IRIS Assessment Plan for Oral Exposure to Vanadium and Compounds

Comments on Key Science Issue 1

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Background

Served as a senior toxicologist in the US FDA Center for Devices and Radiological Health for 25 years.
Responsible for the development of Tolerable Intake (TI) for compounds released from medical devices and for the development of risk assessment guidelines

I currently direct a small firm that provides training and consultation in the toxicological risk assessment.

Revising the chapter on vanadium in Patty's *Industrial Hygiene and Toxicology*

Risk Science Consortium, LLC

Disclaimers

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

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

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.

Points to consider for the IRIS IAP

- Should EPA consider the potential toxicity and toxicokinetic differences across vanadium compounds?
- Can pharmacokinetic data be used to estimate equipotent doses of +5 vanadium from toxicity studies of +4 vanadium?
- Should a PBPK model be used for interspecies extrapolation of dose to derive a HED of vanadium from a PoD in an animal study?
- What critical toxicity endpoints should be considered, regardless of the oxidation state of vanadium?

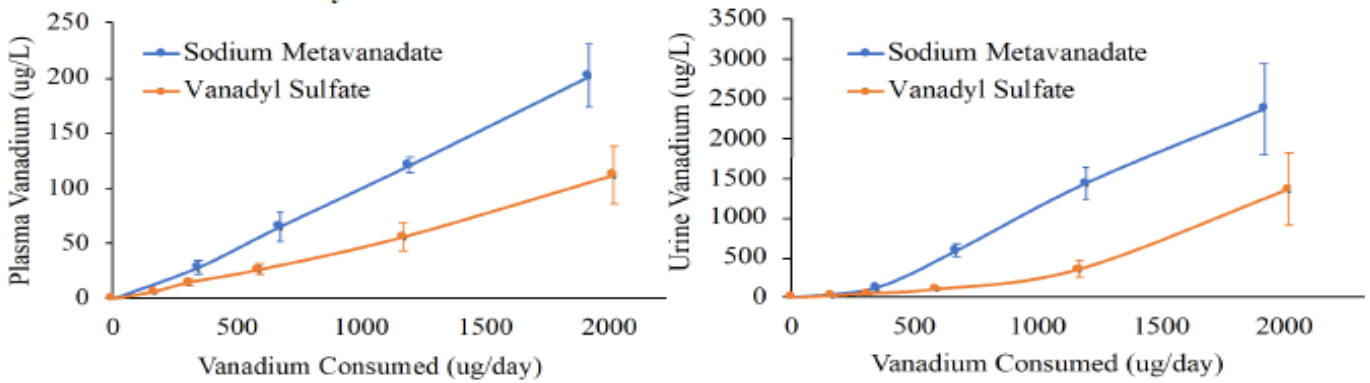
Can PK data from NTP studies be used to convert doses of +4 vanadium to equivalent doses of +5?

Compound	Drinking water concentration at NOAEL (mg/L)	Administered dose at NOAEL (mg/kg/day)
Vanadyl sulfate (+4)	≥ 335	≥ 5-8
Sodium metavanadate (+5)	62.5	25-31

+5 vanadium is at least 5-fold more potent than +4 vanadium

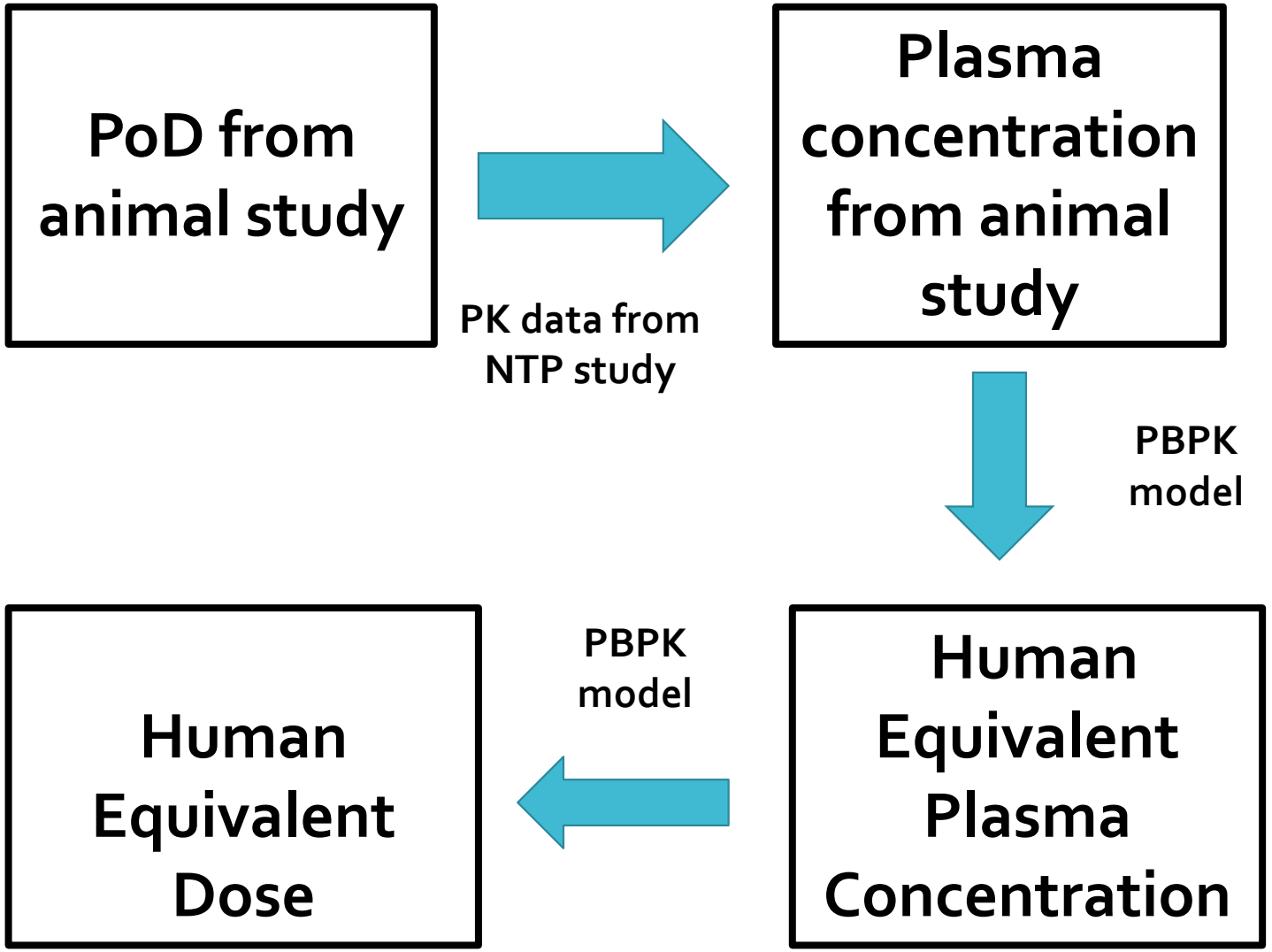
Analysis for Total Vanadium in Plasma and Urine

Figure 5. Total Vanadium Concentration in Plasma and Urine in Male Rats Exposed to Sodium Metavanadate or Vanadyl Sulfate



The IAP should encourage the development of methods to convert oral doses of +4 vanadium to equipotent doses of +5 vanadium so the doses can be interconverted.

Consider using PBPK model for interspecies extrapolation of dose



Agency	HBEL	Compound/ oxidation state	Value (mg/kg/day)	PoD	Duration/ Species	Critical Effect	Study
ATSDR		Sodium metavanadate (+5)		0.12 LOAEL	6 months, Rat	Increased BP	Boscolo et al., 1994
		Ammonium metavanadate (+5)		1.18 LOAEL	Rat	Decreased RBC and Hct	Zaporowski et al., 1993
	MRL	Vanadyl sulfate trihydrate (+4)	0.001	0.12 NOAEL	Human	None	Fawcett et al., 1997
ICH	PDE	Vanadyl sulfate trihydrate (+4)	0.002	0.12 NOAEL	Human	None	Fawcett et al., 1997
EPA	PPRTV	Sodium metavanadate (+5)	0.0007 (subchronic)	0.12 LOAEL	Rat	Kidney damage	Boscolo et al., 1994
EPA	PPRTV	Sodium metavanadate (+5)	0.00007 (chronic)	0.12 LOAEL	Rat	Kidney damage	Boscolo et al., 1994
RIVM	pTDI	Sodium metavanadate (+5)	0.002	2 LOAEL	14d M, 6od F, Rat	Developmental effects	Domingo et al., 1986

Consideration of critical effects at the PoD

- The IAP should recommend that consideration be given to the full range of adverse effects seen in toxicity studies of +4 and +5 vanadium, including safety pharmacology endpoints that were not assessed in the NTP studies. This consideration is especially important if adverse physiological and hemodynamic changes can occur at doses lower than those that produce histopathological effects.

- If the mechanism for vanadium-induced hemodynamic changes (or other effects) in animals is well understood, and if they are relevant for humans, then the IAP may recommend the development of an Adverse Outcome Pathway (AOP) to describe this critical effect.

Summary

Points to consider for the IRIS IAP

The IAP should recommend that:

- **EPA should consider the potential toxicity and toxicokinetic differences across vanadium compounds.**
- **An approach should be developed to use pharmacokinetic data to estimate equipotent doses of +5 vanadium from toxicity studies of +4 vanadium.**
- **The use of a PBPK model for interspecies extrapolation of dose should be explored as a means to derive a HED of vanadium from a PoD in an animal study.**
- **All relevant critical toxicity endpoints should be considered, regardless of the oxidation state of vanadium.**

Separate toxicity evaluations should not result in separate RfDs

- Key Science Issue #1 states, "…*EPA plans to conduct separate toxicity evaluations for different vanadium compounds where the evidence supports such an analysis.*

- The complex speciation of vanadium in exposure media (drinking water, food) results in potential exposure of individuals to vanadium in multiple oxidation states; however, it is not practical to use separate RfD values for different oxidation states of vanadium in a risk assessment. A practical approach should be considered in the IAP that would result in the development of one RfD that is appropriately protective for all oxidation states of vanadium.