4-Chloro-*o*-phenylenediamine

Health-based calculated occupational cancer risk values

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies '4-Chloro-*o*-phenylenediamine'
Uw kenmerk : DGV/MBO/U-932542
Ons kenmerk : U 322/JR/459-S47
Bijlagen : 1
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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 '4-Chloro-*o*-phenylenediamine'. 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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4-Chloro-*o*-phenylenediamine

Health-based calculated occupational cancer risk values

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

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2005/04OSH, 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).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. 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.

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

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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 4-chloor-*o*-fenyleendiamine. Dit carcinogeen is een monocyclisch aromatische amine dat onder andere wordt gebruikt als intermediair in kleurstofproductie. 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 4-chloor-*o*-fenyleendiamine:

- $4x10^{-3}$ bij 40 jaar beroepsmatige blootstelling aan 20 mg/m^3 (inhaleerbare deeltjes en damp);
- $4x10^{-5}$ bij 40 jaar beroepsmatige blootstelling aan 0,2 mg/m^3 (inhaleerbare deeltjes en damp).

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 4-chloro-*o*-phenylenediamine. This carcinogen is a monocyclic aromatic amine that is used as dye or intermediate in dye production. 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 4-chloro-*o*-phenylenediamine amounts to:

- $4x10^{-3}$ for 40 years of occupational exposure to 20 mg/m^3 (inhalable particles and vapour);
- $4x10^{-5}$ for 40 years of occupational exposure to 0.2 mg/m^3 (inhalable particles and vapour).

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 4-chloro-*o*-phenylenediamine. 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 4-chloro-*o*-phenylenediamine has been based on reviews by IARC (IAR82, 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

4-Chloro-*o*-phenylenediamine

2.1 General information

The chemical and physical properties of 4-chloro-*o*-phenylenediamine are shown below (data obtained from Hea95 and IAR82).

Chemical name	:	1,2-benzenediamino, 4-chloro-
CAS registry number	:	95-83-0
EINECS number	:	202-456-8
IUPAC name	:	4-chloro-*ortho*-phenylenediamine
Synonyms	:	2-amino-4-chloroaniline; 4-chloro-1,2-diaminobenzene; 4-chloro-1,2-phenylenediamine; *para*-chloro-*ortho*-phenylenediamine; 1,2-diamino-4-chlorobenzene; 3,4-diamino-chlorobenzene
Description	:	Crystalline powder
Uses	:	It is used as a dye intermediate and is a component of hair-dyes.
Molecular weight	:	142.6
Molecular formula	:	$C_6H_7ClN_2$
Structure	:	
Melting point	:	76 °C
Solubility	:	Slightly soluble in water; soluble in benzene and petroleum ether; very soluble in ethanol and diethyl ether.
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

Human and animal data have been summarized and evaluated by working groups of the IARC (IAR82, IAR87). The IARC concluded that there is sufficient evidence for the carcinogenicity of 4-chloro-*o*-phenylenediamine in experimental animals. In the absence of data on humans, 4-chloro-*o*-phenylenediamine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans. Therefore, IARC classified the compound in category 2B.

In 1995, DECOS concluded that 4-chloro-*o*-phenylenediamine should be considered as a genotoxic carcinogen (Dec95).

2.2.2 Human data

No data on the carcinogenicity in humans have been reported.

2.2.3 Animal data

Animal carcinogenicity studies are limited to two oral studies (see below). No data on inhalation or dermal exposure has been published.

Ono and his colleagues (Ono92) reported on bladder cancer in male Fischer 344 rats. The animals were given clean drinking water or drinking water containing 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamines (BNN, bladder cancer carcinogen) for 4 weeks, and then fed basal diet with or without 4-chloro-*o*-phenylenediamine for another 32 weeks (week 1-2: 3,300 ppm; week 3-32: 825 ppm). The animals had free access to food and water. At the end of the experiment all animals were killed. Histopathologic examination of the urinary bladders in rats without BNN pre-treatment did not reveal (pre)neoplastic lesions. However, in animals pretreated with BNN and treated with the phenylenediamine, significantly increased incidences in papillary or nodular hyperplasia (9/15) and in papillomas (6/15) were observed compared to the control group (2/13 and 0/13, respectively). The investigators did not study carcinogenicity at other sites of the body.

Weisburger and her colleagues (Wei80) performed a 2-year oral exposure study, using male and female Fischer 344 rats and B6C3F_1 mice (n=50/group/sex). Both species were fed basal diets containing various levels of 4-chloro-*o*-phenylenediamine (0 (stock diet), 0.5 and 1.0%) for 18 months, followed by 7 (rats) or 4½ (mice) months on

the stock diet. The animals had free access to food and water. At the end of the experiment, all animals were killed for gross necropsy. Neoplastic and non-neoplastic lesions recorded are shown in Table 2.1 for rats, and Table 2.2 for mice. As a result of the chronic intake, survival was clearly affected in high-dosed male and female rats. Furthermore, as is clear from the data in Table 2.1, in the urinary bladders of rats benign and malignant tumours occurred in a dose-related trend ($p<0.001$). In addition, 4-chloro-*o*-phenylenediamine induced hepatocellular carcinomas in mice ($p<0.05$).

Table 2.1 (Non)neoplastic lesions in *rats* fed 4-chloro-*o*-phenylenediamine for 2 years (Wei80).

Level of 4-chloro-*o*-phenylenediamine	Control		0.5% (5,000 mg/kg food)		1.0% (10,000 mg/kg food)	
	Male	Female	Male	Female	Male	Female
Number of animals used for histologic examination	48	50	47	49	49	48
% Surviving at termination	64	72	80	84	56	54
Urinary bladder						
transitional cell hyperplasia	-	-	3	4	6	4
transitional cell papilloma	-	-	8	10	7	10
transitional cell carcinoma	-	-	7	5	19	22
Forestomach						
squamous cell papilloma	-	-	-	-	2	3
squamous cell carcinoma	-	-	-	-	2	-
Liver (neoplastic nodule)	-	-	4	-	4	2
Squamous cell carcinoma	-	-	-	-	3	1

Table 2.2 (Non)neoplastic lesions in *mice* fed 4-chloro-*o*-phenylenediamine for 2 years (Wei80).

Level of 4-chloro-*o*-phenylenediamine	Control		0.5%[a] (week 1-33: 10,000 mg/kg fd) (week 34-78: 5,000 mg/kg fd)		1.0%[a] (week 1-33: 20,000 mg/kg fd) (week 34-78: 10,000 mg/kg fd)	
	Male	Female	Male	Female	Male	Female
Number of animals used for histologic examination	50	47	49	48	47	48
% Surviving at termination	84	72	84	88	70	78
Liver						
hepatocellular adenoma	5	-	10	7	8	4
hepatocellular carcinoma	10	-	18	4	26	6
Gallbladder hyperplasia	-	-	-	5	1	1

[a] Source national Cancer Institute, 1978a (reported in IAR82).

2.3 Selection of the suitable study for estimating occupational cancer risk

In the absence of long-term inhalation experiments, the committee selected the oral carcinogenicity study by Weisburger *et al*. (Wei80) to estimate the potential cancer risk in humans under workplace exposure conditions. In this study two animal species of both sexes were used, of which male rats showed to be the most sensitive in developing cancer (urinary bladder cancer). For this reason, the committee calculated the potential lifespan cancer risk of 4-chloro-*o*-phenylenediamine in humans with data from these male rats.

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

The lowest dose of 4-chloro-*o*-phenylenediamine at which an increased incidence in urinary bladder cancer in male rats was observed, was 5,000 mg/kg diet. For estimating additional lifetime cancer risk values the concentration should be expressed in mg/kg bw/day. Since the actual values for lifespan, body weight, and daily food intake were not given in the available publications, the standard values for daily food intake as given in the report of the Health Council of the Netherlands on calculating cancer risk were used to calculate the daily dose of the test substance (Hea95)*. Based on these standard values the daily dose of the test substance is equivalent to 5,000/1,000 (mg test substance per g food) x 40 (g food/kg bw/day) = 200 mg/kg bw/day in male rats.

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**:

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

$$I_{dose} = \frac{\left(15/47\right) - \left(0/48\right)}{\left(3.8 \times 10^{-3}\right) \times \left(547/1{,}000\right) \times \left(760/1{,}000\right) \times \left(7/7\right)}$$

* Average body weight values are assumed to be 500 and 350 g for male and female rats, and 30 and 25 g for male and female mice, and average food intake figures 40 and 50 g/kg bw/day for male and female rats, and 120 and 130 g/kg bw for male and female mice (Hea95).

** I is estimated tumour incidence; I_e and I_c are tumour incidences in exposed and control animals, respectively; X_{po} and X_{pe} are exposure and experimental period, respectively; L is the standard lifespan for the animal species in question (L rats is assumed to be 1,000 days)

I_{dose} =3.8 x 10^{-3} *[mg/kg bw/day]*

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 3.8 x 10^{-3} per mg/kg bw/day, the additional lifetime cancer risk per mg/m^3 under occupational exposure conditions, the HBC-OCRV, amounts to

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

$HBC - OCRV$ = (3.8 x 10^{-3}) x 0.53 x 0.92 x 0.71 x 10 x 70^{-1}

$HBC - OCRV$ = 1.9 x 10^{-4} *[mg/m^3]$^{-1}$*

Based on the HBC-OCRV of 1.9 x 10^{-4} per mg/m^3 the additional lifetime cancer risk for 4-chloro-*o*-phenylenediamine amounts to:

- 4 x 10^{-3} for 40 years of exposure to 20 mg/m^3 (inhalable particles and vapour);
- 4 x 10^{-5} for 40 years of exposure to 0.2 mg/m^3 (inhalable particles and vapour).

2.7 Existing occupational exposure limits

No occupational exposure limits for 4-chloro-*o*-phenylenediamine have been established in the Netherlands (SZW04), Germany (Bun03, DFG03), the United Kingdom (HSE02), Scandinavian Countries (Arb02, NBO00), the United States of America (ACGIH, OSHA and NIOSH (ACG04)) and by the SCOEL of the European Union (Hun97).

Based on the IARC evaluations, Denmark included the compound in the list of substances considered to be carcinogenic (Arb02).

2.8 Toxicity profile

2.8.1 Observations in humans

No data were available to the committee concerning non-carcinogenic toxic effects in humans due to 4-chloro-*o*-phenylenediamine exposure.

2.8.2 Observations in animals

No LD_{50} values were available to the IARC Working Group in 1982 (IAR82). McFee *et al*. (McF89) assessed in B6C3F1 mice a maximum tolerable dose (MTD) of 400 mg/kg bw when administered by intraperitoneal injection.

In a short-term study, Weisburger *et al*. (Wei80) reported that all rats and mice that were given basal diet containing 3% 4-chloro-*o*-phenylenediamine (equivalent to 1,300 and 3,700 mg/kg bw/day for rats and mice, respectively), died within 8 weeks. In 25% of the rats and mice fed 1% of the compound (≈ 430 and 1,200 mg/kg bw/day for rats and mice, respectively), weight gain was depressed. Finally, no compound-related organ lesions were observed in rats and mice fed up to 1.4% 4-chloro-*o*-phenylenediamine for 2 years (≈ 600 and 1,700 mg/kg bw/day).

The committee found no data concerning effects of the compound on reproduction and prenatal toxicity.

2.8.3 In vivo and in vitro mutagenicity

IARC (IAR82) reported on a study, in which 4-chloro-*o*-phenylenediamine caused mutations in *Salmonella typhimurium* strain TA98 in the presence of a metabolic activation system.

A few investigators reported on the *in vivo* mutagenicity or genotoxicity in animals. In one, Suter *et al*. (Sut98) determined the *lacI* mutant frequency in the liver of C57BL/6 Big Blue mice, both males and females, which were given 4-chloro-*o*-phenylenediamine in the diet for 26 weeks at doses of 0, 5,000, and 10,000 ppm (corresponding with 0, 2,166 and 4,610 mg/kg/day, respectively). A clear dose-dependent increase in mutant frequencies was observed in the liver of both sexes. Earlier, the same authors reported on the weak mutagenic potential in the same animal species under comparable experimental conditions, but then for a feeding period of 10 to 14 days at a dose level of 200 mg/kg bw/day (Sut96).

Soler-Niedziela *et al*. (Sol91) performed an *in vivo* mouse bone-marrow micronucleus assay using five male CD-1 mice. 4-Chloro-*o*-phenylenediamine was once administered intraperitoneally at doses of 0 (solvent control, DMSO), 100, 200 and 400 mg/kg bw. The animals were than sacrificed at 24, 48 and 72 hours after the injection. The number of micronucleated polychromatic erythrocytes increased significantly in a dose-related manner. The peak response occurred at 24 hours.

McFee *et al*. (McF89) determined chromosome aberrations, sister chromatid exchanges and micronuclei in bone marrow cells in treated male B6C3F1 mice. The treatment consisted of one intraperitoneal injection containing 0 (solvent control, DMSO), 100, 200 or 400 mg/kg bw 4-chloro-*o*-phenylenediamine. The compound induced chromosomal aberrations and micronuclei in bone marrow cells of mice treated up to 400 mg/kg bw. The results of the chromosome aberration tests were characterized by a few cells with very large numbers of aberrations rather than an even distribution of damage among cells.

2.8.4 Conclusion concerning non-carcinogenic toxicity of 4-chloro-o-phenylenediamine

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

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Bun03 Bundesministerium für Arbeit und Sozialordnung. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe; TRGS 900. FRG: Verlag W. Kolhammer, Ausgabe: Okotber 2000, zuletzt geändert BarbBI. Heft 9/2003. [In German]

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A Request for advice

B The Committee

C Comments on the public review draft

Annexes

Chapter 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.

Chapter **B**

The committee

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The first draft of the this report was prepared by 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: F Smith.
Lay-out: J van Kan.

Chapter 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;
- T Scheffers, the Netherlands.