# *Recommendation from the Scientific Committee on Occupational Exposure Limits for Trichloroethylene*

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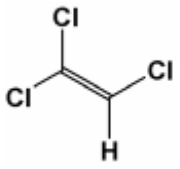
|---|---|
| 8-hour TWA: | 10 ppm [54.7 mg/m$^3$] |
| STEL (15 mins): | 30 ppm [164.1 mg/m$^3$] |
| Additional classification: , | "skin" notation |
| Biological Limit Value (BLV): | 20 mg TCA (trichloroacetic acid) / liter urine |
| [Sampling time: end of the last shift of a workweek or a shift period] | |

**Substance identification**

Trichloroethylene:




Synonyms: Trichloroethene; 1,1,2-Trichloroethylene; Ethene, trichloro-; Ethylene, trichloro-

EC No.: 201-167-4

Annex 1 Index No.: 602-027-00-9

EU-Classification: Carc. Cat. 2; R45 - Muta. Cat. 3; R68 - R67 - Xi; R36/38 - R52-53

CAS No.: 79-01-6

Mwt: 131.39

Conversion factor (20 °C, 101 kPa): 1 ppm = 5.47 mg/m$^3$; 1 mg/m$^3$ = 0.183 ppm

This evaluation is based on Greim (1996), ATSDR (1997), Brüning and Bolt (2000), EPA (2001), Clewell and Andersen (2004), ECB (2004), Harth et al. (2005), NRC (2006), Caldwell and Keshava (2006), Chiu et al. (2006a, b), Scott and Chiu (2006), Lock and Reed (2006), Watson et al. (2006), Lamb and Hentz (2006), the National Health

Council/Committee on Human Health Risk of Trichloroethylene (2006) and the references cited in these reviews.

## 1 Physico-chemical properties

Trichloroethylene (TCE) is a colourless liquid with a characteristic odour similar to chloroform. Of the many values reported for physico-chemical properties, those used in the "Risk Assessment Report" for modelling purposes are given here. The boiling point of the substance is 86-88 °C and the vapour pressure is 86 hPa at 20 °C. The water solubility of TCE is 1.1 g/l at 20 °C and the log $P_{ow}$ is 2.29. The substance has a density of 1.465 g/cm$^3$. No flash point is given (ECB, 2004).

## 2 Occurrence/use and occupational exposure

The production volume of trichloroethylene (TCE) is between 51000 and 225000 tonnes per year (1996). Today, the purity is 99.9% w/w with additives as stabilisers (thymol 51%, triethylamine 51%, 2-methyl-3-butan-2-ol and others with Iower percentage). The substance is mainly used for vapour degreasing and cleaning of metal parts, in adhesives, as a solvent and for synthesis in the chemical industry, e.g. in the production of HFC 134a (1,1,1,2-tetrafluoroethane) and HCFC 133a (1-chloro-2,2,2trifluoroethane). Workplace exposure in metal cleaning is mostly below 30 ppm (164 mg/m$^3$). However, short-term exposure may reach much higher values. Personal exposure data in England (data from the Health and Safety Executive, HSE) in the *years* 1994/1995 showed *an* exposure above 300 ppm (1650 mg/m$^3$) during cleaning of a degreasing bath in 20% of the cases (ECB, 2004).

## 3 Health significance

### 3.1 Toxicokinetics

#### 3.1.1 Human data

TCE is well absorbed via all major routes of exposure. Quantitative data are available for inhalation exposure, for which uptake was between 28% and 80% (ECB, 2004). The absolute uptake increased with increasing physical exercise (Astrand and Ovrum, 1976). Oral uptake was demonstrated after accidental or deliberate ingestion of TCE. However, no quantitative information is available (ECB, 2004). Dermal exposure was tested with volunteers, demonstrating considerable percutaneous absorption as evidenced by measured TCE concentrations in blood or in exhaled air (Sato and Nakajima, 1978; Stewart and Dodd, 1964). The rate of dermal uptake was not determined.

TCE is rapidly distributed throughout the body, crosses the blood-brain barrier and the placental barrier and accumulates in fat tissue (ECB, 2004).

No relevant qualitative differences in metabolism between experimental animals and humans were observed. Major metabolic pathways are described below (animal data). In humans, (free and conjugated) trichloroethanol (TCOH) is found as the dominant excretion product, as well as trichloroacetic acid (TCA), furthermore dichloroacetic acid (DCA) and, to a larger extent than in experimental animals, monochloroacetic acid (Soucek and Vlachova, 1960). N-Hydroxyacetylaminoethanol and N-acetyldichloro vinylcysteine have also been detected in humans. The relative amount of urinary TCA is higher in humans than in experimental animals. Women eliminated less unchanged TCE than did men (Nomiyama and Nomiyama, 1971, 1974a, b).

Regarding the oxidative metabolism by CYP2E1 (see also 3.1.2), it should be noted that there is a variability in expression of this enzyme in humans, especially between different ethnic groups (Bolt et al. 2003).

A steady-state for TCE in blood is reached after continuous exposure after around two hours. Elimination is best described by a three-compartment model composed of richly perfused tissues (half-life of TCE 2-3 minutes), lean body mass (half-life TCE about 30 minutes) and fat-rich tissues (half-life TCE 3.5-5 hours) (Sato et al., 1977). Blood concentrations of TCE increased during five consecutive days of exposure due to accumulation in fat tissue. The half-life of TCOH in blood is 10-12 hours, leading to accumulation during the working week. Steady-state is reached by the fifth day after intermittent exposure to 250 ppm TCE (1770 $mg/m^3$). Following repeated exposure to 50 ppm (275 $mg/m^3$), elimination from blood was complete within 4 days after the last exposure. For TCA, even longer half-lives in blood are reported, caused by its extensive plasma protein binding. Elimination from blood (half-life 70-100 hours) was nearly complete 13 days after the last exposure to 50 ppm TCE following repeated inhalation (Monster et al., 1976, 1979; Soucek and Vlachova, 1960; Ertle et al., 1972; Müller et al., 1972, 1974).

TCE metabolites are mainly excreted via the urine, namely 29-50% of TCE as (free plus conjugated) TCOH and 10-24% of absorbed TCE as TCA (Monster et al., 1976, 1979; Soucek and Vlachova, 1960). Other studies reported that up to 44% of TCE could be excreted as TCA (Nomiyama and Nomiyama, 1971).

In addition to oxidative metabolism, a minor glutathione-dependent reductive pathway (see animal data) is also relevant for humans, as β-lyase activity has been demonstrated in human kidneys by the detection of N-acetyldichloro vinylcysteine in the urine of workers. This metabolite was also excreted by male volunteers after exposure to Iow concentrations (50 ppm and above) of TCE (Lash et al., 1999).

TCE intake interacts with the intake of alcohol, leading to alcohol intolerance in some individuals and inhibition of TCE metabolism (Müller et al., 1975; Davidson and Beliles, 1991).

### 3.1.2 Animal data

TCE is well absorbed by all major routes of exposure. After short-term inhalation exposure of rats to very high concentrations of TCE, 31-79% was retained (Forssman and Holmquist, 1953). In mice, 40-54% uptake was shown (Bergman, 1979). After oral uptake by rats, mice or rabbits, 80-98% of the activity of radiolabelled TCE was recovered in expired air or urine (Prout et al., 1985; Dekant et al., 1984). Oral uptake in mice occurred faster than in rats and higher peak levels were reached (Larson and Bull, 1992). Dermal absorption of liquid TCE through mouse skin was around 8 $\mu g/cm^2$ • minute (Tsuruta, 1978) and around 5.4 $\mu g/cm^2$ minute for absorption through guinea pig skin with TCE in aqueous solutions (Bogen et al., 1992). *In vitro* studies with rat skin indicated dermal uptake of 12 $\mu g/cm^2$ • minute (Tsuruta, 1978).

Similar to humans, TCE is rapidly distributed throughout the body, crosses the blood brain barrier and the placental barrier, and tends to accumulate in fat tissues. In rats, saturation of oxidative metabolism of TCE occurs at lower levels than in mice (ECB, 2004).

Major metabolic pathways are the same for different animal species and for different routes of exposure. However, quantitative differences exist between species and strains. TCE is rapidly oxidised by cytochrome P450 (mainly CYP2E1), via the respective epoxide, to trichloroacetaldehyde (chloral). This metabolite is further metabolised to TCOH or competitively to TCA, both of which are excreted in free or conjugated forms (Caldwell and Kesheva, 2006). Considerably higher levels of TCOH were found in mice compared to rats (Larson and Bull, 1992; Bull et al., 1993). A minor fraction appears as dichloro- and monochloroacetic acid. Other minor pathways result in the formation of carbon dioxide, carbon monoxide, oxalic acid, and glyoxylic acid. From the epoxide also N-hydroxyacetylaminoethanol is formed (reaction with phosphatidylethanolamine as a constituent of lipids). In a recent publication of Ramdhan et al. (2008), the CYP2E1-mediated oxidative metabolism of TCE was viewed in conjunction with heoatotoxicity.

Elevated formic acid levels were found in the urine of experimental animals after exposure to TCE. However, formic acid is not a TCE metabolite. The TCE metabolites TCOH and TCA are suspected to interact with vitamin $B_{12}$ through a free-radical mechanism inducing $B_{12}$ deficiency and, as a consequence, also folate deficiency. As a result of folate deficiency, excess formic acid is excreted in urine (Dow and Green, 2000; Harth et al., 2005).

Apart from oxidative metabolism, TCE is also metabolised via glutathione-S-transferase to S-1,2-dichlorovinyl glutathione and to S-(1,2-dichlorovinyl)-L-cysteine (DCVC). This intermediate may be transformed by three metabolic pathways: either to N-acetyldichloro vinylcysteine by N-acetyltransferase or (by cleavage with β-lyase) to chlorothionoacetyl or chlorothioketene or by flavin monooxygenase to produce dichlorovinylcysteine sulphoxide. The mercapturic acids (N-acetyldichloro vinylcysteine) may be present as regioisomers, which were eliminated by rats in minimal amounts. However, even if mercapturic acids are not detected in urine, the glutathione pathway may be relevant because of the mentioned metabolic activation via β-lyase leading to the toxicologically important chlorothioketenes, which may finally be hydrolysed to monochloroacetic acid. Dichlorovinylcysteine sulphoxide may also be activated as it is a substrate for renal ß-lyase, but it is probably toxicologically active on its own (Lock and Reed, 2006, Chiu et al., 2006b, Greim, 1996, ECB, 2004). Thus, although the glutathione-pathway only contributes slightly to the total elimination of TCE, it may be important because of its toxicologically relevant metabolites.

The half-lives of TCOH in blood of 2-5.3 hours (Sprague-Dawley rats) or 0.5-2.7 hours (B6C3F1 mice) were considerably lower than in humans (10-12 hours). Similarly, the TCA half-lives of 5-7 and 4-7.7 hours in rats and mice, respectively, were much lower than in humans (70-100 hours) (Larson and Bull, 1992; Bull et al., 1993).

Elimination after inhalation exposure of TCE is mainly via the urine after extensive metabolism. Other pathways of excretion are the faeces and exhaled air (carbon dioxide). As shown for the oral pathway, low inhalation exposure of both rats and mice resulted in approximately 65% of the dose being recovered as metabolites in urine, 7-23% as metabolites in faeces, 9-13% were eliminated as $C0_2$ and 1-4% as unchanged TCE in air (Prout et al., 1985; Green and Prout, 1985). In rats, increasing fractions of TCE are excreted unchanged in expired air at higher concentrations (Mitoma et al., 1985). The major metabolite excreted in urine is (conjugated or free) TCOH, with relevant species and strain differences in the quantitative fractions and in the concurrent amount of TCA (Dekant et al., 1984). The fraction of TCOH excretion also changed (reduced) from short-term compared to subchronic or chronic exposure (Green and Prout, 1985). Concentrations of DCA in the urine of rats were minimal after acute exposure to TCE (Chiu et al., 2006b). However, due to inhibition of its metabolism, the role of DCA after chronic exposure may change (Keys et al.,

2004) and is currently insufficiently assessed (Caldwell and Kesheva, 2006).

### 3.1.3 Biological monitoring

Biological monitoring of TCE by measuring TCA concentrations in the urine after shift is well established for a long time. The correlation has been reviewed by Monster and Zielhuis (1983). These authors provided a formula for TCA calculation. According to this formula, 10 ppm TCE (55 mg TCE/$m^3$) in air (8 hrs daily) correspond to 20 mg TCA/I urine, and 50 ppm TCE (273 mg TCE/$m^3$) correspond to 100 mg TCA/l urine (linear transformation). Alternatively, (unconjugated) TCOH in blood may be used. However, this method would be more invasive and is no longer in practical use. Because of the different half-lives, using the sum of TCA plus TCOH, as has been done in some earlier monitoring programmes, is not recommended (Lehnert and Greim, 2003, Henschler and Lehnert, 1983, 1986). Moreover, the ratio between TCOH and TCA apparently varies considerably between individuals. According to the data of a study by Green et al. (2004), this ratio was found to vary between 0.6 and 20.1 (Caldwell and Kesheva, 2006).

As a biomarker for renal toxicity in TCE-exposed persons the urinary excretion of $\alpha_1$-microglobulin has been proposed (Bolt et al., 2004) This effect biomarker would indicate slight impairments of the integrity of the kidney and is observed to be elevated in patients with renal cell cancer and a history of TCE exposure (Brüning et al., 1999). lt is also increased in persons occupationally exposed to TCE without cancer (Green et al., 2004). In controls, urinary $\alpha_1$ -microglobulin excretion is usually below 5 mg/l urine, whereas it may reach much higher concentrations in TCE-exposed persons. Green et al. (2004) reported $\alpha_1$ -microglobulin excretion of 5.06 ± 4.84 mg/g creatinine in 70 TCE-exposed workers (range 0.5-252 ppm, mean 32 ppm) compared to 3.83 ± 1.85 mg/g creatinine in controls (n=54). However, according to Green et al. (2004), other indicators of nephrotoxicity, such as formic acid excretion, may be eventually more sensitive and may be discussed for monitoring in the future (see section "Repeated dose toxicity, human data" for further details).

## 3.2 Acute toxicity

### 3.2.1 Human data

TCE has been used as an anaesthetic with 5,000-20,000 ppm producing light anaesthesia in humans (Reynolds et al., 1989). Most studies in volunteers with controlled conditions showed no or only marginal CNS effects after single inhalation exposure to 300 ppm or below (Stewart et al., 1974; Vernon and Ferguson, 1969; Stopps and McLaughlin, 1969; Winneke et al., 1976; Ettema and Zielhuis, 1975; Windemuller and Ettema, 1978). In contrast, volunteers exposed to 90-130 ppm twice for four hours reported slight dizziness and eye irritation and performed badly in various psycho-physiological tests. A second group of workers, who were accustomed to TCE, was tested with similar results (Salvini et al., 1971). However, the study is poorly reported and the test persons have been aware of the exposure. Subjective signs of CNS depression (fatigue, decreased ability to concentrate) were reported after inhalation exposure of volunteers to 50 and 100 ppm TCE for six hours (Eitle et al., 1972). However, the focus of this study was on metabolism and the circumstances of exposure may have contributed to the observed effects. Nomiyama and Nomiyama (1977) reported irritation (see section "Irritation and corrosivity") and drowsiness at 27 ppm and above as well as headache at 81 ppm after single inhalation exposure to TCE for 2 or 4 hours. These effects have not been reported in other studies at considerably higher

concentrations. Hence, no conclusion may be drawn from the studies at these lower exposure concentrations (ECB, 2004).

Other acute effects like cardiac arrhythmias, hepatotoxicity and nephrotoxicity have occasionally been observed at higher concentrations (ECB, 2004). TCE decomposes in light and with heat or in contact with strong alkali to toxic products like phosgene and dichloroacetylene (Mertens, 1993; Saunders, 1967; Sax and Lewis, 1989). Hence, some of the reported effects, particularly those involving the trigeminal and optic nerves, may be linked to decomposition products (ECB, 2004).

Single oral intakes of about 20 ml (approximately 450 mg/kg body weight(bw), but possibly lower) are associated with CNS effects. Higher doses may lead to cardiac effects as well as liver and kidney toxicity (ECB, 2004).

### 3.2.2 Animal data

Lethal concentrations ($LC_{50}$) in rat are about 12,000 ppm (65,000 mg/m$^3$) after exposure for 4 hours (Siegel et al., 1971). In mice, the $LC_{50}$ was 8,450 ppm (46,000 mg/m$^3$) (Friberg et al., 1953). Main signs of toxicity were CNS depression including anaesthesia, respiratory failure as well as irritation of the eyes and the respiratory tract (Greim, 1996).

Hepatotoxicity, nephrotoxicity and cardiac sensitisation were observed after acute inhalation exposure of experimental animals. Pulmonary effects were seen at low concentrations after single inhalation exposure of mice, but not rats. In mice, vacuolisation of Clara cells was observed at exposure to 20 ppm (109 mg/m$^3$) and above, accompanied by pyknosis of bronchiolar epithelium and focal loss of bronchiolar epithelium at higher concentrations (Odum et al., 1992). Toxicity in Clara cells of the mouse lung may be related to the accumulation of chloral. Mice have a restricted capability to convert this TCE metabolite (ECB, 2004). These observations, indicating the specific sensitivity of mice to pulmonary effects of TCE, were confirmed and substantiated by similar findings in other studies (Villaschi et al., 1991; Forkert et al., 1985; Forkert and Troughton, 1987; Forkert and Birch, 1989).

At high concentrations, behavioural and central nervous system effects were observed after acute inhalation exposure of rodents. Fatigue was increased, motor activities were reduced and T-maze behaviour was changed in rats after a single exposure for 6 hours to 800 ppm (4372 mg/m$^3$), but not to 400 ppm (Grandjean, 1960 and 1963; Grandjean and Battig, 1964; Wolff, 1976). Shock avoidance behaviour in rats was affected at exposure to 250 ppm and above for 4 hours, with no NOAEL demonstrated in this study (Kishi et al., 1993). However, this experiment was poorly reported and is therefore of questionable significance for risk assessment (ECB, 2004).

Immunotoxicity studies in mice measured the response to an induced *Streptococcus* aerosol infection and the pulmonary bactericidal activity against inhaled *Klebsiella pneumoniae* after a single exposure to low concentrations of TCE. Changes in immunological responses were observed at inhalation exposure to 10 ppm or above (Aranyi et al., 1986). However, the toxicological significance of these findings is unclear as these assays are not validated (ECB, 2004).

The oral lethal dose ($LD_{50}$) for TCE ranges between 5,400 and 7,200 mg/kg bw in rats and is about 2,900 mg/kg bw in mice (ECB, 2004). CNS effects were noted as were lesions at necropsy (Jones et al., 1958).

Dermal LD50 have been reported to be greater than 29,000 mg/kg bw (occlusive dressing) in rabbits (Smyth et al., 1962, Smyth et al., 1969).

## 3.3 Irritation and corrosivity

### 3.3.1 Human data

The odour of TCE is detectable at 20 to 30 ppm (110-164 mg/m$^3$) (ECB, 2004). An acceptable odour detection limit of 82 ppm (450 mg/m$^3$) is provided by AIHA (1997). According to other sources, lower concentrations may already be relevant for odour detection. Thus, Abe (1988) stated 8.4 ppm (46 mg/m$^3$) as odour threshold for TCE. A qualified odour recognition level of 108 ppm is documented in AIHA (1997).

Nomiyama and Nomiyama (1977) found irritation of mucous membranes at 27 ppm (148 mg/m$^3$) and above after single inhalation exposure to TCE for 4 hours. These effects have not been reported in most other studies, even at considerably higher concentrations.

Also, Vandervort et al. (1973) mentioned eye Irritation and other symptoms after long-term exposures to 32-78 ppm (175-426 mg/m$^3$) TCE. However, these data were poorly reported and not validated.

Stewart et al. (1970) determined dry throats and an "irritating" sensation (1 of 5 persons) after exposure to 100 or 200 ppm (546-1090 mg/m$^3$) TCE.

TCE is irritating to human skin. Repeated dermal contact may cause de-greasing and lead to erythema and, in rare cases, to generalised exfoliative dermatitis (Irish, 1963; Schirren, 1971; Bauer and Rabens, 1974). TCE (quantity not given) was applied to the unoccluded skin of the forearm of a volunteer for 18 days. No effects on skin fold thickness or erythema were observed. However, the substance may have evaporated readily from the application site (Wahlberg, 1984).

### 3.3.2 Animal data

*Skin*

Undiluted TCE has produced severe skin irritation in several studies on rabbit skin (Duprat et al., 1976; Smyth et al., 1969). Undiluted TCE (0.1 ml), applied to unoccluded rabbit or guinea pig skin daily for 10 days resulted in erythema and oedema with evidence of fissuring and scaling, and increased skin fold thickness (Wahlberg, 1984). Severe skin irritation of TCE in alcohol was confirmed in other guinea pig strains (Anderson et al., 1986).

*Eyes*

The data on eye irritation are contradictory. In one study, the application of 0.1 ml of TCE into the rabbit eye produced mild to moderate conjunctivitis and limited keratosis with complete recovery (Duprat et al., 1976). In another study, the same amount caused necrosis of most of the cornea (Smyth et al., 1969).

## 3.4 Sensitisation

### 3.4.1 Human data

Some case studies report single positive results for skin sensitisation after TCE exposure (Nakayama et al., 1988; Conde-Salazar et al., 1983). TCE exposure is linked to autoimmune effects like *lupus erythematosus,* which in turn may exert skin erythema and other skin reactions (see section "Repeated dose toxicity").

No reports on respiratory sensitisation are available.

3.4.2 Animal data

A link to systemic autoimmune effects and hypersensitivity disorders was corroborated by recent publications (Kajima et al. 2007, 2008) In particular, Tang et al. (2008) has put forward the view that liver injury due to TCE was associated with hypersensitive skin reactions by TCE in the Guinea pig maximisation test.

## 3.5 Repeated dose toxicity

3.5.1 Human data

*CNS effects*

All existing studies with human volunteers or field studies on CNS effects following exposure to TCE include relevant uncertainties.

Stewart et al. (1970) exposed 5 male volunteers on 5 consecutive days (7 h/d) to TCE concentrations of 200 ppm (1090 mg/m$^3$). A second group of 2 persons was exposed to 100 ppm (546 mg/m$^3$; 4 hours, single exposure). The exposed subjects regarded the odour as "moderately strong" or "strong" at the beginning of the experiment but none of them could detect odour at the end of the day. At the beginning, 2/5 persons reported dry throats and 1 person classified the sensation as "irritating". Three out of five volunteers complained throughout the duration of the experiment about "feeling sleepy" when asked to perform certain tasks. Half of the persons reported that it required greater mental effort to perform a modified Romberg test. No objective changes of responses were observed in neurological tests (Stewart et al., 1970). Simon (1997) used pharmacokinetic modelling and Monte-Carlo simulation to extrapolate the results obtained by Stewart et al. to a more representative level. Modelling also included females, who had been regarded as more sensitive to the CNS effects after TCE exposure than men. The authors found that 99% of the females will be protected from CNS effects, if exposure is limited to 30 ppm (165 mg/m$^3$).

In a later study by Stewart et al. (1974), a small number of male volunteers was observed for 4 weeks using exposure to TCE between 20 ppm (first week) and 200 ppm (forth week) with different daily exposure durations. No signs of toxicity and no changes in behavioural test performance were observed. After exposure to 200 ppm (1090 mg/m$^3$), some "minimal" changes in the EEG were found.

Rasmussen and co-workers (1993) examined 96 workers who were exposed either to TCE or to CFC113 during degreasing. No control group was included but the workers were grouped according to exposure history. The maximum concentration of TCA in urine was 26.1 mg/l, the mean was 7.7 mg/l. However, no historical urine levels and no air concentration data were available. Medical history was taken and several psychometric tests were performed. The prevalence of the "psycho-organic syndrome" was 10% for low exposure, 39% for mid exposure and 63% for high exposure. Most of the workers with a "psycho-organic syndrome"

had been exposed to TCE (31/42 predominantly, 7/42 exclusively) (Rasmussen et al., 1993). There is relevant uncertainty on the historical exposure of these workers, including possible peak exposure in the past. However, based on general Danish data for workplace exposure conditions, the usual average exposure in Denmark for such workplaces during the period 1947-1987 was assumed to be below 50 ppm (274 mg/m$^3$) TCE in air (ECB, 2004).

In another study with occupational exposure of degreasers, the TWA values for TCE were 22-66 ppm (mean 38 ppm; 208 mg/m$^3$) with short-term peaks of 77-370 ppm. Nine of 12 exposed workers with mean employment from 4.4 to 9.4 years were medically examined (9 control subjects). Seven of 9 exposed and one of the control persons reported symptoms (mainly fatigue, light headedness, sleepiness, eye irritation and shortness of breath). After three months with reduced exposure concentrations (mean 16 ppm; 88 mg/m$^3$) and peaks up to 74 ppm (404 mg/m$^3$), the number of reported symptoms was slightly reduced (Landrigan and Kominsky, 1987).

There is a large number of similar reports with some variability in results, which do not provide further clarifications on effect levels or thresholds for CNS effects (for review see Greim, 1996; ATSDR, 1997; ECB, 2004).

*Kidney effects*

In a cross-sectional study, 70 workers (58 males, 12 females) exposed to TCE were examined for possible renal dysfunction by Green et al. (2004). The mean exposure concentration was estimated to be 32 ppm (175 mg/m$^3$; range 0.5-252 ppm) based on the urinary elimination of TCA. Average exposure duration was 4.1 years (1-20 years). Exposed workers had elevated N-acetylglucosaminidase (NAG) and albumin excretions, indicative of preclinical nephrotoxicity. However, NAG and albumin levels did not correlate with current urinary levels of TCA or years of employment. There was a trend for increasing urinary glutathione-S-transferase alpha activities with increasing urinary TCA concentrations. In addition, urinary formic acid and methylmalonic acid concentrations were elevated and correlated with TCA concentration. The authors questioned a causal relationship of the elevated NAG and albumin level with TCE exposure and further regarded NAG as an indication of functional changes in the renal tubules and not as an indicator of damage. However, they considered the observed effects as supportive for an influence of TCE exposure on vitamin $B_{12}$ deficiency, induced via the TCE metabolites TCA and TCOH. Vitamin $B_{12}$ deficiency leads to excess formic acid in urine and to excess methylmalonic acid. These acids could contribute to nephrotoxicity by cellular acidosis. No clinically relevant nephrotoxic effects were observed in this study.

In another study, 25 (of 29) Scandinavian workers were exposed to less than 6-10 ppm (33-55 mg/m$^3$) TCE (Seiden et al., 1993). No increase in N-acetyl-D-glucosaminidase excretion was observed. Together with the slight subclinical effects reported in the study by Green et al. (2004), this report (which is rather limited in size and poor in reporting) points to a threshold for subtle preclinical kidney effects by TCE at or around this exposure concentration (6-10 ppm).

The relevance of renal toxicity as a critical endpoint for chronic exposure to TCE was confirmed in a recent case-control study of end-stage renal disease in aircraft workers, in which the risk was significantly elevated and correlated to TCE exposure (Radican et al., 2006). However, no details are available from this study to derive a more precise dose-response relationship.

*Immunologic effects*

A group of male workers "in the printing sector" with at least three years of exposure to TCE (group A) was examined for immunologic changes (Lavicoli et al., 2005). They were compared to an internal control group from the same factory (group B) and an external control group of office workers (group C). Group A exposed to TCE consisted of 35 persons, the control groups of 30 and 40 persons, respectively. The control groups were matched for age, smoking habits and (rural or urban) residence to the exposed group. Air concentrations of TCE were 35 ± 14 mg/m$^3$ (6.4 ± 2.6 ppm). Urinary TCA was 13.3 ± 5.9 mg/g creatinine in group A and 0.02 ± 0.02 mg/g in group B. Means of immunologic parameters were significantly altered in the exposed group (group A) compared to both group B and group C with "type 1" cytokines raised (interleukin-4 (797.9 vs. 705.7 and 730), interferon-gamma (37.1 vs. 22.9 and 22.8)) and "type 2" cytokines lowered (interleukin-2 (3.9 vs. 8.1 and 8.1)). However, the study is of limited reporting quality (only means for the cytokine changes without standard deviation reported, no comment on exposure concentrations in the past).

### 3.5.2 Animal data

*Inhalation*

Sprague-Dawley rats, B6C3F1 mice and Swiss mice were exposed to 0, 100, 300 and 600 ppm (0, 546, 1640, 3280 mg/m$^3$) TCE for 104 weeks (rats) or 78 weeks (mice) (7 hours/day, 5 days/week). In this carcinogenicity study (see section "Carcinogenicity", below) non-cancer effects were only seen in male rats. Kidney tubular mega-nucleocytosis was observed at 300 ppm in 20% and at 600 ppm in 78% of male rats (Maltoni et al., 1986). The NOAEL for kidney toxicity in this study was 100 ppm. No kidney effects were observed in most other studies with repeated inhalation exposure or only at higher concentrations (Adams et al., 1951; Prendergast et al., 1967; Arai et al., 1988; Fonzi et aI.,1967). Increased kidney weights were found in one study in mice at 75 ppm (NOAEL 37 ppm) (Kjellstrand et al., 1981, 1983a, b). The relevance of these changes is uncertain, as effects are regarded as possibly adaptive and no histopathology has been performed (ECB, 2004).

Concentration-dependent liver weight changes were seen in the same study after inhalation exposure of NMRI mice to concentration between 37 and 3,600 ppm (202-20,220 mg/m) TCE for 30 or 120 days. The weight changes were accompanied by changes in the size of the hepatocytes and increased vacuolisation of the cytoplasm (Kjellstrand et al., 1981, 1983a,b). Again, the relevance of these findings is uncertain and is regarded as a possible adaptive response. Mice were more sensitive to liver effects than other species (ECB, 2004). Adverse effects in rat liver occurred at similar or higher concentrations than did kidney effects (Fonzi et al., 1967; Arai et al., 1988; Adams et al., 1951).

Neurotoxicity was examined in F344 rats in a 13-week study in compliance with GLP. Rats were exposed to 0, 250, 800 and 2500 ppm (0, 1366, 4370, 13660 mg/m$^3$; 7 h/d, 5 d/w). Neurotoxicity was evaluated by weekly clinical observations, monthly functional observational battery (FOB), post-exposure testing of evoked potential (visual and auditory chemosensory systems), other tests on trigeminal effects and neuro-histopathology. Lacrimation occurred occasionally at 800 ppm and 2500 ppm. No clearly concentration-related effects were seen in the FOB. Some changes in the visual and auditory somato-sensory systems were observed at 800 ppm and 2500 ppm for the visual system and at 2500 ppm at the auditory system. No trigeminal effects were observed and histopathological findings were limited to the 2500 ppm group (focal loss of hair cells in the cochlea) (Dow Chemical, 1993). From this study, a NOAEL of 250 ppm (1366 mg/m$^3$) can be derived.

A few other neurotoxicological studies with repeated inhalation exposure provided conflicting results. Reduced avoidance behaviour was reported after exposure of rats to 125 ppm (680 mg/m$^3$) TCE for three weeks (Grandjean and Battig, 1964; Goldberg et al., 1964a, b). Increased activity was shown after 5 days exposure of rats to 200 ppm (1090 mg/m$^3$) (Savolainen et al., 1977). However, these studies may have been influenced by the odour of TCE and are less qualified in reporting than the above cited Dow Chemical (1993) study. Mongolian gerbils showed differences in behaviour in the maze test after 71 or 106 days of exposure to 150 ppm (820 mg/m$^3$) TCE. Non-significant changes were still apparent after a recovery period (Kjellstrand et al., 1981). Kyrklund et al. (1983, 1986) also observed minor changes in brain lipid composition in gerbils at 50 ppm (273 mg/m$^3$) exposure for 12 months and in Sprague-Dawley rats at 320 ppm (1750 mg/m$^3$) after 5 days. The relevance of these findings is uncertain and the study results are not used for risk assessment.

Arito et al. (1994) exposed rats to 0, 50, 100 or 300 ppm (0, 270, 546, 1640 mg/m$^3$) TCE (8 h/d) for 6 weeks. They found changes in CNS function at and above 100 ppm, where the circadian heart rhythm was disrupted in a dose-related manner. The NOAEC in this study would be 50 ppm (270 mg/m$^3$). However, the biological significance of these effects is not clear (ECB, 2004).

Ototoxic effects were observed in rats and mice at higher concentrations (for review see ECB, 2004).

Pulmonary toxicity was seen in mice at the only tested concentration of 450 ppm (2460 mg/m$^3$) (subacute duration) with a regenerative process starting after the first days of repeated exposure (Odum et al., 1992).

*Oral*

Similarly to inhalation, kidney toxicity in repeated studies with rats is the most critical effect observed in experimental animals. In a carcinogenicity bioassay, rats received 0, 50 or 250 mg/kg • d by gavage on 4 or 5 days/week for 52 weeks with observation until natural death. 47% of the males showed kidney tubular mega-nucleocytosis at 250 mg/kg • d. No effects occurred in females and the NOAEL for both sexes was 50 mg/kg • d (Maltoni et al., 1986). Nephrotoxicity was also observed in the NTP studies with rats and mice (NTP, 1988; NTP,1990).

Liver toxicity was observed in mice and rats with more distinct effects in mice. Elcombe et al. (1985) administered TCE in corn oil to male Alderly Park and Osborne-Mendel rats as well as to B6C3F1 and to Alderley Park mice. Doses were 500, 1000 and 1500 mg/kg • d for 10 days. Marked liver weight increases were seen in mice and, to a lesser extent, in rats. DNA synthesis was extremely increased in mice (500 % of control values) but not in rats. Hepatomegaly in mice was attributed to hypertrophy and hyperplasia, whereas only cell enlargement was observed in the rat liver. These changes occurred at all three dose levels without a clear dose-response relationship. Only in mice, a concurrent increase of hepatic peroxisomal enzyme activity was observed. This species difference in peroxisome proliferation is thought to be the result of a different rate of TCA formation in mice *vs*. rats, which increases hepatic peroxisomal β-oxidation (Elcombe, 1985).

To investigate possible autoimmune effects caused by TCE, MRL+/+ mice were exposed to 0, 0.1, 0.5 and 2.5 mg TCE/ml (21, 100 and 400 mg TCE/kg • d) in drinking water for 4 and 32 weeks (Griffin et al., 2000). After 32 weeks of treatment, there was a significant increase in hepatic mononuclear infiltration localised to the portal region, a type of hepatic infiltration

consistent with autoimmune hepatitis at and above 100 mg/kg • d. Changes were not significantly different from control at 21 mg/ kg • d. TCE exposure activated $CD4^+$ T-cells after 32 weeks. There were 11, 61, 156% increases in lymph node $CD4^+$ T-cells. Interferon-gamma excreting $CD4^+$ T-cells are involved in the development of autoimmune disease pathology in a similar mouse strain. Therefore, interferon-gamma secretion from $CD4^+$ T-cells isolated after 4 or 32 weeks exposure was measured with a significant increase above control for $CD4^+$ T-cells from animals exposed to 100 mg/kg • d (no significant effect for animals treated with 21 mg TCE/kg • d). In a more recent study of the same group, it was shown that these effects were induced by the metabolites chloral hydrate and TCA as indicated by similar responses at similar doses in *in vivo* testing. Moreover, the $CD4^+$ T-cells showed a decreased susceptibility to the activation-induced cell death form of apoptosis. This kind of defect has been linked with the development of several idiopathic autoimmune diseases such as lupus nephritis, multiple sclerosis, autoimmune haemolytic anaemia and arthritis in both humans and mice (Blossom et al., 2004).

*Dermal*

No studies are available with repeated dermal exposure of experimental animals to TCE.

## 3.6 Genotoxicity

### 3.6.1 In vitro

From earlier studies it was concluded that pure TCE usually did not induce gene mutations or DNA damage in prokaryotic systems. Also, TCE did not induce gene conversion or reverse mutations in *Saccharomyces cerevisiae* (with and without metabolic activation) or mitotic crossing over in *Aspergillus nidulans,* but it did induce forward mutations in *Aspergillus nidulans* (NTP, 2000).

The EU Risk Assessment Report (ECB, 2004), based on a positive Ames test (Crebelli et al. 1982) and a positive mouse lymphoma test (NTP, 1988) concluded that trichloroethylene was an in vitro mutagen.

According to more recent data, no chromosomal aberrations were found in a Chinese hamster lung cell line with or without S9 (Matsuoka et al., 1996). However, a significant and dose-dependent increase in the frequency of DNA single-strand breaks and alkali-labile sites, as measured by the Comet assay, and in micronuclei frequency, was obtained in primary kidney cells from both male rats and humans of both sexes. The test concentration of TCE was between 1 and 4 mM (Robbiano et al., 2004). However, the viability of the cells was clearly compromised at the high concentrations that were tested.

Zefferino et al. (2005) investigated changes in gap junction intercellular communication (GJIC) in serum-free cultured primary human keratinocytes. GJIC was significantly inhibited with 500 µM TCE. According to the authors, this points to a tumour promoting potential of TCE.

### 3.6.2 In vivo - Human data

Results on genotoxic effects after human exposure are contradictory. Higher rates of sister-chromatid exchanges (SCE) in peripheral blood lymphocytes have been observed in a small study with 6 exposed workers (Gu et al., 1981). Also, Seiji et al. (1990) reported increased SCE for male smoking workers exposed to 10-50 ppm (55 - 270 $mg/m^3$) TCE, but not for exposed non-smoking males and for females. Nagaya et al. (1989) saw no increase of SCE

after inhalation exposure to about 30 ppm (164 mg/m$^3$) TCE in another study with small sample sizes.

Rasmussen et al. (1988) found chromosomal aberrations (breaks, translocations, inversions, deletions and gaps) in a group of 15 TCE-exposed workers. Konietzko et al. (1978) described increased levels of leukocyte aneuploidy (hypodiploid cells) in degreasing workers occupationally exposed to TCE. All the reported studies have relevant limitations in the study design not permitting firm conclusions on the genotoxicity of TCE in humans.

Workers occupationally exposed to high concentrations of TCE with kidney tumours are suspected of exhibiting mutations of the von-Hippel-Lindau (VHL) tumour suppressor gene (Brauch et al., 1999, 2004). In an initial study, all of 23 patients with renal cell carcinoma and previous exposure to TCE showed this mutation (Brüning et al., 1997). In a second study, these mutations of the VHL gene were observed in 75% of renal cell carcinoma from 44 TCE-exposed persons. The exposure concentration was positively correlated with the number of mutations in each patient (Brauch et al., 1999). This was confirmed in a subsequent study on 17 TCE-exposed and 21 non-exposed patients with renal cell cancer (Brauch et al., 2004). It is being debated whether the VHL mutations result from a direct genotoxic effect of TCE metabolites or secondary to continuous toxic injury and sustained cell proliferation (Mally et al. 2006).

### 3.6.3 In vivo - Animal data

In earlier studies, TCE gave equivocal results for sex-linked recessive lethal mutations in *Drosophila melanogaster* exposed via feed (NTP, 2000). TCE did not induce mitotic recombination in *Drosophila melanogaster* exposed via inhalation (Vogel and Nivard, 1993).

Based on the review by IARC (1995), TCE administered orally or by intraperitoneal injection gave equivocal results with respect to covalent binding to mouse and rat liver DNA and negative results for binding to mouse spleen, pancreas, lung, testis, kidney or brain DNA. When administered orally or by inhalation, the substance did not induce unscheduled DNA synthesis (UDS) in mouse hepatocytes, SCE in mouse splenocytes or rat lymphocytes. TCE did not induce micronuclei in bone marrow when administered i.p., or in mouse splenocytes, mouse spermatocytes or rat lymphocytes when administered by inhalation. TCE gave both negative and positive results for DNA single-strand breaks or alkali-labile sites in mouse liver (administered i.p. or orally) and positive results for micronucleated polychromatic erythrocytes in mice exposed orally and in rats exposed by inhalation.

A more recent, appropriately designed micronucleus test on TCE in rat bone marrow was negative (Wilmer et al., 2005), thus reducing the weight of earlier positive results (Kligerman et al., 1994).

Tao et al. (1999) exposed mice to 1000 mg/kg • d TCE by gavage for 5 days/week for up to 33 days. TCE decreased methylation of the total DNA and modified the expression of early proto-oncogenes. No UDS was induced in hepatocytes of mice exposed orally (Miyagawa et al., 1995). No base-change or small-deletion mutations were observed in various tissues (including kidney, liver, lung and testicular cells) of *IacZ* transgenic mice exposed to 203 ppm (1110 mg/m$^3$) TCE or above by inhalation for 12 days (Douglas et al., 1999).

### 3.6.4 Genotoxicity of TCE metabolites

*Chloral and chloral hydrate*

Chloral hydrate is a well-established aneuploidogenic agent that also has some mutagenic activity. *In vivo,* it clearly induced aneuploidy and micronuclei in mammals, whereas other tests produced conflicting results. When incubated with calf thymus DNA, chloral hydrate induced the formation of DNA adducts (IARC, 2004). Chloral hydrate is regarded as a low-potency mutagen, with most of the positive results having occurred only at high doses (Moore and Harrington-Brock, 2000).

*Trichloroethanol*

The genotoxic potential of TCOH is insufficiently assessed, with negative results in the *Salmonella* mutagenicity assay (Moore and Harrington-Brock, 2000).

*Trichloroacetic acid*

Trichloroacetic acid caused no mutations in bacteria and no changes in SOS repair. In human cells *in vitro,* it did not induce chromosomal aberrations or DNA strand breaks. However, it was mutagenic in single studies on cultured rodent cells. The substance inhibited intercellular communication.

Studies on DNA adducts, DNA strand breaks and micronuclei *in vivo* gave conflicting results. Trichloroacetic acid induced abnormal sperm in mice and chromosomal aberrations in mouse and chicken bone marrow. It also induced micronuclei in newt salamander (*Triturus*) larvae.

Trichloroacetic acid stimulated cell replication in acute studies (and depressed cell replication in chronic studies). This was correlated with decreased methylation of the promoter regions of proto-oncogenes and increased expression of these genes (IARC, 2004).

*Dichloroacetic acid*

Tests on genotoxicity *in vitro* produced conflicting results. *In vivo*, DCA caused mutations in male transgenic mice harbouring the bacterial *lac1* gene. The substance led to DNA damage in peripheral blood cells in the Comet assay. Exposure of mice also resulted in micronuclei of polychromatic erythrocytes but not in rat bone marrow cells. Tests for the induction of DNA strand breaks and DNA binding assays in mouse liver were inconclusive.

Dichloroacetic acid caused a decrease of 5-methylcytosine in DNA of mouse liver cells. lt affects cell proliferation and cell death in normal livers and tumours in mice. lt causes DNA hypo-methylation (IARC, 2004).

*Monochloroacetic acid*

Monochloroacetic acid is a mutagen in *Salmonella typhimurium* strains, but only at a low potency (Kargalioglu et al., 2002).

*S-1,2-Dichlorovinylcysteine and S-(1,2-dichlorovinyl)glutathione*

DCVC and S-(1,2-dichlorovinyl)-glutathione induced point mutations in bacteria. There is some indication, that DCVC induces primary DNA damage in renal tubular cells in vitro and in vivo. The substance did not induce micronuclei in a Syrian hamster embryo fibroblast system and gave a weak UDS response. It induced the expression of two proto-oncogenes. The genotoxic potency of DCVC and dichlorovinyl-glutathione is currently unknown. However, from the results in the *Salmonella* assay, it may be assumed that DCVC has a

much stronger mutagenic activity compared to dichlorovinyl-glutathione, of which the former is a metabolite (Moore and Harrington-Brock, 2000).

DCVC may react with DNA. However, DNA adducts may not be formed or may not be stable in vivo (Volke and Dekant, 1998; Müller et al., 1998).

A negative result was found in an *ex vivo* Comet assay in rats, who had received up to 10 mg/kg DCVC (single oral dose). Preparations of kidney proximal tubular cells showed no changes in tail length compared to control (CTL 1998).

Gene expression in human renal proximal tubular cells exposed to low (subtoxic) concentrations of DCVC was altered possibly indicating apoptosis, stress response cell proliferation and repair (Lock et al., 2006).

#### 3.6.5 Germ cells

Two positive tests on germ cell mutagenicity have been published, which included i.p. administration of high doses of TCE (Fahrig, 1977 and Schiestl et al., 1997). A mouse spot test with intraperitoneal application of 140 or 350 mg/kg TCE was weakly positive (Fahrig, 1977). Also, in a modified mouse spot test with a single intraperitoneal application of 200 mg/kg TCE to mice post conception induced increased incidences of black spots in the offspring compared to controls at a high level of concurrent embryotoxicity (Schiestl et al., 1997).

*In vivo* tests for chromosomal aberrations in bone marrow or germ cells were negative as well as UDS tests in the liver of rats and mice and mutagenicity tests in various organs of transgenic mice (Douglas et al., 1999; Brüning and Bolt, 2000). Also, additional tests on aneuploidy were negative (see section "Genotoxicity - in vivo - animal data").

### 3.7 Carcinogenicity

#### 3.7.1 Human data

Many epidemiological studies have been performed to assess the potential carcinogenicity of TCE. However, results are often confounded by exposure to mixed solvents or other risk factors. A number of reviews have been published covering most of the cohort, case-control and community-based studies on TCE (Wartenberg et al., 2000; ECB, 2004; Wong, 2004; Scott and Chiu, 2006; Mandel et al., 2006; Alexander et al., 2006). From these reviews and additional more recent studies, it may be concluded that evidence for carcinogenicity by TCE is mainly to be discussed for liver tumours, renal cell carcinoma and non-Hodgkin's lymphoma (NHL). There have been other tumour sites discussed in relation to TCE exposure, but positive results were infrequent and not consistent in these cases. These are not covered below.

The cohort study by Anttila et al. (1995) included 3,089 exposed workers. The urinary excretion of TCA and the latency period (time from first urine samples to death or end of study) were used in the response assessment. Total cancer mortality was not increased in this study (SIR of 1.0; C.I. 0.8-1.2) and total cancer incidence (SIR 1.1 C.I. 0.9-1.2) was only slightly and insignificantly increased compared to the general population in Finland. There was a significant increase for liver cancer in male workers and a latency period of more than 20 years (SIR 13.0, C.I. 2.68-37.9). For kidney cancer, there was no increase, and for NHL the increase was not significant (SIR 1.81; C.I. 0.78-3.56). The authors stated that exposure was usually below 30 ppm (164 mg/m$^3$ TWA). An average exposure of 6.5 ppm was assumed

in a recent assessment (UAIII, 2006).

Another cohort study by Axelson et al. (1994) addressed 1727 workers in Sweden, whose urinary levels of TCA were available from biological monitoring programmes. The standard incidence rates (total cancer mortality, total cancer incidence) were not elevated. For liver cancer, the SIR was 1.4 (C.I. 0.6-3.6), for kidney cancer 1.2 (C.I. 0.5-2.5) and for NHL 1.52 (C.I. 0.49-3.54). Elimination of TCA was usually below 50 mg/I and associated with an average air concentration of about 15 ppm TCE (82 mg/$m^3$). Only few persons were included with higher workplace exposure. This study was a follow-up of an earlier study published by Axelson et al. (1978).

Similarly, the studies by Spirtas et al. (1991) and Blair et al. (1998) on 7204 workers of an aircraft maintenance facility in Utah (USA) provided no evidence of a significant increase for total cancer. Cancers of the liver and kidney as well as NHL were increased insignificantly. There was no appropriate monitoring of TCE exposure in this study (ECB, 2004). Similarly, a large study by Morgan et al. (1998) with 4733 exposed workers revealed only an insignificantly elevated risk for kidney cancer. However, exposure was insufficiently addressed and quantified (ECB, 2004). In another large cohort study in California, the assessment was based on 2267 exposed workers. For those with exposure for more than 5 years, there was an insignificant increase in NHL (Boice et al., 1999).

Henschler et al. (1995) studied 169 male workers who were exposed between 1956 and 1975 for at least 1 year to TCE in the area of Arnsberg/Germany (characterised by metal industry where TCE was used for degreasing). Concentrations of TCE in air were not precisely quantified but episodes of very high exposures were assumed from the reported symptoms. Typical exposure concentrations were estimated to be more than 100 ppm (55 mg/$m^3$), often at or above 500 ppm (2730 mg/$m^3$) TCE. The standard incidence rate for kidney tumours was significantly increased (SIR 8.0; C.I. 3.4-18.6) and the SMR was insignificantly elevated (3.3; C.I. 0.9-11.8). Furthermore, risks for lung tumours and lympho-haematopoetic tumours were insignificantly elevated (no incidence or mortality rate for NHL was described). The study was possibly compromised by a pre-existing cluster of 4 kidney tumours (which were indeed the initial cause of the study project) and was criticised because of discrepancy to earlier studies (Weiss, 1996; McLaughlin and Blot, 1997). Therefore based on the cohort study's results (Henschler et al., 1995), a case-control was supplemented with patients from a local hospital from the same area. It consisted of 58 patients who had been diagnosed with kidney cancer based on nephrectomy results. The odds ratio was 10.8 (CA. 3.36; 34.7). Some confounding factors (e.g. age of control group, other potential selection bias of control) were discussed but should not have had a decisive influence on the outcome of this study (Vamvakas et al., 1998).

Later, Brüning et al. (2003) provided a third consecutive study (case-control) for the area of Arnsberg/Germany. Cases with renal cell carcinoma (n=134) were compared with 401 controls from hospital and nursing homes. Exposure was assessed by job titles. The odds ratio was significantly elevated (OR 2.5; C.I. 1.4-4.5) for the description "if ever worked with TCE" and increased to 2.7 (C.I. 0.8-8.9) if exposure was for 20 years or more. However, the latter was no longer statistically significant. Thirteen of 44 cases with TCE exposure were carriers of the VHL 454 T allele (mutation of a tumour suppressor gene), whereas none of 107 non-exposed cases carried this mutation.

A small study was performed by Hansen et al. (2001) with a workforce size of 803 persons. Like the other Scandinavian studies, elimination of TCA was used for exposure quantification, the latter being assessed as rather Iow (mean 101 mg TCE/$m^3$). For cancers of

the liver and the biliary passages, an insignificantly elevated risk (SIR 2.6; C.I. 0.8-6.9) was calculated. For NHL in men, this study indicated a significantly elevated risk (SIR 3.5; C.I. 1.5-6.90).

Raaschou-Nielsen et al. (2003) provided a large cohort study with 14,360 workers from Denmark. The workers, mainly from small- and medium-sized enterprises, were presumably exposed to higher concentrations of TCE. With regard to NHL (SIR 1.5 (C.I. 1.2-2.0) and to renal cell carcinoma (SIR 1.4; C.I. 1.0-1.8), the cancer risk was significantly or nearly significantly increased. There was no clear link between the SIR for NHL and the lag time, duration of employment, year of first employment or numbers of employers in the company. Renal cell carcinoma increased with increasing lag time and with duration of employment. Furthermore, the risk for this type of tumour was clearly significant if the year of first employment was before 1970 (SIR 1.9; C.I. 1.4-2.6) compared to later years of first employment (SIR 0.7; C.I. 0.4-1.2). The study found elevated SIR for cancer of the liver and biliary passages for women but not for men. However, the lower SIR with increasing duration of employment does not support a causal relationship with TCE exposure.

A case-control study in the Arve valley in France (with a prevalence of metal industry that used TCE for degreasing) included 86 renal cell cancer cases and 316 matched controls (Charbotel et al., 2006). Exposure was quantified by job descriptions and a transformation into exposure bands (Fevotte et al., 2006). After adjustment for tobacco smoking and body mass Index, a significantly increased risk was identified for high cumulative doses (OR= 2.16; CA. 1.02-4.6). A dose-response relationship was shown as was a peak effect. The adjusted OR for the highest class of exposure plus peak was 2.73 (C.I. 1.06-7.07). The study population was regarded as highly exposed with 13.2 % of exposure levels > 50 ppm (270 mg/m3) and 7.5% of exposed jobs having peaks above 200 ppm (1090 mg/m) (Fevotte et al., 2006; Charbotel et al., 2006).

Further studies were performed with TCE in the groundwater and sometimes in the drinking water. In a recent integrated assessment of these studies, Wong (2004) did not find an increased cancer risk, specifically for liver cancer or NHL, from those and the epidemiological studies cited above.

An earlier meta-analysis by IARC (1995) commented that the most informative cohort studies consistently indicated an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases versus 12.87 expected.

Another meta-analysis by Scott and Chiu (2006) has been performed to assess the possibility of an elevated risk of NHL and workplace exposure to TCE. This meta-analysis included most of the cohorts reported above supplemented with a few studies of less quality and a number of case-control studies. The cohort studies for those cohorts for which information TCE exposure was available resulted in a summary relative risk estimate (SRRE) of 1.29 (C.I. 1-1.66). For the seven subcohorts that had a specific exposure to TCE the SRRE was 1.59 (C.I. 1.21-2.08). The significantly elevated risk was driven by European studies (Hansen et al., Raaschou-Nielsen et al., Axelson et al., Anttila et al.), with multiple industry exposures combined, whereas for the U.S. studies with single industry cohorts (Blair et al., Boice et al., Morgan et al.) the risk was only insignificantly elevated. A more detailed analysis of a possible correlation with TCE exposure concentration and/or exposure duration did not demonstrate such a dose-response relationship. Studies with less qualified exposure description and case-control studies showed an insignificant increase in cancer risk when the combined analysis was performed (Mandel et al., 2006). Scott and Chiu (2006) pointed out that the four studies from the Nordic countries (Anttila et al., Axelson et al., Hansen et al.,

Raaschou-Nielsen et al.) all classified NHL identically and all reported consistent findings, whereas other versions of the International Classification of Diseases (ICD) system were used in other studies with sometimes conflicting results. A confounding factor for an appropriate meta-analysis may also have been that the understanding of histopathological and immunological characteristics of lymphoma has changed during the last decades. This leads to problems in the aggregation of earlier and current NHL cases (Scott and Chiu, 2006).

### 3.7.2 Animal data

Inhalation studies on the carcinogenicity of TCE are available for rats, mice and hamsters (Maltoni et al., 1988; Henschler et al., 1980; Fukuda et al., 1983).

One inhalation study showed an increased incidence of lymphomas in mice (Henschler et al., 1980), one study showed increased incidences of liver tumours in mice (Maltoni et al., 1988) and three studies showed increased incidences of lung tumours (Maltoni et al.,1988, Fukuda et al., 1983). Lung tumours were found in female B6C3F1 mice, in male Swiss mice and in female ICR mice. One of three experiments with rats showed an increased incidence of interstitial testicular tumours and a marginal increase in renal cell tumours in males (Maltoni et al.,1988). No increased tumour incidence was observed in one study in hamsters (IARC, 1995).

A slight increase of renal cell tumour incidence was observed in male rats, if aggregated inhalation data are considered (Lock and Reed, 2006).

TCE (with and without stabilisers) was also tested for carcinogenicity by oral exposure. Studies in mice showed significant increases in benign and malign liver tumours (NCI, 1976; NTP, 1990). In two studies, the incidence of uncommon renal cell tumours was significantly increased in male rats (NTP, 1988; NTP, 1990) and in one study an increased incidence of interstitial-cell testicular tumours (NTP, 1988) was observed (IARC, 1995). Kidney tumours were induced in three rat strains: Sprague-Dawley, Fischer-344 and Osborn-Mendel. These effects were consistently only seen in male animals and not in mice. Non-neoplastic nephrotoxicity was found in animals that developed tumours.

In summary, some data point to the possibility of a connection between human TCE exposure and NHL, but the available evidence is not convincing at the present time.

### 3.7.3 Carcinogenicity of metabolites

There are no human data on the carcinogenicity of single major metabolites of TCE available. In experimental animals, chloral hydrate increased the incidence of adenomas in the pituitary gland of female mice after oral application. In dietary restricted mice, there was an increased trend for hepatocellular carcinoma in male animals. Two other oral studies did not show carcinogenic activity. The overall assessment was "*Iimited evidence for carcinogenicity*" of chloral hydrate (IARC, 2004).

In experimental animals, DCA was tested in several studies. Neutralised DCA, administered in the drinking water to mice of both sexes, increased the incidences of hepatocellular adenomas und carcinomas. The substance was also active in rats, however, with a clear sublinear dose-response relationship (DeAngelo et al., 1996). The substance promoted hepatocellular carcinomas in carcinogen-initiated mice. The overall assessment was "*sufficient evidence for carcinogenicity*" of DCA (IARC, 2004).

In experimental animals, TCA was tested in several studies. Neutralised TCA, administered in the drinking water to mice of both sexes, increased the incidences of hepatocellular adenomas und carcinomas. However, there is one study in which the occurrence of tumours was not influenced in male mice. The substance promoted hepatocellular adenomas and/or carcinomas in carcinogen-initiated mice (both sexes) and of kidney tumours in male mice. The overall assessment was "*limited evidence for carcinogenicity*" of TCA (IARC, 2004).

In a recent subchronic gavage study with Eker rats, which are very susceptible to renal cell carcinoma, administered the TCE metabolite dichlorovinylcysteine no neoplastic or preneoplastic changes were observed (Mally et al., 2006).

There are no adequate long-term carcinogenicity studies available for other metabolites of TCE.

### 3.7.4 Mode of action for carcinogenic effects

*Liver tumours*

Mice are generally regarded as a sensitive species for liver tumours. B6C3F1 mice are known to exhibit such tumours especially after exposure to hydrocarbon solvents. In the case of TCE, it has been discussed that the high rate of TCA may lead to peroxisomal proliferation in mouse liver *via* the peroxisome proliferators-activated receptor α (PPAR α). This mechanism is supported by recent studies with wild-type and PPAR□-knock-out mice (Luaghter et al., 2004).The respective PPAR α receptors are only found to a minor degree in humans (Smith et al., 2005).

In humans, conflicting results regarding liver tumours were observed in epidemiological studies. Cohort and case-control studies provided some evidence of the relevance of liver tumours after TCE exposure (see section "Carcinogenicity, human data"; Wartenberg et al., 2000). In a more recent combined assessment (liver and biliary passage cancers), the overall incidence of mortality from these cancers was only slightly and insignificantly elevated. However, in those few studies in which liver cancer was assessed separately from biliary cancer, the risk appears more elevated (Scott and Chiu, 2006). In terms of mechanism it is assumed that, if this tumour location is relevant in humans at all, liver tumours would be induced by a different mode of action in humans compared to mice.

However, Keshava and Caldwell (2006) reported a number of differences in gene expression between the response to typical peroxisomal proliferators and the one observed for TCE or TCA. Liver tumours after exposure to TCE could also be induced (in parts) by DCA. DCA was found to be a hepato-carcinogen in mice and rats. Bull et al. (2002) compared biomarkers from TCA, DCA and TCE-induced tumours, in order to identify the metabolite responsible for liver tumours by looking at the antibody profile and/or the mutational profile. The data were not consistent with the hypothesis that all liver tumours induced by TCE were in fact caused by TCA. DCA induces peroxisomal proliferation in higher doses than the doses associated with liver cancer (Bull, 2004; Walgren et al., 2004). Caldwell and Keshava (2006) noted a variety of effects by DCA consistent with conditions that increase liver cancer risk across species. Recently, DCA has been discussed as the critical metabolite of TCE possibly responsible for the carcinogenic action. DCA may interact with DNA (see section "Genotoxicity"), possibly induces suppression of apoptosis, and affects the lipid and glycogen metabolism, which may be a mode of action for the observed liver tumours induced by TCE (Caldwell and Keshava, 2006). However, very low levels of this substance were found in only some of the highly exposed humans (Fisher et al., 1998) and results from rat

studies support a sublinear dose-response relationship after oral exposure (DeAngelo et al., 1996). But due to the suicide metabolism of DCA the possible participation of this substance in toxicodynamics of TCE in humans may currently not be excluded (Keys et al., 2004).

*Kidney tumours*

Several modes of action have been discussed for the development of renal cell tumours after TCE exposure:

1) Direct interaction with DNA

There is little evidence that TCE acts primarily *via* a direct genotoxic mechanism. Most classic tests for mutagenicity were negative and DNA-binding, if it was noted, was weak or unstable (Lock and Reed, 2006).

2) Indirect interaction with DNA

Some authors propose that DNA damage from TCE is produced via reactive oxygen species, leading to lipid peroxidation and - at least in the liver of rodents - to peroxisome proliferation, which is regarded as an important mechanism for carcinogenicity. However, this mechanism may well be relevant for the liver, but probably not for the kidney (Lock and Reed, 2006).

Lash et al. (2005) performed studies with human proximal tubular cells of the kidney. They exposed the cells to dichlorovinyl-cysteine, a metabolite of TCE discussed as being responsible for nephrotoxicity and carcinogenicity. Cellular necrosis occurred only at high concentrations but relevant changes in the expression of proteins regulating apoptosis, cell growth, differentiation and stress response were seen at much Iower concentrations of dichlorovinyl-cysteine and after shorter duration *in vitro.* The authors discussed that these epigenetic events may relevantly contribute to TCE kidney tumour formation.

3) Hyaline droplet formation

Male rats excrete high amounts of low molecular weight protein, the alpha-2µ-globulin. Some chemicals bind to this protein leading to accumulation of the protein-chemical complex as hyaline droplets, which in turn produces renal tubular hyperplasia, nephrotoxicity and renal cell cancer. This mode of action is regarded as not being relevant for humans. Because of the male rat's sensitivity to TCE-induced renal cancer this mechanism has basically to be considered. However, no hyaline droplets were found after TCE exposure in male rats (Goldsworthy et al., 1988), and therefore this mechanism is not considered as relevant for TCE-induced tumour formation in the kidney.

4) Exaggeration of spontaneous chronic progressive nephropathy

In principle, chronic progressive nephropathy could be a mechanism of tumour formation. Cell proliferation is linked to errors of DNA replication, and this results in a greater opportunity for the fixation of a mutational event as an initial state of a possible tumour. Green et al. (1998) demonstrated that rats exposed to TCE excrete elevated amounts of formic acid. This intermediate is formed *via* the oxidative pathway by the interaction of TCOH and/or trichloroacetic acid with the vitamin $B_{12}$-dependent $C_1$ metabolism (see section "Toxicokinetics"; Dow and Green, 2000). Formic acid is nephrotoxic by induction of cellular acidosis and is already elevated in the urine of rats after subacute exposure to 250 to 500 ppm (1,365-2,730 mg/m$^3$) (Green et al., 1998). Mice eliminate much less formic acid than

rats. This could explain the differences in sensitivity between rats and mice with regard to nephrotoxicity and also to secondary carcinogenesis *via* this tumour-promoting mechanism. However, after chronic intake of high amounts TCOH via drinking water only a moderate increase in renal cell turnover could be demonstrated which was reversible (Green et al., 2003). On the other hand, inhalation exposure of workers already to low concentrations of TCE apparently leads to disturbances of vitamin $B_{12}$ metabolism, elevated formate excretion and first indications of renal injury (Green et al., 2004).

Also, in a recent study by Mally et al. (2006) with subchronic gavage of the TCE metabolite dichlorovinylcysteine to susceptible rats the authors did not find indications for a genotoxic event but only increased cell proliferation. lt was suggested that renal cell cancer after TCE exposure was a consequence of nephrotoxicity and resulting regenerative cell proliferation.

5) Conjugation with glutathione and enzymatic activation to reactive species

The understanding of this proposed mode of action is that the metabolism of TCE *via* the reductive glutathione-dependent pathway leads to nephrotoxic and genotoxic metabolites. Both events in combination are considered responsible for the Iocal carcinogenic effects in the kidney.

For the genotoxic event it is further postulated that this could be a mutation of the VHL gene. The VHL gene damage was often observed in kidney cancer patients exposed to TCE. Subsequent to the damage of this tumour suppressor gene, cell proliferation and renal cell carcinoma may develop.

Principally, identical metabolites were found in humans as in rodents pointing to a human relevance of the tumours observed in animal studies. Moreover, this pathway is less important at lower and more relevant at higher exposure concentrations of TCE, when oxidative metabolism is saturated (Goeptar et al., 1995). There are some contradictions, as S-1,2-dichlorovinyl-glutathione is generated to a larger extent in mice compared to rats, but rats and not mice show increased incidences of kidney cancer. This could be due to the much higher β-lyase activity in rats compared to mice (Green et al., 1997a). Specific sensitivity of male rats is confirmed by *in vivo* comparisons between male and female F344 rats. Similar to mice, female rats generated higher amounts of S-1,2-dichlorovinyl-glutathione in the kidneys; however, the toxicologically relevant DCVC was found in higher concentrations in male animals (Lash et al., 2006). Humans, however, are thought to have a lower β-lyase activity than rats in the renal cytosol, which could render them less susceptible to kidney toxicity and carcinogenicity than rats (Lock and Reed, 2006). On the other hand, it has been discussed that differences between human individuals may more than outweigh this species difference as there may be an up to 50-fold individual variability in the rates of activation versus detoxification *via* mercapturic acids (Altuntas and Kharasch, 2002).

Mally et al. (2006) questioned the influence of genotoxic events via dichlorovinyl-cysteine-dependent metabolites. They conducted a 13-week study with Eker rats, which are very susceptible to renal cell carcinoma, and applied various doses of dichlorovinyl-cysteine to these animals. They observed clear nephrotoxicity at the highest dose and cell proliferation in kidney tubular cells. However, they found no preneoplastic lesions or increased tumours compared to control. These authors suggest that genotoxic events *via* the glutathione-dependent pathway of TCE metabolism are not contributing to the mode of action for TCE-induced kidney cancers.

Epidemiological studies provide different results concerning kidney tumours in humans. In

general, the positive studies were linked to high exposure concentrations (Henschler et al., 1995; Brüning et al., 2003; Vamvakas et al., 1998; Raaschou-Nielsen et al., 2003, Charbotel et al., 2006), at which non-neoplastic nephrotoxic effects occur as well. Especially the implication of very high and repetitive peak concentrations has been emphasised; under such conditions it is plausible that the oxidative metabolism of TCE reaches saturation, so that more TCE proceeds via the glutathione-dependent toxification pathway (Harth et al. 2005). This supports the hypothesis of non-linear increases in the dose-response relationship at high exposure concentrations and of a relevant contribution of cytotoxicity to the mode of action for kidney tumours in humans.

Kidney toxicity was observed in most but not in all of patients with kidney tumours previously exposed to TCE. Bolt et al. (2005) reported that for 15% (3/20) of the exposed persons, no such lesions were found. However, assuming a link between nephrotoxicity and renal cell cancer questioned the exposure quantification in these few cases may be questioned.

*Lymphomas*

There is no sufficient understanding of the mode of action for lymphoma as observed in one experimental animal study after TCE exposure. NHL after exposure to TCE were only described in humans. It may be speculated that the autoimmune effects which are associated with TCE (see section "Repeated dose toxicity") are linked to NHL occurrence. Hardell et al. (1998) have discussed such a mode of action. In general, as indicated in 3.7.2, the available evidence for such a coherence is not convincing at the present time. Moreover, induction of NHL by TCE is not supported by a plausible mode of action, as concerns for genotoxic activity in the blood systems are low.

*Lung tumours*

For lung tumours in mice, a species-specific effect is discussed, because mice are characterised by much higher activities of cytochrome P450 in Clara cells of the respiratory tract than other animal species, including humans. Chloral has been suspected to be the critical metabolite of TCE in mice leading to lung tumours (Green et al., 1997b). Most epidemiological studies do not point to an increased risk for lung cancer in humans after occupational exposure to TCE (Wartenberg et al., 2000).

## 3.8 Reproductive toxicity

### 3.8.1 Human data

*Fertility*

Sperm parameters have been assessed in workers primarily exposed to TCE in a study in Denmark. No differences in sperm count or abnormal sperm heads were found. However, the number of persons examined was very small (Rasmussen et al., 1988). Chia et al. (1996) found that 25% of the sperm obtained from 85 TCE-exposed workers in an electronic factory had normal morphology, which is lower than the percentage considered normal by the World Health Organisation (WHO). Sperm density was reduced in workers exposed to higher concentrations, but was within the normal variation. Neither of these studies provided clear evidence for effects of TCE an the sperm (Lamb and Hentz, 2006).

Elevated concentrations of TCE metabolites were found in semen of eight mechanics who had used TCE and who were classified as infertile according to WHO criteria (Folkert et al.,

2003). Dichloroacetyl adducts and DCVC was found in the epididymus and the efferent ducts of rats (DuTeaux et al., 2003).

Windham et al. (1991) reported increased odd ratios for spontaneous abortion among women exposed occupationally to TCE. Sallmén et al. (1995) discussed a possible increase of the time-to-pregnancy among women exposed to solvents including TCE. Because of mixed exposure to others solvents and possible bias in exposure reporting, this study may not be used for risk assessment.

Taskinen et al. (1989) and Sallmén et al. (1998) did not find associations between the pregnancy outcome and paternal exposure, if specifically restricted to TCE (with differing results for organic solvents in general).

*Developmental toxicity*

No epidemiological studies with occupational inhalation exposure have been located, in which a significant risk for teratogenic effects was specifically related to TCE. However, one study reported an insignificantly elevated risk for abortions related to TCE (Taskinen et al., 1994), and some studies linked risks for developmental effects to exposure to "solvents" in general (Hardin et al., 2005).

Watson et al. (2006) recently reviewed a total of 16 epidemiological studies, 5 of which addressed specifically the question whether TCE contributes to congenital heart disease (CHD), all others may have included TCE but are related to solvents and/or degreasing agents in general, thus not permitting a final conclusion regarding TCE. According to this review, Goldberg et al. (1990) interviewed parents of 246 children with CHD in an area contaminated with up to 239 ppb TCE. Exposure of the mothers could not be determined. Even though there was a significant difference to the control, the incidence of CHD was 6.8/1000, which is well within the background CHD rate. The study was criticised for inappropriate selection of the control group (Hardin et al., 2005). Bove et al. (1995) evaluated the birth register in 75 towns in Northern New Jersey and retrieved 346 infants with CHD. The CHD incidence in this study population was 4/1000. The average contamination of drinking water was 55 ppb. The odds ratio pointed to an insignificantly elevated risk for CHD. Lagakos et al. (1986) reported an the well-known Woburn contaminated site, where the contamination of the drinking water was 267 ppb TCE (with lesser amounts of other contaminants). 43 cases with CHD were identified. A correlation between TCE and CHD was not determined. Other malformations were alleged to be linked to TCE exposure (ear/ear and CNS/chromosomal/oral cleft malformations). An interviewer bias is judged as likely by Watson et al. (2006). ATSDR (1997) investigated a U.S. Marine Corps base in North Carolina with 141 infants born to mothers with short-term TCE exposure and 31 infants of mothers with long-term TCE exposure. The TCE concentration in drinking water varied between 20 and 1400 ppb. No link between TCE exposure and CHD was reported. The birth weight was significantly reduced in males. However, exposure of TCE could not be quantified. Yauck et al. (2004) performed a case-control study in Milwaukee, Wisconsin. The case group consisted of 245 infants with CHD. The amount of TCE was not quantified. The residences of the mothers were within 1.32 miles of TCE emission sources. Older exposed mothers were regarded to be at higher risk to give birth to a child with CHD compared to non-exposed older mothers. Younger mothers were not at higher risk. The group of infants with CHD born to older mothers was rather small (8 of 245; mothers age 38 years). Also, the authors debated the many uncertainties of the study (Scialli and Gibb, 2005). Reviewers concluded from epidemiology that there is insufficient evidence for an elevated risk for CHD after environmental TCE exposure (Hardin et al., 2005, Watson

et al., 2006). However, the negative evidence (no increased risk for CHD) is not very strong as well (Watson et al., 2006).

### 3.8.2 Animal data

*Fertility*

A number of inhalation studies have been performed with experimental animals. Rats did not show adverse effects on male reproductive parameters at 100 ppm (546 mg/m$^3$) (NIOSH, 1980), but after exposure to 376 ppm (2055 mg/m) TCE. At this concentration, testes weights were reduced and sperm counts and motility were decreased (Kumar et al., 2000, 2001).

In mice, the results from three studies are contradictory. There were no changes in sperm parameters after exposure to 200 ppm (1090 mg/m$^3$) TCE in one study (Land et al., 1981), whereas the NIOSH study reported a two-fold increase in abnormal sperm at 100 ppm (546 mg/m$^3$) and above (NIOSH, 1980). No adverse effects on testis weight, sperm count or sperm morphology were reported in a study by Xu et al. (2004) after exposure of mice to 1000 ppm (5460 mg/m$^3$) TCE for up to 6 weeks. However, this concentration decreased the number of sperm bound per egg and the number of fertilised eggs.

Oral exposure of rats to 100 mg/kg • d did not result in adverse effects in one study (Zenick et al., 1984).

No effects on sperm concentration or motility was observed, when male Sprague-Dawley rats or Simonson albino rats received 0.2% or 0.4% TCE in drinking water (emulsified in vehicle; according to the authors corresponding to 1.6-2.0 and 3.4-3.7 mg TCE/kg • d; this conversion is not fully reproducible). However, slight changes were observed in the rat efferent ductile epithelium, sperm exhibited lipid peroxidation, oxidised proteins were found on the spermatozoa from treated animals and *in vitro* fertilisation was adversely affected (DuTeaux et al., 2004). Lamb and Hentz (2006) did not attribute toxicological relevance to these findings, because *in vitro* fertilisation effects are regarded as being not reflective of fertility effects *in vivo* and the low number of animals used in that study would preclude further conclusions. However, concentrations of 0.45% (with 3% vehicle, no dose given) in the drinking water for 2 weeks were recently reported to also affect the fertility of female rats (Wu and Berger, 2005). This report was only published as an abstract.

At much higher doses of TCE, clear cut effects on the fertility of mice were observed. An NTP study showed adverse effects in males (sperm motility, weight of right testes and seminal vesicle) at 845 mg/kg and above, but not below (NTP, 1985).

In summary, unequivocal reproductive effects in experimental animals were only observed at oral doses that were generally toxic with a NOAEL of 100 mg/kg • d after oral application. No adverse reproductive effects are expected at inhalation exposure to 100 ppm (546 mg/m$^3$; NOAEC).

*Developmental toxicity*

TCE has been shown to lead to heart malformations in chick embryos (Elovaara et al., 1979; Loeber et al., 1988). Experimental studies and mechanistic considerations provide evidence that in chickens the stage of development may be crucial for exerting effects at very low doses (Drake et al., 2006, Robbiano et al., 2004). In inhalation studies with rodents, most did not show teratogenic responses, including one study according to OECD guidelines

(Zablotny et al., 2002). In two rat studies, skeletal and soft tissue variations were observed at high concentrations with concurrent maternal toxicity, resorptions were significantly increased and foetal body weights were reduced (Dorfmueller et al., 1979; Hurtt et al., 1993). The effect level was 1800 ppm (9840 mg/m$^3$) or above.

No increased incidences of cardiac malformations were reported after gavage of 500 mg TCE/kg • d an gestation day 6-15 to rats (Fisher et al., 2001). However, "abnormal hearts" were observed in rats exposed to TCE before and during gestation at high concentrations of 1100 mg/l in drinking water (Dawson et al., 1993). In a recent study by Johnson et al. (2003) with rats exposed to TCE in drinking water during gestation (GD 0-22; 0 µg/l, 2.5 µg/l, 250 µg/l, 1.5 mg/l, 110 mg/l) cardiac defects were also observed, when foetuses were examined. However, no dose-response relationship was demonstrated, the report consisted of mixed new and earlier data and the study did not include a concurrent control (Hardin et al., 2005). Finally, a study with direct intrauterine delivery of TCE also showed an increased incidence of cardiac malformations at 1500 mg/l TCE in rats (which is above the maximum solubility in water), but not at 1.5 mg/l (Dawson et al., 1990).

Narotsky et al. (1995a,b) reported a study, in which where F344 rat pups showed a dose-dependent increase of eye defects (anopthalmia, microphthalmia). After oral exposure of the dams to 0, 475, 633, 844 and 1125 mg TCE /kg • d, the incidence in the offspring was 1%, 5.3%, 9.2%, 11.7% and 30%, respectively. The results indicate that TCE and its oxidative metabolites can disrupt ocular development in rats at high doses. EPA (2001) derived a $BMDL_{10}$ of 133 mg/kg • d for this study. Warren et al. investigated the respective dose-response relationship more closely and analysed the potency of the metabolites contributing to effects an eye development. They concluded that this developmental effect would only occur at higher doses although a causal relationship to TCE exposure may not be ignored (Warren et al., 2006).

The potential for trichloroethylene (TCE) (and perchloroethylene) to induce developmental toxicity was investigated in Crl:CD (SD) rats whole-body exposed to target concentrations of 0, 50, 150 or 600 ppm TCE or 0, 75, 250 C for six hours/day, seven days/week on gestation day (GD) 6-20 and 6-19, respectively. Actual chamber concentrations were identical to target. The highest exposure levels exceeded the limit concentration (2 mg/L) specified in the applicable test guidelines. Maternal necropsies were performed the day following the last exposure. Dams exposed to 600 ppm TCE exhibited maternal toxicity, as evidenced by decreased body weight gain (22% less than control) during GD 6-9. There were no maternal effects at 50 or 150 ppm TCE and no indications of developmental toxicity (including heart defects or other terata) at any exposure level tested. Therefore, the TCE NOEC for maternal toxicity was 150 ppm, whereas the embryo/fetal NOEC was 600 ppm (Carney et al. 2006).

## 3.9 Summary of critical endpoints of toxicity and related modes of action

The critical toxicity of trichloroethylene (TCE) is its carcinogenic effect. However, since the carcinogenic effect of TCE may be strongly linked to non-neoplastic organ toxicity, also other systemic effects, especially renal toxicity, become relevant endpoints for the assessment as well. Moreover, there are indications of autoimmune effects and reproductive toxicity, but such data are currently insufficient for a valid assessment. Sensory irritation may occur at similar or higher concentrations compared to (pre-narcotic) CNS effects.It is therefore not regarded as a critical endpoint for TCE risk assessment related to the workplace.

### *3.9.1 Systemic* effects

Based an a subacute study with volunteers exposed to 100 and 200 ppm (546-1090 mg/m$^3$) TCE and on subsequent Monte-Carlo simulation, a conservative NOAEC of 30 ppm (165 mg/m$^3$) was modelled for CNS effects by Simon et al. (1997). Many studies reported CNS effects like fatigue or drowsiness. Formerly, the protection from CNS effects was regarded as decisive for setting an OEL for TCE. Other systemic effects (notably renal toxicity) are today seen in the foreground as the protection from those effects also minimises the risk of carcinogenicity.

In a cross-sectional occupational field study, 70 workers exposed to TCE were examined for possible renal dysfunction by Green et al. (2004). The mean exposure concentration was 32 ppm (175 mg/m$^3$; range 0.5-252 ppm). The workers showed some minor subclinical alterations in renal functional parameters. Exposed workers eliminated higher concentrations of formic acid and methylmalonic acid and had elevated urinary N-acetylglucosaminidase (NAG) and albumin levels (although the latter two parameters did not correlate with the TCA concentrations in urine). This level may be regarded as a marginal LOAEC for nephrotoxicity. At slightly lower concentrations, a NOAEC may be established based on another small study, but basically confirming the results of the study by Green et al. (2004): Seldén et al. (1993) reported no increase of NAG excretion in workers chronically exposed to 6-10 ppm (33-55 mg/m$^3$) TCE.

Hepatotoxic effects are not analysed in detail for humans. From experimental animal experiments it may be expected that adverse liver effects occur at similar or higher doses than kidney toxicity. Therefore, it is plausible to assume that protection from kidney effects does also account for potential liver effects.

*3.9.2 Autoimmune effects*

Occupational inhalation exposure to TCE at low concentrations (mean 6.4 ppm, 35 mg/m$^3$) is associated with significant immunological reactions (activity changes in interferon-gamma, interleukin-2, interleukin-4) (Lavicoli et al., 2005). Similar effects were observed in animal studies with oral chronic application of TCE in drinking water at moderately elevated doses (NOAEL 21 mg/ kg • d; LOAEL 100 mg/ kg • d) (Griffin et al., 2000). At the LOAEL, effects observed were consistent with autoimmune hepatitis. Applying a conservative default route-to-route extrapolation, a NOAEL of 21 mg/m$^3$ (4 ppm) appears plausible. The effects after prolonged exposure to higher doses are similar to the defects that have been linked with the development of several idiopathic autoimmune diseases such as lupus nephritis, multiple sclerosis, autoimmune haemolytic anaemia and arthritis in both humans and mice (Blossom et al., 2004). Chronic exposure to trichloroethylene in contaminated drinking water had been associated with *lupus erythematosus* in earlier studies (Kilburn and Warshaw, 1992). However, the data in humans need to be confirmed, because this single report (Iavicoli et al., 2005) is of limited reporting quality. The relative sensitivity of the mouse strain used for experimental studies precludes a quantitative use of the results for human risk assessment.

*3.9.3 Reproductive Toxicity*

No adverse effects on human male or female fertility were observed for workplace exposures to concentrations, at which no other systemic effects occurred. Similar conclusions were recently derived for male fertility by Lamb and Hentz (2006). However, effects on in vitro fertilisation capacity of rat sperm and slight oxidative damage to the excurrent ducts in rats at much lower doses (observed already at 1.8 mg/kg • d) after oral uptake of TCE (DeTeaux et al., 2004) deserve further clarification, especially in relation to the doses applied and the adverse nature of the effects.

TCE potentially exerts developmental effects (mainly congenital heart disease and eye malformations). However, eye malformations would only be expected at high doses, at which other toxic effects are observed (Warren et al., 2006). Congenital heart disease was demonstrated in chick embryos. Mechanistic considerations also show a link between TCE (and TCA) exposure and developmental impairments for the heart of mammals (Selmin et al., 2005). Epidemiological evidence does not support the occurrence of this teratogenic effect after human uptake of TCE from contaminated drinking water, and animal studies demonstrate such effects at much higher doses than those relevant for OEL derivation (Dawson et al., 1990). In addition, positive results are contradicted by qualified negative studies (Zabiotny et al., 2002). An overall evidence for development of congenital heart disease due to TCE exposure in relevant doses is not sufficiently supported (Watson et al., 2006, Hardin et al., 2005).

*3.9.4 Genotoxicity and carcinogenicity*

A weak mutagenic effect of TCE in vitro may be assumed (Harth et al., 2005). Evidence exists that TCE leads to specific mutations in the kidney at the von-Hippel-Lindau (VHL) tumour suppressor gene (Brauch et al., 1999, 2004). Most appropriately conducted animal tests *in vivo* for genotoxicity were negative. Human *in vivo* data are contradictory and do not permit firm conclusions.

However, some of the metabolites are genotoxic, especially those formed *via* the minor reductive pathway of metabolism, if not eliminated as mercapturic acids. DCVC may possibly react with DNA, and chlorothioketenes are genotoxic (Moore and Harrington-Brock, 2000; Harth et al., 2005). In addition, the assumed minor oxidative metabolite dichloroacetic acid (DCA) is genotoxic in several *in vitro* and *in vivo* assays (IARC, 1995), but is probably of minor relevance in TCE metabolism in humans.

Therefore, it is plausible that genotoxicity may contribute to the genesis of specific local tumours, but that genotoxicity is probably not the general major driving force for carcinogenesis of TCE as with classic DNA-alkylating agents. In general, TCE presumably acts *via* a number of different mechanisms in parallel, some of which result in tumours in experimental animals and in humans (Lock and Reed, 2006).

Conflicting results regarding *liver tumours* were obtained in epidemiological studies. In a recent combined assessment (liver and biliary passage cancers in humans from most existing epidemiological studies), the overall risk for these cancers was only slightly and insignificantly elevated. In those few studies, in which liver cancer was assessed separately from biliary cancer, the risk appears more strongly increased but, is still only insignificantly (Scott and Chiu, 2006). In terms of mechanism, it is assumed that, if this tumour location is relevant in humans at all, liver tumours would be induced by a different mode of action in humans compared to mice. For mice, the TCE metabolite trichloroacetic acid may lead to peroxisomal proliferation in livers via the peroxisome proliferator-activated receptor a (PPARα). This mechanism is supported by recent studies with wild-type and PPARα knock-out mice (Luaghter et al., 2004). The respective PPARα receptors are only found to a minor degree in humans (Smith et al., 2005).

In summary, there is no clear evidence for TCE-induced human liver tumours from epidemiology. Genotoxicity is probably not the determining mode of action for tumours in the liver. However, it is assumed that protection from the risk for kidney tumours would equally protect from the risk for liver tumours. This is based on a similar cytotoxic potency of TCE in the liver and the kidney and on the assumption that a strongly sub-linear dose-

response relationship would be the appropriate and still conservative risk extrapolation method for both tumour locations (Lock and Reed, 2006).

For other possible tumour locations including *non-Hodgkin's lymphoma* (NHL), a risk quantification is again impossible. Even though there is some evidence from a meta-analysis that NHL are indeed possible tumours in humans (Mandel et al., 2006), it is not believed that genotoxicity is an important factor for this type of tumour in the case of TCE. SCOEL considers the evidence for an association of NHL and TCE exposure as being too week to require regulatory attention.

For *kidney tumours*, the evidence from human studies is much stronger, and especially supported by the most recent studies of Brüning et al. (2003), Raaschou-Nielsen et al. (2003) and Charbotel et al. (2006). The results of animal studies in the male rat and data on metabolism and modes of action are supportive of a relevant renal carcinogenicity of TCE (Lock and Reed, 2006). Genotoxicity may contribute to the mechanism because DCVC and its respective β-lyase products have a genotoxic potential. Moreover, mutations of the VHL gene in the kidney tumours of TCE-exposed humans are plausibly associated with a loss of tumour suppression and subsequent growth of renal cell tumours. In general, a mechanism can reasonably be assumed, where kidney toxicity combined with genotoxicity in the kidney are co-carcinogenic factors (Harth et al. 2005). Importantly, tumours in human kidneys were only observed after occupational TCE exposure to very high concentrations, which are clearly nephrotoxic. Such exposures clearly exceeded former exposure limits of 50 ppm, and peak exposures of several hundred ppm very likely involved. At these high dose ranges, it is known that the toxification of TCE *via* the reductive glutathione-pathway is proportionally increased, compared to lower doses where glutathione-dependent metabolism is only marginal. This is because the oxidative CYP-dependent metabolism is saturable. Both aspects, the impact of cytotoxicity and the relative increase of glutathione-dependent metabolism at high doses of TCE, make a sub-linear dose-response relationship at lower exposure concentrations highly plausible (Harth et al., 2005; Lock and Reed, 2006). Therefore, a linear extrapolation of kidney tumour risks should be limited to clearly nephrotoxic concentrations. Even this approach is still conservative, as the relative influence of glutathione-dependent metabolism at slightly nephrotoxic exposure concentrations has probably already decreased, compared to the much higher concentrations at which tumours have been observed.

**Recommendation**

As outlined above, the development of cancer in persons occupationally exposed to TCE is the decisive endpoint for measures of prevention, including setting of an OEL. These matter have been discussed very recently both in Europe (Harth et al. 2005) and in the United States (Chiu et al., 2006a; National Research Council/Committee on Human Health Risks of Trichloroethylene, 2006), and remaining research needs have been addressed. With respect to liver cancer, humans can reasonably be assumed to be much less susceptible than rodents (National Research Council, 2006). The available data on non-Hodgkin lymphoma related to human TCE exposure appear not consistent so far.

Although open questions still remain, it is clear that the key target of human trichloroethylene toxicity and carcinogenesis is the kidney, notably the proximal tubule. Based on several recent studies (see above), human renal cell cancer has been observed in highly and repetitively exposed workers, having used TCE mostly in metal degreasing activities. The mode of action is likely to involve multiple pathways, as discussed above. Several lines of evidence suggest a sub-linear dose-tumour response, as outlined in detail in the preceding chapter. Observations in

experimental systems, as well as in occupationally exposed and diseased persons, lead to the conclusion that human renal cell cancer risk is avoided if exposure to nephrotoxic concentrations of TCE do not occur, including TCE concentrations leading to sub-clinical renal changes that can be monitored by urinary excretion of suitable marker proteins. In the occupational field study by Green et al. (2004) on 70 workers, the mean TCE exposure was 32 ppm (range 0.5-252 ppm). In this cohort some minor sub-clinical alterations in renal functional parameters were observed. This is corroborated by data of Seldén et al. (1993), who found no increase in urinary excretion of the NAG marker protein in workers exposed to a range of 6-10 ppm TCE.

Against this background and with reference to its strategy in the derivation of OELs for carcinogens and mutagens (Bolt and Huici-Montagud, 2008), SCOEL regards TCE as a "*genotoxic carcinogen, for which a practical threshold is supported by studies on mechanisms and/or toxicokinetics*" (group C).

Hence, a health-based OEL may be established based on a NOAEL in exposed humans, which is again related to the avoidance of renal toxicity. Based on the studies of Green et al. (2004) and Seldén et al. (1993), an OEL (TWA) of 10 ppm is therefore proposed for TCE.

As high TCE peak exposures have been described as being critical in the development of human renal cell cancer, a STEL can provide additional protection against potentially hazardous over-exposures. Considering a mean TCE exposure level of 32 ppm reported in the aforementioned field study of Green et al. (2004), a STEL of 30 ppm is proposed, in order to ensure an adequate safety margin to potentially nephrotoxic exposure situations.

*Biological monitoring*

Biological monitoring of TCE is well established by measuring TCA concentrations in the urine after shift. A concentration of 10 ppm TCE in air (i.e., the proposed OEL) corresponds to 20 mg TCA/l urine (Lehnert and Greim, 2003).

Hence, corresponding to the recommended OEL a BLV is proposed of 20 mg trichloroacetic acid (TCA) per litre urine. It should be noted that other chlorinated hydrocarbons, i.e. 1,1,1,-trichloroethane and perchloroethylene, are also converted to trichloroacetic acid, which is excreted in the urine. However, quantitatively 1,1,1,-trichloroethane and perchloroethylene are mostly exhaled unchanged, and only 15% or less of these compounds is metabolised. In industrial practice this must be observed. In view of the very long half-life time of trichloroacetic acid (about 100 h; Henschler and Lehnert, 1983) the urine sampling should be by the end of the last shift of a workweek or a shift period.

In the industrial practice, the monitoring of external and internal exposure can reasonably be supplemented by application of biological effect markers for slight and subclinical nephrotoxicity. This refers to the excretion of marker proteins of tubular damage in the urine (Brüning et al., 1999). For this purpose, NAG (Green et al., 2004; GST-alpha (Brüning et al., 1999a) and $beta_2$-microglobulin (Bolt et al. 2004) have been used successfully. Reference can therefore be made to these publications.

*Other assignments*

A skin notation is recommended, as considerable percutaneous absorption was evidenced in earlier toxicokinetic studies (Stewart and Dodd 1964, Sato and Nakajima 1978). This was supported by Tsuruta (1978) after application of neat TCE to mouse skin.

No indication exists for a relevant skin sensitising potency of TCE. No reports on respiratory sensitisation are available.

At typical workplace exposure concentrations, no analytical difficulties are expected.

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