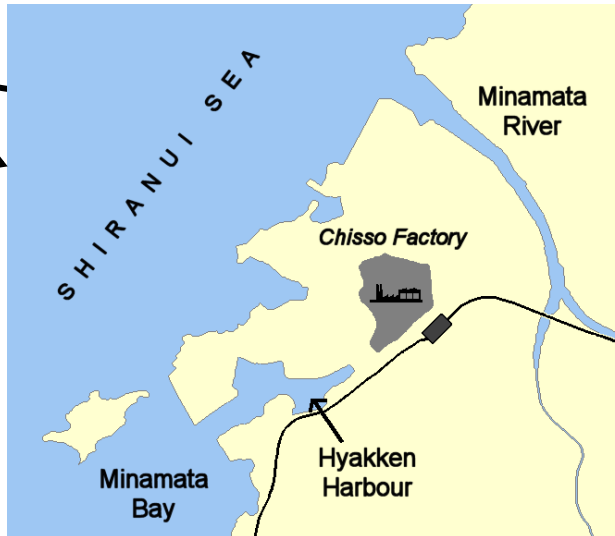
As

Minamata Disease

Hg

Be

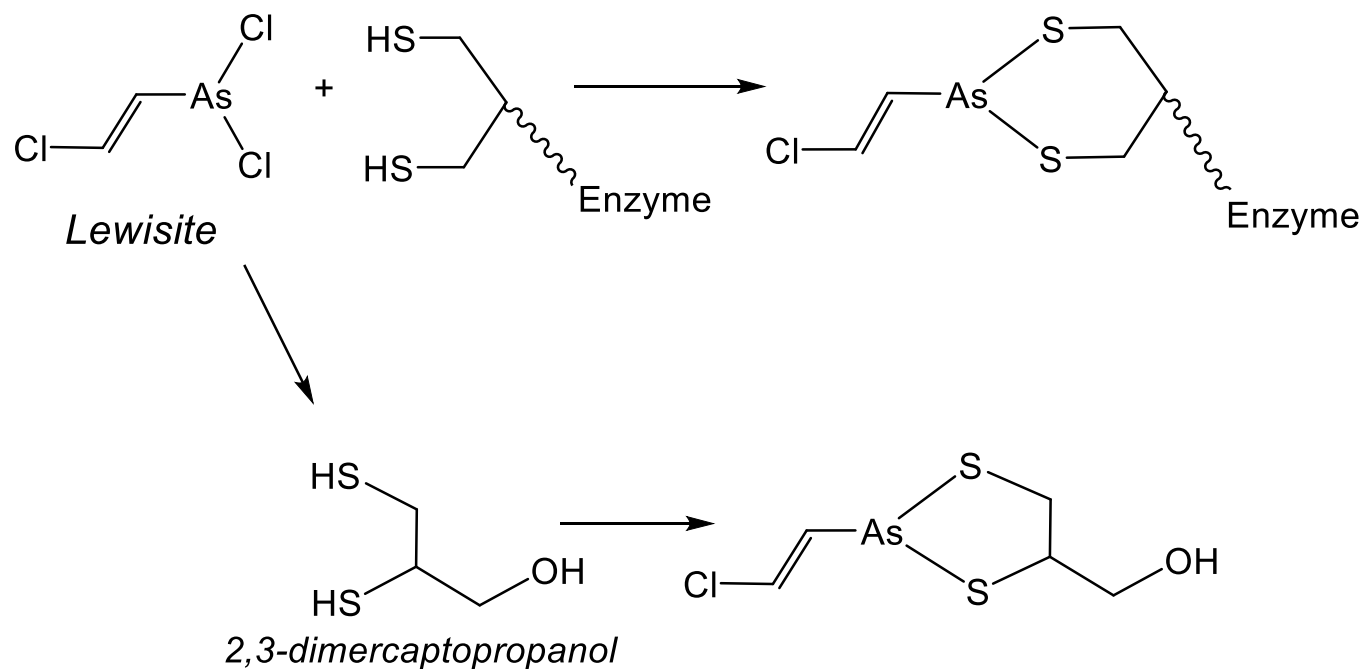
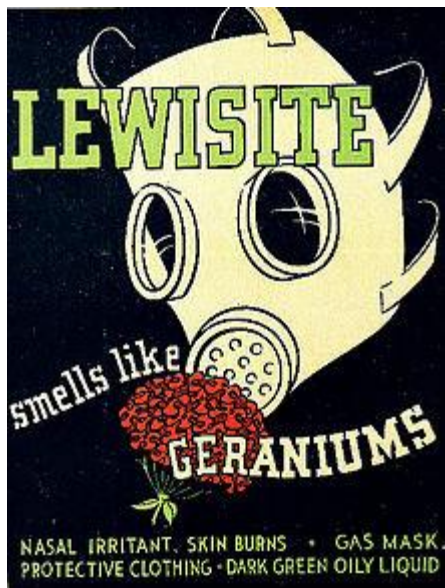
Cr



F

Se

Chelation Therapy

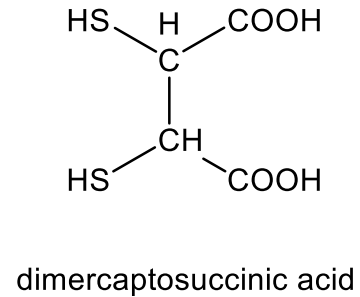
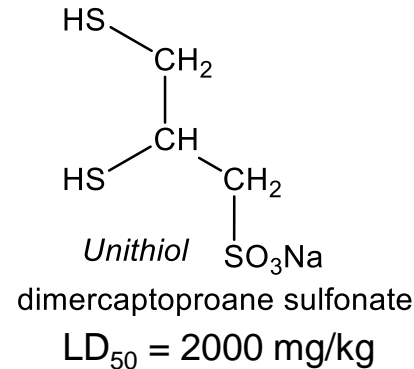
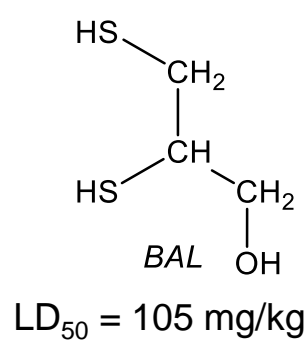


BAL = *British Anti-Lewisite*

Chelation Therapy

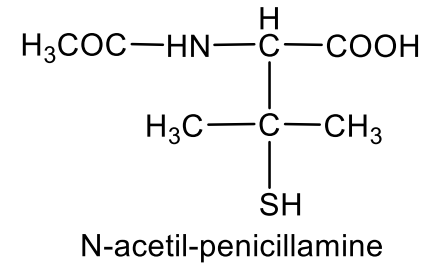
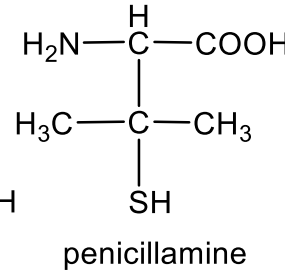
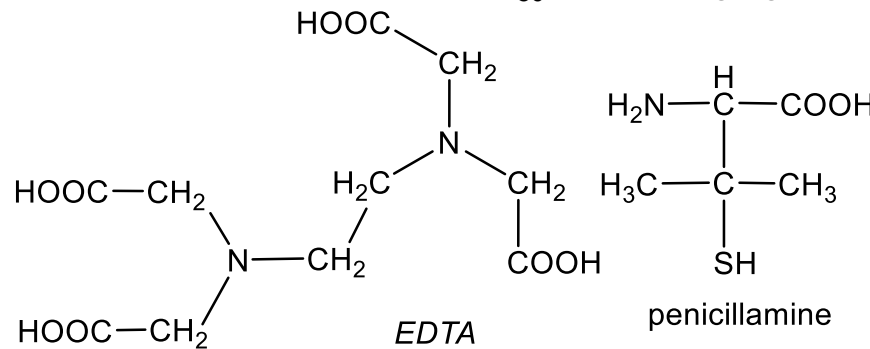
Agent:

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



Adducts:

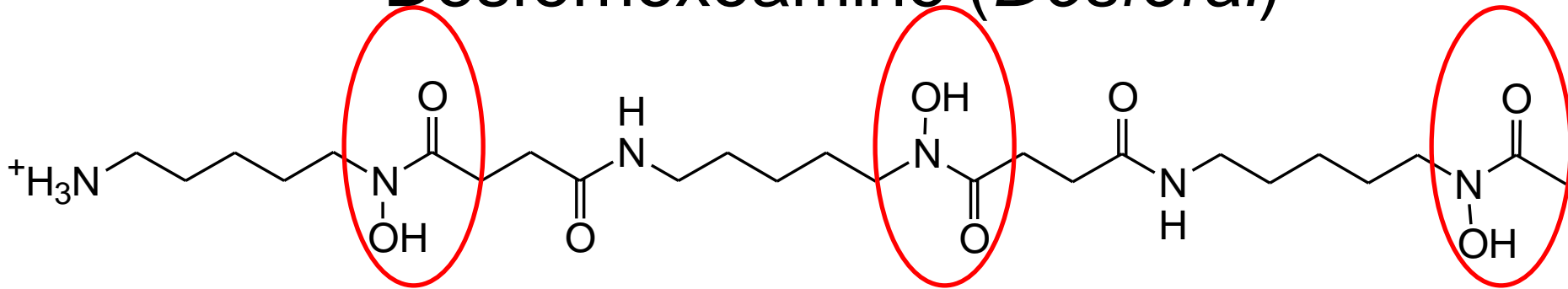
- Stable
- Non toxic
- Highly soluble in water (rapid clearance)
- Resistant to metabolism



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*)

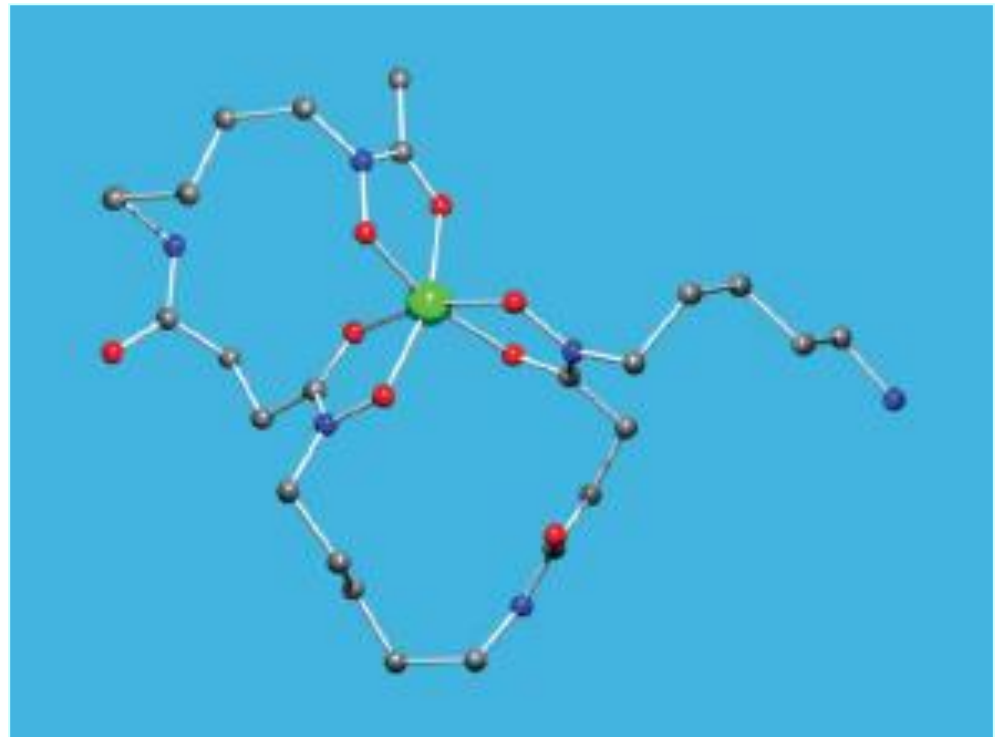
Natural siderophore from *Streptomyces pilosus*

FDA approval: 1968

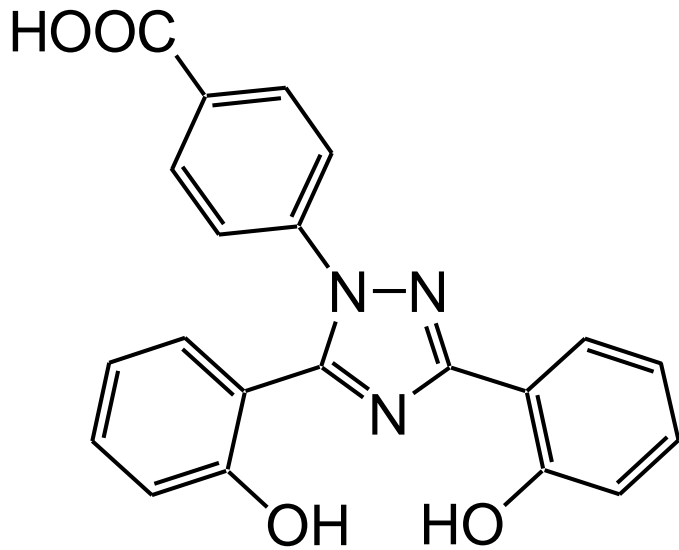
pFe = 26.6

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

Drawback: very long
infusion time: 8 – 12 h



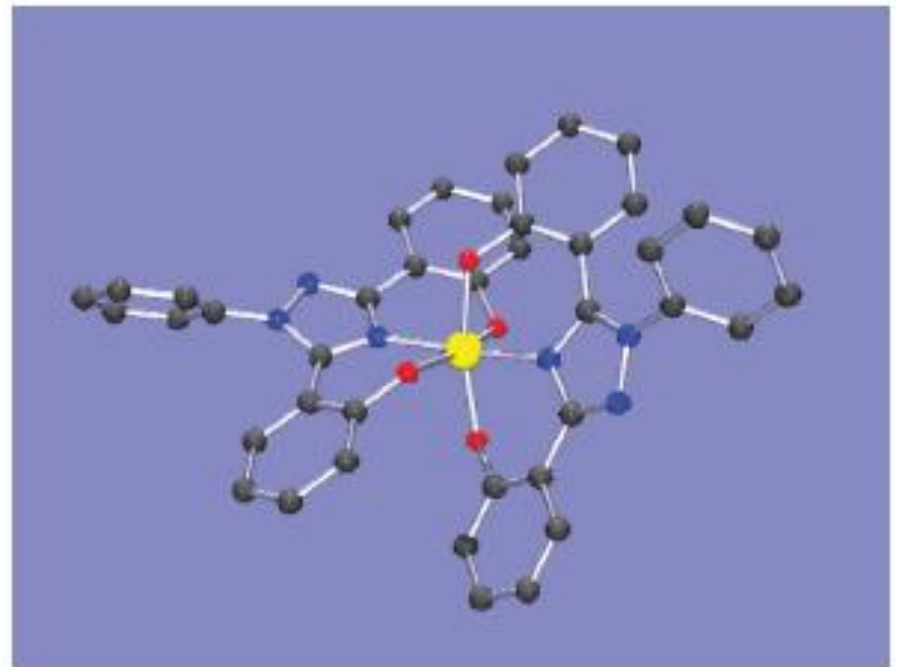
Deferasirox: Orally active



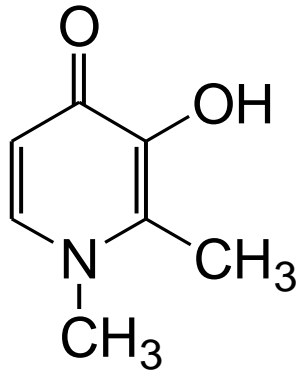
bis-hydroxyphenyl-triazole
deferasirox

pFe = 20

FDA approval: 2005



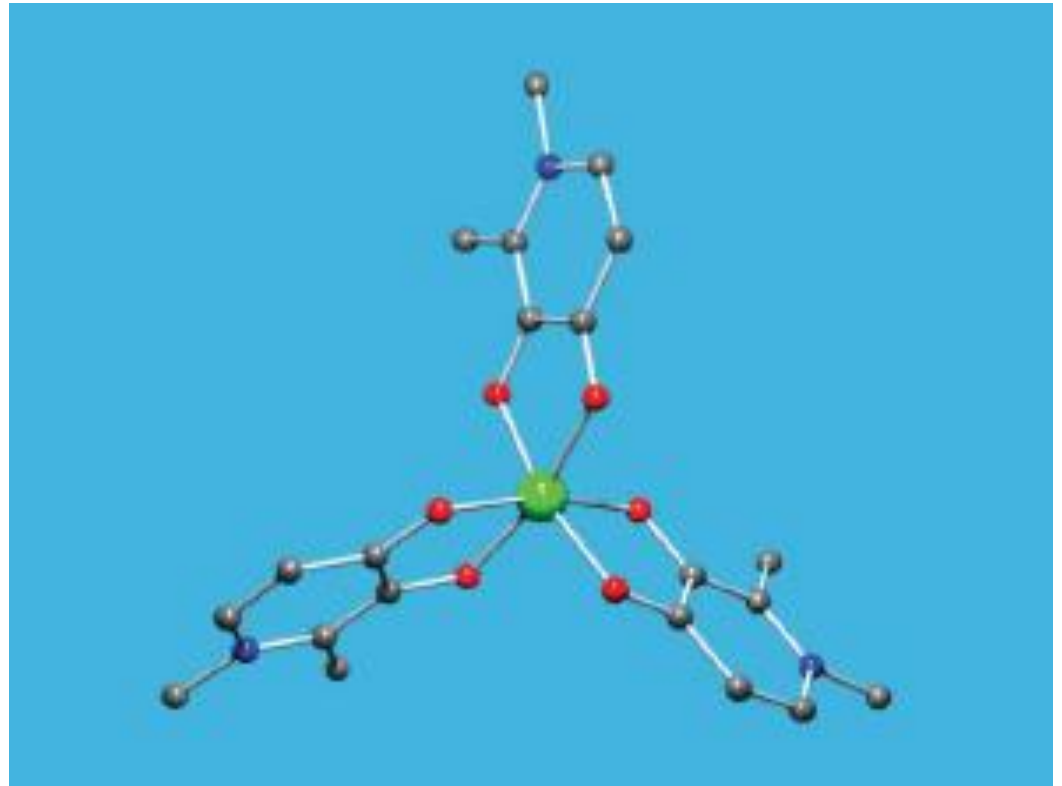
Deferiprone: Orally active

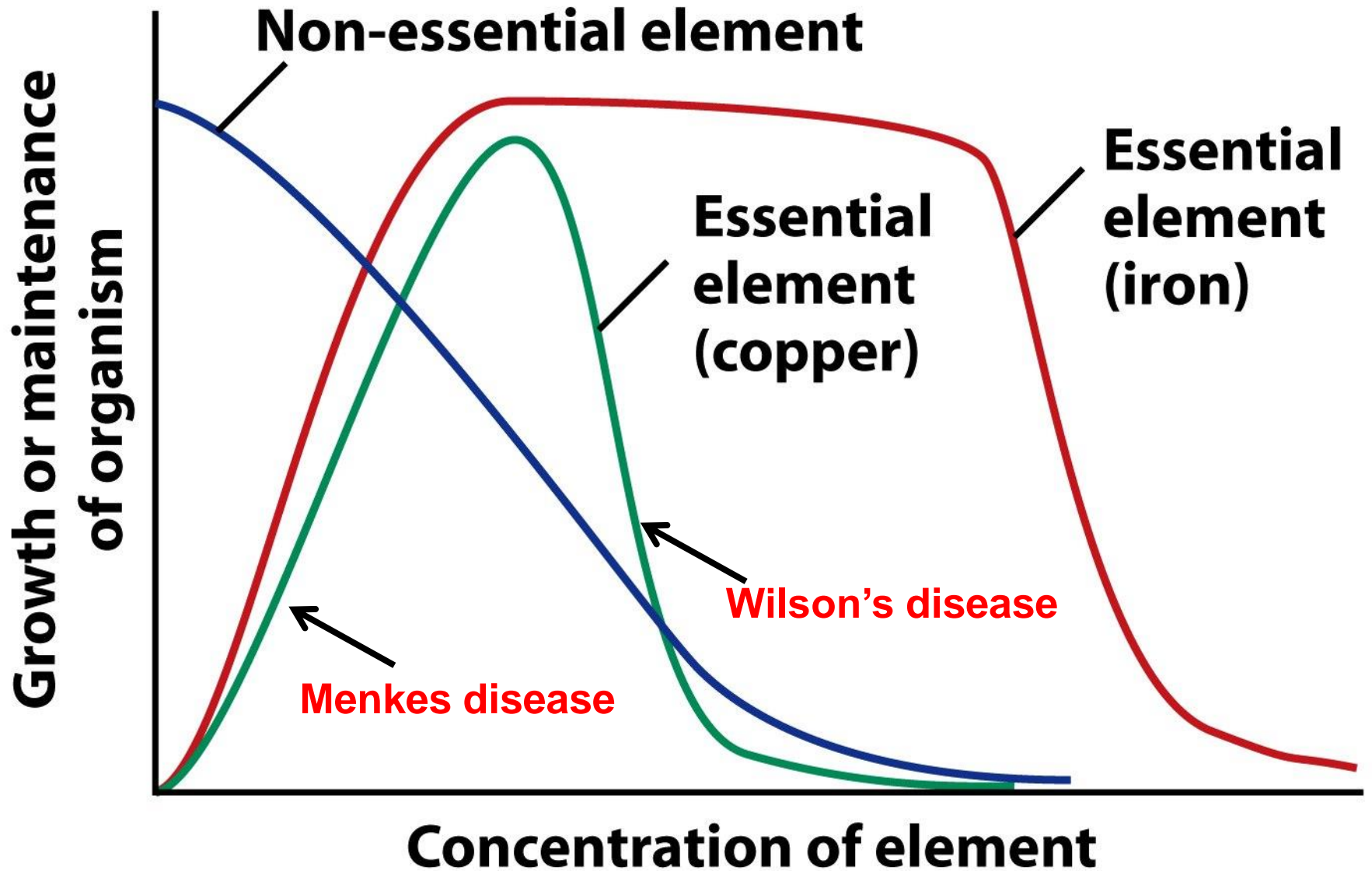


3,4-dihydroxypyridinone
deferiprone

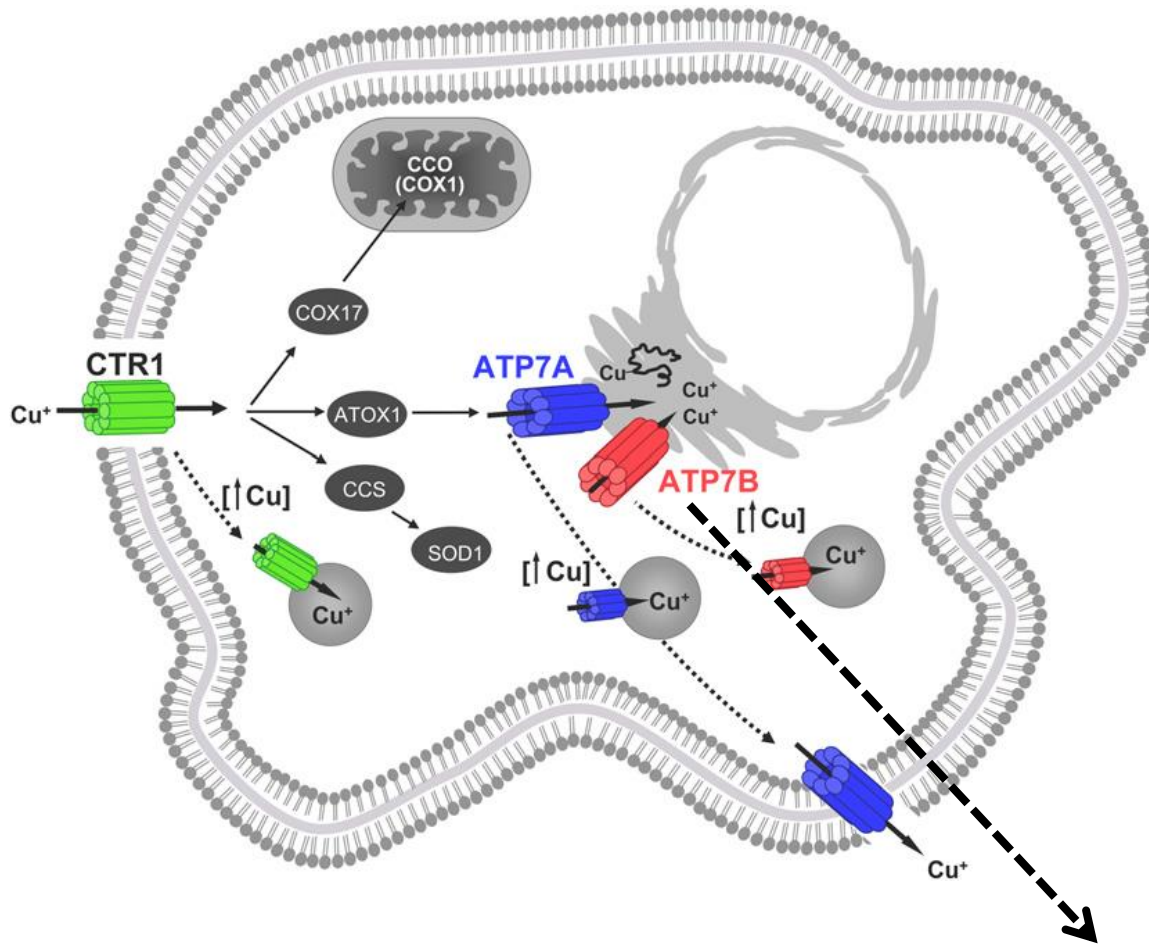
pFe = 20

2011 FDA approval as
second-line oral drug



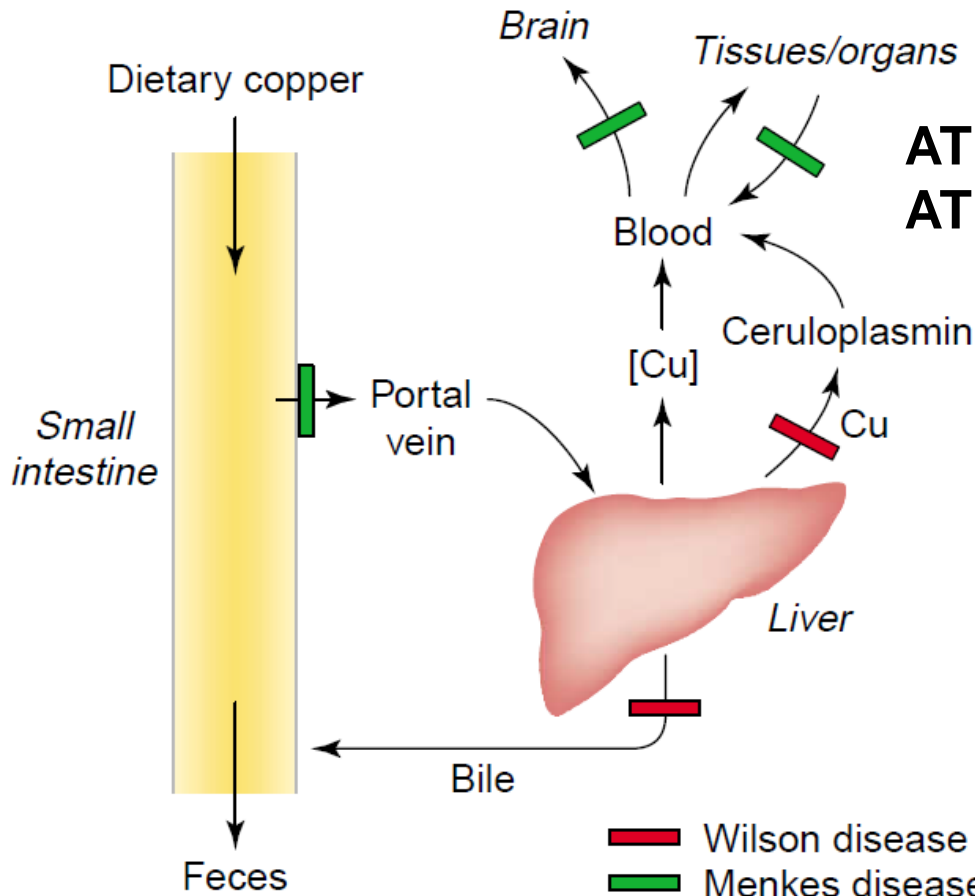


Copper homeostasis



ATP7A: ubiquitous

ATP7B: liver, kidneys, brain

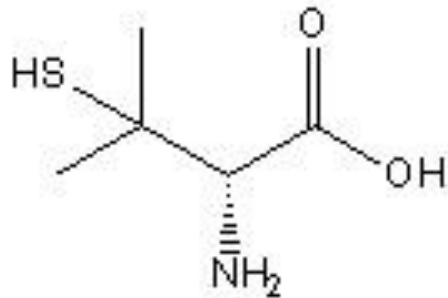


ATP7A: Menkes disease, Cu deficiency
ATP7B: Wilson's disease, Cu overload



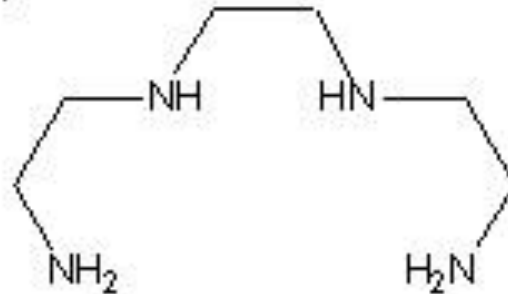
Chelanti per la Sindrome di Wilson (rimozione Cu)

a)



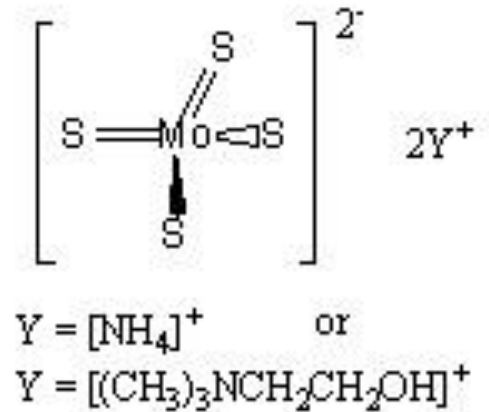
D-penicillamina

b)

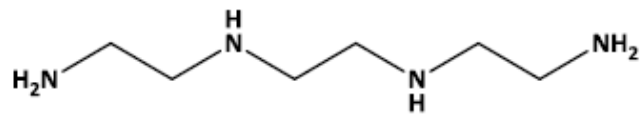


Trien (o *Trientina*)
(tris-etilenetetrammina)

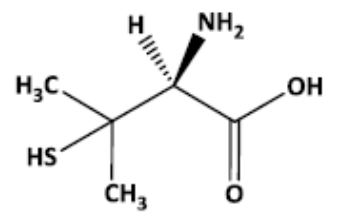
c)



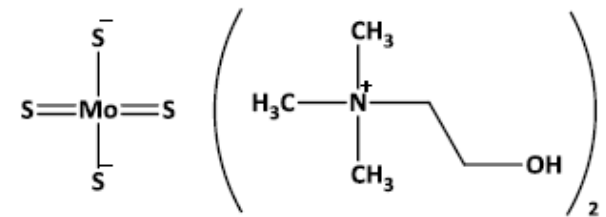
Tetratiomolibdato



a



b



c

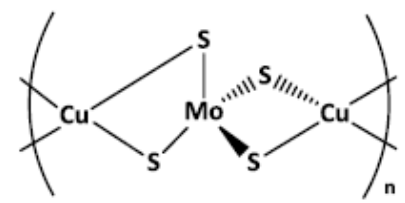
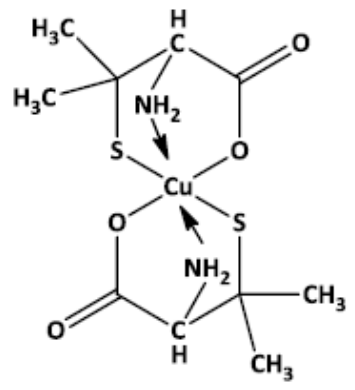
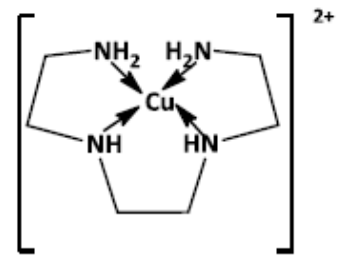


Table 2. Agents for the Treatment of Wilson Disease

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.