From: ITIA [mailto:info@itia.info]
Sent: 09 July 2013 15:14
To: 'science@acgih.org'
Cc: 'Burghard Zeiler'; rlemus@itia.info
Subject: Submission: Tungsten and Compounds (as Tungsten), ACGIH 2013 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), ACGIH 2013 Under Study List.

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Yours faithfully,

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9 July 2013

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

Dear TLV-CS Committee,

Subject: Tungsten and Compounds (as tungsten) – ACGIH 2013 Under Study List

As of 13 June 2013, ACGIH have listed tungsten and compounds (as tungsten) in the Under Study List (USL). As indicated, the USL 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 additional peer review publications sponsored by ITIA and the National Toxicology Program's (NTP) Range-Finding Report on sodium tungstate immunotoxicity which were published during 2012 and 2013.

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 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.

Background

In response to ACGIH 2012 USL for tungsten and compounds (as tungsten) and tungsten carbide, ITIA submitted a letter with several published and unpublished reports on 3 July 2012. The link to access ITIA's last submission to ACGIH is www.itia.info/assets/files/db/2012_acgih.pdf.

After ITIA's response submission, two of the key unpublished studies have been peer reviewed and recently published in scientific journals. One of them is a 28-day repeated dose inhalation study on tungsten blue oxide (CAS# 39318-18-8), and a second one is on the Derived No Effect Level (DNEL) on tungsten substances.

In addition, the US National Toxicology Program (NTP) in October 2012 released a range finding mice study results conducted to establish the potential effects of sodium tungstate dihydrate (CAS# 10213-10-2) on the immune system.

A brief summary of the two new scientific publications and the NTP's latest immunotoxicity findings on sodium tungstate are presented below.

Latest Peer Review Publications

1. **Toxicologic evaluation of tungsten: 28-day inhalation study of tungsten blue oxide in rats (Rajendran et al, 2012).**

   As part of the European Chemical Management Program referred to as REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) the ITIA sponsored an inhalation study as no repeated dose and toxicokinetic studies on sparingly soluble tungsten compounds with sufficient scientific reliability were identified.

   Based on bioavailability studies (data not shown here but final report was previously submitted by ITIA to ACGIH in 2012) conducted on five tungsten sparingly soluble tungsten compounds in alveolar, lysosomal, and interstitial synthetic fluids (as relevant fluids for inhalation exposure), tungsten blue oxide (TBO) was the most bioaccessible substance among the sparingly soluble tungsten substances tested.

   Accordingly, commercially available tungsten blue oxide (TBO), also known as tungsten oxide (CAS# 39318-18-8), was chosen as the test substance for a 28-day inhalation toxicity study which was published at the end of last year. The 28-day test was conducted in accordance with OECD Guideline 412 and under OECD-GLP to assess the systemic repeated dose inhalation toxicity of a sparingly soluble tungsten compound.

   ABSTRACT

   The toxicity and toxicokinetics of tungsten blue oxide (TBO) were examined. TBO is an intermediate in the production of tungsten powder, and has shown the potential to cause cellular damage in in vitro studies. However, in vivo evidence seems to indicate a lack of adverse effects. The present study was undertaken to address the dearth of longer-term inhalation toxicity studies of tungsten oxides by investigating the biological responses induced by TBO when administered via nose-only inhalation to rats at levels of 0.08, 0.325, and 0.65mg TBO/L of air for 6 h/day for 28 consecutive days, followed by a 14-day recovery period. Inhaled TBO was absorbed systemically and blood levels of tungsten increased as inhaled concentration increased. Among the tissues analyzed for tungsten levels, lung, femur and kidney showed increased levels, with lung at least an order of magnitude greater than kidney or femur. By exposure day 14, tungsten concentration in tissues had reached steady-state. Increased lung weight was noted for both terminal and recovery animals and was attributed to deposition of TBO in the lungs, inducing a macrophage influx. Microscopic evaluation of tissues revealed a dose-related increase in alveolar pigmented macrophages, alveolar foreign material and

individual alveolar foamy macrophages in lung. After a recovery period there was a slight reduction in the incidence and severity of histopathological findings. Based on the absence of other adverse effects, the increased lung weights and the microscopic findings were interpreted as nonadverse response to exposure and were not considered a specific reaction to TBO.

2. Development of worker inhalation derived no effect levels for tungsten compounds (Jackson et al, 2013).

REACH requires registrants to develop a Derived No Effect Level (DNEL) for workers and the general population for each potential route of exposure for each substance being registered. 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.

In Jackson's (2013) publication an inhalation DNEL for the worker population was developed using ECHA's Guidance for derivation of DNELs. The 28-day inhalation toxicity study on tungsten blue oxide published by Rajendran et al (2012) (see above) is the key study used to derive the long-term inhalation DNEL for workers.

ABSTRACT

Under the European Community (EC) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), the risk to humans may be considered controlled if the estimated exposure levels to a substance do not exceed the appropriate derived no-effect level (DNEL). In order to address worker exposure, DNELs are derived for the worker population. The most significant route of exposure to workers to both soluble and sparingly soluble tungsten substances is through inhalation. In order to meet the REACH registration requirements, occupational long-term inhalation DNELs were developed according to the European Chemical Agency (ECHA) REACH guidance on characterization of dose-response for human health. The inhalation $DNEL_{long\text{-}term}$ for sodium tungstate, from which all other soluble tungsten substance DNELs were derived, is 3mg sodium tungstate/m^3 (1.7mg W/m^3), and the inhalation $DNEL_{long\text{-}term}$ for tungsten blue oxide, from which all other sparingly soluble tungsten substance DNELs were derived, is 7.3mg tungsten blue oxide/m^3 (5.8mg tungsten/m^3). Although derived using different methodologies and supported by different studies, the occupational inhalation $DNELs_{long\text{-}term}$ for soluble and sparingly soluble tungsten compounds are similar to the current National Institute for Occupational Safety and Health (NIOSH) recommended exposure level (REL) and the American Conference of Industrial Hygienists (ACGIH) threshold limit value (TLV) 8-h time weighted average (TWA) of 1 mg tungsten/m^3 for soluble tungsten compounds and 5 mg tungsten/m^3 as metal and insoluble tungsten compounds.

3. NTP Range-Finding Report: Immunotoxicity of Sodium Tungstate Dihydrate in Female B6C3F1/N Mice (NTP, 2012).

The NTP conducted a dose range-finding study in female B6C3F1/N mice to establish the potential effects of sodium tungstate on the immune system. The mice were exposed to sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) at concentrations of 125, 250, 500, 1000 and 2000mg/L for 28-days via the drinking (tap) water.

Over the 28-day exposure period mice presented no effects on body weight, body weight gain or the weights of major immune system organs (thymus and the spleen). Total splenocyte number and both absolute values and percent values of spleen cell phenotypes were unaffected by $Na_2WO_4 \cdot 2H_2O$ exposure.

No effects were observed on several humoral immunity standard tests such as T-dependent antibody responses (TDAR), as evaluated using the antibody-forming cell (AFC) response, the sheep red blood cell (sRBC) enzyme-linked immunosorbent assay (ELISA), and the keyhole limpet hemocyanin (KLH) ELISA.

No dose-response significant differences were observed in two *ex vivo* cell-mediated assays (ie the mixed leukocyte response [MLR] and the cytotoxic T-lymphocyte [CTL] response). Furthermore, no effects were observed in two cell-mediated immunity tests, the *in vivo* delayed-type hypersensitivity (DTH) response to *C albicans* or in the anti-CD3 mediated proliferation assay.

Finally, innate immunity was not affected by $Na_2WO_4 \cdot 2H_2O$ exposure, as indicated by a lack of effect on both natural killer (NK) cell activity and the functional activity of the mononuclear phagocytic system (MPS).

Absolute bone marrow cell differentials were increased at the 2000mg/L dose for all markers evaluated, except for the $CD3^+$ population, which was unaffected. When evaluated as percent values, bone marrow cell differentials were unaffected overall, with the exception of an increase in TER-119^+cells at the highest dose of 2000 mg/L.

Overall, with the exception of effects on bone marrow differentials at the 2000mg/L dose level, $Na_2WO_4 \cdot 2H_2O$ did not adversely affect innate, humoral or cell-mediated immunity in female B6C3F1/N mice exposed via the drinking water.

Closing

Jackson et al (2013) recent peer review publication presented results that are consistent with historical evaluations conducted in 1977 by NIOSH on establishing 8-h TLV-TWA for soluble and insoluble tungsten compounds (NIOSH, 1977). Using the recently published inhalation toxicity study on tungsten blue oxide (Rajendran et al, 2012), and an unpublished oral study on sodium tungstate (McCain et al, 2009) as DNEL basis demonstrates that the current TLVs of 5mg

tungsten/m^3 (for metal and insoluble tungsten compounds) and 1mg tungsten/m^3 (for soluble tungsten compounds) are adequately protective.

In addition, based on NTP's immunotoxicity studies, sodium tungstate (one the most soluble forms of tungsten) did not adversely affect innate, humoral or cell-mediated immunity in female mice; however the biological relevancy of cell bone marrow differentials observed at high sodium tungstate doses would need to be assessed.

Please contact me at +1 804 852 4439 or via email (info@itia.info) if you have any questions or require further information.

Yours faithfully,

Ranulfo Lemus ScD, DABT
ITIA HSE Director

CC: Dr Burghard Zeiler, *ITIA Secretary-General*

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