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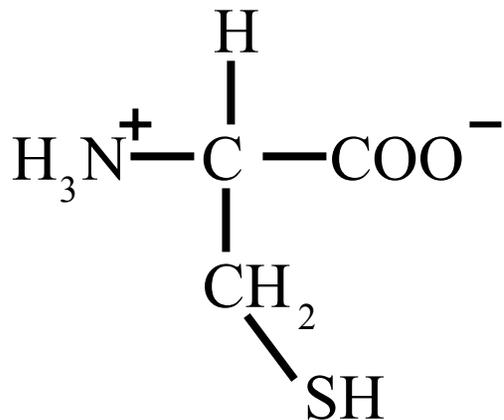
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**INSIGHTS INTO POTENTIAL MECHANISMS OF MERCURY TOXICITY:
IMPACT OF MERCURY ON SELENIUM DEPENDENT PHYSIOLOGY.**

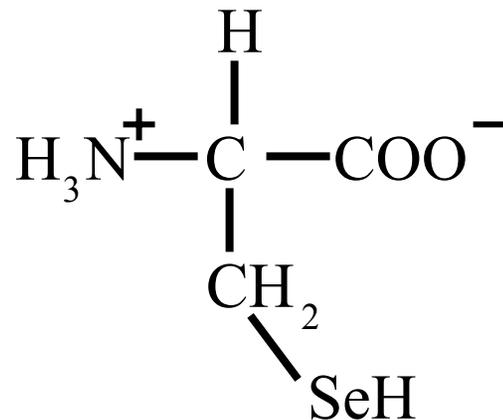
Dr. Nicholas V.C. Ralston
Environmental Health Research Unit
Energy and Environmental Research Center
Grand Forks, North Dakota

BIOLOGICAL HEROES AND VILLAINS (PARTIAL CAST OF CHARACTERS)

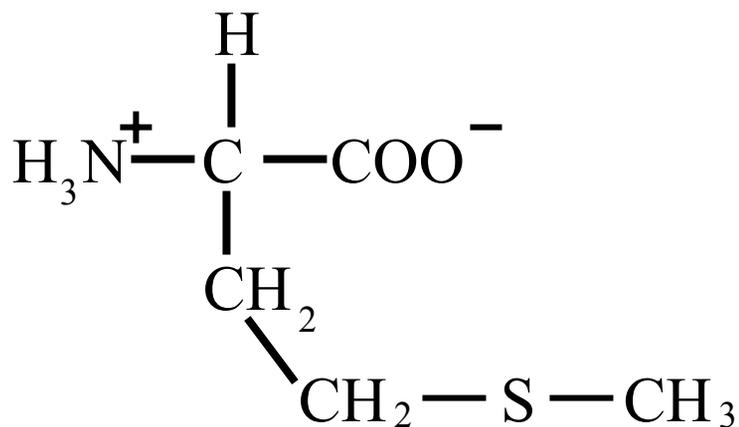
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							He
		B	C	N	O	F	Ne
		Al	Si	P	S	Cl	Ar
Cu	Zn	Ga	Ge	As	Se	Br	Kr
Ag	Cd	In	Sn	Sb	Te	I	Xe
Au	Hg	Ti	Pb	Bi	Po	At	Rn



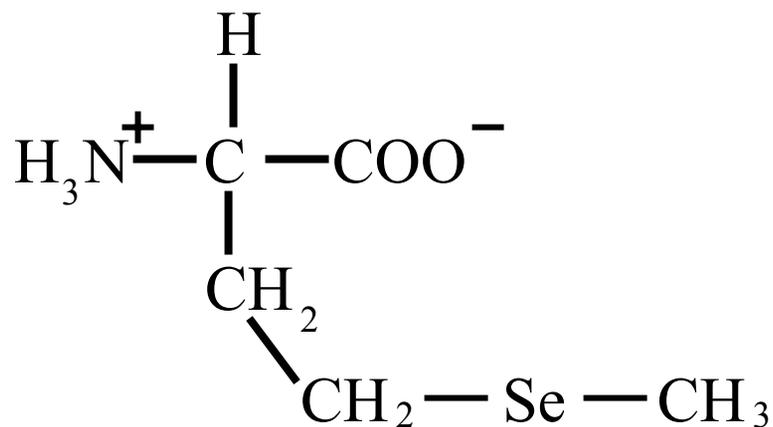
CYSTEINE



SELENOCYSTEINE

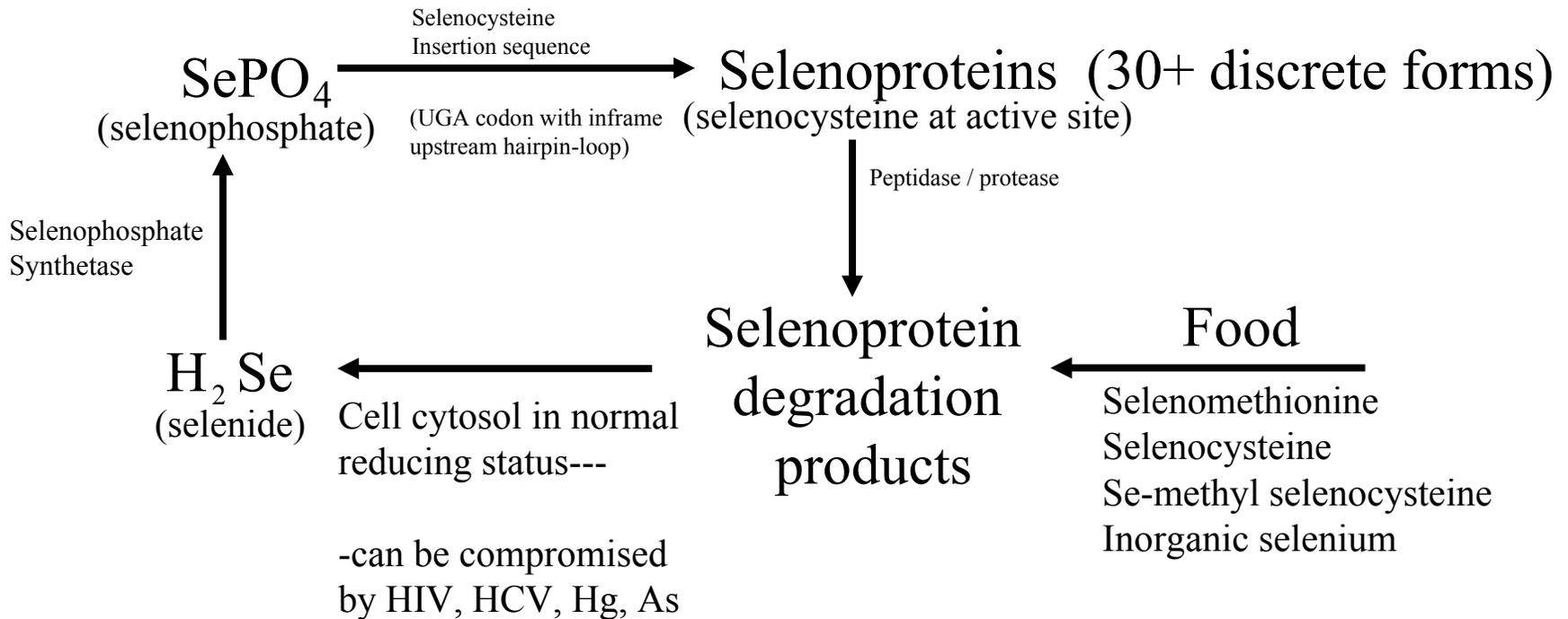


METHIONINE



SELENOMETHIONINE

SELENOPROTEIN SYNTHESIS



Selenocysteine is the only amino acid that must be recreated for each cycle of protein synthesis

SELENOPROTEINS AND SELENOENZYMES

Selenoprotein P; ~65K (10 selenocysteines)

Primary Se transporter in plasma, carries Se to Brain and testes

Thioredoxin reductase ~57K (3 forms)

Active in DNA synthesis, immunoregulatory influences

Selenophosphate synthetase ~50K

Present in all tissues synthesizing selenoproteins

Phospholipid glutathione peroxidase ~27K

Detoxifies lipid peroxides

Cytosolic glutathione peroxidase ~23K

Detoxifies peroxides in aqueous compartment of cytosol

Plasma glutathione peroxidase ~23 K

Primarily synthesized in kidney, main role may be Se transport



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SELENOPROTEINS AND SELENOENZYMES

(continued)

Sperm glutathione peroxidase; ~23K

Required for normal sperm activity, function?

15K selenoprotein ~15K

Discovered in leukocytes, but broadly distributed, function ?

Thyroid hormone 5'deiodinase ~14K

Present in tissues that convert T4 → T3 (thyroxine)

Selenoprotein W ~10K

Found in muscle, but widely distributed, function?

5K selenoprotein -, 7K selenoprotein, 8K selenoprotein

Tissue dependent occurrence and distributions, function?

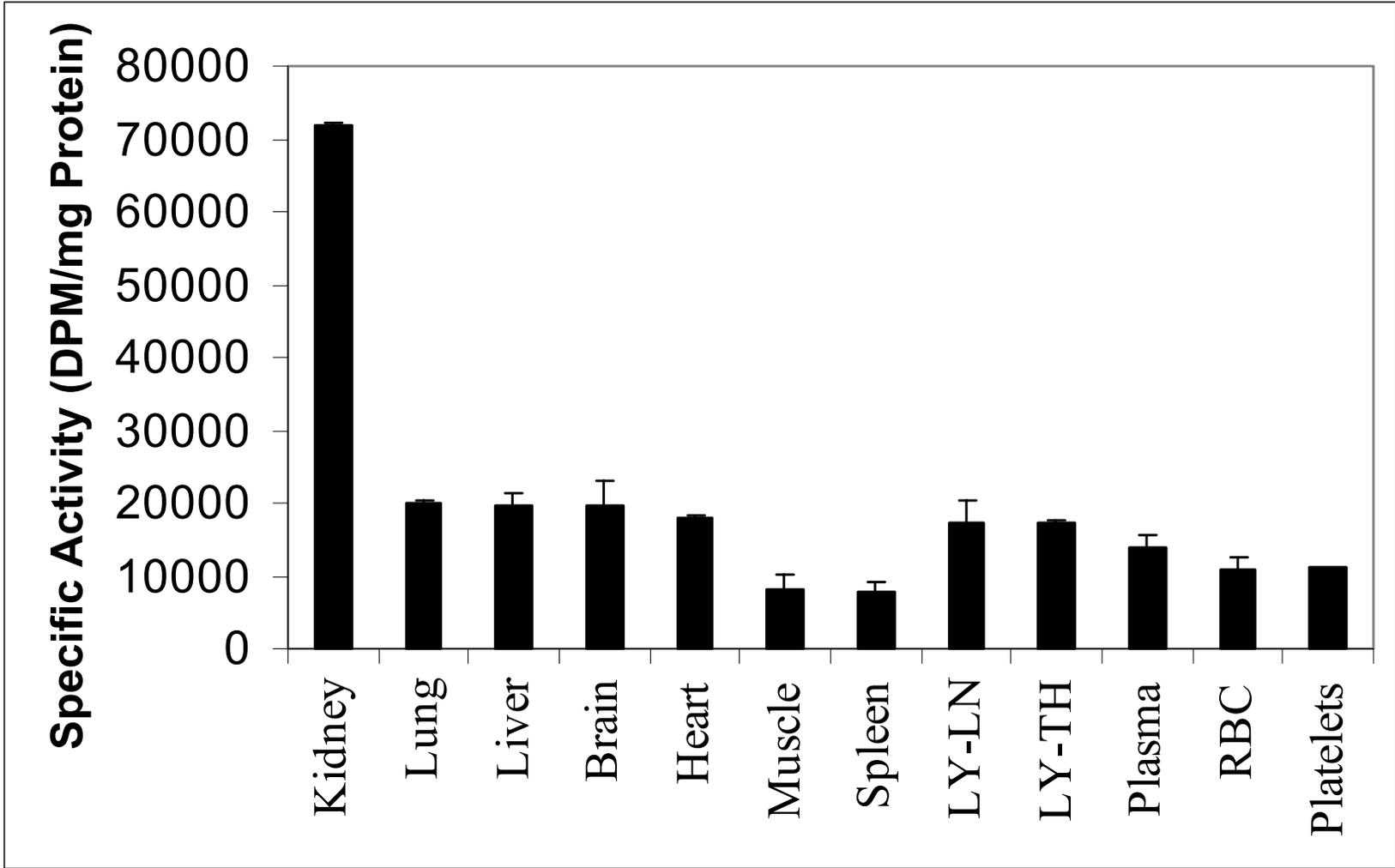
<5K selenomolecules

Abundant in brain, present in leukocytes and platelets, function/s?



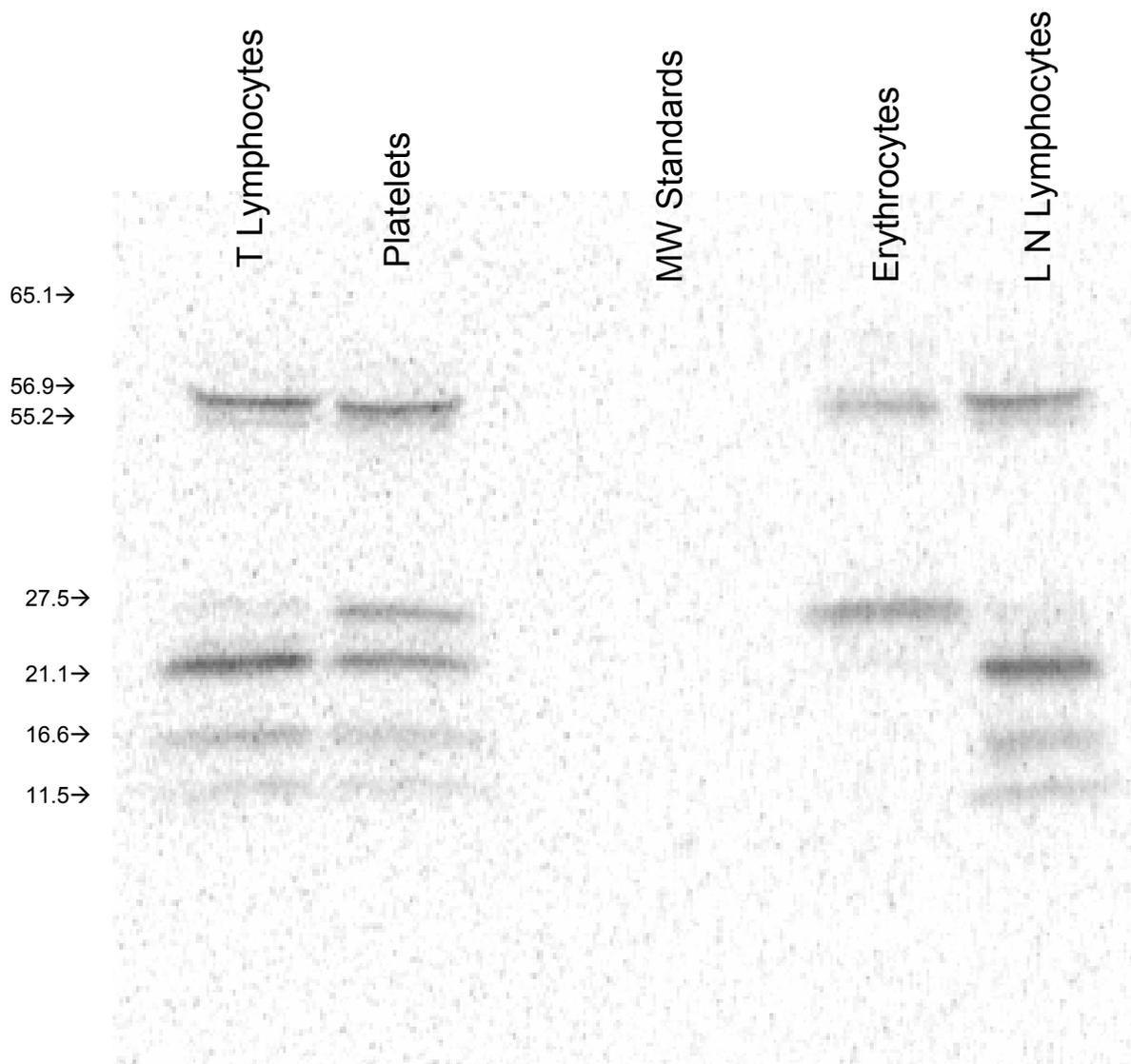
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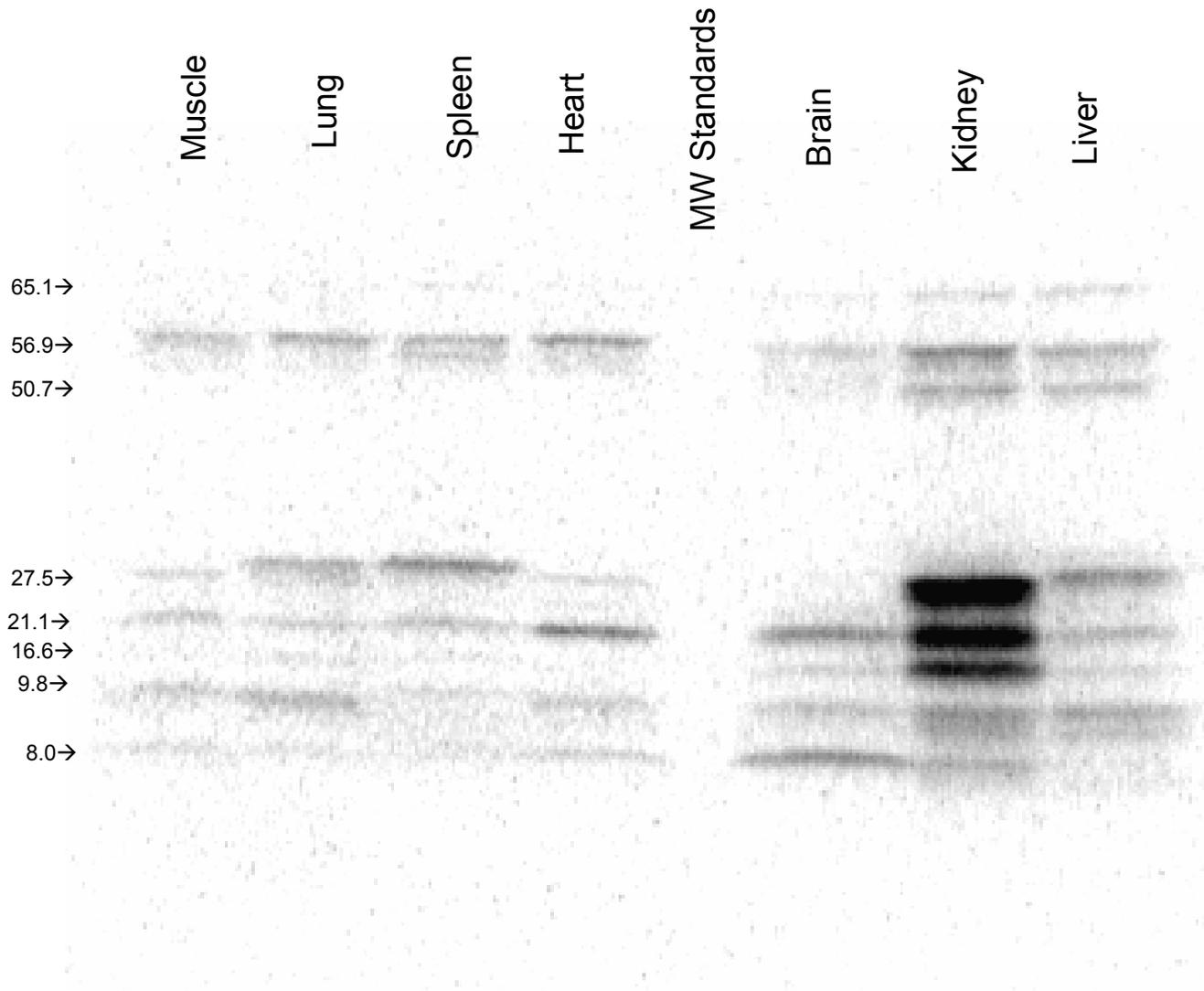
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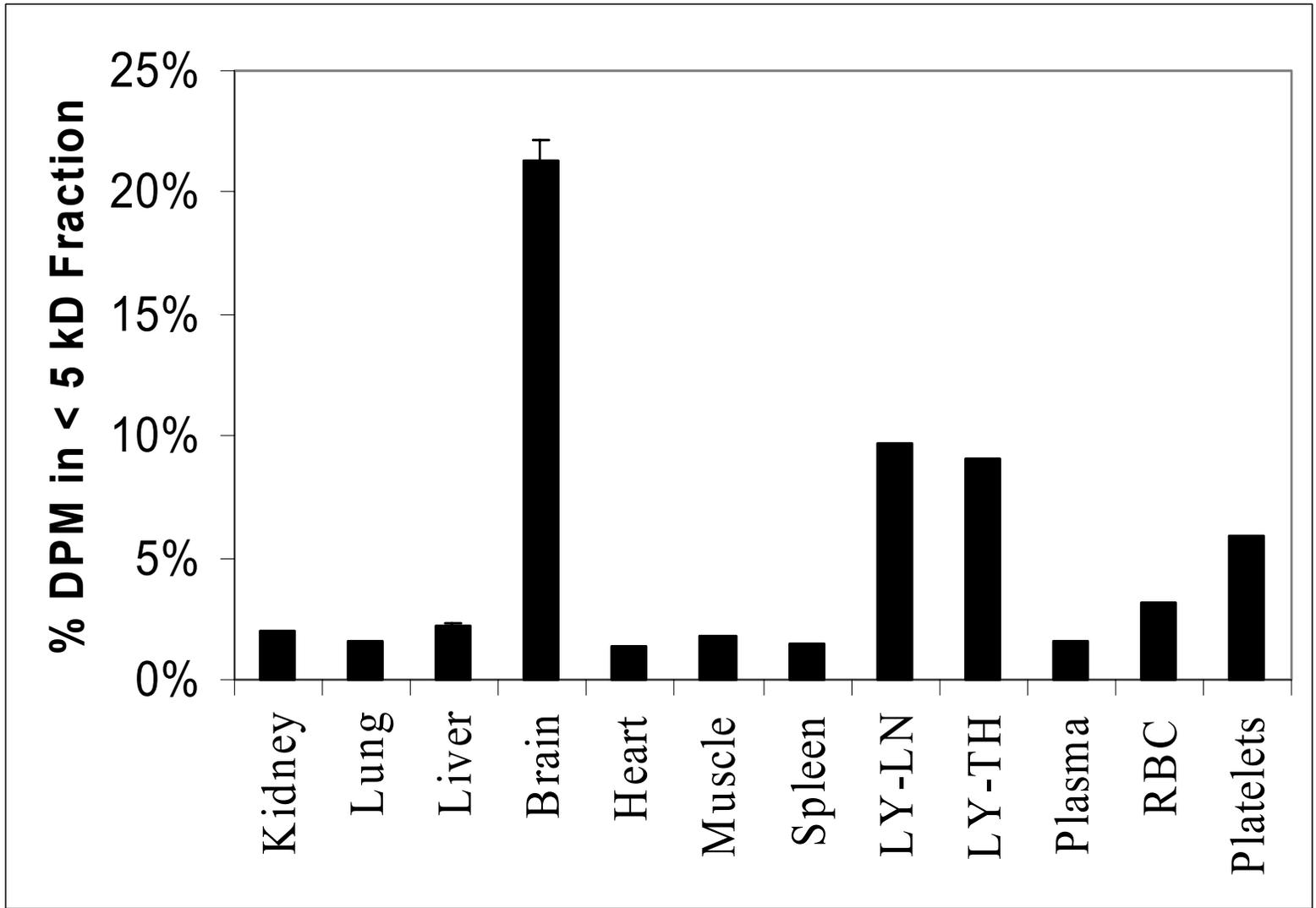
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**IS SELENIUM THE HERO THAT
“PROTECTS” AGAINST MERCURY
TOXICITY, OR IS SELENIUM THE
VICTIM OF MERCURY TOXICITY?**



Image from; J.J. Putman & R.W. Madden (1972) National Geographic 142(4): 506-527



JK

1865 ILLUSTRATION BY JOHN TENNIEL

**Twinkle, twinkle, little bat
How I wonder what you're at**

Spouting one bit of gibberish after another, the Mad Hatter in Lewis Carroll's *Alice's Adventures in Wonderland* exhibited a trait common to many 19th-century hatmakers—incoherent speech. Working long hours with mercury-treated pelts, they absorbed the poison through their skin and inhaled mercury vapor, which caused them to shake and to slur their words.



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MERCURY TOXICITY

- The mechanism of mercury's toxic effects has not been defined.
- Debilitating and/or Lethal toxicity effects noted in adults and newborns in acute high dose Hg poisoning in Japan and Iraq.
- Cumulative effects of chronic low dose exposure unknown.
- Negative neurodevelopmental effects associated with fish/whale consumption (Hg?) apparent in New Zealand and Faroe Islands.
- No such fish consumption effects were noted in the Seychelles.

BACKGROUND

- **Mercury complexes with selenide, forming insoluble precipitates which accumulate in neuronal lysosomes.**
- **Mercury toxicity effects apparent in regions of the world which have low “free” selenium supply from food sources.**
- **Selenium supplementation is known to “protect” against the consequences of toxic doses of mercury.**
- **Brain selenoenzymes are compromised by Hg toxicity.**



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HYPOTHESIS

Selenoenzymes perform vital functions in brain tissues

Free radical detoxification via glutathione peroxidase

T4 → T3 conversion via selenium dependent deiodinases

DNA synthesis via thioredoxin reductase (TR)

Immunocompetence and cell-cell signaling via TR

When excessive quantities of mercury sequester available selenium in insoluble Hg-Se complexes, selenoenzyme synthesis is inhibited

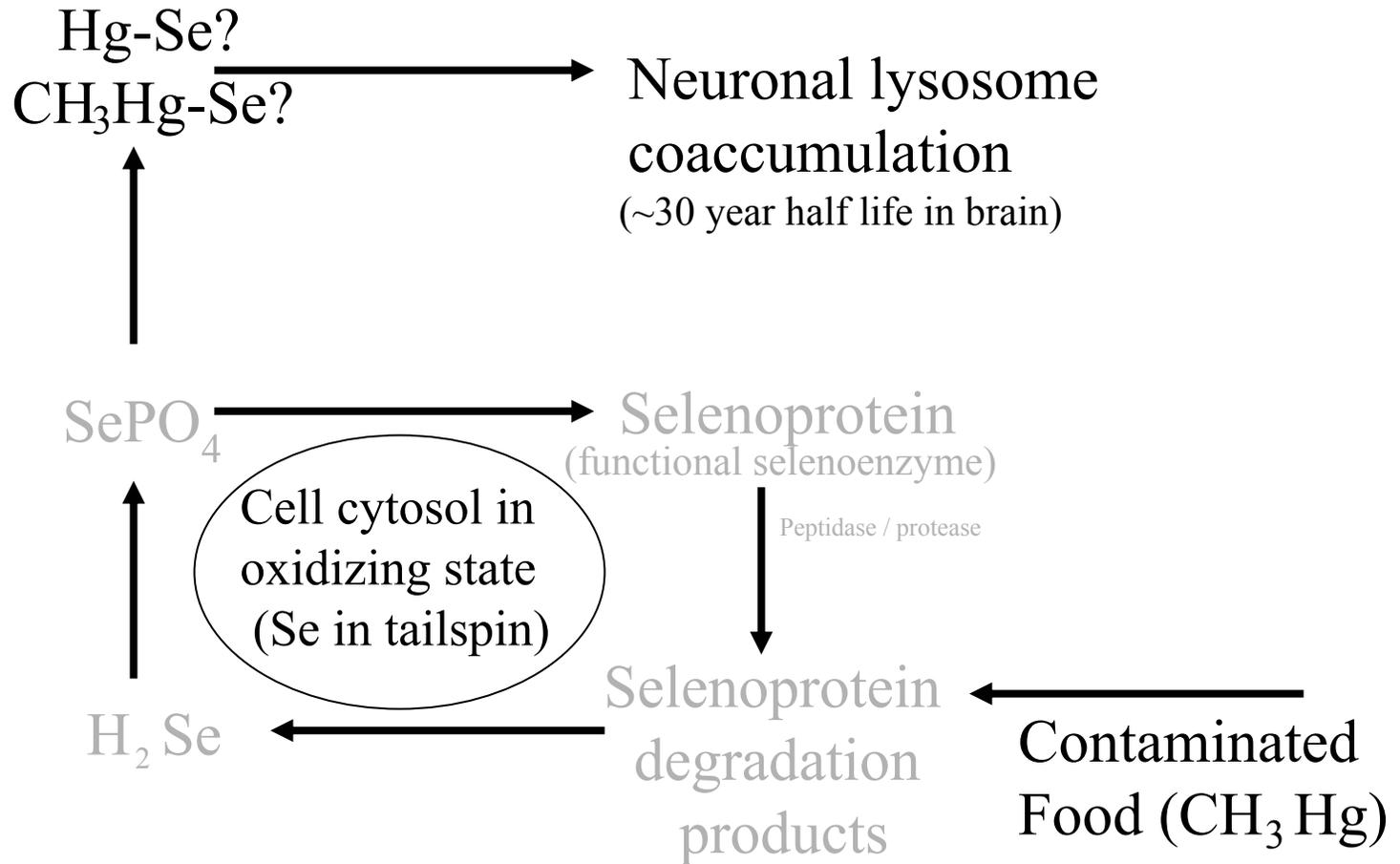
Loss of these selenoenzyme dependent physiological functions results in the signs and symptoms recognized as mercury toxicity



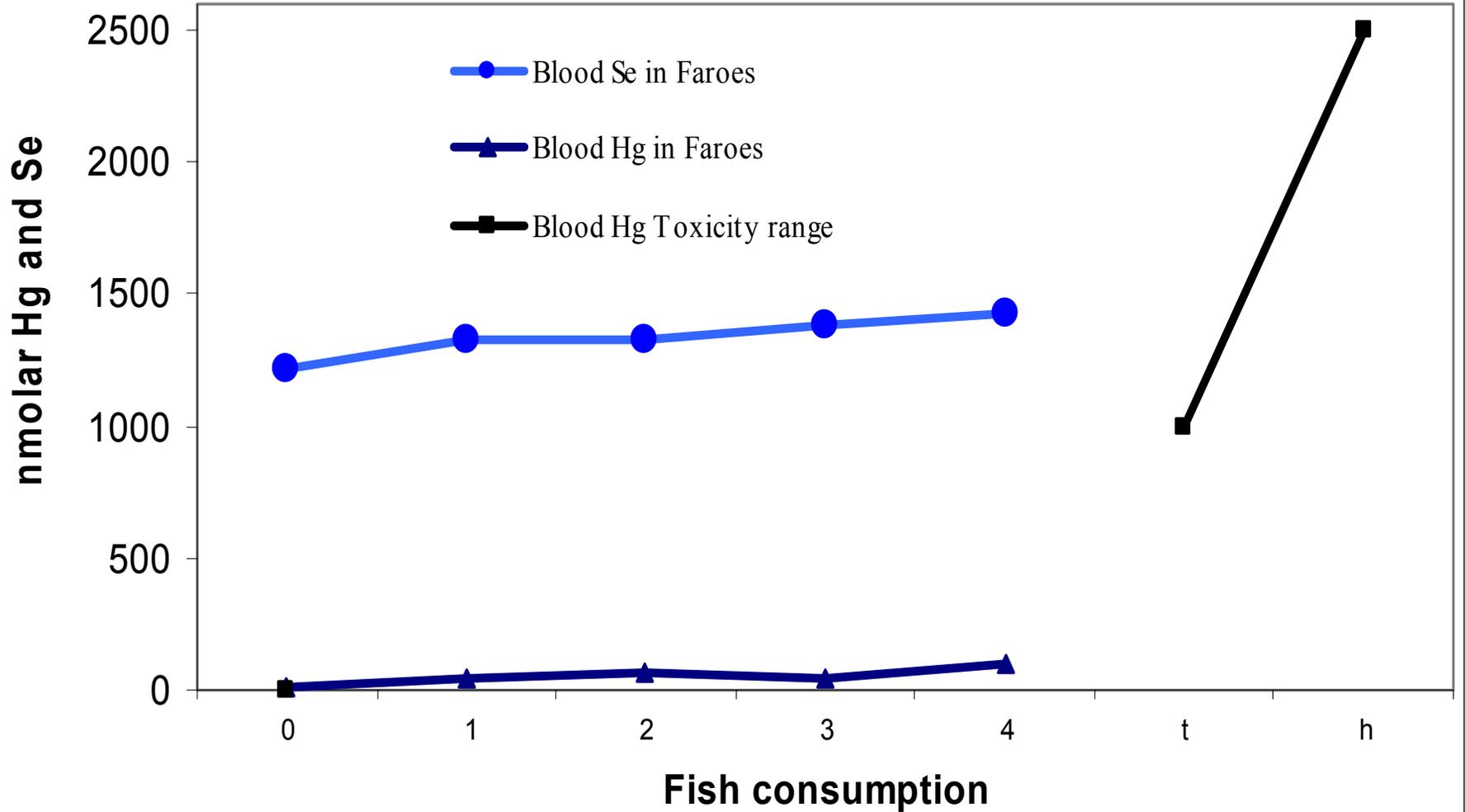
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MERCURY DEPENDENT INTERRUPTION OF SELENOPROTEIN SYNTHESIS



Relation between blood Hg and Se



Biological Concentration Factors of Mercury

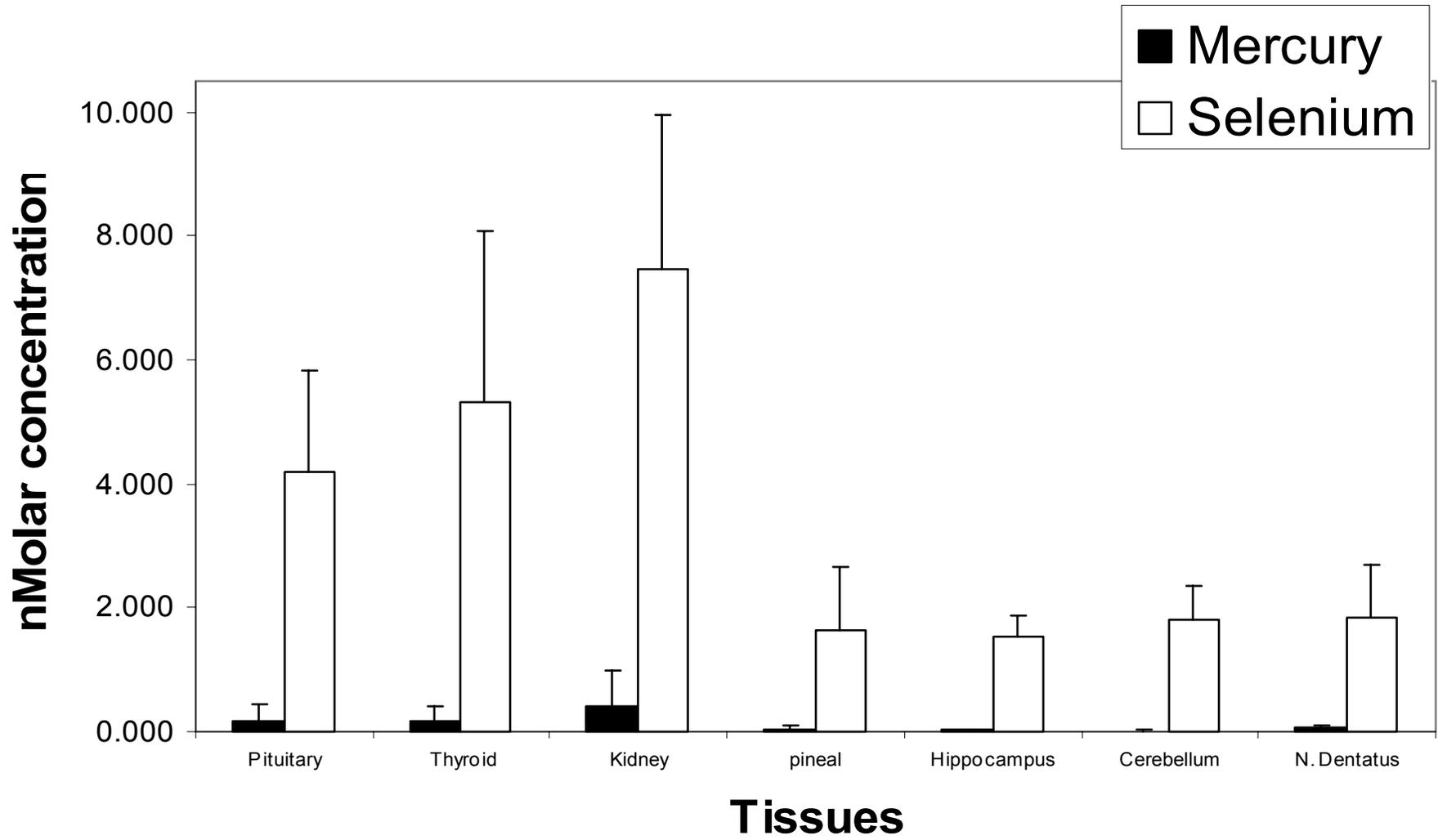
- Water 1
 - Plant 1,000
 - Invertebrates 100,000
 - Fish 1,000
 - Mammals 5
 - Birds 50
-
- (Van Hook, R.I. *Env. Health Perspectives* 27: 303, 1978)



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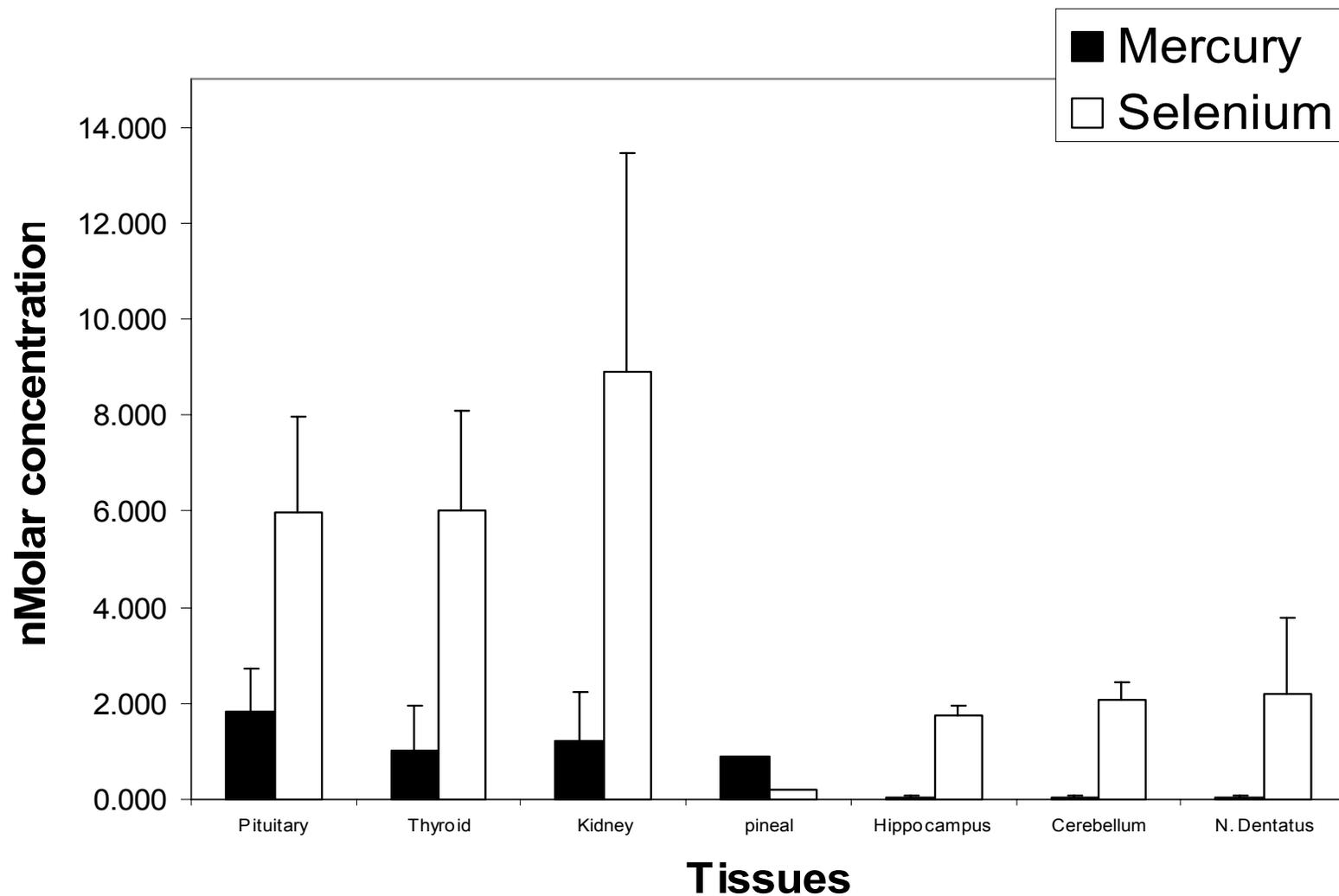
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Hg and Se in Control Tissues



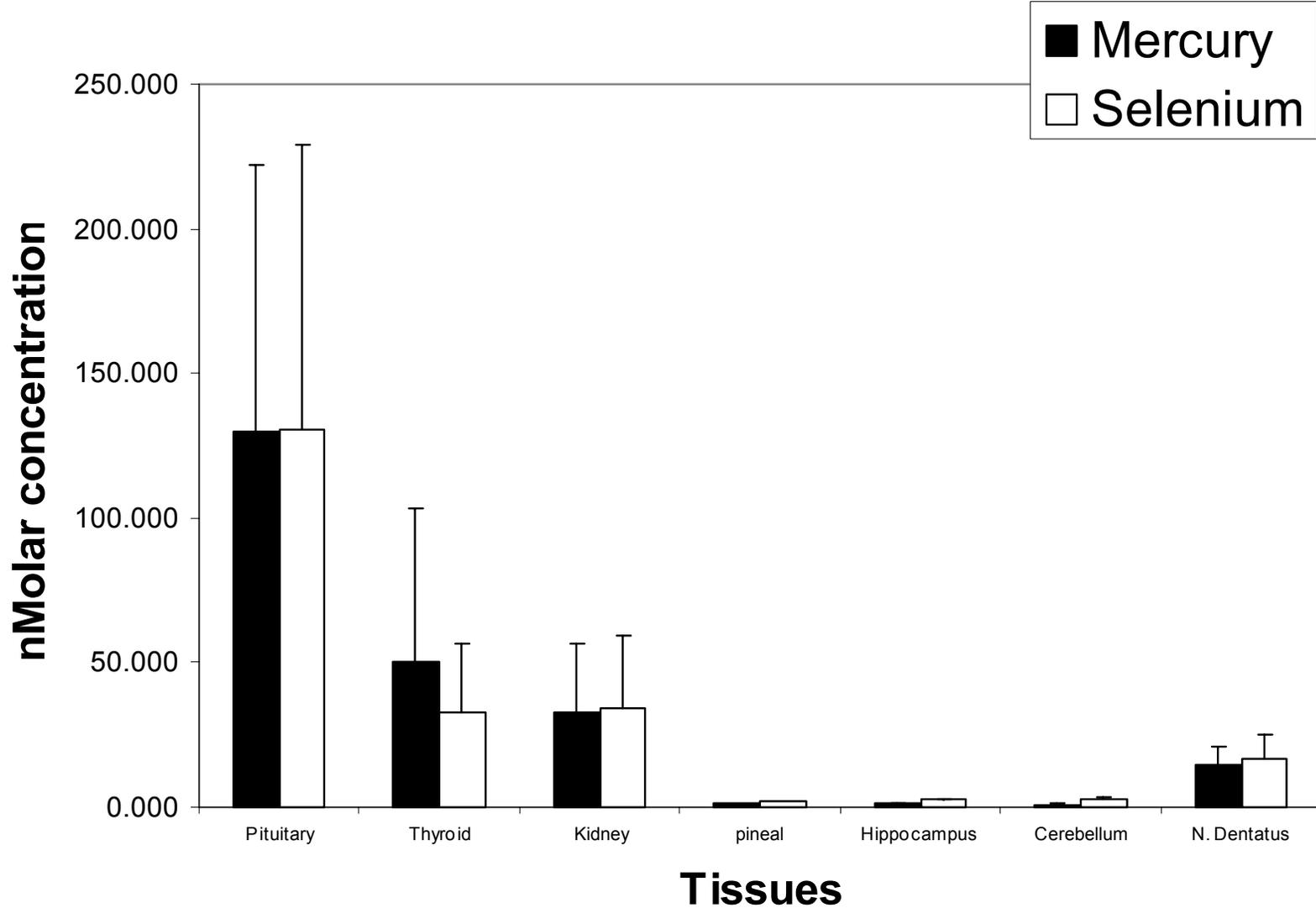
Adapted from; I. Falnoga, et.al., (2000) *Environ Res.*, 84(3):211-8.

Hg and Se in Resident's Tissues



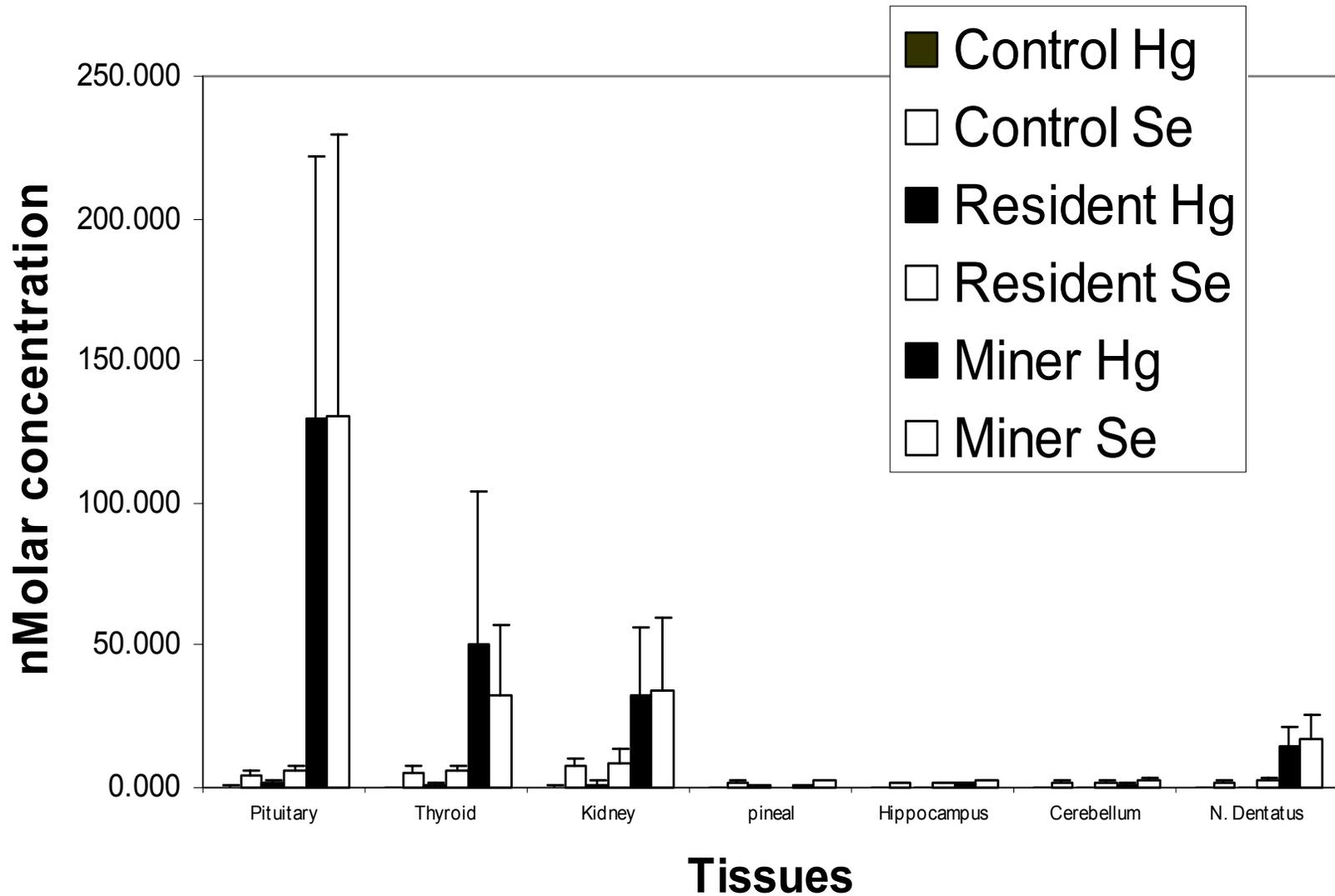
Adapted from; I. Falnoga, et.al., (2000) *Environ Res.*, 84(3):211-8.

Hg and Se in Miner's Tissues



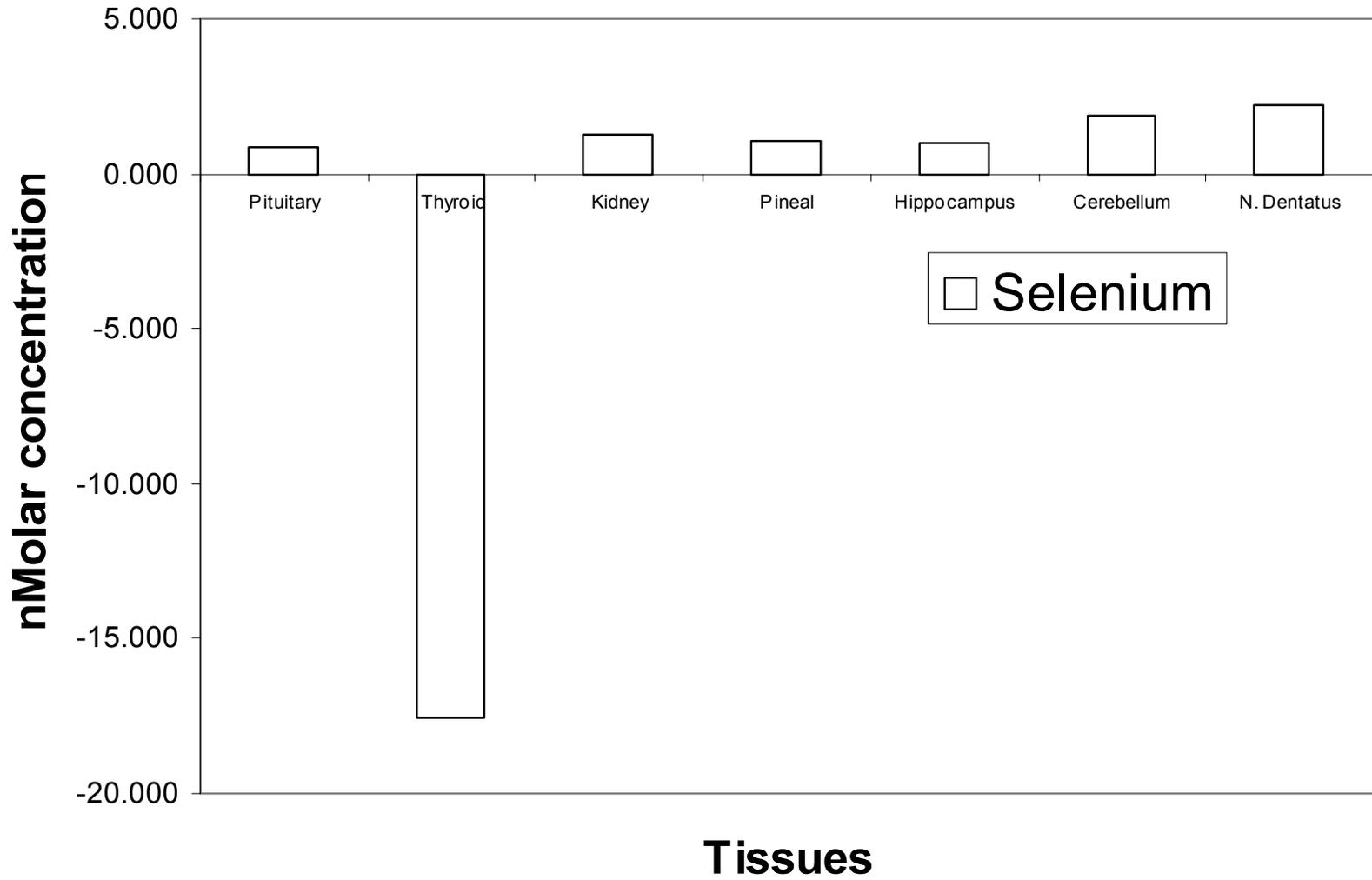
Adapted from; I. Falnoga, et.al., (2000) *Environ Res.*, 84(3):211-8.

Hg and Se in Tissue Samples



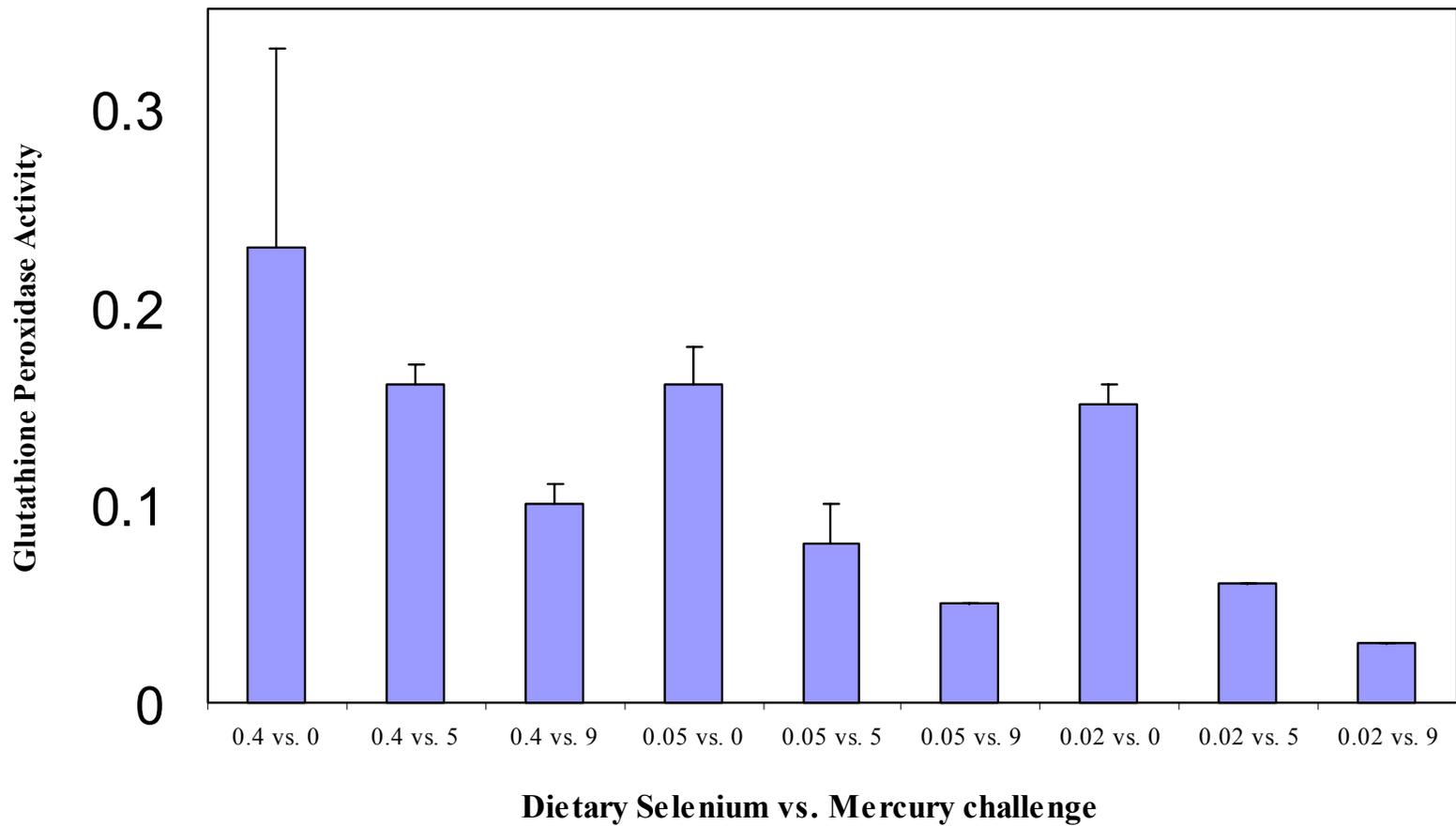
Adapted from; I. Falnoga, et.al., (2000) *Environ Res.*, 84(3):211-8.

Se-Hg in Miner's Tissues



Adapted from; I. Falnoga, et.al., (2000) *Environ Res.*, 84(3):211-8.

Neonatal Brain Glutathione Peroxidase



Adapted from; C. Watanabe, et.al., (1999) *Neurotoxicol Teratol* 21 (1): 83-88.

CONCLUSIONS:

- MECHANISM OF MERCURY TOXICITY MAY INVOLVE INHIBITION OF SELENIUM DEPENDENT PHYSIOLOGY
- SELENIUM STATUS MAY INFLUENCE VULNERABILITY OF MERCURY EXPOSED POPULATIONS
- IN-SILICO, IN-VITRO AND IN-VIVO STUDIES FOCUSED ON EXAMINING THE SELENIUM-MERCURY INTERACTION ARE NEEDED TO CLARIFY TOXICITY MECHANISM/S
- POPULATION STUDIES NEED TO INCLUDE EXAMINATION OF SELENIUM STATUS IN RELATION TO MERCURY EXPOSURE



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