Health Council of the Netherlands

Potassium cyanide

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Potassium cyanide*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U-7041/BvdV/fs/246-Z15
Bijlagen : 1
Datum : 9 maart 2012

Geachte staatssecretaris,

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

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. Daarbij heeft de subcommissie op verzoek van uw ministerie de formulering van de categorie waarin kaliumcyanide valt, aangepast; niet een numerieke aanduiding maar een standaardzin vormt de hoofdformulering. 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. L.J. Gunning-Schepers,
voorzitter

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Potassium cyanide

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 State Secretary of Social Affairs and Employment

No. 2012/03, The Hague, March 9, 2012

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, Agriculture & Innovation, 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.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with health technology assessment.

INAHTA

This report can be downloaded from www.healthcouncil.nl.

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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 kaliumcyanide onder de loep.

Kaliumcyanide is een stof die voornamelijk wordt gebruikt voor galvaniseren, het versterken van staal, de winning van goud en zilver uit erts en de ontsmetting van fruitbomen, schepen, treinwagons en warenhuizen. Daarnaast wordt deze stof breed gebruikt in de synthese van organische en anorganische chemicaliën (bv. cyanides, carboxylzuren, amides, esters, en amines, cyanides van zware metalen) en tijdens de productie van chelerende verbindingen.

De commissie constateert dat de gegevens over kaliumcyanide niet voldoende zijn om de kankerverwekkende eigenschappen te evalueren (categorie 3).*

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

Executive summary

At the 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 Safety of the Health Council, hereafter called the Committee. In this report, the Committee evaluates potassium cyanide.

Potassium cyanide is mainly used for electroplating, steel hardening, extraction of gold and silver from ores, fumigation of fruit trees, ships, railway cars and warehouses. They are also widely used in the synthesis of organic and inorganic chemicals (e.g., nitriles, carboxylic acids, amides, esters, and amines; heavy metal cyanides) and in the production of chelating agents.

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

* According to the new 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 (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 potassium cyanide.

1.2 Committee and procedures

The evaluation is performed by the Subcommittee on Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter (in English) to the State Secretary can be found in Annex C.

In July 2011 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 standardly based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of potassium cyanide such an IARC-monograph is not available. Published data were retrieved from the online databases Medline, Toxline, and Chemical Abstracts, using carcino*, cancer*, mutagen*, chromosom*, genotox* (*: wildcard character) and CAS no. 151-50-8 as key words. The search covered publications till June 2011. The relevant data were included in this report.

Chapter 2

General information

The data have been retrieved from the European Substance Information System (ESIS)*, the Hazardous Substances Data Bank (HSDB)** and the INCHEM database of the International Programme on Chemical Safety (IPCS), which can be accesses via inchem-site***.

* http://esis.jrc.ec.europa.eu/ (February 29, 2012).
** http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB (February 29, 2012).
*** http://www.inchem.org/ (February 29, 2012).

2.1 Identity and physico-chemical properties

Chemical name	:	Potassium cyanide
CAS registry number	:	151-50-8
EINECS number	:	205-792-3 006-007-00-5 (group entry: hydrogen cyanide (Salts of ...) with the exception of complex cyanides such as ferrocyanides, ferricyanides and mercuric oxycyanide
Synonyms	:	Kaliumcyanide, KCN, hydrocyanic acid, potassium salt
Appearance	:	White, granular or crystalline solid. Faint bitter almond-like odor or odor of hydrogen cyanide.
Use	:	Potassium cyanide is mainly used for electroplating, steel hardening, extraction of gold & silver from ores, fumigation of fruit trees, ships, railway cars and warehouses. They are also widely used in the synthesis of organic and inorganic chemicals (e.g., nitriles, carboxylic acids, amides, esters, and amines; heavy metal cyanides) and in the production of chelating agents.
Chemical formula	:	C-K-N
Structural formula		
Molecular weight	:	65.1
Boiling point	:	1625°C
Melting point	:	634°C
Vapour pressure	:	-
Vapour density (air = 1)	:	-
Solubility	:	Soluble in 2 parts cold water and in 1 part boiling water 71.6 g/100 ml
Conversion factor	:	-
EU Classification (100% solution)	:	Acute Tox. 1: H310 (Fatal in contact with skin)
	:	Acute Tox. 2: H300 (Fatal if swallowed)
	:	Acute Tox. 2: H330 (Fatal if inhaled)
	:	EUH032 (Contact with acids liberates very toxic gas)

2.2 IARC classification

Potassium cyanide has not been evaluated by IARC.

Chapter 3

Carcinogenicity

3.1 Observations in humans

No human studies addressing the carcinogenicity of potassium cyanide have been retrieved from public literature.

3.2 Carcinogenicity studies in animals

No in vivo animal studies addressing the carcinogenicity of potassium cyanide have been retrieved from public literature.

Chapter 4

Genotoxicity

No human studies addressing mutagenicity or genotoxicity of potassium cyanide have been retrieved from public literature.

4.1 In vitro assays

In a study of De Flora et al. potassium cyanide was tested in the Ames reverse mutation assay with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100.[1] Potassium cyanide was tested both with and without S9-mix (in duplicate or triplicate plates), and appeared negative in all strains.

In another study of De Flora et al., potassium cyanide again was negative in the Ames test strains TA97 and TA102.[2]

In a study of Kubo et al. potassium cyanide did not show any mutagenicity in the Ames test strains *Salmonella typhimurium* TA98 and TA100 without and with a metabolic activator (S9-mix).[3]

Potassium cyanide was assayed in a liquid DNA-repair test with the 3 isogenic *Escherichia coli* strains WP2 (wild-type repair-proficient), WP67 (*uvr*A- *pol*A-), and CM871 (*uvr*A- *rec*A- *lex*A-) with or without S9-mix.[1] The initial concentrations of potassium cyanide were governed either by its solubility or by its toxic-

ity for bacteria, as inferred from preliminary assays. Potassium cyanide was positive with the *E.coli* strains without S9-mix, but negative with S9-mix.

In 3 studies potassium cyanide was used as test substance in studies aimed at improving the discrimination between cytotoxins (like potassium cyanide) and genotoxins.[4-6]

In a study of Vock et al.to discriminate between direct genotoxicity and cytotoxicity as cause of DNA double-strand breaks, genotoxic agents (melphalan, etoposide and gamma-rays), potassium cyanide and Triton X100 were tested in cultured human lung epithelial cells (A549).[6] DNA fragmentation was assessed by pulsed-field gel electrophoresis and cell viability by measuring the reduction of MTT dye (which can be accomplished by viable cells only). The dose-response relationships for DNA fragmentation and for cell viability were investigated at different times of incubation (8, 24 and 72 hours) in order to discriminate between genotoxicity and cytotoxicity in the pathogenesis of DNA double-strand breaks. Induction of double-strand breaks by potassium cyanide was seen only after cell viability was reduced to less than about 60%, indicating that double-strand breaks were the consequence of cytotoxic damage. For the genotoxic agents double-strand breaks preceded decrease in cell viability. This mechanistic distinction of genotoxins and cytotoxins was also supported by DNA fragment length analysis. DNA fragments induced by potassium cyanide and Triton X100 peaked below 0.5 Mbp, implicating activation of DNA-degrading enzymes as a consequence of cell death. The authors conclude that this study clearly demonstrates the cytotoxic nature of potassium cyanide induced double-strand breaks.

In the study of Henderson et al. potassium cyanide was tested in the alkaline Comet assay in TK6 human lymphoblastoid cells.[4] Potassium cyanide exerts its toxic effect via the cell electron transfer chain. Potassium cyanide produced a significant increase of DNA migration (increase in tail moments) at cell survival levels of $\leq$ 75% at a dose level of 5000 µg/ml. The wide distribution of damaged cells indicated that cells at various stage of necrotic cell death were present. Comparison of the results for cytotoxins and genotoxins showed that cytotoxins are able to induce an increase in DNA migration only when cell viability was $\leq$ 75%.

Storer et al. performed a revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage.[5] This assay is a sensitive assay for genotoxicity, measured as DNA strand breaks induced in primary cultures of rat hepatocytes

after 3-h treatments with test compounds. Since DNA degradation can be rapid and extensive in dead and/or dying cells, the original criteria for a positive result in the assay were that a compound induce a 3.0-fold or greater increase in the elution slope (for the terminal phase of alkaline elution from 3 to 9 h) in the absence of significant cytotoxicity defined as relative cell viability of less than 70% by trypan blue dye exclusion. Potassium cyanide produced no positive result by the proposed criteria. It shows significant increases in both cytotoxicity and in the induced elution slope.

Fornace et al., studied the induction of DNA single strand breaks, and DNA cross-linking by various carcinogens and metabolic inhibitors (including potassium cyanide) in human or mouse fibroblasts in monolayer cultures.[7] To determine the degree of single-strand breaks or cross links induced a method was used of alkaline elution of the cells on polyvinyl chloride filters and measurement of the amount of (previously radiolabeled) DNA retained on the filters. Comparing the amount of DNA retained for cells only treated with the test substance with that of untreated control cells is a measure for the number of single strand breaks. The lower the retention of DNA in treated cells compared to untreated controls, the higher the number of single strand breaks induced.

The difference between the amount of DNA retained on the filter after combined exposure to substance and X-rays compared to the amount of DNA retained after exposure to X-rays alone is a measure of the degree of cross-linking induced: a higher amount of DNA retained after concomitant treatment with the test substance and X-rays indicates cross-linking of DNA has taken place.

No cross-link effects were seen following treatment with potassium cyanide. Also no DNA single-strand breaks were seen after a 1-h exposure to potassium cyanide. After 24-h exposure to potassium cyanide, when the cells showed marked lytic changes, i.e. less than 20% of the cells remained attached, the relative retention did decrease, but again no cross-linking effect was reported.

4.2 *In vivo* assays

Schubert et al. studied the influence of potassium cyanide on the induction of chromosome aberrations in bone marrow cells of male mice as a control in a study that was designed to study the effect of potassium cyanide on induction of these genotoxic effects by single, whole-body ^{60}Co irradiation in male mice.[8] The irradiation dose rate was 1.8 Gy/min, resulting in a total dose of 6.25 Gy (1 joule/kg or 100 rad), while potassium cyanide was injected intraperitoneally at

a non-toxic dose of 5.5 mg/kg bw, 2 min, respectively 20 min prior to irradiation. Although potassium cyanide had a marked reduction in chromosome aberrations 2 min before irradiation, it induced by itself no chromosome aberrations.

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

Potassium cyanide was not evaluated by IARC. In a recent (2010) toxicological review of hydrogen cyanide and cyanide salts the EPA reaffirms that there is 'inadequate information to assess the carcinogenic potential' of cyanide.[9]

The public literature retrieved by the Committee provided no data on the possible carcinogenicity of potassium cyanide in humans and experimental animals.

From in vitro tests that tried to identify genotoxic or mutagenic effects it was found that potassium cyanide was essentially negative. Only in DNA-repair tests with *E-coli* strains potassium cyanide appeared to be positive, though only without S9-mix. However, a couple of more mechanistic studies with mammalian cell cultures showed that DNA damaging effects by potassium cyanide are induced only after it has become cytotoxic.

Only one in vivo study was retrieved from the literature. In mice no cytotoxic effects of potassium cyanide were demonstrated.

5.2 Recommendation for classification

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

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

References

1 De Flora S., Zanacchi P, Camoirano A, Bennicelli C, Badolati GS. Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. Mutat Res 1984; 133(3): 161-198.

2 De Flora S., Camoirano A, Zanacchi P, Bennicelli C. Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other Salmonella strains. Mutat Res 1984; 134(2-3): 159-165.

3 Kubo T, Urano K, Utsumi H. Mutagenicity characteristics of 255 environmental chemicals. J Health Sci 2002; 48(6): 545-554.

4 Henderson L, Wolfreys A, Fedyk J, Bourner C, Windebank S. The ability of the Comet assay to discriminate between genotoxins and cytotoxins. Mutagenesis 1998; 13(1): 89-94.

5 Storer RD, McKelvey TW, Kraynak AR, Elia MC, Barnum JE, Harmon LS et al. Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. Mutat Res 1996; 368(2): 59-101.

6 Vock EH, Lutz WK, Hormes P, Hoffmann HD, Vamvakas S. Discrimination between genotoxicity and cytotoxicity in the induction of DNA double-strand breaks in cells treated with etoposide, melphalan, cisplatin, potassium cyanide, Triton X-100, and gamma-irradiation. Mutat Res 1998; 413(1): 83-94.

7 Fornace AJ, Jr., Little JB. DNA-protein cross-linking by chemical carcinogens in mammalian cells. Cancer Res 1979; 39(3): 704-710.

8 Schubert J, Pan SF, Wald N. Chromosome aberrations reduced in whole-body irradiated mice by pretreatment with cyanide. Mutat Res 1992; 282(2): 107-111.

9 Toxicological review of hydrogen cyanide and cyanide salts. US Environmental Protection Agency (EPA), Washington DC: 2010.

10 Health Council of The Netherlands. Guideline for the classification of carcinogenic compounds. Health Council of The Netherlands, The Hague, The Netherlands: 2010: publication no. A10/07E.

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
- 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 *Potassium cyanide*
Our reference : U-7041/BvdV/fs/246-Z15/E
Your Reference: DGV/MBO/U-932342
Enclosed : 1
Date : March 9, 2012

Dear State Secretary,

I hereby submit the advisory report on the effects of occupational exposure to *Potassium cyanide*.

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 Classifying Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). In addition, at your Ministry's request, the Subcommittee has modified the formulation of the category into which *Potassium cyanide* has been placed; the main formulation is a standard phrase rather than a numerical designation. 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)
Professor L.J. Gunning-Schepers,
President

Annex **D**

Comments on the public review draft

A draft of the present report was released in July 2011 for public review. The following organisation has commented on the draft document:

- National Institute for Occupational Safety and Health, Cincinnati, 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	
		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. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[10]