# SELENITE is not SELENIUM

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## Selenite ($Na_2SeO_3$) ethical concerns

# Conflicts of interest

- Main Shareholder of a very small start up SERENITE-Forceville

  Patent filed in 2015 on a treatment of sepsis combining antioxidant and oxidant selenocompounds

- Working on that field for 30 years

# For details

**2 recent bound review and forum review articles in ARS (Antioxidant and Redox Signaling is a leading journal in oxidation field):**

- **Selenocompounds and Sepsis, Redox Bypass Hypothesis:**
  **Part A: Early acute phase of sepsis an extraordinary redox situation**
  (Leukocyte/Endothelium Interaction Leading to Endothelial Damage)
  X Forceville, P Van Antwerpen, JC Preiser,
  Antioxid Redox Signal. 2021;35(2):113-38.

- **Selenocompounds and Sepsis, Redox Bypass Hypothesis:**
  **Part B: Selenocompounds in the Management of Early Sepsis**
  X Forceville, P Van Antwerpen, D Annane, JL Vincent
  Antioxid Redox Signal., 2022 37(13-15):998-1029

  Free of access via pubmed (in beta version via HAL)

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# Selenite Janus Molecule
# Dual Action (Quantum Chemistry)

LD ≠ weight of 3 caffe beans

## 1- Selenite is a poison as toxic as arsenic LD ≠ weight of

- Oxidant molecule (orally Lethal Dose min. LD ≠ 3-5 mg Se/kg)
- Toxicity is most probably increase in sepsis (i.e. min. LD 0.3-0.6 mg Se/kg)
- But toxicity is most probably more concentration than dose dependent.
- Multiple organ failure (cardiorespiratory distress at foreground)

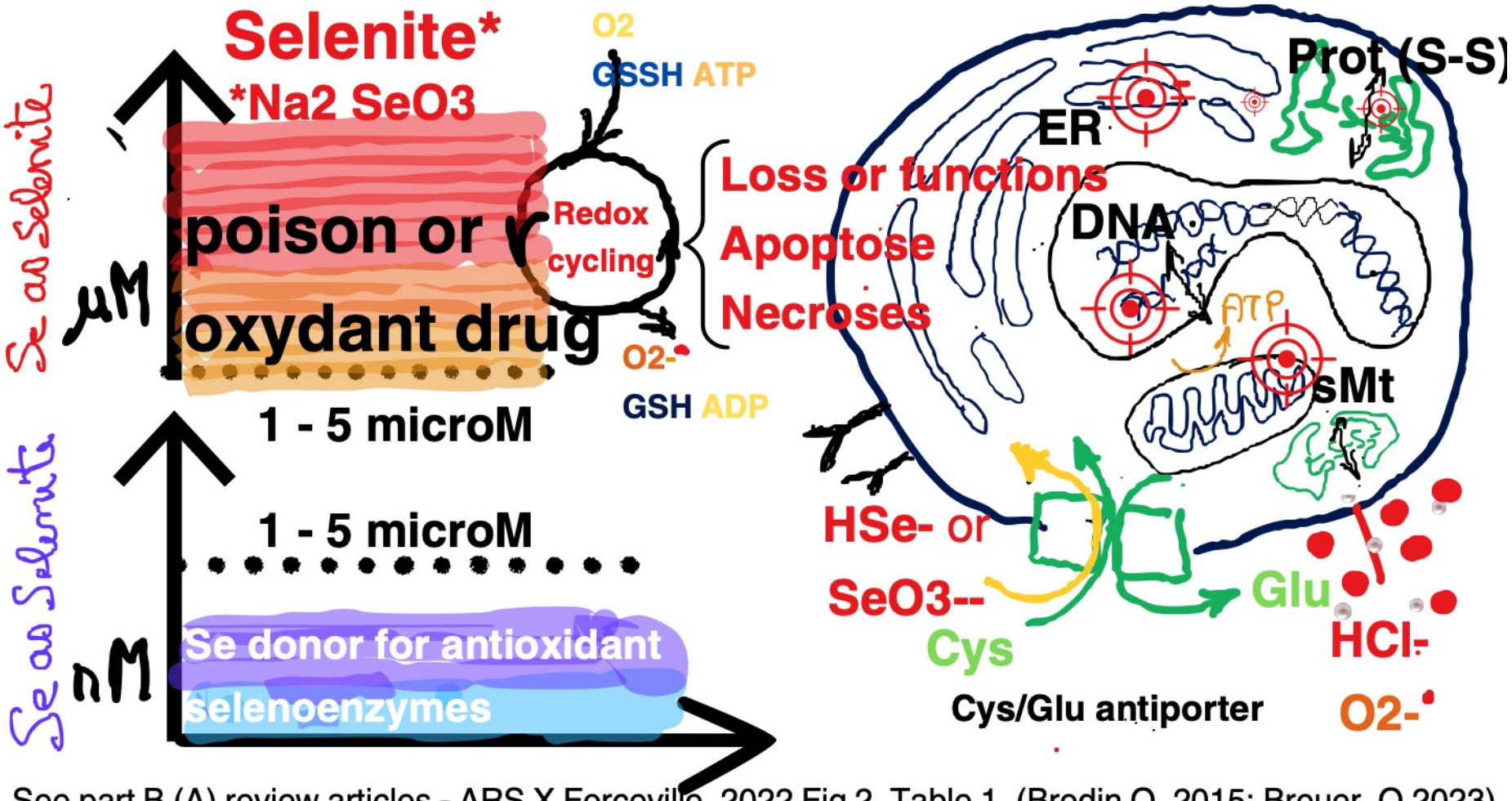
## 2- Selenite is a chemotherapeutic agent (stop in G2M phase):

- Toxicity of selenite is dose but even more concentration dependent. Selenite is cytotoxic for concentration > 1-5 µmole Se/L. Selenite is actively incorporate on active cells and damage many targets in cells :
  - DNA (double strand break),
  - Mitochondria,
  - Endoplasmic reticulum,
  - Proteins (disulfur bridge S-S)

## 3- Selenite could deliver Se after a complex metabolism (pro-antioxidant)

- Physiologically in the liver (3-4 mg Se content)
- Se is essential for vital antioxidant selenoenzymes
- Total body content (TBSe) 10-15 mg Se
- Orally Upper Limit 400 µg Se/d (or 200 µgSe /d), Low Adverse Effect Level 900 µg Se/d

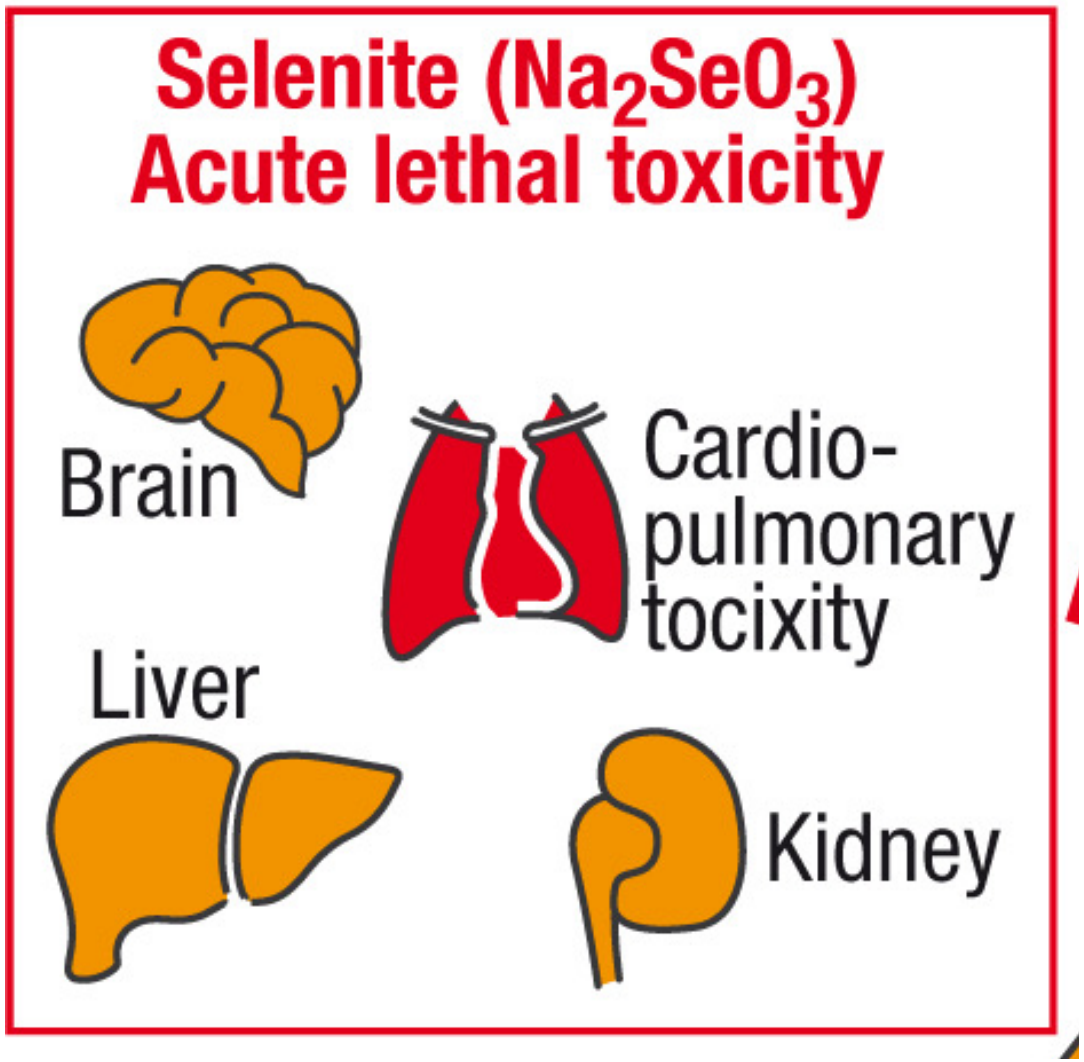
# Selenite Cytotoxicity (in vitro, in animal, in Phase I)




See part B (A) review articles - ARS X Forceville, 2022 Fig 2, Table 1, (Brodin O, 2015; Breuer, O 2023)

Teratogenic, mutagenic, most probably carcinogenic (its metabolite HSe- is carcinogenic)

# 2a - General Acute Toxicity Mimic Septic Shock

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# 4b - Plasma Se and Selenoenzymes (which are decreased in sepsis : 0.3 mg Se - 2% of TBSe)

- Selenocysteine (Sec)
  - **Selenoprotein-P (SELENOP) ≈ 60%**
    - Specific and non-Specific binding (low pH)
    - Double function: Sec Transport and antioxidant enzyme (TXRND)
    - Protection of endothelium against peroxynitrite ($ONOO^-$) ; Endothelium Surface Layer ESL
  - **Glutathion peroxidase 3 (GPX 3) ≈ 30%**
    - Very low glutathione concentration in plasma
    - Could have a protective effect for basal membrane
- Selenomethionine (SeMet)
  - **Albumin ≈ 10%**

**See part B article** for the blockage of SELENOP synthesis in sepsis, and the article of Wang, Forceville, 2010 Shock for selenite action as selenium provider or drug action.

# Dose Expression Problem of Selenite Administration

- **Molecular weight**
  - $Na_2$ ≠ 23 g x2 – Se ≠ 79 g – $O_3$ 16 g x3
  - Se = 0.46 $Na_2SeO_3$

- **Correspondence**
  - 1 mg Selenite ≠ 0.5 mg Se as selenite

- **Mistake**
  - Mistake in expression of delivered amout could lead to a wrong message lowering the administrated dose by a factor 2
  - (e.g. indicating 2 mg selenite for a real administration of 2 mg Se as selenite).

# Main Ethical Concerns for Selenite

- **Selenite should be recognized as drug in cytotoxic range**
  - Above a nutritional dose and especially if reaching cytotoxic concentration (intravenous, and especially if bolus injection reaching concentration > 1-5 µmol Se/L) selenite should be considered as an active ingredient (i.e. drug)

- **When acting as drug it should follow rules of drug development and classified as Active Ingredient (AI) (e.g. drug) by Medicines Agency.**

- **Direct experimentation of selenite in patients in drug range raise ethical concerns and even more in patients with low mortality rate.**
  - Especially as selenite is teratogenic, mutagenic and most probly carcinogenic and there is no pharmacovigilance;
  - Not avoiding acute toxicity, which seems increased in sepsis and difficult to spit from sepsis (or acute inflammation) evolution.