The MAK Collection for Occupational Health and Safety

# 1,4-Dichlorobenzene

## MAK Value Documentation, addendum – Translation of the German version from 2018

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# 1,4-Dichlorobenzene

## MAK Value Documentation

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### Abstract

The German Commission for the investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated 1,4-dichlorobenzene [106-46-7] considering all toxicological endpoints. Available publications and unpublished study reports are described in detail.
In mouse liver, 1,4-dichlorobenzene causes carcinoma after oral and inhalation exposure and is mitogenic and cytotoxic. In reliable studies it is not genotoxic. As a non-genotoxic mechanism is of prime importance and genotoxic effects play at most a minor part, provided the maximum concentration at the workplace (MAK value) is observed, 1,4-dichlororbenzene is now classified in Category 4 for carcinogenic substances.
The chronic local NOAEC of 20 ml/m³ for changes in the olfactory epithelium of the rat nose would correspond to a MAK value of 10 ml/m³. However, the most sensitive toxicological effect is hepatocellular hypertrophy with a LOAEL of 10 mg/kg body weight and day in an oral 52-week study with dogs. Because of the low severity and incidence of the effect, a NAEL (no adverse effect level) of 5 mg/kg body weight and day is assumed. This NAEL is scaled to a MAK value of 2 ml/m³. Since a systemic effect is critical, Peak Limitation Category II is assigned. As it is not known if the effects are due to the metabolites or 1,4-dichlorobenzene itself, the default excursion factor of 2 is assigned.
The NOAECs for developmental toxicity in rats and rabbits are 500 and 100 ml/m³, respectively, and the differences to the MAK value are sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and 1,4-dichlorobenzene is assigned to Pregnancy Risk Group C. Skin contact may contribute significantly to systemic toxicity and 1,4-dichlorobenzene remains designated with an "H" notation. Sensitization is not expected from the limited data.



### Keywords

1,4-dichlorobenzene; p-dichlorobenzene; p-chlorophenyl chloride; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance



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# 1,4-Dichlorobenzene

**[106-46-7]**

**Supplement 2018**

| | | |
|---|---|---|
| **MAK value (2017)** | **2 ml/m³ (ppm) ≙ 12 mg/m³** | |
| **Peak limitation (2017)** | **Category II, excursion factor 2** | |
| **Absorption through the skin (2001)** | **H** | |
| **Sensitization** | **–** | |
| **Carcinogenicity (2017)** | **Category 4** | |
| **Prenatal toxicity (2017)** | **Pregnancy Risk Group C** | |
| **Germ cell mutagenicity** | **–** | |
| **BAT value** | **–** | |
| **EKA (2005)** | **1,4-dichlorobenzene (air)** | **2,5-dichlorophenol (after hydrolysis) (urine)** |
| | **10 ml/m³** | **20 mg/g creatinine** |
| | **20 ml/m³** | **40 mg/g creatinine** |
| | **50 ml/m³** | **100 mg/g creatinine** |

| | |
|---|---|
| Melting point | 52.09 °C (SRC 2015) |
| Boiling point at 1013 hPa | 174.12 °C (ECHA 2015) |
| Vapour pressure at 25 °C | 2.3 hPa (SRC 2015) |
| log $K_{OW}$[1)] | 3.44 (SRC 2015) |
| Solubility at 25 °C | 81.3 mg/l water (SRC 2015) |
| **1 ml/m³ (ppm) ≙ 6.1 mg/m³** | **1 mg/m³ ≙ 0.164 ml/m³ (ppm)** |

Documentation from 1991 (documentation "1,4-Dichlorobenzene" 1992) and a supplement from 2001 (supplement "1,4-Dichlorobenzene" 2003) are available.

As new studies are now available, this supplement has become necessary. It is based mainly on the data compilations in EU (2004) and SCOEL (2014).

1) octanol/water partition coefficient

## 1 Toxic Effects and Mode of Action

1,4-Dichlorobenzene is slightly irritating to the skin and eyes of humans and animals. In long-term inhalation studies with rats and mice, the most sensitive end points were changes in the olfactory and respiratory epithelium of the nose at concentrations of 75 ml/m$^3$ and above. After repeated uptake of 1,4-dichlorobenzene, particularly the liver was found to be the target organ in rats, mice and dogs, and also the kidneys in male rats. At high concentrations of 1,4-dichlorobenzene, increased kidney weights were found also in female rats and in male and female mice.

In mice, ingestion and inhalation of 1,4-dichlorobenzene produced significantly increased incidences of hepatocellular adenomas and carcinomas and also of rare hepatoblastomas, though only at the highest dose and concentration tested of 600 mg/kg body weight and day and 300 ml/m$^3$, respectively. After inhalation exposure, also histiocytic sarcomas occurred in the liver of male mice at 300 ml/m$^3$. After oral administration, 1,4-dichlorobenzene caused carcinomas of the kidneys in male rats, which can be attributed to the species-specific and sex-specific mechanism of $\alpha_{2u}$-globulin nephropathy. This has no relevance for humans. Mononuclear cell leukaemia, which occurs with a high spontaneous incidence, was found in male F344 rats, and in the inhalation study, C-cell adenomas were observed in the thyroid gland of female rats.

In a study of prenatal developmental toxicity in rabbits, the number of resorptions was increased at concentrations of 200 ml/m$^3$ and above, and retro-oesophageal displacement of the right subclavian artery and deformation of the paws on flexion were found at the highest concentration tested of 800 ml/m$^3$. After the administration of 500 mg/kg body weight and day and above by gavage, the foetal weights were reduced and the number of skeletal anomalies after prenatal exposure was increased in rats. In two-generation studies with rats, the litter size was reduced after inhalation exposure to 538 ml/m$^3$ as were the foetal weights at birth after gavage administration of 90 mg/kg body weight and day and above.

The majority of in vitro and in vivo tests did not reveal any genotoxic effects. The few positive results from in vitro studies were either not reproducible or were carried out using test systems not in accordance with test guidelines, and were probably falsely positive as a result of cytotoxicity. Evidence of genotoxic effects in individual organs such as the kidneys and the liver was found in in vivo studies not conforming to the test guidelines. The induction of micronuclei in rat kidney cells stimulated to proliferation was an isolated finding obtained at different time points. Its dose-dependency was not investigated. Overall, the reliable studies show that 1,4-dichlorobenzene does not have genotoxic potential.

As before, no valid clinical or experimental findings are available which indicate that 1,4-dichlorobenzene causes sensitization of the skin or airways.

## 2 Mechanism of Action

**Liver**

In mice, after the ingestion or inhalation of 1,4-dichlorobenzene, carcinogenic effects were found in the liver (Aiso et al. 2005 b; NTP 1987). The hepatocellular carcinomas occurred only at hepatotoxic doses in the mice. In the studies with rats, no carcinogenic effects on the liver were found. In rats, only slight hepatotoxicity was observed. Chlorohydroquinones and their glutathione conjugates could be involved in the carcinogenicity of 1,4-dichlorobenzene via the formation of reactive oxygen species (SCOEL 2014). In haemoxigenase-1 reporter mice, it was found that administering two 1,4-dichlorobenzene doses of 600 mg/kg body weight and day produced a marked induction of oxidative stress in the liver in vivo (Henderson et al. 2015). Several studies demonstrated 1,4-dichlorobenzene to have a mitogenic and promoting response in the mouse liver (Eldridge et al. 1992; Umemura et al. 1996), which is possibly mediated by substituted hydroquinone metabolites (Butterworth et al. 2007). 1,4-Dichlorobenzene caused cellular proliferation in the liver of rats and mice (Umemura et al. 1998). The mitogenic effect of 1,4-dichlorobenzene in the liver was observed also without any marked liver toxicity, so that an exclusively cytotoxic mechanism for liver carcinogenesis in the mouse seems unlikely (Butterworth et al. 2007). However, to date, the relationship between cell proliferation, hepatotoxicity and liver tumours is not clear, especially in view of the species differences in the metabolism (SCOEL 2014).

**Kidneys**

The carcinogenic effects found in the kidneys of male rats can be attributed to the species-specific and sex-specific mechanism of $\alpha_{2u}$-globulin nephropathy. This has no relevance for humans (supplement "1,4-Dichlorobenzene" 2003).

## 3 Toxicokinetics and Metabolism

The toxicokinetics and metabolism of 1,4-dichlorobenzene are presented in detail in the supplement from 2001 (supplement "1,4-Dichlorobenzene" 2003).

### 3.1 Absorption, distribution, elimination

The blood:air partition coefficient of 1,4-dichlorobenzene is 87.6 according to the formula of Buist et al. (2012).

After single oral doses of 1,4-dichlorobenzene, the amounts absorbed in rats and mice were 71% and 72%, respectively, of the administered dose. After repeated ingestion, 62% of the administered dose was absorbed by rats. After inhalation exposure to a concentration of 160 ml/m$^3$, the bioavailable amount was 33% and 59% in rats and mice, respectively. After repeated inhalation exposure of rats to 500 ml/m$^3$ it was 25%; this was attributed to concentration-dependent respiratory depression (supplement "1,4-Dichlorobenzene" 2003).

In US EPA (2006) it is reported that after oral administration to rats, 4% was found in the faeces and 80% in the urine; oral absorption is thus in the range of 90% (Butterworth et al. 2007).

The concentration-time courses of 1,4-dichlorobenzene in the exhaled air and in the serum as well as those of the metabolite 2,5-dichlorophenol in the urine were investigated in seven male volunteers exposed for one hour by inhalation to 2.6 ml/m$^3$. The mean pulmonary retention was 56% ± 9%. Excretion with the urine was the main pathway of elimination, and not exhalation. On average, 7.7% of the absorbed dose was eliminated with the urine in the form of 2,5-dichlorophenol within 9.5 hours after the start of exposure. The elimination rate of the metabolite peaked one hour after the end of exposure. Ten minutes after the end of exposure, the concentration of 1,4-dichlorobenzene in the exhaled air was below the detection limit of 0.02 ml/m$^3$. In all volunteers, the concentration of 1,4-dichlorobenzene in the plasma one hour after the end of exposure (on average 10.8 ng/ml) was below half of the concentration immediately after the end of exposure (on average 34.8 ng/ml). Most of the absorbed substance appears to be rapidly distributed in the tissue and complete elimination requires a longer period of time. Using a linear two-compartment model, daily absorption and internal accumulation were estimated to be 0.27 mg/day and 2.9 mg, respectively, after long-term exposure to 1 µl 1,4-dichlorobenzene/m$^3$ (ppb) (Yoshida et al. 2002).

Studies of the dermal penetration of 1,4-dichlorobenzene are not available. Using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and that of Wilschut et al. (1995), fluxes of 0.217, 0.005 and 0.003 mg/cm$^2$ and hour and therefore absorbed amounts of about 430 mg, 10.4 mg and 5.5 mg, respectively, are obtained after exposure of the hands and forearms (2000 cm$^2$) to a saturated aqueous solution of 1,4-dichlorobenzene for one hour.

Regardless of the exposure route, the highest concentrations of 1,4-dichlorobenzene were determined in adipose tissue, in the liver, the kidneys, the lungs, the gonads and the skin (supplement "1,4-Dichlorobenzene" 2003). In male rats, it can accumulate to a minor extent in the kidneys in the form of a complex with $\alpha_{2u}$-globulin (SCOEL 2014).

The elimination of 1,4-dichlorobenzene takes place rapidly; 91% to 97% of the absorbed dose was eliminated within 5 to 7 days after repeated inhalation or ingestion. Irrespective of the exposure route, more than 70% was eliminated with the urine and 3% to 11% with the faeces. After oral administration, up to 12% was detected in the exhaled air in male F344 rats (supplement "1,4-Dichlorobenzene" 2003).

It can be concluded from the available data that marked enterohepatic circulation of 1,4-dichlorobenzene takes place (supplement "1,4-Dichlorobenzene" 2003).

## 3.2 Metabolism

A diagram of the metabolism of 1,4-dichlorobenzene can be found in the 2001 supplement (supplement "1,4-Dichlorobenzene" 2003). 1,4-Dichlorobenzene is oxidized to 2,5-dichlorophenol and eliminated with the urine in free form as well as in the form of sulfate and glucuronic acid conjugates (SCOEL 2014).

The metabolite 2,5-dichlorohydroquinone was found in F344 rats but not in Wistar rats. In an in vitro study with liver microsomes from mice, the formation of 2,5-di-

chlorohydroquinone during the conversion of 1,4-dichlorobenzene was reported; no in vivo data are available in mice (EU 2004; Hissink et al. 1997).

In vitro studies with liver microsomes have shown that a significant amount (15%) of the 1,4-dichlorobenzene in the mouse liver undergoes conversion to the metabolites, whereas the amount converted with liver microsomes from rats and humans was only 0.3% and 1.1%, respectively (Hissink et al. 1997).

## 4 Effects in Humans

There are no new data available for single exposures and carcinogenicity in humans.

### Repeated exposure

In a cross-sectional study, the level of 2,5-dichlorophenol, the main metabolite of 1,4-dichlorobenzene, in the urine of exposed workers at a moth-ball factory in Taiwan was higher (n = 45, 105.38 µg/l, GSD 6.21) than that in control persons not exposed (n = 29, 1.08 µg/l, GSD 3.73). Data regarding health status were obtained using questionnaires and biochemical tests. The blood leukocyte count and the alanine aminotransferase activity in the serum were significantly increased in the exposed persons and correlated significantly with the 2,5-dichlorophenol concentration in the urine. These correlations remained even after adjustment for sex, age and smoking habits. In addition, the blood urea nitrogen (BUN) levels in the exposed workers were significantly increased (13.28 ± 3.32 mg/dl, 11.85 ± 4.00 mg/dl and 15.18 ± 4.05 mg/dl in control persons, indirectly exposed workers and directly exposed workers, respectively). This was found also for the creatinine-adjusted concentrations (BUN/creatinine ratio: 15.59 ± 5.12 mg/dl, 12.50 ± 4.46 mg/dl and 17.88 ± 6.03 mg/dl in control persons, indirectly exposed workers or directly exposed workers, respectively). The group of control persons not exposed consisted of medical and administrative staff. The indirectly exposed workers were employed in the offices and had no direct contact with the raw materials or intermediate products. The directly exposed workers were in contact with raw materials, intermediate products and final products (Hsiao et al. 2009). Substance concentrations in air are not reported in this study. Biomonitoring investigations determined only the free (unconjugated) 2,5-dichlorophenol in urine, which does not permit a sufficiently exact assessment of the exposure. The differences in clinical parameters obtained are only slight and within normal ranges. The correlations given are weak and the exposed persons and those not exposed differ in a few important aspects such as alcohol consumption and smoking status. The Commission therefore does not consider the study to be sufficiently reliable to be used for the derivation of a limit value.

### Local effects on skin and mucous membranes

Repeated skin contact with 1,4-dichlorobenzene in liquid or vapour form causes slight irritation (burning sensation without cracking of the skin) (EU 2004).

It is reported that irritation of the nose and the eyes occurred in workers at concentrations between 50 and 80 ml/m$^3$. At concentrations of 160 ml/m$^3$ and above, these effects were more pronounced and even affected the respiratory tract. Details of possible co-exposures were not given. No clear correlations between the concentration and effect were found, possibly because the concentrations are only reported as ranges or mean values, but the occurrence of exposure peaks cannot be excluded (EU 2004).

### Allergenic effects

In a man aged 69 years an acute episode of respiratory distress occurred when he used a chair which had just been treated with crystalline 1,4-dichlorobenzene. One to two days later, bilateral petechiae and purpura on the hands, forearms, feet and legs occurred, which were accompanied by swelling of the hands and feet. No patch test or re-exposure to the substance were carried out. In the further course, glomerulonephritis developed. A basophil degranulation test yielded positive results (Nalbandian and Pearce 1965).

### Reproductive and developmental toxicity

The case of a woman is reported who ingested 5 to 10 g 1,4-dichlorobenzene per week during her pregnancy; no evidence was found of anomalies in the child. The mother suffered reversible haemolytic anaemia (EU 2004).

### Genotoxicity

Three healthy volunteers were exposed for one hour to 1,4-dichlorobenzene vapour concentrations of 2.4 to 2.8 ml/m$^3$. Blood samples were taken immediately before and immediately after the exposure and one hour later. The serum was incubated with calf thymus DNA to determine the DNA-binding metabolites. After isolation of the DNA, the DNA adducts were analysed using $^{32}$P-postlabelling. The DNA adduct profiles remained unchanged by the exposure (Tian et al. 2001 b).

## 5 Animal Experiments and in vitro studies

### 5.1 Acute toxicity

Details of the acute toxicity of the substance can be found in the 1991 documentation (documentation "1,4-Dichlorobenzene" 1992) and in the 2001 supplement (supplement "1,4-Dichlorobenzene" 2003). No new results are available for its acute oral, dermal, intraperitoneal and subcutaneous toxicity.

### Inhalation

The $RD_{50}$ in male and female F344 rats was given as 613 and 719 ml/m³, respectively, and in male and female B6C3F1 mice it was 270 and 245 ml/m³. The description of the study conduct is incomplete, and only two to three concentrations were tested, each for the duration of 10 minutes (EU 2004).

Inhalation exposure to a 1,4-dichlorobenzene concentration of 500 ml/m³ for six hours produced a marked decrease in the respiration rate of rats and mice with a 50% reduction in the minute volume (EU 2004).

## 5.2 Subacute, subchronic and chronic toxicity

### 5.2.1 Inhalation

All the relevant and newly available inhalation studies with 1,4-dichlorobenzene are given in Table 1. Further studies can be found in the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003).

In the available studies with rats and mice, particularly the liver and in male rats also the kidneys were found to be the target organs of 1,4-dichlorobenzene toxicity. At high 1,4-dichlorobenzene concentrations, increased kidney weights were found also in female rats and in male and female mice. In the long-term inhalation studies with rats and mice, changes in the olfactory and respiratory epithelium of the nose were the most sensitive end points at and above concentrations of 75 ml/m³ (see Table 2).

### 5.2.2 Oral administration

Oral studies in rats, mice and dogs with repeated administration of 1,4-dichlorobenzene were described in the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003). In these studies, particularly the liver and in male rats also the kidneys are the target organs of 1,4-dichlorobenzene toxicity (supplement "1,4-Dichlorobenzene" 2003). In a 52-week study, the dog was the most sensitive species with initial effects even at the lowest dose tested of 10 mg/kg body weight and day (Monsanto Company 1996; US EPA 1996). The results of this study and of the 4-week study with dogs are shown in Table 3; the histopathological liver findings from the 52-week study are presented in Table 4.

### 5.2.3 Dermal application

In a 21-day study with dermal application of 1,4-dichlorobenzene in mineral oil, no toxic effects and no significant skin irritation were found in groups of five male and five female Sprague Dawley rats given doses of up to 300 mg/kg body weight and day on five days per week (EU 2004).

**Table 1** The effects of 1,4-dichlorobenzene after repeated inhalation exposure

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **rat**,<br>F344,<br>10 ♂, 10 ♀ | **2 weeks**,<br>0, 120, 180, 270, 400, 600 ml/m$^3$,<br>6 hours/day, 5 days/week,<br>purity: > 99.9% | **120 ml/m$^3$ and above**:<br>♂: kidneys: eosinophilic bodies/hyaline droplets (concentration-dependent increase in severity);<br>♀: Hb ↓;<br>**180 ml/m$^3$ and above**:<br>♀: serum: cholesterol ↑;<br>**400 ml/m$^3$ and above**:<br>Hb ↓; serum: cholesterol ↑;<br>**600 ml/m$^3$**:<br>food intake 1st week ↓;<br>♂: thrombocytes ↑; serum: albumin ↑ | JMHLW 1995 a, b |
| **rat**,<br>F344,<br>10 ♂, 10 ♀ | **13 weeks**,<br>0, 25, 55, 120, 270, 600 ml/m$^3$,<br>6 hours/day, 5 days/week,<br>purity: > 99.9% | **55 ml/m$^3$ and above**:<br>♀: urine: pH value ↑;<br>**55 ml/m$^3$**:<br>♀: liver: absolute weights ↑ (10%);<br>**120 ml/m$^3$ and above**:<br>♂: erythrocytes, Hb and Hct ↓; liver: absolute and relative weights ↑ (relative: 120 ml/m$^3$: 7%);<br>**270 ml/m$^3$ and above**:<br>liver: absolute and relative weights ↑ (relative: 270 ml/m$^3$: ♂: 15%, ♀: 8%; 600 ml/m$^3$: ♂: 43%, ♀: 28%);<br>♂: serum: cholesterol ↑, phospholipids ↑, ALT ↓, ALP ↓, calcium ↑; kidneys: absolute and relative weights ↑, hyaline droplets ↑, proximal tubular necrosis ↑, urinary casts ↑; liver: centrilobular hepatocellular hypertrophy (3/10, not significant); | Aiso et al. 2005 a;<br>JMHLW 1995 a, c |

**Table 1** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| | | **600 ml/m³**:<br>food intake at times ↑; serum: total protein ↑, cholesterol ↑, albumin ↑, phospholipids ↑, AST ↓; kidneys: absolute and relative weights ↑; liver: centrilobular hepatocellular hypertrophy (♂: 9/10, ♀: 3/10);<br>♂: MCV and MCH ↓, thrombocytes ↑; serum: triglycerides ↑, urea nitrogen ↑, creatinine ↑; spleen: absolute and relative weights ↑; thymus: relative weights ↓; nasal cavity: goblet cell hyperplasia (2/10, not significant); kidneys: mineralization ↑;<br>♀: soiled genital region (9/10); Hb ↓; serum: glucose ↑ | |
| **rat**,<br>F344,<br>50 ♂, 50 ♀ | **104 weeks**,<br>0, 20, 75, 300 ml/m³,<br>6 hours/day, 5 days/week,<br>purity: > 99.9% | **20 ml/m³**:<br>♀: serum: total protein ↓;<br>**75 ml/m³ and above**:<br>♀: nose: severity of eosinophilic changes ("eosinophilic globules") in the olfactory epithelium ↑;<br>**300 ml/m³**:<br>serum: urea nitrogen ↑; absolute and relative liver weights ↑;<br>♂: survival ↓, MCV ↓, serum: cholesterol ↑, phospholipids ↑, creatinine ↑, calcium ↑; liver: centrilobular hepatocellular hypertrophy ↑; kidneys: absolute and relative weights ↑, papillary mineralization, urothelial hyperplasia of the renal pelvis;<br>♀: serum: total protein ↓, bilirubin ↑, potassium ↑; nose: eosinophilic changes ("eosinophilic globules") in respiratory epithelium ↑, respiratory metaplasia of the glandular epithelium ↑;<br>see also Section 5.7.2 | Aiso et al. 2005 b; JISHA 1995; JMHLW 1995 d, e, f, g |

**Table 1** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **mouse**,<br>BDF1,<br>10 ♂, 10 ♀ | **2 weeks**,<br>0, 120, 180, 270, 400, 600 ml/m³,<br>6 hours/day, 5 days/week,<br>purity: > 99.9% | **120 ml/m³ and above**:<br>♀: serum: cholesterol ↑;<br>**270 ml/m³ and above**:<br>serum: cholesterol ↑;<br>♀: serum: total protein ↑, albumin ↑, ALT ↑;<br>**400 ml/m³ and above**:<br>serum: total protein ↑, albumin ↑, ALT ↑, calcium ↑;<br>♂: piloerection;<br>♀: thrombocytes ↑;<br>**600 ml/m³**:<br>piloerection; food intake in week 2 ↑; serum: chloride ↓; liver: enlarged (♂: 9/10, ♀: 10/10), hepatocellular hypertrophy (♂: 2/2, ♀: 2/2);<br>♂: serum: AST ↑;<br>♀: segmented neutrophil granulocytes ↑ | JMHLW 1995 a, b |
| **mouse**,<br>BDF1,<br>10 ♂, 10 ♀ | **13 weeks**,<br>0, 25, 55, 120, 270, 600 ml/m³,<br>6 hours/day, 5 days/week,<br>purity: > 99.9% | **25 ml/m³ and above**:<br>♂: liver : relative weights ↑ (up to 120 ml/m³: max. 10%, 270 ml/m³: 24%, 600 ml/m³: 62%);<br>**120 ml/m³: NOAEC**;<br>**270 ml/m³ and above**:<br>♂: ALT ↑; kidneys: relative weights ↑; brain: relative weights ↑; liver: centrilobular hepatocellular hypertrophy (10/10), focal necroses (2/10, not significant);<br>♀: liver: absolute and relative weights ↑ (relative: 8%);<br>**600 ml/m³**:<br>serum: total protein ↑, cholesterol ↑, ALT ↑; liver: absolute and relative weights ↑ (relative: ♂: 62%, ♀: 35%), centrilobular hepatocellular hypertrophy with single cell necroses (♂: 10/10, ♀: 10/10);<br>♂: serum: AST ↑, urea nitrogen ↑;<br>♀: body weights ↑; food intake at times ↑; MCH ↑; kidneys: absolute weights ↑ | Aiso et al. 2005 a; JMHLW 1995 a, c |

**Table 1** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **mouse**,<br>BDF1,<br>50 ♂, 50 ♀ | **104 weeks**,<br>0, 20, 75, 300 ml/m³,<br>6 hours/day, 5 days/week,<br>purity: > 99.9% | **20 ml/m³ and above**:<br>♂: slightly increased mortality without concentration-effect relationship (controls: 10/49, 20 ml/m³: 18/49, 75 ml/m³: 18/50, 300 ml/m³: 19/49);<br>**75 ml/m³**:<br>♂: nose: respiratory metaplasia of glandular epithelium ↑, respiratory metaplasia of olfactory epithelium ↑, both without concentration-effect relationship (see Table 2);<br>testes: mineralization ↑;<br>**300 ml/m³**: body weight gains ↓, liver: absolute and relative weights ↑, hepatocellular carcinomas and hepatoblastomas ↑; relative kidney weights ↑;<br>serum: cholesterol ↑, ALT ↑, AST ↑, LDH ↑, ALP ↑;<br>♂: liver : centrilobular hepatocellular hypertrophy ↑, histiocytic sarcomas ↑;<br>testes: relative weights ↑, mineralization ↑;<br>♀: MCH ↓, ratio between eosinophilic leukocytes and total leukocytes ↓, thrombocytes ↑, serum: urea nitrogen ↑, total protein ↑, albumin ↑, bilirubin ↑, calcium ↑; liver : hepatocellular adenomas ↑; absolute and relative kidney weights ↑; nose: respiratory metaplasia of glandular epithelium ↑, respiratory metaplasia of olfactory epithelium ↑; absolute and relative ovary weights ↓;<br>see also Section 5.7.2 | Aiso et al. 2005 b; JISHA 1995; JMHLW 1995 d, e, f, g |

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Hb: haemoglobin; Hct: haematocrit; LDH: lactate dehydrogenase; MCH: mean corpuscular haemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular haemoglobin concentration; NOAEC: no observed adverse effect concentration

**Table 2** Effects of 1,4-dichlorobenzene in the nose of rats and mice after 104-week inhalation exposure (Aiso et al. 2005 b)

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| Concentration (ml/m$^3$) | 0 | 20 | 75 | 300 | 0 | 20 | 75 | 300 |
| **rats** | | | | | | | | |
| number of animals examined | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| eosinophilic changes | | | | | | | | |
| respiratory epithelium [a)] | 4 | 1 | 5 | 4 | 11 | 10 | 14 | 38** |
| grade 1 | 4 | 1 | 5 | 4 | 11 | 10 | 14 | 38 |
| olfactory epithelium | 33 | 22 | 21 | 26 | 49 | 46 | 46** | 50** |
| grade 1 | 32 | 20 | 19 | 19 | 22 | 17 | 7 | 3 |
| grade 2 | 1 | 1 | 1 | 7 | 21 | 27 | 16 | 27 |
| grade 3 | 0 | 1 | 1 | 0 | 6 | 2 | 23 | 20 |
| respiratory metaplasia of glandular epithelium [a)] | 3 | 0 | 0 | 0 | 5 | 4 | 4 | 33** |
| grade 1 | 3 | 0 | 0 | 0 | 5 | 4 | 4 | 33 |
| **mice** | | | | | | | | |
| number of animals examined | 49 | 49 | 50 | 49 | 50 | 50 | 49 | 50 |
| respiratory metaplasia | | | | | | | | |
| glandular epithelium [a)] | 37 | 42 | 47* | 41 | 9 | 6 | 8 | 19 |
| grade 1 | 28 | 29 | 27 | 30 | 9 | 6 | 8 | 18 |
| grade 2 | 9 | 12 | 18 | 11 | 0 | 0 | 0 | 1 |
| grade 3 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 |
| olfactory epithelium [a)] | 23 | 30 | 38** | 24 | 7 | 6 | 2 | 20** |
| grade 1 | 23 | 30 | 37 | 22 | 7 | 6 | 2 | 20 |
| grade 2 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |

[a)] Total number of animals with lesions;
*: $p < 0.05$; **: $p < 0.01$ (Chi Square test)

**Table 3** Effects of 1,4-dichlorobenzene in dogs after repeated oral administration

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **dog**,<br>beagle,<br>2 ♂, 2 ♀ | **4 weeks**,<br>0, 25, 75, 150, 300 mg/kg body weight and day,<br>in gelatine capsules,<br>5 days/week,<br>range-finding study | **25 mg/kg body weight**: NOAEL;<br>**75 mg/kg body weight and above**: absolute and relative liver weights ↑, irritant effect in the gastrointestinal tract;<br>♀: clinico-chemical parameters ↑ (no other details), ALP ↑;<br>**150 mg/kg body weight and above**: body weight gains ↓;<br>♂: clinico-chemical parameters ↑ (no other details);<br>**300 mg/kg body weight**: ♂: mortality 2/2 | US EPA 1996 |
| **dog**,<br>beagle,<br>5 ♂, 5 ♀ | **52 weeks**,<br>0, 10, 50, 75[a)] mg/kg body weight and day,<br>in gelatine capsules,<br>5 days/week,<br>purity: 99.9% | **0 mg/kg body weight**:<br>♂: mortality 1/5;<br>**10 mg/kg body weight and above**:<br>♂ and ♀: GGT ↑ (significant trend);<br>♂: blood: thrombocytes ↑ (significant trend); lungs: foci of chronic active inflammation (2/5 each at 10, 50, 75 mg/kg body weight);<br>♀: serum: ALT ↑ (significant trend); liver: hepatocellular hypertrophy (see also Table 4); kidneys: collecting duct epithelial vacuolization (1/5 each at 10 and 50 mg/kg body weight);<br>**50 mg/kg body weight and above**:<br>♂ and ♀: serum: ALP ↑ (after 6 and 12 months), ALT ↑ (not significant); liver: absolute and relative weights ↑, hepatocellular hypertrophy and pigment deposition;<br>♂: serum: albumin ↓ (after 6 months); liver : periportal inflammation (1/5 at 50 and 2/5 at 75 mg/kg body weight);<br>♀: blood: thrombocytes ↑ (after 6 months); kidneys: relative weights ↑; lungs: foci of chronic active inflammation (1/5 each at 50 and 75 mg/kg body weight); thyroid gland: absolute and relative weights ↑; | Monsanto Company 1996 |

**Table 3** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| | | **75 mg/kg body weight**:<br>♂ and ♀: mortality (2/5 ♂, 1/5 ♀), body weight gains ↓ (up to week 4), blood: erythrocytes ↓ (after 6 months); liver: bile duct hyperplasia (1/5 ♂ and 1/5 ♀); spleen: haematopoiesis ↑, megakaryocyte proliferation; bone marrow: erythroid hyperplasia of rib and sternum;<br>♂: blood: haematocrit ↓ (after 6 months); serum: GGT ↑ (not significant); kidneys: collecting duct epithelial vacuolization (1/5);<br>♀: blood: thrombocytes ↑ (after 6 and 12 months); serum: albumin ↓ (after 6 months), ALT ↑ (after 12 months), GGT ↑ (after 6 and 12 months), kidneys: collecting duct epithelial vacuolization with discoloration of kidneys (2/5); adrenal gland: relative weights ↑; discoloration and enlargement of lymph nodes of mesenterium and pancreas (1/5); spleen: focal dilation (2/5);<br><br>ophthalmology and urinalysis without findings | |

[a)] Time-weighted mean value, initial dose of 150 mg/kg body weight reduced to 100 mg/kg body weight in week 3, without treatment in weeks 4 and 5, in week 6 and beyond 75 mg/kg body weight;
ALP: alkaline phosphatase; ALT: alanine aminotransferase; GGT: γ-glutamyl transpeptidase; NOAEL: no observed adverse effect level

**Table 4** Histopathological liver findings in dogs after 52-week oral administration of 1,4-dichlorobenzene (Monsanto Company 1996)

| Dose (mg/kg body weight and day) | Sex | 0 | 10 | 50 | 75 |
|---|---|---|---|---|---|
| **hepatocellular hypertrophy** | | | | | |
| diffuse | ♂ | 0/5 | 0/5 | 3/5 (3–4)[a)] | 5/5 (3–4) |
| | ♀ | 0/5 | 0/5 | 2/5 (3) | 4/5 (3–4) |
| multifocal | ♂ | 0/5 | 0/5 | 2/5 (2–3) | 0/5 |
| | ♀ | 0/5 | 1/5 (2) | 3/5 (2–3) | 1/5 (3) |
| **pigment deposition, hepatocytes** | | | | | |
| multifocal | ♂ | 0/5 | 0/5 | 2/5 (1) | 2/5 (1–2) |
| | ♀ | 0/5 | 0/5 | 1/5 (2) | 1/5 (4) |

[a)] Grading: 1 (minimal) to 5 (severe)

## 5.3 Local effects on skin and mucous membranes

### 5.3.1 Skin

A 4-hour semi-occlusive application (in accordance with OECD-Test Guideline 404) of 500 mg 1,4-dichlorobenzene mixed with paraffin to the skin of three rabbits caused erythema with a maximum score of 1 on a scale up to 4, which was reversible on day 7. No oedema occurred (ECHA 2015; EU 2004).

No significant skin irritation was found in a 21-day study with Sprague Dawley rats after dermal application (no other details) of 1,4-dichlorobenzene in mineral oil at doses of up to 300 mg/kg body weight and day (EU 2004).

### 5.3.2 Eyes

The administration of 90 mg 1,4-dichlorobenzene mixed with paraffin to three rabbits for the duration of 24 hours produced slight irritation of the eyes with damage to the conjunctiva (score of 1 for erythema and oedema) in one animal. These effects were reversible after 72 hours. No effects on the iris and the cornea were found (EU 2004).

## 5.4 Allergenic effects

In a maximization test, 24 female Hartley guinea pigs (Crl.(HA)BR) underwent intradermal induction with a 0.1% preparation of 1,4-dichlorobenzene in arachis oil and topical induction with a 25% preparation of 1,4-dichlorobenzene in petrolatum. Both preparations were either not or practically not irritating. After intradermal induction there was no reaction to the preparation in any of the animals, and after topical induction there was one weak erythematous reaction (grade 1 on a scale of 0–4) without infiltration (grade 0 on a scale of 0–4) in only one of the 24 animals after 24 hours. In the 24 control animals pretreated with FCA, an erythematous re-

action after one hour or 24 hours (grade 1) was found in one animal in each case on topical treatment with petrolatum. An erythematous reaction (without infiltration) to the topical challenge with the 25% 1,4-dichlorobenzene preparation was seen after 48 hours in 13 of the animals pretreated by induction with 1,4-dichlorobenzene. In five cases this was more pronounced than the reaction to the petrolatum tested as a control (1× grade 1/grade 0, 2× grade 2/grade 1, 1× grade 2/grade 0, 1× grade 3/grade 1). Six of the control animals produced an erythematous reaction to the test preparation after 48 hours, which in three cases was more pronounced than the reaction to petrolatum (2× grade 1/grade 0, 1× grade 2/grade 1). The authors reported that, as regards the two control animals with a grade 1 reaction to the test substance, the test area surrounding the vehicle control was likewise reddened. There was no reaction in any of the animals of either group 24 hours after the end of application (Bornatowicz et al. 1995).

Non-occlusive patch tests with 20 applications of 1%, 3%, 10% or 30% 1,4-dichlorobenzene in paraffin oil yielded negative results in groups of eight guinea pigs. The challenge was carried out two weeks after induction using the same concentrations (Schmidt 1985; EU 2004).

A test for passive cutaneous anaphylaxis in Hartley guinea pigs exposed to a 1,4-dichlorobenzene concentration of 305 mg/m$^3$ for twelve weeks likewise yielded negative results. Two weeks after the end of exposure, the intravenous application of a mixture of 1,4-dichlorobenzene and guinea pig albumin did not produce an anaphylactic reaction (Suzuki et al. 1991). Negative results were obtained also in an in vitro test for microtubule disassembly in the foreskin fibroblasts (AG1522) of humans after three-hour incubation with 40 µM 1,4-dichlorobenzene (5.88 mg/l) and in mouse fibroblasts (Leung et al. 1990).

## 5.5 Reproductive and developmental toxicity

In addition to more recent publications, the studies quoted in the documentation of 1991 (documentation "1,4-Dichlorobenzene" 1992) and the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003) are described in the following section.

### 5.5.1 Fertility

In a two-generation study, male and female Sprague Dawley rats were exposed to nominal 1,4-dichlorobenzene concentrations of 0, 50, 150 or 450 ml/m$^3$ on 7 days per week (6 hours daily) for 10 weeks. The analytically determined concentrations amounted to 0, 66, 211 and 538 ml/m$^3$. Evidence of adverse effects on fertility was seen only in animals of the high concentration group where parental toxicity was already apparent (reduction in body weights and body weight gains, clinical signs of toxicity, effects on the kidneys and the liver). At 538 ml/m$^3$, litter sizes were reduced in the F1 and F2 generations (CMA 1989).

In a dominant lethal test in CD-1 mice exposed by inhalation to 1,4-dichlorobenzene concentrations of 0, 75, 225 or 450 ml/m$^3$ for 6 hours a day for 5 days, the number of successful matings and the pregnancy frequency were decreased at 75 ml/m$^3$; due to the absence of dose-dependency and a high negative control value, this result is not considered to be of biological relevance (ICI 1976).

In a study of the effects on the reproductive organs, the testis and epididymis of Sprague Dawley rats were examined 10 days after a single intraperitoneal injection of 1,4-dichlorobenzene of 800 mg/kg body weight. Examination of the testes using an electron microscope revealed various toxic effects in early spermatids and an increased incidence of sperm head abnormalities (Murthy et al. 1985). Because the histological examination was carried out only 10 days after the injection, the observed effects are considered to be cytotoxic effects and not signs of genotoxicity. To identify sperm head anomalies resulting from genotoxic effects, the examination should be carried out 35 days after the injection.

In a 2-generation study carried out according to OECD Test Guideline 416, in which Sprague Dawley rats were given gavage doses of 1,4-dichlorobenzene of 0, 30, 90 or 270 mg/kg body weight and day, no effects on fertility were found up to the highest dose tested. In the parents, the NOAEL (no observed adverse effect level) was 90 mg/kg body weight and day. At 270 mg/kg body weight and day body weights were decreased (only F1), nephrotoxicity was observed and, in the males, the liver and kidney weights were increased and the spleen weights decreased. The NOAEL for toxic effects in the offspring was 30 mg/kg body weight and day. At 90 mg/kg body weight and day and above, there was increased postnatal mortality in the F1 and F2 offspring, reduced weights at birth in the F1 generation, retarded erection of the ears and opening of the eyes, ring tails (F1 and F2), and slight behavioural changes in the F1 generation in the draw up test (the animal holding on to a horizontally tightened wire with its front paws (gripping reflex) seizes the wire with at least one of its hind legs within five seconds) (Bornatowicz et al. 1994).

In a study of the endocrine effects of 1,4-dichlorobenzene, no reproducible effects on uterine and ovarian weights were found after immature female Sprague Dawley rats and CD-1 mice were given subcutaneous injections of 22 to 67 mg/kg body weight and day. Doses of 800 mg/kg body weight and day caused reduced uterine and ovarian weights. In CD-1 mice, intraperitoneal doses of 1,4-dichlorobenzene of 400 mg/kg body weight and day and above caused significant inhibition of the uterotrophic effect of oestradiol. Intraperitoneal administration of 204 to 400 mg/kg body weight and day prevented the oestradiol-induced uterotrophic effect in Ah-responsive mice (C57BL/6N) in a dose-dependent manner. This effect was not seen in Ah-non-responsive mice (DBA/2N). In vitro, 1,4-dichlorobenzene was found not to bind to the oestrogen receptor (ERα) at concentrations up to $10^{-3}$ M. From these results, the authors concluded that 1,4-dichlorobenzene has weak antioestrogenic/antiuterotrophic activity, possibly due to oestrogen receptor modulation caused by the Ah receptor (Takahashi et al. 2007).

Groups of 8 Wistar rats or CD(ICR) mice were given subcutaneous or intraperitoneal doses of 1,4-dichlorobenzene of 0, 100, 200 or 400 mg/kg body weight and day. The rats were treated for 8 weeks on 4 to 5 days per week, the mice for 2 or 6 weeks. In both species, only slight histopathological effects on the testis and epididymis were observed. A dose-dependent decrease in the daily sperm production was observed in rats and mice at 200 mg/kg body weight and day and above. The serum testosterone levels were not significantly affected in either of the two species. In rats, though not in mice, the relative prostate and seminal vesicle weights were in some cases significantly increased at 100 mg/kg body weight and day and above, but there was no clear dose-dependency. In rats, a single intraperitoneal dose of 1,4-dichlorobenzene

of 800 mg/kg body weight produced a significant increase in morphologically abnormal sperms in the epididymis after 10 days. In the Hershberger assay, subcutaneous administration of 1,4-dichlorobenzene increased the weights of the seminal vesicles and glans penis in castrated Sprague Dawley rats at 100 mg/kg body weight and day and above as well as of the musculus levator ani and musculus bulbocavernosus at 200 mg/kg body weight and day and above. In CD(ICR) mice, the organ weights of the ventral prostate and glans penis were significantly increased at 50 mg/kg body weight and day and above, although without any clear dose-dependency. In vitro, 1,4-dichlorobenzene or its major metabolite 2,5-dichlorophenol did not bind to the androgen receptor up to concentrations of 10 mM (Takahashi et al. 2011).

In in vitro studies with 1,4-dichlorobenzene, a concentration-dependent oestrogenic effect was found in the yeast estrogen screen (YES). The relative potency of the substance compared with that of 17β-oestradiol was $2.2 \times 10^{-7}$. In the zebrafish (Danio rerio) vitellogenin (VTG) assay, after exposure in vivo for 14 days to 1,4-dichlorobenzene concentrations of 0.1 to 32 mg/l water, increased VTG levels were found in the blood of female animals at 32 mg/l. At this concentration, the mortality level was 100% in the male animals and 70% in the females. The induction of VTG is considered to be a biomarker for exposure to oestrogenic substances (Versonnen et al. 2003).

### 5.5.2 Developmental toxicity

The studies of developmental toxicity are described in detail in the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003). In Table 5 these data are once more given in full and complemented by recently available studies.

The studies of the prenatal developmental toxicity of 1,4-dichlorobenzene in rats after inhalation and ingestion of up to 500 ml/m³ and 200 mg/kg body weight and day, respectively, yielded no evidence of developmental toxicity (ICI 1977; Ruddick et al. 1983).

In another study in rats with oral administration of 1,4-dichlorobenzene doses of up to 1000 mg/kg body weight and day, the weights of the foetuses were reduced and the number of skeletal anomalies after prenatal exposure were increased, but not until reaching maternally toxic doses of at least 500 mg/kg body weight and day. The NOAEL for developmental toxicity was 250 mg/kg body weight and day (Giavini et al. 1986).

In rabbits exposed to 1,4-dichlorobenzene concentrations of 300 ml/m³ an increased incidence of resorptions was seen and at 800 ml/m³ displacement of the right subclavian artery (5%, controls: 2%, not significant) into the retro-oesophageal space occurred, as well as deformation of the paws on flexion (5%, controls: 0%) (CMA 1982; Hayes et al. 1985). The NOAEC (no observed adverse effect concentration) for developmental toxicity in rabbits was 100 ml/m³.

In a 2-generation study with rats (see Section 5.5.1) an increase in postnatal or perinatal mortality and reduced body weights in the F1 and F2 generations were recorded only at the parentally toxic 1,4-dichlorobenzene concentration of 538 ml/m³ (CMA 1989). The NOAEC for foetotoxicity was 211 ml/m³.

In another 2-generation study with rats (see Section 5.5.1) the NOAEL for the offspring was 30 mg/kg body weight and day. At dose levels of 90 mg/kg body weight

**Table 5** Studies of the developmental toxicity of 1,4-dichlorobenzene in rats and rabbits

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **Prenatal developmental toxicity** | | | |
| **rat**,<br>Alderley-Park,<br>20–24 ♀ | **GD 6–15**,<br>0, 75, 200, 500 ml/m³,<br>6 hours/day,<br>examination: GD 21,<br>purity: > 99% | **500 ml/m³**:<br>**NOAEC for developmental and maternal toxicity** | ICI 1977 |
| **rat**,<br>Sprague Dawley,<br>♀ | **GD 6–15**,<br>0, 50, 100, 200 mg/kg body weight and day,<br>no data for control group,<br>**gavage**,<br>examination: no data,<br>purity: no data | **200 mg/kg body weight**:<br>**NOAEL for developmental and maternal toxicity** | Ruddick et al. 1983 |
| **rat**,<br>CD,<br>13–17 ♀ | **GD 6–15**,<br>0, 250, 500, 750, 1000 mg/kg body weight and day, in corn oil,<br>**gavage**,<br>examination: GD 21,<br>purity: 99% | **250 mg/kg body weight**:<br>dams: body weight gains ↓ (–18.3%, not significant), food intake ↓ (–11.1%);<br>**NOAEL for maternal toxicity**;<br>**NOAEL for developmental toxicity**;<br><br>**500 mg/kg body weight and above**:<br>dams: body weight gains ↓, food intake ↓;<br>foetuses: number of foetuses with supernumerary ribs ↑;<br><br>**750 mg/kg body weight**:<br>foetuses: skeletal anomalies ↑;<br><br>**1000 mg/kg body weight**:<br>foetuses: mean foetal weights ↓ (–8.1%), skeletal anomalies ↑ | Giavini et al. 1986 |

**Table 5** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **rabbit**,<br>New Zealand White,<br>7 ♀ | **GD 6–18**,<br>0, 300, 600, 1000 ml/m$^3$,<br>6 hours/day,<br>examination: GD 19<br>purity: 99.97% | range-finding study, only dams examined;<br>**600 ml/m$^3$**:<br>**NOAEC for maternal toxicity**;<br><br>**1000 ml/m$^3$**:<br>dams: body weight gains ↓, glycogen accumulation in the liver ↓ | CMA 1982 |
| **rabbit**,<br>New Zealand White,<br>29–30 ♀ | **GD 6–18**,<br>0, 100, 300, 800 ml/m$^3$,<br>6 hours/day,<br>examination: GD 19<br>purity: 99.9% | **100 ml/m$^3$**:<br>**NOAEC for developmental toxicity**;<br><br>**300 ml/m$^3$**:<br>**NOAEC for maternal toxicity**;<br>foetuses: resorptions ↑ (significant, but within range of historical control data);<br><br>**800 ml/m$^3$**:<br>dams: body weights ↓ (GD 6–8), body weight gains ↓ (−4.25%);<br>foetuses: displacement of right subclavian artery into retro-oesophageal space (5%, controls: 2%, not significant), deformation of paws on flexion (5%, controls: 0%) | CMA 1982; Hayes et al. 1985 |

**Table 5** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **Prenatal and postnatal developmental toxicity** | | | |
| **rat**,<br>Sprague Dawley,<br>28 ♂, 28 ♀ | **2-generation study**<br>0, 66, 211, 538 ml/m³,<br>7 days/week, 6 hours/day, 10 weeks, whole-body exposure,<br>examination: PND 0–28,<br>purity: ≤ 100% | **66 ml/m³**:<br>parents: ♂: $\alpha_{2u}$-globulin nephropathy;<br>♀: no effects;<br>offspring: no effects;<br><br>**211 ml/m³**:<br>parents: ♂: $\alpha_{2u}$-globulin nephropathy, relative liver weights ↑;<br>♀: no effects;<br>**NOAEC for foetotoxicity**;<br><br>**538 ml/m³**:<br>parents: body weights and body weight gains ↓, clinical signs of intoxication, effects on kidneys and liver (hepatocellular hypertrophy);<br>offspring: litter size and body weights in F1 and F2 generation ↓, postnatal and perinatal mortality ↑ | CMA 1989 |
| **rat**,<br>Sprague Dawley,<br>24 ♂, 24 ♀ | **2-generation study**<br>0, 30, 90, 270 mg/kg body weight and day, in olive oil,<br>gavage,<br>examination: PND 1–21,<br>purity: 99% | **30 mg/kg body weight**:<br>parents: no effects;<br>**NOAEL foetotoxicity**;<br><br>**90 mg/kg body weight**:<br>parents: no effects;<br>offspring: postnatal mortality in F1 and F2 offspring ↑, weights at birth in F1 generation ↓, dry and flaky skin, ring tails (F1 and F2) and slight behavioural changes in F2 generation in the draw up test; | Bornatowicz et al. 1994 |

**Table 5** (continued)

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| | | **270 mg/kg body weight**:<br>parents: body weights ↓ (only F1), nephrotoxicity; ♂: liver and kidney weights ↑, spleen weights ↓;<br>offspring: number of live offspring at birth ↓, postnatal mortality in F1 and F2 offspring ↑, weights at birth in F1 and F2 generation ↓, body weights ↓ (PND 4, 7, 14, 21), retarded erection of ears (only F2) and opening of eyes, dry and flaky skin, ring tails (F1 and F2) and slight behavioural changes in F1 and F2 generation in draw up test | |
| **rat**,<br>Wistar,<br>6 ♀ | **GD 1–PND 21 (42 days)**,<br>0, 2 mg/kg body weight and day,<br>in diet,<br>examination: PND 1–42,<br>purity: 99.9% | **2 mg/kg body weight**:<br>dams: no effects;<br>offspring: no developmental toxicity; ♀: thymus: weights ↑ (about +36%), no histopathological findings | Makita 2004, 2005 |
| **rat**,<br>Wistar,<br>6 ♀ | **GD 1–PND 21 (42 days)**,<br>0, 2 mg/kg body weight and day,<br>in diet,<br>examination: PND 1–112,<br>purity: 99.9% | **2 mg/kg body weight**:<br>dams: no effects;<br>offspring: no developmental toxicity | Makita 2008 |

GD: gestation day; NOAEC: no observed adverse effect concentration; NOAEL: no observed adverse effect level; PND: postnatal day

and day and above, increased postnatal mortality in the F1 and F2 offspring, reduced weights at birth in the F1 generation, retarded erection of the ears and opening of the eyes, dry and flaky skin as well as ring tails (F1 and F2) and slight behavioural changes in the F1 generation were found in the draw up test (Bornatowicz et al. 1994).

In studies of the prenatal and postnatal developmental toxicity of 1,4-dichlorobenzene in Wistar rats, no developmental toxicity occurred at the only dose investigated of 2 mg/kg body weight and day. The end points examined were litter size, sex ratio, body weights, anogenital distance, time of eye and vaginal opening, preputial separation, oestrous cycle, organ weights, and serum hormone concentrations (Makita 2004, 2005, 2008).

## 5.6 Genotoxicity

### 5.6.1 In vitro

Studies of the genotoxicity of the substance in vitro are described in detail in the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003). These data are again given in full in Table 6 and complemented by new studies.

**Bacteria and yeasts**

In a series of studies of the genotoxicity of the substance in bacteria both in the presence and absence of metabolic activation, exclusively negative results were obtained (see Table 6). In studies with yeasts, some of the results reported were positive (Paolini et al. 1998).

**Mammalian cells**

The studies of the genotoxicity of 1,4-dichlorobenzene in mammalian cells are shown in Table 6.

After the incubation of $^{14}$C-labelled 1,4-dichlorobenzene with isolated calf thymus DNA, an association of radioactivity with the DNA was demonstrated in the presence of microsomes and NADPH from the liver or lungs of rats and mice, though not with those from kidneys of rats and mice or the stomach of mice. After incubation with the cytosolic fraction of these organs and GSH, the result was either negative or, in the case of that from the lungs of rats and mice, the extent of association was only very small. The strongest effect was obtained after incubation with microsomes and cytosol from mouse lung and somewhat less pronounced with that from liver and stomach of rats and mice (Lattanzi et al. 1989). In another study with various subcellular fractions of mouse liver an association of $^{14}$C-labelled 1,4-dichlorobenzene with calf thymus DNA was found (Paolini et al. 1998). Using the $^{32}$P-postlabelling technique, however, no 1,4-dichlorobenzene-induced DNA adducts could be found after the incubation of calf thymus DNA with liver microsomes from rats, mice and human donors (Tian et al. 2001 a).

The investigation of DNA strand breaks by means of alkaline elution after the incubation of hepatocytes from rats and human donors with 1,4-dichlorobenzene yielded negative results (Canonero et al. 1997).

The results of a comet assay in kidney cells from human donors and rats were positive (Robbiano et al. 1999). The cells were obtained from patients with renal adenomas or carcinomas. Details of the presence of apoptotic or damaged cells and of cytotoxicity were not given.

In addition to negative results in an SCE (sister chromatid exchange) test in CHO (Chinese hamster ovary) cells (NTP 1987) positive results were found in a second test with human lymphocytes, although the increase in SCE was only slight and not concentration-dependent (Carbonell et al. 1991).

Two UDS tests in HeLa cells (IRB 1986) and human lymphocytes (Perocco et al. 1983) yielded negative results.

The results of a number of chromosomal aberration tests in CHO and CHL (Chinese hamster lung) cells or human lymphocytes were negative (see Table 6).

In a micronucleus test with hepatocytes from human donors, the incidence of micronuclei was not significantly increased. In rat hepatocytes, significantly increased incidences were found at some concentrations (Canonero et al. 1997). However, there was no concentration-dependency and the results were considered to be equivocal.

In another micronucleus test in kidney cells from human donors and rats, positive results were obtained (Robbiano et al. 1999).

Three HPRT (hypoxanthine guanine phosphoribosyl transferase) tests with CHO or V79 cells yielded negative results (EU 2004; IRB 1986; Tegethoff et al. 2000). The results for the metabolite 2,5-dichlorophenol were likewise negative in an HPRT test with CHO cells in the presence and absence of a metabolic activation system (rat liver S9 mix) (Tegethoff et al. 2000).

No positive results were obtained in a number of studies using the $TK^{+/-}$ mutation test (McGregor et al. 1988; Myhr et al. 1990; NTP 1987).

### 5.6.2 In vivo

Studies of the genotoxicity of the substance in vivo are described in detail in the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003). These data are again given in full in Table 7 and complemented by newly available studies.

In an SLRL test in Drosophila, 1,4-dichlorobenzene yielded negative results (Valencia 1982).

A host mediated assay in mice with oral administration of 1,4-dichlorobenzene likewise yielded negative results (JDIA 1975).

In an investigation of single DNA strand breaks using the comet assay, positive results were obtained in mice after intraperitoneal injection of 1,4-dichlorobenzene only in the liver and spleen and only after three hours, but not after 24 hours, while no DNA damage occurred in the lungs, the kidneys and the bone marrow (Sasaki et al. 1997).

A comet assay yielded positive results in the kidneys of rats after oral administration of 1,4-dichlorobenzene. To stimulate kidney cell proliferation the animals were given an intravenous dose of folic acid after unilateral nephrectomy, prior to oral treatment with 1,4-dichlorobenzene (Robbiano et al. 1999).

**Table 6** Genotoxicity of 1,4-dichlorobenzene in vitro

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | –m. a. | +m. a. | | |
| mitotic recombination | Saccharomyces cerevisiae D3 | not specified | – | – | – | | Waters et al. 1982 |
| differential killing (Rec assay) | Bacillus subtilis H17, M45 | not specified | – | – | not tested | | Waters et al. 1982 |
| | Bacillus subtilis | not specified | – | – | no data | study only insufficiently documented | JETOC 1985 |
| differential killing (polA$^-$) | Escherichia coli W3100, P3478 | not specified | – | – | not tested | | Waters et al. 1982 |
| SOS response (umu test) | Salmonella typhimurium TA1535 (pSK1002) | up to 443 µg/ml | – | – | – | S9 mix: rat | Ono et al. 1991, 1992 |
| gene mutation | Salmonella typhimurium TA98, TA100, TA1535, TA1537 | 1–100 µg/plate | – | – | – | purity: 97%; S9 mix: rat and hamster, vehicle: DMSO; positive controls: NOPD, 2-AA, NA, 9-AA | Haworth et al. 1983; NTP 1987 |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537 | 4–2500 µg/plate | – | – | – | S9 mix: rat, vehicle: DMSO; positive controls: 2-nitrofluorene, CIPN | Loeser and Litchfield 1983 |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537 | 565, 1800, 4100 mg/m$^3$ | – | – | – | S9 mix: rat, gaseous phase | |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1538 | up to 500 µg/plate | – | – | – | | EU 2004 |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | −m. a. | +m. a. | | |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 | 5 doses, not further specified | – | – | – | S9 mix: rat; study only insufficiently documented | Lawlor and Haworth 1979 |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 | up to 10 000 µg/plate | – | – | – | S9 mix: rat | Waters et al. 1982 |
| | Escherichia coli WP2uvrA$^-$ | up to 10 000 µg/plate | – | – | – | | |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 | 51.2–13 105.2 µg/plate | – | – | – | purity: 99%; S9 mix: rat, vehicle: DMSO; positive controls: ENNG, 2-NF, 9-AA, 2-AA | Shimizu et al. 1983 |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 | 50–5000 µg/plate | – | – | – | purity: 99.9%; S9 mix: rat, vehicle: DMSO; positive controls: ENNG, 9-AA, 2-NF, 2-AA | Rhône-Poulenc 1987 |
| | Salmonella typhimurium TA98, TA100, UTH8413, UTH8414 | 10–1000 µg/plate | – | – | – | purity: > 99%; S9 mix: rat, vehicle: DMSO; positive controls: NA, cisplatin, 2-AA | Connor et al. 1985 |
| | no data | not specified | – | – | no data | study only insufficiently documented | JETOC 1985 |
| | Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 | 37–3000 µg/plate | – | – | – | purity: not specified; S9 mix: rat, vehicle: DMSO; positive controls: adriamycin, AfB1, NA, 2-AA, 2-NF | Winker et al. 1993 |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | –m. a. | +m. a. | | |
| | Aspergillus nidulans ($meth_3$ locus) | 0, 200 µg/ml | revertants: controls: $3/10^6$, 200 µg/ml: $10/10^6$ | (+) | not tested | purity: not specified; vehicle: diethyl ether; viability: 39%, controls 60% | Prasad 1970 |
| | Saccharomyces cerevisiae D7 (mitotic gene conversion) | 0.5, 1, 4 mM (74, 147, 588 µg/ml) | 74 µg/ml and above | not tested | + | purity: 98.6%; S9 mix: mouse; cytotoxicity: 65%–80% living cells at 4 mM | Paolini et al. 1998 |
| | Saccharomyces cerevisiae D7 (reverse mutation) | 0.5, 1, 4 mM (74, 147, 588 µg/ml) | 147 µg/ml and above | not tested | + | purity: 98.6%; S9 mix: mouse; cytotoxicity: 65%–80% living cells at 4 mM | |
| DNA associated radioactivity ($^{14}C$) | calf thymus DNA, incubation with microsomes or cytosol from liver, kidneys, lungs, stomach of mice or rats after induction with PB | 19.3 µM (2.8 µg/ml) | DNA association: microsomes with NADH (liver and lungs of rats and mice), cytosol with GSH (lungs of rats and mice; kidneys of mice) | not tested | + | purity: 98% | Lattanzi et al. 1989 |
| | calf thymus DNA, incubation with S9, microsomes or cytosol from ♂ mice livers after induction with PB/βNF or BHA | about 0.1 mM (about 14.7 µg/ml) | DNA association: cytosol (BHA-induced)+GSH: 26.2-fold increase, S9 (PB/βNF or BHA-induced)+NADPH+GSH: around 50-fold increase, microsomes (PB/βNF-induced)+NADPH+GSH: around 120-fold increase | not tested | + | purity: 98.6%; no negative or positive control substances examined | Paolini et al. 1998 |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | –m. a. | +m. a. | | |
| DNA adducts ($^{32}$P-postlabelling), liver | calf thymus DNA, incubation with liver microsomes from rats, mice and humans | 0.1 mM (14.7 µg/ml) | – | not tested | – | purity: not specified; positive control: benzo(a)pyrene | Tian et al. 2001 a |
| DNA strand breaks (alkaline elution) | human hepatocytes (1 donor, ♂) | 1.0–3.2 mM (147–470 µg/ml) | – | – | not tested | purity: 99%; vehicle: ethanol; positive control: NDMA | Canonero et al. 1997 |
| | rat hepatocytes, ♂ | 1.0–3.2 mM (147–470 µg/ml) | – | – | not tested | purity: 99%; vehicle: ethanol, cytotoxicity at and above 5.6 mM; positive control: NDMA | |
| DNA strand breaks (comet assay) | human kidney cells (2 donors, both ♂, with renal carcinomas) | 1.8–5.6 mM (265–823 µg/ml) | 1.8 or 3.2 mM and above | + (both donors) | not tested | purity: 99%; vehicle: ethanol; positive control: NDMA | Robbiano et al. 1999 |
| | rat kidney cells, ♂ | 1.8–5.6 mM (265–823 µg/ml) | 1.8 mM and above | + | not tested | purity: 99%; vehicle: ethanol; positive control: NDMA | |
| SCE | CHO cells | –m. a.: 75–150 µg/ml; +m. a.: 75–125 and 100–150 µg/ml | – | – | –[a)] | purity: 97%; vehicle: DMSO; S9 mix: rat; positive control: mitomycin C or cyclophosphamide | Anderson et al. 1990; Galloway et al. 1987; NTP 1987 |
| | human lymphocytes | donor 1: 0.05, 0.1, 0.2 µg/ml, donor 2: 0.05[b)], 0.1, 0.2 µg/ml | 0.1 µg/ml and above | + at and above 0.1 µg/ml (donor 1 and 2) | not tested | proliferation ↓ at 0.2 µg/ml; increase in SCE only slight and not concentration-dependent | Carbonell et al. 1991 |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | –m. a. | +m. a. | | |
| DNA repair synthesis (UDS) | HeLa cells | –m. a.: 1–500 µg/ml, 0.5–100 µg/ml; +m. a.: 1–500 µg/ml | – | – | – | purity: 99.7%; vehicle: DMSO; S9 mix: rat; positive control: MMS or cyclophosphamide; cytotoxicity: –m. a.: at 50 µg/ml and above, +m. a.: at 500 µg/ml 43% of cells survived | IRB 1986 |
| | human lymphocytes | 0.01–1 mM (1.47–147 µg/ml) | – | – | – | purity: 99%; vehicle: DMSO; S9 mix: rat; cytotoxicity: –m. a.: at 1 mM 50% of cells survived, +m. a.: at 1 mM 100% of cells survived | Perocco et al. 1983 |
| CA | CHO cells | –m. a.: 20–50 µg/ml, 50–150 µg/ml, 150–200 µg/ml; +m. a.: 20–50 µg/ml, 50–200 µg/ml | – | – | – | purity: 99.7%; vehicle: DMSO; S9 mix: rat; positive control: mitomycin C or cyclophosphamide, cytotoxicity: –/+m. a.: at 200 µg/ml and above | US EPA 1982 |
| | CHO cells | –m. a.: 50–150 µg/ml; +m. a.: 25–100 µg/ml | – | – | – | purity: 97%; vehicle: DMSO; S9 mix: rat; positive control: mitomycin C or cyclophosphamide | Anderson et al. 1990; Galloway et al. 1987; NTP 1987 |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | −m. a. | +m. a. | | |
| | CHL cells | 50–200 µg/ml | – | – | – | purity: not specified; vehicle: DMSO; S9 mix: mouse | Ishidate 1988; Sofuni et al. 1985 |
| | CHL cells | 1.25–5 µg/ml | – | – | not tested | purity: not specified; vehicle: DMSO | Ishidate 1988; Ishidate et al. 1988 |
| | human lymphocytes | 1–100 µg/ml | – | – | – | purity: 99.7%; vehicle: DMSO; S9 mix: rat; cytotoxicity at 500 µg/ml; positive control: mitomycin C or cyclophosphamide | IRB 1987 |
| MN | human hepatocytes (2 donors) | 0.56–3.2 mM (82–470 µg/ml) | ♂: in some cases increased by a maximum of 2.1-fold, however not significant | ♀: –; ♂: +/– | not tested | purity: 99%; vehicle: ethanol | Canonero et al. 1997 |
| | rat hepatocytes, ♂ | 0.56–3.2 mM (82–470 µg/ml) | + only at 1.0 mM (1st experiment) or 1.8 mM (2nd experiment), at 3.2 mM negative (1st and 2nd experiment) | +/– | not tested | purity: 99%; vehicle: ethanol; cytotoxicity: 5.6 mM and above; positive control: NDMA | |
| | human kidney cells (2 donors, both ♂, with renal carcinomas) | 1.8–5.6 mM (265–823 µg/ml) | 1.8 or 3.2 mM and above | + (both donors) | not tested | purity: 99%; vehicle: ethanol; cytotoxicity: no data; positive control: NDMA | Robbiano et al. 1999 |
| | rat kidney cells, ♂ | 1.8–5.6 mM (265–823 µg/ml) | 1.8 mM and above | + | not tested | purity: 99%; vehicle: ethanol; cytotoxicity: no data; positive control: NDMA | |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | –m. a. | +m. a. | | |
| gene mutation HPRT | CHO cells | –m. a.: 80–240 µg/ml; +m. a.: 1st experiment: 70–210 µg/ml, 2nd experiment: 70–350 µg/ml | +m. a. (1st experiment): not dose-dependent; controls 1st experiment particularly low | – | +/– (1st experiment) – (2nd experiment) | purity: > 99.9%; vehicle: DMSO; S9 mix: rat; positive control: BrdU or 3-MCA; cytotoxicity: –m. a.: at 240 µg/ml 74% of cells survived, lethal at 320 µg/ml and above; +m. a.: lethal at 350 µg/ml and above | BAYER 1986 a; Tegethoff et al. 2000 |
| | CHO cells | up to 250 µg/ml | – | – | – | purity: 99.7%; S9 mix: rat | EU 2004 |
| | V79 cells | –m. a.: 1–100 µg/ml; +m. a.: 1–200 µg/ml | – | – | – | purity: 99.7%; vehicle: DMSO; S9 mix: rat; positive control: EMS or NDMA; cytotoxicity: –m. a.: 100 µg/ml 55% CFA, +m. a.: 200 µg/ml 32% CFA | IRB 1986 |

**Table 6** (continued)

| End point | Test system | Concentration | Effective concentration | Result | | Remarks | References |
|---|---|---|---|---|---|---|---|
| | | | | −m. a. | +m. a. | | |
| $TK^{+/-}$ mutation test[c)] | L5178Y mouse lymphoma cells | −m. a.: 6.25–100 µg/ml, 30–90 µg/ml, 70–90 µg/ml, 55–105 µg/ml; +m. a.: 60–110 µg/ml, 55–105 µg/ml, 80–105 µg/ml | −m. a.: in 1 experiment in each case positive only at 12.5 or 70 µg/ml; +m. a.: in 1 experiment in each case positive only at 65 and 95 or 100 µg/ml | +/− or − (NTP1987) | +/− or − (NTP 1987) | purity: 97%; vehicle: DMSO; S9 mix: rat; positive control: MMS or 3-MCA; cytotoxicity: −m. a.: lethal in some cases at and above 80–105 µg/ml, +m. a.: lethal at and above 105–110 µg/ml | McGregor et al. 1988; Myhr et al. 1990; NTP 1987 |

[a)] positive only at 75 µg/ml; [b)] in publication presumably wrongly cited as 0.5 µg/ml; [c)] no differentiation between large or small colonies;
−: negative, +: positive, (+): weakly positive, +/−: not clear; 2-AA: 2-aminoanthracene; 9-AA: 9-aminoacridine; AfB1: aflatoxin B1; BHA: butylhydroxyanisol; BrdU: bromodesoxyuridine; CA: test for structural chromosomal aberrations; CFA: colony forming ability; CIPN: 2-(1-chloro-2-isopropylaminoethyl) naphthalene; DMSO: dimethyl sulfoxide; EMS: ethyl methanesulfonate; ENNG: *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine; GSH: glutathione; −m. a.: without metabolic activation; +m. a.: with metabolic activation; 3-MCA: 3-methylcholanthrene; MMS: methyl methanesulfonate; MN: micronucleus test; NA: sodium azide; NDMA: *N*-nitrosodimethylamine; βNF: β-naphthoflavone; 2-NF: 2-nitrofluorene; NOPD: 4-nitro-o-phenylene diamine; PB: phenobarbital; SCE: sister chromatid exchange

Another comet assay in rats yielded positive results after oral administration of 1,4-dichlorobenzene only in the kidneys of the female animals after 16 hours, whereas the results were negative after 24 hours. In the males on the other hand only negative or ambiguous results were obtained (Bayer AG 2002).

In rats, after oral administration of 1,4-dichlorobenzene for 13 weeks, no increase in the level of 8-OHdG (8-hydroxydeoxyguanosine) in the DNA of the kidneys was determined (Umemura et al. 2000).

In studies of DNA binding, after intraperitoneal administration of 1,4-dichlorobenzene, no DNA binding was found in the liver, kidneys, lungs and stomach of rats, whereas, in mice, the DNA binding had increased in these organs after 22 hours, but not after 72 hours (Lattanzi et al. 1989). It is not clear whether the binding was due to covalently bound adducts (EU 2004). In a study using $^{32}$P-postlabelling, no increase in DNA adducts could be found in the liver of rats after intraperitoneal injection of 1,4-dichlorobenzene (Tian et al. 2001 a).

A UDS test carried out with the kidneys of rats and the liver of mice yielded negative results after oral treatment with 1,4-dichlorobenzene (CMA 1987 a, b; Sherman et al. 1998).

1,4-Dichlorobenzene did not increase the frequency of chromosomal aberrations in the bone marrow of rats and mice after inhalation or intraperitoneal injection (EU 2004; Loeser and Litchfield 1983; NTP 1990 a).

A bone marrow micronucleus test in mice yielded positive results after intraperitoneal injection of 1,4-dichlorobenzene (Mohtashamipur et al. 1987). This could not be confirmed after intraperitoneal or oral administration in three other bone marrow tests in mice (Bayer AG 1986 b, 1988; NTP 1990 b). Furthermore, five micronucleus tests in peripheral blood cells of mice yielded negative results after ingestion or intraperitoneal injection of 1,4-dichlorobenzene (Morita et al. 1997; NTP 1987, 1992, 1993).

In a micronucleus test in rats, an increased frequency of micronuclei was detected in the kidneys after oral administration of 1,4-dichlorobenzene (Robbiano et al. 1999).

A dominant lethal test in male CD-1 mice yielded negative results after inhalation exposure to 1,4-dichlorobenzene (ICI 1976).

**Table 7** In vivo studies of the genotoxicity of 1,4-dichlorobenzene

| Test system | | Dose | Result | Remarks | References |
|---|---|---|---|---|---|
| SLRL test | Drosophila, ♂ | 0, 6000, 15 600 ml/m$^3$ × hour, purity: not specified | – | positive control: dibromomethane, mortality up to 23% at 15 600 ml/m$^3$ × hour | Valencia 1982 |
| Host mediated assay (Salmonella typhimurium G45) | mouse, CFLP, 5 ♂ per group | 2000, 4000, 8000 mg/kg body weight, oral, in corn oil, 2× at intervals of 12 or 24 hours[a], purity: not specified | – | positive control: triethylene melamine, mortality 2/5 at 8000 mg/kg body weight | JDIA 1975 |
| DNA single strand breaks, single cell gel electrophoresis (comet assay, alkaline), liver, lungs, spleen, kidneys, bone marrow | mouse, CD-1, 2 ♂ per group | 0, 2000 mg/kg body weight, intraperitoneal, 1×, examined after 3 and 24 hours, purity: not specified | + (liver > spleen only after 3 hours); – (lungs, kidneys, bone marrow after 3 and 24 hours; liver and spleen after 24 hours) | unconventional method, first isolation of nuclei and then comet assay | Sasaki et al. 1997 |
| DNA single strand breaks, single cell gel electrophoresis (comet assay, alkaline), kidneys | rat, Sprague Dawley, 3 ♂ per group | 0, 250 mg/kg body weight, oral, 1×, examined after 48 hours, purity: 99% | + | artificial system: stimulation of kidney cell proliferation by unilateral nephrectomy and intravenous administration of folic acid; dose corresponds to 1/2 $LD_{50}$ | Robbiano et al. 1999 |
| | rat, Sprague Dawley, 3 ♂ per group | 0, 167 mg/kg body weight, oral, 3× at intervals of 24 hours, examined after 12 hours, purity: 99% | + | stimulation of kidney cell proliferation by unilateral nephrectomy and intravenous administration of folic acid; dose corresponds to 1/3 $LD_{50}$ | |

**Table 7** (continued)

| Test system | | Dose | Result | Remarks | References |
|---|---|---|---|---|---|
| DNA single strand breaks, single cell gel electrophoresis (comet assay, alkaline), kidneys | rat, Sprague Dawley, 4 ♂ and 4 ♀ per group | 0, 1000 (only ♂), 2000 mg/kg body weight in corn oil, oral, 1×, examined after 16 (only ♀) and 24 hours, purity: 99.9% | – (1000 mg/kg body weight, only ♂; 2000 mg/kg body weight, ♀, after 24 hours); +/– (2000 mg/kg body weight, ♂); + (2000 mg/kg body weight, ♀, only after 16 hours) | positive control: EMS, signs of toxicity at all doses, no cytotoxicity, authors regarded overall result as positive | Bayer AG 2002 |
| 8-OHdG, kidneys | rat, F344, 5 ♂ per group | 0, 300 mg/kg body weight, oral, 5 days/week, 13 weeks, purity: not specified | – | positive control: potassium bromate | Umemura et al. 2000 |
| DNA binding, liver, kidneys, lungs, stomach (bound radioactivity) | rat, Wistar, 9 ♂, controls 3 ♂ | 0, 433.7 µg/kg body weight (2.95 µmol) in ethanol, intraperitoneal, 1×, examined after 22 hours, purity: 98% | – | no DNA binding, RNA and protein binding demonstrated | Lattanzi et al. 1989 |
| | mouse, BALB/c, 35 ♂, controls 12 ♂ | 0, 433.7 µg/kg body weight (2.95 µmol) in ethanol, intraperitoneal, 1×, examined after 22 hours and after 72 hours (n = 12), purity: 98% | + (22 hours: lungs > liver > kidneys ≥ stomach) – (72 hours: only liver investigated) | covalent character of DNA binding not clearly demonstrated; RNA and protein binding demonstrated | |
| DNA adducts ($^{32}$P-postlabelling), liver | rat, F344/NSIc, 3 ♂ per group | 0, 300, 600 mg/kg body weight in olive oil, intraperitoneal, 1×, examined after 24 hours, purity: not specified | – | no DNA adducts demonstrated in the liver; animals pretreated with ethanol, phenobarbital or 3-methyl cholanthrene to induce CYP, positive control: BaP | Tian et al. 2001 a |

**Table 7** (continued)

| Test system | | Dose | Result | Remarks | References |
|---|---|---|---|---|---|
| UDS test, kidneys | rat, F344, 3–4 ♂ and 3–4 ♀ per group | 0, 300, 600, 1000 mg/kg body weight in corn oil, oral, 1×, examined after 16 hours, purity: 99.5% | – | positive control: streptozotocin | CMA 1987 b; Sherman et al. 1998 |
| UDS test, liver | mouse, B6C3F1, je 3–4 ♂, 3 ♀ | 0, 300, 600, 1000 mg/kg body weight in corn oil, oral, 1×, examined after 16 hours, purity: 99.5% | – | positive control: dimethyl nitrosamine | CMA 1987 a; Sherman et al. 1998 |
| CA, bone marrow | rat, Alderley Park, 3 per group, controls 4 (no other details) | 0, 1831, 4177 mg/m³ (299, 682 ml/m³), 1× 2 hours, purity: not specified | – | positive controls: benzene, vinyl chloride | EU 2004; Loeser and Litchfield 1983 |
| | | 0, 459, 3063 mg/m³ (75, 500 ml/m³), 5 hours/day, 5 days/week, 1 or 12 weeks, purity: not specified | – | | |
| CA, bone marrow | mouse, B6C3F1, 7–8 ♂ per group | 0, 750, 1500, 3000 mg/kg body weight in corn oil, intraperitoneal, 1×, examined after 17 or 36 hours, purity: not specified | – | positive control: dimethyl benzanthracene | NTP 1990 a |
| MN, bone marrow | mouse, NMRI, 5 ♂ and 5 ♀ per group | 0, 2500 mg/kg body weight in corn oil, oral, 1×, examined after 24, 48, 72 hours, purity: ≥ 99.5% | – | positive control: cyclophosphamide | Bayer AG 1986 b; Tegethoff et al. 2000 |

**Table 7** (continued)

| Test system | | Dose | Result | Remarks | References |
|---|---|---|---|---|---|
| MN, bone marrow | mouse, NMRI, 5 ♂ per group | 0; 177.5, 355, 532.5, 710 mg/kg body weight in corn oil, intraperitoneal, 2× at an interval of 24 hours, examined after 6 hours, purity: 99.0% | + | $LD_{50}$ 2000 mg/kg body weight, positive controls: benzene and other halogenated benzene compounds; no data for cytotoxicity; only 10 control animals compared with a total of 180 treated animals (9 test substances) | Mohtashamipur et al. 1987 |
| MN, bone marrow | mouse, NMRI, 5 ♂ and 5 ♀ per group | 0; 177.5; 355 mg/kg body weight in corn oil, intraperitoneal, 2× at an interval of 24 hours, examined after 6 hours, purity: ≥ 99.5% | – | positive control: cyclophosphamide at 355 mg/kg body weight and day decrease in PCE/NCE ratio (93% to 77%) | Bayer AG 1988; Tegethoff et al. 2000 |
| MN, bone marrow | mouse, B6C3F1, 5 ♂ per group | 0, 375, 750, 1500 mg/kg body weight, in corn oil, oral, 3× in 72 hours, examined after 24 hours, purity: not specified | – | positive control: dimethyl benzanthracene, 2 independent assays | NTP 1990 b |
| MN, peripheral blood (erythrocytes) | mouse, B6C3F1, 3–10 ♂ per group | 0, 600, 900, 1000, 1500, 1800 mg/kg body weight and day, oral, 13 weeks, purity: > 99% | – | | NTP 1987 |
| | mouse, B6C3F1, 1–10 ♀ per group | 0, 1200, 1500, 1800 mg/kg body weight and day, oral, 13 weeks, purity: > 99% | – | | |

**Table 7** (continued)

| Test system | | Dose | Result | Remarks | References |
|---|---|---|---|---|---|
| MN, peripheral blood (PCE) | mouse, B6C3F1, 5 ♂ per group | 0, 500, 1000, 1500 mg/kg body weight, in corn oil, oral, 3× in 96 hours, examined after 48 hours, purity: not specified | – | positive control: dimethyl benzanthracene, 2 independent assays | NTP 1992 |
| MN, peripheral blood (NCE) | mouse, B6C3F1, 3–10 ♂ and 1–10 ♀ per group | 0, 84.4 (only ♂), 168.8 (only ♂), 337.5, 675, 900 mg/kg body weight and day, in corn oil, oral, 90× in 90 days, examined after 24 hours, purity: not specified | – | no positive control | NTP 1993; Witt et al. 2000 |
| MN, peripheral blood | mouse, CD-1, 5 ♂ per group | 0, 400, 800, 1600 mg/kg body weight in olive oil, intraperitoneal, 2× at an interval of 24 hours, examined after 24, 48, 72 hours, purity: > 98% | – | $LD_{50}$ 2150 mg/kg body weight | Morita et al. 1997 |
| MN, peripheral blood | mouse, CD-1, 5 ♂ per group | 0, 500, 1000, 2000 mg/kg body weight in olive oil, oral, 2× at an interval of 24 hours, examined after 24, 48, 72 hours, purity: > 98% | – | | |

**Table 7** (continued)

| Test system | | Dose | Result | Remarks | References |
|---|---|---|---|---|---|
| MN, kidney cells | rat,<br>Sprague Dawley,<br>3 ♂ per group | 0, 250 mg/kg body weight,<br>oral, 1×,<br>examined after 48 hours,<br>purity: 99% | + | artificial system: stimulation of kidney cell proliferation by unilateral nephrectomy and intravenous administration of folic acid;<br>dose corresponds to 1/2 $LD_{50}$ | Robbiano et al. 1999 |
| MN, kidney cells | rat,<br>Sprague Dawley,<br>3 ♂ per group | 0, 167 mg/kg body weight,<br>oral, 3× at intervals of 24 hours,<br>examined after 12 hours,<br>purity: 99% | + | artificial system: stimulation of kidney cell proliferation by unilateral nephrectomy and intravenous administration of folic acid;<br>dose corresponds to 1/3 $LD_{50}$ | |
| DLT | mouse,<br>CD-1,<br>16 ♂, controls<br>35 ♂ | 0, 75, 225, 450 ml/$m^3$,<br>6 hours/day, 5 days,<br>purity: not specified;<br>mating lasted for 8 weeks | – | positive controls: cyclophosphamide, EMS, bis-(2-chloroethyl)-methylamine;<br>range-finding: mortality 2/5 at 640 ml/$m^3$;<br>no historical control data given | ICI 1976; EU 2004 |

[a] contradictory data;
BaP: benzo(a)pyrene; CA: test for structural chromosomal aberrations; CYP: cytochrome P450; DLT: dominant lethal test; EMS: ethyl methane sulfonate; MN: micronucleus test; NCE: normochromatic erythrocytes; 8-OHdG: 8-hydroxydeoxyguanosine; PCE: polychromatic erythrocytes; SLRL: Drosophila test for sex-linked recessive lethal mutations; UDS: unscheduled DNA repair synthesis

**Summary:**

In the majority of in vitro and in vivo tests no genotoxic effects were found. There were no gene mutations in bacteria and mammalian cells, and no chromosomal aberrations were induced in mammalian cells. Indicator tests for SCE in CHO cells and human lymphocytes, UDS in HeLa cells and human lymphocytes and DNA adducts in liver cells of rats, mice and humans yielded negative results. Some in vitro studies with positive results were either not reproducible or were carried out using test systems (comet, SCE and alkaline elution assay) not in accordance with test guidelines and are presumed to be falsely positive as a result of high cytotoxicity. The in vivo studies of the induction of DNA adducts ($^{32}$P-postlabelling; bound radioactivity), UDS (kidneys, liver), chromosomal aberrations in the bone marrow (rat, mouse), micronuclei in the bone marrow and peripheral blood (mouse, 3 strains) and of dominant lethal mutations after inhalation (mouse) conforming to OECD Test Guidelines did not reveal systemic genotoxicity. From in vivo studies not in accordance with test guidelines (DNA single strand breaks in the comet assay, DNA binding, micronuclei in kidney cells) there is evidence of a genotoxic effect in individual organs such as the kidneys and the liver. The induction of micronuclei in rat kidney cells stimulated to proliferation was an isolated finding at different time points. Dose-dependency was not investigated.

All in all, the reliable studies show 1,4-dichlorobenzene not to have genotoxic potential.

## 5.7 Carcinogenicity

The studies of the carcinogenicity of 1,4-dichlorobenzene were described in detail in the supplement of 2001 (supplement "1,4-Dichlorobenzene" 2003). No new studies relevant to this evaluation are available.

### 5.7.1 Short-term studies

No increase in the number of transformed colonies was found in an in vitro cell transformation test with BALB/3T3 cells after exposure to 1,4-dichlorobenzene concentrations of 60 to 140 µg/ml for 72 hours and subsequent cultivation for four weeks (EU 2004).

In a short-term test with male F344 rats, no initiating effects of 1,4-dichlorobenzene in the kidneys were found (Umemura et al. 2000).

In another short-term test, no evidence was found of promoting effects of 1,4-dichlorobenzene in the liver of male F344 rats (Gustafson et al. 2000). Similar studies with mice, in which the liver is the main target organ of the carcinogenic effects of 1,4-dichlorobenzene, have not yet been carried out.

## 5.7.2 Long-term studies

**Inhalation**

In an inhalation study with Wistar rats exposed to 1,4-dichlorobenzene concentrations of 0, 75 or 500 ml/m³ for 76 weeks (5 hours/day, 5 days/week) with a 36-week recovery period, one nasal carcinoma (1/60; controls: 0/60) developed in the males of the high concentration group and 2 carcinomas in the thyroid gland (2/58; controls: 0/61) in the female animals of the high concentration group (ICI 1980). The study design does not fulfil present-day requirements for carcinogenicity studies.

In an inhalation study with F344 rats, the animals were exposed to 1,4-dichlorobenzene concentrations of 0, 20, 75 or 300 ml/m³ for 6 hours daily, on 5 days per week, for 104 weeks. The incidence of mononuclear cell leukaemia in male rats was not concentration-dependent, but the Peto test revealed a significantly positive trend. In addition, in the female rats, the incidence of C-cell adenomas of the thyroid gland was significantly increased (9/50; controls: 2/50) in the 75 ml/m³ group (JISHA 1995).

In another inhalation study with BDF1 mice, the animals were exposed to 1,4-dichlorobenzene concentrations of 0, 20, 75 or 300 ml/m³ for 6 hours per day, on 5 days per week, for 104 weeks. Increased incidences of bronchioloalveolar carcinomas in the lungs with a significantly positive trend were found only in the females. The combined incidence of bronchioloalveolar adenomas and carcinomas was, in addition, significantly increased in the high concentration group (7/50; controls: 1/50). In the male mice, the incidence of malignant lymphomas was significantly increased only in the animals of the 75 ml/m³ group (13/50; controls: 4/49) and was therefore not dose-dependent. In the high concentration group, there was a significant increase in the incidence of hepatocellular carcinomas in both sexes. In addition, in the male mice, the incidence of histiocytic sarcomas of the liver was significantly increased (6/49; controls: 0/49) (JISHA 1995).

The inhalation studies in F344 rats and BDF1 mice (JISHA 1995) which were initially available only in the form of an English summary of the Japanese study report, have in the meanwhile been published in a journal (Aiso et al. 2005 b) and the complete study report is available on the internet (JMHLW 1995 d, e, f, g). A summary of the inhalation study in rats states that no significantly increased incidences of neoplastic or tumour-like lesions were found in the organs of the male and female animals. The authors noted that the mortality from leukaemia in the male rats of the 300 ml/m³ group was increased, the incidences of leukaemia, however, were not dose-dependently increased (Aiso et al. 2005 b).

As regards the study with mice, it is reported that the incidence of bronchioloalveolar carcinomas in the females of the high concentration group was still within the upper range of historical control data. In the male and female mice, the incidences of hepatocellular carcinomas and hepatoblastomas were significantly increased in the 300 ml/m³ group. In addition, histiocytic sarcomas occurred in the liver with a significantly increased incidence in the male animals at this concentration (Aiso et al. 2005 b).

**Oral administration**

Male F344 rats were given gavage doses of 1,4-dichlorobenzene of 0, 150 or 300 mg/kg body weight and day on 5 days per week, for 103 weeks. The incidence of mononuclear cell leukaemia showed a significantly positive trend and was significantly increased at 300 mg/kg body weight and day. Furthermore, the incidence of tubular adenocarcinomas in the kidneys was significantly increased in the male animals of the high dose group (NTP 1987).

B6C3F1 mice were given gavage doses of 1,4-dichlorobenzene of 0, 300 or 600 mg/kg body weight and day on 5 days per week, for 103 weeks. In the males the incidence of bronchioloalveolar carcinomas was significantly increased only in the middle dose group, this was found in none of the animals in the high dose group. The incidence of hepatocellular carcinomas in male and female mice was significantly increased only in the high dose group. In addition, very rare hepatoblastomas were found in 4/50 male mice of the high dose group. The incidences of malignant and benign phaeochromocytomas were slightly, but significantly increased in the male mice of the high dose group (NTP 1987).

## 6 Manifesto (MAK value/classification)

The main target organs of 1,4-dichlorobenzene toxicity are the liver and the kidneys.

**Carcinogenicity.** The reliable studies of genotoxicity in animals show 1,4-dichlorobenzene not to have genotoxic potential. The induction of micronuclei in rat kidney cells stimulated to proliferation is an isolated finding obtained at different time points. Dose-dependency was not investigated.

1,4-Dichlorobenzene causes carcinomas of the kidneys in male rats after oral administration (NTP 1987); this can be attributed to the species-specific and sex-specific mechanism of $\alpha_{2u}$-globulin nephropathy. This has no relevance for humans (Hard et al. 1993). The mononuclear cell leukaemia found in the male rats occurs with a high spontaneous incidence in the strain used. The incidences in the inhalation study are not dose-dependent (Aiso et al. 2005 b) and in the study with oral administration (NTP 1987) the incidence is higher than that for the historical controls only in the high dose group. The incidence of C-cell adenomas in the female rats in the inhalation study was not dose-dependent, and corresponding carcinomas were not found.

In mice, ingestion and inhalation of 1,4-dichlorobenzene caused significantly increased incidences of hepatocellular adenomas and carcinomas and rare hepatoblastomas at the respective high dose/concentration tested of 600 mg/kg body weight and day and 300 ml/m$^3$ (Aiso et al. 2005 b; NTP 1987). In addition, histiocytic sarcomas of the liver were found in male mice after inhalation of 300 ml/m$^3$ (Aiso et al. 2005 b). Therefore, for liver carcinogenicity in mice, a NOAEL of 300 mg/kg body weight and day and a NOAEC of 75 ml/m$^3$ are available. Bronchioloalveolar carcinomas were found in mice after oral administration (NTP 1987) without dose-dependency and after inhalation with incidences still within the range of historical control data (Aiso et al. 2005 b). From the data for genotoxicity (see above) and for the mode of action (Section 2), it can be concluded that both mitogenic and cytotoxic mechanisms

are probably responsible for the carcinogenic effects of 1,4-dichlorobenzene on the mouse liver and that there is a non-linear dose-response relationship. Genotoxicity is therefore not the main cause of 1,4-dichlorobenzene carcinogenicity. Therefore, 1,4-dichlorobenzene is classified in Carcinogen Category 4.

**Germ cell mutagenicity** The available reliable studies of the genotoxicity of the substance showed 1,4-dichlorobenzene not to have genotoxic potential. A dominant lethal test in mice with concentrations of up to 450 ml/m³ (2700 mg/m³) yielded negative results. The substance is therefore not classified in one of the categories for germ cell mutagens.

**MAK value.** The cross-sectional study described in Section 4.2.2 (Hsiao et al. 2009), in which liver effects were reported in exposed workers, is not considered reliable by the Commission. Therefore, there are not sufficient data in humans available to derive a MAK value.

In the 2-year inhalation study with rats (Aiso et al. 2005 b), changes in the olfactory epithelium of the nose occurred, the most sensitive end point, at concentrations of 75 ml/m³ and above. The NOAEC in rats was 20 ml/m³. After extrapolation of the data from the animal study to humans (1:2), a MAK value of 10 ml/m³ can be derived.

The most sensitive species after oral administration is the dog. In an oral 52-week study in dogs, initial systemic effects were found at the lowest dose tested of 10 mg/kg body weight and day and above. In the males, increased thrombocyte counts with a significant trend and foci of chronic inflammation in the lungs were found in 2 of 5 animals. In the female dogs, the activity of ALT in the serum was increased; hepatocellular hypertrophy occurred in one animal and vacuolization of epithelial cells of the renal medullary collecting ducts in another. In male and female dogs, the activity of γ-glutamyl transpeptidase in the serum was increased with a significant trend (Monsanto Company 1996).

The findings in the lungs are not considered to be treatment-related, as they occurred only in a few animals and no notable difference in severity between the treated groups was found (US EPA 2006).

Hepatocellular hypertrophy with a LOAEL (lowest observed adverse effect level) of 10 mg/kg body weight and day is the most sensitive end point. As this is only a mild effect (grade 2 of 5) with a low incidence (in 1 of 5 animals), a NAEL of 5 mg/kg body weight and day can be assumed. The following toxicokinetic data are taken into consideration for the extrapolation of the dose of 5 mg/kg body weight and day to a concentration in workplace air: the corresponding species-specific correction value (1:1.4) for the dog, the measured oral absorption for rats (90%, Butterworth et al. 2007; US EPA 2006), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the measured 56% absorption by inhalation. The concentration calculated from this is 40 mg/m³, which corresponds to 6.6 ml/m³. After extrapolation of the data from an experimental study with animals to humans (1:2) and application the preferred value approach, a MAK value of 2 ml/m³ can be derived.

This MAK value therefore also protects against the carcinogenic effects of 1,4-dichlorobenzene. For the liver carcinogenicity in mice, for which both mitogenic and cytotoxic mechanisms are responsible, a NOAEL of 300 mg/kg body weight and day and a NOAEC of 75 ml/m³ are available. The liver toxicity and the marked increase

in liver weights, which can be considered as precursors of liver carcinogenicity in mice, occured in mice in the inhalation studies at concentrations of 270 ml/m³ and above (13 weeks) and 300 ml/m³ (104 weeks), respectively (Aiso et al. 2005 a, b) and, after oral administration, at dose levels of 600 mg/kg body weight and day and above (13 weeks) or 300 mg/kg body weight and day and above (103 weeks) (NTP 1987). In addition, in studies of DNA replication in the liver after single doses or treatment for up to 13 weeks with 1,4-dichlorobenzene doses of 600 or 300 mg/kg body weight and day, respectively, no significant increase was found in B6C3F1 mice (Eldridge et al. 1992; Umemura et al. 1996).

**Peak limitation.** As the MAK value is derived from a systemic effect, 1,4-dichlorobenzene is assigned to Peak Limitation Category II. As it is not known whether the substance itself or a metabolite is responsible for the effects, and data for the half-lives of the metabolites are not available, the default excursion factor of 2 has been set.

**Prenatal toxicity.** In a study of the prenatal developmental toxicity after inhalation exposure, no developmental toxicity occurred in the rat up to the highest concentration tested of 500 ml/m³. In rabbits, the number of resorptions was increased at concentrations of 300 ml/m³ and above. The NOAEC for developmental toxicity in this species is 100 ml/m³. If the increased respiratory volume (1:2) is taken into account, the differences between these NOAECs and the MAK value of 2 ml/m³ are 125-fold and 25-fold for rats and rabbits, respectively.

In rats given gavage doses of 500 mg/kg body weight and day and above, the foetal weights were reduced and the number of skeletal anomalies after prenatal exposure increased. The NOAEL for developmental toxicity was 250 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of the dose of 250 mg/kg body weight and day to a concentration in the workplace air: the species-specific correction value (1:4) for the rat and the other parameters already given above (see MAK value). The concentration calculated from this is 703 mg/m³ (≙ 115 ml/m³). A 58-fold difference between this and the MAK value of 2 ml/m³ is thus obtained. As no malformations occurred in rats and rabbits, the sufficiently large differences between the NOAEC and NOAEL for developmental toxicity and the MAK value of 2 ml/m³ allow the assignment of the substance to Pregnancy Risk Group C.

In 2-generation studies in rats with inhalation exposure, litter size was reduced at the concentration of 538 ml/m³, as were the foetal weights at birth after gavage doses of 90 mg/kg body weight and day and above. The NOAEC and the NOAEL for foetotoxicity were 211 ml/m³ and 30 mg/kg body weight and day, respectively. The differences between the NOAEC and NOAEL of the generation studies after exposure by inhalation (taking the increased respiratory volume (1:2) into consideration) and after administration by gavage, and the MAK value, are, after extrapolation of the 7-day treatment period to the 5-day working week for humans, 74-fold and 10-fold, respectively. The NOAEL for foetotoxicity in the oral 2-generation study might also be higher because the LOAEL was 90 mg/kg body weight and day, which represents a 15-fold difference to the MAK value. The relevant exposure route for the workplace is inhalation, for which reason the 2-generation inhalation study is of greater

significance. The NOAEC and the NOAEL for foetotoxicity from the 2-generation studies allow the assignment of the substance to Pregnancy Risk Group C.

**Absorption through the skin.** From the NAEL of 5 mg/kg body weight and day obtained in the 52-week oral study with dogs, after toxicokinetic correction (1:1.4) and extrapolation of the data from an animal study to humans (1:2), a tolerable daily uptake of 201 mg is calculated when the oral absorption of 90%, the absorption by inhalation of 56% and the body weight of 70 kg are taken into account. The model calculations for dermal absorption yield values of 5.5 mg, 10.4 mg or 430 mg, so that the contribution of absorption through the skin to the total amount absorbed is not negligible and 1,4-dichlorobenzene remains designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

**Sensitization.** As before, no valid clinical or experimental findings are available that indicate a contact sensitization potential of 1,4-dichlorobenzene. In addition, no data for respiratory sensitization are available, so that 1,4-dichlorobenzene is not designated with either "Sh" or with "Sa" (for substances which cause sensitization of the skin or airways).

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