# International Tungsten Industry Association

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United States National Toxicology Program (US NTP)
Public Health Service
US Department of Health and Human Services
Research Triangle Park, NC
USA

Subject: **NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Tungstate Dihydrate (CASRN 10213-10-2) in Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and B6C3F1/N Mice (Drinking Water Studies) – Technical Report 599**

Dear Sir/Madam,

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 22 countries and include mining companies, processors, and manufacturers, consumers, trading companies, and recyclers of tungsten and its compounds. ITIA's membership includes eight US companies, including two of the world's largest tungsten products producers, Global Tungsten & Powders Corp and Kennametal Inc. In addition, many non-US member companies, including HC Stark Tungsten GmbH and Sandvik Machining Solutions AB, maintain extensive operations in the US. Details about ITIA and a list of member companies can be found on www.itia.info.

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

- monitoring proposed legislation, regulatory and/or classification issues,
- developing scientific data on the impact of tungsten on human health and the environment,
- managing the Tungsten Consortium, a collaboration among the world's leading producers and processors of tungsten and tungsten compounds, which was established by ITIA in response to the EU's "REACH" legislation " and to assist the industry in the development of scientific data and to support registration of several soluble and insoluble tungsten compounds.

In response to NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Tungstate Dihydrate (CASRN 10213-10-2) in Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and B6C3F1/N Mice (Drinking Water Studies) – Technical Report 599, ITIA is submitting the following comments for your consideration.

**General Comments**

Overall, the study designs adhered to the recommended testing guidelines. The selected exposure doses fall within the range of doses that other researchers used.

We are in agreement with the identification of the kidney as the critical target organ of tungstate toxicity after oral repeated dose exposure. The results of the NTP study do not support the EPA's use of glandular stomach cell metaplasia (in rats exposed to sodium tungstate via gavage) as the critical effect for deriving the subchronic provisional-RfD for soluble tungsten compounds in the current US EPA Provisional Peer Review Toxicity Value (PPRTV) for soluble tungsten compounds (Superfund Health Risk Technical Support Center, 2015).

The results reported in NTP's sodium tungstate studies corroborate observations reported previously by other researchers which are briefly summarized below (specifically mentioning those studies that were not mentioned in the draft report):

- Kidney as the target organ for tungstate: Sachdeva, et al., (2013) noted an increase in creatinine, and urea levels in rats after rat exposure to 238 mg/kg-day (and intraperitoneal injection of 41 mg/kg-day) for two weeks suggesting renal injury.

- Body weight decreases after tungstate exposure: Body weight reduction in rats (Ballester *et al.*, 2005, 2007) and mice (Kelly *et al.*, 2013) exposed to sodium tungstate via the oral route at similar doses. This body-weight reduction has been suggested to be mediated by the activation of the hypothalamic leptin pathway (Amigó-Correig *et al.*, 2011, 2012). In fact, a proof-of-concept trial on the efficacy of sodium tungstate in human obesity was published by Hanzu *et al.*, (2010).

- Genotoxicity:

    - Standard genotoxicity testing sponsored by industry reported negative genotoxicity in the bacterial reverse mutation assay (OECD TG 471, *in vitro* mammalian cell gene mutation test (OECD TG 476), *in vitro* mammalian chromosome aberration test (OECD TG 473) and in the *in vivo* mammalian erythrocyte micronucleus test (OECD 474) (Lemus and Venezia, 2015).

    - Guilbert *et al.*, (2011) exposed mice to sodium tungstate in the drinking water (15 or 200 mg/mL) for 8 weeks. While tungstate did not significantly alter the total bone marrow cellularity at these concentrations, it was found that tungstate exposure resulted in an increase in DNA damage, as assessed by the Comet assay.

- Fertility/Reproductive:

    - The lack of reproductive toxicity effects is also supported by studies which exposed unmatched male and female rats to sodium tungstate in drinking water. Tungstate administration to healthy male rats (at 2000 mg/L for 3 months) affected the body-weight gain, however, did not alter the reproductive performance of healthy animals; modify the appearance of number of Leydig cells, or change the serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone (Ballester *et al.*, 2005). Healthy female rats exposed to tungstate (at 2000 mg/L for 12-weeks) caused a decrease in the body weight gain but did not modify daily food and water consumption. Tungstate treatment did not modify alanine aminotransferase (ALT) activity, progesterone, FSH or LH. In addition, tungstate treatment did not affect any reproductive parameter or affected the expression of the estrogen receptor. However, in ovaries tungstate treatment had a considerable effect on the expression of the progesterone receptor. In contrast, the uterine expression of the progesterone receptor was not affected by tungstate treatment (Ballester *et al.*, 2007).

    - Osterburg *et al.*, (2014) exposed parental male and female mice orally (via drinking water) to 0, 2, 62.5, 125, 200 mg sodium tungstate/kg bw-day. No statistically significant changes in body weight due to any tungstate dose level, but at the highest dose of 200 mg/kg bw-day males in the parental generation show a consistent trend towards decreased weights. Additionally, no statistically significant changes in the number of live births, litter size, or sex ratio at any dose of tungstate tested.

**Specific Comments**

ITIA recommends the following:

1. **Page xvii Line 2-3 and page 1 Line 16-17:** It will be better to mention "*tungsten minerals are present naturally in the environment and weathering of rocks and soils and can cause tungstate species to enter waterways, the predominate species being the monotungstate*".

2. **Page 1 - Line 24-26:** The statement describes one process by which tungsten is reclaimed from tungsten carbide scrap. However, it should be worth noting here that the vast majority of sodium tungstate produced in the U.S. occurs as an isolated intermediate. The primary method for producing sodium tungstate is via the digestion of tungsten ore concentrates in sodium hydroxide. The resulting solution of sodium tungstate is then converted to ammonium paratungstate, which is further processed to tungsten and tungsten compounds.

3. **Page 2 - Line 7-9:** The ACGIH TLV noted is no longer applicable. In 2017 the ACGIH® Board of Directors adopted a TLV-TWA of 3 $mg/m^3$, as W, Respirable particulate matter, for tungsten and compounds, in the absence of cobalt. The ACGIH no longer makes a distinction between soluble and insoluble tungsten compounds.

## Conclusion

We are in agreement with the conclusions drawn of no evidence of carcinogenic activity of sodium tungstate via the oral route in male rats and female mice (at the doses noted for each of them), and equivocal evidence of carcinogenic activity in female rats and male mice.

Please contact me at [redacted] or via email [redacted] if you have any questions or require further information.

Yours faithfully,

[redacted]

Ranulfo Lemus ScD, DABT
*Health, Safety and Environmental Director*

CC: Dr Burghard Zeiler, *ITIA Secretary-General*
Mr Carmen Venezia, *ITIA Health, Safety and Environmental Specialist*

## Citable Material


Amigó-Correig, M. *et al.* (2011) 'Sodium tungstate regulates food intake and body weight through activation of the hypothalamic leptin pathway', *Diabetes, Obesity and Metabolism*. Blackwell Publishing Ltd, 13(3), pp. 235-242. doi: 10.1111/j.1463-1326.2010.01339.x.

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Ballester, J. *et al.* (2005) 'Tungstate treatment improves Leydig cell function in streptozotocin-diabetic rats.', *Journal of Andrology*, 26(6), pp. 706–15. doi: 10.2164/jandrol.04156.

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Sachdeva, S., Kushwaha, P. and Flora, S. J. S. (2013) 'Effects of sodium tungstate on oxidative stress enzymes in rats.', *Toxicology mechanisms and methods*. Taylor & Francis, 23(7), pp. 519–27. doi: 10.3109/15376516.2013.787132.

Superfund Health Risk Technical Support Center (2015) *Provisional Peer-Reviewed Toxicity Values for Soluble Tungsten Compounds (Various CASRNs)*. Available at: https://hhpprtv.ornl.gov/issue_papers/SodiumTungstate.pdf (Accessed: 16 March 2021).