1,2-Dichloroethane

Health-based calculated occupational cancer risk values

Gezondheidsraad
Health Council of the Netherlands

Voorzitter

Aan de Minister van Volksgezondheid, Welzijn en Sport
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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 om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. Daarnaast verzocht de staatssecretaris om in het geval van beroepsmatige blootstelling aan genotoxisch carcinogene stoffen kankerrisico's te berekenen.

Per 1 januari 1994 heeft mijn voorganger daartoe een commissie ingesteld die de werkzaamheden voortzet van de Werkgroep van Deskundigen (WGD). De WGD was een door genoemde Minister ingestelde adviescommissie.

Hierbij bied ik u - gehoord de Beraadsgroep Toxicologie - een publicatie van de Commissie WGD aan over '1,2-Dichloroethane'.

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

to

the Minister of Health, Welfare and Sport

the Minister and State Secretary of Social Affairs and Employment

No. 1997/01WGD, Rijswijk, 3 July 1997

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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 door de Europese Unie als genotoxisch kankerverwekkend aangemerkte stoffen. In dit rapport maakt zij zo'n schatting voor 1,2-dichloorethaan. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD).

Naar schatting van de commissie is de extra kans op kanker voor 1,2-dichloorethaan:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0,07 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 7 mg/m^3.

Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS) estimates the additional cancer risk associated with occupational exposure to substances that have been classified by the European Union as genotoxic carcinogens. In this report the committee presents such estimates for 1,2-dichloroethane. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genetoxic carcinogens' (1995/06WGD).

The committee estimates that the additional cancer risk for 1,2-dichloroethane amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.07 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 7 mg/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. This evaluation should lead to a health-based recommended exposure limit for the concentration in air of the substance. 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 this case an exposure-response relationship is recommended for use in regulatory standard setting.

1,2-Dichloroethane, the subject of the present report, has been classified as genotoxic carcinogen by the European Union. On request of the Minister of Social Affairs and Employment the committee has established an exposure-response relationship for this substance. This exposure-response relationship is used to calculate a so-called health-based calculated occupational cancer risk value (HBC-OCRV). For the establishment of 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' (GR95). 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-OCRV's to set 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 members of the committee are listed in Annex A. The first draft of this report was prepared by MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

In 1994 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 B. The committee has taken these comments into account in deciding on the final version of the report.

Chapter 2

Derivation of the HBC-OCRV for 1,2-dichloroethane

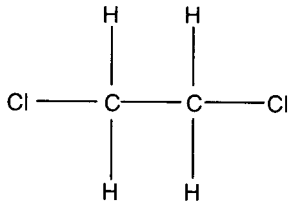
2.1 Introduction

This evaluation of the carcinogenicity and other toxic effects of 1,2-dichloroethane (1,2-DCE) has been based on reviews by the US Agency for Toxic Substances and Disease Registry - ATSDR (ATS94), Deutsche Forschungsgemeinschaft - DFG (Gre95), UK Health and Safety Executive - HSE (HSE94), Netherlands National Institute for Public Health and the Environment - RIVM (Bes84), the Dutch Expert Committee on Occupational Standards (WGD87), and the World Health Organization (WHO95). Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition, literature was retrieved from the on-line data bases Chemical Abstracts, Toxline, and Medline, covering the period January 1988 to the end of October 1995.

2.2 Identity and physical and chemical properties*

Chemical name:	1,2-dichloroethane
CAS registry number:	107-06-2
EEC number:	602-012-00-7
EINECS number:	203-458-1

* data from: ATS94; CEG93; HSE94; Stu95; WHO95

Synonyms:	ethylene dichloride, sym-dichloroethane, 1,2-bichloroethane, acetylenchloride, alpha-, beta-dichloroethane, bichlorure d'ethylene, 1,2-dichloride, ethylene chloride, freon 150, glycol dichloride
Abbreviations:	1,2-DCE; ECD
Description:	1,2-DCE is a clear, dense, mobile, colourless liquid. This synthetic chemical is highly volatile, with a pleasant odour detectable around 80 ppm.
Molecular formula:	$ClCH_2CH_2Cl$
Structure:	
Molecular weight:	98.96
Boiling point (101.3 kPa):	84 °C
Melting point (101.3 kPa):	- 36 °C
Relative density (20 °C/4 °C):	1.3
Vapour density : (air=1; 101.3 kPa)	3.4
Vapour pressure (20 °C):	0.5 kPa
Relative density of saturated: vapour/air mixture (air=1; 20 °C)	1.2
Saturated vapour concentration:	8300 ppm at 20 °C
Flash point:	13 °C
Explosive limits, vol% in air:	6.2-16
Solubility in water (20 °C):	0.9 g/l
Solubility in organic solvents:	miscible with most organic solvents
Log K_{ow}:	1.45, 1.48 (ATS94); 1.76 (WHO95)
Conversion factors: (20 °C, 101.3 kPa)	1 ppm = 4.96 mg/m^3 air 1 mg/m^3 = 0.20 ppm
EEC labeling:	R: 45-11-22-36/37/38 S: 53-45

EEC classification:	F; R 11/ Carc cat 2; R 45/ Xn; R 22/ Xi; R36/37/38

2.3 Carcinogenicity studies and selection of study for risk estimation in the occupational situation

There are only a few reports on the potential carcinogenicity of 1,2-DCE in humans. In two of them (a small case-control and an accompanying historical cohort study), initiated because of the finding of a cluster of brain tumour cases in a petrochemical plant, insufficient evidence was found that these tumours were related to occupational exposure (Aus83a; Aus83b). In another cohort study, an excess in mortality (mainly derived from tumours, but also from circulatory system diseases) and cancer incidence (viz. tumours of the stomach, leukaemia) was observed among workers employed in an ethylene oxide production facility in Sweden. Besides to 1,2-DCE, these workers were exposed to ethylene chlorohydrin, ethylene, small amounts of bis-(2-chloroethyl)ether, ethylene oxide, and traces of other chemicals. However, the excess mortality and cancer incidence could not be attributed to any particular chemical in the ethylene oxide production process (Hog79). In an investigation among workers of a chlorhydrin production plant the mortality due to pancreatic cancer was significantly elevated, and increased with duration of exposure. In addition, a small number of cases of leukaemia was found, but the association with duration of exposure was less consistent. Although workers were principally exposed to 1,2-DCE, other chemicals including bis-chloroethyl ether, ethylene oxide, and ethylene chlorohydrin were involved. No quantitative exposure data were available (Ben93). In an investigation on associations between cancer incidence rates of municipal residents and the level of certain volatile organic contaminants and metals found in finished public drinking water supplies, a statistically significant increase in colon and rectal cancer was found in men aged 55 years or older whose drinking water contained 1,2-DCE levels of 0.1 µg/l or more when compared with men drinking water containing levels of less than 0.1 µg/l). The authors suggested that 1,2-DCE may not be a causal factor, but rather an indicator of possible anthropogenetic contamination of other types (Isa85).

The committee concludes that none of these studies in humans provide conclusive evidence with respect to the possible carcinogenicity of 1,2-DCE in humans. Since the literature search did not reveal any human studies suitable for quantitative cancer risk estimation, animal data are used for estimation of the carcinogenic activity of 1,2-DCE.

The animal carcinogenicity studies are summarized in Table 1.

Table 1 Carcinogenicity studies with 1,2-dichloroethane.

authors (ref)	species/route	experimental	findings, tumours
NCI, 1978 (in IARC79; WGD87;WHO95)	rat (Osborne-Mendel; female, male; n = 50/sex/group) oral (gavage)	TWA[a]: 0, 47, 95 mg/kg bw 5 d/w, 78 w. Experimental period: 93-110 w	tumour incidence observed: male haemangiosarcomas: 1/60, 9/50, 7/50, forestomach squamous cell carcinomas: 0/60, 3/50, 9/50, skin fibromas: 0/60, 5/50, 6/50 at 0, 47, 95 mg/kg/d, resp.; female haemangiosarcomas: 0/59, 4/50, 4/50, mammary gland adenocarcinomas: 1/59, 1/50, 18/50 at 0, 47, 95 mg/kg/d, resp
NCI, 1978 (in IARC79; WGD87; WHO95)	mouse ($B6C3F_1$; female, male ; n = 50/sex/group) oral (gavage)	TWA[b]: male 0, 97, 195; female 0, 149, 299 mg/kg bw, 5 d/w, 78 w. Experimental period: 90 w	tumour incidences observed: male lung adenomas: 0/59, 1/47, 15/48 at 0, 97, 195 mg/kg/d, resp.; female lung adenomas: 2/60, 7/50, 15/48, forestomach squamous cell carcinomas: 1/60, 2/50, 5/45, mammary gland adenocarcinomas: 1/60, 3/49, 4/47, uterus adenocarcinomas/endometrial stromal neoplasms: 0/60, 5/49, 5/47, at 0, 149, 299 mg/kg/d, resp
Cheever *et al* (Che90)	rat (Sprague-Dawley; female, male; n = 50/sex/group) inhalation	0, 200 mg/m^3 (50 ppm) 7 h/d, 5 d/w, 2 y	no statistically significant increase in any type of tumour; non-significant increase in the incidence of mammary gland adenomas (4 vs 2 in controls) and fibroadenomas (21/50 vs 15/50 in controls) in female rats. No compound-related effects found or reported, apart from an increased incidence of testicular lesions (24% vs 10% in controls; no statistics; nature of lesions not specified)
Maltoni *et al* (Mal80)	rat (Sprague-Dawley; female, male; n = 90/sex/group) inhalation	0, 20, 40, 202, 1012 (607[c]) mg/m^3 7 h/d, 5 d/w, 78 w. Experimental period: lifetime	no specific types of tumours, nor changes in the incidence of tumours were found. A not-dose-related increased incidence for fibromas and fibroadenomas of the mammary glands of female rats at 20, 202 and 607 mg/m^3 was observed
Maltoni *et al* (Mal80)	mouse (Swiss; female, male; n = 90/sex/group) inhalation	0, 20, 40, 202, 1012 (607[c]) mg/m^3, 7 h/d, 5 d/w, 78 w. Experimental period: lifetime	no specific types of tumours, nor changes in the incidence of tumours were found
Theiss *et al* (The79)	mouse (A/St; male; n = 20/group) intraperitoneal	0, 20, 40, 100 mg/kg bw, 3 x /w, 8 w. survivors were killed 24 weeks after the first injection	no increase in lung tumours was observed
v.Duuren *et al* (Duu79)	mouse (Ha:1CR Swiss; female; n = 30/group) subcutaneous	0, 42, 126 mg/mouse 3 x /w; 440-594 d	lung papillomas observed were 30/100, 17/30 and 26/30 at 0, 42 and 126 mg/mouse

[a] Time-Weighted Average dose:
high and low doses: 100 and 50 mg/kg bw for 7 w, then 150 and 75 mg/kg bw for 10 w, then 100 and 50 mg/kg bw for 18 w, followedby cycles of 1 treatment-free w and 4 weeks under treatment with the same doses (100 and 50 mg/kw bw) for 43 w (34 w under treatment and 9 treatment-free w).

[b] Time-Weighted Average dose:
high-dose males: 150 mg/kg bw for 8 w, then 200 mg/kg bw for 70 w, followed by 13 w without treatment;
high-dose females: 250 mg/kg bw for 8 w, then 400 mg/kg bw for 3 w, then 300 mg/kg bw for 67 w, followed by 12 w without treatment;
low-dose males: 75 mg/kg bw for 8 w, then 200 mg/kw bw for 3 w, then 150 mg/kg bw for 67 w, followed by 13 w without treatment;
low-dose females: 125 mg/kg bw for 8 w, then 200 mg/kg bw for 3 w, then 150 mg/kg bw for 67 w, followed by 13 w without treatment.

[c] The highest exposure was reduced to 607 mg/m^3 after a few weeks, because of significant mortality.

No compound-related increases in incidences of any tumour were found in inhalation studies using rats and mice. However, these studies suffer from limitations such as one low concentration level, short duration, and high mortality.

Therefore, and in agreement with previous conclusions of the National Institute of Public Health and Environmental Protection (Bes84), The Health Council of the Netherlands (GR86), and DECOS (WGD87), the committee considers the oral NCI study with rats to be the most suitable study to calculate the risk of cancer at the working place.

2.4 Carcinogenic activity in experimental animals, lifetime low-dose exposure

To calculate the carcinogenic activity expressed as the incidence per mg 1,2-dichloroethane per kg bw per day the haemangiosarcomas in male rats (observed in multiple organs, but mainly in the spleen) of the NCI study are used (see IARC79; WGD87; WHO95). The incidence per mg/kg bw per day (lifespan conditions, assuming a linear dose response relationship), I_{dose}, is calculated as follows:

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

$$= \frac{9/50 - 1/60}{47[\text{mg.kg}^{-1}.\text{d}^{-1}] \times (78x7[\text{d}]/1000[\text{d}]) \times (110x7[\text{d}]/1000[\text{d}]) \times 5/7} = 1.2 \times 10^{-2}[\text{mg}^{-1}.\text{kg.d}]$$

2.5 Health risk to humans

To estimate the additional risk of cancer in humans under lifespan conditions it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target susceptibility etc. Furthermore, it is assumed that the standard man lives 75 years, weighs 70 kg and is exposed 24 hours per day, 7 days per week, 52 weeks per year, for lifetime.

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* I_{dose} is the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions assuming a linear dose response relationship, usually expressed per mg per kg body weight per day
I_e and I_c are the tumour incidences in exposed and control animals, respectively
D is the administered daily dose, usually expressed in mg per kg body weight
X_{po} and X_{pe} are the exposure and experimental periods, respectively
L is the standard lifespan for animal species in question

2.6 Calculation of the HBC-OCRV

To estimate the additional lifetime risk of cancer in humans under workplace conditions it is assumed that the standard man is exposed 8 hours per day, during 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, I_{dose}, of 1.2 x 10^{-2} per mg/kg bw per day, the additional lifetime cancer risk per mg/m^3 under occupational conditions, HBC-OCRV, amounts;

$$\text{HBC-OCRV} = I_{dose} \times \frac{40[\text{yr}]}{75[\text{yr}]} \times \frac{48[\text{wk}]}{52[\text{wk}]} \times \frac{5[\text{d}]}{7[\text{d}]} \times (10[\text{m}^3]) \times (70[\text{kg}])^{-1}$$

$$= 1.2 \times 10^{-2}[\text{mg}^{-1}.\text{kg.d}] \times \frac{40[\text{yr}]}{75[\text{yr}]} \times \frac{48[\text{wk}]}{52[\text{wk}]} \times \frac{5[\text{d}]}{7[\text{d}]} \times (10[\text{m}^3]) \times (70[\text{kg}])^{-1} = 6.0 \times 10^{-4}[\text{mg}^{-1}.\text{m}^3].$$

Based on the HBC-OCRV of 6.0 x 10^{-4} per mg/m^3 the reference additional lifetime cancer risks correspond to*

- 4 x 10^{-5} for 40 years of exposure to 0.07 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 7 mg/m^3

2.7 Existing occupational exposure limits

Table 2 summarizes the occupational exposure limits established by Germany, The Netherlands, Sweden, United Kingdom and USA-ACGIH.

2.8 Toxicity profile

The toxicity of 1,2-DCE has been recently reviewed by ATSDR (ATS94), DFG (Gre95), HSE (HSE94), and WHO (WHO95).

According to the CEG, 1,2-DCE is labelled as irritating to eyes, skin, and respiratory tract (CEG93). No quantitative data with respect to irritation were available from the aforementioned reviews, apart from a statement that very high (not quantified) vapour concentrations caused eye and nose irritation in guinea pigs. Following acute inhalatory exposure, 1,2-DCE is of low toxicity, LC_{50}s for rats ranging from 4000 to 6600 mg/m^3. In repeated exposure inhalation studies NOAEL's ranging from approximately 500 (rats, guinea pigs, monkeys) to 2500 mg/m^3 (cats) were reported. Higher le-

* These reference cancer risk values relate to values requested by the Minister of Social Affairs and Employment.

Table 2 Current occupational exposure limits for 1,2-dichloroethane.

country	level		time relation	ref.
	ppm	mg/m^3		
Germany[a] (TRK)	(5)	(20)		DFG95
The Netherlands	50	200	8-h TWA	ISZW95
Sweden[b]	1	4	8-h TWA	NBO93
	5	20	15-min TWA	
UK[c]	5	20	8-h TWA	HSE95
USA-ACGIH[d]	10	40	8-h TWA	ACG96

[a] Classified as a category A2 carcinogen; DFG category A carcinogens are not assigned a health-based occupational exposure limit, but a so called TRK-value (TRK = Technische Richtkonzentration), a concentration feasible with currently available technical means. TRK-values are given in brackets.

[b] Classified as carcinogenic; skin notation added.

[c] Limit is a maximum exposure limit (MEL); skin notation added.

[d] Classified as A4 carcinogen: not classifiable as a human carcinogen.

vels induced effects in mainly liver and kidneys. In a two-year study, no effects were found in rats exposed to 250 mg/m^3, apart from unspecified testicular lesions. Data from oral and inhalation studies investigating different immunological parameters in rats, mice, and rabbits indicate that exposure to 1,2-DCE may impair immune functions in mice and rabbits. Affected antibody responses were reported for rabbits and mice following inhalation and oral 1,2-DCE exposure, while reduced cell mediated immune responses were also observed in mice (see ATS94, WHO95). Furthermore, female mice (n=28/group) exposed to actual concentrations of 5.4 or 10.8 ppm (27 and 54 mg/m^3), for 3 hours, showed significantly increased mortality (observation period: 14 d; times of death not indicated) from streptococcal challenge (five replicates per concentration), whereas a single 3-hour exposure or five consecutive daily 3-hour exposures to 2.3 ppm (10 mg/m^3) had no effect. Macrophage function assays did not reveal any evidence for impaired bactericidal, phagocytic or cytostatic or cytolytic activity in rats or mice. The role of possible effects on neutrophilic granulocytes or humoral responses in the increased susceptibility to streptococcus induced mortality of mice was not evaluated (She87).

Generally, it was noted that 1,2-DCE has a steep dose-response curve.

1,2-DCE is consistently genotoxic when tested in *in vitro* systems. *In vivo*, its genotoxicity is less clear, but its ability to produce somatic and sex-linked recessive lethal mutations in *Drosophila* is beyond doubt.

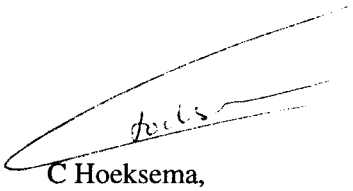
There are no indications for developmental effects at concentrations below those causing other systemic effects.

HSE presented data on effects in humans. Symptoms were reported after exposures of approximately 300 to 5000 mg/m^3 for two months, but not at levels of 50 to 185 mg/m^3. In a separate study, various (not specified) symptoms should have been induced at exposure levels less than 125 mg/m^3, for six months to five years. Many other reports did not contain information on exposure levels. HSE stated that much of the data were of questionable reliability.

Although the infection model as used by Sherwood *et al* is not well validated at the time, the increased mortality following streptococcus challenge should not be ignored. In addition, impairment of immune functions induced by 1,2-DCE has been observed in other studies as well.

In view of the immunotoxicological effects seen in mice at 27 and 54 mg/m^3 (NOAEL: 10 mg/m^3), it is concluded therefore that a health-based occupational exposure limit for 1,2-dichloroethane derived from data other than those on genotoxicity and carcinogenicity would in all likelihood be expected to be in between the concentration levels associated with the referential cancer risk levels.

Rijswijk, 3 July 1997,
for the committee



C Hoeksema,
scientific secretary

professor VJ Feron,
chairman

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Annexes

Annex **A**

The committee

- VJ Feron, *chairman*
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- RB Beems
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Annex **B**

Comments on the public review draft

A draft of the present report was released in 1994 for public review. The following person has commented on the draft document:

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Annex **C**

Abbreviations

ACTS	Advisory Committee on Toxic Substances of the Health and Safety Executive
bw	body weight
DECOS	Dutch Expert Committee on Occupational Standards
HBC-OCRV	health-based recommended occupational cancer risk values
IARC	International Agency for Research on Cancer (WHO)
MEL	maximum exposure limit
$P_{oct/w}$	octanol: water partition coefficient
ppb	parts per billion $(v/v)10^{-9}$
ppm	parts per million $(v/v)10^{-6}$
TWA	time weighted average