NTP Research Concept: Tetravalent and Pentavalent Forms of Vanadium

Project Leader

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Nomination Background and Rationale

Vanadium is an element that exists in a number of oxidation states ranging from -1 to +5. In general, the toxicity of vanadium compounds increases with the valence state. Tetravalent (vanadyl; +4) and pentavalent (vanadate; +5) forms of vanadium were nominated by the National Institute of Environmental Health Sciences and the U.S. Environmental Protection Agency for toxicological characterization, chronic toxicity and carcinogenicity studies via the oral route, and multigeneration reproductive toxicity studies based on widespread occurrence as a contaminant in drinking water (+5), use as a dietary supplement (+4), and the lack of sufficient data to assess human health risks resulting from oral exposures (http://ntp.niehs.nih.gov/go/32744). There is potential for exposure of large populations of humans to water-soluble vanadium compounds. Vanadium remains on the U.S. EPA Drinking Water Contaminant Candidate List (CCL) as a priority contaminant with insufficient information to support a regulatory determination. Based on NTP two-year rodent inhalation studies, the International Agency for Research on Cancer (IARC) concluded that vanadium pentoxide, a pentavalent vanadium compound, is a possible human carcinogen. The similarity of vanadium compounds to chromium compounds warrants further study. Hexavalent chromium (Cr VI) compounds are classified as human carcinogens following inhalation exposure. NTP recently reported that hexavalent chromium is also carcinogenic in rats and mice when administered in the drinking water whereas trivalent chromium was not carcinogenic when administered in the diet. No data are available on the carcinogenic potential of vanadium in humans by the oral route. The existing oral exposure studies in animals are inadequate for a thorough assessment of the carcinogenic potential of vanadium.

Human Exposure

The vast majority of vanadium is used as ferrovanadium or as vanadium carbide in the production of high-resistance carbon steels resulting in occupational exposure through the inhalation route. Food is the major source of exposure to vanadium for the general population although most foods contain low concentrations of vanadium. Daily dietary vanadium intake in the general population has been estimated at 10-60 µg per person per day. Vanadyl sulfate (+4) is a common dietary supplement used at doses up to 60 mg/day to enhance weight training in athletes. There is debate in the literature as to whether vanadium is an essential trace element. Although vanadium does not have a defined biochemical function in humans, it interferes with phosphate-containing enzymes and is a potent inhibitor of the Na+/K+ ATPase pump. A vanadium deficiency disease has not been identified in humans.

The best documented application of vanadium is use as an insulin mimetic. *In vitro* and *in vivo* animal and human studies indicate that vanadium compounds increase glucose transport and improve glucose metabolism. Because vanadium may be useful in future treatment of diabetes, there is increased concern about its long-term toxicity.

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Additional exposure of vanadium by the general population may occur as a result of contamination in drinking water sources. Vanadium dissolved in water is present almost exclusively in the pentavalent form. Its concentration ranges from approximately 0.1 to 220 µg/L in fresh water and up to 100 µg/L in tap water.

Key Issues

Animal studies suggest that the amount of vanadium absorbed by the gastrointestinal tract is <1-2%. Vanadium in the vanadate (+5) state is absorbed about three to five times more effectively by the GI tract than in the vanadyl (+4) state. Based on the poor absorption of vanadium from the GI tract, internal tissue concentrations and toxicity from oral exposure are expected to be low. However, there are few long-term studies in the literature assessing the potential oral toxicity of water soluble vanadium compounds. Based on its similarity to other metals, there is potential for significant tissue uptake and systemic toxicity following oral exposure to vanadium. Since children absorb some metals such as lead more readily than adults they may be more susceptible to vanadium toxicity.

One of the key issues is selection of the appropriate vanadium compounds for study. There are conflicting reports in the literature about the oxidation/reduction potential of vanadium compounds. It is generally accepted that pentavalent salts in the metavanadate form enter cells via anion transport systems where glutathione, ascorbic acid, and other reducing substances in plasma and cells reduce vanadate (+5) to vanadyl (+4). In addition, the standard reduction potentials of vandium favor reduction of vanadate to vanadyl and suggest that vanadyl is unlikely to be oxidized easily to vanadate. However, it has also been reported that vanadyl undergoes spontaneous oxidation to vanadate *in vivo*. This impacts whether to select one or more compounds for study, i.e. a pentavalent and a tetravalent form or only a pentavalent form, which is reported to be the most toxic form of vanadium. In addition, vanadate compounds are able to polymerize and depolymerize under appropriate conditions. It will be important to characterize and monitor the species of vanadium present in dosing formulations and tissues.

Proposed Approach

The overall goal of this research project is to investigate the potential for water-soluble vanadium compounds to cause systemic toxicity and carcinogenicity. Based on the similarity of vanadium to chromium, it is hypothesized that a pentavalent vanadium compound will be more toxic than a tetravalent compound when administered orally. It is proposed to use the most water soluble vanadium salt(s) for oral toxicity and carcinogenicity studies. Dietary supplements are commercially available in the form of vanadyl sulfate (+4). The U.S. EPA Office of Water recommended consideration of a metavanadate species (+5) (i.e. sodium metavanadate or ammonium metavanadate) for study.

Specific Aims

1. Prior to animal studies, we propose to conduct *in vitro* tests to evaluate the stability and speciation of vanadium in the dose formulations. Specifically, we will determine if there is oxidation of vanadyl to vanadate in dosing solutions exposed to air. In addition, we propose to conduct *in vitro* oxidation/reduction experiments using simulated biological fluids to evaluate the interconversion of vanadium species in the presence of various reducing/oxidizing agents and

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under different pH conditions. These studies will be useful in determining the species of vanadium present in dosing formulations and in various biological fluids and tissues.

2. Based on the results of the *in vitro* tests described above, we propose to conduct subchronic perinatal toxicity studies using a tetravalent and a pentavalent vanadium compound by an appropriate route to determine whether there is a difference in toxicity between these forms of vanadium. Toxicokinetic studies will be considered to determine absorption and elimination rates for the different species of vanadium. Based on the results of these studies, we will select one or both compounds for chronic perinatal toxicity and carcinogenesis studies. Based on information in the literature, various endpoints will be considered including clinical pathology, enzyme inhibition assays, cardiotoxicity, neurotoxicity, and immunotoxicity. As part of these studies, vanadium concentrations (total vanadium or speciated vanadium) will be measured in various tissues. If vanadium cannot be speciated in tissues, comparison of total vanadium concentrations in tissues following exposure to pentavalent or tetravalent forms should provide information on the tissue distribution of each species. The relative uptake of the two forms may also aid in predicting or explaining potential differences in toxicity. We also recommend evaluating the genotoxicity of vanadium in various tissues to provide potential mechanistic data.

3. In parallel to the toxicity studies, we propose to conduct reproductive/developmental toxicity studies using a tetravalent and/or a pentavalent vanadium compound. There are limited data in the literature on the potential reproductive and developmental effects of tetravalent vanadium compounds. Studies with pentavalent vanadium compounds indicate that they reduce fertility and fecundity. The available data is insufficient to determine Tolerable Upper Intake Levels (UL) for the intake of vanadium from food for sensitive subpopulations including pregnant and lactating women, children and infants. Studies will also be considered to determine internal dose and speciation of vanadium in pregnant dams and offspring.

Significance and Expected Outcome

Available data are inadequate to evaluate the carcinogenic potential of vanadium compounds when ingested orally as dietary supplements or as a contaminant in drinking water sources. Vanadium remains on the U.S. EPA Drinking Water CCL as a priority contaminant with insufficient information to support a regulatory determination. Studies of vanadium were identified as a research need by the U.S. EPA Office of Water to determine potential human health effects resulting from oral exposure to water soluble vanadium compounds. These data will be used to determine whether drinking water regulations are needed and ultimately could be used as the basis to develop state and federal drinking water standards. In addition, these data could be used to calculate estimates of Tolerable Upper Intake Levels (UL) for the intake of vanadium from food that is unlikely to pose a risk of adverse health effects.

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