# Tungsten and tungsten compounds

(CAS No: 7440-33-7)

Health-based Reassessment of Administrative
Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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## 1 Introduction

The present document contains the health hazard of tungsten and its compounds by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AD Wientjes, M.Sc. and Ir PMJ Bos (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of tungsten has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line databases Medline, Toxline, and Chemical Abstracts covering the periods 1966 to 20 April 1999 (1990420/UP), 1965 to 29 January 1999 (1990126/ED), and 1967 to 10 April 1999, respectively, and using the following key words: tungsten and 7440-33-7. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO99, NLM99). The final literature search was carried out in April 1999.

In September 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

## 2 Identity, physical and chemical properties

Data on tungsten and some selected tungsten compounds are given in Table 1.

Tungsten is a grey, hard, brittle, metallic element in group VIb of the periodic system, and has the highest melting point of all metals (ACG99).

Tungsten exists in several states of oxidation 0, $2^+$, $3^+$, $4^+$, $5^+$, and $6^+$. The most stable is $6^+$, the lower valence states being relatively unstable.

The tungsten of commercial importance includes the water-insoluble compounds (tungsten carbide, sulphide, carbonyl, silicide, and oxide, and tungsten acid) and the water-soluble compounds (tungsten chloride, fluoride, and tungstic acid). According to Beliles (Bel94), soluble compounds are distinctly more toxic than insoluble forms.

*Table 1* Identity and physical and chemical properties of tungsten and some of its compounds.

| name | tungsten | tungsten trioxide | tungsten fluoride | tungsten carbide |
|---|---|---|---|---|
| synonyms | wolfram | tungsten(VI) oxide; tungsten blue; tungsten oxide; tungstic anhydride; tungsten acid anhydride; tungstic oxide; wolframic acid, anhydride | tungsten(VI) fluoride; tungsten hexafluoride | |
| molecular formula | W | $WO_3$ | $WF_6$ | WC |
| CAS number | 7440-33-7 | 1314-35-8 | 7783-82-6 | 12070-12-1 |
| molecular weight | 183.85 | 231.85 | 297.84 | 195.86 |
| melting point[a] | 3410°C | 1473°C | $2.5°C^{420}$ | 2870°C |
| boiling point | 5660°C | - | 17.5°C | 6000°C |
| flash point | - | - | - | - |
| vapour pressure | - | - | - | - |
| solubility in water | i | i | d | i (cold) |
| Log $P_{octanolwater}$ | - | - | - | - |

d: decomposes; i: insoluble; s: soluble.

[a] Number in superscript represents the atmospheric pressure (mmHg) at which the presented value was determined.

*Table 1* Continued.

| name | tungsten disulphide | tungsten carbonyl | tungsten silicide | tungsten chloride | sodium tungstate |
|---|---|---|---|---|---|
| synonyms | tungstenite | | | tungsten hexachloride | disodium tungstate; sodium tungstate(VI); sodium tungsten oxide; tungstic acid, disodium salt |
| molecular formula | $WS_2$ | $W(CO)_6$ | $WSi_2$ | $WCl_6$ | $Na_2WO_4$ |
| CAS number | 12138-09-9 | 14040-11-0 | 12039-88-2 | 13283-01-7 | 13472-45-2 |
| molecular weight | 247.97 | 351.91 | 240.02 | 396.57 | 293.83 |
| melting point [a] | 1250°C[d] | ~150°C[d] | >900°C | 275°C | 698°C |
| boiling point [a] | - | $175°C^{766}$ | - | 346.7°C | - |
| flash point | - | - | - | - | - |
| vapour pressure | - | - | - | - | - |
| solubility in water | i (cold) | i | i | d (hot) | s |
| Log $P_{octanolwater}$ | - | - | - | - | - |

d: decomposes; i: insoluble; s: soluble.

[a] Number in superscript represents the atmospheric pressure (mmHg) at which the presented value was determined.

Data from ACG99, Lid94, NIO99, NLM99, Ric94a, Ric94b.

## 3 Uses

Tungsten is a valuable metal, because it has the highest melting point of all metals, a great strength at high temperatures, and good conductivity for electricity and for heat. It is used to increase the hardness and tensile strength of steel. It plays a vital role in the production of a number of other alloys noted for their hardness, such as the chromium, cobalt, and tungsten alloy use for the tipping and facing lathe tools. It is also used for filaments in incandescent lamps, heating elements, and welding electrodes, in nozzles of rocket motors, in protecting shield for space crafts, and in solar energy devices (ACG99, Kaz79).

Tungsten carbide finds its use in many drills and cutting edges of tools giving them a hardness comparable to that of diamond. The disulphide is used as a solid lubricant, the carbonyl, chloride, and fluoride in deposition of tungsten coatings, and tungstic acid and oxide in the textiles, ceramics, and plastics industries. Tungstates are used in X-rays tubes, fluorescent lamps and lasers, and as pigment in dyes and inks (ACG99, Kaz79).

## 4 Biotransformation and kinetics

The kinetics of tungsten oxide were studied by exposing 6 anaesthetised Beagle dogs via nose-only inhalation to mists of radiolabelled $^{181}WO_3$ of 98 μCi/mL specific activity, for 6 hours; the final air concentration was not reported. Tungstic oxide aerosols were found to have an Activity Median Aerodynamic Diameter of 0.70 μm with a geometric standard deviation of 1.5. The radioactivity deposited in the respiratory tract of each animal was estimated by 3 independent methods: inhaled minus exhaled activity, *in vivo* γ-ray measurements of the body (lung area and posterior part of the dog's body were measured separately), and analyses of activity excreted in urine and faeces during 100 days post-exposure. The fraction excreted during exposure is unknown, the reported excretion will, therefore, be underestimated to an unknown extent (it was, however, mentioned that no faecal excretion occurred before 20 hours post-exposure). The fact that the first method appeared to reveal a higher uptake than the third method confirms an underestimation. However, the results of the excretion analyses were used in the further analyses indicating that about 60% of the inhaled radioactivity was estimated to be deposited in the respiratory tract; half of this fraction was found in the lower portion of the respiratory tract. Under the assumption that oral absorption was approximately

25% (this assumption could not be verified), it was calculated from the excretion data that about 33% of the deposited activity entered the systemic circulation, most of it within 10 days after inhalation. The remaining ca. 66% was cleared from the lungs by way of the ciliary escalator system. Blood measurements indicated that the inhaled tungstic oxide entered the blood quite soon after inhalation. It was concluded that after inhalation, the rate of decrease in radioactivity in blood was clearly slower than after an intravenous injection of $Na_2{}^{181}WO_4$. Based on the excretion analyses, excretion was estimated to occur in 3 phases with half-times of 14 h, 5.8 d, and 63 d, respectively; the average daily urine to faeces $^{181}W$ ratio was 1.92. At sacrifice, 165 days post-exposure, only negligible amounts were found in tissues (Aam75).

Retention and excretion were measured in two 18-month-old Beagle dogs (one male and one female) given intravenous injection of 0.5-2.3 μCi of $^{181}W$ as sodium tungstate in normal saline. After 43 days, a second injection was given to each dog. Retention and excretion were followed for a further 131 days. Urine and faeces were collected separately and body burdens were determined by *in vivo* γ-ray counting. The results obtained from the first 42 days following the second injection (corrected for the expected remaining body burden from the first injection) were combined with those following the first injection. Clearance from the blood was relatively fast in the first 24 hours, and appeared to be 3-phasic with half-times of 36 min, 71 min, and 5 h, respectively. The average plasma to red blood cell $^{181}W$ ratio was 3. Whole body retention was measured by whole-dog γ-ray counting. Removal from the body was estimated to be 4-phasic with biological half-times of 86 min, 8.8 h, 3.7 d, and 99 d, respectively. As to excretion, 91% of the injected radioactivity was excreted in urine within 24 hours. The urine to faeces $^{181}W$ ratio stabilised by day 5, and finally averaged 38, indicating that $^{181}W$ was excreted primarily in the urine (Aam73).

Wide et al. studied the distribution of radiolabelled W (administered as $Na_2{}^{185}WO_4$) by whole-body autoradiography and quantitative measurements in pregnant NMRI mice. As to the autoradiographic experiments, pregnant mice received an intravenous injection of either 0.12 or 20 mg radiolabelled W/kg bw, as $Na_2{}^{185}WO_4$. Three mice received the low dose on gestation day 8, and were killed after 4, 24, or 48 hours. One mouse was administered the high dose and was killed after 48 hours. On gestation day 12, 4 mice received the low dose (sacrificed after 4, 24, or 48 hours, or 6 days), and one mouse the high dose (killed after 48 hours). Two mice were given the low dose at gestation day 17, and killed after 4 and 24 hours. In addition, one non-pregnant female

C57BL mouse (killed after 24 hours) and 3 male NMRI mice (killed 1 hour, 24 hours, or 10 days after injection) were administered the low dose. For quantitative tissue examinations, groups of 4 pregnant NMRI mice (per survival interval) were administered an intravenous dose of 0.12 mg radiolabelled W/kg bw (as $Na_2{}^{185}W\,O_4$ on gestation day 12, and killed after 1, 4, or 48 hours, or on gestation day 17 and killed after 1 or 4 hours. In addition, groups of 4 mice received 20 mg/kg bw on gestation day 12 and were killed after 1 or 8 hours, respectively. Accumulation of radioactivity in adult male as well as in pregnant female mice was observed in the skeleton, liver, and kidney, with rapid excretion to the urine and intestinal contents. Relatively high activity was found in the thyroid, adrenal medulla and outer zone of the adrenal cortex, and pituitary. In the male mice, considerable accumulation was further observed in the seminal vesicles while in the non-pregnant female mouse, the interstitial tissues and ovary follicles showed relatively high concentrations. In pregnant animals, administration on day 8 resulted in accumulation in the zone of the ectoplacental cone, in the visceral yolk, and in the *decidua basalis*. Embryo uptake was considered to be low, but was difficult to evaluate due to the small size of the embryo. After administration on day 12, highest levels of radioactivity found one hour after administration were in the skeleton, kidney, liver, placenta, and fetus. These levels were decreased by approximately 50% 4 hours after injection and to very low levels 48 hours after injection. At 1 hour after administration of the high dose, a relatively lower portion (as % of administered dose) as compared to the low dose, was observed in liver and kidney, but the relative portion distributed in fetus and placenta was comparable to that after the low dose. Four hours after injection, the relative concentrations in fetus and placenta were lower than after administration of the low dose, but still higher than in maternal tissues. Administration of the low dose at day 17 resulted in higher tissue concentrations of W after 1 and 4 hours, as compared to day 12. At 1 hour after exposure, concentrations in fetus and placenta were approximately 70 and 40% higher, respectively, as on day 12, while 4 hours after injection on day 17, the concentration in the fetus was 50% higher when compared to day 12, but was similar in the placenta on both days. On day 12, an accumulation in the nervous tissue of the fetus was observed, as well as in the visceral yolk sac epithelium. The activity in the amniotic fluid was rather high compared to serum. Radioactivity in the fetus on day 17 was high in the skeleton, both at 4 and 24 hours after injection. Furthermore, *in vitro* cytotoxicity experiments showed inhibition by tungstate of cartilage production

in limb bud mesenchymal cultures at concentrations similar to those found *in vivo* (Wid86).

Young et al. administered groups of 7 male rats diets containing 8, 16, or 32 mg W/kg as ammonium tetrathiotungstate, for 4 weeks; in addition the copper content of the diet was varied. Although the time point of plasma sampling is not specified, it is assumed that plasma is sampled at the end of the 4-week exposure period. The plasma tungstate concentrations appeared to be independent of the dietary tungstate content, but were approximately 3- to 4-fold higher at higher dietary copper levels. Liver tungstate concentrations increased with increasing tungstate dose, and were higher at higher copper levels. Copper levels appeared to have less influence on the tungstate levels in the kidneys. Plasma concentrations appeared to be 4- to 5-fold higher in rats administered 32 mg W/kg diet as $WO_2S_2^{2-}$ (dithiotungstate, ammonium salt) for 5 weeks than when administered as $WS_4^{2-}$ for 4 weeks. (Although in the description of the 'Methods'it is stated that tungstate is administered as $WS_4^{2-}$, under 'Results' tungstate is mentioned to be administered as $WO_2S_2^{2-}$, the latter is assumed to be the appropriate form). In contrast, 5-week administration of 32 mg W/kg diet as $WO_2S_2^{2-}$ resulted in a 50% lower liver tungstate content than 4-week administration as $WS_4^{2-}$, whereas the kidney concentration was even 80% lower. Copper supplementation appeared to have less influence on the tissue tungstate concentration when tungstate was administered as $WO_2S_2^{2-}$ (You82).

Two complimentary studies were carried out with adult Rochester strain Wistar rats. Tungstate was administered as a single (unspecified) dose of $WO_4^{2-}$. In the first experiments, 24 female rats were administered $^{187}W$ by gastric intubation. At 0.5, 1, 3, 6, 12, 24, 48, and 72 hours, 3 animals were sacrificed. Carcass, gastrointestinal tract, blood, plasma, urine, and faeces were counted by γ–spectrometry. Tungsten was eliminated from the whole body with an initial biological half-time of 10 h. The gastrointestinal tract and contents accounted for the highest activity for the first 45 hours post-administration. A peak value of 17% of the administered dose was found in the carcass after 1 hour, plasma values also peaked after 1 hour. Excretion via the urine was fast, a steep curve for cumulative urine which crested by 12 hours post-exposure was found. Urinary excretion accounted for approximately 44% of the administered dose. Faecal excretion was slower, finally accounting for 53% of the administered dose after 72 hours. In the second experiment, 90 adult Wistar rats divided evenly between males and females were used. Seventy of the rats received a single dose of $^{185}W$ by gastric intubation and groups of 10 rats (9 rats at the last

2 time points) were killed after 3, 7, 14, 32, 61, 104, and 195 days. At the latter 2 sacrifices, only 4 females were killed, the 2 remaining females were killed after 254 days. Twenty rats were used as controls. In the first week, urinary and faecal collections were carried out daily for the first week on alternating groups of 6 rats (3 males and 3 females). Collections were made every 3-4 days during the following 4 weeks, and at approximately weekly intervals during the remainder of the study (collection of urine and faeces was not 100% efficient). Besides whole blood and plasma, 25 organs and tissues were removed from the animals soon after death and prepared by a special process for liquid scintillation counting of β-activity. Tungsten could not be detected in the faeces after 33 days. Urine sampling was stopped after 191 days, although some activity was still detectable. Highest concentrations in tissues collected after 3 days were found in the spleen (0.013% of the administered dose per g tissue), hair (0.005%), and kidney (0.004%). The concentration in the kidney decreased more rapidly than in the spleen and hair. As to the absolute amount per organ, highest levels were found in the liver (0.03% of the administered dose) (Kay68).

## 5 Effects and mechanism of action

### Human data

Letters sent to the TLV committee by the industry in 1966 reported no pneumoconiosis among workers exposed solely to approximately 5 mg/m$^3$ tungsten or its insoluble compounds and no difficulty in controlling atmospheric concentrations of tungsten and tungsten carbide to workplace air levels considerably below 5 mg/m$^3$ (ACG99).

A young soldier developed seizures and tubular necrosis after drinking 0.25 L of a beverage prepared by rinsing still hot gun-barrels (that had been fired several times) with wine. Tungsten was present in gastric content (concentration: 8 mg/L), blood (serum concentration: 5 mg/L), and urine (concentration: 101 mg/L) of the soldier, as well as in the wine (concentration: 1540 mg/L; estimated by preparing a similar drink several days later) (Mar96, Mar97).

Most of the articles found in the literature search were based on exposure to hard metal. Hard metal is prepared by first heating finely divided tungsten and carbon to form tungsten carbide, and cobalt is added as a binder. Other metal components are also added depending on the specific hard metal to produce.

Therefore, the inhalable dust in hard metal plant may contain tungsten, cobalt, titanium, vanadium, niobium, hafnium, and tantalum both as oxides and as carbides. The major component of dust is, however, tungsten (Sah93). In most of the reports on hard-metal pneumoconiosis, the agent responsible for 'hard metal disease' is believed to be cobalt, but this has not yet been proven (Kaz79). Studies in a number of factories manufacturing tungsten carbide-based products have revealed the presence of respiratory symptoms associated with impaired respiratory functions and radiographic abnormalities in proportion of those exposed. Because of the mixed exposures and the uncertainty which of the above mentioned metals causes the disease, these articles are not included in the present evaluation.

## Animal data

*Irritation and sensitisation*

The committee did not find valid data on eye and skin irritation.

In a briefly reported guinea pig maximisation test, 3 out of 20 guinea pigs showed positive reactions at a challenge concentration of 5% (w/w in saline). No positive reactions were found at lower concentrations (Bom82).

*Acute toxicity*

Female CD-1 mice (n=5; 6- to 8-week old), were submitted to a single intratracheal instillation of 250 µg calcium tungstate ($CaWO_4$) particles suspended in 100 µL of saline. The animals were sacrificed by a lethal dose of diethyl ether 1, 3, 7, 14, and 21 days after the intratracheal instillation. Control animals received 100 µL sterile saline. One additional group of mice was used to collect bronchoalveolar lavage liquid and to evaluate the microanatomy of lung tissue from untreated animals. The effects were studied using 3 microanatomical methods: cytological study of exudates obtained by bronchoalveolar lavage, histological examination of paraffin-embedded sections of lung samples, and scanning electron microscopic (SEM) examination of lung tissues. The metal induced a marked inflammatory response in the bronchoalveolar space characterised by a biphasic attraction of leukocytes with cellular peaks at day 1 and 14. In controls, only the first inflammatory peak was detected. Up to the 14th day after tungsten instillation, the presence of the metal particles attracted significantly higher number of inflammatory cells to the

animal airways than the instillation of saline alone; this difference disappeared after 21 days. Up to day 21, neutrophils were present in significantly higher numbers in the bronchoalveolar lavage preparations of tungsten treated-mice. In the bronchoalveolar lavage from untreated animals, virtually no granulocytes were available. More than 50% of the bronchoalveolar lavage macrophages showed ingested tungsten. Three days after the tungsten instillation, extensive inflammatory exudates were located at the periphery of the bronchus. Twenty-one days after instillation, the lung tissue showed several regions massively invaded by inflammatory cells, mononuclear granulocytes, and cellular debris. In the lung parenchyma, the inflammatory infiltrates were predominantly located at the periphery of the bronchiolar walls (Peã93).

Oral $LD_{50}$ values of sodium tungstate in the rat ranged between 223 to 255 mg/kg. Guinea pigs treated orally or intravenously with tungsten or sodium tungstate developed anorexia, colic, incoordination of movement, trembling, and dyspnoea. When injected subcutaneously, the $LD_{50}$ of sodium tungstate was reported to be between 140-160 mg/kg. Tungsten toxicity appeared to depend on the age and nutritional status of the rat: 30-day-old rats survived a dose that killed older rats; mortality was reduced when animals were fed before tungsten exposure. The $LD_{50}$ by intramuscular injection of sodium tungstate was 105 mg/kg. The intraperitoneal $LD_{50}$ of tungsten metal powder in the rat was 5000 mg/kg (ACG99). The average dose to kill male rabbits and cats (numbers not specified) receiving a continuous intravenous perfusion of sodium tungstate within approximately 1 hour were found to be 105 and 140 mg/kg, respectively (Pha65, Pha67).

*Subacute toxicity*

Young et al. studied the effects of tetrathiotungstate and dithiotungstate on copper metabolism in weanling rats (bw: 40-50 g). Groups of 7 male rats were administered diets containing 8, 16, or 32 mg W/kg as ammonium tetrathiotungstate for 4 weeks. All rats receiving the highest dose and one animal of the mid-dose group died within 1-3 weeks. A dose-related decrease in body weight gain, blood haemoglobin concentration, packed cell volume, and erythrocyte count was observed. No statistical analyses were presented; the decreases for these parameters were 27%, 33%, 31%, and 31%, respectively, in the low-dose group. The growth retardation was related to a decreased feed intake. Supplementation of the diet with copper diminished the tungstate-related toxicity. Ammonium dithiotungstate had no effect on these parameters at doses

up to 32 mg W/kg diet for 4 or 5 weeks. Furthermore, 16 mg W/kg diet as tetrathiotungstate decreased cytochrome oxidase activity by 50% and increased hepatic iron retention. These effects may be an indication of severe copper deficiency in rats. Dithiotungstate up to a dose of 32 mg W/kg diet induced no clinical or biochemical effects indicative of copper deficiency; it rather enhanced the copper content of liver, kidney, and plasma. Plasma ceruloplasmin activity was dose-relatedly decreased when tungstate was administered as tetrathiotungstate (70% reduction in the mid-dose group) while plasma copper concentration was almost doubled. In contrast, dithiotungstate administered at the same dose levels for 4 or 5 weeks rather increased the plasma ceruloplasmin activity and dose-relatedly increased the plasma copper concentration 4- to 5-fold. Administration of 32 mg W/kg diet as tetrathiotungstate inhibited copper absorption from the diet, a smaller fraction of the absorbed copper was retained in liver and kidneys (60 to 75% reduction) while blood levels were relatively increased (expressed as percentage of absorbed dose) (You82).

Following intratracheal instillation of tungsten metal and tungsten carbide dust in guinea pigs at 50 mg/week for 3 weeks, the dusts were reported to be relatively inert. Histological examinations showed moderate interstitial cellular proliferation (ACG99).

*Subchronic toxicity*

Kinard and Van de Erve administered diets containing different percentages of tungsten to groups of 5 to 6 male and 5 to 6 female rats as sodium tungstate (0.1, 0.5, or 2.0% W), tungstic oxide (0.1, 0.5, or 4.0% W), or ammonium paratungstate (0.5, 2.0, or 5.0% W; highest dose to male rats only) for 70 days. However, exact food consumption could not be determined due to occasional spills. (The molecular formula of ammonium paratungstate is unclear, both $(NH_4)_{10}W_{12}O_{41}$ as $(NH_4)_6W_7O_{24}$ are found). The only parameters studied were body weight gain and mortality. As to ammonium paratungstate, the lowest dose resulted in a slight growth retardation (3-6%) compared to controls after 70 days of exposure. Only one male and one female of the mid-dose group survived the 70-day period. Males died after 10-19 days and females after 9-11 days. After an initial weight loss, the male rat gained weight, but the final weight gain was little more than 50% of the weight gain of control males. The surviving female rat still showed a weight loss after 70 days. All male rats of the highest dose group died within 10 days. The lowest dose of tungstic oxide resulted in slight growth retardation (6-7%) after 70 days. One male and one

female (out of 6) rat of the mid-dose group survived the 70 days, but they never regained their initial body weight. Deaths occurred between day 10-23 for males and between day 12-18 for females. All animals of the highest dose group were dead within 4 days. As to sodium tungstate, all animals survived the low dose, but showed growth retardation (9-11%) compared to controls. Two female and 3 male rats (both groups consisted of 6 rats) survived 70 days on the mid-dose administration; these rats never regained their initial body weight. Deaths in males occurred on day 22, females died between day 17 and day 29. At the highest dose, all animals died within 7 days. Although with respect to mortality and body weight gain, ammonium paratungstate appeared to be less toxic (based on consumption of W) than the other 2 compounds, no clear conclusions can be drawn due to the incomplete consumption assessment and the limited number of parameters examined (Kin41).

In a second experiment, Kinard and Van de Erve fed diets containing metallic tungsten (2, 5, or 10%) to groups of 5 male and 5 female rats for 70 days. All animals survived the experiment. Only females of the high-dose group showed growth retardation when compared to controls. No other parameters were investigated (Kin43).

*Chronic toxicity and carcinogenicity*

In a study on the effects of long-term exposure to different trace elements, 54 male and 54 female Swiss Mice (Charles River strain) were exposed to 5 ppm W as sodium tungstate in drinking water for 540 days. The study was focused on the induction of tumours. Compared to controls, no significant effects were observed in body weight gain, longevity, or tumourigenicity (Sch75).

Virgin female rats of the SD strain were fed *ad libitum* a nutritionally adequate semipurified diet and demineralised water; 22 animals were given an intravenous injection of 50 mg *N*-nitroso-*N*-methylurea (NMU)/kg bw after 2 weeks, whereas 10 received only the vehiculum. A third group (n=24) received 150 ppm tungsten (unspecified form) added to the drinking water, starting 2 weeks prior to the NMU injection. Two experimental units were maintained for either 125 (unit I) or 198 (unit II) days following NMU administration; each unit consisted of the same exposure groups. In experimental unit I, the mean terminal body weights were slightly lower (6.5%, not statistically significant) in the tungsten/NMU- and NMU-only-treated groups compared to untreated controls (unit I groups). The tungsten/NMU treatment group exhibited a statistically significant increase in mammary carcinoma incidence compared to

the NMU-only-treated animals (79.2% vs. 50%; $p<0.05$; controls: 0%). There was no difference in the number of carcinomas per carcinoma-bearing rat (1.7 vs. 2.0). The first mammary tumours were identified by palpation 56 and 71 days after NMU treatment in the tungsten/NMU- and NMU-only-treated groups, respectively. In experimental unit II, there was a decrease in body weight of approximately 10% in both treated groups (not statistically significant). The increase in mammary carcinoma incidence amounted to 95.7% and 90.5% (no statistically significant difference) in the tungsten/NMU- and NMU-only-treated groups, respectively, while no such tumours were found in the untreated controls. The first palpable mammary tumours appeared 56 and 85 days after NMU treatment in the tungsten/NMU- and NMU-only-treated group, respectively. The number of carcinoma per tumour-bearing rat was 2.6 and 2.0, respectively. At macroscopic examination, no other tumours were found in any of the treated groups (Wei85).

*Mutagenicity and genotoxicity*

Testing its DNA damaging potential using human peripheral lymphocytes, tungsten carbide did not induce alkaline labile sites and/or DNA single strand breaks detectable by an alkaline elution assay or alkaline single cell gel electrophoresis ('Comet assay') while cobalt and a cobalt-tungsten carbide mixture both caused a dose- and time-dependent increase in single strand breaks, the mixture being more potent than cobalt alone. However, closer examination of the results of the 'Comet assay' (analysis of tail lengths and moments) may suggest that tungsten carbide may either allow some uncoiling of the chromatin loops or induce formation of slowly migrating DNA fragments. By inducing uncoiling, the carbide might increase sensitivity to clastogenic effects (Ana97, Goe97). In human lymphocytes, tungsten carbide produced a statistically significant number of micronuclei at a concentration of 50 µg/mL which did not increase at the next higher doses of 75 and 100 µg/mL (dose range tested: 10-100 µg/mL) (Goe97).

*Reproduction toxicity*

The committee did not find data on the potential reproduction toxicity of tungsten and its compounds.

## 6 Existing guidelines

The current administrative occupational exposure limit (MAC) in the Netherlands is 5 mg/m$^3$, 8-hour TWA, for tungsten and insoluble tungsten compounds and 1 mg/m$^3$, 8-hour TWA, for soluble tungsten compounds.

Existing occupational exposure limits for tungsten in some European countries and in the USA are summarised in the annex.

## 7 Assessment of health hazard

There are no valid data from human studies.

It was reported that in dogs, a large part of inhaled W (as tungsten oxide) was eliminated by secondary ingestion. Excretion of systemic W (as tungsten oxide) via the urine appeared to be relatively fast. Three days after intragastric intubation, only very low levels of radiolabelled W were detectable in tissues. One hour after an intravenous injection, levels of W administered as tungstate were highest in skeleton, intestinal contents, and kidneys. Administration of W through the diet for 4 to 5 weeks resulted in different plasma W concentrations for similar doses of W as tetrathiotungstate or as dithiotungstate. W administered as tungstate was able to reach the fetus, more in late than in early gestation.

Oral $LD_{50}$ values of sodium tungstate in the rat ranged between 223 to 255 mg/kg. For guinea pigs injected subcutaneously with sodium tungstate, an $LD_{50}$ between 140-160 mg/kg is reported. The $LD_{50}$ by intramuscular injection of sodium tungstate in rats is 105 mg/kg. The intraperitoneal $LD_{50}$ of tungsten metal powder in the rat is 5000 mg/kg.

No valid data on eye and skin irritation were reported. As to the skin sensitising potential, only a limited description of a negative sensitisation study was reported.

Several studies have been performed with tungsten (compounds), some of which are rather old. The available studies were either performed to study specific aspects (e.g., on copper metabolism (You82)) or examined only a limited number of parameters (Kin41, Kin43). Furthermore, different tungsten compounds were used. It is noted that the effects on copper metabolism (You82; tungsten administration up to 32 mg W/kg diet) were observed at much lower doses than in the study by Kinard and Van de Erve (Kin41; lowest dose:

1000 mg W/kg diet). The data are insufficient to compare the toxicological potential of different tungsten compounds. Tungsten appears to interfere with copper metabolism, but also with molybdenum metabolism (e.g., increased excretion of molybdenum, decreasing xanthene oxidase activity (Hig56)) inducing effects comparable with copper and molybdenum deficiency. These effects can (partly) be overcome by increasing the intake of the particular trace element. This indicates that the toxicity of tungsten is dependent on the intake of other trace elements, and greater toxicity will be observed (lower NOAELs found) in case subjects consume diets rather deficient in trace elements. In addition, the results of, e.g., Young et al. (You82) show that the interaction with trace elements like copper differed for different forms of tungsten.

Tungsten carbide caused a statistically significant, but not dose-related increase in the frequency of micronuclei but no single strand breaks and/or alkaline labile sites in human lymphocytes. These tests might suggest that tungsten carbide may uncoil chromatin loops and, thus, might increase sensitivity to clastogenic effects by other compounds. The committee did not find other data on the mutagenicity/genotoxicity of tungsten or tungsten compounds.

The committee did not find valid data on the reproduction toxicology of tungsten or its compounds.

The committee considers the toxicological database on tungsten and its compounds too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC value.

## References


Aam73 Aamodt RL. Retention and excretion of injected $^{181}$W labeled sodium tungstate by beagles. Health Phys 1973; 24: 519-24.

Aam75 Aamodt RL. Inhalation of 171W labeled tungstic oxide by six beagles. Health Phys 1975; 208: 733-42.

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Tungsten and compounds. In: TLVs® and other occupational exposure values -1999. [CD-ROM]. Cincinnati OH, USA: ACGIH®, 1999.

ACG02a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2002. Cincinnati OH, USA: ACGIH®, Inc, 2002: 133.

ACG02b American Conference of Governmental Industrial Hygienists (ACGIH). 2002 TLVs® and BEIs®. Threshold Limit Values for chemical substances and fysical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2002: 59.

Ana97 Anard D, Kirsch-Volders M, Elhajouji A, et al. In vitro effects of hard metal particles assessed by alkaline single cell gell and elution assay. Carcinogenesis 1997; 18: 177-84.

Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; (At-vejledning C.0.1).

Arb00b Arbetarskyddstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: National Board of Occupational Safety and Health, 2000: 66; (Ordinance AFS 2000/3).

Bel94 Beliles RP. The metals. In: Clayton GD, Clayton FE, eds. Toxicology. 4th ed. New York: John Wiley & Sons, 1994: 2285-97; (Patty's industrial hygiene and toxicology; Vol II, Pt C).

Bom82 Boman A, Fischer T, Hagelthorn G, et al. Guinea pig maximisation with tungstate. Contact Dermatitis 1982; 8: 344.

CEC00 Commission of the European Communities (CEC). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from risks related to chemical agents at work. Official Journal of the European Communities 2000; L142 (16/06/2000): 47-50.

DFG02 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 2002. Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: Wiley-VCH, 2002: 114 (rep no 38).

Goe97 van Goethem F, Lison D, Kirsch-Volders M. Comparative evaluation of the in vitro micronucleus test and the alkaline single cell gel electrophoresis assay for the detection of DNA damaging agents: genotoxic effects of cobalt powder, tungsten carbide and cobalt-tungsten carbide. Mutat Res 1997; 392: 31-43.

Hig56 Higgins ES, Richert DA. Molybdenum deficiency and tungstate inhibition studies. J Nutr 1956; 59: 539-59.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 28.

Kaz79 Kazantzis G. Tungsten. In: Fribergh L, Nordberg GF, Vouk VB, eds. Handbook on the toxicology of metals. Amsterdam, the Netherlands: Elsevier/North-Holland Biomedical Press, 1979: 637-56 (Chapter 39).

Kay68 Kaye SV. Distribution and retention of orally administered radiotungsten in the rat. Health Phys 1968; 15: 399-417.

Kin41 Kinard FW, van de Erve J. The toxicity of orally ingested tungsten compounds in the rat. J Pharmacol Exp Ther 1941; 72: 196-201.

Kin43 Kinard FW, van de Erve J. Effect of tungsten metal diets in the rat. J Lab Clin Med 1943; 28: 1541-3.

Lid94 Lide DR. CRC Handbook of Chemistry and Physics. 75th edition 1994-1995. Boca Raton FL, USA: CRC Press Florida, 1994: 4-109.

Mar96 Marquet P, François B, Vignon P, et al. A soldier who had seizures after drinking quarter of a litre of wine. Lancet 1996; 348: 1070.

Mar97 Marquet P, François B, Lotfi H, et al. Tungsten determination in biological fluids, hair and nails by plasma emission spectrometry in a case of severe acute intoxication in man. J Forensic Sci 1997; 42: 527-30.

NIO99 US National Institute for Occupational Safety and Health (NIOSH). Tungsten. In: Registry of Toxic Effects of Chemical Substances (RTECS). [CD-ROM], issue July 1999. SilverPlatter International, 1999 (last update tungsten file: July 1999).

NLM99 US National Library of Medicine (NLM). Tungsten. In: Hazardous Substances Data Bank (HSDB). [CD-ROM], issue July 1999. SilverPlatter International, 1999 (last update tungsten file: November 1998).

Pha65 Pham Huu Chanh. The comparative toxicity of sodium chromate, molybdate, tungstate and metavanadate. II Experiments on rabbits. Arch Int Pharmadyn Ther 1965; 157: 109-14.

Pha67 Pham Huu Chanh, Azum-Gelade MC, Som Chanvattey. Toxicité compareé du chromate, du molybdate, du tungstate et du métavanadate de sodium. Agressologie 1967: 8: 51-60.

Peã93 Peão MN, Águas AP, de Sá CM, et al. Inflammatory response of the lungs to tungsten particles: an experimental study in mice submitted to intratracheal instillation of calcium tungstate powder. Lung 1993; 7: 187-201.

Ric94a Richardson ML, Gangolli S, eds. T331 Tungsten, T332 Tungsten carbide and T333 Tungsten hexafluoride. In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1994: 747-50 (Vol 7).

Ric94b Richardson ML, Gangolli S, eds. S98 Sodium tungstate In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1994: 143-4 (Vol 7).

Sah93 Sahle W, Laszlo I, Krantz S, et al. Airborne oxide whiskers in a hard-metal industry. Preliminary findings. An Occup Hyg 1994; 39: 37-44.

Sch75 Schroeder AH, Mitschener M. Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. J Nutr 1975; 105: 452-8.

SZW02 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2002. The Hague, The Netherlands: Sdu, Servicecentrum Uitgevers, 2002: 43.

TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Wei85 Wei H, Luo Z. Yang SP. Effects of molybdenum and tungsten on mammary carcinogenesis in SD Rats. J Natl Cancer Inst 1985; 74: 469-73.

Wid86 Wide M, Danielsson BRG, Dencker L. Distribution of tungstate in pregnant mice and effects on embryonic cells *in vitro*. Environ Res 1986; 40: 487-98.

You82 Young BW, Bremmer I, Mills CF. Effects of tetrathiotungstate and dithiotungstate on copper metabolism in rats. J Inorg Biochem 1982; 16: 121-34.

## Annex

Occupational exposure limits for tungsten and its compounds in various countries.

| country -organisation | occupational exposure limit | | time-weighted average | type of exposure limit | note[a] | reference[b] |
|---|---|---|---|---|---|---|
| | ppm | $mg/m^3$ | | | | |
| the Netherlands | | | | | | |
| -Ministry of Social Affairs and | - | 5[c] | 8 h | administrative | | SZW02 |
| Employment | - | 1[d] | 8 h | | | |
| Germany | | | | | | |
| -AGS | - | 5[c, e] | 8 h | | | TRG00 |
| | - | 1[d, e] | 8 h | | | |
| -DFG MAK-Kommission | - | -[f] | | | | DFG02 |
| Great-Britain | | | | | | |
| -HSE | | 5[c] | 8 h | OES | | HSE02 |
| | | 10[c] | 15 min | | | |
| | | 1[d] | 8 h | OES | | |
| | | 3[d] | 15 min | | | |
| Sweden | - | 5[c] | 8 h | | | Arb00b |
| | - | 1[d] | 8 h | | | |
| Denmark | - | 5[c] | 8 h | | | Arb00a |
| | - | 1[d] | 8 h | | | |
| USA | | | | | | |
| - ACGIH | - | 5[c] | 8 h | TLV | | ACG02b |
| | - | 10[c] | 15 min | STEL | | |
| | - | 1[d] | 8 h | TLV | | |
| | - | 3[d] | 15 min | STEL | | |
| - OSHA | - | - | | | | ACG02a |
| - NIOSH | - | 5[c] | 10 h | REL | | ACG02a |
| | - | 10[c] | 15 min | STEL | | |
| | - | 1[d] | 10 h | REL | | |
| | - | 3[d] | 15 min | STEL | | |
| European Union | | | | | | |
| - SCOEL | - | - | | | | CEC00 |

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Metal (dust/powder) and insoluble compounds.

[d] Soluble compounds.

[e] Measured as the inhalable fraction of the aerosol.

[f] Listed among compounds for which studies of effects in man and in experimental animals have yielded insufficient information for the establishment of MAK values.