IRIS Assessment Plan for Vanadium Compounds (Oral Exposure)

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- 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.

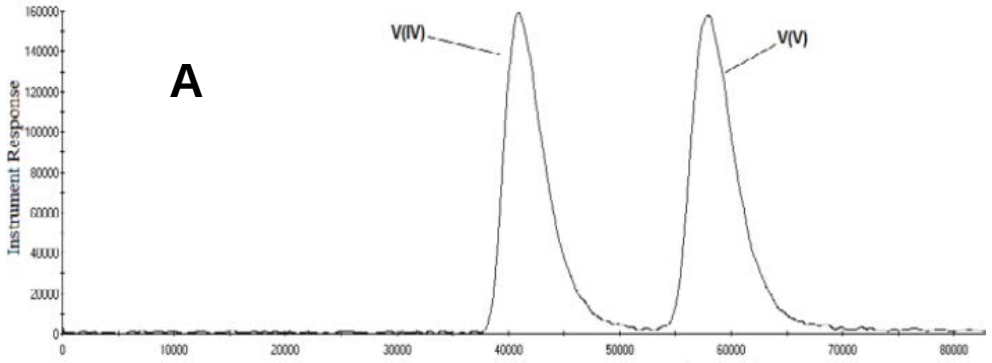
Key science issue #1: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds

Background

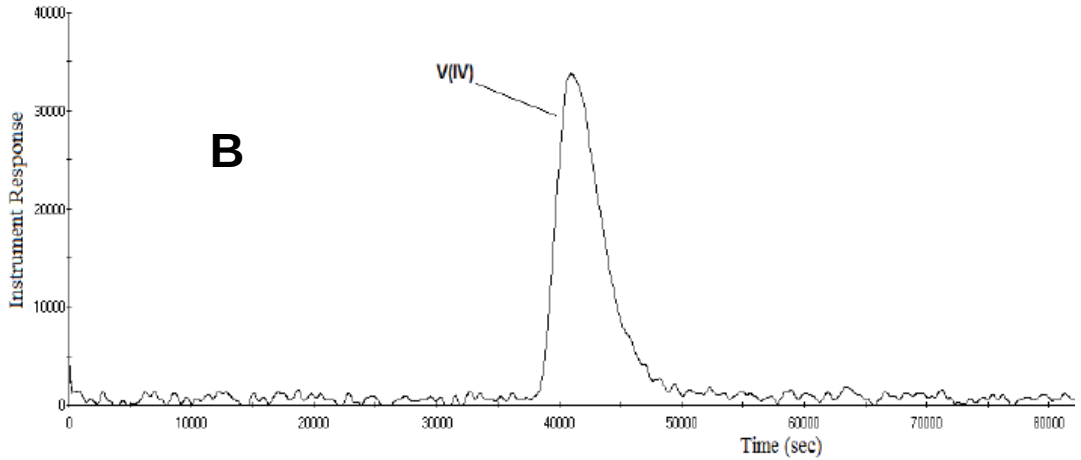
- Differential ADME properties of inorganic V^{+4} and V^{+5} compounds have been reported.
- Higher absorption following exposure to V^{+5} compared to V^{+4} has been observed.
  - V^{+5} oxoanions ($H_2VO_4^-$ and HVO_4^{2-}) are absorbed 3 to 5 times more efficiently than the V^{+4} oxocation, VO_2^+
  - The extent to which these species are formed is determined by various factors including redox conditions, presence of food, enzymes, or other biomolecules.
- Vanadium species are distributed to tissues
  - In blood, vanadium species bind to serum proteins during transport, particularly albumin and transferrin.
  - V^{+4}/V^{+5} can undergo redox reactions in extracellular fluids and interconvert.
  - In intracellular space, the speciation again can vary depending on the specific physiological conditions.
- Hence interconversion between species and oxidation states are likely constantly happening in the body and is challenging to characterize.

Key science issue #1: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds

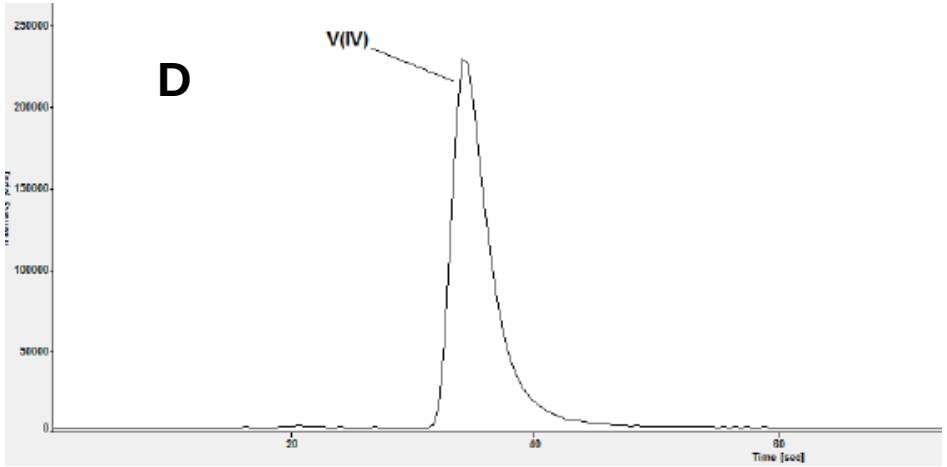
Speciation by mass spectrometry



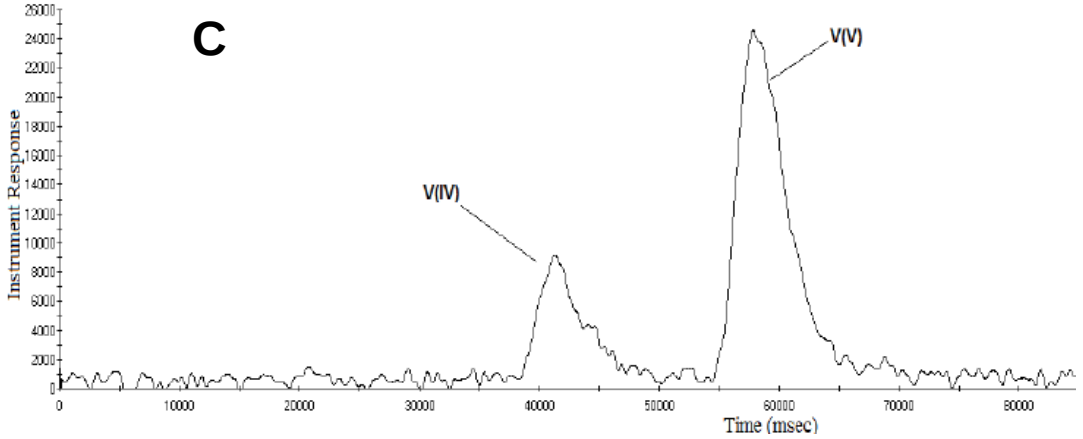
Solvent standards showing stability and separation of V^{+4} and V^{+5}



Plasma matrix standard of V^{+4} showing stability in matrix



Only V^{+4} was observed in rat plasma following V^{+4} or V^{+5} exposure



Plasma matrix standard of V^{+5} showing conversion of V^{+5} to V^{+4}

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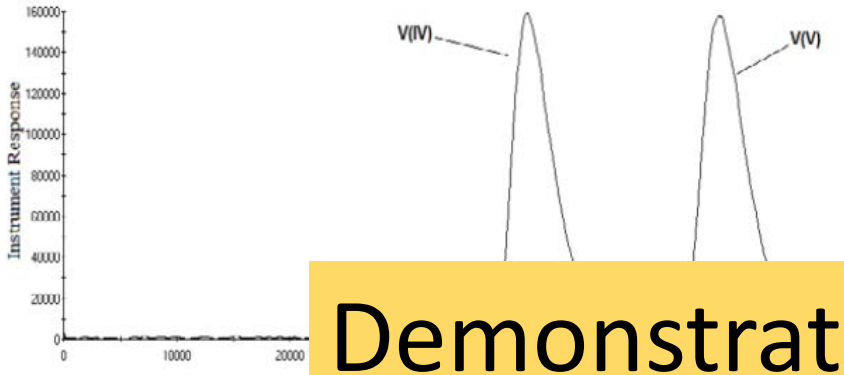
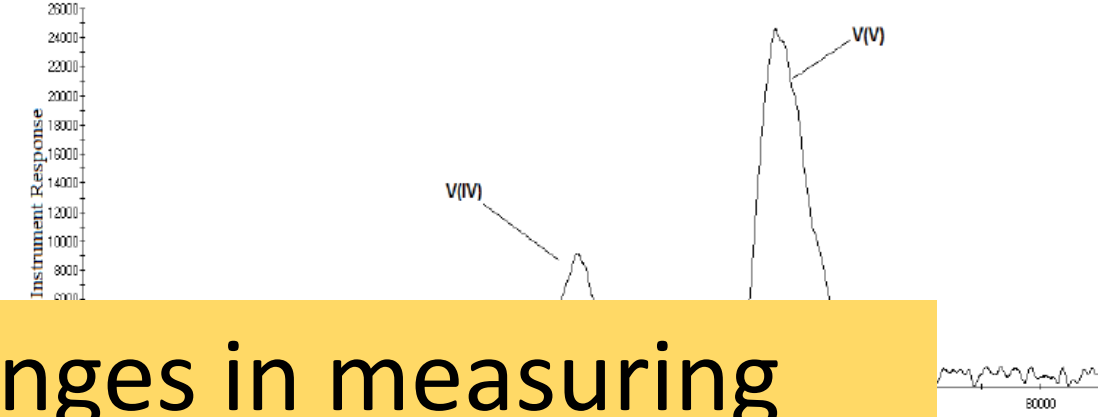
Speciation by mass spectrometry

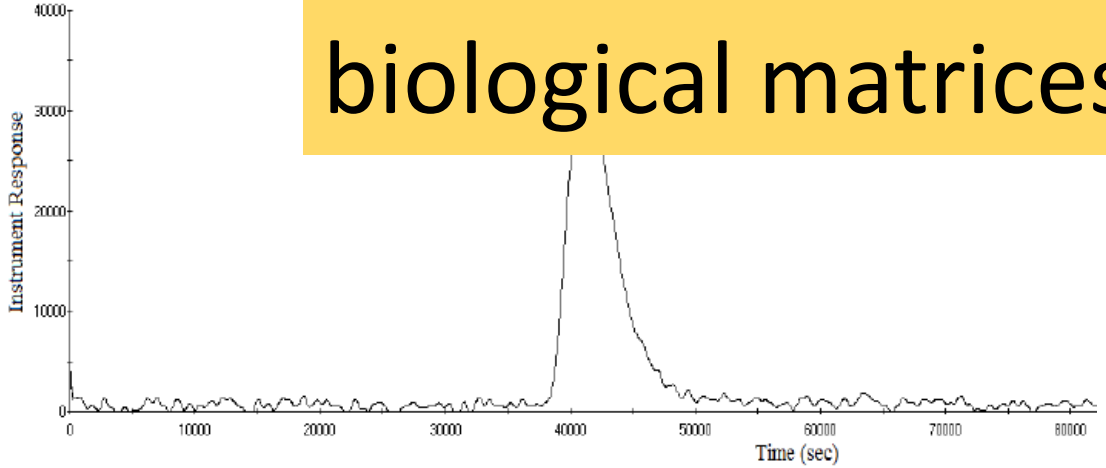


Solvent standards

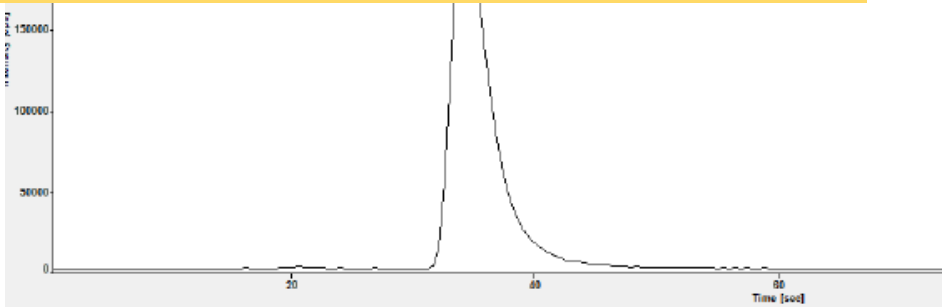


sion of V^{+5} to V^{+4}

Demonstrates challenges in measuring vanadium oxidation states/species in biological matrices.



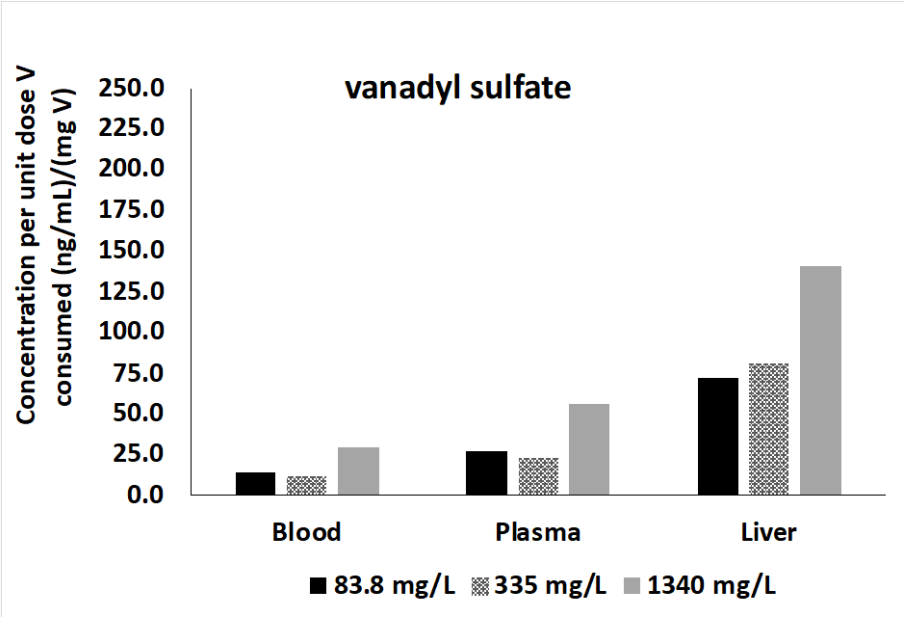
Plasma matrix standard of V^{+4} showing stability in matrix

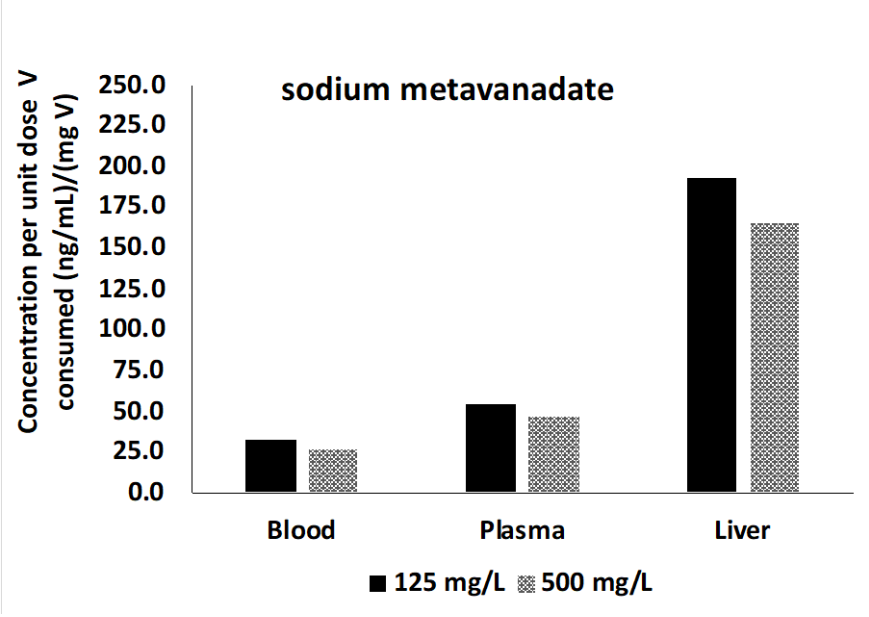


Only V^{+4} was observed in rat plasma following V^{+4} or V^{+5} exposure

Key science issue #1: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds

Internal concentration of vanadium per unit dose of vanadium consumed





- Following exposure via drinking water for 14 d, the internal concentration per unit dose of vanadium consumed is 2- to 3-fold higher following exposure to V^{+5} compared to V^{+4}.
  - It should be noted that the data are from samples collected at one timepoint and may or may not reflect the total internal exposure (concentration X time).
- Based on clinical observations and overt toxicity, V^{+5} appears to be more toxic than V^{+4} following exposure of rats via drinking water for 14 d.
  - Internal concentrations may be related to toxicity and hence potentially a useful endpoint to consider when comparing between studies.

Roberts et al., 2016, 2017; Harrington et al., manuscript in preparation

Key science issue #1: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds

Summary

- Oxidation state of vanadium compounds should be considered when comparing between studies.
- Investigating vanadium speciation in biological media is challenging using commonly available analytical techniques due to interconversion and/or instability of species.
- Total vanadium in blood and tissues may correlate with toxicity and hence is a useful endpoint to consider when comparing between studies.
  - Data available for one timepoint should be considered carefully as they may or may not represent the total internal exposure.
  - Non-linear kinetics should be taken into consideration.