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Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,4-Dichlorobenzene

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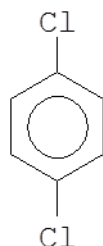
Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,4-Dichlorobenzene

8-hour TWA:	2 ppm (12 mg/m ³)
STEL (15-min.):	10 ppm (60 mg/m ³)
BLV:	-
Additional categorisation:	Carcinogen group D (non-genotoxic carcinogen with threshold)
Notation:	Skin

This evaluation is an update of the SCOEL Recommendation from 1994 and is mainly based on EU (2004) and Greim (2003) and the references cited in these reviews.

1. Substance identification, physico-chemical properties

Chemical name:	1,4-dichlorobenzene
Synonyms:	<i>p</i> -dichlorobenzene; <i>p</i> -chlorophenyl chloride
Molecular formula:	C ₆ H ₄ Cl ₂
Structural formula:	



EC No.:	203-400-5
CAS No.:	106-46-7
Molecular weight:	147.1 g/mol
Boiling point:	174 °C
Melting point:	52.8–53.5 °C
Vapour pressure (55 °C)	13.3 hPa
Conversion factors:	1 ppm = 6.1 mg/m ³
(20 °C, 101.3kPa)	1 mg/m ³ = 0.16 ppm

EU harmonised classification:

Eye Irrit. 2	H319	Causes serious eye irritation
Carc. 2	H351	Suspected of causing cancer
Aquatic Acute 1	H400	Very toxic to aquatic life
Aquatic Chronic 1	H410	Very toxic to aquatic life with long-lasting effects

1,4-Dichlorobenzene is a white crystalline solid with a penetrating, camphoraceous odour. The water solubility of 1,4-dichlorobenzene is 0.1 g/l at 20 °C and the log P_{ow} is 3.37. The substance has flash points of 65–66 °C and 54 °C (closed and open cup, respectively) and a density of 1.23 g/cm³ (ACGIH 2001, ECB 2000).

2. Occurrence/use and occupational exposure

1,4-Dichlorobenzene is used as an insecticide and fumigant. Besides, it is an ingredient for pharmaceutical products, as an intermediate in the production of polyphenylene sulphide, in the production of 1,2,4-trichlorobenzene room deodorant and for moth control, and for the manufacture of 2,5-dichloroaniline and various dyes. Another use of 1,4-dichlorobenzene includes the use as space deodorant for toilets and refuse containers (NTP 2011).

1,4-Dichlorobenzene was detected in food and water, but exposure was generally less than that from air. Especially indoor air concentrations may be 1–3 orders of magnitude higher than outdoor concentrations, which are below $25.2 \mu\text{g}/\text{m}^3$ in urban areas and in the vicinity of hazardous waste sites. Contamination of indoor air with 1,4-dichlorobenzene is a result of its use as a space deodoriser or moth repellent (NTP 2011).

The primary route of occupational exposure to 1,4-dichlorobenzene is inhalation. The substance can be determined in workplace air by means of adsorption on Tenax TA followed by thermal desorption and analysis by gas chromatography with flame ionisation detection. The limit of quantification is estimated to $0.90 \text{ mg}/\text{m}^3$ for an air sample volume of 0.2 l (Tschickardt 2014).

3. Health significance

3.1. Toxicokinetics

3.1.1. Human data

1,4-dichlorobenzene has been identified in human adipose tissue, breast milk, liver and whole blood. It was eliminated with urine and exhaled air. In workers exposed by inhalation to 1,4-dichlorobenzene, the substance itself and the metabolite 2,5-dichlorophenol were determined in urine (Greim 2003, EU 2004).

Yoshida *et al* (2002a) evaluated the toxicokinetics of 1,4-dichlorobenzene in 7 male subjects continuously inhaling about 2.5 ppm of 1,4-dichlorobenzene vapour for 1 hour. Examination of concentration-time courses of 1,4-dichlorobenzene in their exhaled air and serum and of urinary 2,5-dichlorophenol showed that the major route of elimination was urinary excretion followed by metabolism, not exhalation. Most of the absorbed 1,4-dichlorobenzene seemed to be distributed rapidly to the tissues, such as fat, and complete elimination seemed to require a long time. Using a linear two-compartment model, amounts of daily absorption and internal accumulation of chronic exposure to a low concentration of 1 ppb 1,4-dichlorobenzene were estimated to be 0.27 mg/day and 2.9 mg, respectively.

3.1.2. Animal and in vitro data

1,4-Dichlorobenzene is well absorbed through the respiratory tract and following ingestion, with highest concentrations found in the adipose tissue (Greim 2003). Subcutaneous absorption also occurs (EU 2004).

No information was available on dermal absorption. Model calculations (Fiserova-Bergerova *et al* 1990, Guy and Potts 1993, cited in Greim 2003) resulted in absorptions of 318 mg and 8 mg, respectively, for a 1-hour exposure of the hands and forearms ($2\,000 \text{ cm}^2$) to a saturated aqueous solution of 1,4-dichlorobenzene (Greim 2003).

Regardless of exposure route, distribution of 1,4-dichlorobenzene is reported to be similar in fatty tissues, kidney, liver, lungs, gonads and muscle tissues (EU 2004).

1,4-dichlorobenzene is oxidised to 2,5-dichlorophenol, then excreted in the urine both in free and in conjugated form as the sulphate and glucuronide in rodents. In male rats, it can be accumulated to a minor extent as a complex with α_{2u} -globulin in the kidney (Charbonneau *et al* 1989, Greim 2003).

Species differences in metabolism were observed. The metabolite 2,5-dichlorohydroquinone is found in some rat strains (in F344 but not in Wistar) (Muller 2002, EU 2004) but not in mice (EU 2004). Others reported that 2,5-dichlorohydroquinone is produced in liver microsomes of mice in substantial amounts (Muller 2002).

Studies with microsomal preparations indicate that mouse liver is a significant metaboliser of 1,4-dichlorobenzene (15 % being converted to metabolites), whereas rat and human liver microsomes metabolised lower amounts (0.3 and 1.1 %) (Muller 2002).

Elimination is predominantly through urine and faeces (NICNAS 2000).

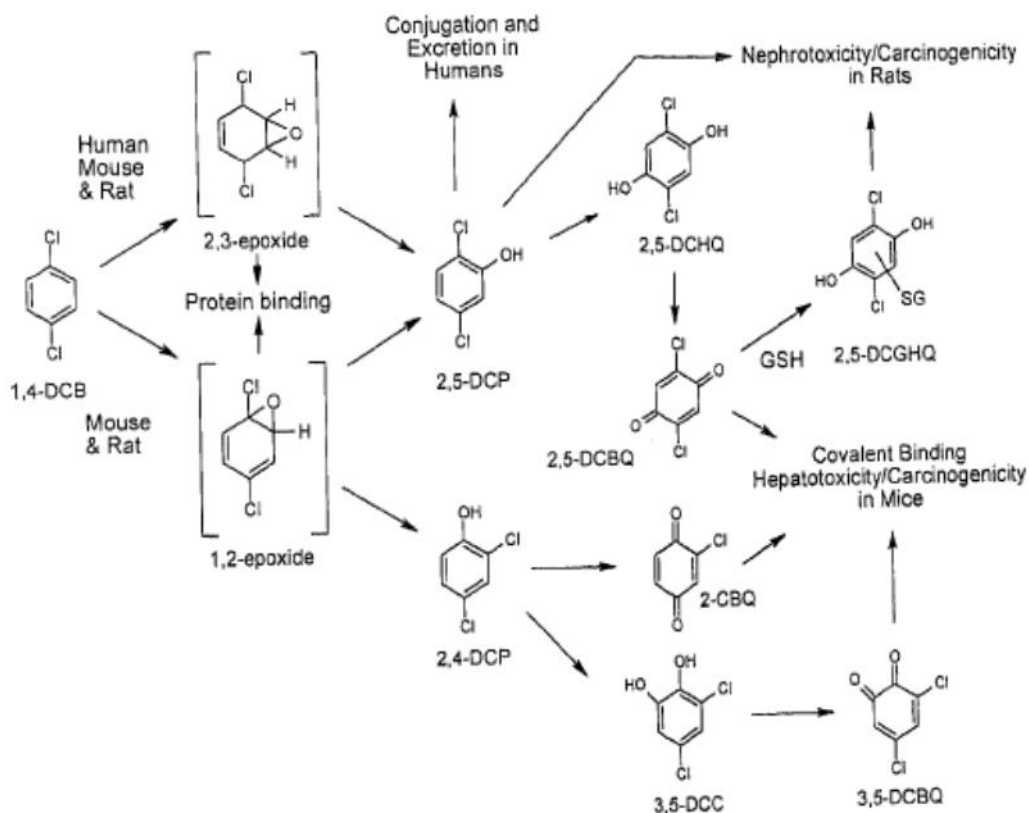


Figure 1. Metabolism of 1,4-dichlorobenzene (1,4-DCB). Pathways for the formation of reactive metabolites by mouse, rat and human microsomes and their proposed effects.

CBQ: Chlorobenzoquinone DBC: dichlorobenzene, DCC: dichlorocatechol, DCGHQ: dichloro-gluthionylhydroquinone, DCHQ: dichlorohydroquinone, DCP: dichlorophenol, DCBQ: dichloro-1,2-benzoquinone, GSH: reduced glutathione, SG: glutathione-S-yl-metabolite (after Den Besten *et al* 1992, Klos & Dekant 1994, Hissink *et al* 1997, all cited in NICNAS 2000).

3.1.3. Biological monitoring

Healthy volunteers (n = 3) were exposed to 2.4–2.8 ppm of 1,4-dichlorobenzene vapour for 1 hour. There were no differences in DNA-adduct profiles of blood samples which were obtained before exposure, immediately at the end of exposure and 1 hour after exposure (EU 2004).

Yoshida *et al* (2002b) showed a strong association between urinary 2,5-dichlorophenol, the major metabolite of 1,4-dichlorobenzene, and airborne 1,4-dichlorobenzene. Personal exposure concentrations of 1,4-dichlorobenzene and 2,5-dichlorophenol excreted in the urine of 119 adults living in Osaka were determined. The median of 1,4-dichlorobenzene exposure concentrations for 24 hours was 2.5 ppb (max. of 33.3 ppb), the median of 2,5-dichlorophenol concentrations in urine was 0.39 mg/g creatinine (max. 3.32 mg/g creatinine), and the Pearson correlation coefficient was 0.81 ($p < 0.001$).

3.2. Acute toxicity

3.2.1. Human data

A limited number of case reports involving intoxication indicated that the minimum dose that leads to adverse acute effects in humans is greater than 300 mg/kg (EU 2004).

3.2.2. Animal data

The acute toxicity appears to be low following inhalation or ingestion (EU 2004).

The 4-hour inhalation LC_{50} in rats (EEC method, GLP, limit test) is $> 5\,070\text{ mg/m}^3$ (845 ppm), with signs of pulmonary irritation (increased respiratory rate up to 4 hours post exposure), piloerection and reversible weight gain losses (EU 2004).

Oral LD_{50} values in rats and mice, as well as dermal LD_{50} values in rats are reported to be $> 2\,000\text{ mg/kg}$ (EU 2004).

A single oral dose of 625 mg/kg administered to male rats, which were sacrificed 24 hours after dosing led to an increase in α_{2u} -globulin in kidneys demonstrated with immunohistochemical staining. Additional renal cell proliferation, a direct cause of α_{2u} -globulin associated toxicity, was measured by immunohistochemical analysis of BrdU incorporation into nuclei. The early events in the α_{2u} -globulin mechanism are the accumulation of α_{2u} -globulin and an increase in regenerative cell proliferation due to necrosis of renal tubule cells. No significant increase in hepatic peroxisome proliferation was observed in the 1,4-dichlorobenzene treated rats (Warnasuriya *et al* 2010).

3.3. Irritancy and corrosivity

3.3.1. Human data

Skin

In EU (2004), it was concluded that 1,4-dichlorobenzene is a slight skin irritant (burning sensation without cracking) at repeated exposure.

Eyes

In EU (2004), it was concluded that ocular irritation symptoms were found at concentrations above 50 ppm.

Respiratory tract

Few reports were available on the effects of 1,4-dichlorobenzene in humans. Hollingsworth *et al* (1956) reported that workers experienced nose and eye irritation at concentrations of 50 to 80 ppm (306–490 mg/m³), with more serious effects extending to the respiratory tract at 160 ppm (979 mg/m³) and above. A degree of acclimatisation was noted after repeated exposures. Data on possible co-exposure are missing. A clear correlation between concentrations and effects could not be found, which may be a result of the fact that concentration data were given as a range and that peak exposure concentrations cannot be excluded.

However, in another study without exposure data, irritation of the mucous membranes was also reported in workers exposed to 1,4-dichlorobenzene (EU 2004).

In EU (2004), it was concluded, that nasal irritation symptoms were found at concentrations above 50 ppm.

Elliott *et al* (2006) showed that, after adjustment for smoking, 1,4-dichlorobenzene concentration in blood was associated with reduced pulmonary function in participants of the Third National Health and Nutrition Examination Survey (NHANES) (1988-1994).

3.3.2. Animal data

Skin

In rabbit dermal irritation studies according to current guideline, 1,4-dichlorobenzene is a slight skin irritant (EU 2004).

Eyes

In rabbit eye irritation studies according to current guideline, 1,4-dichlorobenzene is a slight irritant in the eyes (EU 2004).

Respiratory tract

A 50 % decrease of the mean minute volume and a severe decrease in the respiratory frequency in rats and mice occurred at a 6-hour inhalation exposure of 500 ppm (EU 2004).

3.4. Sensitisation

3.4.1. Human data

Only one, questionable, case report of acute petechial purpura after skin contact with 1,4-dichlorobenzene is reported (Nalbandian 1965, cited in EU 2004).

3.4.2. Animal data

In a Magnusson-Kligman test with guinea pigs, 1,4-dichlorobenzene showed a rather weak sensitisation potential (Bornatowicz 1995, cited in EU 2004). In an open epicutaneous test on guinea pigs, the substance was not skin sensitising (Schmidt 1985, cited in EU 2004). Several other not validated sensitisation tests were also negative with 1,4-dichlorobenzene (Suzuki 1991, Leung 1990, both cited in EU 2004).

In two studies in guinea pigs, no evidence of a sensitising potential of 1,4-dichlorobenzene was found (Greim 2003).

3.5. Repeated dose toxicity

3.5.1. Human data

Inhalation

Few reports were available on the effects of 1,4-dichlorobenzene in humans. Hollingsworth *et al* (1956) reported that workers experienced nose and eye irritation at concentrations of 50 to 80 ppm (306–490 mg/m³), with more serious effects extending to the respiratory tract at 160 ppm (979 mg/m³) and above. A degree of acclimatisation was noted after repeated exposures.

In EU (2004), it was concluded that no studies were available which are suitable for a risk assessment.

In a cross-sectional study, the urinary concentration of 2,5-dichlorophenol, the major metabolite of 1,4-dichlorobenzene, was significantly higher in exposed workers (n = 46; 105.38 µg/l urine, GSD 6.21) than in non-exposed (n = 29; 1.08 µg/l urine, GSD 3.73) workers in mothball manufacture in Taiwan. Health information was collected using questionnaires and biochemical tests. White blood cell counts and serum alanine aminotransferase levels were also significantly increased in exposed workers and significantly correlated with urinary concentrations of 2,5-dichlorophenol. These associations persisted after adjustment for gender, age and smoking habit. Furthermore, the blood urea nitrogen (BUN) level was significantly increased in on-site exposed workers (13.28 ± 3.32 mg/dl, 11.85 ± 4.00 mg/dl and 15.18 ± 4.05 mg/dl in unexposed, non-on-site exposed, on-site exposed, respectively). The same was shown for adjusted BUN levels (BUN/creatinine ratio: 15.59 ± 5.12 mg/dl, 12.50 ± 4.46 mg/dl, and 17.88 ± 6.03 mg/dl in unexposed, non-on-site exposed, on-site exposed, respectively). The non-on-site exposed workers worked in the offices without direct contact with any mothball component or intermediate product. The on-site exposed workers handled the raw materials, intermediate and finished products. The non-exposed control group was medical workers and administrative personnel (Hsiao *et al* 2009).

3.5.2. Animal data

In EU (2004), a full presentation of short and long-term animal studies is given. In the following chapter, only the most relevant long-term studies are described.

Inhalation

The critical effect of 1,4-dichlorobenzene is liver and kidney toxicity. In limited repeated inhalation studies in rats, mice, guinea pigs and rabbits, no effects were observed with exposure to 1,4-dichlorobenzene at 95 ppm (580 mg/m³), 7 hours/day for 6–7 months (Hollingsworth *et al* 1956). Concentrations in the range 155–336 ppm (950–2 050 mg/m³) produced "slight" histopathological changes in the liver, kidneys and lungs of rats, guinea pigs and rabbits. In other studies involving inhalation exposure for 13–18 months and examination 4.5–9 months later, no histopathological effects were noted in rats receiving 74 or 490 ppm (450 or 3 000 mg/m³) 1,4-dichlorobenzene (Riley *et al* 1980a).

For assessment of chronic exposure, there are two carcinogenicity studies (104 weeks) available, one in rats and one in mice (Table 1). In rats exposed to the highest dose of 300 ppm, a statistically significant increase in liver and kidney weights was reported. In males, also mineralisation of the renal papillae and urothelial hyperplasia in the renal pelvis were found. Significant increases in kidney-specific and liver-specific serum parameters and a reduction in total serum protein were observed. Eosinophilic changes in the olfactory epithelium were reported in rats exposed to 75 ppm or more

Table 1. Chronic (104-week) exposure of rats and mice to 1,4-dichlorobenzene (JISHA 1995, cited in Greim 2003); for neoplastic changes, see Section 3.7.2.

Species	Exposure level (ppm)	Results
F344 rat (50/sex)	0, 20, 75, 300 (6 h/d, 5 d/w)	<p>≥ 75 ppm <i>Females:</i> Eosinophilic changes in the olfactory epithelium.</p> <p>300 ppm <i>Males:</i> Increases in mortality, cholesterol, phospholipids, serum urea, creatinine, calcium, liver and kidney weights; decreased haematocrit, eosinophilic changes in the olfactory epithelium, mineralisation of renal papillae, urothelial hyperplasia in renal pelvis. <i>Females:</i> Decreased protein; increases in bilirubin, serum urea, potassium, liver weights; eosinophilic changes in the respiratory epithelium, metaplasia of the glands in the respiratory epithelium.</p>
BDFI mice (50/sex)	0, 20, 75, 300 (6 h/d, 5 d/w)	<p>≥ 20 ppm Slight increase in mortality (females), mineralisation in testes.</p> <p>300 ppm Decreased body weight gain, increases in cholesterol, LDH, ALT, AST, AP, liver weight. <i>Males:</i> Centrilobular hepatocellular hypertrophy. <i>Females:</i> Decreases in MCH, eosinophilic leukocyte ratio, ovary weights; increases in thrombocytes, serum urea, total protein, albumin, bilirubin, calcium, kidney weights.</p>

AP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase
LDH: lactate dehydrogenase, MCH: mean corpuscular haemoglobin.

and in the respiratory epithelium in those exposed to 300 ppm (JISHA 1995, cited in Greim 2003).

For rats, the NOAEC for non-carcinogenic (systemic) effects was 75 ppm for kidney disorder (JISHA 1995, cited in EU 2004), however, eosinophilic changes in the olfactory epithelium of female rats were observed at 75 ppm. ATSDR (2006) concluded that the eosinophilic changes in the nasal olfactory epithelium in female rats are the most sensitive effect and derived a NOAEC of 20 ppm and a LOAEC of 75 ppm.

In mice exposed to the highest dose of 300 ppm, body weight gains were a little lower in both sexes compared to controls. The liver was found to be the main target organ. At 300 ppm, increased liver weights and centrilobular hypertrophy were observed, the latter was considerably more pronounced in males than in females. In addition, liver-specific parameters were increased. Males exposed to 20 ppm or more showed mineralisation in the testes. Haematological parameters were affected only in females exposed to 300 ppm. In females, increased kidney weights were associated with an increase in kidney-specific parameters in the serum, and ovary weights were decreased. For mice, the NOAEC for non-carcinogenic effects was 75 ppm for liver disorder (JISHA 1995, cited in Greim 2002 and EU 2004).

The NOAEC of the older study of Hollingsworth (1956, see above) in rats, mice, guinea pigs and rabbits is in the same range.

Oral

Some effects, principally liver damage, have been observed with repeated oral administration in the region of 300–500 mg/kg/day for up to 2 years in rats (both sexes), mice or rabbits (Hollingsworth *et al* 1956, NTP 1987, cited in Greim 2003).

In EU (2004), it was concluded that the hyaline droplet nephropathy, which was only observed in male rats exposed to 1,4-dichlorobenzene is species specific. The LOAEL for male rats was 75 mg/kg/day. Effects on liver and increased kidney weight and nephropathy were observed in both sexes at 300 mg/kg and higher, therefore the NOAEL for female rats was 150 mg/kg/day. In mice and rabbits, the LOAEL was found to be 300 mg/kg/day or higher with effects on liver and kidney.

The most sensitive species is the dog with a LOAEL of 10 mg/kg/day in a 1-year study (lowest dose tested) (see Table 2). Neoplastic findings were not reported in this study (Naylor 1996, cited in EU 2004).

Dermal

No data were available.

Table 2. Exposure (52-week) of dogs to 1,4-dichlorobenzene (Greim 2003); for neoplastic changes, see Section 3.7.2.

Species	Exposure	Results
Beagle-dog (50/sex)	0, 10, 50, 150 mg/kg bw/d (5 d/w)	≥ 10 mg/kg bw/day <i>Males:</i> Non-significant increase in thrombocytes, foci of chronic inflammation in the lung (2/5 per dose group). <i>Females:</i> Increased ALT (not statistically significant), hepatocellular hypertrophy (1/5), kidney collecting duct epithelial vacuolisation (1/5).
	Highest dose reduced after 3 w to 100 and after 6 w to 75 mg/kg bw/d	≥ 50 mg/kg bw/day Increases in liver weights (absolute and relative), AP activity; hepatocellular hypertrophy (5/5) and pigment deposits (3/20). <i>Males:</i> Decreased albumin. <i>Females:</i> Increases in ALT activity, thrombocytes, relative kidney weights, absolute and relative thyroid weights; lung: foci of chronic inflammation (1/5), kidney: collecting duct epithelial vacuolisation (1/5).
		150 mg/kg bw/day Bile duct hyperplasia (2/10), spleen: increased haemato- poiesis, megakaryocyte proliferation, ribs and sternum: erythroid bone marrow hyperplasia. <i>Males:</i> Non-significant increase in activity of γ -glutamyl transpeptidase, inflammation of liver portal areas (2/5), kidney collecting duct epithelial vacuolisation (1/5), increased relative adrenal weights. <i>Females:</i> Increases in thrombocytes, ALT and γ -glutamyl transpeptidase activity, relative adrenal weights; bone marrow: erythroid hyperplasia; lymph nodes and mesen- terium and pancreas: discoloration and enlargement, spleen: focal enlargement, kidney: collecting duct epi- thelial vacuolisation (2/5) associated with discoloration.

ALT: alanine transaminase, AP: alkaline phosphatase.

3.6. Genotoxicity

Genotoxicity was discussed in detail in the assessments of Greim (2003) and EU (2004). Details on doses and exposure times are therefore not repeated here and can be found in the mentioned assessments. No relevant new studies were located.

3.6.1. Human data

Healthy volunteers (n = 3) were exposed to 2.4–2.8 ppm of 1,4-dichlorobenzene vapour for 1 hour. There were no differences in DNA-adduct profiles of blood samples which were obtained before exposure, immediately at the end of exposure and 1 hour after exposure (EU 2004).

3.6.2. In vitro data

Bacterial studies

There are more than ten mutagenicity tests in *Salmonella typhimurium* and one in *Escherichia coli*, which all show negative results with or without metabolic activation with rat and hamster S9-mix and concentrations of up to 10 000 µg 1,4-dichlorobenzene/plate (ACGIH 2001, Greim 2003, EU 2004). 1,4-dichlorobenzene did not induce mutagenic effects in *Bacillus subtilis* (ACGIH 2001).

Fungal studies

1,4-Dichlorobenzene (200 µg/ml) was mutagenic in *Aspergillus nidulans* without metabolic activation (ACGIH 2001, Greim 2003, EU 2004). According to EU (2004), the experiment appears to have been performed once. Furthermore there was only one dose tested. Therefore this experiment is not used for evaluation of genotoxicity. 1,4-Dichlorobenzene has been found to be negative and positive (with metabolic activation) in *Saccharomyces cerevisiae* (ACGIH 2001, EU 2004).

Mammalian cells

In the mouse lymphoma assay, 1,4-dichlorobenzene has been found to be both negative and positive (ACGIH 2001, Greim 2003). The positive test was assessed as inconclusive by EU (2004). 1,4-Dichlorobenzene did not induce mutations in three independent studies of the *hprt* locus in Chinese hamster ovary (CHO) or V79 cells (EU 2004), while one other study in CHO cells gave an inconclusive result (Greim 2003, EU 2004).

There are four chromosomal aberration tests in CHO, Chinese hamster lung (CHL) cells, and in human lymphocytes which were negative (ACGIH 2001, Greim 2003, EU 2004). 1,4-Dichlorobenzene did not induce sister chromatid exchange (SCE) in CHO cells with or without metabolic activation, but it increased the frequency of SCE in human peripheral blood lymphocytes in the absence of exogenous metabolic activation (Greim 2003, EU 2004).

Neither in HeLa cells, nor in cultured human lymphocytes, did 1,4-dichlorobenzene induce unscheduled DNA synthesis (UDS) (ACGIH 2001, Greim 2003, EU 2004).

Micronucleus tests revealed no significant increase in human hepatocytes but statistically significant increases in micronucleated rat hepatocytes at single concentrations in each experiment (Greim 2003, EU 2004). As a clear dose-dependency was missing and cytotoxicity not estimated, the result is assessed to be inconclusive (EU 2004). In the same laboratory, no DNA strand breaks (alkaline elution assay) were observed in rat or human hepatocytes (Greim 2003, EU 2004).

In rat and human kidney cells, there were dose related increases in micronucleated cells (Robbiano *et al* 1999, cited in Greim 2003, EU 2004). Cytotoxicity was not

estimated in this study. The study also produced positive results in the comet assay (DNA strand breaks) in rat and human kidney cells. In EU (2004), it was pointed out that the existence of apoptotic cells or damaged cells is not mentioned, making it difficult to appreciate the influence of cytotoxicity on the results.

3.6.3. In vivo data

A chromosomal aberration study with inhalation exposure in rats was negative, but is associated with methodological problems (Greim 2003, EU 2004).

Overall there were six micronuclei tests with 1,4-dichlorobenzene in mice available. Only one of the tests is reported to be positive, but was not reproducible by two other laboratories (Greim 2003, EU 2004).

Robbiano *et al* (1999, cited in Greim 2003, EU 2004) found in kidney cells from intraperitoneally (ip) dosed male Sprague-Dawley rats (single dose 250 mg/kg bw or 167 mg/kg bw/day, 3 days) an increase in the frequency of micronucleated cells and a positive comet assay. A further comet assay in male and female Sprague-Dawley-rats with a high ip dose of 2 000 mg/kg bw revealed an inconclusive (males) and a weak positive (female) result (Greim 2003, EU 2004).

Another comet assay in mice liver and spleen gave a positive result (2 000 mg/kg bw, i.p.), whereas lung, kidney and bone marrow showed no significant damage (Sasaki *et al* 1997, cited in Greim 2003; EU 2004).

1,4-Dichlorobenzene was negative in UDS tests in mouse hepatocytes and rat kidney cells (Greim 2003, EU 2004).

1,4-Dichlorobenzene did not produce an increase in dominant lethality in mice or rats (ACGIH 2001, Greim 2003, EU 2004).

DNA adducts could not be found in two studies with male rats in liver and kidney, and in one study investigating lung and stomach (Greim 2003, EU 2004). However, in mice liver, lung, kidney and stomach, Lanzetti *et al* (1989, cited in EU 2004) found adducts 22 hours but not 72 hours after ip injection of 433.7 µg/kg bw of 1,4-dichlorobenzene. In EU (2004), it was pointed out that the procedures used did not demonstrate a covalent nature of the associations with DNA.

3.6.4. Conclusion on genotoxicity

1,4-dichlorobenzene have been investigated in a large number of *in vitro* and *in vivo* tests and the results did not provide a consistent evidence for genotoxicity (EU 2004).

The vast majority of a variety of assays was negative, including *in vitro*: gene mutation in *Salmonella typhimurium*, mouse lymphoma test, DNA damage in rat and human hepatocytes, SCE in CHO cells; and *in vivo*: chromosomal aberrations in rat bone marrow, UDS test in mouse hepatocytes and rat kidney cells, SCE in mouse bone marrow cells and erythrocytes; micronucleus tests in mice and dominant lethal tests in rats and mice (ACGIH 2001, Greim 2003, EU 2004, US EPA 2006). Single positive results *in vitro* were reported, however, these results were not reproducible, some of the test systems were less well validated such as the alkaline elution assay, the comet assay and the SCE assay, and there might be false positives due to cytotoxicity (US EPA 2006). *In vivo* standard tests were mostly negative and evidence on genotoxicity came mostly from non-standard tests such as the comet assay and the observed association of 1,4-dichlorobenzene with DNA. In EU (2004), it was concluded that "the overall weight of evidence from the most reliable studies indicated that 1,4-dichlorobenzene does not have any significant genotoxic potential".

It can therefore be concluded that genotoxicity plays no or at most a minor part in the carcinogenicity of 1,4-dichlorobenzene.

3.7. Carcinogenicity

3.7.1. Human data

No evidence of toxic effects on haematological parameters (leukaemia) was found in workers exposed for several years to 6 and 264 mg/m³ of 1,4-dichlorobenzene (Greim 2003).

There is one report of a worker that used a mixture of 80 % 1,2-dichlorobenzene, 2 % 1,3-dichlorobenzene and 15 % 1,4-dichlorobenzene for many years and developed chronic lymphoid leukaemia. Another worker developed acute myeloblastic leukaemia (Greim 2003). Also in EU (2004), 2 cases of leukaemia were reported and it was concluded that there is no cause-effect relationship.

NTP (2011) concluded that the data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to 1,4-dichlorobenzene. In one cohort study, 5 cases of leukaemia associated with exposure to dichlorobenzenes were reported (IARC 1974, 1982, 1999, cited in NTP 2011).

Overall, available data from epidemiological studies are inadequate to evaluate the carcinogenic potential of 1,4-dichlorobenzene in humans.

3.7.2. Animal data

Inhalation

In (older) inhalation studies, 1,4-dichlorobenzene was not carcinogenic in rats or mice (Riley *et al* 1980 a,b, cited in EU 2004), although these studies would not be considered adequate by current standards.

Additional 2-year inhalation studies in F344 rat and BDF1 mouse (JISHA 1995, cited in EU 2004, Greim 2003) were available and data presented below. Rats and mice were exposed to 0, 20, 75 or 300 ppm for 24 months.

In rats, there was no statistically significant increased incidence in neoplasms except mononuclear leukaemia in male animals, which was dose-dependent or statistically significant (9, 14, 10 and 13 of 50 animals at 0, 20, 75 or 300 ppm, respectively). However, the Peto test revealed a significantly positive trend and the incidence was not within the range of the historical controls. An increased incidence of C cell adenomas (2, 7, 9 and 6 of 50 animals at 0, 20, 75 or 300 ppm) was observed in female rats, which was statistically significant only in the middle dose group. Additionally in female rats, there were a dose-dependent, but not statistically significant increase in the incidence of pheochromocytomas (2, 4, 6 and 5 of 50 animals at 0, 20, 75 or 300 ppm, respectively) (JISHA 1995, cited in Greim 2003).

Mice showed a significant increase in the incidence of hepatocellular carcinomas at 300 ppm in both sexes (males: 12/49, 17/49, 16/50, 38/49 and females: 2/50, 4/50, 2/49, 41/50 at 0, 20, 75 or 300 ppm, respectively). Additionally in males, the rare histiocytic sarcoma in the liver was significantly increased at 300 ppm and malignant lymphomas were dose-dependently increased, but statistically significant only at 75 ppm. A significant increase in the incidence of hepatocellular adenomas was observed in females at ≥ 20 ppm. Additionally in females, combined bronchiolar/alveolar adenomas and carcinomas were increased, carcinomas were not significantly increased but showed a positive trend (JISHA 1995, cited in Greim 2003).

Oral

Prolonged oral administration resulted in kidney tubule cell tumours in male rats and liver tumours in mice (NTP 1987). Both studies are described in detail in Greim (2003) and EU (2004) and summarised in the following:

F344 rats were given 0, 150 and 300 mg/kg bw/day (male), 0, 300 and 600 mg/kg bw/day (female) 5 days per week for 2 years. Survival and body weight gains were reduced in the high dosed males. In males, the kidney was the main target organ, but the haematopoietic system was also affected. A dose-dependent increase in nephropathy was observed (in females at ≥ 300 mg/kg bw/day, in males at ≥ 150 mg/kg bw/day), which was accompanied by renal histological lesions. A dose-dependent increase in the incidence of tubular cell adenocarcinomas (statistically significant at 300 mg/kg bw/day) in male rats (1/50, 3/50, 7/50 at 0, 150 or 300 mg/kg bw/day, respectively) were observed. In addition, probably as a consequence of renal damage, parathyroid gland hyperplasia was observed in male rats. Furthermore at 300 mg/kg bw/day, a marginal increased mononuclear cell leukaemia (5/50, 7/50, 11/50) in males was noted, which was above the range of the historical control data, but within the interval of the study control group, which limits the biological significance of this finding. No significant increases in liver tumours were seen in F344 rats. No increase in the number of malignant tumours was observed in females (NTP 1987, cited in Greim 2003 and EU 2004).

B6C3F1 mice were dosed with 0, 300 and 600 mg/kg bw/day by gavage for 103 weeks. Liver was the main target organ in male and female mice. The incidence of hepatocellular carcinomas was statistically significantly higher in males (14/50, 11/49, 32/50 at 0, 300 and 600 mg/kg/day, respectively) and in females (5/50, 5/48, 19/50). In male mice, a significantly increased incidence of hepatocellular adenomas was seen even in the low-dose group; incidences were in males 5/50, 13/49, 16/50 at 0, 300 and 600 mg/kg bw/day, respectively, and in females 10/50, 6/48, 21/50. Hepatoblastomas (not statistically significant), an extremely rare tumour, were found in 4 male mice of the high-dose group. In male mice, the combined (benign and malignant) incidence of adrenal gland pheochromocytomas (0/47, 2/48, 4/49) was increased and associated with adrenal gland and thyroid hyperplasia (NTP 1987, cited in Greim 2003 and EU 2004).

The incidences of liver tumours in mice in the 2-year gavage studies of 1,4-dichlorobenzene (NTP 1987, cited in Greim 2003) are presented in Table 3.

Table 3. Chronic (103-week) oral exposure of mice to 1,4-dichlorobenzene: incidences of neoplastic liver changes (NTP 1987, cited in Greim 2003).

Dose level (mg/kg bw)	Males			Females		
	0	300	600	0	300	600
No. of mice examined	50	49	50	50	48	50
<i>Lesion</i>						
Hepatocellular degeneration	0	36	39	0	8	36
Cell size alteration	0	38	40	0	4	27
Focal necrosis	1	35	37	1	4	30
Hepatocellular adenoma	5	13	16	10	6	21
Hepatocellular carcinoma	14	11	32	5	5	19
Hepatoblastoma	0	0	4 ^a	0	0	0

^a All hepatoblastomas were observed in mice that had hepatocellular carcinomas.

3.7.3. Summary: carcinogenicity

Inhalation studies showed hepatocellular carcinoma and hepatoblastoma or histiocytic sarcoma in the livers of male and female BDF1 mice from 300 ppm, while no increase in tumours was observed in exposed F344 rats (JISHA 1995, cited in Greim 2003 and EU 2004).

Following chronic oral exposure, 1,4-dichlorobenzene has been clearly shown to induce adenomas and carcinomas in the livers of male and female B6C3F1 mice, with hepatocellular carcinomas from 600 mg/kg/day in both sexes, and of renal tubular cell adenocarcinomas in the kidneys in male F344 rats from the lowest dose of 150 mg/kg/day (NTP 1987, cited in Greim 2003 and EU 2004).

For carcinogenic effects on the liver, the NOAEL is 300 mg/kg/day via the oral route in B6C3F1 mice and 75 ppm via inhalation in BDF1 mice. For kidney adenocarcinomas, no NOAEL can be derived, the LOAEL is 150 mg/kg/day via the oral route in F344 rats.

3.7.4. Mode of action

Kidney

The kidney tumours observed after oral but not after inhalation exposure in male rats have no relevance to humans, as the underlying mechanism is species specific for male rats. Subsequent studies have shown that 1,4-dichlorobenzene produced a marked increase in $\alpha_2\mu$ -globulin accumulation in the proximal tubules in male rats. The following nephropathy was associated with compensatory renal tubule cell proliferation. The male rat kidney tumours were judged to have been produced via a species specific non-genotoxic mechanism and are not relevant for human cancer risk assessments (NTP 1987, cited in Greim 2003, Lock and Hard 2004, Butterworth *et al* 2007, EU 2004).

Liver

The carcinogenic potential of 1,4-dichlorobenzene for the liver has been clearly demonstrated after inhalation and oral exposure in mice. No hepatocarcinomas were observed in the two carcinogenicity studies in rats. As genotoxicity tests for 1,4-dichlorobenzene are primarily negative, a threshold mechanism has to be considered. However, the mode of action by which 1,4-dichlorobenzene produces liver tumours in mice is not clear and evidence for a non-genotoxic mechanism is mixed. Hepatotoxicity and differences in metabolism (rat versus mice) have been discussed. Hepatocellular carcinomas (associated in some cases with rare hepatoblastomas and/or histiocytosarcomas) were found only at doses at which hepatotoxicity was also observed. In contrast, in rats, only slight hepatotoxicity was observed (EU 2004). Chloro(hydro)quinones and their glutathione conjugates could be implicated in carcinogenesis with formation of reactive oxygen species. Several studies have shown that 1,4-dichlorobenzene produces a mitogenic/promotional response in mouse liver, which is discussed by Butterworth *et al* (2007) as possibly mediated by substituted hydroquinone metabolites. Cellular proliferation by 1,4-dichlorobenzene was observed in the liver of rats and mice (Umamura *et al* 1996 and 1998, Eldridge *et al* 1992, Butterworth 1992, cited in EU 2004) and a threshold for this effects is discussed. However, the relationship between cellular proliferation, hepatotoxicity and liver tumours by 1,4-dichlorobenzene is not clear. There are furthermore some species differences in hepatic metabolism between rat, mouse and human; however, these differences cannot at the moment completely explain the liver tumours in mice. In EU (2004), it was finally concluded that the mechanism of induction of the liver tumours in mice was not completely elucidated.

A threshold approach was considered appropriate by EU (2004) with NOAECs for the liver carcinogenic effect of 75 ppm (inhalation) and 300 mg/kg/day (oral).

3.8. Reproductive toxicity

3.8.1. Human data

A case report of a pregnant woman who ingested 5–10 g 1,4-dichlorobenzene daily throughout her pregnancy gave no evidence on abnormalities in the infant. The mother showed a reversible haemolytic anaemia (Campbell 1970, cited in EU 2004).

3.8.2. Animal data

Fertility

A 2-generation study with inhalational exposure (0, 50, 150 or 450 ppm, 6 hours daily, 7 days per week for 10 weeks) of Sprague-Dawley resulted in no evidence of adverse effects on fertility at non-toxic doses. At the highest concentration, reduced body weights and body weight gains, clinical signs of toxicity, effects on the kidneys and liver, as well as reduced litter sizes were observed (Greim 2003).

A 2-generation inhalation study in rats revealed no adverse effects on reproduction. Due to increased perinatal mortality and reduced body weight, the NOAEC for the offspring was 211 ppm (EU 2004).

In a 2-generation study according to OECD TG 416 with gavage up to 270 mg/kg bw/day, no effects on fertility were observed (Bornatowicz 1994, cited in EU 2004). The parental NOAEL was 90 mg/kg bw/day (reduced body weight, increased liver, kidney and spleen weights and nephrotoxicity at 270 mg/kg bw/day). The NOAEL for offspring was 30 mg/kg bw/day (increased early postnatal mortality in F1 and F2 pups, reduced birth weight in F1 pups, slight behavioural changes at 90 mg/kg bw/day).

A dominant lethal test with mice exposed to 1,4-dichlorobenzene up to 450 ppm was negative (Greim 2003, EU 2004).

Various toxic changes in early spermatids and an increased incidence of sperm head anomalies were observed in rats after an ip injection of 800 mg/kg bw of 1,4-dichlorobenzene (Murthy *et al* 1985, cited in Greim 2003; Takahashi *et al* 2011). The observed effects are considered to be cytotoxic effects and not a sign of genotoxicity, as histological examination was carried out only 10 days after the injection (Greim 2003).

Takahashi *et al* (2011) reported that 1,4-dichlorobenzene induced effects on sperm production and morphology in rats and mice independently from androgen receptor binding. 1,4-Dichlorobenzene was administered to rats and mice (each 8 per dose group) subcutaneously (sc) or ip at doses of 0, 100, 200 or 400 mg/kg bw/day. Rats were dosed 4–5 days/week for 8 weeks, mice for 2 or 6 weeks. Both species showed dose dependent histopathological injuries in testis and epididymis, and a dose-dependent decrease in daily sperm production after sc treatment. In rats, relative prostate and seminal vesicle weights were significantly increased at and above 100 mg/kg bw/day. In the Hershberger assay, the following increased organ weights were observed: seminal vesicle, and glans penis in castrated rats (sc \geq 100 mg/kg bw/day), levator ani/bulbocavernosus muscle in castrated rats (sc 200 mg/kg bw/day).

Developmental toxicity

1,4-Dichlorobenzene caused no developmental toxicity in rats (gestation days 6–15) and rabbits (gestation days 6–18) exposed to 100, 300 and 800 ppm (611, 1 833 or 4 888 mg/m³) for 6 hours/day (Hayes *et al* 1985, cited in EU 2004, Greim 2003). Increased number of resorptions at 300 ppm in rabbits was considered as a sign of embryoletality. At 800 ppm, maternal toxicity was observed combined with minor abnormalities, not considered as malformations and not significant. The NOAEC for maternal and developmental toxicity was 300 ppm (EU 2004).

Studies in rats (gestation days 6–15) exposed to 1,4-dichlorobenzene by inhalation (0, 74, 197 or 492 ppm, 6 hours/day) or orally (0, 50, 100 or 200 mg/kg bw) were without effects on foetal development (Greim 2003).

Another study in rats (gestation days 6–15) reported teratogenic effects only at maternally toxic doses of at least 500 mg/kg bw (Giavini *et al* 1986, cited in Greim 2003). Skeletal variations at and above 500 mg/kg bw/day were considered to be linked to maternal toxicity and substance related. The NOAEL for maternal and developmental toxicity was 250 mg/kg bw/day (EU 2004).

4. Recommendation

Systemic toxicity

The main target organs of 1,4-dichlorobenzene are liver and kidney in rats and mice (NOAEC 75 ppm; JISHA 1995, cited in Greim 2003) and dogs (oral LOAEL 10 mg/kg/day - only minor effects observed - which is equivalent to exposure to a concentration of 11 ppm, assuming 100 % absorption by inhalation and by the oral route, a breathing volume of 10 m³ and a body weight of 70 kg; Naylor 1996, cited in EU 2004). Liver and kidney are also target organs in humans (Hsiao *et al* 2009).

Local effects

In rabbits, 1,4-dichlorobenzene is a slight skin and eye irritant, and a respiratory irritant. Limited human data also indicate an irritation potential to skin, eyes and the respiratory tract (EU 2004). In long-term inhalation studies in rats, effects in the nasal epithelium (NOAEC 20 ppm) were observed. This is considered as the most sensitive effect (JISHA 1995, cited in Greim 2003).

Workers experienced nose and eye irritation at concentrations of 50 to 80 ppm (306–490 mg/m³). A degree of acclimatisation was noted after repeated exposures (Hollingsworth *et al* 1956).

Genotoxicity

1,4-dichlorobenzene has been investigated in a large number of *in vitro* and *in vivo* tests and the results do not provide a consistent evidence for genotoxicity (EU 2004).

The vast majority of a variety of assays was negative, including *in vitro*: gene mutation in *Salmonella typhimurium*, mouse lymphoma test, DNA damage in rat and human hepatocytes, SCE in CHO cells; and *in vivo*: chromosomal aberrations in rat bone marrow, UDS test in mouse hepatocytes and rat kidney cells, SCE in mouse bone marrow cells and erythrocytes; micronucleus tests in mice and dominant lethal tests in rats and mice (ACGIH 2001, Greim 2003, EU 2004, US EPA 2006). Single positive results *in vitro* were reported, however, these results were not reproducible, some of the test systems were less well validated such as the alkaline elution assay, the comet assay and the SCE assay, and there might be false positives due to cytotoxicity (US

EPA 2006). *In vivo* standard tests were mostly negative and evidence of genotoxicity came mostly from non-standard tests such as the comet assay and the observed association of 1,4-dichlorobenzene with DNA. In EU (2004) it was concluded that “the overall weight of evidence from the most reliable studies indicated that 1,4-dichlorobenzene does not have any significant genotoxic potential”.

It can therefore be concluded that genotoxicity plays no or at most a minor part in the carcinogenicity of 1,4-dichlorobenzene.

Carcinogenicity

1,4-Dichlorobenzene has been shown to induce kidney tumours in rats and liver tumours in mice.

Kidney tumours were observed in rats at concentrations beginning from 150 mg/kg/day and appear to be species and sex-specific. The underlying mechanism is hyaline droplet nephropathy, which cannot be extrapolated to humans and have no relevance to human health. For kidney adenocarcinomas, no NOAEL can be derived, the LOAEL is 150 mg/kg/day via the oral route in F344 rats (NTP 1987, cited in Greim 2003 and EU 2004).

Hepatocellular carcinomas were observed after chronic oral administration in B6C3F1 mice at 600 mg/kg/day (NTP 1987, cited in Greim 2003 and EU 2004), and in an inhalation carcinogenicity study in BDF1 mice from 300 ppm (JISHA 1995, cited in Greim 2003). For carcinogenic effects on the liver, the NOAEL is 300 mg/kg/day via the oral route in B6C3F1 mice (NTP 1987, cited in Greim 2003 and EU 2004) and 75 ppm via inhalation in BDF1 mice (JISHA 1995, cited in Greim 2003).

For the hepatic tumours in mice, hepatotoxicity, cellular proliferation, mitogenic activity and species differences in metabolism were discussed. In EU (2004), it was finally concluded that the mechanism of induction of the liver tumours in mice was not completely elucidated. A threshold approach was considered appropriate (EU 2004), which is supported by SCOEL.

Developmental toxicity

The results of the two 2-generation studies (Bornatowicz 1994, cited in EU 2004, Greim 2003) and prenatal developmental toxicity studies in rats (Hayes *et al* 1985, Giavini *et al* 1986, cited in Greim 2003) and rabbits (EU 2004) revealed no reproductive toxicity of 1,4-dichlorobenzene regardless of the route of exposure (inhalation or oral).

OEL/STEL

In the long-term inhalation studies in rats, the local NOAEC (effects in the nasal epithelium) is 20 ppm. In the oral study with dogs, marginal effects were observed at 10 mg/kg/day, which is equivalent to exposure to a concentration of 11 ppm. These effects to the main target organs at 10 mg/kg bw included: males: non-significant increase in thrombocytes, foci of chronic inflammation in the lung (2/5 animals per dose group), females: increased ALT activity, hepatocellular hypertrophy (1/5), kidney collecting duct epithelial vacuolisation (1/5). Therefore, 5 ppm is used as a starting point to recommend an OEL. As this value derives from a 52-week exposure study in dogs, a 1.4 allometric scaling factor is applied to extrapolate from dogs to humans ($5/1.4 = 3.6$). Applying the preferred value approach, a recommended OEL of 2 ppm derives.

Since the NOAEC for effects at the nasal epithelium in the long-term inhalation study in rats is 20 ppm, a STEL of 10 ppm is proposed.

Other assignments

Skin: Information on dermal absorption was not available. Model calculations (Greim 2003) resulted in absorptions of up to 318 mg for a 1-hour exposure of the hands and forearms (2 000 cm²) to a saturated aqueous solution of 1,4-dichlorobenzene. Therefore a "skin notation" is strongly recommended

Sensitisation: In EU (2004), it was concluded that 1,4-dichlorobenzene showed a weak sensitisation potential in animals, but the interpretation of the maximisation study was difficult due to limitations in its method. Considering the widespread use of 1,4-dichlorobenzene for many years, and the fact that only one questionable human case report is reported, 1,4-dichlorobenzene should currently not be categorised as a "skin sensitiser".

Biomonitoring

There is a strong association between urinary 2,5-dichlorophenol, the major metabolite of 1,4-dichlorobenzene, and airborne 1,4-dichlorobenzene. This may be a useful method for biological monitoring. However, there are currently no valid data available to establish a biological limit value.

Sampling and analysis

At the recommended OEL, no measurement difficulties are foreseen.

The present Recommendation was adopted by SCOEL on 12 March 2014.

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