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Tungsten toxicity

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ABSTRACT

There is emerging evidence that tungsten has toxic health effects. We summarize the recent tungsten toxicity research in this short review. Tungsten is widely used in many commercial and military applications because it has the second highest melting temperature of any element. Consequently, it is important to elucidate the potential health effects of tungsten.

1. Introduction

Tungsten became a contaminant of high interest in the Fallon, Nevada leukemia cluster as of the open meeting held by the US Centers for Disease Control (CDC) in Fallon, Nevada in early February of 2003. A key announcement at that time was that the tungsten content in the urine of Fallonites was higher than expected [1]. No link was concluded by the CDC between high tungsten levels and leukemia, in part because Fallonites generally, including leukemic case subjects and non-leukemic comparison subjects, showed high body content of tungsten. However, the lack of linkage did not nullify the original finding that Fallonites have high levels of tungsten in their bodies.

2. Fallon research conducted at the University of Arizona

Since the CDC meeting of February 2003 in Fallon, Nevada, my research team has pursued two lines of investigation. Environmentally, we studied Fallon and its surrounding communities to assess tungsten concentrations in airborne and surface dust. The principal finding from that research was that tungsten is elevated in outdoor airborne and surface dust in Fallon relative to other communities of west central Nevada and relative to outlying desert. This consensus was corroborated across multiple techniques of environmental monitoring, including dust collected directly from air [2], dust collected from paved surfaces [3], dust collected from surfaces of tree leaves [4], and tissues of lichens [5]. The outcome of these results was summarized in the special issue of Chemico-Biological Interactions on Fallon [6]. Additionally, tungsten particles collected from airborne dust of Fallon were shown to be anthropogenic in origin, not natural [7].

Biomedically, we worked to create a mouse tungsten exposure model. This research is presented in the present issue of Chemico-Biological Interactions [8]. Briefly, inoculation of C57BL/6J mice with respiratory syncytial virus (RSV) was associated with a neutrophil shift in 56% of 5-month-old mice. When the RSV inoculation was combined with Na_2WO_4 exposure, significant splenomegaly (enlarged spleen) resulted ($p = 0.0406$, 0.0184, 0.0108 for control, Na_2WO_4-only and RSV-only, respectively). We have also studied the health effects of exposure to tungsten in multiple ways. Tungsten ore administered to human leukemia cells in cell culture increased growth of pre-existing leukemia cells by 170% compared to control leukemia cells over a 72-h exposure period [9]. Prenatal exposure to tungstate and/or arsenite decreased DMBT-1 (deleted malignant brain tumor 1 gene) transcriptome expression in mice and altered a cytokine–cytokine receptor interaction pathway associated with lymphocyte activation [10].

3. Biomedical research on tungsten by others

Other research teams have recently published studies on tungsten toxicity. Kalinich and co-workers used military-grade heavy metal tungsten alloys (>90% tungsten) pellets that were implanted intramuscularly into hind legs of male Fischer 344 rats [11]. The high-dose (20 pellets) implanted tungsten alloy rats ($N = 46$) developed extremely aggressive tumors surrounding the pellets within 4–5 months after implantation. The low-dose (4 pellets) tungsten alloy rats ($N = 46$) and nickel-implanted rats ($N = 36$) also developed tumors, characterized as high-grade pleomorphic rhabdomyosarcomas by histopathology and immunohistochemical examination, which rapidly metastasized to the lungs and

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necessitated euthanasia of the animals. In general, metal implants can potentially have carcinogenic effects [12], but these results of Kalinich et al. with tungsten pellets are more severe than a generic effect from implanting metal.

Additionally, the Naval Medical Research Unit at Dayton (NAMRU-D) at Wright-Patterson Air Force Base, OH, has studied the potential reproduction, neurobehavioral, and systemic effects of soluble sodium tungstate in Sprague–Dawley rats [13]. Following 70 days of daily pre- and post-natal exposure via oral gavage to 5, 62.5, and 125 mg/kg/day of exposure, tungsten analysis showed a systemic distribution of sodium tungstate in both parents and offspring with preferential uptake within the immune organs, including the femur, spleen, and thymus. Histopathological evidence suggested no severe or chronic injury or loss of function in these organs. However, the heart showed histological lesions, histiocytic inflammation from minimal to mild with cardiomyocyte degeneration and necrosis in several animals of the 125 sodium tungstate group. The results of this study suggest that pre- and post-natal exposure to sodium tungstate may produce subtle neurobehavioral effects in offspring related to motor activity and emotionality.

Multiple research groups have used cell culture techniques to demonstrate tungsten toxicity. Harris and co-workers used tungsten (91%), nickel (6%), and cobalt (3%) alloys in L6-C11 rat muscle cells [14]. Exposure to this combination of metals produced significant amounts of DNA damage, inhibition of caspase-3, cell hypoxia, and significant cell death within 24 h. Peuster et al. grew primary cultures of human pulmonary arterial endothelial cells, smooth muscle cells, and human dermal fibroblasts on multiplates for 1–10 days with ascending concentrations (0.1–5000 μg/ml) of tungsten [15]. Endothelial cells were most susceptible to tungsten with a LD50 of 50 μg/ml. In contrast, the LD50 was 100 μg/ml for smooth muscle cells and 1000 μg/ml for fibroblasts after 10 days of incubation.

Osterburg et al. identified alterations in isolated human peripheral blood lymphocytes treated with sodium tungstate (0.01, 0.1, 1.0, and 10 mM) [16]. Analysis of apoptosis with annexin V and propidium iodide revealed a dose-and-time dependent increase in the quantity of cells in early apoptosis after tungstate exposure. Finally, Verma and co-workers showed epigenetic modifications, dephosphorylation of H3-Ser 10 in C12C12 cells and hippocampal primary neuronal cultures with H3-hypoacetylation in C12C12 cells, triggered by tungsten alloy exposures [17]. They suggest that tungsten alloy exposure mediates these changes by altering intracellular calcium homeostasis and buffering.

4. Summary

The study of tungsten toxicity is in its infancy. However, the potential involvement of tungsten in the development of cancers and other deleterious health problems needs to be fully elucidated by additional research. It is also notable that chronic exposure to tungsten, even at very low concentration, is important, probably more so than acute toxicity [18].

Conflict of interest statement

Drs. Witten and Sheppard have provided documents, data, and declarations in Case CV03-03482, Richard Jernee et al. vs Kinder Morgan Energy et al. and CV03-05326, Floyd Sands et al. vs Kinder Morgan Energy et al., Second Judicial District Court of Nevada, Washoe County, which are related to the childhood leukemia cluster of Fallon, Nevada. In those cases, the law firm of Dunlap and Laxalt, representing the plaintiffs, with full disclosure to all defendants and their counsel, made an unsolicited donation of $15,000 USD to assist Drs. Witten and Sheppard in furthering their research, with a request that defendants provide similar donations. Neither Witten nor Sheppard have profited personally as a result of doing their research in Fallon or from providing material in these cases. Brandon Witten declares no competing interests.

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