Health Council of the Netherlands

Adriamycin

Health-based calculated occupational cancer risk values

2015/06

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Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Adriamycin*
Uw kenmerk : DGV/BMO/U-932542
Ons kenmerk : U-8338/BvdV/cn/459-R71
Bijlagen : 1
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Geachte minister,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan adriamycine.

Dit advies maakt deel uit van een uitgebreide reeks, waarin concentratieniveaus in lucht worden afgeleid die samenhangen met een extra kans op (overlijden aan) kanker van 4 per 1.000 en 4 per 100.000 door beroepsmatige blootstelling. De conclusies van het genoemde advies zijn opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en omgeving.

In dit advies concludeert de commissie dat adriamycine een carcinogene stof is en beveelt aan om deze stof te classificeren in categorie 1B (de stof moet beschouwd worden als kankerverwekkend voor de mens). De commissie is echter van mening dat wegens gebrek aan adequate humane en dierexperimentele gegevens het niet mogelijk is om de extra kans op kanker na blootstelling aan adriamycine te berekenen.

Ik heb dit 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. J.L. Severens,
vicevoorzitter

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Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2015/06, The Hague, 18 maart 2015

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).

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Samenvatting

Op verzoek van de minister van Sociale zaken en Werkgelegenheid, leidt de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad, de concentraties van een stof in de lucht af die samenhangen met een vooraf vastgesteld extra risico op kanker (4 per 1.000 en 4 per 100.000 individuen) door beroepsmatige blootstelling gedurende het arbeidzame leven. Het gaat om kankerverwekkende stoffen die door de Gezondheidsraad of de Europese Unie geclassificeerd zijn in categorie 1A of 1B en die kankerverwekkend zijn via een stochastisch genotoxisch mechanisme. Voor de schatting maakt de commissie gebruik van de *Leidraad Berekening Risicogetallen voor kankerverwekkende stoffen* van de Gezondheidsraad.[1] In dit advies onderzoekt de commissie de mogelijkheid om zo'n schatting te maken voor adriamycine. Adriamycine is een cytotoxisch anthracycline dat wordt gebruikt in antimitotische chemotherapie.

De commissie concludeert dat adriamycine een carcinogene stof is met een stochastisch genotoxisch werkingsmechanisme. De commissie beveelt aan om deze stof onder te brengen in categorie 1B (*stof moet beschouwd worden als kankerverwekkend voor de mens*).

De commissie is echter van mening dat wegens gebrek aan voldoende gegevens het niet mogelijk is om de extra kans op kanker na blootstelling aan adriamycine te berekenen.

Executive summary

At the request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, derives so-called health-based calculated – occupational cancer risk values (HBC-OCRVs) associated with excess cancer levels of 4 per 1,000 and 4 per 100,000 as a result of working life exposure to substances. It concerns substances which are classified by the Health Council or the European Union in category 1A or 1B, and which are considered stochastic genotoxic carcinogens. For the estimation, the Committee uses the *Guideline for calculating carcinogenic risks* of the Health Council.[1] In this report the Committee evaluates the possibility to establish such estimates for adriamycin. Adriamycin is a cytotoxic anthracycline antibiotic used in antimitotic chemotherapy.

In this report, the Committee concludes that adriamycin is a carcinogenic substance with a stochastic genotoxic mechanism. The Committee recommends adriamycin to be classified in category 1B *(substance presumed to be carcinogenic to humans*).

The Committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional lifetime cancer risk for adriamycin.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for genotoxic chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, at request of the Minister of Social Affairs and Employment (Annex A). For non-stochastic (thresholded) genotoxic substances this evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action is not thresholded, as is the case for substances with stochastic genotoxic carcinogenic properties. In that case, an exposure-response relationship is recommended for use in regulatory standard setting, i.e. the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The Committee calculates HBC-OCRVs for compounds, which are classified as genotoxic carcinogens by the European Union or by the Committee.

For the establishment of the HBC-OCRV's, the Committee generally uses a linear extrapolation method, as described in the Committee's report *Calculating cancer risk due to occupational exposure to genotoxic carcinogens* and *Guideline for calculating carcinogenic risk.*[1,2] The linear model to calculate

occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee. The members of the Committee are mentioned in Annex B. The Committee requested the DECOS Subcommittee on the Classification of Carcinogenic Substances to evaluate the genotoxic mechanism of adriamycin (see Annex F and G). The recommendations of the Subcommittee were used by DECOS to decide on the appropriate approach to risk assessment. The submission letter (in English) to the Minister can be found in Annex C. In July 2014, 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 advisory report. The received comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Data

The Committee's recommendation has been based on scientific data, which are publicly available. Data were obtained from the online databases Chemical Abstracts, XToxline, and Medline, using carcinogen, cancer, tumour or neoplasm, and CAS registry number as keywords. In addition, in preparing this report the following reviews were consulted: IARC monographs from 1976 and 1987.[3,4] The last search was performed in December 2014.

Chapter 2

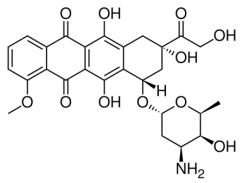
Identity, toxicity profile and classification

2.1 Identity and physical and chemical properties

Adriamycin (doxorubicin) is a cytotoxic anthracycline antibiotic used in antimitotic chemotherapy. It is infused intravenously to treat a variety of cancers.[5] Since 1996, a concentrate of adriamycin hydrochloride in a pegylated liposomal formulation has been authorized in Europe.[6] Occupational exposure might occur during drug preparation and administration or cleanup of medical waste or indirectly during nursing of patients via the dermal route. Inhalation exposure is considered to be negligible taking into consideration the very low vapour pressure of adriamycin and the supply in vials and administration by infusion.[5]

The identity and some physicochemical properties of adriamycin are given below.[4,5,7-10]

Chemical name (CAS)	:	(8S-cis)-10-[(3-amino-2,3,6-trideoxy-L-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphtacenedione
CAS registry number	:	23214-92-8
EC number	:	245-495-6
RTECS number	:	AV9800000
IUPAC name	:	(7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione

Synonyms	: 14-hydroxydaunomycin; Adriablastina; doxorubicin hydrochloride; NCS 123127
Molecular formula	: $C_{27}H_{29}NO_{11}$
Physical description and colour	: red, crystalline solid
Structure	: 
Molar mass	: 543.5 g/mol
Melting point	: 229-231°C
Boiling point	: not available
(Relative) density	: not available
Solubility in water	: 20 g/L (temperature not indicated)
Solubility in organic solvents	: soluble in aqueous alcohols; moderately soluble in anhydrous methanol; insoluble in non-polar organic solvents
Log P (n-octanol/water)	: 1.27 at pH 7.4
Vapour pressure	: 1.20×10^{-22} Pa (calculated)
Relative vapour density	: not available
Flash point (open/closed cup)	: not available
Odour threshold	: not available
Conversion factor (20 °C, 101.3 kPa)	: 1 mg/m^3 = 4.50 ppm; 1 ppm = 0.22 mg/m^3

2.2 Classification as a carcinogenic substance

Adriamycin is not classified by the European Union. In her latest classification (1987) IARC has classified the compound as a 2A carcinogen (*probably carcinogenic to humans*).[3,9] [In 2014 the 13th NTP Report on Carcinogens considers adriamycin as *reasonably anticipated to be a human carcinogen* based on *sufficient evidence* of carcinogenicity from studies in experimental animals.[5]]

In 1995, DECOS concluded that there was *inadequate evidence* that adriamycin was carcinogenic to humans, that adriamycin was carcinogenic in rats by iv, sc and intravesicular administration and that adriamycin was mutagenic to bacteria and mammalian cells in vitro.[11] DECOS, in 1995, classified the compound as *a genotoxic carcinogen*.[11]

In the present evaluation the Committee (DECOS) follows the recommendation of the DECOS Subcommittee on the Classification of Carcinogenic Substances and classified adriamycin in category 1B (*substance presumed to be carcinogenic to humans*)(see Annex F and G).

2.3 Genotoxicity

IARC concluded previously that adriamycin is a potent genotoxicant.[3,4,12] Adriamycin is mutagenic in bacteria, in mammalian cells in vitro, and in vivo in Drosophila.[13-18] It causes chromosomal anomalies in hamster cells and human lymphocytes in vitro and in mouse bone marrow cells in vivo.[19-24] Adriamycin produces cell transformation in mouse fibroblast cells and in Fisher rat embryo cells in vitro.[15,25] Patients treated with adriamycin showed significant increases in the incidence of chromosomal aberrations and sister chromatid exchanges.[26,27] Detailed description of the studies is given in Annex F.

Adriamycin is a chemotherapeutic agent whose mode of action includes intercalation into the DNA double helix thus preventing their unwinding for replication and resulting in DNA damage, binding of DNA-associated enzymes such as topoisomerase II.[28,29] It is very likely that for genotoxicity of adriamycin similar mechanisms as for anti-tumour effects apply. According to the Committee non-covalent inhibition of topoisomerase II (enzyme active in replication) may play an important role but also simple DNA intercalation or generation of oxidative stress may contribute to the development of both mutagenicity and genotoxicity.[6,28,30,31]

The Committee concludes in accordance with the recommendation of the DECOS Subcommittee on the Classification of Carcinogenic Substances (see Annex F) that adriamycin acts by a stochastic genotoxic mechanism.[11,32,33] Therefore, it is recommended that health-based calculated occupational cancer risk values (HBC-OCRVs) should be calculated for regulatory standard setting.

2.4 Non-carcinogenic effects

Limited information is available on uptake, distribution, and excretion of adriamycin after inhalation, or dermal exposure.[34] It is not stable in gastric acid, and animal studies indicate that the drug undergoes little, if any, absorption from the GI tract. The drug is extremely irritating to tissues and, therefore, must be administered intravenously.[9] Adriamycin hydrochloride displays extensive tissue distribution and a rapid elimination clearance (24-73 L/h/m^2).[6]

Sixty seven percent mortality was observed in rats after a single dose of 9 mg/kg bw (route not specified). In dogs, 0.5 mg/kg bw per day iv was lethal after 5-10 doses, while 0.125-0.25 mg/kg bw per day was toxic (inhibition of haemopoiesis) to both dogs and rats, but not lethal.[7] For humans, LD_{Lo}s of 15

mg/kg bw (iv, single dose) and 380 mg /kg bw (31-week, repeated-dose) have been reported.

Clinical observations, supported by studies in vitro and in in experimental animals, report a number of toxic effects. Administration of adriamycin leads to dose-related myelosuppression and mucositis. Adriamycin is a potent myotoxin, causing cardiomyopathy and fibrosis.[34] Cardiotoxicity is considered the most important limitation for high dose adriamycin treatment.[29] The neurotoxic properties of adriamycin are reported to be mediated by transport of the substance to the brain followed by neuronal damage ('suicide retrograde axonal transport').[35,36] Adriamycin is also known to cause hepatotoxicity, related to overproduction of ROS. Moreover, adriamycin may cause nephropathy and proteinuria by injuring glomerular podocytes.[29]

Otterson et al. (2007) evaluated the toxicity profile of inhalational doxorubicin in patients with malignant disease in the lung.[37] The OncoMystModel CDD-2a inhalation device aerosolizes compounds to particles of 2 to 3 µm and prevents exhaled aerosol from escaping into the environment. Treatment was repeated every 3 weeks. No more than moderate pulmonary dysfunction was permitted (forced expiratory volume in 1s, forced vital capacity, and diffusing capacity for carbonmonoxide, all > 50% predicted; resting SaO2 > 90%). Fifty-three patients were enrolled at 13 dose levels ranging from 0.4 to 9.4 mg/m^2.The most common histologic diagnoses were sarcoma (n = 19) and non-small cell lung cancer (n = 16). Dose-limiting pulmonary toxicity (DLT) was observed at the 9.4 mg/m^2 dose level in two of four patients. Of 11 patients treated at the 7.5 mg/m^2 dose level, only one showed DLT consisting of a decline in forced vital capacity of >20% from baseline. No significant systemic drug-related toxicity was observed. Several patients experienced declines in pulmonary function test variables, which were attributed to progressive disease. Observed activity included a partial remission in a patient with metastatic soft tissue sarcoma previously treated with i.v. doxorubicin and ifosfamide. The authors conclude that inhaled doxorubicin is safe up to a dose of 7.5 mg/m^2 every 3 weeks in patients with cancer who had normal to moderately impaired pulmonary function.

Reduction in ovary size and weight, and ovulation rate correlating with a reduction in the population of secondary and primordial follicles was observed up to one month after treatment in female mice injected intraperitoneally with 7.5 mg/kg bw. Oocytes showed no morphological or chromosomal changes.[38] Male rats treated at 15 and 22 days of age with 5 mg/kg bw intraperitoneally showed germ cell depletion, tubular vacuolization, multinucleated formations of

spermatids and germ cells, reduction of seminiferous tubule volume and diameter, and reduced spermatogenesis resulting in infertility.[39]

2.5 Occupational exposure and existing occupational exposure limits

Occupational exposure to adriamycin occurs via inhalation, dermal exposure or ingestion. Probable occupational exposure scenarios are limited to handling of adriamycin in pharmacies, patient handling by hospital staff, sanitary and similar services, research and education (Pieri et al., 2010).[40] The Committee did not find reliable data with regard to the present size of the exposed population (Kauppinen et al., 2000).[41] Although teratogenic and adverse reproductive outcomes and increased cancers have been reported in health care workers exposed to antineoplastic drugs, data on exposure to adriamycin alone are lacking (Connor et al., 2006; Dranitsaris et al., 2005).[42,43]

No occupational exposure limits have been established for adriamycin.

Chapter 3

Carcinogenicity studies

3.1 Human studies

Human carcinogenicity studies have been summarized and evaluated by IARC (IARC 1976, 1982, 1987).[3,4,12] They concluded from the epidemiological data that the evidence for carcinogenicity to humans was *inadequate*.[3,4,12] No epidemiological studies were identified by IARC that evaluated the relationship between human cancer and exposure specifically to adriamycin. However, some cancer patients who received adriamycin in combination with alkylating agents and radiotherapy developed acute non lymphocytic leukemia and bone cancer (osteosarcoma)(IARC 1982).[44]

DECOS did not find any new, published epidemiological data on the effects of exposure to adriamycin alone. Several follow-up studies were performed in which patients with Hodgkin's disease were treated with adriamycin in combination with bleomycin, vinblastine and dacarbazine or patients with Ewing sarcoma or primitive neuroectodermal tumour of bone were treated with adriamycin in combination with vincristine, ifosfamide, cyclophosphamide and etoposide.[3,12,45-49] However, the results of these studies are not suitable for the risk assessment of the carcinogenic risk of adriamycin since adriamycin was always given in combination with other chemotherapeutic agents or radiation. Data on exposure to adriamycin alone are lacking.

3.2 Animal experiments

The compound is carcinogenic to rats after intravenous and subcutaneous injection. Adriamycin produced malignant tumours in the bladder after intravesical instillation.

The animal carcinogenicity data are summarized in Annex E and described in detail in Annex F. These studies include subcutaneous and intravenous studies and one study in which adriamycin was instilled intravesically into the urinary bladder. There were no oral, inhalatory or dermal carcinogenicity studies.

After repeated subcutaneous injections, 0.75 mg/kg/day (2 x 4 days with 3 days in between) adriamycin induced local sarcomas and mammary tumors in CD and Wistar-Lewis rats.[50]

A single intravenous injection of adriamycin in female rats resulted in an increased number of rats with mammary tumours. Most of these tumours were histologically defined as fibroadenomas.[15,51-53]

Intravesicular instillation of adriamycin into the urinary bladder in rats resulted in a low incidence of bladder papillomas (exposure period: 12 weeks, experimental period: 36 weeks). In the same experiment adriamycin appeared to enhance the number of bladder tumors in rats pretreated with *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN).[54]

3.3 Selection of the suitable study for risk estimation in the occupational situation

From the results of the studies summarized above, DECOS concluded that adriamycin is an animal carcinogen. The animal experiments were restricted to single or short-term exposure regimens and no exposure routes relevant for the occupational situation were included. The Committee considered none of the described experiments sufficiently suitable (considering length of exposure and experimental period, relevance of exposure routes, relevance of the tumours, purity of the test substance used, mortality before the end of the experimental period, dose-dependency of tumour development, see Annex E) for calculating the cancer risk of adriamycin under occupational conditions of exposure.

3.4 Calculation of the health-based occupational cancer risk values

Calculation of the health-based occupational cancer risk values is not possible as indicated in paragraph 3.3.

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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

- RA Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, and Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- D.J.J. Heederik
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  Occupational Hygienist, Netherlands Expertise Centre for Occupational Respiratory Disorders (NECORD), Utrecht
- H. van Loveren
  Professor of Immunotoxicology, Maastricht University, Maastricht, and National Institute for Public Health and the Environment, Bilthoven
- A.H. Piersma
  Professor of Reproductive and Developmental Toxicology, Utrecht University, and National Institute for Public Health and the Environment, Bilthoven
- H.P.J. te Riele
  Professor of Molecular Biology, VU University Amsterdam, and Netherlands Cancer Institute, Amsterdam

- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- G.B.G.J. van Rooy
  Occupational Physician, Arbo Unie Expert Centre for Chemical Risk Management, and Radboud UMC Outpatient Clinic for Occupational Clinical Toxicology, Nijmegen
- F. Russel
  Professor of Pharmacology and Toxicology, Radboud University Medical Centre, Nijmegen
- G.M.H. Swaen
  Epidemiologist, Maastricht University, Maastricht
- R.C.H. Vermeulen
  Epidemiologist, Institute for Risk Assessment Sciences, Utrecht
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- B.P.F.D. Hendrikx, *advisor*
  Social and Economic Council, The Hague
- G.B. van der Voet, *scientific secretary*
  Toxicologist, 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**

The submission letter (in English)

Subject : Submission of the advisory report *Adriamycin*
Your Reference : DGV/MBO/U-932342
Our reference : U-8338/BvdV/cn/459-R71
Enclosed : 1
Date : March 18, 2015

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to adriamycin.

This advisory report is part of an extensive series in which carcinogenic substances are evaluated for the possibility to establish health-based occupational cancer risk values in accordance with European Union guidelines. This involves substances to which people can be exposed under working conditions.

The advisory report was prepared by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council. The advisory report has been assessed by the Health Council's Standing Committee on Health and the Environment.

In this report, the Committee concludes that adriamycin is a carcinogenic substance (category 1B, substance presumed to be carcinogenic to humans).

The Committee is of the opinion that due to a lack of adequate data, it is not possible to estimate the additional lifetime cancer risk for adriamycin.

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)
Professor J.L. Severens,
Vice President

Annex **D**

Comments on the public review draft

A draft of the present report was released in July 2014 for public review. The following organization and persons have commented on the draft document:

- T.J. Lentz, T. Connor and L. Rojanasakul. National Institute for Occupational Safety and Health (NIOSH), Cincinnati OH, USA.

Annex **E**

Animal studies

Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
carcinogenicity study; rat, SD; 25F per dose group Bertazolli, 1971[51]	intravenous; 1x 8 mg/kg bw; Xpo = single injection Xpe = 1 year	Incidence of mammary tumours in animals sacrificed at the end of the experiment: Test group: 6/7 mammary tumours, mostly fibroadenomas Controls: 0/25	In the adriamycin group 18 of 25 rats died in the course of the experiment due to severe renal damage or bone marrow aplasia. Only one of these 18 rats had a mammary tumour. No relationship was found between death and presence or absence of tumours.
carcinogenicity study; rat, SD; 25F per dose group Marquardt, 1976[15]	intravenous in femoral vein; 1 x 5 mg/kg bw Xpo = single injection Xpe = 1 year	tumour incidence: Test group 15/17: 19 mammary tumours (16 fibroadenomas, 1 adenocarcinoma), 1 adrenal carcinoma, 1 Schwannoma; Controls: 5/20, 3 mammary tumours (1 fibroadenoma, 2 carcinoma), 1 cervical polyp, 1 lipoma	another group of 20 rats given 1 x 10 mg/kg bw iv died within 15 weeks
carcinogenicity study; rat, CD; 2- to 6-days old at start of treatment treated: 6M + 13F/dose group; controls: 11M +7F Casazza, 1977[50]	subcutaneous; 0.75 mg/kg/day Xpo= 2 x 4 days (3 days in between) Xpe= 2 years	tumour incidence: Males 6/6:2 fibrosarcomas, 1 osteosarcoma, 1 epidermoid carcinoma, 2 unclassified sarcomas. Females 13/13: 5 mammary adenomas, 4 mammary fibroadenomas, 1 mammary adenocarcinoma, 1 fibrosarcoma (with lung metastases), 1 cervical polyp, 1 unclassified sarcoma. Controls: 0/11 males, 3/7 females (3 mammary adenomas)	purity: ?;[a]

carcinogenicity study; rat, Wistar-Lewis, 2- to 6-days old at start of treatment Treated: 20M +18F/ dose group; controls: 23M +19F Casazza, 1977[50]	subcutaneous; 0.5, 0.75 mg/kg/day Xpo= 2 x 4 days (3 days in between) Xpe= 2 years	Males: high dose: 11/20: 6 fibrosarcomas, 1 osteosarcoma, 1 mammary adenocarcinoma, 1 fibroma, 1 schwannoma, 1 neurofibrosarcoma, 1 leiomyoma low dose:10/20: 3 neurofibromas, 2 fibrosarcomas, 1 leiomyosarcoma, 1 leiomyoma, 1 fibrous hystiocytoma, 1 unclassified sarcoma, 1 unclassified tumour controls: 1/23: 1 fibrosarcoma Females: high dose: 12/18: 4 fibrosarcomas, 2 mammary fibroadenomas, 2 mammary adenocarcinomas, 1 leiomyosarcoma, 3 unclassified sarcoma, 1 unclassified tumour low dose: 11/18: 1 mammary adenoma, 1 mammary fibroadenomas, 1 mammary adenocarcinoma, 1 fibroma, 1 schwannoma, 1 leiomyosarcoma, 3 unclassified sarcoma, 1 unclassified tumour controls: 1/19: 1 mammary fibroadenoma	purity: ?;[a]
repeated dose study; rat; n=31-61 F/dose group Ohtani, 1984[54]	intravesical; 4 wks: pretreatment with 0.05% BBN[b]) in drinking water, 1 wk: without treatment, 12 wks: intravesical application of adriamycin (0.15 mg/ 0.3 ml, 0.3 mg/ 0.3 ml) for 1 hour, once per wk controls: 12 wks saline or no treatment or adriamycin (0.3 mg/ 0.3 ml) without pretreatment; Xpo= 12 wks Xpe= 36 wks	Treatment with BBN[b] followed by saline and/ or no treatment induced papillary or nodular hyperplasia, papillomas, and cancer Treatment with adriamycin (without pretreatment) induced only hyperplasia and papilloma After pretreatment with BBN[b] adriamycin induced papillary or nodular hyperplasia, papillomas, and cancer. Two-stage bladder carcinogenesis is promoted by adriamycin.	purity: ?; [a] only bladder effects investigated; adriamycin shows tumour promoting activities
1-y carcinogenicity study; rat, SD; 40M + 40F/dose group/ Jang, 1987[52]	Intravenous in tail vein; 1. single dose, 10 mg/kg bw 2. single dose, 2 mg/kg bw 3. 5 x 2 mg/kg bw within 2 days 4. 5 x 0.9 % NaCl within 2 days Xpo = 1, 2 days Xpe = 1 year	deaths: All high dose animals (group 1), 4M + 4F (group 2), 37M +16F (group 3), 1F (controls) mammary tumors (all rats, except those with advanced autolysis were examined); 1. F 0/34, M 0/33, 2. F 11/37, M 2/40, 3. F 15/37, M 0/37, 4. F 3/40, M 0/40; 22 of these tumors were fibroadenomas, 9 were adenocarcinomas renal effects (only rats surviving until termination) -dysplastic foci: 2. F 1/36, M 6/36; 3. F 8/24, M 0/3; 4. F 0/39, M 0/40 -renal cell tumour: 2. F 2/36, M 3/36; 3. F 1/36, M 0/3; 4.F 0/39, M 0/40	purity : ?;[a] other tumours no significant differences; high mortality due to pulmonary infection and irreversible toxic damage; dysplastic foci are considered to be the earliest manifestation of renal cell tumors.

[a] Purity is not given in publication.
[b] BBN = N-butyl-N-(4-hydroxybutyl)nitrosamine).

Annex **F**

Evaluation of the Subcommittee on the Classification of carcinogenic substances

Adriamycin is not classified by the European Union. In her latest classification (1987) IARC has classified the compound as a 2A carcinogen (*probably carcinogenic to humans*).[1] [In 2014 the 13th NTP Report on Carcinogens considers adriamycin as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.[2]]

In 1995, DECOS concluded that there was *inadequate evidence* that adriamycin was carcinogenic to humans, that adriamycin was carcinogenic to rats by iv, sc and intravesicular administration and that adriamycin is mutagenic to bacteria and mammalian cells in vitro.[3] DECOS, in 1995, classified the compound as *a genotoxic carcinogen*.[3] [This is probably the reason that adriamycin appeared on the list of carcinogenic substances of the Department of Social Affairs and Employment (Staatscourant, 2013).[4]]

In the present update (April 2014) the DECOS Subcommittee on the Classification of Carcinogenic Substances evaluated the existing and new information regarding human, animal and in vitro studies on carcinogenicity and genotoxicity of adriamycin.

Human studies

IARC concluded from the epidemiological data that the evidence for carcinogenicity to humans was inadequate (IARC 1976, 1982, 1987).[1,5,6] No epidemiological studies were identified by IARC that evaluated the relationship

between human cancer and exposure specifically to adriamycin. However, some cancer patients who received adriamycin in combination with alkylating agents and radiotherapy developed acute non-lymphocytic leukemia and bone tumour (osteosarcoma) (IARC 1982).[6]

In the present update the Subcommittee notes that several follow-up studies were performed in which patients with Hodgkin's disease were treated with adriamycin in combination with bleomycin, vinblastine and dacarbazine (IARC 1982, 1987; André et al., 2004; André et al., 1997; Brusamolino et al., 2006; Delwail et al., 2002) or patients with Ewing sarcoma or primitive neuroectodermal tumour of bone were treated with adriamycin in combination with vincristine, ifosfamide, cyclophosphamide and etoposide (Bhatia et al., 2007).[1,7-12] The main objectives of these clinical studies were to test the effectiveness of the chemotherapeutic regimen, to define the risk of developing secondary cancer and late toxicity using this regimen.

The Subcommittee observes that in these studies adriamycin is always given in combination with other chemotherapeutic agents or radiation and that data on exposure to adriamycin alone are lacking. Therefore, the Subcommittee is of the opinion that a conclusion on the carcinogenic risk of adriamycin itself is not possible.

Animal studies

IARC (1987) concluded that the compound is carcinogenic to rats after intravenous and subcutaneous injection. Adriamycin produced tumours in the bladder after intravesical instillation (IARC 1976, 1982, 1987).[1,5,6]

Casazza et al. (1977) treated newborn CD and Wistar-Lewis rats with repeated sc injections (dose groups 0.5 and 0.75 mg/kg/day).[13] Two cycles of 4 treatments each (days 1 to 4 and 8 to 11) were given, with a 3-day rest period between the 2 cycles. CD rats treated with the dose of 0.75 mg/kg/day were observed for 2 years for tumour appearance. In male controls, no tumours were detected; in female controls 3 of 7 rats showed the appearance of mammary tumours that were classified histologically as adenomas. All the rats treated with adriamycin did develop tumours. The most common tumours were sarcomas (fibro-, osteo- and unclassified, all close to the injection site) and mammary tumours in females, most of which were adenomas and fibroadenomas; only 1 of 10 mammary tumours was classified as an adenocarcinoma. Tumours generally appeared after 1 year from the beginning of treatment, except for the adenocarcinoma and 1 sarcoma that occurred earlier in female rats. Also Wistar-Lewis rats treated with 0.5 and 0.75 mg/kg/day were observed for 2 years for

tumour appearance. In the controls, 1 fibrosarcoma was detected in 23 males, and 1 fibroadenoma out of 19 females. In the adriamycin-treated groups, the incidence of rats that developed tumours was about 50% in males and 66% in females. In male rats treated with 0.5 mg/kg/day, 6 of 10 tumours were classified as benign neoplasms, while in male rats treated with the higher dose only 2 of 12 tumours were benign (1 leiomyoma and 1 fibroma). In females, no significant difference was observed as regards malignancy of tumours in the groups treated with the 2 dose levels. In this strain of rats also, tumours generally appeared at least 1 year after the treatment; the majority of tumours (25 of 47 total tumours) appears between 400 and 500 days after treatment. In the animals treated with the higher dose (0.75 mg/kg/day), both males and females, 12 tumours appeared before day 400; while in those treated with the lower dose, only 1 tumour appeared before day 400. Lung metastases were detected in some animals bearing fibrosarcomas, sarcomas and leiomyosarcomas.

Bertazolli et al. (1971) assessed the carcinogenicity of adriamycin in Sprague-Dawley rats. In female rats treated iv with a single high dose of adriamycin (8 mg/kg), high incidence of mammary tumours was observed in a relatively short time.[14] The first adriamycin-induced tumour appeared after 156 days and the mean induction time was 223 days. Besides this, in the adriamycin group 1 meningioma and 2 uterine polypi were noticed. No tumours were found in the control animals. Eighteen of the 25 rats treated with adriamycin died, due to severe renal damage or bone marrow aplasia. In the 7 survivors 6 animals had developed tumours (fibroadenomas). No relationship was found between death and presence or absence of tumours; in fact many rats died before tumour occurrence. After 1 year of observation, all survivors and control rats were sacrificed and examined carefully. In each tumour-bearing rat only 1 breast tumour and no metastases were found on extensive autoptic and histological examination.

Marquard et al. (1976) confirmed the findings of Bertazolli et al. that adriamycin can induce mammary tumours.[15] In this study twenty female Sprague Dawley rats received a single iv injection of 5 mg/kg adriamycin and were observed for the duration of the experiment. By the end of 1 year there were 16 fibroadenomas and 3 adenocarcinomas in 17 adriamycin-treated rats. Another group of 20 rats received adriamycin in the dose of 10 mg/kg. All died without tumours within 15 weeks.

Bucciarelli (1981) administered iv injections of 10 or 5 mg/kg adriamycin in groups of male and female Sprague-Dawley rats (age 30-36 days).[16] Multiple mammary tumors, mostly adenocarcinomas, were observed in 67 and 29% of the females given 5 and 10 mg adriamycin/kg, respectively. The mean induction

time for females receiving 10 mg/kg adriamycin was 135 days, for those receiving 5 mg/kg it was 114 days. Single mammary tumours, also mostly adenocarcinomas, were observed an average of 279 days from injection in 31% of the males given 5 mg/kg adriamycin. No tumours were observed in the males given 10 mg/kg adriamycin but these survived for only 79 days after treatment. It is noted in this study that tumours were induced at a dosage which was lethal in other studies. Remarkable also is the higher prevalence of adenocarcinomas versus fibroadenomas when compared to other studies.

Jang et al. (1987) studied the oncogenic potential of adriamycin in both male and female of Sprague-Dawley rats.[17] Single iv injection of 10 or 2 mg and repeated iv injections of 2 mg adriamycin/kg bw within 2 weeks were performed on rats. Multiple mammary tumours, mostly fibroadenomas, were observed in 30 and 41% of the females given single low (2 mg/kg) or repeated doses (5x2 mg/kg) respectively. These incidences were significantly higher than those for the corresponding control group (8%). Two male rats in the low dose group also developed mammary tumours (fibro- and carcinoadenomas). Both sexes receiving the single high dose (10 mg/kg) injection demonstrated early mortality due to marked toxicity. The mortality of five repeated-treatment group was lower than a single high-dose group. Renal cell tumours were evident in five rats of the single, low dose groups and dysplastic foci of renal tubular epithelium occurred in the groups given a single low or repeated dose of adriamycin.

Othani et al. (1984) studied the effect of weekly intravesicular instillation of adriamycin into the urinary bladder of female F344 rats.[18] Following intravesicular instillation of adriamycin (1 mg/mL) (exposure period: 12 weeks, experimental period: 36 weeks) the incidence of papillary or nodular hyperplasia and papilloma was significantly higher in rats given ADR**,** than in control rats given saline only. In the same experiment, in rats pretreated with N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN), instillation of adriamycin not only enhanced the incidence of papillary or nodular hyperplasia and papilloma but also appeared to enhance the number of bladder tumours.

The Subcommittee notes that there are no oral, inhalatory or dermal carcinogenicity studies. When adriamycin was administered parenterally (iv) to rhesus and cynomolgus monkeys a single malignant tumour was observed at the injection site in one monkey (NTP RoC 2014; Thorgeirsson et al., 1994; Schoeffner & Thorgeirsson 2000).[2,19,20]

The Subcommittee is of the opinion that adriamycin is carcinogenic to animals. However, the increased tumour development is found after exposure to adriamycin along routes which are not relevant for occupational exposure of humans.

Cell transformation assays

Marquard et al. (1976) showed that adriamycin is a powerful transforming agent. Exposure to concentrations of 0.001 to 0.01 µg/mL adriamycin caused transformation of M2 cells (clone of mouse fibroblasts).[15]

Price et al. (1975) observed transformation in Fischer rat embryo cells grown for 4 weeks in a culture medium containing 0.l5 ng/mL adriamycin.[21] Local fibrosarcomas were produced in 3/10 and 4/10 newborn Fischer rats given sc injections of the transformed cells.

Genotoxicity

Mutagenicity assays

In vitro

McCann et al. (1975) observed that adriamycin induced reverse mutations in *Salmonella typhimurium* strain 908 without metabolic activation.[22] Also Matheson et al. (1978) tested adriamycin (0.1-1.0 µg/plate) in *Salmonella typhimurium* strains (TA 1535, 1537, 1538 and TA 98).[23] In this study adriamycin was mutagenic in strain T98 and did not require metabolic activation. Au et al. (1981) tested 6.5, 32.5, 65, and 130 mM of adriamycin in *Salmonella typhimurium* bacterial strains TA98, TA100 and TA1537 with and without S-9.[24] Adriamycin was mutagenic in all strains especially in TA98 and did not require metabolic activation to become mutagenic. Bhuyan et al. (1983) tested bacterial mutagenicity of adriamycin for *Salmonella typhimurium* strains TA98 and TA100 and concluded that adriamycin was a strong mutagen for TA98, both with and without metabolic activation, but was much less mutagenic to TA100.[25]

Marquard et al. (1976) used V79 Chinese hamster cells to determine adriamycin (compared to another tetracycline) induced mutation.[15] The absolute number of mutants in dishes treated with adriamycin was significantly greater than in controls. Adriamycin induced major changes in mutation rate in a dose dependent manner in the concentration range between 0.01 and 0.1 µg/mL. Suter et al. (1980) and Bhuyan et al. (1983) used the same system of V79 Chinese-hamster cells and also found a dose-dependent increase of the mutation frequency (respective concentration ranges 0-0.1 and 0.1-1.0 µg/mL).[25,26]

Matheson et al. (1978) tested a number of antineoplastic agents including adriamycin (0.1-0.5 µg/mL) in a mouse lymphoma cell line.[23] Adriamycin was mutagenic in this assay and did not require metabolic activation.

In vivo

Adriamycin, at concentrations ranging from 250 µg/mL to 1 mg/mL, was shown to be capable of inducing sex-linked recessive lethal mutations in Drosophila (Clements et al. (1984).[27]

Clastogenicity assays

In vitro

Adriamycin (0.01-1.0 µg/mL) was analyzed by Au et al. (1980, 1981) in an in vitro cell culture using a Chinese-hamster ovary (CHO) cell line with respect to its cytogenetic effect with or without metabolic activation using liver fraction S9.[24,28] Adriamycin was most potent in induction of chromosomal breakage, sister chromatid exchange, but its clastogenic activity was reduced after metabolic conversion.

West et al. (1981) studied the action of adriamycin in cultured Chinese-hamster V79 cells in vitro, using cell survival and sister-chromatid exchange as end-points. Adriamycin dose-dependently increased cytotoxicity and levels of sister-chromatid exchanges in V79 cells.[29] Also Bhuyan et al. (1983) studied adriamycin in Chinese-hamster V79 cells in culture on chromosome breakage and sister chromatid exchange (SCE).[25] Adriamycin caused mostly chromosome and chromatid breaks with few chromosome rearrangements. Adriamycin significantly increased the number of sister chromatid exchanges per cell.

Vig (1971) showed that adriamycin caused chromosomal damage when used on human peripheral leukocytes in in vitro cultures at concentrations as low as 0.02 µg/ml for 24 hr or 0.05, 0.10, or 0.15 µg/ml for 3 to 4 hr.[30] Aberrations of all conceivable types (intra- as well as inter-chromatid, -chromosome , and chromatid-chromosome type) are observed.

In vivo

The genotoxic effects of adriamycin on somatic and germinal cells were studied by Au et al. (1980) in mice treated with single injections of 3, 12 or 24 mg/kg of the drug.[31] From 1 to 5 days post-injection, chromosome aberrations were

observed in bone-marrow cell and in diakineses-metaphase 1 cells from the testes. The frequency of chromosome breakages peaked at 5 h or 1 day for the bone marrow and at 3 and 5 days for the testis.

Kram et al. (1979) studied sister chromatid exchange (SCE) frequencies simultaneously studied in fetal cells as well as in maternal bone marrow in pregnant female mice.[32] To examine *in utero* SCE induction adriamycin was injected into pregnant females on day 13 of gestation. Baseline SCE in fetal cells were lower than in maternal cells. SCE induction in fetal cells was one third of that in maternal cells but significantly higher than baseline levels.

Bhuyan et al. (1983) injected Sprague-Dawley rats with adriamycin (1.25 mg/kg) and removed the bone marrow after 30 hr.[25] For each rat, 500 polychromatophilic erythrocytes and, as a control for artifacts, normochromatophilic erythrocytes were examined for micronuclei. Adriamycin significantly increased the number of micronuclei per 500 polychromatophilic erythrocytes.

In peripheral whole blood lymphocyte cultures from a patient studied in a short-term treatment with adriamycin, Nevstad (1978) noted a striking rise in the number of SCEs.[33] Also Musilova et al. (1979) investigated the frequency of structural chromosomal rearrangements and SCEs in peripheral lymphocytes cultured from adriamycin treated patients.[34] The SCE rate was increased and was proportional to the number of chromosome breaks, the ratio of SCE to breaks being about 100: 1. The increase in the SCE number was maintained for several months after the termination of cytostatic therapy.

Mechanism of genotoxicity

IARC concluded previously that adriamycin is a potent genotoxicant.[1,5,6,35] Adriamycin is mutagenic in bacteria (McCann et al. 1976; Matheson et al.,1978; Au et al., 1981; Bhyan et al.,1983), in mammalian cells *in vitro* (Marquard et al., 1976; Suter et al., 1980, Bhyuan et al., 1983; Matheson et al., 1978), and *in vivo* in Drosophila (Clements et al., 1984).[15, 22-27] It causes chromosomal anomalies in hamster cells (Au et al.,1980, 1981; West et al., 1981; Bhyan et al.,1983) and human lymphocytes in vitro (Vig 1971) and in mouse bone marrow cells in vivo (Au et al., 1980; Kram et al., 1979). [24, 25, 28-32] It produces cell transformation in mouse fibroblast cells and in Fischer rat embryo cells (Price et al., 1975; Marquard et al.,1976).[15, 21] Patients treated with adriamycin showed significant increases in the incidence of chromosomal aberrations and sister chromatid exchanges (Musilova et al., 1979; Nevstad 1978). [33, 34]

Adriamycin is a chemotherapeutic agent whose mode of action includes intercalation of adjacent base pairs of the DNA double helix thus preventing their unwinding for replication and resulting in DNA damage, binding of DNA-associated enzymes such as topoisomerase II (enzyme active in replication) (Tacar, 2010; McClendon & Osheroff, 2007).[36, 37] It is very likely that for genotoxicity of adriamycin similar mechanisms as for anti-tumour effects apply. According to the Committee non covalent inhibition of topoisomerase II (McClendon & Osheroff, 2007) may play an important role but also simple DNA intercalation or generation of oxidative stress (Caelix Product Information; Farmaki et al. 2011; Pereira et al., 2011) may contribute to the development of both mutagenicity and genotoxicity.[36, 38-40] The Committee is aware of the ongoing experimental research into the mechanisms of genotoxicity but is of the opinion that this research is not conclusive as yet (Islaih et al., 2005; Spencer et al., 2008; Navarro et al., 2006; Lyu et al., 2007; Lehmann et al., 2003; Valadares et al., 2008; de Rezende et al., 2009; de Rezende, 2011 and Sousa et al., 2009).[41-49]

The Subcommittee concludes that non-thresholded stochastic genotoxic mechanisms are involved.

Recommendation

Epidemological studies are inconclusive regarding carcinogenicity of adriamycin. However, sufficient evidence is available that adriamycin is carcinogenic to animals. Therefore, the Subcommittee recommends to classify adriamycin in category 1B ('substance presumed to be carcinogenic to man').

Furthermore, the Subcommittee is of the opinion that stochastic genotoxic mechanisms are involved.

References

1 Adriamycin (Group 2A). IARC monographs on the evaluation of carcinogenic risks to humans 1987; (Suppl. 7): 82-83.

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Date meeting: April 09, 2014.

Annex **G**

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	
		67/548/EEC before 12/16/2008	EC No 1272/2008 as from 12/16/2008
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 is presumed to be 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. Guidelines to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[33]

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.

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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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