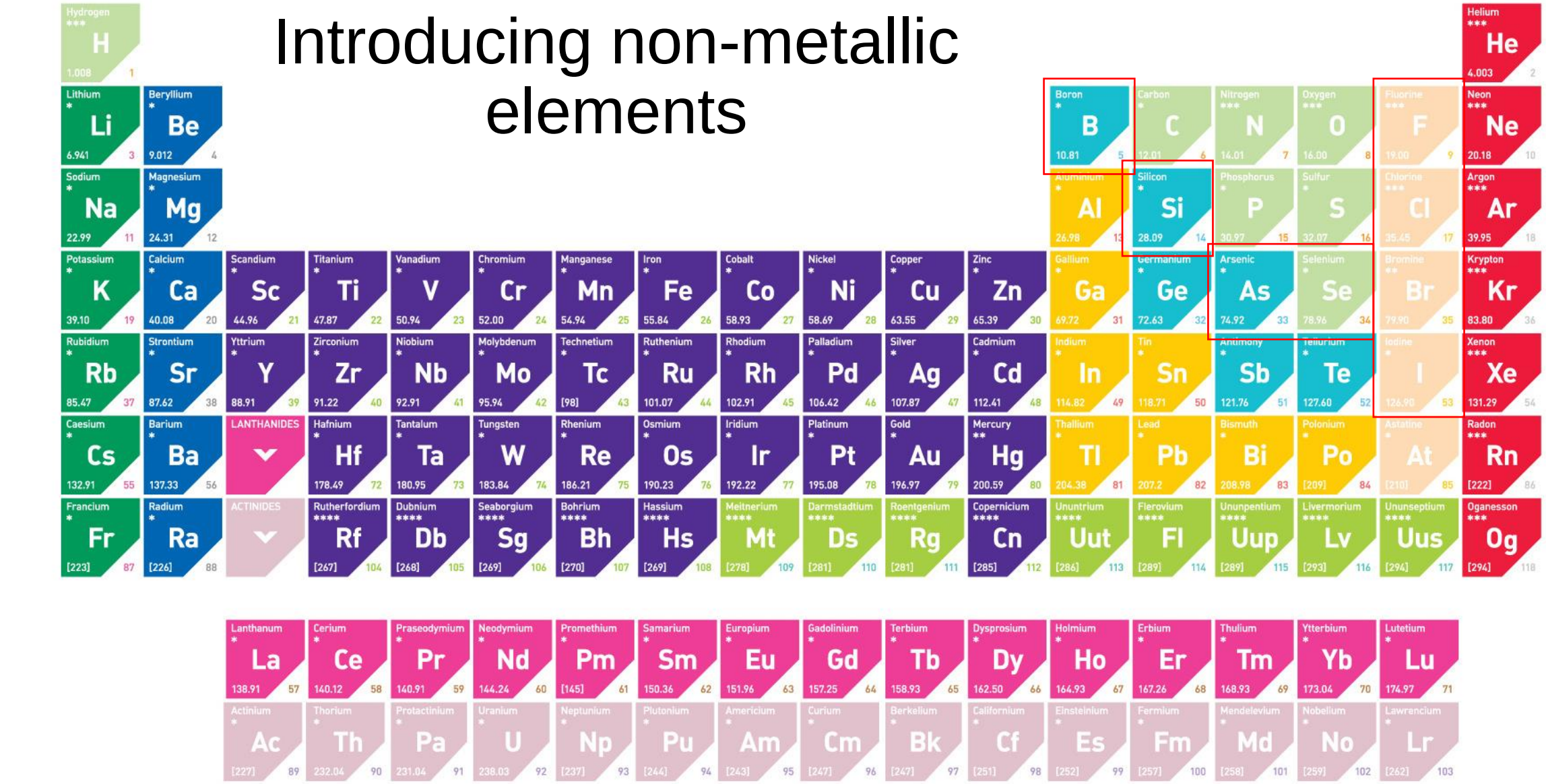
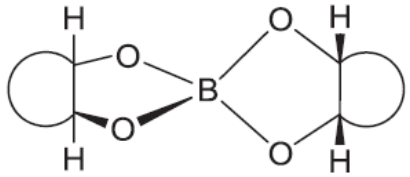
Introducing non-metallic elements



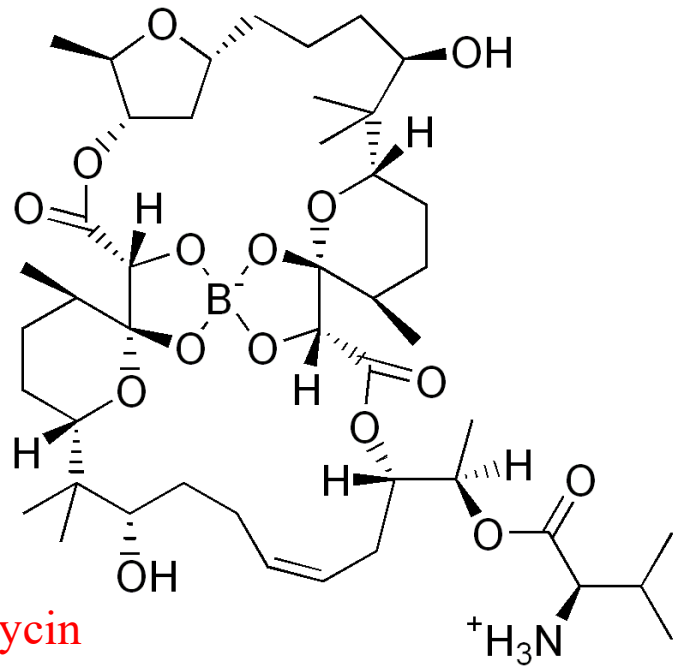
Boron

Role in the crosslinking of carbohydrates in cell membranes

Tendency to **form five-membered ring chelates** with deprotonated *cis*-hydroxy function.
Due to its relatively high concentration in sea water, boron has been found accumulated in some algae and sponges.



A boron-containing natural product, the antibiotic “boromycin”, was isolated in 1967, and borates seem to be essential for the normal growth and infection resistance of (domestic) plants, particularly of tobacco, beet and cabbage species.



Boromycin

Arsenic

Complete lack of arsenic can lead to disorders in the reproduction and growth of land-living animals, particularly with an impaired metabolism of the limiting amino acid methionine.

Arsenic in the soluble form, $As(OH)_3$, of arsenic(III) oxide, As_2O_3, is a **potent poison** and a **carcinogenic substance** for human beings

In **organic form**, especially (bio)methylated, **arsenic compounds are less toxic**

quite common in marine organisms -algae, fish and crustaceans (including lobster)-

Methylation by S-adenosyl methionine and methylcobalamin to give the following substances:

- $O{=}As(CH_3)_2R$, R = OH, CH_3, CH_2CH_2OH, 5'-deoxyribosyl and derivatives;
- $(CH_3)_3As^+–R$, R = 5'-deoxyribosyl and derivatives;
- $(CH_3)_3As^+–CH_2COO^-$ ("arsenobetaine").

Bromine

Bromides have been used as sedatives in the treatment of nervous disorders since the 19th century.

A **modification of the transmembrane ionic non-equilibrium state** is possible when introducing this heavier homologue of chloride, but molecular details of Br effect on ion channels or pumps are not yet known

Fluorine

Important cariostatic effect of trace amounts of fluorides

Hypothesis:

- more effective remineralization, a "hardening" of the tooth enamel surface (e.g. through formation of a particularly compact, acid-resistant crystalline layer under participation of fluoroapatite
- Inhibition of caries-promoting enzymes by fluoride, which dissolves from solid-state depots

Fluoride is used in trace amounts in toothpastes and other medical preparations for the prevention of dental caries. Fluoride-containing compounds are preferred for a better binding by the hydroxyapatite surface of teeth, such as: **monofluorophosphate $PO_3F_2^-$, SnF_2, AlF_3 and organoammonium fluorides**

Due to the importance of Ca^{2+} for so many biochemical processes, the marked insolubility of calcium fluoride, CaF_2 (p*Ksp* =10), renders **acute (→tissue necrosis) and chronic fluoride poisoning very serious**

Small therapeutic window!!

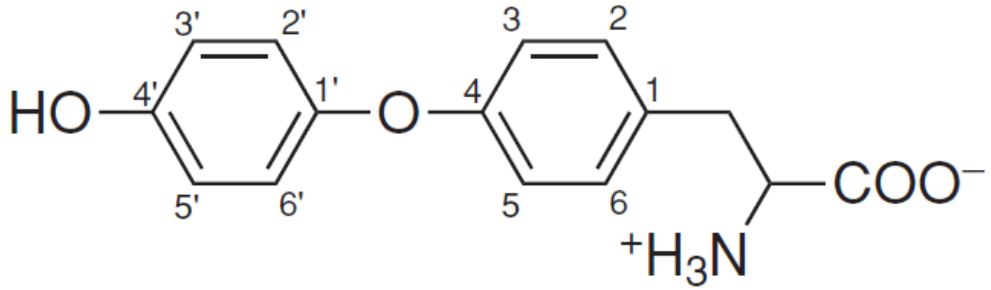
Iodine

The heaviest (and rarest) stable halogen, which was first isolated fror the ashes of marine algae by B. Courtois around 1811, was already recognized as an essential element for higher organisms by the middle of the 19th century

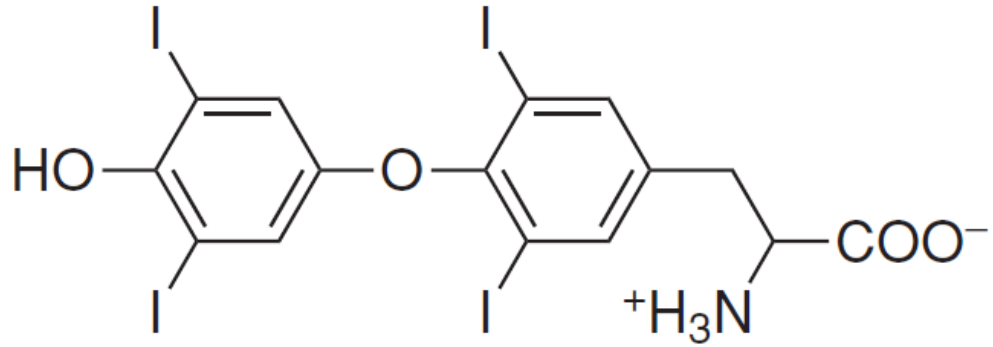
Extreme twofold (physiological *and* intramolecular) enrichment of iodine

Pronounced accumulation in the thyroid gland, where it is present in the form of *polyiodinated* small organic compounds

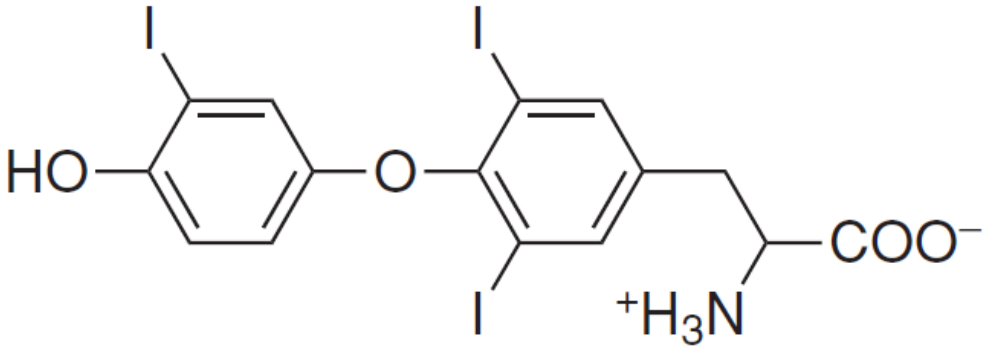
May have developed when organisms were still able to utilize the relatively abundant iodide from seawater



thyronine



thyroxine
(3,5,3',5'-tetraiodothyronine), T_4



3,5,3'-triodothyronine, T_3

Central role of thyroid hormones in the control of energy metabolism and associated processes.

Familiar physiological disorders occur as a result of reduced thyroid activity (ranging from relatively innocuous conditions such as “feeling cold” or tiredness to the severe deficits of congenital hypothyroidism in newborn infants) or hyperactivity (“feeling hot”, restlessness, nervousness).

Low thyroid activity due to iodine deficiency may be compensated for by excessive growth of the organ (goiter, struma)

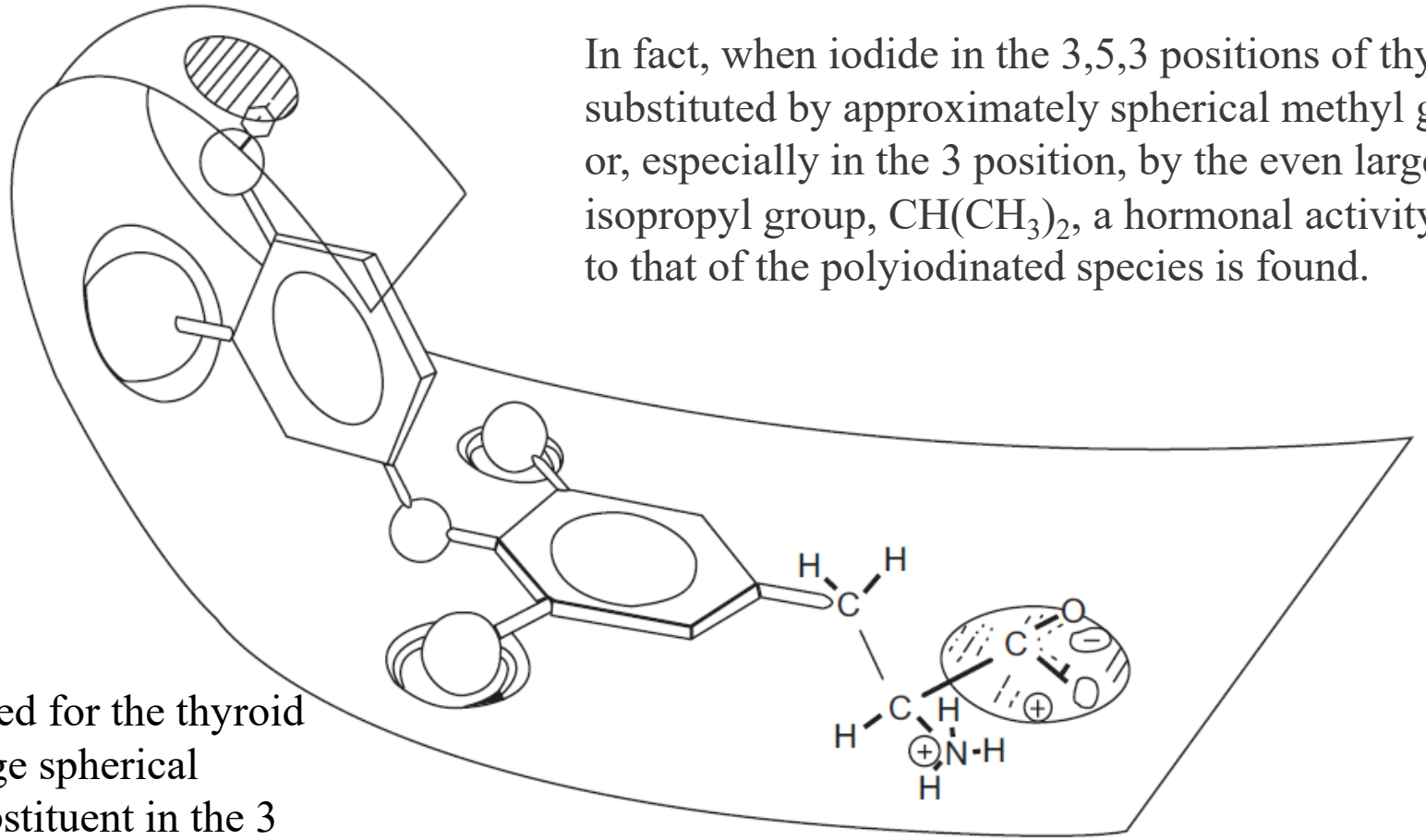
Tumors of the thyroid can be successfully diagnosed and treated using the radioactive isotopes ^{131}I and ^{123}I

What is the function of iodine in the hormones?

In its carbonbound form, iodine is not redox-active at physiological potentials. Furthermore, metal ions are not significantly influenced by the compounds.

But bound iodide, as the heaviest stable halide, is an unusually large, spherical substituent; the ionic radius of I^- (about 220 ppm) is unmatched by other monovalent elemental ions.

In fact, when iodide in the 3,5,3 positions of thyronine is substituted by approximately spherical methyl groups, or, especially in the 3 position, by the even larger isopropyl group, $CH(CH_3)_2$, a hormonal activity similar to that of the polyiodinated species is found.

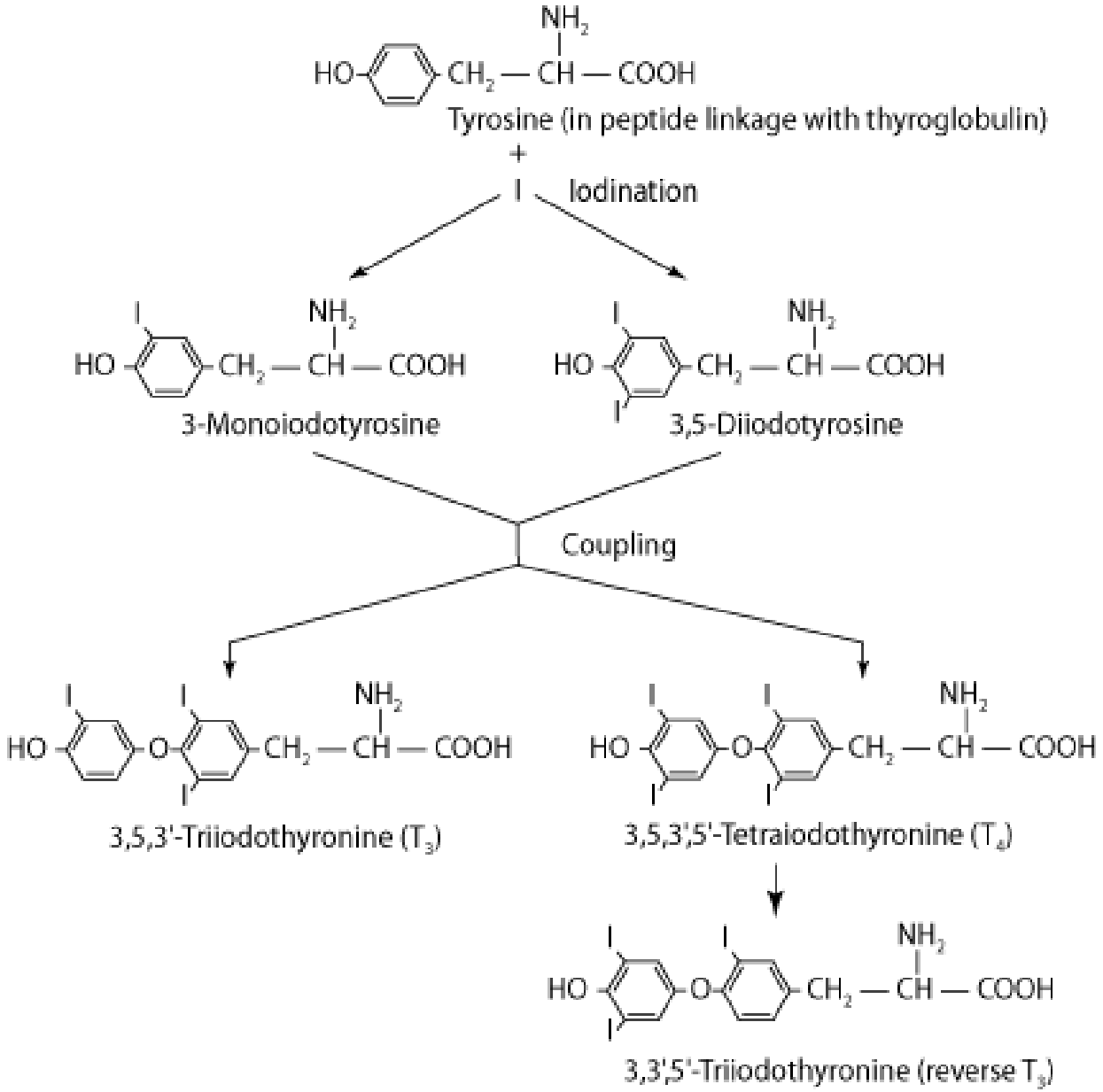


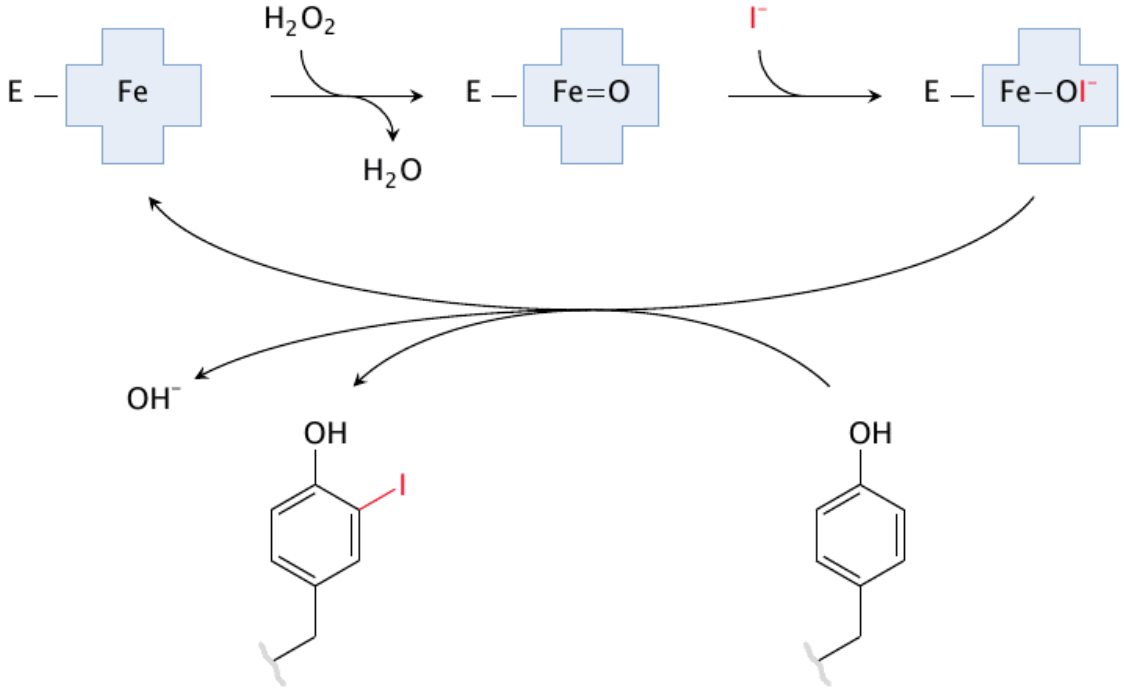
Scheme of a receptor structure assumed for the thyroid hormones, in which normally *one* large spherical "lock" cavity is preformed for the substituent in the 3 position of the hormone "key".

The iodination of thyronine

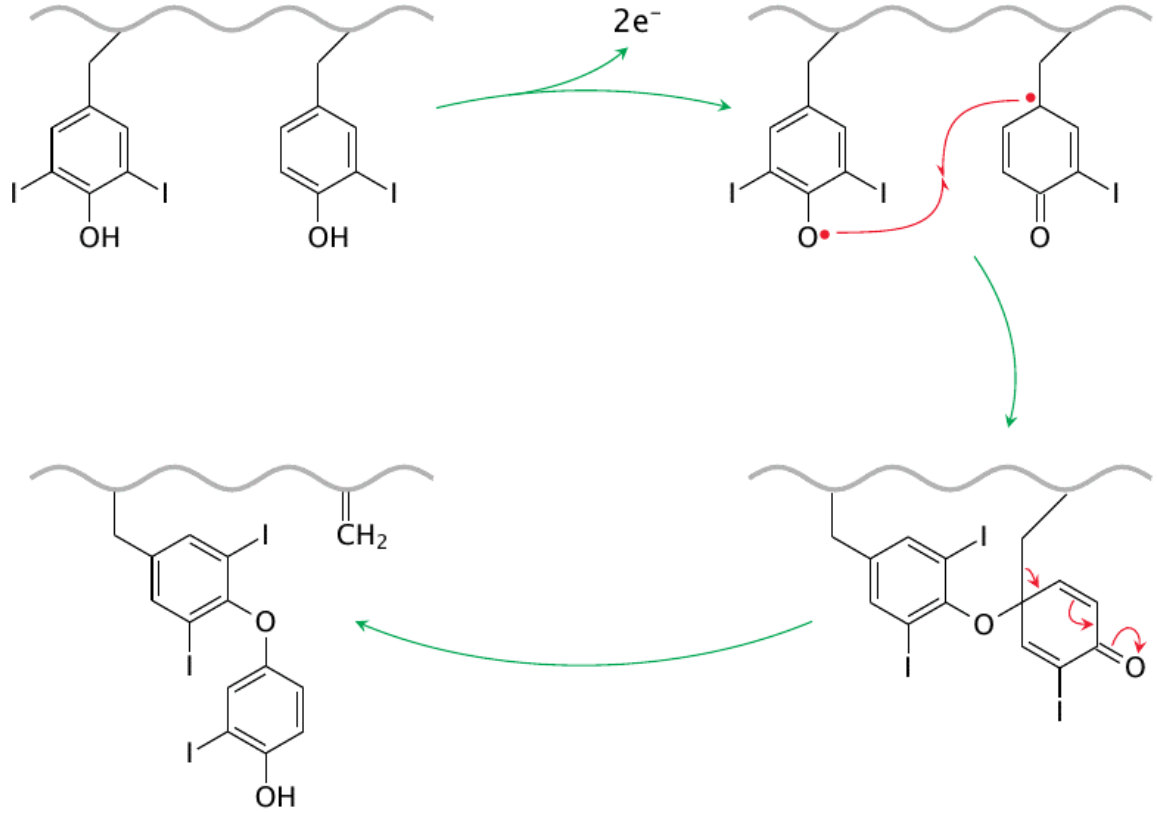
Thyroid hormones are derived from the **amino acid tyrosine** by an **electrophilic substitution** at the phenolic (i.e. electron-rich) aromatic nucleus.

Heme-containing **thyreoperoxidases** are mainly responsible for this reaction, and the 3,5-diiodotyrosine intermediates are oxidatively coupled.
The deiodination of T4 to give the primarily active T3 proceeds via a selenium-containing deiodinase.





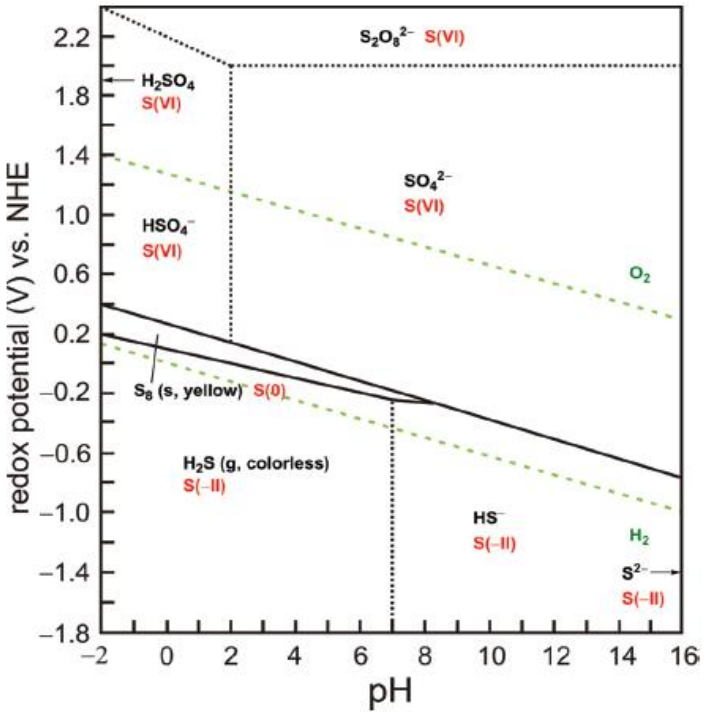
The **first step is the iodination of tyrosyl residues** in thyroglobulin. Thyroid peroxidase contains a heme moiety that generates hypoiodite from iodide and H_2O_2. The hypoiodite then reacts with the hydroxyphenyl side chain of tyrosine.



The **coupling reaction between two iodinated tyrosyl side chains is also catalyzed by thyroid peroxidase**. The enzyme abstracts an electron from each of the substrate side chains, which then undergo radical recombination. The reaction leaves a dehydroalanine residue in the protein backbone.

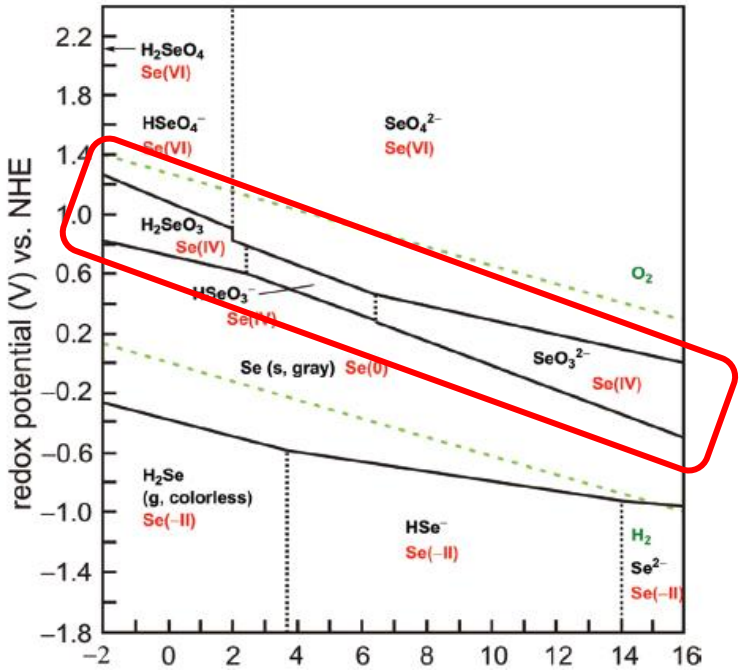
Selenium

As the heavier homologue of sulfur, selenium has recently become the most discussed **essential nonmetallic element** in biology and medicine



The chemistry of selenium qualitatively resembles that of sulfur
BUT

- The selenium analogues of thiols, the **selenols**, feature a **lower redox potential** and can thus be more easily oxidized.
- The **tetravalent state of selenous acid is thermodynamically stable**, in contrast to the metastable sulfites
- The **reactivity of selenium compounds is generally higher** than that of corresponding sulfur analogues, due to longer bonds from Se to coordinated atoms.



Like fluorine, the trace element selenium features a rather **small therapeutic window**: deficiency symptoms (daily dose < 50 mg) / poison effects (>500 mg)

The **high toxicity of selenium compounds** shows characteristic symptoms:

loss of hair and the **excretion** of evil-smelling **dimethylselenium**, $(CH_3)_2Se$, through the breath or skin.

Dimethylselenium is formed via biomethylation and has a garlic-like odor, which is noticeable even in the smallest of concentrations!

Disorders of the central nervous system and characteristic degenerations of keratinous (i.e. disulfide-bridge-containing) tissue such as hairs and hooves have been observed for grazing animals which feed on particularly selenium-rich soil in Central Asia and in parts of the western USA, while.

Selenium – like many other elements – has previously been described as carcinogenic.

Selenium deficiency symptoms can occur on extremely selenium-poor soil, especially for livestock with its specialized diet; muscular degeneration ("white muscle disease") in young animals and reproductive disorders have been observed

Very similar symptoms have been found in the form of the "**Keshan**" disease of adolescent humans, a fatal **weakness of the heart muscle** that occurs in regions of China with very selenium-deficient soil.

Selenium deficiency in mammals can also lead to **liver necroses** and an **increased susceptibility for liver cancer**. The absence of peroxide-destroying selenium enzymes in the eye lens may be connected with the **occurrence of oxidatively induced glaucoma**.

In view of the **antioxidative function of selenium-containing enzymes**, some epidemiological correlations for humans between the availability of selenium in drinking water and the abundance of breast or colon cancers have been noted.

The most abundant selenium-containing compound found in organisms is **selenocysteine**.
The biosynthesis of this "21st proteinogenic amino acid" involves a selenophosphate intermediate.

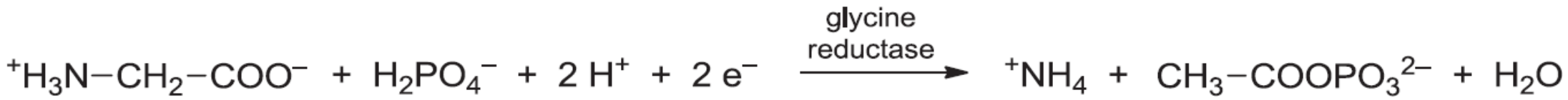
Its coding is unusual, as the codon UGA used in its transcription was once only known as a "stop" or "nonsense" command.

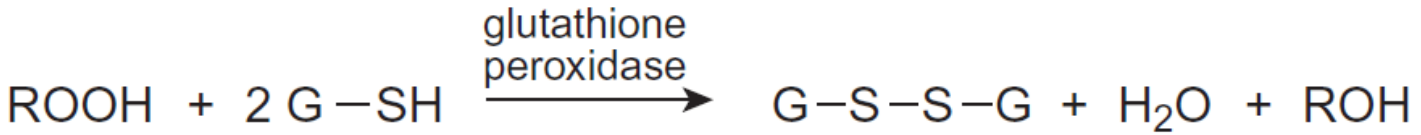
The integration of selenocysteine into proteins is different from that of other amino acids.
It is assumed that the **UGA codon is multifunctional** and can thus induce different responses according to the physiological requirements (flexible genetic code).

Flexibility may be part of a regulatory mechanism in view of the varying supply and demand of selenium.

In the known selenium-containing proteins, selenocysteine appears only once in each polypeptide chain: **Bacters**: formate, xanthine and nicotinic acid dehydrogenases, Ni/Fe/Se hydrogenase and glycine reductase

Mammals: iodothyronine deiodinase and glutathione peroxidase.





G—SH: glutathione, γ-Glu-Cys-Gly

The potentially membrane-damaging lipid hydroperoxide intermediates, ROOH, that can be formed during incomplete O_2 conversion are consumed by a very rapid oxidation of glutathione, G-SH, to the disulfide G-S-S-G. Together with the tripeptide glutathione, this **Se-containing peroxidase enzyme thus functions as an antioxidant**

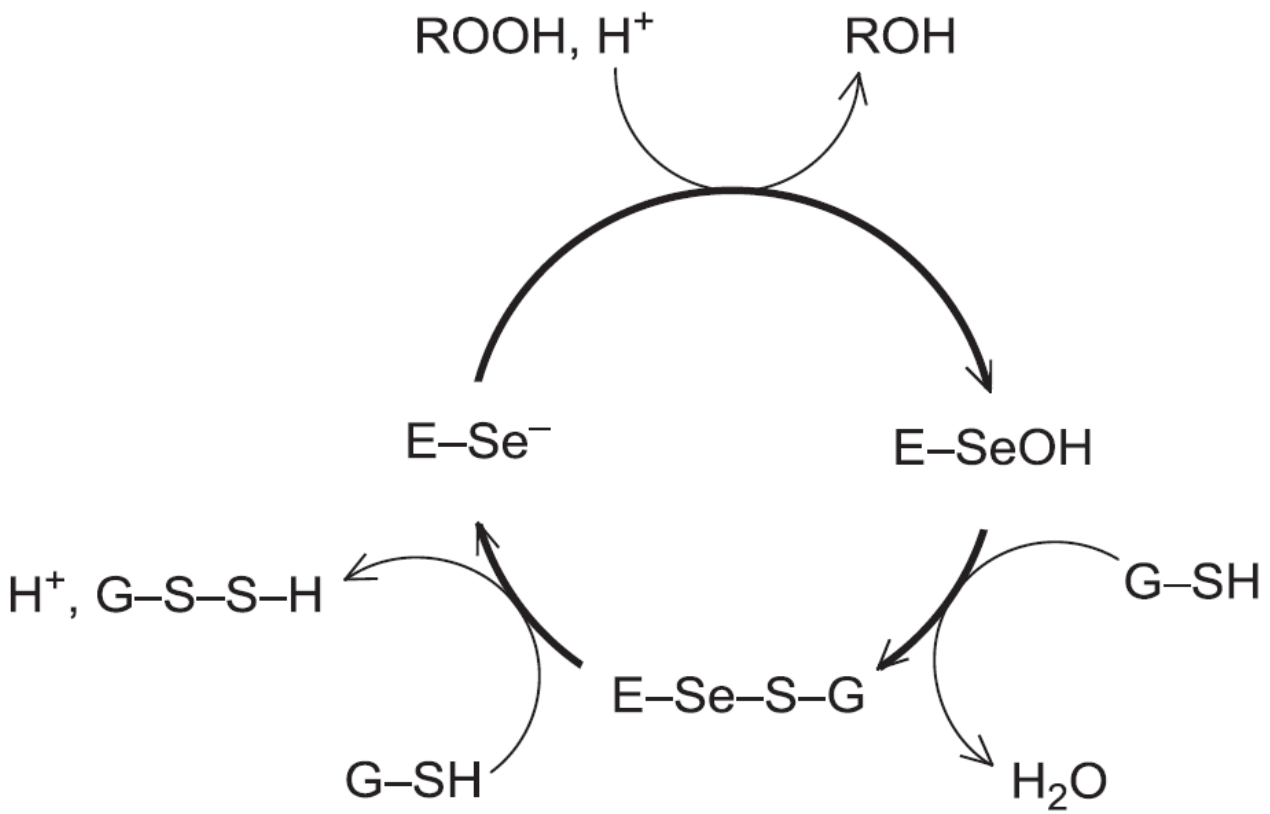
The glutathione peroxidases are tetrameric proteins with subunits of 21 kDa each.

These selenoproteins were first isolated from erythrocytes, which are cells with high “oxidative stress”.

The molecular mechanism of lipid hydroperoxide reaction with selenium-containing glutathione peroxidase is assumed to involve the ionized (i.e. the selenolate) form, RSe^-, of selenocysteine at pH 7.

The degradation of ROOH proceeds very rapidly (nearly diffusion-controlled), thereby justifying the biological use of the otherwise problematic trace element selenium.

A primary oxygen abstraction may lead to the state of selenenic acid, RSeOH.



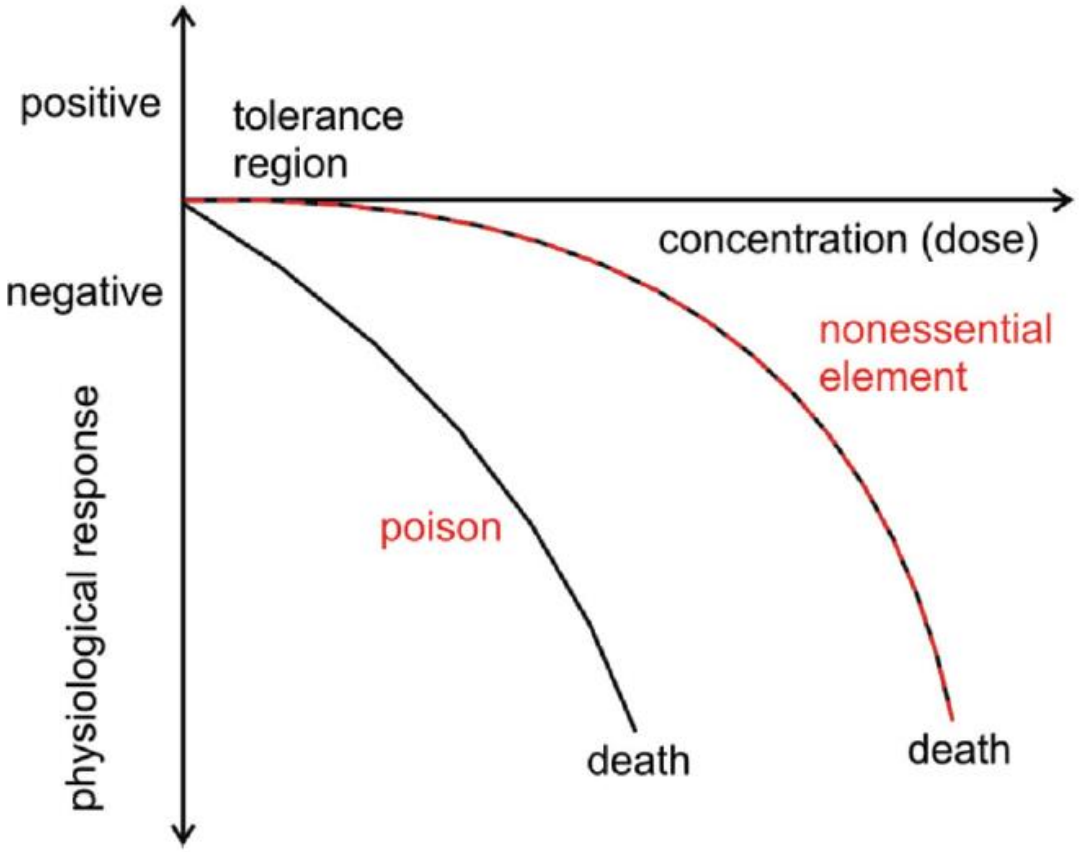
E: Enzym

Quintessentially Toxic Metals

With regard to toxicity, two other, nonbioessential groups of inorganic elements can be distinguished:

- those which have not (yet) been recognized as relevant for life due to low abundance or bioavailability (e.g. insolubility at pH 7)
- those for which exclusively negative effects have been found to date

Among the latter group are the **“soft”, thiophilic heavy metals mercury, thallium, cadmium and lead**.



Dose-effect response diagram

Detoxification strategies

- **Enzymatic transformations** can occur from toxic to less toxic states
  ($Hg^{2+} \rightarrow Hg^{0}$; $As(OH)_3 \rightarrow HAsO_4^{2-}$ or $[AsR_4]^{+}$);
  or to volatile compounds which can be released into the environment
  ($SeO_3^{2-} \rightarrow Me_2Se$).

- **Special membranes** can hinder the passing of highly charged ions into particularly endangered regions such as brain, fetus or cell nucleus.

- **Ion pumps** can remove undesired substances such as AsO_4^{3-} from particularly endangered cellular regions.

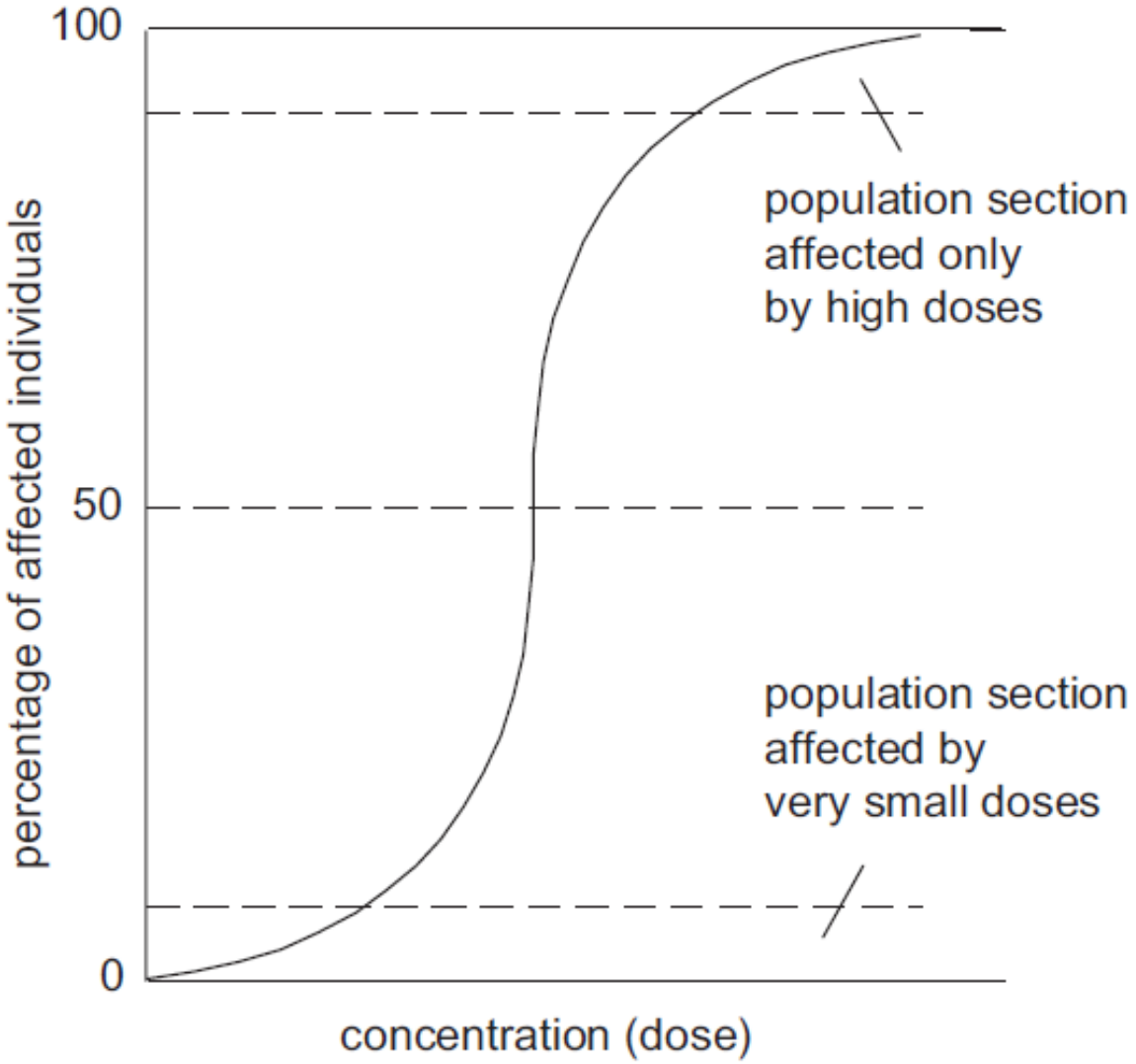
- One can render them less harmful through **complexation or precipitation** with a suitable partner
  (e.g. $Cd^{2+} + S^{2-} \rightarrow CdS\downarrow$).

- **High-molecular-weight compounds such as metallothionein** proteins can bind toxic ions up to a certain storage capacity and thus remove them from circulation.

Legal standards

Based on a ***political assessment***;
they can sometimes be exceeded even in natural soil and often do not take into consideration the chemical form of the element (speciation).

The reaction of a population to varying concentrations of a substance is not uniform but shows a typical S-shape for the idealized case of only quantitative differences; statistical relations of this kind form the basis for the LD_{50} values (lethal dose for 50% of the population) used in toxicological evaluations.



Within a population of more complex organisms, and certainly in comparisons between different species, there may also be qualitative differences in the reaction towards “toxic elements”.

Principali contaminanti	Unità di misura	Acque potabili (D. lgs. 31/01)	Acque minerali (Decreto 542/92 e Decreto 31/05/ 2001)
Antimonio	µg/L	5,0	-
Arsenico (As totale)	µg/L	10	50
Bario	mg/L	-	1
Boro (come B)	mg/L	1,0	5,0
Cadmio	µg/L	5,0	3
Cianuro	µg/L	50	10
Cromo (Cr^{III} + Cr^{VI})	µg/L	50	50
Piombo	µg/L	10 - 25	10
Mercurio	µg/L	1,0	1
Nichel	µg/L	20	-
Rame	µg/L	1000	1000
Selenio	µg/L	10	10
Vanadio	µg/L	50	-
Zinco	µg/L	-	-
Ammonio (come NH_4)	mg/L	0,50	-
Alluminio	µg/L	200	-
Ferro	µg/L	200	-
Manganese	µg/L	50	2000
Fluoruro	mg/L	1,50	-

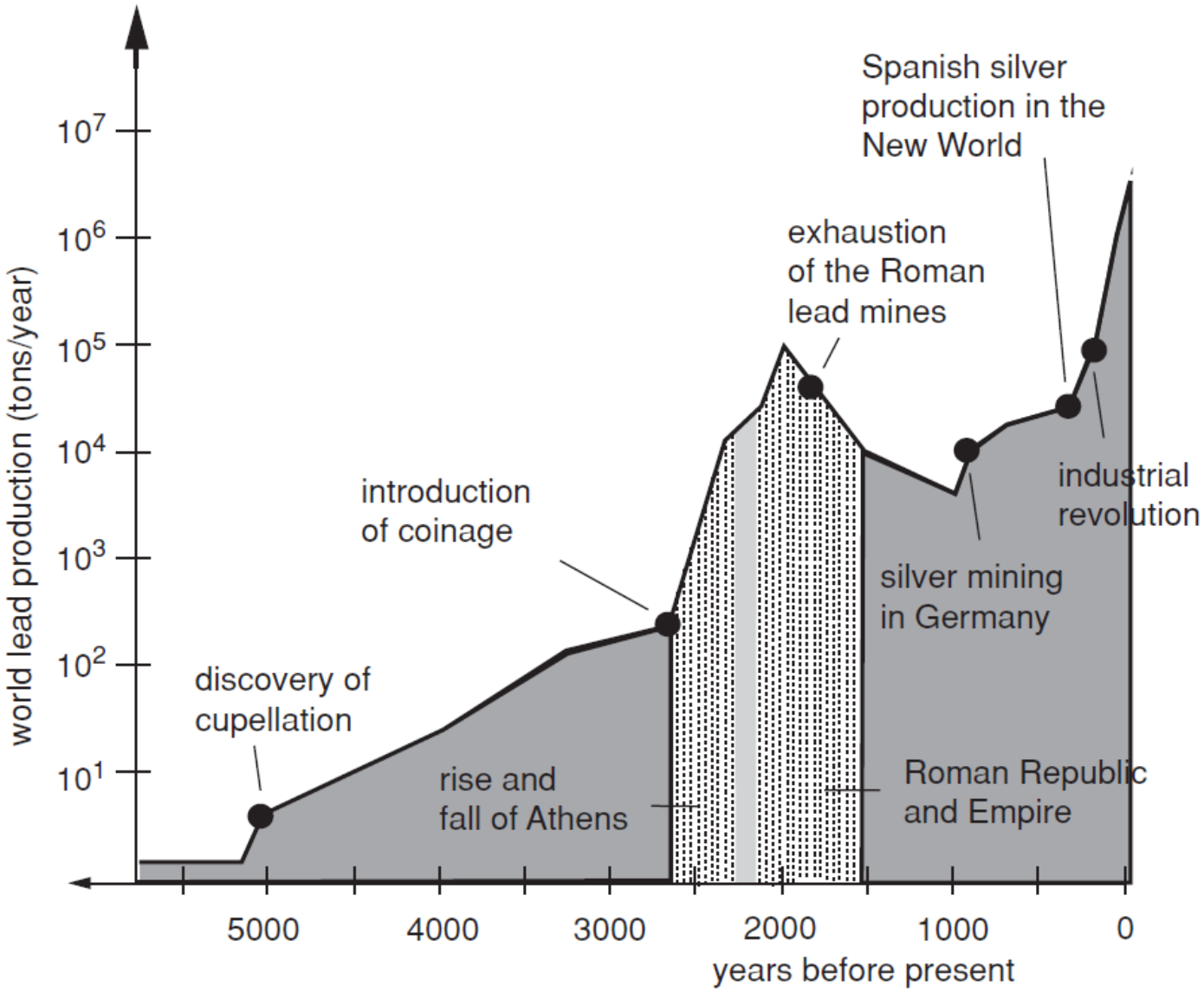
Lead

Historically, lead is the "oldest" recognized toxic metal, and it is also the one which has been most extensively spread into the environment by humans.

In contrast to mercury and cadmium, it is not particularly rare in the earth's crust. Its relatively easy mining and processing, its apparent resistance to corrosion and the not easily recognizable toxicity made it a **highly valuable metal in ancient civilizations**.

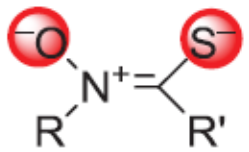
Used in accumulators ("batteries"), solder, optical glasses, pigments ("white lead", $PbCO_3 \times Pb(OH)_2$; "red lead", $Pb_3O_4 = Pb_2[PbO_4]$), radiation protection material
and fuel additives $[Pb(C_2H_5)_4]$.

Only **since the 1980s has lead production leveled off**, but it still ranks sixth behind iron, aluminum, copper, manganese and zinc with regard to worldwide metal production.

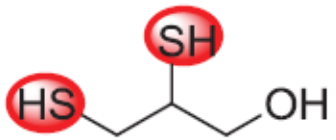


Historically, lead poisoning ("saturnism") is connected not only with **ancient Rome** but also with the **intense mining and smelting activity in medieval Central Europe**.

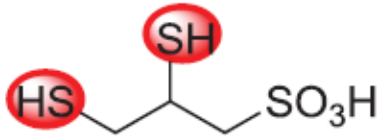
As a counter measure, the consumption of butter was practiced at that time; more recent attempts at detoxification include the combination of **2,3-dimercapto-1-propanol (BAL) with Ca(EDTA)** and the development of specific, **thiohydroxamate-containing ligands** (chelate therapeutics).



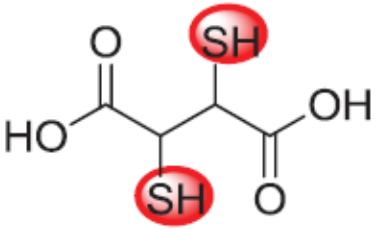
thiohydroxamate



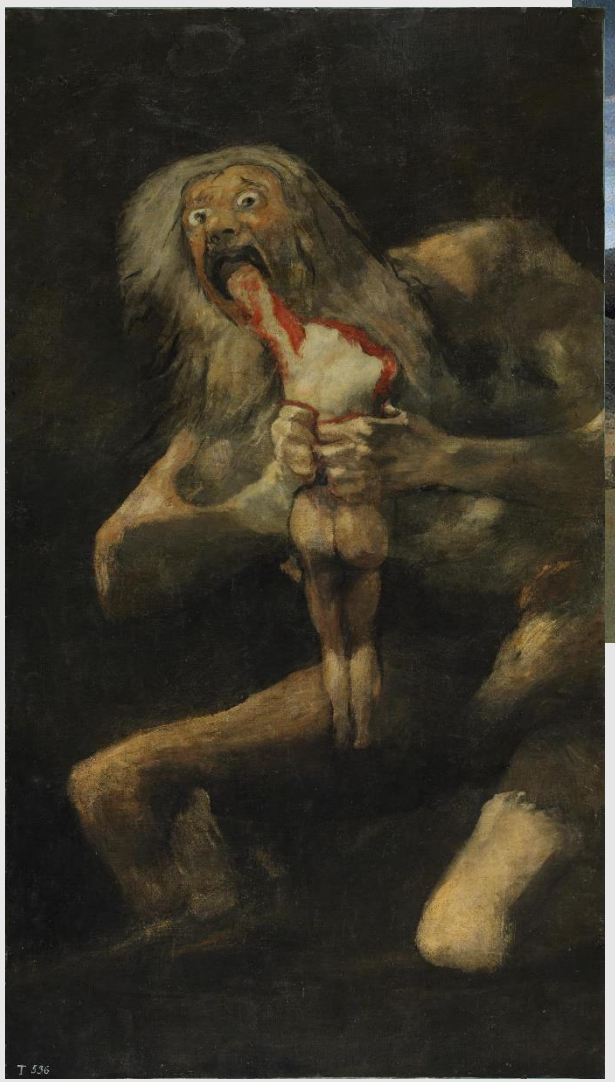
2,3-dimercapto-
1-propanol,
dimercaprol BAL



2,3-dimercapto-
1-propanesulfonic acid



dimercapto-
succinic acid, DMSA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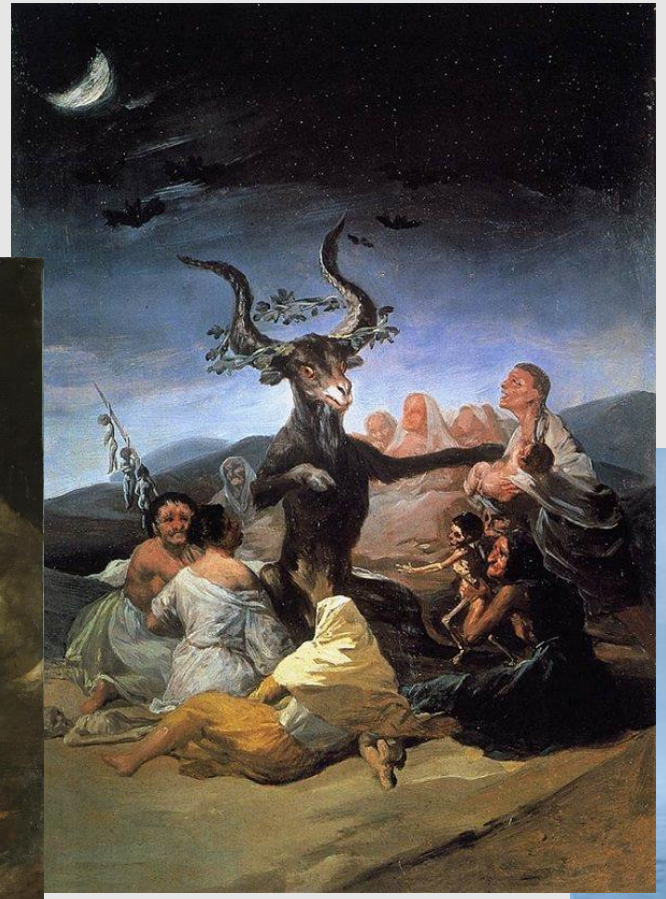


In addition to the **established neurotoxicity,** potential carcinogenic effects led to the classification of lead compounds as “probably carcinogenic to humans” (Group 2A) by the International Agency for Research on Cancer (IARC) and as Group 2 (considered to be carcinogenic to humans based on long-term animal studies) by the German MAK commission.

In blood and soft tissues (liver, kidney), **retention times of about 1 month** are observed; the lead compounds are excreted with urine, sweat or as components of (sulfide-containing) hair and nails. The strong bonding between heavy metals and sulfide-rich keratin in hair and nails (which are very persistent) allows for good forensic proof of heavy-metal poisoning

The major part of incorporated lead is **stored in the bone tissue** due to the similar (in)solubility properties of Pb^{2+} and Ca^{2+} compounds

The triethyl lead cation, $(C_2H_5)_3Pb^+$, is formed from the earlier fuel additive tetraethyl lead by the dissociation of a carbanion.

These organometallic compounds may cause **severe disorders of the central and peripheral nervous system** (cramps, paralysis, loss of coordination).
The toxicity of organometallic cations results from the permeability of membranes, including the very discriminating blood–brain barrier.

Poisoning with **inorganic lead compounds** on the other hand primarily causes **hematological and gastrointestinal symptoms** such as colics

Low concentrations of lead inhibit the zinc-dependent 5-aminolevulinic acid dehydratase (ALAD), which **catalyzes an essential step in porphyrin and thus in heme biosynthesis**

A form of anemia results before long-term neurotoxic symptoms – especially a mental retardation in children – become evident.

Further toxic effects of lead poisoning include **reproductive disorders such as sterility and miscarriages**.

Cadmium

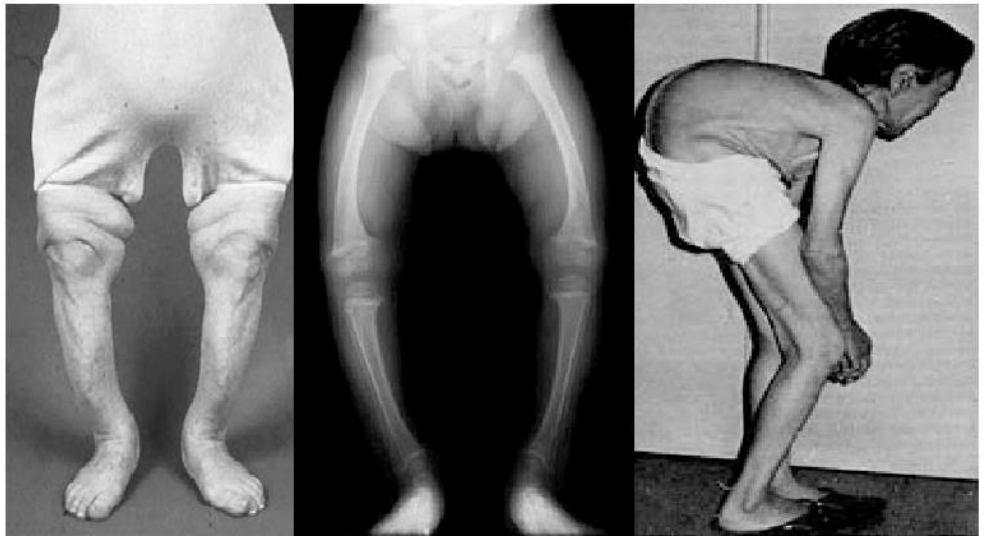
In its ionic form, **Cd^{2+}** (ionic radius 95 pm) shows **great chemical similarity** with two biologically very important metal ions: the lighter homologue **Zn^{2+}** (74 pm) and **Ca^{2+}** (100 pm)

Accordingly, cadmium as the "softer" and more thiophilic metal may displace cysteinate-coordinated zinc from its enzymes and even replace it in special cases, while it can also substitute for calcium in bone tissue.

Cadmium is generally regarded to be far more toxic than lead.

In contrast to many other heavy metals and toxic elements, **cadmium *does not* easily pass into the central nervous system or the fetus**, because, in its ionized form and under physiological conditions, **it cannot be bioalkylated to form stable, membrane-penetrating organometallic compounds.**

Chronic cadmium poisoning can cause **embrittlement of bones and extremely painful deformations of the skeleton**; such symptoms have been observed on a large scale as "**itai-itai disease**" in Japan following the use of cadmium-containing waters to irrigate rice fields during the 1950s.



Although skeletal damage in Cd poisoning is primarily caused indirectly via impairment of renal functions, the **biomineral part of the skeletons of itai-itai patients eventually contained up to 1% cadmium**, a calcium-deficient diet having aggravated the toxic demineralization effect.

Once cadmium is stored in the skeleton, its biological retention time is on the order of decades!

High concentrations of cadmium compounds have proven to be carcinogenic in animal experiments and the IARC has recently classified **cadmium as a human carcinogen (Group 1)**.

Cadmium can be incorporated through food, with the liver and kidney of slaughter animals and wild mushrooms being particularly rich in this element.

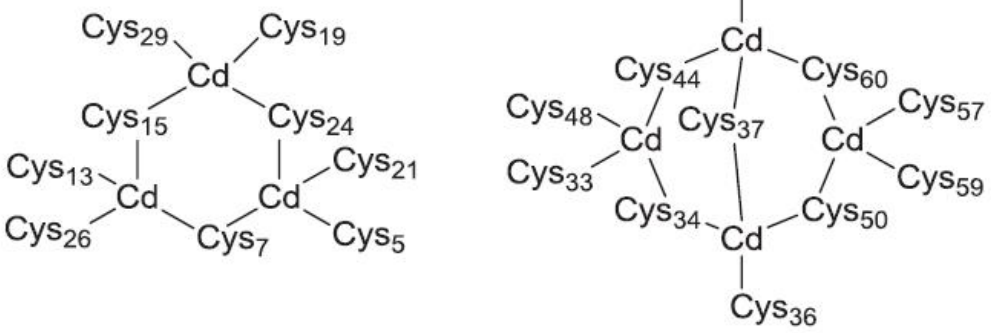
In addition to the liver and kidneys, the small intestines, the pancreas and the testicles of mammals contain larger amounts of these proteins.

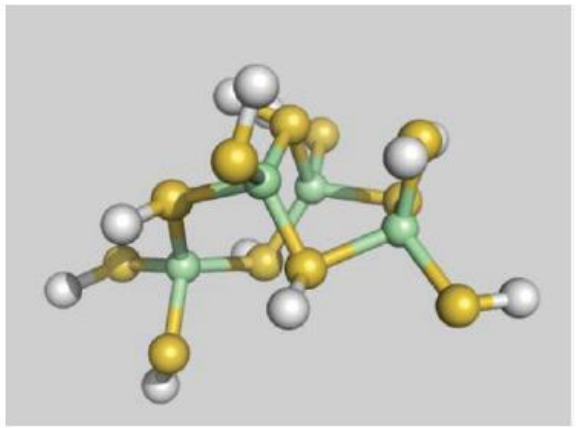
For as yet unknown reasons, **cadmium absorption is especially effective via tobacco smoke**, the Cd content in the blood of smokers being much higher than that of nonsmoker.

Cadmium is also concentrated in the liver and kidney in the human body, where, as in many other organisms, small (6 kDa) and unusually cysteine-rich (≤30%) proteins preferentially bind the soft heavy-metal ion Cd^{2+} in addition to Zn^{2+} and Cu^{+}.

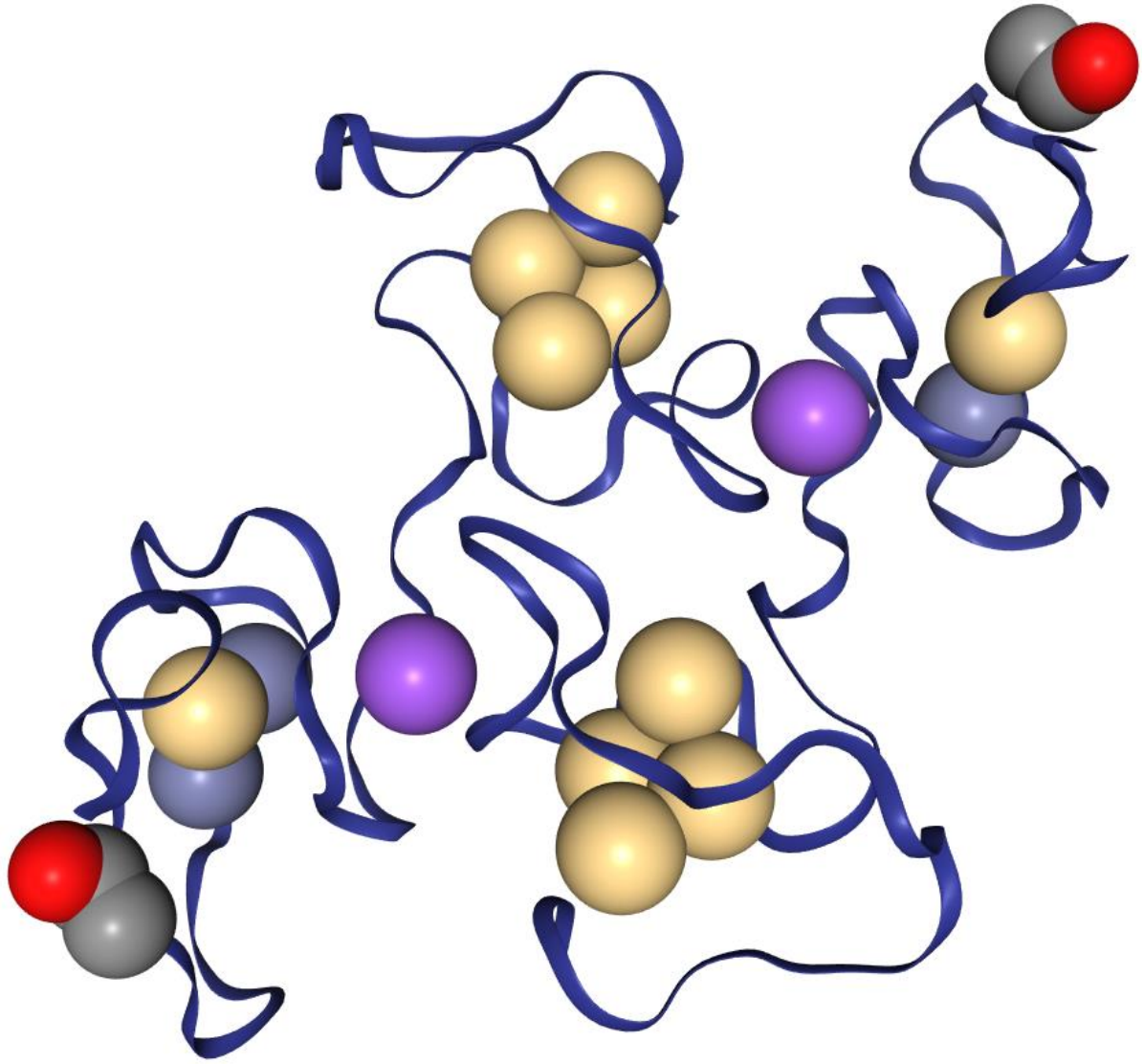
These “metallothionein” proteins feature a highly conserved sequence homology, particularly with regard to the cysteine residues

It has been found that a total of seven metal centers, each of them four-coordinate, **can be bound in two clusters by nine and eleven cysteinate residues**, respectively.





PDB = 4MT2



The **metallothioneins are presumably multifunctional proteins**, the principal function depending on the organism and on the protein variant:

- The not universally accepted **detoxification function** involves mainly Cd(II) but also other thiolate-preferring **heavy-metal centers such as Cu(I), Ag(I) and Hg(II).** In comparison to Cd(II), these ions favor even lower coordination numbers of 3 or 2, so that 12 or **even 18 metal centers can be bound per metallothionein protein**.
- A **storage or "buffering" function** for the essential elements **zinc and copper** may be assumed for metallothionein in unpoisoned organisms where such metals are bound instead of cadmium. Thus, **the ubiquitous metallothioneins can serve in the homeostasis and transport of metal ions with thiolate affinity and with a preference for the coordination number 4**.
- A further function of very **thiolate-rich proteins can be to trap and thus deactivate oxidizing free radicals such as •OH**. The Cu(I)-containing or metalfree metallothioneins are extremely oxidation-sensitive but cannot easily form disulfide bridges due to their specific protein structure.

Thallium

Like cadmium, thallium is a thiophilic heavy metal; **it forms a stable, monovalent cation, Tl^+, under physiological conditions.**

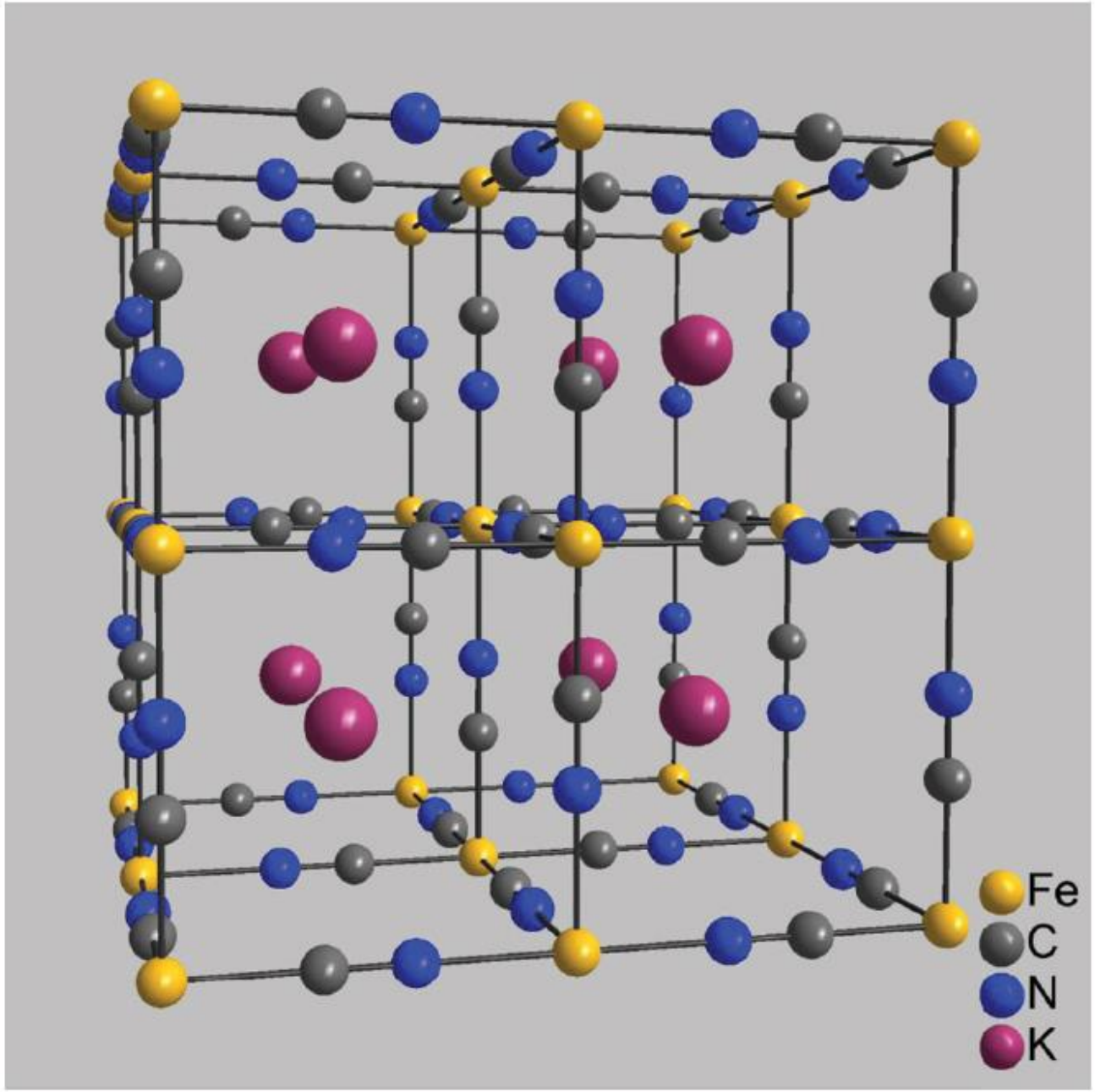
Tl^{3+} (the other stable oxidation state) is easily reduced to Tl^+ ($E0$ = +1.28), the ionic radii of Tl^+ (159 pm) and K^+ (151 pm) (each for coordination number 8) are quite similar and Tl^+ shows a high affinity for inorganic S^{-2} ligands, like Ag^+, but with a slightly better solubility of the chloride salt.

As a "**substitute**" for the **similar K^+** ion, Tl^+ can penetrate membranes via potassium ion channels

Long-term symptoms of **severe thallium poisoning** are **paralysis and impaired sensory perception (→ neurotoxicity)**; the first, typical signs, however, are **gastroenteritis** and the **loss of hair**.

Suitable countermeasures following thallium poisoning include **dialysis and high supplementation with K^+** in combination with **administration of** large quantities of mixed-valent iron cyanide complexes such **as Prussian blue**, simplified as $KFe(III)[Fe(II)(CN)^6]$, in colloidal form.

Due to their "open" structure, the Prussian blue particles are able to function as nontoxic cation exchangers; that is, they do not release significant amounts of cyanide but can bind large monocations such as Tl^+ and Cs^+ instead of K^+.



Mercury

Mercury is an ancient environmental contaminant: already Pliny the Elder (23–79 CE) described the high mortality rate of workers in contemporary mercury mines.

In recent last decades, mercury has become a very thoroughly studied example of a toxic heavy metal. Many of the typical problems arising from heavy-metal pollution have been examined in detail, such as:

- the strong dependence of toxicity on the chemical form of the element;
- the influence of human activity on the global cycle;
- the kinetics of metabolic transformations and the distribution in the human body;
- the genetics of the latent “resistance” of microorganisms against heavy-metal poisoning.

Mercury is a **relatively "noble" heavy metal**; that is, it does not corrode in normal atmosphere, it is **liquid at room temperature and it is comparatively volatile**.

The saturation vapor pressure is about 0.1 Pa, corresponding to 18 mg Hg/m^3, which is significantly higher than the typical permissible limit of 0.1 mg/m^3 air.

In **amalgamated (alloyed) form**, particularly as a component of Ag-, Sn-, Znand sometimes Cu-containing tooth fillings, **mercury is far less volatile and water soluble**; the potential long-term health hazards of additional Hg incorporation in amalgam fillings continue to be a subject of controversy

In its **usual ionic form as Hg^{2+} ion**, mercury is **immediately toxic**, since this species is easily soluble at pH 7 and does not form insoluble compounds with those anions which are abundant in bodily fluids. An **especially toxic form is represented by the organometallic cations**, RHg^+, and particularly by the **methylmercury cation (H_3C-Hg^+)**, which can be formed in the organism from Hg^{2+} through biomethylation

In 1997 the fatal poisoning of the US scientist Karen Wetterhahn shocked the chemical community. Wetterhahn had carried out experiments with dimethyl mercury, Me2Hg, which was used as a standard probe for ^{199}Hg NMR spectroscopy. It turned out that a few spilled drops of Me2Hg (a liquid) rapidly penetrated Wetterhahn's protective gloves, causing severe neurotoxic indications many weeks later, leading to coma and finally to death

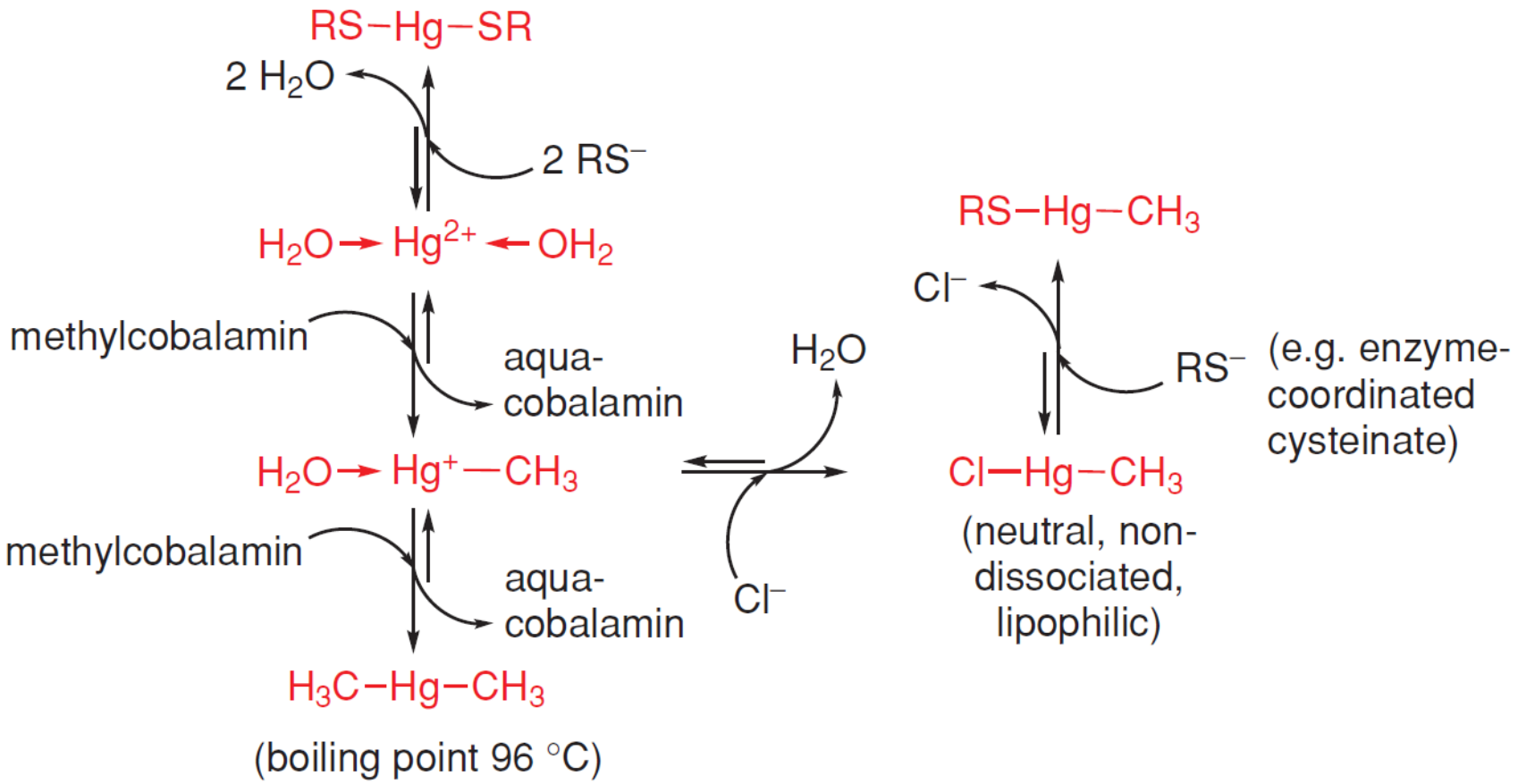
The toxicity of mercury compounds is based on the **strong affinity of this metal for the deprotonated forms of thiol ligands** such as cysteine;
therefore, thiols, RSH, with sulfhydryl groups, -SH, are also called mercaptans (*mer*curium *captans*).

Mercury compounds are distinguished by a **preference for very low coordination numbers** of the metal center, the coordination number 2 with a linear arrangement being highly favored.

mercury is not very susceptible to simple chelate coordination

It is characteristic, however, that the **RHg^+–thiolate bond is kinetically labile despite an extremely favorable equilibrium situation**.

Consequence of easily attainable transition states for an associative substitution with three- or four-coordinate metal

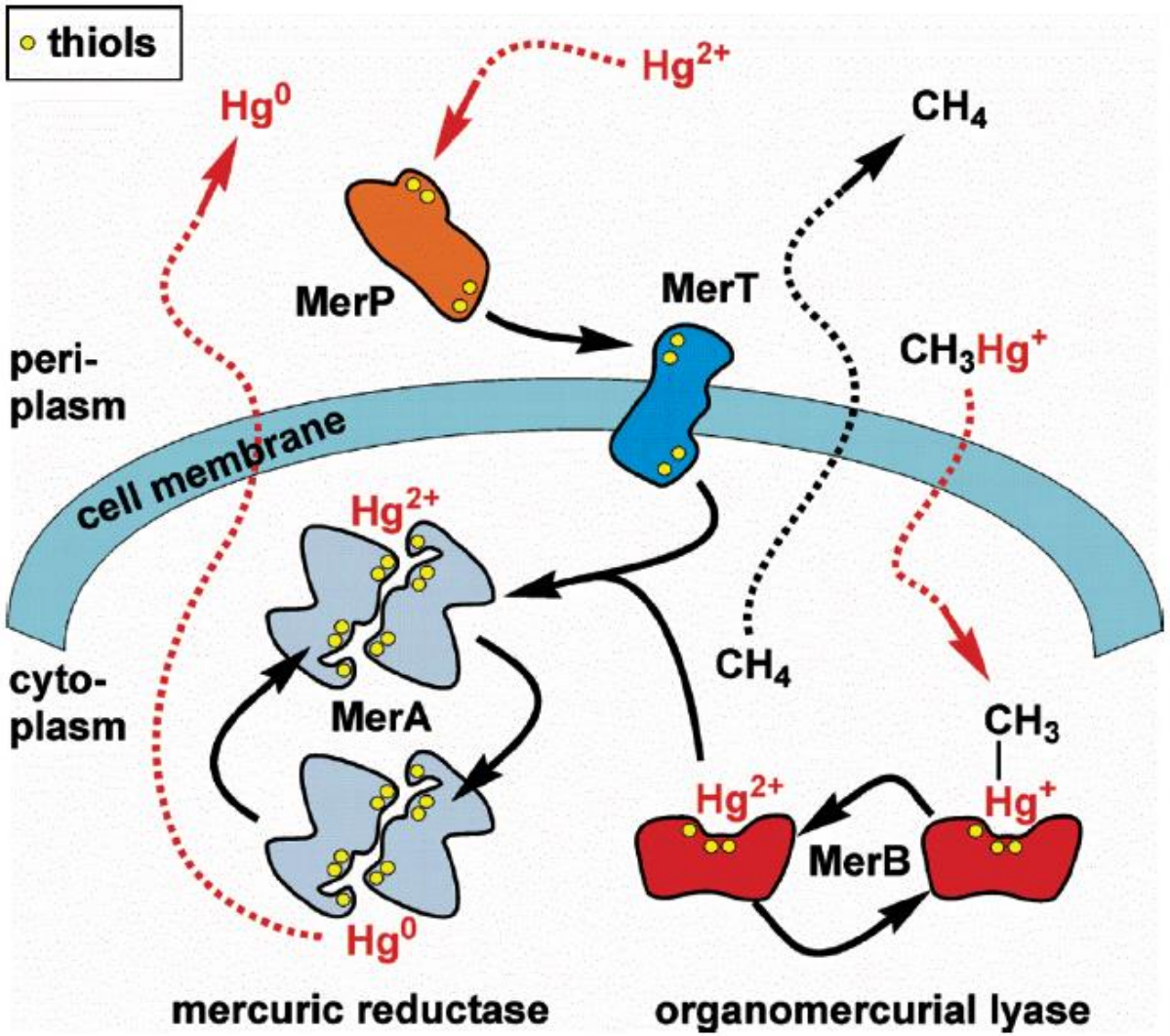


Following an **incorporation of organomercury compounds** (e.g. with food), the **little-dissociated molecules RHgCl** can be formed in the stomach with its high content of hydrochloric acid; **due to their lipophilicity, these molecules can then be efficiently resorbed**.

The relatively low immediate toxicity of elemental mercury and its volatility have enabled bacteria to develop a resistance mechanism towards soluble Hg compounds

***Mer* system**

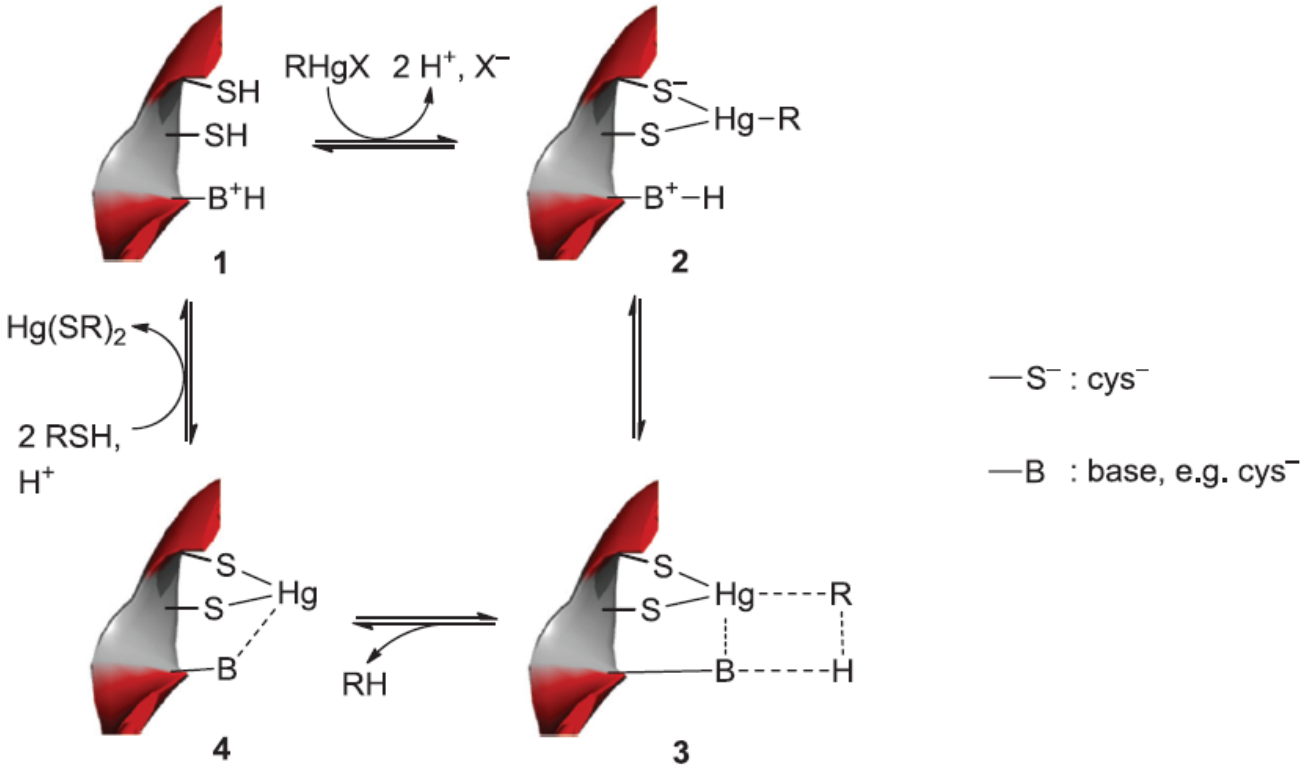
The synthesis of the required proteins (*MerA*, *MerB*, *MerP*, *MerT*) is **triggered and controlled by a metal-selective and gene-regulating sensor protein "*MerR*".**



Two "processing" enzymes are especially interesting: a **specific Hg(II) reductase (*MerA*)** and **organomercury** (or organomercurial) **lyase (*MerB*).**

$$RHgX + H^+ + X^- \rightleftharpoons R{-}H + HgX_2 \qquad X = R'S, Hal$$

Organomercury lyase is a relatively small (22 kDa) monomeric protein which accelerates the cleavage of the otherwise kinetically inert Hg–C bonds by a factor of 10^6–10^7



Reduction of coordinated Hg(II) to the volatile and less toxic elemental mercury is effected by a special HgII reductase, a dimeric flavin- and NADPH-containing protein with a molecular mass of 2 × 60 kDa.

$$Hg(SR)_2 + NADPH + H^+ \rightleftharpoons Hg + NADP^+ + 2\,RSH$$

Aluminum

Aluminum is the **most abundant "true" metallic element** in the earth's crust and, after iron, the **second most produced metal**.
However, according to all accounts, it is an element with almost **no "natural" biochemical function**.

Very **low solubility of Al^{3+}, especially at pH 7,** when it is almost completely present as insoluble hydroxide, $Al(OH)_3$, or its condensation products, $AlO(OH)$ and Al_2O_3.

Soils may be buffered to different extents against added acid

$Al^{3+}(aq)$ in exchange for H^+ at below pH 5

The **hydrated Al^{3+} ion can replace Mg^{2+} with great efficiency** due to its higher charge and smaller ionic radius.

A vast number of **Mg^{2+}/enzyme-induced phosphate transfer reactions can be blocked** by Al^{3+}. The very **high affinity of Al^{3+} towards polyanionic phosphate** groups precludes an efficient catalysis.

Forest damage partly attributed to the acidification of soil by "acid rain" and the resulting release of the rhizotoxic Al^{3+}.

Possible role of Al^{3+} in neuropathological symptoms, the strong tendency of this ion for coordination with deprotonated 1,2-dihydroxy aromatic systems such as the catecholamine neurotransmitters epinephrine and DOPA has been established.

In connection with Alzheimer's disease, there have been conflicting analytical reports.

Encephalopathy, dementia and even mortality have been established for hemodialysis patients who were subjected to an increased level of aluminum.

Other symptoms of Al^{3+} overload include:

- several forms of **anemia** (Al^{3+}/Fe^{3+} antagonism)
- **disorders of the bone metabolism**; an accumulation of Al^{3+}, with its very high affinity towards phosphates, has been observed in bone-forming osteoblasts.

Chelate drugs such as deferrioxamine, which originally target Fe^{3+} have also been used in cases of Al^{3+} poisoning

Chromium

Under physiological conditions, the persistent oxidation states of chromium are Cr(III) and Cr(VI) -as chromate, CrO_4^{2-}, at pH 7-.

Like trivalent aluminum and iron, **trivalent chromium exists as an insoluble hydroxide** at neutral pH

The chromates(VI), which have been recognized as skin irritants ever since the beginning of their industrial use, **are classified as potential carcinogenic substances**.

The uptake of CrO_4^{2-} by organisms seems to be surprising at first because the redox potential for reaction is about +0.6 V at pH 7; that is, **chromate is only metastable in the presence of reducing organic compounds** under physiological conditions.

BUT

the required number of three electrons leaves **only a few special biochemical reduction systems as efficient reductants for chromate**. These include **heme- and flavoproteins (NADH-dependent), thiols such as glutathione, GSH, and ascorbate**.

According to electron paramagnetic resonance (EPR) studies, **highly reactive Cr(V) states with one unpaired 3d electron may be formed** in these reactions.

Due to its structural similarity with the sulfate ion, SO_4^{2-}, **chromate can overcome membrane barriers and reach the cell nucleus** unless it is rapidly reduced.

Chromate can oxidatively damage genetically important components of the cell nucleus. The substitutionally more labile and more strongly oxidizing Cr(V) or Cr(IV) intermediates formed during one-electron reduction steps and the simultaneously produced RS$^\bullet$ and $^\bullet$OH radicals can directly attack the DNA and effect bond cleavage, crosslinking and, as a consequence, faulty gene expression.

The substitutionally *inert* **Cr(III) can irreversibly bind to phosphate-containing DNA** or **free nucleotides** and thus also affect genetic functions.