

Vanadium substances – read-across approach

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Hannover



Registered vanadium substances

Substance	Oxidation state	Molecular formula	CAS #	Registration	Identified hazard
vanadium	metallic	V	7440-62-2	2010	
slags, steelmaking, vanadium	mostly metallic	UVCB	69012-34-6	2010	
vanadium carbide nitride	metalloid	VCN	12069-91-9	2013	
vanadium carbide	metalloid	VC	12070-10-9	2013	
divanadium trioxide	III+	V ₂ O ₃	1314-34-7	2013	(X)
divanadium trisulphate	III+	V ₂ (SO ₄) ₃	13701-70-7	2014	X
vanadium dioxide	IV+	VO ₂	12036-21-4	2013	
vanadium oxide sulfate	IV+	VO(SO ₄)	27774-13-6	2014	X
vanadium, oxalate complexes	IV+	VO(C ₂ O ₄)	98903-75-4	2014	X
divanadium pentaoxide	V+	V ₂ O ₅	1314-62-1	2010	X
ammonium trivanadium octaoxide	V+	NH ₄ V ₃ O ₈	12207-63-5	2013	X
ammonium sodium vanadium oxide	V+	NaNH ₄ V ₆ O ₁₆	39455-80-6	2013	X
ammonium trioxovanadate	V+	NH ₄ VO ₃	7803-55-6	2013	X
potassium vanadium trioxide	V+	KVO ₃	13769-43-2	2013	X
sodium metavanadate	V+	NaVO ₃	13718-26-8	2013	X
aluminum vanadate	V+	AlVO ₄	13530-56-8	2018	X
erbium tetraoxide vanadium	V+	ErVO ₄	13596-17-3	2018	
iron vanadium tetraoxide	V+	FeVO ₄	13977-56-5	2018	X

Vanadium substances & grouping

Vanadium substances:

- vanadium metal & interstitial carbides
- tri-, tetra-, pentavalent vanadium salts & oxides

Solubility of vanadium substances:

- sparingly soluble metal & carbides
- sparingly soluble tri-, tetra-, pentavalent V substances
- soluble tri-, tetra-, pentavalent V substances

Approach for grouping of V substances

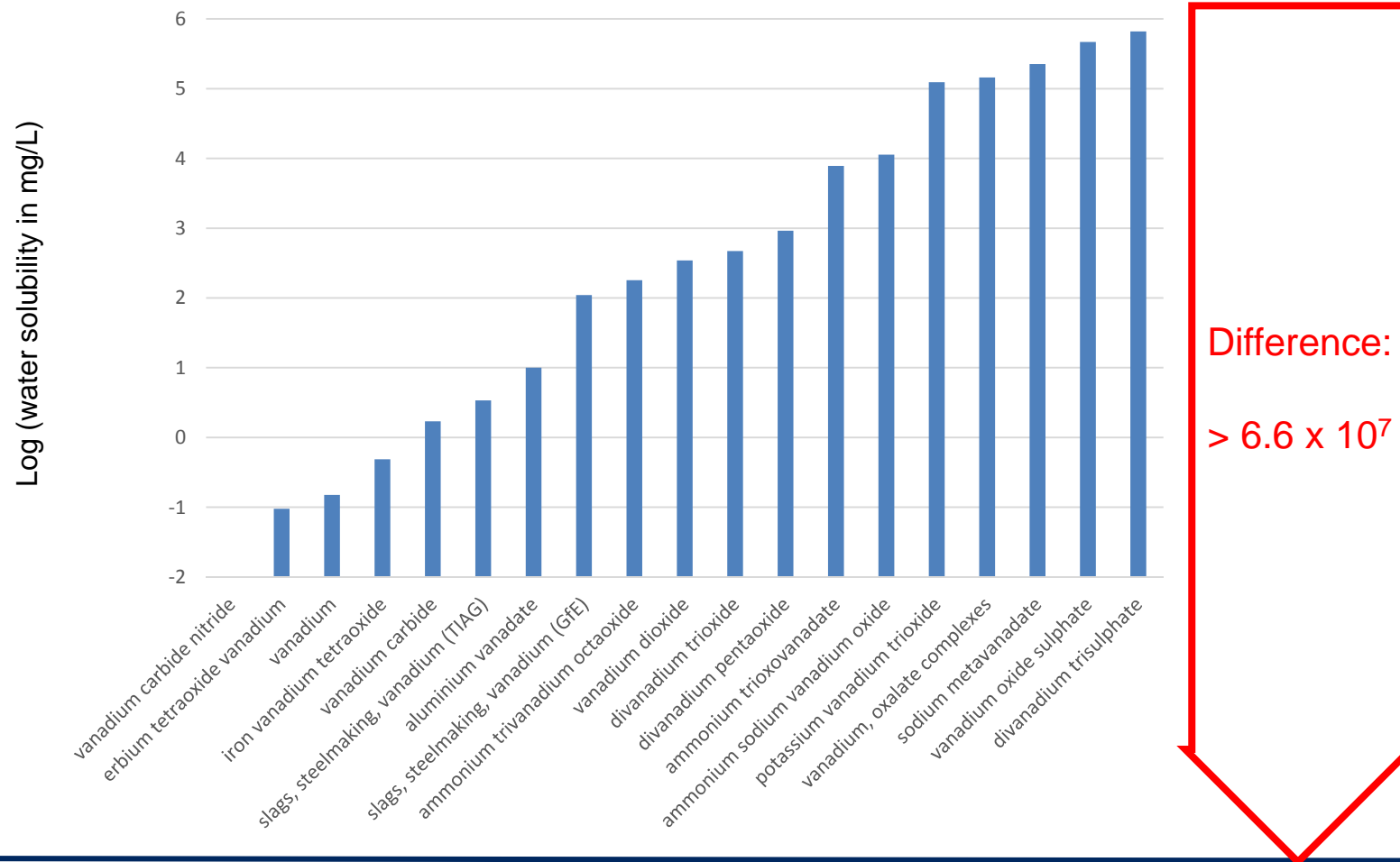
Establishing relative bioavailability:

screening level: water solubility
(all V substances)

advanced level: in-vitro bioaccessibility
(selected candidates)

ultimately: in-vivo toxicokinetics
(only when and if required)

Vanadium substances - water solubility

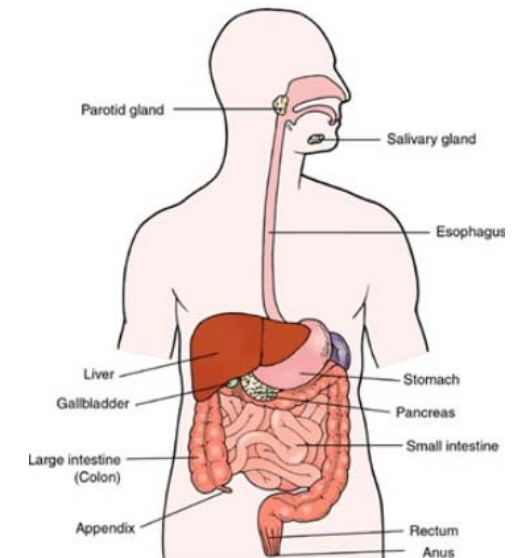
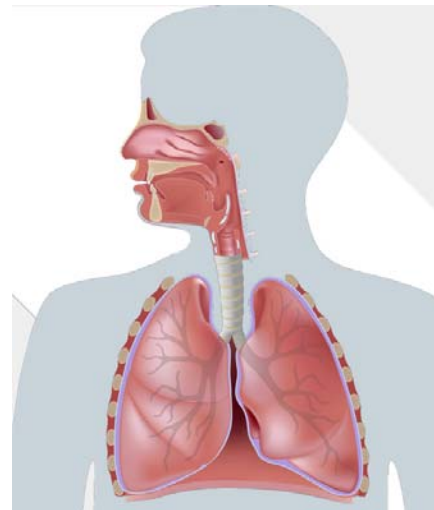
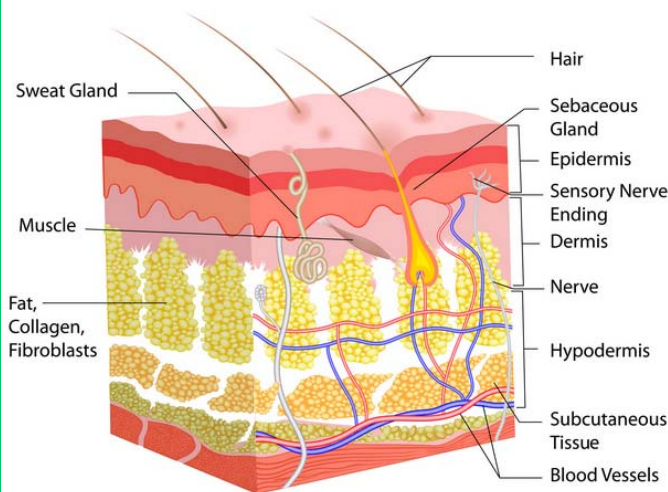


Read-across “nightmare”

- V substances vary between $0.1 < \text{water sol.} < 1,000,000 \text{ mg/L}$
- Different valency states: (III), (IV), (V), (elemental)
- **In theory, 7 different read-across groups feasible**
- Read-across concept is based on:
 - (i) combination of water solubility, in-vitro bioaccessibility, in vivo toxicokinetics
 - (ii) physico-chemistry (oxidising properties / reactivity/acidity)

Bioaccessibility

- Aim: assess the release of metals in a set of artificial physiological media
- Test media selected to simulate relevant human-chemical interactions
 - contact of a test substance with skin
 - a substance entering the human body by inhalation
 - a substance entering the human body by ingestion into the GI tract



Bioaccessibility testing

Solubility testing in surrogate physiological fluids:

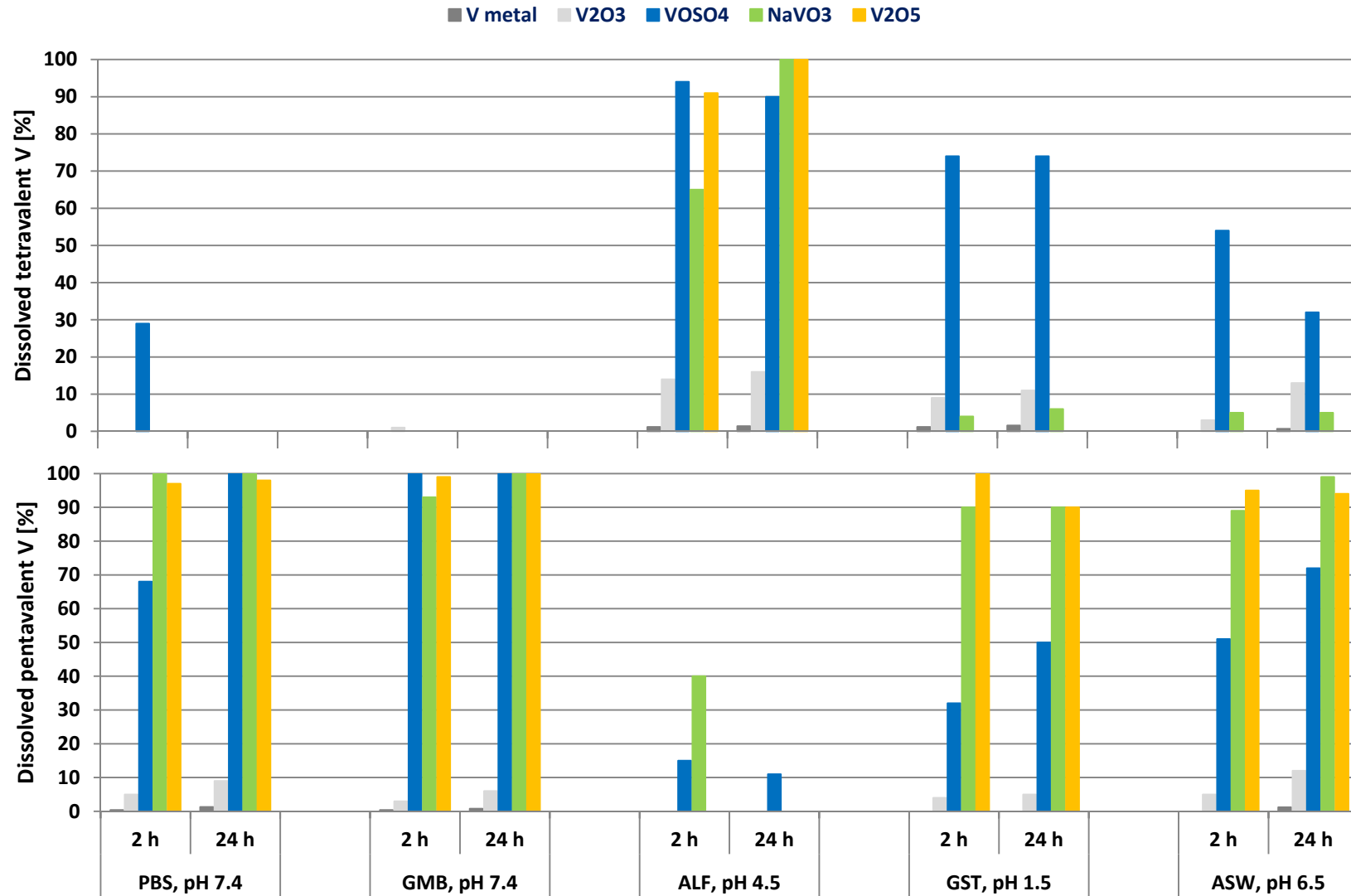
- phosphate-buffered saline (PBS, pH 7.4)
- artificial gastric fluid (GST, pH 1.5)
- artificial lysosomal fluid (ALF, pH 4.5)
- Gamble's solution (GMB, pH 7.4)
- artificial sweat solution (ASW, pH 6.5)
- loading of 100 mg/L (in adaptation of OECD 29)
- measurement of dissolved vanadium & vanadium speciation after 2 h & 24 h



Selected vanadium substances (after screening via water solubility):

- elemental: V metal
- Trivalent: V_2O_3
- Tetravalent: VO_2
- Pentavalent: $NaVO_3$, V_2O_5

Dissolution of V substances in body fluids: dissolved vanadium after 2h & 24 h



Bioaccessibility of vanadium substances

Read-across conclusions

Solubility:

- V metal: 0.5 - 1.6% dissolution in all physiological media
- V_2O_3 : 7 - 20% dissolution in all physiological media
- $VOSO_4$: ~ 100% dissolution in all physiological media
- $NaVO_3$ & V_2O_5 : ~ 100% dissolution in all physiological media

Speciation:

- V substances transform to pentavalent species in all media except in ALF
- In ALF, even pentavalent forms are converted to tetravalent species.

Conclusions - Toxicokinetics

Data for read-across - bioavailability:

- Soluble V (+IV and +V) substances – unlimited read-across
- Poor water solubility indicative of low bioaccessibility (incl. V metal, VC, VCN)

Inhalation absorption:

- PSD and dustiness correction
- Fractional deposition in the resp. tract modelled with MPPD & coupled with oral absorption factors

Dermal absorption:

HERAG approach - Default dermal absorption factor of 1% for screening purposes

Oral absorption:

- Data available for V(IV) and V(V), indicating approx. 3-16% oral absorption
- Most reliable data indicate 16% oral absorption for tetra- & pentavalent V substances
- No data for V(III), extrapolation from the above because of poor solubility in PBS & GMB

V-Substance grouping

- V substances differ substantially in their solubility & bioaccessibility
- V speciation in body fluids depends primarily on medium - not on vanadium source
- V substances expected to differ in acute tox, and particularly for local effects – in consequence, largely addressed with substance-specific experimental data
- systemic toxicity: (IV) and (V) forms occur simultaneously under physiological conditions – apply unlimited read-across based on soluble V substances

Vanadium – read-across

- **Initial grouping:** **7 groups**
 - sparingly soluble metal and carbides
 - soluble & sparingly soluble tri-, tetra-, pentavalent V substances
- **Intermediate grouping after *in vitro* bioaccessibility/speciation: 2 groups**
 - sparingly soluble metal and carbides
 - soluble tri-, tetra- & pentavalent V substances
- **Toxicokinetic data**
 - V(IV) + (V) occur simultaneously under physiol. condition
- **Read-across between V substances for selected HH endpoints**
 - systemic toxicity, genotoxicity & skin sensitisation
- **Read-across for local effects treated separately**

Local effects - read-across matrix for respiratory irritation

	potential to become bioavailable	Potential for acidic injury	potential for inhalability	potential for oxidative injury	potential for irritation of mucous membranes	potential for respiratory irritation
V metal	no	no	yes	no	no	no
VC	no	no	yes	no	no	no
VCN	no	no	yes	no	no	no
V ₂ O ₃	yes	no	yes	no	no*	no
V ₂ (SO ₄) ₃	yes	yes	**	no	yes	yes
VO ₂	yes	no	yes	no	no	no
VO(SO ₄)	yes	yes	**	no	yes	yes
VO(C ₂ O ₄)	yes	yes	**	no	yes	yes
KVO ₃	yes	no	yes	yes	yes	yes
NaNH ₄ V ₆ O ₁₆	yes	no	yes	yes	yes*	yes
NaVO ₃	yes	no	yes	yes	yes	yes
NH ₄ VO ₃	yes	no	yes	yes	yes	yes
NH ₄ V ₃ O ₈	yes	no	yes	yes	yes	yes
V ₂ O ₅	yes	yes	yes	yes	yes	yes

* According to Directive 67/548/EEC, the substance does not require classification for eye irritation whereas according to Regulation (EC) No 1272/2008, the substance classifies as irritating to eyes (Category 2).

** V₂(SO₄)₃, VO(SO₄), and VO(C₂O₄) are manufactured and sold in solution only and as such are not inhaled. However, for pre-cautionary considerations, inhalability was nevertheless assumed.

Local effects - V-Substance grouping

1. Sparingly soluble / insoluble substances
2. Soluble substances with irritation potential
3. Soluble substances without irritation potential

Genotoxicity

Toxicological Data (conducted tests)	V ₂ O ₃	VO ₂	V ₂ O ₅
bacterial reverse mutation assay (OECD 471)	no data, read-across	Negative	Negative
<i>in vitro</i> micronucleus assay (OECD 487)	Positive	Positive	Positive
<i>in vitro</i> mammalian cell gene mutation assay (OECD 476)	Negative	Negative	Negative
<i>in vivo</i> micronucleus test (OECD 474)	read-across	read-across	Negative

- All V substances: no gene mutations
- All V substances: clastogenic effects *in vitro* at high concentrations (common for metals)
- No clastogenic effects of V₂O₅ *in vivo* in bone marrow of rats (exposure confirmed)
- currently no evidence for a germ cell specific mutagen (substances inducing genetic defects in germ cells would also induce them in bone marrow - Shelby et al., 1996, ECHA guidance)
- All V substances: classification is not supported (argumentation based on HERAG)

Vanadium & V oxides: toxicological profile

	V metal	V ₂ O ₃	VO ₂	V ₂ O ₅
Acute toxicity				
Oral (LD50 in mg/kg)	No C&L > 2000 (f)	No C&L 5639 (f)	No C&L RA to V ₂ O ₃ based on similar bioavailability	Cat 4 467 (f)
Inhalation (LC50 in mg/L)	not feasible	No C&L > 6.65	No C&L > 5.05	Cat 4 4.29 (f)
Skin irritation	negative	negative	negative	negative
Eye irritation	negative	Cat 2	negative	Cat 1
Respiratory irritation	No C&L	No C&L	No C&L	STOT SE 3
Skin sensitisation	negative (RA to soluble III, IV & V-valent substances)	negative	negative (RA to soluble IV & V-valent substances)	negative (RA to soluble IV & V-valent substances)
Genotoxicity	No C&L	No C&L	No C&L	Harmonised: Cat 2 Alternative: No C&L
In vitro gene mutation	negative (RA)	negative	Negative (RA)	negative
In vitro clastogenicity		positive		positive
In vivo clastogenicity	negative (RA)	negative (RA)	negative (RA)	negative

Vanadium & V substances: toxicological profile

	V metal	V ₂ O ₃	VO ₂	V ₂ O ₅
Repeated dose inhalation	Not feasible; no RA	no RA based on lack of respiratory irritation potential	no RA based on lack of respiratory irritation potential	STOT RE 1 (local effects)
oral	no RA based on lack of bioavailability	RA (conservative)	RA (conservative)	LOEL = 3 mg V/kg bw/d - red blood cell parameters
Reprotoxicity	no RA based on lack of bioavailability	RA (conservative)	RA (conservative)	Harmonised Repr 2; H361d Maternal toxicity & developmental effects: - NOAEL = 4.2 mg V/kg bw/d
Carcinogenicity	no RA based on lack of inhalability & respiratory irritation potential	no RA based on lack of respiratory irritation potential	no RA based on lack of respiratory irritation potential	C&L pending (CLH proposal) - Local effects - No evidence of systemic effects

Thank you. Any questions?

