Cisplatin

Health-based calculated occupational cancer risk values

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Cisplatin'
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Mijnheer de staatssecretaris,

Bij brief van 3 december 1993, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. Tevens vroeg de Staatssecretaris om in het geval van beroepsmatige blootstelling aan genotoxisch carcinogene stoffen de risico's op sterfte als gevolg van kanker te berekenen.

In dat kader bied ik u hierbij een advies aan over 'Cisplatin'. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving. Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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Health-based calculated occupational cancer risk values

Datch Expert Committee on Occupational Standards
a committee of the Health Council of the Netherlands

to:

the Minister and State Secretary of Social Affairs & Employment

No. 2005/03OSH, The Hague, 19 April 2005

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..." (Section 21, Health Act).

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Contents

Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid, schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen, die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor cisplatine, een genotoxisch chemotherapeuticum. Voor de schatting heeft de commissie gebruik gemaakt van de methode die beschreven is in het rapport 'Berekening van het risico op kanker' (Hea95).

Naar schatting van de commissie is de extra kans op kanker voor cisplatine:

- $4x10^{-3}$ bij 40 jaar beroepsmatige blootstelling aan 5 $\mu g/m^3$;
- $4x10^{-5}$ bij 40 jaar beroepsmatige blootstelling aan 0,05 $\mu g/m^3$.

Executive summary

On request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, estimates the additional cancer risk associated with occupational exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen. In this report the committee presents such estimates for cisplatin, a genotoxic anticancer drug. For the estimation, the committee used the method described in the report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (Hea95).

The committee estimated that the additional lifetime cancer risk for cisplatin amounts to:

- $4x10^{-3}$ for 40 years of occupational exposure to 5 $\mu g/m^3$;
- $4x10^{-5}$ for 40 years of occupational exposure to 0.05 $\mu g/m^3$.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for 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 Standards (DECOS), a committee of the Health Council of the Netherlands, at request of the Minister of Social Affairs and Employment (annex A). 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 cannot be evaluated using a threshold model, as is the case for substances with 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-OCRVs, 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' (Hea95). The linear model 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

This document contains the derivation of HBC-OCRV's by the committee for cisplatin. The members of the committee are listed in Annex B. The first draft of this report was prepared by Ms MI Willems of the TNO Nutrition and Food Research, Zeist, The Netherlands, for the Ministry of Social Affairs and Employment.

In 2004, 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 C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation of the carcinogenicity and other toxic effects of cisplatin has been based on reviews by IARC (IAR81, IAR87). Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition, literature has been retrieved from the online databases Chemical Abstracts, Toxline, and Medline, covering the period 1966 to May 2004.

Chapter 2

Cisplatin

2.1 General information

Cisplatin is an anticancer drug that is used to treat a variety of human malignancies. Its identity, physical and chemical properties are shown below (data obtained from IAR81, Ric93, Sou91 and ROC98).

Chemical name	:	Cisplatin
CAS registry number	:	15663-27-1
EINECS#	:	239-733-8
Chem. Abstr. Name	:	Platinum, diamminedichloro-, (SP-4-2)-
IUPAC name	:	*Cis*-diamminedichloroplatinum
Synonyms	:	CDDP; DDP; *cis*-DDP; *cis*-diaminodichloroplatinum; *cis*-diaminodichloroplatinum (II); *cis*-dichlorodiaminoplatinum (II); *Sp-4-2*-diamminodichloroplatinum; cis-platinum (II); Neoplatin; Platistin
Description	:	Yellow crystalline solid
Occurrence	:	Cisplatin is not known to occur naturally
Molecular weight	:	300.1
Molecular formula	:	*cis*-$[PtCl_2(NH_3)_2]$
Structure	:	
Melting point	:	270 °C

Solubility	:	Slightly soluble in cold water; insoluble in most common solvents except N,N-dimethylformamide
Stability	:	Slowly changes to the *trans*-form in aqueous solution (reaction conditions unknown). It decomposes at approximately 270 °C. When heated to decomposition, cisplatin emits very toxic fumes of chlorine and NO_x
Partition coefficient, log P_{ow}	:	-2.19
EC classification	:	Not classified or labelled according to the 23rd Amendment to Annex I of Directive 67/548/EEC (dated December 5, 1997)

2.2 Carcinogenicity studies

2.2.1 Overall conclusion

IARC (IAR87) has classified cisplatin as probably carcinogenic to humans (Group 2A). The classification is based on sufficient evidence for carcinogenicity in animals, whereas evidence for carcinogenicity in humans was inadequate.

In 1995, DECOS (DEC95) drew the same conclusion as IARC, in that cisplatin should be considered as carcinogenic to humans (comparable with EU category 2). Furthermore, it classified the compound as a genotoxic carcinogen.

2.2.2 Human data

Data obtained on cancer patients, who were treated with platinum containing chemotherapeutics, suggest that these compounds, including cisplatin, may induce secondary malignancies following treatment (Gre92). The type of malignancies described mainly concern acute non-lymphocytic leukaemia and myelodysplasia. For instance, it is reported that cisplatin with either doxorubicin or etoposide, all anticancer drugs, caused leukaemia in humans (Gre92, Vog93). Furthermore, Philpott *et al*. (Phi96) described two cases of secondary acute myeloid leukaemia in which platinum compounds were the sole prior chemotherapy. Overall, however, evidence that cisplatin may cause secondary malignancies is hampered by the fact that anticancer drug are generally used in combination with other anticancer drug. In addition, it is not clear whether secondary malignancies are induced by an individual drug in the chemotherapeutic mixture or by synergistic effects (Vog93).

No additional epidemiological data on the carcinogenic effect of in particular cisplatin is available to the committee.

2.2.3 *Animal data*

No animal data were available to the committee on cisplatin exposure by inhalation or dermal absorption.

In one study cisplatin was given orally to females Sprague-Dawley weanling rats (Ski70). All rats (n=24) receiving cisplatin in their diet (about 7.3 mg/rat/day) developed mammary adenocarcinomas and thymic lymphosarcomas after 18 weeks. However, the rats grew more slowly than the control rats, and only three rats were alive at 18 weeks, whereas all control animals survived that period.

A few studies reported on carcinogenic effects of cisplatin after intraperitoneal injection. In one, Leopold and his colleagues (Leo79) studied the carcinogenic potential of cisplatin by performing several animal experiments. In one experiment the induction of lung adenomas in female A/Jax mice was considered, whereas in the other experiment the induction of skin tumours in female CD-1 mice was investigated.
The experimental design and results on the induction of lung adenomas are shown in Table 2.1. Cisplatin was given once a week by intraperitoneal injections.

Regarding skin tumour induction, none of the mice treated with cisplatin only (n=40; 16 weekly intraperitoneal injections of 1.62 mg/kg bw) developed benign skin papillomas. Also none of the control animals showed any sign of skin tumours. On the other hand, when cisplatin was given in combination with croton oil, a known tumour promotor, at

Table 2.1 Experimental design and induction of lung adenomas in female A/Jax mice by cisplatin (Leo79).

treatment	number of mice		% of mice with lung adenomas	Average no. of adenomas per mouse (± S.D.)
	initial	at 8 months		
Cisplatin in saline solution:				
1) Cisplatin: 3.25 mg/kg bw, 10x[a]	10	9	100	14.2 ± 6.7[b]
2) Cisplatin: 3.25 mg/kg bw, 10x[a] (repeated)	20	17	100[b]	11.4 ± 6.0[b]
3) Cisplatin: 1.62 mg/kg bw, 19x	10	7	100	15.8 ± 4.6[b]
4) Cisplatin: 3.25 mg/kg bw, 5x	20	18	100[b]	7.2 ± 3.1[b]
5) saline solution, 19x	6	6	67	0.8 ± 0.8
Cisplatin in trioctanoin solution:				
1) Cisplatin: 3.25 mg/kg bw, 10x[a]	20	17	100[b]	10.4 ± 3.1[b]
2) Cisplatin: 1.62 mg/kg bw, 10x[a]	20	18	94[b]	5.4 ± 4.7[b]
3) trioctanoin solution	20	19	26	0.5 ± 1.0

[a] Injections interrupted for 1 week owing to poor health of the mice.
[b] Statistically different from controls ($p<0.005$) by a χ^2 test.

week 41, half of the mice (15/30) had developed papillomas with an average of 3.2 papillomas per mouse, whereas croton oil alone did not cause any skin tumours.

In this skin tumour induction experiment, tumours induced by cisplatin were not only found in the skin, but also at other sites of the body (week 41, 30 survivors); one mouse treated with cisplatin alone developed an epidermoid carcinoma in the external ear (different location than treated area) and seven mice of the same group developed neoplasms at other sites than the skin (2 thymic lymphomas, 1 pulmonary adenoma, 3 mammary adenocarcinomas, and 1 subcutaneous fibroliposarcoma). No such tumours were observed in the control group (33 survivors).

A few years later, Leopold and his colleagues (Leo81) presented subsequent experiments, in which the results described in the previous study were confirmed. Concerning lung adenomas, details on the experimental design and the results are shown in Table 2.2. Again, cisplatin was given by intraperitoneal injections. Concerning skin tumour initiation by cisplatin alone (16 weekly intraperitoneal injections, total dose of 86 µmol/kg bw), at the 50th week, 51% of the mice (n=35) developed papillomas, with an average of 1.1 papillomas per mouse. Also, at week 77, four mice had developed epidermoid carcinomas, and 11 mice other tumours (*e.g.* in the mammary gland, the lungs, the ovaries and the abdomen). For comparison reasons, of the control mice (n=35), which were treated with trioctanoin and croton oil: 17% developed skin papillomas, with an average of 0.2 papillomas per mouse; 1 mouse developed epidermoid carcinomas; and, seven mice tumours at other sites than skin.

Kempf and Ivankovic (Kem86a/b) published the preliminary results of a carcinogenicity study on cisplatin. Female and male BD IX rats (n= 25) received cisplatin at a concentration of 1 mg/kg body weight by intraperitoneal injections, 3 times per week for three weeks. Another group of 25 animals received saline only and served as negative control. After 455 days in experiment, 19 animals treated with cisplatin had died, of which 5 of leukemia and 1 of a fibrosarcoma of the kidney. In the control group 6 animals had died, but none of these deaths were caused by cancer.

Table 2.2 Experimental design and induction of lung adenomas in female A/J mice by cisplatin (Leo81).

treatment	number of mice		% of mice with lung adenomas	Average no. of adenomas per mouse (± S.D.)
	initial	at 8 mo.		
Cisplatin in trioctanoin:				
1) *cis*-cisplatin: 10.8 μmol/kg bw, 10x	20	19	100[a]	8.7± 1.9[a]
3) trioctanoin solution	20	19	37	0.6 ± 0.9
Cisplatin in 5% dextrose:				
1) *cis*-cisplatin: 10.8 μmol/kg bw, 10x	25	25	100[a]	9.1 ± 3.9[a]
2) 5% dextrose	25	25	36	0.5 ± 0.8
1) *cis*-cisplatin: 5.4 μmol/kg bw, 10x	25	25	100[a]	4.6 ± 2.1[a]
2) 5% dextrose	25	18	6	0.1 ± 0.2
1) *cis*-cisplatin: 5.4 μmol/kg bw, 10x	25	22	100[a]	5.2 ± 2.8[a]
2) 5% dextrose	26	25	44	0.7 ± 1.0

[a] Statistically different from controls ($p<0.01$) by Fisher's exact or Wilcoxon's rank sum test.

Barnhart and Bowden (Bar85) used a two-stage mouse skin carcinogenesis model to examine the tumour initiating potential of cisplatin. Female CD-1 mice were divided in three experimental groups: i) pre-treatment with TPA (12-*O*-tetradecanoylphorbol-13-acetate; topically applied; twice weekly) plus a single intraperitoneal injection with cisplatin (60, 90 or 120 μg in 200 μL saline) (n=10 animals/dose); ii) no pre-treatment, but treatment with cisplatin as in the previous group (n=10 animals/dose); and, iii) only pre-treatment with TPA (n=50 animals). Also positive control groups were included; these mice received urethane with or without pre-treatment with TPA (n=40 animals/group). Animals were kept in experiment for 50 weeks. During the experiment all animals were tested on the presence of skin tumours.

The authors did not find a significant difference in tumour yield between the different doses of cisplatin. Therefore, they combined data from the different dose groups. Concerning the percentage of mice with skin papillomas, cisplatin alone led to a tumour incidence of 27%, whereas pre-treatment plus cisplatin led to an incidence of 63%. A tumour incidence of 2% (1/50) was found for TPA alone. Concerning the average number of papillomas per mouse, an average of 0.5 per mouse was found for cisplatin alone, and of 2.0 per mouse for pre-treatment plus cisplatin. In addition, only in the group pre-treated with TPA and cisplatin malignant squamous cell carcinomas were observed (incidence 10% (3/30); one tumour in each of the three mice). Based on their results, the authors concluded that cisplatin possesses tumour initiating potential.

2.3 Selection of the suitable study for estimating occupational cancer risk

In the absence of human studies and inhalation studies with animals, the committee selected the carcinogenicity study by Leopold *et al*. (Leo79) to estimate the potential cancer risk in humans under workplace exposure conditions. In this study, CD-1 mice were treated by intraperitoneal injections with cisplatin to investigate skin tumour development. Furthermore, the same mice were examined on the presence of tumours at other sites of the body than the skin.

2.4 Lifetime low-dose exposure: carcinogenic activity in experimental animals

The tumour incidence of cisplatin-treated mice was 8/30. This includes mice with epidermoid carcinomas (n=1), thymic lymphomas (n=2), pulmonary adenoma (n=1), mammary adenocarcinomas (n=3), and fibroliposarcoma (n=1). Although pulmonary adenomas are benign tumours, these are included because of their relevance. In the vehicle-control group none of the mice developed tumours (0/33).

The cisplatin-treated mice were given 16 weekly intraperitoneal injections of 1.62 mg cisplatin per kg bw. For estimating additional lifetime cancer risk values the concentration should be expressed in mg/kg bw/day. Furthermore, the committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate. Therefore, under lifespan conditions, the calculated incidence of tumour-bearing animals per mg/kg bw/day is calculated as follows*:

$$I_{dose} = \frac{I_e - I_c}{D \times \left(X_{po} / L \right) \times \left(X_{pe} / L \right) \times \left(days\ per\ week / 7 \right)}$$

$$I_{dose} = \frac{\left(8/30 \right) - \left(0/33 \right)}{\left(1.62/7 \right) \times \left(112/750 \right) \times \left(364/750 \right) \times \left(7/7 \right)}$$

I_{dose} = 15.5 *[mg/kg bw/day]*

* I is estimated tumour incidence; I_e and I_c are tumour incidences in exposed and control animals, respectively; D is the daily dose (mg/kg bw); X_{po} and X_{pe} are exposure and experimental period, respectively; L is the standard lifespan for the animal species in question (L mice is assumed to be 750 days).

2.5 Human lifetime low-dose exposure

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target susceptibility, etc., unless specific information is available which justifies a different approach. Furthermore, it is assumed that the average man lives 75 years, weighs 70 kg, and is exposed 24 hours per day, 7 days per week, 52 weeks per year for lifetime.

2.6 Calculation of the HBC-OCRV

To estimate the potential additional lifetime risk of cancer in humans under workplace exposure conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years, and inhales 10 m^3 per 8-hour-working day. Using as starting point the estimated incidence of 15.5 per mg/kg bw/day, the additional lifetime cancer risk per mg/m^3 under occupational exposure conditions, the HBC-OCRV, amounts to

$$HBC - OCRV = I_{dose} \times \left({}^{40}\!/_{75\ years} \right) \times \left({}^{48}\!/_{52\ weeks} \right) \times \left({}^{5}\!/_{7\ days} \right) \times \left(10\ m^3 \right) \times \left(70\ kg\ bw \right)^{-1}$$

$HBC - OCRV = 15.5 \times 0.53 \times 0.92 \times 0.71 \times 10 \times 70^{-1}$

$HBC - OCRV = 0.8\ [mg/m^3]^{-1}$

Based on the HBC-OCRV of 0.8 per mg/m^3, the additional lifetime cancer risk for cisplatin amounts to:

- 4×10^{-3} for 40 years of exposure to 5 $\mu g/m^3$;
- 4×10^{-5} for 40 years of exposure to 0.05 $\mu g/m^3$.

2.7 Existing occupational exposure limits

No occupational exposure limits have been established for cisplatin in the Netherlands (SZW04), Germany (Bun03, DFG03), the United Kingdom (HSE02), Scandinavian countries (Arb02, NBO00), the United States of America (ACGIH, OSHA, NIOSH (ACG04) and by the SCOEL of the European Union (Hun97). Instead, the Netherlands, Denmark, and OSHA have included the compound in a list of carcinogenic chemicals. OSHA regulates cisplatin under the Hazard Communication Standard and as a chemical

hazard in laboratories; a Permissible Exposure Limit of 2 μg/m^3 (as Pt; 8-hr TWA) has been established (ROC98).

2.8 Toxicity profile

2.8.1 Human data (IPC91, Ric93)

In humans receiving cisplatin therapeutically, a major side effect of cisplatin is nephrotoxicity. Moreover, it has been shown that renal damage increases by repeated exposure and by higher doses. Eventually, the damage may become irreversible during continued treatment. In addition to nephrotoxicity, toxic effects following therapeutic administration may include myelotoxicity (bone marrow suppression), gastrointestinal toxicity (nausea and vomiting), peripheral neuropathy, and ototoxicity. Ototoxicity is manifested by tinnitus (noise in the ears) with or without clinical loss of hearing. In single cases, allergic phenomena, rash, and asthma have been reported.

2.8.2 Animal data

Lethality, skin and eye irritation. In rats, an LD_{50} of 26 mg/kg bw was found after oral administration (Ric93); in mice, an LD_{50} of 12 mg/kg bw was reported after intravenous injection; and, in rats and mice which received cisplatin by intraperitoneal injection, LD_{50} values of 12 and 13 mg/kg bw were found, respectively (IAR81, IPC91). The minimal lethal dose for dogs after a single intravenous injection was 2.5 mg/kg bw, or after 5 daily consecutive injections 0.75 mg/kg bw (IAR81). In monkeys, the minimum lethal dose was five daily injections of 2.5 mg/kg bw (IAR81). Concerning irritation, in skin testing of albino rabbits and in eye irritation tests, cisplatin showed irritating effects (IPC91).

General toxicity. Cisplatin administered intraperitoneally (6 mg/kg bw) affected gastric emptying in rats (Whitehouse and Garrett, 1984 in IPC91). Furthermore, in dogs it caused complete interruption of interdigestive myoelectric activity of the gastric anthrum, duodenum and jejunum after an intravenous injection (2 mg/kg bw) (Chey *et al*., 1988 in IPC91).

Reproduction toxicity. Male rats administered 5 daily injections of 2 mg cisplatin per kg bw suffered a progressive but reversible loss of germ cells from the seminiferous epithelium of the testes (Ric93). At high doses, cisplatin caused embryo lethality. Diwan *et al*. (Diw95) presented data on the carcinogenic effects in male and female F344 rats, which were transplacentally exposed to cisplatin. Pregnant rats were given a single intraperito-

neal injection of saline (negative control) or cisplatin (5 mg/kg bw) on day 18 of gestation. The experiment was terminated when the offspring was 79 weeks of age. Treatment with cisplatin caused in the offspring renal cell adenomas (incidence males, 2/19), hepatocellular adenomas (incidence both sexes, 9/40), pulmonary tumours (incidence both sexes, 3/40) and brain tumours (incidence both sexes, 2/40). In the control animals, only one hepatocellular adenoma (1/36) and one pulmonary tumour (1/36) was found. Overall, evaluation of the teratogenic potential of cisplatin is hampered by the limited amount of data that is available.

Mutagenicity. Cisplatin is a bacterial mutagen. Furthermore, the compound was found to be genotoxic in various mammalian cell cultures and *in vivo* tests. The genotoxic effects described using these test systems included gene mutations, chromosome aberrations, and primary DNA damage (IAR81, IPC91).

2.8.3 Conclusion

The toxicity data, as summarized in the previous sections, are too limited to allow a conclusion with regard to risk of adverse effects other than carcinogenicity at concentration levels associated with the referential cancer risk levels.

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A Request for advice

B The Committee

C Comments on the public review draft

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

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
  epidemiologist; Environ, the Netherlands
- PJ Boogaard
  toxicologist; SHELL International BV, The Hague
- PJ Borm
  Professor of inhalation toxicology; Heinrich Heine Universität, Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  professor of risk assessment in occupational epidemiology; IRAS, University of Utrecht, Utrecht
- TM Pal
  occupational physician; Dutch Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol; and, professor of working conditions; Free University, Amsterdam
- GMH Swaen
  epidemiologist; DOW benelux NV, Terneuzen
- AA Vijlbrief, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared by Ms MI Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: Ms F Smith.
Lay-out: Ms M Javanmardi.

Annex C

Comments on the public review draft

A draft of the present report was released in 2004 for public review. The following organisations and persons have commented on the draft document:

- R Zumwalde, National Institute for Occupational Safety and Health, the USA;
- B Wierenga, the Netherlands.