July 14, 2021 IRIS Public Science Meeting

Vanadium and Compounds (Inhalation Exposure) IRIS Assessment Plan (IAP)

Comments on Issue #1: relating to issues surrounding chemical speciation of vanadium

By Debbie C. Crans; Colorado State University

Debbie C. Crans, Colorado State University National Academies of Science Expert

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.

Expertise

• I have been working in the area of vanadium science since 1986. As a chemist my initial work focused on developing the chemistry necessary to be able to effectively understand reactions in biological systems. Currently, I am working on problems associated with understanding the effects of vanadium compounds for treatment of cancer and other applications.

Announcement: Re International Vanadium Symposium – Virtual Nov 3-5, 2021

http://vanadium12.com/abstract-paper-submission/

Problem to be Assessed

The following key science issues were identified on the basis of the preliminary literature survey results (see Section 2.3.1) and review of past assessments on inhalation exposure to vanadium and compounds (see Section 2.1).

Issue #1 relates to issues surrounding chemical speciation of vanadium,

Issues #2 and #3 pertain to consideration in interpreting nonneoplastic lesions in the upper and lower respiratory tract and alveolar/bronchiolar neoplasms in rodents,

Issue #4 pertains to evaluating the MOA information relevant to potential carcinogenicity.

Issues identified in U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020

Issue #1 under investigation

Science Issue #1:

- 1a Consideration of **vanadium speciation and oxidation state**. Considering oxidation status could be important as preliminary examination of findings from oral exposure studies in rodents appears to indicate **increased toxicity of vanadium in the +5 oxidation state compared to vanadium +4** (Roberts et al., 2016).
- 1b As noted in Section 2, **vanadium in solution can convert between oxidation states and will form different species as a function of factors including pH, concentration, and redox potential**. Study evaluations for the available **inhalation studies**, to the extent possible, will consider **factors that could affect vanadium oxidation state and speciation** [e.g., study **methods that involved aerosolizing vanadium pentoxide** (or other vanadium compound) from solution, e.g., González-Villalva et al. (2011), **rather than exposure to vanadium as a dust**, e.g., NTP(2002)].
- 1c In addition, data to inform potential **conversion between vanadium oxidation state *(should include "species")* in the body** also will be evaluated and discussed in the assessment.

Issues identified in U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020

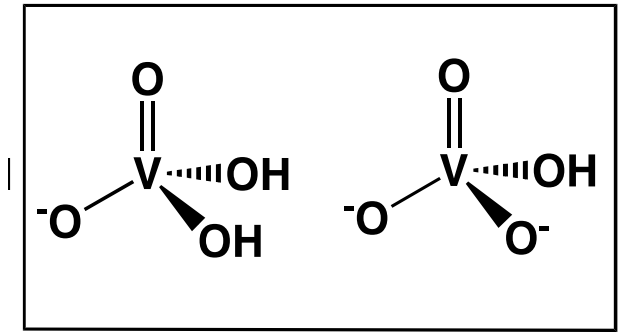
Coverage under Issue #1 (1a, 1b, 1c)

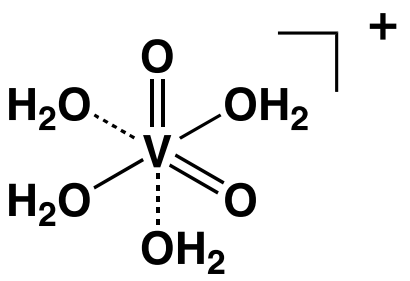
- Vanadium speciation and oxidation state (1a)
  - Pourbaix diagrams.
  - Different species as a function of pH, concentration, and redox potential
  - Solid state and solution
- Speciation of vanadium(V) (+5 oxidation state) (1b)
  - Speciation Profiles
  - Differences in species and interconversions
  - V_2O_5
  - Note – biological system will respond differently to various species (addendum slide)
- Evaluate available inhalation studies and the factors that could affect speciation (1b)
  - Aerosolizing V_2O_5 from solution, rather than exposure to V_2O_5 dust.
  - Model studies of speciation in microemulsions (reverse micelles)
- Conversion to and between vanadium species in the body (1c)
- What was already identified in U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020

V(V) and V(IV) speciation – solid and solution states (1a)

Cationic VO_2^+ and anionic V(V) in solution?

$NaVO_3$ – vanadium(V)



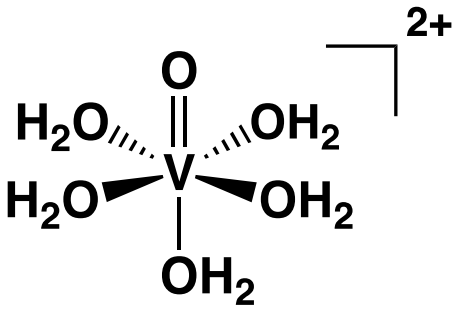


VO_2^+ may be coordinated to H_2O

Anionic vanadate - $H_2VO_4^-$ (and HVO_4^{2-}) – phosphate analog $H_2PO_4^-$ (and HPO_4^{2-})

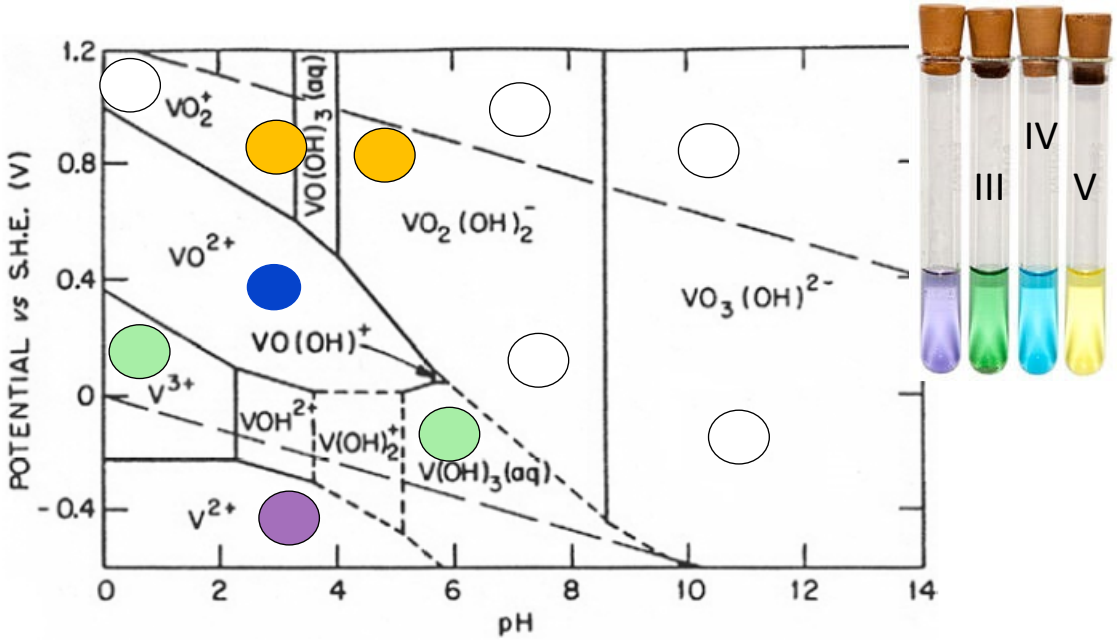
Low pH cationic VO_2^+ Colorless

$VOSO_4$ – vanadium(IV)



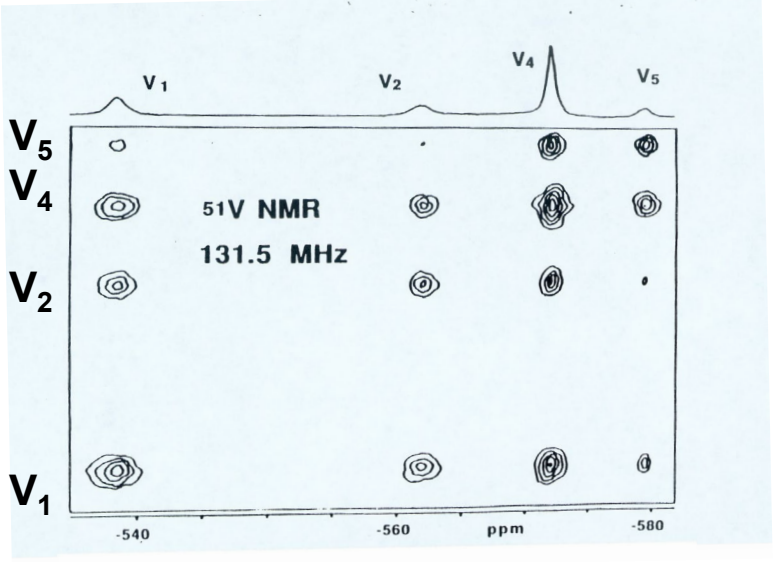
SO_4^{2-}

Spectroscopic studies in solution
Iannuzzi, Rieger *Inorg. Chem.* ***1975,*** *14,* 2895
EXAFS and LAXS (Krakowiak et al *Inorg. Chem.* **2012**



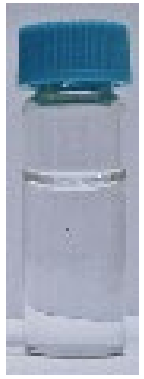
Pourbaux diagram

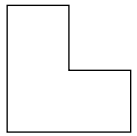
V(IV) and V(V) solution speciation (1b)

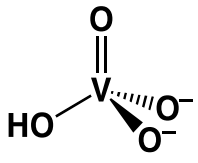


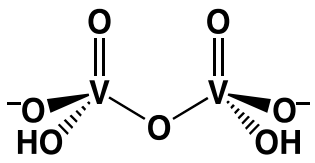
2D EXSY ^{51}V NMR spectroscopy

Crans et al. *J. Am. Chem. Soc.* 1990, *112*, 2901

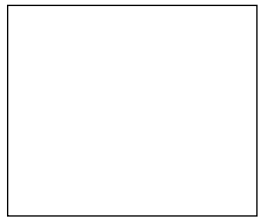


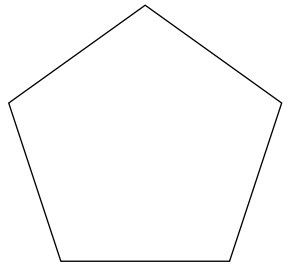


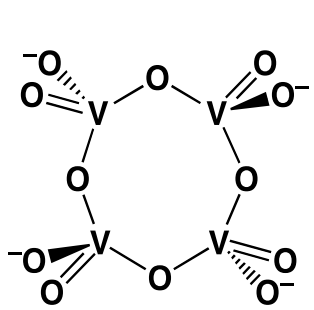


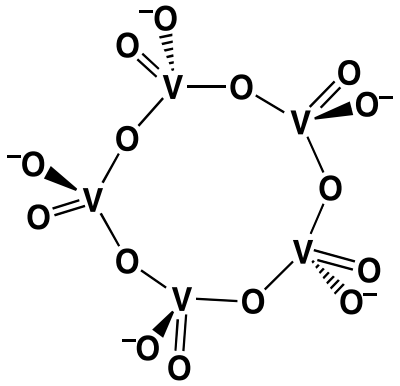


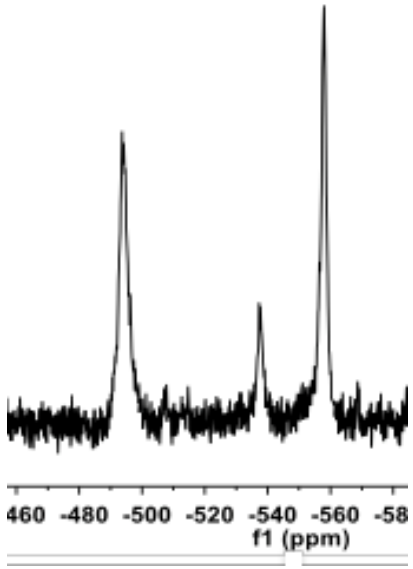
Rapidly exchanging colorless vanadium(V)



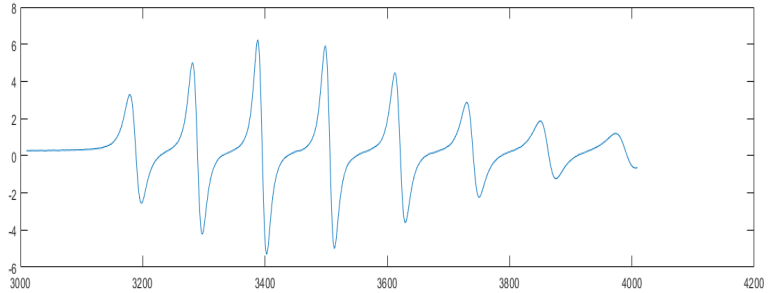


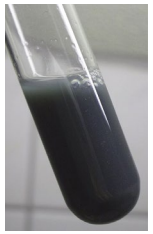






Vanadium(IV) - VO_2^+



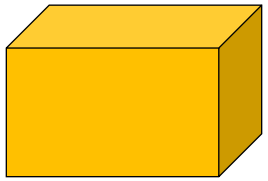


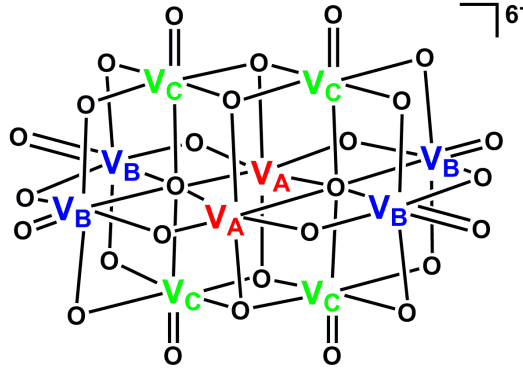
Solution V(IV)

EPR spectrum

Vanadyl

Yellow/orange decavanadate



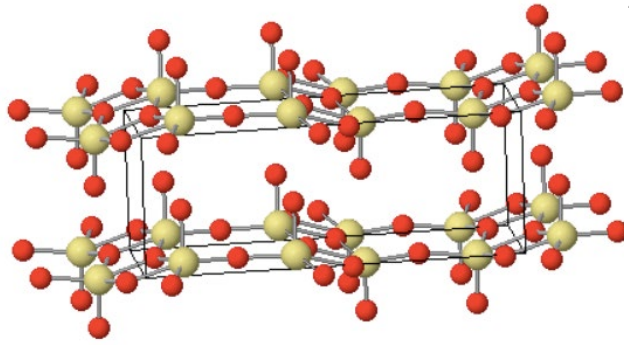


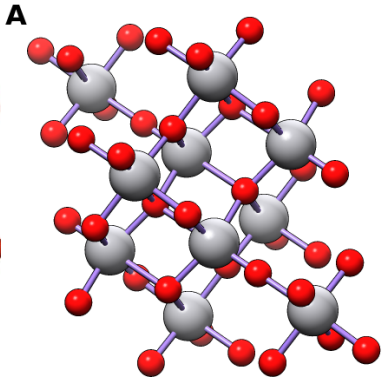
Comparing solid V_2O_5 with $V_{10}O_{28}^{6-}$ (Vanadium(V)) 1a)

V_2O_5

Pure V_2O_5 (orange & brown) – China 99.9%

V_2O_5 - catalyst



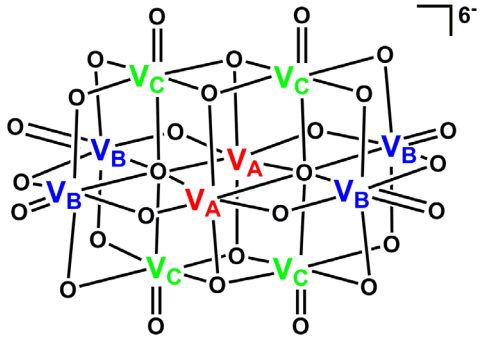


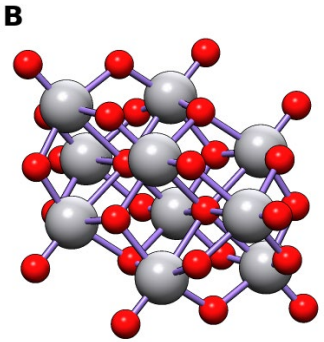
Sheets - polymers

$V_{10}O_{28}^{6-}$

$K_3Na_3V_{10}O_{28}$

$(NH_4)_6V_{10}O_{28}$



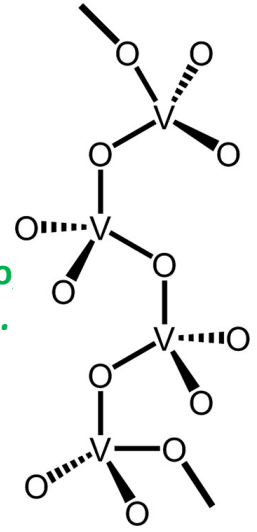


Discrete molecule

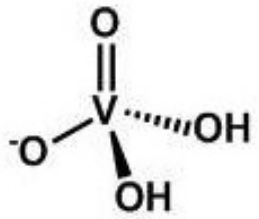
Speciation in V(V)-Chemistry: solid and solution state (1b)

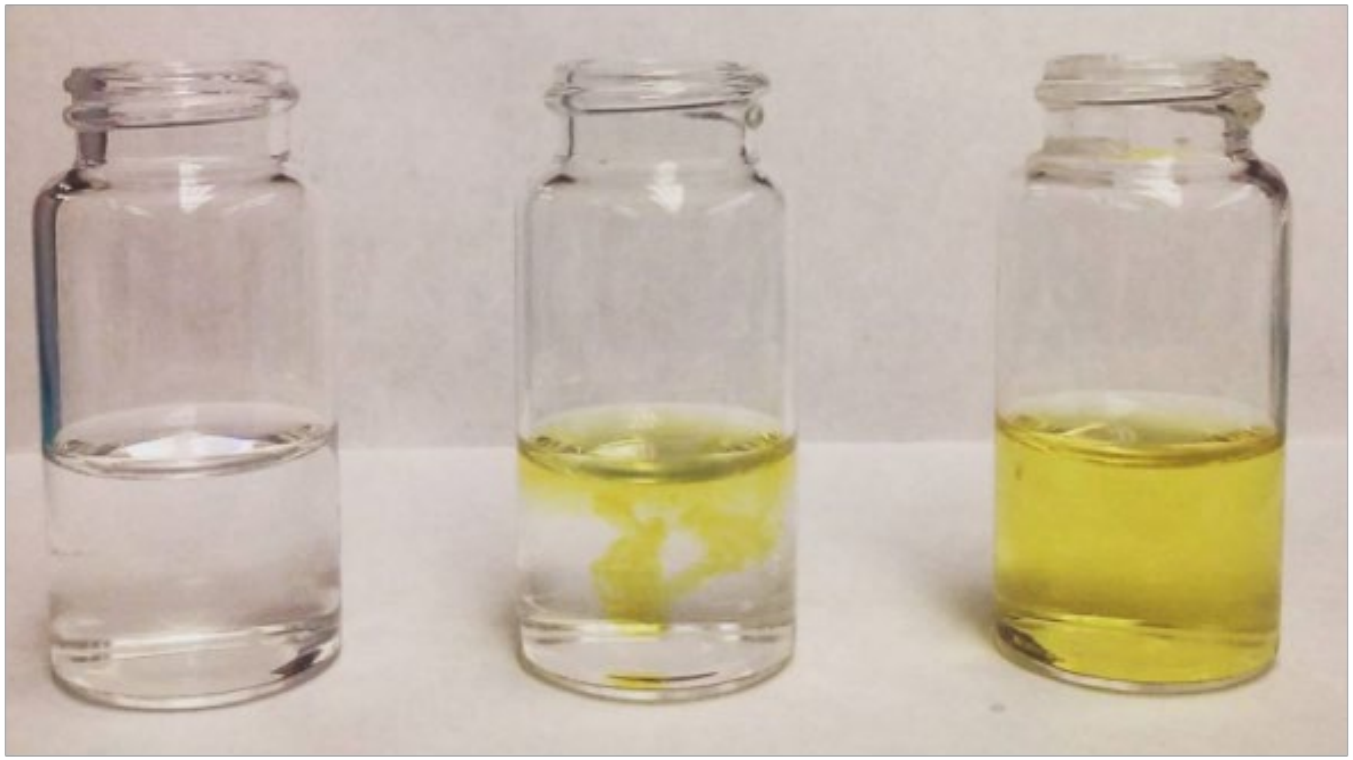
One species in Solid state - $NaVO_3$

Hawthorne & Calvo *J. Solid State Chem.* 1977 22, 157-170.



$NaVO_3$

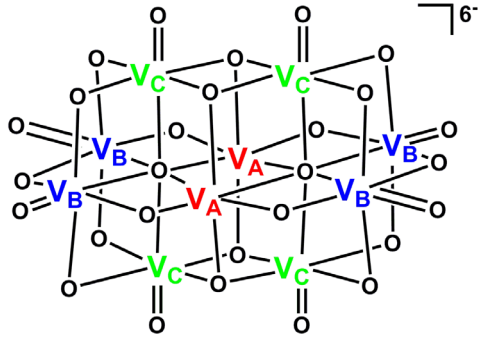




Vanadate (pH 7) **Decavanadate (pH 3)**

$(NH_4)_6V_{10}O_{28}$

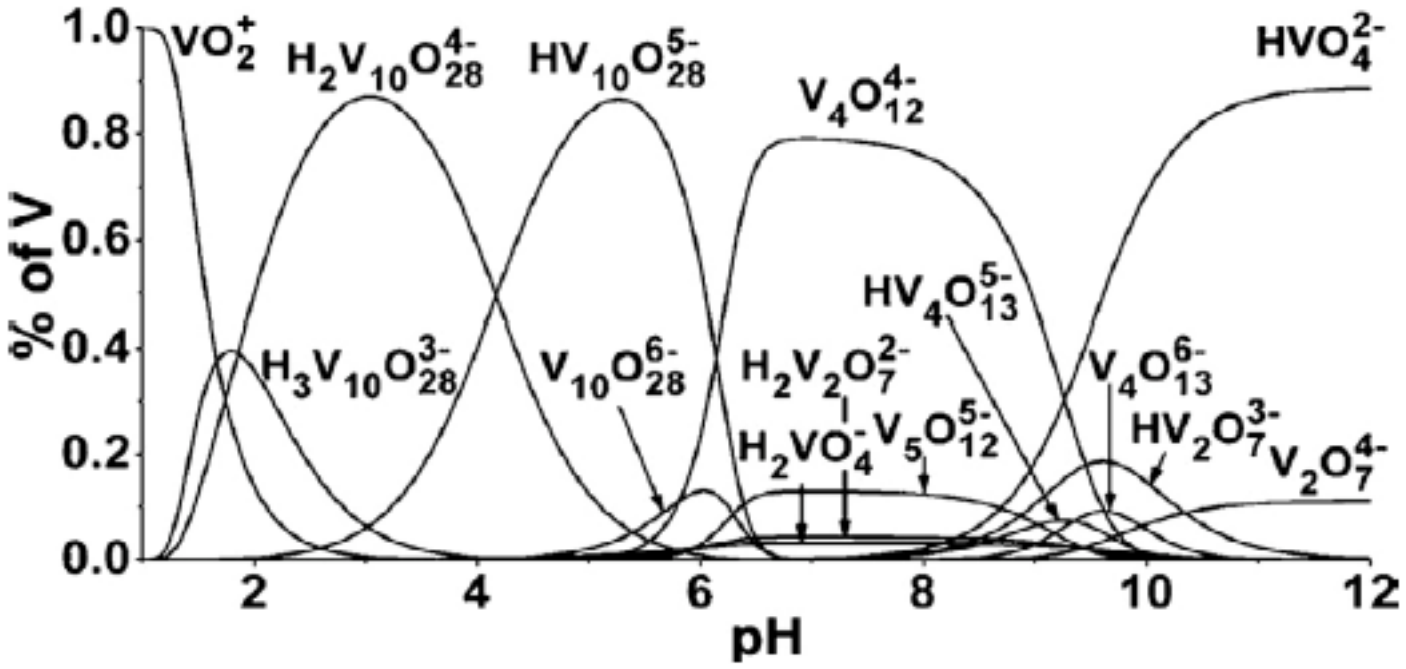
$K_3Na_3V_{10}O_{28}$



Crans *J. Inorg. Chem.* **2000**, 80, 123-131; Crans et al. *Chem. Rev.* **2004**, 104, 849-902; Crans, *Inorg. Chem.*, **2013**, *52*, 12264-12275; Samart *et al., Frontier in Chemistry.* **2018,** *6,* 519.

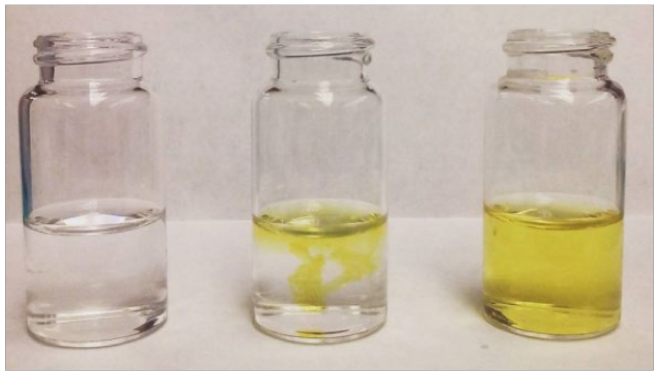
Speciation - Distribution Plot (1b)

Note – no mention of V_2O_5

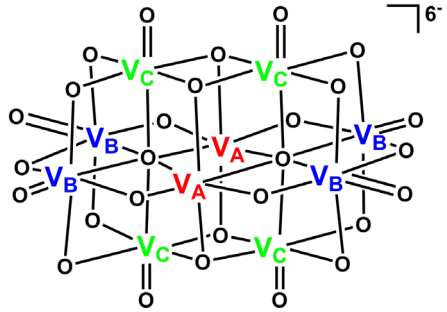


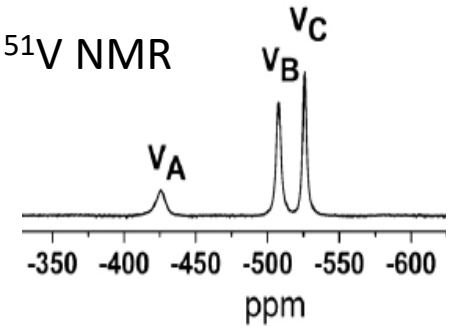
D.C. Crans, N.E. Levinger, Acc. Chem. Res. 45 (2012) 1637–1645.

$K_3Na_3V_{10}O_{28}$



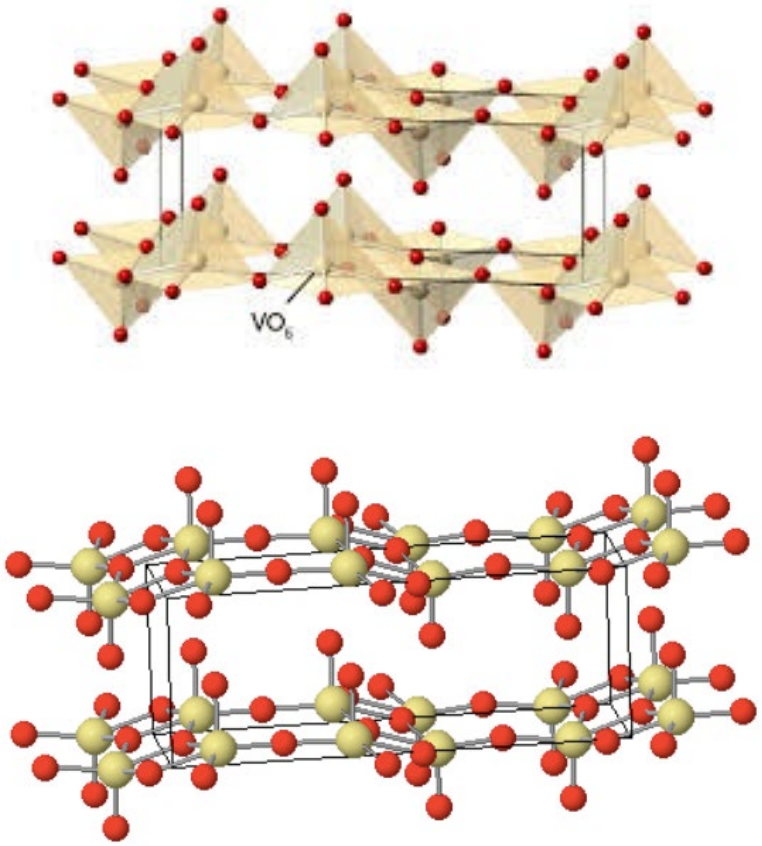
Vanadate (pH 7) Decavanadate (pH 3)





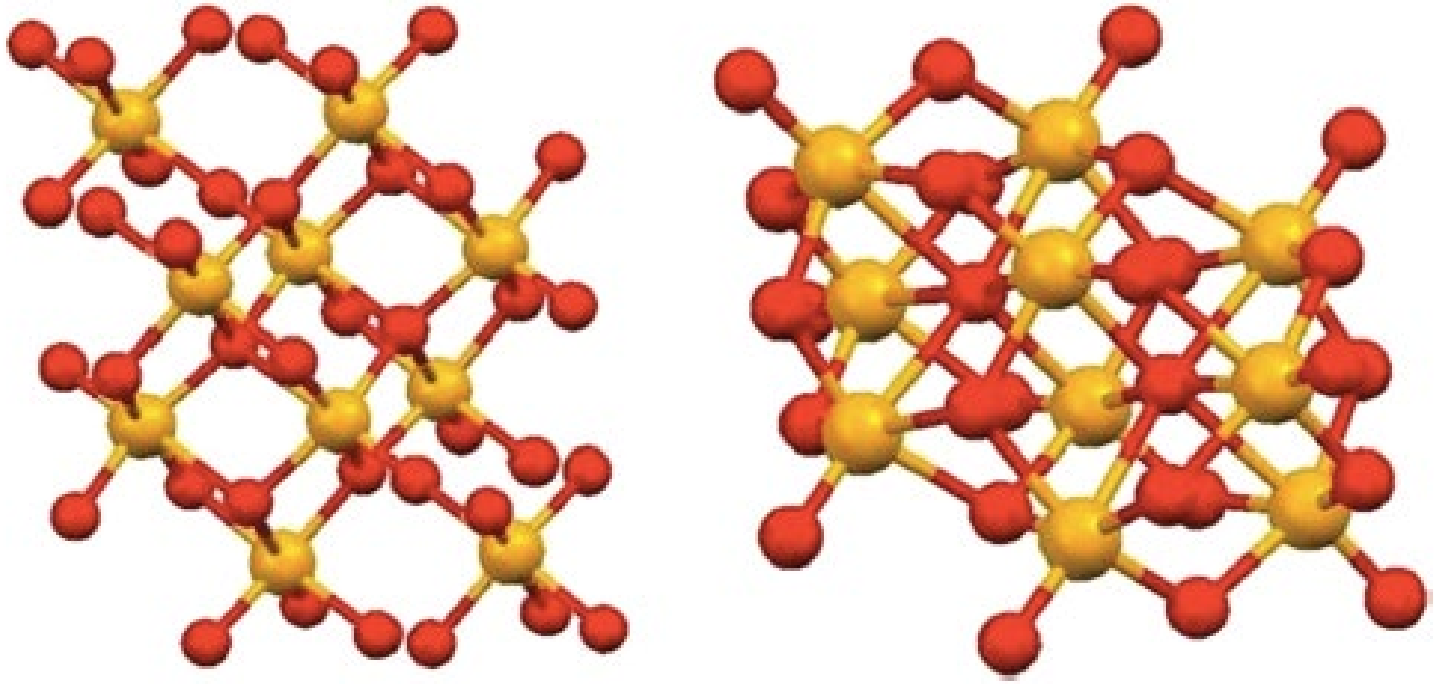
Freshly precipitated V_2O_5 *(Crans asks if it is V_2O_5 or $H_3V_{10}O_{28}^{3-}$?)* by acidifying a solution of a metavanadate with dilute H_2SO_4 to pH near 2. Image credit W. Oelen (Public domain)

Structure of V_2O_5 and $V_{10}O_{28}^{6-}$ (1c)



V_2O_5 - Solid state
Nick Greeves, Creative Comments Lincence

V_2O_5 have been modeled by $V_{10}O_{28}^{6-}$

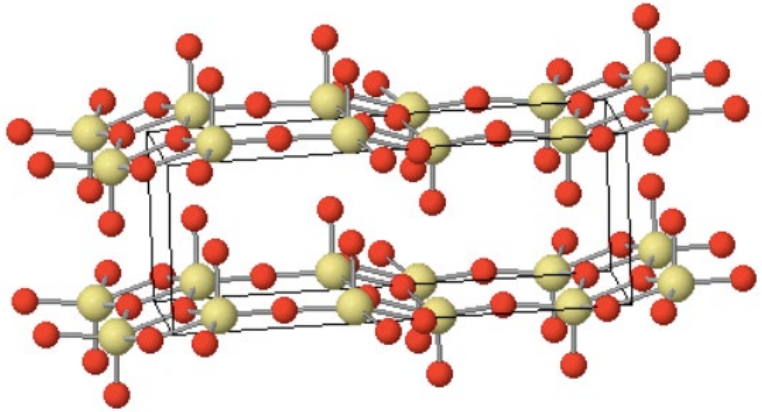


The partial structure for **V_2O_5 sheet** is shown (left). The structure for the **discrete anion (V_{10})** is shown (right). While V_2O_5 falls apart in solution, the discrete V_{10} anion retains its structure upon dissolution.

V_{10} used a s model for V_2O_5 Al-Qatati et al. *Dalton Trans.*, 2013, 42, 11912–11920

How does this translate to the biological experiments?(1c)

- Airborne V_2O_5 **are delivered in aerosols**
- What is speciation in aerosols?
- How are aerosol prepared? From solid or from solution?



V_2O_5 - Solid state
Nick Greeves, Creative Comments Lincence

Fragmenting sheets →

What are the speciation in these aerosols?

Dissolution →

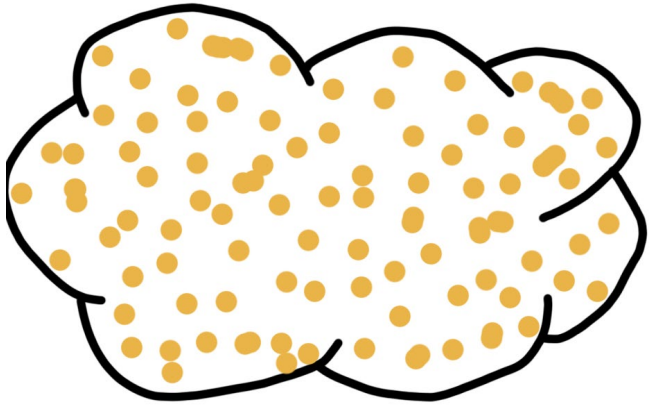
Various protonation states of V_{10}
So what information is available to do accesment?

Speciation Studies in Confined Spaces

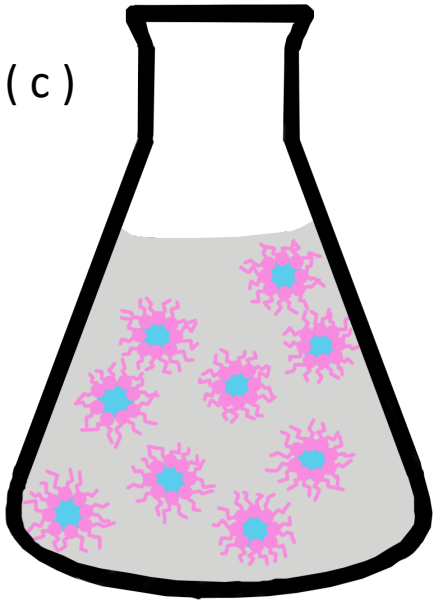
Aerosol definition: A colloidal suspension of particles dispersed in air or gas.

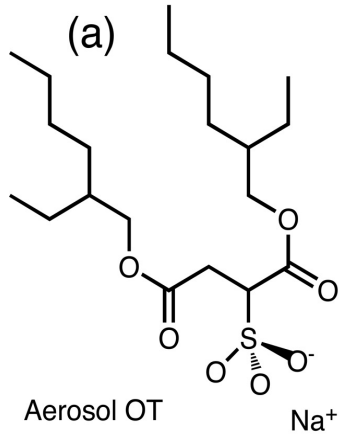
Related System: A colloidal suspension of particles dispersed in solution

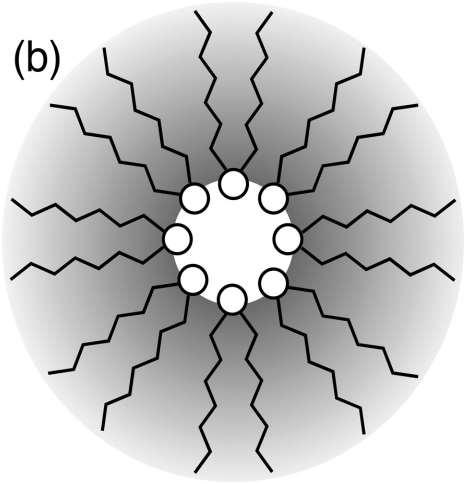
Ternary system consisting of aqueous water pool, Aerosol-OT, organic solvent



Aerosols



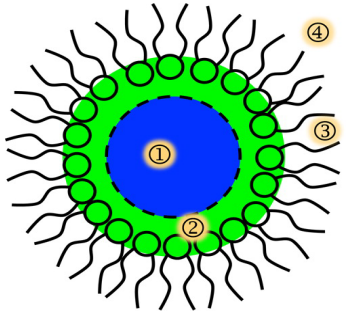




(a) Surfactant aerosol OT (AOT)
(b) Reverse micelle (RM), water pool, surrounded by AOT molecules (gray), organic solvent
(c) Solution of RMs

What is known about speciation in confined spaces? (1c)

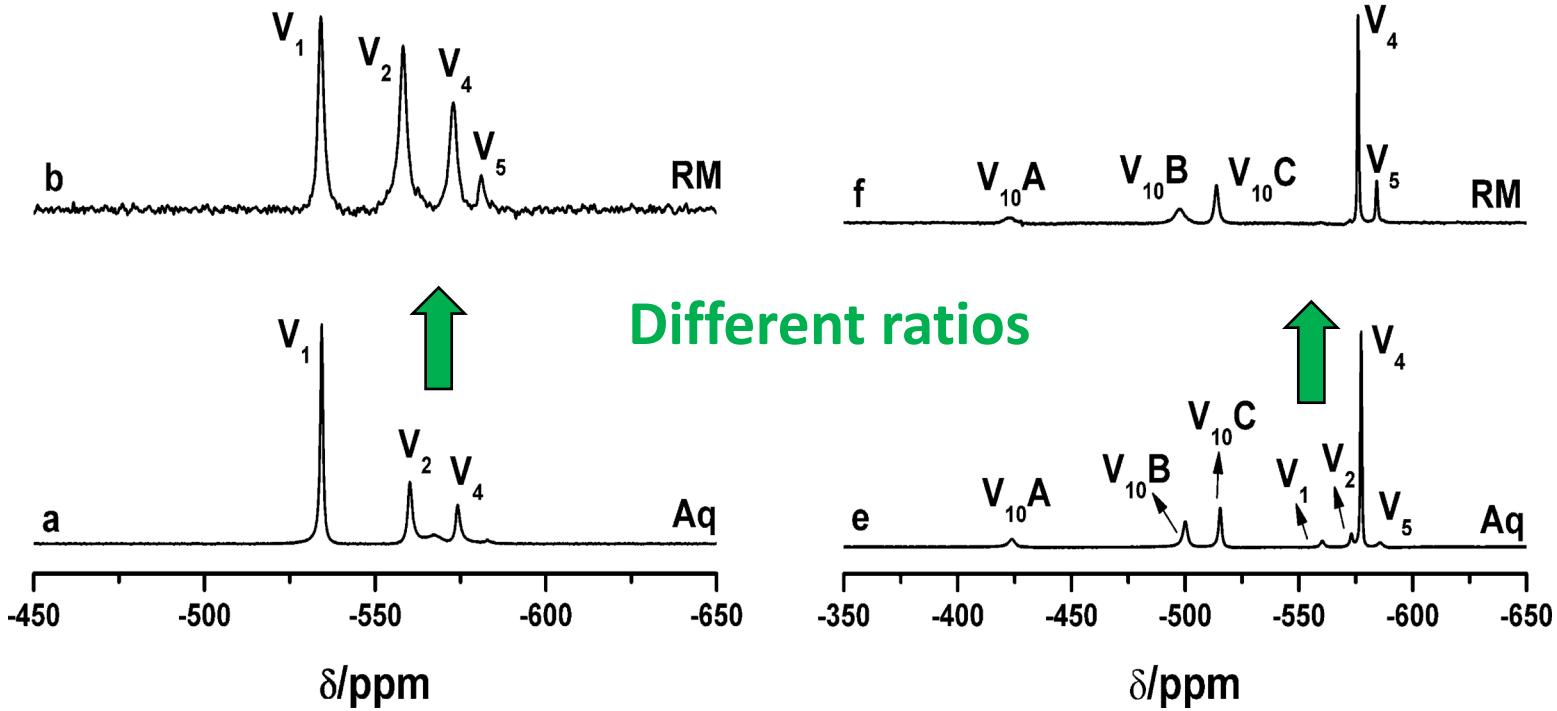
Aerosol OT
Reverse micelle
RM



- Aerosols prepared from Aerosol OT
- Speciation exists in confined space
- **Speciation changed from H_2O to confined space**

Data suggest speciation will change also in aerosols containing dissolved V_2O_5

Aqueous solutions were: pH 9.8 and pH 6.3

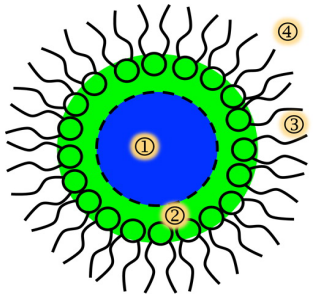


^{51}V NMR spectra of vanadate in aqueous and reverse micelle samples collected at 78.9 MHz of aqueous vanadate solution (50 mM) or in 50 mM vanadate in w_0 = 12 AOT/isooctane RM suspension.

Levinger et al. JACS, 2011, 133, 7205-7213

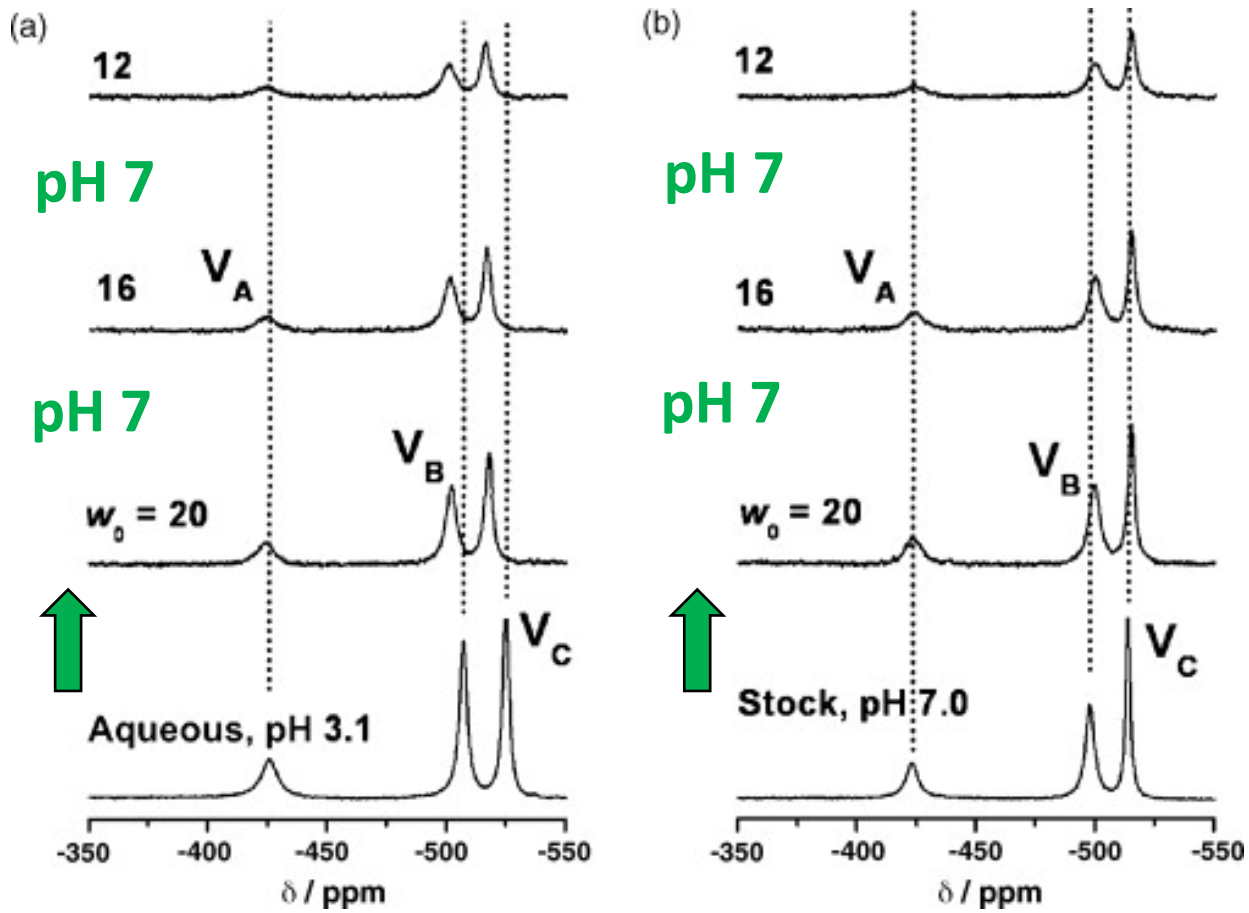
pH values change in confined spaces? (1c)

- Aerosols prepared form Aerosol OT



- pH change in aerosol as shown by speciation vanadate
- **pH changed from aqueous pH to waterpool in RM**

Interpretation: Data suggest pH (and thus speciation) will change in aerosols containing dissolved V_2O_5

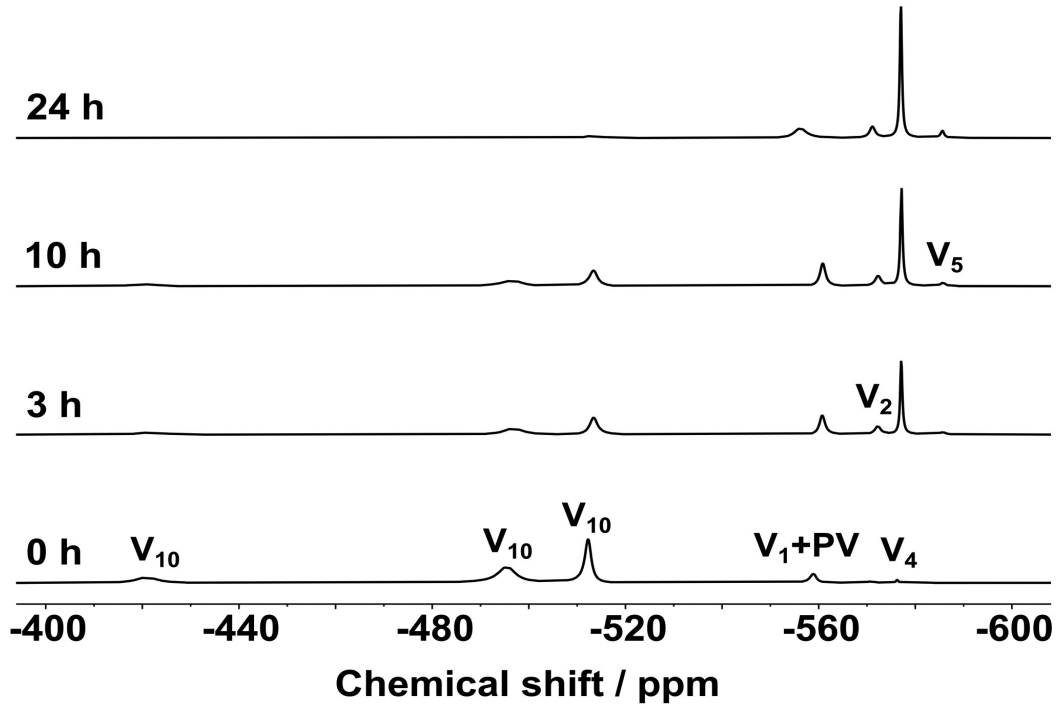


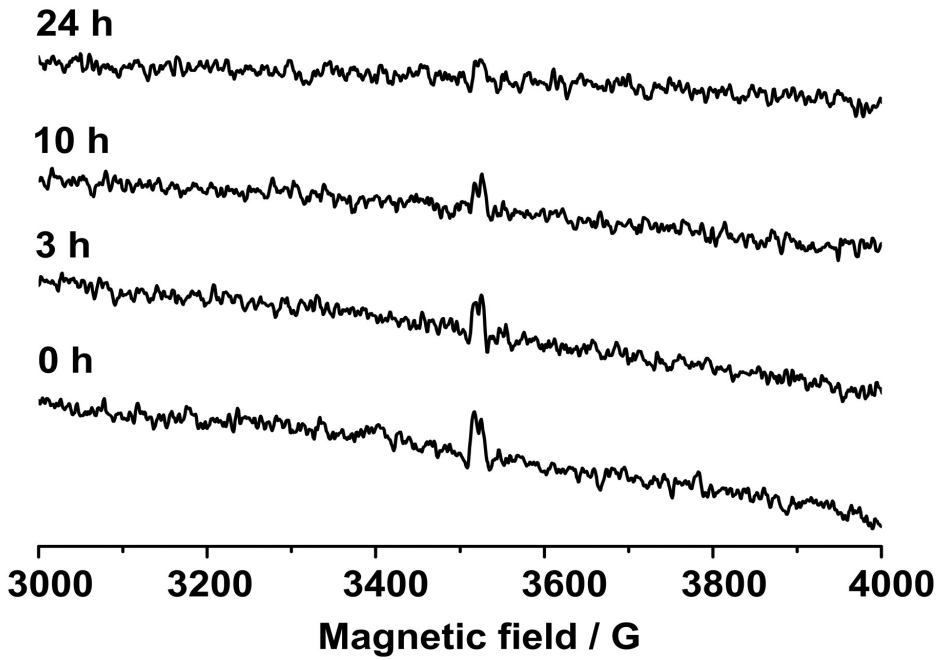
^{51}V NMR spectra of V_{10} in stock 10 mM (100 mM V atoms) solution at pH 3.1 (a) and 7.0 (b) and inside RM
Crans et al. *Coord. Chem. Rev.*, **2009,** *253*, 2178-2185
Baruah et al. JACS 2006, *128*, 12758-12765

What happens to Vanadium in biological systems such as cells?

Studies have been carried out by many groups exploring speciation of vanadium compounds in media and sometimes also in cells. These data show conversion of V(V) to V(IV) and the reverse. Three studies are selected to illustrate phenomenum. Here is shown what happens with V_{10} – using both ^{51}V NMR (for V(V) and EPR(for V(IV)

Result: V_{10} convert in species and also some redox chemistry
implication that V_2O_5 would also convert





Althumairy et al. *Metallomics*, 12, 2020, 1044–1061

What happens to Vanadium in biological systems such as cells?

0 hrs (15 min)

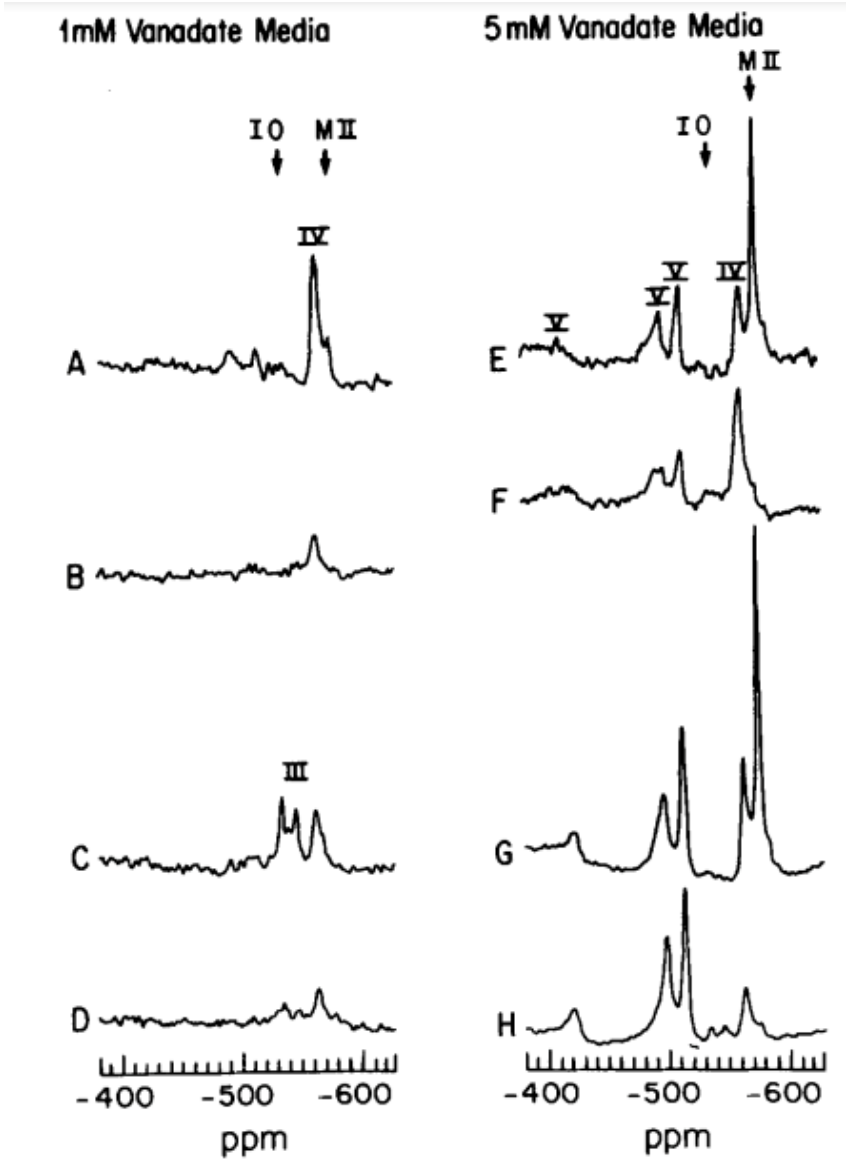
A and E – media of yeast cells

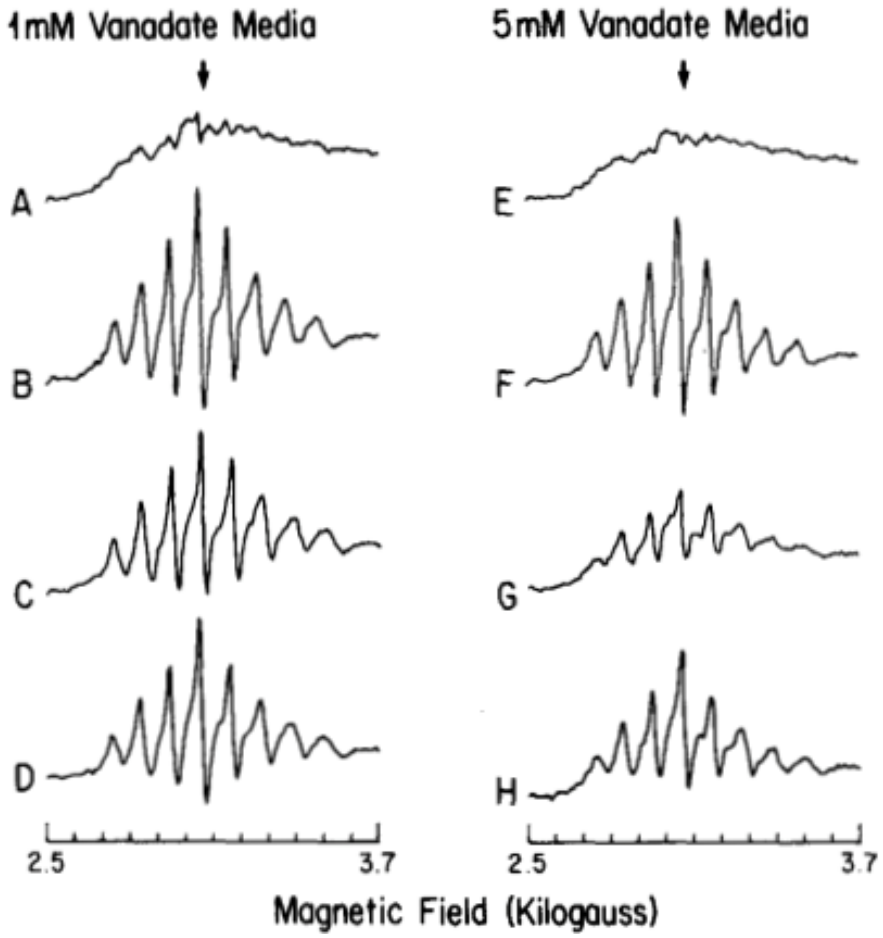
B and F – yeast cells

0 hrs (15 min)

C and G – media of yeast cells

D and H– yeast cells

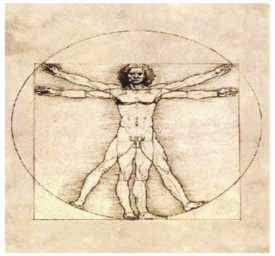




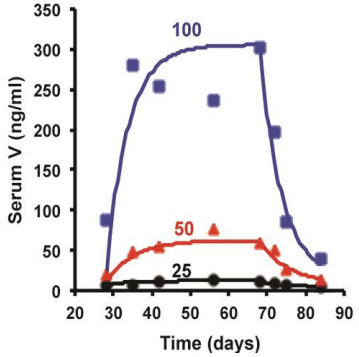
Willsky et al. J. Biol. Chem. 1984, 259, 13273-81

What happens to Vanadium in biological systems such the human body?

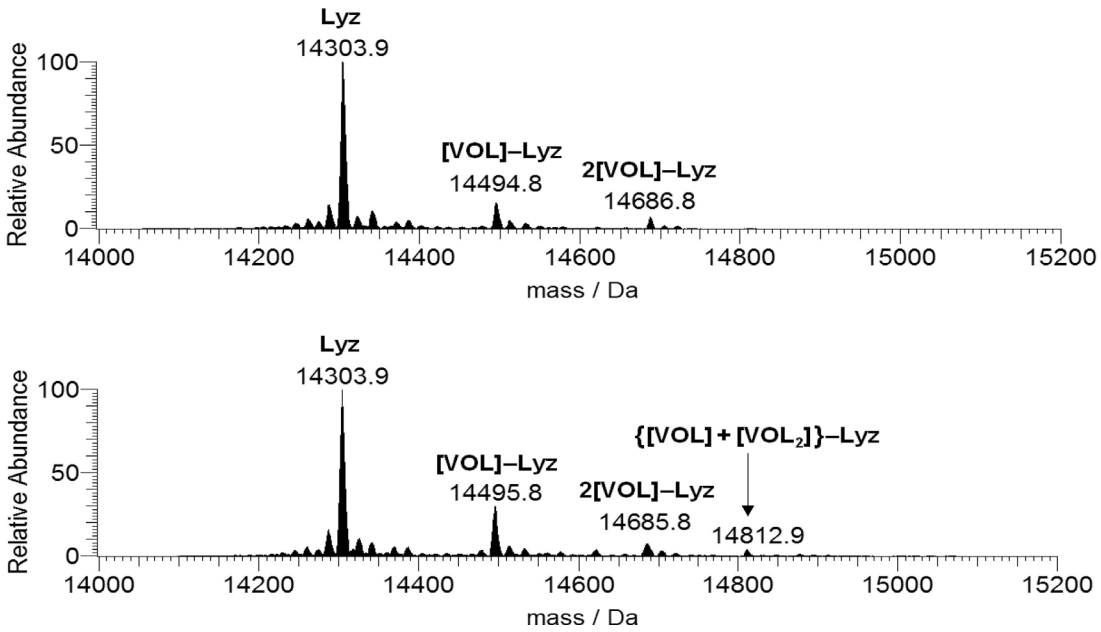
Vanadium in humans – total vanadium measured
Willsky et al. *Metallomics*, 2013, 5, 1491–1502,



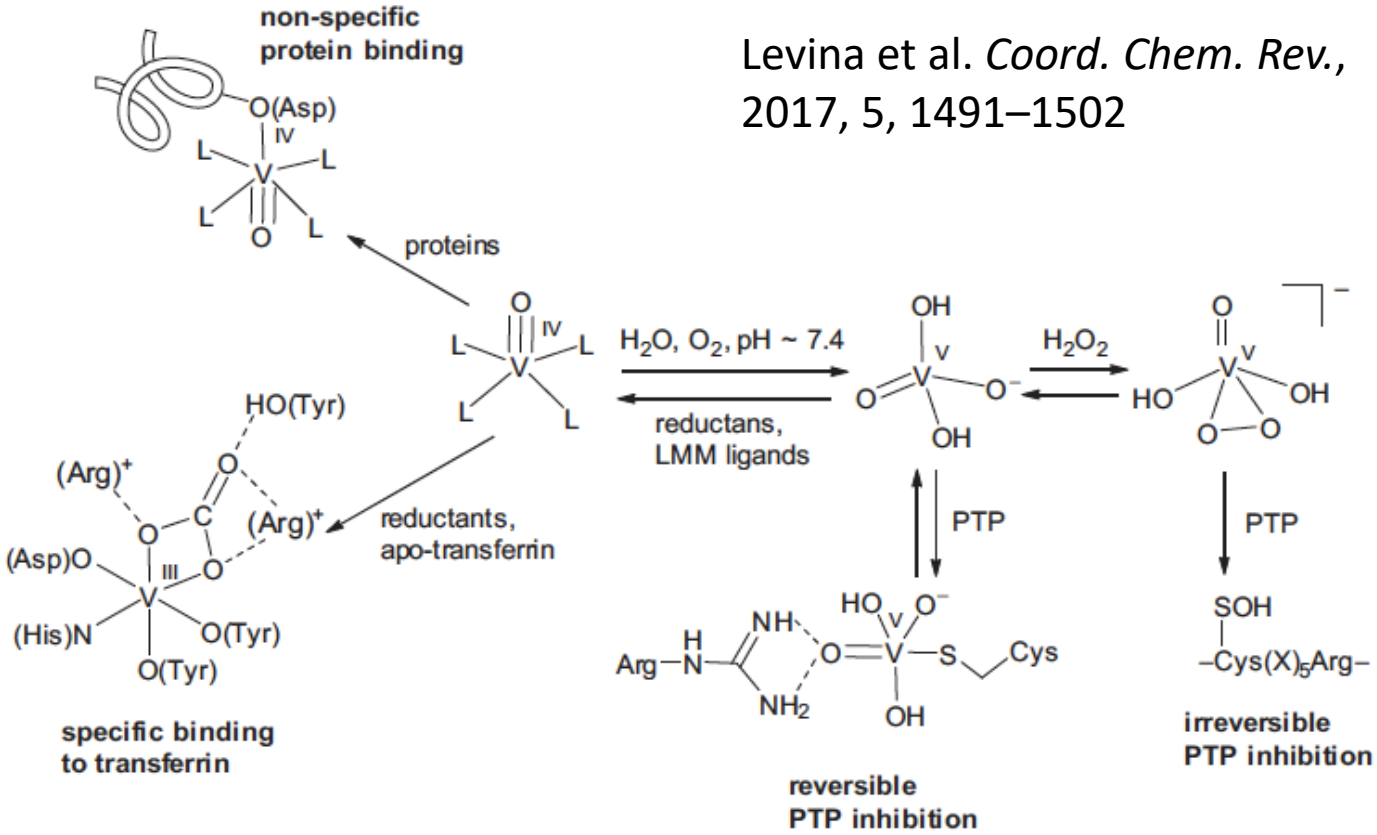
Human



Vanadium accumulation and washout



Confirmation: Conversions of V-species in biology



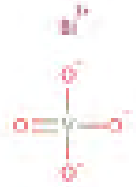
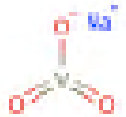
Levina et al. *Coord. Chem. Rev.*, 2017, 5, 1491–1502

Deconvoluted ESI-MS spectra: $[V^{IV}O(ma)_2]$ and lysozyme (50 µM): molar ratios 3:1 (top) & 5:1 (bottom)

Potential compounds under investigation

V_2O_5 - V(V) $NaVO_3$ - V(V) VO_2 - V(IV)

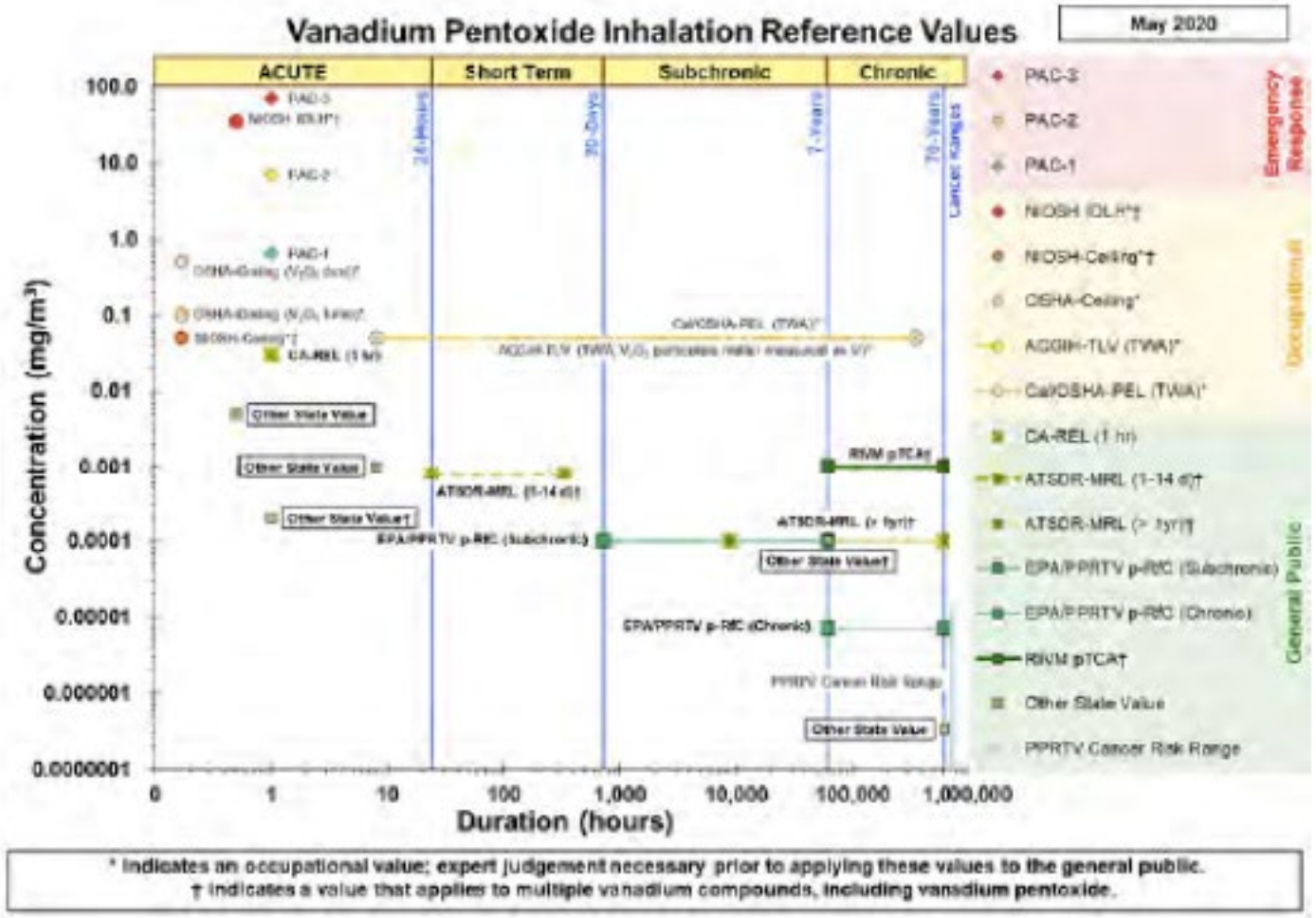
Table 1. Chemical identity and physiochemical properties of vanadium compounds potentially relevant to inhalation exposure

Name	Elemental vanadium	Bismuth orthovanadate	Sodium orthovanadate	Vanadium pentoxide	Sodium metavanadate	Ammonium metavanadate	Vanadium dioxide[a]
CASRN	7440-62-2	14059-33-7	13721-39-6	1314-62-1	3718-26-8	7803-55-6	12036-21-4
DTXSID[b]	2040282	20893971	2037269	2023606	044336	1052533	5065194
Structure	V						
Oxidation state	0	+5	+5	+5	5	+5	+4
Molecular weight (g/mol)	50.942	323.918	183.907	181.878	21.928	116.978	82.94
Molecular formula	V	BiO4V	NaVO3	V2O5	aVO3	NH4VO3	VO2
	V(V)	V(V)	V(V)	V(V)	V(V)	V(V)	V(IV)

Compounds identified in U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020

Information on Vanadium Pentoxide V_2O_5

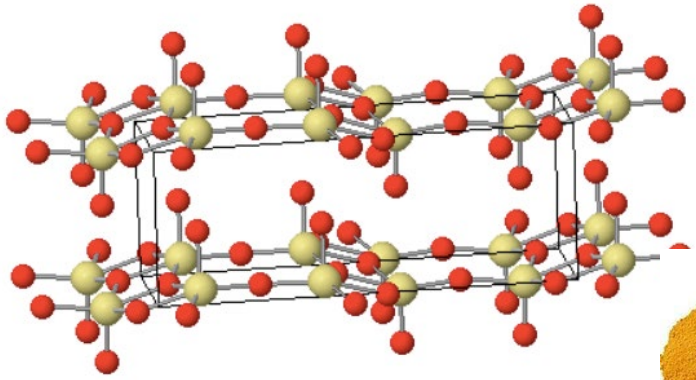
Figure 2. Available health effect reference values for inhalation exposure to vanadium pentoxide.



V_2O_5 listed in IRIS document

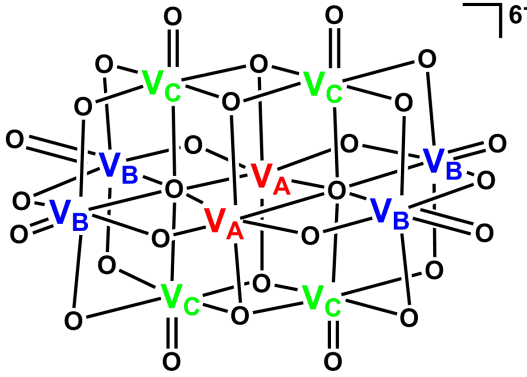
V_2O_5 information summarized in U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020

Summery: How does this impact the inhalation experiments?

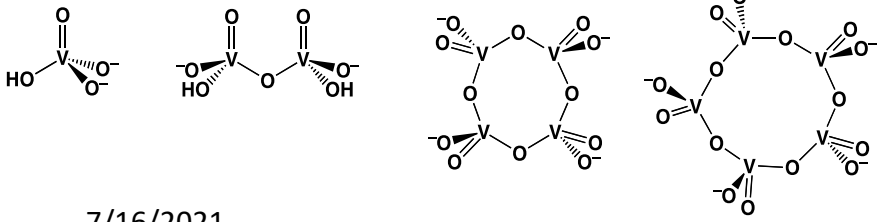


V_2O_5 - Solid state

Nick Greeves, Creative Comments Lincence



Vanadium(V) in solution



- 1a **Vanadium speciation and oxidation state varies. Increased toxicity of vanadium in the +5 oxidation state compared to vanadium +4** (Roberts et al., 2016).
- 1b **Vanadium in solution can convert between oxidation states and will form different species as a function of factors including pH, concentration, and redox potential. Aerosols for the inhalation studies affect vanadium oxidation state and speciation; methods that involved aerosolizing vanadium pentoxide** (González-Villalva et al. (2011), **rather than exposure to vanadium as a dust** (e.g., NTP(2002)].
- 1c **Conversion between vanadium oxidation state *(should include "species")* in the body**
- **Compounds and species identified in** U.S. EPA. ORD Staff Handbook