Integrated Risk Information System (IRIS) Program Public Science Meeting Topic #: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds.

By Debbie C. Crans; Colorado State University

For developing *the* ***Populations, Exposures, Comparators and Outcomes (PECO) criteria for Vanadium*** with the ultimate goal of ***setting guidelines for safe limits in drinking water***

Disclaimer

- 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.

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Topic: Consideration of potential toxicity and toxicokinetic differences across vanadium compounds.

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Vanadium levels in Blood and Plasma

Vanadium salt interact with components in blood; proteins and metabolites

Studies report recycling between oxidation states IV and V

Human study showing blood levels not consistent with observed response

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Uptake depend on cell type/animal and vanadium compound

Cellular uptake difference between vanadyl(V) and vanadium(V(V))

- **Model studies show different interactions and ability to penetrate interfaces / membranes**

Answer: $NaVO_3$ interact differently with the interface than $VOSO_4$

- **Animal cells show difference in toxic responses between $NaVO_3$ and $VOSO_4$**

Answer: Generally $NaVO_3$ slightly more toxic than $VOSO_4$

- **Human cells show difference in toxic responses between $NaVO_3$ and $VOSO_4$**

Answer: $NaVO_3$ slightly more toxic than $VOSO_4$

Are differential effects of vanadium species observed in animal/human studies?

Answer: Sometimes yes / no – in animals and in humans – why?

- **Vanadium(IV) salts given ad libertum can oxidize in the presence of oxygen**
- **The observations can be due to different species or overall concentrations**

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Studies report recycling between oxidation states IV and V

- **Both in vitro and in vivo studies demonstrate that interconversions do occur**

Vanadium in blood / serum can be bound to blood / serum components

- **Key blood/serum metabolites are glutathione and ascorbate**
- **Key blood/serum proteins are transferrin and serum albumin**
- **Extensive chemical work has been reported with these systems**

Human study with Type 2 diabetic patients showing blood levels not consistent with observed response

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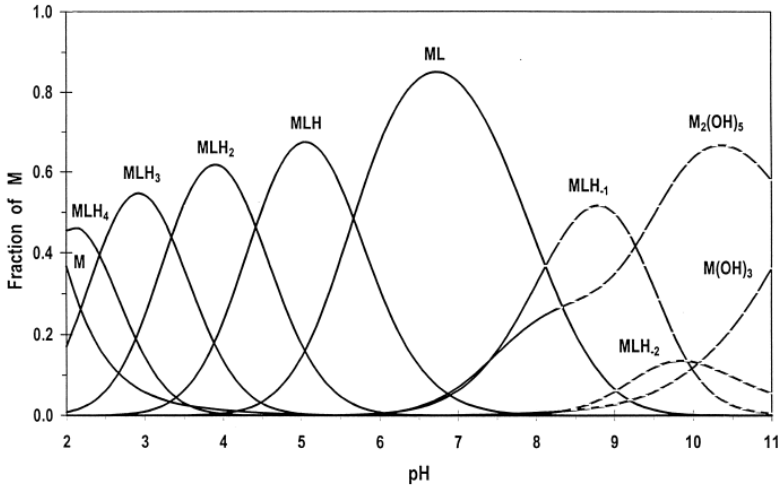
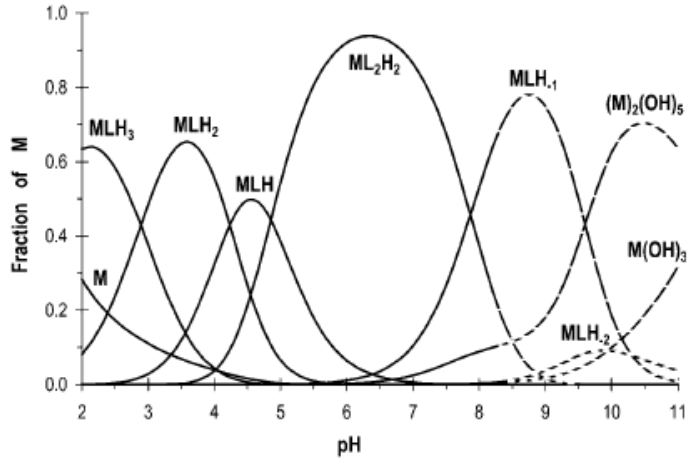
Vanadium and gluthathione

- Vanadium(V) and vanadium(IV) form both complexes with gluthathione (GSH)
- Vanadium(IV) form complexes with gluthathione (GSSG)
- Vanadium(V) can be reduced by GSH; metabolizing and can form both the V(IV)-GSH and V(IV)-GSSG complexes



The $V(IV)^{2+}$-GSSG system V(IV) 7 mM and 70 mM GSSG

- **Conclusion:** Vanadium in blood or plasma is likely to be in part in the form of a V(IV)-GSH and possible also a V(IV) complex



The $V(IV)O^{2+}$-GSH system with V(IV) 10 mM and 250 mM GSH

Pessoa et al. *J. Inor. Biochem.* 2001, 84, 259-270

Pessoa et al. *J. Biol. Chem.* 2002, 7, 225-240

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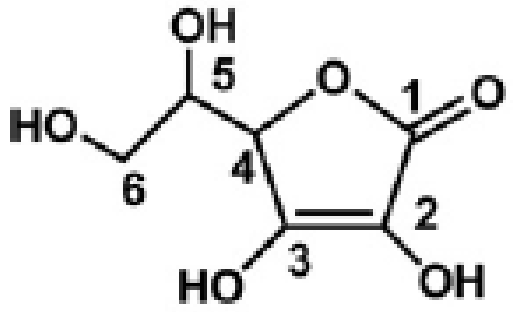
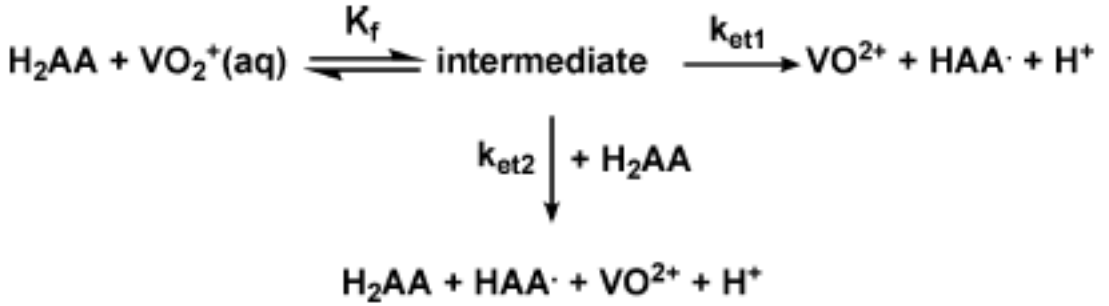
Vanadium and Ascorbate



Ascorbic acid



Scheme 1. Detailed mechanism for the ascorbic acid reduction by VO_2^+ presented previously [14].

- Vanadium for complexes with ascorbate
- Vanadium(V) is reduced by ascorbate
- The reaction contribute to convert any potential vanadium(V) compounds to vanadium(IV)

Reaction supportive of the possibility that vanadium(V) complexes converts to vanadium(IV) in blood or plasma

"Impairment of ascorbates' anti-oxidant properties in confined media: Inter and intramolecular reactions with air and with vanadate at acidic pH," Debbie C. Crans, Bharat Baruah, Ernestas Gaidamauskas, Brant G. Lemons and Michael D. Johnson, *J. Inorg. Biochem,* **2008**, *102*, 1334-1347 and references therein

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Vanadium and proteins in blood (transferrin and albumin)

- Vanadium in oxidation states III, IV and V are known to bind tightly to transferrin and transferred readily in blood
- Vanadium also is known to bind to serum albumin (both bovine and human serum albumin)
- Such interactions can be measured using MS methods

Very active research area:
D. Sanna, L. Biro, P. Buglyo, G. Micera and E. Garribba, *Metallomics***, 2012**, 4, 33–36.
J. C. Pessoa and I. Tomaz, *Curr. Med. Chem.,* 2010, 17, 3701–3738.
Recently reviewed in "Developing vanadium as an antidiabetic drug: A clinical and historical perspective" Debbie C. Crans, LaRee Henry, Gabriel Cardiff and Gary Posner, *Met. Ions Life Sci,* **2019**, *19*, 203-230

Recent publications that may be of relevance
"Speciation of metal drugs, supplements and toxins in media and bodily fluids controls *in vitro* activities" Aviva Levina, Debbie C. Crans, Peter A. Lay *Coor. Chem. Rev.* **2017**, *352,* 473-498.
"ESI-MS Study of the Interaction of Potential V^{IV} Drugs and Amavadin with Proteins" Valeria Ugone, Daniele Sanna, Giuseppe Sciortino, Debbie C. Crans, and Eugenio Garribba *Inorg. Chem.* **2020**, 59, 9739-9755.
Levina and Lay *Inorg. Chem*. **2020**, ASAP

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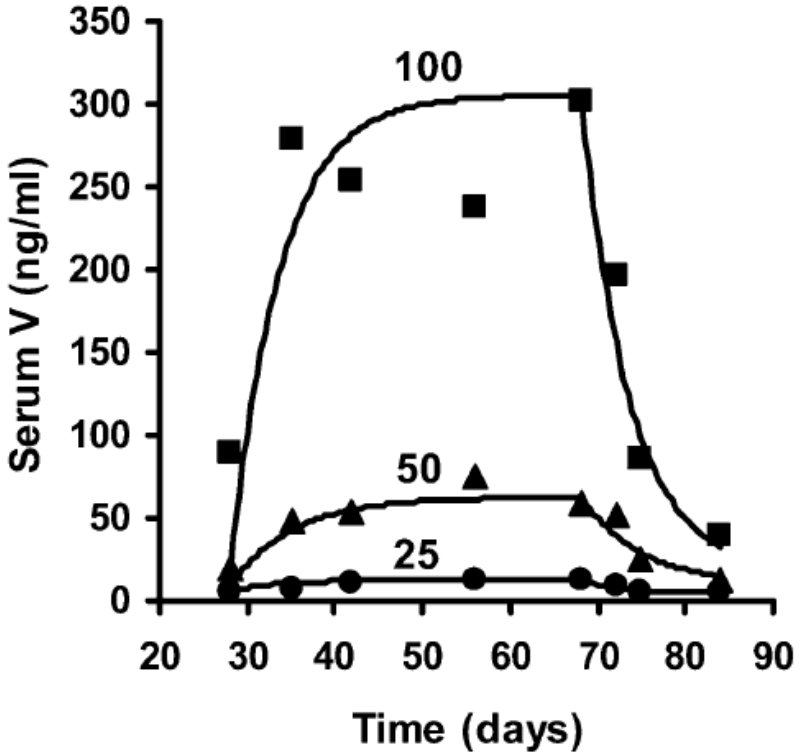
Examination of administration of $VOSO_4$ to humans

Type 2 diabetic patients were given 25, 50 or 100 mg $VOSO_4$ 3 times daily. Vanadium levels was measured using Graphite Furnace Atomic Absorption Spectroscopy

Figure Caption: Serum vanadium accumulation for all patients dosed at 25, 50, and 100 mg V as vanadyl sulfate. A one-compartment open model using the equation Ct = baseline concentration + $C_o e^{-kt}$. Mean serum V levels are indicated by (•) for the 25 mg V dose, (solid triangle) for the 50 mg V dose, and (solid square) for the 100 mg V dose.



Observation: Non-linear response between serum level and amount administered

Conclusion: The total vanadium pool is not the active pool of vanadium

"Coordination chemistry may explain pharmacokinetics and clinical response of vanadyl sulfate in type 2 diabetic patients," Gail R. Willsky, Katherine Halvorson, Michael E. Godzala III, Lai-Har Chi, Mathew Most, Peter Kaszynski, Debbie C. Crans, Allison B. Goldfine and Paul J. Kostnyniak, *Metallomics,* **2013**, *5,* (11) 1491-1502.

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Take home messages:

Vanadium levels in Blood and Plasma

- **Uptake depend on speciation and should be measured**
- **Interaction with the membrane exist and several uptake mechanisms documented**

Are differential effects of vanadium species observed?

- **Yes studies have been reported with both diabetic animals and human beings**
- **Some of these effects are due to different vanadium compounds but in the case of salts may also be due to overall concentrations**

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Take home messages:

Presence in blood / serum depend on blood / serum components

- **Blood Components: gluthathione, ascorbate, transferrin and serum albumin all bind vanadium and can be measured**
- **Presence in blood may change as a function of time; more data is needed on changes as a function of time**
- **Method has now been reported to measure the protein-vanadium complexes**

Study with human Type 2 diabetic patients showing vanadium blood and serum levels did not correlate with the observed antidiabetic effects

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