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Sent via Email to: biomonitoring@oehha.ca.gov

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Biomonitoring California
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland
CA 94612
USA

Dear Sir/Madam,

Re: Listing Tungsten as a Potential Priority Metal in the California Biomonitoring Program

The International Tungsten Industry Association (ITIA) is registered under Belgian law as a not-for-profit association with scientific purposes in support of the tungsten industry. ITIA's members are from 20 countries and include mining companies, processors, consumers, trading companies and recyclers as well as the world's leading manufacturers, importers, and users of tungsten and its compounds. There are eight member companies in the US including Global Tungsten & Powders Corp and Kennametal Inc, and operations in the US of member companies from overseas, ie Sandvik Machining Solutions AB and HC Starck GmbH. Details about ITIA and list of ITIA's member companies and can be found on our website - www.itia.info.

One of our major tasks is to co-ordinate the extensive work programme of the Health, Safety and Environment issues related to tungsten and its compounds including:

- regulatory and classification issues,
- monitoring proposed legislation,
- developing scientific data on the impact of tungsten on human health and the environment,
- managing the Tungsten Consortium which was established by ITIA in response to the EU's "REACH" legislation "

ITIA is pleased to provide the following comments regarding the potential listing of tungsten as a priority chemical under the California's Environmental Contaminant Biomonitoring Program.

Biomonitoring programs are important when conducting human risk assessment as such programs measure background chemicals levels in the general population due to exposures resulting from the environment. However, one of the most common misperceptions is that the mere detection of a chemical in our bodies suggests a health hazard rather than simply providing a measure of exposure. Then, it is important that the State of California which is designing and conducting the

biomonitoring program carefully considers how the data should be interpreted and how that information should be conveyed to the public.

Tungsten has been previously biomonitored under different country-wide programs such as United States' National Health and Nutrition Examination Survey (NHANES) and Canada's Human Biomonitoring of Environmental Chemicals; as well as on inhabitants of two Italian regions (Bocca et al. 2010) or in a subpopulation of Spanish athletes (Llerena et al. 2012).

ITIA does not oppose the biomonitoring of tungsten by the State California, but its inclusion needs to be based on the current and accurate scientific information available. However, based on our scientific opinion the March 27, 2014 Summary Table that lists the potential priority chemicals for biomonitoring presents an incomplete and inaccurate summary of the exposure and toxicity information available for tungsten. In particular, the table summary fails to mention the critical non-carcinogenicity evidence for tungsten and its compounds. Therefore, we would like to provide details evidencing that tungsten is not carcinogenic:

- The United States Center for Disease Control (CDC) reports no direct link between tungsten and the incidence of leukaemia (Rubin et al. 2007; CDC 2003).
- The scientific evidence of rodent carcinogenicity is associated exclusively with the military grade heavy alloy made of tungsten-cobalt-nickel (Kalinich 2011).
- The carcinogenic effect of the tungsten-cobalt-nickel alloy can be attributed to galvanic corrosion that causes mobilization of carcinogenic metals such as cobalt and nickel which causes the muscle tumour in rodents (Schuster et al. 2012).

The scientific and technical information presented in this document are studies published by a variety of entities including CDC (Rubin et al. 2007), and the US Armed Forces Radiobiology Research Institute (Kalinich et al 2005; Kalinich et al 2011; Schuster et al 2012).

This document summarises the findings of these peer reviewed and publication studies divided into two main sections: (1) carcinogenicity and toxicity; and (2) degree of potential exposure.

1) Carcinogenicity and Toxicity

a. Childhood Leukaemia Cluster

This section briefly discusses the relevant information relating to metals, and will not examine the other substances that were part of CDC's assessment such as pesticides, polychlorinated biphenyls (PCB), or volatile organic compounds (VOCs).

The March 27, 2014 Summary Table that lists tungsten as a potential priority chemical for biomonitoring, does not mention that in addition to tungsten, arsenic was also identified in tap water samples of Churchill County, Nevada community (CDC 2003; Rubin et al. 2007). Tungsten metal is not listed or classified as human carcinogen (Table 1); however arsenic (as inorganic arsenic compound) is considered according to the International Agency for Research on Cancer as *carcinogenic to humans* (Group 1), listed as *known to cause cancer* by the State of California (Prop 65); and considered by National Toxicology Program as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans.

The potential priority chemical summary table also omits the odds ratio (OR) that defines the association between metal exposures with leukaemia. Tungsten (OR 0.78, p-value 0.57), arsenic (OR 0.60 p=0.22) and the rest of the metals (antimony, barium, cesium, cobalt, molybdenum and uranium) ORs did not suggest increased risk, and Rubin et al. (2007) concludes that "no exposure

consistent with leukaemia risk was identified". Overall, "tungsten and arsenic levels in urine and water samples were significantly higher than national comparison values; however, levels were similar among case and comparison groups".

b. Rodent Carcinogenicity

In the US Armed Forces Radiobiology Research Institute studies (Kalinich et al. 2005; Kalinich 2011) tumour formation was only observed in animals implanted with tungsten-cobalt-nickel alloy (a military relevant alloy). Follow-up studies with other tungsten combinations such as tungsten-nickel-iron (a military relevant alloy), tungsten-tantalum, tungsten-nickel-tantalum, tungsten-cobalt-tantalum, and tungsten-iron-tantalum did not produce a carcinogenic effect.

When evaluating the Kalinich et al. (2005) study it is useful to review the human carcinogenicity evidence of individual components in the heavy alloy that produced tumours when is embedded in the rat muscle (Table 1).

Tungsten metal is not listed or classified as human carcinogen, while cobalt and nickel are considered human carcinogens by IARC, US NTP, and the State of California; and classified as carcinogens according to EU CLP/ UN GHS guidelines. It is reasonable to assume that the carcinogenic activity on the carcinogenic pellet is conferred by cobalt and/or nickel in the presence of tungsten. But is not caused by the tungsten. This is confirmed (see below for more details) by a subsequent embedded pellet study by Kalinich (2011) that reported negative carcinogenic potential for tungsten-tantalum, tungsten-nickel-tantalum, tungsten-cobalt-tantalum and nickel-cobalt-tantalum pellets (Note: tantalum is a biologically inert metal).

Table 1. Human Carcinogenicity Classifications of W, Co & Ni

Metal	Carcinogenicity Classification			
	IARC[1]	State of California Proposition 65	US NTP[2]	EU CLP[3]/ UN GHS[4]
Tungsten (W) CAS No 7440-33-7 EC No 231-143-9	Not Listed	Not Listed	Not Listed	Not Classified
Cobalt (Co) CAS No 7440-48-4 EC No 231-158-0	Possibly carcinogenic to humans (Group 2B).	Listed	Reasonably anticipated to be a human carcinogen*	Substances presumed to have carcinogenic potential for humans (Category 1B)
Nickel (Ni) CAS No 7440-02-0 EC No 231-111-4	Possibly carcinogenic to humans (Group 2B).	Listed	Reasonably anticipated to be a human carcinogen	Suspected human carcinogens (Category 2)

* Not listed in 12th Report of Carcinogens (RoC), but it is expected to be as the US NTP 2013 rodent carcinogenicity study on cobalt metal reports a "clear evidence of carcinogenic activity".

[1] International Agency for Research on Cancer; [2] United States National Toxicology Program;

[3] European Union Classification, Labelling and Packaging; [4] United Nations Globally Harmonized System

As the March 27, 2014 Summary Table mentions the peer-review publication written by Kalinich et al. (2005) we will not spend a substantial amount of time discussing this publication as we are not refuting the results and it is assumed that the State of California is well familiar with the study design and results (Table 2). We would like to draw your attention to the follow-up study conducted by the same investigator in 2011 and it concludes that not all the tungsten based alloys are carcinogenic, and the adverse effects are only specifically seen with the tungsten-cobalt-nickel alloy.

Kalinich (2011) follow-up study in mice focuses on two tungsten alloys of special interest to the military: tungsten 91.1% tungsten -6% nickel-2.9% cobalt and 91% tungsten-7% nickel-2% iron; and the rest of the study design included several treatment groups consisting of various controls, tungsten alloy metal tests, and a toxicity reference metal (lead) (Table 2).

The follow-up study also found rhabdomyosarcomas- type tumours in mice with embedded tungsten-nickel-cobalt and 100% nickel (positive control) pellets. No tumors were found in any other treated group (Table 2).

Table 2. US Armed Forces Radiobiology Research Institute Embedded Tungsten Alloy Studies

Reference & Study Design	Pellet Compositions Tested	Results	
		Tumour Development	Comments
Kalinich et al. (2005) Male rats (n= 46 per group) were implanted intramuscularly with 4 (low dose) or 20 pellets (high dose) of weapons-grade tungsten alloy. Tantalum (20 pellets; n=46) and nickel (20 pellets; n=36) served as negative and positive controls	1) 100% Ta 2) 100% Ni 3) W 91.1%-Co 2.9%-Ni 6.0%	No Yes Yes	The tungsten-cobalt-nickel alloy high-dose-implanted rats developed aggressive tumours surrounding the pellets within 4–5 months after implantation. The tungsten-cobalt-nickel alloy low-dose-implanted rats and nickel-implanted rats also developed tumours surrounding the pellets but at a slower rate. Rats implanted with tantalum did not develop tumours. Rhabdomyosarcoma tumor yield was 100% in both the tungsten-cobalt-nickel alloy low- and high-dose groups.
Kalinich (2011) Male mice (n= 20 per group) were implanted in the quadriceps muscle with 2 (low dose) or 4 pellets (high dose) of variety alloys. Tantalum and nickel served as negative and positive controls. Serial collection of tissues was conducted at 1, 3, 6, and 12 months post-implantation aimed at identifying early changes relevant to the development of carcinogenic endpoints.	1) 100% Ta 2) 100% Pb 3) 100% Ni 4) 91.1% W-2.9% Co-6.0% Ni 5) 91.0% W-7% Ni-2%-Fe 2.0% 6) 91.1%W-8.9% Ta 7) 6% Ni-94% Ta 8) 2.9% Co-97.1% Ta 9) 2% Fe-98% Ta 10) 91.1% W-6% Ni-2.9% Ta 11) 91.1% W-2.9% Co-6%Ta 12) 91.0% W-2.0% Fe- 7.0% Ta 13) 6.0% Ni-2.0% Fe-92.0% Ta 14) 6.0% Ni-2.9% Co-91.1% Ta	No No Yes Yes No No No No No No No No No No	Mice in tungsten-nickel-cobalt and positive control (100% nickel) low- and high-dose groups developed tumors (rhabdomyosarcomas) at the pellet implantation sites. No tumours were found in any other treated group. Time to tumour development in the mouse was far slower than rat and did not metastasize to other organs. This was not unexpected considering the long latency period for implanted-metal carcinogenesis in mouse reported by others investigators. Hematological and splenic changes induced by tungsten-nickel-cobalt in the rat were not observed in the mouse.

Schuster et al (2012) conducted electron microscopy of pellets extracted from rats after being embedded for 6-months. Progressive galvanic corrosion of the matrix phase of the tungsten-cobalt-nickel was observed and was accompanied by high urinary concentrations of nickel and cobalt. The galvanic corrosion takes place because of the difference in electrode potential between the matrix phase (anode) and the W phase (cathode).

In contrast, non-carcinogenic tungsten-nickel-iron pellets were minimally corroded and urinary metals were low; but this was not progressive and decreased over time. In addition, over time these pellets developed a surface oxide layer (passivation) *in vivo* that may have restricted further anodic dissolution of the matrix phase. The formation of a "protective skin" on pellets greatly limited corrosion and mobilization of carcinogenic nickel (Schuster et al. 2012).

Overall, Kalinich's follow-up study confirms (using another rodent species) that the carcinogenic effect is associated exclusively with tungsten-cobalt-nickel alloy, and it shows that the carcinogenic activity cannot be associated with all tungsten alloys, as it depends greatly on the mobilization carcinogenic metals by galvanic corrosion, and this corrosion can be restricted by passivation.

c. Neurobehavioral Effects

The neurobehavioral effects mentioned in potential priority chemical summary table they still need to be confirmed as the study design has some limitations as described below.

The neurobehavioral assessment of pups born and lactated from WO_4^{-2} (as sodium tungstate) exposed rats found elevation of distress vocalizations in the 125 mg/kg/day group, and the righting reflex showed unexpected sex differences (but not dose dependent) where males demonstrated faster righting than females (McInturf et al. 2008; McInturf et al. 2011). When looking closer to these results, it can be noted that the statistical difference observed in righting reflex between males and females was due to a decrease in male righting reflex with increasing dose (but not statistically significant) combined with a numerical increase in the righting reflex among females (Jackson et al. 2013).

Locomotor activity was affected in both 5 and 125 mg/kg/day groups of dams without affecting maternal retrieval and no apparent effects of treatment on F1 acoustic startle response or water maze navigation (McInturf et al. 2008; McInturf et al. 2011).

McInturf's study only used two neurobehavioral tests and these measured only very early reflexive behavioral responses. In addition, no histopathology effects were noted that indicate effects in the brain. Based on the results, one could conclude that sodium tungstate may produce subtle neurobehavioral effects in offspring related to motor activity and emotionality; however, the collection of results are insufficient to delineate a clear dose response in either the pups or dams and deserves further investigation.

2) Degree of Potential Exposure

The potential priority chemical summary table includes tungsten exposure from a faulty shielding device used in testing of a new radiation treatment for breast cancer patients shed tungsten particles in the breast tissue of the study participants (n = 30).

These particles can be mistaken for cancer and produce possible false positive breast exams. However, it does not mention that in 2011 the manufacturer of the medical device issued a recall notice which was posted on the US Food and Drug Administration website, overall removing the tungsten exposure to additional cancer patients.

Furthermore, the recall notice also indicates that based on a risk assessment conducted by the shield's manufacturer concluded that there is "no permanent impairment of bodily functions or permanent damage to body structures is anticipated". Therefore, the exposures from use of these shields should not be included in the table as they are no longer relevant.

Closing

Four criteria (among these criteria the degree of potential exposure to the public, and the likelihood of a chemical to be a carcinogen or toxicant), are used by the Scientific Guidance Panel (SGP) to recommend priority chemicals. These criteria are summarized on the March 27, 2014 Summary Table, and the accuracy of such information is critical on the SGP review process. Therefore, it is of some importance that the information summarized on the table is scientifically reliable, but this is not the case as the table currently presents an incomplete and inaccurate summary of the exposure and carcinogenicity/toxicity information available for tungsten.

ITIA does not oppose to the biomonitoring of tungsten by the State California, but its inclusion needs to be based on the current and accurate scientific information available indicating the unconfirmed neurodevelopmental effects, the lack of leukemic association as suggested by an OR below one, and the carcinogenic effect is associated exclusively with tungsten-cobalt-nickel alloy, and it cannot be associated with other tungsten alloys, as it depends greatly on the mobilization carcinogenic metals by galvanic corrosion, and this corrosion can be restricted by passivation. Finally, the potential means of exposure should also be accurately stated and should not include exposures which are no longer relevant.

Therefore, the information included in this letter can be used by the State of California to update accordingly the March 27, 2014 Summary Table before the SGP review is conducted.

I, the HSE Director of the Association, am available to provide further information, answer questions either to in person or through email.

Yours faithfully,

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