IRIS Assessment Plan for Vanadium Compounds (Oral Exposure)

Suramya Waidyanatha

Chemistry and ADME Resources Group Leader

Division of National Toxicology Program

National Institute of Environmental Health Sciences

- I do not have any financial relationships with persons or organizations having an interest in a toxicological review of vanadium compounds.

- No interested party had reviewed the input I am providing at the meeting today.

Key science issues identified by EPA

- **Key science issue #1: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds.**
  - Differential absorption has been observed across inorganic vanadium compounds. For instance, as described earlier in this document, studies in progress by NTP preliminarily report that drinking water exposure to sodium metavanadate (+5) in rats led to higher levels of vanadium in plasma and urine as compared to vanadyl sulfate (+4) at similar vanadium exposure levels. This is consistent with reports that vanadate (+5) is absorbed more readily in the gastrointestinal tract compared to vanadyl (+4) (Treviño et al., 2019; Nielsen, 1995). Absorption may be correlated with toxicity, as the effects observed by NTP were more pronounced following exposure to sodium metavanadate compared to vanadyl sulfate. To address these apparent differences, in addition to more fully characterizing the toxicokinetic differences across compounds (including potential interconversion within the body), EPA plans to conduct separate toxicity evaluations for different vanadium compounds where the evidence supports such an analysis.

- **Key science issue #2: Consideration of vanadium speciation.**
  - Available information indicates that vanadium in solution can readily interconvert between oxidation states and will form different spectrums of species as a function of factors including pH, concentration, and redox potential. For instance, tetravalent vanadium in drinking water is stable at acidic pH but can convert to pentavalent species at neutral or basic pH (Mutlu et al., 2017). Given the apparent toxicokinetic (and, likely, toxicity) differences across vanadium compounds (see Key Science Issue #1), study evaluations will, to the extent possible, consider factors that could affect vanadium oxidation state and speciation in the available toxicity studies. Speciation of vanadium at low environmental concentrations will also be of particular interest.

Key science issue #2: Consideration of vanadium speciation

Background

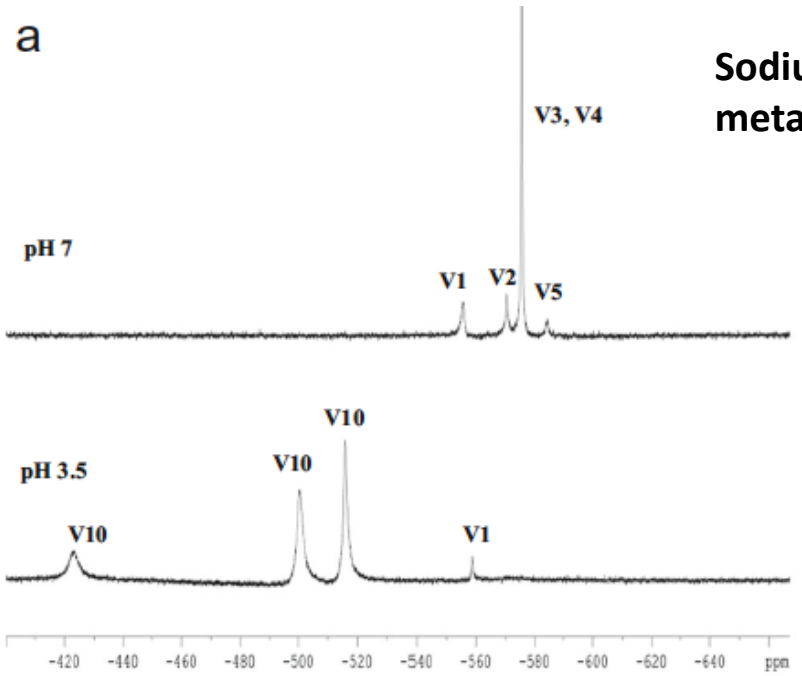
- Vanadium and compounds are ubiquitous in the environment.
  - Oral exposure to inorganic vanadium compounds occur from food, drinking water, and dietary supplements.
  - Hence important to determine any adverse human health effects following oral exposure.

- Chemistry of vanadium is complex
  - Multiple oxidation states (+2 to +5), numerous species, and charges.
  - V^{+4} and V^{+5} are the predominant oxidation states and are most relevant to oral exposure.
  - Interconversion between vanadium oxidation states could occur depending on the pH, presence of oxidation/reduction equivalents, and other factors.
    - In acidic pH and sub oxic and/or mildly reducing conditions, vanadyl (V^{+4}) and corresponding oxocation (VO^{+2}) predominates.
      - V^{+4} converts to V^{+5} in neutral-basic pH.
    - In basic pH and oxic conditions, vanadate (V^{+5}) and corresponding oxoanions ($H_2VO_4^-$, HVO_4^{-2}) predominate.

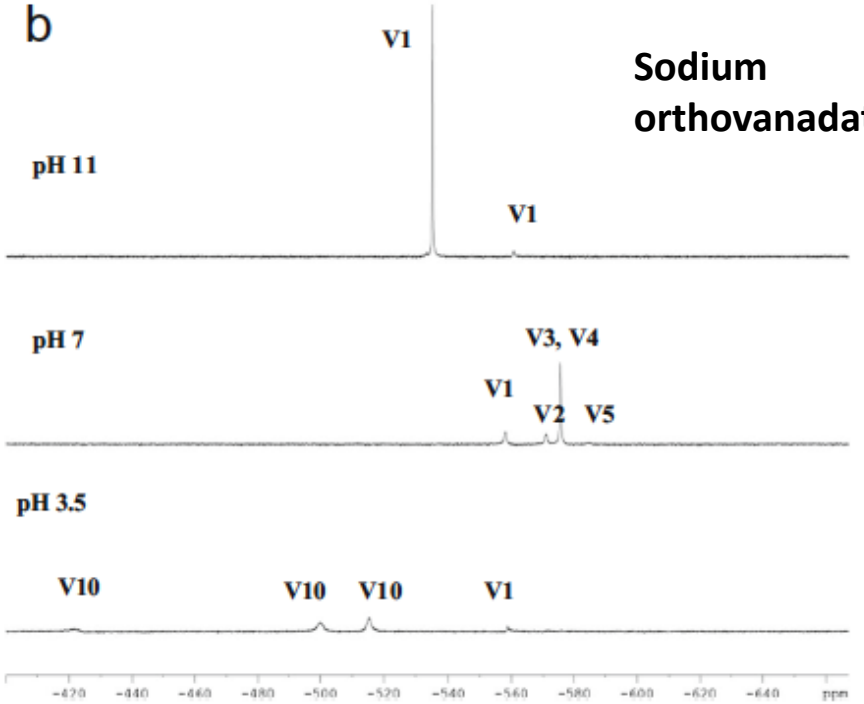
- Important to know the oxidation state and potentially species present when comparing across studies.

Key science issue #2: Consideration of vanadium speciation

Speciation of V^{+5} in drinking water formulations by ^{51}V NMR spectroscopy



Sodium metavanadate



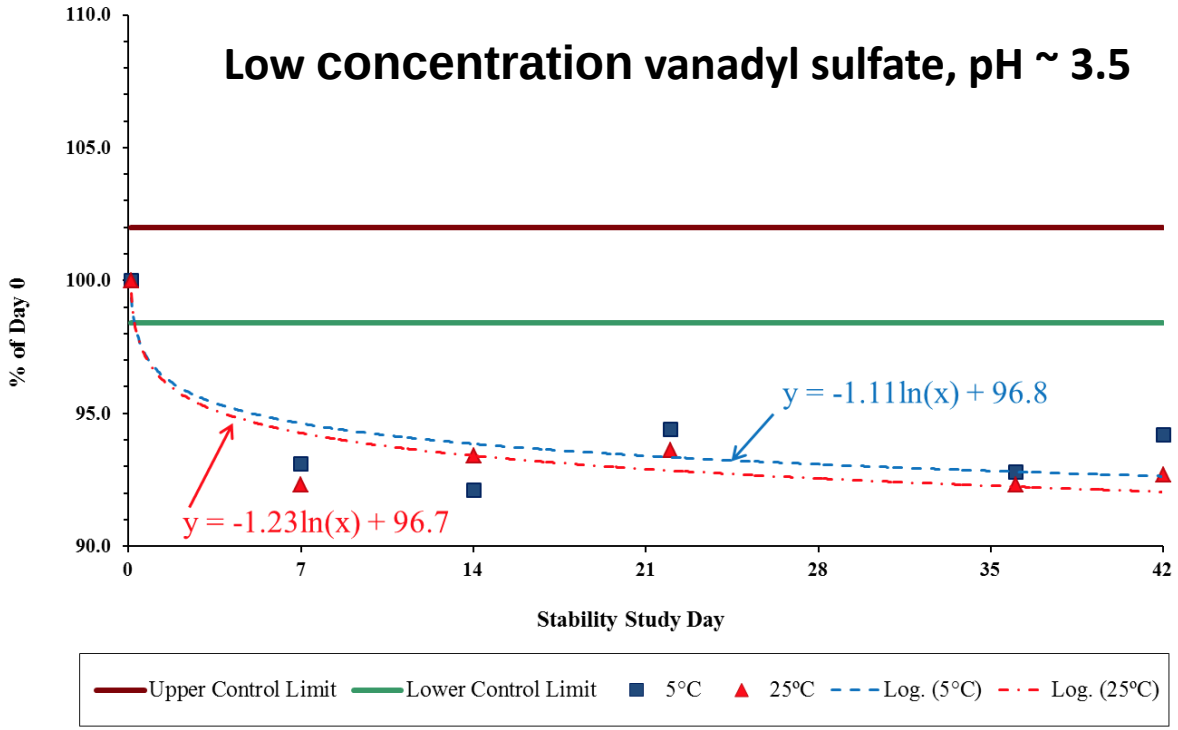
Sodium orthovanadate

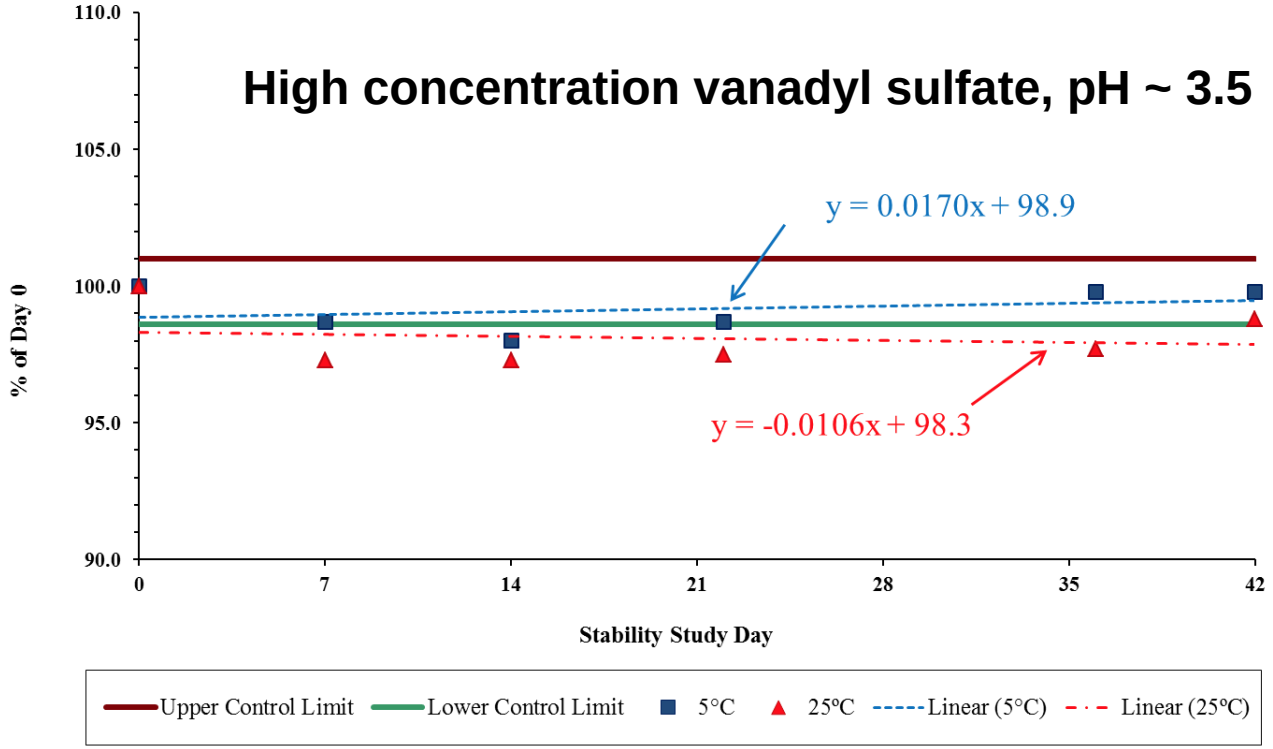
- Types of oxovanadate species present are influenced by pH.
  - In basic pH, monomers predominate (e.g., VO_3^-, $H_2VO_4^-$).
  - A mixture of oligomers are formed around neutral pH (e.g., $V_2\ O_6^{2-}$, $V_4\ O_{12}^{4-}$).
  - In acidic pH, vanadate decamers predominate (e.g., V ($V_{10}\ O_{26}^{6-}$, $HV_{10}\ O_{28}^{5-}$).
- Species formed were similar between inorganic V^{+5} compounds.

Mutlu et al., 2017

Key science issue #2: Consideration of vanadium speciation

Stability of V^{4+} in aqueous dose formulations



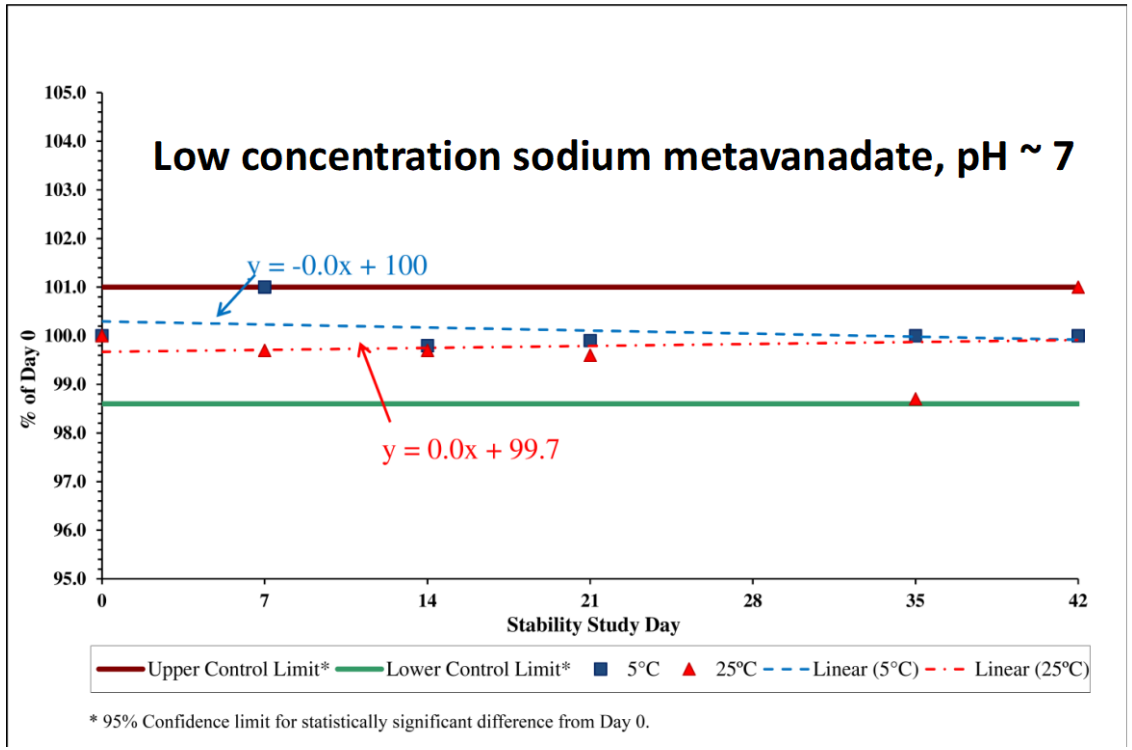


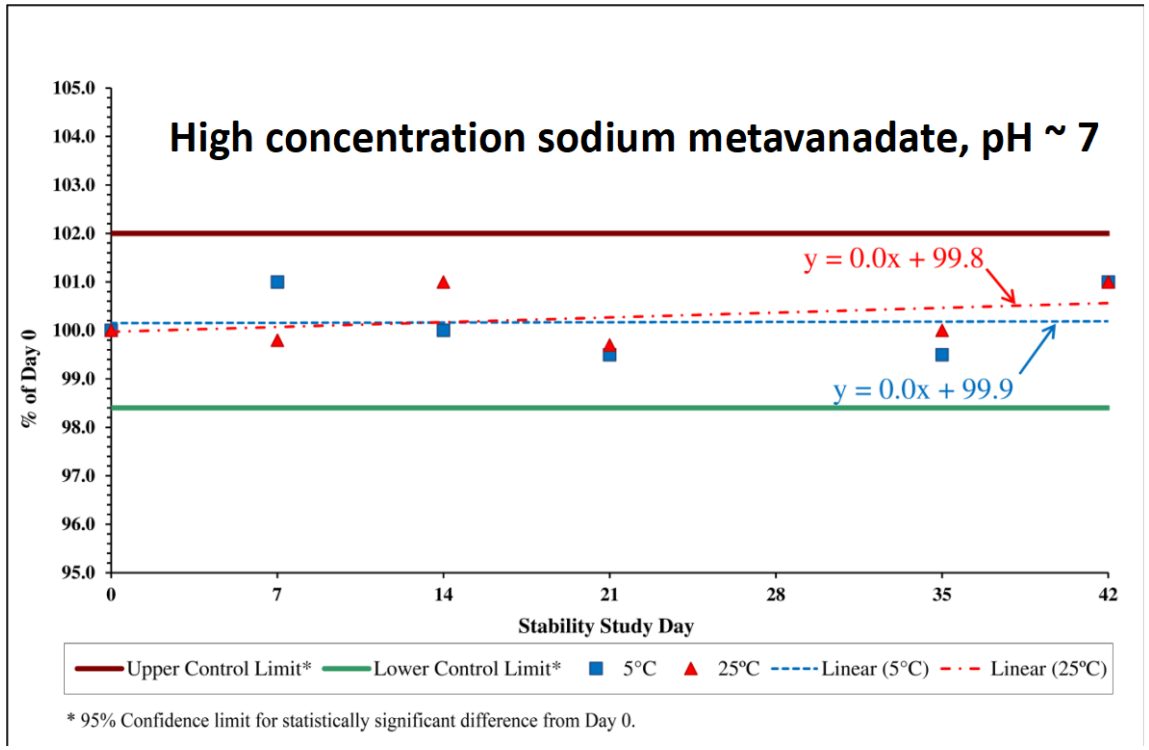
Mutlu et al., 2017

- Observation of concentration-dependent effect.
  - Initial drop in concentration followed by negligible decline. Small % of V^{+5} was formed.
  - The low concentration of V^{+4} was still within 10% of target concentration.
- No apparent difference in behavior of V^{+4} in tap or deionized water formulations.

Key science issue #2: Consideration of vanadium speciation

Stability of V^{5+} in aqueous dose formulations





Mutlu et al., 2017

- No concentration- or time-dependent change in V^{+5} concentration.
- No difference in behavior of V^{+5} in tap or deionized water formulations.
- Types of oxovanadate species present were similar at day 0 and 42.

Key science issue #2: Consideration of vanadium speciation

Summary

- Factors that affect the oxidation state and speciation should be carefully considered.
  - Dose formulation vehicle and pH should be a consideration among other factors when comparing across studies to ensure exposure to similar vanadium species.
  - Some consideration should be given to evaluate vanadium species across formulation concentrations and duration used.