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1,1,2-Trichloroethane

MAK Value Documentation, supplement – Translation of the German version from 2020

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)

Keywords

1,1,2-trichloroethane; short-term exposure; irritation; maximum workplace concentration; MAK value; toxicity; hazardous substance; peak limitation; carcinogenicity

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group of 1,1,2-trichloroethane [79-00-5]. The critical effects are local irritation after inhalation or dermal exposure and liver toxicity after oral administration. Inhalation of 15 ml/m^3 leads to vacuolization of the olfactory epithelium after 13-week exposure of rats. A NAEC of 5 ml/m^3 was calculated. As a result of the local irritation, the MAK value has been lowered to 1 ml/m^3. As the critical effect of 1,1,2-trichloroethane is local, Peak Limitation Category I has been assigned. The excursion factor of 2 is retained. 1,1,2-Trichloroethane is classified in Pregnancy Risk Group D because sufficient data for developmental toxicity are not available. 1,1,2-Trichloroethane is still a suspected carcinogen and remains in Carcinogen Category 3 B. 1,1,2-Trichloroethane can be absorbed via the skin in toxicologically relevant amounts and remains designated with "H". A sensitizing potential is not expected from the data available.

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MAK value (2019)	**1 ml/m³ (ppm) ≙ 5.5 mg/m³**
Peak limitation (2019)	**Category I, excursion factor 2**
Absorption through the skin (1981)	**H**
Sensitization	**–**
Carcinogenicity (1989)	**Category 3 B**
Prenatal toxicity (2019)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
CAS number	79-00-5
Molar mass	133.42 g/mol
Density at 20 ℃	1.44 g/cm³ (ECHA 2017)
Vapour pressure at 20 ℃	22.25 to 25.35 hPa (ECHA 2017)
log K_{OW}	2.05–2.49 (ECHA 2017)
Solubility at 25 ℃	3500 mg/l water (ECHA 2017)
1 ml/m³ (ppm) ≙ 5.536 mg/m³	**1 mg/m³ ≙ 0.181 ml/m³ (ppm)**

Documentation for 1,1,2-trichloroethane was published in 1981 (Henschler 1981, available in German only) followed by a supplement on peak limitation in 2002 (Greim 2002, available in German only).

This supplement evaluates whether the MAK value for 1,1,2-trichloroethane and other classifications should be amended as a result of the findings of recent studies.

1 Toxic Effects and Mode of Action

Gavage doses of 1,1,2-trichloroethane induced liver carcinomas in mice, but not in rats. An initiation–promotion study carried out in rats after partial hepatectomy found an increased number of preneoplastic foci in the liver.

An inhalation study in rats reported irritation of the olfactory epithelium at concentrations of 15 ml/m³ and above. In a 90-day drinking water study, glutathione was decreased in the liver of male mice and cytochrome P450 (CYP) enzymes were inhibited in female mice at doses of 45 mg/kg body weight and day and above.

1,1,2-Trichloroethane was slightly irritating to the skin and eyes in rabbits.

In a screening test with gavage administration of 1,1,2-trichloroethane, a dose of 350 mg/kg body weight and day did not induce embryotoxic or foetotoxic effects in female rats.

1,1,2-Trichloroethane was not found to have a marked genotoxic potential in vitro and in vivo.

There are no data for sensitizing effects.

2 Mechanism of Action

1,1,2-Trichloroethane is metabolically activated by the CYP system. Chloroacetyl chloride and chloroacetaldehyde probably form as reactive intermediates, and may be responsible for the toxic and carcinogenic effects of 1,1,2-trichloroethane (BUA 1995; Henschler 1981).

The metabolites were found to contain sulfur, which suggests that glutathione *S*-transferase is involved in the metabolic pathway, possibly via the conjugation of the intermediates chloroacetaldehyde and chloroacetic acid or of 1,1,2-trichloroethane itself. A possible pathway involves the reaction of 1,1,2-trichloroethane with glutathione to form an episulfonium ion, which is the pathway followed by the structurally similar 1,2-dichloroethane. However, this is considered unlikely because only 1,2-dichloroethane was activated in the Salmonella mutagenicity test by the addition of glutathione, and not 1,1,2-trichloroethane (Rannug et al. 1978).

In addition, radicals may form during reductive dechlorination (see Section 3.2); these radicals may likewise bind to macromolecules and lead to genotoxic effects (Mazzullo et al. 1986). However, studies that investigated the reductive dechlorination of various chloroalkanes using the liver microsomes and hepatocytes of rats demonstrated that there is no correlation between the extent of dechlorination or radical formation and the carcinogenic potential of the chloroalkanes in the liver of mice (Nastainczyk et al. 1982; Salmon et al. 1981, 1985; Thompson et al. 1984; Tomasi et al. 1984). For this reason, it is unclear how the formation of radicals contributes to the carcinogenic effects in the liver.

The toxicokinetic data do not explain why 1,1,2-trichloroethane induces carcinogenic effects in mice, but not in rats (see Section 3.1). Studies using microsomal and cytosolic fractions from the liver found a higher affinity for binding to the hepatic DNA of mice than to that of rats (see Section 5.6). This is supported by evidence from a carcinogenicity study in mice, which found that the liver is the target organ (see Section 5.7.2).

The covalent binding index determined in mice was of an order of magnitude typical for weak genotoxic carcinogens and in a range similar to the indices for 1,1-dichloroethane and 1,2-dichloroethane. The binding index for rat DNA is lower than that for mouse DNA (Mazzullo et al. 1986). The findings of this study do not indicate whether DNA adducts were actually formed. However, evidence of this was provided by in vitro studies that found that 1,1,2-trichloroethane and its metabolites bind to the DNA (see Section 5.6.2). They bind also to the RNA and to proteins. These effects are blocked by glutathione (see Section 5.6.1).

After treatment of mice with 1,1,2-trichloroethane, cell proliferation was increased in the liver (Mirsalis et al. 1989). As a high incidence of spontaneous tumours was found in the liver of B6C3F1 mice, it can be assumed that the number of initiated cells was increased. Therefore, a possible explanation for the formation of liver tumours would involve a combination of the proliferation of previously initiated cells and the weak genotoxic effects of 1,1,2-trichloroethane.

In an initiation–promotion study with 1,1,2-trichloroethane in Osborne Mendel rats, no initiating effect was found, but a promoting effect on the induction of γ-glutamyltranspeptidase-positive (GGT^+) liver foci (Story et al. 1986). Unlike B6C3F1 mice, rats do not have a high incidence of spontaneous liver tumours. This finding, together with a lower affinity for DNA binding, may explain why a higher incidence of liver tumours was not found in rats.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

1,1,2-Trichloroethane is readily absorbed after inhalation, oral and dermal exposure (BUA 1995; Henschler 1981). After inhalation exposure of mice to 1,1,2-trichloroethane at a concentration of 1000 ml/m^3 for 1 hour, the tissue concentrations of 1,1,2-trichloroethane were determined either immediately or up to 120 minutes after exposure. The partition coefficients were found to be: blood:air 58.0 ± 1.1; fat:air 1438 ± 58; liver tissue:air: 73.1 ± 0.8 and muscle tissue:air 22.9 ± 0.8. On the basis of the decrease in 1,1,2-trichloroethane concentrations, elimination was found to occur in two phases from the blood, liver, kidneys and heart and in one phase from the spleen, lungs, brain and adipose tissue. The

half-lives in phase 1/phase 2 were 19/134 minutes in the blood, 10/82 minutes in the liver, 127/248 minutes in the kidneys and 24/1096 minutes in the heart. On the basis of these values, the half-life in the body as a whole was calculated to be 49.3 minutes (ATSDR 1989; BUA 1995; Takahara 1986).

Groups of 3 female Fischer 344 rats or 3 female B6C3F1 mice were exposed by inhalation to 1,1,2-trichloroethane at a concentration of 100 ml/m^3 for 4 weeks. 1,1,2-Trichloroethane concentrations in the blood were determined 5, 7, 7.25 and 9 hours after the beginning of a 6-hour exposure period on day 1 of exposure week 4 and 4, 6, 6.25 and 8 hours after the beginning of a 6-hour exposure period on days 3 or 5 of exposure week 4. In rats, the highest concentration of 2.3 ± 0.35 µg/g blood was determined 7 hours after the beginning of exposure on day 1. In mice, the highest concentration of 2.2 ± 0.37 µg/g blood was determined 6 hours after 5 days of exposure in exposure week 4. The concentrations in the blood remained at about the same level from days 1 to 5 and decreased markedly in all cases 2 hours after the end of exposure. Thus, after exposure for 4 weeks, the concentration in the blood did not increase over the course of the week (Pacific Northwest National Laboratory 2003).

The 1,1,2-trichloroethane concentrations in the blood were determined after the substance was administered daily by gavage for 5 days to groups of 36 female Fischer 344 rats at a dose level of 91 mg/kg body weight and day in corn oil or 1.5 mg/kg body weight and day in water and to groups of 12 female B6C3F1 mice at a dose level of 366 mg/kg body weight and day in corn oil or 9.5 mg/kg body weight and day in water. On days 1, 3 and 5, blood samples were taken from 3 animals of each group 0.5, 1, 2 and 8 hours after administration of the substance in corn oil and 6, 15, 30 or 60 minutes after administration of the substance in water. In the groups given the substance in corn oil, the highest concentrations of 1,1,2-trichloroethane in the blood were determined in mice 30 minutes (25 µg/g) after administration of the fifth dose (day 5) and in rats 30 minutes (16.6 µg/g) after the first dose (day 1). In the groups given the substance in water, the highest concentrations in the blood were determined in mice 6 minutes (0.25 µg/g) after administration of the first dose and in rats 6 minutes (0.065 µg/g) after the fifth dose (Pacific Northwest National Laboratory 2003).

After oral doses of [^{14}C]-1,1,2-trichloroethane were given to male Osborne Mendel rats and B6C3F1 mice, in the protein fraction of the liver homogenate a higher level of radioactivity was found in mice than in rats (BUA 1995; Mitoma et al. 1985).

After oral or intraperitoneal administration of [^{14}C]-1,1,2-trichloroethane to rats and mice, 7% to 10% were exhaled as unidentified metabolites, 3% to 7% as CO_2 and 72% to 87% of the radioactivity (metabolites) was recovered in the urine. The oral doses were chosen to be almost equivalent to the maximum tolerable dose (MTD). Although mice received a dose of 300 mg/kg body weight, which was 4.3 times as great as the dose of 70 mg/kg body weight administered to rats, the mice were able to metabolize the same percentage of the dose (ATSDR 1989; Mitoma et al. 1985; Yllner 1971).

After intraperitoneal injection of a [^{14}C]-1,1,2-trichloroethane dose of 100 to 200 mg/kg body weight in mice, 16% to 22% of the dose was exhaled, 60% of this as CO_2 and 40% as unchanged substance (Henschler 1981; Yllner 1971).

A blood:air partition coefficient of 37 was determined for 1,1,2-trichloroethane according to the formula of Buist et al. (2012). A blood:air partition coefficient of 71 was determined for mice (Pacific Northwest National Laboratory 2003).

In rats, the tissue:air partition coefficients of 1,1,2-trichloroethane were 43 (spleen:air) and 56 (brain:air) (Pacific Northwest National Laboratory 2003).

Studies in guinea pigs demonstrated that 1,1,2-trichloroethane is absorbed through the skin. The concentration of 1,1,2-trichloroethane in the blood increased within 30 minutes of dermal application (Boman et al. 1989). Dose-dependent systemic effects, including the death of the animals, were induced by the treatment (Henschler 1981). Fifteen minutes after dermal application of 0.5 ml of the substance, 0.763 mg of the substance was absorbed in mice. During this period of time, 0.3% was exhaled and 99.7% of the absorbed substance remained in the body of the animals. The absorbed amount was used to calculate a flux of 130 nmol/cm^2 and minute, which is the equivalent of 1.04 mg/cm^2 and hour (Tsuruta 1975). On the basis of this value, 2.08 g of 1,1,2-trichloroethane would be absorbed through the skin after 1-hour exposure of both hands and forearms (surface area of 2000 cm^2).

An extensive review of the studies of the toxicokinetics of the substance can be found in the report of the Advisory Council on Existing Chemicals of Environmental Relevance (Beratergremium für umweltrelevante Altstoffe (BUA)) (BUA 1995).

3.2 Metabolism

After intraperitoneal and oral exposure of mice, the metabolites chloroacetic acid, *S*-carboxymethylcysteine and thiodiacetic acid were detected in the urine. Glycolic acid, 2,2-dichloroethanol, 2,2,2-trichloroethanol, oxalic acid and trichloroacetic acid were found in trace amounts (Henschler 1981; Mitoma et al. 1985; Yllner 1971). The trichloroethanol and trichloroacetic acid can probably be attributed to impurities in the 1,1,2-trichloroethane samples used (ATSDR 1989).

Inhalation exposure of male Wistar rats to 1,1,2-trichloroethane concentrations of 200 to 800 ml/m^3 led to the exhalation of acetone at a level of 65 ± 5 ml/m^3, which suggests that enzymes of the citric acid cycle were inhibited by the formation of the metabolite chloroacetic acid (Filser et al. 1982).

Monochloroacetic acid was identified as the main metabolite in the liver microsomes of rats treated with phenobarbital after the addition of 1,1,2-trichloroethane under aerobic conditions (Ivanetich and van den Honert 1981).

1,1,2-Trichloroethane may follow a similar metabolic pathway to that of 1,1-dichloroethane as both substances form chloroacetic acid via an acid chloride (Ivanetich and van den Honert 1981; Mazzullo et al. 1986).

The dechlorination rates demonstrated that 1,1,2-trichloroethane is extensively metabolized in isolated rat liver microsomes under aerobic conditions (Salmon et al. 1981).

Ivanetich and van den Honert (1981) suggested the following reaction scheme for the metabolism of 1,1,2-trichloroethane to chloroacetic acid:

[$HOCl_2C{-}CH_2Cl$] forms from 1,1,2-trichloroethane ($Cl_2HC{-}CH_2Cl$) as an unstable intermediate. This intermediate rearranges to chloroacetyl chloride ($ClH_2C{-}COCl$) by splitting off HCl, followed by hydrolysis and the splitting off of another HCl to form chloroacetic acid ($ClH_2C{-}COOH$).

A study using perfused rat liver demonstrated that 1,1,2-trichloroethane is metabolized via the CYP system (Takano et al. 1985).

Bioactivation by microsomal rat liver fractions or the CYP inhibitor SKF 525-A likewise demonstrated that the initial dechlorination step is catalysed by the CYP system (Henschler 1981).

After intraperitoneal injection of the substance in male CD-1 mice, the expression and activity of the CYP2B1 isoform in liver microsomes was increased, while total CYP activity was reduced (Paolini et al. 1992).

A comparison of the metabolic pathways of 1,1,2-trichloroethane and its monodeuterated analogue in rat liver microsomes demonstrated that, under aerobic conditions, an H radical is abstracted during CYP-catalysed oxidation of 1,1,2-trichloroethane and recombination of the chloroalkane intermediate occurs via a radical mechanism (Hales et al. 1987). Figure 1 presents a schematic depiction.

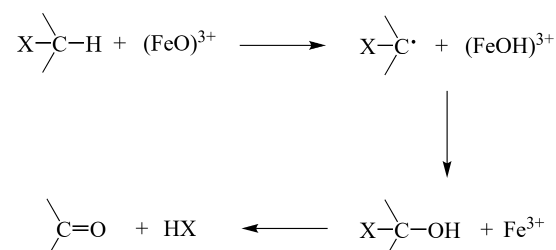

Fig. 1 Schematic depiction of CYP-catalysed oxidation (according to Hales et al. 1987)

Vinyl chloride (chloroethylene) was detected under anaerobic conditions after the addition of 1,1,2-trichloroethane to liver microsomes of rats treated with phenobarbital (Thompson et al. 1985). 1,1,2-Trichloroethane was found to be metabolized only slowly in this system as determined by substrate consumption (Thompson et al. 1984).

Small amounts of radicals were detected by electron spin resonance (ESR) spectroscopy in isolated rat hepatocytes after the addition of 1,1,2-trichloroethane under hypoxic conditions (Tomasi et al. 1984).

The high level of metabolites containing sulfur in the urine demonstrates that intermediates are conjugated by glutathione; this is a detoxification pathway for chloroacetaldehyde and chloroacetic acid (Henschler 1981).

An unlikely pathway would involve the conjugation of 1,1,2-trichloroethane with glutathione through a dechlorination reaction directly catalysed by glutathione *S*-transferase and the formation of a highly reactive glutathione episulfonium ion through a further dechlorination reaction via *S*-(2-chloroethyl)glutathione. The metabolite glutathione episulfonium is regarded as responsible for DNA adduct formation and has been shown to induce the carcinogenic effects of 1,2-dichloroethane (ATSDR 2001; Mazzullo et al. 1986). A bacterial mutagenicity test with Salmonella typhimurium yielded negative results after glutathione was added with 1,1,2-trichloroethane; positive results had been obtained with 1,2-dichloroethane under the same test conditions. This demonstrates that the episulfonium ion is not a metabolite of 1,1,2-trichloroethane (Rannug et al. 1978).

Figure 2 presents a possible metabolic pathway of 1,1,2-trichloroethane involving the CYP system and glutathione *S*-transferase (Mazzullo et al. 1986). As explained above, the c) pathway is unlikely. Glutathione *S*-transferase probably catalyses the binding of glutathione with intermediates of 1,1,2-trichloroethane.

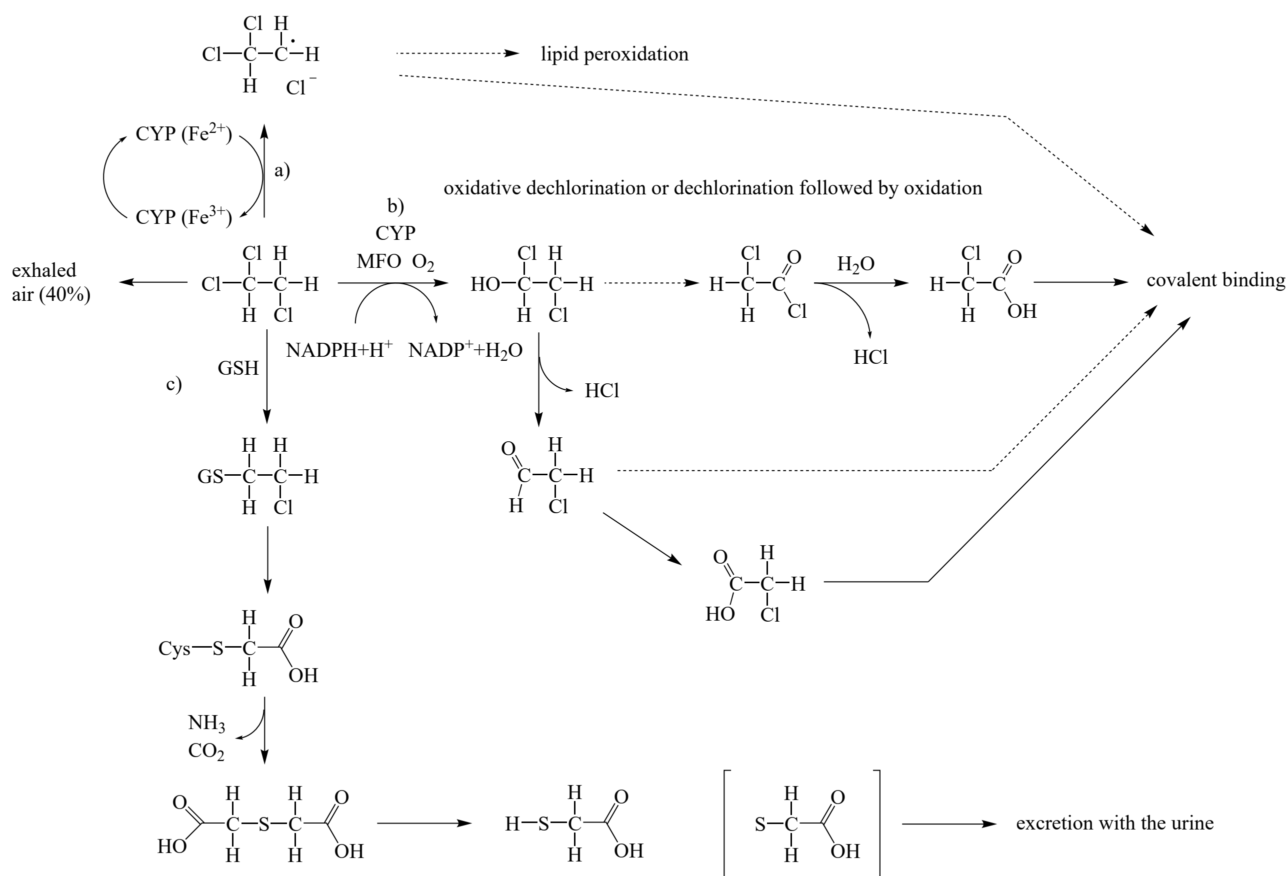

Fig. 2 Metabolism of 1,1,2-trichloroethane (according to Mazzullo et al. 1986, with modification)

4 Effects in Humans

The substance is described as being irritating to the conjunctiva of the eyes, the mucosa of the upper respiratory tract and the outer surface of the skin. Exact data are not available. Effects on the upper gastrointestinal tract, the kidneys and the lungs have been reported after long periods of exposure. The data available for humans are not sufficient for the derivation of a threshold value (Henschler 1981).

It was shown that in 95% of the persons examined of the general population in the US the 1,1,2-trichloroethane levels in blood were below the methodological detection limit (ATSDR 2010).

Single exposures

Five-minute topical application of 1.5 ml 1,1,2-trichloroethane to the skin on the forearm of a test person induced hyperaemia, whitening of the skin and a burning sensation on the skin (Wahlberg 1984).

Reproductive and developmental toxicity

In a population-based case-control study, the data for 60 613 cases recorded in the Texas Birth Defects Registry from 1996 to 2008 and for 244 927 controls were evaluated by the Center for Health Statistics at the Texas Department of State Health Services for exposure of the mothers to industrial air. The Texas Birth Defects Registry collects data for live births, foetal deaths, the termination of pregnancy because of congenital malformations, neural tube defects, missing or malformed body parts, cleft palates and congenital heart defects. Emissions data from industrial plants in Texas for 14 chlorinated solvents were taken from the US EPA Toxic Release Inventory Program database. The residential exposure of the pregnant women was estimated using a modified version of the emission weighted proximity model. An analysis of the data found a correlation between exposure to 1,1,2-trichloroethane and an increased incidence of neural tube defects (odds ratio (OR) 1.56 with 95% confidence interval (CI): 1.11–2.18) and spina bifida (OR 1.94 with 95% CI: 1.32–2.84), but not of anencephaly (OR 0.97 with 95% CI: 0.42–2.21). The OR for the incidence of cleft palates was 1.51 (95% CI: 0.97–2.34); however, exposure was not associated with an increased incidence of cleft lips (OR 1.0). The association between exposure and foetal defects was stronger for pregnant women older than 35 years than for pregnant women under 35 years of age (Brender et al. 2014). However, because of the limited reliability of the study in terms of the exposure data and the possibility of exposure to a mixture of substances, the data are not sufficient to establish a causal relationship between exposure to 1,1,2-trichloroethane and foetal defects.

Carcinogenicity

The risk of renal cell carcinomas caused by occupational exposure to chlorinated hydrocarbons was investigated by comparing a group of cases (n = 438) with a control group (n = 687). For 9 substances, a priori job exposure matrices were applied to determine whether an increased risk was associated with exposure to the individual substances. The risk of renal cell carcinomas was not found to be increased with statistical significance after exposure to 1,1,2-trichloroethane (ATSDR 2010; Doherty et al. 1996).

5 Animal Experiments

5.1 Acute toxicity

The acute toxic effects were found to be irritation of the upper respiratory tract and the gastrointestinal tract, lung damage, CNS depression as well as liver and kidney damage (ATSDR 1989; Henschler 1981; White et al. 1985 b).

5.1.1 Inhalation

The 8-hour LC_{50} values for 1,1,2-trichloroethane in rats ranged from 500 to 999 ml/m^3 and the 6-hour LC_{50} value was 1654 ml/m^3 in rats and 416 ml/m^3 in mice (ATSDR 1989).

Four-hour exposure to 500 ml/m^3 led to the death of 50% of the treated rats. In mice, exposure to 3750 ml/m^3 induced unconsciousness after 18 minutes and a statistically significant increase in alanine aminotransferase (ALT). After 10 hours, 50% of the mice had died (Henschler 1981).

Whole-body exposure of groups of 5 female B6C3F1 mice to 1,1,2-trichloroethane concentrations of 250, 500 or 1000 ml/m^3 induced lethargy in the high concentration group after 2 hours, followed by a loss of coordination and laboured breathing after 4 hours and a loss of consciousness after 6 hours. After a 6-hour observation period, 1 animal had died and the others were lethargic and uncoordinated. Four hours after exposure to 500 ml/m^3, 2 animals were in a dazed state and 3 lethargic. No effects were noticeable after exposure to 250 ml/m^3 (Pacific Northwest National Laboratory 2003).

Groups of 10 male and 10 female F344 rats were exposed whole-body for 4 hours to 1,1,2-trichloroethane concentrations of 0, 58, 181 or 1527 ml/m^3 (nominal: 0, 50, 200 or 1500 ml/m^3). Lethargy, ataxia, reduced breathing, reduced body weights and discharge from the eyes were observed in the high concentration group. As 3 females had died, 5 other female animals were exposed to 1000 ml/m^3; the same symptoms were observed. Reduced phagocytic activity was observed after bronchoalveolar lavage in 5 animals of each group; this was not dependent on the concentration and was therefore not regarded as substance-induced by the authors. Centrilobular hepatocellular necrosis was found in 4 of 5 female animals at 200 ml/m^3 and above. Minimal to slight necrosis of the olfactory epithelium was observed in all female animals and in 2 of 5 male animals even after exposure to the low concentration (WIL Research Laboratories 2001).

5.1.2 Oral administration

In rats, the LD_{50} after oral administration was 840 mg/kg body weight. In mice, the LD_{50} after oral administration was 378 mg/kg body weight in the females and 491 mg/kg body weight in the males. Irritation in the gastrointestinal tract was observed in all mice given a single 1,1,2-trichloroethane dose of 500 or 600 mg/kg body weight with the drinking water (ACGIH 2001; ATSDR 1989; Henschler 1981; White et al. 1985 b).

After 8 hours of fasting, female Wistar rats (group size not specified) were given a single gavage dose of 1,1,2-trichloroethane of 0 or 0.5 mmol/kg body weight (about 66.7 mg/kg body weight) in arachis oil. The substance was administered again after another 4 hours of fasting, followed by sacrifice after 6, 12, 24, 36, 48 or 72 hours. Blood and liver samples were collected for further examination. In the serum of the treated animals, the activities of ALT, sorbitol dehydrogenase (SDH) and glutamate dehydrogenase (GLDH) were significantly increased. 1,1,2-Trichloroethane caused a statistically significant increase in free radical formation in the liver. Treatment of the isolated perfused livers of previously untreated rats with 0.5 mmol 1,1,2-trichloroethane likewise increased the activities of ALT, SDH and GLDH (ATSDR 2010; Xia and Yu 1992).

A single gavage dose of 1,1,2-trichloroethane of 0, 200, 500 or 600 mg/kg body weight given to male and female B6C3F1 mice led to an increase in S-phase synthesis in the hepatocytes in the females at dose levels of 200 mg/kg body weight and above and in the males at 500 mg/kg body weight and above in comparison with the levels determined in the controls. This is evidence of increased proliferation (BUA 1995; IARC 1999; Mirsalis et al. 1989).

A single gavage dose of 1,1,2-trichloroethane of 0, 55, 95 or 200 mg/kg body weight in corn oil given to groups of 12 Crl:CD (SD)IGS BR rats led to hypoactivity in the test for locomotor activity, impaired habituation to the test and reduced body temperatures in the 95 and 200 mg/kg groups. The effects were no longer noticeable after an observation period of 7 days. An examination of the neuropathological end points did not determine any changes (WIL Research Laboratories 2004). The NOAEL (no observed adverse effect level) of this study is 55 mg/kg body weight.

5.1.3 Dermal application

The dermal LD_{50} was 3.73 ml/kg body weight (5380 mg/kg body weight) in rabbits (Smyth et al. 1969).

5.1.4 Intraperitoneal, intravenous and subcutaneous injection

The LD_{50} values ranged from 405 to 936 mg/kg body weight after intraperitoneal injection in rats (ACGIH 2001).

Intravenous injection of a 1,1,2-trichloroethane dose of 1.33 mg/kg body weight and minute in the tail vein suppressed the vestibulo-ocular reflex in female rats. After a single 1,1,2-trichloroethane dose of 0, 3, 10, 30, 100 or 300 mg/kg body weight was given to male CD-1 mice, the animals exhibited taste aversion to a saccharine solution at doses of 100 mg/kg body weight and above. This effect was dependent on the dose and statistically significant. Subcutaneous injection of single 1,1,2-trichloroethane doses of 173 to 347 mg/kg body weight led to central nervous system depression with ataxia and loss of the righting reflex in addition to a prolonged pentobarbital-induced sleep duration in male mice (BUA 1995).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

After groups of 10 male and 10 female rats were exposed 16 times to a 1,1,2-trichloroethane concentration of 30 ml/m^3 for 7-hour periods, minor fatty changes and cloudy swellings were determined in the liver of female rats. A slight, but not statistically significant increase in the incidence of pneumonia was observed in the male animals (no other details; Torkelson and Rowe 1981).

Groups of 10 male and 10 female Fischer 344 rats underwent whole-body exposure to 1,1,2-trichloroethane concentrations of 0, 15, 40 or 100 ml/m^3 for 6 hours a day, on 5 days a week, for 13 weeks. The 1,1,2-trichloroethane had a purity of 99.55%. The examination included body weight gains and feed consumption, the haematological system, ophthalmological effects, serum and urine parameters, organ weights, and visible gross-pathological and histopathological changes. Vacuoles and microcysts were observed in the olfactory epithelium at concentrations of 15 ml/m^3 and above. Atrophy was observed at 40 ml/m^3 and above and respiratory metaplasia in the olfactory epithelium at 15 ml/m^3 and above. The severity of the effects and the number of symptomatic animals increased in the higher concentration groups (Table 1). Minimal vacuolation in the hepatocytes was noted in 3 of 10 females in the 15 and 40 ml/m^3 groups in addition to 5 of 10 males and 10 of 10 females of the high concentration group. The absolute and relative liver weights were not increased in any of the animals. Liver enzyme activities were likewise not increased. Other substance-related effects were not observed (WIL Research Laboratories 2002). The LOAEC (lowest observed adverse effect concentration) of this study was 15 ml/m^3. A NOAEC (no observed adverse effect concentration) could not be derived.

An important factor that needs to be taken into consideration is that 15% of the inhaled air in rats and 7% in humans reaches the olfactory epithelium (Frederick et al. 1998).

Tab. 1 Effects in the olfactory epithelium in rats after 13-week inhalation exposure to 1,1,2-trichloroethane (WIL Research Laboratories 2002)

	Vacuolation		Atrophy		Respiratory metaplasia	
	♂	♀	♂	♀	♂	♀
0 ml/m^3	1/10	1/10	0/10	0/10	0/10	0/10
15 ml/m^3	2/10	4/10	0/10	0/10	1/10	0/10
40 ml/m^3	6/10	4/10	6/10	7/10	1/10	1/10
100 ml/m^3	10/10	8/10	7/10	10/10	3/10	5/10

No differences between control and treated animals were found after the exposure of male and female rats, guinea pigs and rabbits to 1,1,2-trichloroethane at concentration levels of 0 or 15 ml/m^3 for 6 months. The animals were exposed on 5 days a week for 7 hours a day. Histopathological, haematological and clinico-chemical parameters were investigated in addition to mortality, body weight gains and organ weights (no other details; BUA 1995; Torkelson and Rowe 1981). The method used by this study was not described in sufficient detail.

5.2.2 Oral administration

The data of the studies with oral administration are shown in Table 2.

1,1,2-Trichloroethane given by gavage to groups of 36 female Fischer 344 rats for 1, 3 and 5 days in doses of 91 mg/kg body weight and day in corn oil or 1.5 mg/kg body weight and day in water and to groups of 12 female B6C3F1 mice in doses of 366 mg/kg body weight and day in corn oil or 9.5 mg/kg body weight and day in water did not lead to statistically significant changes in the weights of the lungs, kidneys, spleen and brain. In the mice of the group treated with 366 mg/kg body weight, the absolute liver weights increased by 27% after the fifth dose in comparison with the weights determined after the first dose. As the body weights had not changed significantly over the 5 days and the study did not include a control group, it is assumed that the relative liver weights were increased by about 30%. No statistically significant changes were observed in the other dose groups (see Section 3.1; Pacific Northwest National Laboratory 2003). The report did not include histopathological data.

In an initiation–promotion study, gavage doses of 1,1,2-trichloroethane of 70 mg/kg body weight and day given to rats for 7 weeks led to a marked reduction in body weights and decreased absolute liver weights (Milman et al. 1988; see also Section 5.7.1).

In a carcinogenicity study, gavage doses of 1,1,2-trichloroethane of 0, 46 or 92 mg/kg body weight given to rats for 78 weeks induced effects such as hunched posture, eye discharge and changes to the fur, but no histopathological effects at doses of 46 mg/kg body weight and day and above. No non-neoplastic effects were observed in mice treated with doses of up to 390 mg/kg body weight and day (NCI 1978; see Section 5.7.2).

Gavage doses of 1,1,2-trichloroethane of 0, 3.8 or 38 mg/kg body weight and day given to CD-1 mice for 14 days induced slight effects on the absolute, but not on the relative brain, thymus and testis weights of male mice in the high dose group. No effects were determined in the haematological examination and there were no changes in the immune status (White et al. 1985 b).

In a 90-day drinking water study with 1,1,2-trichloroethane given to male and female CD-1 mice in doses of 4.4/3.9, 46/44 or 305/384 mg/kg body weight and day, the body weights in the male animals at the end of the study and the body weight gains were reduced by up to 10% in comparison with the values of the controls. These effects were dependent on the dose. In addition, the initial weights of the exposed animals were slightly lower than those of the control animals. This explains the increased relative testis weights and reduced absolute organ weights of the liver and kidneys. The absolute and relative liver weights were increased in the female animals at 384 mg/kg body weight and day. In the male animals, the levels of the B-cells involved in primary antibody production (IgM) were increased after immunization with sheep erythrocytes at doses of 4.4 mg/kg body weight and above. The increase was attributed to the unusually low control values. A marked increase was not found when the levels were compared with those of the historical controls. Haemagglutination was reduced in both sexes at 44 and 46 mg/kg body weight and above (Sanders et al. 1985; White et al. 1985 a, b). The LOAEL (lowest observed adverse effect level) of this study is about 45 mg/kg body weight and day; however, hepatic glutathione levels and CYP enzyme activities were only slightly decreased at this dose.

After 1,1,2-trichloroethane was given to groups of 10 male and 10 female Fischer F344 rats in concentrations of 0, 170, 570 or 1350 mg/l drinking water for 13 weeks, thus male animals were administered 0, 12.1, 37.7 and 86.0 mg/kg body weight and day and female animals 0, 17.1, 55.9 and 98.2 mg/kg body weight and day. Motor functions were observed and the motor activity evaluated (Functional Observational Battery (FOB)) prior to exposure and again after 4, 8 and 13 weeks. The neuropathological effects were investigated in 5 animals from each dose group after 13 weeks. Sections of the olfactory bulb, the cerebrum (frontal, parietal, temporal and occipital lobes), the thalamus/hypothalamus, the mesencephalon, the pons, the cerebellum and the medulla oblongata were taken from the other 5 animals of each group and examined for changes. No effects were determined. The observed decrease in body weights correlated with reduced water and feed consumption (Dow Chemical Company 2005).

Tab. 2 Studies of toxicity after oral administration of 1,1,2-trichloroethane

Species, strain, number per group	Dose	End point	References
rat, Wistar	**7 days**, 0, 180 mg/kg body weight and day, gavage	**180 mg/kg body weight**: body weights ↓, $NADH_2$-cytochrome c reductase ↓*, glucose-6-phosphate dehydrogenase ↑*	BUA 1995; Platt and Cockrill 1969
rat, Osborne Mendel, 10 ♂	**7 weeks**, 0, 70 mg/kg body weight and day, gavage, 5 days/week	**70 mg/kg body weight**: body weights ↓ (40% of the control values), absolute liver weights ↓, no other end points examined	Milman et al. 1988
rat, Fischer 344, 10 ♂, 10 ♀	**13 weeks**, ♂: 0, 12.1, 37.7, 86.0 mg/kg body weight and day, ♀: 0, 17.1, 55.9, 98.2 mg/kg body weight and day, administration of 0, 170, 570, 1350 mg/l drinking water, 7 days/week	♂: **86.0 mg/kg body weight**: **NOAEL**, ♀: **98.2 mg/kg body weight**: **NOAEL**, end points examined: observation of functions and assessment of motor activity (FOB), body weight gains, feed consumption, eyes, histopathological examination of the CNS and PNS (5 animals per group)	Dow Chemical Company 2005
rat, Osborne Mendel, 50 ♂, 50 ♀, controls 20 ♂, 20 ♀	**78 weeks**, 0, 46, 92 mg/kg body weight and day, gavage, 5 days/week, observation period: 33–35 weeks	**46 mg/kg body weight and above**: hunched posture, rough fur, stained abdomen, blinking with reddish discharge from the eyes, dyspnoea, no histological lesions	NCI 1978
mouse, CD-1, 12 ♂, 12 ♀	**14 days**, 0, 3.8, 38 mg/kg body weight and day, gavage, 7 days/week	**3.8 mg/kg body weight**: **NOAEL**, relative liver weights ↑* (10% of the control values); **38 mg/kg body weight**: ♂: absolute weights ↑* (brain, thymus, testis), relative liver weights ↑ (6% of the control values, not statistically significant), LDH ↓*, no histological examination	White et al. 1985 b
mouse, CD-1, 11–12 ♂	**14 days**, 0, 3.8, 38 mg/kg body weight and day, gavage, 7 days/week	**38 mg/kg body weight**: **NOAEL**, only immune status investigated	Sanders et al. 1985
mouse, CD-1, 32 ♂, 32 ♀, controls 48 ♂, 48 ♀	**90 days**, ♂: 0, 4.4, 46, 305 mg/kg body weight and day, ♀: 0, 3.9, 44, 384 mg/kg body weight and day, drinking water, 7 days/week	**4.4/3.9 mg/kg body weight**: **NOAEL**, ♀: blood: fibrinogen ↑* (not dose dependent); **46/44 mg/kg body weight and above**: ♂: body weights ↓ (not statistically significant), absolute weights ↓ (liver, kidneys), relative weights ↑ (testis), liver: GSH ↓* (83% of the control values); ♀: blood: AP ↑* (not dose dependent), CYP activity ↓* (90% of the control values), aniline hydroxylase ↓* (86% of the control values); fibrinogen ↑* (not dose dependent), prothrombin ↓*; **305/384 mg/kg body weight**: ♂: body weights ↓*, water consumption decreased by 30%*, blood: AP ↑*, liver: glutathione ↓* (72% of the control values); ♀: liver weights ↑* (absolute by 32%, relative by 26%), absolute weights ↑* (spleen, kidneys), blood: haemoglobin ↓*, erythrocytes ↓, haematocrit ↓*, AST ↑*, ALT ↑*, cholesterol ↑*, fibrinogen ↑* (not dose dependent), prothrombin ↓*, liver: glutathione ↑* (87% of the control values), CYP activity ↓* (74% of the control values), aniline hydroxylase ↓* (53% of the control values), no histological examination	White et al. 1985 b

Tab. 2 *(continued)*

Species, strain, number per group	Dose	End point	References
mouse, CD-1, 8–23 ♂, 8–23 ♀	**90 days**, ♂: 0, 4.4, 46, 305 mg/kg body weight and day, ♀: 0, 3.9, 44, 384 mg/kg body weight and day, drinking water, 7 days/week	**4.4/3.9 mg/kg body weight**: **NOAEL**; **46/44 mg/kg body weight and above**: haemagglutination ↓*; **305/384 mg/kg body weight**: ♀: RES: liver ↑*, spleen ↓*, ♂: capability for phagocytosis ↓	Sanders et al. 1985
mouse, B6C3F1, 50 ♂, 50 ♀ controls 20 ♂, 20 ♀	**78 weeks**, 0, 195, 390 mg/kg body weight and day, gavage, 5 days/week, observation period: 12–13 weeks	**195 mg/kg body weight**: ♀: abdominal swelling (liver carcinomas) 6/50; **390 mg/kg body weight**: from week 46 onwards: abdominal swelling (liver carcinomas), no other histological lesions	NCI 1978

*$p < 0.05$; ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CNS: central nervous system; CYP: cytochrome P450; FOB: Functional Observational Battery; LDH: lactate dehydrogenase; PNS: peripheral nervous system; RES: functional activity of the reticuloendothelial system

Summary: In a 90-day drinking-water study, at the 1,1,2-trichloroethane dose of 45 mg/kg body weight and day, the glutathione level in the liver of male mice was reduced and the activity of CYP enzymes was inhibited in the females (White et al. 1985 b). As the effects were only slight, the actual NAEL (no adverse effect level) is probably higher than the NOAEL of 4 mg/kg body weight determined in the study. Therefore, a NAEL (NAEL = LOAEL/3) of 15 mg/kg body weight and day has been estimated.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

1,1,2-Trichloroethane was slightly irritating to the rabbit skin and severely irritating after occlusive application to the abraded rabbit skin (index of 5.2 on a scale with a maximum value of 8) (BUA 1995; Duprat et al. 1976; Smyth et al. 1969).

1,1,2-Trichloroethane caused cracked and scaly skin in addition to increased skin-fold thickness in guinea pigs and rabbits after daily application of 144 mg for 10 days (no other details; ACGIH 2001).

5.3.2 Eyes

1,1,2-Trichloroethane was only slightly irritating to the eyes with an index of 2 (maximum: 10) (ECHA 2017; Smyth et al. 1969).

In a study of eye irritation in female New Zealand White rabbits, 1,1,2-trichloroethane (0.1 ml, purity 98%) was slightly irritating to the eyes with a primary irritation index of 8 on a scale with a maximum of 110. The conjunctiva was reddened and discharge from the eye was observed in addition to damage to the epithelium and epithelial keratosis (Duprat et al. 1976).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

1,1,2-Trichloroethane given to mice with the drinking water at dose levels of 38 mg/kg body weight and day led to increased relative testis weights after 90 days (see Section 5.2; White et al. 1985 b). In a 78-week carcinogenicity study with oral doses of 0 to 92 mg/kg body weight and day given to rats and oral doses of 0 to 390 mg/kg body weight and day given to mice, no histological changes in the reproductive organs were observed (NCI 1978).

5.5.2 Developmental toxicity

In a screening test with female ICR/SIM rats given gavage doses of 1,1,2-trichloroethane of 350 mg/kg body weight and day from days 8 to 12 of gestation, no embryotoxic or foetotoxic effects were observed. Three of the 30 dams died (control 0/30). The body weight gains of the dams were not affected (Seidenberg et al. 1986).

Studies with chicken embryos found a very slight teratogenic potential for 1,1,2-trichloroethane (Henschler 1981).

5.6 Genotoxicity

5.6.1 In vitro

1,1,2-Trichloroethane did not induce the SOS response in Escherichia coli PQ37 either in the presence or in the absence of a metabolic activation system. In a large number of bacterial mutagenicity tests using the Salmonella typhimurium strains TA97, TA98, TA100, TA102, TA1535, TA1537 and TA1538, 1,1,2-trichloroethane was not found to have mutagenic potential with or without metabolic activation (ATSDR 1989, 2010; IARC 1999; Mersch-Sundermann 1989; Mitoma et al. 1984, 1985). Only one study reported the induction of point mutagenic effects in the Salmonella typhimurium strains TA97, TA100 and TA104; however, the effects were not dependent on the dose. A range-finding study was not performed to investigate cytotoxicity. The cytotoxic concentration was not reached in the tests (Strobel and Grummt 1987). The incidence of aneuploidy in Aspergillus nidulans P1 was increased with statistical significance without metabolic activation (BUA 1995; Crebelli et al. 1988). Positive results were obtained in yeasts after metabolic activation (no other details; Bronzetti et al. 1987). The binding affinity of 1,1,2-trichloroethane to calf thymus DNA was 5 times as high after incubation with microsomes from BALB/c mice treated with phenobarbital than with microsomes of mice that were not pretreated with phenobarbital. The addition of glutathione inhibited DNA binding (Mazzullo et al. 1986). In a comet assay with human lymphocytes, DNA strand breaks were detected without the addition of metabolic activation (Tafazoli and Kirsch-Volders 1996). Positive results were obtained in a UDS (DNA repair synthesis) test with primary rat hepatocytes, but not in a test with primary mouse hepatocytes. These results contradict the findings of carcinogenicity studies that observed the development of tumours only in mice. The study report did not include data for the tested concentration and did not describe the method in sufficient detail. Therefore, the results cannot be included in the evaluation (ATSDR 2010; BUA 1995; Milman et al. 1988). In micronucleus tests in human lymphocytes, 1,1,2-trichloroethane was found to be clearly genotoxic in one test and weakly genotoxic in another; in both cases without metabolic activation. Micronuclei were not induced with metabolic activation. Micronuclei were found in the MCL-5 and h2E1 cell lines, which express high levels of CYP activity, but not in the AHH-1 cell line with basal expression of CYP enzymes (ATSDR 2010; Doherty et al. 1996; IARC 1999; Tafazoli and Kirsch-Volders 1996). Chromosomal aberrations and sister chromatid exchanges were observed in CHO cells (a cell line derived from Chinese hamster ovary) in the presence and in the absence of metabolic activation (NTP 1986 a).

1,1,2-Trichloroethane was found to be a spindle toxin in the V79d-MZ cell line, which does not express CYP (Kim et al. 2002).

The data are shown in detail in Table 3. Unless specified otherwise, microsomal fractions from the liver of rats treated with Aroclor 1254 were used for metabolic activation.

Tab. 3 Genotoxicity of 1,1,2-trichloroethane in vitro

End point	Test system	Concentration [μg/ml]	Effective concentration	Cytotoxicity	Results		References
					–m. a.	+m. a.	
induction of the SOS response	Escherichia coli PQ37	0.1–10 000 nl/ batch		1 μl	–	–	ATSDR 2010; Mersch-Sundermann et al. 1989
gene mutation	Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537, TA1538	0.01–10 000		cytotoxic concentration reached	–	–	ATSDR 1989, 2010; IARC 1999 (15 tests in total)
	Salmonella typhimurium TA102	0.01–10 000		no data	–	–	Mersch-Sundermann 1989
	Salmonella typhimurium TA97	0.01–1 mg/plate	0.01 mg/plate (no dose dependency)	–	+	+	Strobel and Grummt 1987
	Salmonella typhimurium TA98	0.01–1 mg/plate		–	–	–	Strobel and Grummt 1987
	Salmonella typhimurium TA100	0.01–1 mg/plate	0.01 mg/plate (no dose dependency)	–	+	–	Strobel and Grummt 1987
	Salmonella typhimurium TA104	0.01–1 mg/plate	0.01 mg/plate (no dose dependency)	–	–	(+)	Strobel and Grummt 1987
forward mutation (Ar2 test)	Salmonella typhimurium	500		no data	–	n. t.	IARC 1999
gene mutation	Saccharomyces cerevisiae D7 (growth phase: CYP level high = metabolic activity)	no data	no data	no data	–	+	Bronzetti et al. 1987
aneuploidy	Aspergillus nidulans P1	360–1440	1080 μg/ml	1440 μg/ml	+	n. t.	BUA 1995; Crebelli et al. 1988
mitotic crossing-over	Aspergillus nidulans P1	360–1440		1440 μg/ml	–	n. t.	Crebelli et al. 1988; IARC 1999
covalent DNA/ RNA/protein binding	calf thymus DNA, microsomal RNA, microsomal proteins using the microsomal or cytosolic liver fraction of mice or rats treated or untreated with phenobarbital (100 mg/kg body weight, intraperitoneal)	25 μCi ^{14}C-1,1,2-trichloroethane			DNA +	+ (5×) after treatment with phenobarbital	Mazzullo et al. 1986
					RNA +	+ (2.8×) after treatment with phenobarbital	
					protein +	+ (6.5×) after treatment with phenobarbital	
covalent DNA binding	calf thymus DNA	133 (1 mM)	133 μg/ml		+	n. t.	DiRenzo et al. 1982
DNA damage by means of comet assay	human lymphocytes	333 (2.5 mM)	333 μg/ml		+	+	Tafazoli and Kirsch-Volders 1996
UDS	primary hepatocytes rat (♂ Osborne Mendel)	no data	no data	no data	+	n. t.	ATSDR 2010; Milman et al. 1988

Tab. 3 *(continued)*

End point	Test system	Concentration [µg/ml]	Effective concentration	Cytotoxicity	Results		References
					−m. a.	+m. a.	
	primary hepatocytes mouse (♂ B6C3F1)	no data		no data	–	n. t.	ATSDR 2010; Milman et al. 1988
SCE	CHO cells	166.7–5000	1700 µg/ml	3750/5000 µg/ml	+	+	NTP 1986 a
CA	CHO cells	377–5000	5000 µg/ml	4400/5000 µg/ml	+	+	NTP 1986 a
micronucleus test (experiment 1)	human lymphocytes	13.3–665 (0.1–5.0 mM)	−m. a.: 13.3 µg/ml (no dose dependency), +m. a.: 333 µg/ml	665 µg/ml	(+)	+	Tafazoli and Kirsch-Volders 1996
(experiment 2)	human lymphocytes	13.3–665 (0.1–5.0 mM)	−m. a.: 13.3 µg/ml (no dose dependency)	665 µg/ml	(+)	–	Tafazoli and Kirsch-Volders 1996
	MCL-5[a)]	1.33–665 (0.01–5 mM)	133 µg/ml (1 mM)	266 µg/ml	+[a)]	n. t.	ATSDR 2010; Doherty et al. 1996
	h2E1[a)]	1.33–665 (0.01–5 mM)	133 µg/ml (1 mM)	266 mg/ml	+[a)]	n. t.	ATSDR 2010; Doherty et al. 1996
	AHH-1 (lymphoblastoid cell line)	1.33–665 (0.01–5 mM)		665 µg/ml	–	n. t.	ATSDR 2010; Doherty et al. 1996

[a)] cell line with a high level of CYP expression
CA: chromosomal aberrations; −m. a./+m. a.: without a metabolic activation system/with a metabolic activation system; n. t.: not tested;
SCE: sister chromatid exchanges; UDS: DNA repair synthesis

5.6.2 In vivo

Genotoxic effects were not detected in the sex-linked recessive lethal test (SLRL) in Drosophila; however, weak effects were found at cytotoxic concentrations in the SMART eye mosaic test (somatic mutation and recombination test) (ATSDR 2010; IARC 1999; Vogel and Nivard 1993). After intraperitoneal injection of [^{14}C]-1,1,2-trichloroethane in rats and mice, the substance bound to the DNA, RNA and proteins of the liver, kidneys, lungs and stomach. A much higher level of radioactivity was found in the mouse liver DNA fraction than in the rat liver DNA fraction. No differences in RNA and protein binding were found between the species. The covalent binding index for liver DNA was 26 in rats and 73 in mice. This is regarded as evidence that the substance is a weak initiator (Mazzullo et al. 1986). DNA adducts were not determined.

In the UDS test, 1,1,2-trichloroethane administered to mice in 3 gavage doses did not lead to an increase in DNA repair synthesis at dose levels up to 1000 mg/kg body weight and day (IARC 1999; Mirsalis et al. 1989). 1,1,2-Trichloroethane increased replicative DNA synthesis (RDS) in the hepatocytes of B6C3F1 mice given a single gavage dose of 100 or 200 mg/kg body weight (Miyagawa et al. 1995). No micronuclei were observed in the polychromatic erythrocytes of mice following gavage administration. The polychromatic/normochromatic erythrocytes ratio was reduced in the erythrocytes at the high dose. It can therefore be assumed that the bone marrow was reached. The test was carried out according to OECD Test Guideline 474 (MHLW 2002). Likewise, no micronuclei were observed after intraperitoneal administration and no strand breaks were observed after alkaline unwinding (ATSDR 2010; Crebelli et al. 1999; Taningher et al. 1991).

The data are shown in detail in Table 4.

Tab. 4 In vivo studies of the genotoxicity induced by 1,1,2-trichloroethane

Test system		Dose	Results	References
SMART, eye mosaic test	Drosophila	cytotoxic concentration	(+) no dose dependency	ATSDR 2010; Vogel and Nivard 1993
SLRL	Drosophila	1000 mg/l feed 3300 mg/l injection solution	–	ATSDR 2010; Foureman et al. 1994
DNA binding, liver, kidneys, lungs, stomach	rat, Wistar, groups of 4 ♂	0.8 mg ^{14}C-1,1,2-trichloroethane/kg body weight, single dose in DMSO, intraperitoneal, sacrificed after 22 hours	+	IARC 1999; Mazzullo et al. 1986
DNA binding, liver, kidneys, lungs, stomach	mouse, BALB/c, groups of 12 ♂	0.8 mg ^{14}C-1,1,2-trichloroethane/kg body weight, single dose in DMSO, intraperitoneal, sacrificed after 22 hours	+	IARC 1999; Mazzullo et al. 1986
RNA/protein binding, liver, kidneys, lungs, stomach	rat, Wistar, groups of 4 ♂	0.8 mg ^{14}C-1,1,2-trichloroethane/kg body weight, single dose, intraperitoneal, sacrificed after 22 hours	+	IARC 1999; Mazzullo et al. 1986
RNA/protein binding, liver, kidneys, lungs, stomach	mouse, BALB/c, groups of 12 ♂	0.8 mg ^{14}C-1,1,2-trichloroethane/kg body weight, single dose, intraperitoneal, sacrificed after 22 hours	+	IARC 1999; Mazzullo et al. 1986
DNA strand breaks, alkaline unwinding, liver	mouse, BALB/c, 16 ♂	900 mg/kg body weight, intraperitoneal	–	BUA 1995; Taningher et al. 1991
UDS, liver	mouse, B6C3F1, groups of 3 ♂, 3 ♀	0, 50, 200, 1000 mg/kg body weight, single dose in corn oil, gavage, sacrificed after 2 or 12 hours	–	IARC 1999; Mirsalis et al. 1989
RDS, liver	mouse, B6C3F1, groups of 4–5 ♂	0, 100, 200 mg/kg body weight, single dose in corn oil, gavage, sacrificed after 24, 39 or 48 hours	+	Miyagawa et al. 1995
MN, bone marrow	mouse, CD-1, groups of 5 ♂, 5 ♀	0, 200, 400 mg/kg body weight, single dose in olive oil, intraperitoneal, sacrificed after 24 or 48 hours	–	ATSDR 2010; Crebelli et al. 1999
MN, bone marrow, (OECD 474)	mouse, CD-1, groups of 5 ♂	0, 100, 200, 400 mg/kg body weight, single dose in olive oil, gavage, sacrificed after 24 or 48 hours	–	MHLW 2002

DMSO: dimethyl sulfoxide; MN: micronuclei; RDS: replicative DNA synthesis; SLRL: sex-linked recessive lethal; SMART: somatic mutation and recombination test; UDS: DNA repair synthesis

5.6.3 Summary

No mutagenic effects were found in bacterial mutagenicity tests. Positive results were obtained in vitro with 1,1,2-trichloroethane both in the UDS test and comet assay and in the SCE and CA tests in various cell lines. In vitro, micronuclei were induced in human lymphocytes and in cell lines which express high levels of CYP. In vivo, 1,1,2-trichloroethane was not found to induce genotoxicity in the SLRL, UDS and micronucleus tests. The only exception was a weak effect observed in the cytotoxic range in the SMART eye mosaic test. Binding to the DNA, RNA and proteins of various organs was observed after intraperitoneal injection.

Most halogenated hydrocarbons do not induce micronuclei in the bone marrow in vivo. The negative results of a single in vivo micronucleus test are not sufficient to invalidate the genotoxic effects determined in vitro. Additional in vivo tests need to be carried out, particularly in the target organs of the respective substances (Crebelli et al. 1999).

Therefore, the effects caused by exposure to 1,1,2-trichloroethane are characteristic of the weak genotoxicity induced by chlorinated hydrocarbons.

5.7 Carcinogenicity

5.7.1 Short-term studies

5.7.1.1 In vitro

In a cell transformation test in BALB/c-3T3 embryonic cells, the transformation efficiency was increased at a 1,1,2-trichloroethane concentration of 25 or 50 µg/ml without metabolic activation. Although slight, the increase was statistically significant (BUA 1995; IARC 1999; Tu et al. 1985). Another transformation test likewise demonstrated an increase in cell transformation efficiency in BALB/c-3T3 cells. Exact data for the severity of the effects, the concentration and the method used are not available (ATSDR 2010; BUA 1995; Milman et al. 1988).

5.7.1.2 In vivo

In an initiation study, a single 1,1,2-trichloroethane dose of 0 or 70 mg/kg body weight given to groups of 10 male Osborne Mendel rats 24 hours after partial hepatectomy followed by the administration of phenobarbital with the feed for 7 weeks at a concentration of 0.05% (w/w) did not lead to an increased incidence of GGT^+ liver foci. Therefore, the initiation study did not find evidence of a carcinogenic potential (BUA 1995; Milman et al. 1988; Story et al. 1986).

In a promotion study, male Osborne Mendel rats (10 animals per group) first underwent a partial hepatectomy followed by treatment with 1,1,2-trichloroethane by gavage at a dose level of 70 mg/kg body weight and day on 5 days a week for 7 weeks. The increase in the incidence of GGT^+ foci ($p < 0.05$) was statistically significant both after initiation with a single intraperitoneal injection of diethylnitrosamine at a dose level of 30 mg/kg body weight and without the administration of an initiator. Of all the investigated chlorinated hydrocarbons, 1,1,2-trichloroethane induced the highest number of foci. However, a large fraction of the foci only weakly expressed GGT and could be differentiated only with difficulty from the surrounding tissues by histomorphological examination. When only clearly differentiated foci were examined, no statistically significant tumour promoting effects were determined (BUA 1995; Milman et al. 1988; Story et al. 1986). The size of the foci was not specified in the study report and was thus not included in the evaluation.

5.7.2 Long-term studies

In groups of 50 male and 50 female B6C3F1 mice given 1,1,2-trichloroethane by gavage on 5 days a week for 78 weeks in average doses of 0, 195 or 390 mg/kg body weight and day followed by an observation period of 12 to 13 weeks, the incidence of hepatocellular carcinomas was significantly increased in the animals of the two dose groups. The incidences in the control group and in the low and high dose groups were 10% to 12%, 37% and 76%, respectively, in the males and 0 to 10%, 33% and 89%, respectively, in the females. In addition, the incidences of phaeochromocytomas in the adrenal glands were increased with statistical significance in the high dose group. The incidences were 0%, 0% and 17%, respectively, in the males and 0%, 0% and 28%, respectively, in the females. The body weight gains of the treated animals were in the range of the control values (BUA 1995; Henschler 1981; NCI 1978). The report did not describe non-neoplastic effects in the liver, but these may have regressed during the observation period. The incidence of hepatocellular carcinomas is regarded as very high.

1,1,2-Trichloroethane given by gavage to groups of 50 male and 50 female Osborne Mendel rats for 78 weeks in average doses of 0, 46 or 92 mg/kg body weight and day followed by an observation period of 33 to 35 weeks led to isolated neoplastic findings, which were not considered to be substance-induced. The findings of this study cannot be regarded as evidence of the induction of carcinogenic effects in rats by 1,1,2-trichloroethane. The body weight gains of the treated animals were in the range of the controls (BUA 1995; Henschler 1981; NCI 1978). It is unclear whether the MTD was reached in this study. Initial toxic symptoms were observed at doses of 46 mg/kg body weight and above (see Section 5.2.2).

In a 2-year study, groups of 35 to 50 male and 35 to 50 female Sprague Dawley rats received 1,1,2-trichloroethane in DMSO once a week by subcutaneous injection at dose levels of about 0, 9, 11 or 28 mg/kg body weight and day. A larger

number of sarcomas were found in the groups of treated male animals than in the control animals. In comparison with the incidence of sarcomas found in the vehicle control group (in 2 of 35 animals), a dose-dependent increase in the incidence was observed at a dose of 11 mg/kg body weight and day (in 4 of 50 animals) and at 28 mg/kg body weight and day (in 8 of 50 animals); however, the increase was not statistically significant. No sarcomas were observed in the untreated control group consisting of 35 males and 50 females. The sarcomas were found in different organs and thus did not target specific organs. The incidence of benign mesenchymal and epithelial tumours and the mean survival were in the range of the values for the controls for both dose groups (BUA 1995; Norpoth et al. 1988).

6 Manifesto (MAK value/classification)

The critical effects in humans and animals are irritation after inhalation exposure and after dermal application.

After oral administration to male and female B6C3F1 mice, GSH levels in the liver were reduced, CYP enzymes were inhibited and liver carcinomas developed.

MAK value. In a 13-week inhalation study in rats (WIL Research Laboratories 2002), a LOAEC of 15 ml/m^3 was derived for vacuolation in the olfactory epithelium induced by 1,1,2-trichloroethane. The NAEC (no adverse effect concentration = LOAEC/3) was estimated to be 5 ml/m^3. By applying the method described by Brüning et al. (2014) and taking into consideration a possible intensification of the effects after long-term exposure (1:2) and the extrapolation of the data from animal studies to humans (1:2), this results in a concentration in the air of 1.25 ml/m^3.

In a carcinogenicity study with gavage administration to rats, clinical symptoms such as hunched posture and dyspnoea were observed at the low 1,1,2-trichloroethane dose of 46 mg/kg body weight and day (NCI 1978). As no NOAEL is available, a NAEL of 15.3 mg/kg body weight and day has been estimated (NAEL = LOAEL/3). The following toxicokinetic data are taken into consideration for the extrapolation of the NAEL of 15.3 mg/kg body weight to a concentration in workplace air: the corresponding species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. Using the values obtained by extrapolating the data from the animal study to the human (1:2), a concentration of 13.4 mg/m^3 ≙ 2.4 ml/m^3 is calculated.

In the 90-day study with administration of 1,1,2-trichloroethane in the drinking water, at the dose level of 45 mg/kg body weight and day the GSH level in the liver of male mice was reduced and the activity of CYP enzymes was inhibited in the females. A histopathological examination was not performed, however (White et al. 1985 b). As the findings were negligible, the actual dose at which no effects are to be expected is probably higher than the NOAEL of 4 mg/kg body weight determined in the study. For this reason, a NAEL of 15 mg/kg body weight and day has been estimated (NAEL = LOAEL/3). In the chronic study of the NCI (1978), no non-neoplastic histopathological effects were found in the liver of mice at 390 mg/kg body weight and day. Therefore, the NAEL from the 90-day study should also be sufficient to prevent histopathological effects. The effects on the CYP enzymes and GSH should have reached their maximum levels after 90 days.

For the toxicokinetic extrapolation of this NAEL of 15 mg/kg body weight to a concentration in workplace air, the above factors are taken into consideration in addition to the corresponding species-specific correction value for the mouse (1:7). After extrapolating the data from animal studies to humans (1:2), a concentration of 10.5 mg/m^3 ≙ 1.9 ml/m^3 is calculated.

By applying the preferred value approach, a MAK value of 1 ml/m^3 has been derived from the data for the effects in the rat nose.

Peak limitation. As the MAK value was derived based on irritation, the substance has been classified in Peak Limitation Category I. As the effects induced in the olfactory epithelium of rats at 15 ml/m^3 were minimal, an excursion factor of 2 is deemed appropriate instead of the default excursion factor of 1.

Prenatal toxicity. The only available study is a screening study that investigated a single 1,1,2-trichloroethane dose of 350 mg/kg body weight and day. As no foetotoxic effects were induced at this dose (Seidenberg et al. 1986) and no teratogenicity studies are available, 1,1,2-trichloroethane has been classified in Pregnancy Risk Group D.

Carcinogenicity. 1,1,2-Trichloroethane is suspected of having a carcinogenic potential. This has not been invalidated by the in vitro findings of genotoxic effects in mammalian cells, the lack of in vivo genotoxicity studies, the tumour-promoting activity in rats and the high incidence of hepatocellular carcinomas in B6C3F1 mice. Also, a complete 2-year carcinogenicity study with oral exposure of rats and mice is not available. For this reason, 1,1,2-trichloroethane remains in Carcinogen Category 3 B.

Germ cell mutagenicity. After the administration of a single dose to rats and mice by intraperitoneal injection, radioactively labelled 1,1,2-trichloroethane bound to the DNA, RNA and proteins in the liver, kidneys, lungs and stomach. A much higher level of radioactivity was determined in the fraction from mouse liver DNA than in the fraction from rat liver DNA (Mazzullo et al. 1986).

The results of the in vitro and in vivo tests demonstrate that 1,1,2-trichloroethane causes clastogenic or aneugenic effects in vitro. However, the genotoxic effects in vivo are not of sufficient severity and have not been investigated in the target organ. 1,1,2-Trichloroethane does not have a marked genotoxic potential. Therefore, the effects caused by exposure to 1,1,2-trichloroethane are characteristic of the weak genotoxicity induced by halogenated hydrocarbons.

Mutagenic effects were not observed in bacterial mutagenicity tests carried out with 1,1,2-trichloroethane. In vitro, positive results were obtained with 1,1,2-trichloroethane in the test for UDS, in the comet assay and in the tests for sister chromatid exchange and structural chromosomal aberrations using various cell lines. In vitro, micronuclei are induced in human lymphocytes and cell lines that express high levels of CYP. The clastogenic effects were not evident in a micronucleus test in vivo, which is typical for halogenated hydrocarbons. Weak clastogenic effects were observed in the SMART eye mosaic test in the cytotoxic range.

There are no studies available that investigated the effects induced in the germ cells of mammals. Negative results were obtained in an SLRL test in Drosophila. On the basis of the available data, 1,1,2-trichloroethane has not been classified in a category for germ cell mutagens.

Absorption through the skin. There are data available from animal studies for the absorption of 1,1,2-trichloroethane through the skin. The substance is readily absorbed through the skin of mice and guinea pigs. In guinea pigs, dermal application of the substance led to systemic effects including the death of the animals. The results of a study in mice were used to estimate that 2080 mg of 1,1,2-trichloroethane would be absorbed via the skin by humans under standard conditions (skin surface of 2000 cm^2, 1-hour exposure) (Section 3.1). Using the concentration of 13.4 mg/m^3 calculated above as the starting point and assuming a respiratory volume of 10 m^3 and 100% absorption by inhalation, the systemically tolerable amount is 134 mg. As absorption through the skin is thus relevant for systemic toxicity, 1,1,2-trichloroethane continues to be designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available for sensitization. The substance is therefore not designated with “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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