



# **SCOEL/REC/302**

# **1,2-Dichloroethane**

# **(Ethylene dichloride)**

Recommendation from the  
Scientific Committee on Occupational Exposure Limits



H.M. Bolt, A. Moretto, I. Rietjens, D. Papameletiou, C. L. Klein  
*Adopted December 2016*



**EUROPEAN COMMISSION**

Directorate-General for Employment, Social Affairs and Inclusion  
Directorate B — Employment  
Unit B.3 — Health and safety

*Contact:* Dr. Christoph Klein

*E-mail:* [EMPL-SCOEL@ec.europa.eu](mailto:EMPL-SCOEL@ec.europa.eu)  
[Christoph.Klein@ec.europa.eu](mailto:Christoph.Klein@ec.europa.eu)

*European Commission*  
*B-1049 Brussels*

**SCOEL/REC/302**  
**1,2-Dichloroethane**  
**(Ethylene dichloride)**

Recommendation from the  
Scientific Committee on Occupational Exposure Limits



***Europe Direct is a service to help you find answers  
to your questions about the European Union.***

**Freephone number (\*):**

**00 800 6 7 8 9 10 11**

(\*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

#### **LEGAL NOTICE**

This document has been prepared for the European Commission however it reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

More information on the European Union is available on the Internet (<http://www.europa.eu>).

Luxembourg: Publications Office of the European Union, 2016

ISBN: 978-92-79-64564-8 (PDF)

doi: 10.2767/100789 (PDF)

© European Union, 2016

Reproduction is authorised provided the source is acknowledged.

## Contents

1.	CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES .....	11
2.	EU HARMONISED CLASSIFICATION AND LABELLING .....	12
3.	CHEMICAL AGENT AND SCOPE OF LEGISLATION .....	12
4.	EXISTING OCCUPATIONAL EXPOSURE LIMITS .....	13
	<b>EU</b> .....	14
	<b>Non-EU</b> .....	14
5.	OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE .....	15
6.	MONITORING EXPOSURE.....	17
	<b>6.1 EXTERNAL EXPOSURE</b> .....	17
	<b>6.2 INTERNAL EXPOSURE/BIOMONITORING OF EXPOSURE</b> .....	20
7.	HEALTH EFFECTS.....	20
	7.1. Toxicokinetics (absorption, distribution, metabolism, excretion) .....	20
	7.1.1. Human data .....	20
	7.1.2. Animal data.....	20
	7.1.3. In vitro data .....	22
	7.1.4. Toxicokinetic modelling .....	23
	7.1.5. Biological monitoring .....	23
	7.2. Acute toxicity .....	23
	7.2.1. Human data .....	23
	7.2.2. Animal data.....	24
	7.2.3. In vitro data .....	25
	7.3. Specific Target Organ Toxicity/Repeated Exposure .....	25
	7.3.1. Human data .....	25
	7.3.2. Animal data.....	26
	7.3.3. In vitro data .....	28
	7.4. Irritancy and corrosivity .....	28
	7.4.1. Human data .....	28
	7.4.2. Animal data.....	28
	7.4.3. In vitro data .....	28
	7.5. Sensitisation .....	29
	7.5.1. Human data .....	29
	7.5.2. Animal data.....	29
	7.5.3. In vitro data .....	29
	7.6. Genotoxicity .....	29
	7.6.1. Human data .....	30
	7.6.2. Animal data.....	30

7.6.3. In vitro.....	31
7.7. Carcinogenicity .....	31
7.7.1. Human data .....	31
7.7.2. Animal data.....	32
7.7.3. Summary of experimental carcinogenicity data.....	37
7.7.4 Quantitative risk assessment. ....	37
7.8. Reproductive toxicity .....	42
7.8.1. Human data .....	42
7.8.2. Animal data.....	43
7.8.3. In vitro data .....	43
7.9. Mode of action and adverse outcome pathway considerations .....	44
7.10. Lack of specific scientific information .....	45
8. GROUPS AT EXTRA RISK .....	45
9. REFERENCES .....	46
10. ANNEX .....	55

**RECOMMENDATION FROM THE  
SCIENTIFIC COMMITTEE ON OCCUPATIONAL  
EXPOSURE LIMITS  
FOR  
1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE)**

8-hour TWA:	not assigned
STEL:	not assigned
BLV:	not assigned
BGV:	
Additional categorisation:	SCOEL carcinogenicity group A (genotoxic carcinogen, non-threshold)
Notation:	'skin'
Carcinogenic risk assessment:	<i>see below: Recommendation Executive Summary / 7.7.4</i>

**The present Recommendation was adopted by SCOEL on 2016-12-13.**

This evaluation is based on DFG (1992), IPCS (1995), IARC (1999), ATSDR (2001), Gwinn (2011), NTP (2011), the references cited in these reviews and a PubMed search (Nov 2014/Feb 2016).



## RECOMMENDATION EXECUTIVE SUMMARY

1,2-Dichloroethane (ethylene dichloride) is metabolised to reactive and toxic intermediates. High acute and subacute experimental animal exposures have led to liver, kidney and lung damage. Triggered by human case studies, recent interest has been focussed on CNS effects. The NOEC for behavioural neurotoxicity in rats was 200 ppm 1,2-dichloroethane for 4 h. Taking the specific endpoint of olfactory degeneration after acute exposure, a NOAEC of 50 ppm has been reported after an 8 h exposure.

The critical endpoint to discuss an OEL is carcinogenicity. As specified in sections 7.7.3 and 7.9, 1,2-dichloroethane is carcinogenic at multiple sites in rats and mice, both by oral dosing and by inhalation. Upon inhalation, there were clear indications of carcinogenicity at exposure levels of 160 ppm in rats and 90 ppm in mice, respectively. The assumed mode of action is genotoxic, based on generation of DNA-reactive intermediate(s) and not entirely consistent results in genotoxicity tests, since there is no evidence of an alternative non-genotoxic mode of action. There are arguments based on quantitative metabolic data that the dose-tumour response probably is non-linear. Taking all this information together, 1,2-dichloroethane is categorised as a genotoxic carcinogen into the *SCOEL carcinogen Group A*. Therefore, no safe health-based OEL can be supported.

Available data show skin permeability is a relevant factor for occupational 1,2-dichloroethane exposure. Therefore, a "skin" notation is applied. It is possible to measure 1,2-dichloroethane in blood, but this method has not been used in an occupational context. Therefore, it is at this stage not possible to recommend a BGV or BLV.

### **Carcinogenic risk assessment (for details, see 7.7.4)**

Based on well-conducted experimental data (Nagano et al. 2006), the BMD10 of 37.8 ppm for the combination of adenoma and fibroadenoma in the mammary gland of the female rats was taken as the most conservative starting point and adjusted to the workplace situation. Acceptable goodness of fit was found for all models used. This refers to benign tumours and to the combination of benign and malignant tumours. In the present case, benign tumours were included as possible pre-stages of malignancy, because this broadens the data-base of the benchmark calculation. It is noted by SCOEL that this leads to very conservative risk figures.

The following adjustment to the workplace situation was made:

Corrected BMD10 = BMD10 × 6.7 m<sup>3</sup>/10 m<sup>3</sup> × 75 years/40 years × 6 hours/8 hours × 52 weeks/48 weeks.

This results in a corrected BMD10 = POD of 38.58 ppm. Using this value the following risk numbers were derived:

Cancer risk estimate with an excess lifetime cancer risk of 10<sup>-1</sup> = 38.6 ppm (158660 µg/m<sup>3</sup>)

Cancer risk estimate with an excess lifetime cancer risk of 10<sup>-3</sup> = 0.386 ppm (1586.6 µg/m<sup>3</sup>)

Cancer risk estimate with excess lifetime cancer risk of  $10^{-4}$  = 0.0386 ppm (158.66  $\mu\text{g}/\text{m}^3$ )

Cancer risk estimate with excess lifetime cancer risk of  $10^{-5}$  = 0.00386 ppm (15.866  $\mu\text{g}/\text{m}^3$ )

*It is stressed that the presented risk values are rather conservative (see 7.7.4.2).*

**RECOMMENDATION FROM THE  
SCIENTIFIC COMMITTEE ON OCCUPATIONAL  
EXPOSURE LIMITS  
FOR  
1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE)**

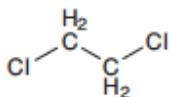
**RECOMMENDATION REPORT**

**1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES**

The compound is a colourless liquid with a pleasant odour (IARC 1999).

Name: 1,2-dichloroethane  
Synonyms: ethylene dichloride, EDC, 1,2-bichloroethane, 1,2-DCE, *sym*-dichloroethane, ethane dichloride, glycol dichloride  
Molecular formula: C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>

Structural formula:



EC No.: 203-458-1  
CAS No.: 107-06-2  
Molecular weight: 98.96 g/mol  
Melting point: -35.5°C  
Boiling point: 83.5°C  
Conversion factors: 1 ppm = 4.110 mg/m<sup>3</sup>  
(20 °C, 101.3kPa) 1 mg/m<sup>3</sup> = 0.243 ppm

(DFG 1992, IARC 1999, NTP 2011)

*Note: Some inhalation studies, which are evaluated here, give 1,2-dichloroethane concentrations in mg/m<sup>3</sup>, others in ppm. In this document, the respective original values are given. For information, the corresponding ppm or mg/m<sup>3</sup> figure may be calculated based on a rounded conversion factor of 4 from ppm to mg/m<sup>3</sup> or the exact factors indicated above.*

## 2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for 1,2-dichloroethane is provided by ECHA (2016), as summarised in Table 1.

**Table 1:** Classification according to CLP [Regulation \(EC\) No 1272/2008](#), Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances"

Index no.	CAS no.	EC / List no.	EC / List name	IUPAC Name	
602-012-00-7	107-06-2	203-458-1	1,2-dichloroethane	1,2-dichloroethane	
Classification		Labelling		Specific Concentration Limits, M-factors	Notes
Hazard Class & Category Codes	Hazard Statement Codes	Hazard Statement Codes	Pictograms, Signal Word Codes		
Flam. Liq. 2	H225	H225	GHS07 GHS02 GHS08 Dgr	-	-
Acute Tox. 4 *	H302	H302			
Skin Irrit. 2	H315	H315			
Eye Irrit. 2	H319	H319			
STOT SE 3	H335	H335			
Carcinogenicity Category 2 , 1B (2015)	H351	H351			
Mutagenicity Category 2	H341	H341			

Explanations: based on C&L GHS 2009; H225 Highly flammable liquid and vapour; H302 Harmful if swallowed; H315 Causes skin irritation; H319 Causes serious eye irritation; H335 May cause respiratory irritation; H350 May cause cancer; 'Dgr' Danger.

\* The classification as obtained from the Annex VII shall then substitute the minimum classification indicated in this Annex if it differs from it.

## 3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

1,2-Dichloroethane is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

1,2-Dichloroethane is also a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

#### 4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

1,2-Dichloroethane has been classified as genotoxic carcinogen by many national regulatory authorities. However, there is no entry for genotoxicity in the CLP [Regulation \(EC\) No 1272/2008](#), see chapter 2. The reason may be that in the past under the Dangerous Substances Directive 67/548, classification as Carc. Cat. 2 (now 1B) was often used for genotoxic carcinogens. Additional classification as Mut. Cat. 3 (now 2) could have been regarded 'double classification'. Based on the considered genotoxic mode of action, some organisations (e.g. Germany DFG) did not derive an OEL (DE DFG 2013). Several countries in and outside the EU did. A number of relevant OEL's globally are presented in Table 3.

At EU level, no *OEL* has been adopted. Yet, the ECHA Committee for Risk Assessment (RAC) delineated a cancer risk of  $6.0 \times 10^{-7}$  per  $\mu\text{g}/\text{m}^3$  ( $= 6.0 \times 10^{-4}$  for  $1 \text{ mg}/\text{m}^3$ ) (ECHA 2015).

No indications for any existing *BLV* (Biological Limit Value) were found.

**Table 3:** Overview of selected existing OELs for 1,2-dichloroethane

EU	TWA (8 hrs)		STEL (15 min)		Remarks	References
	ppm	mg/m <sup>3</sup>	ppm	mg/m <sup>3</sup>		
Austria	5	20	20	80	TRK	AT GKV (2011)
Belgium	10	41	-	-		BE KB (2014)
Finland	1	4	5	20	Skin notation	FI MSAH (2012)
France	10	40	-	-	VME	FR INRS (2012)
Germany	-	-	-	-	Skin notation	DE DFG (2013) DE DFG (2015)
Germany	0.2 <sup>1</sup>	0.8 <sup>1</sup>	-	-	Acceptable concentration (risk level 4:10 <sup>4</sup> ); Skin notation	DE BAuA (2016) <sup>1</sup>
Germany	1 <sup>1</sup>	4 <sup>1</sup>	-	-	Tolerated concentration (risk level 4:10 <sup>3</sup> ); Skin notation	DE BAuA (2016) <sup>1</sup>
Ireland	5	20	10	40		IE HSA (2016)
Netherlands	-	7 <sup>2</sup>	-	-		NL SER (2007)
Spain	5	20	-	-		ES INSHT (2011)
Sweden	1	4	5	20	Skin notation	SWE SWEA (2015)
UK	5	21	-	-	Skin notation	GB HSE (2002)
<b>Non-EU</b>						
Australia	10	40	-	-		AU SWA (2011)
Canada (Ontario)	10	-	-	-	TWA	CA OML (2013)
Canada (Québec)	1	4	2	8	TWAEV / STEV	CA IRSST (2010)
New Zealand	5	21	-	-	Skin notation	NZ HS (2013)
Norway	1	4	-	-	Skin notation	NO NLIA (2011)
Switzerland	5	20	-	-	VME; skin notation	CH SUVA (2016)
US (OSHA)	50	-	100	-	PEL (TWA, TWAC)	US OSHA (2006)
US (ACGIH)	10	-	-	-	TLV-TWA	US ACGIH (listed 2015)
US (NIOSH)	1	4	2	8	REL (TWA, ST)	US NIOSH (2016)

- PEL = Permissible Exposure Level (OSHA)
- REL = Recommended Exposure Limit (NIOSH)
- TRK [Technische RichtKonzentration] = indicative concentration. Used when no 'safe' exposure level can be derived. Value based on technical feasibility.
- TWA = Time-Weighted Average (usually 8 hours average); STEL = Short Term Exposure Limit (usually 15 minutes average).
- TWAEV = Time-Weighted Average Exposure Value = TWA; STEV = Short Term Exposure Value
- VME [Valeur Moyenne d'Exposition] = TWA.

<sup>1</sup> Not a formal OEL but a 'risk number'-based concentration [Draft, not yet officially published in the *Gemeinsames Ministerialblatt* at the time of adoption of this Recommendation by SCOEL]

<sup>2</sup> Not clear whether a formal OEL or a 'risk number'-based concentration.

## 5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

### 5.1 Occurrence

There are no known natural sources of 1,2-dichloroethane other than anaerobic biodegradation of tetrachloroethane (NTP 2014). Most 1,2-dichloroethane released into the environment is from emissions into the air linked to its production, use, storage, distribution, and disposal of 1,2-dichloroethane (ATSDR 2001, NTP 2014). It is moderately persistent in air; the estimated atmospheric lifetime is between 43 and 111 days. Small amounts of 1,2-dichloroethane are transported to the stratosphere, where photolysis may produce chlorine radicals, which may in turn react with ozone (Spence & Hanst 1978). 1,2-Dichloroethane may be released in industrial effluents to the aquatic environment, from where it is removed rapidly by volatilization. It may also leach to groundwater near industrial waste sites. It is not expected to bio-concentrate in aquatic or terrestrial species (WHO/IPCS 1998). It has been detected at low levels in ambient and urban air, groundwater and drinking-water samples (NTP 2014).

### 5.2 Production and use

#### Production

According to IOM (2011), 1,2-dichloroethane is produced either by the direct reaction of chlorine with ethylene (known as direct chlorination) or by the reaction of hydrochloric acid and oxygen on ethylene (known as oxy-chlorination). They referred to the European Council of Vinyl Manufacturers (ECVM) which includes all 14 European polyvinylchloride (PVC) resin producers noting the annual production and import volume in EU of  $>1 \times 10^6$  tonnes to be spread as follows:

- Eastern Europe (Czech Republic, Hungary, Poland, Romania, Slovakia): 15%,
- Central and Northern Europe (Germany, Sweden): 38%,
- Western Europe (Belgium, Netherlands, France, UK): 35%,
- Southern Europe (Italy and Spain): 12%.

1,2-Dichloroethane ranks among the highest production volume chemicals in the USA. Annual production plus imports totalled over 35 billion pounds ( $>15 \times 10^6$  tonnes) from 1986 to 2006 (NTP 2014).

#### Use

More than 95% of produced 1,2-dichloroethane is used to manufacture vinyl chloride, mostly for PVC production (WHO/IPCS 1995; IARC 1999). The remaining 5% is used in the manufacturing of chlorinated solvents (IOM 2011). Formerly 1,2-dichloroethane was used as a solvent for processing pharmaceutical products, for fats, oils, waxes, gums, resins, rubber and in several removers (HSDB 2016). It was also used as an insecticide, as cleaner for upholstery and carpets, as a solvent in textile cleaning and metal degreasing, as a lead scavenger in antiknock gasoline, a starting material for chlorinated solvents such as vinylidene chloride, ethylenediamines, tri- and tetrachloroethylene (IOM 2011), a dispersant for plastics and elastomers such as synthetic rubber, an ore flotation compound, an extractant in certain food processes (IARC 1979; HSDB 2016) and as a general anaesthetic instead of chloroform (HSDB 2016; NTP 2014). Exposures in the pharmaceutical industry are expected to be intermittent and long term time-weighted average exposures are expected to be low

(IOM 2011). The global 1,2-dichloroethane market was growing at 3.5-4% per year in the past but this changed abruptly in 2008 when PVC demand collapsed due to deteriorating economic conditions and destocking in the vinyl's chain (IOM 2011).

### **5.3 Occupational exposure**

#### Numbers of sites and people exposed

Occupational exposure to 1,2-dichloroethane in North America occurs mainly among workers involved in the production of vinyl chloride (WHO/IPCS 1998). A national occupational exposure survey (conducted from 1981 to 1983) estimated that 83,246 workers in 1,526 plants potentially were exposed to 1,2-dichloroethane (NIOSH 1990). According to IARC (1999) 28% of employees working with adhesives and solvents were exposed to 1,2-dichloroethane.

In European countries, most occupational exposures to 1,2-dichloroethane occur in the manufacturing industry. The number of workers exposed in VCM manufacturing facilities is approximately 2,264 (in the year 2009). Based on the estimates of the regional proportions of VCM production capacity, the number of workers exposed in different EU regions is as follows:

- Eastern Europe: 340 (15%)
- Central and Northern Europe: 860 (38%)
- Western Europe: 790 (35%)
- Southern Europe: 270 (12%)

An estimated 460 workers are involved in the use of 1,2-dichloroethane as a solvent in pharmaceutical processing (IOM 2011).

#### Levels of exposure

Mean concentrations of 1,2-dichloroethane at three production plants in the UK in 1990 were 2.8, 3.2 and 6.8 mg/m<sup>3</sup>; 95% remained below 20 mg/m<sup>3</sup>, while maximum values at the plants were 18, 80 and 160 mg/m<sup>3</sup> (IARC 1999). In 2006 industry completed a survey on the exposure to 1,2-dichloroethane in the European plastics manufacturing industry. A total of 1,653, 8h TWA exposure measurements were taken across different manufacturing sites and job groups. Levels ranged from 0.2 to 10 ppm with an average of 0.48 ppm across all job groups and sites. The highest exposures were seen during decommissioning, product sampling, and loading and unloading during transport. On the basis of this information, an estimated 11% of manufacturing workers would be exposed to TWAs above 1 ppm and only 0.36% of workers would be exposed to TWAs above 5 ppm. No data were available on the levels of exposure of the workers in the pharmaceutical industry using 1,2-dichloroethane as solvent. The OECD Screening Information Data Set (SIDS) mentioned concentrations ranging from 0.122 to 3.72 ppm for VCM production between the year 1995 and 1999. The average exposure was 1.12 ppm. An average exposure of 0.48 ppm is assumed representative for 2006. Over the period 1997 to 2006 an annual decline of 9% was calculated (IOM 2011).



### **5.4 Routes of exposure and uptake**

The routes of potential human exposure to 1,2-dichloroethane encompass inhalation, ingestion, and dermal contact (IARC 1979). Because of the volatile nature of 1,2-dichloroethane, the inhalation route is most important. 1,2-Dichloroethane has been detected in ambient air (urban and rural) and indoor air of residences near hazardous-waste disposal sites and in surface water, groundwater, and drinking water (ATSDR 2001). Drinking-water samples from a number of urban and rural locations in the United States have been reported as being contaminated with 1,2-dichloroethane (NTP 2014).

For the general population, the greatest source of exposure is inhalation of contaminated ambient or indoor air, with a minor contribution from ingestion of contaminated drinking water (ATSDR 2001). Ingestion of 1,2-dichloroethane in contaminated drinking water is expected to be an important source of exposure for 4% to 5% of the U.S. population. 1,2-Dichloroethane has also been detected in food items and in human breath, urine, and milk (ATSDR 2001; NTP 2014).

## **6. MONITORING EXPOSURE**

### **6.1 External exposure**

1,2-Dichloroethane can be monitored in the workplace air using the following methods:

- NIOSH (2003). Method 1003 for halogenated hydrocarbons
- OSHA (1979). Method ORG-03 for organic vapours
- OSHA (2000). Method ORG-07 for ethylene dichloride
- DFG (1999). Method for determination of 1,2-dichloroethane
- EPA (1999). Method TO-17 for volatile organic compounds
- UK HSE (1993). Method MDHS 72 for volatile organic compounds (active sampler)
- UK HSE (2000). Method MDHS 96 for volatile organic compounds (active sampler)
- UK HSE (1995). Method MDHS 80 for volatile organic compounds (diffusive sampler)
- UK HSE (1997). Method MDHS 88 for volatile organic compounds (diffusive sampler)
- ISO (2001). Method ISO 16200-1 for volatile organic compounds (active sampler)
- ISO (2000). Method ISO 16200-2 for volatile organic compounds (diffusive sampler)

In all eleven methods 1,2-dichloroethane is sampled from the air in the workplace by adsorption onto a solid sorbent, followed by extraction with an organic solvent or thermal desorption. The 1,2-dichloroethane-containing extract is subsequently analysed by (head-space) gas chromatography (GC), using mass spectrometry (MS), flame ionisation detection (FID), photo-ionization detection (PID) or electron capture detection (ECD) as shown in Table 4.

Table 4: Overview of sampling and analytical methods for monitoring 1,2-dichloroethane in workplace air.

Method	Filters/ adsorbent	Desorption solution	Analysis	EE (%)	LOD/LOQ	Concentration range	Flow rate / sample volume / time	Evaluation #	Refs
<b>NIOSH Method 1003</b>	Coconut shell charcoal	CS <sub>2</sub>	GC-FID	94*	0.7 (LOD) µg analyte /sample  2.3 (LOQ) µg analyte /sample	Working range 16 to 1320 ppm at max sample volume	0.1 to 0.2 L/min/  1 L at 50ppm (minimum) 50 L (maximum)	Partially	NIOSH (2003)
<b>OSHA Method ORG-03</b>	Charcoal	O-xylene	GC with electron capture detector	87.9**	0.05 ppm (LOD) at recommended air volume	n.s.	0.2 L/min 10 L	Fully	OSHA (1979)
<b>OSHA Method ORG-07</b>	Charcoal	Organic solvent	GC-FID	n.s.	n.s.	n.s.	n.s.	***	OSHA (2000)
<b>DFG 1999</b>	Activated carbon	Dimethyl- acetamine/ water (3:1)	Head space GC- FID	>95****	0.08 mg/m <sup>3</sup> (LOQ) for 10 L air sample	n.s.	1.2-4 L/h max 10L	n.s.	DFG (1999)
<b>EPA Method TO-17</b>	Activated charcoal or activated charcoal/ silica gel mixture	Thermal desorption	Capillary GC- MS/FID/ ECD detector	n.s.	n.s.	n.s.	Sampling rate at a settable value in the range 10 to 200 mL/min; collection of 1 and 4 liter total sample volume	n.s.	EPA (1999)
<b>UK HSE Method MDHS 72 (active sampler)</b>	Tenax	Thermal desorption	GC-FID	n.s.	n.s.	0.2-100 mg/m <sup>3</sup> For samples of 2.5 L of air	Flow rates between 5 and 500ml/min (optimum 50 ml/min)	n.s.	UK HSE (1993)

SCOEL/REC/302 1,2-Dichloroethane (Ethylene dichloride)

Method	Filters/ adsorbent	Desorption solution	Analysis	EE (%)	LOD/LOQ	Concentration range	Flow rate/ sample volume/ time	Evaluation <sup>#</sup>	Refs
<b>UK HSE Method MDHS 96 (active sampler)</b>	Charcoal	CS <sub>2</sub>	GC- MS/FID or other selective detector	n.s.	n.s.	1-1000 mg m <sup>3</sup> Of VOCs for a 10L sample size	n.s.	n.s.	UK HSE (2000)
<b>UK HSE Method MDHS 80 (diffusive sampler)</b>	Chromo- sorb 102	Thermal desorption	GC-FID	n.s.	n.s.	1-1000 mg m <sup>3</sup> Individual organic for exposure times between 30 min and 8h	Diffuse sampling exposure times between 30 min and 8 h	n.s.	UK HSE (1995)
<b>UK HSE Method MDHS 88 (diffusive sampler)</b>	Activated carbon	CS <sub>2</sub>	GC- MS/FID or other selective detector	n.s.	n.s.	1-1000 mg m <sup>-3</sup> Of VOCs for exposure times between 30 min and 8h	Diffuse sampling exposure times between 30 min and 8 h	n.s.	UK HSE (1997)
<b>ISO 16200-1 (active sampler)</b>	Activated coconut shell charcoal	CS <sub>2</sub>	GC- MS/FID/ PID or other suitable detector	n.s.	n.s.	Is dependent on the volume sampled	n.s.	n.s.	ISO (2001)
<b>ISO 16200-2 (diffusive sampler)</b>	Activated coconut shell charcoal	CS <sub>2</sub>	GC- MS/FID/ PID or other suitable detector	n.s.	n.s.	1-1000 mg m <sup>3</sup> individual organic for an exposure time of 8 h	Diffuse sampling exposure times between 30 min and 8 h	n.s.	ISO (2000)

*n.s.* not specified; *LOD*:Limit of Detection (for the overall procedure); *LOQ*:Limit of Quantification; *EE*: Extraction efficiencies (average)

\* Desorption efficiency at 2.5-2500 µg

\*\* Desorption efficiency (average) at 0.1 to 0.4 mg per tube

\*\*\* With slight modification, this method is a generalized version of validated NIOSH methodology.

\*\*\*\* Recovery in the range of 7.5-450 µg 1,2-dichloroethane

# Any evaluation statement is as given in the original method description. Wording may have different meanings in different methods.

## 6.2 Internal exposure/Biomonitoring of exposure

Biomonitoring of 1,2-dichloroethane exposures in the workplace can be carried out by the measurement of 1,2-dichloroethane in blood, and can be quantitated by head-space chromatography (DFG 1981). Biological monitoring based on excretion of urinary metabolites would be a potential means for industrial exposure control, however, no studies are available so far on which a biological limit value could be based.

Table 5: Overview of the available method for bio-monitoring of occupational exposures to 1,2-dichloroethane.

Method	Application	Analysis	Standard deviation (rel)(Sw)	Prognostic range(u)	Recovery (%)	Detection limit	References
DFG 1981	In blood	Head-space GC	9.5-3.2%	21.7-7.2%	97-106	0.082 mg/L 1,2-dichloroethane	DFG (1981)

## 7. HEALTH EFFECTS

1,2-Dichloroethane is a central nervous system depressant and causes damage to liver and kidneys. Very high concentrations of the vapour cause mucosal irritation and relatively low concentrations inhaled in animal studies result in pulmonary oedema. 1,2-Dichloroethane vapour may cause corneal damage. Liquid 1,2-dichloroethane can induce dermatitis. 1,2-Dichloroethane has proved to be genotoxic in a number of test systems *in vitro*, and less conclusively *in vivo*. A carcinogenic effect of 1,2-dichloroethane has been seen in mice and rats after long-term oral administration (DFG 1992).

### 7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

#### 7.1.1. Human data

The analysis of several tissues of humans who died following acute oral poisoning with 1,2-dichloroethane showed that 1,2-dichloroethane is widely distributed throughout the human body. Concentrations ranged from 1 to 50 mg/kg in the spleen and 100 to 1000 mg/kg in the stomach; levels in the liver and kidney were approximately 10 times lower than those in the stomach (Luznikov et al., 1985, IARC 1999).

Dichloroethane was detected in the breast milk of exposed female workers (Muchametova and Wosabaja 1972).

#### 7.1.2. Animal data

##### *Absorption*

1,2-Dichloroethane is rapidly absorbed, both after inhalation and oral dosage, and is distributed rapidly to various organs in the blood stream (DFG 1992).

After occlusive dermal application of 2 ml undiluted 1,2-dichloroethane, or a saturated or one-third saturated aqueous solution of 1,2-dichloroethane on the shaved skin of the rat for 24 hours, rapid percutaneous absorption was observed. Over the whole exposure period there was a continuous increase in 1,2-dichloroethane concentrations in blood. The peak level of 1,2-dichloroethane detected in blood (135 mg/L) was markedly higher

than the peak concentrations of other solvents investigated in the same way (e.g. benzene, ethylbenzene, tetrachloroethene, chloroform, toluene, xylene) (Morgan et al. 1991). This was taken as an indication of substantial skin absorption (DFG 2013).

### Distribution

1,2-Dichloroethane is rapidly distributed to various organs in the blood stream. The highest concentrations are found in adipose tissue followed by liver and lungs from which the substance is eliminated relatively rapidly, and more slowly with increasing dose (DFG 1992, Gwinn et al 2011). 1,2-Dichloroethane easily crosses the placental barrier (Payan et al 1995).

### Metabolism

In evaluating the genotoxicity of 1,2-dichloroethane, it is important to consider the metabolic pathways and the formation of genotoxic metabolites. Metabolism occurs rapidly with a reported half-life in blood of 20-30 min in male Osborne-Mendel rats following inhalation or oral dosing (Gwinn et al 2011).

For details of the metabolism of 1,2-dichloroethane, reference can be made to comprehensive reviews (DFG 1992, IPCS 1995, IARC 1999, Gwinn 2011). The knowledge on pathways is based on the metabolites identified from in vivo and in vitro studies of both 1,2-dichloroethane and its bromine analogue, 1,2-dibromoethane. *Figure 1* shows the most relevant routes, as proposed by IARC (1999).

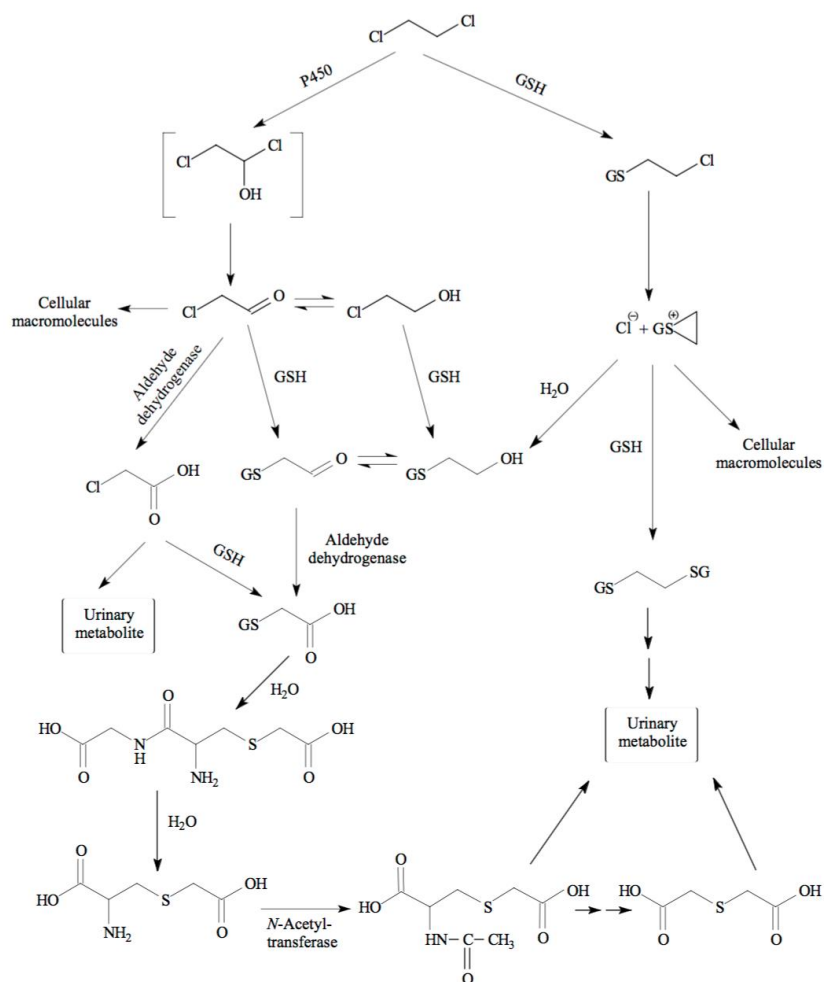


Figure 1: Proposed metabolic pathways of 1,2-dichloroethane (IARC 1999).

Basically, metabolism occurs *via* two principal pathways, catalysed by cytochrome P-450 and by glutathione S-transferase (*Figure 1*). Cytochrome P-450 (CYP) enzymes catalyse oxidative transformation of 1,2-dichloroethane to 2-chloroethanol (proposed), to 2-chloroacetaldehyde and then to 2-chloroacetic acid (Guengerich *et al.*, 1980), which are conjugated both enzymatically and non-enzymatically with glutathione (GSH). The other pathway involves direct conjugation with GSH to form S-(2-chloroethyl)glutathione, which is a sulfur half mustard. A non-enzymatic reaction of this half mustard leads to an alkylating agent (episulfonium or thiiranium ion), which may react with water to form S-(2-hydroxyethyl)glutathione, with thiols such as GSH to form ethene bis-glutathione, or with DNA to form DNA-adducts (IARC 1999). Key isoenzymes for the oxidative and reductive (glutathione-dependent) pathways are the cytochrome P-450 isoform CYP2E1 and the glutathione S-transferase isoform GSTT1-1, respectively (Guengerich *et al* 1991, Thier *et al* 1995, 1996).

The available animal data provide evidence that the majority of absorbed 1,2-dichloroethane is normally metabolised *via* the oxidative pathway, with the reductive glutathione-dependent conjugation representing a minor pathway. For low 1,2-dichloroethane concentrations this is likely to be the case as CYP-mediated oxidation of 1,2-dichloroethane has been shown to exhibit high affinity, but low capacity metabolism. Conversely, the glutathione-dependent pathway displays low affinity but high capacity. Therefore, as blood and tissue levels of 1,2-dichloroethane increase, oxidative metabolism likely becomes saturated, and glutathione conjugation becomes the predominant metabolic pathway. This metabolic saturation through the CYP2E1 pathway appears to occur at 1,2-dichloroethane blood levels of 5–10 mg/ml, which corresponds to inhalation exposures of 150 ppm in rats (Gwinn *et al* 2011).

As much of the information on metabolic pathways of 1,2-dichloroethane is deduced by analogy from experiments with 1,2-dibromoethane, Watanabe *et al* (2007) treated rats and mice (*i.p.*) with <sup>14</sup>C-labelled 1,2-dichloroethane or 1,2-dibromoethane (5 mg/kg *b.w.*). Hepatic and renal DNA was digested and analysed for using accelerator mass spectrometry. The DNA-adduct level in liver or kidney of S-[2-(N(7)-guanyl)ethyl]glutathione in rats treated with 1,2-dibromoethane was approximately 1 adduct/10<sup>5</sup> DNA bases; in male or female mice, the level was approximately one-half of this. The levels of DNA-adducts from 1,2-dichloroethane were 10-50-fold lower. Thus, DNA binding occurs with metabolites of 1,2-dichloroethane, but this is considerably less than binding with 1,2-dibromoethane metabolites *in vivo*.

### *Excretion*

The pattern of elimination of metabolites was similar in rats and mice 48 h after administration of oral doses of radiolabelled 1,2-dichloroethane (100 and 150 mg/kg *bw*, respectively). In rats, 8.2 and 69.5% of the radiolabelled dose was recovered as exhaled CO<sub>2</sub> and in the excreta (principally urine), respectively, compared with 18 and 82% in mice. The overall recovery was reported to be nearly quantitative (96 in rats, 110% in mice; Mitoma *et al* 1985). In rats exposed by inhalation to 600 mg/m<sup>3</sup> [150 ppm] 1,2-dichloroethane for 6 h or administered 150 mg/kg *bw* by gavage, there was no significant difference in the route of excretion of non-volatile metabolites (Reitz *et al* 1982). The major urinary metabolites identified following exposure of rats by either route were thiodiacetic acid (67–68%) and thiodiacetic acid sulfoxide (26–29%) as metabolites of the oxidative CYP-dependent pathway (IARC 1999).

### **7.1.3. In vitro data**

Ward (1992) reported a low level of absorption of approximately 1.5% in a study on occluded human skin *in vitro* within one hour.

By contrast, Frasch *et al* (2007) studied skin permeability and lag time for the three neat chemicals diethyl phthalate (slightly volatile), 1,2-dichloroethane (highly volatile), and

naphthalene (solid) in two different laboratories. One laboratory also measured fluxes and lag times from saturated aqueous vehicle. Static diffusion cells, hairless Guinea pig skin, and gas chromatography were used. In the two laboratories, the steady state fluxes [means  $\pm$  SD] of 1,2-dichloroethane were  $6280 \pm 1380$  and  $3842 \pm 712$   $\mu\text{g} \times \text{cm}^{-2} \times \text{hour}^{-1}$ . This was interpreted to indicate a potential for significant dermal penetration.

In a study of Gajjar and Kasting (2014) the absorption of 1,2-dichloroethane and several other VOCs (volatile organic compounds) was tested on human skin *in vitro*. However, the *in vitro* system allowed the evaporation of the product at the surface of the skin. Quantitative conclusions can therefore not be drawn.

#### **7.1.4. Toxicokinetic modelling**

Physiologically based pharmacokinetic (PBPK) modelling for route-to-route extrapolation in experimental animals has been reported. Sweeney et al (2008) updated existing model structure and parameter values for 1,2-dichloroethane, including the kinetics of the metabolic pathway mediated by glutathione-S-transferases, which was not part of preliminary models. The model structure also considered extrahepatic metabolism by unspecified enzymes. However, extrapolations to relevant situations in humans were not included.

#### **7.1.5. Biological monitoring**

Although 1,2-dichloroethane levels in blood can be analytically determined (DFG 1981), no applications in occupationally exposed human populations are reported. This may be due to the very short half-life of the compound in the blood (7.1.2.). There are some NHANES data regarding the general population, which were usually below LOD (CDC 2013). Studies of biological monitoring by analysis of urinary metabolites have not been reported.

### **7.2. Acute toxicity**

#### **7.2.1. Human data**

Systemic intoxications in humans, often in children, have been caused by accidental oral intake of unknown concentrations or amounts of such liquids as cleaning fluids, face lotion or even so-called "*Nervenbalsam*". There is one known case of a lethal intoxication after intentional ingestion of about 15 ml to produce a state of euphoria (a "high"). Post mortem examination revealed necrosis of the liver, kidneys and adrenals. There have also been frequent reports of acute and sometimes lethal occupational intoxications with 1,2-dichloroethane. The intoxication can have two phases. It begins with headache, nausea as well as a marked state of excitation and irritability, which can rapidly progress after high doses to deep, sometimes lethal narcosis. The second gastroenteric phase is characterised by frequent vomiting, diarrhoea that is sometimes bloody and abdominal colic. During this phase severe liver damage can occur, possibly with liver necrosis and kidney damage. Mild intoxications by inhalation have been described in which, after exposure periods of 2–5 months, depression of central nervous system activity and gastrointestinal symptoms with nausea and vomiting developed. Tremor and nystagmus have also been observed. Two other cases were characterised by mostly neurovegetative symptoms (DFG 1992).

## 7.2.2. Animal data

### *Inhalation*

Data on acute experimental toxicity are reported in the older literature (see DFG 1992). Thus, for an exposure period of 31.8 min the LC<sub>50</sub> for 1,2-dichloroethane in the rat was indicated to be 12000 ppm, for 165 min 3000 ppm and for 432 min 1000 ppm. The highest concentrations survived by rats were 20000 ppm for 12 min, 3000 ppm for 1 hour and 300 ppm for 7 hours; the highest concentrations tolerated without symptoms were 12000 ppm for 6 min, 1000 ppm for 90 min and 200 ppm for 7 h. Inhalation of 3000 ppm for 7 hours was lethal for mice, rats, guinea pigs and rabbits. 5000 ppm produced anaesthesia in the mouse. Exposure to 10000 ppm for 2 hours produced deep anaesthesia in cats, rabbits and guinea pigs. The anaesthesia was deeper and longer lasting than that produced after similarly long inhalation of 10000 ppm carbon tetrachloride or 10000 ppm chloroform. The liver function disorder produced by 1,2-dichloroethane was, however, less severe and more rapidly reversible than that produced by carbon tetrachloride. In cats paralysis of the extremities was seen after inhalation of 1,2-dichloroethane. Histological examination after short-term 1,2-dichloroethane inhalation revealed pulmonary oedema, liver and kidney damage as well as occasional necrosis and bleeding in the adrenal cortex. In addition, 1,2-dichloroethane may cause irritation of the gastrointestinal tract and haemorrhage in the mesenterium and in the intestinal mucosa, as well as myocardial degeneration (DFG 1992).

Triggered by industrial observations of neurotoxicity caused by 1,2-dichloroethane (see 7.3.1.), Hotchkiss et al (2010) studied acute neurotoxic effects in Fischer 344 rats exposed to 0, 50, 200, 600, or 2000 ppm 1,2-dichloroethane for 4 h or 0, 50, 100 or 150 ppm for 8 h. Neurobehavioral and neuropathologic effects were assessed using a functional observational battery (FOB; baseline, days 1, 8, and 15), and by light microscopy, respectively. Acute toxic effects were assessed by broncho-alveolar lavage and histopathology of the respiratory tract and selected target organs. Neurobehavioral effects consistent with central nervous system (CNS) depression were present at concentrations >200 ppm and were restricted to day 1. There were no neuropathologic changes in the CNS, however, olfactory epithelial regeneration 15 days after exposure to P200 ppm was observed. The no-observed-effect concentration (NOEC) for behavioural neurotoxicity was 200 ppm 1,2-dichloroethane for 4 h. There were no effects on BAL parameters in any exposure group. Exposure to 2000 ppm EDC altered adrenal gland, kidney, and liver weights, and resulted in morphologic alterations in the kidney and liver. Degeneration/necrosis of the olfactory epithelium was observed at 200 ppm for 4 h and 100 ppm for 8 h. Based on olfactory epithelial degeneration/necrosis, the most sensitive indicator of toxicity in this study, the overall NOEC was assessed to be 50 ppm 1,2-dichloroethane for up to 8 h in rats.

### *Oral exposure*

The toxicity of orally ingested 1,2-dichloroethane has been well studied in animals. Targets of 1,2-dichloroethane toxicity in orally exposed animals included the immune system, central nervous system, liver, and kidney. For details of studies and results, reference may be made to ATSDR (2001).

A single oral dose ( $\geq 400$  mg/kg bw) of 1,2-dichloroethane to B6C3F1 mice induced an elevation of alanine aminotransferase activity and an increase in relative liver weight, and some mortality occurred. The lowest intraperitoneal dose inducing an elevation of these enzymes was 500 mg/kg b.w.; intraperitoneal doses of up to 600 mg/kg bw did not kill any of the animals (n = 5). Inhalation exposure to 500 ppm [2000 mg/m<sup>3</sup>] for 4 h was hepatotoxic to some of the mice, while at 150 ppm [600 mg/m<sup>3</sup>] no toxicity was observed. Relative kidney weight was elevated after 300 mg/kg b.w. orally, 400 mg/kg b.w. intraperitoneally and after a 4-h exposure to 500 ppm 1,2-dichloroethane (Storer et al 1984; IARC 1999).

### *Dermal exposure*



The REACH joint registration dossier on the ECHA webpage for registered substances reports of an unpublished acute dermal toxicity study, where groups of male rabbits (6 - 11 animals/dose level) were dermally exposed to 1,2-dichloroethane at doses of 3972, 5000, 5594 or 6285 mg/kg bw with an observation time of 14 days. Mortality was observed in 2/6 at 3972 mg/kg bw within 5 -10 days, 3/11 at 5000 mg/kg bw within 1 -5 days, 8/9 at 5594 mg/kg bw within 1 -11 days and 5/6 at 6285 mg/kg bw within 1 day. Most survivors showed weight loss. No adverse effects were reported after gross necropsy. The calculated LD<sub>50</sub> by the method of probits was 3.89 mL/kg bw [3.40 -4.46 mL/kg bw] or 4890 mg/kg bw [4270-5600 mg/kg bw] (Anonymous, 2002, cited in the REACH joint registration dossier: <http://echa.europa.eu/information-on-chemicals/registered-substances>).

### **7.2.3. In vitro data**

Studies on effects on cell proliferation and apoptosis in vitro have been conducted, including SW620 cells (Li et al 2012) and Jurkat T cells (McDermott and Heffron 2013). Increased reactive oxygen production played a role in decreased cell proliferation by 1,2-dichloroethane; this effect was lower than that of other chlorinated solvents (perchloroethylene, trichloroethylene, dichloromethane; McDermott and Heffron 2013).

## **7.3. Specific Target Organ Toxicity/Repeated Exposure**

### **7.3.1. Human data**

Toxicity of 1,2-dichloroethane on the central nervous system of exposed workers has been the matter of recent studies and case reports.

Bowler et al (2003) investigated a group of 221 hazardous clean-up workers exposed to 1,2-dichloroethane. Chronic exposure incurred without protective equipment. A quantitative exposure monitoring and possible exposures to additional chemicals were not mentioned. As surrogate for exposure, certain variables available through clinical interviews included the following: smelling odours, skin becoming wet while working with (toxic) materials, dirt, mud or dust on skin, dirt, mud or dust on clothes, feet becoming soaked with water or toxic materials, working with boots in water, water or liquid soaking through clothes. Each variable was rated for frequency, i.e., whether exposure took place on a daily basis, more than twice a month, less than twice a month, or never. A clinical history and the following neuropsychological tests were administered: WHO Adult Environmental Neurobehavioral Test Battery (AENTB), Wechsler Adult Intelligence Scale (WAIS-III), Wechsler Memory Scale (WMS-III); WRAT 3 Reading, Cancellation H, Trail Making, Stroop, Rey Osterreith, Animal Naming, COWAT, TOMM, Rey 15, Lanthony d-15 Color Vision, and Vistech Contrast Sensitivity. Mood and symptoms were assessed with the SCL90-R, BDI, BAI and IES. The neuropsychological evaluation indicated lower neuropsychological functioning in the domains of processing speed; attention; cognitive flexibility; motor coordination and speed; verbal memory; verbal fluency; and visuo-spatial abilities. The workers also showed disturbed mood and impaired vision. There were dose-response relationships between exposure to 1,2-dichloroethane and the test scores.

Liu et al (2010) described clinical and neuroimaging features of five patients diagnosed with 1,2-dichloroethane toxic encephalopathy (1998-2009). All were female workers who had been in contact with 1,2-dichloroethane and subsequently had had seizures or symptoms of intracranial hypertension, including headache, nausea, and vomiting. The

cranial MRI showed extensive brain oedema in either the subcortical white matter, bilateral globus pallidus, and cerebellar nucleus dentatus, or the cortices. Of the five patients in the study, three had vasogenic oedema, one had cytotoxic oedema, and one had both types of oedema. Following treatment with steroids and mannitol for 3 to 10 weeks, all patients made either a partial or complete recovery. The imaging findings were resolved on a follow-up MRI. It was indicated that occupational exposure to 1,2-dichloroethane could have caused the severe toxic encephalopathy.

In a case report, Zhan et al (2011) described the history of a 20-y old man, who had been occupationally exposed to 1,2-dichloroethane for 6 months and presented himself to the hospital with headache, dizziness, nausea, vomiting and "slow response to verbal commands". Extensive CNS imaging was performed, pointing to brain oedema that was compatible with the clinical symptoms. The authors discussed that the oedema was mainly cytotoxic in the acute stage, and vasogenic in the subacute stage. These observations were considered consistent with similar previous case reports from China (Zhang et al 2006, Liu et al 2009).

### **7.3.2. Animal data**

#### *7.3.2.1. Inhalation*

Older inhalation studies were summarised by DFG (1992). Repeated 2 hour exposures of several species to 10000 ppm 1,2-dichloroethane brought about mucosal irritation, occasional vomiting, coordination disorders and narcosis and sometimes convulsions and spasms as well as paralysis of the hind limbs (DFG 1992). Even a concentration of 500 ppm was still toxic for rabbits, guinea pigs and rats (Hofmann et al 1970). Daily 6h inhalation of 500 ppm (5 times weekly) was lethal for rabbits after 10–17 exposures, for Guinea pigs after 4–14 and for rats generally after only 1–5 exposures. It was concluded that in this concentration range 1,2-dichloroethane is more toxic than carbon tetrachloride (Hofmann et al 1970). Cats, on the other hand, survived 30 exposures without clinically or chemically detectable damage (Hofmann et al 1970). Histological examination of the animals that died and of the survivors killed after 6 weeks exposure revealed cardiac dilation in cats and rabbits, pulmonary hyperaemia and occasionally slight oedema in rats as well as fatty infiltration and necrosis of the myocardium and the liver with lipoid nephrosis and mobilisation in the adrenals particularly in rats and Guinea pigs.

In other subacute toxicity studies with 1,2-dichloroethane in which animals inhaled 1000 ppm (8 h/day, 5 days/week), guinea pigs died after 2 exposures, rats after 3–14 and rabbits after 2–64 exposures. Dogs, cats and monkeys tolerated 23–50 exposures with only very low mortality. Histological examination revealed fatty infiltration of the liver in rats, guinea pigs, rabbits, cats and monkeys. Inhalation of 400 ppm for up to about 3 months also led to high mortality and various signs of liver damage in rats, Guinea pigs and rabbits. Dogs survived 177 exposures (about 8 months) to 400 ppm. On the other hand, the inhalation of 200 ppm for 7 hours daily up to 125 times (for about 51/2 months) increased mortality in rats and guinea pigs but was tolerated by rabbits and monkeys without symptoms. 100 ppm was the highest concentration tolerated for long periods without symptoms by rats and guinea pigs (Heppel et al 1946). Other studies produced essentially similar results (Spencer et al 1951, Hofmann et al 1970).

More recently, studies were focussed on neurotoxicity and neurobehaviour. Deng et al. (2014) reported on a study in rats. Sixty Sprague-Dawley rats were divided into five groups: negative control, positive control, low-dose 1,2-dichloroethane (1472 mg/m<sup>3</sup>), mid-dose (2550 mg/m<sup>3</sup>), and high-dose (4418 mg/m<sup>3</sup>) [360, 640 and 1100 ppm]. The three treated groups were exposed to 1,2-dichloroethane via inhalation for 6 hours a day for 6 consecutive days. The positive control group received intraperitoneal injection of lipopolysaccharide (5 mg/kg) and was sacrificed 8 hours after injection. Blood and brain tissue were collected, followed by determination of brain water content and HE staining

for pathological examination of brain tissue. The rats in the 1,2-dichloroethane groups suffered from decreased body weight with increasing dose ( $p < 0.01$ ), and brain water content rose with increasing dose. The brain water content of the mid-dose ( $80.09 \pm 0.14\%$ ) and high-dose 1,2-dichloroethane ( $80.28 \pm 0.10\%$ ) groups increased significantly, compared with that of the negative control group ( $79.46 \pm 0.23\%$ ;  $p < 0.001$ ). Optical microscopy discovered loose structure and vasodilation in the brain tissue of the mid-dose group, pointing to brain oedema; the high-dose 1,2-dichloroethane group and the positive control group had spongiform and vacuolated brain tissues with severe vascular dilation, indicating severe brain oedema.

In mice, Qi et al (2011) and Wang et al (2013) explored effects of subacute exposures to 1,2-dichloroethane (1,2-DCE) on mouse behaviour and related mechanisms. Thirty mice were randomly divided into 4 groups (untreated control, 225, 450 and 900 mg/m<sup>3</sup> 1,2-dichloroethane) [0, 56, 110, 225 ppm]. Inhalation was for 3.5 h/day for 10 days. Mouse behaviour was examined by open field test. Levels in the brain of nitric oxide (NO), malondialdehyde (MDA) and nonprotein sulfhydryl (NPSH) and activity of inducible nitric oxide synthase (iNOS) and superoxide dismutase (SOD) were determined by colorimetric method. Contents of glutamate (Glu), aspartate (Asp) and gamma-aminobutyric acid (GABA) were evaluated by high-performance liquid chromatography. Reduced locomotor and exploratory activities and increased anxiety were found in 450 and 900 mg/m<sup>3</sup> 1,2-dichloroethane-treated mice. In contrast, increased excitability was found in 225 mg/m<sup>3</sup> 1,2-dichloroethane-treated mice. Compensatory antioxidant status and increased NOS activity and NO level in the brain were found in treated mice. Moreover, Glu contents in treated mice and GABA contents in 900 mg/m<sup>3</sup> 1,2-dichloroethane-treated mice increased, whereas GABA contents in 225 mg/m<sup>3</sup> 1,2-dichloroethane-treated mice decreased significantly compared with control. The interpretation by the authors was that mouse behaviour could be disturbed by subacute exposures to 1,2-dichloroethane, and that changes of amino acid neurotransmitters in the brain might be related to these behavioural effects.

#### 7.3.2.2. Oral exposure

In a 13-week study, using administration of 1,2-dichloroethane in the drinking-water, the highest dose used, 8000 ppm (corresponding to 515–727 mg/kg b.w. per day), no histological evidence of toxicity was observed in male Fischer 344/N rats or Osborne-Mendel or Sprague-Dawley rats of either sex. Minimal histological damage was observed in the kidney of female Fischer 344/N rats. Equivalent doses given by gavage to Fischer 344 rats were more toxic than those introduced in the drinking water and caused substantial mortality. However, no histological damage to the liver or kidney was observed in the gavage experiments (Morgan et al., 1990).

In a 10-day toxicity study (Daniel et al., 1994), Sprague-Dawley rats of each sex were given 1,2-dichloroethane at dose levels of 10, 30, 100 or 300 mg/kg b.w. per day by gavage. Although 8/10 males and all females in the high-dose group died, no haematological or clinical chemical changes were observed. The only histopathological effect was a slight inflammation of the forestomach in the 100-mg/kg b.w. group. In a subsequent 90-day study at dose levels of 37.5, 75 and 150 mg/kg b.w. per day, no treatment-related effect on mortality or gross histopathology was observed.

Mild forestomach hyperplastic changes and hyperkeratosis were observed in 2/8 male Fischer 344/N rats given 1,2-dichloroethane (350 or 700 mg/kg b.w.) by gavage (five days per week for two weeks), while no such changes were observed in 16 vehicle-treated animals (Ghanayem et al., 1986). The difference between treated animals and controls was not significant.

When CD-1 mice were given 1,2-dichloroethane by gavage for 14 days at a level of 4.9 or 49 mg/kg b.w. per day (0.01 and 0.1 x LD<sub>50</sub>, as determined in an acute toxicity study), the number of splenic IgM antibody-forming cells in response to sheep red blood

cells showed a dose-dependent suppression (Munson et al., 1982); no significant effect was observed in the cell-mediated immune response to sheep erythrocytes. In a 90-day study (0.02, 0.2 or 2.0 mg/L in the drinking-water, calculated to yield 3, 24, or 189 mg/kg bw per day 1,2-dichloroethane), no effect on antibody-forming cell number, splenic response to the B-cell mitogen *Salmonella* lipopolysaccharide or to the T-cell mitogen concanavalin A, or vascular clearance of <sup>51</sup>Cr-labelled sheep erythrocytes was observed.

#### *7.3.2.3. Dermal exposure*

No dermal repeated-dose toxicity studies were reported.

#### **7.3.3. In vitro data**

No in vitro data were retrieved.

### **7.4. Irritancy and corrosivity**

#### **7.4.1. Human data**

No human data were reported.

#### **7.4.2. Animal data**

##### *7.4.2.1. Skin*

When 1 ml undiluted 1,2-dichloroethane was applied directly to the clipped skin of Guinea pigs for up to 12 h in occluded patch tests, no gross skin reactions were visible (Jakobson et al., 1982). Microscopic changes appeared 4 h after application, comprising karyopyknosis, perinuclear oedema, spongiosis and junctional separation (Kronevi et al., 1981). In Draize tests on rabbits, moderate erythema and oedema were observed 24 h after application (dose not specified). Microscopy on the third day revealed necrosis and other lesions such as ulcerations and acanthosis. The severity of the changes was not indicated (Duprat et al., 1976).

##### *7.4.2.2. Eyes*

Instillation of 0.1 ml undiluted 1,2-dichloroethane into the conjunctival sac of the eye of rabbits generated reversible, mild irritation characterized by conjunctivitis and epithelial abrasion. Epithelial keratitis, described as being "in a state of repair", was observed microscopically 7 days after application (Duprat et al., 1976). Reversible clouding of the cornea was observed in dogs within 10 h of subcutaneous administration of undiluted 1,2-dichloroethane at 0.9 mg/kg body weight. The clouding continued up to 48 h, but the corneas appeared clear after 5 days. Histological changes, including necrosis of the corneal endothelium, partially denuded Descemet's membrane, formation of excess basement membrane, and swelling of the corneal stroma, were also observed in dogs, cats and rabbits after ocular injection of 1.8 mg 1,2-dichloroethane (0.15 ml of a 1% solution) into the anterior chamber (Kuwabara et al., 1968).

#### **7.4.3. In vitro data**

No relevant in vitro data were reported.

## **7.5. Sensitisation and immunotoxicity**

### **7.5.1. Human data**

No studies were located regarding immunological effects in humans after inhalation exposure to 1,2-dichloroethane.

### **7.5.2. Animal data**

Acute intermittent exposure to 1,2-dichloroethane caused chronic splenitis in rats exposed to 1,000 ppm for 14 days (Heppel et al 1946), but this exposure was lethal in most of the animals tested. There is evidence that acute exposure to 1,2-dichloroethane affects the ability to fight infection arising from inhaled microbial pathogens in animals. Female mice (4–5 weeks old) exposed to 5.4–10.8 ppm of 1,2-dichloroethane for 3 hours exhibited increased susceptibility to *Streptococcus zooepidemicus* (i.e., increased mortality following infection), suggesting reduced pulmonary defence in the exposed mice (Sherwood et al 1987); male mice were not evaluated. No effect was observed at 2.3 ppm. Additionally, female mice that were similarly exposed to 10.8 ppm had reduced bactericidal activity in the lungs 3 hours after exposure to *Klebsiella pneumoniae*. Male rats exposed to 100 ppm for 5 hours/day for 12 days, or to a single 5-hour exposure to 200 ppm, did not exhibit reduced bactericidal activity after *K. pneumoniae* challenge (female rats were not evaluated); mortality following *S. zooepidemicus* challenge was not evaluated in rats. In addition, no effects on lymphocyte function (as indicated by blastogenesis to T- and B-cell mitogens) were seen in rats exposed to 100 ppm 5 hours/day for 12 days. Results reported in Sherwood et al. (1987) suggest that rats may be less susceptible to the detrimental immunological effects of 1,2-dichloroethane than mice and/or that male rodents are less susceptible than females. The relevance of the immunological effects in mice to human immunotoxicity is uncertain, since the massive bacterial challenges given to mice in the study are unlikely to be representative of normal immunological challenges in humans.

The REACH joint registration dossier on the ECHA webpage for registered substances reports a murine local lymphnode assay (LLNA) with 1,2-dichloroethane on female CBA mice conducted according to OECD guideline 429 and under GLP in 2010. Neither mortality nor clinical signs were observed during the study. No cutaneous reactions and no notable increase in ear thickness were observed in the animals of the treated groups. All four test concentrations 10, 25, 50 and 100% did not induce delayed contact hypersensitivity or local irritation effects and 1,2-dichloroethane was therefore suggested not to cause skin sensitization under the conditions of this test (Study report, 2010, cited in the REACH joint registration dossier: <http://echa.europa.eu/information-on-chemicals/registered-substances>).

### **7.5.3. In vitro data**

No relevant in vitro studies were located.

## **7.6. Genotoxicity**

The available genotoxicity studies have been reviewed by IARC (1999), ATSDR (2001) and Gwinn et al (2011). For more details, reference can be made to these compilations.

### 7.6.1. Human data

No human studies on genotoxicity were located.

### 7.6.2. Animal data

In a study investigating the relationship between inhalation exposure to 1,2-dichloroethane and covalent binding to liver and lung DNA, female Fischer-344 rats were exposed either to 80 ppm of 1,2-dichloroethane for 4 hours ("constant-low" exposure) or 4,400 ppm for a few minutes ("peak" exposure) (Baertsch et al. 1991). The DNA "covalent binding index" was elevated, compared to controls, after both exposure scenarios. However, in both the liver and the lung, the effect was much greater (approximately 35 times greater; CBI = 69 vs. 1.8) after peak exposure, suggesting that acute exposure to highly concentrated 1,2-dichloroethane may pose a greater genotoxic hazard than protracted low-level exposure. The results of this study support the notion that increased toxicity of 1,2-dichloroethane is associated with saturation of cytochrome P-450 enzymes (see 7.9.).

A single oral non-necrogenic dose of 100 mg/kg of 1,2-dichloroethane produced irreversible DNA damage in B6C3F1 mice, as revealed by single-stranded breaks in hepatocytes (Storer et al. 1984). Hepatic DNA damage was also induced in female rats receiving two oral gavage doses of 1,2-dichloroethane (in corn oil) at 134 mg/kg each, but not in rats receiving two doses of 13.4 mg/kg (Kitchin and Brown 1994).

The level of covalent DNA-binding produced from <sup>14</sup>C-labelled 1,2-dichloroethane was similar in rats that had previously been exposed via inhalation to 50 ppm of 1,2-dichloroethane vapour for 2 years, and in rats that had served as controls in the 2-year study (Cheever et al. 1990).

The ability of 1,2-dichloroethane to bind DNA in rodents in vivo has been well established in the liver as well as in other organs such as the kidney and lung. DNA binding in these organs has been observed not only after inhalation and oral exposures, but also in rats and mice administered a single i.p. injection of 1,2-dichloroethane (6.35 µmol/kg; Prodi et al 1986). Actual structural damage to DNA, in the form of single-stranded breaks and unwinding of the DNA molecule, has also been demonstrated in mice after single intraperitoneal injections of 45–360 mg/kg. Genotoxicity assays for clastogenic effects obtained mixed results, with a positive effect on sister chromatid exchange (believed to be caused by strand breakage) in mouse bone marrow cells of mice administered a single intraperitoneal injection of up to 16 mg/kg, but no effect on micronucleus formation in mice after 14 weeks of daily gavage administrations of up to 300 mg/kg/day or in mice after a single intraperitoneal injection of between 45–400 mg/kg (ATSRR 2001).

1,2-Dichloroethane also produces both somatic and sex-linked recessive lethal mutations in *Drosophila melanogaster* in vivo (ATSDR 2001). Formation of the specific DNA adduct S-[2-(N7-guanyl)ethyl]glutathione from 1,2-dichloroethane has also been demonstrated in catfish (*Ictalurus punctatus*). Pre-treatment with the glutathione-depleting agent diethylmaleate led to non-detectable levels of this DNA adduct (Jemal et al 2010), suggesting that the formation of DNA adducts is related to the activation of the GSH pathway.

In a recent study sponsored by the 1,2-dichloroethane REACH Consortium and conducted by the DOW Chemical Company, the potential mode of action of 1,2-dichloroethane-induced mammary tumors was investigated in female F344/DuCrI rats. In this GLP study female rats were exposed to 0 or 200 ppm of 1,2-dichloroethane vapour for 28 consecutive days (28 – 31 exposures). The study parameters of interest for the endpoint genotoxicity were the Comet Assay in mammary tissue and the DNA adducts 8-hydroxy-2'-deoxyguanosine and the predominant adduct formed after exposure to 1,2-dichloroethane, S-[2-(N7-guanyl)ethyl]glutathione, in mammary (target tissue) and liver (non-target) tissue. As a positive control for the Comet Assay, a further group of 3 rats

received N-nitroso-N-methylurea via oral gavage three hours before to the scheduled necropsy. Compared to control rats, 1,2-dichloroethane exposure had no effect on 8-hydroxy-2'-deoxyguanosine adduct levels in mammary tissue but the respective levels in the liver of exposed rats were significantly less than control rats. Endogenous S-[2-(N7-guanyl)ethyl]glutathione adduct was not quantifiable in mammary or liver tissue isolated from control rats. Although a statistically significant increase in S-[2-(N7-guanyl)ethyl]glutathione adduct levels was observed in both tissues, the adduct levels in the liver of 1,2-dichloroethane exposed rats were approximately ~54% higher than in the mammary tissue. The Comet Assay showed no DNA damage in the tested mammary epithelial cells. In summary, the study reports no exposure-related genotoxic effects in the Comet Assay or relevant specific DNA adducts in the mammary tissue after repeated inhalation of 1,2-dichloroethane (Dow Chemical Company, 2014; unpublished study, cited in the REACH joint registration dossier: <http://echa.europa.eu/information-on-chemicals/registered-substances>).

### 7.6.3. In vitro

The results of in vitro genotoxicity clearly indicate that 1,2-dichloroethane is capable of interacting with DNA to produce genotoxic effects in vitro. It caused point mutations in human and animal cells, and bacteria, unscheduled DNA synthesis (i.e., DNA repair activity) in human and animal cells, DNA binding in animal cells, and mitotic segregation aberrations leading to aneuploidy in fungi. The results in bacterial mutagenicity assays suggest that 1,2-dichloroethane is a very weak, direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione S-transferases (DeMarini and Brooks 1992). Mutagenicity was increased in TA100 strain *Salmonella typhimurium* expressing the alpha class (Simula et al. 1993) and the theta class (Thier 1996) of human glutathione S-transferase, but not in bacteria expressing the pi class of human glutathione S-transferase (Simula et al. 1993). S-(Chloroethyl)-cysteine, an analogue of the proposed intermediate product of the conjugation of 1,2-dichloroethane with glutathione, was a potent inducer of unscheduled DNA synthesis and micronucleus formation in mammalian cells in vitro (Vamvakas et al. 1988). S-(2-Chloroethyl)glutathione itself was found to be a potent mutagen in *S. typhimurium*. Although it produced only intermediate levels of alkylation, the results indicated that the guanyl adduct that is formed appears to be unusually mutagenic.

### 7.6.4 Summary of genotoxicity data

1,2-Dichloroethane is genotoxic *in vitro* as it induced gene mutations, unscheduled DNA synthesis and micronuclei and can form DNA-adducts in the presence of a metabolic activation system. A proposed mechanism proceeds via glutathione conjugation. However, the *in vivo* data are inconsistent and do not allow a definitive conclusion of the mutagenic potential of 1,2-dichloroethane in somatic cells. 1,2-Dichloroethane induced the formation of DNA adducts and SCE but not of micronuclei, dominant lethal effects or DNA damage in the Comet assay. Nevertheless, since there is no evidence of an alternative non-genotoxic mode of action for the induction of carcinogenicity after 1,2-dichloroethane exposure in animal experiments, the default assumption of a non-threshold mechanism of action is adopted.

## 7.7. Carcinogenicity

### 7.7.1. Human data

Five cohort studies and one nested case-control study of brain tumours have examined the risk of cancer among workers with potential exposure to 1,2-dichloroethane. Excesses of lymphatic and haematopoietic cancers were observed in three studies and of stomach cancer in one study, while an excess of pancreatic cancer was observed in one

study. All the cohort studies included workers with potential exposure to multiple agents and were not able to examine the excess risk associated with 1,2-dichloroethane. For details, see IARC (1999).

### **7.7.2. Animal data**

Studies of cancer in experimental animals upon application of 1,2-dichloroethane have been compiled and evaluated by IARC (1999). [Note by SCOEL: Nagano et al (2006) published 2-year carcinogenicity bioassays with 1,2-dichloroethane by inhalation in both rats and mice. Preliminary data of this study (Nagano et al 1998) had been included in the documentation by IARC (1999), but these were not fully evaluated at that time because of missing details and unspecified statistics.]

#### *Mouse inhalation studies*

Groups of 90 male and 90 female Swiss mice, 11 weeks of age, were exposed to concentrations of 5, 10, 50 or 250 ppm [20, 40, 200 or 1000 mg/m<sup>3</sup>] 1,2-dichloroethane for 7 h/d on five days per week for 78 weeks. After several days of exposure to 250 ppm, the concentration was reduced to 150 ppm because of severe toxic effects. A group of 115 males and 134 females kept in a nearby room served as controls. At the end of the treatment period, the animals were kept until spontaneous death. The experiment lasted 119 weeks. Survival at 78 weeks of age was 42/115, 26/90, 34/90, 30/90 and 26/90 in control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm males and 76/134, 68/90, 50/90, 49/90 and 44/90 in control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm females, respectively. No specific types of tumour or changes in the incidence of tumours normally occurring in the strain of mice used were observed in the treated animals (Maltoni et al 1980). [IARC (1999) noted the low survival rates, especially in males.]

Groups of 50 male and 50 female BDF1 mice, six weeks of age, were exposed by whole-body inhalation to 0, 10, 30 or 90 ppm [0, 40, 120 or 360 mg/m<sup>3</sup>] 1,2-dichloroethane (purity, > 99%) for 6 h/d on five days per week for 104 weeks at JBRC, Japan. The maximum exposure concentration (90 ppm) was selected on the basis of the result of a 13-week study. In males, significantly increased incidences of liver haemangiosarcomas were observed at mid and high-dose (controls: 0/50; 10 ppm: 4/49; 30 ppm: 6/50; 90 ppm: 5/50). Historical JBRC controls ranges from 0/50 to 5/50 hepatic haemangiosarcomas. In females, increased incidence of bronchiolar-alveolar adenomas and carcinomas, hepatocellular adenomas, adenocarcinomas of the mammary gland and endometrial stromal polyps occurred, with a significantly positive trend (Nagano et al 2006). Results of this study are shown in [Table 6](#).



(A) Male							
Group Name	Control	10 ppm	30 ppm	90 ppm	Peto's test	JBRC historical control data	
Number of animals	50 (%)	49 <sup>a)</sup> (%)	50 (%)	50 (%)		Incidence <sup>b)</sup> (%)	Min.–Max. <sup>c)</sup> (%)
Liver							
Hemangiosarcoma	0 (0.0)	4 (8.2)	<u>6</u> * (12.0)	5* (10.0)		27/748 (3.6)	0/50 – 5/50 (0.0 – 10.0)
(B) Female							
Group Name	Control	10 ppm	30 ppm	90 ppm	Peto's test	JBRC historical control data	
Number of animals	49 <sup>a)</sup> (%)	50 (%)	50 (%)	50 (%)		Incidence <sup>b)</sup> (%)	Min.–Max. <sup>c)</sup> (%)
Lung							
Bronchiolo-alveolar adenoma	4 (8.2)	1 (2.0)	3 (6.0)	<u>8</u> (16.0)	↑	29/749 (3.9)	0/50 – 5/50 (0.0 – 10.0)
Bronchiolo-alveolar carcinoma	1 (2.0)	0 (0.0)	1 (2.0)	3 (6.0)	↑	21/749 (2.8)	0/50 – 3/50 (0.0 – 6.0)
Combined bronchiolo-alveolar adenoma and bronchiolo-alveolar carcinoma	5 (10.2)	1 (2.0)	4 (8.0)	<u>11</u> (22.0)	↑↑	49/749 (6.5)	0/50 – 6/50 (0.0 – 12.0)
Uterus							
Endometrial stromal polyp	2 (4.1)	0 (0.0)	1 (2.0)	<u>6</u> (12.0)	↑↑	26/748 (3.5)	0/50 – 4/50 (0.0 – 8.0)
Mammary gland							
Adenocarcinoma	1 (2.0)	2 (4.0)	1 (2.0)	<u>6</u> (12.0)	↑↑	20/749 (2.7)	0/50 – 4/50 (0.0 – 8.0)
Liver							
Hepatocellular adenoma	1 (2.0)	1 (2.0)	1 (2.0)	<u>6</u> (12.0)	↑↑	33/749 (4.4)	1/50 – 4/50 (2.0 – 8.0)
Hepatocellular carcinoma	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)		23/749 (3.1)	0/50 – 4/50 (0.0 – 8.0)
Combined hepatocellular adenoma and hepatocellular carcinoma	2 (4.1)	1 (2.0)	2 (4.0)	6 (12.0)	↑↑	54/749 (7.2)	1/50 – 6/50 (2.0 – 12.0)
Lymph node							
Malignant lymphoma	6 (12.2)	17* (34.0)	22** (44.0)	12 (24.0)		214/749 (28.6)	7/50 – 23/50 (14.0 – 46.0)

\* and \*\*: Significantly different from the control group at  $p \leq 0.05$  and  $p \leq 0.01$  by Fisher's exact test, respectively.

↑ and ↑↑: Significantly different at  $p \leq 0.05$  and  $p \leq 0.01$  by Peto's test, respectively.

<sup>a)</sup>: One mouse died accidentally during the 2-yr exposure period.

<sup>b)</sup>: Number of animals bearing tumor / number of animals examined in the 15 historical inhalation studies.

<sup>c)</sup>: Number of animals bearing tumor / number of animals examined in a single historical study.

The underlined values indicate the tumor incidences exceeding the maximum tumor incidence in the JBRC historical control data.

**Table 6:** Numbers of tumour-bearing mice exposed by inhalation to 1,2-dichloroethane for 2 years (Nagano et al 2006)

### Rat inhalation studies

Groups of 90 male and 90 female Sprague-Dawley rats, 12 weeks of age, were exposed to concentrations of 5, 10, 50 or 250 ppm [20, 40, 200 or 1000 mg/m<sup>3</sup>] 1,2-dichloroethane for 7 h/d on five days per week for 78 weeks. After several days of exposure to 250 ppm, the concentration was reduced to 150 ppm because of severe toxic effects. A group of 90 males and 90 females kept in an exposure chamber under the same conditions for the same amount of time as the exposed animals served as chamber controls. Another group of 90 males and 90 females kept in a nearby room served as untreated controls. At the end of the treatment period, the animals were kept until spontaneous death. The experiment lasted for 148 weeks. Survival at 104 weeks of age was 16/90, 12/90, 45/90, 13/90, 17/90 and 10/90 in control, chamber-control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm males and 36/90, 22/90, 48/90, 26/90, 29/90 and

21/90 in control, chamber-control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm females, respectively. The incidence of mammary fibromas and fibroadenomas in females was 47/90, 27/90, 56/90, 33/90, 49/90 and 47/90 in control, chamber-control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm groups, respectively. The increase in the incidence of these mammary tumours was significant (chi square test) in the 150–250-ppm ( $p < 0.001$ ), 50-ppm ( $p < 0.01$ ) and 5 ppm ( $p < 0.001$ ) groups, in comparison to chamber controls. The difference between the incidences in the two control groups was also significant ( $p < 0.01$ ) (Maltoni et al 1980). [IARC (1999) noted the low and variable survival rates.]

Groups of 50 male and 50 female Sprague-Dawley rats, 5.5–6 weeks of age, were exposed to concentrations of 0 or 50 ppm [ $200 \text{ mg/m}^3$ ] 1,2-dichloroethane (purity  $>99\%$ ) for 7 h per day on five days per week for 24 months. A complete autopsy was carried out on each animal and histological examination was performed on almost all organs and all gross lesions and tissue masses. Survival was 58% and 60% among the control and treated males and 54% and 64% among the control and treated females, respectively. There were no significant differences in the incidence of tumours between the control and treated groups (Cheever et al 1990). [IARC (1999) noted the low exposure level.]

Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were exposed at JBRC, Japan, by whole-body inhalation to 0, 10, 40 or 160 ppm [0, 40, 160 or  $640 \text{ mg/m}^3$ ] 1,2-dichloroethane (purity,  $>99\%$ ) for 6 h per day on five days per week for 104 weeks. The maximum exposure concentration (160 ppm) was selected on the basis of the result of a 13-week study. In males, increased incidences of fibromas of the subcutis, fibroadenomas of the mammary gland and mesotheliomas of the peritoneum occurred, with a significantly positive trend [statistics not specified]. In females, increased incidences of fibromas of the subcutis and fibroadenomas, adenomas and adenocarcinomas of the mammary gland occurred, with a significantly positive trend (Nagano et al 2006). Results of this study are shown in [Table 7](#). At the time of evaluation by IARC (1999) the present study was not yet published and therefore not included in the IARC evaluation.

#### *Skin application*

A group of 30 female Ha:ICR Swiss mice, six to eight weeks of age, received skin applications of 126 mg/animal 1,2-dichloroethane [purity unspecified] in 0.2 mL acetone three times per week for life [survival and duration of treatment unspecified]. A group of 30 mice that received applications of 0.1 mL acetone alone served as controls. A complete autopsy was carried out and histological examinations were performed on the skin, liver, stomach, kidney and all abnormal-appearing tissues and organs. An increased incidence of lung tumours was observed in the high-dose treated group (26/30) compared with controls (11/30) ( $p < 0.0005$ , chi-square test). No skin tumours were observed in treated mice or controls (Van Duuren et al 1979). [IARC noted inadequate reporting.]

(A) Male							
Group Name	Control	10 ppm	40 ppm	160 ppm	Peto's	JBRC historical control data	
Number of animals	50	50	50	50	test	Incidence <sup>a)</sup>	Min.–Max. <sup>b)</sup>
	(%)	(%)	(%)	(%)		(%)	(%)
Subcutis							
Fibroma	6 (12.0)	9 (18.0)	<u>12</u> (24.0)	<u>15</u> (30.0)	↑	55/749 (7.3)	1/50 – 10/50 (2.0 – 20.0)
Mammary gland							
Adenoma	1 (2.0)	2 (4.0)	0 (0.0)	2 (4.0)		7/749 (0.9)	0/50 – 2/50 (0.0 – 4.0)
Fibroadenoma	0 (0.0)	0 (0.0)	1 (2.0)	<u>5</u> * (10.0)	↑↑	13/749 (1.7)	0/50 – 3/50 (0.0 – 6.0)
Combined adenoma and fibroadenoma	1 (2.0)	2 (4.0)	1 (2.0)	<u>7</u> * (14.0)	↑↑	19/749 (2.5)	0/50 – 4/50 (0.0 – 8.0)
Peritoneum							
Mesothelioma	1 (2.0)	1 (2.0)	1 (2.0)	<u>5</u> (10.0)	↑	16/749 (2.1)	0/50 – 4/50 (0.0 – 8.0)
(B) Female							
Group Name	Control	10 ppm	40 ppm	160 ppm	Peto's	JBRC historical control data	
Number of animals	50	50	50	50	test	Incidence <sup>a)</sup>	Min.–Max. <sup>b)</sup>
	(%)	(%)	(%)	(%)		(%)	(%)
Subcutis							
Fibroma	0 (0.0)	0 (0.0)	1 (2.0)	<u>5</u> * (10.0)	↑↑	8/747 (1.1)	0/50 – 4/50 (0.0 – 8.0)
Mammary gland							
Adenoma	3 (6.0)	5 (10.0)	5 (10.0)	<u>11</u> * (22.0)	↑↑	28/747 (3.7)	0/50 – 9/50 (0.0 – 18.0)
Fibroadenoma	4 (8.0)	1 (2.0)	6 (12.0)	<u>13</u> * (26.0)	↑↑	76/747 (10.2)	0/50 – 8/50 (0.0 – 16.0)
Combined adenoma and fibroadenoma	7 (14.0)	6 (12.0)	<u>11</u> (22.0)	<u>22</u> * (44.0)	↑↑	103/747 (13.8)	2/50 – 10/50 (4.0 – 20.0)
Adenocarcinoma	1 (2.0)	2 (4.0)	0 (0.0)	<u>5</u> (10.0)	↑	5/747 (0.7)	0/50 – 2/50 (0.0 – 4.0)
Combined adenoma, fibroadenoma and adenocarcinoma	8 (16.0)	8 (16.0)	<u>11</u> (22.0)	<u>25</u> ** (50.0)	↑↑	104/747 (13.9)	2/50 – 10/50 (4.0 – 20.0)

\* and \*\*: Significantly different from the control group at  $p \leq 0.05$  and  $p \leq 0.01$  by Fisher's exact test, respectively.

↑ and ↑↑: Significantly different at  $p \leq 0.05$  and  $p \leq 0.01$  by Peto's test, respectively.

<sup>a)</sup>: Number of animals bearing tumor / number of animals examined in the 15 historical inhalation studies.

<sup>b)</sup>: Number of animals bearing tumor / number of animals examined in a single historical study.

The underlined values indicate the tumor incidences exceeding the maximum tumor incidence in the JBRC historical control data.

Table 7: Numbers of tumour-bearing rats exposed by inhalation to 1,2-dichloroethane for 2 years (Nagano et al 2006)

### Oral application studies

Groups of 50 male and 50 female mice were administered technical 1,2-dichloroethane dissolved in oil by gavage 5 times weekly for 78 weeks and were then observed for 12 to 13 weeks. The average doses were 195 or 97 mg/kg body weight for the male rats and 299 or 148 mg/kg body weight for the females. Lung adenomas developed in 31 % of the male mice in the higher dose group and in 2 % in the lower dose group. In the female mice lung adenomas developed in both dose groups (31 % and 14 %, controls 5 %) and also adenocarcinomas of the mamma (15 % and 18 %), squamous epithelial carcinomas of the forestomach (10 % and 4 %) and adenocarcinomas (9 % and 6 %) and sarcomas (6 % and 4 %) of the uterus (NCI 1978).

In the same way as described above for the mice, groups of 50 male and 50 female rats were treated for 69 weeks and then observed for 32 weeks. The average doses for both male and female animals were 95 and 47 mg/kg body weight. In the male animals of both dose groups squamous epithelial carcinomas were found in the forestomach (18 % and 6 %), haemangiosarcomas in the spleen (14 % and 18 %) and subcutaneous fibromas (12 % and 10 %) as well. In the female rats of the higher dose group mammary adenomas (36 %) developed but no other tumour incidences were significantly increased in this group. Among the treated rats but not in the control group, a small number of haemangiosarcomas was observed in various organs (NCI 1978).

#### *Multistage protocols and preneoplastic lesions*

In a two-stage mouse-skin assay, a group of 30 female Ha:ICR Swiss mice, six to eight weeks of age, received a single skin application of 126 mg per animal 1,2-dichloroethane [purity unspecified] in 0.2 mL acetone, followed 14 days later by 5 µg per animal phorbol myristyl acetate in 0.2 mL acetone three times weekly for life. Survival was described as excellent, the median survival for the various groups in the study [that included some groups exposed to chemicals other than 1,2-dichloroethane and the controls] ranging from 429 to 576 days. Animals treated with phorbol myristyl acetate alone served as controls. There were no significant differences in the occurrence of skin tumours between controls (total, 7 papillomas in 6/90 mice) and treated groups (total, 3 papillomas in 3/30 mice) (Van Duuren et al 1979).

Groups of 25 male B6C3F1 mice, 30 days of age, received drinking water containing 10 mg/L *N*-nitrosodiethylamine (NDEA) for four weeks. Animals were then given drinking-water containing 0 (controls), 835 or 2500 mg/L 1,2-dichloroethane [purity unspecified] for 52 weeks. The highest concentration of 1,2-dichloroethane was that which failed to cause mortality in eight-week-old B6C3F1 mice after a four-week exposure period. A complete autopsy was carried out and histological examination was performed on the liver, kidney and lung. There were no significant differences in either tumour incidence or number of tumours per mouse in any organ between the controls and 1,2-dichloroethane-treated groups. The incidences of liver tumours were 25/25, 25/25 and 23/25 in control, low-dose and high-dose mice, respectively, and the numbers of liver tumours per mouse were  $29.30 \pm 15.40$ ,  $34.50 \pm 17.40$  and  $25.20 \pm 16.70$ , respectively. The incidences of lung tumours were 18/25, 12/25 and 23/25, respectively, and the numbers of lung tumours per mouse were  $1.40 \pm 1.40$ ,  $1.00 \pm 1.10$  and  $2.60 \pm 2.00$ , respectively (Klaunig et al 1986). [IARC noted that the tumour incidences in controls were too high for evaluation of a promoting effect of 1,2-dichloroethane.]

In an initiation study, one group of 10 male Osborne-Mendel rats, weighing 180–230 g, was given a two-thirds partial hepatectomy and, 24 h later, a single dose of 100 mg/kg bw 1,2-dichloroethane (purity, 97–99%) (maximum tolerated dose) in corn oil by gavage. Similar groups of animals were treated with 2 mL/kg bw corn oil alone (vehicle controls) or 30 mg/kg bw *N*-nitrosodiethylamine (positive controls) followed by a two-thirds partial hepatectomy. Starting six days after partial hepatectomy, the rats received 500 mg/kg of diet (0.05% w/w) phenobarbital for seven weeks, then control diet for seven more days, after which time they were killed and the livers were examined histologically for gamma-glutamyltranspeptidase (gamma-GT)-positive foci. There was no significant increase in the number of total gamma-GT-positive foci ( $1.02 \pm 0.55$  and  $0.27 \pm 0.19/\text{cm}^2$  in the 1,2-dichloroethane group and vehicle controls, respectively). NDEA treatment increased the numbers of gamma-GT-positive foci ( $4.04 \pm 1.47/\text{cm}^2$ ) (Milman et al 1988). [IARC noted the small number of animals.]

In a promotion study, groups of 10 male Osborne-Mendel rats, weighing 180–230 g, were given a single intraperitoneal injection of 30 mg/kg bw *N*-nitrosodiethylamine 24 h after a two-thirds partial hepatectomy. Starting six days later, the rats received daily 100 mg/kg b.w. 1,2-dichloroethane (purity, 97–99%) (maximum tolerated dose) in corn oil by gavage on five days per week for seven weeks. Control rats received corn oil alone

instead of 1,2-dichloroethane. After the promotion phase, the rats were held for seven more days, after which they were killed and the livers were examined histologically for gamma-GT-positive foci. There was no significant difference in the number of total gamma-GT-positive foci between the 1,2-dichloroethane group and controls ( $1.54 \pm 0.54$  and  $1.62 \pm 0.33/\text{cm}^2$ , respectively) (Milman *et al.*, 1988). [IARC noted the small number of animals.]

A group of 50 male and 50 female Sprague-Dawley rats, 5.5–6 weeks of age, was exposed by inhalation to 50 ppm [200 mg/m<sup>3</sup>] 1,2-dichloroethane (purity, >99%) for 7 h/d on five days per week and to 500 mg/kg of diet (0.05%) disulfiram (purity, 98%) for 24 months. A complete autopsy was carried out on each animal and histopathological examination was performed on almost all organs and all gross lesions and tissue masses. In the liver, increased incidences of intrahepatic bile duct cholangiomas (0/50 untreated control males, 9/49 treated males, 0/50 untreated control females and 17/50 treated females), intrahepatic bile duct cysts (1/50 control males, 12/49 treated males, 1/50 untreated control females and 24/50 treated females) and neoplastic nodules in males (0/50 untreated controls and 6/49 treated) were observed in the treated group ( $p < 0.05$ ; Fisher's exact test). The incidence of adenocarcinomas of the mammary gland in females (4/50 controls and 12/48 treated) and that of interstitial-cell tumours of the testis in males (2/50 controls and 11/50 treated) were increased in the treated group ( $p < 0.05$ ) (Cheever *et al.* 1990).

### 7.7.3. Summary of experimental carcinogenicity data.

1,2-Dichloroethane was tested in one experiment in mice and in one in rats by *oral* administration (NCI 1978). In mice, it produced benign and malignant tumours of the lung and malignant lymphomas in animals of each sex, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. In rats, it produced carcinomas of the forestomach in males, benign and malignant mammary tumours in females and haemangiosarcomas in animals of each sex (IARC 1999).

No increase in tumour incidence was found after *inhalation* exposure in one experiment in rats in one experiment in mice (Maltoni *et al.* 1980), but these studies were considered to be inadequate (IARC 1999). In two other inhalation studies, one in mice and one in rats, 1,2-dichloroethane increased the incidence of tumours at various sites including the liver, lung and mammary gland (Nagano *et al.* 2006; Tables 6 and 7).

In a multistage study measuring gamma-glutamyl transpeptidase (gamma-GT)-positive foci in the liver of male rats, single administration of 1,2-dichloroethane by gavage after a two-thirds partial hepatectomy followed by treatment with phenobarbital (initiation study) or repeated administration of 1,2-dichloroethane by gavage after a two-thirds partial hepatectomy and initiation by *N*-nitrosodiethylamine (promotion study) did not increase the number of gamma-GT-positive foci. In a two-stage mouse-skin assay, 1,2-dichloroethane was not active as an initiator of skin carcinogenicity.

### 7.7.4 Quantitative risk assessment.

#### 7.7.4.1 Selection of the most relevant data and the point of departure

The older studies by NCI (1978) and by Maltoni *et al.* (1980) were considered inadequate or inappropriate for a quantitative risk assessment.

By contrast, the recent Nagano studies in mice and rats were considered adequate. These studies were performed according to the recent OECD guideline and under GLP

standards. They do not show major limitations and represent a relevant basis for qualitative risk assessment. 1,2-Dichloroethane increased the incidence of tumours at various sites including the liver, lung and mammary gland (Nagano et al 2006).

As specified in chapter 7.7.2, groups of 50 male and 50 female BDF1 mice, six weeks of age, were exposed by whole-body inhalation to 0, 10, 30 or 90 ppm [0, 40, 120 or 360 mg/m<sup>3</sup>] 1,2-dichloroethane (purity, > 99%) for 6 h/d on five days per week for 104 weeks. The maximum exposure concentration (90 ppm) was selected on the basis of the result of a 13-week study. In males, significantly increased incidences of liver haemangiosarcomas were observed at mid and high-dose (controls: 0/50; 10 ppm: 4/49; 30 ppm: 6/50; 90 ppm: 5/50). Historical controls range from 0/50 to 5/50 hepatic haemangiosarcomas. Therefore, the relevance of these findings is questionable and might not be related to the exposure to 1,2-dichloroethane. In females, increased incidence of bronchiolar-alveolar adenomas and carcinomas, hepatocellular adenomas, adenocarcinomas of the mammary gland and endometrial stromal polyps occurred, with a significantly positive trend but no statistically significant differences to the control groups. Results of this study are shown in *Table 6*.

*Table 7* shows that the predominant tissue in exposed rats with a statistically significant, dose related increase in tumor incidences compared to the control was the mammary tissue with an increase in mammary gland tumours in female rats above the historical control range at 40 and 160 ppm and a statistically significant increase at 160 ppm.

While 1,2-dichloroethane was shown to be genotoxic *in vitro*, the *in vivo* data are inconsistent and do not allow a definitive conclusion of the mutagenic potential of 1,2-dichloroethane in somatic cells. 1,2-Dichloroethane induced the formation of DNA adducts and SCE but not of micronuclei, dominant lethal effects or DNA damage in the Comet assay. In addition, in a recently conducted study (discussed in chapter 7.9) no exposure-related genotoxic effects in the Comet Assay or relevant specific DNA adducts in the mammary tissue after inhalation exposure to 200 ppm for 28 days of 1,2-dichloroethane were observed.

In conclusion, available data suggest that effective doses are those that cause a shift in the metabolic pathway with formation of GSH-derived metabolites. In fact, DNA damage has not been observed at exposure levels associated with increased mammary tumours, that significantly occur at the highest doses tested. However, there are no strong data to support a non-genotoxic mode of action for the induction of carcinogenicity after 1,2-dichloroethane exposure in animals. Therefore, a conservative position would be that to apply the default assumption of a non-threshold mechanism of action due to *i.a.* possible direct interaction of reactive metabolites of 1,2-dichloroethane with DNA. This leads to the most conservative linear approach and an extrapolation from the high dose effects to lower doses for the assessment of the quantitative cancer risk.

#### 7.7.4.2 Benchmark-Dose Modelling

The Benchmark-Dose (BMD) approach is a scientifically advanced method for deriving a point-of-departure (POD) for risk assessment purposes, as it provides a quantification of the uncertainties in the dose-response data from animal studies and makes extended use of these data to better characterise and quantify potential risks. It is therefore applicable to the quantitative risk assessment of genotoxic carcinogens. Furthermore, it leads to a more consistent POD, as a consequence of the specified benchmark response.

The BMD approach aims at estimating the dose that corresponds to a low, but measurable change in response (BMDR) for an effect relative to the background response rate predicted by a fitted model (5% or a 10% increase in the incidence of tumours from the modelled background response, "BMRF"). The choice of 10 or 5% for the BMDR is dependent on the toxic effect and conservatism of the evaluator and is calculated by fitting mathematical models to the dose-response data. A number of models are available

to calculate a one-sided confidence limit of the BMD (typically 95%) (BMDL) which accounts for elements of experimental uncertainty, including sample size, response variability and high background response. From those models considered compatible with the data (*i.e.* that pass the goodness-of-fit test) the lowest AIC (Akaike’s Information Criterion) is used to identify the best-fitted model (the lower the AIC, the better) when the BMDLs are sufficiently close. When the ratio of BMD and BMDL is more than 3-fold, the model with the lowest BMDL is chosen instead of the model with the lowest AIC. Finally, the BMDL is typically used as the POD. At least 2 test groups and a control, together with a dose-response relationship, are needed in order to use this approach.

For the modelling of the POD for the tumour incidences seen in the Nagano study, the US EPA BMD software Version 2.6 was used to calculate the BMD10 with an extra risk of 10%. To take into account background tumour incidences the extra risk method was chosen. To find the model with the lowest AIC, all models of the EPA software that are suitable for dichotomous data were used. P-values were derived reflecting the degree of the quality of modulation. Restrictions for the respective models which are commonly used were made. For instance, restrictions for the multistage model were made to ensure a monotone dose response relationship. Restrictions for the LogLogistic and LogProbit model were made to assure a sub-linear (convex) dose response relationship. This includes the assumption that at the high dose group a plateau is not reached and further testing of higher doses would lead to a further increase in tumour incidences. The results for all tumour types with a statistically significant increase compared to the control group and the combination of these tumour types can be found in the following tables.

Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	2	yes	0.915	46.519	157.1	99.2	1.58
Logistic	Extra	0.1	na	2	yes	0.569	47.690	160.5	131.6	1.21
LogLogistic	Extra	0.1	yes	2	yes	0.916	46.593	157.3	98.1	1.60
Probit	Extra	0.1	na	2	yes	0.603	47.548	159.8	126.1	1.27
LogProbit	Extra	0.1	yes	2	yes	0.418	47.693	148.0	101.6	1.46
Weibull	Extra	0.1	yes	2	yes	0.913	46.602	157.4	99.6	1.58
Multistage 3° Cancer	Extra	0.1	yes	2	yes	0.890	46.695	158.3	99.6	1.59
Multistage 2°	Extra	0.1	yes	2	yes	0.890	46.695	158.3	99.6	1.59
Quantal-Linear	Extra	0.1	na	1	yes	0.945	44.985	177.0	96.7	1.83

Table 8 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *mammary gland fibroadenoma found in male rats*.

Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	3	yes	0.474	83.384	155.8	87.0	1.79
Logistic	Extra	0.1	na	2	yes	0.661	81.725	147.5	111.3	1.32
LogLogistic	Extra	0.1	yes	3	yes	0.474	83.383	157.5	85.3	1.85
Probit	Extra	0.1	na	2	yes	0.645	81.786	146.4	106.0	1.38
LogProbit	Extra	0.1	yes	3	yes	0.474	83.383	155.5	101.2	1.54
Weibull	Extra	0.1	yes	3	yes	0.474	83.383	157.6	87.0	1.81
Multistage 3° Cancer	Extra	0.1	yes	2	yes	0.754	81.434	151.7	86.4	1.76
Multistage 2°	Extra	0.1	yes	2	yes	0.696	81.604	148.7	84.6	1.76
Quantal-Linear	Extra	0.1	na	2	yes	0.535	82.335	148.2	78.0	1.90

Table 9 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *mammary gland adenoma & fibroadenoma found in male rats*.

Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	2	yes	0.915	46.519	157.1	99.2	1.58
Logistic	Extra	0.1	na	2	yes	0.569	47.690	160.5	131.6	1.22
LogLogistic	Extra	0.1	yes	2	yes	0.916	46.593	157.3	98.1	1.60
Probit	Extra	0.1	na	2	yes	0.603	47.548	159.8	126.0	1.27
LogProbit	Extra	0.1	yes	2	yes	0.418	47.693	148.0	101.6	1.46
Weibull	Extra	0.1	yes	2	yes	0.913	46.602	157.4	99.6	1.58
Multistage 3° Cancer	Extra	0.1	yes	2	yes	0.890	46.695	158.3	99.6	1.59
Multistage 2°	Extra	0.1	yes	2	yes	0.890	46.695	158.3	99.6	1.59
Quantal-Linear	Extra	0.1	na	1	yes	0.945	44.985	176.9	96.7	1.83

Table 10 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *subcutis fibroma found in female rats*.

Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	2	yes	0.823	144.78	97.6	52.4	1.86
Logistic	Extra	0.1	na	2	yes	0.816	144.81	116.6	81.7	1.43
LogLogistic	Extra	0.1	yes	2	yes	0.820	144.79	94.5	47.3	2.00
Probit	Extra	0.1	na	2	yes	0.819	144.80	113.8	77.3	1.47
LogProbit	Extra	0.1	yes	2	yes	0.745	145.02	124.9	81.4	1.53
Weibull	Extra	0.1	yes	2	yes	0.823	144.78	97.6	52.4	1.86
Multistage 3° Cancer	Extra	0.1	yes	3	yes	0.538	146.78	105.9	52.4	2.02
Multistage 2°	Extra	0.1	yes	3	yes	0.535	146.78	101.7	52.4	1.94
Quantal-Linear	Extra	0.1	na	2	yes	0.823	144.78	97.6	52.4	1.86

Table 11 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *mammary gland adenoma found in female rats*.

Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	3	yes	0.117	140.56	78.9	43.4	1.82
Logistic	Extra	0.1	na	2	yes	0.263	138.88	96.9	74.7	1.30
LogLogistic	Extra	0.1	yes	3	yes	0.118	140.54	76.8	39.3	1.95
Probit	Extra	0.1	na	2	yes	0.269	138.82	92.4	69.7	1.32
LogProbit	Extra	0.1	yes	2	yes	0.221	139.13	94.8	64.9	1.46
Weibull	Extra	0.1	yes	3	yes	0.116	140.58	79.2	43.4	1.83
Multistage 3° Cancer	Extra	0.1	yes	3	yes	0.109	140.72	79.4	42.9	1.85
Multistage 2°	Extra	0.1	yes	3	yes	0.109	140.72	79.4	42.9	1.85
Quantal-Linear	Extra	0.1	na	2	yes	0.268	138.79	69.2	42.7	1.62

Table 12 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *mammary gland fibroadenoma found in female rats*.

Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	3	yes	0.544	204.85	44.4	25.0	1.77
Logistic	Extra	0.1	na	2	yes	0.741	203.08	58.6	45.7	1.28
LogLogistic	Extra	0.1	yes	3	yes	0.563	204.81	43.0	19.9	2.16
Probit	Extra	0.1	na	2	yes	0.760	203.03	55.6	43.0	1.29
LogProbit	Extra	0.1	yes	2	yes	0.650	203.32	62.8	43.7	1.44
Weibull	Extra	0.1	yes	3	yes	0.539	204.86	44.0	25.0	1.76
Multistage 3° Cancer	Extra	0.1	yes	3	yes	0.519	204.90	41.7	24.9	1.67
Multistage 2°	Extra	0.1	yes	3	yes	0.519	204.90	41.7	24.9	1.67
Quantal-Linear	Extra	0.1	na	2	yes	0.805	202.92	37.8	24.9	1.52

Table 13 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *mammary gland adenoma & fibroadenoma found in female rats*.



Model Type	Risk Type	BMRF	Restricted Model	No of Parameters	Model accepted	p-value (goodness of fit)	AIC	BMD	BMDL	BMD / BMDL
Gamma	Extra	0.1	yes	3	yes	0.908	215.95	50.3	22.6	2.22
Logistic	Extra	0.1	na	2	yes	0.980	213.98	51.0	40.1	1.27
LogLogistic	Extra	0.1	yes	3	yes	0.915	215.95	49.7	18.2	2.74
Probit	Extra	0.1	na	2	yes	0.978	213.99	48.5	38.0	1.28
LogProbit	Extra	0.1	yes	2	yes	0.969	214.00	56.0	39.5	1.42
Weibull	Extra	0.1	yes	3	yes	0.895	215.96	50.6	22.6	2.24
Multistage 3° Cancer	Extra	0.1	yes	3	yes	0.850	215.98	51.7	22.6	2.29
Multistage 2°	Extra	0.1	yes	3	yes	0.850	215.98	51.7	22.6	2.29
Quantal-Linear	Extra	0.1	na	2	yes	0.830	214.31	32.9	22.1	1.49

Table 14 : Calculation of BMD10 as possible point of departure for human health risk assessment for the *mammary gland adenoma & fibroadenoma & adenocarcinoma found in female rats*.

The tables show acceptable goodness of fit for all models used. This refers to benign tumours (Tables 8-13) and to the combination of benign and malignant tumours (Table 14). In the present case, benign tumours were included as possible pre-stages of malignancy, because this broadens the data-base of the benchmark calculation. It is noted by SCOEL that this leads to very conservative risk figures.

Since the ratios of BMD and BMDL in Tables 8-14 do not differ more than 3-fold, the model with the lowest AIC was chosen to identify the BMD10 as the POD (highlighted in yellow). Of these BMD10, the BMD10 with the lowest value has to be chosen as the overall POD. In this case, table 13 showing the BMD10 for human health risk assessment for the mammary gland adenoma & fibroadenoma found in female rats indicates the lowest BMD10 of all modulations. The curve modelling for the most conservative BMD10 of all models used are given in the ANNEX.

Therefore, the BMD10 of 37.8 ppm of the combination of adenoma and fibroadenoma in the mammary gland of the female rats is taken as the most conservative starting point and is adjusted to the workplace situation.

*Adjustment to the workplace situation:*

Corrected BMD10 = BMD10 × 6.7 m<sup>3</sup>/10 m<sup>3</sup> × 75 years/40 years × 6 hours/8 hours × 52 weeks/48 weeks.

This results in a corrected BMD10 = POD of 38.58 ppm. Using this value the following risk numbers were derived:

Cancer risk estimate with an excess lifetime cancer risk of 10<sup>-1</sup> = 38.6 ppm (158660 µg/m<sup>3</sup>)

Cancer risk estimate with an excess lifetime cancer risk of 10<sup>-3</sup> = 0.386 ppm (1586.6 µg/m<sup>3</sup>)

Cancer risk estimate with excess lifetime cancer risk of 10<sup>-4</sup> = 0.0386 ppm (158.66 µg/m<sup>3</sup>)

Cancer risk estimate with excess lifetime cancer risk of 10<sup>-5</sup> = 0.00386 ppm (15.866 µg/m<sup>3</sup>)

To put the derived cancer risk estimates into perspective, 1,2-dichloroethane can be compared to another analogous substance that has been assessed by SCOEL in recent years. The activation pathway of 1,2-dichloroethane and 1,2-dibromoethane are similar in both cases but 1,2-dibromoethane is a much more potent in DNA adduct formation

(induction is 10-50 times higher than for 1,2-dichloroethane; Watanabe et al., 2007) although both substances have been categorised into the SCOEL carcinogen group A (Bolt and Huici-Montagud, 2008), as a genotoxic carcinogen for which the absence of threshold is postulated. Therefore, the above BMD10 modelling can be seen as a very conservative approach since 1,2-dichloroethane has been assumed to be a genotoxic carcinogen for the derivation of a POD for risk assessment due to the lack of an alternative, non-genotoxic mode of action for tumor induction.

Taking together the several issues that were discussed above, SCOEL underlines that the present assessment of derived cancer risk estimates for 1,2-dichloroethane is very conservative.

#### *Published quantitative risk assessments*

The U.S. EPA has derived a slope (potency) factor ( $q_1^*$ ) of  $0.091 \text{ (mg/kg/day)}^{-1}$  for cancer risk associated with oral exposure to 1,2-dichloroethane based on the study by NCI (1978) in rats (IRIS 2001). This slope factor corresponded to a drinking water unit risk of  $2.6 \times 10^{-6} \text{ (}\mu\text{g/L)}^{-1}$  and an inhalation unit risk of  $2.6 \times 10^{-5} \text{ (}\mu\text{g/m}^3\text{)}^{-1}$ . Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks of  $10^{-4}$ ,  $10^{-5}$ ,  $10^{-6}$ , and  $10^{-7}$  are  $1 \times 10^{-3}$ ,  $1 \times 10^{-4}$ ,  $1 \times 10^{-5}$ , and  $1 \times 10^{-7}$  mg/kg/day, respectively. These risk levels correspond to one excess cancer death in 10,000, 100,000, 1 million, and 10 million persons, respectively, and were derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane. (ATSDR 2001).

In a quantitative risk assessment published by ECHA (2015), the combined frequency of mammary tumours (adenomas, fibroadenomas, adenocarcinomas) from the Nagano study in rats (Nagano et al., 2006) was taken as point of departure for deriving risk values using the T25 approach. The  $T25_{\text{inhalation}}$  for workers was calculated to be 100.8 ppm (414.4 mg/m<sup>3</sup>). Assuming linearity of response, the cancer risk for lifetime exposure to each unit amount of 1,2-dichloroethane was calculated to be:

Workplace concentration	Cancer risk
1 $\mu\text{g/m}^3$	$6.0 \times 10^{-7}$
10 $\mu\text{g/m}^3$	$6.0 \times 10^{-6}$
100 $\mu\text{g/m}^3$	$6.0 \times 10^{-5}$

## **7.8. Reproductive toxicity**

The overall evidence from inhalation studies in rats and rabbits indicates that 1,2-dichloroethane is not a developmental toxicant (ATSDR 2001).

### **7.8.1. Human data**

During examination of 360 female workers from a rubber-processing factory in which, together with gasoline and dichloromethane, 1,2-dichloroethane was used, adverse effects on pregnancy and birth were reported. The number of miscarriages and early births as well as cases of preeclampsia was claimed increased, as was the frequency of early rupture of the embryonal membranes and of foetal asphyxia (6.8 % of cases; 2.6 % in the control group). The total gynaecological morbidity was increased, in particular in the form of disturbed menstrual cycles and genital inflammation. Dichloroethane and dichloromethane were detected in the breast milk of the workers (Muchametova and Wosabaja 1972).

## **7.8.2. Animal data**

### *7.8.2.1 Fertility*

In a study with only small numbers of animals, daily 4 hour exposures of rats to 1,2-dichloroethane concentrations of 15 mg/m<sup>3</sup> (3.7 ml/m<sup>3</sup>), repeated 6 times weekly for a period of 4 months, was reported to reduce the conception rate and increase the pre-implantation mortality by a factor of five. The effect was increased if 1,2-dichloroethane was inhaled simultaneously with "gasoline" (Vozowaya 1976).

### *7.8.2.2 Developmental toxicity*

In a teratology study (Rao et al 1980), rats and rabbits were exposed to 100 or 300 ppm [400 or 1200 mg/m<sup>3</sup>] 1,2-dichloroethane for 7 h per day on days 6 through 15 (rats) or 6 through 18 (rabbits) of gestation. In rats, 10/16 dams died at the high dose, one exhibited implantation sites but all the implantations were resorbed. At 100 ppm, 1,2-dichloroethane was not overtly toxic to the dam and did not induce foetotoxicity, teratogenicity or skeletal variations with the exception of a decrease in the number of bilobed thoracic centres. In rabbits, 3/19 dams died at the high dose; there were no adverse effects on foetal or embryonic development.

In a reproduction study (Rao et al 1980), rats were exposed to 25, 75 or 150 ppm [100, 300 or 600 mg/m<sup>3</sup>] 1,2-dichloroethane for 60 days before breeding (6 h per day, five days per week) and thereafter to similar concentrations for 6 h per day on seven days per week, with the exception of day 21 of gestation through day 4 postpartum. No effect on the reproductive performance or on the development (until day 21) of the F1A or F1B (bred 21 days after F1A birth) litters was observed.

In a two-generation reproduction study (Lane et al 1982), ICR Swiss mice were continuously administered 1,2-dichloroethane in the drinking water (30, 90 or 290 mg/L with the aim of producing daily doses of 5, 15 or 50 mg/kg bw) starting five weeks before mating of the F0 generation. No treatment-related effect on fertility, gestation, viability, pup survival, weight gain or teratogenicity was observed.

1,2-Dichloroethane administration (1.2, 1.6, 2.0 or 2.4 mmol/kg b.w. per day by gavage or by inhalation of 150, 200, 250 or 300 ppm [600, 800, 1000 or 1200 mg/m<sup>3</sup>] for 6 h per day on days 6 through 20 of gestation) induced no embryo- or foetotoxicity, changes in foetal growth or teratological effects. Maternal toxicity, as indicated by smaller weight gain, was observed at the highest inhalation dose level and two highest oral dose levels (Payan et al 1995).

### *Neurotoxicity*

No studies on developmental neurotoxicity were located.

## **7.8.3. In vitro data**

No relevant in vitro data were located.

### **7.9. Mode of action and adverse outcome pathway considerations**

There is compelling evidence that toxicity and carcinogenicity of 1,2-dichloroethane are associated with its metabolism to active intermediates. Studies in rats and mice indicate that 1,2-dichloroethane is metabolised to 2-chloroacetaldehyde, S-(2-chloroethyl)glutathione, and other putative reactive intermediates capable of binding covalently to cellular macromolecules. The level of glutathione present in the liver appears to modulate effects of 1,2-dichloroethane in animals. Glutathione is involved in the biotransformation of 1,2-dichloroethane. The metabolic pathway of 1,2-dichloroethane is linear at low doses, but at higher concentrations, as CYP enzymes become saturated, the amount of glutathione conjugate produced rises disproportionately with increasing administered dose; at very high doses, the GSH pathway is also saturated, and the glutathione conjugate produced declines disproportionately with increasing dose. It has been suggested that 1,2-dichloroethane-induced toxicity occurs when the CYP-mediated biotransformation processes are saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body and conjugate with glutathione instead of being detoxified and eliminated. This might explain the observation that large drinking water doses fail to produce the same toxic effects as smaller gavage doses. Gavage administration involves the placement of large bolus doses in the stomach that are absorbed at one time, thereby leading to spikes in blood levels and the subsequent expression of toxicity. However, drinking water exposure results in ingestion of contaminated water in small doses spread out over the course of a day. In such instances, biotransformation processes are not as likely to become saturated, and the risk of adverse effects is not as high as would be predicted from gavage administration of equivalent doses. This would cause a non-linear dose-response with respect to carcinogenicity.

Quantitative differences in carcinogenic response have been discussed between application by oral gavage and by inhalation study. Route-related differences in carcinogenic response may be explained on the basis of metabolic differences and the saturation of the detoxification/ excretion mechanism occurring between the gavage dose and the longer-term inhalation dose, as proposed by Reitz et al (1982).

A recent mechanistic study (Hotchkiss et al 2014) investigated the potential mode of action (MoA) of 1,2-dichloroethane-induced mammary tumors seen in the study of Nagano et al. (2006). In this study female F344/DuCrI rats were exposed to 0 or 200 ppm of 1,2-dichloroethane vapour for 28 days. The study parameters investigated were oestrous evaluations, serum prolactin levels, cell proliferation (Ki-67), morphometric evaluation of mammary gland structure, histopathology of the mammary tissue, cell proliferation (Ki-67), and Comet assay in mammary tissue. Furthermore, the DNA adducts 8-hydroxy-2'-deoxyguanosine and S-[2-(N7-guanyl)ethyl]glutathione in mammary tissue and liver, reduced (GSH) and oxidized (GSSG) glutathione, and the glutathione conjugates S-(2-hydroxyethyl) glutathione hydrochloride and S,S'-ethylene-bis-glutathione were determined. In summary, the study reported no exposure-related genotoxic effects in the Comet assay or relevant specific DNA adducts in the mammary tissue after repeated inhalation of 1,2-dichloroethane. Another group of six animals were administered diethyl maleate *i.p.*, two hours prior to necropsy, which served as a positive control for depletion of glutathione in mammary and liver tissues. The repeated inhalation exposure showed no effects on histopathology of the mammary tissue, serum prolactin levels, mammary gland morphology, mammary epithelial cell proliferation or GSH or GSSG levels in mammary tissue. Liver GSH and GSSG levels were decreased by approximately 72 and 62 %, respectively, but the GSH/GSSG ratio remained essentially unchanged. No 1,2-dichloroethane-glutathione conjugates were measured in mammary or liver tissue in the control and exposed group. Compared to control rats, 1,2-dichloroethane exposure had no effect on 8-hydroxy-2'-deoxyguanosine adduct levels in mammary tissue but the respective levels in the liver of exposed rats were significantly less than control rats. Endogenous S-[2-(N7-guanyl)ethyl]glutathione adduct was not quantifiable in mammary or liver tissue isolated from control rats. Although a statistically significant increase in S-[2-(N7-guanyl)ethyl]glutathione adduct levels were observed in both tissues, the adduct levels in the liver of 1,2-dichloroethane exposed rats were

approximately ~54% higher than in the mammary tissue. The Comet assay showed no DNA damage in the tested mammary epithelial cells. In summary, the study reported no exposure-related genotoxic effects in the Comet assay or relevant specific DNA adducts in the mammary tissue after repeated inhalation of 1,2-dichloroethane.

Nevertheless, there is clear evidence of genotoxicity of 1,2-dichloroethane in vitro, which is mediated by metabolic activation to intermediates that bind to DNA. However, this genotoxic effect is much less compared to the analogue 1,2-dibromoethane (DFG 1992). The spectrum of tumours appears not only confined to the mammary tissue and is similar upon oral gavage and inhalation of 1,2-dichloroethane, both in rats and mice (see the detailed comparison by Nagano et al 2006).

### **7.10. Lack of specific scientific information**

In total, 1,2-dichloroethane is a well-investigated compound. There is no specific lack of toxicological information for an evaluation, although the carcinogenic effect and its mode of action could be better characterised. Field studies on biological monitoring (based on urinary metabolite excretion) would be desirable, as 1,2-dichloroethane has a potential for penetration through the skin.

## **8. GROUPS AT EXTRA RISK**

As stated in section 7.1, 1,2-dichloroethane is metabolised by two competing metabolic pathways, by oxidation (CYP-dependent) and by glutathione conjugation (GSH dependent). Key isoenzymes in these pathways are CYP2E1 and GSTT1-1 (theta class GST), respectively (7.6.3). The expression of CYP2E1 enzyme activity shows remarkable inter-individual and inter-ethnic differences (Bolt et al 2003), and the GSTT1 gene is deleted in 15-25% of the European and 50-60% of the East Asian population (Bolt and Thier 2006). This coincidence points to the possibility of major human inter-individual variability in susceptibility to 1,2-dichloroethane toxicity. However, human studies to verify such an assumption are lacking.

## 9. REFERENCES

AT GKV [Grenzwerteverordnung] (2011) BGBl. II Nr. 429/2011. Verordnung des Bundesministers für Arbeit, Soziales und Konsumentenschutz über Grenzwerte für Arbeitsstoffe sowie über krebserzeugende und über fortpflanzungsgefährdende (reproduktionstoxische) Arbeitsstoffe, (Grenzwerteverordnung 2011 – GKV 2011), Austria.

<http://www.auva.at/portal27/portal/auvaportal/content/contentWindow?&contentid=10008.542565&action=b&cacheability=PAGE> Accessed 2016.05.06

ATSDR [The Agency for Toxic Substances and Disease Registry] (2001) Toxicological Profile for 1,2-Dichloroethane. <http://www.atsdr.cdc.gov/toxprofiles/tp38.pdf> Accessed 2016.04.26

AU SWA [Safe Work Australia] (2011) Workplace exposure standards for airborne contaminants date of effect: 22 December 2011, Australia. [http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace Exposure Standards for Airborne Contaminants.pdf](http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace%20Exposure%20Standards%20for%20Airborne%20Contaminants.pdf) Accessed 2016.04.29

Baertsch A, Lutz WK, Schlatter C (1991) Effect of inhalation exposure regimen on DNA binding potency of 1,2-dichloroethane in the rat. Arch Toxicol, 65: 169-176.

BE KB (2002) [Koninklijk Besluit - Royal Decision] (2002) Revised version valid for after July 2014. Koninklijk besluit van 11 maart 2002 betreffende de bescherming van de gezondheid en de veiligheid van de werknemers tegen de risico's van chemische agentia op het werk, Belgium. <https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwj7h0am8f7LAhWBORoKHcMgAp4QFggcMAA&url=http%3A%2F%2Fwww.werk.belgie.be%2FDownloadAsset.aspx%3Fid%3D2162&usq=AFOjCNGhKN3FmC8o8vps9iLtBYFpdxEBXg&sig2=R62PTd6ymNQtn9MW1tggZw&bvm=bv.119028448,d.d2s&cad=rja>

Bolt HM, Huici-Montagud A (2008) Strategy of the Scientific Committee on Occupational Exposure Limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. Arch Toxicol 82: 56-69.

Bolt HM, Roos PH, Thier R (2003) The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int Arch Occup Environ Health 76:174-185.

Bolt HM, Thier R (2006) Relevance of the deletion polymorphism of the glutathione S-transferases GSTT1 and GSTM1 in pharmacology and toxicology. Current Drug Metabolism 7:613-628.

Bowler RM, Gysens S, Hartney C (2003) Neuropsychological effects of ethylene dichloride exposure. NeuroToxicology 24:553-562.

CA IRSST [Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail] (2010) Québec, Canada. <http://www.irsst.qc.ca/en/laboratories/references-tools/workplace-air-contaminant/substance/i/57> Accessed 2016.04.29

CA OML [Ontario Ministry of Labour] (2013) Current Occupational Exposure Limits for Ontario Workplaces Required under Regulation 833, Canada. [http://www.labour.gov.on.ca/english/hs/pubs/oel\\_table.php](http://www.labour.gov.on.ca/english/hs/pubs/oel_table.php) Accessed 2016.04.29

CDC [Center for Disease Control and Prevention] (2013) National biomonitoring program, biomonitoring summary, other halogenated solvents. Last updated Dec 2013. [https://www.cdc.gov/biomonitoring/OtherHalogenatedSolvents\\_BiomonitoringSummary.html](https://www.cdc.gov/biomonitoring/OtherHalogenatedSolvents_BiomonitoringSummary.html) Accessed 2016-07-05.

Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. CTL/L/4546.  
Owner Company: ICI Chemicals and Polymers 1992-04-10.

CH SUVA [Schweizerische Unfallversicherungsanstalt] (2016) Grenzwerte am Arbeitsplatz 2015. MAK-Werte, BAT-Werte, Grenzwerte für physikalische Einwirkungen Switzerland. [https://extra.suva.ch/suva/b2c/download/\(layout=7.01-15\\_1\\_71\\_68\\_6\\_125&uiarea=1&care=50328D134DA837E0E10080000A630358&citem=50328D134DA837E0E10080000A6303584BE36A0936148016E10080000A630387\)/.do;jsessionid=Ax9Bf-vMX-vSaIHzG4I9HPMom4f1UwFzkRoe\\_SAPW5jysT93Gt3nXMIRx2HFbmCH;saplb\\_\\*\(J2EE505057620\)505057651?doctype=pdf&docid=00000000000004490&file=1903\\_F.pdf](https://extra.suva.ch/suva/b2c/download/(layout=7.01-15_1_71_68_6_125&uiarea=1&care=50328D134DA837E0E10080000A630358&citem=50328D134DA837E0E10080000A6303584BE36A0936148016E10080000A630387)/.do;jsessionid=Ax9Bf-vMX-vSaIHzG4I9HPMom4f1UwFzkRoe_SAPW5jysT93Gt3nXMIRx2HFbmCH;saplb_*(J2EE505057620)505057651?doctype=pdf&docid=00000000000004490&file=1903_F.pdf)  
Accessed 2016.04.29

Cheever KL, Cholakis JM, el-Hawari AM, Kovatch RM, Weisburger EK (1990) Ethylene dichloride: the influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. *Fundam Appl Toxicol* 14(2):243-261.

Daniel FB, Robinson M, Olson GR, York RG, Condie LW (1994) Ten and ninety-day toxicity studies of 1,2-dichloroethane in Sprague-Dawley rats. *Drug Chem Toxicol* 17: 463-477

DE BAuA [Bundesanstalt für Arbeitsschutz und Arbeitsmedizin / Federal Institute for Occupational Safety and Health] (2016) AGS-Geschäftsführung - BauA. [http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/AGS/pdf/TRGS-910-Aenderung.pdf?\\_blob=publicationFile&v=4](http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/AGS/pdf/TRGS-910-Aenderung.pdf?_blob=publicationFile&v=4) . Accessed 2016-05-05. Or: [http://www.baua.de/SiteGlobals/Forms/Suche/Servicesuche\\_Formular.html?nn=666838&resourceId=709354&input\\_ =666838&pageLocale=de&searchEngineQueryString=107-06-2&sortString=score+desc&sortString.HASH=4fd26e0322fe2da3060e&searchArchive=0&searchArchive.HASH=ec5ba6961456f3e706a6&searchIssued=0&searchIssued.HASH=b4bd81f61454d48704a4&submit=Suche+starten](http://www.baua.de/SiteGlobals/Forms/Suche/Servicesuche_Formular.html?nn=666838&resourceId=709354&input_ =666838&pageLocale=de&searchEngineQueryString=107-06-2&sortString=score+desc&sortString.HASH=4fd26e0322fe2da3060e&searchArchive=0&searchArchive.HASH=ec5ba6961456f3e706a6&searchIssued=0&searchIssued.HASH=b4bd81f61454d48704a4&submit=Suche+starten) . Accessed 2016.05.05

DE DFG [Deutsche Forschungsgemeinschaft] (2015) List of MAK and BAT Values 2014 <http://onlinelibrary.wiley.com/doi/10.1002/9783527695539.ch2/pdf> Accessed 2016.04.29

DeMarini DM, Brooks HG (1992) Induction of prophage lambda by chlorinated organics: detection of some single species / single site carcinogens. *Environ Mol Mutagen* 19(2): 98-111.

Deng Y, Zhu W, Wei B, Zhou X, Su Y, Gao Y, Liu Y (2014) Establishment of a rat model of subacute toxic encephalopathy induced by 1,2-dichloroethane [in Chinese]. *Zhonghua Lao Dong Wei Sheng Zhi Bing Za Zhi* 32(4): 260-263.

DFG [Deutsche Forschungsgemeinschaft] (1981) 1,2-Dichloroethan. Analytische Methoden, Analysen im biologischen Material. Wiley-VCH, Weinheim. Available online: <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>

DFG [Deutsche Forschungsgemeinschaft] (1991) Method for the determination of 1,2-dichloroethane. Carcinogenic substances, established methods. Wiley-VCH, Weinheim. Available online via: <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>

DFG [Deutsche Forschungsgemeinschaft] (1992) 1,2-Dichloroethane. In: Occupational Toxicants, Vol.3, 137-147. Wiley-VCH, Weinheim. Available online via: <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>

DFG [Deutsche Forschungsgemeinschaft] (1999) Method for the determination of 1,2-dichloroethane

<http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am10706e0004/pdf>. Accessed 2016.05.0E

DFG [Deutsche Forschungsgemeinschaft] (2013) 1,2-Dichloroethane (Absorption through the Skin). In: Occupational Toxicants, The MAK Collection, Part I, MAK Value Documentations 2013. Wiley-VCH, Weinheim. Available online via: <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>

Duprat P, Delsaut L, Gradiski D (1976) Pouvoir irritant des principaux solvants chlorés aliphatiques sur la peau et les muqueuses oculaires du lapin. Eur J Toxicol 9: 171-177.

ECHA (2015) Application for authorisation: Establishing a reference dose response relationship for carcinogenicity of 1,2-dichloroethane. Rev1. Final. RAC/33/2015/09. ECHA Risk Assessment Committee. Helsinki, 05 June 2015. [http://echa.europa.eu/documents/10162/13641/rac\\_33\\_dose\\_response+1\\_2dichloroethane\\_en.pdf](http://echa.europa.eu/documents/10162/13641/rac_33_dose_response+1_2dichloroethane_en.pdf).

ECHA [European Chemicals Agency] (2016) ECHA inventory database <http://echa.europa.eu/it/information-on-chemicals/cl-inventory-database/-/discli/details/98649>. Accessed 2016.04.21

EPA [Environmental Protection Agency] (1999) Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes Compendium Method TO-17 EPA/625/R-96/010b. <https://www3.epa.gov/ttnamti1/files/ambient/airtox/to-17r.pdf>. Accessed 2016.05.03

ES INSHT [Instituto Nacional de Seguridad e Higiene en el Trabajo] (2011). Limites de Exposicion profesional para agentes quimicos en Espana, Spain. [http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores\\_Limite/Limites2011/Limites2011web.pdf](http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_Limite/Limites2011/Limites2011web.pdf) Accessed 2016.04.29

FI MSAH [Ministry of Social Affairs and Health] (2012) HTP-värden 2012. Koncentrationer som befunnits skadliga. Social- och halso vardsministeriets publikationer 2012:6, Finland. [http://www.ttk.fi/files/2610/STM\\_2012\\_6\\_HTP\\_SWE\\_web.pdf](http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf) Accessed 2016.04.29

FR INRS (2012) Valeurs limites d'exposition professionnelle aux agents chimiques en France, Institut National de Recherche et de Sécurité (INRS), France <http://www.inrs.fr/media.html?refINRS=ED%20984> Accessed 2016.04.29

Frasch HF, Barbero AM, Alachkar H, McDougal JN (2007) Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutan Ocul Toxicol 26(2):147-160.

Gajjar, R.M. and Kasting, G.B. (2014) Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicol. Appl. Pharmacol. 281, 109-117.

GB HSE [Health and Safety Executive] (2011) EH40/2005 Workplace Exposure Limits. EH40 (Second edition, published 2011). Health and Safety Executive (HSE), UK. <http://www.hse.gov.uk/pUbns/priced/eh40.pdf> Accessed 2016.04.29

Ghanayem BI, Maronpot RR, Matthews HB (1986) Association of chemically induced forestomach cell proliferation and carcinogenesis. Cancer Lett 32: 271-278

Guengerich FP, Crawford WM Jr, Domoradzki JY, Macdonald TL, Watanabe PG (1980) In vitro activation of 1,2-dichloroethane by microsomal and cytosolic enzymes. Toxicol Appl Pharmacol 55: 303-317



Guengerich FP, Kim DH, Iwasaki M (1991) Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. *Chem Res Toxicol* 4: 168-179

Gwinn MR, Johns DO, Bateson TF, Guyton KZ (2011) A review of the genotoxicity of 1,2-dichloroethane (EDC). *Mutation Res* 727:42-53

Heppel LA, Neal PA, Perrin TL, Endicott KM, Porterfield VT (1945) The toxicology of 1,2-dichloroethane (ethylene). III. Its acute toxicity and the effect of protective agents. *J Pharmacol Exp Ther* 84: 53-63.

Heppel LA, Neal PA, Perrin TL, Endicott KM, Porterfield VT (1946) The toxicology of 1,2-dichloroethane (ethylene). III. Its acute toxicity and the effect of protective agents *J industry Hyg* 28:113-120

Hofmann HTh, Birnstiel H, Jobst P (1970) Naunyn-Schmiedeberg's Arch Pharmacol 266:360

Hotchkiss JA, Andrus AK, Johnson KA, Krieger SM, Woohiser MR, Maurisson JP (2010) Acute toxicologic and neurotoxic effects of inhaled 1,2-dichloroethane in adult Fischer 344 rats. *Food Chem Toxicol* 48:470-481.

Hotchkiss JA, Marshall VA, Luna L, Sura R, Visconti N (2014) Investigation of the mode of action for 1,2-Dichloroethane-induced mammary tumors in female F344/DuCrI rats. Dow Chemical Company, unpublished data. Data provided to SCOEL by the REACH Consortium.

HSDB [Hazardous Substances Data Bank] (2016) National Library of Medicine. Search term 1,2- Dichloroethane, database HSDB. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~hxx7XQ:3> Accessed 2016.04.28

IARC [International Agency for Research on Cancer] (1979) 1,2-Dichloroethane. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Volume 20:429-448. Lyon, France. <http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono20.pdf> Assessed 2016.05.12

IARC [International Agency for Research on Cancer] (1999) 1,2-Dichloroethane. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Volume 71:501-529. Lyon, France. <http://monographs.iarc.fr/ENG/Monographs/vol71/mono71.pdf> Assessed 2016.05.12

IE HSA [Health and Safety Authority] (2016) 2016 Code of Practice for the Chemical Agents Regulations (S.I. No. 619 of 2001), Health and Safety Authority, Ireland [http://www.hsa.ie/eng/Publications\\_and\\_Forms/Publications/Chemical\\_and\\_Hazardous\\_Substances/Chemical\\_Agents\\_COP\\_2016.pdf](http://www.hsa.ie/eng/Publications_and_Forms/Publications/Chemical_and_Hazardous_Substances/Chemical_Agents_COP_2016.pdf) Accessed 2016.05.06

IOM [Institute of Occupational Medicine] (2011) Health, socio-economic and environmental aspects of possible amendments to the EU Directive on the protection of workers from the risks related to exposure to carcinogens and mutagens at work. 1,2-Dichloroethane. SHEcan Report P937/17 [https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEWij07iSjrHMAhUCkSwKHecaCJ4QFggqMAA&url=http%3A%2F%2Fec.europa.eu%2Fsocial%2FBlobServlet%3FdocId%3D10170%26langId%3Den&usq=AFQjCNGIU43Tkph8EKAnT9XaFBH0cIBF0Q&sig2=eajCZuo7bWCiL6MHZ8\\_ZIQ&cad=rja](https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEWij07iSjrHMAhUCkSwKHecaCJ4QFggqMAA&url=http%3A%2F%2Fec.europa.eu%2Fsocial%2FBlobServlet%3FdocId%3D10170%26langId%3Den&usq=AFQjCNGIU43Tkph8EKAnT9XaFBH0cIBF0Q&sig2=eajCZuo7bWCiL6MHZ8_ZIQ&cad=rja). Accessed 2016.04.29

IPCS [International Programme on Chemical Safety] (1995) 1,2-Dichloroethane (Second Edition). Environmental Health Criteria 176. Available online via:

ISO [International Standards Organization] (2000) Method ISO 16200-2 for volatile organic compounds. Workplace air quality. Sampling and analysis of volatile organic compounds by solvent desorption/gas chromatography-diffusive sampling method.

ISO [International Standards Organization] (2001) Method ISO 16200-1 for volatile organic compounds. Workplace air quality. Sampling and analysis of volatile organic compounds by solvent desorption/gas chromatography-pumped sampling method.

Jakobson I, Wahlberg JE, Holmberg B, Johansson G (1982) Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. *Toxicol Appl Pharmacol* 63: 181-187.

Jean PA, Reed DJ (1992) Utilization of glutathione during 1,2-dihaloethane metabolism in rat hepatocytes. *Chem. Res. Toxicol* 5: 386-391

Jemal A, Barker SA, Means JC (2010) Dose-response relationship, kinetics of formation, and persistence of S-[2-(N7-guanyl)-ethyl]glutathione-DNA adduct in livers of channel catfish (*Ictalurus punctatus*) exposed to ethylene dichloride. *Environ Toxicol Chem* 29(7):1537-1544.

Kitchin KT, Brown JL (1994) Dose-response relationship for rat liver DNA damage caused by 49 rodent carcinogens. *Toxicology* 88(13):31-49.

Klaunig JE, Ruch RJ, Pereira MA (1986) Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. *Environ Health Perspect* 69: 89-95.

Kronevi T, Wahlberg JE, Holmberg B (1981) Skin pathology following epicutaneous exposure to seven organic solvents. *Int J Tissue React* 3: 21-30.

Kuwabara T, Quevedo AR, Cogan DG (1968) An experimental study of dichloroethane poisoning. *Arch Ophthalmol*, 79: 321-330.

Lane RW, Riddle BL, Borzelleca JF (1982) Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. *Toxicol. Appl Pharmacol* 63: 409-421.

Li C, Zhang WM, Luo MJ, Yang J, Wang J (2012) The effects of 1,2-dichloroethane on the cellular proliferation, cellular cycle and apoptosis in SW620 cells in vitro [in Chinese] (2012) *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 30(3):213-216.

Liu JR, Fang S, Ding MP, Chen ZC, Zhou JJ, Sun F, Jiang B, Huang J (2010) Toxic encephalopathy caused by occupational exposure to 1,2-dichloroethane. *J Neurol Sci* 292:111-113.

Liu QX, Xia S, Qi J (2009) Imaging features to toxic encephalopathy and the values of DWI. *Chin J Med Imaging Technol* 25:54-57.

Luznikov, E.A., Lisovik, Z.A. & Novikovskaya, T.V. (1985) Metabolism of 1,2-dichloroethane in human body after acute poisonings. *Foren Med Expert*, 2: 47-49 (in Russian; cited by IARC 1999)

Maltoni C, Valgimigli L, Scarnato C (1980) Long-term carcinogenic bioassays on ethylene dichloride administered by inhalation to rats and mice. In: Ames BN, Infante P, Reitz R ed. *Ethylene dichloride: A potential health risk?* Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, pp 3-33 (Banbury Report No. 5).

McDermott C, Heffron JJ (2013) Toxicity of industrially relevant chlorinated organic solvents in vitro. *Int J Toxicol* 32(2):136-145.

Milman HA, Storystorey DL, Riccio ES, Sivak A, Tu AS, Williams GM, Tong C, Tyson CA (1988) Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. *Ann NY Acad Sci* 534: 521-530.

Mitoma C, Steeger T, Jackson SE, Wheeler KP, Rogers JH, Milman HA (1985) Metabolic disposition study of chlorinated hydrocarbons in rats and mice. *Drug Chem Toxicol* 8: 183-194.

Morgan DL, Bucher JR, Elwell MR, Lilja HS, Murthy AS (1990) Comparative toxicity of ethylene dichloride in F344/N, Sprague-Dawley and Osborne-Mendel rats. *Food Chem Toxicol* 28: 839-845

Morgan DL, Cooper SW, Carlock DL, Sykora JJ, Sutton B, Mattie DR, McDougal JN (1991) Dermal absorption of neat and aqueous volatile organic chemicals in Fischer 344 rat. *Environ Res* 55: 51-63

Muchametova GM, Wosabaja MA: *Gig. Tr. prof. Zabol.* No. 11, 6 (1972); cited in UWD [Umweltschutzdienst]-Information für Umweltfragen, No. 8 (1973). As referenced by DFG (1992)

Munson AE, Sanders VM, Douglas KA, Sain LE, Kauffmann BM, White KL (1982) In vivo assessment of immunotoxicity. *Environ Health Perspect* 43: 41-52

Nagano K, Nishizawa T, Yamamoto S, Matsushima T (1998) Inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice. In: Chiyotani K, Hosoda Y, Aizawa Y, eds, *Advances in the Prevention of Occupational Respiratory Diseases*, Amsterdam, Elsevier, pp. 741-746

Nagano K, Umeda Y, Senoh H, Gotoh K, Arito H, Yamamoto S, Matsushima T (2006) Carcinogenicity and chronic toxicity in rats and mice exposed by inhalation to 1,2-dichloroethane for two years. *J Occup Health* 48:424-436.

NCI [National Cancer Institute] (1978) Bioassay of 1,2-dichloroethane for possible carcinogenicity. *Techn. Rep. Ser. No. 55, DHEW Publ. No. (NIH) 78-1361*, National Technical Information Service, US Dept. of Commerce, Springfield, VA, USA.

NIOSH [National Institute for Occupational Safety and Health] (1990) National Occupational Exposure Survey (1981-83). National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/24130sic.html>. Accessed: 2016.04.28

NIOSH [National Institute for Occupational Safety and Health] (2003) Hydrocarbons, halogenated Method 1003 NIOSH Manual of Analytical Methods (NMAM), Fourth Edition <http://www.cdc.gov/niosh/docs/2003-154/pdfs/1003.pdf>. Accessed 2016.05.03

NL SER [Sociaal-Economische Raad / Social-Economic Council] (1998) Subcommission MAC-Values. Advice OEL 1,2-dichloorethaan. <http://www.ser.nl/documents/24775.pdf>. Accessed 2016.05.05.

NL SER [Sociaal-Economische Raad / Social-Economic Council] (2007) Dichloorethaan - OEL. <http://www.ser.nl/en/sitecore/content/internet/nl/grenswaarden/1%202%20dichloorethan.aspx>. Accessed 2016.04.29

NO NLIA [Norwegian Labour Inspection Authority] (2011) Administrative normer for forurensning i arbeidsatmosfære, Norway. Arbeidstilsynet. Veiledning, best.nr. 361 <http://www.arbeidstilsynet.no/binfil/download2.php?tid=77907> Accessed 2016.04.29

NTP [National Toxicology Program] (2011) Rep Carcinog 13:145-148. Available via: <http://ntp.niehs.nih.gov/go/roc13>

NTP [US NIEHS National Toxicology Program] (2014) Report on Carcinogens, Thirteenth Edition. U.S. Department of Health and Human Services, Public Health Service. <http://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloroethane.pdf>. Accessed 2016.04.28

NZ HS [Health and Safety] (2013) Workplace Exposure Standards and Biological exposure Indices Effective from February 2013 7th Edition. The Ministry of Business, Innovation and Employment, New Zealand. <http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices/workplace-exposure-standards-and-biological-indices-2013.pdf> Accessed 2016.04.29

OSHA [Occupational Safety and Health Administration] (1979) Ethylene Dichloride OSHA Method ORG-03 <https://www.osha.gov/dts/sltc/methods/organic/org003/org003.html>. Accessed 2016.05.03

OSHA [Occupational Safety and Health Administration] (2000) Ethylene Dichloride OSHA Method ORG-07 <https://www.osha.gov/dts/sltc/methods/organic/org007/org007.html#51>. Accessed 2016.05.03

Payan JP, Saillenfait AM, Bonnet P, Fabry JP, Langonne I, Sabate JP (1995) Assessment of the developmental toxicity and placental transfer of 1,2-dichloroethane in rats. *Fundam Appl Toxicol* 28(2):187-198

Prodi G, Arfellini G, Colacci A, Grilli S, Mazzullo M (1986) Interaction of halocompounds with nucleic acids. *Toxicol Pathol* 14(4):438-444.

Qi Y, Shi L, Gao LY, Wang GY, Lv XQ, Jin YP (2011) Influence of 1,2-dichloroethane on open field behaviour and levels of neurotransmitters in brain of mice [in Chinese]. *Zhonghua Lao Dong Wei Sheng Zhi Bing Za Zhi* 29(6):413-416.

Rao KS, Murray JS, Deacon MM, John JA, Calhoun LL, Young JT (1980) Teratogenicity and reproduction studies in animals inhaling ethylene dichloride. In: Ames BN, Infante P, Reitz R, eds, *Ethylene Dichloride: A Potential Health Risk?* (Banbury Report No. 5), Cold Spring Harbor, NY, CSH Press, pp. 149-166

REACH joint submission dossier: [http://echa.europa.eu/information-on-chemicals/registeredsubstances?p\\_auth=9JaQTjjM&p\\_p\\_id=registeredsubstances\\_WAR\\_regsupportlet&p\\_p\\_lifecycle=1&p\\_p\\_state=normal&p\\_p\\_mode=view&p\\_p\\_col\\_id=column1&p\\_p\\_col\\_pos=2&p\\_p\\_col\\_count=3&\\_registeredsubstances\\_WAR\\_regsupportlet\\_java\\_x.portlet.action=registeredSubstancesAction](http://echa.europa.eu/information-on-chemicals/registeredsubstances?p_auth=9JaQTjjM&p_p_id=registeredsubstances_WAR_regsupportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column1&p_p_col_pos=2&p_p_col_count=3&_registeredsubstances_WAR_regsupportlet_java_x.portlet.action=registeredSubstancesAction)

Reitz RH, Fox TR, Ramsey JC, Quast JF, Langvardt PW, Watanabe PG (1982) Pharmacokinetics and macromolecular interactions of ethylene dichloride in rats after inhalation or gavage. *Toxicol Appl Pharmacol* 62: 190-204

SE SWEA (2015) Hygieniska gränsvärden. Arbetsmiljöverkets författningssamling, AFS 2015:7. Arbetsmiljöverket, Stockholm (in Swedish): <https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf>.

Simula TP, Glancey MG, Wolf CR (1993) Human glutathione S-transferase-expressing Salmonella typhimurium tester strains to study the activation/detoxification of mutagenic compounds: studies with halogenated compounds, aromatic amines and aflatoxin B1. *Carcinogenesis*, 14: 1371-1376.

Spence JW and Hanst PL, (1978) Oxidation of Chlorinated Ethanes, *Journal of the Air Pollution Control Association*, 28:3, 250-253, DOI:10.1080/00022470.1978.10470599

Spencer HC, Rowe VK, Adams EM, McCollister DD, Irish DD (1951) Vapor toxicity of ethylene dichloride determined by experiments on laboratory animals. *Arch Industr Health* 4: 482-493.

Storer RD, Jackson NM, Conolly RB (1984) In vivo genotoxicity and acute hepatotoxicity of 1,2-dichloroethane in mice: comparison of oral, intraperitoneal and inhalation routes of exposure. *Cancer Res* 4: 4267-4271

Thier R, Müller M, Taylor JB, Pemble SE, Ketterer B, Guengerich FP. (1995) Enhancement of bacterial mutagenicity of bifunctional alkylating agents by expression of mammalian glutathione S-transferase. *Chem Res Toxicol* 8(3):465-472.

Thier R, Pemble SE, Kramer H, Taylor JB, Guengerich FP, Ketterer B (1996) Human glutathione S-transferase T1-1 enhances mutagenicity of 1,2-dibromoethane, dibromomethane and 1,2,3,4-diepoxybutane in Salmonella typhimurium. *Carcinogenesis* 17(1):163-166.

UK HSE [Health and Safety Executive] (1993) Volatile organic compounds in air MDHS 72. <http://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs72.pdf>. Accessed 2016.05.03

UK HSE [Health and Safety Executive] (1995) Volatile organic compounds in air MDHS 80. <http://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs80.pdf>. Accessed 2016.05.03

UK HSE [Health and Safety Executive] (1997) Volatile organic compounds in air MDHS 88 <http://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs88.pdf>. Accessed 2016.05.03

UK HSE [Health and Safety Executive] (2000) Volatile organic compounds in air MDHS 96 <http://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs96.pdf>. Accessed 2016.05.03

US ACGIH [American Conference of Governmental Industrial Hygienists] (2015). TLVs® and BEIs®. ISBN: 978-1-607260-77-6. ACGIH®. USA. <https://www.acgih.org/forms/store/ProductFormPublic/2015-tlvs-and-beis>

US NIOSH [US National Institute for Occupational Safety and Health] (2016) NIOSH Publications & Products. Immediately Dangerous To Life or Health (IDLH). Chemical Listing and Documentation. Immediately Dangerous to Life or Health Concentrations (IDLH). <http://www.cdc.gov/niosh/npg/npgd0271.html> Accessed 2016.04.29

US OSHA [Occupational Safety and Health Administration] (2006). Annotated PELs; Table Z2. Air Contaminants, USA. <https://www.osha.gov/dsg/annotated-pels/tablez-2.html> Accessed 2016.04.29

Vamvakas S, Dekant W, Schiffmann D, Henschler W (1988) Induction of unscheduled DNA synthesis and micronucleus formation in Syrian hamster embryo fibroblasts treated with cysteine S-conjugates of chlorinated hydrocarbons, *Cell Biol Toxicol* 4:393-403.

Van Duuren BL, Goldschmidt BM, Loewengart G, Smith A, Mechionne S, Seldman I, Roth D (1979) Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J Natl Cancer Inst* 63: 1433-1439.

Vozowaya MA (1976) Gig i Sanit 6:100 (as cited by ATSDR 2001).

Wang G, Qi Y, Gao L, Li G, Lv X, Jin Yp (2013) Effects of subacute exposure to 1,2-dichloroethane on mouse behaviour and the related mechanisms. Hum EXP TOXICOL 32(9):983-991.

Ward, R.J. (1992) In vitro absorption through human and rat epidermis. Testing lab: ICI

Watanabe K, Liberman RG, Skipper PL, Tannenbaum SR, Guengerich FP (2007) Analysis of DNA adducts formed in vivo in rats and mice from 1,2-dibromoethane, 1,2-dichloroethane, dibromomethane, and dichloromethane using HPLC/accelerator mass spectrometry and relevance to risk assessment. Chem Res Toxicol 20(11):1594-1600.

WHO/IPCS [International Programme on Chemical Safety] (1995) Environmental Health Criteria No. 176. 1,2-Dichloroethane <http://www.inchem.org/documents/ehc/ehc/ehc176.htm>. Accessed 2016.04.29

WHO/IPCS [World Health Organization / International Programme on Chemical Safety] (1998) 1,2-Dichloroethane CICAD 1 (Concise International Chemical Assessment Document. <http://www.who.int/ipcs/publications/cicad/en/cicad01.pdf>. Accessed 2016.04.29

Zhan F, Zheng W, Liu L, Kong L (2011) Diagnosis and prognosis evaluation of 1,2-dichloroethane encephalopathy – magnetic resonance imaging combined with diffusion tensor imaging and magnetic resonance spectroscopy study. Neurol India 59(1):108-110.

Zhang QL, Wang LP, Guo XL (2006) Effect of 1,2-dichloroethane on blood brain barrier. Chin J Ind Hyg Occup Dis 24:239-242.

### 10. ANNEX

The curve modelling for the most conservative BMD10 of all models used can be seen in the following figures.

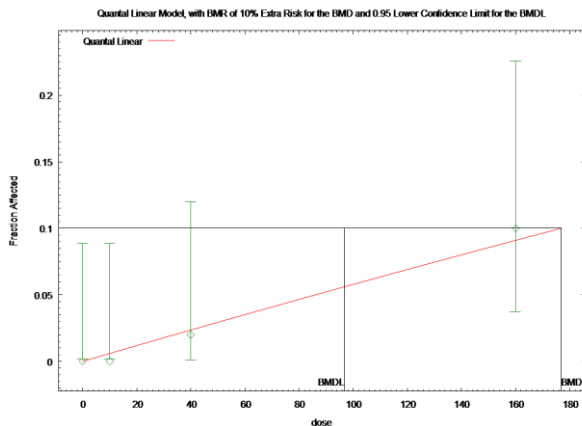


Figure 1 : Quantal linear model with the lowest AIC for the **mammary gland fibroadenoma found in male rats.**

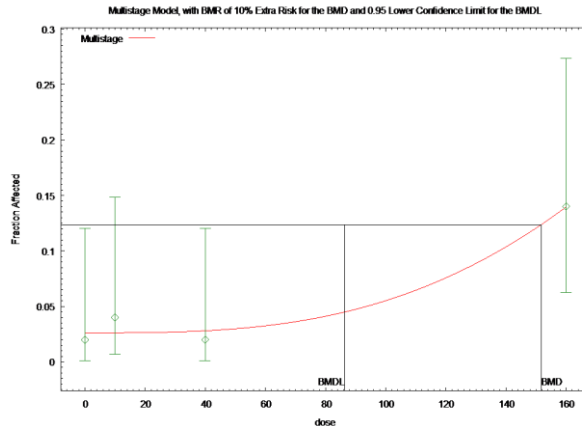


Figure 2 : Multistage 3° cancer model with the lowest AIC for the **mammary gland adenoma & fibroadenoma found in male rats.**

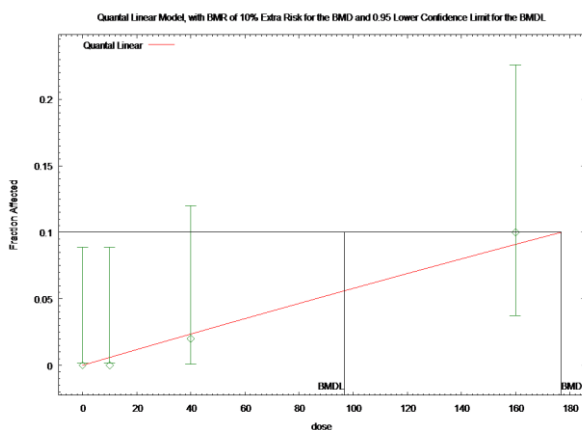


Figure 3 : Quantal linear model with the lowest AIC for the **subcutis fibroma found in male rats.**

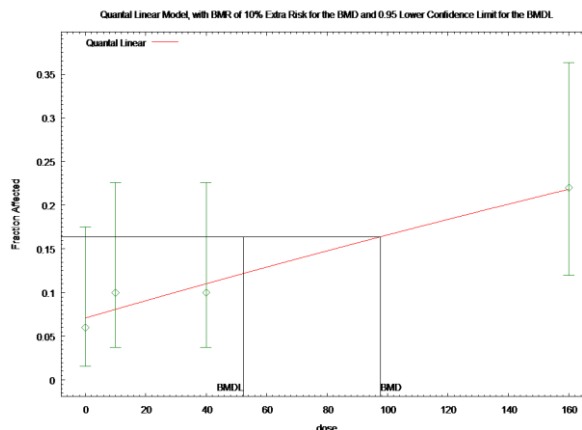


Figure 4 : Quantal linear model with the lowest AIC for the **mammary gland adenoma found in female rats.**

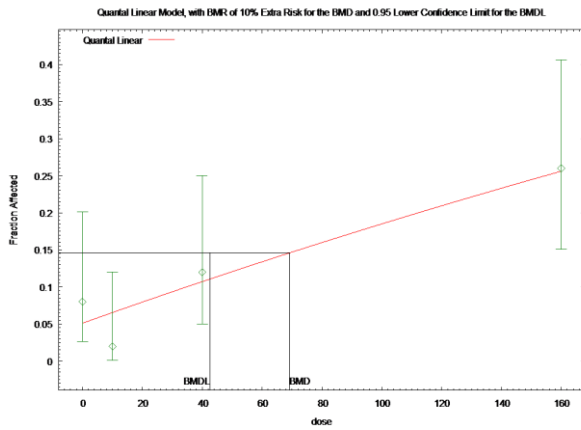


Figure 5 : Quantal linear model with the lowest AIC for the **mammary gland fibroadenoma found in female rats.**

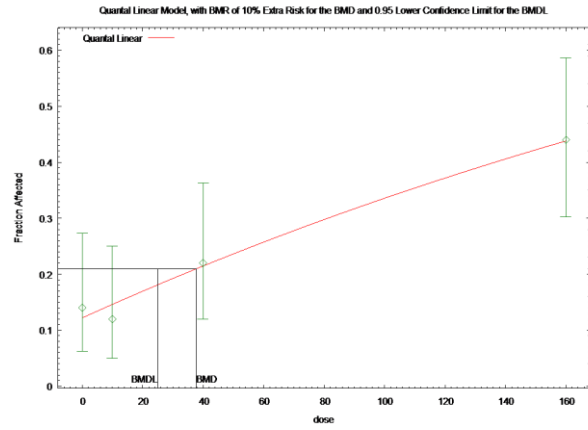


Figure 6 : Quantal linear model with the lowest AIC for the **mammary gland adenoma & fibroadenoma found in female rats.**

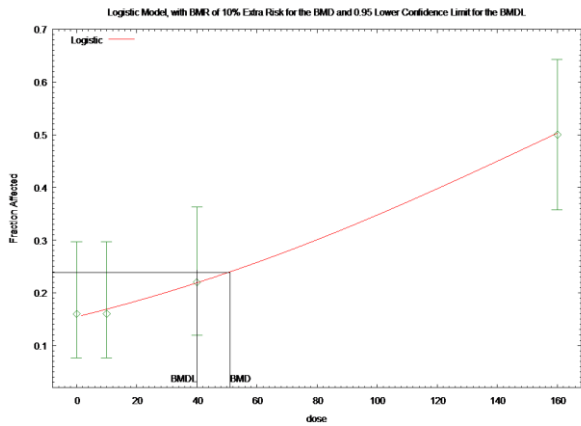


Figure 7 : Quantal linear model with the lowest AIC for the **mammary gland adenoma & fibroadenoma & adenocarcinoma found in female rats.**



## **HOW TO OBTAIN EU PUBLICATIONS**

### **Free publications:**

- one copy:  
via EU Bookshop (<http://bookshop.europa.eu>);
- more than one copy or posters/maps:  
from the European Union's representations ([http://ec.europa.eu/represent\\_en.htm](http://ec.europa.eu/represent_en.htm));  
from the delegations in non-EU countries  
([http://eeas.europa.eu/delegations/index\\_en.htm](http://eeas.europa.eu/delegations/index_en.htm));  
by contacting the Europe Direct service ([http://europa.eu/europedirect/index\\_en.htm](http://europa.eu/europedirect/index_en.htm))  
or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (\*).

(\*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

### **Priced publications:**

- via EU Bookshop (<http://bookshop.europa.eu>).

### **Priced subscriptions:**

- via one of the sales agents of the Publications Office of the European Union  
([http://publications.europa.eu/others/agents/index\\_en.htm](http://publications.europa.eu/others/agents/index_en.htm)).



Publications Office

doi: 10.2767/100789

ISBN 978-92-79-64564-8