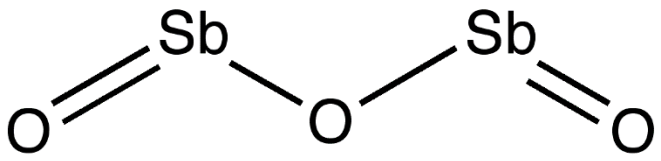
Disposition and Toxicokinetics



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National Institute of Environmental Health Sciences

January 24, 2018

Antimony Disposition & Toxicokinetics

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

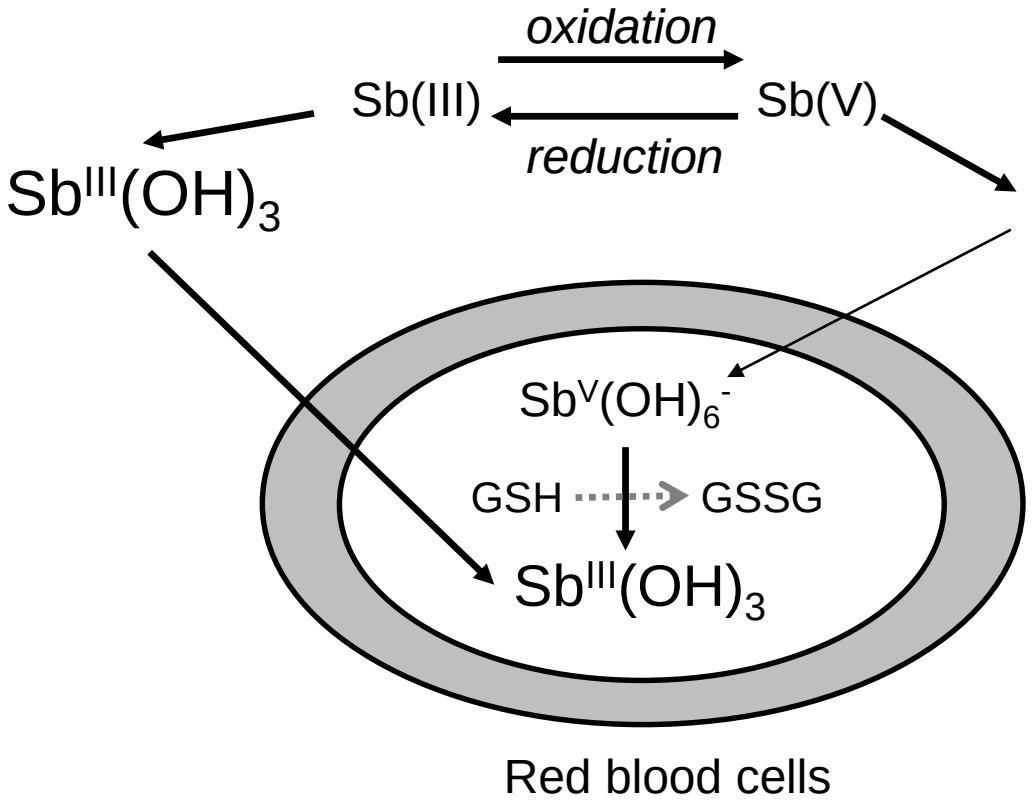
Excretion: Elimination from the body as evidence for absorption

Distribution: Tissues where antimony is present in the body

Toxicokinetics: Effects of antimony accumulation

Antimony Metabolism

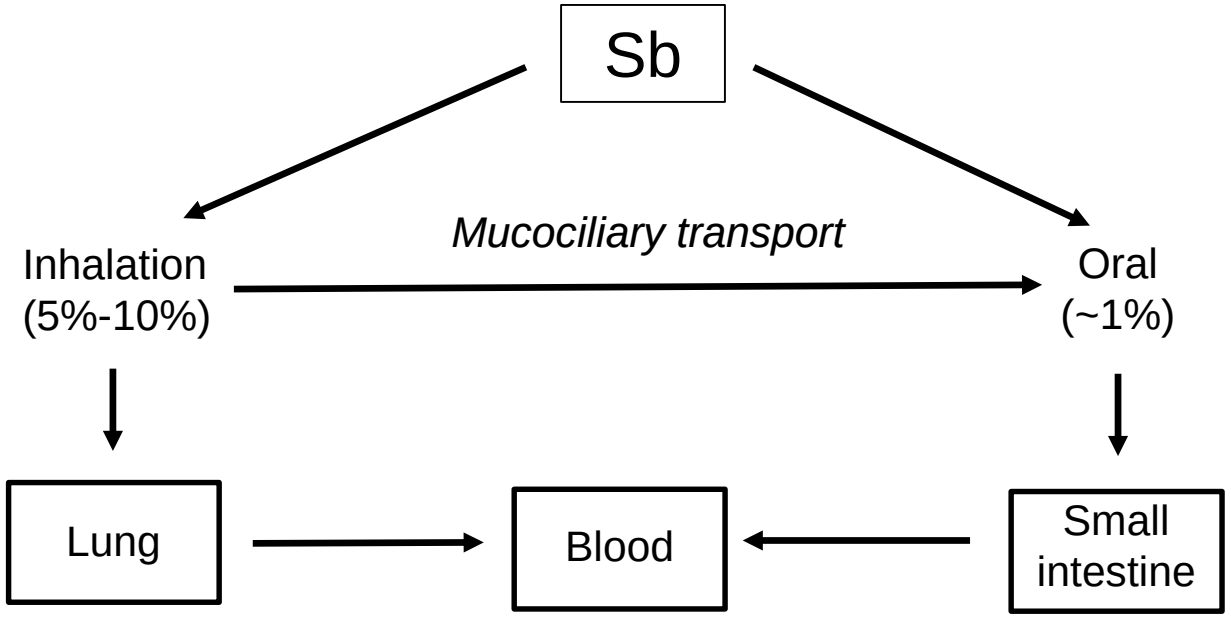
The chemical form of antimony trioxide changes once it dissolves in bodily fluids, where it forms the hydroxides, $Sb^{III}(OH)_3$ and $Sb^{V}(OH_6^-)$, which have limited solubility



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

Absorption of Antimony

Absorption



- 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.

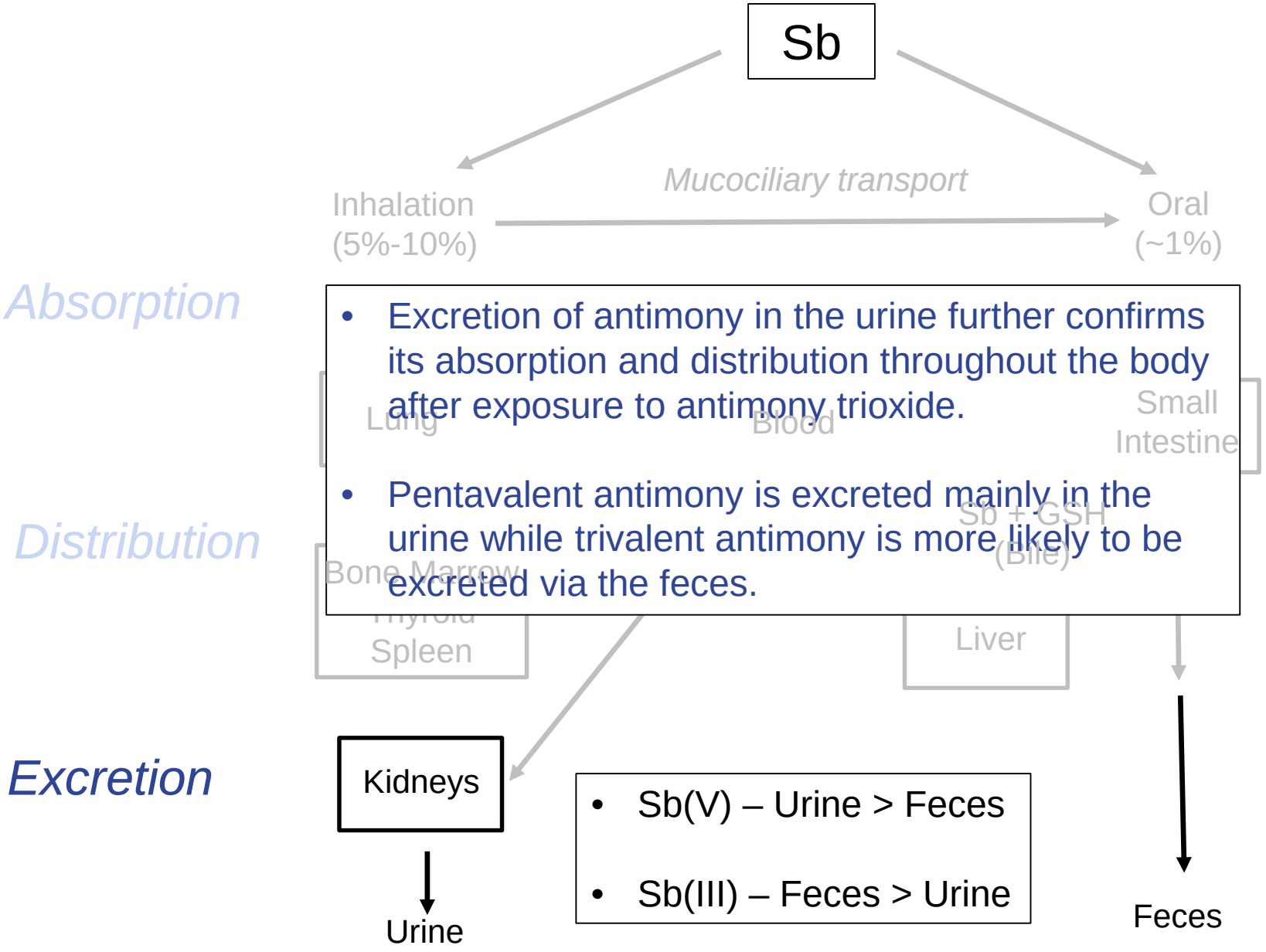
Inhalation Exposure Results in Excretion

Exposure to Sb_2O_3 (Reference)	N	Air Sb Levels (μg/m³)	Urine Sb Levels (μg/g creatinine)
Lead battery production (Kentner *et al.* 1995)	7	4.5	3.9
Antimony(III) trioxide production (Kim *et al.* 1999)	12	766[a]	419.8 (μg/L)

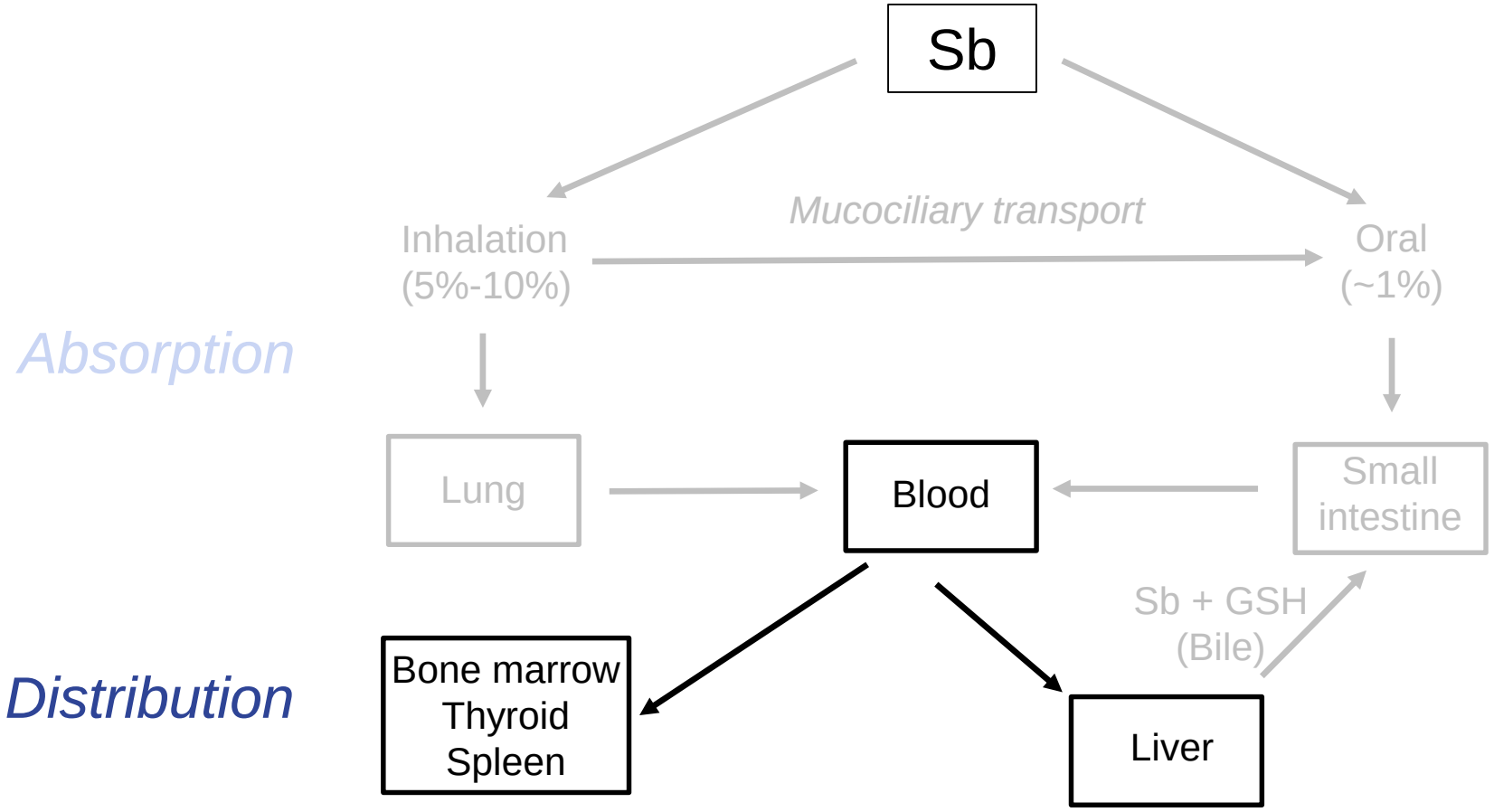
[a]Exceeds ACGIH TLV of 500 ug/m³

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

Excretion of Antimony

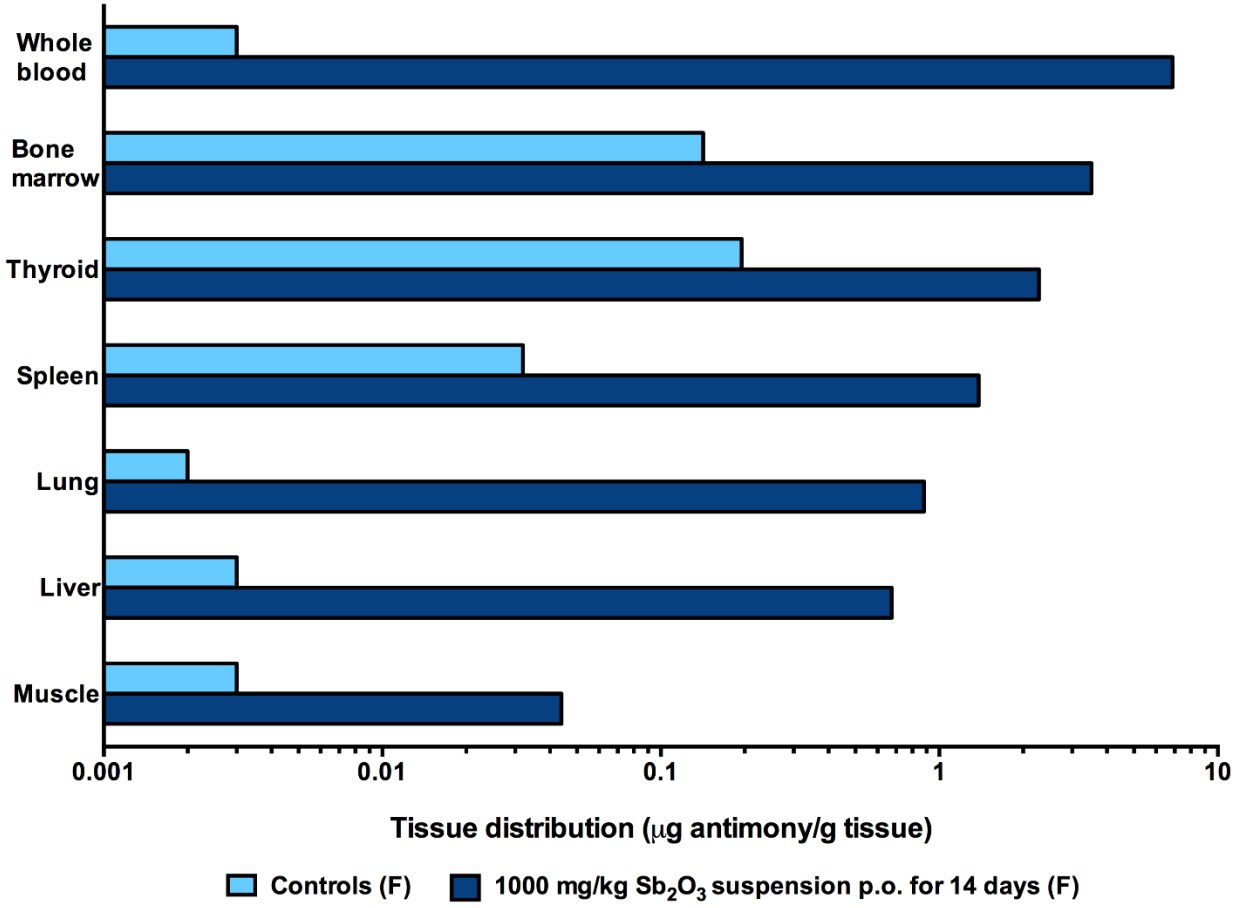


Distribution of Antimony



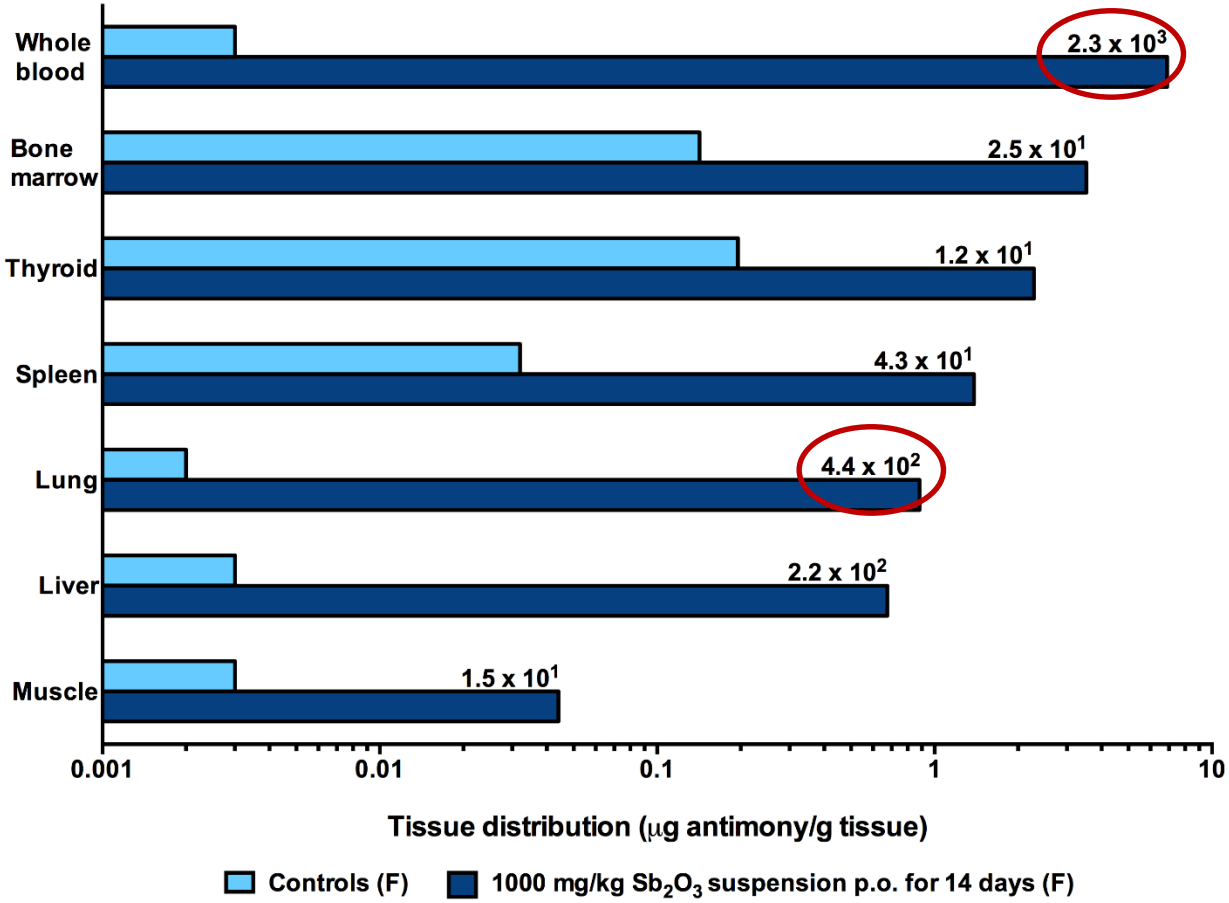
- Antimony distributes to multiple tissues.

Antimony Tissue Distribution



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

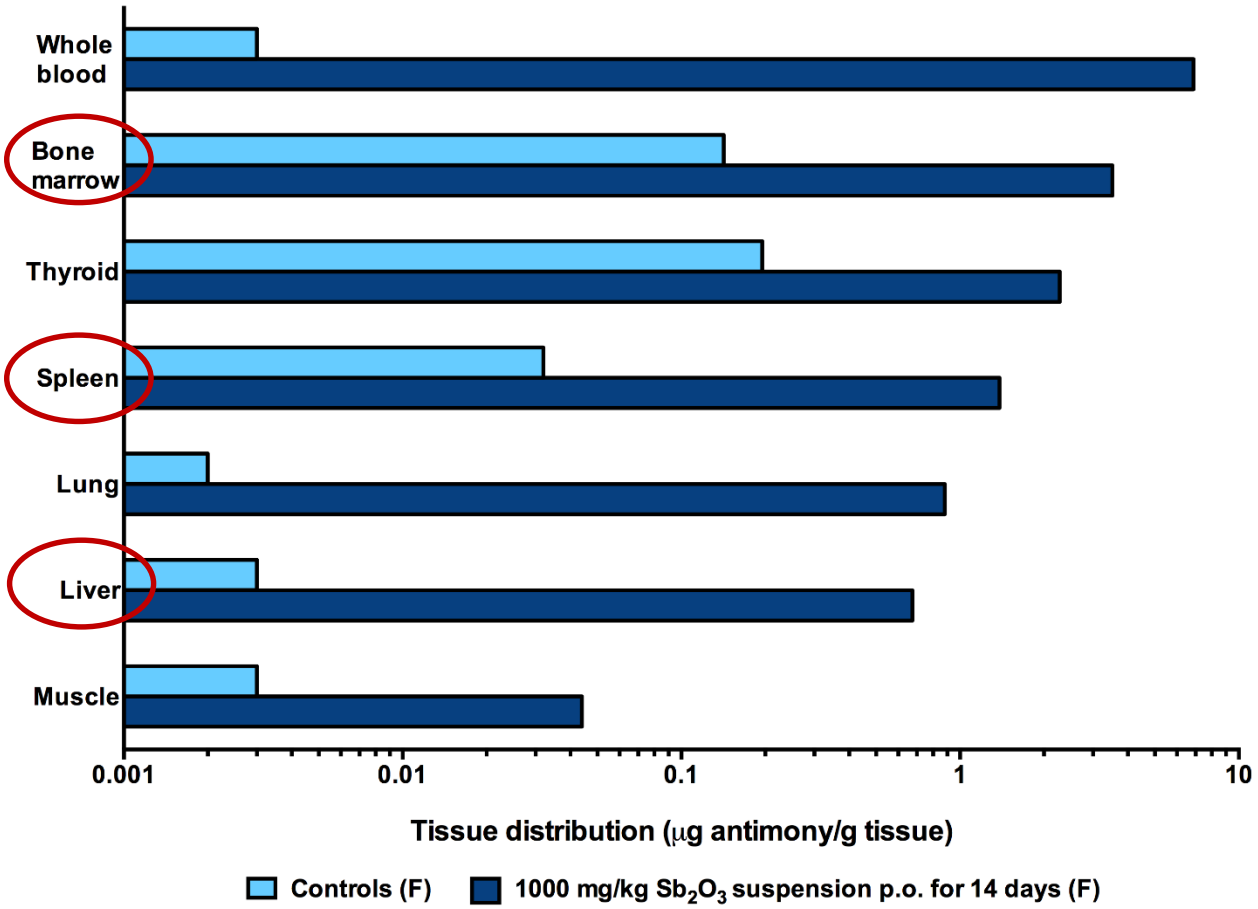
Antimony Tissue Distribution



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

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

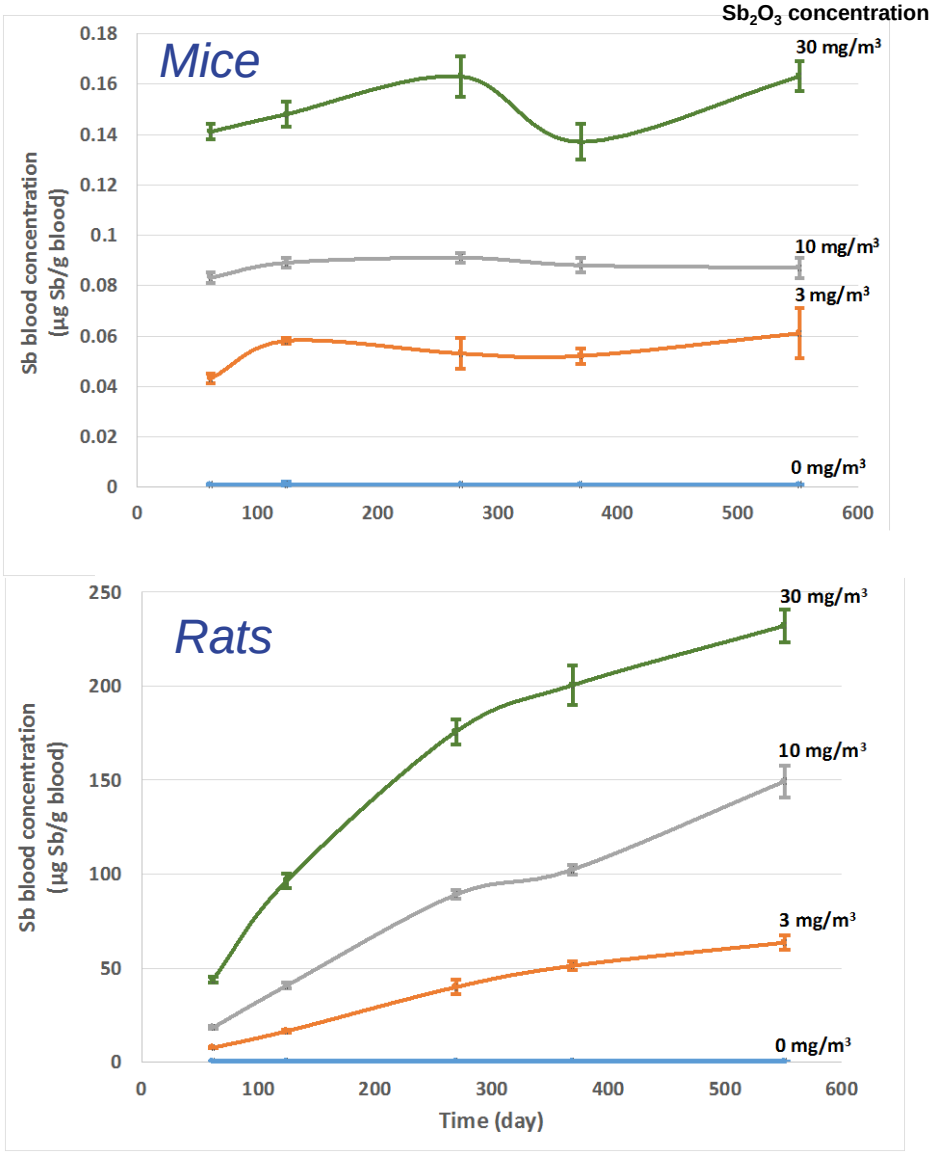
Antimony Tissue Distribution



- Antimony is generally highest in tissues with reticuloendothelial cells.

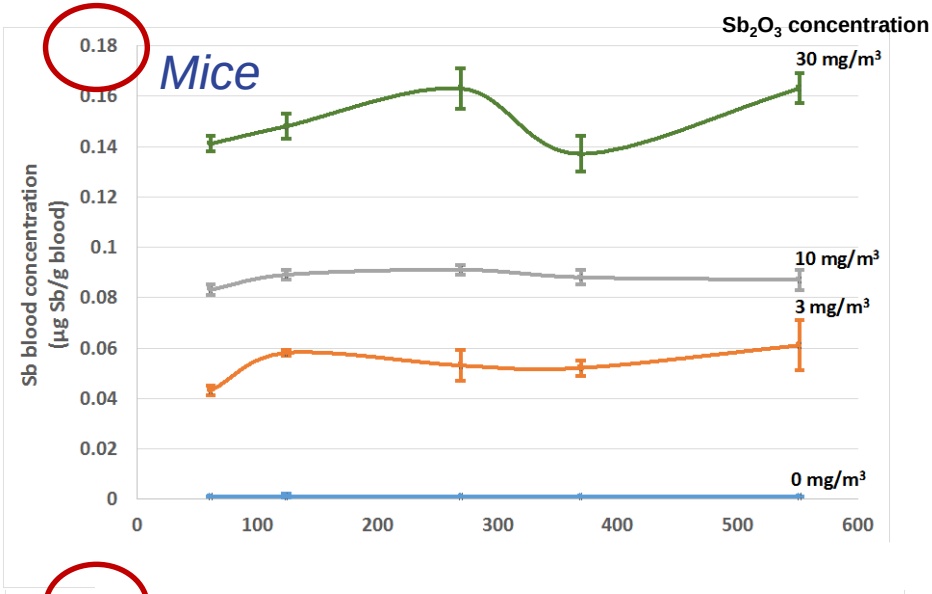
Source: TNO Quality of Life 2005 (as reported in EU 2008)

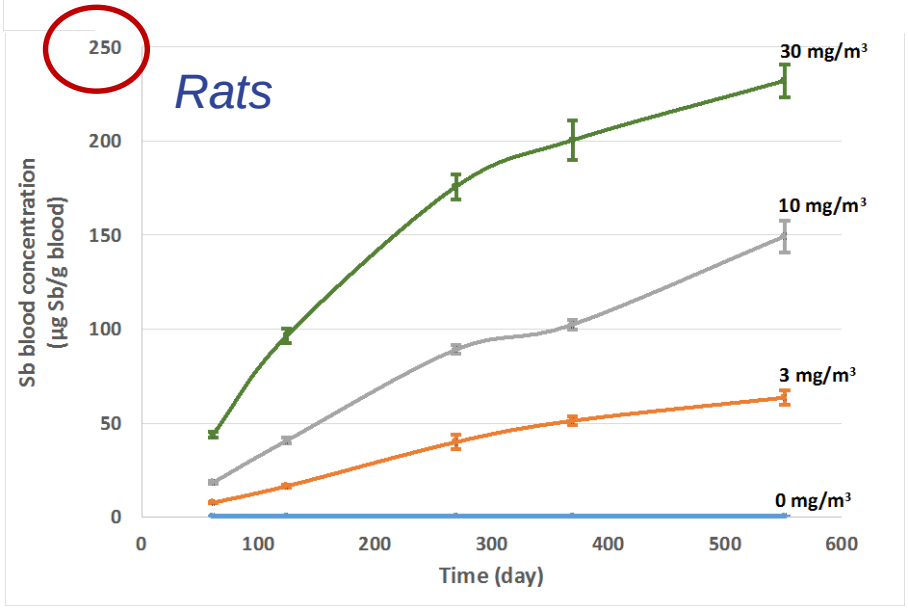
Toxicokinetics: Blood Antimony Levels



Source: NTP 2017.

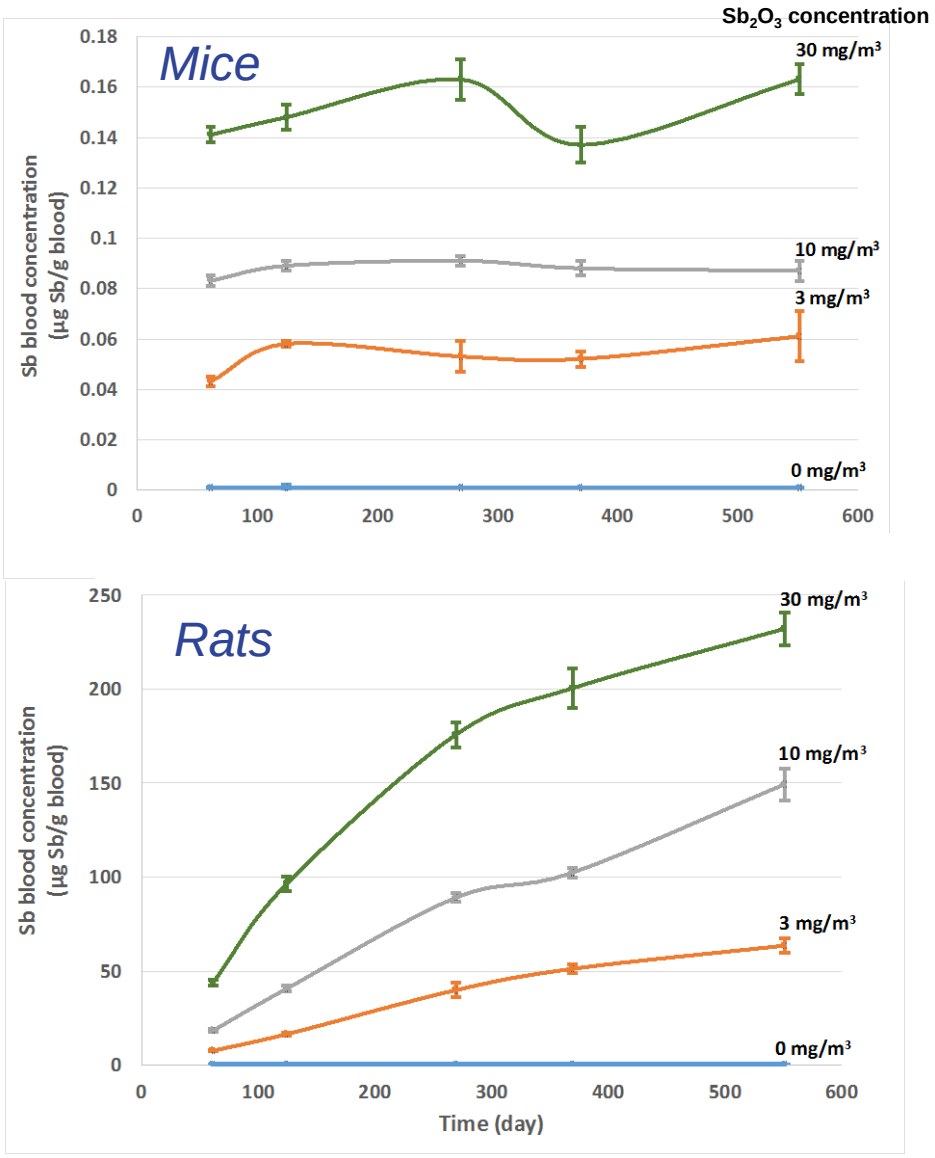
Toxicokinetics: Blood Antimony Levels





Source: NTP 2017.

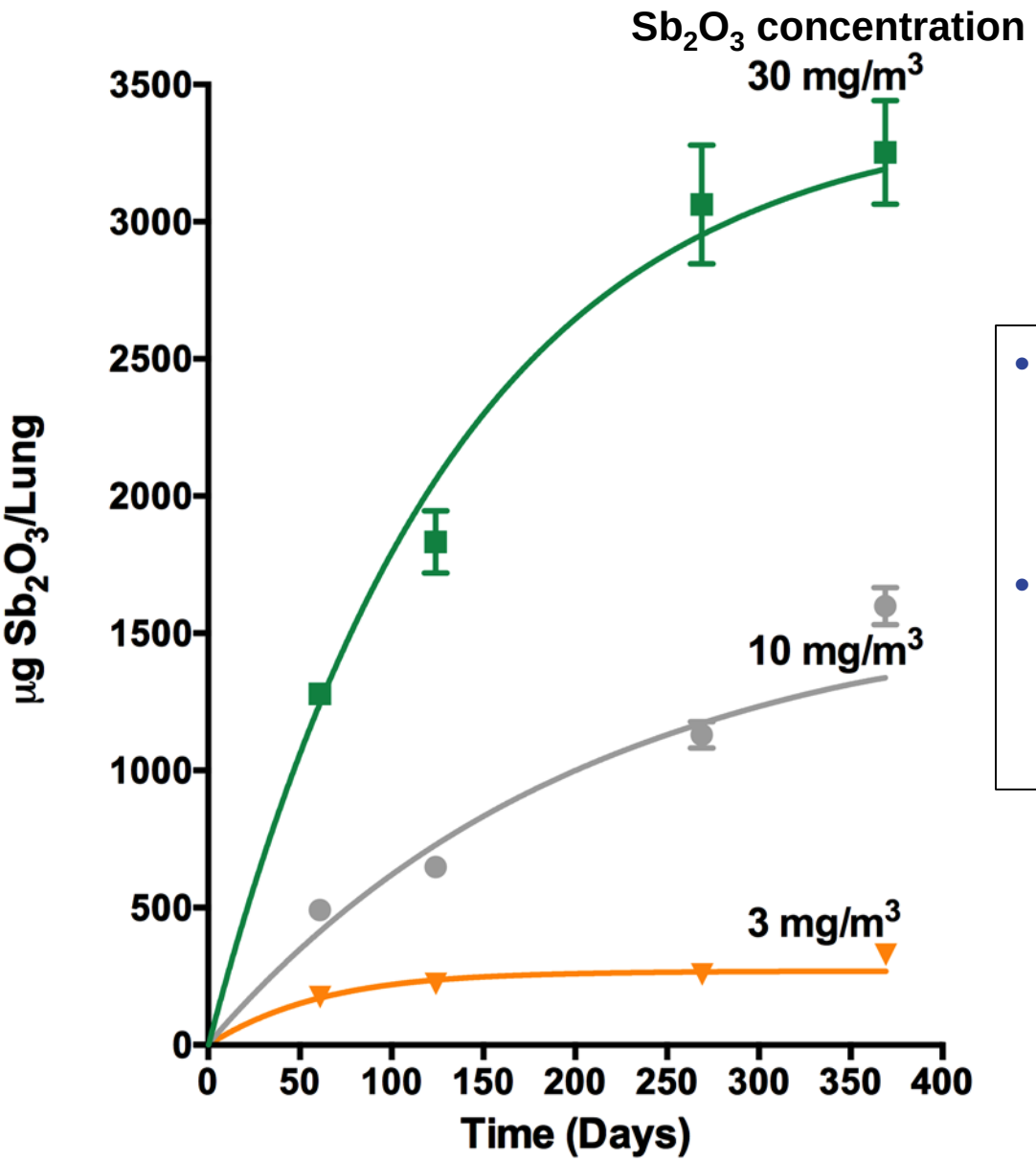
Toxicokinetics: Blood Antimony Levels



- 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.

Source: NTP 2017.

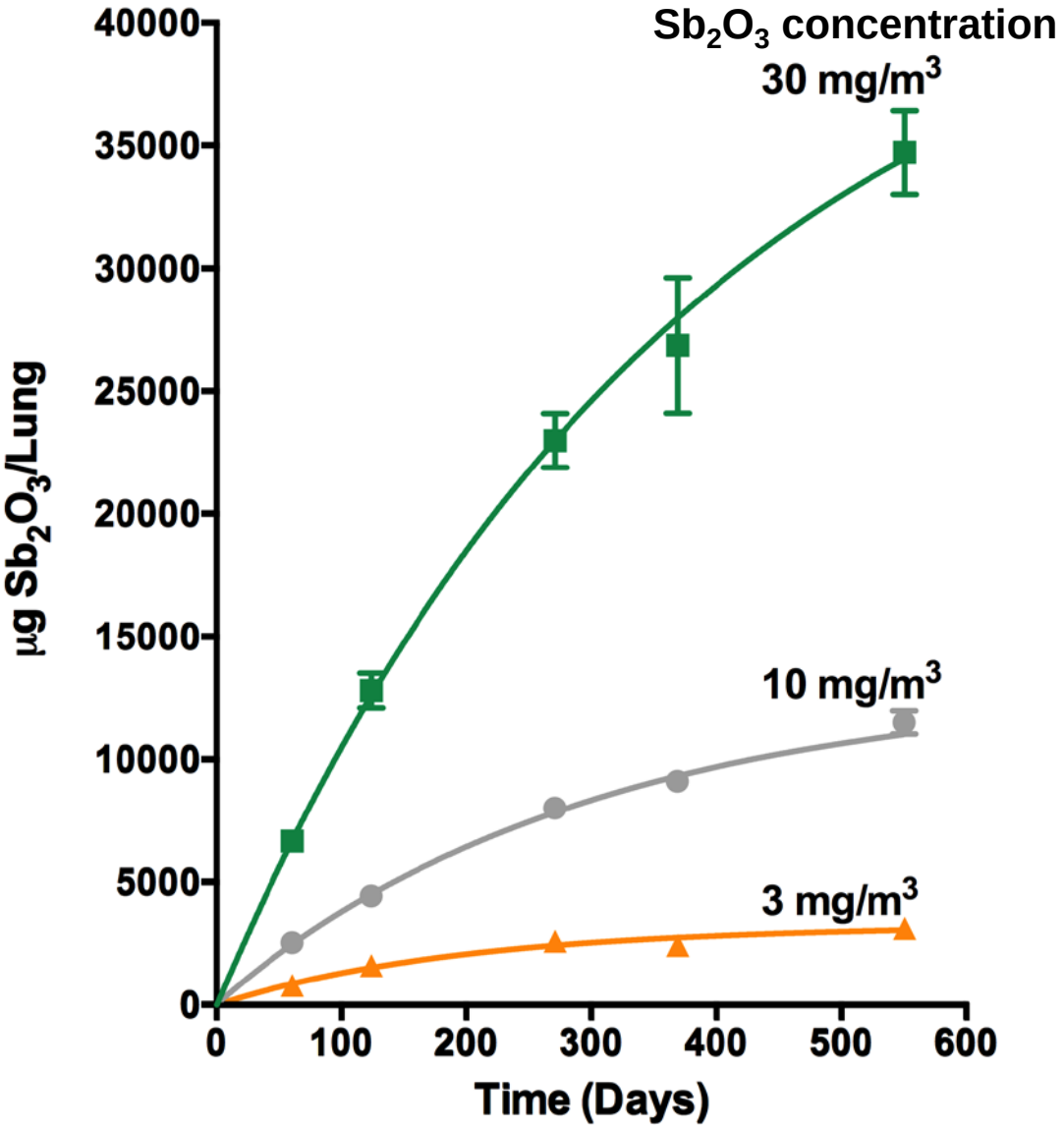
Toxicokinetics: Lung Burdens in Female Mice



- 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.

Source: NTP 2017.

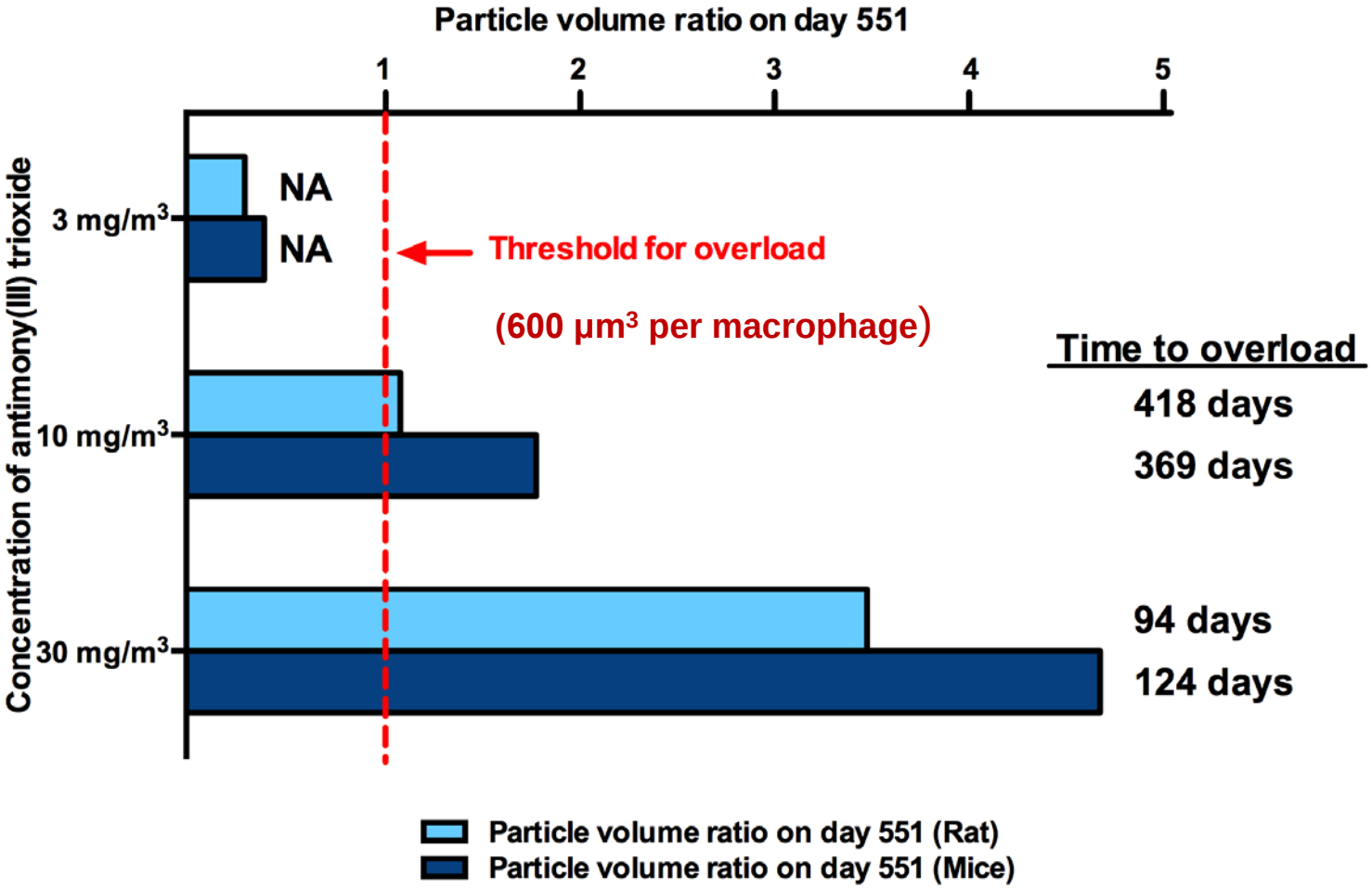
Toxicokinetics: Lung Burdens in Female Rats



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

Source: NTP 2017.

Lung Overload in Rats and Mice



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

Source: NTP 2017.

Summary

- 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