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CONTENTS

Editorial

Prevention and control of silicosis: A national challenge
G. K. Kulkarni ....................................................................................................................................... 95

Review Article

Vanadium pentoxide inhalation
Ross G. Cooper .................................................................................................................................... 97

Original Articles

Occupational injury surveillance: A study in a metal smelting industry
Asim Saha, Sunil Kumar, D. M. Vasudevan .............................................................................................. 103

Do bullae and emphysema increase risk of pneumothorax in silicosis?
Iraj Mohebbi, Ebrahim Hassani, Shaker Salarilak, Abdul Rahman Bahrami ................................................. 108

Brief Communication

Climate change: The challenges for public health preparedness and response-
An Indian case study
Rajan R. Patil, T. M. Deepa .................................................................................................................... 113

Letter to Editor

E-waste management in India: An emerging environmental and health issue
Harshal Pandve .................................................................................................................................... 116

Obituary

.......................................................................................................................................................... 117

Branch Activities

....................................................................................................................................................... 118

Author Index - 2007

....................................................................................................................................................... 000

Title Index - 2007

....................................................................................................................................................... 000

Announcement

....................................................................................................................................................... 000

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Vanadium pentoxide inhalation

Abstract

Context: This mini-review describes the toxic effects of vanadium pentoxide inhalation principally in the workplace and associated complications with breathing and respiration. Although there are some material safety data sheets available detailing the handling, hazards and toxicity of vanadium pentoxide, there are only two reviews listed in PubMed detailing its toxicity. Aim: To collate information on the consequences of occupational inhalation exposure of vanadium pentoxide on physiological function and wellbeing. Materials and Methods: The criteria used in the current mini-review for selecting articles were adopted from proposed criteria in The International Classification of Functioning, Disability and Health. Articles were classified from an acute and chronic exposure and toxicity thrust. Results: The lungs are the principal route through which vanadium pentoxide enters the body. It can injure the lungs and bronchial airways possibly involving acute chemical pneumonitis, pulmonary edema and/or acute tracheobronchitis. It may adversely influence cardiac autonomic function. It stimulates the secretion of cytokines and chemokines by hepatocytes and disrupts mitochondria function. It disrupts the permeability of the epithelium and promotes access of inflammatory mediators to the underlying neuronal tissue causing injury and neuronal death. When renal brush border membrane vesicles are exposed to vanadium pentoxide, there is a time-dependent inhibition of citrate uptake and Na⁺K⁺ATPase in the membrane possibly contributing to nephrotoxicity. Exposure results in necrosis of spermatogonium, spermatocytes and Sertoli cells contributing to male infertility. Conclusion: Vanadium pentoxide certainly has adverse effects on the health and the wellbeing and measures need to be taken to prevent hazardous exposure of the like.

Key words: Breathing, dust, exposure, fumes, occupation, respiration, vanadium pentoxide

INTRODUCTION

This mini-review describes the toxic effects of vanadium pentoxide inhalation principally in the workplace and associated complications with breathing and respiration.[1] Vanadium is a by-product of oil-burning furnaces when vanadium pentoxide (M₆ 181.88) is deposited in the flues. It is an odorless gas.[2] Inhalation is the principal route of entry into the body and may result acutely in severe pneumonitis with associated mucus membrane irritation and gastrointestinal disturbances. Ambient vanadium pentoxide dust produces irritation of the eyes, nose and throat.[3] Over long periods, inhalation may potentiate chronic bronchitis, eczematous skin lesions, fine tremors of the extremities and greenish discoloration of the tongue.[4] As it has a rapid renal clearance, it may be monitored in urine specimens to determine exposure to vanadium pentoxide (American Conference of Governmental Industrial Hygienists, ACGIH and British Education Index, BEI) 50 µg.g⁻¹ creatinine for an end-of-shift, end-of-workweek sample.[5] Most absorbed vanadium is excreted in the urine within one day after a long-term moderate exposure to vanadium dust.[6] During its measurement vanadium oxide is sampled onto a PVC filter in a Higgins and Dewell cyclone for subsequent analysis using X-ray powder diffraction.[3] The workplace exposure limit for vanadium pentoxide is according to the Health and Safety Executive (HSE), 0.05 mg.m⁻³/8h.[1] MSDS[2] details airborne exposure limits of 0.5 mg.m⁻³ (ceiling) for vanadium respirable dust and 0.1 mg.m⁻³ (ceiling) for vanadium fumes.

Studies in laboratory rats have shown that one acute inhalation study available reported an LC67 of 1440 mg/m³ following a 1-h exposure of rats to vanadium pentoxide dust.[5] Oral studies in rats and mice demonstrate greater toxicity of vanadium as oxidation state increases. The lungs are a significant site of entry of vanadium in the case of community exposure. The distribution pattern of particles and the solubility of vanadium compounds, as well as alveolar and mucociliar clearance, are important factors that
The biological monitoring of vanadium is widely used. Urine testing, in preference for plasma testing, assumes that vanadium is excreted with a half-life of 15-40h.[22] Pre- and post-shift urine vanadium levels measured at the beginning and the end of a working week will, therefore, give a measure of daily absorption and accumulated dose from exposures over the preceding days.[19]

Environmental monitoring of vanadium employs various methods for the analysis of air samples of vanadium in air, surface waters and biota. For example, flameless AAS[23] gives a detection limit of 1 ng/ml in air, corresponding to an absolute sensitivity of 0.1 ng vanadium. ICP-AES has a working range of 5-2000 µg/m³ for a 500-litre air sample.[20]

Although there are some material safety data sheets available detailing the handling, hazards and toxicity of vanadium pentoxide,[12,24] there are only two reviews listed in PubMed detailing its toxicity.[25,26] The aim of this article therefore was to collate information on the consequences of occupational inhalation exposure of vanadium pentoxide on physiological function and wellbeing. An attempt to classify the like according to functionality of certain selected organ systems was decided.

MATERIALS AND METHODS

The criteria used in the current mini-review for selecting articles to be included were both theoretically and practically motivated and adopted from proposed criteria in The International Classification of Functioning, Disability and Health - ICF.[27] These criteria were as follows:

- Articles were chosen only with internationally recognized impact factors greater than 0.10.
- Articles were chosen based upon the impact of lifestyle, stress and/or environmental factor/s predisposing vanadium pentoxide exposure.
- Criteria for selection of literature used included yes-no responses to: the appropriateness of methodology; adequacy of subject numbers; specificity of sex and/or age of subjects; and statistically significant response rates to survey questionnaires. Due consideration was given to a comparative effect between acute and chronic exposure to vanadium pentoxide. Additionally, it was noted whether the studies occurred in laboratory animal or human subjects.

- The timeframe used was principally 1990-2007 inclusive, although articles of extreme importance from earlier decades were used where appropriate.
- A multi-factorial overview of the factors eschewed concerning vanadium pentoxide exposure was elucidated. It was presumed that collective articles detailing known factors of usage were not necessarily correlated with
functionality and health.

- Compilation of materials for the mini-review started with published literature or easily accessible academic research.
- The articles were accessible from on-line sources - PubMed and Medline (abstracts of journal articles); Cochrane (reviews of clinical evidence); Clinical Trials (reports); Dissertation.com (summaries of journal articles); and Occupational Health and Safety Information Services (full-text guidance material).

Articles were categorized according to their focus on acute or chronic exposure and toxicity, respectively (Table 1).

**RESULTS**

From the data elucidated in Table 1, the differences between total articles chosen in the acute exposure versus other categories, was 42.9% (chronic exposure), 15.3% (acute toxicity) and 31.6% (chronic toxicity). Using similar determinations, included articles were 44.1, 13.1 and 41.7%, respectively. The excluded articles were judged via chronic toxicity comparison with the other categories giving differences of 22.2% (acute exposure), 50% (chronic exposure) and 44.4% (acute toxicity).

**Lungs:** Vanadium pentoxide is regarded as a less soluble form of vanadium and is therefore eliminated from the lungs at a slow rate. Inhalation of vanadium pentoxide can injure the lungs and bronchial airways, possibly involving acute chemical pneumonitis, pulmonary edema and/or acute tracheobronchitis. Symptoms include irritation and inflammation of the mucus membranes, nasal passages and pharynx. Clinical complications include a persistent cough, shortness of breath, bronchiolar constriction, tightness of the chest and a pseudo-asthmatic inflammation. In a study of 40 plant workers previously free of lung disease and exposed to vanadium pentoxide, 12 had bronchial hyper-reactivity and symptoms of asthma. Vanadate acts directly on human bronchial smooth muscle promoting the release of Ca2+ from intracellular store via the production of inositol phosphate second messengers and inhibition of Ca2+-ATPase and causing spasms. Occasionally pulmonary edema and/or pneumonia may result with fatal consequences. First aid measures following inhalation include removing the patient into fresh air and applying artificial respiration if breathing has expired. Oxygen is needed if breathing is labored and it is essential to seek medical attention. Vanadium pentoxide dust may be a potential mutagen via induced chromosomal aberrations in man and hamsters. Alveolar/bronchiolar neoplasms developed in male rats exposed to 0.5 and 2 mg.m-3 vanadium pentoxide, with only a marginal increase thereof in female rats exposed to 0.5 mg.m-3. There were associated increase in inflammation, fibrosis and alveolar and bronchiolar hyperplasia/metaplasia and squamous metaplasia in both male and female rats. In an investigation of cynomolgus monkeys exposed to vanadium pentoxide dust for six hours per day, five days per week for 26 weeks, it demonstrated that airway obstruction accompanied a significant influx of inflammatory cells into alveolar tissue. In an earlier study, it was suggested that vanadium-induced pulmonary inflammatory changes involving polymorphonuclear leukocytes may play an important role in air-flow limitation. Exposure to vanadium may cause a metal fume fever-like syndrome associated with neutrophilic alveolitis associated with marked neutrophilia. Respiratory tract inflammation following inhalation of vanadium particles is characterized by abundant neutrophilia initiated by alveolar macrophages and release of proinflammatory cytokines. Short-term, repeated inhalation of occupationally relevant levels of vanadium by rats results in pulmonary immunocompetence via cytokine production and pulmonary macrophage induction. Wang et al. describes the mechanism of multiple reactive oxygen species induced by vanadium involves activation of an NADPH oxidase complex and the mitochondrial electron transport chain, with hydrogen peroxide playing a major role in lung inflammation and apoptosis. There may be a pathological pattern within the lung which may be associated with the pattern and/or extent of vanadium deposition. Its cumulative effect in lung tissue possibly contributes to the development lung cancer. Indeed, in lung tissue excised from post-mortem investigations, the mean vanadium concentrations of 1.36 ± 0.08 (sd) (1990s) were higher than 1.04 ± 0.05 in the 1960s. The free-radical redox cycling of vanadium in the rat lung involving vanadium (V) undergoing one-electron redox cycling in the rat lung biomembranes and re-oxidation of vanadium (IV) initiating lipid peroxidation, possibly contribute to pulmonary toxicity.

**Circulatory system:** Chronically, exposure to airborne metals including vanadium may result in alterations in cardiac autonomic function. Vanadium induces thrombocytosis and may be associated with various thromboembolic diseases. Acute studies of vanadium pentoxide inhalation on the heart in experimental animals revealed that there was myocardial vascular congestion was observed, with focal perivascular haemorrhages. Studies in humans has revealed palpitation of the heart, high incidence of extrasystoles, changes in the blood picture (anemia, leukopenia, punctatebasophilia of the erythrocytes) and reduced levels of cholesterol in the blood. Limited studies have suggested a positive correlation between...
vanadium inhalation in urban air and mortality from cardiac failure, despite an absence of lifestyle determination.\[^{46}\]

**Liver**: Acutely, vanadium is a potent inhibitor of many enzymes, while it stimulates adenylate cyclase. It has been shown to inhibit cholesterol biosynthesis and lower plasma cholesterol levels. Vanadium can also directly influence glucose metabolism *in vitro* and may play a role in its regulation. Lipid peroxidation of rat liver microsomes and mitochondria was induced by sulphite and accelerated by the presence of vanadium compounds.\[^{48}\] Severe acute exposure (tens of mg/m\(^3\)) is responsible for systemic effects. Most frequent findings in animal experiments were in the liver, kidneys, gonads and the nervous, hematological and cardiovascular systems.\[^{15}\] Chronically, histopathological changes observed in the liver following the higher level of inhalation exposure (27 µg/m\(^3\) for 70 days) included central vein congestion with scattered small hemorrhages and granular degeneration of hepatocytes.\[^{6}\]

Vanadium concentrations of 10 µg/g dry weight (dw) in the liver is associated with mortality in ducks acutely exposed to sodium metavanadate.\[^{47}\] Chronic exposure to increasing dietary concentrations of sodium metavanadate (38.5-2651 ppm) over 67 days resulted in vanadium accumulation in the liver of 25.2 µg/g dwt.\[^{47}\] It is unlikely though that such concentrations would have been achieved via inhalation. Vanadium pentoxide exposure stimulates the secretion of cytokines and chemokines by hepatocytes and associated epithelium and promotes access of inflammatory mediators to the underlying neuronal tissue causing injury and neuronal death.\[^{51}\] Within the ependymal epithelium, cilia loss, cell sloughing and cell layer detachment occur after vanadium pentoxide inhalation.\[^{53}\] The damage results in disrupted permeability of the epithelium and promotes access of inflammatory mediators to the underlying neuronal tissue causing injury and neuronal death.\[^{53}\] In humans, severe chronic exposure results in general symptomatology including nervous disturbances, neurasthenic or vegetative symptoms.\[^{6}\]

**CNS**: Severe acute exposure to vanadium pentoxide has major pathophysiological manifestations on the nervous system.\[^{48}\] Inhalation thereof produces a time-dependent loss of dendritic spines, necrotic-like cell death and considerable alterations of the hippocampus CA1 neurophile, all associated with spatial memory impairment.\[^{52}\] Additionally, there is a decrease in the number of tyrosine hydroxylase immunoreactive neurones in the substantia nigra pars compacta.\[^{52}\] Within the ependymal epithelium, cilia loss, cell sloughing and cell layer detachment occur after vanadium pentoxide inhalation.\[^{53}\] The damage results in disrupted permeability of the epithelium and promotes access of inflammatory mediators to the underlying neuronal tissue causing injury and neuronal death.\[^{53}\] In humans, severe chronic exposure results in general symptomatology including nervous disturbances, neurasthenic or vegetative symptoms.\[^{6}\]

**Kidneys**: Severe acute exposure (tens of mg/m\(^3\)) is responsible for aberrations in renal function.\[^{46}\] Vanadium concentrations of 25 µg/g dw. in the kidneys are associated with mortality in ducks acutely exposed to sodium metavanadate.\[^{47}\] Chronic exposure to increasing dietary concentrations of sodium metavanadate (38.5-2651 ppm) over 67 days resulted in vanadium accumulation in the kidneys of 13.6 µg/g dw.\[^{47}\] It is unlikely though that such concentrations would have been achieved via inhalation. When renal brush border membrane vesicles are exposed to vanadium pentoxide, there is a time-dependent inhibition of citrate uptake in the membrane possibly contributing to nephrotoxicity.\[^{15}\] In studies on dog and human kidney enzymes, vanadium may inhibit the Na\(^+\)K\(^+\)ATPase, a process independent of enzyme protein concentrations.\[^{54}\] The authors suggested that vanadium inhibits the ATPase at the site activated by Na\(^+\) and ATP protects the enzyme by either binding vanadium or by competing for a mutual receptor on the enzyme. Chronically in experimental animals, histopathological changes observed in the kidneys following the higher level of inhalation exposure (27 µg/m\(^3\) for 70 days) included marked granular degeneration of the epithelium of the convoluted tubules. Dose-dependent histological changes, included corticomедullary microhaemorrhagic foci in the kidneys.\[^{25}\]

Chronically, absorbed vanadium in either pentavalent or tetravalent states is distributed mainly to the bone (around 10-25% of the administered dose three days after administration) and to a lesser extent to the kidney (about 4%).\[^{56}\] Distribution studies in which rats received a total of approximately 224 and 415 mg vanadium pentoxide/kg in drinking-water over a period of 1 and 2 months indicated that the vanadium content (assessed in 13 specific tissues) was greatest in the kidneys, spleen, tibia and testes.\[^{57}\]

**Testicles**: Chronic ingestion of vanadium may have significant consequences for infertility by damaging spermatogenesis. Studies in mice have demonstrated that inhalation of vanadium pentoxide results in necrosis of spermatogonium, spermatocytes and Sertoli cells.\[^{58}\] Vanadium accumulates in the testes and attenuates the percentage of gamma-tubulin in all analysed testicular cells, suggesting changes in microtubules used in cell division.\[^{59}\] Vanadium also induces DNA damage.\[^{60}\] Leydig cells may not be affected by vanadium pentoxide as testosterone levels remain unchanged.\[^{61}\]

**DISCUSSION**

This mini-review has contributed to a brief synthesis of the literature which is currently rather scattered in nature into a compact format. Its main thrust was from both an acute and chronic exposure and toxicity angle. Vanadium pentoxide has adverse effects on health and well-being and measures need to be taken to prevent hazardous exposure of the like. Medical monitoring of workers exposed to the dust or fumes; workplace
monitoring and measurement of ambient concentrations; dealing with contaminated attire and establishing personal hygienic procedures; dealing with emergency spills of dust; enforcing protocols for emergencies and hazardous waste management; and the use of insulated respiratory and personal protective equipment, are all essential in reducing toxic exposure.

Vanadium pentoxide exposure (acutely and chronically) in both experimental animal and human studies indicates a systemic patho-physiological and pathological influence on cell metabolism and tissue function. Therefore procedures need to be implemented in environments which potentially expose workers to vanadium pentoxide including influences on respiratory function and appropriate quality guidelines enforced. The lungs are likely to accumulate more vanadium particles than elsewhere particularly from polluted air. The lowest observed-adverse-effect level for acute exposure can be considered to be 60 μg vanadium per m³. Indeed, chronic exposure emanates as slight changes in the upper respiratory tract, with irritation, coughing and injection of pharynx, to more serious effects such as chronic bronchitis and pneumonitis. Persons suffering from lung problems including asthma and cystic fibrosis would need to ensure that they take adequate measures to prevent vanadium irritation of the mucosa. Obviously, however, a systemic assessment via renal and liver function tests needs to be completed in order to make an accurate clinical assessment of the influence of vanadium on body function and ultimately the efficient maintenance of homeostasis. More research is required to establish and add to the limited existing knowledge on the toxicokinetic and toxicological database on vanadium pentoxide. Indeed, there is limited understanding of the potential for dermal absorption and the potential long term effects as a result of sequestration in body tissues such as bone.

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