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Differences in Bioavailability – Example Selenium

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Sicherheit von Lebensmitteln
Die Rolle der Bioverfügbarkeit im Rahmen der Risikobewertung am Beispiel Spurenelemente.
BfR-Symposium, 16.-17. Jan 2013, Berlin.

Selenium

What is Selenium?

What is it good for?

In which form?

How much is enough?

Selenium

What is Selenium?

Selenium is not an antioxidant
Selenium is an element which can be used for a high number of different molecules.

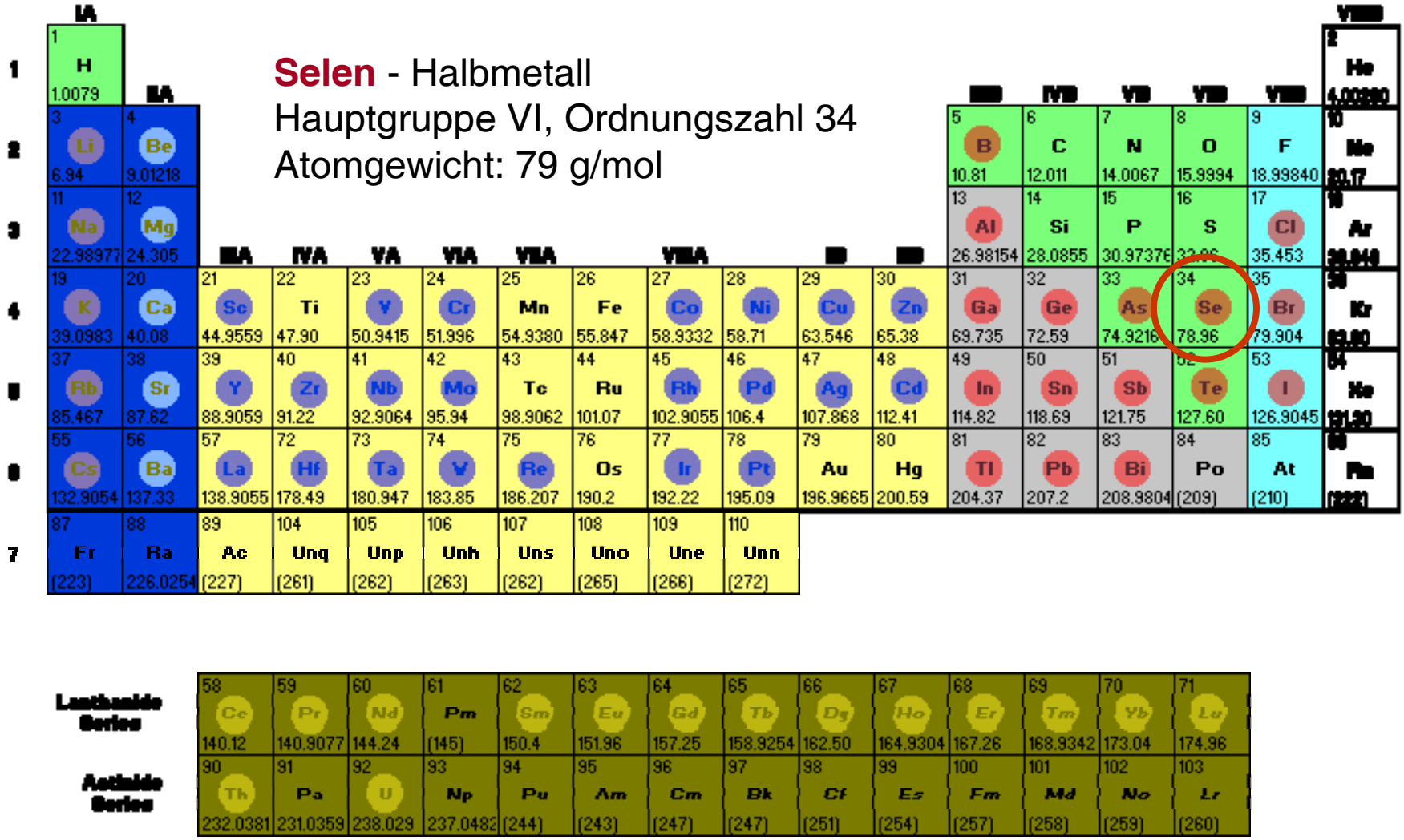
What is it good for?

In which form?

How much is enough?

Periodic system of elements

Selen - Halbmetall
Hauptgruppe VI, Ordnungszahl 34
Atomgewicht: 79 g/mol



Selenium - From a toxin to an essential trace element -

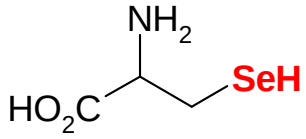
1817 Jöns Jakob Freiherr von Berzelius discovered a novel element selenium (seléne, griech. = godess of the moon)

1937 Selenium is toxic for livestock

1957 Selenium is an essential micronutrient, Klaus Schwarz

1973 Identification of the first selenoprotein, GPx1
Flohé et al., Rotruck et al.

1986 Selenocysteine is the 21. amino acid and is encoded by the stop codon “TGA“ Chambers et al.



1996 Selenium decreases cancer mortality and incidence, Clark et al.

2003 The human genome contains gene for at least 25 selenoproteins, Kryukov et al.

Selenium

What is Selenium?

What is it good for?

Mammals need it
for Selenoproteins

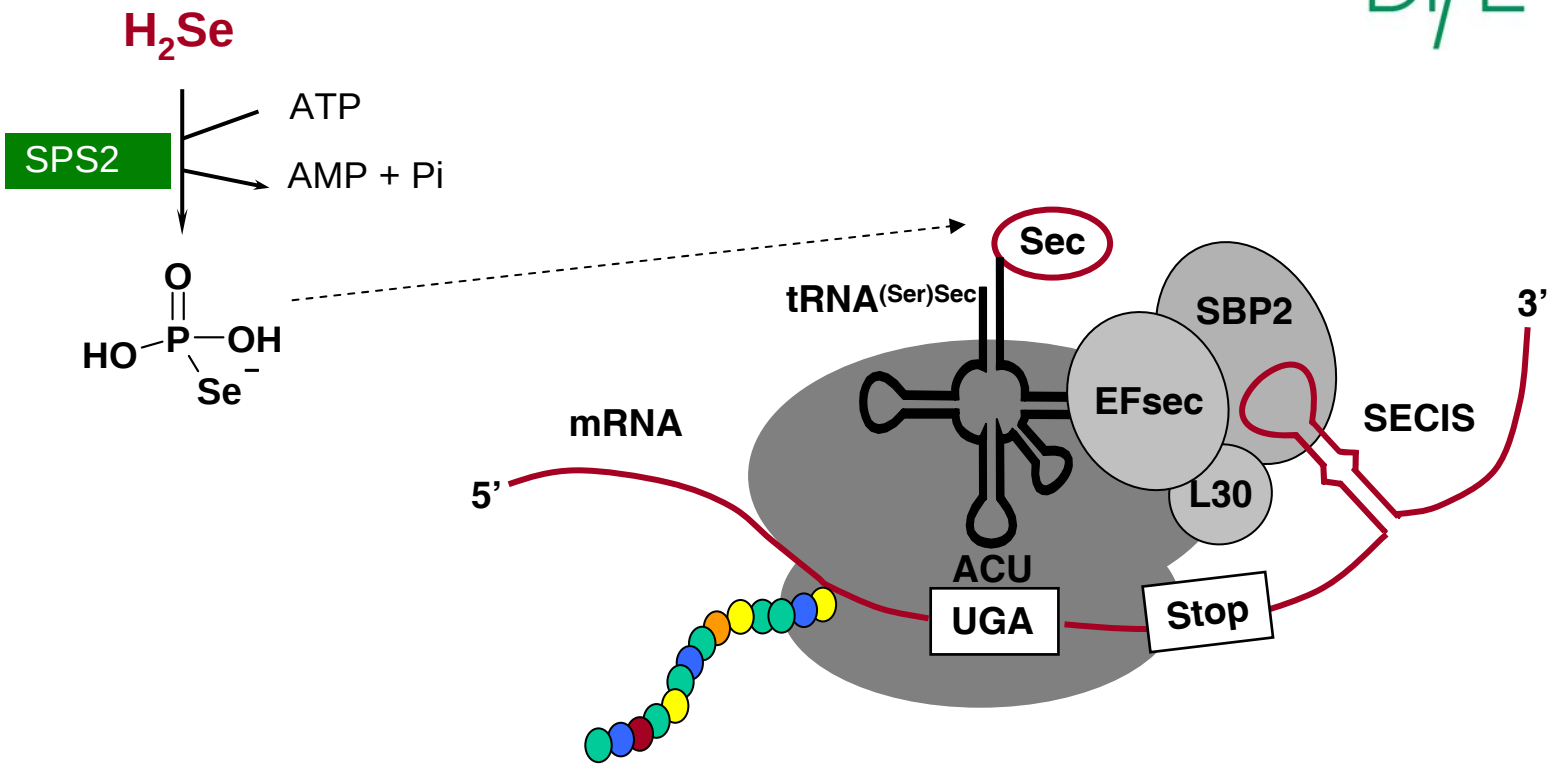
In which form?

How much is enough?

Mammalian Selenoproteins

Selenoprotein	Abbreviation	Function
Glutathione peroxidases	**GPx**	Reduction of hydroperoxides (some with peroxynitrite).
cytosolic or classical GPx	cGPx, GPx-1	Antioxidant
Phospholipid hydroperoxide GPx	PHGPx, GPx-4	Reduction von lipophilic hydroperoxides, building of the mitochondrial capsule of spermatids, male fertility. Removal of 12,15 LOX products, inhibition of apoptosis.
Plasma GPx	pGPx, GPx-3	Reduction of H_2O_2 in the thyroid?
gastrointestinal GPx	GI-GPx, GPx-2	Prevention of hydroperoxide resorption? Involved in mucosal self-renewal. Anti-inflammatory. Role in cancer?
GPx3-Homolog	GPx-6	Role in the olfactory system?
Iodothyronine deiodinases		Metabolism of thyroid hormones
5'-deiodinase-1	5'DI-1	Activation of T4 to T3
5'-deiodinase-2 (SelY)	5'DI-2	Activation of thyroid hormones
5-deiodinase-3	5-DI-3	Inactivation of thyroid hormones
Thioredoxin reductases		Reduction of oxidized Trx, regulation of cellular redox state
Thioredoxin reductase-1	TR-1, TrxR-1	cytosolic
mitochondrial TrxR	TR-2, TrxR-2	mitochondrial
Thioredoxin/Glutathionreductase	TGR	testes-specific
Selenophosphate synthetase-2	SPS2	Selenophosphate synthesis
15-kDa selenoprotein (T cells)	Sel15	complex with UDP-glucose:glycoprotein glucosyltransferase-1 in ER. Protein folding?
Selenoprotein P	SelP, SePP	Selenium transport and distribution
Selenoprotein R (also SelX)	MsrB1	Reduction of methionine sulfoxide in proteins
Selenoprotein S	SelS	Human homolog of Tanis, a Type-2 diabetes-associated protein in mice. Elimination of misfolded proteins
Selenoprotein N	SelN	ER Protein, associated with *rigid spine disease*. Glycosylation of dystroglycan? Role in muscle development?
Redoxin proteins, CxxC or CxxU:		
Selenoprotein W	SelW	Muscle protein, interaction with 14-3-3, muscle function development?
Selenoprotein H	SelH	DNA-binding protein? Regulation of phase II enzyme expression?
Selenoprotein T	SelT	Golgi protein, function unknown
Selenoprotein V	SelV	Testis variant of SelW
Selenoprotein M	SelM	Protein folding
Selenoprotein I, K, O		unknown

Co-translational incorporation of selenocysteine into proteins simplified scheme



Sources for selenoproteins are only Se compounds from which Se can be transformed into selenide

Explanation to the previous slide

Selenocysteine (Sec) is encoded by TGA which usually is a stop codon. To discriminate between TGA meaning stop or Sec, respectively, organisms have developed a complex mechanism which is unique in protein synthesis.

1. The selenoprotein mRNA has a stem-loop structure in its 3‘untranslated region called SECIS for selenocysteine incorporation sequence.

2. A number of proteins are needed to support building the selenocysteine incorporation complex. These proteins link the SECIS element, the ribosome and the Sec-specific $tRNA^{(ser)sec}$.

3. The Sec-specific $tRNA^{(ser)sec}$ is first loaded with serine. Then the -OH group of serine is exchanged by -SeH to form Sec. This process requires selenophosphate which is build by selenophosphate synthetase-2 (SPS2) from selenide (H_2Se) and ATP.

➡ Thus, only selenium compounds which can be metabolized to selenide are selenium sources suitable for selenoprotein biosynthesis.

Selenium

What is Selenium?

What is it good for?

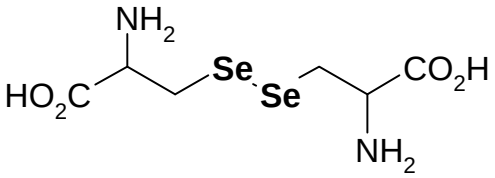
In which form?

Dietary selenium exists in many different forms

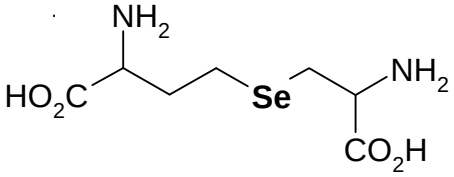
How much is enough?

Selenium in plants - example: compounds in selenium-enriched **garlic**

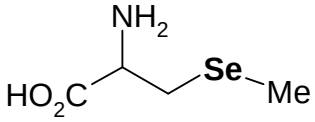
SeO_4^{2-}, Selenate 2%



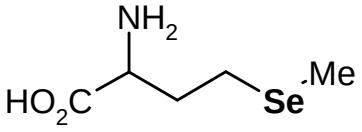
Selenocystine 0.5%



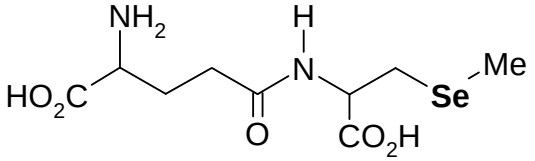
Selenocystathionine 0.5%



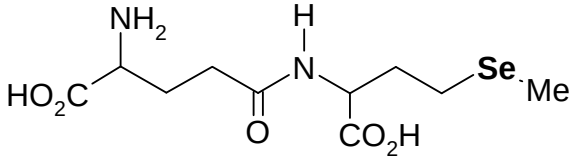
Se-Methyl selenocystein 3-60% *



Selenomethionine 13%



γ-Glutamyl-*Se*-methylselenocysteine 73 – 10% *



γ-Glutamyl-selenomethionine 4%

Kotrebai et al. *Anal Commun* **1999**, *36*, 249-252.

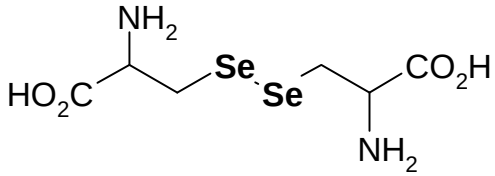
Kotrebai et al. *Analyst* **2000**, *125*, 71-78.

* dependent on the total Se-content in garlic

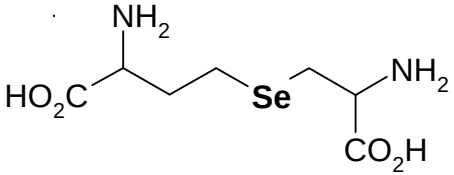
Selenium compounds in selenium-enriched yeast

(varies with the total Se content in yeast)

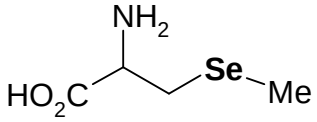
SeO_3^{2-} , Selenite 1%



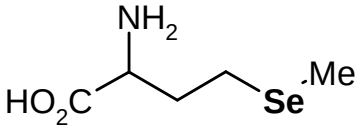
Selenocystine 0.5%



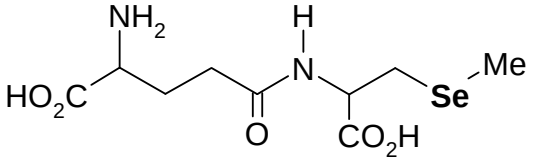
Selenocystathionine 1%



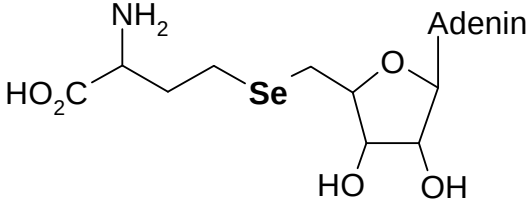
Se-Methyl-selenocysteine 0.5%



Selenomethionine 85%



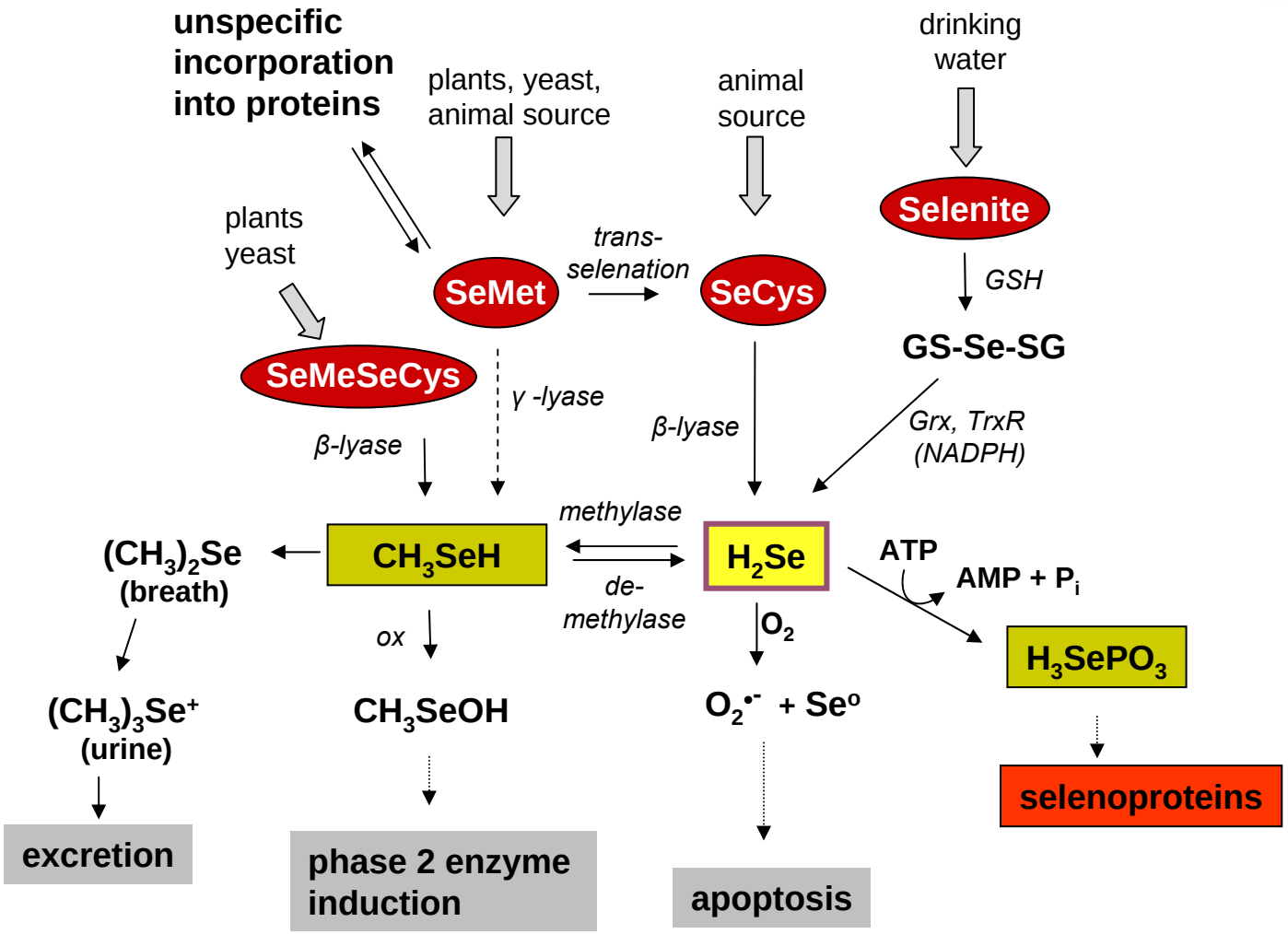
γ-Glutamyl-*Se*-methylselenocysteine 0.5%



Se-Adenosyl-selenohomocysteine 3%

Kotrebai et al. *Analyst* **2000**, *125*, 71-78.

Selenium metabolism in mammals



Forms of selenium in foods (see also: Fairwheater-Tait et al. AJCN 2010 Rayman, Br.J.Nutr. 2008)

Plant	Selenium compounds	Se-content [µg/g]
Cereals		
Wheat	Selenate, SeMet, SeCys, Se-methyl-SeCys	≤ 0.1
Wheat flour	Selenate, SeMet	≤ 0.4 - 0.5
Maize	SeMet, SeCys	0.6 - 44
Nuts		
Brazil nuts	SeMet	2.54
Walnuts	SeMet	0.38
Vegetables		≤ 0.01
Broccoli (Se)	Se-methyl-SeCys	≤ 11
Cabbage (Se)	Se-methyl-SeCys, SeMet, Selenate	94
Onions (Se)	SeCys, Se-methyl-SeCys	96
Garlic	γ-Glu-Se-methyl-SeCys, SeMet, Se-methyl-SeCys	≤ 0.5
Garlic (Se)	Se-methyl-SeCys, SeCys, SeMet	1355
Leek (Se)	γ-Glu-Se-methyl-SeCys, SeMet, Se-methyl-SeCys, Selenate, Se-cystathionine	up to 524
Chive	Se-Cystine, Se-methyl-SeCys, SeMet	222

Forms of selenium in foods (see also: Fairwheater-Tait et al. AJCN 2010, and Rayman, Br.J.Nutr. 2008)

Animals	Selenium compound	Se-content [µg/g]
Meat		≤ 0.3
Beef, pork, lamb	SeCys und SeMet	0.03 - 0.15
Turkey		0.1 – 0.2
Liver, kidney		0.2 – 2.0
Fish		
Blue Marlin		2.5 – 4.2
Macarel		0.26, 0.13
Sardines	SeMet	0.4 – 0.9
Tuna	Selenat	0.36 – 1.33
Crustaceans	Selenat	0.15 – 4.15
Milk(products)		
Cow‘s milk	As so far unknown selenoamino acids in milkproteins	0.013 - 0.022
Yoghurt		0.022 – 0.027
Butter		0.005 – 0.014
Eggs		0.7 – 172 µg/egg

Biomarkers

Success of absorption

- **Selenium**
  content in plasma, erythrocyte, whole blood

Functional markers

- **Enzymes** (activity or protein levels)
  plasma SelP, GPx3
  erythrocyte GPx1
  platelet GPx

Molecular biological markers

- **RNA** of hierarchical low ranking selenproteins
  GPx1, **SelW**

An example:

Burk RF, Norsworthy BK, Hill KE, Motley AK and Byrne DW

Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial

Cancer Epidemiol. Biomarkers Prev. 15, 804-810 (2006)

The paper describes a randomized, placebo-controlled intervention study in which 200, 400, or 600 µg/d selenium in the forms sodium selenite, high selenium yeast (YS), or selenomethionine (SeMet) was applied to healthy volunteers. As markers plasma selenium, plasma GPx activity, and plasma selenoprotein P content was measured.

Outcome:

- Selenite was without any effect
- SeMet increased plasma selenium but not enzymes (unspecific incorporation into plasma proteins)
- Selenium yeast worked as SeMet since YS mainly contains SeMet

- Note: participants were already ‘replete‘ (122 µg/L)
- Participants with a low selenium state would have responded differently

Our interest: glutathione peroxidase-2 (GPx2)

- In a model of inflammation-triggered colon carcinogenesis (AOM/DSS), GPx2 KO mice develop a significantly more severe inflammation than wildtype mice and in the following a higher number of tumors/animal. The effect was especially high in selenium-deficiency.

  ⇒ GPx2 acts antiinflammatory and inhibits tumorigenesis if mediated by inflammation Krehl *et al*. Carcinogenesis 2012

- In a xenograft model, HT-29 cells in which GPx2 was down-regulated developed much smaller tumors than cells containing intact GPx2.

  ⇒ GPx2 supports tumor cell growth Banning *et al*. Canc Res 2008

The effect of selenium and/or specific selenoproteins on cancer development depends on the stage of cancer and the mode of initiation.

In general:
the effect of selenium supplementation depends on:

the selenium compound
the concentration
the use of biomarker
the selenium state when supplementation starts

Selenium

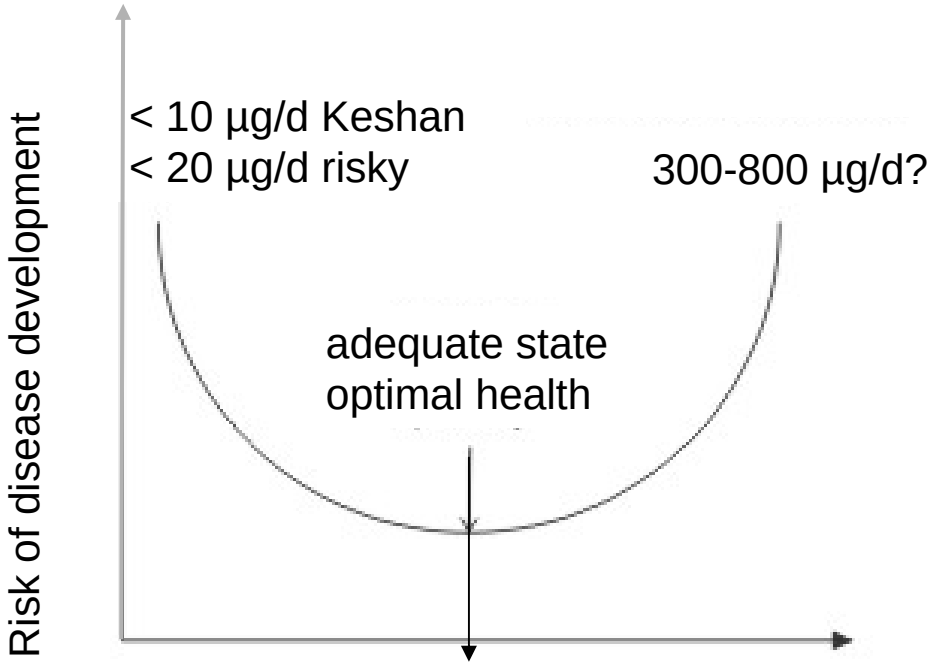
What is Selenium?

What is it good for?

In which form?

How much is enough?

How much selenium is too low, adequate or too high?



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