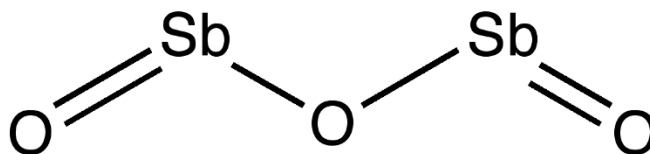


# Disposition and Toxicokinetics



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National Institute of Environmental Health Sciences

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# Antimony Disposition & Toxicokinetics

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The following topics will be addressed for ADMET of antimony from antimony trioxide:

*Metabolism:* Transformation of antimony in the body

*Absorption:* Entry of antimony into the body

*Excretion:* Elimination from the body as evidence for absorption

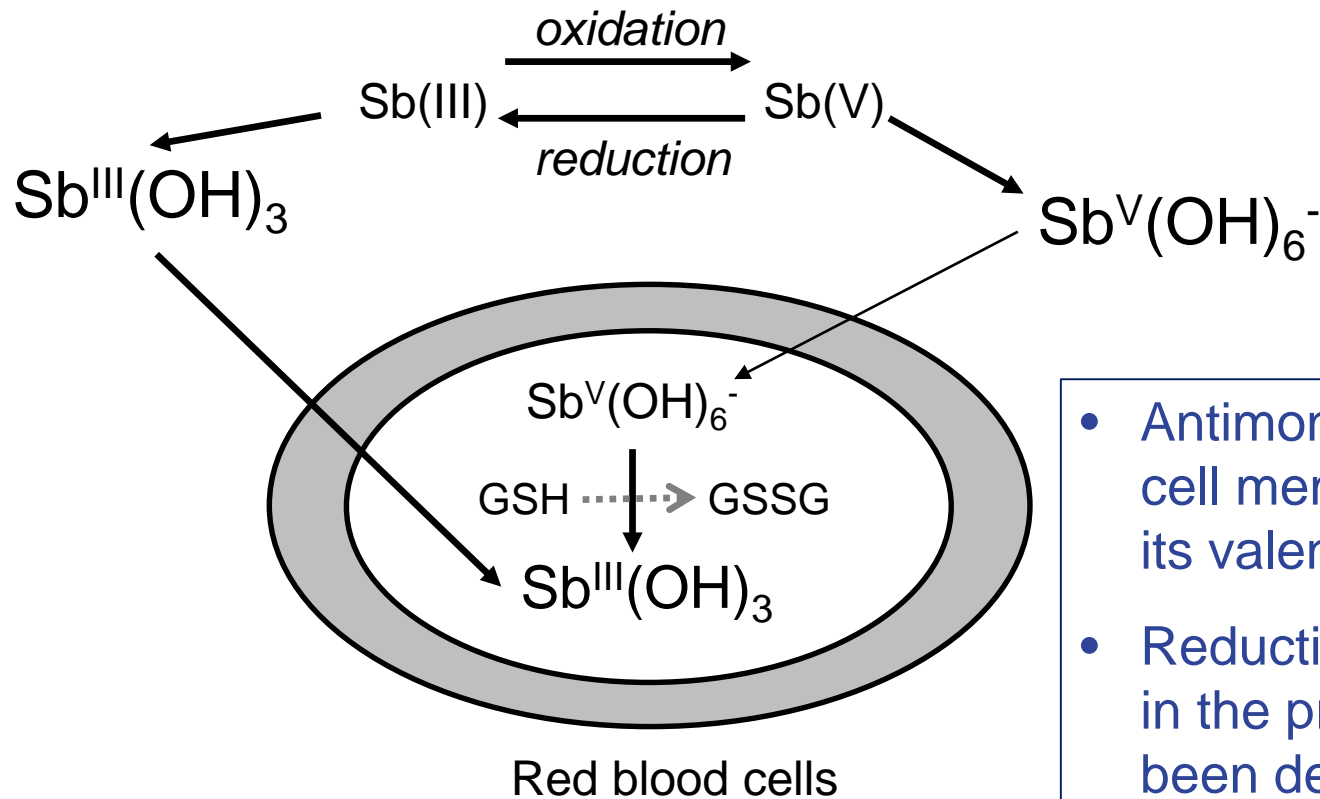
*Distribution:* Tissues where antimony is present in the body

*Toxicokinetics:* Effects of antimony accumulation



# Antimony Metabolism

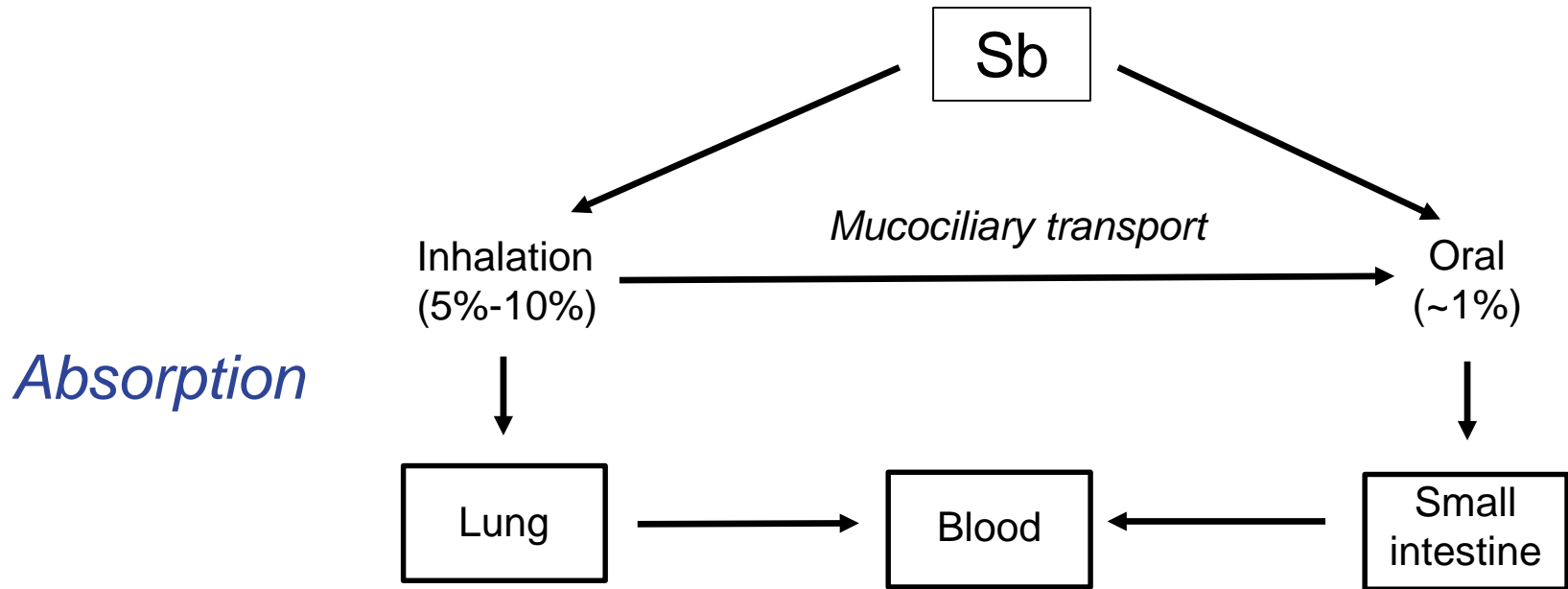
The chemical form of antimony trioxide changes once it dissolves in bodily fluids, where it forms the hydroxides,  $\text{Sb}^{\text{III}}(\text{OH})_3$  and  $\text{Sb}^{\text{V}}(\text{OH})_6^-$ , which have limited solubility



- Antimony's ability to cross cell membranes varies with its valence.
- Reduction of  $\text{Sb}^{\text{V}}$  to  $\text{Sb}^{\text{III}}$  in the presence of thiols has been demonstrated *in vitro*.
- Valence also impacts tissue distribution and excretion.



# Absorption of Antimony



- Dermal absorption also occurs, particularly for workers and consumers through contact with fire retardant treated materials.
- Absorption of antimony trioxide is greater with inhalation than with oral ingestion for both valences, but mucociliary transport can result in oral absorption for some inhaled antimony trioxide.



# Inhalation Exposure Results in Excretion

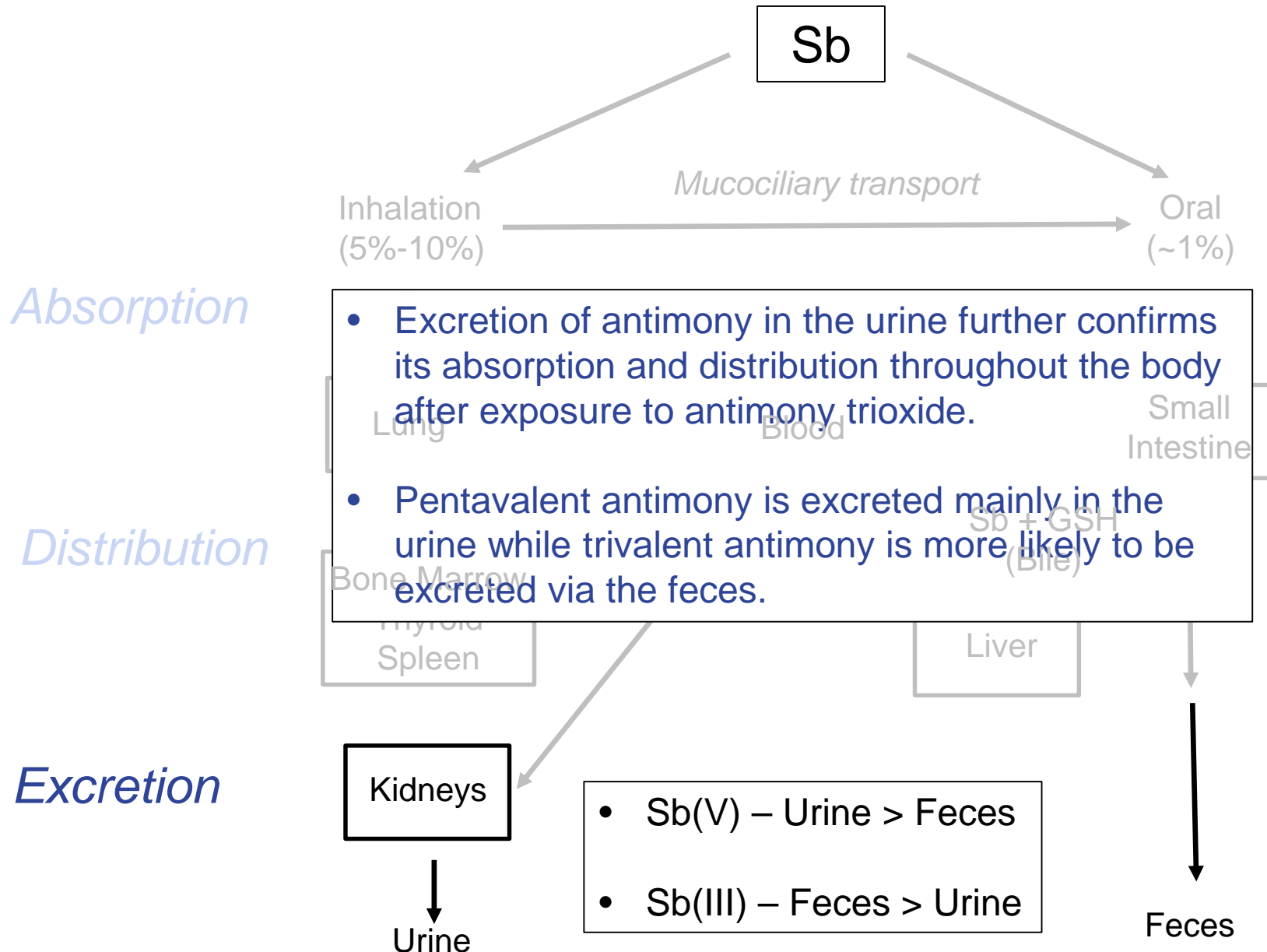
Exposure to Sb <sub>2</sub> O <sub>3</sub> (Reference)	N	Air Sb Levels (µg/m <sup>3</sup> )	Urine Sb Levels (µg/g creatinine)
Lead battery production (Kentner <i>et al.</i> 1995)	7	4.5	3.9
Antimony(III) trioxide production (Kim <i>et al.</i> 1999)	12	766 <sup>a</sup>	419.8 (µg/L)

<sup>a</sup>Exceeds ACGIH TLV of 500 µg/m<sup>3</sup>

- Workers exposed to antimony trioxide by inhalation excrete more antimony in the urine, confirming human absorption from these exposures.

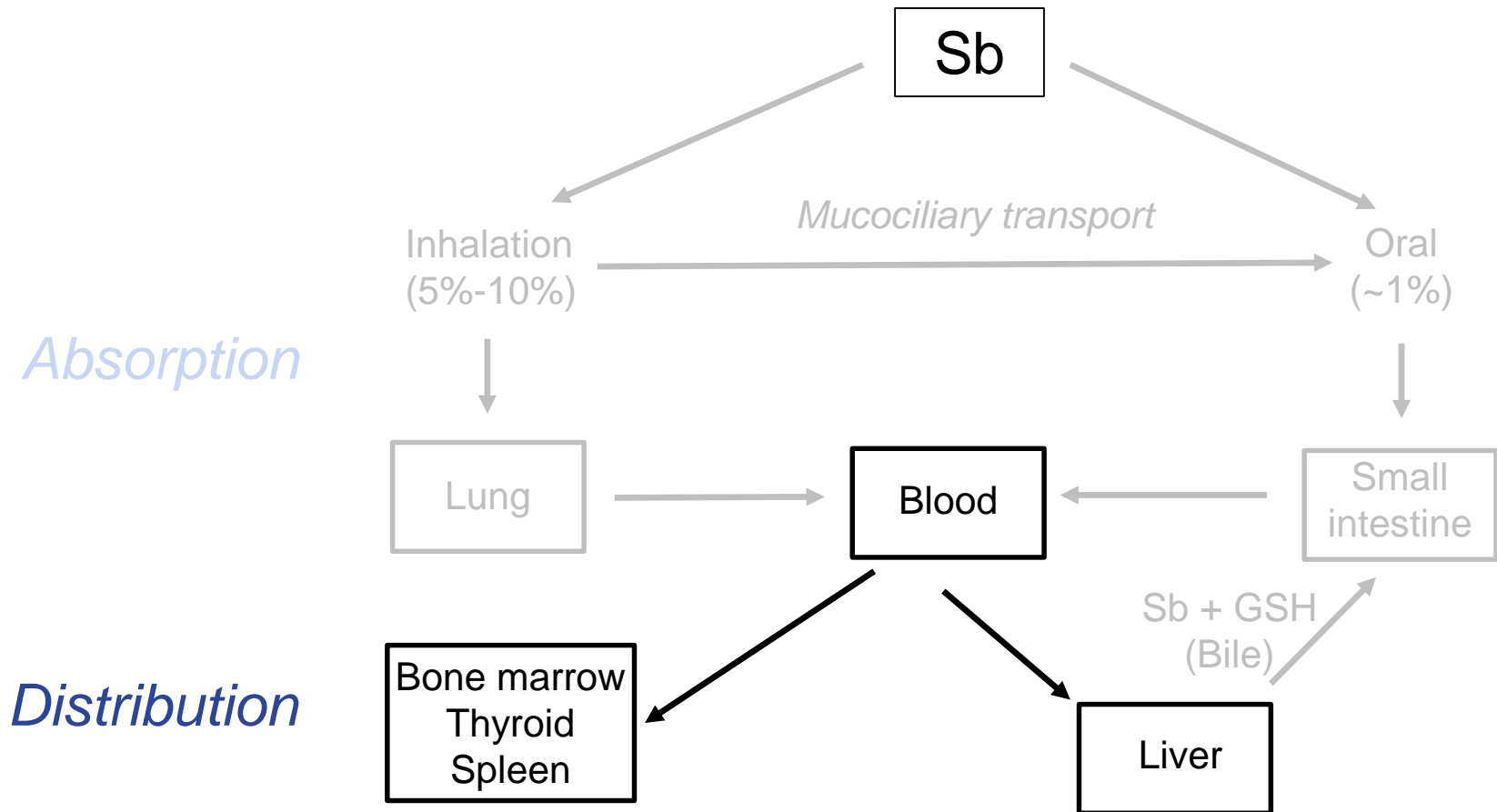


# Excretion of Antimony





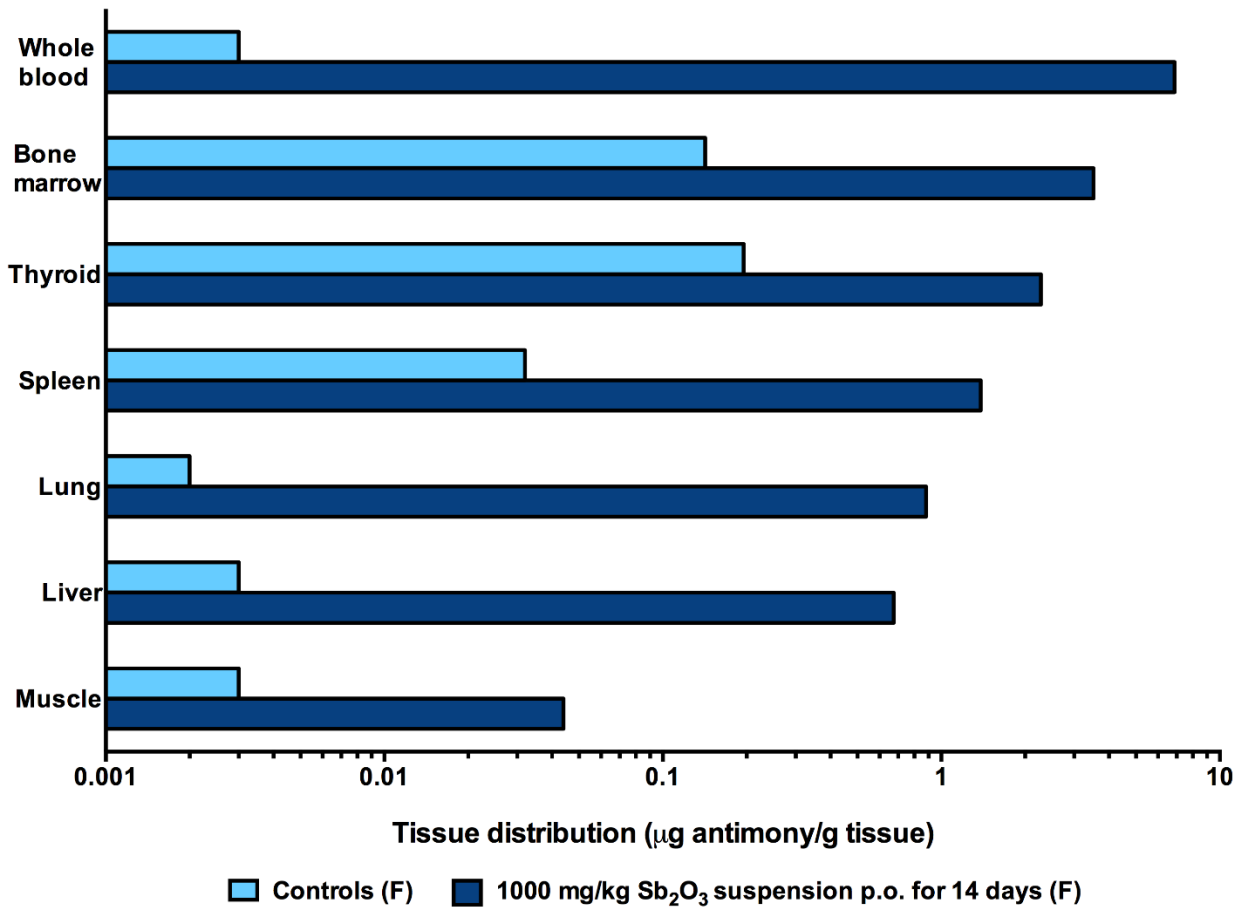
# Distribution of Antimony



- Antimony distributes to multiple tissues.



# Antimony Tissue Distribution

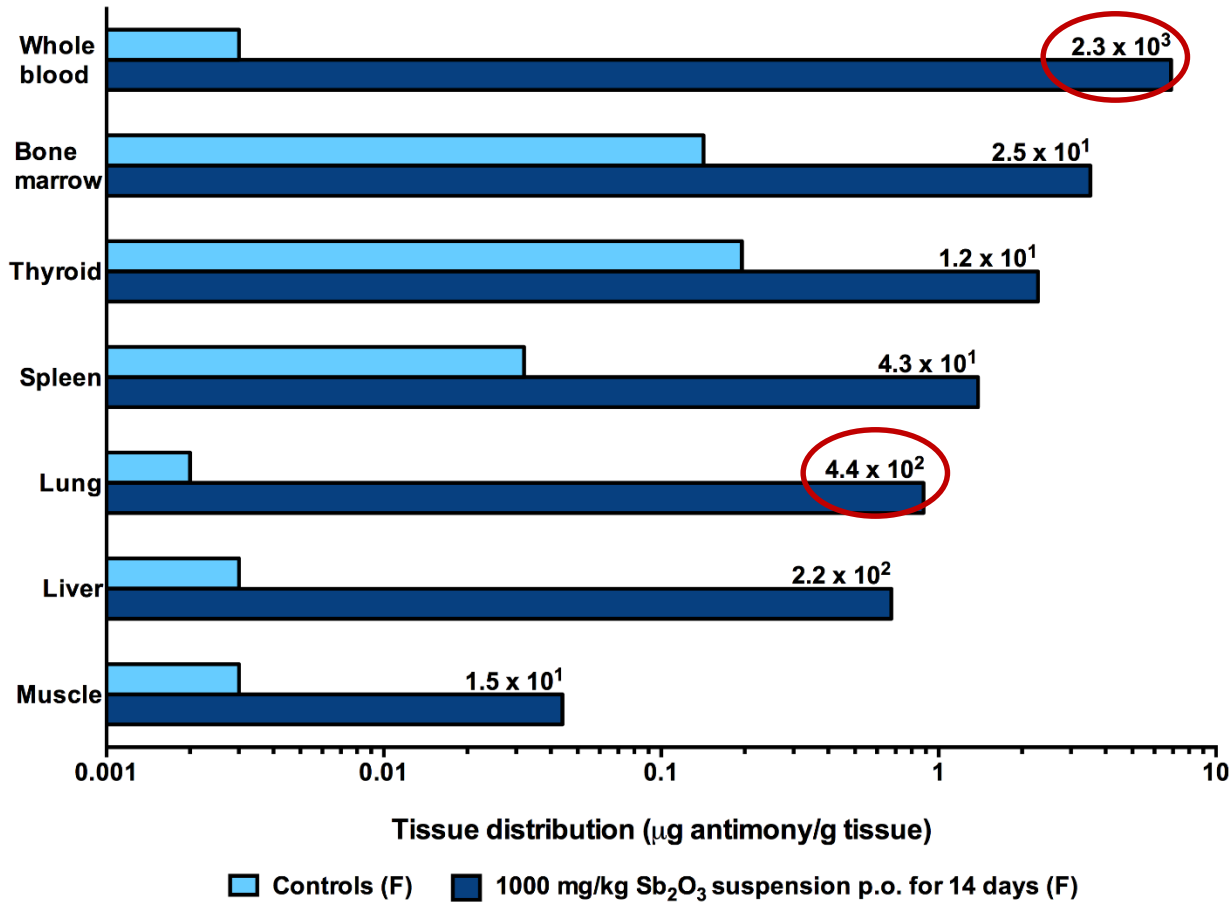


Source: TNO Quality of Life 2005 (as reported in EU 2008)





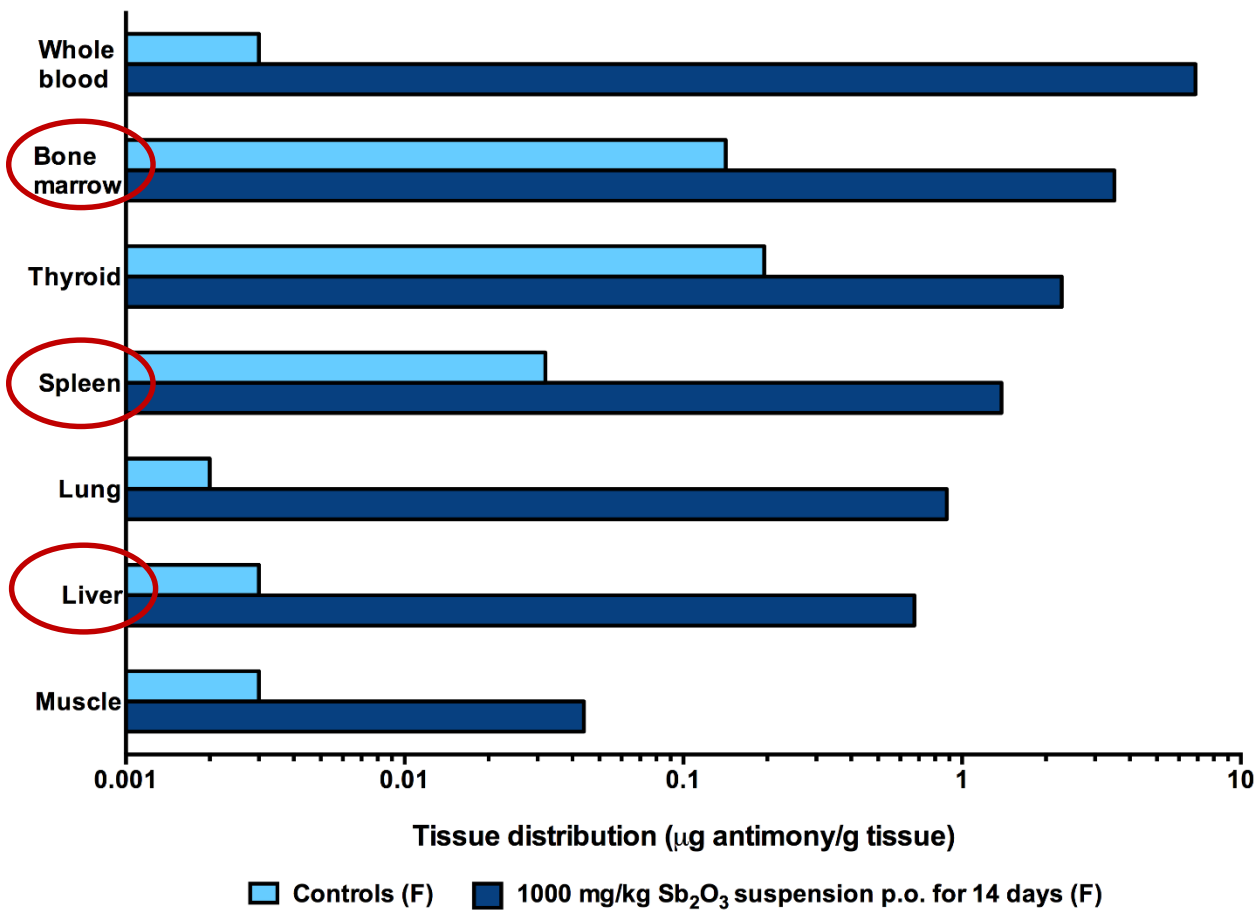
# Antimony Tissue Distribution



- Antimony accumulates to higher levels in tissues after oral exposure to antimony trioxide but increases in blood and lung are much greater after exposure.



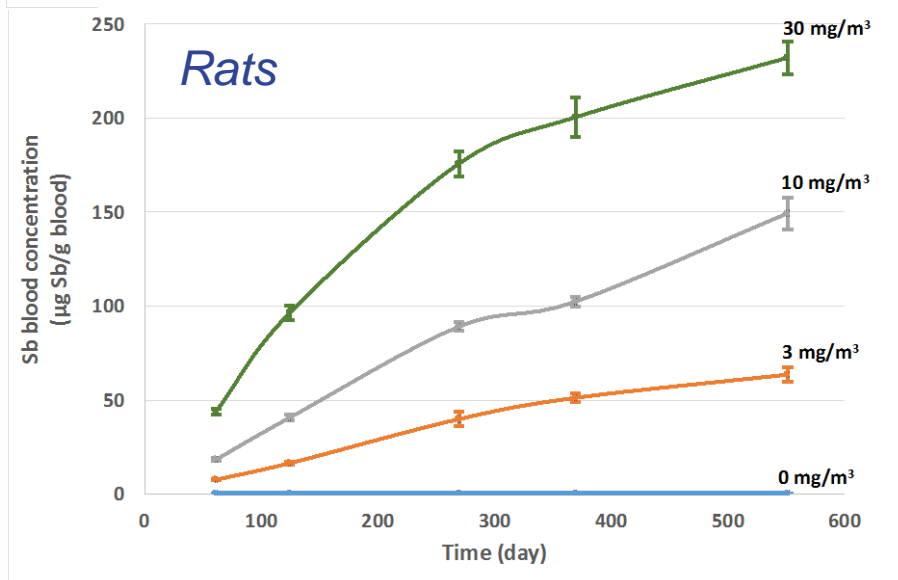
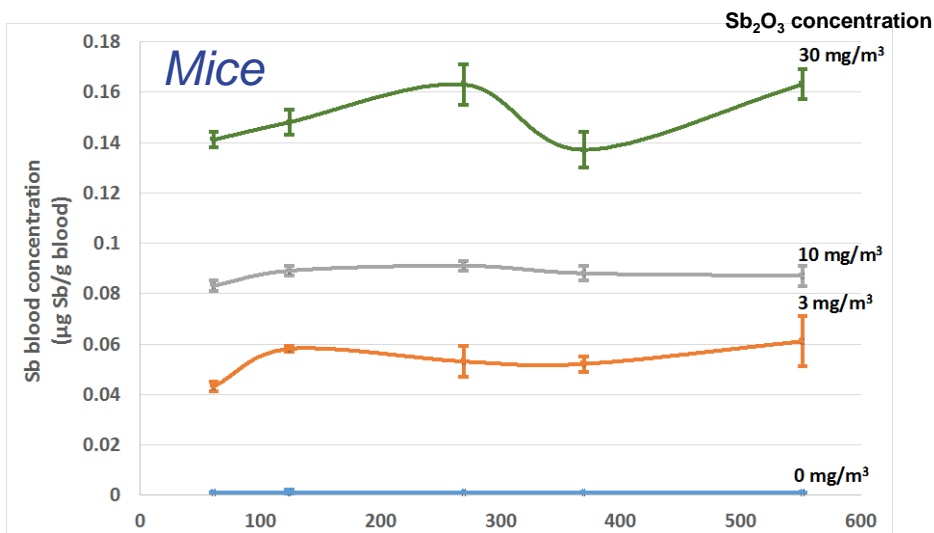
# Antimony Tissue Distribution



- Antimony is generally highest in tissues with reticuloendothelial cells.



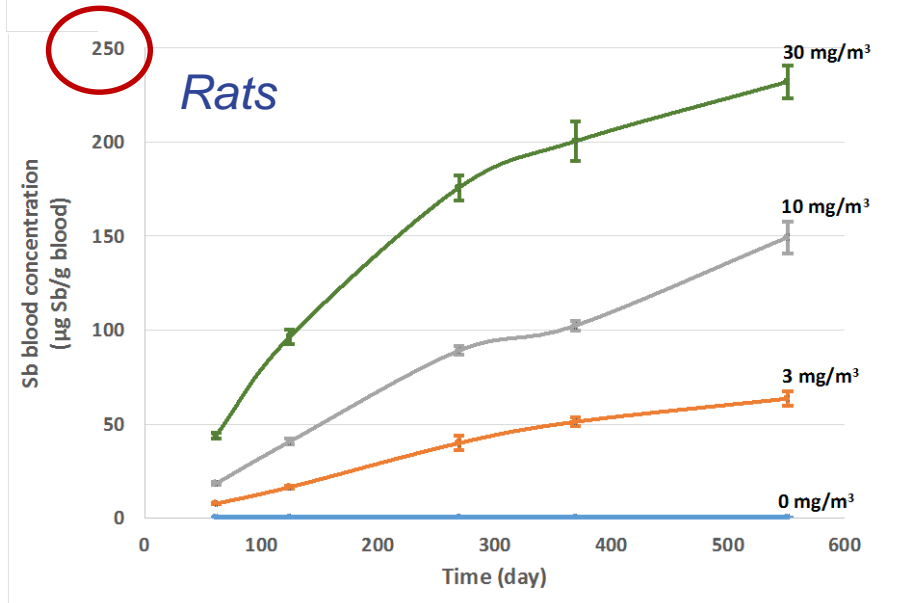
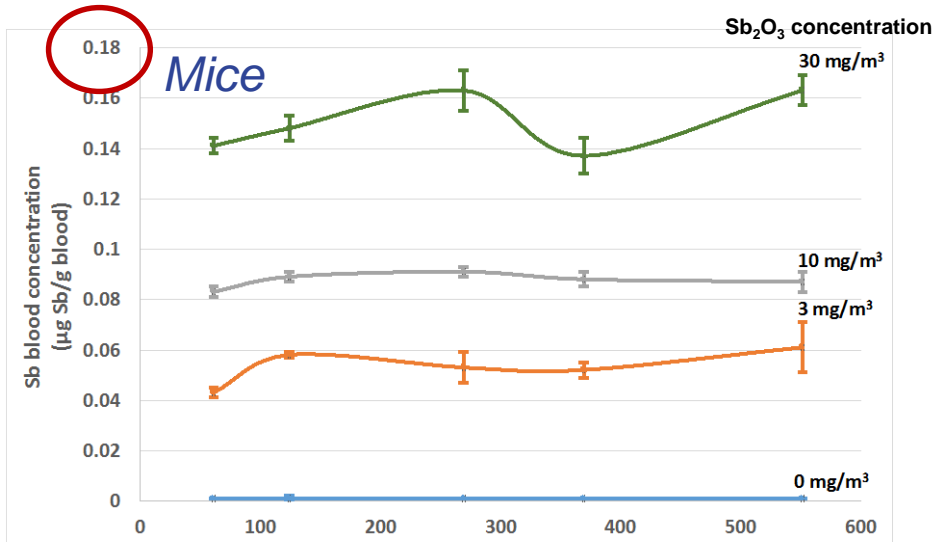
# Toxicokinetics: Blood Antimony Levels



Source: NTP 2017.



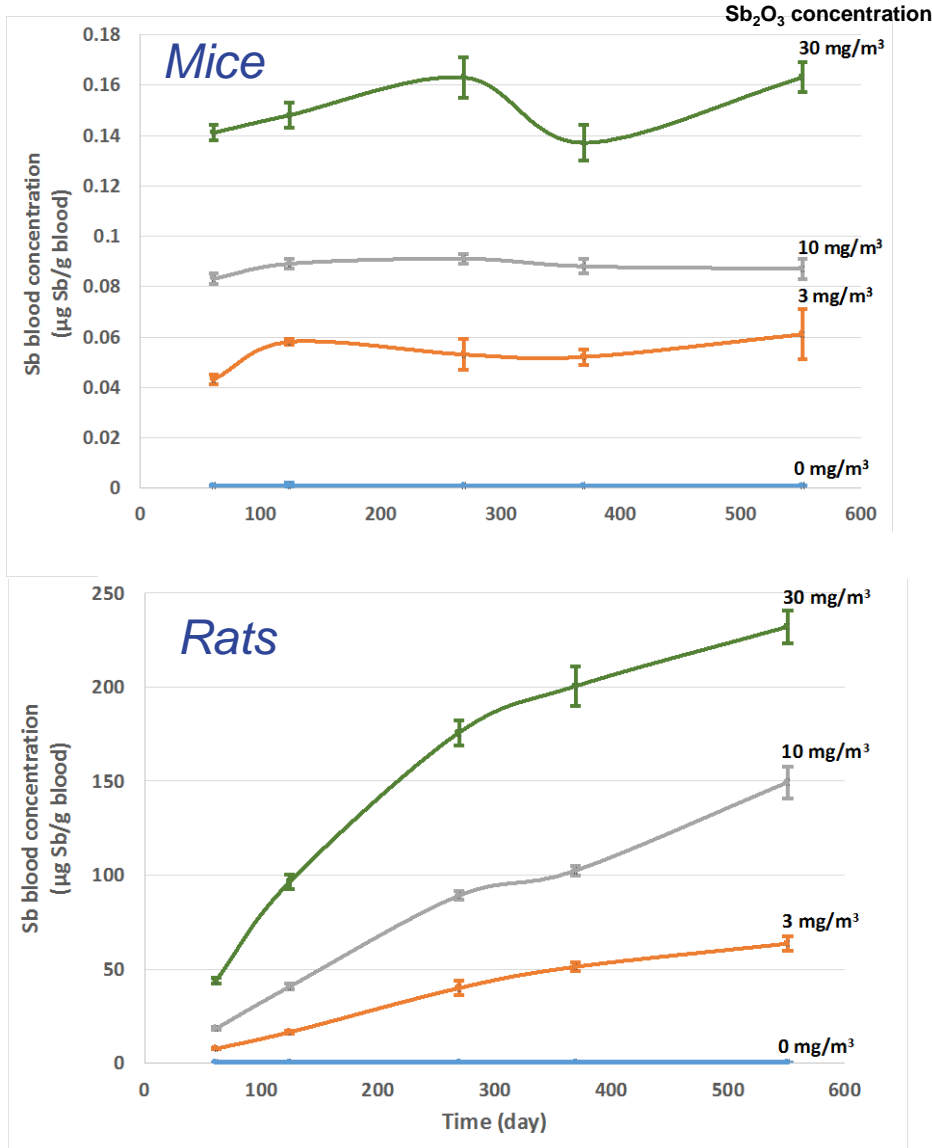
# Toxicokinetics: Blood Antimony Levels



Source: NTP 2017.



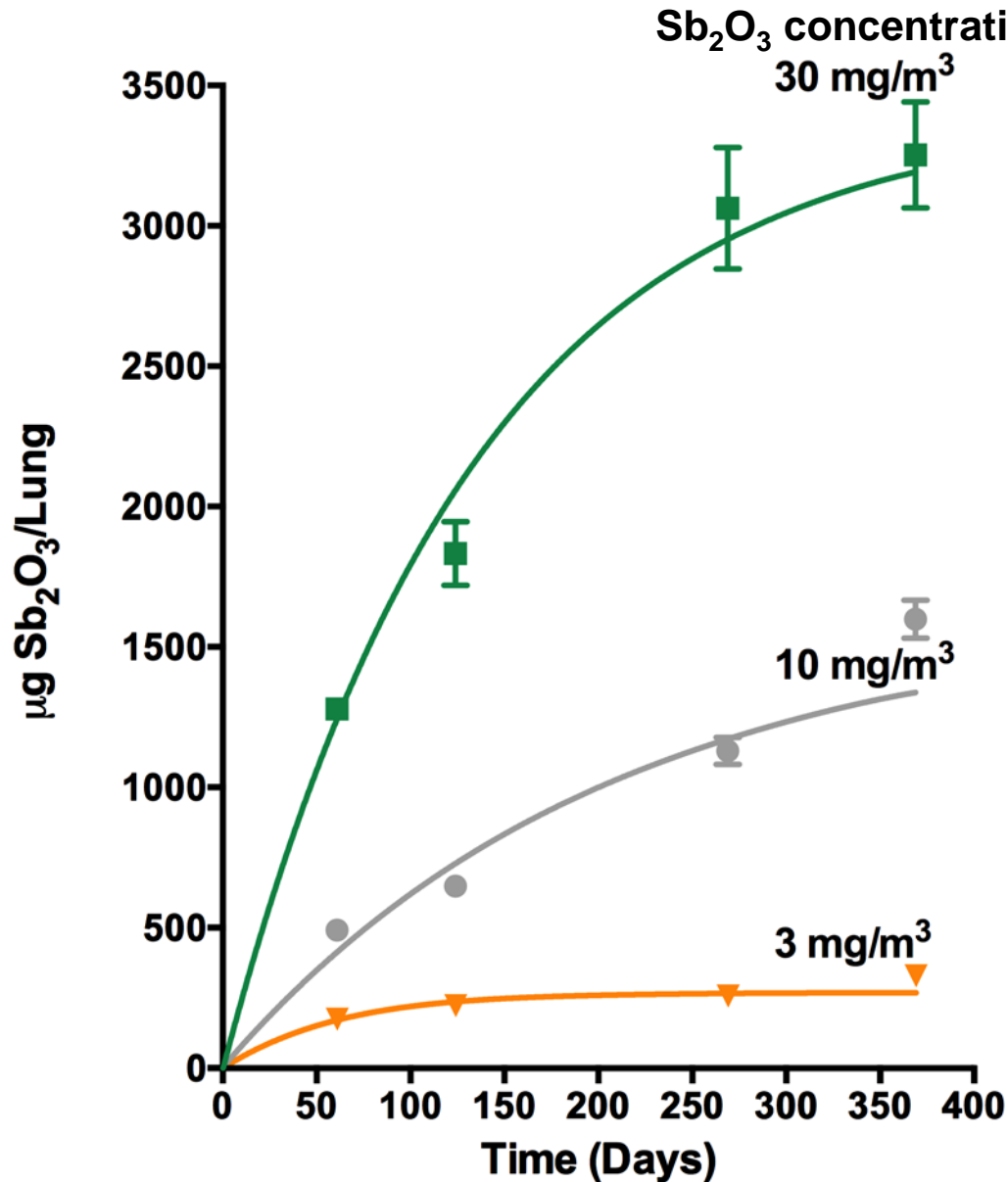
# Toxicokinetics: Blood Antimony Levels



- Blood levels increased in female mice with dose, but only slightly with time.
- Blood levels of antimony in female rats increased with both exposure time and dose.
- At the highest dose and duration, mouse blood concentration was 0.002% of lung concentration compared with 7% in rats.



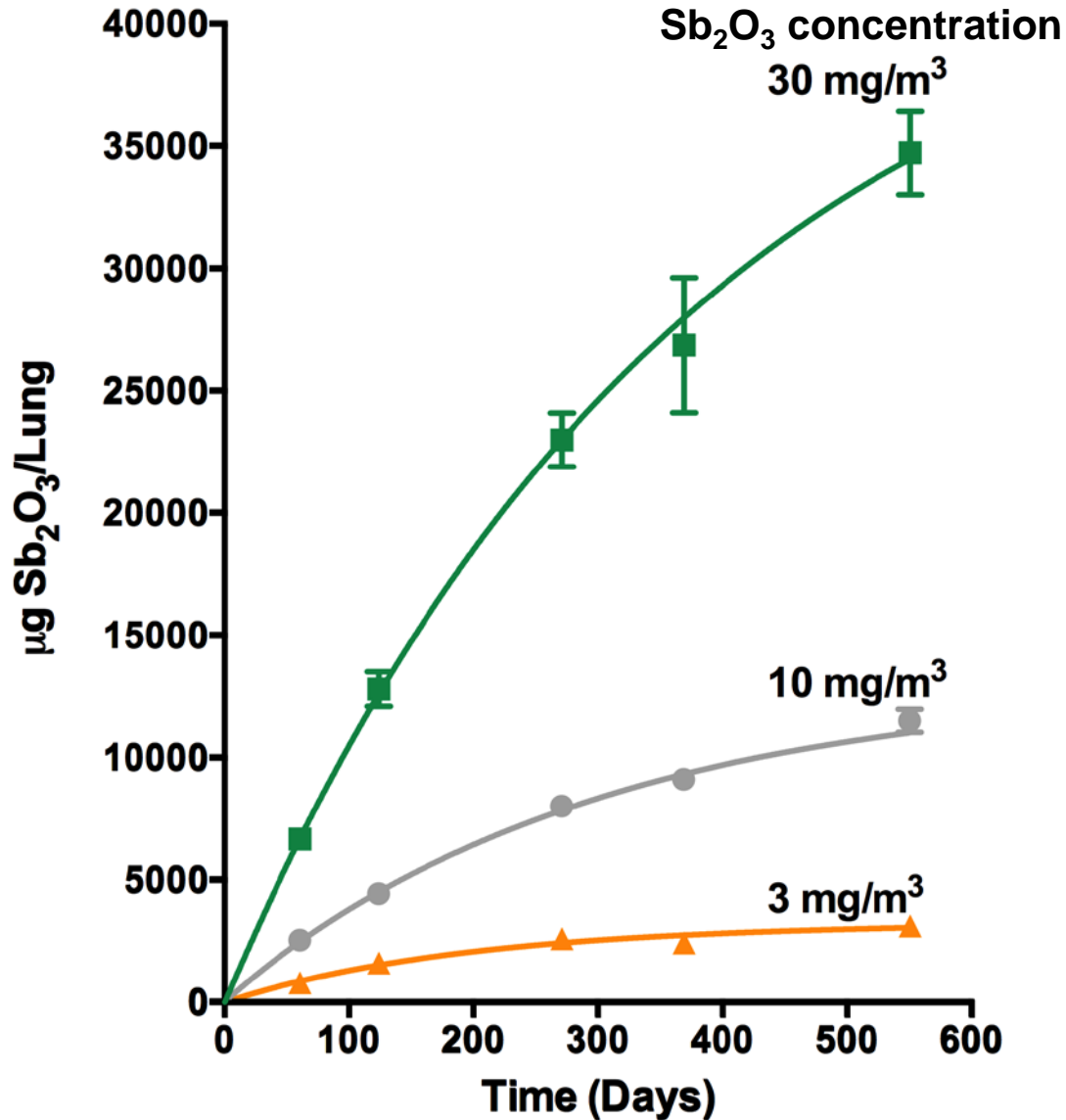
# Toxicokinetics: Lung Burdens in Female Mice



- Antimony accumulated in the lung in female mice, but the fit to the model is poor.
- Day 551 lung burdens were considerably higher than the calculated curves and are not shown here.



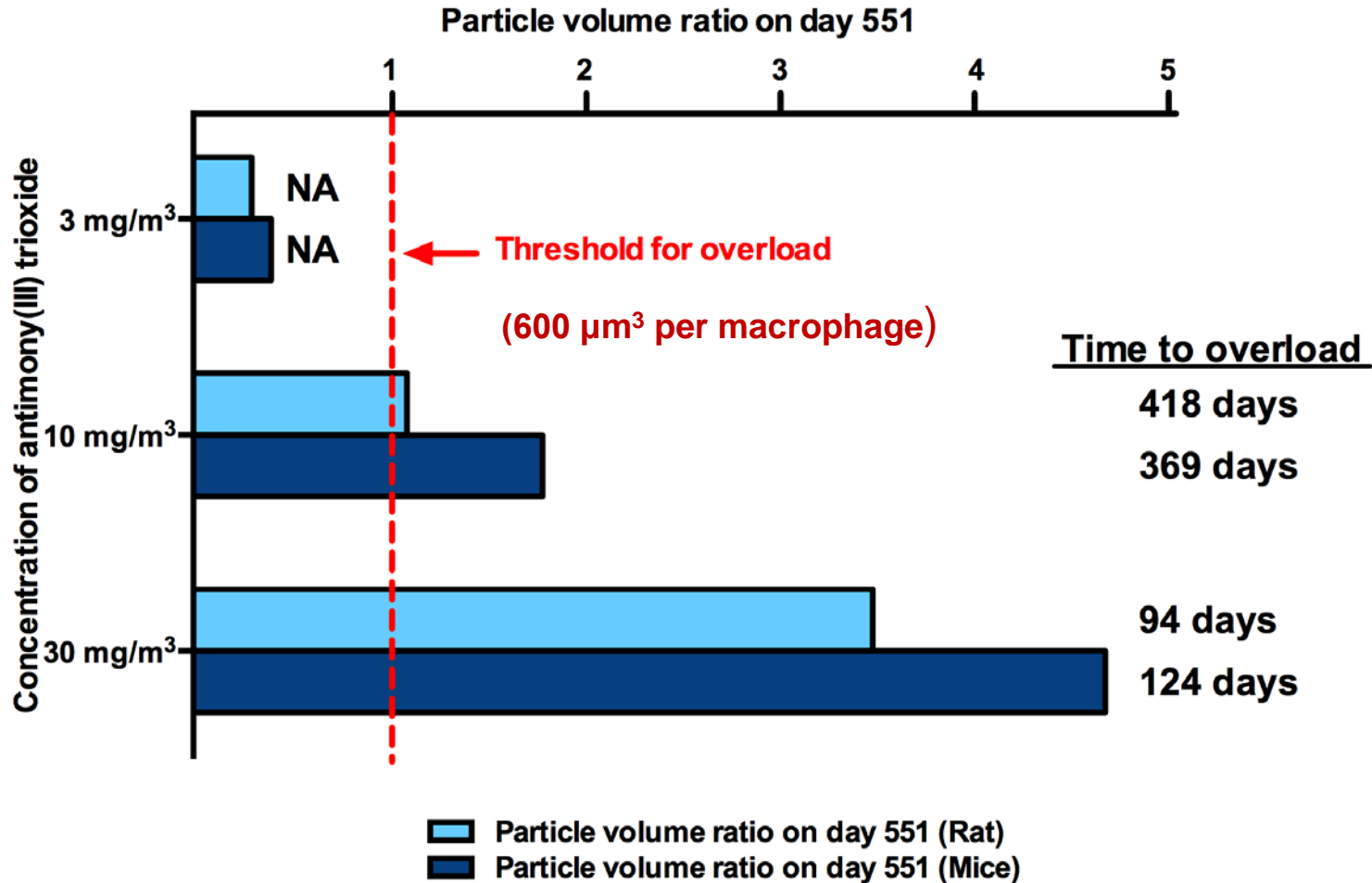
# Toxicokinetics: Lung Burdens in Female Rats



- A better fit to the model was obtained for data from female rats.
- Rats exposed to 3 or 10, but not 30  $\text{mg}/\text{m}^3$ , approached steady state.
- Reduced pulmonary clearance is likely associated with lung overload at the higher doses.



# Lung Overload in Rats and Mice



- Similar results were seen for lung overload based on particle surface area in both species.





- The most common metabolic change *in vivo* is the reduction of Sb(V) to Sb(III) in the presence of intracellular thiol groups.
- Antimony(III) trioxide has low solubility in water, but absorption and distribution results in increased excretion with higher levels of exposure by inhalation in workers and by distribution to tissues in animals, particularly to organs rich in reticuloendothelial cells, e.g., spleen, liver, bone marrow.
- The 2-year bioassay data on lung burden with inhalation exposure to antimony(III) trioxide indicate that both rats and mice were exposed to concentrations that resulted in the absence as well as the presence of lung overload.



## Disposition and Toxicokinetics

- **Comment on whether the information on Disposition and Toxicokinetics (Section 3 and Appendix B) is clear, technically correct, and objectively presented.**
  - Identify any information that should be added or deleted.



# Disposition of Antimony

