



International Tungsten Industry Association

The Tungsten Reference Dose (RfD)

**Beyond Science and Decisions:
From Problem Formulation to Risk Assessment
Virtual Workshop XVI**

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Background

- Tungsten (W) is a rare metal used in numerous industrially important products, notably in machine tools, catalysts, and superalloys.
 - Most notably hard metals used in cutting and drilling tools.
- W^{+6} is the most common formal oxidation state of tungsten but exhibits all oxidation states from -2 to $+6$.
- The most water-soluble form of tungsten is tungstate (WO_4^{-2}).
- Tungsten was selected for study under the National Toxicology Program (NTP), and in 2011, it was nominated by the US EPA for risk assessment under the Integrated Risk Information System (IRIS) program.

Soluble Tungsten Compounds Provisional Peer-Review Toxicity Value (PPRTV)

- The [2015 PPRTV](#) document has identified the increased incidence of glandular stomach cell metaplasia as the critical effect to establish subchronic toxicity values for soluble tungsten substances.
 - Histopathological changes in a **90-day gavage study** ([McCain et al., 2015](#)) were observed in the glandular stomach including inflammation and metaplasia in the high-dose groups (125 or 200 mg/kg/d) of both sexes of rats.
- On that basis, the subchronic and chronic provisional Reference Doses (p-RfDs) were derived from a BMDL10 of 2.3 mg W/kg-day in a 90-day gavage study, with uncertainty factors of 300 and 3,000, producing values of 0.008 and 0.0008 mg W/kg-day, respectively

NTP's 2-yr Carcinogenicity Sodium Tungstate (ST) Study

- In both the 90-day and 2-year drinking water studies, the kidney was identified as the primary target organ in rats and mice.
- Using US EPA BMD Software, and applying both frequentist and Bayesian modelling approaches, BMD values and their corresponding 95% lower confidence limit (BMDL) values were estimated for each sex and species ([Gadagbui et al., 2026](#)).
- After applying the appropriate Uncertainty Factors (UFs) to the lowest (most conservative) BMDL values, subchronic and chronic oral RfDs of 0.2 and 0.02 mg ST/kg bw/day, respectively, were derived, equivalent to 0.1 and 0.01 mg/kg bw/day for elemental tungsten.
- The most sensitive reproductive toxicity observed in rats (namely decreased dam body weight) occurred at doses well above the kidney effects, hence these RfDs are protective of such effects.

PPVRT RfD vs Gadagbui et al (2026) RfD

	PPVRT (2015)	Gadagbui et al (2026)
Critical Effect	Gastrointestinal - Glandular stomach goblet cell metaplasia	Urinary - Renal tubule regeneration
POD Reference	McCain et al 2015	US NTP 2021
Study Duration	90-days	2-yr
Route of Exposure	Gavage	Drinking water
Species	Rat	Mice
Subchronic BMDL10 (W mg/kg-day)	2.3	5.9
Chronic BMDL10 (W mg/kg-day)	2.3	0.6
Assessment Factors	300 (subchronic) 3000 (chronic)	30
Interspecies (UFA)	10	3
Intraspecies (UFH)	10	10
Quality of Database (UFD)	3	1
Point of Departure (UFL)	1	1
Study Duration (UFS)	10	1
Reference Dose (RfD, W-basis)		
Subchronic RfD (W mg/kg-day)	0.008	0.10
Chronic RfD (W mg/kg-day)	0.0008	0.01

The new estimated RfD based on kidney lesions is one order of magnitude higher than the one based on stomach lesions.

PPVRT – Target Organ Selection

As part of the PPRTV evaluation (page 37), US EPA states that, *“selection of stomach lesions in SD rats as the critical effect has some uncertainty, because the occurrence of these lesions was not mentioned in the available reports of a reproductive study for a duration equivalent to subchronic study (70 days, including 14 days pre-mating, 14 days mating, 22 days gestation, and 20 days post-parturition) in SD rats exposed by gavage to sodium tungstate in water (McInturf et al., 2008, 2011), or in any other study”*.

- Route: Gavage - McInturf et al ([2008](#), [2011](#)): 5, 62.5 and 125 mg/kg-d
- Route: Drinking Water - [McCain et al \(2015\)](#): 10, 75, 125, or 200 mg/kg-d

Critical effect - Glandular Stomach Toxicants

- The glandular stomach (including inflammation and metaplasia) in the sodium tungstate high-dose groups (125 or 200 mg/kg/d) of both sexes of rats was selected by PPRTV as the critical effect.
- Several toxicants and experimental agents can produce **injury, proliferative lesions, or tumors in the rat glandular stomach**

Toxicant/agent	Typical glandular-stomach effect
N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG)	Potent direct-acting mutagen; experimentally induces gastric adenocarcinoma
N-Methyl-N-nitrosourea (MNU)	DNA alkylation; widely used to induce glandular-stomach carcinogenesis
N-nitroso compounds	DNA damage and mutations; some can produce gastric tumors
Catechol	At sufficiently high experimental exposures, can cause gastric epithelial injury/proliferation and promote carcinogenesis
High concentrations of irritant/corrosive chemicals	Erosion/ulceration followed by regenerative epithelial hyperplasia; chronic injury may contribute to tumor development
Certain pharmaceuticals/chemicals producing prolonged gastric irritation	Depending on the compound, may cause inflammation, erosion, hyperplasia, or other proliferative lesions

Route of Exposure - Gavage vs Drinking Water

Feature	Oral gavage	Drinking water
Exposure pattern	Large dose delivered rapidly	Smaller amounts consumed repeatedly
Gastric concentration	Often a high transient concentration	Usually lower, distributed concentrations
Peak systemic concentration (Cmax)	Often higher	Often lower
Stomach contact	Bolus exposure	Intermittent throughout drinking periods
Local irritation/cytotoxicity	Greater potential for concentration-driven effects	Often less severe at equivalent daily dose
Relevance to typical human exposure	Depends on scenario; sometimes less representative	Often more representative of continuous environmental exposure
Dose control	Very precise	Depends on water consumption
Stress/procedural effects	Restraint and dosing procedure	Minimal dosing-related handling

Gavage delivers a bolus directly into the stomach and may produce high local concentrations and prolonged contact with the gastric mucosa, particularly in the rodent forestomach. For irritating substances, these exposure conditions may contribute to localized mucosal injury (IARC, 2003; Frederick et al., 1990).

Quality of Database – PPVRT, 2015

Neurotoxicity – Low Confidence

Table 8. Uncertainty Factors for the Subchronic p-RfD for Soluble Tungsten Compounds

UF	Value	Justification
UF _A	10	A UF _A of 10 is applied to account for uncertainty in extrapolating from animals to humans, in the absence of information to assess species differences in toxicokinetic and toxicodynamic characteristics of soluble tungsten compounds, and in the absence of a rationale to support use of HED for a POD based on portal-of-entry effects.
UF _H	10	A UF _H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of soluble tungsten compounds in humans.
UF _D	3	A UF _D of 3 is applied because the database contains several adequately designed subchronic-duration animal toxicity studies of sodium tungstate that collectively identify glandular stomach lesions as a critical effect occurring at dose levels that do not cause reproductive, developmental, or immune system effects (Osterburg et al., 2014; Kelly et al., 2013; McInturf et al., 2011; McInturf et al., 2008; USACHPPM, 2007a, b). However, there is indication of neurotoxicity effects (Nadeenko, 1966), which was not comprehensively investigated.
UF _L	1	A UF _L of 1 is applied because the POD is a BMDL.
UF _S	1	A UF _S of 1 is applied because the POD comes from a subchronic-duration study of rats.
UF _C	300	Composite Uncertainty Factor = UF _A × UF _H × UF _D × UF _L × UF _S .

Table 11. Confidence Descriptors for the Chronic p-RfD for Soluble Tungsten Compounds

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study is high because the study design and conduct was in accordance with EPA Health Effects Testing Guidelines for a study of 90-d oral toxicity in rodents. In addition, the results were published in a peer-reviewed paper McCain et al. (2015).
Confidence in database	L	Confidence in the database is low, because it contains no comprehensive studies of toxic endpoints in humans or animals orally exposed to tungstate for chronic durations, and there is limited information regarding neurotoxicity (Nadeenko, 1966).
Confidence in chronic p-RfD ^a	L	The overall confidence in the chronic p-RfD is low.

^aThe overall confidence cannot be greater than the lowest entry in the table.

H = high; L = low.

Neurotoxicity	Albino rats were orally exposed to 0, 0.005, 0.05, or 0.5 mg/kg-d of sodium tungstate for 7 mo. Strain, sex, and animal number were not reported. Neurobehavioral testing (conditioned reflexes to a light and bell) was conducted at an unspecified time point during the study. Details on the neurobehavioral protocol and endpoints examined are limited. Brains were examined microscopically at 8 mo.	Impaired conditioned responses were reported in rats from the 0.05- and 0.5-mg/kg-d groups. No brain lesions were reported.	Due to inadequate reporting of study design and results, findings are difficult to interpret. As such, reliable NOAEL/LOAEL determinations cannot be made.	Nadeenko (1966)
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Test	Materials and Methods	Results	Conclusions	References
Neurotoxicity	Albino rabbits (7/group) were exposed to 0, 0.005, 0.05, 0.5, or 5 mg/kg-d of sodium tungstate for 8 mo. Strain and sex and animal number were not reported. Blood cholinesterase activity was measured monthly and brains were examined microscopically at 8 mo.	Blood cholinesterase activity in rabbits was significantly decreased in the 5-mg/kg-d group from 4 to 8 mo and in the 0.5-mg/kg-d group at 8 mo. Unspecified lesions were observed in the cerebral cortex of rabbits in the 0.5 and 5-mg/kg-d groups. No neurotoxic effects were reported for lower dose groups.	Due to inadequate reporting of study design and results, findings are difficult to interpret. As such, reliable NOAEL/LOAEL determinations cannot be made.	Nadeenko (1966)

Quality of Database – Neurotoxicity

Gadagbui et al., 2026

- New evidence - Sequani Limited (2016). Rats are the preferred species for neurotoxicity testing according to EPA, OECD, and ICH guidelines.
- GLP-compliant study conducted according to guidelines (International Conference on Harmonization) Harmonised Tripartite Guideline (ICH (2005, 2009) administered ST by oral gavage to four groups of female CD (SD) rats (22 females/dose group) at a dose of 0, 40, 80 or 160 mg/kg-day from GD 5 to LD 20.
- Selected pups were tested for learning and memory using a water-filled E-maze, monitored by an automated video-tracking system during Weeks 1 and 2 of the F1 maturation phase, and all groups were tested during Week 1 for learning ability.
- As there was no test-item related effect on learning, during Week 2, only the control and 160 mg/kg-day groups were tested for memory. Auditory function of each selected animal in the control and 160 mg/kg-day dose group was assessed using the auditory startle test during Week 0 of the F1 maturation phase. Motor activity of each selected animal in the control and 160 mg/kg-day dose groups was assessed during Week 0 of the F1 maturation phase, using an automated infrared beam activity monitoring system.
- There was **no effect** of maternal administration of ST on (1) learning and memory of the F1 generation as assessed by the E-maze test, (2) the hearing ability of the F1 generation; all animals in the control and the 160 mg/kg-day dose groups passed the auditory startle reflex assessment, and (3) on motor activity.

Discussion

- Critical effect and target organ used to develop the current version of PPRTV for Soluble Tungsten Compounds needs to be updated.
 - Based on the latest sodium tungstate evidence available from the US NTP (database and scientific panel approved 90-day and 2-year study conclusions), the selection of goblet cell metaplasia observed in the glandular stomach as the critical effect should be replaced with renal tubule regeneration.
 - The current oral p-RfD based on the glandular stomach lesions should be revised to one based on kidney toxicity, which is one order of magnitude higher.
 - Quality of the database should be revised accordingly, based on no new evidence that neurotoxicity is not a health concern.