



NTP
National Toxicology Program

Vanadium: Tetravalent and Pentavalent Forms

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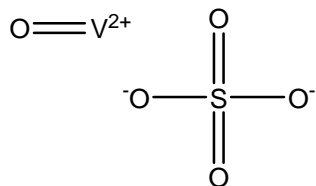


Nomination of Vanadium Compounds

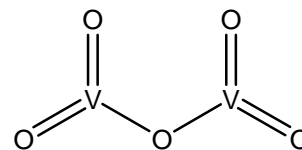
- Nominated by NIEHS and U.S. EPA for:
 - Toxicological characterization
 - Chronic toxicity and carcinogenicity studies by the oral route
 - Multigeneration reproductive toxicity studies
- Nomination based on:
 - Potential for exposure of large populations of humans
 - Use as a dietary supplement (tetravalent)
 - Occurrence as a contaminant in drinking water (pentavalent)
 - Listed on EPA's Contaminant Candidate List
 - Lack of sufficient data to assess human health risks from oral exposures
 - NTP 2-year inhalation studies of vanadium pentoxide
 - Similarity to chromium compounds



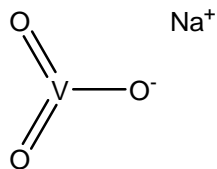
Common Forms of Tetravalent and Pentavalent Vanadium



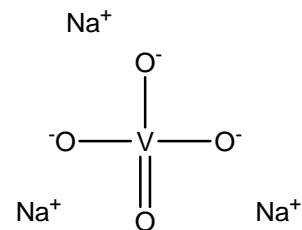
Vanadyl Sulfate



Vanadium Pentoxide



Sodium Metavanadate



Sodium Orthovanadate



Human Exposure to Vanadium Compounds

- Occupational exposure to ferrovandium or vanadium carbide through the inhalation route
- Food is the major source of exposure for the general population
 - Most foods contain low concentrations of vanadium
 - Highest concentrations found in black pepper (987 $\mu\text{g}/\text{kg}$), dill seed (431 $\mu\text{g}/\text{kg}$), mushrooms, parsley, shellfish, spinach, and some prepared foods (11-93 $\mu\text{g}/\text{kg}$)
 - Estimated daily dietary intake for the US population is 10-60 $\mu\text{g}/\text{day}$
- Additional exposure through contamination in drinking water sources
 - Primarily pentavalent form
 - Concentrations up to 100 $\mu\text{g}/\text{L}$ in tap water, mean of ~ 5 $\mu\text{g}/\text{L}$



Putative Therapeutic Uses of Vanadium Compounds

- Vanadium does not have a defined biochemical function in humans
 - Interferes with phosphate-containing enzymes
 - Potent inhibitor of the Na⁺/K⁺ ATPase pump
- Common dietary supplement
 - Vanadyl sulfate (tetravalent) used at doses up to 60 mg/day (18.6 mg vanadium/day) to enhance performance in weight training
- Antidiabetic effects
 - Increase glucose transport and improve glucose metabolism
- Reduction of hyperlipidemia and hypertension
- Treatment for osteoporosis
- Antitumor activity





Background Information on Vanadium

- Exists in a number of oxidation states ranging from -1 to +5
 - Tetravalent/pentavalent are the most stable oxidation states
 - Standard reduction potentials favor reduction of pentavalent to tetravalent
 - Oxidation of tetravalent to pentavalent *in vivo*?
- Pentavalent form able to polymerize/depolymerize depending on conditions
- Interconversion of pentavalent vanadium compounds?



Absorption, Distribution, Metabolism, and Excretion Information on Vanadium

- Poorly absorbed by the GI tract (<5%)
 - Vanadium in the vanadate (pentavalent) state is absorbed 3 times more effectively than in the vanadyl (tetravalent) state
 - Pentavalent compounds enter cells via anion transport systems
 - Reduced by glutathione, ascorbic acid, and other reducing agents
 - Tetravalent form predominates intracellularly- binds to proteins
- Distributed to multiple tissues- liver, kidney, spleen, bone
- Stomach converts most forms of vanadium into the tetravalent form
- Absorbed vanadium excreted relatively rapidly
- Unabsorbed vanadium excreted primarily in the feces



Genotoxicity of Vanadium Compounds

- Generally do not induce gene mutations in bacterial or mammalian cells
- Pentavalent and tetravalent forms produce aneuploidy, polyploidy, endoreduplication etc. *in vitro and in vivo*
- Produce DNA damage *in vitro and in vivo* probably due to ROS
- Evidence for clastogenic effects (structural chromosomal aberrations) is mixed



Proposed Research Program

- Overall goal is to investigate the potential for water soluble vanadium compounds to cause systemic toxicity and carcinogenicity
- Hypothesis is that a pentavalent vanadium compound will be more toxic than a tetravalent compound when administered orally
- A key issue is the selection and chemical characterization of appropriate vanadium compounds for study
 - Propose to use the most water soluble vanadium salt(s)
 - Vanadyl sulfate (tetravalent)
 - Sodium/ammonium metavanadate or orthovanadate (pentavalent)



Specific Aim 1

- Prior to animal studies, conduct *in vitro* tests to evaluate the speciation and stability of vanadium compounds
 - Determine if there is oxidation of vanadyl to vanadate in dosing solutions exposed to air
 - Identify and characterize the vanadium species that may be formed *in vivo* under various physiological conditions
 - A variety of methods will be considered
 - Various reducing/oxidizing agents
 - Under different pH conditions





Specific Aim 2

- Conduct *in vivo* toxicity studies based on the results of the *in vitro* tests
 - Subchronic studies in Wistar Han rats (perinatal) and B6C3F1 mice
 - Compare toxicities of a tetravalent and a pentavalent compound
 - Chronic studies
 - Select one or more compounds
 - Vanadium tissue concentrations (speciated)
 - *In vivo* genotoxicity
- Evidence in the literature suggests additional endpoints should be considered including TK, clinical pathology, enzyme inhibition, cardiotoxicity, neurotoxicity, and immunotoxicity



Specific Aim 3

- Conduct developmental/reproductive toxicity studies
 - Limited studies on tetravalent and pentavalent compounds suggest developmental/reproductive toxicity
 - Decreased fertility and litter size
 - Decreased survival rate at weaning
 - Delayed growth
 - Most did not identify a No Observed Adverse Effect Level
 - Available data is insufficient to determine Tolerable Upper Intake Levels for sensitive subpopulations including pregnant and lactating women, children and infants



Significance and Expected Outcome

- Available data inadequate to evaluate the carcinogenic potential of vanadium compounds when ingested orally
- Available data inadequate to evaluate the reproductive/developmental toxicity of vanadium compounds when ingested orally
- Listed on US EPA CCL as a priority contaminant
 - Determine whether drinking water regulations are needed
 - Could be used as the basis to develop drinking water standards
- Data could be used to calculate estimates of Tolerable Upper Intake Levels for the intake of vanadium from food including for sensitive subpopulations