Health Council of the Netherlands

Tungsten and tungsten compounds

Evaluation of the carcinogenicity and genotoxicity

2013/16

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Tungsten and tungsten compounds*
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Geachte minister,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan wolfraam- en wolfraamverbindingen.

Dit advies maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb het advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. W.A. van Gool,
voorzitter

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Tungsten and tungsten compounds

Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of the
Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2013/16, The Hague, July 12, 2013

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de Subcommissie Classificatie van carcinogene stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie wolfraam en wolfraamverbindingen onder de loep. Wolfraam wordt, vaak als legering, toegepast onder andere als gloeidraad in lampen, in onderdelen van röntgenbuizen, in dartpijlen en in onderdelen van golfclubs. De hardheid en de hoge dichtheid van wolfraam maakt ook militaire toepassingen in doordringende projectielen mogelijk. De niet-gelegeerde vorm van wolfraam wordt voornamelijk gebruikt in elektrische toepassingen. Wolfraamverbindingen worden voornamelijk industrieel toegepast, als katalysatoren, en verder onder andere in keramische pigmenten en beschermende coatings. Wolfraamcarbide wordt gebruikt voor de productie van instrumenten om harde materialen te vermalen en te snijden.

Op basis van de beschikbare gegevens is de commissie van mening dat de gegevens over wolfraam en wolfraamverbindingen niet voldoende zijn om de kankerverwekkende eigenschappen te evalueren (categorie 3).*

* Volgens het classificatiesysteem van de Gezondheidsraad (zie bijlage E).

Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the Subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the Committee. In this report, the Committee evaluates tungsten and tungsten compounds. Tungsten is used, often as alloy, amongst others as light bulb filaments, as part of x-ray tubes, in darts and in golf club components. Tungsten's hardness and high density give it also military applications in penetrating projectiles. Pure tungsten is used mainly in electrical applications. Chemical compounds of tungsten are mainly used in industry, as catalysts, and in ceramic pigments and protective coatings. Tungsten carbide is used to make grinding and cutting tools.

The Committee concludes that the available data are insufficient to evaluate the carcinogenic properties of tungsten and tungsten compounds (category 3).*

* According to the classification system of the Health Council (see Annex E).

Chapter 1

Scope

1.1 Background

In the Netherlands, a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances and to propose a classification with reference to an EU-directive (see Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex E).

This report contains the evaluation of the carcinogenicity and genotoxicity of tungsten and tungsten compounds (tungsten dioxide, tungsten trioxide, tungsten carbide, ditungsten carbide, hexacarbonyl-tungsten, tungsten hexachloride, disodium wolframate, sodium tungstate (anhydrous), sodium tungsten hydroxide oxide phosphate, ammonium wolframate, and tungsten hexafluoride).*

* The scope of the report is limited to tungsten, and tungsten compounds that are anticipated to display toxicity that is reasonably attributable to tungsten. Results on tungsten alloys with toxic metals (such as cobalt, nickel or cadmium) do not provide specific information on tungsten, and are therefore not taken into account in this report.

1.2 Committee and procedures

The evaluation is performed by the Subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter to the Minister can be found in Annex C.

In 2013, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the Committee is commonly based on scientific data, which are publicly available. The starting points of the Committee's reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). In the case of tungsten and tungsten compounds such an IARC-monograph is not available.

Alternatively, the toxicological profile of tungsten as described by The Agency for Toxic Substances and Disease Registry (ATSDR) has been used as starting point.[1] This means that the original sources of the studies, which are mentioned in the toxicological profile published by the ATSDR, have only been reviewed by the Committee when these are considered relevant in assessing the carcinogenicity and genotoxicity of the substance in question.

An additional search was conducted from 2004 till September 2012 using online databases Medline, Toxline, and Chemical Abstracts, using carcino*, mutagen*, genotox* and CAS numbers 7440-33-7, 12036-22-5, 1314-35-8, 12070-12-1, 11130-73-7, 12070-13-2, 14040-11-0, 13283-01-7, 10213-10-2, 13472-45-2, 51312-42-6, 12028-06-7, or 7783-82-6 as key terms. The relevant data were included in this report. As no specific data were retrieved on nanoparticles derived from, or containing tungsten, these are not further addressed in this evaluation.

Chapter 2

General information

Tungsten is a naturally occurring element found in the earth's surface rocks. Tungsten metal typically does not occur as the free element in nature. Tungsten forms a variety of different compounds, such as tungsten trioxide, tungsten carbide, and ammonium paratungstate.[1]

The identity and some of the physico-chemical properties of tungsten and tungsten compounds are specified in Table 1. The data have been retrieved from the toxicological profile for tugsten by the ATSDR[1], the European Substance Information System (ESIS)*, the Hazardous Substances Data Bank (HSDB)**, and the INCHEM database of the International Programme on Chemical Safety (IPCS)***.

* ttp://ecb.jrc.ec.europa.eu/esis/.
** ttp://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
*** http://www.inchem.org/.

2.1 Identity and physico-chemical properties

Table 1 Identification of the evaluated tungsten compounds (adapted from ATSDR[1]).

	Molecular formula	Synonyms	CAS#	EINECS#	appearance
Tungsten	W	Wolfram; VA (tungsten)	7440-33-7	231-143-9	Steel-gray to tin-white solid metal
Tungsten dioxide	WO_2	Tungsten oxide	12036-22-5	234-842-7	Blue solid
Tungsten trioxide	WO_3	Tungsten blue; tungsten oxide (WO_3; tungsten(VI) oxide; tungstic acid; tungstic acid anhydride; tungstic anhydride; tungstic oxide; wolframic acid, anhydride	1314-35-8	215-231-4	Canary-yellow solid; dark orange when heated
Tungsten carbide	WC	Tungsten carbide; tungsten monocarbide	12070-12-1	235-123-0	Grey solid
Ditungsten carbide	W_2C	Tungsten carbide	12070-13-2	235-124-6	Solid
Hexacarbonyl-tungsten	WC_6O_6	Tungsten carbonyl; tungsten hexacarbonyl	14040-11-0	237-880-2	White solid
Tungsten hexachloride	WCl_6	Tungsten chloride Hexachlorotungsten; wolfram hexachloride	13283-01-7	236-293-9	Purple solid
Disodium wolframate	$Na_2WO_4 \cdot 2H_2O$ (dihydrate)	Sodium tungstate, Disodium tetraoxatungstate (2-), dihydrate; tetraoxotungstate (2-); disodium tungstate, dihydrate; sodium tungsten oxide, dihydrate; sodium wolframate, dihydrate; tungstic acid, disodium salt, dihydrate	13472-45-2	236-743-4	White solid
Sodium tungsten hydroxide oxide phosphate	ca. $2Na_2OP_2O_5 \cdot 12WO_3 \cdot 18H_2O$	Sodium phosphotungstate Sodium tungstophosphate; tungstophosphoric acid, sodium salt; sodium-12- tungstophosphate	51312-42-6	257-132-9	White solid
Ammonium wolframate	$(NH_4)6W_7O_{24}$	Ammonium paratungstate	12028-06-7	234-732-9	White solid
Tungsten hexafluoride	WF_6	Tungsten fluoride	7783-82-6	232-029-1	Colorless; pale yellow liquid

Table 1 (cont.) Identification of the evaluated tungsten compounds (adapted from ATSDR[1]).

	Molecular weight	Boiling point	Melting point	Solubility	Density (g/cm^3)
Tungsten	183.8	5,900 °C	3,410 °C	Insoluble in water; Soluble in mixture of nitric acid and hydrofluoric acid	18.7
Tungsten dioxide	215.84	Not applicable	1,500-1,700 °C (decomposes)	Insoluble in water and organic solvents	10.82 (theoretical)
Tungsten trioxide	231.85	No data	1,472 °C	Insoluble in water; Caustic alkalies; very slightly soluble in acids; slightly soluble in hydrofluoric acid	7.2
Tungsten carbide	195.85	6,000 °C	2,785 °C	Insoluble in water; Soluble in nitric acid/ hydrogen fluoride; aqua regia	15.6
Ditungsten carbide	379.69	No data	~2,800 °C	Insoluble in water	14.8
Tungsten carbonyl	351.90	Not applicable	170 °C (decomposes)	Insoluble in water; soluble in organic solvents	2.65
Tungsten hexachloride	396.56	346.75 °C	275 °C	Decomposes in water; soluble in ethanol, organic solvents, lingroine	3.52
Disodium wolframate	329.85	Not applicable	Decomposes at 100 °C with loss of water and then melts at 692 °C	Highly soluble in water; Insoluble in alcohol and acids	3.25
Sodium tungsten hydroxide oxide phosphate	No data	No data	No data	Very soluble in water; very soluble in alcoholse	No data
Ammonium wolframate	1779.16	No data	No data	Soluble in water; insoluble in alcohol	No data
Tungsten hexafluoride	297.83	17 °C	2.3 °C	Reacts with water; dissolves in benzene, cyclohexane, or dioxane; soluble in anhydrous hydrogen fluoride	12.173

2.2 IARC classification

Tungsten and tungsten compounds have not been evaluated by IARC.

Chapter 3

Carcinogenicity studies

3.1 Observations in humans

The only available study addressing the potential carcinogenic effects of tungsten in humans is a cross-sectional exposure assessment by the Centers for Disease Control and Prevention (CDC).[2,3] The purpose of this investigation was to identify contaminants unique to the Churchill County community, which might be associated with the elevated number of children in Churchill County, Fallon, Nevada in whom acute lymphocytic leukaemia (ALL) had been diagnosed.

The study population consisted of children already enrolled in a Nevada State Health Division leukaemia investigation, and who resided in Churchill County before diagnosis of their ALL or acute myelocytic leukaemia. These cases were randomly matched by sex and age with other children from this region. The cross-sectional exposure assessment included everyone else living in the children's current home (i.e. all siblings, parents, guardians, and other adults). The study enrolment comprised a total of 205 participants from 14 case families and 55 comparison families. Biological and environmental samples were tested for heavy metals, persistent and non-persistent pesticides, polychlorinated biphenyls (PCBs), and volatile organic compounds (VOCs).

Community-wide, an elevated level of exposure to the element tungsten was found. However there was no statistically significant association with an increase in leukaemia for cases versus controls (OR 0.78, p-value 0.57).

A recent environmental study of metal accumulation in tree rings from different time periods (dendrochemistry) suggested increased tungsten and cobalt concentrations in Churchill County at the time of the onset of excessive childhood leukaemia.[4] Overall, the lack of association between childhood leukaemia and environmental contaminants (including tungsten) do not indicate an environmental contaminant as a cause.

3.2 Carcinogenicity studies in animals

3.2.1 Carcinogenicity studies

Carcinogenicity studies that have been described for tungsten or tungsten compounds only involve exposure to sodium tungstate.

Inhalation studies

No inhalation studies are available.

Oral administration

Sodium tungstate was administered at a level of 5 ppm in drinking water (equivalent to a daily dose of approximately 0.6 mg sodium tungstate/kg bw; calculated using default values for body weight and water consumption[5]) to male and female rats for life.[6] Treatment caused a slight increase in body weight gain in both sexes and reduced lifespan significantly in males when compared to controls. However, no increase in (gross) tumour incidence was found: 4 (2 considered malignant)/25 in treated animals versus 4 (2)/26 in controls for males and 17 (8)/24 in treated animals vs 13 (5)/20 in controls for females.

In a similar study design, sodium tungstate (specified as 5 ppm tungsten, equivalent to a daily dose of approximately 1 mg tungsten/kg bw[5]) was studied as part of a panel of trace metals in male and female mice.[7] Although no significant effect on body weight was observed, the longevity (mean age of the last surviving 10%) of males appeared reduced. The authors stated that no trace metal was tumourigenic, however they did not show any specific data on the tungsten exposed groups.[7]

Sodium tungstate was used as an inhibitor of molybdenum absorption, to study the effect of molybdenum on the induction of esophageal and forstomach tumours in rats by N-nitrososarcosine ethyl ester (NSEE).[8] Sodium tungstate itself, at a reported concentration of 100 ppm added to the drinking water

(equivalent to a dose of 12 mg/kg bw/day[5]), did not induce oesophageal and forestomach tumours when administrated for 19 or 30 weeks.

Gunnison et al. used sodium tungstate as a mean to induce sulfite oxidase deficiency and increase systemic sulphite in rats, for studying the effect of systemic sulfite on benzo[a]pyrene-induced lung carcinomas.[9] In this study, two groups of male Sprague-Dawley rats were exposed to sodium tungstate only (100 or 400 ppm in drinking water for 21 weeks; approximating 12 or 49 mg/kg bw/day, respectively[5]). A complete necropsy was performed on each animal with particular attention given to the respiratory tract. No increase in lung tumours was observed. The incidence of mammary tumours (fibroadenoma and adenocarcinoma) was increased with increasing concentration of tungsten, however this increase was not statistically significant.

The Committee notes the limitations in study design (relatively short exposure period, limited pathological analyses) and subsequent reporting of the available oral carcinogenicity studies.

Dermal application

No dermal studies are available.

3.2.2 Tumour promotion studies

Both positive and negative data on tumour promoting activity of sodium tungstate have been reported, depending on the initiator used and the route of exposure applied.

In the study by Gunnison et al. the effect of sodium tungstate was studied on benzo[a]pyrene-induced lung carcinomas in rats.[9] In this study, sodium tungstate (100 or 400 ppm in drinking water; 12 or 49 mg/kg bw/day, respectively[5]) did not statistically significantly affect the initiation of squamous cell carcinoma of the respiratory tract or incidences of mammary gland tumours of rats treated with benzo[a]pyrene by instillation.

Sodium tungstate administered at 100 ppm in drinking water (12 mg/kg bw/day[5]) for 19 weeks did not enhance the effect of NSEE administrated by gastric intubation in rats.[8] However, at a concentration of 200 ppm (24 mg/kg bw/day[5]), an increase in precancerous lesions of the oesophagus was noted compared to NSEE alone.

In a study by Wei et al., rats received an intravenous injection of 5 mg N-nitroso-N-methylurea (NMU)/100 g bw daily for fifteen days, and were continuously exposed to 150 ppm tungsten in drinking water (21 mg/kg

bw/day[5]).[10] Mammary tumours were scored by palpation, of which only histologically confirmed carcinomas were used for analysis. The tungsten-supplemented group was the first to develop palpable mammary tumours, resulting in a significant increase in the incidence of histologically confirmed mammary carcinomas, 125 days after NMU administration (75.2% compared to 50% for NMU alone). No difference was observed 198 days after NMU administration (91.1% compared to 90.7%).

In view of its use in ammunition, the carcinogenic effect of tungsten alloy has been investigated.

Intramuscular implantation of weapons-grade tungsten alloy pellets consisting of tungsten, nickel and cobalt have been studied in male F344 rats.[11] All animals (n = 92) developed local, extremely aggressive rapidly metastasizing tumours (high-grade pleomorphic rhabdomyosarcomas) necessitating euthanasia of these animals. Nickel pellets caused malignancy comparable to that induced by the alloy pellets.

Unfortunately, tungsten pellets were not included as a control. Since both nickel[12] and cobalt[13,14] have previously been reported to be carcinogenic when administrated intramuscularly, no conclusions could be made on the carcinogenic effect of tungsten alone.

3.3 Transformation assays

Results obtained with transformation assays are negative. Sodium tungstate did not induce morphological transformation in primary Syrian embryo hamster cells at concentrations up to 20 µg/mL.[15]

Using human osteoblast cells, Miller et al.[16] found that tungsten (46 µg/mL) was not capable to transform immortalised HOS cells to the tumourigenic phenotype (characterized by anchorage-dependent growth, tumour formation in nude mice and a high expression level of the K-*ras* oncogene) above untreated control levels.

3.4 Conclusion

Epidemiological studies are not available. The available animal carcinogenicity studies show severe limitations in design and reporting; no transformation capability has been observed. The Committee therefore cannot draw any conclusions on the carcinogenic properties of tungsten and tungsten compounds.

Chapter 4

Genotoxicity

4.1 Gene mutation assays

In vitro assays

In an Ames test conducted by the NTP, tungsten trioxide did not induce mutations in bacterial strain TA 100, TA 98 and *E. coli* pKM101 (with and without 10% rat S9).[17] Sodium tungstate demonstrated mutagenic activity in a bacterial bioluminescence test in *P. fischeri* (Pf-13), at a concentration which was specified by the authors as 2-3 times lower than the toxic range.[18]

Sodium tungstate was included in a preliminary screen using *S. cerevisiae* D7 sensitive to gene conversion at the *trp* locus and reverse mutation at the *ilv* locus.[19] Incubation with sodium tungstate resulted in a concentration gradient (concentration further unspecified) with some degree of toxicity evident as an area of cell death and the result was reported as 'weak positive'. In *S. cerevisiae* strain DIS13, sodium tungstate at a concentration range of 7-44 mg/mL caused a minor increase in recombinant frequency and a more pronounced induction of diploid spores.[20] The results of both studies in *S. cerevisiae* are difficult to interpret due to the high and toxic concentrations used.

Tungsten anion showed positive results (a 3-fold induction compared to control) at 'relatively non-toxic levels' in the *Hprt* forward mutation assay using Chinese hamster lung V79 cells.[21] Further details have not been provided in this abstract.

In vivo assays

No in vivo mutagenicity assays with tungsten (and tungsten compounds) are available.

4.2 Cytogenetic assays

In vitro assays

Van Goethem et al. studied the induction of micronuclei formation in human peripheral lymphocytes after treatment with tungsten carbide (up to 100 µg/mL), cobalt (up to 6 µg/mL) and equivalents of tungsten carbide-cobalt alloy.[22] A pronounced induction of cells with micronuclei was observed after incubation at the highest concentration with either tungsten carbide-cobalt alloy (51.0 ± 8.5%) or cobalt alone (51.5 ± 0.7%), compared with the control (10.5 ± 0.7%). Micronucleus induction by tungsten carbide also reached statistical significance (maximum of 25.0 ± 2.8% at 50 µg/mL), however, at relatively high concentrations and this effect was not concentration-dependent.

Sodium tungstate (tested up to 10 µg/mL) did not induce chromosome aberrations in human lymphocytes or Syrian hamster embryo cells, nor did it induce sister chromatid exchange (SCE) in human whole blood cultures.[23]

Cobalt and tungsten carbide-cobalt alloy induced a concentration – and time-dependent increase of single strand breaks up to 100 µg total powder/mL (cobalt ranging from 0-6 µg/mL) in human peripheral lymphocytes in a single-cell gel electrophoresis ('Comet') assay. Tungsten itself however, did not when tested up to a concentration of 100 µg/mL.[24] Similar results were found when tungsten carbide and tungsten carbide-cobalt alloy were tested at a concentration range of 25-250 µg/mL in an alkaline elution test.

Van Goethem et al. reported a positive response in the comet assay for tungsten carbide-cobalt at 0-100 µg/mL alloy with a 0-6 µg/mL cobalt equivalent). Tungsten carbide alone (10-100 µg/mL) caused a small but significant response, however this response was not concentration-dependent.[22]

In a more recent DNA single-strand break analysis using alkaline elution of HOS cells, extrafine tungsten metal (d_{50} 1-3 µm) tested positive, but only at the highest, somewhat cytotoxic concentrations tested (i.e. 92 and 184 µg/mL) and not in a dose-dependent manner. Tungsten alloys showed responses of a magnitude higher and at lower mass concentrations.[16]

Kühne et al. tested tungsten carbide in the non-nano form in an in vitro micronucleus assay.[25] No increase in the number of micronucleated HepG2 cells was observed at concentrations up to 30 µg/mL.

In vivo assays

No in vivo chromosomal aberrations assays with tungsten (and tungsten compounds) are available.

4.3 Miscellaneous

In a DNA damage microscreen using *E. coli* WP2sλ, sodium tungstate (-S9) induced prophages (which occurs when the host SOS response is triggered by DNA damage) up to 4-fold compared to the background growth at a concentration of 412 µg/mL.[26]

4.4 Conclusion

Limited genotoxicity data are available. Several tungsten compounds have been tested in in vitro tests, however, in vivo data are lacking. The Committee concludes that the available data are insufficient for drawing conclusions on the genotoxic properties of tungsten and tungsten compounds.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

Tungsten and tungsten compounds have not been evaluated by IARC.

The public literature retrieved by the Committee provided little data on the possible carcinogenicity of tungsten and tungsten compounds. A single exposure assessment raised concern due to relatively high exposure to the element tungsten, and the observation of an elevated incidence of acute lymphocytic leukaemia (ALL), however no association could be established.

The only animal carcinogenicity data on single-substance exposure to tungsten or tungsten compounds consist of one study in rats and one in mice, both with sodium tungstate. In both studies, no increase in tumours was noted. These studies, however, show methodological limitations and especially the latter was poorly reported.

The Committee therefore cannot draw any conclusions on the carcinogenic properties of tungsten and tungsten compounds.

Inconsistent results have been observed in in vitro genotoxicity tests, whereas in vivo genotoxicity data are lacking. The Committee cannot draw any conclusions on the genotoxicity of tungsten.

5.2 Recommendation for classification

The Committee concludes that the available data are insufficient to evaluate the carcinogenic properties of tungsten and tungsten compounds (category 3). *

* According to the classification system of the Health Council (see Annex E).

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A	Request for advice
B	The Committee
C	Submission letter
D	Comments on the public review draft
E	Classification of substances with respect to carcinogenicity

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. van Benthem
  Genetic Toxicologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- Ms. M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Chemicals NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- S.R. Vink, *scientific secretary*
  Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Submission letter

Subject : Submission of the advisory report *Tungsten and tungsten compounds*
Your Reference : DGV/MBO-U-932542
Our reference : I-7820/SV/fs/246-Q18
Enclosed : 1
Date : July 12, 2013

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to tungsten and tungsten compounds.

This advisory report is part of an extensive series in which carcinogenic substances are classified in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Subcommittee on the Classification of Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The advisory report has been assessed by the Health Council's Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)

Prof. dr. W.A. van Gool,
President

Annex **D**

Comments on the public review draft

A draft of the present report was released in 2013 for public review. The following organisations and persons have commented on the draft document:

- Mr. T.J.Lentz, National Institute for Occupational Safety and Health, USA.

Annex **E**

Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category (before 16 December 2008)	Comparable with EU Category (as from 16 December 2008)
1A	The compound is known to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound should be regarded as carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	not applicable	not applicable
(4)	The compound is probably not carcinogenic to man.	not applicable	not applicable

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[27]

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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