The MAK Collection for Occupational Health and Safety

Tetrachloroethylene

MAK Value Documentation, addendum – Translation of the German version from 2017

A. Hartwig[1,*], MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

***** *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

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Tetrachloroethylene / 1,1,2,2-Tetrachloroethene

MAK Value Documentation

A. Hartwig[1,*], MAK Commission[2,*]

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated tetrachloroethylene [127-18-4] to derive a maximum concentration at the workplace (MAK value), considering all toxicity endpoints. Available study reports and publications are described in detail.
Results from human studies do not point to a genotoxic potential of tetrachloroethylene. In vitro and in vivo studies in mammalian cells do not show a distinct genotoxic potential. From epidemiologic and animal studies there is concern that tetrachloroethylene could be carcinogenic for humans; therefore, tetrachloroethylene has been classified in Carcinogen Category 3B. However, since carcinogenic effects are judged to be not predominantly caused by genotoxic mechanisms, a MAK value can be derived.
Neurotoxicity is considered the most sensitive endpoint for tetrachloroethylene. In volunteers, repeated daily 4-hour inhalation exposure caused small but significant effects on visual evoked potentials. The NOAEC was 10 ml/m³, but as only weak effects were observed at the LOAEC of 50 ml/m³, 20 ml/m³ is regarded as the NAEC. As a doubling of uptake is expected under workplace conditions, a MAK value of 10 ml/m³ has been set. As the critical effect is systemic, tetrachloroethylene is assigned to Peak Limitation Category II. The default excursion factor of 2 is set as the half-life in the central nervous system is unknown.
There is limited evidence suggesting that women working in a dry-cleaner have an increased risk of spontaneous abortion. But the limited validity of the studies is not sufficient to prove a causal relationship. In developmental toxicity studies, NOAECs for developmental toxicity of 65 and 217 ml/m³ in rats, 500 ml/m³ in rabbits, and a LOAEC of 217 ml/m³ in mice were obtained. The NOAEC for behavioural toxicity in the offspring of treated rats was 100 ml/m³. The differences between these NOAECs as well as the LOAEC and the MAK value are considered so large that damage to the embryo or foetus is unlikely when the MAK value is observed. Therefore, tetrachloroethylene is classified in Pregnancy Risk Group C.
Sensitization is not expected due to results of animal studies and experience in humans. Skin contact is expected to contribute significantly to the systemic toxicity of tetrachloroethylene. Therefore, designation with an "H" is confirmed.

Keywords

tetrachloroethylene; perchloroethylene; per; ethylene tetrachloride; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany
[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Tetrachloroethylene

[127-18-4]

Supplement 2017

MAK value (2016)	**10 ml/m³ (ppm) ≙ 69 mg/m³**
Peak limitation (2016)	**Category II, excursion factor 2**
Absorption through the skin (1974)	**H**
Sensitization	**–**
Carcinogenicity (1988)	**Category 3B**
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

EKA (2001)

Tetrachloroethylene (air)	**Tetrachloroethylene (whole blood)**
10 ml/m³	**0.2 mg/l**
20 ml/m³	**0.4 mg/l**
30 ml/m³	**0.6 mg/l**
50 ml/m³	**1.0 mg/l**

Synonyms	perchloroethylene tetrachloroethene
Chemical name	1,1,2,2-tetrachloroethene
CAS number	127-18-4
Structural formula	$Cl_2C{=}CCl_2$
Molecular formula	C_2Cl_4
Molar mass	165.83 g/mol
Melting point	–22.3 °C (SRC 2014)
Boiling point	121.3 °C (SRC 2014)
Density at 20 °C	1.623 g/cm³ (IARC 2014)
Vapour pressure at 25 °C	24.7 hPa (SRC 2014)

log K_{OW}[1)]	3.4 (SRC 2014)
Solubility	206 mg/l at 25 °C (SRC 2014)
1 ml/m³ (ppm) ≙ 6.881 mg/m³	**1 mg/m³ ≙ 0.145 ml/m³ (ppm)**

Documentation for tetrachloroethylene was published in 1974, followed by supplements in 1983, 1988 (these three documents were combined into one translation: documentation "Tetrachloroethylene" 1992) and 1997 (supplement "Tetrachloroethylene" 1997).

This supplement is based primarily on the reviews by NEG (2003), SCOEL (2009), US EPA (2012), ATSDR (2014) and IARC (2014).

1 Toxic Effects and Mode of Action

Tetrachloroethylene is readily absorbed by inhalation, through the skin and from the gastro-intestinal tract and is exhaled mainly in unchanged form by humans and animals. A small fraction of the tetrachloroethylene is metabolized, mainly via the oxidative pathway and, to a very slight extent, via the reductive pathway.

The hepatocarcinogenicity observed in mice is attributed to the metabolites of oxidative bioactivation, whereas the nephrotoxic and nephrocarcinogenic effects found in rats are caused by the conversion products of glutathione conjugation. Like all halogenated hydrocarbons, tetrachloroethylene induces central nervous depression. Neuropsychological tests carried out after long-term exposure at the workplace revealed significant differences between persons exposed to high levels and low levels of the substance, suggesting a LOAEC (lowest observed adverse effect concentration) of 40 ml/m³. After repeated short-term exposure to tetrachloroethylene, effects were observed at 50 ml/m³ during the determination of event-related potentials in the electroencephalogram.

Tetrachloroethylene causes skin irritation.

The results of in vitro and in vivo studies of genotoxicity showed that tetrachloroethylene has only a very weak genotoxic potential. In vivo, high doses induced DNA single strand breaks in the liver and kidneys or micronuclei in the liver.

Epidemiological studies yielded positive associations for bladder cancer. Tetrachloroethylene induced hepatocellular adenomas and carcinomas, and haemangiosarcomas of the spleen and liver in mice, and mononuclear leukaemia and kidney tumours in rats.

The evidence for an association between the employment of women in dry cleaning and an increased risk of spontaneous abortions is not strong enough to establish a causal relationship because the studies are of limited statistical power. Studies of developmental toxicity after inhalation reported initial effects of minimal toxicological relevance on the foetal weights of rats at 249 ml/m³ and above. In another study, reduced foetal weights and an increase in the number of delayed ossifications and malformations were observed at 652 ml/m³. Inhalation exposure in mice caused reduced body weights and delayed ossification at 300 ml/m³ and an increased number

1) octanol/water partition coefficient

of malformations of the internal organs at 217 ml/m³. In rabbits, post-implantation losses were detected at 652 ml/m³. Studies that investigated developmental neurotoxicity in rats reported decreased performance in behavioural tests (ascent and rotarod test) at 900 ml/m³.

There are no conclusive positive findings available from humans for sensitizing effects on the skin or respiratory tract. A valid local lymph node assay in mice reported weakly positive results only, which in the light of the irritation caused by tetrachloroethylene are to be regarded as negative.

2 Mechanism of Action

Hepatotoxicity

Trichloroacetic acid, the main metabolite of tetrachloroethylene, caused hepatocellular adenomas and carcinomas in mice, but not in rats (supplement "Trichloressigsäure" 2016, available in German only). Therefore, the liver tumours observed in mice after exposure to tetrachloroethylene may have been caused by the formation of trichloroacetic acid during the oxidative metabolism of tetrachloroethylene (Odum et al. 1988; Sweeney et al. 2009), although this assumption is a matter of controversy because other metabolites and several mechanisms might be involved (US EPA 2012).

Under identical exposure conditions, the concentrations of covalent protein adducts from oxidative metabolism are much lower in the blood of humans than in the blood of rats (see Section 3.2, Pähler et al. 1999 a, b). It can thus be assumed that compared with rats, humans are less sensitive to the hepatotoxicity caused by tetrachloroethylene. Mice are assumed to be more sensitive to hepatotoxicity than rats because the capacity to metabolize tetrachloroethylene by oxidation is several times higher in mice than in rats (supplement "Tetrachloroethylene" 1997).

Nephrotoxicity

The formation of dichlorothioketene in the kidneys as a reactive metabolite of glutathione-dependent metabolism has been suggested as a mechanism of nephrotoxicity and nephrocarcinogenicity. However, the metabolic flux via glutathione conjugation and β-lyase cleavage seems to be much lower in humans than in rats. This is supported by the fact that the capacity of the human liver to form trichlorovinylglutathione is much lower than that of the rat liver (see Section 3.2, Dekant et al. 1998), the elimination of N-acetyl-S-trichlorovinyl-L-cysteine is one order of magnitude lower in humans under identical exposure conditions (see Section 3.2, Völkel et al. 1998) and the β-lyase activity in the human kidneys is also about one order of magnitude lower (Green et al. 1990). In addition, covalent protein adducts from the glutathione-dependent β-lyase pathway were not detected in the blood of humans unlike in the blood of rats that had been exposed under identical conditions (see Section 3.2, Pähler et al. 1999 a, b). It can thus be assumed that compared with rats, humans are markedly less sensitive to nephrotoxicity and possible nephrocarcinogenicity caused by tetrachloroethylene.

Furthermore, the formation of sulfoxides from N-acetyl-S-trichlorovinyl-L-cysteine and trichlorovinylcysteine was detected in rat liver microsomes; these sulfoxides

are α,β-unsaturated compounds that may cause cytotoxic effects in kidney cells of rats and are more toxic than their parent compounds (Elfarra and Krause 2007; Werner et al. 1996).

Germ cell mutagenicity

A dominant lethal test in rats yielded negative results. However, like the β-lyase-dependent pathway in the kidneys, the formation of reactive metabolites might also affect the germ cells.

At least 11 enzymes with β-lyase activity have been detected in the tissues of mammals to date. Glutamine transaminase K (GTK) and mitochondrial aspartate aminotransferase are the most important enzymes. These enzymes are widespread in the tissues of mammals. For example, GTK is detected in almost all examined tissues of rats (Cooper et al. 2010; Cooper and Pinto 2006).

In rats, this specific GTK activity is detected in the kidneys and liver as well as in the testes and seven other tissues. Determined on the basis of the conversion of DCVC (dichlorovinylcysteine, a metabolite of trichloroethylene), the β-lyase activity was found to be 3.05 or 1.32 nmol/min/mg protein in the kidneys, 0.84 or 0.22 in the liver and 0.40 or 0.07 in the testes in the presence or absence of an activating α-keto acid, respectively (Jones et al. 1988). Therefore, β-lyase activity is 8 or 19 times higher in the kidneys than in the testes.

The authors concluded from a study with trichloroethylene in rats that there is only little evidence of β-lyase activity in the epididymis and efferent ducts, the connecting duct between the testis and epididymis (DuTeaux et al. 2003).

Solvent effect/effects on the CNS

Tetrachloroethylene is a highly volatile chlorinated hydrocarbon that is used as a solvent. The sedative effects of this type of substance, which occur primarily after acute exposure, are probably caused by effects on ligand-gated and voltage-gated ion channels in the CNS (Bushnell et al. 2010). This end point was examined in detail for tetrachloroethylene (Bale et al. 2005). In vitro experiments yielded IC_{50} values of about 0.02 mM (human nAChR and nAChR in rats) for the inhibition of various nicotinic acetylcholine receptors of humans and rats. Acetylcholinergic neurotransmission plays an important role in cognitive processes that are associated with visual attention (Klinkenberg et al. 2011); therefore, this neurotoxic mechanism might be involved in the behavioural toxicity of tetrachloroethylene.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

3.1.1 Absorption

Tetrachloroethylene is readily absorbed by inhalation and after oral or dermal exposure (supplement "Tetrachloroethylene" 1997).

After inhalation, equilibrium is reached only after several hours. Systemic absorption is proportional to the respiration rate, the duration of exposure and the con-

centration of exposure. After 6-hour exposure to a concentration of 1 ml/m^3, peak levels of tetrachloroethylene were detected in the venous blood of humans towards the end of the exposure period. The alveolar retention determined in volunteers was on average 65% (IARC 2014; US EPA 2012).

The blood:air partition coefficient of tetrachloroethylene in humans was given as 10 to 20 (US EPA 2012).

Likewise, animal studies showed that tetrachloroethylene was readily absorbed after inhalation exposure (IARC 2014; US EPA 2012). The blood:air partition coefficients of tetrachloroethylene for rodents are in the range from 13 to 21 (IARC 2014).

Quantitative estimates of oral absorption in humans are not available. A case study of a 6-year-old boy reported a concentration of 21.5 µg/ml blood after ingestion. Tetrachloroethylene is almost completely absorbed by rats, mice and dogs after ingestion (IARC 2014; US EPA 2012).

Dermal absorption of tetrachloroethylene from the gaseous phase by humans makes up only about 1% of the amount absorbed by inhalation (IARC 2014). Animal studies confirmed slight dermal absorption from the gaseous phase compared with the amount absorbed by inhalation (US EPA 2012).

Dermal absorption of tetrachloroethylene from contaminated soil material was investigated in rats and humans. Permeability coefficients of about 0.1 cm/hour in rats were calculated by analysing tetrachloroethylene in the exhaled air and by means of physiologically based pharmacokinetic (PBPK) modelling. Lower values averaging 0.0009 cm/hour were determined for humans. Immersion of a hand in a mass containing a tetrachloroethylene dose of 30 g/kg led to a total amount absorbed of 20.2 ± 7.77 mg in 3 volunteers within 2 hours (Poet et al. 2002). Other animal studies confirmed the absorption of tetrachloroethylene through the skin (Bogen et al. 1992; Jakobson et al. 1982; Morgan et al. 1991; Tsuruta 1975).

After the immersion of one thumb (about 20 cm^2) in tetrachloroethylene for 30 minutes, a concentration of 0.31 ml/m^3 was determined in the exhaled air. This corresponds to the uptake by inhalation after exposure to 2 to 5 times the concentration in the air over the same period (Stewart and Dodd 1964). For the area of 2000 cm^2 assumed under standard conditions, this would result in a concentration 100 times as high as in the exhaled air, namely 31 ml/m^3. Therefore, the corresponding concentration in the air for absorption by inhalation only would be 60 to 150 ml/m^3.

The penetration of liquid tetrachloroethylene through the skin led to similar results in an in vitro model with human skin and hairless guinea pig skin (permeability coefficients: 0.14 to 0.19 cm/hour) (Frasch and Barbero 2009). A permeability coefficient of 0.018 cm/hour was determined in another in vitro study in human skin (Nakai et al. 1999). In addition, a dermal penetration rate of 0.554 nmol/cm^2 and minute (5.5 µg/cm^2 and hour) was reported for tetrachloroethylene in an in vitro study in rat skin (Tsuruta 1977).

3.1.2 Distribution

Tetrachloroethylene accumulates in fatty tissue (SCOEL 2009).

Tissue examinations after accidental poisonings in humans have shown that there is wide systemic distribution of tetrachloroethylene in the blood and across all the tested organs such as the lungs, liver, heart, kidneys and brain (IARC 2014). Likewise,

animal studies demonstrated the wide distribution of tetrachloroethylene across all organs. In rats, the highest concentrations were found in the fatty tissue, liver and brain (60, 5 and 4 times higher than in the blood, respectively). Tetrachloroethylene can pass the blood–brain barrier and reach the placenta (IARC 2014).

Volunteer studies with repeated daily exposure by inhalation revealed the accumulation of tetrachloroethylene in the body and an increase in the concentrations in the blood for several days (IARC 2014).

3.1.3 Elimination

Exhalation is the main route of elimination. Regardless of the route of exposure, about 95% of the amount absorbed is exhaled in the form of unchanged substance (SCOEL 2009). At the end of exposure, the substance is eliminated in humans from the different tissues via the lungs in multiple phases with initial half-lives in the range of 5 to 20 minutes, several intermediate phases and terminal half-lives of 50 to 65 hours. About 1% to 3% of absorbed tetrachloroethylene is eliminated with the urine in the form of trichloro metabolites (predominantly trichloroacetic acid). The fraction of metabolites derived from conjugation with glutathione is considerably smaller. In addition, it is possible that the studies did not record other metabolized products including carbon monoxide, carbon dioxide, oxalic acid and additional glutathione conjugation products, such as sulfoxides and reactive thiols. Based on the most recent PBPK model estimates, it is assumed that the amounts eliminated by humans via exhalation are 90% to 99% after exposure to tetrachloroethylene by inhalation and 81% to 99% after ingestion (IARC 2014).

The half-lives in rats and mice are in the order of hours, and pulmonary elimination is virtually complete within 24 hours. This indicates that elimination is much more rapid in rodents than in humans. The percentage of unchanged tetrachloroethylene in the exhaled air is dependent on the species and concentration. As exposure levels increase, the percentage of substance eliminated in unchanged form increases, suggesting saturation of the metabolism of tetrachloroethylene. For exposures below the saturation level, the PBPK models predict the fraction of tetrachloroethylene exhaled unchanged to be 90% to 95% in rats and 40% to 80% in mice, depending on the route of uptake (IARC 2014).

3.2 Metabolism

While most of the tetrachloroethylene (about 95%) is exhaled unchanged, the remaining fraction undergoes oxidative (cytochrome P450 (CYP)-dependent) metabolism and, to a lesser extent, glutathione-dependent reductive metabolism (see Figure 1 and Figure 2). Compared with in rats and humans, oxidative metabolism is more pronounced in mice, whereas reductive metabolism plays a more important role in rats than in mice and humans. Findings from in vitro studies indicate that reductive metabolism is of lesser relevance in humans compared with in rats and mice (supplement "Tetrachloroethylene" 1997; SCOEL 2009).

The 1997 supplement (supplement "Tetrachloroethylene" 1997) described a study in which dry cleaners who worked only with tetrachloroethylene were exposed to average concentrations in the air of 50 ± 4 ml/m^3. Two workers were exposed for

8 hours daily and another two were exposed for 4 hours daily. Trichloroethanol and N-acetyl-S-trichlorovinyl-L-cysteine were identified in the urine of all workers. Trichloroacetic acid was found in the urine only after exposure for 8 hours. Compared with the total amount of trichloroacetic acid and trichloroethanol eliminated, the amount of N-acetyl-S-trichlorovinyl-L-cysteine eliminated was 3000 to 6000 times lower (Birner et al. 1996). Trichloroethanol was not detected in the urine in a later study; this was explained by possible co-exposure to trichloroethylene (Völkel et al. 1998).

An in vitro study demonstrated the CYP3A-dependent sulfoxidation of N-acetyl-S-trichlorovinyl-L-cysteine in liver microsomes of untreated male rats. Sulfoxidation was not observed in kidney or liver microsomes of untreated female rats. After CYP3A enzymes were pretreated with phenobarbital or dexamethasone, sulfoxidation was determined also in liver microsomes of females and an increase in sulfoxidation was observed in liver microsomes of males (Werner et al. 1996).

Other studies described the sulfoxidation of S-trichlorovinyl-L-cysteine in liver microsomes of rabbits and in liver and kidney microsomes of rats by flavin-dependent monooxygenase 3 (FMO3) or CYP enzymes (Elfarra and Krause 2007; Ripp et al. 1997).

Species differences between humans and rats

A study investigated the metabolism of tetrachloroethylene in Wistar rats (3 ♂ and 3 ♀) and humans (3 ♂ and 3 ♀) after inhalation exposure in exposure chambers to concentrations of 10, 20 or 40 ml/m^3 for 6 hours. Another group of rats was exposed to 400 ml/m^3. In volunteers, trichloroacetic acid was determined as the main metabolite in the urine collected at several intervals over a 78-hour period. The cumulative elimination of the trichloroacetic acid that formed as a product of oxidative metabolism was 100 times higher than that of N-acetyl-S-trichlorovinyl-L-cysteine, which is a product of the glutathione-dependent metabolic pathway. The concentrations of the two metabolites in the urine increased linearly with the increase in the exposure concentration. There was no evidence of saturation of the metabolic pathways. The concentration of dichloroacetic acid, which is probably also a product of the glutathione-dependent metabolic pathway, was below the limit of detection of about 50 ng/ml in all urine samples. Sex-specific differences were not observed in the volunteers. Trichloroacetic acid was likewise the main metabolite in the urine in rats. In addition, dichloroacetic acid was detected in the urine of the animals of both sexes. The cumulative elimination of dichloroacetic acid was one order of magnitude (factor of 10) lower than that of trichloroacetic acid. In a concentration range of up to 40 ml/m^3, the elimination of N-acetyl-S-trichlorovinyl-L-cysteine in the urine corresponded to about 1% of the amount of trichloroacetic acid. At various times after exposure, the concentration of trichloroacetic acid in the blood was much higher in rats than in humans. In rats, too, the concentration of the metabolites in urine increased linearly with the increase in the exposure concentration of up to 40 ml/m^3. In the males, a more than linear increase in the cumulative elimination of N-acetyl-S-trichlorovinyl-L-cysteine was observed at 400 ml/m^3. In the females, saturation of oxidative metabolism occurred at this concentration, and there was evidence of saturation of the glutathione-dependent pathway. At the high concentration, the males eliminated 3 times more N-acetyl-S-trichlorovinyl-L-cysteine in the urine than the

females (Völkel et al. 1998). The authors concluded that tetrachloroethylene undergoes a higher level of glutathione-dependent metabolism and higher bioactivation of the intermediate trichlorovinylcysteine by β-lyase cleavage in rats than in humans.

Another study investigated the dose-dependent formation of protein adducts in blood samples from humans and rats and in the liver and kidneys of rats after 6-hour inhalation exposure to tetrachloroethylene concentrations of 10, 20 or 40 ml/m³ (rats additionally to 400 ml/m³). Oxidative metabolism of tetrachloroethylene leads to the formation of N^{ε}-(trichloroacetyl)-L-lysine in proteins via trichloroacetyl chloride, whereas the glutathione-dependent β-lyase pathway leads to the formation of N^{ε}-(dichloroacetyl)-L-lysine in proteins via the reactive dichlorothioketene. In rats, the dose-dependent formation of protein adducts was detected in the blood and in subcellular fractions from the liver and kidneys. The highest concentrations of N^{ε}-(dichloroacetyl)-L-lysine in proteins were found in kidney mitochondria, followed by kidney cytosol. Only low concentrations were found in liver proteins. The concentrations of N^{ε}-(dichloroacetyl)-L-lysine in proteins in the blood were 5 to 10 times lower than in kidney mitochondria. After exposure to 400 ml/m³, the concentration of N^{ε}-(dichloroacetyl)-L-lysine in renal mitochondrial proteins of male rats was higher than in those of female rats. The highest concentrations of N^{ε}-(trichloroacetyl)-L-lysine in proteins were detected in microsomal and cytosolic proteins from the liver of exposed rats. In human blood samples, low concentrations of proteins containing N^{ε}-(trichloroacetyl)-L-lysine were found immediately and 24 hours after exposure. Proteins containing N^{ε}-(dichloroacetyl)-L-lysine were not detected in the blood of volunteers (Pähler et al. 1999 a, b). The authors concluded from their findings that the concentrations of covalent protein adducts in the blood of humans were much lower than in the blood of rats exposed under identical conditions. It can thus be assumed that compared with rats, humans are less sensitive to nephrotoxicity and possible nephrocarcinogenicity caused by tetrachloroethylene.

In an in vitro study, the conjugation with glutathione of tetrachloroethylene was compared in subcellular fractions from the liver and kidneys of rats, mice and humans. The formation of trichlorovinylglutathione was not observed in liver or kidney microsomes from rats, mice or humans. In liver cytosol from male rats, the rate of trichlorovinylglutathione formation (84.5 ± 12 pmol/mg per minute) was about 4 times as high as in female rats (19.5 ± 8 pmol/mg per minute) and about 3 times as high as in male and female mice (27.9 ± 6 and 26.0 ± 4 pmol/mg per minute, respectively). Low formation rates (12 ± 6 pmol/mg per minute) were determined for trichlorovinylglutathione in kidney cytosol from mice, but not from rats. There was no evidence of trichlorovinylglutathione formation in human liver fractions although glutathione S-transferase activity was detected in liver cytosol in the same order of magnitude as that in rats and mice. Therefore, in human liver samples, the rate of trichlorovinylglutathione formation was at least 20 times lower than in liver cytosol from male rats and 5 times lower than in liver cytosol from female rats (Dekant et al. 1998).

An in vitro study that was already included in the 1997 supplement (supplement "Tetrachloroethylene" 1997) reported that β-lyase activity for the cleavage of trichlorovinylcysteine in kidney cytosol from humans (and mice) was only about 5% of the corresponding value in rats (Green et al. 1990).

In summary, the β-lyase activity in the kidneys of humans is probably only low and the glutathione-dependent β-lyase pathway in humans (and probably in mice) is likely to be at least 40 times less active than that in rats (SCOEL 2009).

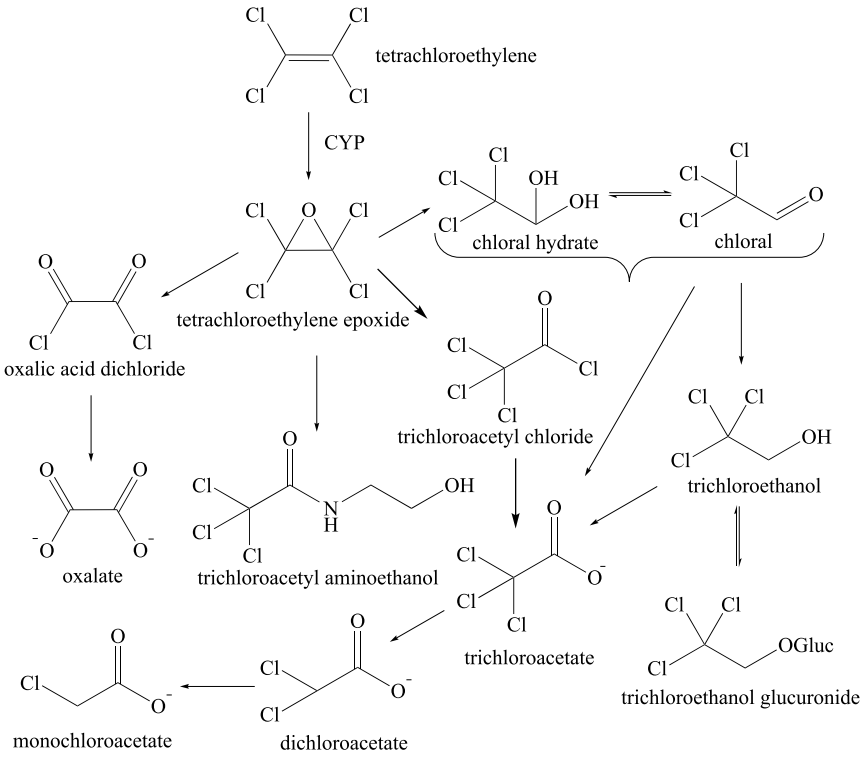

Figure 1 CYP: cytochrome P450
Oxidative metabolism of tetrachloroethylene (according to IARC 2014)

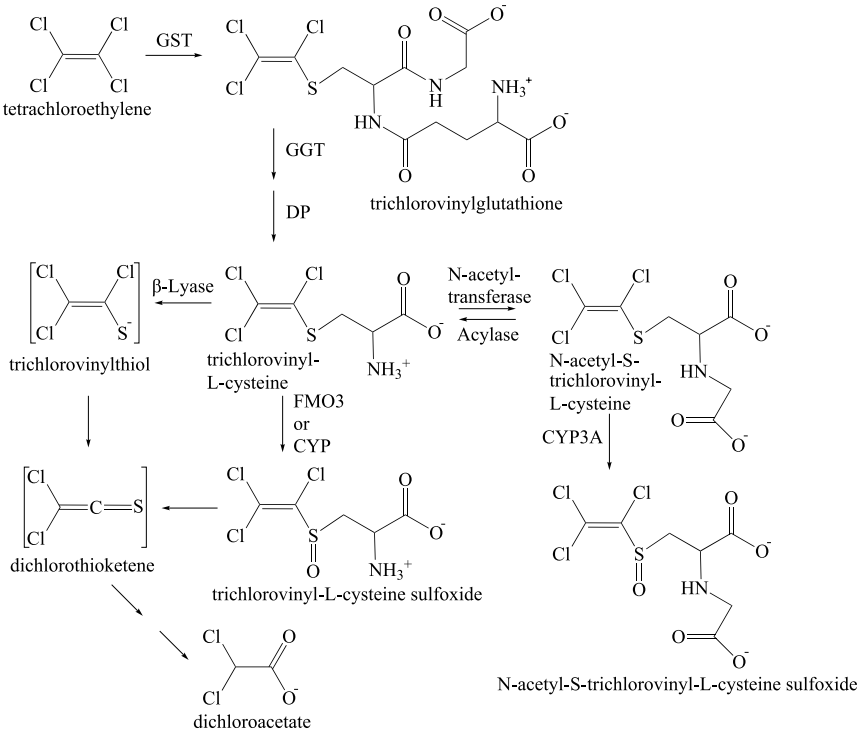

Figure 2 CYP: cytochrome P450, DP: dipeptidase, FMO: flavin-dependent monooxygenase, GGT: γ-glutamyltransferase, GST: glutathione S-transferase
Glutathione-dependent metabolism of tetrachloroethylene (according to IARC 2014)

4 Effects in Humans

Effects in humans were already described in the 1974 documentation and in the 1983 and 1997 supplements (see documentation "Tetrachloroethylene" 1992 and supplement "Tetrachloroethylene" 1997). In addition to case reports and epidemiological studies, volunteer studies are available for tetrachloroethylene. Only the studies that are relevant to the evaluation are described below.

Criteria for evaluating studies

To evaluate the quality of the studies and the end points used, the "classical" neurophysiological (for example, visually evoked potentials (VEPs); Altmann et al. 1990) and neuropsychological methods (Wechsler Adult Intelligence Scale – revised (WAIS-R); Echeverria et al. 1995) and the effects observed after exposure to tetrachloroethylene are of greater importance than effects on colour vision and contrast sensitivity (Cavalleri et al. 1994; Gobba et al. 1998). Studies in animals substantiated

that the visual system is particularly sensitive to neurotoxic effects caused by tetrachloroethylene (Boyes et al. 2009); however, the Commission regards these effects as adverse only if they contribute to effects on behaviour (visual memory performance), for example.

Additional criteria used to evaluate the studies are selection of participants, recording of exposure levels, consideration of relevant confounders, experimental design and statistical evaluation carried out (NRC 2010).

4.1 Single exposures

The effects on the CNS are the prime effects after single exposures to tetrachloroethylene by inhalation. Dizziness, drowsiness, sleepiness, loss of consciousness, nausea, headaches and tinnitus were observed as symptoms (documentation "Tetrachloroethylene" 1992; supplement "Tetrachloroethylene" 1997). The case reports of acute fatal poisonings after exposure by inhalation do not include any data for the tetrachloroethylene concentrations in the air. The concentrations determined in the blood after death were in a range between 44 and 66 mg/l (ATSDR 2014).

After exposure to an average 216 ml/m^3 for 45 minutes to 2 hours, 4 volunteers reported irritation of the eyes, fatigue, mild dizziness, congestion of the frontal sinuses and slight nasal discharge (Rowe et al. 1952).

When 6 volunteers were exposed to an average 106 ml/m^3 for 1 hour, they all reported short-term, very mild irritation of the eyes, which the authors attributed to short-term concentration peaks in the exposure chamber (Rowe et al. 1952).

In another volunteer study, 16 men and 1 woman were exposed once for 7 hours to a tetrachloroethylene concentration of 100 ml/m^3. Subjective effects such as headache, fatigue, difficulties in speaking and dizziness were described by 25% to 40% of the test persons. Within the first 2 hours, 60% reported mild irritation of the eyes, nose or throat, which in most cases was no longer felt by the end of the exposure period. The Romberg test revealed effects on the sense of balance in 4 test persons (Stewart et al. 1970).

Another volunteer study reported very slight irritation of the eyes in the form of mild burning 1 to 4 minutes after the beginning of exposure to tetrachloroethylene concentrations of 75 to 80 ml/m^3. The volunteers no longer perceived any irritation after a few minutes (Stewart et al. 1961).

Conclusions:

Earlier studies in volunteers did not use sufficiently valid behavioural methods to record the neurotoxic or chemosensory effects caused by tetrachloroethylene. The Romberg test is the only standard method of neurological evaluation that can be used to determine acute neurotoxic effects "in an objective way". A NOAEC (no observed adverse effect concentration) cannot be derived from these studies. However, the fact that sensory irritation is very likely to occur at 100 ml/m^3 should be included in the assessment of peak limitation because it was repeatedly reported in the studies. However, the data cannot be evaluated quantitatively (see also Section 4.3). The study of Stewart et al. (1970) provides clear evidence of acute behavioural effects at a LOAEC of 100 ml/m^3.

4.2 Repeated exposure

In addition to neurotoxicity (see Table 1 and Table 2), effects on the liver and kidneys (see Table 3) were investigated after repeated exposure to tetrachloroethylene by inhalation.

Neurotoxicity

Repeated short-term exposure

Individual volunteer studies (Table 1) observed initial effects at 100 ml/m^3 and above (Hake and Stewart 1977; NIOSH 1981; Stewart et al. 1970). One study (Altmann et al. 1990, 1992) described effects at 50 ml/m^3. Two studies reported NOECs (no observed effect concentrations) of 10 and 20 ml/m^3, respectively (Altmann et al. 1990, 1992; Hake and Stewart 1977). The validity of the volunteer studies is restricted by the absence of control exposures, small group sizes, short periods of exposure and only a few exposure concentrations.

The studies of Altmann et al. (1990, 1992) are the most relevant of the experimental exposure studies (volunteer studies), in spite of the fact that these earlier studies were often carried out with a very small number of persons. However, these studies suggest that effects on the nervous system are to be found at 50 ml/m^3. Altmann et al. (1990) investigated visually evoked potentials (VEPs) for 6 different stimuli and evaluated the latencies of early event-related potentials (ERPs for sensory processes) in the electroencephalogram. At 50 ml/m^3, these ERPs were significantly delayed and there was a significant correlation with the blood concentration of tetrachloroethylene for N150 (VEP component at 150 ms). The results and the entire study are regarded as valid. The study included repeated determinations because the volunteers were investigated on 6 consecutive days and were exposed from days 2 to 5. Therefore, the significant effects of the VEP latencies resulted from statistical comparisons with control day 1. These differences in latency, although nominally rather small, were very stable over the 4 exposure days in the entire group of 10 volunteers exposed to tetrachloroethylene at 50 ml/m^3 (see Fig. 2 in Altmann et al. 1990). This concentration is regarded as the LOAEC because neurotoxic effects were recorded at 50 ml/m^3. The tetrachloroethylene concentration of 10 ml/m^3 that was also investigated can be regarded as the NOAEC because no changes in neurophysiological parameters were observed.

Chronic exposure at the workplace

The studies that investigated the neurotoxicity of tetrachloroethylene in occupationally exposed persons are summarized in Table 2.

Qualitatively, the study of Echeverria et al. (1995) is regarded as the best study because relevant confounders were considered and indoor air monitoring of tetrachloroethylene was described in detail. After adjusting for the relevant confounders, several neuropsychological tests revealed significant differences between persons exposed to high levels and low levels of the substance, suggesting a LOAEC of 40 ml/m^3 (exposure period: about 14 years). Hardly any effects on test performance were observed in the middle concentration group exposed to only about 20 ml/m^3, which is regarded as the NOAEC.

The studies with environmental exposure to tetrachloroethylene are characterized by very low exposure concentrations. A causal relationship with the reduced

Table 1 Volunteer studies with inhalation exposure to tetrachloroethylene

Test persons	Exposure	Observations	Notes	References
5 men, age: 36–64 years	100 ml/m³ (range: 62–137 ml/m³), 7 hours/day, 5 days	**100 ml/m³**: mild frontal headaches during exposure (1/5 with slight chronic sinusitis), mild irritation of eyes and throat (2/5), impairment of the sense of balance (Romberg test) within the first 3 hours (3/5); other clinical examinations, blood parameters and urinalysis normal	no control exposure	Stewart et al. 1970
6 men, 6 women	0, 25, 100 ml/m³, 5.5 hours/day, 11 weeks	**up to 100 ml/m³**: blood count and urinalysis normal, no evidence of a change in response to diazepam or ethanol		NIOSH 1977 a; Hake and Stewart 1977
3–4 men, 2–4 women per exposure period	0, 20 (only ♂), 100[a], 150 (only ♂) ml/m³, 1, 3 or 7.5 hours/day, 5 days/week, 1 week	**20 ml/m³**: NOAEC; **up to 100 ml/m³ (♀)/150 ml/m³ (♂)**: no effects on the composition of the urine, liver enzyme activity or lung function (only ♂ in the group exposed for 7.5 hours); no balance disorders (modified Romberg and heel-to-toe equilibrium tests), no significant effects on visually evoked responses (♂ and ♀ only in the group exposed for 7.5 hours); **100 ml/m³ (7.5 hours)**: changes in EEG patterns as in the case of drowsiness, indicative of cortical depression; **150 ml/m³ (7.5 hours)**: significant decrease in coordination performance (only ♂ examined)		Hake and Stewart 1977; NIOSH 1981
22 men, age: 23–35 years	10, 50 ml/m³, 4 hours/day, 4 days	**10 ml/m³** (n = 12): NOAEC; **50 ml/m³** (n = 10): effects on visually evoked potentials; auditory evoked potentials normal; significant deficits in vigilance performance and eye-hand coordination, simple reaction times significantly prolonged; results did not worsen over the 4-day period; no significant trend for visual contrast sensitivity		Altmann et al. 1990, 1992

[a] additional group (only ♂) with fluctuating exposure of 50–150 ml/m³;
EEG: electroencephalogram

Table 2 Studies of the neurotoxicity of tetrachloroethylene in exposed persons

Participants	Age (years), duration (years)	Exposure	Observations	Notes	References
18 dry cleaners (9 ♂, 9 ♀), 9 control persons (♀) from laundries	♂: 40.9 ± 15.0; 9.8 ± 6.9; ♀: 46.2 ± 17.2; 6.7 ± 6.1; controls: 37.0 ± 10.9	18 ml/m³ (8-hour mean, range: 1–37 ml/m³); ♂: 32 ml/m³ (8-hour mean)	significant deviations in neurological tests in 2/11 variables were attributed to exposure to Stoddard Solvent		NIOSH 1977 b
112 workers exposed in railway repair shops, 100 control persons	44.6 ± 10.0; 11.5 ± 5.5; controls: 40.1 ± 10.1	0.2–50 ml/m³ (75% of determinations), earlier determinations: 56% > 100 ml/m³, 28% > 400 ml/m³, exposure for 73 hours per month on average	subjective complaints during exposure: dizziness (44.6%), skin rash (31.3%), nausea (17.9%), loss of appetite (15.2%), but no objective evidence of neurological effects; hepatotoxicity and nephrotoxicity were the subject of the study	in numerous cases, concentrations often exceeded the limit values valid at that time; at the time of the study, exposure of most workers had been markedly reduced for > 2 years	Essing 1975
26 dry cleaners (24 ♂, 2 ♀), 33 control persons	32.9; 6.4; controls: 34.5	21 ml/m³ (mean; range: 9–38 ml/m³)	increased incidences for 17 of 22 symptoms (not significant); psychomotor test results normal		Lauwerys et al. 1983
101 dry cleaners (low exposure: n = 57; high exposure: n = 44), 84 control persons	low exposure: 38.2 ± 11.2; 11.8 ± 9.3; high exposure: 38.4 ± 9.7; 10.6 ± 7.8; controls: 31.8 ± 10.1	30 ml/m³ (mean; 88%: < 50 ml/m³), low exposure: 12 ml/m³, high exposure: 53 ml/m³	significant impairment in performance in perceptual speed, sensorimotor accuracy, attention and digit reproduction as a memory test, but changes were in the reference range; no significant concentration–effect relationship, no significant differences between low and high exposure groups		Seeber 1989

Table 2 (continued)

Participants	Age (years), duration (years)	Exposure	Observations	Notes	References
139 dry cleaners	not specified; 9.8	20–25 ml/m^3	neuropsychological and neurovegetative symptoms, correlated with exposure period but not with the level of exposure		Müller et al. 1989
56 dry cleaners (29 ♂, 27 ♀), 69 control persons (32 ♂, 37 ♀)	35.1 (17–55); 3.0 (0.08–10); controls: 34.5 (19–65)	20 ml/m^3 (geometric mean from 8-hour mean values)	subjective symptoms for CNS effects and local effects on skin and mucous membranes		Cai et al. 1991
60 (♀) dry cleaners, 30 control persons (♀)	39.7 ± 13.6; 10.1 ± 9.2; controls: 37.6 ± 10.9	15 ml/m^3 (median; range: 1–67 ml/m^3)	reaction times significantly prolonged, but no indication of dose-dependent or time-related effects; prolactin levels significantly increased in exposed persons during the proliferative phase of the menstrual cycle, but still within the normal range		Ferroni et al. 1992
64 dry cleaners (30 ♂, 34 ♀), 120 control persons (48 ♂, 72 ♀)	34.2 ± 11.3 (♂) or 35.3 ± 7.8 (♀); not specified; controls: 34.0 ± 7.1 (♂) or 32.6 ± 5.9 (♀)	15.3 ml/m^3 (♂) or 10.7 ml/m^3 (♀)	no blue-yellow colour vision loss	test method not sensitive enough	Nakatsuka et al. 1992

Table 2 (continued)

Participants	Age (years), duration (years)	Exposure	Observations	Notes	References
22 dry cleaners, 35 control persons	35 ± 10; 8.83 ± 7.67; controls: 35 ± 11	7.3 ml/m³ (range: 0.38–31 ml/m³), single determination	colour vision (colour confusion index, CCI) reduced (mainly in the blue-yellow range)	follow-up study (Gobba et al. 1998): CCI not better after 2 years with reduced exposure	Cavalleri et al. 1994
65 dry cleaners (35 ♂), 3 groups with low (n = 24), medium (n = 18) and high (n = 23) exposure	42; 2, 4, 14	3 groups: 11, 23, 41 ml/m³ (estimated by calculation); 0.6, 12, 42 ml/m³ (determined)	significant reduction in performance in 3 tests of memory performance (visual reproduction and recognition) with an increase in cumulative exposure (not current exposure), NOAEC: 23 ml/m³	no control group, previous exposure to solvents not specified	Echeverria et al. 1995
14 residents exposed in neighbourhoods close to dry-cleaning shops without occupational exposure, 23 control persons	39.2 ± 10.7; 10.6 on average	0.2 ml/m³ indoor air concentration	prolonged reaction times, reduced memory performance and vigilance; no significant effects on visually evoked potentials	causal relationship questionable, has not been included in the evaluation; environmental exposure not comparable with workplace, insufficient matching of the control group	Altmann et al. 1995
17 residents (13 adults, 4 children) exposed in neighbourhoods close to dry-cleaning shops 17 control persons	34.3 ± 4.4; 5.8; controls: 33.2 ± 4.4	0.05–0.3 ml/m³	no significant change in visual acuity; colour confusion index increased, but no significant change; significant decrease in visual contrast sensitivity	environmental exposure not comparable with workplace	Schreiber et al. 2002

Table 2 (continued)

Participants	Age (years), duration (years)	Exposure	Observations	Notes	References
9 exposed day care workers (♀), workplace in neighbourhoods close to dry-cleaning shops, 9 control persons	27.2 ± 3.0; about 4; controls: 27.7 ± 2.8	0.3 ml/m^3 (mean, range: 0.26–0.35 ml/m^3)	no significant change in visual acuity; no significant change in colour confusion index; significant decrease in visual contrast sensitivity	environmental exposure not comparable with workplace	Schreiber et al. 2002
55 adult residents exposed in neighbourhoods close to dry-cleaning shops, 49 control persons	low exposure: 44.6 ± 5.9; 10.4 ± 8.0; high exposure: 35.0 ± 9.5; 9.7 ± 7.6; controls: 44.3 ± 7.8	0.0004 ml/m^3 (n = 49, control group); 0.002 ml/m^3 (n = 43); 0.07 ml/m^3 (n = 12)	visual contrast sensitivity in adults not associated with exposure	environmental exposure not comparable with workplace; critical review of the study in Bukowski 2012	Storm et al. 2011

Table 3 Studies of the effects of tetrachloroethylene on the liver and kidneys in exposed workers

Participants	Age (years), duration (years)	Exposure	Observations	References
112 workers exposed in railway repair shops, 100 control persons	44.6 ± 10.0; 11.5 ± 5.5; controls: 40.1 ± 10.1	0.2–50 ml/m³ (75% of the determinations), earlier determinations: 56% > 100 ml/m³, 28% > 400 ml/m³, exposure for 73 hours per month on average	no evidence of effects on liver or kidney function	Essing 1975
26 dry cleaners (2 ♂, 24 ♀), 33 control persons	32.9 (15–53); 6.4 (0.1–25); controls: 34.5 (20–57)	21 ml/m³ (mean, range: 9–38 ml/m³)	no evidence of effects on liver or kidney function (β2-microglobulin, albumin and RBP in the urine and ALT and GGT in serum in the normal ranges)	Lauwerys et al. 1983
57 dry cleaners, 80 control persons	43.0 ± 9.1; 13.9 ± 9.8; controls: 37.9 ± 14.3	about 10 ml/m³ (calculated from TCA concentration in the urine)	urine: 2-fold increase in lysozymuria, β-glucuronidase activity ↑ (+50%); total protein and albumin in the normal ranges; according to the authors: subclinical impairment in kidney function	Franchini et al. 1983
16 dry cleaners (♀), 13 control persons (♀)	42 ± 10; 11; controls: 36 ± 6	23 ml/m³ (mean, range: 1.3–116 ml/m³)	urine: 4-fold increase in lysozyme activity, no correlation with concentration or period of exposure; albumin, β2-microglobulin, creatinine, glucose, LDH and protein in the urine in the normal ranges	Vyskocil et al. 1990
56 dry cleaners (29 ♂, 27 ♀), 69 control persons (32 ♂, 37 ♀)	35.1 (17–55); 3.0 (0.08–10); controls: 34.5 (19–65)	20 ml/m³ (geometric mean from 8-hour mean values)	no evidence of effects on liver (AST, ALT, GGT, ALP/LAP, bilirubin) or kidney function (BUN, creatinine) or effects on blood parameters (erythrocytes, Hb, Hct, leukocytes)	Cai et al. 1991
192 dry cleaners, no control persons	not specified; 12	14 ml/m³ (mean)	no evidence of nephrotoxicity (protein, albumin and NAG activity in the urine)	Solet and Robins 1991

Table 3 (continued)

Participants	Age (years), duration (years)	Exposure	Observations	References
141 dry cleaners (17 ♂, 124 ♀), 130 control persons (24 ♂, 106 ♀)	43 ± 8 (20–58); 12.3 ± 4.4; 41 ± 9 (23–56)	< 50 ml/m³ (8-hour mean values, mean: 11.3 ml/m³)	no clear effects on liver enzymes (ALT, AST, ALP, LDH, 5′-NU), GGT activity ↑, but no correlation with level or duration of exposure	Gennari et al. 1992
50 dry cleaners (9 ♂, 41 ♀), 50 control persons	41; 10; controls: 40	15 ml/m³ (median, range: 0.1–85 ml/m³)	1.5 to 4-fold increase in 8 proteins in the urine and 2 serum proteins, 12 other proteins in the normal ranges; slight but significant impairment in glomerular and tubular kidney function, according to the authors generalized membrane disturbances in the kidneys; no concentration–effect relationship; according to the authors relevance of the findings unclear, either physiological adaptation or early signs of renal disease	Mutti et al. 1992
27 dry cleaners, 26 control persons	46 ± 16; 20 ± 18; controls: 38 ± 10	16 ml/m³ (8-hour mean, range: 0.4–83 ml/m³)	slight changes in liver parenchyma detected by sonographic examination in 13/27 (controls: 4/26), moderate to severe changes in 5/27 (controls: 6/26); no significant changes in serum ALT, AST, GGT, ALP	Brodkin et al. 1995
82 dry cleaners, 19 control persons	34 ± 10; 3.9 (GM); controls: 32 ± 7	1.1 ml/m³ (8-hour mean, range: 0.1–32 ml/m³)	NAG, β-galactosidase, alanine aminopeptidase and albumin in the urine in the normal ranges, 2-fold significant increase in RBP; no correlation with exposure concentration or cumulative dose; mean RBP concentration in the normal range (US EPA 2012)	Verplanke et al. 1999

Table 3 (continued)

Participants	Age (years), duration (years)	Exposure	Observations	References
40 dry cleaners (♀), 45 control persons (♀)	41.3 ± 10.3; 15.3 ± 9.2; controls: 28.8 ± 10.2	8.7 ml/m³ (8-hour mean, range: 0.04–35.3 ml/m³)	positive correlation between the concentration of tetrachloroethylene in the urine at the beginning of the shift and the sum of the dissolved substances or total protein in the urine and between the concentration of tetrachloroethylene in the urine at the end of the shift and the GS activity in the urine; no significant differences in the mean values in the urine (related to creatinine) of: sum of the dissolved substances, total protein, ACE, NAG, GS; AST ↑, but no correlation with exposure, was probably age-related, serum ALT and GGT in the normal ranges	Trevisan et al. 2000

ACE: angiotensin converting enzyme; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GGT: γ-glutamyltransferase; GM: geometric mean; GS: glutamine synthetase; Hb: haemoglobin concentration; Hct: haematocrit level; LDH: lactate dehydrogenase; NAG: N-acetylglucosaminidase; 5′-NU: 5′-nucleotidase; RBP: retinol-binding protein; TCA: trichloroacetic acid

performance observed in these studies is to be regarded very critically because no significant concentration–effect relationships were detected in the workplace studies after exposure to higher concentrations.

Results for the effects on colour vision are inconsistent (Nakatsuka et al. 1992; Cavalleri et al. 1994); the toxicological relevance of these findings is unclear.

Hepatotoxicity and nephrotoxicity

The studies of hepatotoxicity and nephrotoxicity caused by tetrachloroethylene primarily in dry cleaners are shown in Table 3. There was no conclusive evidence of adverse effects on the liver and kidneys at mean exposure concentrations of about 20 ml/m^3 and below.

In one of the studies of hepatotoxicity, sonographic examinations revealed slight changes of the hepatic parenchymal tissue in persons exposed to tetrachloroethylene (8-hour mean: 16 ml/m^3). The incidence in exposed persons was 48% (13/27), which is higher than the 15% incidence observed in the control group (4/26). The frequency of moderate to severe changes of around 20% was about the same in both groups. No significant changes in serum transaminases were observed after comparing the groups (Brodkin et al. 1995). It is unclear whether the observed changes have any relevance as indicators of hepatotoxicity (NRC 2010). In another study, exposure to an average tetrachloroethylene concentration of 11 ml/m^3 induced an increase in GGT activity, but this increase did not correlate with the level or duration of exposure. Moreover, the other parameters of hepatotoxicity that were examined yielded no unusual findings (Gennari et al. 1992).

In one of the studies of nephrotoxicity, increased lysozyme and β-glucuronidase activities were determined in the urine of persons exposed to a tetrachloroethylene concentration of about 10 ml/m^3, whereas total protein and albumin were unchanged. The findings led the authors to conclude that there was a subclinical impairment in kidney function (Franchini et al. 1983). In another study, exposure to an average concentration of 23 ml/m^3 caused an increase in lysozyme activity in the urine, but this increase did not correlate with the level or duration of exposure. All the other markers that were examined in the urine were in the normal range (Vyskocil et al. 1990). In a study of workers exposed to 15 ml/m^3, the authors concluded that there was a slight disturbance in glomerular and tubular kidney function. There was no concentration–effect relationship. The findings may be interpreted as a physiological adaptation or as an early sign of renal disease (Mutti et al. 1992). At a mean exposure level of 1.1 ml/m^3, retinol-binding protein (RBP) was significantly increased in the urine of workers, but there was no correlation with the exposure concentration or the cumulative dose. Moreover, all other markers in the urine were normal (Verplanke et al. 1999). The mean RBP concentration of the exposed persons was in the normal range (US EPA 2012). At a mean exposure to 8.7 ml/m^3 in another study, several positive correlations between the tetrachloroethylene concentration in the urine and markers of effect were observed, but there were no significant differences in the mean values (Trevisan et al. 2000).

Conclusions:

A LOAEC of 50 ml/m^3 was derived from volunteer studies with repeated short-term exposure for 4 hours; no effects were observed at 10 ml/m^3. After reviewing the

human studies with long-term exposure at the workplace, a NOAEC of 20 ml/m³ is assumed for the neurotoxicity of tetrachloroethylene whereas a number of human studies reported weak neurotoxic symptoms below this concentration (see Table 2).

The majority of the studies that investigated the effects of tetrachloroethylene on the liver and kidneys of exposed persons (Table 3) did not reveal clearly adverse effects after mean exposure concentrations of about 10 to 20 ml/m³.

4.3 Local effects on skin and mucous membranes

Several case reports described tetrachloroethylene as clearly irritating to the skin of humans (NEG 2003). Extensive erythema and blistering were reported in a worker who had lain unconscious in a pool of solvents for about 5 hours (NEG 2003). The same symptoms were observed in a worker who had been unconscious for about half an hour wearing tetrachloroethylene-soaked clothes. The symptoms decreased considerably within 5 days, although there was still dryness, discoloration and irritation of the injured areas after 4 months (NEG 2003).

Irritation of the airways was observed in workers exposed to concentrations of 1600 to 2656 mg/m³ (232 to 385 ml/m³) while degreasing metal parts (SCOEL 2009).

After exposure to an average 216 ml/m³ for 45 minutes to 2 hours, 4 volunteers reported irritation of the eyes. In addition, irritation of the airways occurred at higher concentrations of 600 ml/m³ (10 minutes) and 1000 ml/m³ (1–2 minutes) (Rowe et al. 1952).

When 6 volunteers were exposed to an average 106 ml/m³ for 1 hour, they all reported short-term, very mild irritation of the eyes, which the authors attributed to short-term concentration peaks in the exposure chamber (Rowe et al. 1952).

In another volunteer study, 16 men and 1 woman were exposed once for 7 hours to a tetrachloroethylene concentration of 100 ml/m³. Within the first 2 hours, 60% reported mild irritation of the eyes, nose or throat, which in most cases was no longer felt by the end of the exposure period.

Another volunteer study reported very slight irritation of the eyes in the form of mild burning 1 to 4 minutes after the beginning of exposure to tetrachloroethylene concentrations of 75 to 80 ml/m³. The volunteers no longer perceived any irritation after a few minutes (Stewart et al. 1961).

In a study in which 8 to 11 male volunteers were exposed for 90 seconds (by means of an exposure mask) to a mixture of 20 ml tetrachloroethylene/m³ and 1 ml NO_2/m³ that was heated and irradiated with light, eye irritation was not observed compared with the control exposure (Wayne and Orcutt 1960).

At a tetrachloroethylene concentration of 20 ml/m³ (geometric mean of 8-hour mean values, range: 3.8–94.4 ml/m³), dry cleaners complained of irritation of the nose (significant) and throat (not significant) more frequently than persons from the control group (Cai et al. 1991). However, the reported symptoms are subjective and were not substantiated by objective methods.

4.4 Allergenic effects

There is no conclusive clinical evidence showing that tetrachloroethylene causes contact-sensitizing effects. A metal worker who had been exposed to a lubricating oil and tetrachloroethylene developed acute contact eczema on the hands. A patch test with 1% tetrachloroethylene in olive oil yielded positive results. Patch tests with 1% and 50% formulations of the lubricating oil in petrolatum and an open test with undiluted tetrachloroethylene produced no reaction. However, the time of reading was not reported. Control patch tests in which the author applied the substances to himself yielded negative results for all substances (Vail 1974).

Another publication reported positive patch test results with tetrachloroethylene in a female employee of a semiconductor manufacturing facility, but did not include any other details. The authors assumed that residues of tetrachloroethylene used in the dry cleaning of the garments might have caused presumably irritant dermatitis in this employee and in 5 other persons (Redmond and Schappert 1987).

4.5 Reproductive and developmental toxicity

In the 1997 supplement (supplement "Tetrachloroethylene" 1997), the epidemiological data were not regarded sufficient to evaluate the reproductive and developmental toxicity of tetrachloroethylene in humans. Studies that investigated the reproductive toxicity of tetrachloroethylene in humans are shown in Table 4.

The findings of these studies may have been affected by confounders such as exposure to other solvents (for example trichloroethylene), smoking, alcohol consumption, diseases, medication, parity (number of births), previous abortions, reproductive behaviour, age and physical workload. Most of these were small studies with unclear control populations that frequently failed to record relevant confounders. The study results are heterogeneous.

Overall, there is evidence of an association between the employment of women in dry cleaning and an increased risk of spontaneous abortions. However, there are only sparse data that relate this specifically to exposure to tetrachloroethylene. There is also very limited evidence of an association between exposure to tetrachloroethylene and disturbances in the menstrual cycle. There is no evidence of an association between exposure to tetrachloroethylene and congenital malformations or between paternal exposure and an increased risk of spontaneous abortions. There is no conclusive evidence of effects on male fertility, although the available data indicate that there may have been slight effects (SCOEL 2009). In many of these studies, exposure was defined only by the type of employment, without analysing tetrachloroethylene exposure at the workplace. According to a review of studies that investigated workplace exposure to tetrachloroethylene, in the dry cleaning industry in the 1970s and 1980s mean exposure levels were often in the range of 50 ml/m^3, and in some cases even above 100 ml/m^3, depending on the type of employment (Gold et al. 2008). In addition, in some studies, there may have been co-exposure to other solvents. Therefore, no reliable conclusions can be drawn from the available studies about the effect that tetrachloroethylene has on the end points of fertility and developmental toxicity in humans.

Table 4 Studies of the reproductive toxicity of tetrachloroethylene in humans

Description of the study	Results	Comments	References
male fertility			
927 couples with impaired fertility, 3728 control couples	male dry cleaners: no anomalies in the spermiogram (OR: 1.0; 95% CI: 0.5–2.0) time to conception not prolonged (OR: 1.2; 95% CI: 0.7–1.9)	questionnaires to establish job description; no specific evaluation for tetrachloroethylene	Rachootin and Olsen 1983
34 male dry cleaners, 48 male laundry workers	sperm concentration and proportion of abnormal sperm in the normal range; differences in sperm morphology and motility of unclear relevance	exposure index derived from tetrachloroethylene concentration in exhaled air and questionnaires about working conditions	Eskenazi et al. 1991 b
17 male dry cleaners, 32 male laundry workers	incidences of conception and of spontaneous abortions in wives of dry cleaners in the normal range; time to conception prolonged (not significantly) in wives of dry cleaners	subcollective from Eskenazi et al. 1991 b	Eskenazi et al. 1991 a
male workers with exposure to various chemicals	exposure to solvents: spontaneous abortions not increased in wives of exposed men (OR: 0.86; 95% CI: 0.69–1.08)	exposure levels not recorded; no specific evaluation for tetrachloroethylene	Lindbohm et al. 1984
120 cases of spontaneous abortions, 251 control persons (from a cohort of 6000 male workers with exposure to solvents)	no association between spontaneous abortions (n = 4, controls: n = 17) and paternal exposure to tetrachloroethylene (OR: 0.5; 95% CI: 0.2–1.5)	evaluation of exposure from reported working conditions and in some cases from biological monitoring	Taskinen et al. 1989
male workers with exposure to organic solvents, exposure to tetrachloroethylene at n = 17	likelihood of conception in wives of exposed men reduced, but not significantly (low exposure, n = 9, FDR: 0.86; 95% CI: 0.40–1.84; high exposure, n = 8, FDR: 0.68; 95% CI: 0.30–1.53)	assessment of exposure from reported working conditions and, in some cases, from biological monitoring; various confounders considered; limitations due to the method (retrospective self-evaluation questionnaires); small number of exposed persons; study based on Taskinen et al. 1989	Sallmén et al. 1998

Table 4 (continued)

Description of the study	Results	Comments	References
female fertility			
68 female dry cleaners, 76 female laundry workers	disturbances in the menstrual cycle more frequent in dry cleaners, no differences in length of menstrual cycle	small number of exposed persons; exposure levels not recorded; effects reported in questionnaires; confounders not sufficiently considered	Zielhuis et al. 1989
927 couples with impaired fertility, 3728 control couples	female dry cleaners: risk of idiopathic infertility increased (OR: 2.7; 95% CI: 1.0–7.1), time to conception not prolonged (OR: 1.6; 95% CI: 0.9–2.9)	questionnaires to establish job description; no specific evaluation for tetrachloroethylene	Rachootin and Olsen 1983
197 female workers with exposure to organic solvents; exposure to tetrachloroethylene: high (n = 7), low (n = 13), none (n = 177)	fertility (likelihood of conception) in persons exposed to tetrachloroethylene reduced, but not significantly (low exposure: IDR: 0.63; 95% CI: 0.31–1.52)	evaluation of exposure from reported working conditions and in some cases from biological monitoring; small number of exposed persons; study based on Lindbohm et al. 1990	Sallmén et al. 1995
9000 female chemical workers, 52 cases of spontaneous abortions	spontaneous abortions (n = 7) increased in laundry workers compared with the female population in Finland (proportion of abortions/pregnancies: 16.67%, control population: 7.98%)	exposure levels not recorded; possible confounders (for example physical workload) not sufficiently considered; small number of cases	Hemminki et al. 1980
female workers with exposure to various chemicals	exposure to solvents: spontaneous abortions in exposed women (730 pregnancies) not increased (OR: 0.79; 95% CI: 0.58–1.07); spontaneous abortions in laundry workers significantly increased (416 pregnancies, OR: 1.48; 95% CI: 1.09–2.02)	exposure levels not recorded; no specific evaluation for tetrachloroethylene; confounders not sufficiently considered	Lindbohm et al. 1984
56 female dry cleaners, 46 housewives	incidence of spontaneous abortions (8.9%, n = 5) higher (not significantly) than in housewives (2.2%, n = 1); no significant differences in low birth weights, stillbirths, congenital malformations	method of recording exposure levels: determination of trichloroacetic acid in the urine, 4 times higher in exposed women than in housewives; small number of exposed persons and small number of cases; confounders not sufficiently considered	Bosco et al. 1987

Table 4 (continued)

Description of the study	Results	Comments	References
cross-sectional study of 56 067 women questioned after delivery or spontaneous abortion, 202 of them laundry workers and dry cleaners	no association between employment in laundries or dry cleaning shops and spontaneous abortions (n = 36), low birth weights (n = 15), stillbirths (n = 3) or congenital malformations (n = 9)	exposure levels not recorded (only type of employment considered); small number of cases	McDonald et al. 1987
cohort of 5700 female dry cleaners and laundry workers, 130 cases of spontaneous abortions, 289 control persons	significant association between high exposure to tetrachloroethylene and spontaneous abortions (OR: 3.4; 95% CI: 1.0–11.2), no association with congenital malformations (OR: 0.8; 95% CI: 0.2–3.5)	assessment of exposure from reported working conditions and in some cases from biological monitoring (n = 7) in the blood; confounders for spontaneous abortions (such as heavy lifting, high consumption of alcohol and exposure to other solvents) considered	Kyyrönen et al. 1989
female dry cleaners and female laundry workers, 112 cases of spontaneous abortions, 232 control persons	no increased risk of spontaneous abortions after low and high exposures; risk not significantly increased (OR: 1.5; 95% CI: 0.4–6.3) after very high exposure (4 cases, 6 controls)	assessment of exposure from reported working conditions (questionnaires); confounders extensively considered; small number of persons exposed to high levels and small number of cases	Ahlborg 1990
female workers with exposure to organic solvents, 73 cases, 167 control persons	slightly increased risk (OR: 2.5; 95% CI: 0.6–10.5) of spontaneous abortions after high exposure to tetrachloroethylene (5 cases, 6 controls)	assessment of exposure from reported working conditions and in some cases (5%) from biological monitoring; confounders considered (previous abortions, parity, smoking, alcohol consumption, exposure to other solvents); small number of exposed persons	Lindbohm et al. 1990
female dry cleaners and laundry workers, 159 cases of spontaneous abortions, 436 control persons	slightly increased risk (OR: 2.9; 95% CI: 0.98–8.44) of spontaneous abortions after high exposure to tetrachloroethylene, no association with congenital malformations, stillbirths or low birth weights	assessment of exposure from reported working conditions (questionnaires and interviews); confounders not considered sufficiently; small number of persons exposed to high levels and small number of cases; study based on data from Sweden, Denmark and Finland; 118 cases from Kyyrönen et al. 1989, 31 cases from Ahlborg 1990	Olsen et al. 1990

Table 4 (continued)

Description of the study	Results	Comments	References
case–control study in 626 women with spontaneous abortions before week 20 of pregnancy, 1300 control persons	significant association between spontaneous abortions and exposure to tetrachloroethylene (5 cases, 2 controls; OR: 4.7; 95% CI: 1.1–21.1)	assessment of exposure from reported working conditions (telephone interview); confounders not considered sufficiently; small number of cases (n = 5) and co-exposure to trichloroethylene (n = 4)	Windham et al. 1991
683 pregnant female dry cleaners, 408 of them machine operators	increased risk of spontaneous abortions in female machine operators in dry cleaning units compared with other workers in dry cleaning (OR: 1.63; 95% CI: 1.01–2.66); no increased risk in dry cleaners compared with laundry workers	assessment of exposure from reported working conditions (questionnaires); confounders considered in some cases	Doyle et al. 1997
postnatal developmental toxicity			
prospective population-based cohort study, 88 829 individuals born in Jerusalem from 1964 to 1976, followed from birth to between ages 21 and 33	schizophrenia in 4 of 144 offspring of dry cleaners (RR: 3.4; 95% CI: 1.3–9.2, p = 0.01)	important confounders considered, but small number of cases and no evaluation of exposure	Perrin et al. 2007

CI: confidence interval; FDR: fecundability density ratio; IDR: incidence density ratio; OR: odds ratio; RR: relative risk

Several epidemiological studies are available that investigated the relationship between exposure to tetrachloroethylene via the drinking water and reproductive toxicity (see ATSDR 2014 and US EPA 2012). These studies were not included in the evaluation of the reproductive and developmental toxicity of tetrachloroethylene at the workplace and are therefore not described in detail here.

Conclusions:

There is evidence of an association between the employment of women in dry cleaning and an increased risk of spontaneous abortions, but it is not sufficient to establish a causal relationship because of the uncertainties and shortcomings of the studies as regards exposure levels, possible co-exposures, the small number of exposed persons, etc.

4.6 Genotoxicity

Studies that investigated the genotoxic effects of tetrachloroethylene in exposed workers were described in the supplements published in 1988 (documentation "Tetrachloroethylene" 1992) and in 1997 (supplement "Tetrachloroethylene" 1997).

A study with 18 women exposed to tetrachloroethylene (dry cleaning, 8-hour mean values of 2.4 and 3.8 ml/m^3) and 20 control persons (laundry; 8-hour mean values of < 0.02 ml/m^3) revealed significantly reduced 8-hydroxydeoxyguanosine levels in the leukocytes of exposed female workers. Exposure to tetrachloroethylene was not clearly identified as the cause of this effect. Other biomarkers of oxidative stress did not significantly differ between the groups (Toraason et al. 2003).

There was a significant increase in the incidence of sister chromatid exchange (SCE) in smokers exposed to tetrachloroethylene (average concentration 10 ml/m^3) compared with that in non-smoking control persons. Exposure to tetrachloroethylene alone or smoking did not induce increased SCE frequencies (Seiji et al. 1990).

Increased frequencies of chromosomal aberrations or SCE in lymphocytes were not detected in workers from metal degreasing workshops at mean exposure concentrations of 92 ml/m^3 (IARC 2014; Ikeda et al. 1980).

A study of dry cleaners (exposure concentration not specified) did not reveal any differences between exposed and control persons with regard to chromosomal aberrations or SCE (Böttger and Elstermeier 1989).

Another study reported a markedly increased incidence of dicentric chromosomes in peripheral lymphocytes of female workers exposed to tetrachloroethylene concentrations of 20 to 50 ml/m^3 compared with that in control persons (Fender 1993). However, there was simultaneous exposure to trichloroethylene (IARC 2014).

In a cross-sectional study of 18 women exposed to tetrachloroethylene (dry cleaning; 8-hour mean value: 3.8 ml/m^3) and 18 control persons (laundry; 8-hour mean value: < 0.02 ml/m^3), chromosome painting was used to analyse chromosomal aberrations in peripheral blood cells; a standardized method (Tucker et al. 1995) was then applied to classify them according to chromosomal translocations, insertions, exchanges, which were referred to as colour junctions, and dicentric and acentric fragments. In the exposed women, a significant correlation was observed between tetrachloroethylene concentrations in the blood and the incidence of acentric frag-

ments. However, the incidence of all chromosomal changes compared with the control value was not significantly increased. The authors concluded that in this study population, which had been exposed to low levels only, tetrachloroethylene exposure did not have any marked effect on the chromosomes (Tucker et al. 2011). The evaluation included 6 stained chromosome pairs and was not carried out per cell (metaphase), but as genome equivalents.

Conclusions:

Recent studies have not substantiated the genotoxic effects suggested by earlier investigations; however, these earlier studies involved exposure to mixtures of substances.

4.7 Carcinogenicity

Epidemiologic studies that investigated the carcinogenic effects of tetrachloroethylene in exposed workers were described in the supplements published in 1988 (documentation "Tetrachloroethylene" 1992) and in 1997 (supplement "Tetrachloroethylene" 1997). A current review of the epidemiological data may be found in IARC (2014). Only the studies that specifically considered exposure to tetrachloroethylene or employment in dry cleaning are included here. The results of these studies are described below.

4.7.1 Case–control studies

The case–control studies (Asal et al. 1988; Delahunt et al. 1995; Harrington et al. 1989; Mandel et al. 1995; McCredie and Stewart 1993; Mellemgaard et al. 1994; Schlehofer et al. 1995; Sharpe et al. 1989) described in the 1997 supplement (supplement "Tetrachloroethylene" 1997) did not reveal sufficiently consistent results for renal cell carcinomas. No significant associations could be established (see supplement "Tetrachloroethylene" 1997) for liver cancer (Bond et al. 1990) and astrocytomas (Heineman et al. 1994).

The relevant case–control studies published since then that were described in IARC (2014) reported cancer of the bladder, upper respiratory tract, lymphatic and haematopoietic system, kidneys, breast, lungs, liver and brain (see Table 5).

Bladder

An association between bladder cancer and exposure to tetrachloroethylene or employment in dry cleaning was investigated in 9 studies. In most studies, the odds ratio was not significantly increased and the number of exposed cases was usually small (Aschengrau et al. 1993; Burns and Swanson 1991; Christensen et al. 2013; Colt et al. 2011; Gaertner et al. 2004; Schoenberg et al. 1984; Steineck et al. 1990; Swanson and Burns 1995). One study described a statistically significant increase in the odds ratio for urothelial carcinomas in the group of men with the highest exposure (see Table 5) (Pesch et al. 2000 a).

Table 5 Case–control studies of the cancer risk for occupational exposure to tetrachloroethylene (according to IARC 2014)

Study population, country, period	Number of cases/controls	Exposure	Relative risk (95% CI)	Influencing factors, comments	References
bladder					
Germany, 5 regions, 1991–1995	704/2650 (population controls)	interview, JEM and JTEM for tetrachloroethylene	JEM, men, medium exposure: 162 exposed cases, 1.1 (0.9–1.3); JEM, women, medium exposure: 21 exposed cases, 1.8 (1.0–3.0); JEM, men, high exposure: 172 exposed cases, 1.2 (1.0–1.5); JEM, women, high exposure: 15 exposed cases, 1.0 (0.6–1.9); JEM, men, substantial exposure: 71 exposed cases, 1.4 (1.0–1.9); JEM, women, substantial exposure: 3 exposed cases, 0.7 (0.2–2.5); JTEM, men, medium exposure: 37 exposed cases, 1.0 (0.7–1.5); JTEM, men, high exposure: 47 exposed cases, 1.2 (0.8–1.7); JTEM, men, substantial exposure: 22 exposed cases, 1.8 (1.1–3.1)	age, smoking, study centre; no JTEM data for women	Pesch et al. 2000 a

Table 5 (continued)

Study population, country, period	Number of cases/controls	Exposure	Relative risk (95% CI)	Influencing factors, comments	References
lymphatic and haematopoietic system					
Seattle-Puget Sound/Detroit, USA, 2000–2002	181 with multiple myelomas/481 controls	interview, JEM for tetrachloroethylene	JEM: 29 exposed cases, 1.4 (0.9–2.4); highest category of cumulative exposure: 14 exposed cases, 2.5 (1.1–5.4)	age, ethnicity, study site, gender, years of education	Gold et al. 2011
kidneys					
Germany, 1991–1995	935/4298 (population controls)	interview, JEM and JTEM	German JEM, men, persons not exposed and < 30th percentile: exposed cases: not specified, 1.0 (ref); medium exposure, > 30th–60th percentile: 154 exposed cases, 1.4 (1.1–1.7); high exposure, > 60th–90th percentile: 119 exposed cases, 1.1 (0.9–1.4); substantial exposure, > 90th percentile: 50 exposed cases, 1.4 (1.0–2.0); German JEM, women, persons not exposed and < 30th percentile: exposed cases: not specified, 1.0 (ref); medium exposure, > 30th–60th percentile: 12 exposed cases, 0.7 (0.4–1.3);	age, study centre, smoking, responses: 88% (cases), 71% (controls)	Pesch et al. 2000 b

Table 5 (continued)

Study population, country, period	Number of cases/controls	Exposure	Relative risk (95% CI)	Influencing factors, comments	References
			high exposure, > 60th–90th percentile: 19 exposed cases, 1.1 (0.7–1.9); substantial exposure, > 90th percentile: 4 exposed cases, 0.7 (0.3–2.2); JTEM, men, persons not exposed and < 30th percentile: exposed cases: not specified, 1.0 (ref); medium exposure, > 30th percentile: 44 exposed cases, 1.2 (0.9–1.7); high exposure, > 60th–90th percentile: 39 exposed cases, 1.1 (0.7–1.5); substantial exposure, > 90th percentile: 15 exposed cases, 1.3 (0.7–2.3); JTEM, women, persons not exposed and < 30th percentile: exposed cases: not specified, 1.0 (ref); medium exposure, > 30th–60th percentile: 8 exposed cases, 2.2 (0.9–5.2); high exposure, > 60th–90th percentile: 6 exposed cases, 1.5 (0.6–3.8); substantial exposure, > 90th percentile: 3 exposed cases, 2.0 (0.5–7.8)		

Table 5 (continued)

Study population, country, period	Number of cases/controls	Exposure	Relative risk (95% CI)	Influencing factors, comments	References
lungs					
Missouri, USA, 1986–1991	429/1021 (population controls)	interview	dry cleaners (all cases): 30 exposed cases, 1.8 (1.1–3.0); dry cleaners (lifetime non-smokers): 23 exposed cases, 2.1 (1.2–3.7)	age, history of previous lung diseases, smoking habits, responses: 69% (cases), 73% (controls)	Brownson et al. 1993
Montreal, Canada, 1980–1986 (study 1), 1995–2001 (study 2)	2016/2001 (study 1: 851/533; study 2: 430 women, 735 men/570 women, 898 men), (population controls)	personal interview	any exposure to tetrachloroethylene: 23 exposed cases, 2.5 (1.2–5.6); substantial exposure to tetrachloroethylene: 10 exposed cases, 2.4 (0.8–7.7)	age, smoking habits, educational attainment, socioeconomic status, ethnicity, exposure to 8 known carcinogens, responses: 79/86% (cases), 70/70% (controls)	Vizcaya et al. 2013

JEM: job exposure matrix; JTEM: job–task exposure matrix

Upper respiratory tract

An association between cancer of the upper respiratory tract and exposure to tetrachloroethylene or employment in dry cleaning was investigated in 2 case–control studies. Odds ratios > 1 were reported, but these were not statistically significant, and concentration–effect or exposure duration–effect relationships were observed for laryngeal cancer. However, the number of cases was small (Vaughan et al. 1997). In the second study, none of the cases of oesophageal cancer had been exposed to tetrachloroethylene (Christensen et al. 2013).

Lymphatic and haematopoietic system

An association between cancer of the lymphatic and haematopoietic system and exposure to tetrachloroethylene was investigated in 5 studies (Christensen et al. 2013; Gold et al. 2011; Kato et al. 2005; Miligi et al. 2006; Seidler et al. 2007). In one of the studies, a significant increase in the odds ratio of 2.5 (95% CI: 1.1–5.4) was found for multiple myelomas in the highest exposure category and there was a significant trend with increasing cumulative exposure (Gold et al. 2011).

Kidneys

An association between cancer of the kidneys and exposure to tetrachloroethylene was investigated in 7 case–control studies. The 1997 supplement reviewed 3 of these studies (Asal et al. 1988; Delahunt et al. 1995; Mandel et al. 1995); the results were not regarded as sufficiently consistent.

Only one (Pesch et al. 2000 b) of the new studies (Christensen et al. 2013; Dosemeci et al. 1999; Karami et al. 2012; Pesch et al. 2000 b) reported a statistically significant increase in the odds ratio in men, but not in women. However, no trend was observed with the increase in exposure levels. If exposure was classified by means of the more conclusive job–task exposure matrix, the odds ratio was not significantly increased for any exposure group, however, the number of cases was greatly reduced.

Breast

A study re-evaluated the data of drinking water contaminated with tetrachloroethylene in Massachusetts (USA). A significantly increased odds ratio was obtained only for an estimated exposure greater than the 75th percentile (OR: 1.6; 95% CI: 1.1–2.4). There was no significant increase in the odds ratio at the 90th percentile or using different exposure modelling (Gallagher et al. 2011).

Lungs

An association between cancer of the lungs and occupational exposure to tetrachloroethylene or employment in dry cleaning was investigated in 2 case–control studies. Statistically significant increases in the odds ratio were determined in both studies (Brownson et al. 1993; Vizcaya et al. 2013).

In a number of persons who had been exposed to tetrachloroethylene levels in the drinking water above the 90th percentile, the adjusted odds ratios for lung cancer were markedly increased and were dependent on whether or not a latency period was assumed (odds ratio: 3.7 (95% CI: 1.0–11.7), 3.3 (0.6–13.4), 6.2 (1.1–31.6) and 19.3 (2.5–141.7) for a latency period of 0, 5, 7 and 9 years, respectively) (Paulu et al. 1999).

Liver

An association between cancer of the liver and occupational exposure to tetrachloroethylene or employment in dry cleaning was investigated in 3 case–control studies. The number of exposed cases was small, and none of the studies reported a statistically significant increase in the odds ratio (Bond et al. 1990; Christensen et al. 2013; Suarez et al. 1989).

Brain

An association between cancer of the brain and exposure to tetrachloroethylene was investigated in 3 case–control studies. None of the studies reported a statistically significant increase in the odds ratio (Heineman et al. 1994; Neta et al. 2012; Ruder et al. 2013), not even after exposure to tetrachloroethylene with the drinking water (Paulu et al. 1999).

Prostate gland

An association between cancer of the prostate gland and occupational exposure to tetrachloroethylene was investigated in 1 case–control study. Substantial exposure to tetrachloroethylene was associated with a significantly increased risk of cancer of the prostate gland (odds ratio: 6.0; 95% CI: 1.2–30; 9 exposed cases) (Christensen et al. 2013).

4.7.2 Cohort studies

The studies described in the 1988 supplement (Blair 1980; Blair and Mason 1980; Blair et al. 1979; Brown and Kaplan 1987; Kaplan 1980) did not provide evidence of a carcinogenic risk for humans (see documentation "Tetrachloroethylene" 1992).

The cohort studies (Anttila et al. 1995; Blair et al. 1990; Duh and Asal 1984; Ruder et al. 1994; Spirtas et al. 1991) described in the 1997 supplement (supplement "Tetrachloroethylene" 1997) did not reveal consistent results for cancer of the oesophagus, bladder or kidneys. The persons included in the studies were only rarely exposed to tetrachloroethylene only (see supplement "Tetrachloroethylene" 1997).

The relevant cohort studies published since then and that were described in IARC (2014) are summarized in Table 6.

A retrospective study analysed mortality in the period up to 1996 among aircraft-manufacturing workers who were exposed to chromate, tetrachloroethylene, trichloroethylene and various other solvents in 1960 or later. A subcohort of 2631 persons was regularly exposed to tetrachloroethylene, but also to other substances. There was no significant change in the SMR (standardized mortality ratio) among these workers for the types of cancer that were investigated or for mortality from all types of cancer (Boice et al. 1999).

A follow-up study analysed mortality in the period from 1979 to 1993 among 5369 workers who were employed in dry cleaning shops in the United States and had been members of a union since 1948. The mortality from all cancer types was slightly increased (SMR: 1.2; 95% CI: 1.1–1.3; n = 590). A significant increase in mortality from cancer of the oesophagus, lungs and cervix was observed (see Table 6). There was a slight, but not significant increase in mortality for bladder cancer (SMR: 1.3;

95% CI: 0.7–2.4; n = 12) (Blair et al. 2003). There was only little evidence of an exposure–response effect. The increase in mortality caused by oesophageal cancer may have been an effect of smoking (IARC 2014).

A cohort of 46 768 laundry workers and dry cleaners from Denmark, Finland, Norway and Sweden (period from 1970 to 2001) was analysed in a nested case–control study. A significantly increased risk of bladder cancer (RR: 1.4; 95% CI 1.1–1.9; n = 93) that was not associated with the duration of employment was observed among 695 dry cleaners. No statistically significant increase in the risk was observed for other tumour localizations, including the oesophagus (Lynge et al. 2006).

A follow-up study with 14 455 aircraft-maintenance workers in the United States (period from 1973 to 2000) included a subgroup of 851 persons who had worked with tetrachloroethylene at some time. The emphasis of the study was on exposure to trichloroethylene. Among the persons exposed to tetrachloroethylene, the hazard ratios were significantly increased for cancer of the lymphatic and haematopoietic system (in men) and multiple myelomas (in women) (Radican et al. 2008). However, the study was based on a small number of cases.

A follow-up study of a cohort of 1704 dry cleaners in the United States with exposure to tetrachloroethylene for the duration of at least 1 year revealed a significant increase in mortality from cancer (SMR: 1.22; 95% CI 1.09–1.36; n = 322). Significant increases in the SMR were found for the following tumour localizations (see Table 6): oesophagus, tongue and trachea, bronchi and lungs. When a duration of employment of ≥ 5 years and a latency period of ≥ 20 years was considered, the SMRs were increased for cancer of the oesophagus and bladder. The SMR for cancer of the tongue was significantly increased in a subcohort of 618 persons who were employed in dry-cleaning shops in which tetrachloroethylene was used as the main solvent. The increased SMRs were not statistically significant in other organs (Calvert et al. 2011).

A follow-up study of a cohort of 9440 dry cleaners and laundry workers in Sweden analysed the cancer incidences in the period from 1985 to 2006. A subgroup of 6356 persons worked in shops in which only tetrachloroethylene was used. No significantly increased incidences of cancer were observed for oesophagus, larynx, cervix, liver, kidneys or bladder. Statistically significant increases in cancer incidences were observed for non-Hodgkin's lymphomas in men of the subgroup exposed to tetrachloroethylene (Seldén and Ahlborg 2011).

In the NOCCA (Nordic Occupational Cancer) study, case–control analyses were carried out for liver and kidney cancer, non-Hodgkin's lymphomas and multiple myelomas with regard to exposure to tetrachloroethylene in a cohort consisting of 30 to 64-year-old census participants in Finland, Iceland, Norway and Sweden in 1960, 1970, 1980/81 and 1990. There was evidence of an association between exposure and the incidence of liver cancer in men and women and non-Hodgkin's lymphomas in men. Furthermore, a low additional risk was observed for the incidence of multiple myelomas in men and women with high exposure to tetrachloroethylene. There

Table 6 Cohort studies of the cancer risk for occupational exposure to tetrachloroethylene (according to IARC 2014)

Study population, country, period	Number of persons	Exposure	Effects	References
aircraft-manufacturing workers, California, USA, 1960–1996	2631	regular exposure to tetrachloroethylene; JEM without quantitative assessment of the exposure level	oesophagus: n = 6, SMR: 1.47 (0.54–3.21); cervix: n = 0; 0.47 expected cases; kidneys: n = 2, SMR: 0.69 (0.08–2.47); bladder and urogenital tract: n = 2, SMR: 0.70 (0.09–2.53); NHL: n = 8, SMR: 1.70 (0.73–3.34); Hodgkin's lymphomas: n = 0; 0.63 expected cases; bronchi, trachea and lungs: n = 46, SMR: 1.08 (0.79–1.44)	Boice et al. 1999
dry cleaners, Missouri, USA, 1948 (1979?)–1993	5369	exposure assessment in 3 categories: no/little, medium, high exposure	kidneys: little/no exposure: n = 1, SMR: 0.3 (< 0.1–1.6); medium/high exposure: n = 7, SMR 1.5 (0.6–3.1); overall: n = 8, SMR: 1.0 (0.4–2.0); bladder: little/no exposure: n = 5, SMR: 1.4 (0.4–3.2); medium/high exposure: n = 7, SMR: 1.5 (0.6–3.1); overall: n = 12, SMR: 1.3 (0.7–2.4); liver: overall: n = 10, SMR: 0.8 (0.4–1.5); breast: little/no exposure: n = 30, SMR: 0.8 (0.6–1.2); medium/high exposure: n = 29, SMR: 1.2 (0.8–1.7); overall: n = 68, SMR: 1.0 (0.8–1.3); lymphatic and haematopoietic system: little/no exposure: n = 18, SMR: 1.0 (0.6–1.5); medium/high exposure: n = 17, SMR: 0.9 (0.5–1.4); overall: n = 39, SMR: 1.0 (0.7–1.3); NHL: overall: n = 12, SMR: 0.9 (0.5–1.6);	Blair et al. 2003

Table 6 (continued)

Study population, country, period	Number of persons	Exposure	Effects	References
			Hodgkin's lymphomas: overall: n = 5, SMR: 2.0 (0.6–4.6); oesophagus: little/no exposure: n = 7, SMR: 2.1 (0.9–4.4); medium/high exposure: n = 16, SMR: 2.2 (1.2–3.5); overall: n = 26, SMR: 2.2 (1.5–3.3); cervix: little/no exposure: n = 12, SMR: 1.5 (0.8–2.7); medium/high exposure: n = 11, SMR: 1.4 (0.7–1.7); overall: n = 27, SMR: 1.6 (1.0–2.3); lungs: overall: n = 125, SMR: 1.4 (1.1–1.6)	
dry cleaners, Denmark, Finland, Norway, Sweden, 1970–2001	46 768 (laundry workers and dry cleaners); nested case–control study with 2420 persons not exposed, 695 dry cleaners, 183 other workers	exposure categories: group A: dry cleaners and other workers in dry cleaning shops with < 10 workers, group B: other workers in dry cleaning shops, group C: laundry workers not exposed	group A: oesophagus: n = 8, RR: 0.76 (0.34–1.69); gastric cardia: n = 9, RR: 0.69 (0.31–1.53); liver: n = 11, RR: 0.76 (0.38–1.52); pancreas: n = 57, RR: 1.27 (0.90–1.80); cervix: n = 36, RR: 0.98 (0.65–1.47); kidneys: n = 29, RR: 0.67 (0.43–1.05); bladder: n = 93, RR: 1.44 (1.07–1.93); NHL: n = 42, RR: 0.95 (0.65–1.41)	Lynge et al. 2006
aircraft-maintenance workers, Hill Air Force Base, Utah, USA, 1973–2000	14 455 (851 exposed to tetrachloroethylene at some time)	exposure to tetrachloroethylene	lymphatic and haematopoietic system (men): n = 14, HR: 1.92 (1.00–3.69); NHL (men): n = 5, HR: 2.32 (0.75–7.15); NHL (women): n = 2, HR: 2.35 (0.52–10.71); multiple myelomas (men): n = 3, HR: 1.71 (0.42–6.91); multiple myelomas (women): n = 2, HR: 7.84 (1.43–43.06); non-malignant respiratory diseases (men): n = 46, HR: 1.83 (1.28–2.60)	Radican et al. 2008

Table 6 (continued)

Study population, country, period	Number of persons	Exposure	Effects	References
dry cleaners, California, Illinois, Michigan, New York, USA, 1940–2004	1704 (618 exposed to tetrachloroethylene only)	exposure categories: exposure to tetrachloroethylene for at least one year before 1960 (total cohort), exposure to tetrachloroethylene only, further classification according to duration of employment and latency period	kidneys: total cohort: n = 5, SMR: 1.1 (0.4–2.7); tetrachloroethylene only: n = 2, SMR: 1.4 (0.2–4.9); bladder: total cohort: n = 10, SMR: 1.8 (0.9–3.3); employment ≥ 5 years, ≥ 20 years since first employment: n = 9, SMR: 4.1 (2.1–7.1); tetrachloroethylene only: n = 0; liver: total cohort: n = 1, SMR: 0.1 (0.0–0.7); tetrachloroethylene only: n = 0; breast: total cohort: n = 28, SMR: 1.1 (0.7–1.5); tetrachloroethylene only: n = 10, SMR: 1.1 (0.5–1.9); lymphatic and haematopoietic system: total cohort: n = 19, SMR: 0.9 (0.5–1.4); tetrachloroethylene only: n = 11, SMR: 1.5 (0.8–2.7); NHL: total cohort: n = 11, SMR: 1.6 (0.8–2.8); tetrachloroethylene only: n = 6, SMR: 2.5 (0.9–5.4); oesophagus: total cohort: n = 16, SMR: 2.4 (1.4–4.0); employment ≥ 5 years, ≥ 20 years since first employment: n = 11, SMR: 4.8 (2.7–7.9); tetrachloroethylene only: n = 6, SMR: 2.7 (0.98–5.8); tongue: total cohort: n = 5, SMR: 4.5 (1.5–10.5); tetrachloroethylene only: n = 3, SMR: 8.0 (1.7–23.5); cervix: total cohort: n = 13, SMR: 1.8 (0.98–3.1); tetrachloroethylene only: n = 5, SMR: 2.1 (0.7–4.9); trachea, bronchi, lungs: total cohort: n = 77, SMR: 1.3 (1.0–1.6); tetrachloroethylene only: n = 26, SMR: 1.3 (0.8–1.8)	Calvert et al. 2011

Table 6 (continued)

Study population, country, period	Number of persons	Exposure	Effects	References
dry cleaners and laundry workers, Sweden, 1985–2006	9440 (6356 in tetrachloroethylene group)	exposure categories: tetrachloroethylene group (dry cleaners and laundry workers who used tetrachloroethylene only), laundry group (laundry workers without exposure to tetrachloroethylene), combined group (exposure to various substances used in dry cleaning), further classification according to duration of employment	liver, gallbladder: tetrachloroethylene group (men): n = 8, SIR: 2.14 (0.92–4.21); breast: tetrachloroethylene group (women): n = 140, SIR: 0.85 (0.72–1.00); Hodgkin's lymphomas: tetrachloroethylene group (men): n = 3, SIR: 3.22 (0.66–9.40); NHL: tetrachloroethylene group (men): n = 15, SIR: 2.02 (1.13–3.34); tetrachloroethylene group (women): n = 18, SIR: 1.14 (0.68–1.81); oesophagus: tetrachloroethylene group (women): n = 3, SIR: 1.25 (0.26–3.65); cervix: tetrachloroethylene group (women): n = 16, SIR: 1.19 (0.64–1.93); lungs: tetrachloroethylene group (men): n = 23, SIR: 1.30 (0.82–1.94); tetrachloroethylene group (women): n = 35, SIR: 1.09 (0.76–1.51)	Seldén and Ahlborg 2011

Table 6 (continued)

Study population, country, period	Number of persons	Exposure	Effects	References
occupational exposure to tetrachloroethylene, Finland, Iceland, Norway, Sweden, 1961–2005	15 million (Nordic Occupational Cancer Study)	quantitative exposure assessment based on JEMs; classification according to tertile of cumulative exposure or analysis of high exposure group only or use of cumulative exposure as a continuous variable	liver: group with high exposure: men and women: n = 38, HR: 1.26 (0.88–1.80); men: n = 11, HR: 1.31 (0.67–2.56); women: n = 27, HR: 1.24 (0.81–1.89); NHL: group with high exposure: men and women: n = 113, HR: 1.23 (1.00–1.52); men: n = 30, HR: 1.74 (1.15–2.64); multiple myelomas: group with high exposure: men: n = 12, HR: 1.22 (0.65–2.30); women: n = 44, HR: 1.28 (0.92–1.78)	Vlaanderen et al. 2013

HR: hazard ratio; JEM: job exposure matrix; NHL: non-Hodgkin's lymphomas; RR: rate ratio; SIR: standardized incidence ratio; SMR: standardized mortality ratio

was no evidence of a relationship with the incidence of kidney cancer (Vlaanderen et al. 2013). The authors admitted that thestudy limitations were the low exposure prevalence and the limited exposure estimates.

4.7.3 Meta-analyses

Cancer of the kidneys

The studies described in the 1997 supplement (supplement "Tetrachloroethylene" 1997) yielded no evidence of an exposure–response relationship for cancer of the kidneys. More recent studies are not available.

Cancer of the bladder

A meta-analysis reported an SRR (summary relative risk) of 1.27 (95% confidence interval: 0.95–1.71) for bladder cancer among laundry workers (category: launderers). Exposure to tetrachloroethylene was not explicitly mentioned in the study (Reulen et al. 2008).

Another meta-analysis differentiated between workers exposed to tetrachloroethylene and dry cleaners. The meta-relative risk (mRR) for bladder cancer among workers exposed to tetrachloroethylene was 1.08 (95% confidence interval: 0.82–1.42; 3 studies; 463 exposed cases). For dry cleaners, the mRR was 1.47 (95% CI: 1.16–1.85; 7 studies; 139 exposed cases) or, based on studies adjusted for smoking, 1.50 (95% CI: 0.80–2.84; 4 case–control studies) (Vlaanderen et al. 2014).

Conclusions:

The data derived from the epidemiological studies are not sufficient to classify tetrachloroethylene in Carcinogen Category 1. Positive associations were observed for cancer of the bladder, but there are no reliable mechanistic hypotheses. The data for cancer of the kidneys provide even less evidence of a risk. Overall, the evidence is scanty, the exposure was not sufficiently recorded in the studies and clear dose–response relationships were not detected.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

A large number of studies were described in the 1974 documentation (see documentation "Tetrachloroethylene" 1992).

In rats, LC_{50} values of 4100 and 5027 ml/m^3 were reported after exposure by inhalation for 6 hours and 8 hours, respectively (NEG 2003). After exposure for 4 hours, LC_{50} values of 4000 and 5200 ml/m^3 were established for rats and mice, respectively (ACGIH 2001). Acute inhalation exposure induced neurotoxic symptoms such as hyperactivity, hypoactivity, hypotonia, loss of reflexes, drowsiness, trembling, ataxia and impaired respiration close to the lethal dose (NEG 2003). Other effects included

hepatotoxicity, immune disorders and effects on the kidneys in mice at high concentrations and cardiac arrhythmia in rabbits (NEG 2003).

Exposure of dogs to 68 900 mg/m^3 (10 000 ml/m^3) for 10 minutes induced irritation of the respiratory tract; no effects were observed after exposure to 34 450 mg/m^3 (5000 ml/m^3) (SCOEL 2009).

5.1.2 Oral administration

LD_{50} values of 3835 and 3005 mg/kg body weight were reported after acute oral exposure in male and female rats, respectively (NEG 2003). After acute exposure of mice, oral LD_{50} values of 4700 to 5000 mg/kg body weight were determined and an oral LD_{50} of 7814 mg/kg body weight was reported after the administration of undiluted tetrachloroethylene (NEG 2003).

5.1.3 Dermal application

In rabbits, the LD_{50} was greater than 10 000 mg/kg body weight after occlusive dermal exposure to tetrachloroethylene doses of 1300, 2500, 5000, 10 000 or 20 000 mg/kg body weight for 24 hours. Necrosis at the application sites was observed at all dose levels (Dow Europe GmbH 2014).

5.1.4 Intraperitoneal and intravenous injection

After single intraperitoneal injections, the LD_{50} was 4600 to 5671 mg/kg body weight in mice and 3163 mg/kg body weight in dogs (NEG 2003).

In mice, an LD_{50} of 5000 mg/kg body weight was reported after subcutaneous injection (NEG 2003).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The studies that investigated the toxicity of tetrachloroethylene after repeated inhalation exposure are shown in Table 7.

After exposure by inhalation, the liver and kidneys were the most important target organs of tetrachloroethylene, and effects on the central nervous system were observed at high concentrations. In the 13-week and 2-year studies in rats, only the liver weights were increased after exposure to 50 ml/m^3 (6.5% and 11%, respectively); as the concentration increased, survival was slightly reduced in the long-term study (no other details). The 13-week studies in mice reported NOAECs of 100 to 115 ml/m^3; in a 2-year study, survival was slightly reduced at 10 ml/m^3 and above (no other details) and there was a significant increase in the liver enzymes in serum at 50 ml/m^3 and above (JMHLW 1992 b, c, d).

Table 7 Studies of the toxicity of tetrachloroethylene after repeated exposure by inhalation

Species, strain, number per group	Exposure	Findings	References
rat, F344, 3 ♂	**1, 5 or 10 days**, 0, 1000 ml/m³, 6 hours/day, whole body	**1000 ml/m³**: kidneys: hyaline deposits in the tubular epithelium ↑ (after 10 days)	Green et al. 1990
rat, Sprague Dawley, ♂	**4 days**, 0, 200 ml/m³, 6 hours/day	**200 ml/m³**: behavioural changes	ATSDR 2014
rat, F344, ♂	**4 days**, 0, 800 ml/m³, 6 hours/day	**800 ml/m³**: changes in FEP, SEP and EEG	Mattsson et al. 1998
rat, F344/N, 5 ♂, 5 ♀	**14 days**, 0, 100, 200, 425, 875, 1750 ml/m³, 6 hours/day, 5 days/week, whole body	**up to 875 ml/m³**: NOAEC; **1750 ml/m³**: mortality (2/5 ♂, 3/5 ♀), dyspnoea, hypoactivity, ataxia; ♂: body weights ↓; range-finding study	NTP 1986
rat, F344/DuCrj, 10 ♂, 10 ♀	**2 weeks**, 0, 200, 400, 800, 1600, 3200 ml/m³, 6 hours/day, 5 days/week, whole body	**1600 ml/m³ and above**: body weight gains ↓, feed consumption ↓, piloerection; **3200 ml/m³**: lacrimation, irregular respiration, mortality (5/10 ♂, 7/10 ♀); range-finding study	JMHLW 1992 a, c
rat, Wistar, 22 ♀	**18 days**, 0, 400 ml/m³, 7 hours/day, 14 whole-body exposures	**400 ml/m³**: NOAEC	Rowe et al. 1952
rat, Wistar, 5 ♂, 5 ♀	**18 days**, 0, 2500 ml/m³, 7 hours/day, up to 13 whole-body exposures	**2500 ml/m³**: mortality (4/5 ♂, 4/5 ♀), severe CNS depression, loss of consciousness, liver: cloudy swelling with diffusely distributed fat vacuoles	Rowe et al. 1952

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 8 ♀	**25 days**, 0, 1600 ml/m^3, 7 hours/day, 18 whole-body exposures	**1600 ml/m^3**: marked effects on behaviour, body weights ↓, enlarged liver and kidneys, no histopathological findings	Rowe et al. 1952
rat, F344, 5 ♂, 5 ♀	**14, 21 or 28 days**, 0, 400 ml/m^3, 6 hours/day, whole body	**400 ml/m^3**: liver: hardly any evidence of peroxisomal proliferation (cyanide-insensitive palmitoyl-CoA oxidation, electron microscopy), centrilobular hypertrophy	Odum et al. 1988
rat, F344, 5 ♂, 5 ♀	**28 days**, 0, 200 ml/m^3, 6 hours/day, whole body	**200 ml/m^3**: liver: hardly any evidence of peroxisomal proliferation (cyanide-insensitive palmitoyl-CoA oxidation, electron microscopy); ♂: liver: centrilobular hypertrophy	Odum et al. 1988
rat, F344, 5 ♂, 5 ♀	**28 days**, 0, 400 ml/m^3, 6 hours/day, whole body	**400 ml/m^3**: NOAEC	Green et al. 1990
rat, no other details	**30 days**, 0, 200, 400, 800 ml/m^3, 24 hours/day	**200 ml/m^3 and above**: brain: glutamine, threonine and serine ↑, GABA ↓, acetylcholine in the striatum ↓	NEG 2003
rat, no other details	**30 days**, 0, 320 ml/m^3, 24 hours/day	**320 ml/m^3**: brain: slight decrease in cholesterol and phospholipids, changes in fatty acid composition	NEG 2003

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 16 ♀	**4 weeks**, 0, 100, 300, 1000 ml/m³, 6 hours/day, 5 days/week whole body	**100 ml/m³**: NOAEC; **300 ml/m³ and above**: liver: relative weights ↑, slight hypertrophy of centrilobular hepatocytes; **1000 ml/m³**: transient decrease in body weights; no evidence of immunotoxicity (antibody response to sheep erythrocytes; phagocytic activity of alveolar macrophages)	Boverhof et al. 2013
rat, Sprague Dawley, 8 ♂	**4 or 12 weeks**, 0, 300, 600 ml/m³, 24 hours/day	**600 ml/m³**: brain: body weight gains ↓, DNA, total protein and weights of frontal cerebral cortex and brain stem ↓; frontal cerebral cortex: cytoskeletal proteins in glial and neuronal cells ↓; glial proteins ↓ (in hippocampus, brain stem and frontal cerebral cortex)	Wang et al. 1993
rat, Sprague Dawley, 8 ♂	**90 days**, 0, 320 ml/m³, 24 hours/day, with and without recovery for 30 days	**320 ml/m³**: liver: relative weights ↑; brain: slight changes in fatty acid composition of phospholipids, reversible in most cases; slight persistent changes in cholesterol content	Kyrklund et al. 1990
rat, F344/N, 10 ♂, 10 ♀	**13 weeks**, 0, 100, 200, 400, 800, 1600 ml/m³, 6 hours/day, 5 days/week, whole body	**0 ml/m³**: liver: congestion (1/10 ♂, 0/9 ♀); **200 ml/m³**: liver: congestion (2/10 ♂, 1/10 ♀); **400 ml/m³**: liver: congestion (3/10 ♂, 5/10 ♀); **800 ml/m³**: liver: congestion (5/10 ♂, 5/10 ♀); **1600 ml/m³**: mortality (4/10 ♂, 7/10 ♀), body weights ↓ (♂: 20%, ♀: 11%), lungs: congestion (7/10 ♂, 7/10 ♀), liver: congestion (7/10 ♂, 8/9 ♀)	NTP 1986

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344/DuCrj, 10 ♂, 10 ♀	**13 weeks**, 0, 50, 115, 265, 609, 1400 ml/m^3, 6 hours/day, 5 days/week, whole body	**50 ml/m^3 and above**: ♀: relative liver weights ↑ (6.5–15.4%); **609 ml/m^3 and above**: relative liver weights ↑; ♂: cholesterol ↑, relative kidney weights ↑; **1400 ml/m^3**: absolute and relative kidney weights ↑; ♂: body weight gains ↓, urine: pH and protein ↑, relative adrenal gland and testis weights ↑	JMHLW 1992 b, c
rat, F344/N, 12 ♂, 12 ♀	**13 weeks**, 0, 50, 200, 800 ml/m^3, 6 hours/day, 5 days/week whole body	**200 ml/m^3**: NOAEC; **800 ml/m^3**: increase in FEP amplitude; no clinical or neuropathological findings	Mattsson et al. 1998
rat, Wistar, 15 ♂, 15 ♀	**183 days**, 0, 400 ml/m^3, 7 hours/day, 130 whole-body exposures	**400 ml/m^3**: NOAEC	Rowe et al. 1952
rat, no other details	**7 months**, 0, 70, 230, 470 ml/m^3, 8 hours/day, 5 days/week	**70 ml/m^3**: NOAEC; **230 ml/m^3**: liver: glycogen ↓; **470 ml/m^3**: kidneys: mild nephropathy; study from 1937	ATSDR 2014
rat, Sprague Dawley, 94 ♂, 91–94 ♀, controls: 189 ♂, 189 ♀	**12 months**, 0, 300, 600 ml/m^3, 6 hours/day, 5 days/week, whole body, life-long observation (for a maximum 31 months)	**300 ml/m^3**: NOAEC; **600 ml/m^3**: ♂: mortality ↑ (months 5–24) presumably because of earlier beginning of chronic nephropathy; liver: relative weights ↑; no treatment-related histopathological changes	Rampy et al. 1978

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344/N, 50 ♂, 50 ♀	**104 weeks**, 0, 200, 400 ml/m³, 6 hours/day, 5 days/week, whole body	**200 ml/m³**: kidneys: karyomegaly ↑ (♂: 37/49, controls: 1/49; ♀: 8/49, controls: 0/50), tubular cell hyperplasia (♂: 3/49, controls: 0/49; ♀: 0/49, controls: 0/50); mononuclear cell leukaemia ↑; ♂: nasal cavity: squamous metaplasia (♂: 5/50, controls: 0/50); adrenal medulla: hyperplasia ↑; **400 ml/m³**: kidneys: karyomegaly ↑ (♂: 47/50, controls: 1/49; ♀: 20/50, controls: 0/50), tubular cell hyperplasia (♂: 5/50, controls: 0/49; ♀: 1/50, controls: 0/50); mononuclear cell leukaemia ↑; ♂: survival ↓ (as of week 102); forestomach: ulcers (♂: 5/49, controls: 0/48); nasal cavity: thrombosis (♂: 19/50, controls: 9/50), squamous metaplasia (♂: 5/50, controls: 0/50); adrenal medulla: hyperplasia ↑; ♀: adrenal cortex: hyperplasia (♀: 11/47, controls: 4/50); see also Section 5.7.2	NTP 1986

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344/DuCrj, 50 ♂, 50 ♀	**104 weeks**, 0, 50, 200, 600 ml/m^3, 6 hours/day, 5 days/week whole body	**50 ml/m^3 and above**: decrease in survival in relation to the concentration (no data for significance); **50 ml/m^3**: ♀: absolute liver weights ↑ (11%); **200 ml/m^3 and above**: ♂: kidneys: absolute and relative weights ↑; spleen: extramedullary haematopoiesis ↓; ♀: relative heart, lung, kidney and liver weights ↑, serum: ALT ↑, urea nitrogen ↑; **200 ml/m^3**: kidneys: karyomegaly of tubular epithelial cells (♂: 23/50, controls: 0/50; ♀: 1/50, controls: 0/50); ♀: body weight gains ↓, relative adrenal gland weights ↑; **600 ml/m^3**: body weight gains ↓, serum: ALT ↑; kidneys: karyomegaly of tubular epithelial cells (♂: 48/50, controls: 0/50; ♀: 16/50, controls: 0/50), atypical dilation in proximal tubules (♂: 24/50, controls: 0/50; ♀: 6/50, controls: 0/50); liver: relative weights ↑; ♂: liver: spongiosis hepatitis ↑; ♀: absolute liver weights ↑ (11%), MCH ↑, serum: triglycerides ↓, potassium ↑; see also Section 5.7.2	JMHLW 1992 d, e, 1993 a
mouse, ddY, 16 ♂, controls: 8 ♂	**5 days**, 0, 300 ml/m^3, 6 hours/day, whole body, examination 1–7 days after exposure	**300 ml/m^3**: nose: olfactory epithelium: degeneration and dilation of Bowman's glands (days 1–7 after exposure), atrophy of olfactory nerves (days 4–7 after exposure); effects less pronounced in the respiratory epithelium	Aoki et al. 1994

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, ddY, 20 ♂, controls: 10 ♂	**5 days**, 0, 300 ml/m³, 6 hours/day, whole body, examination 2 weeks to 3 months after exposure	**300 ml/m³**: nose: some of the olfactory epithelium replaced by ciliated epithelium, atrophy of olfactory nerves and Bowman's glands (up to 3 months after exposure); effects in the respiratory epithelium less persistent	Suzaki et al. 1997
mouse, B6C3F1, 5 ♂, 5 ♀	**14 days**, 0, 100, 200, 425, 875, 1750 ml/m³, 6 hours/day, 5 days/week, whole body	**up to 425 ml/m³**: NOAEC; **875 ml/m³**: liver: fatty vacuolation of hepatocytes (4/5 ♂); **1750 ml/m³**: dyspnoea, hypoactivity, hyperactivity, anaesthesia, ataxia; body weights ↓ (♂: 6%, ♀: 7%); liver: fatty vacuolation of hepatocytes (5/5 ♂, 5/5 ♀); range-finding study	NTP 1986
mouse Crj:BDF1, 10 ♂, 10 ♀	**2 weeks**, 0, 200, 400, 800, 1600, 3200 ml/m³, 6 hours/day, 5 days/week, whole body	**400 ml/m³ and above**: pale liver; **800 ml/m³ and above**: kidneys: necrosis and regeneration in the proximal tubule; AST and ALT ↑; **1600 ml/m³ and above**: swelling of the liver; **3200 ml/m³**: mortality (9/10 ♂, 7/10 ♀); body weight gains ↓; range-finding study	JMHLW 1992 a, c
mouse, B6C3F1, 5 ♂, 5 ♀	**14, 21 or 28 days**, 0, 400 ml/m³, 6 hours/day, whole body	**400 ml/m³**: liver: relative weights ↑, centrilobular eosinophily and fatty vacuolation, cyanide-insensitive palmitoyl-CoA oxidation ↑, peroxisomal proliferation (electron microscopy)	Odum et al. 1988
mouse, B6C3F1, 5 ♂, 5 ♀	**28 days**, 0, 200 ml/m³, 6 hours/day, whole body	**200 ml/m³**: liver: relative weights ↑, centrilobular lipid accumulation, cyanide-insensitive palmitoyl-CoA oxidation ↑, peroxisomal proliferation (electron microscopy)	Odum et al. 1988

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 5 ♂, 5 ♀	**28 days**, 0, 400 ml/m^3, 6 hours/day, whole body	**400 ml/m^3**: NOAEC	Green et al. 1990
mouse, no other details	**30 days**, 0, 9, 75 ml/m^3, 24 hours/day	**9 ml/m^3**: liver: weights ↑, hypertrophy and vacuolation; **75 ml/m^3**: liver: weights ↑ (100%), hypertrophy and vacuolation	NEG 2003
mouse, no other details	**up to 8 weeks**, 0, 200 ml/m^3, 4 hours/day, 6 days/week	**200 ml/m^3**: liver: increase in severity of effects with an increase in the number of exposures; after 8 weeks: massive, central infiltration with fat in about 80% of the liver	NEG 2003
mouse, B6C3F1, 10 ♂, 10 ♀	**13 weeks**, 0, 100, 200, 400, 800, 1600 ml/m^3, 6 hours/day, 5 days/week, whole body	**100 ml/m^3**: NOAEC; **200 ml/m^3**: kidneys: karyomegaly (6/10 ♂, 8/10 ♀); ♂: liver: mitotic change (3/10); **400 ml/m^3**: kidneys: karyomegaly (10/10 ♂, 10/10 ♀); liver: infiltration of leukocytes, centrilobular necrosis, biliary stasis (8/10 ♂, 5/10 ♀); ♂: liver: mitotic change (5/10); **800 ml/m^3**: kidneys: karyomegaly (10/10 ♂, 10/10 ♀); liver: infiltration of leukocytes, centrilobular necrosis, biliary stasis (10/10 ♂, 10/10 ♀); ♂: liver: mitotic change (5/10) ; **1600 ml/m^3**: mortality (2/10 ♂, 4/10 ♀), kidneys: karyomegaly (7/7 ♂, 6/7 ♀); liver: infiltration of leukocytes, centrilobular necrosis, biliary stasis (10/10 ♂, 8/9 ♀); ♂: body weights ↓ (8%); liver: mitotic change (1/10)	NTP 1986

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse Crj:BDF1, 10 ♂, 10 ♀	**13 weeks**, 0, 50, 115, 265, 609, 1400 ml/m³, 6 hours/day, 5 days/week, whole body	**115 ml/m³**: NOAEC; **265 ml/m³ and above**: relative liver weights ↑, swelling of the liver (50%–100% of animals); ♂: absolute liver weights ↑, ALP ↑; **609 ml/m³ and above**: ALT ↑, relative lung weights ↑, kidneys: nuclear enlargement of proximal tubules (90%–100% of animals); ♂: body weight gains ↓, Hb and Hct ↓, kidney weights ↓, relative adrenal gland and spleen weights ↑; **1400 ml/m³**: CPK ↑; kidneys: regeneration of proximal tubules (5/10 ♂, 6/10 ♀); ♂: pH ↓; ♀: body weight gains ↓; absolute liver weights ↑	JMHLW 1992 b, c
mouse, B6C3F1, 50 ♂, 50 ♀	**104 weeks**, 0, 100, 200 ml/m³, 6 hours/day, 5 days/week, whole body	**100 ml/m³**: kidneys: casts (♂: 9/49, controls: 3/49; ♀: 4/49, controls: 4/48), karyomegaly (♂: 17/49, controls: 4/49; ♀: 16/49, controls: 0/48), nephrosis (♂: 24/49, controls: 22/49; ♀: 14/49, controls: 5/48); ♂: survival ↓; liver: degeneration (♂: 8/49, controls: 2/49), necrosis (♂: 6/49, controls: 1/49), nuclear inclusions (♂: 5/49, controls: 2/49); **200 ml/m³**: survival ↓; kidneys: casts (♂: 15/50, controls: 3/49; ♀: 15/50, controls: 4/48), karyomegaly (♂: 46/50, controls: 4/49; ♀: 38/50, controls: 0/48), nephrosis (♂: 28/50, controls: 22/49; ♀: 25/50, controls: 5/48); liver: degeneration (♂: 14/50, controls: 2/49; ♀: 13/50, controls: 1/49), necrosis (♂: 15/50, controls: 1/49; ♀: 9/50, controls: 3/48), nuclear inclusions (♂: 9/50, controls: 2/49); see also Section 5.7.2	NTP 1986

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse Crj:BDF1, 50 ♂, 50 ♀	**104 weeks**, 0, 10, 50, 250 ml/m³, 6 hours/day, 5 days/week whole body	**10 ml/m³ and above**: decrease in survival in relation to the concentration (no data for significance); **50 ml/m³ and above**: ♂: serum: AST and ALT ↑; **50 ml/m³**: liver: degeneration (♂: 4/50, controls: 1/50; ♀: 2/50, controls: 0/50); kidneys: karyomegaly tubular epithelial cells (♂: 6/50, controls: 0/50; ♀: 1/50, controls: 0/50); ♂: liver: angiectasis (12/50, controls: 1/50); **250 ml/m³**: body weight gains ↓; feed consumption ↓; erythrocyte count and Hct ↑; serum: total bilirubin ↑, AST, ALT, LDH and ALP ↑, chloride ↓; relative weights of heart, lungs, kidneys and brain ↑; liver: angiectasis (♂: 33/50; ♀: 25/50, controls: 6/50), degeneration (♂: 37/50; ♀: 30/50), hepatocellular adenomas and carcinomas ↑; kidneys: karyomegaly of tubular epithelial cells (♂: 38/50 ♀: 49/50); spleen: extramedullary haematopoiesis ↑; ♂: MCV, MCH, MCHC and platelets ↓; serum: total protein, cholesterol and calcium ↑, glucose, triglycerides and urea nitrogen ↓; absolute and relative kidney, spleen and liver weights ↑; relative adrenal gland and testis weights ↑; liver: focal necrosis (13/50; controls: 3/50); ♀: haemoglobin ↑; serum: potassium ↓; kidneys: atypical dilation in proximal tubules (6/50, controls: 0/50); see also Section 5.7.2	JMHLW 1992 d, e, 1993 b
rabbit, 2 ♂	**39 days**, 0, 2500 ml/m³, 7 hours/day, 28 whole-body exposures	**2500 ml/m³**: severe CNS depression; liver: degeneration of the parenchyma	Rowe et al. 1952

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rabbit, 15 (no other details)	**45 days**, 0, 2790 ml/m³, 4 hours/day, 5 days/week	**2790 ml/m³**: serum: AST, ALT and GDH ↑; liver: damage to cytoplasmic and mitochondrial structures in the parenchyma	NEG 2003
rabbit, 2 ♂, 2 ♀	**222 days**, 0, 400 ml/m³, 7 hours/day, 159 whole-body exposures	**400 ml/m³**: NOAEC	Rowe et al. 1952
guinea pig, 7 ♂	**10 days**, 0, 1600 ml/m³, 7 hours/day, 8 whole-body exposures	**1600 ml/m³**: body weights ↓; liver: weights ↑, moderate fatty degeneration, testes: slight degenerative changes in germinal epithelium	Rowe et al. 1952
guinea pig, 7 ♀	**17 days**, 0, 100 ml/m³, 7 hours/day, 13 whole-body exposures	**100 ml/m³**: NOAEC	Rowe et al. 1952
guinea pig, 15 ♂, 5 ♀	**18 days**, 0, 200 ml/m³, 7 hours/day, 14 whole-body exposures	**200 ml/m³**: body weight gains ↓; liver: weights ↑, mild fatty degeneration	Rowe et al. 1952
guinea pig, 15 ♂	**18 days**, 0, 400 ml/m³, 7 hours/day, 14 whole-body exposures	**400 ml/m³**: body weight gains ↓; liver: weights ↑, mild to moderate fatty degeneration; kidneys: weights ↑	Rowe et al. 1952

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
guinea pig, 4 ♂, 4 ♀	**24 days**, 0, 2500 ml/m³, 7 hours/day, 18 whole-body exposures	**2500 ml/m³**: severe CNS depression; body weights ↓; liver: weights ↑, fatty degeneration; kidneys: weights ↑, cloudy swelling of tubular epithelium	Rowe et al. 1952
guinea pig, no other details	**30 days**, 0, 160 ml/m³, 24 hours/day	**160 ml/m³**: brain: changes in fatty acid composition, no increased sensitivity of the animals during gestation	NEG 2003
guinea pig, 7 ♂, 4 ♀	**185 days**, 0, 100 ml/m³, 7 hours/day, 132 whole-body exposures	**100 ml/m³**: liver: few small fat vacuoles (2/5 ♂, 4/4 ♀); ♀: liver: relative weights ↑ (18%)	Rowe et al. 1952
guinea pig, 8 ♂, 8 ♀	**220 days**, 0, 200 ml/m³, 7 hours/day, 158 whole-body exposures	**200 ml/m³**: body weight gains ↓; liver: relative weights ↑, fatty degeneration, fat and esterified cholesterol ↑	Rowe et al. 1952
guinea pig, 8 ♂, 8 ♀	**236 days**, 0, 400 ml/m³, 7 hours/day, 169 whole-body exposures	**400 ml/m³**: body weight gains ↓; liver: weights ↑, fatty degeneration with slight cirrhosis, fat and esterified cholesterol ↑	Rowe et al. 1952
Mongolian gerbil, no other details	**30 days**, 0, 320 ml/m³, 24 hours/day	**320 ml/m³**: brain: changes in fatty acid composition	NEG 2003
Mongolian gerbil, no other details	**3 months**, 0, 320 ml/m³, 24 hours/day	**320 ml/m³**: brain: slight decrease in weight, slight changes in fatty acid composition of phospholipids	NEG 2003

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
Mongolian gerbil, no other details	**3 months**, 0, 60, 320 ml/m³, 24 hours/day, 4 months recovery	**60 ml/m³ and above**: cerebral cortex: slight decrease in DNA concentration, evidence of loss of neuronal and glial cells in the frontal cortex; **320 ml/m³**: brain: slight increase in astroglial protein S100 (in hippocampus, occipital cerebral cortex and cerebellum)	NEG 2003
Mongolian gerbil, no other details	**12 months**, 0, 120 ml/m³, 24 hours/day	**120 ml/m³**: brain: slight changes in fatty acid composition of phospholipids	NEG 2003
Rhesus monkey, 2 ♂	**250 days**, 0, 400 ml/m³, 7 hours/day, 179 whole-body exposures	**400 ml/m³**: NOAEC	Rowe et al. 1952

ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; EEG: electroencephalogram; FEP: flash evoked potential; GABA: γ-aminobutyric acid; GDH: glutamate dehydrogenase; Hb: haemoglobin; Hct: haematocrit; LDH: lactate dehydrogenase; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean erythrocyte volume; SEP: somatosensory evoked potential

5.2.2 Oral administration

The studies that investigated the toxicity of tetrachloroethylene after repeated oral exposure are shown in Table 8. After oral administration of tetrachloroethylene, the liver and kidneys were the main target organs in rats and mice.

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

When testing skin irritation in rabbits according to Draize, the average degree of skin irritation caused by tetrachloroethylene (99.95%) was given a score of 4 of a maximum of 4 for erythema (severe erythema and slight eschar formation) and of 1.7 of a maximum of 4 for oedema (slight oedema). The findings were reversible after 16 days, but had not completely subsided. The effects were no longer visible after a total of 5 weeks (van Beek 1990). Tetrachloroethylene thus caused irritation of the skin (supplement "Tetrachloroethylene" 1997).

In a Draize test in female New Zealand White rabbits, tetrachloroethylene ("very pure"; 0.5 ml; occlusive; 24 hours) caused severe skin irritation; the primary dermal irritation index was 6.1 of 8 (Duprat et al. 1976; ECHA 2014).

Another study reported moderate necrosis in groups of 4 rabbits after 24-hour occlusive application of undiluted tetrachloroethylene in doses of 1300 and 2500 mg/kg body weight and severe necrosis at higher doses (no other details) (ECHA 2014).

In guinea pigs, however, no gross-pathological changes of the skin were observed after treatment with tetrachloroethylene (1 ml in glass rings on the backs of the animals) for 16 hours. The microscopic examination revealed degenerative changes in the epidermis, junctional separation and cellular infiltration in the dermis (ECHA 2014; NEG 2003).

5.3.2 Eyes

After tetrachloroethylene was sprayed directly into the eyes of rabbits, blepharospasms, a granular and optically irregular appearance of the corneal epithelium and the loss of patches of epithelium were observed. The effects were completely reversible within 2 days (NEG 2003).

In a study of the irritant effects of tetrachloroethylene (0.1 ml; "very pure") in the eyes of female New Zealand White rabbits, the substance caused slight irritation of the eyes with a primary irritation index of 4 of 110. Redness of the conjunctiva with discharge, and damage and keratosis of the epithelial cells were observed in the animals (Duprat et al. 1976; Dow Europe GmbH 2014).

Table 8 Studies of the toxicity of tetrachloroethylene after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, ♂	**5 days**, 0, 500, 1000, 2000 mg/kg body weight and day, daily, gavage	**1000 mg/kg body weight**: liver: relative weights ↑, induction of CYP2B and phase II enzymes; **2000 mg/kg body weight**: body weights ↓ (16%); spleen: atrophy, thymus: atrophy	ATSDR 2014
rat, F344, 4 ♂	**7 days**, 0, 1000 mg/kg body weight and day, daily, gavage	**1000 mg/kg body weight**: kidneys: hyaline droplets in tubular epithelium ↑	Potter et al. 1996
rat, F344, ♂	**10 days**, 0, 1000 mg/kg body weight and day, daily, gavage	**1000 mg/kg body weight**: liver: relative weights ↑; no evidence of peroxisomal proliferation in the liver and kidneys (no increase in cyanide-insensitive palmitoyl-CoA oxidase)	ATSDR 2014; NEG 2003
rat, F344, ♂, ♀	**10 days**, 0, 1000 mg/kg body weight and day, daily, gavage	**1000 mg/kg body weight**: ♂: kidneys: hyaline deposits and α2u globulin in tubular epithelium ↑, cell replication ↑	ATSDR 2014; NEG 2003
rat, F344, ♂	**11 days**, 0, 100, 250, 500, 1000 mg/kg body weight and day, daily, gavage	**1000 mg/kg body weight**: body weight gains ↓ (22%); liver: changes in cell staining of centrilobular hepatocytes	ATSDR 2014; NEG 2003
rat, F344, ♀	**14 days**, 0, 500, 1500 mg/kg body weight and day, 7 days/week, gavage	**1500 mg/kg body weight**: liver: relative weights ↑, hepatocellular hypertrophy; serum: ALT ↑	ATSDR 2014

Table 8 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, ♀	**14 days**, 0, 1000 mg/kg body weight and day, 7 days/week, gavage	**1000 mg/kg body weight**: liver: minimal periportal lymphocytic infiltration, inflammation, hepatocellular necrosis; serum: AST, ALT, ALP ↑	ATSDR 2014
rat, Wistar, ♂	**2 or 4 weeks**, 0, 0.01, 1 mg/l drinking water (about 0, 0.0012, 0.12 mg/kg body weight and day[a)])	**0.0012 mg/kg body weight and above**: increased dermal lymphocyte infiltration and perivascular mast cell accumulation; mesenteric lymph nodes: relative weights ↑, enlargement with visible germinal centres; relevance of the findings unclear	ATSDR 2014
rat, F344, ♂, ♀	**4 weeks**, 0, 500 mg/kg body weight and day, 7 days/week, gavage (in corn oil)	**500 mg/kg body weight**: kidneys: accumulation of protein droplets (S2 segment of the proximal tubule), less pronounced in ♀; urine: protein elimination ↑ (albumin: ♂: up to 15-fold above control group, ♀: slight increase; α2u globulin: ♂: transient increase, ♀: up to 4-fold above control group; RBP: ♂: up to 2-fold above control group, ♀: slight increase; NAG: ♂: transient increase, ♀: slight increase)	NEG 2003
rat, Wistar, 5 ♀	**32 days**, 0, 600, 2400 mg/kg body weight and day, 7 days/week, gavage	**2400 mg/kg body weight**: mortality (1/5); severe, but transient CNS depression; liver: relative weights ↑; kidneys: relative weights ↑, multifocal tubular vacuolation and karyomegaly; serum: AST and ALT ↑; urinalysis: volume ↑, protein ↑, GGT, ALP, LDH and NAG ↑	Jonker et al. 1996
rat, F344, 10 ♂	**42 days**, 0, 1500 mg/kg body weight and day, 7 days/week, gavage (in corn oil)	**1500 mg/kg body weight**: kidneys: relative weights ↑, hyaline deposits in tubular epithelium ↑, tubular casts, focal tubular regeneration; urine: volume ↑, glucose ↑, ALP ↑, NAG ↑	Green et al. 1990

Table 8 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Osborne Mendel, 5 ♂, 5 ♀	**6 weeks**, 0, 316, 562, 1000, 1780, 3160 mg/kg body weight and day, 5 days/week, gavage, 2-week observation	**up to 1000 mg/kg body weight**: no mortality, no reduced body weight gains; **1780 mg/kg body weight and above**: mortality; range-finding study	NCI 1977
rat, Sprague Dawley, ♂	**8 weeks**, 0, 5, 50 mg/kg body weight and day, 5 days/week, gavage	**5 mg/kg body weight and above**: impaired nociception (latency period ↑), increased threshold for seizure initiation; **50 mg/kg body weight**: motor activity ↓	ATSDR 2014
rat, Sprague Dawley, ♂, ♀	**90 days**, 0, 14, 400, 1400 mg/kg body weight and day, drinking water	**14 mg/kg body weight**: NOAEL; **400 mg/kg body weight**: ♂: kidneys: relative weights ↑; ♀: body weight gains ↓ (18%); **1400 mg/kg body weight**: body weight gains ↓ (24%); liver: relative weights ↑; kidneys: relative weights ↑	ATSDR 2014; NEG 2003
rat, Osborne Mendel, 50 ♂, 50 ♀; controls with gavage: 20 ♂, 20 ♀; controls without gavage: 20 ♂, 20 ♀	**78 weeks**, 0, 471/474, 941/949 mg/kg body weight and day, 5 days/week, gavage (in corn oil), 32-week observation	**471 mg/kg body weight**: kidneys: nephropathy ↑; dose-dependent increase in mortality; **941 mg/kg body weight**: kidneys: nephropathy ↑; 50% mortality: ♂: week 44, ♀: week 66; pneumonia in almost all animals (including controls)	NCI 1977
rat, 40 ♂, 40 ♀; controls: 50 ♂, 50 ♀	**104 weeks**, 0, 500 mg/kg body weight and day, 4–5 days/week, in olive oil, gavage	**500 mg/kg body weight**: no increase in tumour incidence; ♂: kidneys: cytomegaly or karyomegaly of tubular cells (in 32% of the animals)	NEG 2003

Table 8 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, ♂	**10 days**, 0, 1000 mg/kg body weight and day, daily, gavage	**1000 mg/kg body weight**: liver: relative weights ↑; peroxisomal proliferation in the liver and kidneys (cyanide-insensitive palmitoyl-CoA oxidase ↑)	ATSDR 2014; NEG 2003
mouse, B6C3F1, ♂	**11 days**, 0, 100, 250, 500, 1000 mg/kg body weight and day, daily, gavage	**100 mg/kg body weight and above**: liver: hepatocellular swelling, DNA content ↓, DNA synthesis ↑	ATSDR 2014; NEG 2003
mouse, Swiss Webster, ♂, ♀	**15 days**, 0, 3000 mg/kg body weight and day, 7 days/week, gavage	**3000 mg/kg body weight**: liver: relative weights ↑, focal necrosis, change in glycolytic and gluconeogenic enzyme activities; kidneys: relative weights ↑, hypercellular glomeruli; blood: leukocytes ↑, Hb, Hct, erythrocytes and platelets ↓	ATSDR 2014
mouse, ICR, no data	**2 or 4 weeks**, 0, 0.0025, 0.26 mg/kg body weight and day, drinking water	**< 0.1 mg/kg body weight**: increase in passive anaphylactic reaction of the skin, only after 4 weeks, no effects after 2 weeks	ATSDR 2014
mouse, Swiss Webster, 4 ♂ per time	**7, 14 or 30 days**, 0, 150, 500, 1000 mg/kg body weight and day, 7 days/week, gavage	**150 mg/kg body weight and above**: plasma: ALT ↑ (as of day 1–14); liver: replicative DNA synthesis ↑ (after 7 days); **500 mg/kg body weight and above**: liver: centrilobular fatty degeneration, single cell necrosis, reduced damage as of day 30, beginning tissue repair, replicative DNA synthesis ↑ (after 14 days); **1000 mg/kg body weight**: mortality (2/20); no evidence of nephrotoxicity (histopathology, urea nitrogen in the blood)	Philip et al. 2007

Table 8 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, Swiss Cox, ♂, no other details	**6 weeks**, 0, 20, 100, 200, 500, 1000, 1500, 2000 mg/kg body weight and day, 5 days/week, gavage	**20 mg/kg body weight**: NOAEL; **100 mg/kg body weight and above**: liver: relative weights ↑ triglycerides ↑; **200 mg/kg body weight and above**: liver: degeneration and necrosis	ATSDR 2014; NEG 2003
mouse, B6C3F1, 5 ♂, 5 ♀	**6 weeks**, 0, 562, 1000, 1780, 3160, 5620 mg/kg body weight and day, 5 days/week, gavage, 2-week observation	**562 mg/kg body weight**: ♂: body weight gains unchanged; ♀: body weight gains ↓ (30%); **1000 mg/kg body weight**: ♂: body weight gains ↓ (22%); ♀: body weight gains ↓ (15%); range-finding study	NCI 1977
mouse, no other details	**7 weeks**, 0, 0.05, 0.1 mg/kg body weight and day, drinking water	**0.05 mg/kg body weight and above**: body weights ↓; spleen: relative weights ↑, haemosiderin in the macrophages of the red pulpa ↑, erythrocyte count in red pulpa ↑; kidneys: relative weights ↑; serum: LDH activity ↑	NEG 2003
mouse, B6C3F1, 50 ♂, 50 ♀; controls with gavage: 20 ♂, 20 ♀; controls without gavage: 20 ♂, 20 ♀	**78 weeks**, ♂/♀: 0, 536/386, 1072/772 mg/kg body weight and day, 5 days/week, gavage (in corn oil), 12-week observation	**536/386 mg/kg body weight**: kidneys: nephropathy; liver: hepatocellular carcinomas (see also Section 5.7.2)	NCI 1977

[a)] conversion factor 0.12 according to EFSA (2012);
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BrdU: bromodeoxyuridine; GGT: γ-glutamyltransferase; Hb: haemoglobin; Hct: haematocrit; LDH: lactate dehydrogenase; NAG: N-acetylglucosaminidase; PCNA: proliferating cell nuclear antigen; RBP: retinol-binding protein

5.4 Allergenic effects

A local lymph node assay carried out in female CBA/J mice according to OECD Test Guideline 429 tested tetrachloroethylene in 5% and 25% concentrations in acetone/olive oil (4:1) and undiluted (25 µl/ear). Stimulations indices of 0.9, 1.4 and 4.3 were determined for the 3 concentrations. The concentration that led to a 3-fold increase in lymphocyte proliferation was 66.4%. The test substance contained 0.4% of an undefined stabilizer that itself has a weak sensitizing potential (no other details) (Dow Europe GmbH 2014; ECHA 2014). Moreover, the irritant activity of tetrachloroethylene might have led to the weakly positive result. Therefore, and because of the lack of a structural alert, this result is not a sufficiently valid argument for a contact-allergenic potential of tetrachloroethylene.

Likewise, the negative results obtained in a modified split adjuvant test with 9 animals (Rao et al. 1981) cannot be used to evaluate the sensitizing potential of tetrachloroethylene because of methodological inadequacies and a lack of data for the concentrations used and the vehicle.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a multi-generation study, male and female Alpk:APf SD rats were exposed to tetrachloroethylene concentrations of 0, 100, 300 or 1000 ml/m^3 by inhalation for 6 hours a day. At 300 ml/m^3 and above, the body weights of the parental animals were decreased concentration-dependently. In addition, at 1000 ml/m^3, damage to the liver and kidneys was found and the number of live-born and surviving pups was reduced. As this increase in mortality was not observed when exposed males were mated with control animals, it is assumed to be caused by exposure of the dams to the test substance. The weights of the pups were reduced at 300 ml/m^3 and above. In the second generation, the testis weights were reduced at 300 ml/m^3 and above, but there was no evidence of histopathological lesions. Fertility was not impaired. Therefore, toxic effects on reproduction occurred only at parentally toxic doses (Halogenated Solvents Industry Alliance 1995).

In rats, tetrachloroethylene was not found to cause sperm head abnormalities, whereas in mice, positive results were obtained with tetrachloroethylene of low purity (91.4%) (NIOSH 1980). The Sprague Dawley rats and CD-1 mice were exposed to 0, 100 or 500 ml/m^3 for 7 hours a day on 5 days. Examinations were carried out 1, 4 or 10 weeks after the last exposure. After 4 weeks, the percentages of abnormal sperm were 6.0%, 10.3% and 19.7%, respectively (NIOSH 1980).

In a study from 1937, exposure of rats to tetrachloroethylene concentrations up to 470 ml/m^3 for 7 months had no adverse effects on the tested reproductive parameters (number of pregnant animals, number of litters and litter size). The validity of the study is restricted because of the incidence of intercurrent diseases, inadequate controls and because the procedure does not comply with current standards and rats of undefined strain were used (ATSDR 2014).

The in vitro fertilizability of oocytes from female rats that had been treated with tetrachloroethylene for 2 weeks was slightly reduced after exposure by inhalation

(1700 ml/m³; 2× 1 hour/day). After tetrachloroethylene was administered with the drinking water (0.9% in water with 3.5% Tween 20, 60 or 80), the number of ovulating animals was significantly reduced, but the fertility of the oocytes was not impaired (Berger and Horner 2003).

5.5.2 Developmental toxicity

The data for the developmental toxicity of tetrachloroethylene available at the time were summarized in the chapter on MAK values and pregnancy from 1987 (Sammelkapitel "MAK-Werte und Schwangerschaft" 1987, available in German only). The studies are shown in Table 9.

Prenatal developmental toxicity

Sprague Dawley rats were exposed to a tetrachloroethylene concentration of 300 ml/m³ for 7 hours a day from days 6 to 15 of gestation. The mean body weights of the dams were slightly reduced. No signs of foetal toxicity or malformations were found except for a slight increase in the incidence of resorptions (Schwetz et al. 1975).

Groups of Sprague Dawley rats and New Zealand White rabbits were exposed to tetrachloroethylene concentrations of 0 or 500 ml/m³ for 7 hours a day on 5 days a week. During gestation, the rats were exposed from days 0 to 18 or from days 6 to 18 and the rabbits were exposed from days 0 to 21 or from days 7 to 21. Half of the animals per group were exposed for 3 weeks before mating. No significant treatment-related effects were observed in the dams of either species. There was no evidence of developmental toxicity or teratogenicity in the foetuses of either rats or rabbits (NIOSH 1980).

Groups of 30 female Long Evans rats were exposed to tetrachloroethylene concentrations of 0 or 1000 ml/m³ for 6 hours a day. Group A was exposed for 2 weeks before mating up to day 20 of gestation, group B was exposed only for 2 weeks before mating, group C was exposed only from days 0 to 20 of gestation, and the control group was exposed to filtered air 2 weeks before mating up to day 20 of gestation. Half of the animals were sacrificed on day 21 of gestation and used for examination of teratogenicity. Manson et al. (1981) reported the results for the animals with postnatal exposure (see below). Increases in the relative liver weights of the dams and decreases in foetal weights were observed in groups A and C. Increases in the incidence of skeletal variations were found in the foetuses of group A, and there was an increase in the incidence of kidney dysplasia in group C (Tepe et al. 1980).

CFY rats were exposed to tetrachloroethylene concentrations of 0, 217, 652 or 1232 ml/m³ for 8 hours a day from days 1 to 20 of gestation. The animals were sacrificed on day 21 of gestation and the foetuses were examined. At 217 ml/m³, no significant effects on the dams or foetuses were observed. At the middle concentration and above, the body weight gains of the dams were significantly reduced, and there was a significant increase in pre-implantation losses. At 652 ml/m³ and above, the body weights of the foetuses were significantly reduced, post-implantation losses were increased and significant increases in the incidences of delayed skeletal ossification, supernumerary ribs and in the total number of malformations were observed (Szakmáry et al. 1997). In this study, the NOAEC for maternal and developmental toxicity was 217 ml/m³.

Table 9 Studies of the developmental toxicity of tetrachloroethylene

Species, strain, number per group	Exposure	Findings	References
prenatal developmental toxicity			
rat, Sprague Dawley, 17 ♀, controls: 30 ♀	**GD 6–15**, 0, 300 ml/m^3, 7 hours/day, examination: GD 21	**300 ml/m^3**: dams: body weights ↓ (4%–5%); foetuses: resorptions ↑ (9%, controls: 4%)	Schwetz et al. 1975
rat, Sprague Dawley, 30 ♀	**GD 0–18 or 6–18**, with and without 3-week pre-exposure; 0, 500 ml/m^3, 7 hours/day, 5 days/week, examination: GD 20	**500 ml/m^3**: dams: no significant treatment-related effects; foetuses: no foetotoxic or teratogenic effects	NIOSH 1980
rat, Long Evans, 15 ♀	**2 weeks before mating up to GD 20 (group A)**, or **2 weeks before mating only (group B)**, or **GD 0–20 only (group C)**; 0, 1000 ml/m^3, 6 hours/day, 5 days/week, GD 1–20: 6 hours/day, 7 days/week, examination: GD 21	**1000 ml/m^3**: dams: relative liver weights ↑ (groups A and C); foetuses: body weights ↓ (groups A and C), skeletal variations ↑ (group A), kidney dysplasia ↑ (group C)	Tepe et al. 1980

Table 9 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, CFY, 20–22 ♀	**GD 1–20**, 0, 217, 652, 1232 ml/m³, 8 hours/day, examination: GD 21	**217 ml/m³: NOAEC** for developmental toxicity; dams: decrease in body weight gains (not significant) (13%), increase in pre-implantation losses (not significant) (49%); foetuses: increase in post-implantation losses (not significant) (38%), increase in incidences of delayed body weight gains (3.4-fold), skeletal retardations (48%) and malformations (2.3-fold) (all not significant); **652 ml/m³**: dams: significant decrease in body weight gains (37%), relative liver weights ↑ (10%); significant increase in pre-implantation losses (133%); foetuses: increase in post-implantation losses (not significant) (80%), significant decrease in foetal weights, significant increase in skeletal retardations and supernumerary ribs, significant increase in the total number of malformations (6.4%, controls: 2.0%); **1232 ml/m³**: dams: significant decrease in body weight gains (40%), relative liver weights ↑ (6%); significant increase in pre-implantation losses (117%); foetuses: increase in post-implantation losses (not significant) (80%), significant decrease in foetal weights, significant increase in skeletal retardations and supernumerary ribs, significant increase in the total number of malformations (15.7%, controls: 2.0%)	Szakmáry et al. 1997

Table 9 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 22 ♀	**GD 6–19**, 0, 65, 249, 600 ml/m³, 6 hours/day, 7 days/week, examination: GD 20	**65 ml/m³**: **NOAEC** for developmental toxicity; dams: no effects; **249 ml/m³**: **NOAEC** for maternal toxicity; dams: significant decrease in placental weights (12.3%, within range of historical controls); foetuses: significant decrease in mean foetal weights (4.3%, within range of historical controls); **600 ml/m³**: dams: significant decrease in body weight gains (GD 6–9 only), significant decrease in uterus weights (9.4%), significant decrease in placental weights (15.8%, outside range of historical controls); foetuses: significant decrease in mean foetal weights (9.4%, outside range of historical controls), increase in incomplete ossification of thoracic vertebral centra (not significant, but outside range of historical controls)	Carney et al. 2006
rabbit, New Zealand White, 25–30 ♀	GD 0–21 or 7–21, with and without 3-week pre-exposure; 0, 500 ml/m³, 7 hours/day, 5 days/week, examination: GD 30	**500 ml/m³**: dams: no effects; foetuses: no foetotoxic or teratogenic effects	NIOSH 1980
rabbit, New Zealand White, 16 ♀, controls: 10 ♀	**GD 7–20**, 0, 652 ml/m³, 8 hours/day, examination: GD 30	**652 ml/m³**: dams: body weight gains ↓, significant increase in relative liver weights; abortions in 2/16; foetuses: total resorption in 4 litters, significant increase in post-implantation losses	Szakmáry et al. 1997
mouse, Swiss Webster, 17 ♀	**GD 6–15**, 0, 300 ml/m³, 7 hours/day, examination: GD 18	**300 ml/m³**: dams: relative liver weights ↑; foetuses: foetal weights ↓, delayed ossification of skull and sternebrae ↑	Schwetz et al. 1975

Table 9 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, C57Bl, 10 ♀, controls: 77 ♀	**GD 7–15**, 0, 217 ml/m³, 8 hours/day, examination: GD 19	**217 ml/m³**: dams: significant increase in relative liver weights; foetuses: significant increase in malformations of internal organs (14.3%, controls: 0.8%)	Szakmáry et al. 1997
guinea pig, no other details, 4 ♀	**GD 33–65**, 0, 160 ml/m³ continuous, examination: GD 65	**160 ml/m³**: dams: no effects; foetuses: slight change in fatty acid pattern in the brain, no change in lipid composition in the brain	Kyrklund and Haglid 1991
prenatal and postnatal developmental toxicity			
rat, Sprague Dawley, 3–10 ♀	**GD 7–13 or 14–20**, 0, 900, 1800, 3600 ml/m³, 7 hours/day, examination: GD 21 or PND 35 pilot study	**900 ml/m³**: foetuses: no skeletal effects; offspring: (GD 14–20): body weights ↓ (about 20% in weeks 3–5); **1800 ml/m³ and above**: dams: narcosis; **1800 ml/m³**: dams: only few surviving animals (no other details); foetuses: resorptions ↑, no malformations	Nelson et al. 1980
rat, Sprague Dawley, 13–21 ♀	**GD 7–13 or 14–20**, 0, 100 (GD 14–20 only), 900 ml/m³, 7 hours/day, examination: up to PND 46	**100 ml/m³**: **NOAEC** for developmental neurotoxicity (GD 14–20) and maternal toxicity; **900 ml/m³**: dams: decrease in body weight gains and feed consumption (GD 7–13 only); offspring: GD 7–13: performance in some behavioural tests ↓ (ascent and rotarod tests), acetylcholine and dopamine in the brain ↓ (PND 21 only); GD 14–20: performance in some behavioural tests ↓ (ascent test, GD 14 only), in other tests ↑ (rotarod test), exploratory activity ↑; acetylcholine in the brain ↓ (PND 21 only)	Nelson et al. 1980

Table 9 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Long Evans, 11–15 ♀	**2 weeks before mating up to GD 20 (group A)**, or **2 weeks before mating only (group B)**, or **GD 0–20 only (group C)**; 0, 1000 ml/m^3, 6 hours/day, 5 days/week, GD 1–20: 6 hours/day, 7 days/week, examination: up to 18 months	**1000 ml/m^3**: dams: no data; offspring: no effects on survival, growth, behaviour (open field test: PND 10 and 20, activity in the activity wheel: PND 40–100, visual discrimination test: PND 130–170), pathology (after 6 or 18 months)	Manson et al. 1981
rat, Alpk:APfSD; F0: 24 ♂, 24 ♀	**11 weeks before mating, GD 0–20 and PND 6–29**, 0, 100, 300, 1000 ml/m^3, 6 hours/day, 5 days/week before mating and daily afterwards, ♂ F0 and F1 exposed for 19 or 35 weeks	**100 ml/m^3**: dams: no effects; offspring: no effects; **300 ml/m^3**: dams: body weights ↓, liver weights ↑; offspring: body weights ↓ (not significant), testis weights ↓ (F2); **1000 ml/m^3**: parental animals: F0 and F1: body weights ↓; kidney and liver weights ↑; kidneys: histological changes (♂: F0 and F1; ♀: F0); offspring: body weights ↓ (10%), number of live-born and surviving pups ↓ (hyperthermia, sedation)	Halogenated Solvents Industry Alliance 1995
rat, F344, 17–21 ♀	**GD 6–19**, 0, 900, 1200 mg/kg body weight and day, in corn oil, gavage, examination: up to PND 6	**900 mg/kg body weight**: dams: ataxia, body weight gains ↓ (GD 6–8 and GD 6–20); offspring: significant decrease in number of live-born pups per litter ↓ (PND 1: 5.2 ± 1.5; controls: 7.7 ± 0.7; PND 6: 4.9 ± 1.2; controls: 7.7 ± 0.7), body weights ↓ (PND 1 and 6), postnatal mortality ↑, microphthalmia/anophthalmia ↑; **1200 mg/kg body weight**: dams: body weight gains ↓ (GD 6–8); offspring: no live-born pups (PND 1), total resorptions, about 100% decrease in foetuses per litter	Narotsky and Kavlock 1995

Table 9 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, CFY, 15 ♀	**GD 1–20**, 0, 217, 652 ml/m³, 8 hours/day, examination: up to PND 100	**217 ml/m³**: offspring: transient slight decrease in exploratory behaviour and muscular strength (reversible up to PND 51, exposure concentration unclear), motor activity normal (activity wheel) [a]; **652 ml/m³**: offspring: survival index ↓ (no other details), ♀: significant increase in motor activity (PND 100); **up to 652 ml/m³**: no effects on postnatal development, functional observation battery, testis descent or vaginal opening, no abnormalities in pathological examination (PND 100)	Szakmáry et al. 1997
postnatal developmental toxicity			
mouse, NMRI, 4 ♂	**PND 10–16**, 0, 5, 320 mg/kg body weight and day, gavage, examination on PND 17 and 60	**5 mg/kg body weight and above**: PND 17: no significant effects; PND 60: significant increase in total activity and locomotion; **320 mg/kg body weight**: PND 60: significant decrease in rearing	Frederiksson et al. 1993

[a] statement is not in agreement with the result described in the discussion of the publication (decrease in motor activity);
GD: gestation day; PND: postnatal day

Sprague Dawley rats were exposed to tetrachloroethylene concentrations of 0, 65, 249 or 600 ml/m^3 for 6 hours a day, on 7 days a week, from days 6 to 19 of gestation. The dams were sacrificed on day 20 of gestation and the foetuses were examined. In the low concentration group, significant effects were not observed either in the dams or in the foetuses. At 249 ml/m^3, the placental weights were significantly reduced in the dams, but the values were within the range of the historical controls. At this concentration, the mean foetal weights were significantly reduced, but they were within the range of the historical controls, and no effects on the uterus weights were observed during gestation. Transient decreases in body weight gains and significant decreases in placental and uterine weights, which correlated with the significantly reduced mean foetal weights, were recorded in the dams at the high concentration. In addition, incomplete ossification of thoracic vertebral centra was found in the foetuses; the incidence was outside the range of the historical controls (Carney et al. 2006). The NOAEC for maternal toxicity was 249 ml/m^3, and the NOAEC for developmental toxicity was 65 ml/m^3; however, the effects on foetal weights observed at the LOAEC of 249 ml/m^3 are of minimal toxicological relevance.

New Zealand White rabbits were exposed to tetrachloroethylene concentrations of 0 or 652 ml/m^3 for 8 hours a day from days 7 to 20 of gestation. On day 30 of gestation, the animals were sacrificed and the foetuses were examined. The body weight gains of the dams were reduced and abortions occurred in 2 of 16 dams. Post-implantation losses were significantly increased, and total resorptions were reported in 4 litters (Szakmáry et al. 1997). In this study, the LOAEC for developmental toxicity was 652 ml/m^3.

C57Bl mice were exposed to tetrachloroethylene concentrations of 0 or 217 ml/m^3 for 8 hours a day from days 7 to 15 of gestation. On day 19 of gestation, the animals were sacrificed and the foetuses were examined. The number of malformations of internal organs was significantly increased in the foetuses (Szakmáry et al. 1997). In this study, the LOAEC for developmental toxicity was 217 ml/m^3.

Swiss Webster mice were exposed to a tetrachloroethylene concentration of 300 ml/m^3 for 7 hours a day from days 6 to 15 of gestation. Slight maternal toxicity was observed in the form of an increase in relative liver weights. Malformations were not found, but there was a slight delay in the ossification of the skull and ribs. This can be explained by the fact that the mean weights of the foetuses from exposed dams were somewhat lower than the weights of the corresponding control foetuses (Schwetz et al. 1975).

Pregnant guinea pigs were exposed continuously to a tetrachloroethylene concentration of 160 ml/m^3 from days 33 to 65 of gestation. The concentration was reduced to 80 ml/m^3 on the first day and on the last 4 days of exposure. The lipid composition and fatty acid pattern in the brains of the foetuses were examined and compared with those in the untreated control group. There was a slight change in the fatty acid pattern, but no significant changes in the lipid composition in the brain (Kyrklund and Haglid 1991).

Prenatal and postnatal developmental toxicity

In a combined study that investigated both developmental toxicity and developmental neurotoxicity, Sprague Dawley rats were exposed to a tetrachloroethylene concentration of 900 ml/m^3 for 7 hours a day from days 7 to 13 or from days 14 to 20

of gestation. This concentration caused maternal toxicity, and feed consumption and body weight gains were reduced. No toxic effects on the prenatal development of the foetuses were observed. During the first few weeks after birth, the pups were subjected to a series of behavioural tests. In some of these tests, their performance was poorer, and in some tests their performance was better than that of the control animals. The examination of the pups of dams that had been exposed to a concentration of 100 ml/m^3 from days 14 to 20 of gestation did not reveal any significant differences in the behaviour or performance as compared with pups from control dams (Nelson et al. 1980).

The offspring of female Long Evans rats that had been exposed to tetrachloroethylene concentrations of 0 or 1000 ml/m^3 for 6 hours a day (Tepe et al. 1980, see above) were subjected to various examinations and behavioural tests up to the age of 18 months. There were no effects on survival, growth, behaviour (open field test on postnatal days 10 and 20), motor activity in an activity wheel (postnatal days 40 to 100), in the visual discrimination test (postnatal days 130 to 170) or in the pathological examination after 6 or 18 months (Manson et al. 1981).

In a multi-generation study, male and female Alpk:APf SD rats were exposed to tetrachloroethylene concentrations of 0, 100, 300 or 1000 ml/m^3 by inhalation for 6 hours a day (see Section 5.5.1). At 300 ml/m^3 and above, the body weights of the offspring were reduced, and there was a decrease in the testis weights of the F2 generation without a histopathological correlate. In addition, the number of liveborn and surviving pups was reduced at 1000 ml/m^3 (Halogenated Solvents Industry Alliance 1995).

After pregnant F344 rats were given gavage doses of tetrachloroethylene of 0, 900 or 1200 mg/kg body weight and day from days 6 to 19 of gestation, a significant increase in resorptions was observed. At 1200 mg/kg body weight and day, no live offspring were born on day 22 of gestation, and at 900 mg/kg body weight and day, the number of live offspring per litter was significantly reduced. The examination of the implantation sites suggested that the embryos died early in the treatment period. In addition, decreases in body weights, an increase in postnatal mortality and increased incidences of microphthalmia and anophthalmia were reported at 900 mg/kg body weight and day (Narotsky and Kavlock 1995).

Groups of 8 offspring from 15 litters of CFY rats that had been exposed to tetrachloroethylene concentrations of 0, 217 or 652 ml/m^3 for 8 hours a day from days 1 to 20 of gestation were observed up to postnatal day 100 to evaluate the effects of prenatal exposure on postnatal development. Pre-weaning observations on postnatal day 21 included body weights (postnatal days 1, 7, 14 and 21), pinna detachment, incisor eruption, eye opening and development of the nervous system (forward movement, surface righting reflex, grasping ability, swimming ontogeny, rotating activity, auditory startle reflex and development of stereoscopic vision). After weaning, the exploratory activity in an open field (open field test), motor activity (activity wheel) and development of muscular strength (inclined plane) were examined and on postnatal day 100 a pathological examination was carried out. The authors reported a decrease in the survival index at 652 ml/m^3 (no other details). There was a transient slight decrease in exploratory activity and muscular strength (exposure concentration unclear). On postnatal day 100, the motor activity of the females was significantly

increased in the high concentration group. All other test results were in the normal range (Szakmáry et al. 1997). The publication did not give any other details.

Postnatal developmental toxicity

In a study that investigated the toxic effects on postnatal development, groups of young male NMRI mice were given gavage doses of tetrachloroethylene of 0, 5 or 320 mg/kg body weight and day from postnatal days 10 to 16. Signs of toxicity were not observed. The activity of the animals (locomotion, rearing and total activity) was determined on postnatal days 17 and 60. On postnatal day 17, no significant changes in activity were observed in any group. On postnatal day 60, a significant increase in locomotion and total activity was found in both dose groups and there was a significant decrease in rearing in the high dose group (Frederiksson et al. 1993).

In vitro

In the whole embryo culture test, embryos from Sprague Dawley rats were removed on day 10 of gestation and incubated with 2.5 to 15 mM tetrachloroethylene for 46 hours. Concentration-related effects on growth and development occurred at 3.5 mM and above. Lethal effects were observed in 10% and 83.5% of the embryos at 7.5 and 15 mM, respectively. The presence of rat liver microsomes reduced the embryotoxic effects (Saillenfait et al. 1995).

Conclusions:

Studies that investigated developmental toxicity after inhalation reported initial effects on the foetal weights of rats at 249 ml/m^3 and above that were of minimal toxicological relevance (Carney et al. 2006); reduced foetal weights and an increase in the number of delayed ossifications and in malformations were observed at 652 ml/m^3 and above (Szakmáry et al. 1997). The NOAECs for developmental toxicity in rats were 65 ml/m^3 (Carney et al. 2006) and 217 ml/m^3 (Szakmáry et al. 1997).

Inhalation exposure of mice caused reduced body weights and delayed ossification at 300 ml/m^3 (Schwetz et al. 1975) and an increased number of malformations of internal organs at 217 ml/m^3 (Szakmáry et al. 1997). It was not possible to derive a NOAEC for developmental toxicity. In rabbits, post-implantation losses were observed at 652 ml/m^3 (Szakmáry et al. 1997), but in another study there was no evidence of toxic effects on development at 500 ml/m^3 (NIOSH 1980). Therefore, the NOAEC for developmental toxicity in rabbits was 500 ml/m^3.

There are 3 studies available for developmental neurotoxicity. In behavioural tests (ascent and rotarod tests), there was a decrease in performance at 900 ml/m^3. The NOAEC for developmental neurotoxicity was 100 ml/m^3 (Nelson et al. 1980).

5.6 Genotoxicity

An important factor in evaluating the studies that investigated the genotoxicity of tetrachloroethylene is information about the purity of the test substance. This is because impurities and genotoxic stabilisers may lead to positive results (documentation "Tetrachloroethylene" 1992; SCOEL 2009).

5.6.1 In vitro

Bacteria and yeasts

There are many studies that investigated the genotoxicity of tetrachloroethylene in bacteria and yeasts; these have been summarized in recent reviews (IARC 2014; US EPA 2012). Most yielded negative results.

In individual cases, positive findings were obtained with tetrachloroethylene in bacteria and yeasts; in these cases, the purity was not known or the tetrachloroethylene contained genotoxic stabilizers (documentation "Tetrachloroethylene" 1992).

Tetrachloroethylene was not mutagenic in Escherichia coli or Salmonella typhimurium without the addition of S9 mix or under conditions that would enable only oxidative metabolism. However, if reductive bio-activation of tetrachloroethylene was possible, potent β-lyase-dependent mutagenic effects were observed (supplement "Tetrachloroethylene" 1997).

Recent bacterial mutagenicity tests confirmed these results (US EPA 2012).

Mammalian cells

The in vitro studies that investigated genotoxic effects in mammalian cells are summarized in Table 10.

A comet assay carried out with tetrachloroethylene in human leukocytes both with and without the addition of metabolic activation yielded no evidence of DNA damage (Hartmann and Speit 1995).

Studies with tetrachloroethylene in Chinese hamster ovary (CHO) cells and human leukocytes did not reveal increased incidences of sister chromatid exchanges (Anderson et al. 1990; Galloway et al. 1987; Hartmann and Speit 1995; NTP 1986).

An increase in DNA synthesis was observed in human lymphocytes only at the highest concentration tested and only without metabolic activation. The purity of the tetrachloroethylene was reported to be 99% (Perocco et al. 1983).

Tetrachloroethylene yielded negative results in the available UDS (unscheduled DNA synthesis) tests in the hepatocytes of rats and mice and in human fibroblasts (Costa and Ivanetich 1984; Milman et al. 1988; NIOSH 1980; Shimada et al. 1985).

In chromosomal aberration tests in Chinese hamster lung (CHL) and CHO cells, tetrachloroethylene led to negative results both with and without the addition of metabolic activation (Anderson et al. 1990; Galloway et al. 1987; NTP 1986; Sofuni et al. 1985).

A micronucleus test yielded negative results with tetrachloroethylene in the absence of metabolic activation in CHL cells (Matsushima et al. 1999), whereas positive results were obtained in CHO cells (Wang et al. 2001). In another micronucleus test, positive results were obtained with human lymphoblastoid cell lines with increased metabolic activity (Doherty et al. 1996). The purity of the tetrachloroethylene was not reported in this study.

In the TK gene mutation assay in L5178Y cells, tetrachloroethylene yielded negative results both with and without the addition of metabolic activation (McGregor et al. 1988; Myhr et al. 1990; NTP 1986), whereas the overall result of several test series with metabolic activation was reported to be "questionable" (Myhr et al. 1990); no information is available about the purity of the test substance.

Table 10 Genotoxicity of tetrachloroethylene in vitro

End point	Test system	Concentration, purity	Effective concentration	Cytotoxicity	Result		References
					−m. a.	+m. a.	
gap junction intercellular communication	rat hepatocytes	0.01, 0.1, 1 mM	0.1 mM, inhibition of intercellular communication				Benane et al. 1996
single cell gel electrophoresis (comet assay)	human leukocytes	1–5 mM, purity: no data	–	viability: 59% at 5 mM	–	–	Hartmann and Speit 1995
SCE	CHO cells	16.4–164 µg/ml (−m. a.), 5.45–125 µg/ml (+m. a.), purity: technical grade	–	no data	–	–	Anderson et al. 1990; Galloway et al. 1987
	CHO cells	16.4–164 µg/ml (−m. a.), 80.36–124.60 µg/ml (+m. a.), purity: unclear (99.9% or technical grade)	–	no data	–	–	Galloway et al. 1987; NTP 1986
	human leukocytes	50 µM–20 mM, purity: no data	–	−m. a.: 20 mM: toxic	–	–	Hartmann and Speit 1995
DNA synthesis	human lymphocytes	0.1–10 mM, purity: 99%	10 mM	−m. a.: 10 mM: 30% viability, +m. a.: 10 mM: 100% viability	+	–	Perocco et al. 1983

Table 10 (continued)

End point	Test system	Concentration, purity	Effective concentration	Cytotoxicity	Result		References
					–m. a.	+m. a.	
DNA repair synthesis (UDS)	primary rat hepatocytes	0.1–2.5%, purity: 99.99%	–	1.0% and above	–	not examined	Shimada et al. 1985
	primary rat and mouse hepatocytes	no data, purity: no data	–	no data	–	not examined	Milman et al. 1988
	rat hepatocytes	2.5 mM, purity: no data	–	no data	–	not examined	Costa and Ivanetich 1984
	human fibroblasts (WI-38)	0.1–5.0 µl/ml, purity: 91.43%	–	5 µl/ml and above	–	–	NIOSH 1980
CA	CHL cells	0.06–0.5 mg/ml (–m. a.), 0.13–0.5 mg/ml (+m. a.)	–	–m. a.: 0.5 mg/ml, +m. a.: > 0.5 mg/ml	–	–	Sofuni et al. 1985
	CHO cells	17–136.3 µg/ml (–m. a.), 17–68.1 µg/ml (+m. a.), purity: unclear (99.9% or technical grade)	–	no data	–	–	Anderson et al. 1990; Galloway et al. 1987; NTP 1986
MN	CHL cells	31–250 µg/ml, purity: no data	–	no data	–	not examined	Matsushima et al. 1999
	CHO cells	5–20 µl (24 hours), purity: 99%	5 µl and above (about 1.85 µg/ml medium)	cell growth: 5 µl: 65%, 10 µl: 35%, 20 µl: 20%	+	not examined	Wang et al. 2001
	human lymphoblastoid cell lines (AHH-1, h2E1, MCL-5)	0.01–5 mM, purity: no data	1 mM (h2E1, MCL-5), 5 mM (AHH-1)	no data	+	not examined	Doherty et al. 1996

Table 10 (continued)

End point	Test system	Concentration, purity	Effective concentration	Cytotoxicity	Result		References
					−m. a.	+m. a.	
gene mutation, TK	L5178Y cells	12.5–150 nl/ml (−m. a.), 6.25–100 nl/ml (+m. a.), purity: 99.9%	–	−m. a.: 75 nl/ml and above (RTG: < 50%) +m. a.: 100 nl/ml and above (RTG: < 50%)	–	–	Myhr et al. 1990; NTP 1986
	L5178Y cells	12.5–225 µg/ml (−m. a.), 25–225 µg/ml (+m. a.), purity: no data	–	200 µg/ml and above	–	–	McGregor et al. 1988; Myhr et al. 1990
	L5178Y cells	3.13–200 µg/ml (−m. a.), 3.13–300 µg/ml (+m. a.), purity: no data	–	−m. a.: 75–200 nl/ml and above +m. a.: 100 nl/ml and above	–	+/−	Myhr et al. 1990

m. a.: metabolic activation; CA: chromosomal aberrations; MN: micronuclei; SCE: sister chromatid exchange; TK: thymidine kinase locus

5.6.2 In vivo

The available in vivo tests are summarized in Table 11.

Tests for sex-linked recessive lethality in Drosophila (SLRL test) yielded no evidence of genotoxic effects after inhalation exposure to tetrachloroethylene (up to 500 ml/m^3; 7 hours) or after tetrachloroethylene was administered to males with the diet or by injection (NIOSH 1980; NTP 1986; Valencia et al. 1985).

A study, which was published only as an abstract, reported positive results in a host-mediated assay with tetrachloroethylene in mice (Cerna and Kypenova 1977); however, the findings were not dose-dependent and the purity of the test substance was not specified.

A host-mediated assay with Salmonella typhimurium in mice yielded positive results; however, at 91.43%, the purity of the test substance was rather low and positive results were observed in the females only at the high concentration of 500 ml/m^3 and in the males only at the low concentration of 100 ml/m^3. Moreover, the concurrent positive control 2-aminoanthracene did not lead to the expected results (NIOSH 1980).

Another host-mediated assay with Saccharomyces cerevisiae in mice yielded negative results (Bronzetti et al. 1983); however, the test procedure was unusual and a positive control was not included (NEG 2003).

Intraperitoneal injection of tetrachloroethylene induced DNA single strand breaks in the liver and kidneys of male mice, but not in the lungs. These effects were reversible after 24 hours (Walles 1986). DNA strand breaks were not observed in the kidneys of rats that were repeatedly given gavage doses of tetrachloroethylene of 1000 mg/kg body weight (Potter et al. 1996).

After oral administration to male CD-1 mice of tetrachloroethylene doses of 1000 or 2000 mg/kg body weight, liver and kidney cells were examined by means of alkaline single cell gel electrophoresis (comet assay). There was no evidence of DNA damage in the kidneys, whereas a slight, statistically significant increase in tail intensity was observed in hepatocytes (Cederberg et al. 2010). The statistical and biological relevance of this finding has been disputed (Lillford et al. 2010). Methodological bias was suggested in a comment published on this study (Struwe et al. 2011).

When male rats were given a single intraperitoneal injection of tetrachloroethylene, there was no increase in the 8-hydroxydeoxyguanosine (8-OHdG) levels in the DNA of the liver or kidneys or in the urine (Toraason et al. 1999).

After oral or inhalation exposure of mice to radioactively labelled tetrachloroethylene, no radioactivity was found bound to DNA of the liver (Schumann et al. 1980). However, the sensitivity of the test was relatively low (WHO 2006).

After intraperitoneal injection of ^{14}C-tetrachloroethylene (1.4 mg/kg body weight), in male Wistar rats and male BALB/c mice there was evidence of covalent binding of the radioactivity to DNA, RNA and proteins. Binding to DNA was highest in mouse livers, while binding to RNA was highest in rat kidneys. The covalent binding indices (according to Lutz) were in the range of weak initiators (10 to 100 pmol/mg). However, this study has not been included in the evaluation because the incorporation of radioactively labelled carbon via the C1 pool was not examined (Mazzullo et al. 1987).

A UDS test in the rat kidney, which was published only as an abstract, yielded negative results after oral administration of a tetrachloroethylene dose of 1000 mg/kg body weight (Goldsworthy et al. 1988).

Repeated inhalation exposure to tetrachloroethylene (up to 600 ml/m^3) did not induce chromosomal aberrations in the bone marrow of rats (Rampy et al. 1978). Repeated inhalation exposure (for 7 hours a day on 5 days) to tetrachloroethylene concentrations of up to 500 ml/m^3 yielded negative results in the chromosomal aberration test in the bone marrow of rats, whereas acute exposure (a single exposure for 7 hours) led to negative results in the female animals and weakly positive results in the males. However, at 91.4%, the purity of the test substance was rather low (NIOSH 1980). Single or repeated intraperitoneal injections of tetrachloroethylene did not cause chromosomal aberrations in the bone marrow of mice. The abstract provides only an inadequate description of the doses used and of the study itself (Cerna and Kypenova 1977).

In another chromosomal aberration test in mice with negative results, males were given single intraperitoneal doses of up to 2500 mg/kg body weight. The concurrent positive controls led to the expected results (NTP 1993 a).

After intraperitoneal injection of tetrachloroethylene doses of up to 2000 mg/kg body weight, the incidences of micronuclei were not increased in the bone marrow of mice. A significant, dose-dependent increase in micronuclei was observed in hepatocytes when mice were treated according to the same procedure following partial hepatectomy. There was only a slight increase in the incidence of micronuclei from 0.39 ± 0.07 in the control group to 0.62 ± 0.15 and 0.68 ± 0.10 at 1000 and 2000 mg/kg body weight, respectively. The concurrent positive controls led to the expected results (Murakami and Horikawa 1995).

The NTP described another micronucleus test with negative results in male B6C3F1 mice. The concurrent positive controls led to the expected results (NTP 1993 b).

A dominant lethal test in male rats yielded negative results after exposure to 100 to 500 ml/m^3 (689 to 3445 mg/m^3 for 7 hours a day) on 5 days. At 91.43%, the purity of the tetrachloroethylene was rather low. The positive control group (triethylenemelamine) led to the expected findings (NIOSH 1980).

Conclusions:

In vitro and in vivo studies found that tetrachloroethylene has only a very weak genotoxic potential. In vivo, high doses induced DNA single strand breaks in the liver and kidneys or micronuclei in the liver.

Table 11 Studies of the genotoxicity of tetrachloroethylene in vivo

Test system		Dose/Concentration	Results	References
SLRL test	Drosophila, ♂	up to 500 ml/m³, 7 hours, purity: 91.43%	–	NIOSH 1980
SLRL test	Drosophila, ♂	4000 mg/l diet, 1000 mg/l injection, purity: technical grade	–	NTP 1986; Valencia et al. 1985
host-mediated assay (Salmonella typhimurium)	mouse, ICR, ♀	purity: no data	+	Cerna and Kypenova 1977
host-mediated assay (Salmonella typhimurium)	mouse, CD-1, ♂, ♀	100, 500 ml/m³, purity: 91.43%	+ (100 ml/m³ (♂), 500 ml/m³ (♀))	NIOSH 1980
host-mediated assay (Saccharomyces cerevisiae D7)	mouse, CD-1, ♂, ♀	11 000 mg/kg body weight, once orally (gavage), purity: 99.5%	– (liver, lungs, kidneys)	Bronzetti et al. 1983
		2000 mg/kg body weight, 12 times orally (gavage), purity: 99.5%	– (liver, lungs, kidneys)	
DNA single strand breaks (alkaline unwinding), liver, kidneys, lungs	mouse, NMRI, 5–7 ♂	0, 660, 990, 1160, 1300 mg/kg body weight, once intraperitoneally, purity: 99.8%	+ (liver, kidneys); – (lungs)	Walles 1986
DNA single strand breaks, kidneys	rat, F344, ♂	1000 mg/kg body weight and day, 7 days, orally (gavage), purity: no data	–	Potter et al. 1996
DNA single strand breaks, single cell gel electrophoresis (comet assay, alkaline), liver, kidneys	mouse, CD-1, ♂	0, 1000, 2000 mg/kg body weight and day, twice orally (gavage), 24 h apart, purity: 99.96%	+/– (liver); – (kidneys)	Cederberg et al. 2010

Table 11 (continued)

Test system		Dose/Concentration	Results	References
8-OHdG, liver, lymphocytes, urine	rat, F344, ♂	100, 500, 1000 mg/kg body weight, once intraperitoneally, purity: 99.5%	– (limited validity because of mortality)	Toraason et al. 1999
DNA binding, liver (bound radioactivity)	mouse, B6C3F1, ♂	600 ml/m^3, 6 hours, purity: > 99%	– (liver)	Schumann et al. 1980
		500 mg/kg body weight, once orally (gavage), purity: > 99%	– (liver)	
DNA/RNA binding, liver, kidneys, lungs, stomach	mouse, BALB/c, ♂	1.4 mg/kg body weight, once intraperitoneally, purity: 97%	+ (DNA, RNA)	Mazzullo et al. 1987
	rat, Wistar, ♂	1.4 mg/kg body weight, once intraperitoneally, purity: 97%	+ (DNA, RNA)	Mazzullo et al. 1987
UDS, kidneys	rat, F344, ♂	1000 mg/kg body weight, orally (gavage), purity: no data	–	Goldsworthy et al. 1988
CA, bone marrow	rat, 10 ♂, 10 ♀	100 or 500 ml/m^3, 7 hours, 1 day, examination after 6, 24, 48 hours, purity: 91.43%	– (♀); (+) (♂)	NIOSH 1980
	rat, 10 ♂, 10 ♀	100 or 500 ml/m^3, 7 hours/day, 5 days, examination after 6 hours, purity: 91.43%	–	NIOSH 1980
CA, bone marrow	rat, 3 ♂, 3 ♀	0, 300 or 600 ml/m^3, 6 hours/day, 5 days/week, 12 months, purity: > 99%	–	Rampy et al. 1978

Table 11 (continued)

Test system		Dose/Concentration	Results	References
CA, bone marrow	mouse, ICR, ♀	once intraperitoneally, purity: no data	–	Cerna and Kypenova 1977
		once daily, 5 days, intraperitoneally, purity: no data	–	
CA, bone marrow	mouse, B6C3F1, 7–8 ♂	0, 1000, 1500, 2000, 2500 mg/kg body weight, once intraperitoneally	–	NTP 1993 a
MN, reticulocytes	mouse, ddY, 5 ♂	0, 500, 1000, 2000 mg/kg body weight, once intraperitoneally, purity: 99.8%, examination after 0, 24, 48, 72 hours	–	Murakami and Horikawa 1995
MN, hepatocytes	mouse, ddY, 5 ♂	0, 500, 1000, 2000 mg/kg body weight, once intraperitoneally (24 hours after partial hepatectomy), purity: 99.8%, examination after 72 hours	+ (1000 mg/kg body weight and above)	Murakami and Horikawa 1995
MN, hepatocytes	mouse, ddY, 5 ♂	2000 mg/kg body weight, once intraperitoneally (1, 5 or 7 days before partial hepatectomy), purity: 99.8%, examination after 72 hours	–	Murakami and Horikawa 1995
MN, bone marrow	mouse, B6C3F1, 5 ♂	0, 500, 1000, 2000 mg/kg body weight, 3 times intraperitoneally in 72 hours	–	NTP 1993 b
DLT	rat, Sprague Dawley, 10 ♂	100 or 500 ml/m^3, 7 hours/day, 5 days, purity: 91.43%	–	NIOSH 1980

CA: test for structural chromosomal aberrations; DLT: dominant lethal test; MN: micronucleus test; SLRL: Drosophila test for X-chromosomal recessive lethal mutations; UDS: test for DNA repair synthesis

5.7 Carcinogenicity

5.7.1 Short-term studies

Negative results were obtained with tetrachloroethylene in 2 cell transformation assays with BALB/c-3T3 cells (NEG 2003). Another cell transformation assay with rat embryo cells (F1706p108) that were infected with Rauscher leukaemia virus yielded positive results (NEG 2003).

In a study mentioned in the 1988 supplement (documentation "Tetrachloroethylene" 1992), groups of 20 male A/St mice (sensitive to the development of lung tumours) were given intraperitoneal injections of tetrachloroethylene of 0, 80, 200 or 400 mg/kg body weight 3 times a week. After up to 24 injections, the animals were sacrificed 24 weeks after the beginning of treatment and examined for lung tumours. Tetrachloroethylene did not increase the number of adenomas per mouse compared with that in the controls (IARC 2014). This result was confirmed in another study in male and female A/St mice (Maronpot et al. 1986).

Initiation–promotion studies

After initiation or promotion with tetrachloroethylene (purity: 97% to 99%), foci positive for γ-glutamyltranspeptidase (GGT) were determined in the livers of male Osborne-Mendel rats. In the initiation study, 10 animals underwent partial hepatectomy, followed 24 hours later by gavage doses of tetrachloroethylene of 1000 mg/kg body weight. The rats were then given 0.05% phenobarbital with the diet for 7 weeks followed by untreated feed for 7 days. Finally, the animals were sacrificed and examined. Control animals were given a single dose of corn oil or diethylnitrosamine (DEN) (30 mg/kg body weight) followed by untreated feed or phenobarbital for 7 weeks. Tetrachloroethylene did not cause significant changes in the number of GGT-positive foci compared with that in the controls. In the promotion study, 10 rats were given single intraperitoneal injections of DEN (30 mg/kg body weight) or water 24 hours after partial hepatectomy; after 6 days, they were given gavage doses of tetrachloroethylene of 1000 mg/kg body weight daily, on 5 days a week, for 7 weeks. The control animals were given corn oil. The animals were sacrificed and examined after they had received untreated feed for another 7 days. After initiation with DEN, tetrachloroethylene caused a significant increase in the number of GGT-positive foci in the liver compared with that in the controls. Even without initiation with DEN, after administration of tetrachloroethylene for 7 weeks the number of GGT-positive foci in the liver was significantly increased compared with that in the control group without initiation (Story et al. 1986; Milman et al. 1988).

Another study in male Sprague Dawley rats did not reveal tumour-promoting activity in the liver after partial hepatectomy, initiation with DEN and subsequent administration of gavage doses of tetrachloroethylene of 1100 mg/kg body weight on 5 days a week for 7 weeks (Lundberg et al. 1987).

A single dose of 163 mg tetrachloroethylene in 0.2 ml acetone was applied to the dorsal skin of groups of 30 female Swiss mice. After 14 days, 5 µg phorbol ester (phorbol 12-myristate-13-acetate) in 0.2 ml acetone were applied as a tumour promoter 3 times a week for at least 61 weeks. Only phorbol ester was applied to a control group of 90 animals. Tetrachloroethylene did not cause increased incidences of papillomas (IARC 2014).

5.7.2 Long-term studies

The carcinogenic potential of tetrachloroethylene could not be evaluated conclusively in the 1988 supplement (documentation "Tetrachloroethylene" 1992) on the basis of the long-term studies available at that time because of reduced survival (NCI 1977) or short exposure period (Rampy et al. 1978).

The inhalation study (NTP 1986) described in the 1988 supplement (documentation "Tetrachloroethylene" 1992) reported a significant increase in the incidence of hepatocellular carcinomas in female and male mice. An increased incidence of mononuclear leukaemia was observed in F344/N rats after exposure by inhalation. The spontaneous incidences of this tumour are also very high in control animals of this strain. In addition, a non-significant increase in the incidence of renal cell tumours was observed in male F344/N rats after exposure to tetrachloroethylene concentrations of 200 or 400 ml/m^3. The spontaneous incidence of this tumour is very low in the rat strain used. Nephrotoxicity and histopathological precursors of renal cell tumours (karyomegaly and hyperplasia) were observed in the treated animals of both sexes (see Table 12 and Table 13).

In another study (see Table 12), groups of 50 male and 50 female F344/DuCrj rats were exposed to tetrachloroethylene (purity: 99.0%) concentrations of 0, 50, 200 or 600 ml/m^3 for 6 hours a day, on 5 days a week, for 103 weeks. The number of animals that survived the treatment was reduced, but this finding was not evaluated statistically. Increased incidences of mononuclear leukaemia were observed with significantly positive trends in male and female rats. At the high concentration, these incidences were significantly higher than in the concurrent controls and were above the reported incidences of the historical controls. As in the earlier inhalation study (NTP 1986), increased incidences of karyomegaly of the tubular epithelial cells were observed in the males and females. In addition, individual renal cell adenomas were found in males and a rare renal cell carcinoma was observed in 1 female of the high concentration group. The number of fibroadenomas of the mammary gland was significantly increased only in the females of the low concentration group (JMHLW 1993 a; US EPA 2012).

Groups of 50 male and 50 female Crj:BDF1 mice were exposed to tetrachloroethylene (purity: 99.0%) concentrations of 0, 10, 50 or 250 ml/m^3 for 6 hours a day, on 5 days a week, for 103 weeks (see Table 13). The number of animals that survived was reduced in relation to the concentration, but this finding was not evaluated statistically. Significantly positive trends were observed for hepatocellular adenomas, carcinomas and the combined evaluation. At the high concentration, the incidences of these neoplasms were significantly increased compared with those in the controls. Likewise, the incidences of degeneration of the liver were significantly increased in both sexes at the high concentration. Positive trends were reported for the incidences of haemangiosarcomas of the liver and spleen in males, haemangiomas and haemangiosarcomas (combined) for all organs in males and females and adenomas of the Harderian gland in the males. Likewise, the incidences of karyomegaly of the tubular cells were significantly increased in males and females at the high concentration (JMHLW 1993 b; US EPA 2012).

In a study mentioned in the 1988 supplement (documentation "Tetrachloroethylene" 1992), groups of 30 female Swiss mice were dermally exposed to doses of 18 or 54 mg tetrachloroethylene per animal (in 0.2 ml acetone) 3 times a week for at least

63 weeks. A control group was treated with acetone only. A papilloma was found in 1 animal of the low dose group; no papillomas or carcinomas of the skin were observed in any other animal. Limitations of the study included the small number of animals tested, the short exposure period, the lack of information about the purity of the test substance, the incomplete reporting of results and the failure to take into consideration losses resulting from the volatility of the test substance (IARC 2014).

Conclusions:

Mononuclear leukaemia is a neoplasm with a high spontaneous incidence in F344 rats. In a detailed evaluation, the US EPA concluded that the significant increase in incidences observed in the carcinogenicity studies with tetrachloroethylene resulted from treatment (US EPA 2012). However, the relevance of this finding for humans remains unclear.

Likewise, a high spontaneous incidence of liver tumours is observed in B6C3F1 mice. In the NTP inhalation study, hepatocellular adenomas and carcinomas were significantly increased in male and female mice at the lowest concentration tested of 100 ml/m^3 and above. The incidences were above the historical control incidences. Other tumours were not observed (NTP 1986).

Another inhalation study (JMHLW 1993 b) reported an increase in the incidence of hepatocellular carcinomas in male and female BDF1 mice that was significant and above the historical control incidences only at the highest concentration tested of 250 ml/m^3. The historical control incidences in BDF1 mice are similar to those in B6C3F1 mice.

In addition, in the recent inhalation study in mice, the incidences of haemangiosarcomas of the spleen and liver were increased with a significant trend (JMHLW 1993 b). However, the incidences were not statistically significantly increased when the groups were compared pairwise with the controls.

The inhalation studies in rats did not report increased incidences of liver tumours up to 600 ml/m^3.

Trichloroacetic acid, the main metabolite of tetrachloroethylene, caused hepatocellular adenomas and carcinomas in mice (see supplement "Trichloressigsäure" 2016, available in German only). The liver tumours observed in mice after exposure to tetrachloroethylene may have been caused by the formation of trichloroacetic acid during the oxidative metabolism of tetrachloroethylene (Odum et al. 1988; Sweeney et al. 2009), but this assumption is a matter of controversy because other metabolites and mechanisms might be involved (US EPA 2012).

In the NTP inhalation study, a non-significant increase in the incidence of rare renal cell tumours was observed in male rats at tetrachloroethylene concentrations of 200 ml/m^3 and above (NTP 1986). This finding was not confirmed in the second inhalation study in rats (JMHLW 1993 a), even when higher concentrations were tested. In both studies, nephrotoxicity was observed in male and female rats at 200 ml/m^3 and above. Nephrotoxicity and possible carcinogenicity were caused by the formation of reactive metabolites of the glutathione-dependent β-lyase pathway. The studies described in Section 3.2 (Pähler et al. 1999 a, b) found that, unlike in rats, no protein adducts from the glutathione-dependent β-lyase pathway were detected in the blood of humans after exposure to a tetrachloroethylene concentration of 40 ml/m^3. Taking the other arguments into account (see Section 2), it can be assumed that humans are markedly less sensitive than rats to the nephrotoxicity and possible nephrocarcinogenicity of tetrachloroethylene.

Table 12 Studies of the carcinogenicity of tetrachloroethylene in rats

Author:		NTP 1986		
Substance:		tetrachloroethylene (purity: 99.9%)		
Species:		**rat**, F344/N, 50 ♂, 50 ♀		
Administration route:		inhalation		
Concentrations:		0, 200, 400 ml/m³		
Duration:		103 weeks, 5 days/week, 6 hours/day		
Toxicity:		see also Section 5.2.1 **200 ml/m³**: ♂: nasal cavity: squamous metaplasia; adrenal medulla: hyperplasia; **400 ml/m³**: ♂: survival ↓ (as of week 102); forestomach: ulcers; nasal cavity: thrombosis, squamous metaplasia; adrenal medulla: hyperplasia; ♀: adrenal cortex: hyperplasia		
		exposure concentration (ml/m³)		
		0	200	400
surviving animals	♂	23/50 (46%)	20/50 (40%)	12/50 (24%)
	♀	23/50 (46%)	21/50 (42%)	24/50 (48%)
tumours and pre-neoplasms				
mononuclear leukaemia	♂	28/50 (56%)[a), c)] 64.6%[b)]	37/50 (74%)* 80.1%	37/50 (74%)* 90.8%
	♀	18/50 (36%)[a), d)] 53.8%[b)]	30/50 (60%)* 71.4%	29/50 (58%)* 66.3%
kidneys				
karyomegaly	♂	1/49 (2%)	37/49 (76%)	47/50 (94%)
	♀	0/50 (0%)	8/49 (16%)	20/50 (40%)
tubular cell hyperplasia	♂	0/49 (0%)	3/49 (6%)	5/50 (10%)
	♀	0/50 (0%)	0/49 (0%)	1/50 (2%)
tubular cell adenomas	♂	1/49 (2%)[e)]	3/49 (6%)	2/50 (4%)
tubular cell adenocarcinomas	♂	0/49 (0%)	0/49 (0%)	2/50 (4%)
tubular cell adenomas and carcinomas	♂	1/49 (2%)[a)] 4.3%[b)]	3/49 (6%) 10.8%	4/50 (8%) 22.4%
brain				
gliomas	♂	1/50 (2%)[a), f)] 4.3%[b)]	0/50 (0%) 0.0%	4/50 (8%) 17.3%
	♀	1/50 (2%)[a)]	0/50 (0%)	2/50 (4%)

*$p \leq 0.05$; **$p \leq 0.01$ (Fisher's exact test)
a) overall rate (number of animals with tumours per number of examined animals)
b) adjusted rate (tumour incidence at the end of the study estimated according to Kaplan-Meier after correction for intercurrent mortality)
historical controls of study laboratory or in NTP studies (incidence, mean ± standard deviation):
c) 117/250 (47% ± 15%) or 583/1977 (29% ± 12%)
d) 73/249 (29% ± 6%) or 375/2021 (19% ± 7%)
e) 1/249 (0.4% ± 0.9%) or 4/1968 (0.2% ± 0.6%), no carcinomas observed
f) 3/247 (1.2%) or 16/1971 (0.8%)

Table 12 (continued)

Author:	JMHLW 1993 a; JISA 1993
Substance:	tetrachloroethylene (purity: 99.0%)
Species:	**rat**, F344/DuCrj, 50 ♂, 50 ♀
Administration route:	inhalation (whole body)
Concentrations:	0, 50, 200, 600 ml/m³
Duration:	104 weeks, 5 days/week, 6 hours/day
Toxicity:	see also Section 5.2.1 **50 ml/m³ and above**: concentration-related decrease in survival; **50 ml/m³**: ♀: absolute liver weights ↑; **200 ml/m³ and above**: ♂: kidneys: absolute and relative weights ↑; spleen: extramedullary haematopoiesis ↓; ♀: relative heart, lung, kidney and liver weights ↑, serum: ALT ↑, urea nitrogen ↑; **200 ml/m³**: kidneys: karyomegaly of tubular epithelial cells; ♀: body weight gains ↓, relative adrenal gland weights ↑; **600 ml/m³**: body weight gains ↓, serum: ALT ↑; kidneys: karyomegaly of tubular epithelial cells, atypical dilation in the proximal tubule; liver: relative weights ↑; ♂: liver: spongiosis hepatis ↑; ♀: absolute liver weights ↑, MCH ↑, serum: triglycerides ↓, potassium ↑

		exposure concentration (ml/m³)			
		0	50	200	600
surviving animals	♂	37/50 (74%)	34/50 (68%)	30/50 (60%)	28/50 (56%)
	♀	42/50 (84%)	34/50 (68%)	34/50 (68%)	34/50 (68%)
tumours					
mononuclear leukaemia	♂	11/50 (22%)[b)] trend test: p = 0.0001	14/50 (28%)	22/50 (44%)	27/50 (54%)*
	♀	10/50 (20%)[c)] trend test: p = 0.0571[a)]	17/50 (34%)	16/50 (32%)	19/50 (38%)
kidneys					
adenomas	♂	1/50 (2%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
	♀	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
carcinomas	♂	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
	♀	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
mammary gland					
fibroadenomas	♀	3/50 (6%)	13/50 (26%)*	1/50 (2%)	0/50 (0%)

*p ≤ 0.05 (Fisher's exact test); trend test: Peto test (combined analysis)
a) p = 0.046 in poly-3 test (US EPA 2012)
historical controls (inhalation and feeding studies) (incidence, range):
b) 147/1149 (13%), 6.0–22.0%
c) 147/1048 (14%), 2.0–26.0%

Table 13 Studies of the carcinogenicity of tetrachloroethylene in mice

Author:		NTP 1986		
Substance:		tetrachloroethylene (purity: 99.9%)		
Species:		**mouse**, B6C3F1, 50 ♂, 50 ♀		
Administration route:		inhalation		
Concentrations:		0, 100, 200 ml/m³		
Duration:		103 weeks, 5 days/week, 6 hours/day		
Toxicity:		see also Section 5.2.1 **100 ml/m³**: kidneys: casts, karyomegaly, nephrosis; ♂: survival ↓; liver: degeneration, necrosis, nuclear inclusions; **200 ml/m³**: survival ↓; kidneys: casts, karyomegaly, nephrosis; liver: degeneration, necrosis, nuclear inclusions		
		exposure concentration (ml/m³)		
		0	100	200
surviving animals	♂	46/50 (92%)	25/50 (50%)	32/50 (64%)
	♀	36/50 (72%)	31/50 (62%)	19/50 (38%)
tumours and pre-neoplasms				
liver				
adenomas	♂	12/49 (24%)[a)] 26.1%[b)]	8/49 (16%) 29.9%	19/50 (38%) 55.4%
	♀	3/48 (6%) 7.5%	6/50 (12%) 18.7%	2/50 (4%) 6.1%
carcinomas	♂	7/49 (14%) 14.9%	25/49 (51%)*** 58.3%	26/50 (52%)*** 58.3%
	♀	1/48 (2%) 2.8%	13/50 (26%)*** 35.5%	36/50 (72%)*** 91.7%
adenomas and carcinomas	♂	17/49 (35%)[c)] 36.1%	31/49 (63%)** 73.0%	41/50 (82%)*** 89.0%
	♀	4/48 (8%)[d)] 10.1%	17/50 (34%)** 46.7%	38/50 (76%)*** 92.2%

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 (Fisher's exact test)
[a)] overall rate (number of animals with tumours per number of examined animals)
[b)] adjusted rate (tumour incidence at the end of the study estimated according to Kaplan-Meier after correction for intercurrent mortality)
historical controls of study laboratory or in NTP studies (incidence, mean ± standard deviation):
[c)] 83/249 (33% ± 7%) or 627/2084 (30% ± 8%)
[d)] 19/248 (8% ± 4%) or 181/2080 (9% ± 5%)

Table 13 (continued)

Author:	JMHLW 1993 b; JISA 1993
Substance:	tetrachloroethylene (purity: 99.0%)
Species:	**mouse**, Crj:BDF1, 50 ♂, 50 ♀
Administration route:	inhalation (whole body)
Concentrations:	0, 10, 50, 250 ml/m^3
Duration:	104 weeks, 5 days/week, 6 hours/day
Toxicity:	see also Section 5.2.1 **10 ml/m^3 and above**: concentration-related decrease in survival; **50 ml/m^3 and above**: ♂: serum: AST and ALT ↑; **50 ml/m^3**: liver: degeneration; kidneys: karyomegaly of tubular epithelial cells; ♂: liver: angiectasis; **250 ml/m^3**: body weight gains ↓; feed consumption ↓; erythrocyte count and Hct ↑; serum: total bilirubin ↑, AST, ALT, LDH and ALP ↑, chloride ↓; relative heart, lung, kidney and brain weights ↑; liver: angiectasis, degeneration; kidneys: karyomegaly of tubular epithelial cells; spleen: extramedullary haematopoiesis ↑; ♂: MCV, MCH, MCHC and platelets ↓; serum: total protein, cholesterol and calcium ↑, glucose, triglycerides and urea nitrogen ↓; absolute and relative kidney, spleen and liver weights ↑; relative adrenal gland and testis weights ↑; liver: focal necrosis; ♀: haemoglobin ↑; serum: potassium ↓; kidneys: atypical dilation of the proximal tubule

		exposure concentration (ml/m^3)			
		0	10	50	250
surviving animals	♂	31/50 (62%)	35/50 (70%)	28/50 (56%)	22/50 (44%)
	♀	32/50 (64%)	27/47 (57%)	22/49 (45%)	17/50 (34%)
tumours and pre-neoplasms					
liver					
adenomas	♂	7/50 (14%)[b)] trend: $p < 0.001$	13/50 (26%)	8/50 (16%)	26/50 (52%)**
	♀	3/50 (6%)[c)] trend: $p < 0.001$	3/47 (6%)	7/49 (14%)	26/49 (53%)***
carcinomas	♂	7/50 (14%)[d)] trend: $p < 0.001$	8/50 (16%)	12/50 (24%)	25/50 (50%)**
	♀	0/50 (0%)[e)] trend: $p < 0.001$	0/47 (0%)	0/49 (0%)	14/49 (29%)***

Table 13 (continued)

adenomas and carcinomas	♂	13/50 (26%) trend: $p < 0.001$	21/50 (42%)	19/50 (38%)	40/50 (80%)**
	♀	3/50 (6%) trend: $p < 0.001$	3/47 (6%)	7/49 (14%)	33/49 (67%)***
all organs, haemangiosarcomas [a)]	♂	2/50 (4%) trend: $p < 0.05$	1/50 (2%)	6/50 (12%)	8/50 (16%)*
	♀	1/50 (2%) trend: $p < 0.05$	0/47 (0%)	2/49 (4%)	3/49 (6%)
spleen, haemangiosarcomas	♂	1/50 (2%)[f)] trend: $p = 0.034$	1/50 (2%)	3/50 (6%)	5/50 (10%)
liver, haemangiosarcomas [h)]	♂	1/50 (2%) trend: $p < 0.033$	1/50 (2%)	5/50 (10%)	5/50 (10%)
Harderian gland, adenomas	♂	2/50 (4%)[g)] trend: $p < 0.01$	2/50 (4%)	2/50 (4%)	8/50 (16%)

*$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$ (Fisher's exact test); trend test: Peto test

[a)] incidences could not be verified on the basis of the original data (JMHLW 1992 e)
historical controls (inhalation and feeding studies) (incidence, range):

[b)] 165/947 (17.4%), 4.0–34.0%

[c)] 50/949 (5.3%), 2.0–10.0%

[d)] 215/947 (22.7%), 2.0–42%

[e)] 22/949 (2.3%), 0–8.0%

[f)] 30/946 (3.2%), 0–8.0%

[g)] 42/947 (4.4%), 0–10.0%

[h)] a re-evaluation of the individual animal data by the US EPA (2012) yielded the following incidences for haemangiomas and haemangiosarcomas of the liver in ♂: 4/50, 2/50, 7/50, 11/50*

6 Manifesto (MAK value/classification)

The critical effects are the neurotoxic, hepatotoxic and nephrotoxic effects and the carcinogenic effects that were observed in animal studies.

Carcinogenicity. The human data available for the genotoxic effects of tetrachloroethylene did not suggest a genotoxic potential. In vitro and in vivo studies in mammalian cells found that tetrachloroethylene has only a very weak genotoxic potential. In vivo, high doses induced micronuclei in the liver and DNA single strand breaks in the liver and kidneys, which are the target organs of tetrachloroethylene. Therefore, genotoxicity may have been involved in the formation of tumours in the liver and kidneys. The in vitro and in vivo data available for genotoxicity do not suggest a primarily genotoxic mechanism of carcinogenicity. An initiation-promotion study (Milman et al. 1988) did not provide evidence of an initiating effect of tetrachloroethylene in the liver of rats.

On the basis of the data obtained from epidemiological studies, tetrachloroethylene is suspected of having carcinogenic effects in humans. Animal studies also suggested a carcinogenic potential, although it is unclear whether the findings obtained in the livers and spleens of mice and the kidneys of rats, as well as the increased incidence of leukaemia in the F344 strain of rats, are relevant to humans. Therefore, classification in Carcinogen Category 3B has been retained.

Germ cell mutagenicity. The human data (chromosomal aberrations and sister chromatid exchanges) do not suggest a genotoxic potential. In vitro and in vivo studies in mammalian cells found that tetrachloroethylene has only a very weak genotoxic potential. In vivo, high doses induced micronuclei in the liver or DNA single strand breaks in the liver and kidneys, which are the target organs of tetrachloroethylene. Tetrachloroethylene was not found to have genotoxic potential in the dominant lethal test. Therefore, classification in one of the germ cell mutagen categories is not required.

MAK value. Neurotoxicity and effects on the liver and kidneys were the primary effects induced by inhalation exposure to tetrachloroethylene.

The evaluation does not include the results relating to hepatotoxicity from animal studies because the oxidative metabolism of tetrachloroethylene is considerably less important in humans, particularly compared with that in mice, and the animal studies are therefore of only little relevance for the evaluation.

Studies that investigated the effects of tetrachloroethylene on the liver and kidneys in exposed workers did not reveal any clearly adverse effects at mean exposure concentrations of mostly 10 to 20 ml/m^3.

Neurotoxicity is considered to be the most sensitive end point in humans. On the basis of the human studies with long-term exposure at the workplace a NOAEC of 20 ml/m^3 can be assumed for the neurotoxicity of tetrachloroethylene. Among the studies with repeated daily 4-hour exposure of volunteers, the study of Altmann et al. (1990) reported slight, but significant effects on visually evoked potentials (VEPs) at 50 ml/m^3; this concentration is regarded as the LOAEC. This study found no effects at 10 ml/m^3. As this level is 5 times lower than the LOAEC, at which only weak effects were observed, 20 ml/m^3 is regarded as the NAEC (no adverse effect concentration).

As the volunteers were exposed for 4 hours only under resting conditions, but absorption is expected to be about twice as high under workplace conditions (documentation "Tetrachloroethylene" 1992), a MAK value of 10 ml/m^3 has been established. Irritation is unlikely to result from exposure at the level of the MAK value (see Section 4.3).

Peak limitation. As the MAK value has been derived from a systemic effect, tetrachloroethylene is classified in Peak Limitation Category II.

There are no data available for the half-life of tetrachloroethylene in the target organ the CNS. Therefore, the default excursion factor of 2 has been established. No irritation of any relevance is expected to occur at the concentration of 20 ml/m^3 because such effects were not described in the study of Altmann et al. (1990) at 50 ml/m^3.

Prenatal toxicity. In humans, there is some evidence of an association between the employment of women in dry cleaning and an increased risk of spontaneous abortions. There is no evidence of an association between exposure to tetrachloroethylene and congenital malformations or between paternal exposure and an increased risk of spontaneous abortions. These studies include possible confounders, such as exposure to other solvents (for example trichloroethylene), smoking, alcohol consumption, diseases, medication, parity, previous abortion, reproductive behaviour, age and physical workload. Most of the available studies were small studies with unclear control populations that frequently failed to record relevant confounders. The study results are heterogeneous. In many studies, exposure was defined only by the type of work carried out, and most did not analyse tetrachloroethylene at the workplace. The evidence of an association between the employment of women in dry cleaning and an increased risk of spontaneous abortions is not strong enough to establish a causal relationship because the studies are of limited statistical power.

Animal studies that investigated developmental toxicity after exposure by inhalation reported initial effects on the foetal weights of rats at 249 ml/m^3 and above that were of minimal toxicological relevance (Carney et al. 2006). In another study, reduced foetal weights and an increase in the number of delayed ossifications and malformations were observed at 652 ml/m^3 (Szakmáry et al. 1997). The NOAECs for developmental toxicity in rats were given as 65 ml/m^3 (Carney et al. 2006) and 217 ml/m^3 (Szakmáry et al. 1997); the first value is presumably too low in view of the large difference to the LOAEC of 249 ml/m^3 while the second is probably close to the actual NOAEC.

After exposure of mice by inhalation, reduced body weights and delayed ossification were observed at 300 ml/m^3 (Schwetz et al. 1975) and an increase in the number of malformations of the internal organs was found at 217 ml/m^3 (Szakmáry et al. 1997). It was not possible to derive a NOAEC for developmental toxicity. In rabbits, post-implantation losses were observed at 652 ml/m^3 (Szakmáry et al. 1997) and another study found no evidence of toxic effects on development at 500 ml/m^3 (NIOSH 1980). Therefore, the NOAEC for developmental toxicity in rabbits is 500 ml/m^3.

The margins between the NOAECs for toxic effects on prenatal development and the MAK value of 10 ml/m^3 of 6 or 22 (rats), 22 (LOAEC for mice) and 50 (rabbits) times are thus sufficiently large. This would suggest classification in Pregnancy Risk Group C. However, tetrachloroethylene has neurotoxic effects. There are 3 studies of developmental neurotoxicity in rats available that the Commission considers suitable for assessing this end point. In behavioural tests (ascent and rotarod tests), a decrease in performance occurred at 900 ml/m^3. The NOAEC for developmental neurotoxicity was 100 ml/m^3 (Nelson et al. 1980); the 10-fold margin between this level and the MAK value of 10 ml/m^3 is also sufficiently large. Tetrachloroethylene has therefore been classified in Pregnancy Risk Group C.

Absorption through the skin. The body burden resulting from dermal exposure of both hands and forearms for 1 hour corresponds to an external concentration of up to 150 ml/m^3 (Section 3.1.1), which is higher than that after 8-hour exposure by inhalation at the level of the MAK value. Tetrachloroethylene is thus designated with "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no conclusive positive findings in humans available for sensitizing effects on the skin or respiratory tract. A local lymph node assay in mice reported weakly positive results only, which are regarded more or less as negative primarily because of the irritation caused by tetrachloroethylene. Tetrachloroethylene is therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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