NST 160

Theil Selenium Lecture 1

October 27, 2004

Selenium Nutrition and Physiology

Reading

Chapter 12: Insel, P., R.E. Turner, and D. Ross. *Nutrition*, 2nd Ed.

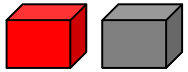
Chapter 34: (Reserve BioSci Library) Stipanuk -*Biochemical and Physiological Aspects of Human Nutrition*

Driscoll and Copeland, Annu Rev Nutr. 2003; 23:17-40

NST 160 website:

http://nutrition.berkeley.edu/undergrad_class/nst1-60/

Selenium - Chemistry



Metallic Se

Atomic number : 34

Periodic Table: Se (34) - same <u>group</u> as S (16) and O (8).

Se (34) - same <u>period</u> as Mn(25), Fe(26), Cu(29), Zn(30)

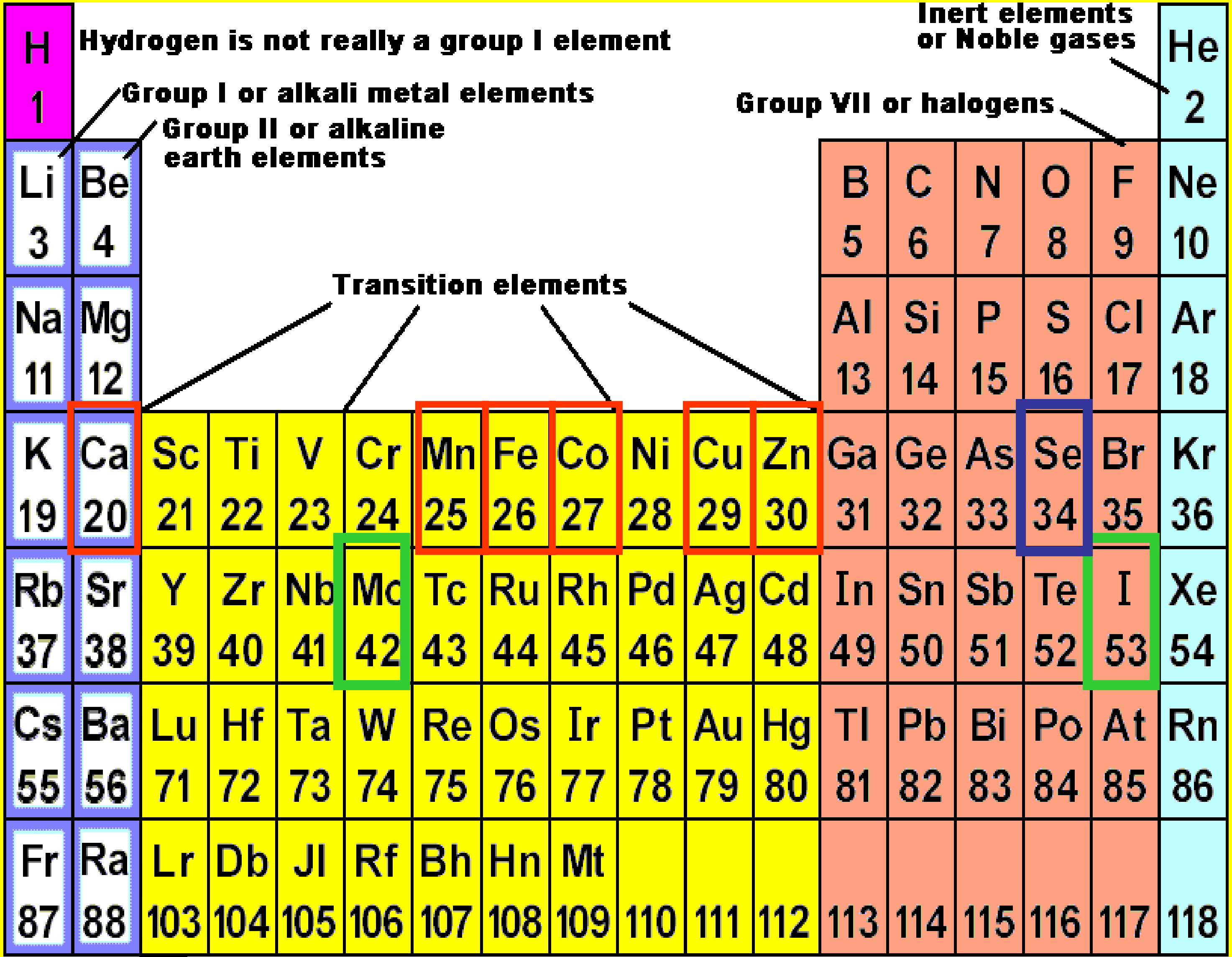
Atomic weight (FW) g/mole: 78.9

Outer electron configuration:*3d* = 10 (like Zn); *4s* = 2; *4P* = 4,

Se^{4+} and Se^{6+}; semiconductor

Solubility: $Na_2SeO_4^{-2}$ - 4.4 M

Elements of Life- Abundance: Period 1 > 2 > 3 > 4



Period

1. H

2. C,N,O

3. Na, Mg, P, S, Cl

4. Trace/micro"

5. Micro

6. -

7. -

Selenium - Physiology

Plasma concentration: (6-8 µg/L)

Plasma transport: in SelP (selenoprotein) and on serum albumin as selenite and selenide

Content (human body): 13-23 mg / 70 kg

Tissue distribution: 61% + muscle + liver+ kidney + blood); 30% in bone (related to thyroxine activity)

Recognition of biological relevance very recent!

1957 –Animal Se deficiency; 1980's: Humans - Keshan Disease

Selenium - Nutrition

UL (Safe daily intake upper limit): 400 μg/day
RDA: 55 μg/day

Most American diets are Se sufficient.

Sources:
Organ meats: seafoods, muscle meats
Examples: beef liver, lobster tail, shrimp. tuna steak, pork loin
Plants: Variable with soils
Absorption: Seleno-amino acids are 50-90% absorbed

Enhancers: Vitamins A, C, E

Low soil Se/ high vegetable consumption $\rightarrow$ Se deficiency (Example: Keshan province in China)

Se Toxicity: Rare overall except in selected geographic areas

Originally thought to be environmental toxin for livestock (1949 = "Awful poison")

High Se soil

Botanical Se indicator

Natural: North and South Dakota, Colorado

Irrigation- San Joaquin Valley reservoir

High Se plants-absorb soluble Se $\rightarrow$Se-methionine, Se cysteine)

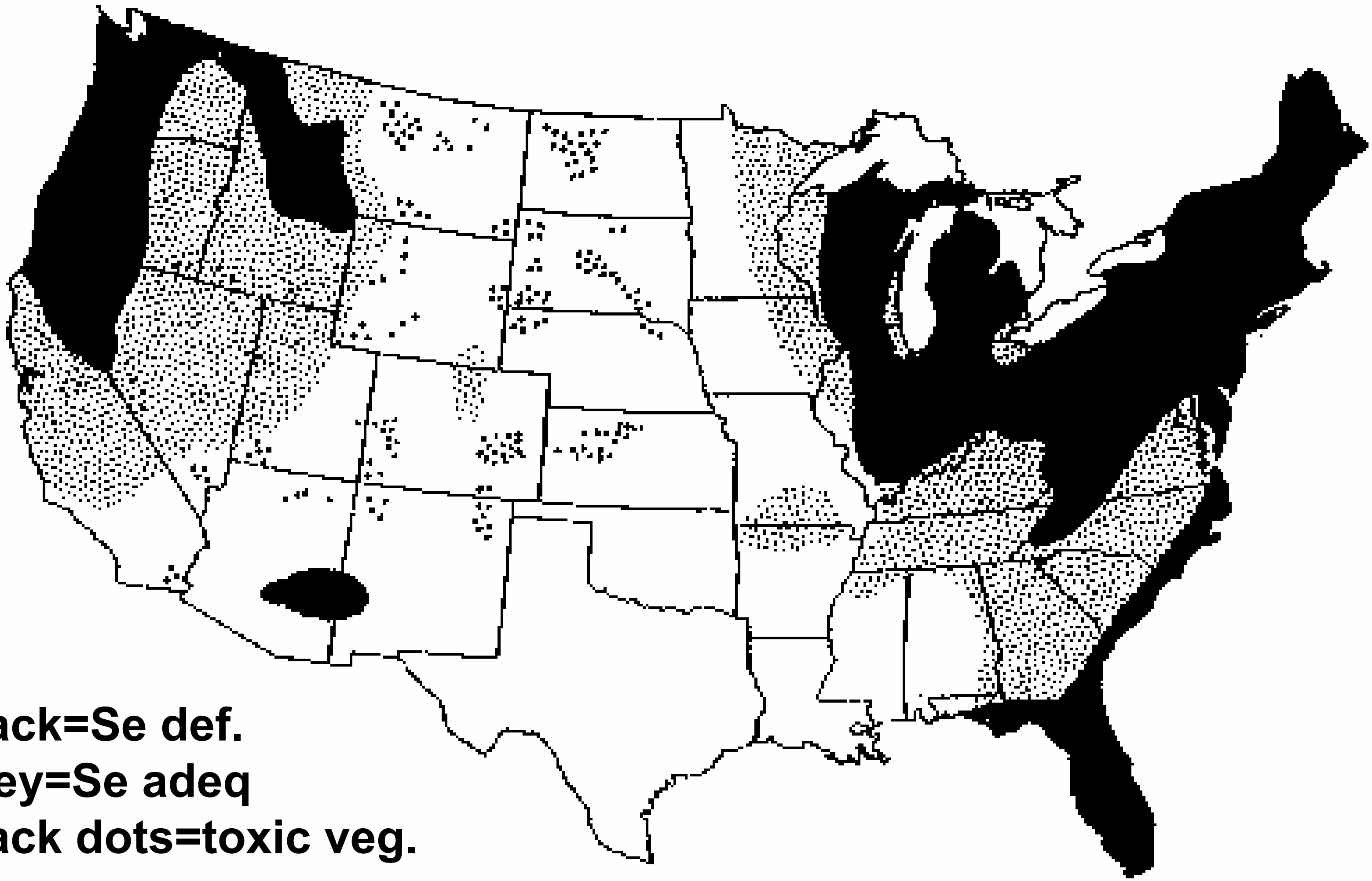
Toxic effects:Cattle, sheep "blind staggers" /alkaline (soil) disease;anemia, hair loss, paralysis

Toxicity:

Chronic: > 5 ppm in total diet

Acute : 1-10 mg/Kg

Selenium Distribution in the U.S.



Black=Se def.
Grey=Se adeq
Black dots=toxic veg.

Selenium - Deficiency

Keshan's Disease- Discovered in the 1980's

- **Readily treated by Se Supplementation- Na SeO_3**
- **Mainly in rural poor –low Se soil, low meat diet**
- **Urban population – higher meat intake, little affect**
- **Myocardial necrosis (Oxidative damage?).**

(Thyroxine deiodinase, key to active hormone synthesis, is an Se protein

***Kashan-Beck: Osteoarthiritis – China; may be Se + I deficiencies**

***Other: Goiter – New Zealand; linked to iodine deficiency**

***Not fully characterized**

Selenium and Cancer

Selenium compounds appear to have "anti-cancer" properties

Mechanism:

Human metabolism of plant selenomethionine?

Se-protein catalysts?

Both?

Anti-oxidant Se proteins

Glutathione peroxidase, thioredoxin reductase,

Met sulfoxide reductase

Methylselenol (CH_3SeH) has anticancer activity:

Se Met (Dietary Plants) $\rightarrow CH_3SeH \rightarrow$ apoptosis of malignant cells

Selenium Biochemistry

1973: glutathione peroxidase recognized as Se-protein

Se in two amino acids:

Selenocysteine (Sec)

Synthesized in plants, animals and bacteria

Selenomethionine Se-Met:

Synthesized in plants.

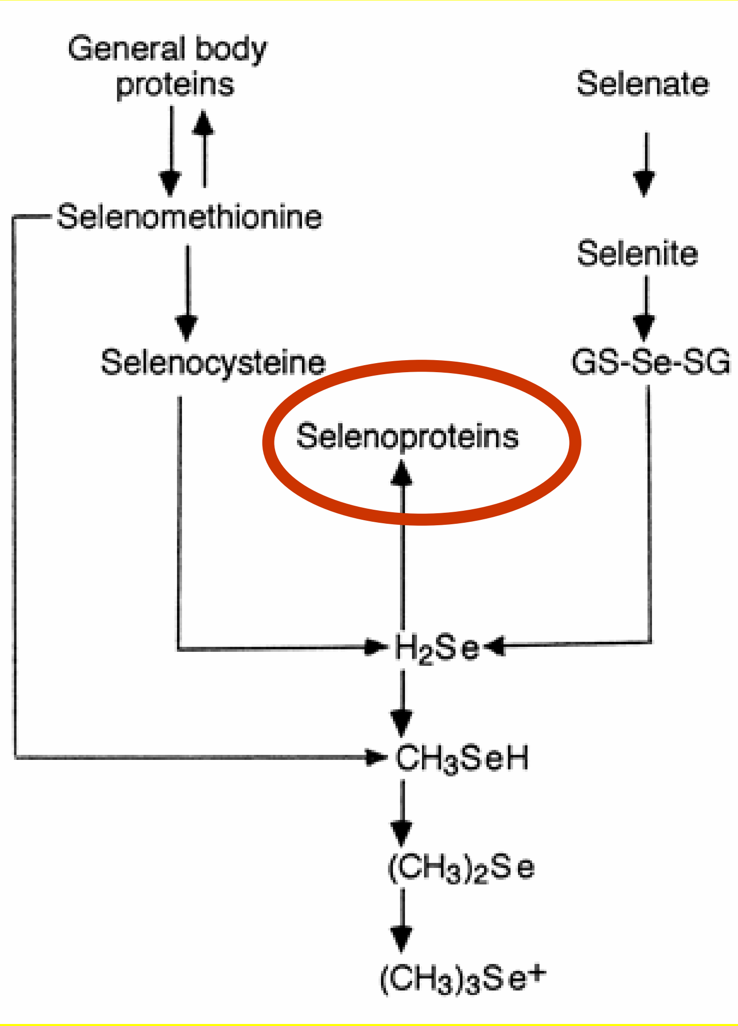
Found in human diets - cereals, vegetables.

Converted to Sec

pka: selenocysteine- 5.3

pKa: cysteine - 8.3

Sec is negatively charged at pH 7 like aspartate and glutamate.



Modified from: Schrauzer,
J. Nutr. 30:1653 (2000)

Selenium- Selenoproteins

1. Oxidative metabolism rates: Tissue T4 deiodinases - convert T4 to T3

Thyroxine (T4) made in thyroid, circulates in blood; cells convert T4 to T3, which binds thyroid hormone receptor;
Multiple forms, many cell types

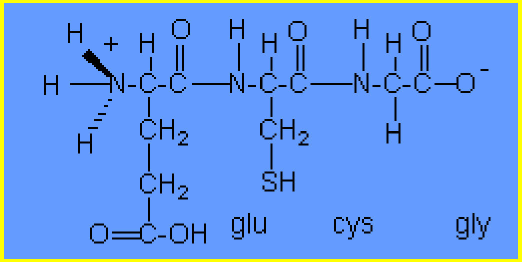
2. Cellular redox control: Thioredoxin* (Trx) Reductase (TrRX)

$$\text{Trx-S}_2 + \text{NADPH} + \text{H+} \rightarrow \text{Trx-(SH)}_2 + \text{NADP}^+$$

All cell types-multiples forms

Expression changes in differentiation and cancer

*Thioredoxins: a group of small (~ 12 kDa) redox proteins, present in all cells converts glutathioneox , a hexa –peptide (GS-SG) to 2 glutathione (GSH), a tripeptide



Selenium- Selenoproteins (cont.)

3. Resistance to oxidative damage - Glutathione Peroxidase (GPX)

Reverse membrane (lipid) oxidation; destroy H_2O_2.

2 GSH + ROOH $\rightarrow$ ROH + H_2O + GSSG; R= fatty acid

Multiple GPX forms

RBC GPx, first Se-protein identified; all cells-GPX1

Plasma- GPX 3

Enterocyte GPX-2*

Liver GPX -1,3,4

Se dietary deficiency response is hierarchal

GPX4<GPx3 < GPX 1

*Predict GPx 3 sensitivity [Se]- High? Low?

Selenium- Selenoproteins (cont.)

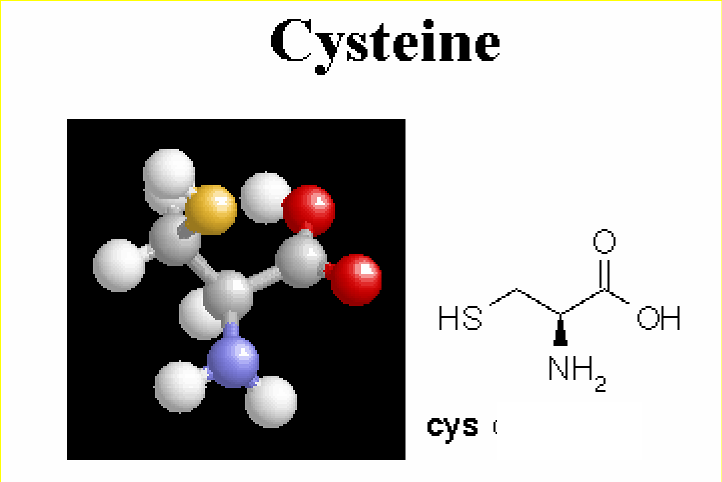
4- Plasma Se transport, antioxidative activity - Sel P

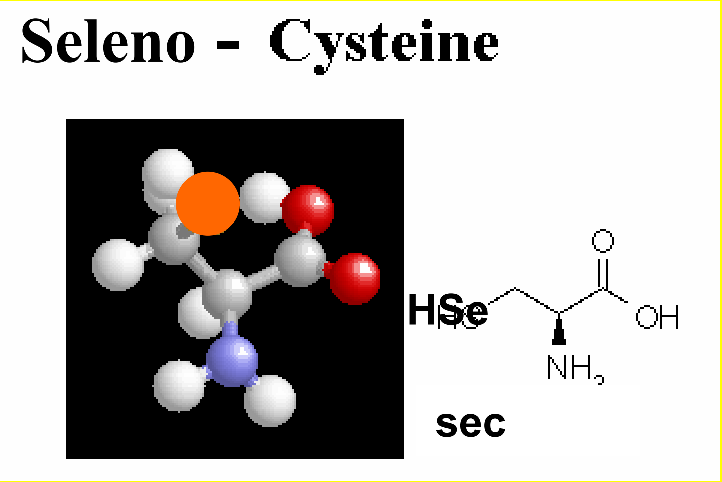
5. Methionine sulfoxide reductase- Sel R

6- "Orphan" Se proteins: ~ 10-30

Detected with surveys of DNA sequences for SECIS (<u>Se</u>c Insertion <u>S</u>equence) elements

Selenocysteine – Structure, DNA Code





Cysteine	UGU
Cysteine	UGC
Selenocysteine	UGA
Stop	UGA

One codon – two uses

AUG	Methionine
AUG	Start

Summary

Selenium Nutrition and Physiology

a) Toxicity: known before physiological requirement
b) Sufficiency: range narrow
c) Deficiency: cardiomyopathy ; Goiter (+ I^- def.); osteoarthritis
d) Cancer: Se derivatives have anti-tumor activity
e) Distribution:
    All cells
    Hi-Blood, Liver, muscle, bone
    Cell-specific isoforms
f) Source: Cereals, vegetables

Selenium Biochemistry

a) Two amino acids:
    Selenocysteine – synthesis: humans, animals, plants, bacteria
    Selenomethionine- synthesis:plants, converted to Sec in animals and humans
b) Se catalysts: antioxidant peroxidases, reductases (GPx, TrRX, SelR) and T4 deiodinases
c) Se regulation: protein- specific and hierarchal
d) Sec DNA code: 21st codon; second use UGA termination codon