From: ITIA [mailto:info@itia.info]
Sent: 03 July 2012 17:15
To: 'science@acgih.org'
Subject: Submission: Tungsten and Compounds (as Tungsten) and Tungsten Carbide, ACGIH 2012 Under Study List

To : American Conference of Industrial Hygienists
Attn : Threshold Limited Values for Chemical Substances Committee

Dear Sirs,

Attached is our submission document regarding Tungsten and Compounds (as Tungsten) and Tungsten Carbide, ACGIH 2012 Under Study List.

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Yours faithfully,

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3 July 2012

Threshold Limit Values for Chemical Substances Committee (TLV-CS)
American Conference of Industrial Hygienists (ACGIH)
1330 Kemper Meadow Drive
Cincinnati
Ohio 45240
USA

Subject: Tungsten and Compounds (as tungsten) and Tungsten Carbide
ACGIH 2012 Under Study List

Dear TLV-CS Committee,

As of January 2012, ACGIH have listed tungsten and compounds (as tungsten) and tungsten carbide (WC) in the Under Study list (USL). As indicated, the Under Study list serves as a notification and invitation to interested parties to submit substantive data and comments to assist the Committee in its deliberations.

In response to your solicitation of information which may assist in ACGIH's deliberations regarding the tungsten substances listed in the USL, the International Tungsten Industry Association (ITIA) is submitting for your consideration new studies on tungsten and compounds.

The ITIA is registered under Belgian law as a not-for-profit association with scientific purposes in support of the tungsten industry. ITIA's members represent 18 countries and include mining companies, processors, consumers and trading companies as well as the world's leading manufacturers, importers, and users of tungsten and its compounds.

Study Summaries Background

The technical information presented in this document represents studies sponsored by a variety of entities including the ITIA, the Tungsten Consortium, individual members of the ITIA, and the US Department of Defense, US Army Center for Health Promotion and Preventative Medicine, and the Naval Health Research Center Environmental Health Effects Laboratory. These studies were used to support the registration of tungsten substances under the European Chemical Management Program referred to as REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals).

The following sections describe standard toxicity studies for tungsten and compounds conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practices (GLP).

***In vitro* Bioaccessibility Study**

Most exposures to tungsten and its compounds in occupational environments occur during production of tungsten metal from the ore, and preparation of tungsten carbide powders. The most significant route of tungsten exposure for workers is by inhalation of dusts. In some instances inhalation toxicity data were not available for specific tungsten substances being registered under REACH.

REACH established procedures for use of read-across strategies for similar substances to fill data gaps. This strategy is intended to reduce animal testing. In support of REACH registration for sparingly soluble tungsten substances, a 28-day inhalation toxicity study was conducted.

In order to determine which of the substances to evaluate in a repeated dose inhalation toxicity study, *in vitro* bioaccessibility testing was conducted on five sparingly soluble tungsten substances in alveolar, lysosomal, and interstitial synthetic fluids (as relevant fluids for inhalation exposure). The testing was conducted in accordance with OECD-GLP and consistent with the Draft Guidance for RIP 3.6: Bioavailability and Read-Across for Metals and Minerals (Eurometaux, 2008). Detailed results from this testing can be found at European Chemicals Agency's (ECHA's) website (ECHA, 2012) for each of the substances tested.

A summary of the *in vitro* bioaccessibility test results are provided in Table 1. Of the substances tested, tungsten blue oxide (TBO) was the most bioaccessible of the sparingly soluble tungsten substances (IITRI, 2010a). Accordingly, TBO was chosen as the test substance for a 28-day inhalation toxicity study. The 28 day test was conducted in accordance with OECD Guideline 412 and under OECD-GLP to assess the systemic repeated dose toxicity of sparingly soluble tungsten compounds (IITRI, 2010b).

Table 1: Summary of *in vitro* Bioaccessibility Testing

Tungsten Substance	CAS Number	Synthetic fluid release (% tungsten/total tungsten in substance ± std dev)		
		Lysosomal	Alveolar	Interstitial
Tungsten Trioxide	1314-35-8	38 ± 1.30	34 ± 6.10	39 ± 1.60
Tungsten Blue Oxide	39318-8-8	60 ± 5.80	41 ± 5.40	40 ± 0.59
Tungsten Metal	7440-33-7	0.97 ± 0.38	0.97 ± 0.13	0.71 ± 0.37
Tungsten Carbide	12070-12-1	0.41 ± 0.28	0.48 ± 0.06	0.13 ± 0.05
Fused Tungsten Carbide	12070-13-2	4.3 ± 0.07	3.2 ± 2.00	0.60 ± 0.01

TBO 28-Day Inhalation Toxicity Study

In support of the data requirements under REACH for repeated dose toxicity, a 28-day inhalation toxicity study on TBO was conducted in accordance with OECD Guideline 412 (IITRI, 2010b). In this study, five rats per sex per dose were given TBO nose-only for 6 hours per day, 7 days per week, for 28 days at doses of 0 (control), 0.08, 0.325, and 0.65 mg TBO/L air. Using the Guyton's formula (where respiratory vol/min in mL = 2.10 x $[\text{weight(g)}]^{0.75}$) these animal exposure

concentrations represent an estimated rat inhalable TBO dose of 15, 62 and 124 mg/kg-day. The inhaled doses of this study correspond to approximately 39, 157, or 315 times the inhalable dose of tungsten for a person working at the tungsten TLV of 5 mg/L (as metal and insoluble compounds).

All animals underwent daily clinical observations during the exposure and recovery periods. Body weights and food consumption for the core and recovery animals were measured on study days 1, 8, 15, 22 and 28. On day 29 measurement of body weights (recovery animals), food consumption (core and recovery animals), and a fasted body weight (core animals only) were taken. During the recovery period, body weights and food consumption were measured on study days 36 and 42, and a fasted body weight on study day 43.

Clinical pathology, necropsy, organ weight measurement, and histopathological evaluation were performed at the end of the exposure period and after the recovery period. Based on the results of the testing, no toxicologically significant effects were observed and, therefore, the NOAEL was deemed to be greater than 0.65 mg TBO/L air (650 mg TBO/m^3).

Sodium Tungstate 90-day Oral Toxicity Study

The US Army Center for Health Promotion and Preventative Medicine conducted a 90-day subchronic toxicity study in accordance with 40 CFR 798.2650 (McCain et al, 2009). In this study, male and female Sprague-Dawley rats were given 10, 75, 125 and 200 mg/kg/day sodium tungstate by oral gavage (7 days per week) for 90 days. Food consumption and body weight measurements were conducted, and hematology, clinical chemistry and histopathological analyses were performed.

Histological examination revealed mild to severe regeneration of cortical tubules of the kidneys of male and female rats for the 125 and 200 mg/kg/day dose groups. Based on kidney effects, the authors concluded that the Lowest Observable Adverse Effect Level (LOAEL) was 125 mg sodium tungstate/kg/day and the No Observable Adverse Effect Level (NOAEL) was 75 mg sodium tungstate/kg/day (McCain et al, 2009).

Sodium Tungstate Reproductive Toxicity Study

In a reproductive toxicity study conducted similar to EPA OPPTS 870.3650, 40 rats per sex were exposed for 70 days to 5, 62.5, 125, and 250 mg/kg/day sodium tungstate via oral gavage (McInturf et al, 2008 and 2011). Animals were dosed for a period of 70 days including 14 days prior to mating, a 14-day mating period, a 22-day gestation period, and through postnatal day (PND) 20.

Offspring (F1 generation) were monitored until PND70. In addition to standard reproductive and developmental assessments, a small battery of neurobehavioral exams was used to assess exposed dams and their offspring. No significant effects on reproductive success were reported following exposure to any of the doses.

Gestation lengths (22.08 +/- 0.089) in days for the 125 mg/kg/day group were significantly different ($p<0.05$; $n>37$) from controls (21.548 +/- 0.097); however, this effect is not considered to be toxicologically significant as the gestation length in the 125 mg/kg/day dose group is within historical control values. No effects on pup survival, M:F ratio, litter size, or clinical signs were observed in the F1 litters. No treatment-related effects were reported on the gestational weight gain in the dams, number of pups born, or physical birth defects. The results of the neurobehavioral

exams indicated that the righting reflex for male pups was generally faster than for female pups in both the low and high dose groups.

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 non-significant increase in the righting reflex among females. In addition, as a measure of separation distress, pups in the high dose treatment group vocalized significantly more than both control and low dose groups during the 60-second time period. As noted by the authors, only two neurobehavioral tests were used and they measured only very early, reflexive behavioral responses.

No histopathology effects were noted that indicate effects in the brain. Based on the results, the authors concluded 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 (McInturf et al, 2008 and 2011).

Based on the lack of toxicologically significant effects directly attributable to sodium tungstate, the NOAEL for both reproductive and developmental toxicity was considered to be 125 mg sodium tungstate/kg/day.

Mutagenicity / Genotoxicity Studies

A summary of some of mutagenicity studies that may have not been previously available is provided below. Please note that while a number of mutagenicity studies are presented in the REACH dossier for tungsten carbide, much of this data was previously available in the OECD SIDS document for tungsten carbide (OECD, 2005). Therefore, only the mutagenicity data that may not have been previously available are summarized below, and detailed summary of these studies is available on ECHA's website.

Overall, the weight of evidence on bacterial and mammalian *in vitro* systems demonstrates that insoluble and soluble tungsten substances are not genotoxic.

Tungsten Metal

- Negative in an *in vitro* bacterial reverse mutation assay conducted according to OECD 471 (Covance Laboratories Inc, 2004a)
- Negative in an *in vitro* chromosome aberration assay conducted according to OECD 473 (Covance Laboratories Inc, 2004b)
- Negative in an *in vitro* L5178Y TK +/- Mouse Lymphoma Forward Mutation Assay conducted according to OECD 476 (Covance Laboratories Inc, 2004c)

Tungsten Carbide

- Negative in an *in vitro* chromosome aberration assay conducted according to OECD 473 (Covance Laboratories Inc, 2008)

Sodium Tungstate

- Negative for mutagenicity in an *in vitro* bacterial reverse mutation assay conducted according to OECD 471 (Covance Laboratories Inc, 2004d)

- Negative in an *in vitro* chromosome aberration assay conducted according to OECD 473 (Covance Laboratories Inc, 2003)
- Negative in an *in vitro* L5178Y TK +/- Mouse Lymphoma Forward Mutation Assay conducted according to OECD 476 (Covance Laboratories Inc, 2004e)
- Negative in an *in vivo* micronucleus assay conducted according to OECD 474 (Covance Laboratories Inc, 2004f).

Tungsten Trioxide

- Negative for mutagenicity in an *in vitro* chromosome aberration assay conducted according to OECD Guideline 473. (IITRI, 2009)

Tungsten Blue Oxide

- Negative for mutagenicity in an *in vitro* bacterial reverse mutation assay conducted according to OECD 471 (ARC Seibersdorf Research GmbH-Environmental and Life Sciences Toxicology, 2003).

Derivation of an Inhalation DNEL for Sparingly Soluble Tungsten Substances for the Worker

REACH requires the registrant to develop a Derived No Effect Level (DNEL) for each substance being registered in accordance with ECHA Guidance (2010). The DNEL is equivalent to the relevant dose descriptor from the key study divided by the total Assessment Factor (AF) to account for inter- and intra-species variability, and differences in duration of exposure between the experimental animals and that of the human population.

An inhalation DNEL for the worker population was developed using ECHA's Guidance (2010) for derivation of DNELs. Inhalation was selected as the key worker protection criterion since mutagenicity / genotoxicity testing was negative. Based on a review of the available toxicity data, the key inhalation toxicity study was the 28-day inhalation toxicity study conducted on TBO (described above).

Using the data from the 28-day inhalation toxicity study, the doses utilized in the study needed to be modified to adjust for differences in experimental exposure conditions and those of the worker. The experimental animals were exposed for 6 hours per day, whereas workers are typically exposed for 8 hours per day. In addition, the starting dose needed to be modified to account for respiratory volume under standard conditions (6.7 m^3/person) versus under conditions of light activity for workers (10 m^3/person). Therefore, accounting for these differences, the adjusted dose used for the derivation of the inhalation DNEL is 330 mg TBO/m^3.

AFs were applied to the corrected dose from the 28-day toxicity study for calculation of the DNEL in accordance with ECHA's Guidance and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2010).

As indicated previously, the DNEL is equivalent to the relevant dose descriptor from the key study divided by the total AF. Therefore, using the corrected NOAEL of 330 mg/m^3 from the 28-day inhalation toxicity study and the corresponding AF of 45, the worker $DNEL_{long\text{-}term}$ for the inhalation

route is 7.3 mg TBO/m^3. The worker $DNEL_{long\text{-}term}$ for tungsten using the molecular formulas and molecular weights for TBO and tungsten is 5.8 mg tungsten/m^3.

This long-term inhalation DNEL is consistent with the current ACGIH threshold limit value (TLV) 8-hour time weighted average (TWA) for tungsten (as metal and insoluble compounds) of 5 mg tungsten/m^3 which is also the current NIOSH Recommended Exposure Limit (REL). The 5 mg tungsten/m^3 is also the ambient workplace standard for insoluble tungsten compounds in several European countries.

Although the methods and data from which the DNEL and the TLV were derived are different, the values derived are similar. Therefore, based on the comparison to the derived long-term inhalation DNEL, the current TLV of 5 mg/m^3 is protective of the worker and the current data does not suggest that this level needs to be revised.

Derivation of an Inhalation DNEL for Soluble Tungsten Substances for the Worker

Considering the lack of toxicologically significant effects clearly attributed to sodium tungstate in the reproductive study, the 90-day oral toxicity study was deemed as the key study and the kidney effects was the key endpoint from which the inhalation $DNEL_{long\text{-}term}$ was derived. Utilizing the kidney data from the McCain et al. (2009) 90-day oral toxicity study, Schell and Pardus (2009) used the US EPA's Benchmark Dose Software (BMDS, Version 1.4.1) to derive a benchmark dose low at the 10% response (BMDL10) for sodium tungstate.

From this analysis, the lowest (most precautionary) BMDL10 for the renal toxicity endpoint in the 90-day oral toxicity study was 102 mg/kg bw/day. Therefore, the BMDL10 of 102 mg/kg/day was used for derivation of the $DNEL_{long\text{-}term}$ for sodium tungstate.

The most significant route of exposure to the worker is the inhalation route. No repeated dose inhalation studies were available on sodium tungstate or other soluble tungsten substances; therefore, route-to-route extrapolation was used to extrapolate the oral BMDL10 derived from the 90-day oral toxicity study on sodium tungstate to an inhalation $DNEL_{long\text{-}term}$ for the worker.

Insufficient data are available on the bioavailability of sodium tungstate in rats versus humans for the oral route of administration. The default situation, in the absence of sufficient information, is to assume the same bioavailability for experimental animals and humans for a particular exposure route (ECHA, 2010).

For route-to-route extrapolation from an oral dose to an inhalation dose the starting point needs to be modified to correct for the breathing volume of the rat (0.38 m^3/kg) and respiratory volume under standard conditions (6.7 m^3/person) versus under conditions of light activity for workers (10 m^3/person) (ECHA, 2010). Based on ECHA's recommendations, it is assumed that respiratory absorption is equivalent between the animals and humans.

In addition, ECHA recommends in the absence of route-specific information on the starting route, to include a default factor of 2 (i. e. the absorption percentage for the starting route is half that of the end route) in the case of oral-to-inhalation extrapolation (ECHA, 2010). Application of these factors to the BMDL10 of 102 mg/kg/day results in a starting dose of 90 mg/m^3 (102 mg/kg/day x [1/0.38 m^3/kg] x [6.7m^3/10m^3] x 0.5).

As indicated previously, the DNEL is equivalent to the relevant dose descriptor from the key study divided by the total AF accounting for inter- and intra-species variability (2.5 and 3, respectively), differences in duration of exposure between the experimental animals and that of the human population (2), as well as an additional factor to account for the severity of the effect (2). Therefore, applying the total AF of 30 to the starting dose of 90 mg/m^3 results in an inhalation $DNEL_{long\text{-}term}$ for the worker of 3 mg sodium tungstate/m^3. The worker $DNEL_{long\text{-}term}$ for tungsten using the molecular formulas and molecular weights for sodium tungstate and tungsten is 1.7 mg tungsten/m^3.

This long-term inhalation DNEL for soluble tungsten substances is consistent with the ACGIH TLV of 1 mg tungsten/m^3 for soluble tungsten substances (which is also the current NIOSH REL). Therefore, based on the comparison to the derived long-term inhalation DNEL, the current TLV of 1 mg/m^3 for soluble tungsten substances is protective of the worker and the current data does not suggest that this level needs to be revised.

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Closing

Recent toxicological studies using soluble and insoluble tungsten substances have yielded results that are consistent with historical evaluations. Using the recent studies as a basis for worker protection demonstrates that the current TLVs of 5 mg tungsten/m^3 (for metal and insoluble tungsten compounds) and 1 mg tungsten/m^3 (for soluble tungsten compounds) are adequately protective.

Please contact me at +44 20 8996 2221 or via email (info@itia.info) if you have any questions or require further information.

Yours faithfully,

Dr Burghard Zeiler
Secretary-General

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