



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

An overview of the available data on the **reproductive and developmental toxicity** of **1,4-dichlorobenzene**

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reproductive and developmental toxicity of
1,4-dichlorobenzene**

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Colophon

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Synopsis

An overview of the available data on the reproductive and developmental toxicity of 1,4-dichlorobenzene

1,4-dichlorobenzene is a substance used to kill insects, for example as an ingredient in mothballs. It is also an important ingredient in products such as medicines, polyphenylene sulphide (PPS) resin and paint. In addition, it is used as an air freshener, for example for toilets and waste containers.

The question is whether 1,4-dichlorobenzene poses a hazard to the fertility of humans and the unborn child. The National Institute for Public Health and the Environment (RIVM) has examined the scientific literature to determine what is known about these two potentially harmful properties of the substance. RIVM has summarised the results of studies conducted in laboratory animals and cells.

It was commissioned to do so by the Health Council of the Netherlands (*Gezondheidsraad*). The Health Council will propose that the substance be assigned to a specific 'hazard class'. To prepare its proposal, the Health Council will use the RIVM's overview to assess whether 1,4-dichlorobenzene is hazardous to fertility and the unborn child. The Minister of Social Affairs and Employment (SZW) requested this advice.

Keywords: 1,4-dichlorobenzene, reproductive toxicity, reproduction, developmental toxicity

Publiekssamenvatting

Een overzicht van de beschikbare informatie over de reproductietoxische en ontwikkelingsgiftige effecten van 1,4-dichloorbenzeen

De stof 1,4-dichloorbenzeen wordt gebruikt als middel om insecten te doden, zoals in mottenballen. Ook is het een belangrijk ingrediënt in producten als medicijnen, polyfenyleensulfide (PPS) hars, en verf. Verder wordt het gebruikt als luchtverfrisser voor bijvoorbeeld toiletten en afvalcontainers.

De vraag is of 1,4-dichloorbenzeen gevaarlijk is voor de vruchtbaarheid van mensen en het ongeboren kind. Het RIVM heeft in de wetenschappelijke literatuur onderzocht wat er bekend is over deze twee schadelijke eigenschappen van de stof. Het RIVM heeft de resultaten van studies met proefdieren en cellen samengevat.

Het RIVM deed dat in opdracht van de Gezondheidsraad. De Gezondheidsraad gaat een voorstel doen om de stof in een bepaalde 'gevaarenklasse' in te delen. Als voorbereiding daarop gebruikt de Gezondheidsraad het overzicht van het RIVM om te beoordelen of 1,4-dichloorbenzeen gevaarlijk is voor de vruchtbaarheid en het ongeboren kind. De minister van Sociale Zaken en Werkgelegenheid (SZW) heeft om dit advies gevraagd.

Kernwoorden: 1,4-dichloorbenzeen, reproductietoxiciteit, voortplanting, ontwikkelingstoxiciteit

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Summary

RIVM has summarised the available literature on the potential reproductive toxicity and developmental toxicity of 1,4-dichlorobenzene. 1,4-Dichlorobenzene is mostly used for the production of air care products, insecticide and fumigant, as well as a key ingredient in various products such as pharmaceuticals, polyphenylene sulphide (PPS) resin, and dyes. Its primary applications include use as air freshener, space deodorant for toilets, and refuse containers.

In the current report, studies were summarised that include information on fertility, developmental toxicity and lactation in animals, as well as studies providing human relevant information. The data found were summarised. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the reproduction toxic properties and to provide a recommendation for classification. Such an assessment was beyond the scope of the current report

1 Introduction

The aim of current research is to identify and summarize the available data from studies with laboratory models, test animals and humans on the substance 1,4-dichlorobenzene. The focus of current literature review will be on the reproductive toxic properties of this substance. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the reproductive toxic properties and to provide a recommendation for its classification. The assessment will be performed by the Health Council's Subcommittee on Classification of Reproductive Toxic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

Current RIVM report does not include an assessment of the reported reproductive toxic properties of 1,4-dichlorobenzene, nor does it provide a recommendation for classification of these substances based on the CLP-criteria (Regulation EC No 1272/2008).

The literature search which forms the basis of current literature overview is summarized in chapter 2. In chapter 3, the substance identification of 1,4-dichlorobenzene is provided. Chapter 4 presents information on international classifications of 1,4-dichlorobenzene. Available information on monitoring (i.e. environmental and biological exposure monitoring) and manufacture and use is presented in chapters 5 and 6, respectively. A summary of the (toxico)kinetics of 1,4-dichlorobenzene is described in chapter 7. Chapter 8 describes an overview of the data on reproductive toxicity: data on adverse effects on fertility and sexual function, on development and on or via lactation.

2 Literature search

The Health Council of the Netherlands has performed a literature search using PubMed and Scopus. Relevant in vitro, in vivo and epidemiology studies were selected for an extensive summary by the Health Council. This resulted in animal fertility and developmental studies in rats, mice, rabbits, guinea pigs and monkeys. Furthermore, human biomonitoring studies were found.

RIVM also consulted the REACH registration dossier of 1,4-dichlorobenzene (publicly available on the ECHA CHEM website)¹ and secondary sources, which included the Toxicological profile of Agency for Toxic Substances and Diseases Registry (ATSDR) for 1,4-dichlorobenzene [1], a National Toxicology Program (NTP) report on 1,4-dichlorobenzene [2], an Australian National Industrial Chemicals Notification and Assessment Scheme report on 1,4-dichlorobenzene [3], an European Union Risk assessment report on 1,4-dichlorobenzene [4], a U.S. Environmental Protection Agency [5], and a MAK (Maximale Arbeitsplatz-Konzentration) value documentation on 1,4-dichlorobenzene [6]. These were used to retrieve information on substance identification, classification, manufacture, monitoring, toxicokinetics and to identify additional relevant studies to ensure completeness of the evidence base.

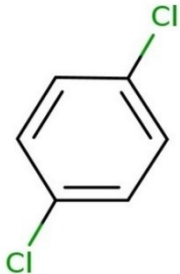
¹ Registration Dossier - ECHA

3 Substance identification

3.1 Name and other identifiers of the substance

The identity of 1,4-dichlorobenzene is presented in **Fout!**
Verwijzingsbron niet gevonden. below.

Table 1 Substance identity and information related to the molecular and structural formula of 1,4-dichlorobenzene [7].

Identifier	Value
Name(s) in the IUPAC nomenclature or other international chemical name(s)	1,4-dichlorobenzene 1,4-dichlorbenzol 1,4-diclorobenceno 1,4-DCB p-dichlorbenzol p-dichlorobenzene PDB PDCB DCB
Other names (usual name, trade name, abbreviation)	SANTOCHLOR PARADICHLOROBENZENE PARADOW PARAMOTH DI-CHLOROCIDE
ISO common name (if available and appropriate)	N/A
EC/EINECS number (if available and appropriate)	203-400-5
EC name (if available and appropriate)	1,4-dichlorobenzene
CAS number	106-46-7
Other identity code (if available)	N/A
Molecular formula	C ₆ H ₄ Cl ₂
Structural formula	
SMILES notation (if available)	<chem>C1=CC(=CC=C1Cl)Cl</chem>
Molecular weight or molecular weight range	147.00 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A

Identifier	Value
Description of the manufacturing process and identity of the source (for UVBC substances only)	N/A
Degree of purity (%) (if relevant for the entry in Annex VI) [8]	Pure-grade para-dichlorobenzene consists of > 99.8% para-dichlorobenzene, < 0.05% chlorobenzene and trichlorobenzene and < 0.1% ortho- and meta-dichlorobenzene

N/A: Not applicable

3.2 Physico-chemical properties of 1,4-dichlorobenzene

The physico-chemical properties of 1,4-dichlorobenzene are presented in Table 2.

Table 2 Summary of physico-chemical properties of 1,4-dichlorobenzene

Properties	Value	Reference
State of the substance at normal temperature and pressure	Solid	ECHA CHEM [7]
Melting/freezing point	53.3°C at 101.3 kPa	ECHA CHEM [7]
Boiling point	174.12 °C at 101.3 kPa	ECHA CHEM [7]
Relative density	1.46 at 20 °C	ECHA CHEM [7]
Vapour pressure	53 Pa at 25 °C	ECHA CHEM [7]
Surface tension	Surface activity is not a desired property of the substance and, based on structure, surface activity is not expected	ECHA CHEM [7]
Water solubility	51.2 mg/L at 10 °C, 82.9 mg/L at 25 °C	ECHA CHEM [7]
Partition coefficient n-octanol/water	3.37 at 25 °C and pH ca. 7	ECHA CHEM [7]
Flash point	66 °C at 101.3 kPa	ECHA CHEM [7]
Flammability	The substance does not have pyrophoric properties.	[4]
Explosive properties	Vapour can form explosive mixtures with air within the range of 1.7% to 5.9% by volume	[4]
Self-ignition temperature	500 °C	ECHA CHEM [7]

Properties	Value	Reference
Oxidising properties	The substance does not contain a chemical moiety suggesting an oxidising potential	ECHA CHEM [7]
Granulometry	N/A	
Stability in organic solvents and identity of relevant degradation products	The substance does not contain chemical moieties or reactive groups suggesting instability in organic solvents.	ECHA CHEM [7]
Dissociation constant (pKa)	The substance does not contain structural moieties or groups which could act as a proton donator or acceptor. The determination of a pKa-value is technically not feasible	ECHA CHEM [7]
Viscosity	The substance is a solid under environmental conditions.	ECHA CHEM [7]

N/A: Not applicable

4 International classifications

4.1 European Commission

1,4-Dichlorobenzene has currently a harmonized classification (human health) in Annex VI of the CLP-Regulation (EC) 1272/2008 [7] for:

- Eye irrit. 2 (H319, causes serious eye irritation)
- Carc. 2 (H351, suspected of causing cancer)

4.2 The Health Council

1,4-Dichlorobenzene has not previously been evaluated by the Health Council of the Netherlands.

4.3 Other countries

1,4-Dichlorobenzene is classified by IARC as a group 2B carcinogen.²

The MAK commission has classified 1,4-dichlorobenzene as pregnancy risk group C, i.e. damage to the embryo or foetus is unlikely when the MAK value or the BAT value is observed. 1,4-Dichlorobenzene is further classified as a category 4 carcinogen, i.e. substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans and for which a MAK value can be derived.³

In Germany, 1,4-dichlorobenzene is not included in the list of additional CMR substances in the context of worker protection.⁴

1,4-Dichloroethane is listed as 'reasonably anticipated to be a human carcinogen' by the NTP.⁵

The state of California has included 1,4-dichlorobenzene in their safe drinking water and toxic enforcement act as a chemical known to the state to cause cancer.⁶

² <https://publications.iarc.fr/91>

³ https://series.publisso.de/sites/default/files/documents/series/mak/lmbv/Vol2024/Iss2/Doc002/mbwl_2024_eng.pdf

⁴ <https://www.baua.de/DE/Angebote/Regelwerk/TRGS/TRGS-905>

⁵ https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf

⁶ <https://oehha.ca.gov/media/downloads/proposition-65/p65list091319.pdf>

5 Monitoring and Exposure

5.1 Environmental exposure monitoring

Depending on the sample matrix very low levels (low ppb range) of 1,4-dichlorobenzene concentrations can be measured in environmental media. For methods used specifically for 1,4-dichlorobenzene (so not as part of a mixture) recoveries range from ± 12.5 from workplace air to 107% from drinking water. The lowest detection limits reported are for 1,4 dichlorobenzene in drinking water at 0.006 $\mu\text{g/L}$ using GC/PID or GC/MS. For solid waste the lowest reported detection limits are 0.01 $\mu\text{g/L}$ using a Hall electrolytic conductivity detector (HECD) (table 3).

Table 3 Overview of methods for the analysis of 1,4 dichlorobenzene in environmental samples. The references quoted are from the original ATSDR report [1]

Sample matrix (analyte)	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (1,4-DCB)	Collection on charcoal tubes; desorption with CS ₂	GC/FID	10 $\mu\text{g}/\text{sample}^a$	± 12.5	Method 1003 NIOSH 1994
Ambient air (VOCs including DCBs)	Collection in canisters; cryofocussing; thermal desorption	cap. GC with FID, ECD or MS	No data	No data	Method TO-14 EPA 1988a
Air-emission sources (selected compounds)	MM5 sampling train (condensate, filter, adsorbent); condensate, impinger and rinses, solvent extraction, evaporation; XAD-2 adsorbent and filters, Soxhlet extraction, concentration	cap. GC/MS	No data	-13 to -16	Method 0010 EPA 1994f
Air-emission sources (volatile organics)	VOST sampling train (sorbent traps); thermal desorption	GC/MS	No data	No data	Method 0030 EPA 1994h

Sample matrix (analyte)	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water (1,4-DCB)	Purge and trap	GC/HECD; conf. on second col. or GC/MS	<0.01 µg/L for most VOCs	90	Method 502.1 EPA 1991a
Drinking water (1,4-DCB)	Purge and trap	GC/PID-HECD; conf. by GC/MS	0.01–0.03 µg/L (PID); 0.01–0.04 µg/L (HECD)	97–103 (PID); 97–98 (HECD)	Method 502.2 EPA 1991b
Drinking water (1,4-DCB)	Purge and trap	GC/PID; conf. on second col. Or GC/MS	0.006 µg/L	91–107	Method 503.1 EPA 1991c
Drinking water	Purge and trap	cap. GC/MS	0.03–0.05 µg/L	93–97	Method 524.2 EPA 1992a
Drinking water	Purge and trap	cap. GC/MS	0.05–0.12 µg/L	87–100	Method 524.2 EPA 1992a
Drinking water	Purge and trap	cap. GC/MS	0.03–0.04 µg/L	93–103	Method 524.2 EPA 1992a
Waste water	Purge and trap	GC/HECD; conf. on second col. Or GC/MS	0.15 µg/L	ND–208	Method 601 EPA 2002c
Waste water	Purge and trap	GC/HECD; conf. on second col. or GC/MS	0.32 µg/L	7–187	Method 601 EPA 2002c
Waste water	Purge and trap	GC/HECD; conf. on second col. or GC/MS	0.24 µg/L	42–143	Method 601 EPA 1984c; EPA 2002c
Waste water	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.4 µg/L	37–154	Method 602 EPA 2002d
Waste water	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.3 µg/L	50–141	Method 602 EPA 2002d
Waste water	Purge and trap	GC/PID; conf. on second col. or GC/MS	0.3 µg/L	42–143	Method 602 EPA 1984f; EPA 2002d
Waste water	Solvent extraction; optional Florisil column clean-up	GC/ECD	1.14 µg/L	9–160	Method 612 EPA 2002b
Waste water	Solvent extraction; optional Florisil column clean-up	GC/ECD	1.19 µg/L	DL–150	Method 612 EPA 2002b

Sample matrix (analyte)	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	Solvent extraction; optional Florisil column clean-up	GC/ECD	1.34 µg/L	13–137	Method 612 EPA 1984c; EPA 2002b
Waste water (1,2- and 1,4-DCB)	Purge and trap	GC/MS	No data	18–190	Method 624 EPA 1984d; EPA 2002a
Waste water	Purge and trap	cap. GC/MS	0.031 µg/L	106	Method 6200B APHA 1998
Waste water	Purge and trap	cap. GC/MS	0.045 µg/L	108	Method 6200B APHA 1998
Waste water	Purge and trap	cap. GC/MS	0.033 µg/L	106	Method 6200B APHA 1998
Waste water/ Drinking water (1,4-DCB)	Purge and trap	cap GC/HECD, PID	0.059 µg/L (HECD); 0.061 µg/L (PID)	91 (HECD); 70 (PID)	Method 6200 APHA 1998
Drinking water (VOCs)	Purge and trap	GC	low µg/L	99	Method D 3871 ASTM 1994
Solid waste (VOCs)	Closed system purge and trap and extraction	GC/ECD, FID, MS	Not reported	Not reported	Method 5035 EPA 1996c
Solid waste (1,4-DCB)	Purge and trap, direct injection, headspace, or vacuum distillation	GC/HECD, PID	0.01 µg/L (HECD); 0.07 (PID)	98 (HECD); 103 (PID)	Method 8021B EPA 1996d
Solid waste (1,4-DCB)	Solvent extraction	Single or dual cap. GC/ECD	0.89 µg/L	104	Method 8121 EPA 1994

aEstimated limit of detection

cap. - capillary; conf. - confirmation; col. - column; DL - detection limit;

ECD -electron capture detector; FID - flame ionization detector;

GC - gas chromatography; HECD - Hall electrolytic conductivity detector;

MS - mass spectrometry; ND - not detected; PID - photoionization detector; VOC - volatile organic compound

5.2 Biological exposure monitoring

Exposure to 1,4 dichlorobenzene may be evaluated by measuring its level in blood, breath, milk, and adipose tissue or by measuring 2,5-dichlorophenol in urine, the major metabolite of 1,4-dichlorobenzene. Concentrations have been determined in these biological fluids and tissues using a range of different analytical methods. Separation from blood, urine and tissues is achieved by purging with an inert gas, followed by trapping on an absorbent cartridge or by extracting with hexane or carbon tetrachloride. However, the purge and trap method is the more sensitive of the two. Extraction from exhaled breath does not

require preparation but collection requires use of a spirometer and collection onto a sorbent cartridge or into passivated canisters [1].

Analysis is commonly done using gas chromatography (GC) coupled with a detector. Of the different detectors that can be used to identify dichlorobenzenes, the mass spectrometer (MS) is the only one that can also quantify dichlorobenzenes in biological media.

For determination of 1,4 dichlorobenzene in blood, methods using capillary GC/MS methods with recoveries ranging from 93 to 98% with detection limits in the low-ppb range have been developed. For determination in adipose tissue and mother's milk recoveries range from > 80% with detection limits in the low-ppb range when GC coupled with an electron capture device (ECD) or a photoionization detector (PID) is used. The reported recoveries for 1,4 dichlorobenzene from breath ranges from 49 to 98%. Detection limits have not been reported. Table 4 contains a representative list of the different analytical methods used for biological exposure monitoring [1].

Table 4 Overview of methods for determining 1,4 dichlorobenzene in biological materials. This list was obtained from ATSDR (2006). The references quoted are from the original ATSDR report (2006)[1]

Sample matrix (analyte)	Preparation method	Analytical method	Sample detection limit (µg/L)	Percent recovery	Reference
Blood (1,4-DCB)	Solvent extraction; silica gel column clean-up	GC/PID	3.0	89	Langhorst and Nestruck (1979)
Blood (1,4-DCB)	Solvent extraction	GC/ECD	2	81.6	Bristol et al. (1982)
Blood (1,4-DCB)	Purge and trap	cap. GC/MS	0.04	93–98	Ashley et al. (1992)
Blood, urine (unspecified DCBs)	Purge-and-trap, thermal desorption cap	GC/MS	No data	No data	Barkley et al. (1980)
Urine (1,4-DCB)	Solvent extraction; silica gen column clean-up	GC/PID	0.75	81	Langhorst and Nestruck (1979)
Urine (model compounds)	Headspace purge; thermal desorption	cap. GC/MS	Low µg/L	48–110 (model compounds)	Michael et al. (1980)
Adipose tissue (model compounds)	Maceration; headspace purge; thermal desorption	cap. GC/MS	Low µg/L	13–80 (model compounds)	Michael et al. (1980)
Human milk (chloro-benzene)	Headspace purge; thermal desorption	GC/MS	0.6	>80	Erickson et al. (1980)
Human milk (unspecified DCBs)	Solvent extraction; cleanup with	GC/ECD	No data	>80	Jan (1983)

Sample matrix (analyte)	Preparation method	Analytical method	Sample detection limit (µg/L)	Percent recovery	Reference
	sulfuric acid, Florisil				
Adipose tissue (unspecified DCBs)	Solvent extraction; cleanup with sulfuric acid, Florisil	GC/ECD	No data	56.5	Jan (1983)
Breath (unspecified DCBs)	Collection using a spirometer; adsorption on Tenax traps; thermal desorption cap	cap. GC/MS	No data	No data	Barkley et al. (1980)
Breath (1,4-DCB)	Collection into canisters using spirometer; cryofocussing; thermal desorption	cap. GC/MS-SIM	Low µg/m ³	49-80	Thomas et al. (1991)

cap – capillary; ECD – electron capture device; GC = gas chromatography; MS = mass spectrometry; PID = photoionization detector; SIM = selected ion monitoring

5.3 General population exposure

1,4-Dichlorobenzene enters the environment primarily as releases to air when it is used as a room deodorant, toilet deodorizer, and moth repellent. It predominantly exists as a vapour and has been detected in rainwater possibly due to washout from the atmosphere. It is expected to volatilise from surface water and soil surfaces to the atmosphere [1]. Due to its ready sublimation at room temperature, exposure is mainly via the inhalation route [9]. Exposure is also possible via oral, dermal and ocular routes [8, 10].

1,4-Dichlorobenzene has been detected in meat and eggs from exposed animals, in fish from contaminated waters and in fresh vegetables [11]. It has also been detected in a range of table-ready food items in the USA and Canada. This includes in chocolate-chip cookies, soft drinks, cream, butter, margarine, peanut butter and milk [1]. In the UK it has been detected in carrots, potatoes, cauliflowers and lettuce [1]. In Slovenia and the Gulf of Triest, former Yugoslavia it has been detected in trace amounts up to 0.45 µg/kg in the edible tissue of various species of trout, nase, whiting, mullet, and pilchard fresh water fish [1].

The use of 1,4-dichlorobenzene in household products such as air deodorants, pesticides and mothballs increases the chance of indoor exposure of the general population. Chronic exposure to low concentrations is possible due to its use in long-life materials with low release rates (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment) [7]. Populations living close to sites where

dichlorobenzenes are produced or disposed of, can have potentially higher exposures than the general population [1]. Because it is primarily used indoors, indoor concentrations tend to be higher than outdoor concentrations [11].

Saijo et al. (2004) [12] reported average indoor air concentrations of 1,4-dichlorobenzene of 26.7 $\mu\text{g}/\text{m}^3$ with a range of <3.8 $\mu\text{g}/\text{m}^3$ to 1028.9 $\mu\text{g}/\text{m}^3$. These estimates were based on measurements collected in the living rooms of 191 Japanese dwellings over a 1-week period. This is similar to the levels reported for studies conducted in Germany and The Netherlands based on measurements in more than 100 homes per country. In Germany an arithmetic mean concentration of 1,4-dichlorobenzene in indoor air of 14 $\mu\text{g}/\text{m}^3$ with a maximum concentration of 1260 $\mu\text{g}/\text{m}^3$ was reported. In The Netherlands the median concentration was 1 $\mu\text{g}/\text{m}^3$ with maximum levels of 299 $\mu\text{g}/\text{m}^3$ [8]. In the same study the mean concentrations in homes in the USA were 25 $\mu\text{g}/\text{m}^3$ with maximum levels of 1600 $\mu\text{g}/\text{m}^3$. Median levels measured in indoor air under varying conditions range from 0.58 to 339 $\mu\text{g}/\text{m}^3$ [1]. Outdoor concentrations levels are generally lower than indoor levels and median concentration levels range from below the limit of quantification in rural settings to 0.3 $\mu\text{g}/\text{m}^3$ in urban settings [1].

Table 5 gives an overview of studies that have reported exposure estimates for the general population based on environmental monitoring.

Table 5 General population exposure to 1,4 dichlorobenzene based on environmental monitoring

Country	Exposure details	Exposure estimates	Reference
Indoor air 1,4-dichlorobenzene			
Germany	Measured in more than 100 homes	AM - 14 $\mu\text{g}/\text{m}^3$; Max - 1260 $\mu\text{g}/\text{m}^3$	Wallace 1991 as quoted in IARC 1999 [8]
Netherlands	Measured in more than 100 homes	Median - 1 $\mu\text{g}/\text{m}^3$; max - 299 $\mu\text{g}/\text{m}^3$;	Wallace 1991 as quoted in IARC 1999 [8]
USA	Measured in more than 100 homes	AM - 25 $\mu\text{g}/\text{m}^3$; Max - 1600 $\mu\text{g}/\text{m}^3$	Wallace 1991 as quoted in IARC 1999 [8]
Canada	Nationwide study. Measured in homes	Mean (Winter) – 36 $\mu\text{g}/\text{m}^3$ Mean (Spring) – 15 $\mu\text{g}/\text{m}^3$ Mean (Summer) – 11 $\mu\text{g}/\text{m}^3$ AM (Autumn) – 15 $\mu\text{g}/\text{m}^3$	Fellin & Otson (1994) as quoted in IARC 1999 [8]

Country	Exposure details	Exposure estimates	Reference
Japan	Measured in 191 houses; 1-week passive sampling at 100–150 cm above the floor.	Mean - 26.7 µg/m ³ Min-Max - <3.8-1028.9	Saijo et al. (2004) [12]
Outdoor air 1,4-dichlorobenzene			
USA	Rural settings	Median: < LOD	Shah and Heyerdahl (1988) as quoted in ATSDR 2006 [1]
USA	Urban settings	Median: 0.3 µg/m ³	Shah and Heyerdahl (1988) as quoted in ATSDR 2006 [1]

N – number of samples; LOD – Limit of Detection

With regard to prevalence of detectable levels in human fluids and tissue based on personal biological monitoring, 98% of a sample of 1000 US adults had 2,5-dichlorophenol in their urine and 96% had 1,4-dichlorobenzene in their blood [9]. In a nationwide US study conducted in the early eighties, 1,4-dichlorobenzene was detected in 100% of 46 composite human adipose tissue samples at levels ranging from 12 – 500 µg/kg [1]. In a sample of 3617 participants who took part in the USA's National Health and Nutrition Examination Survey (NHANES) 2007-2010, the geometric mean (GM) creatinine-corrected concentration of urinary 2,5-dichlorophenol was 7.03 µg/L (95% CI 6.04 to 8.19) [13]. For female participants 20 years of age or older (N=4459) who participated in NHANES (2003-2016), the weighted GM urinary concentration of 2,5-dichlorophenol was 5.92 µg/g creatinine with a range of 5.54 – 6.32) [10]. The 95th-percentile concentration of 1,4-dichlorobenzene in whole blood for the US general population was 1.07 µg/L, based on a sample of 3,172 individuals that took part in the 2013-2014 NHANES survey [2].

In a study conducted in 5 different regions in Canada, 100% of 210 breast milk samples contained detectable levels of 1,3- and 1,4-dichlorobenzene together [1]. Mean and maximum milk concentrations of 1,4-dichlorobenzene were 6 and 75 µg/L, respectively and mean and maximum concentrations in milkfat were 161 and 4,180 µg/kg, respectively [1].

In Japan 99% of 119 urine samples from adults in Osaka tested positive for the presence of 2,5-dichlorophenol [9].

In Slovenia and former Yugoslavia in early eighties, concentrations 1,4-dichlorobenzene in breast milk samples was 640 µg/kg [1]. Studies on the prevalence of detectable levels of 1,4-dichlorobenzene or its

metabolites among the European general population are generally scarce; as are studies on personal exposure levels.

Table 6 gives an overview of studies that have reported exposure estimates for the general population based on environmental monitoring.

Table 6 General population exposure to 1,4-dichlorobenzene based on biological monitoring.

Country	Exposure details	Exposure estimates	Reference
Breast milk 1,4-dichlorobenzene			
Slovenia, former Yugoslavia	Breast milk Milkfat	Mean - 25 µg/kg Mean: 640 µg/kg	Jan 1983 as quoted in ATSDR 2006 [1]
Canada	210 breast milk samples from 5 regions	100% of samples had detectable levels of 1,3- and 1,4-dichlorobenzene. Mean - 6 µg/L Max - 75 µg/L	Mes et al. (1986) as quoted in ATSDR 2006 [1]
Canada	210 milkfat samples from 5 regions	Mean - 161 µg /kg Max - 4,180 µg /kg	Mes et al. (1986) as quoted in ATSDR 2006 [1]
Urine 2,5-dichlorophenol			
USA	Urine of 1000 adults	98% of urine samples had detectable levels of 2,5-dichlorophenol.	Hsaio et al. (2009) [9]
USA	NHANES (2007-2010)	2,5-dichlorophenol: GM - 7.03 µg/L (95% CI 6.04 to 8.19)	Rooney et al. (2019) [13]
	NHANES (2003-2016)	2,5-dichlorophenol: GM 5.92 µg/g creatinine with a range of 5.54 - 6.32	Pridgen et al. (2023) [10]
Japan	Urine of adults in Osaka. N=119 urine samples	99% of urine samples had detectable levels of 2,5-dichlorophenol.	Hsaio et al. (2009) [9]
Blood 1,4-dichlorobenzene			
USA	NHANES (2013-2014) Whole blood. US general population. N = 3172 participants	95th-percentile concentration: 1.07 µg/L	CDC 2018 as quoted in RoC 2021 [11]
USA	NHANES III, N = 1100	Median: 0.33 µg/L	Buckley et al. (1997) as quoted in ATSDR 2006 [1]

Country	Exposure details	Exposure estimates	Reference
USA	Non-occupationally exposure individuals. N = 1037	Median: 0.33 µg/L Mean: 1.9 µg/L	Ashley et al. (1994, 1996) as quoted in ATSDR 2006 [1]
USA	Adults. N = 1000	Range: ≤49 µg/L Median: 0.33 µg/L Mean: 2.1 µg/L	Hill et al. (1995) as quoted in ATSDR 2006 [1]
Alaska, USA	N = 48	Range: <LOD – 7.10 µg/L Median: 0.02 – 0.04 µg/L	Backer et al. (1997) as quoted in ATSDR 2006 [1]
British Columbia, Canada	N = 25	Range: ≤14.29 µg/L Median: < 3.12 µg/L	Mes 1992 as quoted in ATSDR 2006 [1]

N – number of samples; LOD – Limit of Detection; NHANES – National Health and Nutrition Examination Survey

5.4 Occupational exposure

Occupational exposure to 1,4 dichlorobenzene occurs during its manufacture, during its conversion to polyphenylene sulphide, and during other industrial uses [11]. This includes the use of products that may contain 1,4 dichlorobenzene such as fillers, putties, plasters, modelling clay, metal surface treatment products, non-metal-surface treatment products and heat transfer fluids [7]. Exposure has also been associated with the use of photocopier operators with personal exposure levels ranging from 0.1 to 3.7 µg/m³ in the personal breathing zone of operators in photocopy centres [1].

Inhalation is the primary exposure route in occupational settings [14] but exposure by dermal and ocular contact is also possible [8]. In occupational exposure assessment studies concentrations of 2,5-dichlorophenol in urine, which is well correlated with 1,4-dichlorobenzene concentrations in air, have been measured [9].

Workers in manufacturing facilities, janitors and cleaners, mortuary employees and workers in pest control are likely to be exposed [8]. Workers from manufacturing facilities have relatively high exposure with concentrations in workplace air ranging from 32.5 to 4352 mg/m³ (IARC 1982 as quoted in ATSDR 2006) [1].

Data on occupational exposure to 1,4-dichlorobenzene is generally limited and exposure data collected in Europe were not identified.

6 Manufacture and uses

Manufacture

1,4-Dichlorobenzene is registered under the REACH Regulation and manufactured in/or imported to the European Economic Area at a total tonnage of $\geq 10,000$ tonnes⁷.

The manufacture of 1,4-dichlorobenzene involves the fluid phase chlorination of benzene in the presence of a catalyst, typically ferric chloride, aluminium chloride, or stannous tetrachloride, at temperatures ranging from 20 to 80°C. By adjusting the temperature and the molar ratio of benzene to chlorine, the yield of chlorinated products can be controlled [3].

A batch process using two moles of chlorine per mole of benzene, in the presence of ferric chloride and sulfur monochloride, can yield up to 98% dichlorobenzene [11]. The process produces a mixture of chlorobenzene isomers, primarily 1,2- and 1,4-dichlorobenzene, with smaller amounts of 1,3-dichlorobenzene and higher chlorinated benzenes. The exact ratio of 1,2- to 1,4-dichlorobenzene depends on the catalyst used. The resulting dichlorobenzene mixture is purified through distillation and fractional crystallization, producing 1,4-dichlorobenzene with less than 0.5% of 1,2- and 1,3-dichlorobenzene and less than 0.1% of monochlorobenzene and trichlorobenzene [3].

Uses

1,4-Dichlorobenzene is used by consumers in air care products, in articles, by professional workers (widespread use), in formulation or re-packing, and at industrial sites and in manufacturing .

1,4-Dichlorobenzene is widely used as an insecticide and fumigant, as well as a key ingredient in various products such as pharmaceuticals, polyphenylene sulphide (PPS) resin, and dyes. Its primary applications include use as air freshener, space deodorant for toilets, and refuse containers [1].

⁷ Registration dossier - ECHA

7 (Toxico)kinetics

7.1 Summary

This summary of the toxicokinetics of 1,4-dichlorobenzene is based on chapter 3.4 of the ATSDR report published in 2006 [1].

Briefly,

- *Absorption:* The absorption of 1,4-dichlorobenzene is quick and nearly complete when inhaled or ingested. Although specific data on absorption through the skin are lacking, it is thought to be minimal based on the very high dermal LD₅₀ (>6 g/kg bw) observed in rats and the absence of systemic effects in humans who handled solid 1,4-dichlorobenzene.
- *Distribution:* 1,4-Dichlorobenzene is distributed throughout the body but tends to accumulate most in fat, liver, and kidneys.
- *Metabolism:* The metabolism of 1,4-dichlorobenzene starts with oxidation to an epoxide, followed by conversion to 2,5-dichlorophenol. It undergoes extensive phase II metabolism, with the resulting metabolites mainly excreted as sulphate, glucuronide, or mercapturic acid conjugates.
- *Excretion:* 1,4-Dichlorobenzene is primarily eliminated through urine, mostly in the form of 2,5-dichlorophenol conjugates.

7.2 Human data

The information in this paragraph is based on chapter 3.4 of the ATSDR report published in 2006. The references shown can be found in the original ATSDR report [1].

7.2.1 Absorption

Inhalation: Quantitative data on the absorption of 1,4-dichlorobenzene in humans following inhalation exposure are lacking.

Oral: There are no quantitative data available on how much 1,4-dichlorobenzene is absorbed in humans after oral exposure.

Dermal: No studies have specifically investigated the rate or extent of 1,4-dichlorobenzene absorption through the skin in humans or animals. When solid 1,4-dichlorobenzene is held against the skin for a prolonged period, it can cause a burning sensation but does not lead to irritation or systemic effects (Hollingsworth et al. 1956).

However, the presence of 1,4-dichlorobenzene in human tissues, such as blood (Bristol et al. 1982; Hill et al. 1995), urine (Ghittori et al. 1985; Hill et al. 1995; Pagnotto and Walkley 1965), adipose tissue (Jan 1983), and breast milk (Jan 1983), provides evidence that absorption does occur. While these studies do not quantify the rate or amount of 1,4-dichlorobenzene absorbed or clarify the specific route of exposure, they do demonstrate that 1,4-dichlorobenzene is indeed taken up by the human body.

7.2.2 *Distribution*

There are no quantitative data on the distribution of 1,4-dichlorobenzene in humans. However, 1,4-dichlorobenzene has been detected in human blood (Bristol et al. 1982; Hill et al. 1995), urine (Hill et al. 1995; Ghittori et al. 1985; Pagnotto and Walkley 1965), adipose tissue (Jan 1983), and breast milk (Jan 1983), indicating that 1,4-dichlorobenzene is distributed to at least these tissues and matrices.

7.2.3 *Metabolism*

The metabolism of 1,4-dichlorobenzene follows similar steps to those of other dichlorobenzene isomers. The process begins with cytochrome P-450 (CYP) enzymes, mainly CYP2E1, oxidizing 1,4-dichlorobenzene to an epoxide, which is then further converted to 2,5-dichlorophenol. This compound can either undergo further oxidation to form dichlorocatechols or dichlorohydroquinone, or it can be conjugated through several phase II metabolic pathways. Evidence for this CYP-mediated oxidation and subsequent conjugation comes from studies using human microsomes and cell lines expressing CYP enzymes. In one case, urine analysis of a 3-year-old boy who had been exposed to 1,4-dichlorobenzene revealed the presence of 2,5-dichlorophenol and four other unidentified phenols, which were found to be conjugated with glucuronic and sulfuric acids (Hallowell 1959).

7.2.4 *Elimination*

Quantitative data on the elimination of 1,4-dichlorobenzene in humans are not available. However, the presence of 1,4-dichlorobenzene metabolites in the urine of exposed individuals (Ghittori et al. 1985; Hill et al. 1995; Pagnotto and Walkley 1965) confirms that 1,4-dichlorobenzene is eliminated through the urinary system in humans.

A study on workers exposed to dichlorobenzenes, mainly 1,4-dichlorobenzene, found that urinary excretion of the major metabolite, 2,5-dichlorophenol, began soon after exposure, peaking at the end of the exposure period. Air concentrations of dichlorobenzene ranged from 8 to 49 ppm, with urinary dichlorophenol levels between 10 and 233 mg/l. The excretion pattern was biphasic, with a rapid initial decrease followed by a slower decline in urinary metabolites over several days (Pagnotto and Walkley, 1965). Another study by Hill et al. (1995) in 1,000 adults found a strong correlation between mainly 1,4-dichlorobenzene levels in the blood and urinary p-dichlorophenol concentration.

7.3 **Animal data**

The information in this paragraph is based on chapter 3.4 of the ATSDR report published in 2006. The references shown can be found in the original ATSDR report [1].

7.3.1 *Absorption*

Inhalation: Studies providing quantitative data on the rate or extent of 1,4-dichlorobenzene absorption through inhalation in animals are not available. However, evidence of systemic toxicity from inhalation exposure suggests that 1,4-dichlorobenzene is absorbed. Additional evidence comes from studies detecting the compound or its metabolites

in various peripheral tissues after inhalation exposure. In one study, rats exposed to radiolabelled 1,4-dichlorobenzene through single or multiple 3-hour inhalation sessions showed the label in all tested tissues (liver, kidneys, lungs, muscle, fat, and blood plasma), indicating significant absorption (Hawkins et al. 1980). The amount of label in tissues did not increase significantly with additional exposures beyond the first. Similarly, in another study, a single 24-hour inhalation exposure in rats resulted in a rapid increase in 1,4-dichlorobenzene levels in the liver, kidneys, fat, and blood within the first 6 hours, followed by a slower rise for the remainder of the exposure period as the levels began to equilibrate between the body and blood (Umemura et al. 1998). This suggests an initial rapid absorption, followed by a slower absorption phase.

Oral: Evidence of 1,4-dichlorobenzene absorption in animals comes from studies showing toxicity after oral exposure and the presence of 1,4-dichlorobenzene or its metabolites in peripheral tissues. These latter studies suggest that 1,4-dichlorobenzene is absorbed rapidly and nearly completely. For example, in rats exposed to radiolabelled 1,4-dichlorobenzene, the label was found in all major tissues (liver, kidneys, lungs, muscle, fat, and blood plasma), indicating significant absorption (Hawkins et al. 1980). The amount of label in tissues did not significantly increase with additional exposures beyond the first. Further evidence includes data showing that 70–85% of a single dose of radiolabelled 1,4-dichlorobenzene was eliminated in the urine within 72 hours (Hissink et al. 1996b), suggesting extensive absorption. However, another study reported that approximately 41% of the labelled dose was recovered in the urine after 72 hours (Klos and Dekant 1994).

Dermal: There are no studies that specifically investigate how much or how quickly 1,4-dichlorobenzene is absorbed through the skin in animals. In toxicity studies involving Sherman rats, the dermal LD₅₀ for 1,4-dichlorobenzene was found to be over 6,000 mg/kg bw for both genders (Gaines and Linder 1986), suggesting that dermal exposure to 1,4-dichlorobenzene has low systemic toxicity and is not significantly absorbed through the skin in animals.

7.3.2 *Distribution*

Animal studies demonstrate that once absorbed, 1,4-dichlorobenzene is rapidly distributed throughout the body. 1,4-Dichlorobenzene accumulates primarily in adipose tissues but is not retained long-term. Studies show very little of the compound remains in tissues 72 hours after exposure, indicating quick clearance (Hissink et al. 1996b; Klos and Dekant 1994; Umemura et al. 1998).

Following a 24-hour inhalation exposure, serum levels of 1,4-dichlorobenzene rise quickly within the first six hours and then gradually increase over the next 18 hours before decreasing sharply (Umemura et al. 1990). Fat tissues consistently exhibit the highest concentrations of 1,4-dichlorobenzene, with liver and kidney levels being significantly lower.

Similar distribution patterns are observed with oral exposures, with the highest concentrations of radiolabelled 1,4-dichlorobenzene found in fat

tissues, followed by kidneys, liver, blood plasma, lungs, and muscle (Hawkins et al. 1980). Post oral dosing, radiolabel increases in the blood are observed for the first 8–10 hours, followed by a steady decline over the next 40 hours (Hissink et al. 1997a). Additionally, unique sulphur-containing metabolites of 1,4-dichlorobenzene, specifically 2,5-dichlorophenyl methyl sulfoxide, and 2,5-dichlorophenyl methyl sulfone, were identified in various tissues including blood, urine, fat, liver, and kidneys shortly after exposure (Kimura et al. 1979).

7.3.3 *Metabolism*

In F344 rats treated with 1,4-dichlorobenzene, the primary metabolic reaction involves CYP-dependent oxidation to 2,5-dichlorophenol. This metabolite is mainly conjugated to sulphate or glucuronic acid and then excreted in the urine, along with mercapturic acids (Hissink et al. 1996b; Klos and Dekant 1994). After oral exposure in male Wistar rats, significant metabolites identified in the urine included 2,5-dichlorophenyl methyl sulfoxide (M1) and methyl sulfone (M2), with M2 showing higher and more persistent levels in the blood (Kimura et al. 1979).

Further studies with male Wistar rats exposed to varying doses of 1,4-dichlorobenzene (up to 250 mg/kg bw) showed about 90% of it metabolized to 2,5-dichlorophenol, appearing in the urine as sulphates (50-60%), glucuronides (20-30%), and free forms (5-10%), with the major bile metabolite being glucuronide of 2,5-dichlorophenol (Hissink et al. 1997a). In Chinchilla rabbits, a high percentage of 2,5-dichlorophenol was also excreted in the urine as glucuronic or sulfuric acid conjugates (Azouz et al. 1955), and these sulphur metabolites were found to induce cytochrome P450 activity (Kimura et al. 1983).

7.3.4 *Elimination*

Animal studies on the elimination of 1,4-dichlorobenzene show that the compound is primarily excreted through the urine as metabolites, with minimal presence of the unchanged parent compound. In experiments involving male Wistar rats given single oral doses ranging from 10 to 250 mg/kg bw of ¹⁴C-labeled 1,4-dichlorobenzene, the urine primarily contained sulphate (60%) and glucuronide (30%) conjugates, while bile excretion was dose-dependent, with more being excreted at higher doses (Hissink et al. 1996b; Hissink et al. 1997a). Notably, the majority of the administered dose was recovered in the urine (75-85%), with only a small fraction found in the faeces (2-5%).

In a similar study on F344 rats given a high single dose of 900 mg/kg bw of ¹⁴C-1,4-dichlorobenzene, the peak excretion in urine occurred between 24 and 36 hours post-dosing, with 41.3% of the dose recovered from urine and only 3.6% from faeces in both males and females (Klos and Dekant 1994). Following both oral and inhalation exposures, levels of 1,4-dichlorobenzene and its metabolites in the liver, kidneys, fat, and plasma decreased only slightly during the first 8 hours but then declined rapidly, becoming nearly undetectable by 120 hours post the final exposure (Hawkins et al. 1980). Overall, 97% of the radiolabelled compound was eliminated via the urine, with negligible amounts released through expired air, accounting for less than 1% of the total (Hawkins et al. 1980).

8 Toxicity on reproduction

8.1 **Adverse effect on sexual function and fertility**

Human data are not available. The studies of 1,4-dichlorobenzene in experimental animals, i.e. mating studies and repeated dose/inhalation studies, are summarized in table 7 followed by a summary in text. These include studies in rats, mice, guinea pigs, monkey and rabbits upon inhalation, oral, subcutaneous and intraperitoneal exposure. In general, only statistically significant results are presented in the table below. Regarding the repeated dose/inhalation studies, only the studies in which reproductive organs were examined are described in this summary. In addition, two in vitro (receptor binding) studies with 1,4-dichlorobenzene are available and summarized in table 8.

8.1.1 *Human data*

Human data regarding adverse effects on fertility and sexual function were not available for 1,4-dichlorobenzene.

8.1.2 Animal data

Table 7 Reproductive toxicity studies on 1,4-dichlorobenzene – animal data

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
<i>Inhalation – rats</i>						
Hollingsworth et al. (1956) [15]	Rats, strain not specified, male and female 96 and 158 ppm: n=10/sex 173 ppm: n=5/sex 341 ppm: n=20 males 798 ppm: n=19 males, 15 females	Repeated inhalation study <i>Exposure:</i> 7h/day, 5d/week (except highest concentration: 8h/day, 5d/week) 96 ppm: exposure during 6-7 months 158 ppm: exposure during 157-219 days 173 ppm: exposure during 16 days 341 ppm: exposure during 6 months 798 ppm: male rats exposed during 1-46 days, females during 9-69 days	1,4-dichlorobenzene (>99% purity) Inhalation, whole body 0, 96, 158, 173, 341, 798 ppm (0.58, 0.95, 1.04, 2.05, 4.8 mg/L) (average analytical concentrations) Control: not described	96 ppm: average kidney weight increased in males (+9.4%, p<0.05) 158 ppm: increased average kidney weight (males: +12.5%, p<0.008, females: +8.0%, p<0.05) and liver weight (males: +9.8%, p<0.008, females: +12.0%, p<0.008), slight changes in liver (cloudy swelling) or granular degeneration of questionable significance in the parenchymal cells in the central zones 173 ppm: increased average kidney weight (males: +15.2%, p<0.05, females: +20.5%, p<0.008) and liver weight (males: +26.6%, p<0.008), females: +18.8%, p<0.008), slight changes in lungs (slight interstitial oedema, congestion, alveolar haemorrhage) of males and slight congestion and	No significant changes in testes weight in males at either concentration. Effects on other reproductive toxicity endpoints not described or not studied	Non-guideline, non-GLP Where table in the report showed "p≥0.05", it was assumed "p<0.05" was meant Also oral effects and occupational exposure studied, but not included in this report, because no reproductive or developmental toxicity endpoints were described or investigated

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Examinations:</i> Final body and organ weight, gross pathology, histopathology (incl. testes) <i>Statistical analysis:</i> Fisher <i>t</i>-test		granular degeneration in central areas of liver of females <i>341 ppm:</i> slight increase in average liver and kidney weight in males (data not shown) <i>798 ppm:</i> 4 rats died during exposure period, an undefined number of animals were moribund when killed, tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness were observed, slight to moderate changes in liver (cloudy swelling and central necrosis), slight cloudy swelling of tubular epithelium of kidneys in females		
Riley et al. (1980) [16]	Wistar rats, male and female n=75-79 sex/concentration)	Repeated inhalation toxicity study <i>Exposure:</i> 5h/day, 5 days/week for 76 weeks Recovery phase until either 80% mortality or 2 years after the start of the experiment	1,4-dichlorobenzene (>99.8% purity) Inhalation, whole body 0, 75 or 500 ppm (analytical concentrations:	<i>500 ppm:</i> increased liver weight (+10.0%, $p<0.05$) and increased kidney weight (+20.8%, $p<0.01$) in females, increased heart weight (males: +15.1%, $p<0.05$, females: +16.7%, $p<0.01$) and lung weight (males: +16.6%, $p<0.05$, females: +18.5%, $p<0.01$), decreased brain weight in males (-3.4%, $p<0.01$)	No effects on reproductive organs observed at any concentration level	According to GLP; non guideline Study mainly focuses on the carcinogenic effects of 1,4-dichlorobenzene, tumour incidences not

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		Interim kills: 5 rats/group/sex sacrificed and autopsied at week 26, 52 and 76. <i>Examinations:</i> clinical signs, bw, food and water consumption, clinical chemistry, haematology, organ weight (incl. gonads), pathology (incl. epididymis, prostate, seminal vesicles, testes, cervix, uterus, ovaries), residue analysis in fat, liver, plasma and urine <i>Statistical analysis:</i> Student's <i>t</i>-test (two-sided)	0, 75, 490-499 ppm, corresponding to 0, 0.45 or 2.95-3.00 mg/L)^a Control: clean air			included in this literature overview
Tyl and Neeper-Bradley (1989) [17]	Sprague-Dawley rats, male and female	Two-generation reproductive toxicity study <i>Exposure:</i> F0-generation: 6h/day, 7 days/ week	1,4-dichlorobenzene (100% purity) Inhalation, whole-body	F0-generation: 50 ppm: increased relative kidney (+11.4%, p<0.01) and relative liver weight (+4.8%, p<0.05) in males, microscopic pathology observations in kidneys of males	No effects on reproductive parameters observed See table 9 for adverse effects on development	According to GLP; non-guideline Large discrepancy between target

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
	n=28/sex/concentration (F0 and F1)	for 10 weeks prior to mating, during mating, during gestation until GD 19. Exposure continued from PND5 until sacrifice at weaning. Mothers were separated from their pups for the exposure period. Males sacrificed after successful mating. F1-generation (parents): 6h/day, 7 days/ week for 11 weeks prior to mating, during mating, during gestation until GD 19. Exposure continued from PND 5 until sacrifice at weaning. Mothers were separated from their pups for the exposure period. Males sacrificed after successful mating. <i>Examinations:</i> body weight, food consumption, clinical	0, 50, 150 and 450 ppm (analytical concentrations: 0, 66.3, 211.0, 538.0 ppm, corresponding to 0.398, 1.27, 3.23 mg/L)^a Control: filtered compressed air	<i>150 ppm:</i> increased relative liver weight (males +13.9%, $p<0.01$, females: +9.4%, $p<0.05$) and increased relative kidney weight in males (+19.4%, $p<0.01$), microscopic pathology observations in kidney of males, gestational BW of females decreased at GD20 (-4.7%, $p<0.05$) <i>450 ppm:</i> toxic clinical observations in males and females (tremor, unkempt body, urine stains, periocular encrustation, salivation, perioral encrustation, fur wetness, $p<0.01$), decreased male BW in multiple pre-mating and mating weeks (ranging from -7.0% to -15.3%, $p<0.01$), decreased female BW in pre-mating week 2 (-2.79%, $p<0.01$), decreased male BW gain after multiple pre-mating weeks (ranging from -9.5% to -276.8%, $p<0.01$), increased male BW gain in week 13-14 (during mating period) (+228.1%, $p<0.01$) and week 15-16 (+61.4%, $p<0.01$),		and analytical concentration was noted. Condensation may have occurred.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		signs, gross and microscopic pathology, reproductive parameters and indices, litter size, sex ratio, pup bw, pup and litter viability. <i>Statistical analysis:</i> Levene's test for equal variances, ANOVA and t-tests for the quantitative continuous variables, Kruskal-Wallis test, Mann-Whitney U test and Fisher's exact test for nonparametric data.		decreased female BW gain in pre-mating week 0-1 (-3250.0%, $p < 0.01$) and pre-mating week 6-7 (-35.3%, $p < 0.05$), decreased female BW at GD20 (-6.4%, $p < 0.01$), decreased female BW gain GD0-20 (-12.3%), increased female lactational BW gain at LD14-21 (+112.4%, $p < 0.01$) and LD0-28 (+210.9%, $p < 0.01$), decreased food consumption in week 0-1 (males: -23.7%, females: -24.4%, $p < 0.01$) and increased food consumption week 2-3 in females (+9.9%, $p < 0.05$), increased relative liver (males: +52.1%, $p < 0.01$, females: +31.0%, $p < 0.01$) and relative kidney (males: +43.7% $p < 0.01$, females: +11.4%, $p < 0.01$) weight and relative brain (+11.3%, $p < 0.01$) and testes (+10.1%, $p < 0.01$) weight in males, microscopic pathology observations in male kidneys F1-generation (parents): 50 ppm: increased relative kidney weight in males (+11.7%, $p < 0.01$)		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				<i>150 ppm</i>: increased relative kidney (+16.5%, $p<0.01$) and relative liver (+6.7%, $p<0.05$) weight in males, decreased male BW gain during week 1-2 (-15.6%, $p<0.01$) and increased male BW gain during week 7-8 (+45.1%, $p<0.01$) and week 10 to 11 (+60.2%, $p<0.01$), increased female lactational BW gain LD21-28 (+26.0%, $p<0.01$) and LD0-28 (+91.8%, $p<0.01$), increased male food consumption in week 7-8 (+6.3%, $p<0.05$) and increased female food consumption in week 8-9 (+14.0%, $p<0.05$) <i>450 ppm</i>: decreased male BW in multiple pre-mating and mating weeks (ranging from -15.0% to -22.5%, $p<0.01$), decreased male BW gain after multiple pre-mating weeks (ranging from -212.2%, $p<0.01$ to -19.5%, $p<0.05$), reduced female BW during multiple pre-mating weeks (ranging from -15.5% to -10.1%, $p<0.01$), reduced female BW gain during pre-mating week 6-7 (-33.6%, $p<0.01$), gestational BW of females decreased at day 0, 7, 13 and 20 (-		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				11.6%, -10.5%, -9.8% and -9.8%, resp., $p < 0.01$), reduced female lactational BW LD0 (-10.6%, $p < 0.01$) LD4 (-7.8%, $p < 0.05$), LD7 (-7.9%, $p < 0.05$), increased female lactational BW gain LD0-28 (+172%, $p < 0.01$), reduced food consumption occasionally during premating and mating in males (ranging from -26.3% to -8.1%, $p < 0.01$) and in females during week 0-1 (-19.7%, $p < 0.01$), increased food consumption in females during week 4-5 (+21.2%, $p < 0.01$) and 8-9 (+15.8%, $p < 0.01$), toxic clinical observations in males and females ($p < 0.01$), increased relative liver weight (males: +43.7%, $p < 0.01$, females: +19.6%, $p < 0.01$), increased relative kidney (+48.0%, $p < 0.01$), brain (+20.1%, $p < 0.01$) and testes (+18.8%, $p < 0.01$) weight in males, microscopic pathology observations in liver		
Japan Bioassay Research Center	F344 rats, male and female	Repeated inhalation study	1,4-dichlorobenzene (>99.9% purity)	600 ppm: decreased BW gain after week 1 in males (-5.8%, $p < 0.05$), decreased food consumption after	A dilated lumen of the uterus in single females of the 120 and 400 ppm groups was observed	Non-guideline, probably according to GLP based on

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
(1995) [18] [19]	n=10/sex/concentration	<i>Exposure:</i> 6h/day, 5 days/week, 2 weeks <i>Examinations:</i> clinical signs, body weight, food consumption, haematology, biochemistry, gross and histopathology (description of which organs were examined is limited) <i>Statistical analysis:</i> not described	Inhalation, whole body 0, 120, 180, 270, 400, 600 ppm (analytical concentrations: 0, 119.3, 182.0, 274.4, 403.8, 597.4 ppm, corresponding to 0, 0.72, 1.1, 1.6 2.4, 3.6 mg/L)^a Control: clean air	week 1 in males (-14.9%, p<0.01) and females (-5.7%, p<0.05)		the other Japan Bioassay Research Center (1996) [20]/Aiso et al. (2005) studies [21] Study report not available, summary based on tables only[22]
Japan Bioassay Research Center (1995) [18] [23]/ Aiso et al. (2005) [21]	F344 rat, male and female n=10/sex/concentration	Repeated inhalation study <i>Exposure:</i> 6h/day, 5 days/week, 13 weeks <i>Examinations:</i> clinical signs, body weight, food consumption, haematology, blood chemistry, urinalysis,	1,4-dichlorobenzene (>99.9% purity) Inhalation, whole body 0, 25, 55, 120, 270, 600 ppm (analytical	<i>55 ppm:</i> increased absolute liver weight in females (+10.5%, p<0.01), changes in food consumption in females (+9.5%, p<0.01) <i>120 ppm:</i> increased absolute and relative liver weight in males (+10.0% and +6.9% resp., p<0.05), decreased RBC count and hematocrit (-2.0% and -2.5%,	No effects on reproductive organs observed	According to OECD TG 413 and GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		histopathology, organ weight and gross findings (description of which organs were examined is limited) <i>Statistical analysis:</i> Bartlett's test, one-way ANOVA, Kruskal-Wallis rank sum test, Dunnett's multiple comparison test, two-sided analysis, Chi-square test	concentrations: 0, 27.4, 54.4, 120.0, 267.4, 601.5 ppm, corresponding to 0.16, 0.33, 0.72, 1.6, 3.6 mg/L)^a Control: clean air	p<0.05) and hemoglobin (-2.5%, p<0.01) in males. 270 ppm: increased absolute and relative kidney weight in males (+15.4% and +9.6% resp., p<0.01), increased absolute and relative liver weight in males (+21.3% and +15.3% resp., p<0.01) and females (+9.0%, p<0.05 and +7.5%, p<0.01, resp.), increased absolute brain weight in males (+3.0%, p<0.05), increased male kidney hyaline droplets (5/10 moderate^b 5/10 marked, p<0.01), eosinophilic body (5/10 moderate 5/10 marked, 0>0.01), granular casts (9/10 slight 1/10 moderate, p<0.01), proximal tubular cell necrosis (9/10 slight 1/10 moderate, p<0.01) and cytoplasmic basophilia (9/10 moderate 1/10 marked, p<0.01), changes in food consumption in males week 12 (+10.2%, p<0.05), decreased RBC count, hemoglobin and hematocrit in males (-5.24%, -5.0% and -5.3%, p<0.01)		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				600 ppm: decreased BW gain in week 1 in males (-5.1%, $p < 0.05$), changes in food consumption in males in week 1 (-12.2%, $p < 0.01$), week 9 (+13.5%, $p < 0.01$), week 11 (+9.4%, $p < 0.01$), week 12 (+10.2%, $p < 0.01$), week 13 (+12.2%, $p < 0.01$) and females in week 1 (-11.2%, $p < 0.01$), week 6 (+10.5%, $p < 0.01$), week 9 (+8.8%, $p < 0.05$), week 12 (+9.1%, $p < 0.01$), increased absolute and relative kidney weight in males (+57.5% and +55.8% resp., $p < 0.01$) and females (+18.2% and +15.1% resp., $p < 0.01$), increased absolute and relative liver weight in males (+44.9% and +43.4% resp., $p < 0.01$) and females (+32.7% and +27.9% resp., $p < 0.01$), increased absolute and relative spleen weight in males (+11.5% and +10.3% resp., $p < 0.01$), decreased relative thymus weight in males (-11.4%, $p < 0.05$), increased hepatocellular centrilobular hypertrophy in liver males (9/10, $p < 0.01$), increased male kidney hyaline droplets (1/10 slight 2/10 moderate 5/10 marked, $p < 0.01$), eosinophilic body (1/10		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				slight 4/10 moderate 5/10 marked, $p<0.01$), granular casts (1/10 slight 1/10 moderate 8/10 marked, $p<0.01$), mineralization of papilla (7/10 slight, $p<0.01$), proximal tubular cell necrosis (10/10 marked, $p<0.01$) and cytoplasmic basophilia (2/10 moderate 8/10 marked, $p<0.01$), decreased RBC count, hemoglobin, hematocrit, MCV, MCH and increased platelet in males (-7.2%, -9.3%, -9.1%, -2.0%, -2.9% and +18.1%, $p<0.01$) and decreased hemoglobin in females (-3.8%, $p<0.05$)		
Japan Bioassay Research Center (1995) [20]/ Aiso et al. (2005) [22]	F344 rats, male and female n=50/sex/concentration	Repeated inhalation study <i>Exposure:</i> 6h/day, 5 days/week, 104 weeks <i>Examinations:</i> Clinical signs, body weight, food consumption, urinalysis, blood chemistry and haematology, organ weight, gross and histopathology (incl. reproductive organs)	1,4-dichlorobenzene (>99.9% purity) Inhalation, whole body 0, 20, 75, 300 ppm (analytical concentrations: 0, 19.8, 74.8, 298.4 ppm, corresponding to 0.12, 0.45	<i>20 ppm:</i> sign. decreased total protein and increased total bilirubin, urea nitrogen, potassium in females (p-value not given) <i>75 ppm:</i> increased incidence of marked eosinophilic globules in olfactory epithelium in females (23/50 vs. 6/50 in control, sign. unknown), sign. difference in total amount of eosinophilic globules in olfactory epithelium in females (7/50 slight, 16/50 moderate, 23/50 marked vs. 22/50 slight,	No effects on reproductive organs observed	According to OECD TG 453 and GLP Study mainly focussed on carcinogenic effects, tumour incidences not considered in this summary

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Statistical analysis:</i> Chi-square test, Dunett's test, Kaplan-Meier method, log-rank test, Fisher's exact test, Peto test, Cochran-armitage linear trend test	and 1.79 mg/L) ^a Control: clean air	21/50 moderate, 6/50 marked in controls, $p < 0.01$) <i>300 ppm:</i> increased incidence of slight eosinophilic globules in respiratory epithelium of females (38/50 vs. 11/50 in control, $p < 0.01$), increased incidence of slight respiratory metaplasia in nasal gland in females (33/50 vs. 5/50 in control, $p < 0.01$), increased incidence of eosinophilic globules in olfactory epithelium in females (3/50 slight, 27/50 moderate, 20/50 marked vs. 22/50 slight, 21/50 moderate, 6/50 marked in control, $p < 0.01$), increased incidence of hepatocellular centrilobular hypertrophy in males (5/50 vs. 0/50 in control, $p < 0.05$), increased incidence of kidney mineralization in papilla (41/50 vs. 0/50 in control, $p < 0.01$), kidney urothelial hyperplasia in pelvis (32/50 vs. 7/50 in control, $p < 0.01$), increased absolute and relative liver weight in males (+15.0% and +18.6% resp., $p < 0.01$) and females (+15.1% and +19.5% resp., $p < 0.01$), increased		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				absolute and relative kidney weight in males (+19.6% and +24.1% resp., $p < 0.01$), MCV sign. decreased in males (p-value not given), total cholesterol, phospholipid, urea nitrogen, creatinine, calcium increased in males and total bilirubin, urea nitrogen, potassium sign. increased in females and total protein sign. decreased in females (p-value not given)		
<i>Inhalation - mice</i>						
Hollingsworth et al. (1956) [15]	Mice, strain not specified, male and female <i>96 ppm:</i> n=10 females <i>158 ppm:</i> n=10 males	Repeated inhalation study <i>Exposure:</i> 7h/day, 5d/week <i>96 ppm:</i> exposure during 6-7 months <i>158 ppm:</i> exposure during 157-219 days <i>Examinations:</i> Final body and organ weight, gross pathology, histopathology.	1,4-dichlorobenzene (>99% purity) Inhalation, whole body 0, 96, 158 ppm (0.58, 0.95 mg/L) (average analytical concentrations) Control: not described	No general toxicity observed	Effects on reproductive toxicity endpoints were not specifically described for this species (in contrast to rat and guinea pig) or not investigated.	Non-guideline, non-GLP Also oral effects and occupational exposure studied, but are not relevant for this report, because no reproductive or developmental toxicity endpoints were described or investigated

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		Statistical analysis: Fisher <i>t</i> -test				
Anderson and Hodge (1976) [24]	CD-1 mice, male n=20 exposed initially but 16 selected for study/concentration for the treatment group; 35 for negative control; 5-13 for positive controls)	Dominant lethal assay <i>Exposure</i> : 6h/day, for 5 days Treated males were mated during 5 days with untreated virgin females. This mating was repeated until the treated male mice had been mated at weekly intervals for 8 weeks with virgin females. Female mice killed 13 days after the assumed date of fertilisation (i.e. 15 or 16 days after caging females with males). Males were killed with no further examination. <i>Examinations</i> : Clinical signs, uteri examined for live implantations, early deaths and late deaths.	1,4-dichlorobenzene (purity unknown) Inhalation, whole-body 0, 75, 225, 450 ppm (target concentrations corresponding to 0, 0.45, 1.35, 2.71 mg/L) (analytical concentrations determined though not reported) Positive controls: cyclophosphamide (200 mg/kg bw, single ip injection), ethyl methanesulpho	75 ppm: one male died at week 3 of mating	75 ppm: decreased pregnancy frequency in week 6 (83.3% vs 95.7% in control, $p<0.05$) and week 7 (73.3% vs 90.0% in control, $p<0.05$), decreased average number of implants (11.5 vs 12.4 in control, $p<0.05$) in week 8 225 ppm: increased early deaths in week 1 (based on percentage of pregnant females with at least one early death: 75.9% vs. 50% in control, $p<0.05$) and in week 6 (based on mean percentage of early deaths per total implants per pregnancy: 10.3% vs. 5.3% in control, $p<0.05$) 450 ppm: decreased average number of implants (10.8 vs. 12.4 in control, $p<0.01$) in week 8	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Statistical analysis:</i> simple 2 X 2 Chi-square, a week by week hierarchical analysis of variance, Dunnett's t-test (one-sided)	nate (150 mg/kg bw/day, orally 1x/day for 5 days), nitrogen mustard (2.5 mg/kg bw/day single ip injection) Control: clean air		Appropriate results obtained for the positive controls	
Japan Bioassay Research Center (1995) [19] [18]	BDF1 mice, male and female n= 10/sex/concentration	Repeated inhalation study <i>Exposure:</i> 6h/day, 5 days/week, 2 weeks <i>Examinations:</i> clinical signs, body weight, food consumption, haematology, biochemistry, gross and histopathology <i>Statistical analysis:</i> not described	1,4-dichlorobenzene (>99.9% purity) Inhalation, whole body 0, 120, 180, 270, 400, 600 ppm (analytical concentrations: 0, 124.3, 181.2, 274.1, 406.7, 599.9 ppm, corresponding to 0, 0.75, 1.1,	<i>180 ppm:</i> decreased food consumption after week 1 in males (-9.8%, p<0.01) <i>270 ppm:</i> increased food consumption after week 2 in females (+12.9%, p<0.01), decreased food consumption after week 1 in males (-9.8%, p<0.01) <i>400ppm:</i> increased food consumption after week 2 in females (+12.9%, p<0.01) <i>600ppm:</i> decreased food consumption after week 1 (-12.2%, p<0.01) and increased after week 2 (+13.5%, p<0.01) in males,	No effects on reproductive organs observed	TG guideline unknown, but probably according to GLP based on the other Japan Bioassay Research Center (1996) [20, 23]/Aiso et al. (2005[21, 22]) studies No reproductive endpoints results included in the tables for female mice

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
			1.6, 2.4, 3.6 mg/L) ^a Control: clean air	increased food consumption after week 2 in females (+32.3%, p<0.01), enlarged liver in males (9/10) and females (10/10) (no p-value described)		Study report not available, summary based on tables only
Japan Bioassay Research Center (1995) [18, 23]/ Aiso et al. (2005) [21]	BDF1 mice, male and female n=10/sex/concentration	Repeated inhalation study <i>Exposure:</i> 6h/day, 5 days/week, 13 weeks <i>Examinations:</i> clinical signs, body weight, food consumption, haematology, biochemistry, urinalysis, organ weight, gross and histopathology (incl. reproductive organs)	1,4-dichlorobenzene (>99.9% purity) Inhalation, whole body 0, 25, 55, 120, 270, 600 ppm (analytical concentrations: 0, 24.6, 54.6, 119.4, 268.0, 597.3 ppm, corresponding to 0.15, 0.33, 0.72, 1.6, 3.6 mg/L) ^a Control: clean air	<i>25 ppm:</i> increased relative heart weight in males (+14.0%, p<0.01) and females (+7.8%, p<0.05), increased relative liver weight in males (+9.7%, p<0.05) <i>55 ppm:</i> decreased BW gain in week 6 in females (-5.6%, p<0.05), changes in food consumption in males in week 3 (-5.3%, p<0.05) and week 11 (-11.9%, p<0.01), increased relative heart weight in males (+11.6%, p<0.05), increased relative brain weight in males (+11.7%, p<0.05), increased relative liver weight in males (+9.7%, p<0.05) <i>120 ppm:</i> changes in food consumption in males in week 8 (-12.2%, p<0.01), increased relative liver weight in males (+10.1%, p<0.05)	<i>270 ppm:</i> increased relative testes weight (+16.0%, p<0.05)	According to OECD TG 413 and GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				270 ppm: increased relative liver weight in males (+23.9%, $p < 0.05$) and females (+ 10.6%, $p < 0.05$ and +8.1%, $p < 0.01$, resp.), increased relative heart weight in males (+13.1%, $p < 0.05$), increased relative brain weight in males (+12.1%, $p < 0.05$), increased relative kidney weight in males (+12.5%, $p < 0.01$), increased hepatocellular centrilobular hypertrophy in liver males (10/10, $p < 0.01$) 600ppm: increased female BW gain week 5 (+6.2%, $P < 0.01$), week 7 (+5.5%, $p < 0.05$), week 8 (+7.6%, $p < 0.01$), week 9 (+8.9%, $p < 0.01$), week 10 (+8.4%, $p < 0.01$), week 12 (+9.0%, $p < 0.01$) and week 13 (+6.3%, $p < 0.05$), changes in food consumption in males in week 2 (+8.3%, $p < 0.01$) and females in week 2 (+12.6%, $p < 0.01$), week 3 (+8.6%, $p < 0.05$), week 5 (+10.8, $p < 0.05$), week 8 (+10.0%, $p < 0.05$), week 10 (+9.8%, $p < 0.05$), week 13 (+9.5%, $p < 0.05$), increased absolute and relative liver weight in males		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				(+48.6% and +62.6% resp., $p < 0.01$) and females (+42.9% and +34.6% resp., $p < 0.01$), increased relative kidney weight in males (+12.1%, $p < 0.01$), increased absolute kidney weight in females (+10.8%, $p < 0.01$), increased relative brain weight in males (+11.8%, $p < 0.05$), increased hepatocellular centrilobular hypertrophy in liver males and females (both 10/10, $p < 0.01$), vacuolization of proximal tubule cells in kidney males (1/10, $p < 0.01$), increased MCH in females (+2.0%, $p < 0.05$), decreased amount of ketone bodies in males (8/10 no ketone bodies vs 2/10 in control, $p < 0.05$)		
Japan Bioassay Research Center (1995) [20]/ Aiso et al. (2005) [22]	BDF1 mice, male and female n=50/sex/concentration	Repeated inhalation study <i>Exposure:</i> 6h/day, 5 days/week, 104 weeks <i>Examinations:</i> Clinical signs, body weight, food consumption, urinalysis, blood chemistry and	1,4-dichlorobenzene (>99.9% purity) Inhalation, whole body 0, 20, 75, 300 ppm (analytical concentrations:	<i>75 ppm:</i> increased incidence in respiratory metaplasia in olfactory epithelium (38/50 vs. 23/50 in control, $p < 0.05$) and nasal gland (47/50 vs. 37/50 in control, $p < 0.01$) in males <i>300 ppm:</i> decreased body weight in males (-11.5%, $p < 0.01$), increased incidence of hepatocellular centrilobular	<i>20 ppm:</i> increased mineralization of testis (35/49 vs. 27/49 in control, sign. unknown). <i>75 ppm:</i> increased mineralization of testis (42/50 vs. 27/49 in control, sign. unknown).	According to OECD TG 453 and GLP Study mainly focussed on carcinogenic effects, tumour incidences not extensively

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		haematology, organ weight, gross and histopathology (incl reproductive organs) <i>Statistical analysis:</i> Chi-square test, Dunett's test, Kaplan-Meier method, log-rank test, Fisher's exact test, Peto test, Cochran-armitage linear trend test	0, 19.9, 74.8, 298.3 ppm, corresponding to 0.12, 0.45, 1.79 mg/L) ^a Control: clean air	hypertrophy in males (34/49 vs. 0/49 in control, $p < 0.01$), increased incidence of respiratory metaplasia of olfactory epithelium in females (20/50 vs. 7/50 in controls, $p < 0.01$), increased absolute and relative liver weight in males (+85.8% and +104.3 resp., $p < 0.01$) and females (+238.2% and +258.2% resp., $p < 0.01$), increased relative kidney weight in males (+16.0%, $p < 0.01$) and females (+18.7, $p < 0.01$), increased absolute kidney weight in females (+10.1%, $p < 0.05$), MCH and eosinophilic leukocyte ratio sign. decreased and platelet number sign. increased in females (p-value not given), total cholesterol, T-cholesterol, GOT, GPT, LDH, ALP activity sign. increased in males and T-protein, albumin, T-bilirubin, T-cholesterol, BUN, calcium, GOT, GPT, LDH, ALP activity sign. increased in females (p-value not given).	300 ppm: increased mineralization of testis (41/49 vs. 27/49 in control, sign. unknown).	considered in this summary
<i>Inhalation – other species</i>						
Hollingsworth et al. (1956)	Rabbits, strain not specified,	Repeated inhalation study	1,4-dichlorobenzene	173 ppm: slight changes in lungs (slight interstitial oedema,	Effects on reproductive toxicity endpoints were not specifically described for this	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
[15]	male and female 96 ppm: n=1/sex 158 ppm: n=1/sex 173 ppm: n=1/sex 798 ppm: n=8/sex	<i>Exposure:</i> 7h/day, 5d/week (except highest concentration: 8h/day, 5 d/week) 96 ppm: exposure during 6-7 months 158 ppm: exposure during 157-219 days 173 ppm: exposure during 16 days 798 ppm: males during 1-62 days, females during 2-62 days <i>Examinations:</i> Final body and organ weight, gross pathology, histopathology. <i>Statistical analysis:</i> Fisher <i>t</i> -test	e (>99% purity) Inhalation, whole body 0, 96, 158, 173, 798 ppm (analytical concentrations: 0, 0.5, 0.95, 1.04, 4.8 mg/L) Control: not described	congestion, alveolar haemorrhage) of females. 798 ppm: 4 animals died during exposure period, moribund when killed (number unknown), tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness, slight to moderate changes in liver (cloudy swelling and central necrosis), reversible nonspecific eye ground changes, slight congestion and emphysema in lungs of two animals	species (in contrast to rat and guinea pig) or not investigated.	Also oral effects and occupational exposure studied, but are not relevant for this report, because no reproductive or developmental toxicity endpoints were described or investigated
Hollingsworth et al. (1956) [15]	Guinea pig, strain not specified, male and female	Repeated inhalation study <i>Exposure:</i> 7h/day, 5d/week (except	1,4-dichlorobenzene (>99% purity)	96 ppm: average liver weight increased in female guinea-pigs (+9.1%, p=0.05)	No significant changes in testes weight in male animals were observed at either concentration. Effects on other reproductive	Non-guideline, non-GLP Also oral effects and

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
	<i>96 and 158 ppm:</i> n=8/sex <i>173 ppm:</i> n=5/sex <i>341 ppm</i> n=8/sex <i>798 ppm</i> n=16 males, 7 females	highest concentration: 8h/day, 5d/week) <i>96 ppm:</i> exposure during 6-7 months <i>158 ppm:</i> exposure during 157-219 days <i>173 ppm:</i> exposure during 16 days <i>341 ppm:</i> exposure during 6 months <i>798 ppm:</i> males exposed for 1-23 days, females for 11-20 days <i>Examinations:</i> Final body and organ weight, gross pathology, histopathology <i>Statistical analysis:</i> Fisher <i>t</i>-test	Inhalation, whole body 0, 96, 158, 173, 341, 798 ppm (analytical concentrations: 0, 0.58, 0.95, 1.04, 2.05, 4.8 mg/L) Control: not described	<i>158 ppm:</i> average liver weight increased in female guinea-pigs (+7.8%, $p<0.04$), decreased body weight (male: -10.6%, $p<0.04$, female: -9.5%, $p<0.04$) <i>173 ppm:</i> decreased average spleen weight in males (-31.6%, $p<0.04$), slight changes in lungs (slight interstitial oedema, congestion, alveolar haemorrhage) of females <i>341 ppm:</i> slight histologic changes in liver (cloudy swelling, fatty degeneration, focal necrosis, slight cirrhosis) of males <i>798 ppm:</i> 2 animals died during exposure period, moribund when killed (unknown number), tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness, slight to moderate changes in liver (cloudy swelling and central necrosis)	toxicity endpoints were not described or not investigated	occupational exposure studied, but are not relevant for this report, because no reproductive or developmental toxicity endpoints were described or investigated
Hollingsworth et al. (1956) [15]	Monkey, strain not specified, female	Repeated inhalation study	1,4-dichlorobenzene (>99% purity)	No general toxicity observed	Effects on reproductive toxicity endpoints were not specifically described (in	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
	n=1 female monkey/concentration	<i>Exposure:</i> 7h/day, 5d/week <i>96 ppm:</i> exposure during 6-7 months <i>158 ppm:</i> exposure during 157-219 days <i>Examinations:</i> Final body and organ weight, gross pathology, histopathology. <i>Statistical analysis:</i> Fisher <i>t</i>-test	Inhalation, whole body 0, 96, 158 ppm (analytical concentrations: 0, 0.58, 0.95 mg/L) Control: not described		contrast to rat and guinea pig) or not investigated.	Also oral effects and occupational exposure studied, but are not relevant for this report, because no reproductive or developmental toxicity endpoints were described or investigated
<i>Oral - rats</i>						
NTP (1987) [2] Study 1 of 2	F344/N rats, male and female n=10/sex/dose	Repeated dose toxicity study <i>Exposure:</i> once a day, 5 days per week for 13 weeks <i>Examinations:</i> body weight, organ weights, gross lesions and histopathological changes (incl. reproductive organs),	1,4-dichlorobenzene (>99% purity) Oral, gavage 0, 300, 600, 900, 1200 or 1500 mg/kg bw/day	<i>300 mg/kg bw/day:</i> decreased male BW gain (-12.8%, $p<0.05$), renal tubular cell degeneration in males, decreased hematocrit ($p<0.05$), hemoglobin, RBC, alkaline phosphatase, total protein and triglyceride ($p<0.01$) and increased reticulocytes and glucose ($p<0.01$) in males <i>600 mg/kg bw/day:</i> decreased male BW gain (-24.1%, $p<0.01$), renal tubular cell degeneration in	<i>300 mg/kg bw/day:</i> decreased uterus to brain weight ratio in females (-51.1%, $p<0.01$) <i>600 mg/kg bw/day:</i> decreased uterus to brain weight ratio in females (-56.5%, $p<0.01$) <i>900 mg/kg bw/day:</i> decreased uterus to brain	Non- guideline, according to GLP Due to high mortality in the high dose females, additional parameters were not examined in this group. This

Reference	Species	Experimental period and design	Dose/concent ration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		and blood and urine parameters <i>Statistical analysis:</i> Dunnett's test, Williams' test, Jonckheere's test	Control: corn oil only	males, lymphocytic perivascularitis in male lungs, increased kidney to brain weight ratio in males (+8.5%, $p<0.05$), decreased hematocrit, hemoglobin, RBC, alkaline phosphatase, total protein, triglyceride ($p<0.01$) and total bilirubin ($p<0.05$) and increased cholesterol and glucose ($p<0.01$) in males, decreased MCV in females ($p<0.01$) <i>900 mg/kg bw/day:</i> 1/10 males + 2/10 females died (vs. 1 male and no females in control), decreased male BW gain (-26.7%, $p<0.01$), renal tubular cell degeneration in males, lymphocytic perivascularitis in male lungs, increased liver to brain weight ratios in males and females (males: +19.4% ($p<0.01$); females: +21.3% ($p<0.01$)), increased kidney to brain weight ratio in males (+14.6%, $p<0.01$), decreased hemoglobin, MCV, RBC, alkaline phosphatase, triglyceride ($p<0.01$) and hematocrit, total bilirubin, total protein ($p<0.05$) and increased reticulocytes, cholesterol and blood urea nitrogen	weight ratio in females (-45.2%, $p<0.01$) <i>1200 mg/kg bw/day:</i> decreased uterus to brain weight ratio in females (-52.2%, $p<0.01$) <i>1500 mg/kg bw/day:</i> no effects on reproductive organs observed in males or in case of females not examined (due to high mortality)	also partly applies to high dose males.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				($p < 0.01$) in males, decreased MCV ($p < 0.01$) and reticulocytes ($p < 0.05$) and increased cholesterol ($p < 0.01$) and total protein ($p < 0.05$) in females. <i>1200 mg/kg bw/day</i>: 5/10 males + 1/10 females died (vs. 1 male in control), decreased male BW gain (-39.0%, $p < 0.01$), decreased female BW gain (-27.1%, $p < 0.01$), tremors, poor motor response, and ocular discharge in males, renal tubular cell degeneration in males, degeneration and necrosis of hepatocytes, hypoplasia of bone marrow, lymphoid depletion of spleen and thymus, epithelial necrosis and villar bridging of small intestinal mucosa, and epithelial necrosis of nasal turbinates, increased liver to brain weight ratios in males and females (males: +18.4% ($p < 0.01$); females: +27.3% ($p < 0.01$), increased kidney to brain weight ratio in males (+10.5%, $p < 0.05$), decreased spleen to brain weight ratio in females (-14.5%, $p < 0.01$), decreased hemoglobin, MCV,		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				alkaline phosphatase, triglyceride ($p < 0.01$) and hematocrit, RBC ($p < 0.05$) and increased cholesterol, urinary coproporphyrin, blood urine nitrogen ($p < 0.01$) and urinary uroporphyrin ($p < 0.05$) in males, decreased MCV ($p < 0.01$) and increased cholesterol, total bilirubin ($p < 0.01$) and alkaline phosphatase and urinary coproporphyrin ($p < 0.05$) in females <i>1500 mg/kg bw/day</i>: 8/10 males + 9/10 females died (vs. 1 male in control), decreased male BW gain (-51.3%, $p < 0.01$), tremors, poor motor response, and ocular discharge in both sexes, renal tubular cell degeneration in males, degeneration and necrosis of hepatocytes, hypoplasia of bone marrow, lymphoid depletion of spleen and thymus, epithelial necrosis and villar bridging of small intestinal mucosa, and epithelial necrosis of nasal turbinates, increased liver to brain weight ratios in males (+10.1%, $p < 0.05$), decreased thymus to brain weight		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				ratio in males (-47.0%, $p < 0.01$), decreased hematocrit, hemoglobin, RBC ($p < 0.01$) and MCV ($p < 0.05$) and increased urinary coproporphyrin ($p < 0.01$) and urinary uroporphyrin ($p < 0.05$) in males		
NTP 1987 [2] Study 2 of 2	F344/N rats, male and female n=10/sex/dose	Repeated dose toxicity study <i>Exposure:</i> once a day, 5 days per week for 13 weeks <i>Examinations:</i> body weight, organ weights, gross lesions and histopathological changes (incl. reproductive organs), and blood and urine parameters <i>Statistical analysis:</i> Dunnett's test, Williams' test, Jonckheere's test	1,4-dichlorobenzene (>99% purity) Oral, gavage 0, 37.5, 75, 150, 300 or 600 mg/kg bw/day Control: corn oil only	<i>600 mg/kg bw/day:</i> increased incidence and severity kidney cortical tubular degeneration in males (9/10 moderate vs. 7/10 mild in control)	No effects on reproductive organs observed	Non- guideline, according to GLP
NTP 1987 [2]	F344/N rats, male and female	Carcinogenicity study	1,4-dichlorobenzene	<i>150 mg/kg bw/day (males only):</i> increased average severity of nephropathy and epithelial	No effects on reproductive organs observed	Non- guideline, according to GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
	n=50/sex/dose	<i>Exposure:</i> once a day, 5d/ week for 103 weeks Examinations: Body weight, organ weight, gross lesions and histopathological changes (incl. reproductive organs). Statistics: Dunnett's test, Williams' test, Jonckheere's test	e (>99% purity) Oral, gavage 0, 150 or 300 mg/kg bw/day for males and 0, 300 or 600 mg/kg bw/day for females Control: corn oil only	hyperplasia of the renal pelvis (30/50 vs. 1/50), increased incidence of mineralization of collecting tubules in renal medulla (46/50 vs. 4/50) <i>300 mg/kg bw/day (males & females):</i> sign. reduced survival in males (32/50 vs. 20/50), sign. reduced BW in males (-5-8% after week 38), increased average severity of nephropathy and epithelial hyperplasia of the renal pelvis in males (31/50 vs. 1/50), focal hyperplasia of renal tubular epithelium in males (9/50 vs 0/50), increased incidence of mineralization of collecting tubules in renal medulla of males (47/50 vs. 4/50), increased incidences of nephropathy in females (32/50 vs. 21/49) <i>600 mg/kg bw/day (female only):</i> reduced BW (-5-8% after week 55), increased incidences of nephropathy (41/49 vs. 21/49)		Study mainly focussed on carcinogenic effects, tumour incidences not extensively considered in this summary.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
Bornatowicz et al. (1994) [25]	Sprague-Dawley rats, male and female n=24/sex/dose (both generations)	Two-generation reproduction toxicity study <i>Exposure:</i> F0: 7d/week, males 77 days, females 14 days before mating; followed by exposure during mating for both sexes. Females additionally exposed during gestation and lactation until weaning F1: 7d/week, both sexes 84 days before mating; followed by exposure during mating for both sexes. Females additionally exposed during gestation and lactation until weaning <i>Examinations:</i> Fertility and reproductive indices, general observation for physical or behavioral changes, body weight, feed	1,4-dichlorobenzene (99% purity) Oral, gavage 0, 30, 90 and 270 (279 in developmental milestone test) mg/kg bw/day Control: olive oil only	F0-generation: <i>270 mg/kg bw/day:</i> food consumption partly sign. decreased in females during LD 1-14; absolute and/or relative weight of liver and kidney increased and of spleen decreased in males, kidney lesions in males F1-generation (parents): <i>90 mg/kg bw/day:</i> increased relative liver weight in males <i>270 mg/kg bw/day:</i> food consumption partly sign. decreased in females during LD 1-14; reduced body weight (about 20g less for males, 10g less for females; not further specified), absolute and/or relative weight of liver and kidney increased and of spleen decreased in males, kidney lesions in males	The fertility index ranged from 71% to 100% in both generations but with no significant difference between the groups (though results for individual groups not quantified). One dam of the high dose group of both F0 and F1 was pregnant but not yet delivered by GD24 (late-dead foetuses and resorption sites). No further reproductive effects observed See table 9 for the effects on development.	According to OECD TG 416, according to GLP Limited quantitative details presented on the general toxicity and reproductive parameters

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		consumption, organ weights, histopathological changes of parent animals (though not systematically done in control and high dose F0 and F1), litter size and pup mortality, sex ratio, reflexes and behavior of pups, developmental milestones, body weight of pups, and malformations (only for pups that died before LD4, and pups excluded after culling) were examined. <i>Statistical analysis:</i> one-way ANOVA, Scheffé's test, Kruskal-Wallis or Wilcoxon-Mann-Whitney, Chi-square or Fisher exact				
Makita (2004) [26]	Wistar rats, female	Perinatal developmental toxicity study focussing on the development, onset of puberty and	1,4-dichlorobenzene (purity 99.9%)	No maternal effects observed	No reproductive effects observed	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
	n=6 pregnant females/dose	reproductive organs of the female offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND42. <i>Examinations:</i> Maternal animals: body weight, food consumption. Offspring: body weight, food consumption after weaning, sex, viability, gross malformations,	Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)		See table 9 for the effects on development	This study only includes the effects on female offspring until 6 weeks of age. The effects on male offspring up to week 6 are presented by Makita (2005). Given the similar reproductive outcomes for the dams in these two papers, it may be assumed that the data originate from the same experiment

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		organ weights, histopathology, eye opening, anogenital distance, vaginal opening, blood LH and FSH <i>Statistical analysis:</i> two-way analysis of variance (two-way ANOVA), with dam data on individual basis, and offspring data with litter as unit. Significant level was set at $P < 0.05$.				
Makita (2005) [27]	Wistar rats, female n=6 pregnant females/dose	Perinatal developmental toxicity study focussing on the development, onset of puberty and reproductive organs of the male offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with	1,4-dichlorobenzene (purity 99.9%) Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)	No maternal effects observed	No reproductive effects observed See table 9 for the effects on development.	Non-guideline, non-GLP This study only includes the effects on male offspring until 6 weeks of age. The effects on female offspring up to week 6 are presented by Makita (2004).

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND42. <i>Examinations:</i> Maternal animals: body weights, food consumption; Offspring: body weight, food consumption after weaning, sex, viability, gross malformations, organ weights, histopathology, eye opening, anogenital distance, preputial separation, blood testosterone, LH and FSH <i>Statistical analysis:</i> two-way analysis of variance (two-way				Given the similar reproductive outcomes for the dams in these two papers, it may be assumed that the data originate from the same experiment.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		ANOVA), with dam data on individual basis, and offspring data with litter as unit. Significant level was set at $P < 0.05$.				
Makita and Omura (2006) [28]	Wistar rats, female n=6 pregnant females/dose	Perinatal developmental toxicity study focussing on the development, onset of puberty and reproductive organs of the male offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND112.	1,4-dichlorobenzene (purity 99.9%) Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)	No maternal effects observed	No reproductive effects observed See table 9 for the effects on development	Non-guideline, non-GLP This study focusses on male offspring until 16 weeks of age. The effects on female offspring up to week 16 are presented by Makita (2008). When compared to Makita (2005), current study includes additionally analysis of sperm.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Examinations:</i> Maternal animals: body weights, food consumption; Offspring: body weight, food consumption after weaning, sex, viability, gross malformations, organ weights, histopathology, sperm analysis (count, motility, morphology), eye opening, anogenital distance, preputial separation, blood testosterone, FSH and LH <i>Statistical analysis:</i> two-way analysis of variance (two-way ANOVA), with dam data on individual basis, and offspring data with litter as unit				Given the different reproductive outcomes for the dams in these two papers, it is assumed that the data originate from different experiments.
Makita (2008) [29]	Wistar rats, female	Perinatal developmental toxicity study focussing on the development, onset of puberty and	1,4-dichlorobenzene (purity 99.9%)	No maternal effects observed	No reproductive effects observed	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
	n=6 pregnant females/dose	reproductive organs of the female offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND112 <i>Examinations:</i> Maternal animals: body weights, food consumption. Offspring: body weight, food consumption after weaning, sex, viability, gross malformations,	Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)		See table 9 for the effects on development	This study focusses on female offspring until 16 weeks of age. The effects on male offspring up to week 16 are presented by Makita and Omura (2006). When compared to Makita (2004), current study includes additionally analysis of oestrus cyclus. Given the different reproductive outcomes for the dams in these two papers, it is assumed that

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		organ weights, histopathology, oestrus cyclus, eye opening, anogenital distance, vagina opening, blood testosterone, oestradiol, FSH and LH, <i>Statistical analysis:</i> two-way analysis of variance (two-way ANOVA) plus Fisher's least significant difference procedure. Dam data on individual basis, and offspring data with litter as unit				the data originate from different experiments.
<i>Oral - mice</i>						
NTP 1987 [2] Study 1 of 2	B6C3F1 mice, male and female n= 10/sex/dose	Repeated dose toxicity study <i>Exposure:</i> once a day, 5d/week for 13 weeks <i>Examinations:</i> Body weight, organ weights, gross lesions and histopathological changes (incl. reproductive organs),	1,4-dichlorobenzene (>99% purity) Oral, gavage 0, 600, 900, 1000, 1500 or 1800 mg/kg bw/day	<i>0 mg/kg bw/day:</i> 1/10 males died <i>600 mg/kg bw/day:</i> decreased BW gain (males: -34.7%, p<0.05); females: -39.9%, p<0.01), increased hepatocellular degeneration (males: 7/10; females: 9/10), decreased kidney to brain weight ratio in males (-10.7%, p<0.05), decreased spleen to brain weight ratio in males (-24.0%, p<0.01), decreased WBC,	<i>1800 mg/kg bw/day:</i> increased ovary to brain weight ratio (+131.5%, p<0.01)	Non-guideline, according to GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		and blood and urine parameters <i>Statistical analysis:</i> Dunnett's test, Williams' test, Jonckheere's test	Control: corn oil only	segmented neutrophils and increased RBC ($p < 0.05$) in males and increased hemoglobin ($p < 0.05$) in females. <i>900 mg/kg bw/day:</i> decreased BW gain (males: -25.6%, $p < 0.05$; females: -27.0%, $p < 0.01$), increased hepatocellular degeneration (males: 10/10; females: 10/10), increased liver to brain weight ratio (males: +24.2%; females: +43.2% (both $p < 0.01$), decreased kidney to brain weight ratio in males (-11.9%, $p < 0.05$), decreased spleen to brain weight ratio in males (-36.1%, $p < 0.01$), decreased WBC, segmented neutrophils ($p < 0.01$) and lymphocytes ($p < 0.05$) and increased cholesterol ($p < 0.05$) in males, increased platelets and alkaline phosphates ($p < 0.05$) in females <i>1000 mg/kg bw/day:</i> 1/10 males died, decreased BW gain (males: -23.1%, $p < 0.05$; females: -29.2%, $p < 0.01$), increased hepatocellular degeneration (males: 10/10;		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				females: 10/10), increased liver to brain weight ratio (males: +34.2%; females; +28.6% (both $p < 0.01$), decreased spleen to brain weight ratio in males (-33.1%, $p < 0.01$), decreased WBC, segmented neutrophils ($p < 0.01$) and lymphocytes ($p < 0.05$) and increased liver porphyrine ($p < 0.05$) and cholesterol ($p < 0.01$) in males, decreased WBC ($p < 0.05$) and increased platelets and liver porphyrin ($p < 0.05$) in females <i>1500 mg/kg bw/day</i>: 3/10 males and 5/10 females died, decreased BW gain in males (-48.8%, $p < 0.05$), increased hepatocellular degeneration (males: 10/10; females: 10/10), lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia of the spleen and bone marrow observed in animals that died before end of study, increased liver to brain weight ratio (males: +65.5%; females; +90.2% (both $p < 0.01$), increased kidney to brain weight ratio in females (+17.4%, $p < 0.01$), decreased spleen to brain		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				weight ratio in males (-36.9%, $p < 0.01$), increased thymus to brain weight (females: +56.2%, $p < 0.01$), decreased WBC, segmented neutrophils ($p < 0.01$) and lymphocytes ($p < 0.05$) and increased cholesterol, liver porphyrin, total protein and triglycerides ($p < 0.01$) in males, decreased WBC ($p < 0.01$) and increased platelets ($p < 0.01$) in females <i>1800 mg/kg bw/day</i>: 7/10 males and 9/10 females died, decreased BW gain in males (-25.6%, $p < 0.05$), increased hepatocellular degeneration (males: 5/10; females: 6/10), lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia of the spleen and bone marrow observed in animals that died before end of study, increased liver to brain weight ratio (males: +74.2%, $p < 0.01$), decreased heart to brain weight (males: -19%, $p < 0.01$), decreased spleen to brain weight ratio in males (-39.9%, $p < 0.01$), decreased platelets		

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				($p < 0.01$), WBC and segmented neutrophils ($p < 0.05$) and increased alkaline phosphatase, cholesterol, liver porphyrin, total protein and triglycerides ($p < 0.01$) in males		
NTP 1987 [2] Study 2 of 2	B6C3F1 mice, male and female n=10/sex/dose	Repeated dose toxicity study <i>Exposure:</i> once a day, 5d/week for 13 weeks <i>Examinations:</i> body weight, organ weights, gross lesions and histopathological changes (incl. reproductive organs), and blood and urine parameters <i>Statistical analysis:</i> Dunnett's test, Williams' test, Jonckheere's test	1,4-dichlorobenzene (>99% purity) Oral, gavage 0, 84.4, 168.8, 337.5, 675 or 900 mg/kg bw/day Control: corn oil only	<i>675 mg/kg bw/day:</i> increased centrilobular to midzonal hepatocytomegaly (males: 8/10, females: 4/10, sign., p-value unknown) <i>900 mg/kg bw/day:</i> increased centrilobular to midzonal hepatocytomegaly (males: 9/10, females: 10/10, sign., p-value unknown)	No effects on reproductive organs observed	Non-guideline, according to GLP
NTP 1987 [2]	B6C3F1 mice, male and female n=50/sex/dose	Carcinogenicity study <i>Exposure:</i> once a day, 5d/week for 103 years	1,4-dichlorobenzene (>99% purity)	<i>300 mg/kg bw/day:</i> hepatocellular degeneration (males: 36/49 vs. 0/50 in control, females: 8/48 vs. 0/50 in control), cell necrosis (males: 35/49 vs. 1/50 in control, females: 4/48 vs. 1/50 in control)	No effects on reproductive organs observed	Non-guideline, according to GLP Study mainly focussed on

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Examinations:</i> body weight, organ weight, gross lesions and histopathological changes (inc. reproductive organs) <i>Statistical analysis:</i> Kaplan Meier, Cochran-Armitage trend test, Fisher Exact test	0, 300, 600 mg/kg bw/day Control: corn oil only	and cell size alteration (males: 38/49 vs. 0/50 in control, females: 4/48 vs. 0/50 in control), increased focal hyperplasia of adrenal gland capsule in males (21/48 vs. 11/47 in control), thyroid follicular cell hyperplasia in males (4/48 vs 1/47 in control), increased incidence of nephropathy (males: 12/50 vs 6/50 in control; females: 3/47 vs. 0/50 in control), renal tubular regeneration in females (7/47 vs. 4/50 in control) <i>600 mg/kg bw/day:</i> hepatocellular degeneration (males: 39/50 vs. 0/50 in control, females: 36/50 vs. 0/50 in control), cell necrosis (males: 37/50 vs. 1/50 in control, females: 30/50 vs. 1/50 in control) and cell size alteration (males: 40/50 vs. 0/50 in control, females: 27/50 vs. 0/50 in control), increased focal hyperplasia of adrenal gland capsule in males (28/49 vs. 11/47 in control), thyroid follicular cell hyperplasia in males (10/47 vs 1/47 in control), increased incidence of nephropathy (males: 15/47 vs 6/50 in control,		carcinogenic effects, tumour incidences not further described in this summary

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
				females: 3/46 vs. 0/50 in control), renal tubular regeneration in females (13/46 vs. 4/50 in control)		
<i>Subcutaneous/intraperitoneal - rats</i>						
Murthy et al. (1987) [30]	Sprague Dawley rats, male n=not described	Single dose study <i>Exposure:</i> single dose <i>Examinations:</i> sperm morphology (1000 sperm cells examined in triplicates), testicular morphology Euthanasia 10 days post exposure <i>Statistical analysis:</i> student's <i>t</i> -test	1,4-dichlorobenzene (purity unknown) Intraperitoneal injection (i.p.) 0, 800 mg/kg bw Control: chloroform	No general toxicity described	800 mg/kg bw: increased total abnormal sperm heads (+800.3%, $p < 0.001$), increased average % abnormal heads (11.02 vs. 1.72, $p < 0.001$), increased total abnormal sperm tails (+250.0%, $p < 0.02$), increased average abnormal sperm heads (8.26 vs. 2.92, $p < 0.05$). Lysosomal-like structures along with pleomorphic membranous bodies in early spermatids with fragmented nuclear material in the cytoplasm. Membranous aggregates associated with numerous vesicles, electron dense structures and lipids in the lumen of seminiferous tubules.	Non-guideline, non-GLP
Takahashi et al. (2007)	Crj:CD(SD)IG S rats, female, 19-22 d	Uterotrophic assay	1,4-dichlorobenzene (>98.0% purity)	No general toxicity described	22 mg/kg bw/day: in one out of two experiments decreased absolute and	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
[31]	n=5-10 females/dose	<i>Exposure:</i> once a day, for three consecutive days Euthanasia 19-22h after final dose <i>Examinations:</i> uterine and in some assays also ovarian and pituitary weights <i>Statistical analysis:</i> Student's t-test or Dunnett's parametric or non-parametric test Experiments were partially repeated	Subcutaneous injections 0, 22, 67, 200, 400, or 800 mg/kg bw/day Control: olive oil		relative ovarian weights ($p < 0.05$) <i>67 mg/kg bw/day:</i> in one out of four experiments decreased absolute ovarian and uterine weights ($p < 0.05$), in one experiment increased pituitary weights (data not described, p-value unknown) <i>200 mg/kg bw/day:</i> no sign. change in absolute and relative uterine and ovarian weights. <i>400 mg/kg bw/day:</i> no sign. change in absolute and relative uterine and ovarian weights. <i>800 mg/kg bw/day:</i> sign. decreased absolute uterine weights (-20%)	Data only presented in figures, no quantitative data available 2,5-DCP (major metabolite) did not show any uterotrophic or anti-uterotrophic activities DCHQ and DCBQ (minor metabolites) were acutely toxic
Takahashi et al. (2011) [32]	Jcl:SD rats, male n=3/dose	Single dose study Sacrifice 10 days after injection.	1,4-dichlorobenzene (>98.0% purity)	Reduced BW at 1 st day upon injection, with gradual recovery to control level at 10 th day (data not quantified)	<i>800 mg/kg bw:</i> increased abnormal headed sperm number (39.1% vs. 2.1% in control, $p < 0.01$), increased abnormal tailed sperm	Non-OECD guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Examinations:</i> clinical signs, body weight, epididymal cauda weight, sperm motility and morphology <i>Statistical analysis:</i> Bartlett's test followed by ANOVA (if non-significant) or Kruskal-Wallis (if significant). Groups were compared with F-test, followed by Student's t-test or Wilcoxon's rank-sum test.	Single intraperitoneal injection with 0 or 800 mg/kg bw Control: olive oil		number (21.0% vs. 1.6% in control, $p < 0.01$), increased sperm abnormalities: - detached head (2.8% vs. 1.8% in control, $p < 0.05$) - reduced hook (30.8% vs. 0.8% in control, $p < 0.01$) - bent neck (7.6% vs. 0.4% in control, $p < 0.01$) - coiled flagellum (0.8% vs. 0.2% in control, $p < 0.01$) - bent flagellum (9.8% vs. 0.9% in control, $p < 0.01$) - bent flagellum tips (9.9% vs. 0.5% in control, $p < 0.01$)	This study aimed to reconfirm the results as reported by Murthy et al. (1987) This study also described other experiments
Takahashi et al. (2011) [32]	Wistar rats, male n=8/dose	Repeated dose toxicity study <i>Exposure:</i> once a day, 4–5 times per week for 8 weeks Total dosing times: 37 in 56 days	1,4-dichlorobenzene (>98.0% purity) Subcutaneous injection	No general toxicity observed	<i>100 mg/kg bw/day:</i> increased relative seminal vesicles weight (+14.3%, $p < 0.05$), increased absolute and relative ventral prostate gland weight (+19.4%; +19.6%, resp., $p < 0.05$), minor vacuolar changes and disappearance of	Non-guideline, non-GLP Data on sperm production shown in a figure

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		Sacrifice 4-5 days after last injection Rats killed by decapitation 4 or 5 days after last administration <i>Examinations:</i> clinical signs, body weight, organ weights and histopathology of preputial glands, testis and epididymis, ventral, lateral and dorsal prostate glands, seminal vesicles with coagulation gland prostate and seminal vesicles. Testicular sperm content, daily sperm production, and serum testosterone <i>Statistical analysis:</i> Bartlett's test followed by ANOVA (if non-significant) or Kruskal-Wallis (if significant). Groups were compared	0, 100, 200 and 400 mg/kg bw/day (cumulative dose: 0, 65, 131 and 262 mg/kg bw/day) Control: olive oil		seminiferous tubules (sign., no quantitative data described), Sertoli cell nuclei were changed into clear type (no details described), desquamated round germ cells and leukocytes sign. increased in epididymal sperm populations (only photo available, no quantitative data), spermatozoa leakages into interstitial tissues of epididymal caput and cauda (also in control; only photo available, no quantitative data) <i>200 mg/kg bw/day:</i> increased relative seminal vesicles weight (+16.5%, $p < 0.05$), increased relative dorsolateral prostate gland weight (+15.7%, $p < 0.05$), decreased DSP/testis and DSP/g testis ($p < 0.05$; $p < 0.01$, resp., details only displayed in figure, no quantitative data described), minor vacuolar	This study also describes other experiments

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		with F-test, followed by Student's t-test or Wilcoxon's rank-sum test. Pathological data analysed using chi-square and Fisher's exact test			changes and disappearance of seminiferous tubules (sign., no quantitative data described), Sertoli cell nuclei were changed into clear type (no details described), sign. increased vacuoles in epididymal ductal epithelia (details not described), desquamated round germ cells and leukocytes sign. increased in epididymal sperm populations (only photo available, no quantitative data), spermatozoa leakages into interstitial tissues of epididymal caput and cauda (also in control; only photo available, no quantitative data). <i>400 mg/kg bw/day:</i> increased absolute and relative seminal vesicles weights (+14.7%; +14.7% p<0.05), decreased DSP/testis and DSP/g testis (p<0.01, details only displayed in figure, no	

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
					quantitative data described), minor vacuolar changes and disappearance of seminiferous tubules (sign., no quantitative data described), Sertoli cell nuclei were changed into clear type (no details described), sign. increased vacuoles in epididymal ductal epithelia (details not described), desquamated round germ cells and leukocytes sign. increased in epididymal sperm populations (only photo available, no quantitative data), spermatozoa leakages into interstitial tissues of epididymal caput and cauda (also in control; only photo available, no quantitative data)	
Takahashi et al. (2011) [32]	Jcl:SD rats, male n=8 castrated males/dose	Hershberger assay <i>Exposure:</i> daily injection for 15 days Sacrifice 1 day after last injection	1,4-dichlorobenzene (>98.0% purity) Subcutaneous injection	No general toxicity observed	<i>100 mg/kg bw/day:</i> increased absolute and relative ventral prostate gland weight ($p<0.05$, data displayed in graph, no quantitative data), increased absolute ($p<0.05$)	Non-OECD guideline, non-GLP Results of organ weight

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Examinations:</i> clinical signs, body weight, weights of ventral prostate glands, seminal vesicles with coagulation glands, levator ani and bulbocavernosus muscle, glans penis and Cowper's gland. <i>Statistical analysis:</i> Dunnett's test	0, 100 and 200 mg/kg bw/day Control: olive oil		and relative ($p < 0.01$) seminal vesicles and coagulation glands and glans penis weights (data displayed in graph, no quantitative data) <i>200 mg/kg bw/day:</i> increased absolute and relative seminal vesicles and coagulation glands and glans penis weights ($p < 0.01$, data displayed in graph, no quantitative data), increased levator ani and bulbocavernosus muscles weight ($p < 0.01$)	presented only in figure This study also described other experiments
<i>Subcutaneous/intraperitoneal - mice</i>						
Takahashi et al. (2007) [31]	Crlj:CD-1(ICR) mice, female, 19-22 d n=5-10 females/dose	Uterotrophic assay <i>Exposure:</i> once a day, for three consecutive days Euthanasia 19-22h after final dose Experiments were partially repeated multiple times	1,4-dichlorobenzene (>98.0% purity) Subcutaneous (four studies) or intraperitoneal injections (one study)	Not described	S.c. exposure <i>22 mg/kg bw/day:</i> in one out of two experiments increased absolute and relative uterine weight ($p < 0.05$) <i>67 mg/kg bw/day:</i> In one out of three experiments a decreased absolute and relative uterine weight ($p < 0.05$)	Non-guideline, non-GLP Data only presented in figures, no quantitative data available

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		<i>Examinations:</i> absolute and relative uterine and/or ovarian weights. Additionally, uterine peroxidase activity was measured. <i>Statistical analysis:</i> Student's t-test, Wilcoxon rank sum test, Barlett's test, one-way analysis of variance, Kruskal-Wallis test, and Dunnett's parametric or non-parametric test.	S.c. injection: 0, 22, 67, 200, 400, 600, or 800 mg/kg bw/day I.p. injection: 0, 50, 100, 200, or 400 mg/kg bw/day Control: olive oil		<i>200 mg/kg bw/day:</i> No significant changes in absolute and relative ovarian weights. <i>400 mg/kg bw/day:</i> No significant changes in absolute and relative uterine and ovarian weights. <i>800 mg/kg:</i> decreased uterine weight ($p < 0.01$), relative ovarian weight ($p < 0.05$). I.p. exposure Non-sign. changes in absolute and relative uterine weights observed. Absolute and relative ovarian weights not studied. Uterine peroxidase activity no changes on uterine peroxidase activity.	
Takahashi et al. (2007)	Crlj:CD-1(ICR) mice,	Anti-uterotrophic assay <i>Exposure:</i>	1,4-dichlorobenzene	<i>600 mg/kg bw/day:</i> deaths in 5/8 mice	Uterine weights with E2 <i>Single dose 1,4-dichlorobenzene - single</i>	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
[31]	female, 19-22 d n=7-8 /group	- One study single dose of 1,4-dichlorobenzene and E2 via s.c. dose - One study with three successive s.c. doses 1,4-dichlorobenzene and single i.p. dose E2 on third day - Three studies with three successive i.p. doses of 1,4-dichlorobenzene and E2 Euthanasia 19-22h after final dose <i>Examinations:</i> uterine weights (5 studies). In addition, uterine peroxidase activity was measured per mg uterus, whole uterus and mg uterine protein combined with E2 (4 studies) <i>Statistical analysis:</i> Student's t-test, Wilcoxon rank sum test, Barlett's test, one-	e (>98.0% purity) 0, 8, 80, 100, 200, 400, 600, or 800 mg/kg bw/day Subcutaneous (four experiments) or intraperitoneal injections (one experiment) β-estradiol (E2): 0, 1, 2 μg/kg bw/day Control: olive oil or DMSO	800 mg/kg bw/day: deaths occurred on second, third and fourth day in 5/10 mice Massive lung hemorrhages in all mice that died	dose E2: no effects on E2-induced uterine growth <i>Three doses 1,4-dichlorobenzene - single dose E2:</i> no E2-induced uterine growth, though decreased uterine weights (non-sign.) upon 800 mg/kg bw/day 1,4-dichlorobenzene <i>Three doses 1,4-dichlorobenzene - three doses E2:</i> 400 mg/kg bw/day: reduced E2-induced increase in uterine weight (-30% for 2 μg/kg E2; -20% for 1 μg/kg E2) ($p < 0.05$) 600 mg/kg bw/day: reduced E2-induced increase in uterine weight (-30% for 2 μg/kg E2) ($p < 0.05$) 800 mg/kg bw/day: inhibition of 2 μg/kg/day E2-induced uterine hypertrophy ($p < 0.01$)	The text under figure 3 states that five out of ten mice exposed to 800 mg/kg died in one study (nr 15). In the sentence before that one they describe that each group in study nr 15 contains eight mice.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		way analysis of variance, Kruskal-Wallis test, and Dunnett's parametric or non-parametric test			Uterine peroxidase activity <i>800 mg/kg bw/day:</i> decreased activity of E2-induced uterine peroxidase per whole uterus in one experiment ($p < 0.05$)	
Takahashi et al. (2007) [31]	C57BL/6NCrlCrlj mice, female, 19-22 days n=8/dose	Anti-uterotrophic assay <i>Exposure:</i> 1,4-dichlorobenzene and E2 simultaneously once a day, for three days Euthanasia 19-22h after final dose <i>Examinations:</i> uterine weight, uterine peroxidase activity per mg uterus, whole uterus and mg uterine protein combined with E2 <i>Statistical analysis:</i> Student's t-test,	1,4-dichlorobenzene (>98.0% purity) Intraperitoneal injection 0, 204, 285, 400 mg/kg bw/day β -estradiol (E2): 0, 1 μ g/kg bw/day Control: olive oil	Not described	Uterine weights <i>204 mg/kg bw/day:</i> inhibition of E2-induced increase of absolute and relative uterine weight ($p < 0.05$) <i>285 mg/kg bw/day:</i> inhibition of E2-induced increase of absolute and relative uterine weight ($p < 0.05$) <i>400 mg/kg bw/day:</i> inhibition of E2-induced increase of absolute ($p < 0.01$) and relative uterine weight ($p < 0.05$)	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		Wilcoxon rank sum test, Barlett's test, one-way analysis of variance, Kruskal-Wallis test, and Dunnett's parametric or non-parametric test			Uterine peroxidase activity <i>400 mg/kg bw/day:</i> decreased E2-induced activity of uterine peroxidase (expressed per mg protein)	
Takahashi et al. (2007) [31]	DBA/2NCrCrj mice, female, 19-22 days old n=8/dose	Anti-uterotrophic assay <i>Exposure:</i> 1,4-dichlorobenzene and E2 simultaneously once a day, for three days Euthanasia 19-22h after final dose <i>Examinations:</i> uterine weight, uterine peroxidase activity per mg uterus, whole uterus and mg uterine protein combined with E2 <i>Statistical analysis:</i> Student's t-test, Wilcoxon rank sum test, Barlett's test, one-way analysis of	1,4-dichlorobenzene (>98.0% purity) Intraperitoneal injection 0, 204, 285, 400 mg/kg bw/day β -estradiol (E2): 0, 1 μ g/kg bw/day Control: olive oil	Not described	Uterine weights: <i>204 mg/kg bw/day:</i> increased absolute uterine weight ($p<0.05$) <i>285 mg/kg bw/day:</i> increased absolute uterine weight ($p<0.05$) <i>400 mg/kg bw/day:</i> increased absolute and relative uterine weight ($p<0.01$) Uterine peroxidase activity no effect on E2-induced peroxidase activity	Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		variance, Kruskal-Wallis test, and Dunnett's parametric or non-parametric test				
Takahashi et al. (2011) [32]	Crlj:CD(ICR) mice, male n=8/dose	Repeated dose study <i>Exposure:</i> once a day, 4–5 times per week for 2 or 6 weeks. Total dosing times: 11 in 15 days (2 weeks) or 29 in 42 days (6 weeks) Sacrifice 1 day after last injection <i>Examinations:</i> clinical signs, body weight, organ weights and histopathology of preputial glands, testis and epididymis, ventral, lateral and dorsal prostate glands, seminal vesicles with coagulation glands and seminal vesicles. Testicular sperm content, daily sperm	1,4-dichlorobenzene (>98.0% purity) Intraperitoneal injection 0, 100, 200 and 400 mg/kg bw/day (cumulative doses; 2-week exposure: 0, 73, 147 and 293 mg/kg bw/day 6-week exposure: 0, 68, 137 and 273 mg/kg bw/day) Control: olive oil	No general toxicity observed	2 weeks No clear information on results 6 weeks <i>100 mg/kg bw/day:</i> increased absolute epididymal weight (sign. no quantitative data), indistinct lumen-side border of caput duct walls, increased spermatozoa leakages (no tails) into interstitial tissues of caput and cauda epididymis <i>200 mg/kg bw/day:</i> decreased DSP/testis ($p<0.05$) and DSP/g testis ($p<0.01$) (data displayed in graph, no quantitative data), disappearance of seminiferous tubules (lacked part of germ cells and/or disruption), indistinct lumen-side border of caput	Results for the weights and histopathology of reproductive organs are mentioned in text, data and level of significance of the effects are not stated Data on sperm production shown in a figure This study also described other experiments Non-guideline, non-GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
		production, and serum testosterone <i>Statistical analysis:</i> Bartlett's test followed by ANOVA (if non-significant) or Kruskal-Wallis (if significant). Groups were compared with F-test, followed by Student's t-test or Wilcoxon's rank-sum test. Pathological data analysed using chi-square and Fisher's exact test			duct walls, increased spermatozoa leakages (no tails) into interstitial tissues of cauda epididymis <i>400 mg/kg bw/day:</i> decreased DSP/testis and DSP/g testis ($p < 0.01$, data displayed in graph, no quantitative data), decrease in sperm stages IX and X (no details described), increased vacuolar degenerations in ductal epithelia of epididymis, indistinct lumen-side border of caput duct walls, increased spermatozoa leakages (no tails) into interstitial tissues of cauda epididymis Other minor and no significant changes in epididymis were also found (data not shown).	
Takahashi et al. (2011)	Crlj:CD(ICR) mice, male	Hershberger assay <i>Exposure:</i> daily injection for 10 days	1,4-dichlorobenzene (>98.0% purity)	No effects observed	<i>50 mg/kg bw/day:</i> increased absolute and relative ventral prostate gland and glans penis	Results of organ weights presented in a figure.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on reproductive organs or fertility	Remarks
[32]	n=8 castrated males/concentration	Sacrifice 1 day after last injection <i>Examinations:</i> clinical signs, body weight, weights of ventral prostate glands, seminal vesicles with coagulation glands, levator ani and bulbocavernosus muscle, glans penis and Cowper's glands. <i>Statistical analysis:</i> Dunnett's test	Intraperitoneal injection 0, 50, 100 and 200 mg/kg bw/day Control: olive oil		weights ($p < 0.05$, data displayed in graph, no quantitative data) <i>100 mg/kg bw/day:</i> increased absolute and relative glans penis weight ($p < 0.05$, data displayed in graph, no quantitative data) <i>200 mg/kg bw day:</i> increased absolute ventral prostate gland weight ($p < 0.05$, data displayed in graph, no quantitative data).	This study also described other experiments. Non-guideline, non-GLP

^a: converted conform the CLP-guidance (https://echa.europa.eu/documents/10162/2324906/clp_part3_en.pdf/42e0397a-73f2-0583-958f-3830928e1604?t=1730718832043)

^b: Lesions were divided into four different grades of severity: slight, moderate, marked and severe.

BW: body weight, PND: post-natal day, LH: luteinizing hormone, FSH: follicle stimulating hormone, DSP: daily sperm production, resp.: respectively, DMSO: dimethyl sulfoxide, sign.: significant; i.p: intraperitoneally; s.c.: subcutaneous; vs.: versus

8.1.2.1 Inhalation

8.1.2.1.1 *Rats***Hollingsworth et al. (1956)**

In a repeated inhalation toxicity study (non-guideline, non-GLP) conducted by Hollingsworth et al. (1956) [15], rats (strain not specified) were exposed whole body to 1,4-dichlorobenzene (99% purity) vapour for 7h/day, 5 days/week, except at the highest concentration (798 ppm) where animals were exposed for 8h/day, 5 days/week. The animals were exposed to analytical concentrations of 0, 96, 158, 173, 341 or 798 ppm (0.58, 0.95, 1.04, 2.05, 4.8 mg/L). Exposure periods ranged from 6 to 7 months (96 ppm), from 157 to 219 days (158 ppm), 16 days (173 ppm), 6 months (341 ppm), male during 1 to 46 days, females during 9 to 69 days (798 ppm). The number of animals was 10/sex (96; 158 ppm), 5/sex (173 ppm), 20 males (341 ppm), 19 males and 15 females (798 ppm).

Results showed at 96 ppm a significant average increased kidney weight in male rats. At 158 ppm the average kidney and liver weights were significantly increased in male and female rats, in addition to slight changes in the liver (cloudy swelling) or granular degeneration of questionable significance in the parenchymal cells in the central zones. At 173 ppm the average kidney and liver weights were significantly increased in male and female rats, in addition to slight changes in the lungs (slight interstitial oedema, congestion, alveolar haemorrhage) of male rats. At 341 ppm a slight increase in average liver and kidney weight of male rats occurred. At 798 ppm, 4 rats died during the exposure period. An undefined number of animals were moribund when killed. Tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness were observed. Slight to moderate changes in the liver (cloudy swelling and central necrosis), slight cloudy swelling of the tubular epithelium of the kidneys in female rats. Regarding the reproductive effects, no significant changes in testes weight in male animals were observed at either concentration. Effects on other reproductive toxicity endpoints were not described or not investigated.

Riley et al. (1980)

The non-guideline repeated inhalation study performed by Riley et al. (1980) [16] involved Wistar rats (n=75-79/sex/concentration). The rats were whole body exposed to 1,4-dichlorobenzene (purity>99.8%) via inhalation for 5 hours per day, 5 days a week, over a period of 76 weeks. A recovery phase was included, extending until 80% mortality was reached or until two years after the experiment began. Periodic sacrifices for autopsy were performed at weeks 26, 52, and 76, with 5 rats from each group per sex. The concentrations of 1,4-dichlorobenzene used were 0 (air control), 75, and 500 ppm (analytical concentrations: 0, 75, 490-499 ppm, corresponding to 0, 0.45 or 2.95-3.00 mg/L).

No effects from the treatment were found on mortality, clinical condition, body weight, food or water consumption, blood biochemistry, haematology, or general histopathology. Liver, kidney, heart and lung weights were increased, and brain weight was decreased at 500 ppm. No significant effects were observed on the weights of the gonads or on pathologies of the testes, prostate, epididymis, uterus, ovaries, cervix.

Tyl and Neeper-Bradley (1989)

In a two-generation reproduction toxicity study (non-guideline) performed by Tyl and Neeper-Bradley (1989) [17], Sprague-Dawley rats (n=28/sex/concentration) were exposed to 1,4-dichlorobenzene (100% purity) via inhalation at target concentrations of 0, 50, 150 and 450 ppm (analytical concentrations 0.0, 66.3, 211.0, 538.0 ppm corresponding to 0, 0.398, 1.27, and 3.23 mg/L). Exposure was applied for 10 weeks (F0) or 11 weeks (F1) prior to mating, during mating, and during gestation until GD19. Exposure continued from PND 5 until sacrifice at weaning. Mothers were separated from their pups for the exposure period. Males were sacrificed after successful mating. A large discrepancy between target and analytical concentration was noted. Condensation may have occurred. Five adult animals (1 male control and 1 female each of control, mid and high in the F0 generation, 1 male of the low concentration in the F1 generation) died during the study. Clinical signs such as tremors, unkempt appearance, encrustation (perioral, perinasal, periocular) were observed at high concentration F0 and F1 animals. Body weights of the F0 and F1 males were significantly decreased at the high concentration group during multiple weeks of the premating and mating period.

Body weight gain of high concentration F0 males was in general reduced during premating, though an increase was observed during some of the mating weeks. In F1 males, body weight gain was occasionally reduced at high concentration during premating and mating. In F0 and F1 high concentration females, body weight and body weight gain were reduced during premating. Gestational body weights of females of the F0 generation were significantly decreased at GD 20 in the mid and high concentration group (-4.7% and -6.4%, respectively), and the body weight gains were reduced during GD 0-20 in the high concentration group (-12.3%). Gestational body weight of females of the F1 generation was significantly decreased at day 0, 7, 13 and 20 in the high concentration group only (-11.6%, -10.5%, -9.8% and -9.8%, respectively). F0 maternal lactational body weights were unaffected throughout lactation, but F0 lactational body weight gains were increased during LD14-21 and LD0-28 at high concentration. For F1 female adult animals of the high concentration group, lactational BW was reduced at LD0 (-10.6%), LD4 (-7.8%) and LD7 (-7.9%). Lactational BW gain in adult F1 females was however increased at LD0-28 at high concentration, and increased during LD21-28 and LD0-28 in mid concentration.

In addition, food consumption was reduced in high concentration F0 males and females (week 0-1) and occasionally during premating and mating period in high concentration F1 males and females.

In addition to increased kidney and liver weights (mainly in F0 and F1 males), also histopathological lesions in kidney of F0 and F1 males were noted.

No effects on reproductive parameters were observed in this study. The effects on development and on/via lactation observed in this study are summarised in sections 8.2 and 8.3, respectively.

Japan Bioassay Research Center (1995) (2-weeks study)

In a repeated inhalation toxicity study performed by Japan Bioassay (1995) [18, 19], F334 rats (n=10/sex/concentration) were whole body exposed to 0, 120, 180, 270, 400 or 600 ppm (analytical concentrations: 0, 119.3, 182.0, 274.4, 403.8, 597.4 ppm, corresponding to 0, 0.72, 1.1, 1.6, 2.4, 3.6 mg/L) 1,4-dichlorobenzene (> 99.9 % purity) via inhalation for 6h/day, 5 days/week, over a period of 2 weeks.

Body weight gain was significantly decreased after week 1 in males and food consumption was decreased in both sexes after week 1. No significant effects on reproductive organs were observed, except for a dilated lumen of the uterus in a single female of the 120 and 400 ppm groups.

Aiso et al. (2005)/Japan Bioassay Research Center (1995) (13-weeks study)

In a repeated inhalation toxicity study (OECD TG 413/GLP) performed by Aiso et al. (2005)[21]/Japan Bioassay Research Center (1995) [18, 23], F334 rats (n=10/sex/concentration) were whole body exposed to 0, 25, 55, 120, 270 or 600 ppm (analytical concentrations: 0, 27.4, 54.4, 120.0, 267.4, 601.5 ppm, corresponding to 0.16, 0.33, 0.72, 1.6, 3.6 mg/L) 1,4-dichlorobenzene (> 99.9% purity) via inhalation for 6h/day, 5 days/week, over a period of 13 weeks.

Significantly decreased BW gain was observed in males at 600 ppm after week 1. Changes in food consumption were observed at 600 ppm in males after week 1 (decrease), and week 9, 11, 12 and 13 (increase), and in females after week 1 (decrease), and week 6, 9 and 12 (increase). Absolute and relative liver weight was significantly increased in males after exposure to ≥ 120 ppm and in females after exposure to ≥ 270 ppm. Absolute liver weight was also significantly increased in females of the 55 ppm group. Absolute and relative kidney weight was significantly increased in males after exposure to 270 and 600 ppm and in females of the high concentration group only. In male kidneys, also increased hyaline droplets, granular casts, mineralization of papilla, proximal tubular cell necrosis and cytoplasmic basophilia were observed in either the high concentration group only or after exposure to ≥ 270 ppm, depending on the histopathological effect. In addition, increased hepatocellular centrilobular hypertrophy was observed in the liver of males after exposure to 600 ppm. In the two highest concentration groups, a significant increase of absolute brain weight (270 ppm), an increase of absolute and relative spleen weight (600 ppm), and a decrease of relative thymus weight (600 ppm) were observed in males only. Haematological effects included decreased RBC count, hemoglobin, hematocrit in 120 ppm males and above, decreased Hb in 600 ppm females, and decreased MCV, MCH and increased platelets in 600 ppm males.

No significant effects on reproductive organs (i.e. testes, ovaries) were observed.

Aiso et al. (2005)/ Japan Bioassay Research Center (1995) (2-year study)

In a repeated inhalation toxicity study (according to OECD TG 453 and GLP) performed by Japan Bioassay Research Center (1995) [20]/ Aiso et

al. (2005)[22], F344 rats (n=50/sex/concentration) were whole body exposed to 1,4-dichlorobenzene (> 99.9% purity) via inhalation to concentrations of 0, 20, 75 or 300 ppm (analytical concentrations: 0, 19.8, 74.8, 298.4 ppm, corresponding to 0.12, 0.45 and 1.79 mg/L) for 6h/day, 5 days/week, over a period of 104 weeks.

No clinical findings and no effects on bw or food consumption were observed. Absolute and relative liver weights were significantly increased in both males and females at 300 ppm. Absolute and relative kidney weight was significantly increased at 300 ppm in males only. Histopathological examinations revealed eosinophilic globules in the olfactory epithelium in females at ≥ 75 ppm and in the respiratory epithelium of females at 300 ppm, increased incidence of respiratory metaplasia in the nasal glands of females at 300 ppm, increased incidence of hepatocellular centrilobular hypertrophy in males at 300 ppm, increased incidence of kidney mineralization in the papilla and kidney urothelial hyperplasia in the pelvis of males of the high concentration group. Haematology and blood chemistry analyses revealed *decreased total protein and increased* total bilirubin, urea nitrogen, potassium in 20 ppm and 300 ppm females, and decreased MCV and increased total cholesterol, phospholipid, urea nitrogen, creatinine, calcium in 300 ppm males.

No significant effects on reproductive organs (i.e. testes, epididymis, seminal vesicle, prostate, ovaries, vagina, uterus and mammary gland) were observed.

8.1.2.1.2 Mice

Hollingsworth et al. (1956)

In a repeated inhalation toxicity study (non-guideline, non-GLP) conducted by Hollingsworth et al. (1956) [15], mice (strain not specified) were whole body exposed to 1,4-dichlorobenzene vapour (>99% purity) for 7h per day, 5 days/week. Mice were exposed at concentrations of 0, 96 (n=10 females), 158 ppm (n=10 males) (0.58, 0.95 mg/L) (average analytical concentrations). Exposure periods were 6 to 7 months (96 ppm), and 157 to 219 days (158 ppm).

No general toxicity was observed. Effects on reproductive toxicity endpoints were not specifically described for this species (in contrast to rat and guinea pig) or not investigated.

Anderson and Hodge (1976)

In a dominant lethal assay (non-guideline, non-GLP), conducted by Anderson and Hodge (1976) [24], male CD-1 mice (n=20/concentration) were whole body exposed to 0, 75, 225 or 450 ppm (target concentrations, corresponding to 0, 0.45, 1.35 or 2.71 mg/L) 1,4-dichlorobenzene (purity unknown), for 6h/day for 5 days and mated with untreated females.

There was one dead male at week 3 at 75 ppm.

There were no clear concentration-related reductions in either the percentage of male mice mating successfully or the percentage and numbers of females becoming pregnant. Pregnancy was only significantly decreased at the low concentration at mating week 6 (83.3% vs 95.7% in control) and week 7 (73.3% vs 90.0% in control), but not at the mid and high concentrations or in other weeks.

There were no differences in the mean total number of implants per pregnant female, except in mating week 8 when there was a significant

decrease observed in the low and high (and not mid) concentration groups (i.e. 12.4, 11.5, 12.2 and 10.8 for control, low, mid and high, resp.). Also no concentration related difference in the early deaths were observed. Solely for the mid concentration group increased early deaths were observed, dependent on the manner of analysis, in either mating week 1 (based on percentage of pregnant females with at least one early death: 75.9% vs. 50% in control) or mating week 6 (based on mean percentage of early deaths per total implants per pregnancy: 10.3% vs. 5.3% in control). Late deaths were not affected.

Japan Bioassay Research Center (1995) (2-weeks study)

In a repeated inhalation toxicity study performed by Japan Bioassay Research Center (1995) [18, 19], BDF1 mice (n=10/sex/concentration) were whole body exposed to 0, 55, 120, 270 or 600 ppm (analytical concentrations: 0, 124.3, 181.2, 274.1, 406.7, 599.9 ppm, corresponding to 0.75, 1.1, 1.6, 2.4, 3.6 mg/L) 1,4-dichlorobenzene (> 99.9 % purity) via inhalation for 6h/day, 5 days/week, for a period of 2 weeks.

Food consumption was significantly increased after week 2 in females after exposure to ≥ 270 ppm, and significantly decreased after week 1 (180, 270, 600 ppm) and increased after week 2 in males (600 ppm). Enlarged livers were observed in both males (9/10) and females (10/10) at 600 ppm (no p-value described). No significant effects on reproductive organs (i.e. testes, epididymis, seminal vesicle, prostate, ovaries, vagina, uterus and mammary gland) were observed.

Aiso et al. (2005)/Japan Bioassay Research Center (1995) (13-weeks study)

In a repeated inhalation toxicity study (OECD TG413 and GLP) performed by Aiso et al. (2005) [21]/Japan Bioassay Research Center (1995) [18, 23], BDF1 mice (n=10/sex/concentration) were whole body exposed to 0, 55, 120, 270 or 600 ppm (analytical concentrations: 0, 24.6, 54.6, 119.4, 268.0, 597.3 ppm, corresponding to 0.15, 0.33, 0.72, 1.6, 3.6 mg/L) 1,4-dichlorobenzene (> 99.9 % purity) via inhalation for 6h/day, 5 days/week, for a period of 13 weeks.

There was a decrease in body weight gain observed in females in week 6 after exposure to 55 ppm. After exposure to 600 ppm, a significant increase in body weight gain was observed in week 5 and 7-13.

Significant changes in food consumption were observed in males after exposure to 55 ppm in week 3 (decrease) and week 11 (decrease), 120 ppm in week 8 (decrease) and 600 ppm in week 2 (increase). In females, an increased food consumption was only observed in animals of the high concentration group in week 2, 3, 5, 8, 10 and 13.

In all concentration groups, the relative liver weight in males was significantly increased. After exposure to 55 ppm, relative heart and brain weight were significantly increased in males. Relative heart, brain and kidney weights were significantly increased in males of the 270 ppm group. In addition, after exposure to 600 ppm, absolute liver, relative kidney and brain weight were significantly increased. In females, relative liver weight was significantly increased after exposure to ≥ 270 ppm, and absolute liver and kidney weight was increased in the high concentration group only.

Histopathological findings are an increase in hepatocellular centrilobular hypertrophy in the liver of males after exposure to 270 ppm and in both

sexes of the high concentration group, and vacuolization of proximal tubule cells in the kidney of males.

Haematology and blood chemistry analyses revealed increased MCH in 600 ppm females, decreased amount of ketone bodies in 600 ppm males. The only significant effect on reproductive organs (i.e. testes, ovaries) was a significant increase in relative testis weight in the 270 ppm animals.

Aiso et al. (2005)/Japan Bioassay Research Center (1995) (2-year study)

In a repeated dose toxicity study (according to OECD TG 453 and GLP) performed by Japan Bioassay Research Center (1995) [20]/ Aiso et al. (2005) [22], BDF1 mice (n=50/sex/concentration) were whole-body exposed to 0, 20, 75 or 300 ppm (analytical concentrations: 0, 19.9, 74.8, 298.3 ppm, corresponding to 0.12, 0.45, 1.79 mg/L) 1,4-dichlorobenzene (> 99.9 % purity), for 6h/day, 5 days/week for two years.

Clinical findings showed a significantly decreased body weight in males in the high concentration group by the end of the 2-y exposure period. In the high concentration group, absolute and relative liver weights and relative kidney weights were significantly increased in males and females, and absolute kidney weight was increased in females only. Histopathological examinations revealed a significantly increased incidence in respiratory metaplasia in the olfactory epithelium and nasal gland in males at 75 ppm. At 300 ppm, the incidence of hepatocellular centrilobular hypertrophy was increased in males and the incidence of respiratory metaplasia of the olfactory epithelium was increased in females. Increased mineralization of the testis was observed in males at all concentrations, but significance was not described.

8.1.2.1.3 *Rabbits*

Hollingsworth et al. (1956)

In a repeated inhalation toxicity study (non-guideline, non-GLP) conducted by Hollingsworth et al. (1956) [15], rabbits (strain not specified) were exposed whole body to 1,4-dichlorobenzene vapour (>99% purity) for 7h per day, 5 days/week, except at the highest concentration (798 ppm) where animals were exposed for 8h daily, 5 days/week. The concentrations used were 0, 96, 158, 173, 798 ppm (0.58, 0.95, 1.04, 4.8 mg/L). Exposure time were from 6 to 7 months (96 ppm), from 157 to 219 days (158 ppm), 16 days (173 ppm), 6 months (341 ppm), male on days 1-46, females on days 9-69 (798 ppm). The number of animals were 1/sex (96; 158; 173 ppm), 8/sex (798 ppm).

Results showed that at 798 ppm, 4 rabbits died during the exposure period. An undefined number of animals were moribund when killed. Tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness were observed. Slight to moderate changes in the liver (cloudy swelling and central necrosis), and emphysema in the lungs of two rabbits. At 173 ppm, slight changes in the lungs (slight interstitial oedema, congestion, alveolar haemorrhage) of female rabbit. At 158 ppm, no adverse effects on growth or mortality of rabbits were found. At 96 ppm, no adverse effects on growth or mortality of rabbits were found. Effects on reproductive toxicity endpoints were not specifically

described for this species (in contrast to rat and guinea pig) or not investigated.

8.1.2.1.4 *Other species*

Hollingsworth et al. (1956) – guinea pigs

In a repeated inhalation toxicity study (non-guideline, non-GLP) conducted by Hollingsworth et al. (1956) [15], guinea pigs (strains not specified) were exposed whole body to 1,4-dichlorobenzene vapour (>99% purity) for 7h per day, 5 days/week, except at the highest concentration (798 ppm) where animals were exposed for 8h daily, 5 days/week. The concentrations used were 0, 96, 158, 173, 798 ppm (0.58, 0.95, 1.04, 4.8 mg/L). Exposure time were from 6 to 7 months (96 ppm; n=8/sex), from 157 to 219 days (158 ppm; n=8/sex), 16 days (173 ppm; n=5/sex), 6 months (341 ppm; n=8/sex), male on days 1-46, females on days 9-69 (798 ppm; n=16 males, 7 females). Results showed that, at 798 ppm, 2 guinea-pigs died during the exposure period. An undefined number of animals were moribund when killed. Tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness were observed. Slight to moderate changes in the liver (cloudy swelling and central necrosis). At 341 ppm, slight histologic changes in liver (cloudy swelling, fatty degeneration, focal necrosis, slight cirrhosis) of male guinea-pigs. At 173 ppm, average spleen weight increased in male guinea-pigs (sign.), slight changes in the lungs (slight interstitial oedema, congestion, alveolar haemorrhage) of female guinea-pigs. At 158 ppm, average liver weight increased in female guinea-pigs (sign.). At 96 ppm, average kidney weight increased in male rats (sign.) and average liver weight increased in female guinea-pigs (sign.).

No significant changes in testes weight in male animals were observed at either concentration. Effects on other reproductive toxicity endpoints were not described or not investigated.

Hollingsworth et al. (1956) - monkey

In a repeated whole body inhalation toxicity study (non-guideline, non-GLP) conducted by Hollingsworth et al. (1956) [15], female monkey (strain not specified, n=1/concentration) were exposed whole body to 0, 96, 158 ppm (0.58, 0.95 mg/L) 1,4-dichlorobenzene vapour (>99% purity) for 7h per day, 5 days/week. Exposure period was 6 to 7 months (96 ppm), 157 to 219 days (158 ppm).

General toxicity was not observed. Effects on reproductive toxicity endpoints were not specifically described for this species (in contrast to rat and guinea pig) or not investigated.

8.1.2.2 Oral

8.1.2.2.1 *Rats*

NTP 1987 (F344/N rats, 13-weeks, study 1 of 2)

In a NTP study (pre-guideline, GLP compliance) [2], an oral repeated dose study was performed in F344 rats (n=10/sex/dose). The rats received 1,4-dichlorobenzene (>99% purity) in corn oil through gavage at doses of 0, 300, 600, 900, 1200 or 1500 mg/kg bw/day once a day, 5 days a week for 13 weeks.

Clinical findings upon exposure to 1,4-dichlorobenzene included mortality (≥ 900 mg/kg bw/day, though also 1 dead male in control group). Due to high mortality in the high dose females, additional

parameters were not examined in this group. This also partly applies to high dose males. Reduced body weight gain (all dose levels), tremors, poor motor response, and ocular discharge (≥ 1200 mg/kg bw/day) were further noticed. Organ weights (relative to brain weight) were affected, i.e. liver (increased in males/females ≥ 900 mg/kg bw/day), kidney (increased in males, ≥ 600 mg/kg bw/day, though not at high dose), thymus (decreased in high dose males), and spleen (decreased in females, 1200 mg/kg bw/day). Histopathological examinations revealed a.o. degeneration and necrosis of hepatocytes, hypoplasia of the bone marrow, lymphoid depletion of the spleen and thymus, epithelial necrosis and villar bridging of the small intestinal mucosa, and epithelial necrosis of the nasal turbinates in the two highest dose groups, and renal tubular cell degeneration in males of all dose groups. Regarding the reproductive organs, uterus weight to brain weight ratios were significantly decreased in all dose groups. No significant effects on other reproductive organs (i.e. testes, ovaries) were observed.

NTP 1987 (F344/N rats, 13-weeks, study 2 of 2)

In the second 13-week NTP study (non-guideline, GLP compliance) [2], an oral repeated dose study was performed in F344 rats (n=10/sex/dose). The rats received 1,4-dichlorobenzene (>99% purity) in corn oil through gavage at dose levels of 0, 37.5, 75, 150, 300 or 600 mg/kg bw/day once a day, 5 days a week for 13 weeks. No compound related deaths or changes in body weight (change) were observed. An increase in the incidence and severity of kidney cortical tubular degeneration was observed in male rats receiving 600 mg/kg bw/day of 1,4-dichlorobenzene. Effects on reproductive organs were not observed.

NTP 1987 (F344/N rats, 2-years)

The NTP (non-guideline, GLP compliance) [2] performed an oral carcinogenicity study in F344/N rats (n=50/sex/concentration). The rats received 1,4-dichlorobenzene (>99% purity) in corn oil through gavage at dose levels of 0, 150 or 300 mg/kg bw/day for males and 0, 300 or 600 mg/kg bw/day for females once a day, 5 days a week for two years. The survival rate of high dosed males was reduced. Histopathological examinations identified the kidney as the primary target organ with nephropathy (increased incidence in females, increased severity in males), focal hyperplasia of the renal tubular epithelium, epithelial hyperplasia of the renal pelvis, increased incidence of mineralization of collecting tubules in renal medulla of males. Neoplastic lesions are not described here. Effects on reproductive organs were not observed.

Bornatowicz et al. (1994)

In an oral two-generation reproduction toxicity study (GLP compliance; OECD TG 416), Bornatowicz et al. (1994) [25] exposed Sprague-Dawley rats to 0, 30, 90 and 270 mg/kg bw/day 1,4-dichlorobenzene (99% purity) by gavage, 7 days/week. The F0 generation consisted of 24 rats/sex/dose and were treated for 77 days (males) or 14 days (females) before mating, followed by exposure of both sexes during mating. Females were exposed for an additional period during gestation and lactation until weaning of the F1 pups on postnatal day 21. The F1 generation consisted of 24 rats/sex/dose and both sexes were exposed for 84 days before mating, followed by exposure during mating. Females

were exposed for an additional period during gestation and lactation. Weaning of the F2 pups on postnatal day 21 was the end of the study. General toxicity showed only partly significantly decreased food consumption in the high dosed F0 and F1 dams between LD1 and 14. In the F1-generation, four animals from the high-dose group had to be euthanized early due to a poor general condition, whereas one low dose animal died spontaneously. In addition, mean F1 maternal and paternal BW was significantly decreased at the high dose. At the high dose F0 and F1 males, absolute and/or relative weight of liver and kidney was increased and of spleen was decreased, in addition to kidney lesions in these animals, and in F1 mid dosed males an increased relative liver weight only.

No statistically significant effects on fertility were noted. The fertility index ranged from 71% to 100% in both generations, but with no significant difference between the groups (though results for individual groups not quantified). One dam of the high dose group of both F0 and F1 was pregnant but not yet delivered by GD24 (late-dead fetuses and resorption sites).

The effects on developmental toxicity observed in this study are summarised in section 8.2. Effects on/via lactation are summarised in section 8.3.

Makita (2004), Makita (2005), Makita and Omura (2006), Makita (2008)

In perinatal developmental toxicity studies (non-guideline, non-GLP), Makita (2004) [26], Makita (2005) [27], Makita and Omura (2006) [28] and Makita (2008) [29] exposed pregnant Wistar rats (n=6/dose) via diet to 0 or 25 ppm (0 and 2 mg/kg bw/day) 1,4-dichlorobenzene (99.9% purity) from gestation day 1 to postnatal day 21 (total 42 days). On PND 2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND42 or PND96. Makita (2004) and Makita (2008) focussed on the development, onset of puberty and reproductive organs of the female offspring, whereas Makita (2005) and Makita and Omura (2006) focussed on these effects in male offspring.

No maternal toxicity (i.e. no effect on bw and food consumption) was observed in any of these studies.

No adverse effect on the onset of puberty was observed in both male as well as female offspring, i.e. no effects on anogenital distance, vaginal opening, or preputial separation.

Blood hormone levels, i.e. testosterone, oestradiol, LH and FSH were not significantly affected in the offspring though it is noted that some hormone levels varied within groups.

Regarding the reproductive organs, no significant histopathological changes, effect on sperm (count, motility, morphology) or on oestrus cycle was observed in the offspring.

The effects on developmental toxicity observed in this study are summarised in section 8.2.

8.1.2.2.2 *Mice***NTP 1987 (B6C3F1 mice, 13-week, study 1 of 2)**

The NTP performed (non-guideline, GLP compliance) [2] an oral repeated dose study in B6C3F1 mice (n=10/sex/dose) [2]. The mice received 1,4-dichlorobenzene (>99% purity) in corn oil through gavage at doses of 0, 600, 900, 1000, 1500 or 1800 mg/kg bw/day once a day, 5 days a week for 13 weeks.

Mortality was observed in males (≥ 1000 mg/kg bw/day, also one dead male in control) and females (≥ 1500 mg/kg bw/day). Due to high mortality in the high dose females, additional parameters were not examined in this group. Body weight gain was reduced in males and females at all dose levels (except 1500 mg/kg bw/day in females). Organ weights (relative to brain weight) were affected, i.e. liver (increased in males/females ≥ 900 mg/kg bw/day), kidney (decreased in males, 600+900 mg/kg bw/day; increased in females at 1500 mg/kg bw/day), spleen (decreased in males at all dose levels), thymus (increased in females ≥ 900 mg/kg bw/day).

Histopathological examinations revealed an increased incidence of hepatocellular degeneration in all groups of dosed mice. The hepatocellular degeneration was centrilobular in distribution and was associated with cytomegaly, variation in nuclear shape, karyomegaly, and granular amphophilic cytoplasm. The severity of this change was dose related. Lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia of the spleen and bone marrow were also noted in animals of the two highest dosed groups which died before the end of the study.

1,4-Dichlorobenzene produced significant dose-dependent increases in liver to brain weight ratios in male and female mice receiving doses of 900 mg/kg bw/day or more. Kidney to brain weight ratios were decreased significantly ($p < 0.05$) in male mice, at doses of 600 and 900 mg/kg bw/day, and in female mice increased only in the 1500 mg/kg bw/day group.

Spleen to brain weight ratio was dose-dependent significantly decreased in male, but not in female, mice at all dosed groups. A significant increase in thymus to brain weight was observed in females. A significant decrease in heart to brain weight ratio was observed in males of the high dose group.

No significant effects on testis and uterus weight to brain weight ratios were observed. Ovary weight to brain weight ratios were significantly increased in the highest dosed group. No effects on other reproductive organs were observed.

NTP 1987 (B6C3F1 mice, 13-weeks, study 2 of 2)

In a second oral 13-week repeated dose toxicity NTP study (non-guideline, GLP compliance) [2], B6C3F1 mice (n=10/sex/dose) were administered 1,4-dichlorobenzene (>99% purity) in corn oil through gavage at dose levels of 0, 84.4, 168.8, 337.5, 675 or 900 mg/kg bw/day once a day, 5 days a week for 13 weeks.

No compound related deaths or significant changes in body weight (change) were observed. Centrilobular to midzonal hepatocytomegaly was observed at significantly increased incidences and severity in male and female mice that received 675 mg/kg bw/day or 900 mg/kg bw/day.

No effects on the reproductive organs were observed.

NTP 1987 (B6C3F1 mice, 2-years)

NTP performed (non-guideline, GLP compliance) an oral carcinogenicity study in B6C3F1 mice (n=50/sex/dose) [2]. The mice received 1,4-dichlorobenzene (>99% purity) in corn oil through gavage at doses of 0, 300 or 600 mg/kg bw/day once a day, 5 days a week for two years. No effects on mortality rate were observed. Histopathological examinations identified liver and kidney as the primary target organs with liver degeneration, cell necrosis and cell size alteration, and nephropathy, renal tubular regeneration. In addition, focal cell hyperplasia of the adrenal gland capsule and thyroid follicular cell hyperplasia were observed in males. Neoplastic lesions are not considered in this literature overview. Effects on reproductive organs were not observed.

8.1.2.3 Subcutaneous/intraperitoneal

8.1.2.3.1 *Rats***Murthy et al. (1987)**

In the non-guideline study performed by Murthy et al. (1987) [30] male Sprague Dawley rats were exposed intraperitoneally (i.p.) to 1,4-dichlorobenzene (purity unknown) at a single dose of 800 mg/kg bw in 0.5 mL chloroform. Euthanasia was performed 10 days post exposure and analysis included sperm morphology (1000 sperm cells were examined in triplicates) and testes morphology.

Results showed a significant increase of total abnormal heads as well as average abnormal heads. Additionally, a significant increase in total abnormal sperm tails and average abnormal sperm heads was found. Lysosomal-like structures along with pleomorphic membranous bodies were observed in early spermatids with, in addition, fragmented nuclear material in the cytoplasm. Membranous aggregates associated with numerous vesicles, electron dense structures and lipids in the lumen of seminiferous tubules were noticed.

Takahashi et al. 2007 (uterotrophic assay with CRJ:CD(SD)IGS rats)

In a study conducted by Takahashi et al. (2007)[31], uterotrophic assays were performed in immature female CRJ:CD(SD)IGS rats (n=5-10/group), divided over seven separate experiments. 1,4-Dichlorobenzene (>98.0% purity) dissolved in olive oil was injected subcutaneously at doses of 0, 22, 67, 200, 400 and/or 800 mg/kg bw/day, once a day for three successive days.

No reproducible effects on uterine and ovarian weights were found upon 22 to 67 mg/kg bw/day. Doses of 800 mg/kg bw/day induced reduced uterine weights.

Takahashi et al. (2011) (Jcl:SD rats; single dose study)

In the non-guideline study by Takahashi et al. (2011) [32], focusing on sperm parameters, Jcl: SD rats (n=3 males/dose) received single ip injection of either 0 or 800 mg/kg bw of 1,4-dichlorobenzene (> 98.0% purity). This study aimed to reconfirm the results as reported by Murthy et al. (1987).

A decrease in body weight was noted on the first day post-injection, which then gradually recovered over the following days (no quantitative details described). Abnormal headed sperm number and abnormal tailed sperm number were significantly increased (39.1% vs. 2.1% in control;

21.0% vs. 1.6% in control). Sperm abnormalities such as detached head (2.8% vs. 1.8% in control), reduced hook (30.8% vs. 0.8% in control), bent neck (7.6% vs 0.4% in control), coiled flagellum (0.8% vs. 0.2% in control), bent flagellum (9.8% vs. 0.9% in control), and bent flagellum tips (9.9% vs. 0.5% in control) were significantly increased in the treated group. Other misshapen sperms were also observed but those changes were minor or not treatment-related.

Takahashi et al. (2011) (Wistar rats; repeated dose toxicity study)

In a non-guideline repeated dose study focussing on male reproductive organ by Takahashi et al. (2011) [32], eight male Wistar rats per group were subjected to subcutaneous injections of 1,4-dichlorobenzene (> 98.0% purity) at doses of 0, 100, 200, and 400 mg/kg bw/day, administered once a day, 4–5 times per week for 8 weeks.

Injection site injuries were noted at the highest dose. There was a significant increase in relative seminal vesicles weights at all dosages. Absolute seminal vesicles weight was significantly increased in the high dose group only. Significant increased ventral prostate gland weight (absolute and relative) was only observed in the 100 mg/kg bw/day group. The relative dorsolateral prostate gland weight was only significantly increased at 200 mg/kg bw/day. Additionally, a significant reduction in daily sperm production was observed at doses of 200 and 400 mg/kg bw/day (details only displayed in figure, no quantitative data described). Major histopathologic injuries were not found in testis and epididymis of rats. Only minor changes were detected (data not described). Minor vacuolar changes and disappearance of seminiferous tubules were significantly increased in a dose-dependent manner. Sertoli cell nuclei were changed into clear type in treated groups (no details described). Vacuoles were significantly increased in epididymal ductal epithelia of rats administered 1,4-dichlorobenzene at doses of 200 and 400 mg/kg bw/day (only photo available, no quantitative data). Desquamated round germ cells and leukocytes were significantly increased in epididymal sperm populations of treated rats (only photo available, no quantitative data). Spermatozoa leakages into interstitial tissues of epididymal caput and cauda were observed in the control and treated groups (only photo available, no quantitative data). Almost all the leaked sperm consisted of only heads without tails. A tendency of increase in sperm leaked was found in rats treated with 1,4-dichlorobenzene at a lower dose. The leakages were significantly decreased in the middle and high dose groups.

1,4-dichlorobenzene administration did not significantly change the serum testosterone level in rats (data not described). There were no significant changes in the weights of the testes, epididymis, or preputial glands, nor were there any effects on serum testosterone levels.

Takahashi et al. (2011) (Jcl:SD rats; Hershberger assay)

In the Hershberger assay performed by Takahashi et al. (2011) [32], 8 castrated male rats/group received daily subcutaneous injections of 1,4-dichlorobenzene (>98.0% purity) for 15 days at dose levels of 0, 100, and 200 mg/kg bw/day. No significant changes in body weight were observed. There was a significant increase in the (absolute and relative) weights of the seminal vesicle and coagulation gland and glans penis in both exposure groups. The (absolute and relative) weight of ventral

prostate was only increased in the 100 mg/kg bw/day group and the (absolute and relative) weight of the levator ani and bulbocavernosus muscle was only increased in the 200 mg/kg bw/day group.

8.1.2.3.2 *Mice*

Takahashi et al. 2007 (uterotrophic assay in Crlj:CD-1(ICR) mice)

Another segment of the Takahashi study [31] included an uterotrophic assay in mice. Immature female Crlj:CD-1(ICR) mice (n=7-10/group) received subcutaneous injections of 1,4-dichlorobenzene (>98.0% purity) dissolved in olive oil at doses of 0, 22, 67, 200, 400, 600 or 800 mg/kg bw/day once a day for three successive days, divided over four experiments. In a fifth experiment, eight mice/group received intraperitoneal injections at doses of 0, 50, 100, 200 or 400 mg/kg bw/day.

Results are only presented in figures, no quantitative data were available. No reproducible effects on uterine and ovarian weight were observed upon s.c. 22 and 67 mg/kg bw/day. At 800 mg/kg bw/day administered subcutaneously, absolute and relative uterine weights were decreased.

Takahashi et al. 2007 (anti-uterotrophic assay in Crlj:CD-1(ICR) mice)

The effect of 1,4-dichlorobenzene on the uterotrophic activity of β -estradiol (E2) in immature female Crlj:CD-1 (ICR) mice was studied in five experiments conducted by Takahashi et al.[31] The mice received β -estradiol (E2) at doses of 0, 1 or 2 μ g/kg bw/day simultaneously with the 1,4-dichlorobenzene. The experiments were conducted as follows:

- single subcutaneous doses of E2 (2 μ g/kg bw) with or without 1,4-dichlorobenzene in DMSO (8, 80 or 800 mg/kg bw) (N=7-8), or
- single intraperitoneal dose of E2 in olive oil (2 μ g/kg bw) with or without three successive subcutaneous doses of 1,4-dichlorobenzene in olive oil (8, 80 or 800 mg/kg bw/day) (N=8), or
- three separate experiments with each three successive intraperitoneal administered doses of E2 (1 or 2 μ g/kg bw/day) with or without 1,4-dichlorobenzene (8, 80, 800 mg/kg bw/day; 200, 400 and 600 mg/kg bw/day; or 100, 200 and 400 mg/kg bw/day) (N=8).

Results are only presented in figures, no quantitative data were available. Mice administered 800 mg/kg bw/day, crouched down and slightly trembled 1.5h after intraperitoneal injection. Two mice died a day after. Deaths also occurred at the third and fourth day. Massive hemorrhages in lungs were observed in all dead mice. Doses were lowered, but deaths also occurred at 600 mg/kg bw/day. In total 5/8 or 5/10 mice died at 600 or 800 mg/kg bw/day, respectively.

Intraperitoneal doses of 1,4-dichlorobenzene of 400 mg/kg bw/day and higher caused significant inhibition of the uterotrophic effect of oestradiol. Three successive doses of 400 and 600 mg/kg bw/day 1,4-dichlorobenzene significantly reduced the uterotrophic effect of E2 (2 μ g/kg/day, three consecutive doses) by 30%, and a 20% reduction of the uterotrophic effect of 1 μ g/kg bw/day E2 (three consecutive doses)

was observed upon three consecutive doses of 400 mg/kg bw/day 1,4-dichlorobenzene. In the study with a single E2 dose and three consecutive 1,4-dichlorobenzene doses, no increased uterine weight was observed upon treatment with E2 only, though at co-exposure with 800 mg/kg bw/day 1,4-dichlorobenzene a significantly reduced uterine weight was noticed.

In addition to examining the anti-uterotrophic effect of 1,4-dichlorobenzene, the effect of 1,4-dichlorobenzene on (E2-induced) uterine peroxidase activity was studied in CD-1 mice (N=8 in most experiments). Administration of E2 increased uterine peroxidase activities per mg uterus, per uterus, and per mg uterine protein. Only co-administration of 800 mg/kg bw/day 1,4-dichlorobenzene decreased the uterine peroxidase activity. However, this was only measured in three mice instead of 8 that were used in most cases.

Takahashi et al. 2007 (anti-uterotrophic assay in C57BL/6NCrCrIj and DBA/2NCrCrIj mice)

In another segment of the Takahashi study [31], an anti-uterotrophic assay was performed in female C57BL/6NCrCrIj and DBA/2NCrCrIj mice (n=8 mice/concentration) to study the strain differences (Ah-response vs. Ah-non-responsive). The mice were subjected to simultaneous intraperitoneal injections of 1,4-dichlorobenzene (>98.0% purity) dissolved in olive oil at doses of 0, 204, 285 and 400 mg/kg bw/day and β -estradiol (E2) at doses of 0 or 1 μ g/kg bw/day, once a day for three successive days.

Results are only presented in figures, no quantitative data were available. E2 significantly increased uterine weight by 2.6 and 2.1 times in C57BL/6N and DBA/2N mice, respectively. 1,4-Dichlorobenzene inhibited the uterotrophic effect of E2 in all doses with a dose-response relationship by 22–33% in C57BL/6N mice but not in DBA/2N mice. In DBA/2N mice, 1,4-dichlorobenzene rather increased the uterine weight. In C57BL/6N mice, E2 (1 μ g/kg bw for 3 days) increased uterine peroxidase activities per mg uterus, per whole uterus and per mg uterine protein, by 2 (not sign.), 6, and 5 times, respectively. A decrease was only observed in activity per mg uterine protein in the 400 mg/kg bw/day 1,4-dichlorobenzene group.

In DBA/2N mice, E2 (1 μ g/kg bw for 3 days) increased uterine peroxidase activities per mg uterine, per whole uterus and per mg uterine protein, by 4, 9 and 8 times, respectively. 1,4-Dichlorobenzene did not decrease this activity.

Takahashi et al. (2011) (mice; repeated dose study)

In the non-guideline repeated dose study focussing on male reproductive organ conducted by Takahashi et al. (2011) [32], CrIj:CD(ICR) mice (n=8 males/group) were exposed via i.p. injections of 1,4-dichlorobenzene (> 98.0% purity) once a day, 4-5 times per week, for either 2 or 6 weeks. The doses administered were 0, 100, 200, and 400 mg/kg bw/day.

The results of the 2-week exposure period are not clearly presented. No significant differences in body weight were observed in this study. Notable findings included an increase in epididymal weight at the 100 mg/kg bw/day dose for the 6-week exposure period. There were no significant changes in the weights of the testes, prostate glands, seminal vesicles, or preputial glands, nor were there any effects on serum

testosterone levels. Daily sperm production was significantly decreased at 200 and 400 mg/kg bw/day. Vacuolar degenerations were observed in the ductal epithelia of the epididymis at the 400 mg/kg bw/day dose, and there was increased leakage of tailless spermatozoa in the cauda epididymis across all dose groups.

Takahashi et al. (2011) (mice; Hershberger assay)

The Hershberger assay performed by Takahashi et al. (2011) [32] involved daily i.p. injections using Crlj:CD(ICR) mice, eight castrated male mice per group, for 10 days at doses of 0, 50, 100, and 200 mg/kg bw/day. No effects were found on body weight. There was a significant increase in the weights of the ventral prostate (low dose: absolute and relative weight, high dose: absolute weight) and glans penis (low and mid dose, both absolute and relative weight) in the treated groups.

8.1.3 Other data

Table 8 Reproductive toxicity studies on 1,4-dichlorobenzene - other data

Reference	Experimental design	Concentration	Results	Remarks
Takahashi et al. (2007) [31]	Estrogen-receptorα competitor screening assay ERα Competitor Screening Kit <i>Examinations:</i> determine amount of ligands between fluorescein labeled E2 and plate-coated recombinant human ERα	1,4-dichlorobenzene (>98.0% purity) Up to 10⁻³ M (dissolved in DMSO) tested, individual test concentrations not specified Positive control: bisphenol A	1,4-Dichlorobenzene did not bind to ER α up to 10 ⁻³ M.	Non-guideline, non-GLP
Takahashi et al. (2011) [32]	Androgen receptor binding assay (in ventral prostate) Ventral prostate glands obtained from 19-week old Jcl:SD rats, 24h after castration Test chemical and [³H]testosterone added to prostate cytosol, mixed and incubated at 4 °C for 18–20h. Upon removal of unabsorbed labelled [³H] testosterone, supernatants containing receptor bound [³H]testosterone were counted with LSC	1,4-dichlorobenzene (>98.0% purity) Up to 10⁻³ M tested, individual test concentrations not specified Positive controls: testosterone and dihydrotestosterone	1,4-Dichlorobenzene did not bind to AR up to 10⁻³ M Positive controls: binding of [³H]testosterone to AR was inhibited by testosterone and dihydrotestosterone with 50% inhibitory concentrations of 3×10⁻⁹ and 3×10⁻⁸ M resp.	Non-guideline, non-GLP

ER: estrogen receptor, AR: androgen receptor; LSC: liquid scintillation counting ; DMSO: dimethyl sulfoxide

Takahashi et al. 2007 (estrogen-receptor α binding)

Takahashi et al. (2007) [31] conducted an estrogen-receptor α (ER α) competitor screening assay to examine the inhibitory activity of 1,4-dichlorobenzene against ER α binding. A ER α Competitor Screening Kit was used for this purpose. Bisphenol A was used as positive control. The results were expressed as 50% inhibitory concentration (IC₅₀). 1,4-dichlorobenzene did not bind to ER α up to 10⁻³ M.

Takahashi et al. 2011 (Androgen receptor binding)

Takahashi et al. (2011) [32] conducted an androgen-receptor (AR) binding assay to examine the inhibitory activity of 1,4-dichlorobenzene for the binding of testosterone to AR. The binding of [³H]testosterone to AR was inhibited by testosterone and dihydrotestosterone with the 50% inhibitory concentrations of 3×10⁻⁹ and 3×10⁻⁸ M, respectively. 1,4-Dichlorobenzene did not bind to AR up to 10⁻³ M.

8.2 Adverse effects on development

There are both human data and animal studies on developmental toxicity of 1,4-dichlorobenzene available. The human data are summarized in section 8.2.1. The studies with experimental animals are summarized in table 9 followed by a summary in text in section 8.2.2. These include studies in rats and rabbits, after inhalation and oral exposure.

Only statistically significant results are presented, unless specified otherwise.

8.2.1 Human data**Campbell and Davidson (1970)**

Campbell and Davidson (1970) [33] described a human case report on a pregnant patient that consumed toilet blocks containing 1,4-dichlorobenzene throughout her pregnancy (1-2 per week), due to pica. At 34 weeks, routine peripheral blood examination showed hypochromic, microcytic anaemia with excessive polychromasia and marginal nuclear hyper segmentation of the neutrophils. Peripheral blood parameters returned to normal post pregnancy. No adverse effects on development were observed in this case. Standard neonatal examination revealed no clinical abnormality and haematological analysis of the infants blood appeared normal.

8.2.2 Animal data

Table 9 Developmental toxicity studies in animals on 1,4-dichlorobenzene

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
<i>Inhalation – rats</i>						
Hodge et al. (1977) [34]	Alderley-Park rats, female n=results of 20-24/concentration were presented At start 4 batches of 32 females were included for mating and randomly allocated to treatment groups, to achieve a minimum of 20 pregnancies	Prenatal developmental toxicity study <i>Exposure:</i> 6h/day from GD 6-15 C-section and sacrifice on GD 21 <i>Examinations:</i> clinical signs and BW dams, gross pathology, histopathology of maternal heart lung, liver, kidney, adrenal, ovary and uterus (in case if any foetus was abnormal), plus additionally liver and lung (10 animals/group), implantations, resorptions (early/late), viable foetuses, corpora	1,4-dichlorobenzene (>99% purity) Inhalation, whole-body 0, 75, 500 ppm (analytical concentrations: 0, 74.7, 198.6, 508.4 ppm, corresponding to 0, 0.449, 1.19, 3.06 mg/L) ^a Control: air only	75 ppm: uteri from three females with excessive blood (in one case associated with a dead foetus)	No adverse effects on development	Non-guideline, non-GLP The study authors excluded data of nine females that littered on day 21 (i.e. 2, 2, 5 for low, mid, high concentration).

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
	in any one group	lutea, mean foetal and litter weight, sex ratio, external, skeletal and visceral examination of fetuses <i>Statistical analysis:</i> student's <i>t</i> -test				
Tyl and Neeper-Bradley (1989) [17]	Sprague-Dawley rats, male and female n=28/sex/concentration (F0 and F1)	Two-generation reproductive toxicity study <i>Exposure:</i> F0: 6h/day, 7 days/week for 10 weeks prior to mating, during mating, during gestation until GD 19. Exposure continued from PND 5 until sacrifice at weaning. Mothers were separated from their pups for the exposure period. Males sacrificed after successful mating F1: exposure 6h/day, 7 days/ week for 11	1,4-dichlorobenzene (100% purity) Inhalation, whole-body 0, 50, 150 and 450 ppm (analytical concentrations: 0, 66.3, 211.0, 538.0 ppm, corresponding to 0.398, 1.27, 3.23 mg/L) ^a Control: filtered compressed air	See section 8.1 'Adverse effects on sexual function and fertility' for full details on general/parental toxicity	F1-generation (pups): <i>50 ppm:</i> reduced nr of stillborn pups (1 vs 34 in control, $p < 0.01$; see column 'remark') <i>150 ppm:</i> reduced nr of stillborn (10 vs 34 in control, $p < 0.01$; see column 'remark') <i>450 ppm:</i> reduced litter size at LD4 (10.5 vs 12.9 in control $p < 0.05$), increased nr of dead pups at LD4 (47 vs 17 in control, $p < 0.01$), decreased 4-day pup survival index (82.0% vs 93.8% in control, $p < 0.05$), decreased pup weight at LD0 (-12.5%), LD4	Non-guideline, according to GLP Large discrepancy between target and analytical concentration was noted. Condensation may have occurred. It is noted that of the 34 stillborn pups in control, 27 were from only two litters

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		weeks prior to mating, during mating, during gestation until GD 19. Exposure continued from PND 5 until sacrifice at weaning. Mothers were separated from their pups for the exposure period. Males sacrificed after successful mating <i>Examinations:</i> body weight, food consumption, clinical signs, gross and microscopic pathology, reproductive parameters and indices, litter size, sex ratio, pup bw, pup and litter viability. <i>Statistical analysis:</i> Levene's test for equal variances, ANOVA and t-tests for the quantitative continuous variables.			(precll:-17.2%, postcll: -17.0%), LD7 (-21.6%), LD14 (-21.3%), LD21 (-21.7%), LD28 (-18.7%) (all $p<0.01$)), decreased pup bw gain during LD0-4 (-24.7%, $p<0.05$), LD4-7 (-31.9%, $p<0.01$), LD7-14 (-20.8%, $p<0.05$), LD14-21 (-22.3%, $p<0.01$), LD21-28 (-14.8%, $p<0.01$) F2-generation (pups): 450 ppm: reduced total born alive/litter (10.7 vs 14.0 in control, $p<0.01$), increased nr of stillborn (14 vs 2 in control, $p<0.01$), increased nr of dead pups at LD4 (54 vs 3 in control, reduced litter size at LD4 (10.7 vs 13.9 in control, $p<0.01$), decreased 4-day survival index (71.3% vs 99.1% in control, $p<0.01$), decreased pup weight at LD0 (-12.8%), LD4 (precll: -22.9%, postcll: -21.6%), LD7 (-23.6%), LD14 (-	

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		Kruskal-Wallis test, Mann-Whitney U test and Fisher's exact test for nonparametric data			22.6%), LD21 (-16.3%), LD28 (-16.0%) (all $p < 0.01$) (all $p < 0.01$), decreased pup BW gain during LD0-4 (-37.3%), LD4-7 (-25.6%), LD7-14 (-21.2%), LD21-28 (-15.5%) (all $p < 0.01$) See table 7 for adverse effects on reproduction	
<i>Inhalation – rabbits</i>						
Hayes et al. (1982) [35]	New Zealand White rabbits, females n=7 /concentration (artificially inseminated)	Dose range finder study <i>Exposure:</i> 6h/day, from GD6-18 (day of insemination considered as GD0) C-section and sacrifice at GD19 <i>Examinations:</i> clinical signs, maternal body weights, organ weights (liver, kidney), gross pathology, histological examination (liver	1,4-Dichlorobenzene (99.97% purity) Inhalation, whole body 0, 300, 600 or 1000 ppm (analytical concentrations: 0, 297, 575, 933 ppm, corresponding to 1.79, 3.46, 5.61 mg/L) ^a	Significant linear trend for a decreased BW gain. No further significant maternal toxicity was observed.	No adverse effects on development	Non-guideline, according to GLP Based on this probe study, exposure levels of 100, 300 and 800 ppm are selected for main prenatal developmental toxicity study (see Hayes et al. 1982, 1985)

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		only), number of corpora lutea, number and position of the live, dead and resorbed fetuses, <i>Statistical analysis:</i> Wilcoxon test (for frequency pre-implantation loss, resorptions), Fisher exact probability test (for other incidence data), parametric or non-parametric analysis of variance followed by Dunnett's test or distribution free multiple comparison (other data)	Control: air only			
Hayes et al. (1982, 1985) [35, 36]	New Zealand white rabbits, female n=29-30/concentration	Prenatal developmental toxicity study <i>Exposure:</i> 6h/day from GD 6-18 (day of insemination considered GD0)	1,4-dichlorobenzene (99.9% purity) Inhalation, whole body	<i>300 ppm:</i> one female died on GD10, with multiple large intrathoracic abscesses which interfered with both circulatory and respiratory systems (not treatment related) <i>800 ppm:</i> decreased BW gain during GD6-8 (-1125%, p<0.05),	<i>300 ppm:</i> increased pale liver-torsion of a portion of a lobe (8% vs. 0% in control in fetuses, 18% vs. 0% in control in litter, p<0.05), increased % of implantations resorbed (16% vs. 7% in control, p<0.05), increased % of	Non-guideline, according to GLP

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
	(artificially inseminated)	C-section and sacrifice at GD29 <i>Examinations:</i> clinical signs, maternal body weights, maternal organ weights (liver and kidney), number and position of foetuses in utero, number of live and dead foetuses, number and position of resorption sites, number of corpora lutea, foetal sex, body weights and crown-rump length, foetal external, soft tissue and skeletal alterations <i>Statistical analysis:</i> Bartlett's test for equality of variance, subsequent ANOVA followed by either Dunnett's test or the Wilcoxon rank-sum test with Bonferroni's correction (bw and	0, 100, 300 or 800 ppm (analytical concentrations: 0, 103, 306 or 791 ppm, corresponding to 0, 0.619, 1.84, 4.76 mg/L)^a Control: air only	increased BW gain during GD19-28 (+200.0%, $p < 0.05$)	litters with resorptions (63% vs. 29% in control, $p < 0.05$; though within range of HCD of 22 studies of 0-70% (mean 40%)) <i>800 ppm:</i> increased incidence of retroesophageal right subclavian artery (5% vs. 1% in control in foetuses, 18% vs. 4% in control in litter, $p < 0.05$)	

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		organ weights), sensored Wilcoxon test (foetal alterations and resorptions), Fisher exact probability test (other data)				
<i>Oral - rats</i>						
Ruddick et al. (1983) [37]	Sprague-Dawley rats, female n=unknown	Prenatal developmental toxicity study <i>Exposure:</i> from GD 6 to 15 Day of C-section and sacrifice: not specified <i>Examinations:</i> maternal BW gain, histopathology and biochemical analysis (not further specified) in dams, litter size, foetal weight, skeletal and visceral examinations, residue analysis and microscopy	1,4-dichlorobenzene (purity unknown) Oral, via gavage 50, 100, and 200 mg/kg bw/day Control: unknown	No maternal toxicity observed	No teratological effects observed	TG guideline and GLP unknown Abstract only available, limited information available

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		<i>Statistical analysis:</i> not described				
Giavini et al. (1986) [38]	CD-rats, female n=13-17 mated/dose	Prenatal developmental toxicity study <i>Exposure:</i> from GD6-15 C-section and sacrifice at GD 21 <i>Examinations:</i> clinical signs, food consumption and bw dams, gross pathology, histopathology of liver, number of corpora lutea, live/dead/reabsorbed fetuses, foetal weight, skeletal and visceral examinations <i>Statistical analysis:</i> analysis of variance, 2×2 contingency chi-square test	1,4-dichlorobenzene (99% purity) Oral, via gavage 0, 250, 500, 750, 1000 mg/kg bw/day Control: corn oil	<i>250 mg/kg bw/day:</i> decreased food consumption (-11.1%, p<0.01) during GD6-15 <i>500 mg/kg bw/day:</i> one dead dam, decreased weight gain (-20.4%, p<0.05) and decreased food consumption (-11.1%, p<0.01) during GD6-15 <i>750 mg/kg bw/day:</i> decreased weight gain (-22.3%, p<0.05) and decreased food consumption (-14.1%, P<0.01) during GD6-15 <i>1000 mg/kg bw/day:</i> one dead dam, decreased weight gain (-55.0%, p<0.01) and decreased food consumption (-20%, p<0.01) during GD6-15	<i>500 mg/kg bw/day:</i> increased number of extra ribs (15 vs. 7 in control, p<0.05) <i>750 mg/kg bw/day:</i> increased number of fetuses with skeletal variations (50.0% vs. 35.7% in control, p<0.05), increased number of extra ribs (35 vs. 7 in control, p<0.05) <i>1000 mg/kg bw/day:</i> decreased foetal BW (-8.1%, p<0.01), increased number of fetuses with skeletal variations (50.6% vs. 35.7% in control, p<0.05), increased number of extra ribs (26 vs. 7 in control, p<0.05)	Non-guideline, non-GLP Reason of maternal deaths in 500 and 1000 mg/kg bw/day groups are described as technical error, with no further details.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
Bornatowicz et al. (1994) [25]	Sprague-Dawley rats, male and female n=24/sex/dose (both generations)	Two-generation reproduction toxicity study <i>Exposure:</i> F0: males 77 days, females 14 days before mating; followed by exposure during mating for both sexes. Females additionally exposed during gestation and lactation until weaning F1: both sexes 84 days before mating; followed by exposure during mating for both sexes. Females additionally exposed during gestation and lactation until weaning <i>Examinations:</i> Fertility and reproductive indices, general observation for physical or behavioral changes, body weight, feed	1,4-dichlorobenzene (99% purity) Oral, gavage 0, 30, 90 and 270 mg/kg bw/day Control: olive oil only	See section 8.1 'Adverse effects on sexual function and fertility' for full details on general/parental toxicity	F1-generation (pups): <i>90 mg/kg bw/day:</i> decreased pup BW at birth (-8.4%, p<0.05), tail constrictions (ring tail) <i>270 mg/kg bw/day:</i> decreased pup BW at birth (-22.6%, p<0.05), LD7 (-27.0%, p<0.05), LD14 (-18.6%, p<0.05) and LD21 (-16.5%, p<0.05), increased pup mortality between birth and LD4 (62 vs. 3 in control, p<0.05), increased pup mortality between day 5-21 (5 vs. 1 in control, p<0.05), decreased total number of pups born alive (192 vs. 205 in control, p<0.05), increased number of stillborn pups (39 vs. 9 in control, p<0.05), tail constrictions (ring tail), average delayed eye opening (day 15.79 vs. 14.94 in control, p<0.05),	OECD TG 416, according to GLP Limited quantitative details presented on the general toxicity and reproductive parameters See table 7 for adverse effects on reproduction, see section 8.3 for effects on lactation

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		consumption, organ weights, histopathological changes of parent animals (though not systematically done in control and high dose F0 and F1), litter size and pup mortality, sex ratio, reflexes and behaviour of pups, developmental milestones, body weight of pups, and malformations (only for pups that died before LD4, and pups excluded after culling) were examined. <i>Statistical analysis:</i> one-way ANOVA, Scheffé's test, Kruskal-Wallis or Wilcoxon-Mann-Whitney, Chi-square or Fisher exact			behavioural changes in draw up test. F2-generation (pups): <i>90 mg/kg bw/day:</i> increased pup mortality between birth and day 4 (17 vs. 3 in control, $p < 0.05$), tail constrictions (ring tail), behavioural changes in draw up test <i>270 mg/kg bw/day:</i> decreased pup BW weight at birth (-16.7%, $p < 0.05$), at LD4 (-20.7%, $p < 0.05$), at LD7 (-25.8%, $p < 0.05$), at LD14 (-19.0%, $p < 0.05$) and LD21 (-17.8%, $p < 0.05$), increased pup mortality between birth and day 4 (31 vs. 3 in control, $p < 0.05$), increased pup mortality between day 5-21 (6 vs. 1, $p < 0.05$), decreased total number of pups born alive (226 vs. 286 in control, $p < 0.05$), increased number of stillborn pups (27 vs. 8 in	

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
					control, $p < 0.05$), tail constrictions (ring tail), average delayed eye opening (day 15.94 vs. 15.35 in control, $p < 0.05$), delayed eye opening for all pups (day 17.31 vs. 16.40 in control, $p < 0.05$), delayed erection of ears for all pups (day 4.63 vs. 3.80 in control, $p < 0.05$), behavioural changes in draw up test.	
Makita (2004) [26]	Wistar rats, female n=6 pregnant females/dose	Perinatal developmental toxicity study focussing on the development, onset of puberty and reproductive organs of the female offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with	1,4-dichlorobenzene (purity 99.9%) Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)	No maternal effects observed	Increased thymus weight at PND42 (not quantified; results presented in graph) See table 7 for the effects on onset of puberty and reproductive organs	Non-guideline, non-GLP This study only includes the effects on female offspring until 6 weeks of age. The effects on male offspring up to week 6 are presented by Makita (2005).

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND42. <i>Examinations:</i> Maternal animals: body weight and food consumption Offspring: body weight, food consumption after weaning, sex, viability, gross malformations, organ weights, histopathology, eye opening, anogenital distance, vaginal opening, blood LH and FSH <i>Statistical analysis:</i> two-way analysis of variance (two-way				Given the similar reproductive outcomes for the dams in these two papers, it may be assumed that the data originate from the same experiment.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		ANOVA), with dam data on individual basis, and offspring data with litter as unit				
Makita (2005) [27]	Wistar rats, female n=6 pregnant females/dose	Perinatal developmental toxicity study focussing on the development, onset of puberty and reproductive organs of the male offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal	1,4-dichlorobenzene (purity 99.9%) Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)	No maternal effects observed	No developmental effects observed See table 7 for the effects on onset of puberty and reproductive organs	Non-guideline, non-GLP This study only includes the effects on male offspring until 6 weeks of age. The effects on female offspring up to week 6 are presented by Makita (2004). Given the similar reproductive outcomes for the dams in these two papers, it may be assumed that the data originate from

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		feed until sacrifice at PND42 <i>Examinations:</i> Maternal animals: body weights, food consumption Offspring: body weight, food consumption after weaning, sex, viability, gross malformations, organ weights, histopathology, eye opening, anogenital distance, preputial separation, blood testosterone, LH and FSH <i>Statistical analysis:</i> two-way analysis of variance (two-way ANOVA), with dam data on individual basis, and offspring data with litter as unit				the same experiment.

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
Makita and Omura (2006) [28]	Wistar rats, female n=6 pregnant females/dose	Perinatal developmental toxicity study focussing on the development, onset of puberty and reproductive organs of the male offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND 2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND112 <i>Examinations:</i>	1,4-dichlorobenzene (purity 99.9%) Oral, via diet 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)	No maternal effects observed	No developmental effects observed See table 7 for the effects on onset of puberty and reproductive organs.	Non-guideline, non-GLP This study focusses on male offspring until 16 weeks of age. The effects on female offspring up to week 16 are presented by Makita (2008). When compared to Makita (2005), this study includes additionally analysis of sperm. Given the different reproductive outcomes for the dams in these two

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		Maternal animals: body weight Offspring: body weight, food consumption after weaning, gross malformations, organ weights, histopathology, sperm analysis (count, motility, morphology), eye opening, anogenital distance, preputial separation, blood testosterone, FSH and LH <i>Statistical analysis:</i> two-way analysis of variance (two-way ANOVA), with dam data on individual basis, and offspring data with litter as unit				papers, it is assumed that the data originate from different experiments.
Makita (2008) [29]	Wistar rats, female n=6 pregnant females/dose	Perinatal developmental toxicity study focussing on the development, onset of puberty and	1,4-dichlorobenzene (purity 99.9%) Oral, via diet	No maternal effects observed	No developmental effects observed See table 7 for the effects on onset of puberty and reproductive organs.	Non-guideline, non-GLP This study focusses on female

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		reproductive organs of the female offspring <i>Exposure:</i> GD1 till PND21 (42 days total) On PND2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND112 <i>Examinations:</i> Maternal animals: body weights, food consumption Offspring: body weight, food consumption after	Dose: 0 or 25 ppm (0 or 2 mg/kg bw/day) Control: CE-2 only (rat chow)			offspring until 16 weeks of age. The effects on male offspring up to week 16 are presented by Makita and Omura (2006). When compared to Makita (2004), this study includes additionally analysis of oestrus cyclus Given the different reproductive outcomes for the dams in these two papers, it is assumed that the data originate from

Reference	Species	Experimental period and design	Dose/concentration and route	General toxicity	Effects on development	Remarks
		weaning, gross malformations, organ weights, histopathology, oestrus cyclicity, eye opening, anogenital distance, vaginal opening, blood testosterone, oestradiol, FSH and LH <i>Statistical analysis:</i> two-way analysis of variance (two-way ANOVA) plus Fisher's least significant difference procedure. Dam data on individual basis, and offspring data with litter as unit. Significant level was set at $P < 0.05$.				different experiments

^a: converted conform the CLP-guidance (https://echa.europa.eu/documents/10162/2324906/clp_part3_en.pdf/42e0397a-73f2-0583-958f-3830928e1604?t=1730718832043)

GD: gestation day; PND: post-natal day; LD: lactation day; HCD: historical control data; BW: body weight; resp.: respectively

8.2.2.1 Inhalation

8.2.2.1.1 *Rats***Hodge et al. (1977)**

In a prenatal developmental toxicity study conducted by Hodge et al. (1977) [34] (non-guideline, non-GLP), groups of pregnant Alderley-Park rats were whole-body exposed via inhalation to 0 (air only), 75, 200 or 500 ppm (analytical concentrations: 0, 74.7, 198.6, 508.4 ppm, corresponding to 0, 0.449, 1.19, 3.06 mg/L) 1,4-dichlorobenzene for 6h/day from gestation day 6 to 15. Rats were killed on day 21 of the pregnancy and the foetuses removed and examined. The results of 20-24 pregnant females/concentration were presented.

No maternal toxicity was observed, except for three 75 ppm females with excessive blood in uteri (in one case associated with a dead foetus). No statistically significant effects were observed on number of implantations, resorptions, viable foetuses or corpora lutea, or on mean foetal or litter weight, on sex ratio, or on implantation efficiency (i.e. numbers of numbers of implantations/corpora lutea). No increase in the number of runts was observed. Anomalies were low in number, not statistically significantly increased upon treatment, or reported to be within the normal range.

Tyl and Neeper-Bradley (1989)

In a two-generation reproduction toxicity study (non-guideline) performed by Tyl and Neeper-Bradley (1989) [17], Sprague-Dawley rats (n=28/sex/concentration) were whole-body exposed via inhalation to 1,4-dichlorobenzene (100% purity) at target concentrations of 0, 50, 150 and 450 ppm (analytical concentrations 0.0, 66.3, 211.0, 538.0 ppm; corresponding to 0, 0.398, 1.27, and 3.23 mg/L). Exposure was applied for 10 weeks (F0) or 11 weeks (F1) prior to mating, during mating, and during gestation until GD19. Exposure continued from PND 5 until sacrifice at weaning. Mothers were separated from their pups for the exposure period. Males sacrificed after successful mating.

A large discrepancy between target and analytical concentration was noted. Condensation may have occurred.

See section 8.1 for full details on general/parental toxicity.

The highest tested concentration resulted in perinatal pup mortality. This included reduced total born alive/litter (F2: 10.7 vs 14.0 in control), increased nr of stillborn (F2: 14 vs 2 in control), increased nr of dead pups at LD4 (F1: 47 vs 17 in control, F2: 54 vs 3 in control), a reduced litter size at LD4 (F1: 10.5 vs 12.9 in control and F2: 10.7 vs 13.9), decreased 4-day pup survival index (F1: 82.0% vs 93.8% in control, F2: 71.3% vs 99.1%). In addition, pup weight and pup weight gain of the high concentration F1 and F2 were reduced not only at LD0, but this also remained during the lactation period up to LD28, albeit not statistically significant on D14-21. The effects on reproduction observed in this study are summarised in section 8.1. The effects on/via lactation are summarised in section 8.3.

8.2.2.1.2 *Rabbit***Hayes et al. (1982)**

A dose range finding study (non-guideline, GLP-compliant) was performed by Hayes et al. (1982) [35]. New Zealand white rabbits (n=7/concentration) were artificially inseminated and whole-body exposed via inhalation to target concentrations of 0, 300, 600 or 1000

ppm (analytical concentrations: 0, 297, 575, 933 ppm, corresponding to 1.79, 3.46, 5.61 mg/L) 1,4-dichlorobenzene (>99.97% purity) vapour. The rabbits were exposed for 6h/day from day 6 through 18 of gestation. On day 19 of gestation animals were sacrificed and examined. No significant maternal toxicity occurred, except for a significant linear trend for a decreased BW gain. Adverse effects on development were not observed.

Hayes et al. (1982)/ Hayes et al. (1985)

In a prenatal developmental toxicity study (non-guideline; GLP compliant) performed by Hayes et al. (1982, 1985) [35, 36], 30 New Zealand white female rabbits/concentration were whole body exposed via inhalation to 1,4-dichlorobenzene (99.9% purity) for 6h/day from day 6 to 18 of gestation (artificial insemination). The tested concentrations were 0, 100, 300, and 800 ppm (analytical concentrations: 0, 103, 306 or 791 ppm, corresponding to 0, 0.619, 1.84, 4.76 mg/L).

Results showed one dead female at 300 ppm on GD 10. The necropsy showed that the animal had multiple large intrathoracic abscesses which interfered with both circulatory and respiratory systems. Other maternal effects observed were limited to a significantly lower body weight gain at 800 ppm.

The number of corpora lutea, implantation, number of live foetuses, foetus and litter weight, and the sex ratio were not significantly different from those of the control group. At 300 ppm an increase of resorptions was observed (63% of litters with resorptions compared to 29% in control). However, no dose-response was noticed (no such effect in 100 ppm and 800 ppm groups) and the value for the 300 ppm group was within the historical control values of the laboratory. Regarding the foetal alterations various effects were observed in single cases for all groups including the controls. Only for the 800 ppm group, a significant increase in incidence of a retroesophageal right subclavian artery was observed (6 foetuses (5 litters) vs. 1 foetus (1 litter) in control).

8.2.2.2 Oral

8.2.2.2.1 Rats

Ruddick et al. (1983)

In the prenatal developmental toxicity study performed by Ruddick et al. (1983) [37] female Sprague-Dawley rats (number/group not specified) were exposed during gestation day 6 to 15 to 1,4-dichlorobenzene (unknown purity) via oral gavage at doses of 0, 50, 100, and 200 mg/kg bw/day. Details about the control group are not provided. The findings indicated no maternal toxicity and no teratological effects in the rats. However, the information available from this study is limited as only an abstract is accessible.

Giavini et al. (1986)

In the non-guideline prenatal developmental toxicity study performed by Giavini et al. (1986) [38], female CD-rats (n=13-17/dose) were exposed by oral gavage to 1,4-dichlorobenzene (99% purity). Exposure occurred from gestation day 6 to 15. The dose levels used were 0, 250, 500, 750, and 1000 mg/kg bw/day in corn oil.

After dosing of ≥ 500 mg/kg bw/day, maternal BW weight gain was significantly decreased during GD 6-15, associated with a significant

food consumption decrease in all dosing groups. Maternal deaths were observed in the 500 and 1000 mg/kg bw/day groups (one in each group) which were, according to the study authors, due to 'a technical error'.

Foetal body weight was significantly reduced in the high dose group. A significant increase in the number of skeletal variations was observed at 750 and 1000 mg/kg bw/day. Specifically an increase in the frequency of extra ribs was observed at doses of ≥ 500 mg/kg bw/day.

Bornatowicz et al. (1994)

In an oral two-generation reproduction toxicity study (GLP compliance; OECD TG 416), Bornatowicz et al. (1994) [25] exposed Sprague-Dawley rats to 0, 30, 90 and 270 mg/kg bw/day 1,4-dichlorobenzene (99% purity) by gavage, for 7 days/week. The F0 generation consisted of 24 rats/sex/dose and were treated for 77 days (males) or 14 days (females) before mating, followed by exposure of both sexes during mating. Females were exposed for an additional period during gestation and lactation until weaning of the F1 pups on postnatal day 21. The F1 generation consisted of 24 rats/sex/dose and both sexes were exposed for 84 days before mating, followed by exposure during mating. Females were exposed for an additional period during gestation and lactation. Weaning of the F2 pups on postnatal day 21 was the end of the study. In the 90 mg/kg bw/day group, a decreased pup BW at birth (F1 pups), a significant increase in pup mortality between birth and day 4 (F2 pups) and tail constrictions (ring tail) (F1 and F2 pups) were observed. In the 270 mg/kg bw/day group, reduced pup BW at birth and during lactation, a significant increased pup mortality between birth and day 4, an increased pup mortality between day 5-21, a decreased total number of pups born alive, and an increased number of stillborn pups were observed in both generations. In addition to these effects in the high dose group, tail constrictions (ring tail), behavioural changes in draw up test and a delayed average eye opening (both generations) and delayed erection of ears (F2 pups) were shown.

The effects on general toxicity and reproductive toxicity observed in this study are summarised in section 8.1. Effects on lactation are summarised in section 8.3.

Makita (2004), Makita (2005), Makita and Omura (2006), Makita (2008)

In perinatal developmental toxicity studies (non-guideline), Makita (2004) [26], Makita (2005) [27], Makita and Omura (2006) [28] and Makita (2008) [29] exposed pregnant Wistar rats (n=6/dose) via diet to 0 or 25 ppm (0 and 2 mg/kg bw/day) 1,4-dichlorobenzene (99.9% purity) from GD1 to PND 21 (total 42 days). On PND 2, litters were culled to 4 male and 4 female pups per litter. After parturition, the pups were kept with their respective dams until weaning on PND21. On PND 22 the pups were weaned and housed separately by gender in each litter. These pups received normal feed until sacrifice at PND42 or PND96. Makita (2004) and Makita (2008) focussed on the development, onset of puberty and reproductive organs of the female offspring, whereas Makita (2005) and Makita and Omura (2006) focussed on these effects in male offspring.

No maternal toxicity (i.e. no effect on bw and food consumption) was observed in any of these studies.

Except for an increased thymus weight in female offspring (only observed in the 2004 study of Makita and not in the 2008 study), no adverse effects on development were observed in these studies, i.e. no effect on pup bw, food consumption after weaning, viability, gross malformations, day of eye opening, organ weights and histopathology. See chapter 8.1 for a description of the onset of puberty and reproductive organs.

8.3 Adverse effects on or via lactation

There are two human and six animal studies available in which effects of 1,4-dichlorobenzene on/via lactation are described. The human studies are summarized in chapter 8.3.1. The study with experimental animals is summarized in chapter 8.3.2. This concerns a two-generation study in rats upon inhalation and one upon oral exposure, in addition to a combination of four perinatal developmental toxicity studies in rats. Only statistically significant results are presented, unless specified otherwise.

8.3.1 Human data

Table 10 Studies on or via lactation with 1,4-dichlorobenzene – human data

Reference	Species	Experimental period and design	General toxicity	Remarks
Blount et al. (2010) [39]	Human women n=12	Women breastfeeding and at least in 30 days <i>post-partum</i> Different collection methods tested: - Manual expression directly into a Vacutainer® - Manual expression into a 30 mL glass jar then immediate transfer to a Vacutainer® - Breast pump then immediate transfer to a Vacutainer® Around 7.5 mL collected	Median concentration of 1,4-dichlorobenzene = 0.170 ng/mL, range from 0.120-0.59 ng/mL	Study primarily focussed on development of method for collection, storing and analysis of breast milk samples for VOCs
Juvancz et al. (2010) [40]	Human women n=1	N.A.	0.8 µg/L was measured in a human milk sample from a mother one week after her first delivery	

Blount et al. (2010)

Blount et al. (2010) [39] evaluated the concentration of 1,4-dichlorobenzene in 12 women breastfeeding who are at least in 30 days *post-partum*. Different sampling methods were used to collect the breastmilk: manual expression directly into a Vacutainer®, manual expression into a 30 mL glass jar then immediate transfer to a Vacutainer®, or breast pump then immediate transfer to a Vacutainer®. For every sample around 7.5 mL was collected. Results showed that the

median concentration of 1,4-dichlorobenzene in the breastmilk of these women was 0.170 ng/mL with a range from 0.120-0.59 ng/mL.

Juvancz et al. (2010)

Juvancz et al. (2010) [40] studied the concentrations 1,4-dichlorobenzene in a variety of environmental matrices, including human breast milk. A concentration of 0.8 µg/L 1,4-dichlorobenzene was found in a human milk sample from a single mother one week after her first delivery.

8.3.2

Animal data

Tyl and Neeper-Bradley (1989)

In a two-generation reproduction toxicity study (non-guideline) performed by Tyl and Neeper-Bradley (1989) [17], Sprague-Dawley rats were exposed to 1,4-dichlorobenzene (100% purity) via inhalation at target concentrations of 0, 50, 150 and 450 ppm (analytical concentrations 0.0, 66.3, 211.0, 538.0 ppm corresponding to 0, 0.398, 1.27, and 3.23 mg/L). Exposure was applied for 10 weeks (F0) or 11 weeks (F1) prior to mating, during mating, and during gestation until GD19. Exposure continued from PND 5 until sacrifice at weaning.

Mothers were separated from their pups for the exposure period. A large discrepancy between target and analytical concentration was noted. Condensation may have occurred.

The effects on reproductive toxicity observed in this study are summarised in section 8.1. The effects on developmental toxicity are summarised in section 8.2.

Specifically during the lactation period, some maternal toxicity was observed. F0 maternal lactational body weights were unaffected throughout lactation, but lactational body weight gains were increased during LD14-21 and LD0-28 at high concentration. For F1 female adult animals of the high concentration group, lactational BW was reduced at LD0 (-10.6%), LD4 (-7.8%) and LD7 (-7.9%). Lactational BW gain in adult F1 females was however increased at LD0-28 at high concentration, and increased during LD21-28 and LD0-28 in mid concentration.

Effects on the pups were observed during the lactation period. This included increased nr of dead pups at LD4 (F1: 47 vs 17 in control, F2: 54 vs 3 in control), a reduced litter size at LD4 (F1: 10.5 vs 12.9 in control and F2: 10.7 vs 13.9), decreased 4-day pup survival index (F1: 82.0% vs 93.8% in control, F2: 71.3% vs 99.1%). In addition, pup weight and pup weight gain of the high concentration F1 and F2 were reduced not only at LD0, but this also remained during the lactation period up to LD28.

No treatment-related gross lesions were observed in F1 and F2 pups that died during lactation.

Bornatowisz et al. (1994)

In an oral two-generation reproduction toxicity study (GLP compliance; OECD TG 416), Bornatowicz et al. (1994) [25] exposed Sprague-Dawley rats to 0, 30, 90 and 270 mg/kg bw/day 1,4-dichlorobenzene by gavage, for 7 days/week. The F0 generation consisted of 24 rats/sex/dose and were treated for 77 days (males) or 14 days (females) before mating, followed by exposure of both sexes during mating. Females were exposed for an additional period during gestation

and lactation until weaning of the F1 pups on postnatal day 21. The F1 generation consisted of 24 rats/sex/dose and both sexes were exposed for 84 days before mating, followed by exposure during mating. Females were exposed for an additional period during gestation and lactation. Weaning of the F2 pups on postnatal day 21 was the end of the study. The effects on general toxicity and reproductive toxicity observed in this study are summarised in section 8.1. Effects on developmental toxicity are summarised in section 8.2.

Specifically during lactation period, increased pup mortality was observed between birth and LD4 of the F1-generation in the high dose group (62 vs. 3). In this generation, in the same dose group also increased pup mortality between LD5-21 (5 vs. 1, $p < 0.05$) and decreased pup BW at LD7 (-27.0%, $p < 0.05$), LD14 (-18.6%, $p < 0.05$) and LD21 (-16.5%, $p < 0.05$) were observed. In the F2 generation, an increased pup mortality was observed between birth and LD4 after dosing of 90 mg/kg bw/day (17 vs. 3). In the high dose group, increased pup mortality was observed between birth and LD4 (31 vs. 3)), as well as an increased pup mortality between LD5-21 (6 vs. 1) and decreased pup BW weight at LD4 (-20.7%, $p < 0.05$), at LD7 (-25.8%, $p < 0.05$), at LD14 (-19.0%, $p < 0.05$) and LD21 (-17.8%, $p < 0.05$)

Makita (2004), Makita (2005), Makita and Omura (2006), Makita (2008)

The perinatal developmental toxicity studies (non-guideline) of Makita (2004) [26], Makita (2005) [27], Makita and Omura (2006) [28] and Makita (2008) [29] included the lactation phase as well. The studies focussed on the development, onset of puberty and reproductive organs of the offspring. See paragraph 8.1 and 8.2 for full details on the conduct of the study. No adverse effects were observed during lactation phase.

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