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2 April 2015

Submitted Online - www.regulations.gov

US Department of Labor (DOL)
29 CFR Parts 1910, 1915, 1917, 1918, and 1926
[Docket No. OSHA 2012-0023]
RIN 1218-AC74

Occupational Safety and Health Administration (OSHA)
Chemical Management and Permissible Exposure Limits (PELs)
ACTION: Request for Information (RFI)

Dear Sirs,

Subject: Use of REACH Data to Support Occupational Exposure Assessments and Development of Permissible Exposure Levels

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 GmbH and Sandvik Machining Solutions AB, maintain extensive operations in the US. Details about ITIA and list of ITIA's 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 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.

ITIA supports the Agency's initiative to develop an effective and timely means for updating Permissible Exposure Limits (PELs). In response to OSHA' Request for Information, ITIA is submitting information, for your consideration, to answer the question – Should US Occupational Safety and Health Administration (OSHA) pursue efforts to obtain data from ECHA that companies are required to provide under the European Union's (EU) Regulation on the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) in support of updating Permissible Exposure Levels (PELs) for chemical substances? The information below provides an example of how information required by REACH regulations was used to calculate of a long term Derived No Effect Level (DNEL) for tungsten compounds. The DNEL is analogous to the Low-End Toxicity Exposure (LETE).

Executive Summary

The current OSHA's PELs for soluble and insoluble tungsten compounds are 1 and 5 mg W/m^3 as time weighed averages (TWA), respectively. These limits were based on the 1967 ACGIH Threshold Limit Values (TLVs) for soluble and insoluble tungsten compounds. The same limits were recommended by the National Institute for Occupational Safety and Health's (NIOSH) in its 1977 criteria document on Tungsten and Cemented Tungsten Carbide.

In 2010, the Tungsten Consortium developed a long term inhalation Derived No Effect Level (DNEL) for workers as a REACH registration requirement for several soluble and insoluble tungsten compounds. REACH defines the DNEL as "the level of exposure above which humans should not be exposed". Long-term inhalation DNELs were estimated using dose descriptor from recent key animal studies (not available for NIOSH to considered in 1977) divided by the total assessment factor as recommended by the European Chemicals Agency's (ECHA) REACH Guidance on Information Requirements and Chemical Safety Assessments to account for inter- and intra-species variability, and differences in duration of exposure between the experimental animals and that of the human population.

The Tungsten Consortium's DNEL derivation of soluble and insoluble tungsten compounds is described in great detail by Jackson et al (2013). This recent peer review publication presents results that are consistent with historical evaluations conducted in 1977 by NIOSH on establishing RELs for tungsten compounds. 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, 2010) as DNEL basis, it was demonstrated that the current PELs-TWA of 5 mg tungsten/m^3 (for metal and insoluble tungsten compounds) and 1 mg tungsten/m^3 (for soluble tungsten compounds) continue to be adequately protective after being recommended 38-years ago by NIOSH.

A. Background

The current OSHA's PELs-TWA, American Conference of Governmental Industrial Hygienist's (ACGIH) 8-h TLV-TWA, and NIOSH's RELs-TWA for soluble and insoluble tungsten compounds are 1 and 5 mg W/m^3, respectively (OSHA 2015a,b; NIOSH 2015a,b). The RELs were initially developed in 1977 by NIOSH (NIOSH, 1977), and while initially developed by NIOSH, these

occupational exposure limits are used by other agencies and/or countries, including some European countries as the basis to control worker exposure to tungsten compounds.
In 2010, the Tungsten Consortium developed a long-term inhalation DNEL for workers for tungsten compounds as required for the REACH registration. This DNEL REACH requirement revisited the NIOSH's RELs initially proposed in 1977 by taking into account recent inhalation and oral rodent studies. This tungsten compound long-term worker's DNELs were supported by the following key studies:

- A recently peer-review published inhalation toxicity study on tungsten blue oxide (Rajendran et al, 2012).
- An unpublished rat oral study on sodium tungstate sponsored by the US Army (McCain et al, 2010) [*Note: This study was recently submitted for peer-review publication considerations in the International Journal of Toxicology*].

This development of the tungsten long-term inhalation DNELs is described in great detail by Jackson et al (2013) a peer review publication that we are enclosing herein for your review and consideration.

In the sections below we briefly describe in the sections below the key considerations that the Tungsten Consortium took into account when estimating the long-term inhalation DNELs. This DNEL REACH requirement confirmed that the current TLVs of 1 and 5 mg tungsten/m^3 for soluble and insoluble tungsten compounds, respectively; continue to be adequately protective for individuals working in the Tungsten Industry.

B. Key developing considerations when estimating the tungsten long-term inhalation DNELs

DNELs are developed by Industry using ECHA's guidance (ECHA, 2012); the substance's lead registrant has the final decision on the selection of the key studies, endpoints of concern, and the assessment factors to account for sources of uncertainty. In the case of the REACH registrations, this was done as part of a collaborative process among the leading companies in the industry based on the existing science. By comparison, currently accepted occupational exposure levels (OELs), such as OSHA's PELs, NIOSH's RELs, or ACGIH TLVs, may have been derived using different methods, some of which incorporate economic and technical feasibility concerns and/or health-based assessment. Below we discuss the key considerations used to estimate the tungsten long-term inhalation DNELs following ECHA's Guidance on Information Requirements and Chemical Safety Assessments (ECHA, 2012).

1. Data availability

   Under REACH specific human health endpoints need to be fulfilled and to do this additional toxicological testing may have to be conducted to support the registration of chemicals. This new toxicological data may not have been available to the US OSHA, NIOSH or ACGIH when deriving the PELs, RELs or TLVs.

When estimating the DNELs, the Tungsten Consortium sponsored a new 28-day rat inhalation study on tungsten blue oxide (TBO) (Rajendran et al, 2012), and also make use of a 90-day rat oral study on sodium tungstate (Na_2WO_4) sponsored by the US Army (McCain et al, 2010) to fulfill REACH requirements for inhalation and oral repeated exposure toxicological endpoints. Both studies are the cornerstone of the inhalation long-term DNELs for soluble and insoluble tungsten compounds.

NIOSH based RELs on radiological examination of workers with pulmonary fibrosis exposed to tungsten. Using the weight of evidence from these key data along with other supporting animal data, NIOSH concluded that dusts of insoluble tungsten compounds pose a hazard somewhat greater than a nuisance dusts, and therefore exposure to insoluble tungsten compounds should be limited to below the respirable nuisance dust standard of 5 mg/m^3 (NIOSH, 1977). The TLV of 1 mg/m^3 for soluble tungsten compounds was based on a comparison between the available acute LD_{50} values for tungstic oxide and sodium tungstate in which a 3.5- fold difference was observed (NIOSH, 1977). Applying this 3.5-fold difference to the TLV of 5 mg/m^3 resulted in a limit of 1.4 mg/m^3. However, NIOSH (1977) determined that an increased margin of safety was needed beyond the 3.5-fold difference and recommended a limit of 1 mg/m^3 for soluble tungsten compounds.

2. Basis for benchmark value

One key difference between the OSHA's PELs and the Tungsten Consortium's DNELs for soluble tungsten compounds reside on the critical endpoint or point of departure selected. OSHA's PEL for soluble tungsten compounds are intended to protect against the accumulation of soluble compounds on the central nervous system (metabolic poison); whereas the DNEL critical endpoint for soluble tungsten compounds is kidney toxicity. For insoluble tungsten compounds both PEL and DNEL share the same critical effect of lung accumulation.

3. Default assumptions used to derive the DNEL values

The Tungsten Consortium long-term inhalation DNELs were estimated using dose descriptor from recent key animal studies divided by the total Assessment Factor (AF). These AF (or default/uncertainty factors) may differ from regulatory agency to the next one. Although the derivation of benchmark values allow for the use of scientific judgment in the selection of assessment/uncertainty factors, some of the default factors do differ. For example, ECHA's default AF to account for duration differences between the length of the study and actual exposure includes an AF of 2 when extrapolating from a sub-chronic study to chronic exposure and an AF of 6 when extrapolating from a sub-acute study to chronic exposure. Typically, other regulatory agencies traditionally use a default value of 10 when extrapolating from a sub-chronic study to chronic exposure.

Jackson et al (2013) describes the AF used when estimating the long-term inhalation DNELs and these are presented in the following summary table:

Parameter/Assessment Factor	Soluble Tungsten	Insoluble Tungsten
Starting Dose	90 mg Na_2WO_4/m^3	330 mg TBO/m^3
Inter-species	2.5	2.5
Intra-species	3	3
Exposure duration	2	6
Severity of Effect	2	--
Total AF	30	45
Long-term inhalation DNEL†	3 mg Na_2WO_4/m^3 (equivalent to 1.7 mg W/ m^3)	7.3 mg TBO/m^3 (equivalent to 5.8 mg W/ m^3)

†DNEL= Starting Dose/Total AF; Na_2WO_4: sodium tungstate; TBO: tungsten blue oxide

When adjusting the sodium tungstate and tungsten blue oxide DNELs by the tungsten molecular weight, the DNEL (as W) are in the same order of magnitude (1.7 and 5.8 mg W/m^3) than the respective PELs (1 and 5 mg W/m^3).

C. Closing

The current OSHA's PELs for soluble and insoluble tungsten compounds are 1 and 5 mg W/m^3 time weighed average (TWA), respectively; and are based on the 1967 ACGIH TLVs for soluble and insoluble tungsten compounds. The same limits were recommended by the 1977 NIOSH's RELs criteria document.

For REACH registration purposes the Tungsten Consortium developed inhalation long term DNELs for workers for soluble and insoluble tungsten compounds. The DNELs were estimated using dose descriptor from two rodent studies not available to NIOSH in 1977.

The Tungsten Consortium's derivation of DNELs for soluble and insoluble tungsten compounds is described in great detail by Jackson et al (2013). This recent peer review publication presents results that are consistent with NIOSH 1977's RELs criteria document for tungsten compounds. Using these recent toxicity studies as the DNEL basis, it was demonstrated that the current PELs-TWA of 1 and 5 mg tungsten/m^3 for soluble and insoluble compounds, respectively; continue to be adequately protective after being recommend by NIOSH 38-years ago. In conclusion, ITIA supports the idea of sharing information and having similar interpretation of the data in both the EU and the US. We believe that information developed for REACH registration purposes can be used to support occupational exposure assessments and Permissible Exposure Limits.

We hope that this information will be helpful to you. 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,

Ranulfo Lemus ScD, DABT
Health, Safety & Environmental Director

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

Enc: Peer Review Publication of "Development Of Worker Inhalation Derived No Effect Levels For Tungsten Compounds

Citable Material

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Journal of Toxicology and Environmental Health, Part B: Critical Reviews
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uteb20

Development Of Worker Inhalation Derived No Effect Levels For Tungsten Compounds

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To cite this article: Mark Jackson , Ranulfo Lemus-Olalde , Christina Inhof , Carmen Venezia & Michael Pardus (2013): Development Of Worker Inhalation Derived No Effect Levels For Tungsten Compounds, Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 16:2, 114-126

To link to this article: http://dx.doi.org/10.1080/10937404.2013.775050

Journal of Toxicology and Environmental Health, Part B, 16:114–126, 2013

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937404.2013.775050

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DEVELOPMENT OF WORKER INHALATION DERIVED NO EFFECT LEVELS FOR TUNGSTEN COMPOUNDS

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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 3 mg sodium tungstate/m^3 (1.7 mg 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 7.3 mg tungsten blue oxide/m^3 (5.8 mg 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.

Most exposures to tungsten (W) and its compounds in occupational environments occur during production of W metal from the ore, and preparation of tungsten carbide (WC) powders (ATSDR, 2005). In these occupation environments, the inhalation route of exposure is of greatest concern and W-specific occupational exposure limits have been developed. The current U.S. occupational recommended exposure level (REL) and threshold limit value (TLV) 8-h time weighted average (TWA) for soluble W and W as metal and insoluble compounds are 1 and 5 mg W/m^3, respectively (NIOSH, 2010; ACGIH, 2012). The RELs were initially developed in 1977 by the National Institute for Occupational Safety and Health (NIOSH, 1977) and serve as the basis for the American Conference of Industrial Hygienists (ACGIH) TLV. While initially developed by NIOSH, these occupational exposure limits are used by other countries, including some European countries such as the United Kingdom, as the basis to control worker exposure to W and W-compounds. Although these

The authors are grateful to the staff of IIT Research Institute (IITRI), the U. S. Army Center for Health Promotion and Preventative Medicine, for conducting many of the key studies used for derivation of the DNELs. Funding for some the research presented in this article was provided by the Tungsten REACH Consortium. All studies and results were developed in support of registration of tungsten compounds in accordance with the EU legislation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

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RELs are currently being used to control exposures to W and W-compounds and were initially proposed in 1977, these values have not yet been reassessed to determine whether the use of more current data and information would result in different exposure limits.

Under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), the European Community regulation on chemicals and their safe use, manufacturers, importers, and downstream users need to ensure that they manufacture, import, market, or use a substance in a manner that does not adversely affect the environment or human health (EC, 2006). REACH requires that manufacturers and importers are responsible for evaluating whether any environmental or human health hazards for a given substance are controlled during the life cycle (manufacture, use, and disposal) of that substance (EC, 2006).

REACH defines the derived no-effect level (DNEL) as the level of exposure above which humans should not be exposed. In the Chemical Safety Assessment (CSA) for a substance, the exposure of each human population known to be or likely to be exposed is compared with the appropriate DNEL. The risks to humans can be considered to be controlled if the estimated exposure levels do not exceed the appropriate DNEL. A DNEL (or DNELs) needs to be derived for all compounds subject to registration that are manufactured, imported, or used in quantities of 10 tonnes or more per year (ECHA, 2012). The DNELs need to reflect the likely route(s), duration, and frequency of exposure (ECHA, 2012).

In order to meet the requirements under REACH, Chemical Safety Reports (CSRs) were submitted to the European Chemicals Agency (ECHA) for specific soluble (sodium tungstate, ammonium metatungstate, and ammonium paratungstate) and sparingly soluble tungsten compounds (tungsten carbide, fused tungsten carbide, tungsten metal, tungstic acid, tungsten trioxide, and tungsten blue oxide). Although W has a long history of use, there was a lack of long-term toxicity data available from which a DNEL could be derived for each of the W-compounds. Of these nine W compounds, adequate repeated-dose toxicity data were only available for sodium tungstate (Na_2WO_4) and tungsten blue oxide (TBO), and these two compounds were the basis for the derivation of the DNEL for soluble and sparingly soluble compounds. The methodology and key data used to derive the inhalation DNEL for both Na_2WO_4 and TBO are detailed herein. Because of the requirements under REACH to compile and critically evaluate the most up-to-date and available toxicological data for the development of DNELs, comparing these inhalation DNELs to the relevant REL/TLV can confirm the protection that these exposure control limits currently offer to workers in the W industry.

The DNELs for soluble and sparingly soluble W compounds were developed according to Chapter 8 of ECHA's REACH "Guidance on Information Requirements and Chemical Safety Assessment—Characterisation of Dose [Concentration]-Response for Human Health" (ECHA, 2012). Briefly, the DNEL development followed these steps: (1) identification of appropriate toxicity endpoints; (2) identification of critical effects and key toxicity studies; (3) calculation of starting dose; and (4) selection of assessment factors. Once the starting dose was identified from the key study based on the critical effect, this starting dose was divided by the applicable assessment factors. The resulting worker DNELs were then compared to the available occupational limits for tungsten. These steps are described in more detail in the following.

INHALATION WORKER DNEL DERIVATION FOR SOLUBLE W COMPOUNDS

Repeat-dose toxicity data are available for only a few W compounds. In water, Na_2WO_4 produces soluble ionic tungstate (WO_4^{-2}), which is the common ion among the W compounds of interest. Because Na_2WO_4 has higher water solubility in comparison to other W compounds, and hence likely higher bioavailability, Na_2WO_4 has become one of the more studied W-containing compounds.

Identification of Appropriate Toxicity Endpoint

Under REACH, the DNELs need to reflect the likely route(s), duration, and frequency of exposure (ECHA, 2012). For the worker population, the oral route is not considered to be a relevant route of exposure for purposes of derivation of a DNEL (ECHA, 2012). Although the dermal route is a relevant route of exposure for workers and was derived in support of REACH, the inhalation route of exposure is considered the most significant route of exposure and is the focus of this review. Based on the available acute toxicity data for inhalation and dermal routes, Na_2WO_4 is not classified under the European Union (EU) classification, labeling, and packaging (CLP) regulation (EC, 2008) as an acute dermal or inhalation toxicant (Table 1). The acute oral toxicity data dictate a Category 4 classification under CLP, which suggests that Na_2WO_4 is more toxic through the oral route than through the inhalation or dermal routes of exposure. In accordance with ECHA (2012), unless a substance has been classified as an acute toxicant, an acute DNEL does not need to be developed. Because Na_2WO_4 was not classified as an acute inhalation or dermal toxicant, and the oral route is not relevant for the worker population, an acute DNEL was thus not derived. Na_2WO_4 was not classified as a skin or eye irritant, and was not sensitizing to the skin in standard tests (Table 1); therefore, derivation of a DNEL for local effects is not required (ECHA, 2012). Na_2WO_4 was negative for mutagenicity in various in vitro and in vivo mutagenicity studies (Table 1). Based on the lack of mutagenicity and no evidence of hyperplasia and/or preneoplastic lesions in the repeated-dose oral toxicity studies with Na_2WO_4, development of a derived minimal effect level (DMEL) for nonthreshold toxicity (e.g., carcinogenicity, mutagenicity) is not required (ECHA, 2012). Therefore, the inhalation $DNEL_{long\text{-}term}$ is expected to be sufficient to control any potential risks associated with inhalation exposure by workers to Na_2WO_4.

TABLE 1. Summary of the Toxicological Data Set For Sodium Tungstate

Endpoint	Guideline[a]	Species	Results	Classification under CLP	Reference
Acute oral toxicity	OECD 401	Rats	LD50 = 1453 mg/kg	Category 4	Huntingdon Life Sciences Ltd., 1999a
Acute dermal toxicity	OECD 402	Rats	LD50 > 2000 mg/kg	Not classified	Huntingdon Life Sciences Ltd., 1999b
Acute inhalation toxicity	OECD 403	Rats	LC50 > 5.01 mg/L	Not classified	Huntingdon Life Sciences Ltd., 1998
Skin irritation	OECD 404	Rabbits	Not irritating	Not classified	Huntingdon Life Sciences Ltd., 1999c
Eye irritation	OECD 405	Rabbits	Slightly irritating	Not classified	Huntingdon Life Sciences Ltd., 1999d
Skin sensitization	OECD 406	Guinea pigs	Not sensitizing	Not classified	Huntingdon Life Sciences Ltd., 1999e
Mutagenicity	OECD 471 (in vitro), OECD 473 (in vitro), OECD 476 (in vitro), OECD 474 (in vivo)	Mice (in vivo)	Negative	Not classified	Covance Laboratories Inc., 2004a Covance Laboratories Inc., 2003 Covance Laboratories Inc., 2004b Covance Laboratories Inc., 2004c Reddy et al., 2007
Repeat-dose toxicity	40 CFR 798.2650	Rats	NOAEL = 75 mg/kg LOAEL = 125 mg/kg	Not classified	McCain et al., 2009
Reproductive toxicity	U.S. EPA OPPTS 870.3650	Rats	NOAEL = 125 mg/kg/day	Not classified	McInturf et al., 2008, 2011

[a]The guidelines followed include several from the Organisation for Economic Cooperation and Development (OECD) Guidelines for Testing of Chemicals series, a U.S. Environmental Protection Agency (EPA) guideline on subchronic oral toxicity published in the U.S. Code of Federal Regulations (40 CFR 798.2650), and a U.S. EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) harmonized test guideline on reproductive toxicity (OPPTS 870.3650).

Identification of Critical Effect and Key Toxicity Studies

Based on the available data just summarized, derivation of a $DNEL_{long\text{-}term}$ would be sufficiently protective of any potential risks associated with Na_2WO_4. In accordance with ECHA's Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2011), the available data that were evaluated as part of the CSA were assessed for reliability using the procedures of Klimisch et al. (1997). According to Klimisch et al. (1997), those studies that were conducted according to standard test guidelines and performed according to good laboratory principles (GLP) are considered to be more reliable than those that are not conducted using standard methods.

Based on the review of the available literature, only two repeated-dose studies of sufficient quality were available on Na_2WO_4 from which a $DNEL_{long\text{-}term}$ could be derived: a 90-d repeated-dose oral toxicity study in rats (McCain et al., 2009), and a reproductive toxicity study (McInturf et al., 2008; 2011) in rats.

The 90-d repeated-dose toxicity study was conducted in accordance with 40 CFR 798.2650 (McCain et al., 2009). Male and female Sprague-Dawley rats were given 10, 75, 125, or 200 mg Na_2WO_4/kg/day by oral gavage (7 d/wk) for 90 d. 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/d dose groups. Based on kidney effects, data indicated that the lowest-observable-adverse-effect level (LOAEL) was 125 mg Na_2WO_4/kg/d and the no-observable-adverse-effect level (NOAEL) was 75 mg Na_2WO_4/kg/d (McCain et al., 2009). Utilizing the kidney data from the McCain et al. (2009) 90-d oral toxicity study, Schell and Pardus (2009) used the U.S. Environmental Protection Agency (EPA) Benchmark Dose Software (BMDS, Version 1.4.1) to derive a benchmark dose low at the 10% response (BMDL10) for Na_2WO_4. From this analysis, the lowest (most precautionary) BMDL10 for the renal toxicity endpoint in the 90-d oral toxicity study was 102 mg/kg body weight (bw)/d.

In the reproductive toxicity study, 40 rats per gender were exposed for 70 d to 5, 62.5, 125, or 250 mg/kg/d Na_2WO_4 via oral gavage (McInturf et al., 2008, 2011). Animals were dosed for a period of 70 d, including 14 d prior to mating, a 14-d mating period, a 22-d 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/d group were significantly different ($n > 37$) 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/d dose group is within historical control values. No marked effects on pup survival, M:F ratio, litter size, or clinical signs were observed in the F1 litters. No significant 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 numerical 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-s time period. As noted by McInturf et al. (2008, 2011), only two neurobehavioral tests were used and these measured only very early, reflexive behavioral responses.

No histopathology effects were noted that indicate effects in the brain. Based on the results, it was concluded that Na_2WO_4 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, 2011). Based on the lack of toxicologically significant effects directly attributable to Na_2WO_4, the NOAEL for both reproductive and developmental toxicity was considered to be 125 mg Na_2WO_4/kg/d.

Considering the lack of toxicologically significant effects clearly attributed to Na_2WO_4 in the reproductive study, the 90-d oral toxicity study was deemed the key study and the kidney effects was the key endpoint from which the oral $DNEL_{long\text{-}term}$ was derived. Therefore, the BMDL10 of 102 mg/kg/d was used for derivation of the oral $DNEL_{long\text{-}term}$ for Na_2WO_4.

Calculation of Starting Inhalation Dose

As stated previously, the most significant route of exposure to the worker is the inhalation route. No repeated-dose inhalation studies were available on Na_2WO_4 or other soluble W compounds; therefore, route-to-route extrapolation was used to extrapolate the oral BMDL10 derived from the 90-d oral toxicity study on Na_2WO_4 to an inhalation $DNEL_{long\text{-}term}$ for the worker. Insufficient data are available on the bioavailability of Na_2WO_4 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, 2012).

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, 2012). Based on ECHA's recommendations, it is assumed that respiratory absorption is equivalent between animals and humans. In addition, ECHA recommends, in the absence of route-specific information on the starting route, including 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, 2012). Application of these factors to the BMDL10 of 102 mg/kg/d resulted in a starting dose of 90 mg/m^3 (102 mg/kg/d $\times$ [1/0.38 m^3/kg] $\times$ [6.7 m^3/10 m^3] $\times$ [1/2]).

Selection of Assessment Factors

In accordance with ECHA's Guidance R.8 (ECHA, 2010), assessment factors (AF) need to be applied to account for differences between the experimental data and human exposure. The AF used in the derivation of a DNEL account for interspecies and intraspecies differences, exposure duration differences, issues related to dose response, and the overall quality of the toxicity database for a substance.

The interspecies AF is the product of an allometric scaling (AS) factor and an additional factor of 2.5. However, when the starting dose descriptor is an inhalation dose, an AS factor is not required. Therefore, only an interspecies factor of 2.5 was used (ECHA, 2012).

ECHA's default AF for intraspecies variation for the worker population is 5 (ECHA, 2012); however, in order to be consistent with procedures used by other REACH consortia in the derivation of DNEL for other metal compounds, the Eurometaux (2010) recommended AF of 3 for intraspecies variability for the worker population was used in the derivation of the DNEL for Na_2WO_4. The AF of 3 as recommended by Eurometaux (2010) was taken directly from an assessment conducted by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) and presented in its technical report on the Guidance on Assessment Factors to Derive a DNEL (ECETOC, 2010). The ECETOC AF of 3 for intraspecies variability for workers is based on a detailed analysis and comparison of the data sets of Hattis et al. (1987, 1999) and Renwick and Lazarus (1998) to estimate the total intraspecies variability

for toxicokinetic and toxicodynamic parameters. This AF of 3 is recommended for the more homogeneous worker population as in this cohort; the more susceptible groups are typically excluded and/or may be protected from specific exposures. Therefore, the normal industrial hygiene practices that are required in the workplace may serve to compensate in the management of risk, and lower values of the AF for intraspecies variability are considered appropriate (ECETOC, 2003).

The ECHA-recommended AF for extrapolation from a subchronic toxicity study to a chronic exposure is 2 (ECHA, 2012). In addition, ECHA (2012) allows for the addition of an assessment factor that can be used to account for "exceptional cases of serious effects." ECHA's Guidance on DNEL Development also recommends using a BMD5, and "if other BMD indicators are used, e.g., a BMD10, it should be considered on a case-by-case basis whether an additional dose-response assessment factor is needed." Because of the severity of the effect reported in the 90-d oral toxicity study on Na_2WO_4, that is, kidney toxicity, and because a BMDL10 and not a BMD5 was derived by Schell and Pardus (2009), an additional AF of 2 was used. Therefore, the total AF used to derive the systemic $DNEL_{long\text{-}term}$ from the 90-d oral toxicity data was 30 ($2.5 \times 3 \times 2 \times 2$).

Derivation of Long-Term Inhalation DNEL

In accordance with ECHA's Guidance (ECHA, 2012), the DNEL is equivalent to the relevant dose descriptor from the key study divided by the total AF. Using the adjusted BMDL10 of 90 mg/m^3 for the kidney toxicity data from the 90-d oral toxicity study on Na_2WO_4 and the corresponding AF of 30, the $DNEL_{long\text{-}term}$ was 3 Na_2WO_4/m^3 (1.7 mg tungsten/m^3). DNEL for other soluble W substances such as ammonium metatungstate and ammonium paratungstate were calculated based on the molecular weight of the substance as well as number of moles of W in the substance to yield an equivalent of 1.7 mg W/m^3 (Table 2). Based on comparisons of available acute toxicity data on ammonium metatungstate, ammonium paratungstate, and sodium tungstate (data not shown on ammonium metatungstate and ammonium paratungstate), use of sodium tungstate as a surrogate for chronic toxicity is appropriate. A specific read-across strategy was developed in support of REACH registration documenting these comparisons, but is not included as part of this review.

INHALATION WORKER DNEL DERIVATION FOR SPARINGLY SOLUBLE W COMPOUNDS

Adequate repeated-dose toxicity data were not available for any of the sparingly soluble W compounds being registered under REACH. Therefore, in vitro testing bioaccessibility (data not shown) was conducted on several sparingly soluble W compounds in alveolar and lysosomal synthetic fluids (as relevant fluids for inhalation exposure) (IITRI, 2010). Data indicated that TBO was the most bioaccessible sparingly soluble W substance. Based on these results, TBO was selected as the test substance for a 28-d inhalation toxicity study conducted in accordance with OECD Guideline 412 and under Good Laboratory Practices (GLP) to assess the systemic long-term toxicity of sparingly soluble tungsten compounds (Rajendran et al., 2012). The composition of TBO (WO_n, where $n = 2.99 - 2.90$) is variable depending on the conditions under which it is formed. For purposes of the 28-d inhalation toxicity study, the most commonly used commercial form ($WO_{2.9}$, molecular weight of 230) was tested.

Identification of Appropriate Toxicity Endpoint

As indicated previously, the inhalation route is the most likely route of exposure to TBO for workers. In accordance with ECHA (2012), unless a substance has been classified as an acute toxicant, an acute DNEL does not need to be developed. Based on the available acute toxicity data (oral, dermal, inhalation), TBO is not likely an acute toxicant and therefore derivation of $DNEL_{acute}$ is not required (Table 3).

TABLE 2. Summary of Long-Term Inhalation DNELs

Tungsten substance	CAS number	Long-term inhalation DNEL (mg/m^3)[a]	Molecular weight (g)	Molecular formula
Soluble substances[b]				
Sodium tungstate	13472-45-2	3 mg sodium tungstate/m^3	330	$Na_2WO_4 \cdot 2H_2O$
APT	11120-25-5	2.4 mg APT/m^3	3132	$[(NH_4)_{10}\ H_2W_{12}O_{42}] \cdot 4H_2O$
AMT	12028-48-7	2.2 mg AMT/m^3	2956	$[(NH_4)_6(H_2W_{12}O_{40})] \cdot 3H_2O$
Sparingly soluble substances				
TBO	39318-8-8	7.3 mg TBO/m^3	232	WO_3
Tungsten trioxide	1314-35-8	7.3 mg WO_3/m^3	232	WO_3
Tungsten metal	7440-33-7	5.8 mg W/m^3	184	W
Tungsten carbide	12070-12-1	6.2 mg WC/m^3	196	WC
Fused tungsten carbide	12070-13-2	6 mg W_2C/m^3	380	W_2C
Tungstic acid	7783-03-1	7.9 mg H_2WO_4/ m^3	250	H_2WO_4

[a]DNELs for APT, AMT, WO_3, tungsten metal, WC, W2C, and tungstic acid were calculated by adjusting the DNEL for the base substance (sodium tungstate for soluble tungsten substances and TBO for sparingly soluble substances) by the molecular weight of the substance and the number of moles of W in the substance. Example: 3 mg sodium tungstate/m^3 × (1 mol sodium tungstate/330 g) × (1 mol W/1 mol sodium tungstate) × (1 mol APT/12 mol W) × (3132 g/1 mol APT) = 2.4 mg APT/m^3.

[b]Converting the DNELs of sodium tungstate, APT, and AMT to mg W results in a DNEL of 1.7 mg/m^3.

TABLE 3. Summary of Mammalian Toxicological Studies for TBO

Endpoint	Guideline	Species	Results	Classification under CLP	Reference
Acute oral toxicity	OECD 423	Rats	LD50 > 2000 mg/kg	Category 4	ARC Seibersdorf Research GmbH–Environmental and Life Sciences Toxicology, 2003a
Acute dermal toxicity	OECD 402[a]	Rats	LD50 > 2000 mg/kg	Not classified	Huntingdon Life Sciences Ltd., 1999b
Acute inhalation toxicity	OECD 403[b]	Rats	LC50 > 5.36 mg/L	Not classified	ARC Seibersdorf Research Environmental and Life Sciences Toxicology, 2002a
Skin irritation	OECD 404[b]	Rabbits	Not irritating	Not classified	ARC Seibersdorf Research GmbH–Environmental Life Sciences and Toxicology, 2002b
Eye irritation	OECD 405	Rabbits	Not irritating	Not classified	ARC Seibersdorf Research GmbH–Environmental and Life Sciences Toxicology, 2003b
Skin sensitization	OECD 406[b]	Guinea pigs	Not sensitizing	Not classified	ARC Seibersdorf Research GmbH–Environmental and Life Sciences Toxicology, 2002c
Mutagenicity	OECD 471 (in vitro), OECD 473[b] (in vitro), OECD 476[a] (in vitro), OECD 474[a] (in vivo)	Mice (in vivo)	Negative	Not classified	ARC Seibersdorf Research GmbH–Environmental and Life Sciences Toxicology, 2003c IIT Research Institute, 2009 Covance Laboratories, Inc., 2004b Covance Laboratories, Inc., 2004c
Repeat-dose toxicity	OECD 412	Rats	NOAEL > 0.65 mg/L	Not classified	Rajendran et al., 2012

[a]Data from sodium tungstate were used for read across to TBO for this endpoint.

[b]Data on tungsten trioxide were used for read across to TBO for this endpoint.

In addition, based on the available data, TBO is not likely to be irritating to either the eyes or skin, or sensitizing to the skin (Table 3); therefore, derivation of a DNEL for local effects is not required (ECHA, 2012). The in vitro and in vivo mutagenicity data set for TBO suggests that TBO is not mutagenic (Table 3). Based on the lack of mutagenicity and no evidence of hyperplasia and/or preneoplastic lesions in the repeated-dose inhalation toxicity study with TBO, development of a DMEL for nonthreshold toxicity (e.g., carcinogenicity, mutagenicity) is not required. Therefore, the inhalation $DNEL_{long\text{-}term}$ is expected to be sufficient to control any potential risks associated with inhalation exposure of TBO to the worker.

Identification of Critical Effects and Key Toxicity Studies

The only repeat-dose toxicity study available for TBO was a 28-d repeat-dose inhalation toxicity study with rats conducted in accordance with OECD Guideline 412. In this study, 5 rats per gender per dose were given TBO nose-only for 6 h/d, 7 d/wk, for 28 d at doses of 0 (control), 0.08, 0.325, or 0.65 mg TBO/L air. The exposure concentrations were selected based on guidance values recommended by CLP Regulation EC 1272/2008 (EC, 2008) to classify compounds as specific target organ toxicity (STOT)—repeated exposure. Briefly, the guidance values refer to effects seen in a standard 90-d toxicity study conducted in rats. They may be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. For a 28-d study the guidance values were increased by a factor of 3 as recommended under the CLP regulation.

Using the Guyton (1947) formula (where respiratory vol/min in mL $= 2.10 \times [\text{weight(g)}]^{0.75}$) these animal exposure concentrations represent estimated rat inhalable TBO doses of 15, 62, and 124 mg/kg-d that correspond to approximately 39, 157, or 315 times the inhalable dose of tungsten for a person working under the tungsten (as metal and insoluble compounds) TLV of 5 mg/L.

No toxicologically significant effects were reported, and therefore the NOAEL was deemed to be greater than 0.65 mg TBO/L air (650 mg TBO/m^3). For purposes of derivation of the DNEL, as a conservative assumption the NOAEL was assumed to be equal to 650 mg TBO/m^3.

Calculation of Starting Inhalation Dose

In order to account for the differences between exposure conditions in the 28-d inhalation toxicity study and those of the worker, the dose descriptor needed to be modified accordingly. The experimental animals were exposed for 6 h/d, whereas workers are typically exposed for 8 h/d. In addition, the starting dose needed to be modified to correct 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 corrected dose used for the derivation of the inhalation DNEL is 330 mg TBO/m^3 (650 mg TBO/m^3 $\times$ 6 h/8 h $\times$ 6.7 m^3/10 m^3).

Selection of Assessment Factors

The same interspecies and intraspecies AFs (2.5 and 3, respectively) that were used in the derivation of the inhalation DNEL for Na_2WO_4 were also used in the derivation of the inhalation DNEL for TBO.

The ECHA-recommended AF for extrapolation from a subacute study to chronic endpoint is 6. Therefore, the overall AF used to derive the systemic $DNEL_{long\text{-}term}$ for the inhalation route for the worker was 45 ($2.5 \times 3 \times 6$).

Derivation of Long-Term Inhalation DNEL

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-d 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 (5.8 mg W/m^3). DNELs for other sparingly soluble W substances such as tungsten carbide, fused tungsten carbide, tungstic acid, and tungsten trioxide were calculated based on the molecular weight of the substance as well as number of moles of W in the substance to yield an equivalent of 5.8 mg W/m^3 (Table 2). Based on comparison of the available acute toxicity data on tungsten carbide, fused tungsten carbide, tungstic acid, tungsten trioxide, and TBO, the use of TBO as a surrogate for chronic toxicity is appropriate. A specific read-across strategy was developed in support of REACH registration documenting these comparisons but is not included as part of this review.

Using the procedures consistent with the ECHA Guidance (2012) for derivation of DNEL, the inhalation long-term DNELs for the worker population for Na_2WO_4 (soluble tungsten substance) and TBO (sparingly soluble tungsten substance) are 3 mg Na_2WO_4/m^3 and 7.3 mg TBO/m^3, respectively. These inhalation DNELs for Na_2WO_4 and TBO were then used to derive DNELs for other soluble and sparingly soluble tungsten substances. When the DNELs for Na_2WO_4 and TBO are converted to milligrams W per cubic meter, the values of 1.7 and 5.8 mg tungsten/m^3 are consistent with the current U.S. occupational REL and TLV 8-h TWA for soluble tungsten and tungsten (as metal and insoluble compounds) of 1 and 5 mg W/m^3, respectively (ACGIH, 2012).

Although the inhalation DNEL and the REL/TLV for soluble and sparingly soluble W compounds are similar, data and methods on which they were developed are different. The REL of 5 mg W/m^3 is based on an assessment conducted by NIOSH in which the available epidemiological and animal toxicological data were evaluated (NIOSH, 1977). The majority of the available epidemiological data was based on exposures from dusts in the production of cemented WC. Two of the key epidemiological studies used to support the REL investigated occupational exposure to W and compounds without concurrent exposure to cobalt (Mezentseva, 1967; Kaplun and Mezentseva, 1959). Based on radiological examination of workers exposed to W, there was an increased incidence of 9–11% in pulmonary fibrosis in the exposed workers. Using the weight of evidence from these key data along with other supporting animal data, NIOSH concluded that dusts of insoluble W compounds pose a hazard somewhat greater than a nuisance dusts, and therefore exposure to insoluble W compounds should be limited to below the respirable nuisance dust standard of 5 mg/m^3 (NIOSH, 1977). While the effects reported in the two key studies were used to support the conclusion that insoluble W compounds represent a hazard slightly greater than that of a nuisance dust, the exposure concentrations were not specifically used to derive the REL. The concentration range as reported in the study by Mezentseva (1967) was from 1.3 to 83 mg/m^3, whereas in the study by Kaplun and Mezentseva (1959) it was from 8.6 to 106 mg/m^3.

In accordance with ECHA Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2011), each study being evaluated as part of the CSA is assessed for reliability using the procedures of Klimisch et al., (1997). Based on the data as presented in the NIOSH (1977) report as well as the Mezentseva (1967) study, there were insufficient details provided on which to adequately evaluate the quality of the studies. Insufficient details were provided on how the concentrations of W were measured, which compounds were analyzed in the measurements, and the depth of questions the workers were asked to reduce any confounding factors. Based on the lack of sufficient details provided as well as the large range in concentrations reported, these studies are not sufficient on which to derive a DNEL.

In addition, the TLV of 1 mg/m^3 for soluble W compounds was based on a comparison between the available acute LD50 values for tungstic oxide and Na_2WO_4 in which a 3.5-fold difference was observed (NIOSH, 1977). Applying this 3.5-fold difference to the TLV of 5 mg/m^3 resulted in a limit of 1.4 mg/m^3. However, NIOSH (1977) determined that an increased margin of safety was needed beyond

the 3.5-fold difference and recommended a limit of 1 mg/m^3 for soluble W compounds.

While the inhalation DNELs for the worker population for representative soluble and sparingly soluble W compounds were derived using data and methods different than those used in the development of the current TLV for tungsten compounds, the resulting limits are similar. Based on the comparison of these limits, the current TLV for tungsten compounds appear to be adequately protective of worker health.

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