Masten, Scott (NIH/NIEHS)

From: BlakeInt@aol.com
Sent: Friday, January 30, 2004 10:44 AM
To: Masten, Scott (NIH/NIEHS)
Subject: Re. Tungsten Toxicity

To: Dr. Scott A. Masten
Office of Chemical Nomination and Selection
Environmental Toxicology Program
National Institute of Environmental Health Sciences
P.O. Box 12233, MD A3-07
111 T.W. Alexander Drive
Research Triangle Park, NC

Dear Sir

I am writing regarding the notice regarding Substances Nominated to the NTP for Toxicological Studies and Testing Recommendations Made by the NTP Interagency Committee for Chemical Evaluation and Co-ordination (ICCEC) on June 10, 2003, with a particular reference to Tungsten.

As you may be aware tungsten is becoming increasingly promulgated as a non-toxic substitute for lead and other heavy metallic materials. It is increasingtly used in wildfowel shooting and as a lead substitute in military small calibre rounds.

There is a significant body of information which suggest the Tungsten is significantly more harmful than promulgated and that the available evidence is being ignored by those promoting tungsten as a non-toxic and inert material. In particular we draw your attention to the references below implicating tungsten cancer antagonist and a potentially genotoxic and mutagenic agent.

We respectfully submit that the toxicity of tungsten metal with regard to its potentially carcinogenic properties are long overdue for evaluation.

Yours sincerely

Dr Peter J. Hurley

Blake International Limited
Huddersfield
United Kingdom

REFERENCES:

Title:[Effect of molybdenum and tungsten on mammary carcinogenesis in Sprague-Dawley (SD) rats]
Author
Wei HJ; Luo XM; Yang XP
Address
Cancer Institute, Chinese Academy of Medical Sciences, Beijing.
Source
Chung Hua Chung Liu Tsa Chih, 9(3):204-7 1987 May
Abstract

Virgin female rats of SD strain were given ad libitum a nutritionally adequate semipurified diet containing 0.026 ppm molybdenum and deionized water (groups 1-3) or the same diet with 150 ppm tungsten and the drinking water (group 4). Group 1 was used as control. After 15 days, all the animals in groups 2-4 received an intravenous injection of N-nitroso-N-methylurea (NMU) 5 mg/100 g body weight. One week after administration of carcinogen, 10 ppm Mo was added to the drinking water in group 3. After 125 days, the mammary cancer incidence in group 4 (79.2%) was significantly higher than that in group 2 (50.0%) or group 3 (45.5%) (P less than 0.05). After 198 days, the average number of mammary cancer in each animal and mammary cancer incidence in group 3 (1.5 and 50.0%) were obviously lower than those in group 2 (2.0 and 90.5%) or group 4 (2.6 and 95.7%). The first palpable mammary tumor was found in the W-supplemented group only 56 days after the injection of NMU, whereas in the W-unsupplemented and Mo-supplemented groups, the first mammary tumor was observed 71 and 85 days after NMU treatment. Of these 181 mammary tumors, 177 (97.8%) were adenocarcinoma or papillary carcinoma, only 4 (2.2%) fibroadenocarcinoma. The results of this study show, for the first time, the inhibitory effect of Mo on the mammary carcinogenesis and promoting effect of Tungsten, an antagonist of molybdenum, on the tumor growth.

JOURNAL OF ATHEROSCLEROSIS AND THROMBOSIS 1998;5(1):13-20
Influences of supplementary dietary tungsten on methionine metabolism in rabbits fed a low-cholesterol plus methionine diet.
Takagi S, Nakajima S, Fukuo Y, Terashi A
Department of Internal Medicine, Nippon Medical School, Tokyo, Japan.

Hyperhomocysteinemia results from an impaired methionine metabolism. Sulfite oxidase, which is an important enzyme in methionine metabolism, contains molybdenum. In contrast, tungsten has a molybdenum-antagonistic effect. Thus, we hypothesized that dietary tungsten may decrease plasma homocysteine levels and influence methionine metabolism. Male New Zealand White rabbits (n=15) were fed a low-cholesterol basal diet and then placed on three different diets: 0.1% cholesterol (Chol), Chol plus 1% methionine (Met), and Chol plus Met plus 0.1% tungsten (W). The animals received these diets for 20 weeks. Biochemical tests of blood and urine were performed. Plasma homocysteine levels were significantly lower in the Chol+Met+W group than in the Chol+Met group. Plasma levels of total cholesterol, triglyceride, lipid peroxide, and urinary 24-h taurine concentrations were higher in the Chol + Met + W group than in the Chol + Met group. In comparison, concentrations of 2, 3-diphosphoglycerate (2, 3-DPG), reduced glutathione (GSH) in erythrocytes, and urinary 24-h SO4(2) were lower in the Chol+Met+W group than in the Chol+Met group. From these results, tungsten could be expected to exhibit an antiatherogenic effect. Conversely, it may have effects on atherogenic factors. Thus, tungsten may play a number of roles in the methionine metabolism.

Carcinogenesis, Vol. 22, No. 1, 115-125, January 2001 Oxford University Press
CANCER BIOLOGY
Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy metal-tungsten alloy particles: induction of genotoxic effects
Alexandra C. Miller3, Steve Mog1, LuAnn McKinney1, Lei Luo2, Jennifer Allen, Jiaquan Xu and Natalie Page2
Applied Cellular Radiobiology Department and
1 Veterinary Sciences Department, Armed Forces Radiobiology Research Institute, Bethesda, MD 20889-5603 and
2 Molecular Oncology Branch, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Heavy metal-tungsten alloys (HMTAs) are dense heavy metal composite materials used primarily in military applications. HMTAs are composed of a mixture of tungsten (91-93%), nickel (3-5%) and either cobalt (2-4%) or iron (2-4%) particles. Like the heavy metal depleted uranium (DU), the use of HMTAs in military munitions could result in their internalization in humans. Limited data exist, however, regarding the long-term health effects of internalized HMTAs in humans. We used an immortalized, non-

tumorigenic, human osteoblast-like cell line (HOS) to study the tumorigenic transforming potential of reconstituted mixtures of tungsten, nickel and cobalt (rWNiCo) and tungsten, nickel and iron (rWNiFe). We report the ability of rWNiCo and rWNiFe to transform immortalized HOS cells to the tumorigenic phenotype. These HMTA transformants are characterized by anchorage-independent growth, tumor formation in nude mice and high level expression of the K-ras oncogene. Cellular exposure to rWNiCo and rWNiFe resulted in 8.90 ± 0.93- and 9.50 ± 0.91-fold increases in transformation frequency, respectively, compared with the frequency in untreated cells. In comparison, an equivalent dose of crystalline NiS resulted in a 7.7 ± 0.73-fold increase in transformation frequency. The inert metal tantalum oxide did not enhance HOS transformation frequency above untreated levels. The mechanism by which rWNiCo and rWNiFe induce cell transformation in vitro appears to involve, at least partially, direct damage to the genetic material, manifested as increased DNA breakage or chromosomal aberrations (i.e. micronuclei). This is the first report showing that HMTA mixtures of W, Ni and Co or Fe cause human cell transformation to the neoplastic phenotype. While additional studies are needed to determine if protracted HMTA exposure produces tumors in vivo, the implication from these in vitro results is that the risk of cancer induction from internalized HMTAs exposure may be comparable with the risk from other biologically reactive and insoluble carcinogenic heavy metal compounds (e.g. nickel subsulfide and nickel oxide).

Title: Carcinogenic Potential of Depleted Uranium and Tungsten Alloys
Synopsis: This study in animals is designed to determine whether or not embedded fragments of depleted uranium (DU) cause changes in cells suggestive of cancer.
Overall Project Objective: This project seeks to assess the degree of carcinogenic potential and determine the mechanism of action of embedded fragments of DU and a proposed surrogate metal, heavy metal tungsten alloy (HMTA) using both cell culture and animal studies.
Status/Results to Date: Previous studies at AFFRI indicate that exposure to DU or HMTA causes changes in cells, both in vivo and in vitro, suggesting that DU has carcinogenic potential. DU induces a dose- and time-dependent increase in the expression of specific oncogenes in kidney, muscle, and liver of rats implanted with pellets of DU. No oncogene increases were observed in rodents implanted with the non-toxic metal tantalum. Significant increases in both micronuclei and sister chromatid exchanges, indicators of genotoxic damage, were measured in lymphocytes obtained from DU-implanted rats 18 months after implantation, but not in tantalum-implanted rats. Injection of sodium tungstate into Fischer rats produced significant increases in both micronuclei and SCE. Urine from DU-implanted animals was mutagenic; a consequence of the presence of excreted DU. Exposure of cultured human bone cells to DU or HMTA resulted in a transformation of those cells to a type with biochemical and growth characteristics typical of tumor cells. The magnitude of transformation observed with DU and HMTA was similar to that observed with the known heavy metal carcinogen, nickel. These cells, once transformed, produced tumors when injected into immune deficient mice. DU and HMTA were also shown to be genotoxic and mutagenic in model system studies.
Project: DoD-122
Agency: Department Of Defense
Location: Armed Forces Radiobiology Research Institute (AFRRI)

P.I. Name: Alexandra C Miller, Ph. D.
Research Type: Mechanistic
Research Focus: Depleted Uranium
Focus Category: Cancer
Status: Ongoing
Study Start Date:
Estimated Completion Date: December 31,2004
Specific Aims: This project seeks to determine whether exposure to embedded fragments of DU and HMTA cause cancer in a rat model and to investigate potential mechanisms of action. The animal study will provide data from two general treatment groups that include a carcinogenicity/rat longevity study. A parallel study to analyze tissues obtained at various time points to investigate cellular changes associated with the metal exposures will also be conducted. Cell culture studies will be used to examine additional mechanisms and the role radiation plays in DU-induced effects.

Methodology: Rats will be implanted with pellets of DU, HMTA, the known metal carcinogen nickel (positive controls), the suspected carcinogen lead, and the biologically inert metal tantalum (negative control). Longevity studies will be carried out under guidelines suggested by the National Toxicology Program. Tissue analyses after necropsy will be used to determine the cause of death and the nature of any abnormal tissues observed. Subgroups of animals will be similarly implanted but euthanized at various times after tissue implantation to correlate tissue metal content with long-term biological effect analysis. Mutagenicity, cytogenicity, and genomic instability will be assessed. Experiments using an in vitro cell model were designed to determine the role alpha particle radiation plays in DU effects and examine other mechanisms of neoplastic transformation.

Pharmacol Toxicol. 1997 Aug;81(2):74-80.
In vitro toxicity of cobalt and hard metal dust in rat and human type II pneumocytes.
Roesems G, Hoet PH, Demedts M, Nemery B.
Laboratory of Pneumology (Unit of Lung Toxicology), K.U.Leuven, Belgium.

It has been demonstrated that hard metal dust, which consists of a mixture of cobalt and tungsten carbide, is more toxic toward mouse peritoneal and rat alveolar macrophages than pure cobalt (Co) or tungsten carbide (WC). The aim of this study was to investigate the toxic effects of Co and hard metal dust on alveolar epithelial type II cells (AT-II), and to compare these with alveolar macrophages. Freshly isolated rat and human AT-II and rat alveolar macrophages were exposed for 18 hr to particles of Co, WC or Co/WC. As an index for cell toxicity, release of lactate dehydrogenase was measured. For rat AT-II, TD50 values per 10(5) cells were 672 micrograms (95% C.I. = 264-1706 micrograms) for pure Co and 101 micrograms (95% C.I. = 59-172 micrograms) for Co in Co/WC mixture. For rat alveolar macrophages, TD50 values per 10(5) cells were 18 micrograms (95% C.I. = 15-24 micrograms) for pure Co and 5 micrograms (95% C.I. = 5-6 micrograms) for Co in Co/WC mixture. WC only caused an increase in lactate dehydrogenase at high concentrations. No toxicity was found in human AT-II for either Co, WC or Co/WC. These results indicate that 1) rat AT-II are less sensitive to Co than rat alveolar macrophages, 2) human AT are less sensitive to Co than rat AT-II, 3) the toxicity of Co is increased by the presence of WC.