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1,1,2,2-Tetrachloroethane

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

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Keywords

1,1,2,2-tetrachloroethane; liver; maximum workplace concentration; MAK value; toxicity; hazardous substance; carcinogenicity; mode of action; skin absorption

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 carcinogenicity classification of 1,1,2,2-tetrachloroethane [79-34-5]. Available publications and unpublished study reports are described in detail. The critical effect is liver toxicity in humans, rats and mice. Valid inhalation studies are not available. After oral application, 1,1,2,2-tetrachloroethane is a liver tumour promoter and induces neoplastic nodules and carcinomas in rats and mice. The NOAEL for carcinogenic effects in rats is 43 mg/kg body weight. 1,1,2,2-Tetrachloroethane is not genotoxic. The mechanism responsible for tumour development in the liver is most likely the formation of reactive metabolites, e.g. dichloroacetic acid and free radicals. As the primary mode of action is non-genotoxic, 1,1,2,2-tetrachloroethane is classified in Carcinogen Category 4. After 14-week oral application, the NOAELs for liver effects are 20 and 80 mg/kg body weight for rats and male mice, respectively. Based on the NOAEL of 20 mg/kg body weight, a MAK value of 2 ml/m^3 is derived. Irritation is not expected to occur at this concentration because 10-minute exposure of volunteers to 13 ml/m^3 did not induce local effects. As the critical effect of 1,1,2,2-tetrachloroethane is systemic and its half-life is not known, the assignment to Peak Limitation Category II and the excursion factor of 2 are retained. 1,1,2,2-Tetrachloroethane remains classified in Pregnancy Risk Group D because sufficient data for developmental toxicity are not available. 1,1,2,2-Tetrachloroethane 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)	**2 ml/m³ (ppm) ≙ 14 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 2**
Absorption through the skin (1958)	**H**
Sensitization	**–**
Carcinogenicity (2019)	**Category 4**
Prenatal toxicity (1994)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**

Synonyms	acetylene tetrachloride
Chemical name (IUPAC name)	1,1,2,2-tetrachloroethane
CAS number	79-34-5
Structural formula	$Cl_2HC–CHCl_2$
Molecular formula	$C_2H_2Cl_4$
Molar mass	167.85 g/mol
Melting point	−43.8 °C (NLM 2019)
Boiling point at 1013 hPa	146.5 °C (NLM 2019)
Density at 20 °C	1.597 g/cm³ (IFA 2019)
Vapour pressure at 20 °C	6.4 hPa (IFA 2019)
log K_{OW}	2.39 (NLM 2019)
Solubility at 25 °C	2830 mg/l water (NLM 2019)
1 ml/m³ (ppm) ≙ 6.950 mg/m³	**1 mg/m³ ≙ 0.144 ml/m³ (ppm)**

New findings for the induction of toxic effects in animals and in humans have become available since the publication of the documentation (Henschler 1973, available in German only) and a supplement (Greim 2002, available in German only), making a re-evaluation necessary.

1,1,2,2-Tetrachloroethane was once used as a refrigerant, widely as a solvent, to clean and degrease metals, in paint removers, varnishes and lacquers, to extract oils and fats and in the production of trichloroethylene, tetrachloroethylene and 1,2-dichloroethylene. Today, the substance is only an intermediate in closed systems (OECD 2002; US EPA 2010).

1 Toxic Effects and Mode of Action

After inhalation exposure, 60% of the inhaled amount of 1,1,2,2-tetrachloroethane is absorbed. The substance is almost completely absorbed after oral administration. Most of the substance is metabolized to CO_2 via dichloroacetic acid. High concentrations of 1,1,2,2-tetrachloroethane induce narcotic effects and severe toxic effects in the liver in humans, rats and mice. After rats were given oral doses for 14 weeks, increased liver weights and reduced sperm motility were found at 40 mg/kg body weight and above. As the dose increased, also liver hypertrophy and liver necrosis were

observed. Long-term studies with inhalation exposure are not available. The odour threshold is 3 ml/m^3. Irritation of the mucous membranes was reported in humans after short-term exposure at a concentration of 146 ml/m^3.

1,1,2,2-Tetrachloroethane induces carcinogenic effects in the liver of rats and mice. According to the in vivo data, the clastogenic potential of the substance is slight at most.

Teratogenicity was not evaluated in any of the studies of developmental toxicity.

No data for sensitizing effects are available.

2 Mechanism of Action

Covalent bonds were formed with the DNA, RNA and proteins in the liver, kidneys, lungs and stomach of Wistar rats and BALB/c mice 22 hours after a single dose of radioactively labelled 1,1,2,2-tetrachloroethane was administered by intravenous injection. 1,1,2,2-Tetrachloroethane induces tumour-promoting effects in the liver of rats. In vitro data in bacteria and mammalian cells do not provide evidence of a marked mutagenic or clastogenic potential. In vivo studies demonstrated that 1,1,2,2-tetrachloroethane induces slight clastogenic effects in mice. It is likely that the toxic and carcinogenic effects in the liver are caused by the formation of carcinogenic and reactive metabolites such as dichloroacetic acid and free radicals during reductive dechlorination. However, studies investigating reductive dechlorination in rat liver microsomes and hepatocytes using different chloroalkanes demonstrated that the extent of dechlorination and radical formation does not correspond to the carcinogenic potential of the chloroalkanes in the mouse liver (Nastainczyk et al. 1982; Salmon et al. 1981, 1985; Thompson et al. 1984; Tomasi et al. 1984). Therefore, it is unclear how the formation of radicals contributes to the induction of carcinogenic effects in the liver.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

3.1.1 Absorption

Humans: A male volunteer inhaled a single breath of ^{38}Cl-1,1,2,2-tetrachloroethane (2.5 mg in about 1.5 l air). After the volunteer held his breath for 20 seconds, the radioactivity in the exhaled air was determined over the following hour. Absorption was calculated to be 97% (Morgan et al. 1970). As the steady state is not reached in the body after exposure for such a short period of time, the amount absorbed by inhalation cannot be calculated from this study.

A study published by Yllner (1971) reports 80% absorption by inhalation, but does not give any other details.

After repeated exposure by inhalation to 20 to 2300 mg/m^3 for 30 minutes per exposure, 2 subjects retained 49% to 62% of the inhaled amount (Lehmann and Schmidt-Kehl 1936). Even though this study does not meet present-day standards, the reported percentage of absorbed substance is plausible, as 60% absorption by inhalation was determined for other substances with a blood:air partition coefficient similar to that of 1,1,2,2-tetrachloroethane (see Section 3.1.2) (Kumagai and Matsunaga 2000). On the basis of these findings, humans are considered to absorb 60% of the inhaled amount of 1,1,2,2-tetrachloroethane.

Animals: After exposure to radioactively labelled 1,1,2,2-tetrachloroethane at a concentration of 10 ml/m^3 for 6 hours, a body burden of 38.7 µmol equivalents/kg body weight was determined for male Osborne Mendel rats and 127 µmol equivalents/kg body weight for B6C3F1 mice. Mice therefore absorb proportionally more 1,1,2,2-tetrachloroethane per body weight than rats (US EPA 2010).

After male Osborne Mendel rats and B6C3F1 mice were exposed to a single oral dose of radioactively labelled 1,1,2,2-tetrachloroethane in corn oil of 150 mg/kg body weight, only 4% to 6% of the radioactivity was recovered in the

faeces after 72 hours. More than 90% of the radioactivity was found in both species as metabolites in the urine (US EPA 2010). The amount absorbed after oral exposure was 94% to 96% with a mean of 95%.

1,1,2,2-Tetrachloroethane is rapidly absorbed after oral exposure. Only 60 minutes after the administration of a single oral dose of 143.5, 287, 574 or 1148 mg/kg body weight to rats, the first signs of hepatotoxic effects were observed in the form of increased aspartate aminotransferase and alanine aminotransferase activities in the serum (Cottalasso et al. 1998).

In a study of dermal absorption, 1 ml of undiluted 1,1,2,2-tetrachloroethane was applied to the backs of guinea pigs (skin area: 3.1 cm^2) for 15 minutes under occlusive conditions. The 1,1,2,2-tetrachloroethane concentration was determined in the arterial blood at various time points after the beginning of exposure. The blood samples were taken by a catheter that had been laid before exposure began. After 30 minutes, the 1,1,2,2-tetrachloroethane concentration determined by the authors was 1.1 µg/ml blood; after 6 hours, the concentration was 1.5 µg/ml. In an experiment with 2 simultaneously applied depots, a concentration of 3.3 µg/ml was determined after 30 minutes and 4.5 µg/ml after 6 hours. This shows that 1,1,2,2-tetrachloroethane is absorbed rapidly also through the skin (Jakobson et al. 1982).

After occlusive application of 0.5 ml of 1,1,2,2-tetrachloroethane to the skin of mice (skin area: 2.92 cm^2) for 15 minutes, absorption through the skin was determined by analysing the total amount present in the body and the concentration of the substance in the exhaled air. A flux of 619 µg/cm^2 and hour (61.5 nmol/cm^2 and minute) was calculated (Tsuruta 1975).

The findings of Tsuruta (1975) were applied to calculate the total amount of undiluted 1,1,2,2-tetrachloroethane absorbed through the skin under the standard conditions for dermal exposure at the workplace (2000 cm^2 of skin on the hands and forearms, exposure for 1 hour). The amount was calculated to be 1240 mg. Additionally, models based on a saturated aqueous solution were applied; an absorbed amount of 58 mg was determined using the algorithm of the IH SkinPerm model (Tibaldi et al. 2014) while 967 mg was calculated using the model of Fiserova-Bergerova et al. (1990).

3.1.2 Distribution

In humans, the blood:air partition coefficient of 1,1,2,2-tetrachloroethane is in the range from 72.6 to 116. The tissue:air partition coefficients in rats are 142 in the blood, 3767 in fat, 196 in the liver and 101 in muscles (Gargas and Andersen 1989; Meulenberg and Vijverberg 2000; Morgan et al. 1970).

Female C57B1 mice were given a single intravenous injection of radioactively labelled 1,1,2,2-tetrachloroethane (3 mg/kg body weight; 9 µCi). Radioactivity was determined in the mucosal tissues of the olfactory and tracheobronchial regions and in the mucosa of the oral cavity, tongue, nasopharynx, oesophagus and the forestomach 1 minute to 4 hours after exposure. High levels of radioactivity were found also in the liver, the gall bladder, the adrenal cortex, in the interstitium of the testes and in the urine (metabolites) (Eriksson and Brittebo 1991).

3.1.3 Elimination

In volunteers exposed by inhalation to radioactively labelled 1,1,2,2-tetrachloroethane, 0.015% of the absorbed radioactivity was excreted per minute with the urine (Morgan et al. 1970).

Male Osborne Mendel rats and B6C3F1 mice were exposed to radioactively labelled 1,1,2,2-tetrachloroethane at a concentration of 10 ml/m^3 for 6 hours. More than 90% of the absorbed dose was metabolized and eliminated by both species within 72 hours. The percentage of radioactivity recovered in the rats was 33% in the exhaled air (25% as CO_2 and 8% as the unchanged compound), 19% in the urine and 5% in the faeces. The percentage of radioactivity recovered in the mice was 34% in the exhaled air (32% as CO_2 and 2% as the unchanged compound), 26% in the urine and 6% in the faeces (US EPA 2010).

After male Osborne Mendel rats and B6C3F1 mice were given a single oral dose of radioactively labelled 1,1,2,2-tetrachloroethane in corn oil of 150 mg/kg body weight, only 4% to 6% of the radioactivity was recovered in the faeces after 72 hours. In both species, more than 90% of the radioactivity was recovered in the form of metabolites. Rats exhaled

32% of the radioactivity as CO_2 and 9% as the unchanged compound and excreted 23% with the urine and 4% with the faeces. Mice exhaled 50% as CO_2 and 1% in unchanged form and excreted 22% with the urine and 6% with the faeces (US EPA 2010).

Male Osborne Mendel rats (100 mg/kg body weight) and male B6C3F1 mice (200 mg/kg body weight) were first given oral doses of 1,1,2,2-tetrachloroethane on 5 days a week for 4 weeks, followed by radioactively labelled 1,1,2,2-tetrachloroethane. Both species exhaled between 7% and 9% of the radioactivity (rat: 2% as CO_2, mouse: 10% as CO_2), 31% to 46% was excreted with the urine and the faeces and 27% to 31% remained in the animal. The amount of recovered substance was 77% to 86% (Mitoma et al. 1985).

3.2 Metabolism

The following discussion of the metabolism of 1,1,2,2-tetrachloroethane is based mainly on the data reported by the US EPA (US EPA 2010).

Studies investigating the metabolism of the substance in humans are not available. In vitro and in vivo studies in rats and mice suggest a number of different metabolic pathways after exposure to 1,1,2,2-tetrachloroethane: hydrolytic cleavage, oxidative degradation by cytochrome P450 (CYP) enzymes, non-enzymatic dehydrochlorination, oxidation and reductive dechlorination (see Figure 1).

Hydrolytic cleavage and oxidative degradation by CYP: The main metabolic pathway for 1,1,2,2-tetrachloroethane is stepwise hydrolytic cleavage and oxidation via dichloroacetaldehyde and dichloroacetic acid to form first glyoxylic acid and then formic acid and carbon dioxide. Oxalic acid is another product that may form from glyoxylic acid. Overall, between 68% and 9% of the applied dose is metabolized by rats and mice. Dichloroacetic acid may be formed via dichloroacetyl chloride along other metabolic pathways involving different CYP enzymes of the CYP2A, CYP2B, CYP2E and CYP3A families.

After intraperitoneal injection of doses of 210 to 320 mg/kg body weight, the main metabolite found in mice was dichloroacetic acid with 27% recovered in the urine within 24 hours. Other metabolites were trichloroacetic acid (4%), trichloroethanol (10%), oxalic acid (7%), glyoxylic acid (0.9%), glycine (20–23%) and urea (2%).

In mice, the metabolic activity for 1,1,2,2-tetrachloroethane related to the body weight was 1.1 to 3.5-fold as high as in rats.

1,1,2,2-Tetrachloroethane inactivated phenobarbital-inducible CYP isoenzymes. When Swiss albino mice were examined 24 hours after exposure to a single 1,1,2,2-tetrachloroethane dose of 300 or 600 mg/kg body weight, CYP activity was reduced in the males by 44% and 85% and in the females by 37% and 74%, respectively. Additionally, glutathione *S*-transferase (GST) activity was reduced in both sexes in the high dose group (Paolini et al. 1992). Dichloroacetic acid inhibits GST zeta, which in turn inhibits the metabolism of dichloroacetic acid, thus leading to accumulation.

Non-enzymatic dehydrochlorination and oxidation: A smaller fraction of 1,1,2,2-tetrachloroethane is first metabolized to trichloroethylene by the non-enzymatic cleavage of hydrogen chloride and then further to trichloroacetaldehyde, trichloroethanol or trichloroacetic acid. Another possible metabolic pathway is oxidation to tetrachloroethylene, which in turn may be further metabolized by CYP isoenzymes to trichloroacetic acid and oxalic acid. After inhalation exposure of rats for 8 hours, trichloroethanol and trichloroacetic acid were recovered in the urine; the levels of trichloroethanol were 4 times as high as those of trichloroacetic acid.

Reductive dechlorination: Spin-trapping experiments demonstrated the presence of free radicals during the metabolism of 1,1,2,2-tetrachloroethane; these were probably the product of reductive dechlorination (ATSDR 2008; Tomasi et al. 1984).

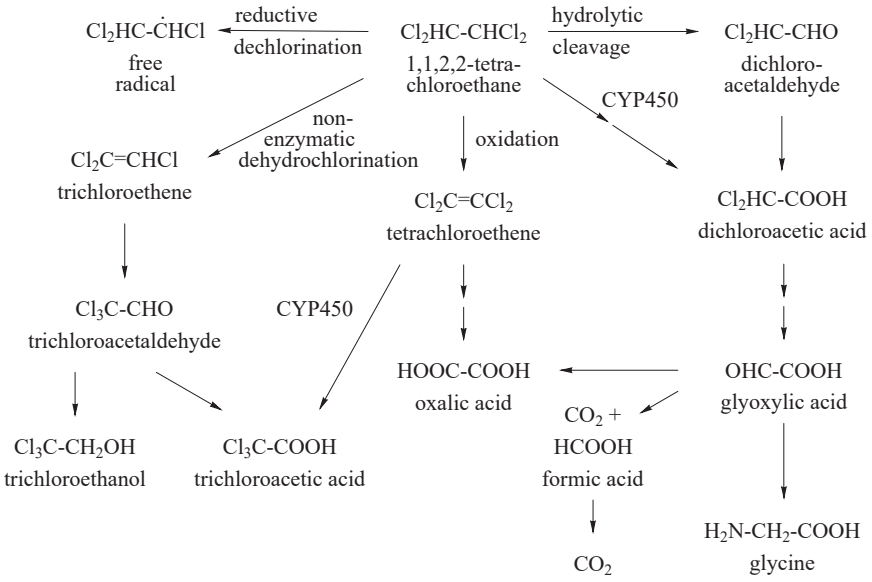

Fig. 1 Metabolic pathways of 1,1,2,2-tetrachloroethane in animals (according to US EPA 2010)

In the mouse, 1,1,2,2-tetrachloroethane was metabolized more extensively by homogenates of the olfactory mucosa than by those of the liver (Eriksson and Brittebo 1991). The identities of potential metabolites and modified proteins and phospholipids were not determined. The radioactivity in the proteins may have been incorporated glycine that was formed metabolically (US EPA 2010).

4 Effects in Humans

4.1 Single exposures

Two subjects inhaled 1,1,2,2-tetrachloroethane at different concentrations for 30 minutes. On the basis of the study findings, the odour threshold is calculated to be 3 ml/m^3. Exposure to 13 ml/m^3 was tolerated for 10 minutes without effects, while exposure to 146 ml/m^3 for 30 minutes or to 335 ml/m^3 for 10 minutes caused irritation of the mucous membranes, pressure in the head, vertigo and fatigue (US EPA 2010).

4.2 Repeated exposure

In humans, inhalation exposure at the workplace caused enlargement of the liver, nervous or gastrointestinal complaints, anaemia, headache, vertigo and fine tremor. The exposure concentrations were in the range from 9 to 98 ml/m^3. The effects could not be attributed to specific exposure concentrations. As a result of the insufficient documentation, these studies cannot be used for the evaluation of toxicity in humans (Henschler 1973).

1,1,2,2-Tetrachloroethane was used as an emulsifier at a penicillin production plant. A cohort of 34 to 75 workers was examined for 3 years. The workers were exposed to 1,1,2,2-tetrachloroethane concentrations of 2 to 248 ml/m^3 in the first year, 1 to 124 ml/m^3 in the second year and 1 to 36 ml/m^3 in the third year. The workers spent only very short amounts of time in high concentration areas (no other details) and wore face masks. Every 2 months, haematological parameters and bilirubin levels were determined in the blood of the workers and liver function tests were carried out. The hippuric acid levels in the urine were determined every 6 months. In the first year, 31% of the exposed workers had gastrointestinal complaints, 66% of these reported feeling pressure in the vicinity of the liver. In addition, 38% of the examined workers had an enlarged liver, 50% urobilinogenuria and the liver was palpable in 31% of the workers

with urobilinogenuria. The fraction of workers with an enlarged liver decreased in the second year to 20.5% and in the third year to 5%. A positive correlation was found between the duration of exposure and positive findings in liver function tests that represented significant deviations (thymol and Takata-Ucko liver function tests). In the third year, the erythrocyte concentrations, haemoglobin and hippuric acid levels were within the normal range. Serum bilirubin levels (> 10 mg/l) were increased in 20% of the workers in the first year, in 18.7% in the second year and in 7.6% in the third year (US EPA 2010).

In 2008, 5 men and 13 women who were exposed to 1,1,2,2-tetrachloroethane in a factory manufacturing plastic products were admitted to hospital with fatigue, poor appetite, nausea, vomiting, abdominal distension, other gastrointestinal disorders and discoloration of the urine. Five patients had a fever and 3 women menstrual cycle disorders. Up until that point, the plant employees had been exposed to 1,1,2,2-tetrachloroethane for 8 to 12 hours a day on an average of 33 days (13 to 57 days) through the adhesive they used, which was made up of 99.76% 1,1,2,2-tetrachloroethane. The room was 60 m^2 in size and equipped only with a ceiling fan, no ventilation system or other detoxification apparatus. The patients were examined by ultrasound and the prothrombin time, alanine aminotransferase and aspartate aminotransferase, alkaline phosphatase and γ-glutamyl transferase activities and total bilirubin were determined in the blood. The patients were tested for hepatitis B and C. A liver biopsy was carried out in 16 patients. After 3 and 6 months, liver function tests were carried out again in 17 patients. One female patient died of severe jaundice during the 3-month observation period. In all patients, the liver parameters were markedly increased at the time the patient was hospitalized in comparison with the values determined at the end of the 3 and 6-month observation periods. The eosinophilic lymphocytes were increased in 16 patients and the prothrombin time was extended in 6 patients. Two patients had positive test results for hepatitis B. The liver biopsies yielded findings of swollen, fatty and degenerated hepatocytes in the lobular area. Lymphocytes and neutrophils were observed in the hepatic sinusoids. Necrotic hepatocytes and mononuclear cells were found in the acinar zones III and I with neutrophil and lymphocyte infiltration. Cholestasis was diagnosed in 1 patient and the portal area was expanded with inflammatory cell infiltration and necrosis. Infiltration of Kupffer's cells was found in 12 patients. Spotty necrosis with little or no inflammation was determined in 14 patients. In all patients, small amounts of fibrous tissue were found in the portal area. The liver functions of all 16 patients had returned to "normal" at the end of the observation periods of 3 to 6 months. No data were given for the level of exposure (Zheng et al. 2012).

Both studies provide evidence that 1,1,2,2-tetrachloroethane induces severe toxic effects in the liver in humans. However, because of the lack of a control group, incomplete documentation (US EPA 2010) and no data for the level of exposure (Zheng et al. 2012), neither of the studies are suitable for the derivation of a quantitative concentration–effect relationship.

4.3 Local effects on skin and mucous membranes

There are no data available.

4.4 Allergenic effects

There are no data available.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

In a cohort of 3859 army personnel exposed to 1,1,2,2-tetrachloroethane by means of an impregnation solvent (no other details), the incidences of genital cancer, leukaemia and lymphomas were slightly increased. However, because of confounding factors, an association between the increased incidence and the use of 1,1,2,2-tetrachloroethane could not be established with confidence (ATSDR 2008; OECD 2002).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

The acute toxicity of 1,1,2,2-tetrachloroethane is minimal. The primary target organs are the central nervous system and the liver. After inhalation exposure for 4 hours, the LC_{50} for 1,1,2,2-tetrachloroethane was in the range from 640 to 1200 ml/m^3 in rats and 2800 ml/m^3 in rabbits. After exposure by gavage, the LD_{50} for 1,1,2,2-tetrachloroethane was in the range from 250 to 800 mg/kg body weight in rats and mice. The dermal LD_{50} for 1,1,2,2-tetrachloroethane was 6360 mg/kg body weight in rabbits (ATSDR 2008; OECD 2002).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Groups of 7 male rats (strain not specified) were exposed to 1,1,2,2-tetrachloroethane at a concentration of 15 mg/m^3 for 4 hours a day on 10 days. Additional, animals were given ethanol by gavage (4 g/kg body weight) immediately after undergoing inhalation exposure on the first, third and seventh day. The rats were examined after the second, fourth and eight exposure. Increased testis weights were determined only in the group after exposure to ethanol. The total protein level in serum was increased in all exposed rats; this increase was statistically significant after the first examination. The total liver fat content remained unchanged. During exposure, slight inflammatory changes such as round cell infiltration of the periportal fields, stellate granulomas and also necrosis of the liver were determined in all exposure groups. Atrophy of the seminiferous tubules with severely limited or absent spermiogenesis and a thickened basal membrane were observed. The kidney fat content was decreased only in the groups treated with ethanol. Inflammatory reactions in the thyroid gland were not observed (Gohlke and Schmidt 1972; Schmidt et al. 1972). Interstitial pneumonia was determined in all rats in varying degrees of severity.

Additionally, groups of 147 animals per control and exposure group were exposed to 1,1,2,2-tetrachloroethane at a concentration of 15 mg/m^3 for 4 hours a day for 11 months. Seven animals per group were examined on days 110, 265 and 325 of exposure. The body weights were reduced in the exposed rats; this decrease was statistically significant from exposure days 90 to 170. A statistically significant increase in the β1-globulin levels and the number of leukocytes was determined on day 110 and in the γ-globulin and neutrophil levels on day 265. Additionally, the total liver fat content was increased. A statistically significant decrease was noted in the number of lymphocytes on day 265 and in the adrenocorticotropic activity of the pituitary gland at all examination time points. The authors reported that most of the changes were only noticeable for a short period of time. The fat content in the liver was the only exception, and increased over the entire duration of exposure. Morphological changes and impaired functioning of the liver did not correlate with the accumulation of fatty deposits. It was further noted that the parameters that yielded reactions were almost exclusively those that are to be regarded as non-specific for toxicity induced by chlorinated ethanes (Schmidt et al. 1972). These studies did not report any data for the incidence and the severity of the findings. In addition, the concentrations in air are unclear. The concentration determined in air of 15 mg/m^3 would be equivalent to a dose of 1.7 mg/kg body weight and day in rats (respiratory volume of 0.8 l/min/kg body weight, 60% absorption), which is lower than the NOAEL of 20 mg/kg body weight for oral exposure by a factor of 11 (Section 5.2.2). It is not plausible that inflammatory effects in the liver would occur at such a low concentration in the subacute study, but not in the

chronic study with exposure to doses higher by a factor of 11. For this reason, the two studies are not used for the derivation of the MAK value.

5.2.2 Oral administration

Groups of 50 male and 50 female Osborne Mendel rats were given 1,1,2,2-tetrachloroethane (90% purity) by gavage on 5 days a week for 78 weeks. The control group was made up of 20 males and 20 females. The mean doses administered to the males were 0, 62 or 108 mg/kg body weight and day and to the females 0, 43 or 76 mg/kg body weight and day. The study included an observation period of 32 weeks. Reduced body weight gains were observed in the males and the females in both dose groups. Within the first 5 weeks, 20% of the females in the high dose group died, 8 of these of pneumonia; the cause of death was not reported for 2 of the animals. Beginning in the first week, the animals displayed hunched posture, reddened, in some cases encrusted eyes, laboured, wheezy breathing, nasal discharge and urine stains on the abdomen. Additionally, groups of 50 male and 50 female B6C3F1 mice were given gavage doses of 1,1,2,2-tetrachloroethane of 142 and 284 mg/kg body weight and day, respectively, for 78 weeks. A slight reduction in body weights was observed in the male mice of the control group and of the exposure groups from week 40 onwards. From week 14 onwards, a higher incidence of alopecia (mostly in the females), hunched posture, anal irritation, rough and stained fur, reddened eyes and palpable nodules were observed. Several animals in the high dose group had a swollen stomach from week 60 onwards; this effect was observed in 95% of the females from week 78 until the end of the study. The increase in mortality observed in the males and females was dose-dependent and statistically significant. In weeks 69 and 70, 33 males of the high dose group died from acute toxic tubular nephrosis. Hepatocellular carcinomas were found in all animals (see Section 5.7.2) (NCI 1978).

Male and female F344 rats and B6C3F1 mice were given doses of 1,1,2,2-tetrachloroethane per kg body weight and day in microcapsules with the feed for 15 days or 14 weeks (doses specified in Table 1). The administered substance had a purity of 99%. All of the animals survived the 14-week exposure period. Feed consumption decreased as the dose increased; in male rats, consumption decreased from 16.6 g per animal at the low dose level to 8 g per animal and in the female rats from 10.1 g per animal to 5.8 g per animal. The functional observation battery test did not yield evidence of neurotoxicity in rats or in mice. A dose-dependent and time-dependent increase in the activities of alanine aminotransferase and sorbitol dehydrogenase was observed in both male and female rats; this is regarded as evidence of liver cell damage. It was not possible to determine a NOAEL for mice because of the toxic effects in the liver. At the low dose of 20 mg/kg body weight and day, vacuolation of the hepatocytes was determined only in the male rats. No other cytotoxic changes in the liver were observed and the activities of the liver enzymes were not increased. This dose is therefore regarded as the NOAEL (NTP 2004).

Tab. 1 Effects after exposure via the feed for 15 days and 14 weeks (NTP 2004)

Species, strain, number per group	Exposure	Findings [mg/kg body weight and day]
rat, F344, 5 ♂, 5 ♀	**15 days**, 0, 300, 400, 500, 1000, 2000 mg/kg body weight and day, feed	**300 and above**: ♂ and ♀: body weights ↓, feed consumption ↓, relative kidney weights ↑ and absolute kidney weights ↓, **400 and above**: ♂ and ♀: relative and absolute thymus weights ↓, ♀: emaciated, hepatodiaphragmatic nodules 1/5, **500 and above**: ♂ and ♀: hepatodiaphragmatic nodules 2/10, ♂: emaciated, absolute liver weights ↓, ♀: alopecia 4/5, correlation with acanthosis, **1000 and above**: all animals sacrificed as moribund on day 11 of exposure, ♂ and ♀: hepatodiaphragmatic nodules 3/10, **2000**: ♂ and ♀: lethargy, alopecia 7/10

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings [mg/kg body weight and day]
rat, F344, 10 ♂, 10 ♀	**14 weeks**, 0, 20, 40, 80, 170, 320 mg/kg body weight and day, feed	**20 and above**: ♂ and ♀: feed consumption ↓, thin, ♂: hepatocyte vacuolation, **40 and above**: ♂ and ♀: relative liver weights ↑ (♂ > 20%), ♂: sperm motility ↓, hepatocyte vacuolation, ♀: body weights ↓ (not statistically significant), **80 and above**: ♂ and ♀: spleen pigmentation, body weights ↓, ♂: alanine aminotransferase and sorbitol dehydrogenase activity ↑, 5′-nucleotidase ↑, absolute epididymis weights ↓, ♀: cholesterol ↓, 5′-nucleotidase ↑, **170 and above**: liver: ♂ and ♀: lean and pale, yellow-brown pigmentation, hypertrophy and necrosis, basophilic or eosinophilic foci, relative kidney weights ↑, leukocyte count ↓, lymphocyte count ↓, bile acid ↑, alkaline phosphatase ↑, creatinine ↓, haemoglobin ↓, haematocrit ↓, atrophy of the bone marrow, ♂: atrophy of the spleen, ♀: bile duct hyperplasia, atrophy of the clitoral gland and the uterus, alanine aminotransferase and sorbitol dehydrogenase activity ↑, shorter pre-oestrus, oestrus and post-oestrus cycle, **320**: ♂ and ♀: atrophy of the spleen, relative organ weights: kidneys ↑, heart ↑, lungs ↑, liver ↑, absolute thymus weights ↓, ♂: smaller testes; atrophy of the prostate gland, preputial glands and seminal vesicles, bile duct hyperplasia, ♀: relative thymus weights ↓, erythrocytosis, cytoplasmic changes in the ovarian interstitial cells
mouse, B6C3F1, 5 ♂, 5 ♀	**15 days**, 0, 3325, 6650, 13 300, 26 600, 53 200 mg/kg feed, about 0, 665, 1330, 2660, 5320, 10 640 mg/kg body weight and day[a)]	**about 665 and above**: ♂ and ♀: body weights ↓, hyperactivity, relative and absolute thymus weights ↓, relative liver weights ↑, pale and spotty liver, hepatocellular degeneration, swelling, necrosis, mononuclear infiltrates **about 2260**: ♂: mortality 2/5, **about 5320**: ♂: mortality 5/5, **about 10 640**: ♂ and ♀: mortality 10/10
mouse, B6C3F1, 10 ♂, 10 ♀	**14 weeks**, 0, 589, 1120, 2300, 4550, 9100 mg/kg feed, ♂: 0, 100, 200, 370, 700, 1360 mg/kg body weight and day, ♀: 0, 80, 160, 300, 600, 1400 mg/kg body weight and day	**100/80 and above**: ♂: atrophy of the preputial glands 4/10, ♀: body weights ↓, relative liver weights ↑, pale liver, 2/10 minimal to mild hepatocellular hypertrophy, **200/160 and above**: ♂ and ♀: minimal to moderate hepatocyte hypertrophy, cholesterol ↓, bile acids ↑, ♂: protein concentration ↓, sorbitol dehydrogenase activity ↑, relative liver weights ↑, ♀: alanine aminotransferase activity, 5′-nucleotidase and sorbitol dehydrogenase activity ↑, **370/300 and above**: ♂ and ♀: body weights ↓, protein concentration ↓, liver: necrosis, pigmentation, hyperplasia of the bile ducts, alkaline phosphatase ↑, ♂: relative kidney weights ↓, pale liver, alanine aminotransferase and 5′-nucleotidase activity ↑, bile acids ↑, **700/600 and above**: ♂ and ♀: animals emaciated, ♂: reduced feed consumption, pale kidneys, absolute testis weights ↓, epididymis weights ↓, **1360/1400**: ♂ and ♀: absolute thymus weights ↓, ♂: atrophy of the preputial glands, sperm motility ↓, ♀: extended oestrus cycle

[a)] Feed consumption could not be determined conclusively, conversion factor 0.2 (for subacute studies) according to EFSA (2012)

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Undiluted 1,1,2,2-tetrachloroethane (0.01 ml) was applied to the skin of 5 rabbits. 1,1,2,2-Tetrachloroethane was classified as highly irritating to the skin (irritation index 6 on a scale with a maximum of 8) (no other details) (OECD 2002).

5.3.2 Eyes

Undiluted 1,1,2,2-tetrachloroethane (0.1 ml) was instilled into the eyes of 6 rabbits. 1,1,2,2-Tetrachloroethane was classified as irritating (irritation index 42.5 on a scale with a maximum of 110) (no other details) (OECD 2002).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no fertility studies or generation studies available.

A screening programme investigated 1,1,2,2-tetrachloroethane for genotoxicity and toxic effects on sperm (Inveresk Research International Limited 1980) (see Section 5.6.2). B6C3F1 mice were exposed to 1,1,2,2-tetrachloroethane at concentrations of 0, 5 or 50 ml/m^3 for 7 hours a day on 5 successive days. The mice did not exhibit signs of toxicity at any of the tested concentrations. After exposure to 1,1,2,2-tetrachloroethane at a concentration of 50 ml/m^3, the incidence of morphological changes to the sperm hook (upright or elongated) was slightly increased by a factor of 2.4. The authors did not consider this finding adverse because the increase was only slight and its biological significance doubtful (Inveresk Research International Limited 1980).

In a 14-week study in male and female F344 rats given 1,1,2,2-tetrachloroethane in microcapsules with the feed, sperm motility was reduced in the epididymis of male rats at doses of 40 mg/kg body weight and day and above in comparison with the levels determined in the control animals. The absolute epididymis weights were decreased at dose levels of 80 mg/kg body weight and day and above and the absolute weights of the left cauda epididymis were reduced concurrently with a decrease in body weights at doses of 170 mg/kg body weight and day and above. At the high dose of 320 mg/kg body weight and day, minimal to moderate atrophy of the preputial glands, the prostate gland, the seminal vesicles and the germinal epithelium was observed. In the females, minimal to slight atrophy of the uterus and the clitoral gland were found at dose levels of 170 mg/kg body weight and day and above, minimal to slight atrophy and cytoplasmic changes in the interstitial cells of the ovaries were determined at 320 mg/kg body weight and day. Additionally, female rats spent more time in the dioestrus phase and less time in the prooestrus, oestrus and metoestrus phases after exposure to 170 mg/kg body weight and day in comparison with the times determined for the control animals (see Section 5.2.1; NTP 2004).

In the corresponding 14-week study in B6C3F1 mice, the absolute weights of the left testis were reduced at dose levels of 700 mg/kg body weight and day and above and the absolute weights of the left epididymis were reduced at 1360 mg/kg body weight and day in comparison with the organ weights determined in the control animals. At 1360 mg/kg body weight and day, sperm motility in the epididymis was reduced in comparison with the motility observed in the control

animals. The oestrus cycle of female mice was longer than that of the control animals at 1400 mg/kg body weight and day (see Section 5.2.1; NTP 2004).

The shortcomings of a 10-day study with an exposure period of 8 days that observed atrophy of the seminiferous tubules (Gohlke and Schmidt 1972; Schmidt et al. 1972) and an 11-month study of reproductive toxicity in male rats with a limited scope (Schmidt et al. 1972) have been discussed above (see Section 5.2.1).

5.5.2 Developmental toxicity

Studies of the toxic effects of 1,1,2,2-tetrachloroethane on development are shown in Table 2.

Tab. 2 Studies of the toxic effects on development of 1,1,2,2-tetrachloroethane

Species	Exposure	Findings	References
rat, Sprague Dawley, groups of 8–9 ♀	**GD 4–20**, 0, 0.045%, 0.135%, 0.27%, 0.405%, 0.54% in microcapsules with the feed; 0, 34, 98, 180, 278 330 mg/kg body weight and day, examination on GD 20	**teratogenicity not investigated**; **34 mg/kg body weight and day and above**: dams: feed consumption ↓; **98 mg/kg body weight and day**: dams: complete resorption of a litter (1/8 animals); **98 mg/kg body weight and day and above**: dams: body weights ↓ (98, 180, 278, 330 mg/kg body weight: 9%, 11%, 14%, 24%); foetuses: body weights ↓ (98, 180, 278, 330 mg/kg body weight: 3.9%, 12.7%, 10.5%, 20.6%); **278 mg/kg body weight and day and above**: dams: ruffled fur; **330 mg/kg body weight and day**: dams: gravid uterine weights ↓; complete resorption of a litter (4/9 animals); dams: no mortality; no noticeable changes: number of live and dead foetuses per litter, number of resorptions per litter, number of implantations per litter; original study not available; the inconsistencies between the complete resorption observed in 4/9 dams at 330 mg/kg body weight and the changes in the number of resorptions per litter (not statistically significant) cannot be explained without the original study, according to OECD Test Guideline 414: data given for developmental end points for all litters with implantations	US EPA 2010
mouse, CD-1, groups of 5–11 ♀	**GD 4–17**, 0, 0.5%, 1.0%, 1.5%, 2.0%, 3.0% in microcapsules with the feed; 0, 987, 2120, 2216, 4575 mg/kg body weight and day, no determination for 3% in the feed as all animals died; examination on GD 17	**teratogenicity not investigated**; **987 mg/kg body weight and day and above**: dams: food consumption ↓; **2120 mg/kg body weight and day and above**: dams: mortality ↑, body weights ↓, resorptions of litters ↑; original study not available	US EPA 2010

GD: gestation day

The studies of the toxic effects on prenatal development in Sprague Dawley rats and CD-1 mice did not include an investigation of teratogenicity. The original publications are not available, but based on the list of references included in the report published by the US EPA, these were dose-finding studies (US EPA 2010). The scope of the studies is not sufficient for a complete evaluation of developmental toxicity.

The report published by the NTP includes a study with inhalation exposure of rats to 1,1,2,2-tetrachloroethane at a concentration of 2 ml/m^3 for 325 days. No changes in the number of litters or offspring were determined in comparison with the values of the controls (no other details; NTP 2004).

5.6 Genotoxicity

5.6.1 In vitro

DNA binding in the presence of a metabolic activation system was observed in calf thymus DNA. This was inhibited by the addition of SKF-525A, indicating that metabolic activation is required. However, DNA adducts were not identified (US EPA 2010).

The in vitro data for genotoxicity are shown in Table 3. 1,1,2,2-Tetrachloroethane induced DNA damage in Escherichia coli (DNA repair, induction of prophage λ) in the presence of a metabolic activation system. The results obtained in bacterial mutagenicity tests with various Salmonella typhimurium strains were mostly negative, even at toxic concentrations. Treatment with high concentrations induced gene conversions and mitotic recombination in yeasts (Saccharomyces cerevisiae); chromosomal malsegregation was induced in Aspergillus nidulans. No mutagenic effects were induced in mammalian cells (L5178 mouse lymphoma cells) up to cytotoxic concentrations. 1,1,2,2-Tetrachloroethane did not lead to DNA repair synthesis (UDS) in the primary hepatocytes of mice and rats. A UDS test with human embryonic intestinal fibroblasts yielded negative results after treatment for 3 hours with concentrations up to 15 869 µg/ml. By contrast, an increase in sister chromatid exchange (SCE) was observed in CHO (a cell line derived from Chinese hamster ovary) and BALB/c 3T3 cells with and without a metabolic activation system. Positive results were produced in BALB/c 3T3 cells at test concentrations above 500 µg/ml and in CHO cells at concentrations above 55.8 µg/ml. However, chromosomal aberrations were not induced in CHO cells at much higher concentrations up to cytotoxic concentrations of 653 µg/ml.

Summary: Studies investigating the mutagenicity of 1,1,2,2-tetrachloroethane in bacteria yielded mainly negative results. Gene conversions and mitotic recombination were observed in yeasts at high concentrations. 1,1,2,2-Tetrachloroethane did not induce mutagenicity in mammalian cells. Tests for UDS in the primary hepatocytes of mice and rats and with embryonic intestinal fibroblasts yielded negative results. Sister chromatid exchange was induced in CHO cells; a chromosomal aberration test with exposure at higher concentration levels yielded negative results. Overall, the in vitro data do not provide evidence of a mutagenic or clastogenic potential for 1,1,2,2-tetrachloroethane.

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

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Results		References
					–m.a.	+m.a.	
DNA damage, polA assay	Escherichia coli pol A^+/pol A_1^-	10 µl/plate (16 mg/plate)	10 µl/plate (16 mg/plate)		+	n.t.	Brem et al. 1974; Rosenkranz 1977; US EPA 2010
DNA damage, DNA repair	Escherichia coli $WP2_S(\lambda)$	–m.a.: 7.4–236.3 mM (1242–39 663 µg/ml) +m.a.: 14.8–473 mM (2484–79 393 µg/ml)	≥ 4952 µg/ml	–m.a.: 39 663 µg/ml +m.a.: 79 393 µg/ml	–	+	DeMarini and Brooks 1992
gene mutation	Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537	(1) 10–1000 µg/plate (2) 33–3333 µg/plate	–	≥ 1000 µg/plate	–	–	Haworth et al. 1983; NTP 2004
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	not specified	–	4000 µg/plate	–	–	Nestmann et al. 1980
	Salmonella typhimurium TA1535, TA1538 (filter discs)	10 µmol/plate (1679 µg/plate)		not specified	–	n.t.	Brem et al. 1974; Rosenkranz 1977; US EPA 2010

Tab. 3 *(continued)*

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Results		References
					–m. a.	+m. a.	
	Salmonella typhimurium TA1530 (filter discs)	5–24 µmol/plate (839–4028 µg/plate)	1679 µg/plate		+	n. t.	
	Salmonella typhimurium TA98, TA100, TA1535, TA1537 (plates in desiccator)	not specified	–	not specified	–	–	Milman et al. 1988; SRI International 1984
forward mutation	Salmonella typhimurium BA13	0.060–2979 nmol/plate (0.01–500 µg/plate)	–	300 µg/plate	–	–	Roldán-Arjona et al. 1991
gene conversion	Saccharomyces cerevisiae D7, duration of exposure: 1 hour	3.1–7.3 mM (520–1225 µg/ml)	870 µg/ml	≥ 870 µg/ml	+	n. t.	Callen et al. 1980
	Saccharomyces cerevisiae D7, duration of exposure: 24 hours	not specified	–	not specified	–	n. t.	Nestmann and Lee 1983
gene reversion	Saccharomyces cerevisiae D7	3.1–7.3 mM (520–1225 µg/ml)	870 µg/ml	≥ 870 µg/ml	+	n. t.	Callen et al. 1980
	Saccharomyces cerevisiae D7, duration of exposure: 24 hours	not specified	–	not specified	–	n. t.	Nestmann and Lee 1983
gene re-combination	Saccharomyces cerevisiae D7	3.1–7.3 mM (520–1225 µg/ml)	870 µg/ml	≥ 870 µg/ml	+	n. t.	Callen et al. 1980
mitotic crossing-over	Aspergillus nidulans P1	0.01%–0.04% (160–639 µg/ml)	≥ 320 µg/ml	639 µg/ml	+	n. t.	Crebelli et al. 1988
SCE	CHO cells	–m. a.: 16.8–168 µg/ml +m. a.: 451–588 µg/ml	–m. a.: 55.8 µg/ml +m. a.: ≥ 451 µg/ml	–	+	+	Galloway et al. 1987; NTP 2004
	BALB/c 3T3 cells	–m. a.: 1000 µg/ml +m. a.: 500 µg/ml	–m. a.: 1000 µg/ml +m. a.: 500 µg/ml	–	+	+	Colacci et al. 1992
UDS	rat hepatocytes	95 µM (15.9 µg/ml)	–	–	–	n. t.	Milman et al. 1988; Williams et al. 1989
	human embryonic intestinal fibroblasts	–m. a.: 124–15 869 µg/ml +m. a.: (1) 8–250 µg/ml (2) 1.3–10 µg/ml	–	–m. a.: ≥ 7935 µg/ml +m. a.: > 250 µg/ml	–	–	Inveresk Research International Limited 1980
CA	CHO cells	–m. a.: 453–653 µg/ml +m. a.: 503–653 µg/ml	–	–/+m. a.: 653 µg/ml	–	–	Galloway et al. 1987; NTP 2004
gene mutation $TK^{+/-}$	L5178Y mouse lymphoma cells	–m. a.: 60–300 nl/ml (96–480 µg/ml) +m. a.: 50–500 nl/ml (80–800 µg/ml)	–	480 µg/ml	–	–	NTP 2004

CA: structural chromosomal aberrations; m. a.: metabolic activation; n. t.: not tested; SCE: sister chromatid exchange; UDS: DNA repair synthesis

5.6.2 In vivo

The data for genotoxicity in vivo are shown in Table 4.

1,1,2,2-Tetrachloroethane did not induce mitotic recombination (SMART) or sex-linked recessive lethal mutations (SLRL) in Drosophila melanogaster after exposure by inhalation, injection or via the diet (Inveresk Research International Limited 1980; NTP 2004; Vogel and Nivard 1993; Woodruff et al. 1985).

1,1,2,2-Tetrachloroethane bound to the DNA, RNA and protein in the liver, kidneys, lungs and stomach of rats and mice treated with a single intravenous injection of the substance. However, no adducts were identified and a possible metabolic incorporation of radioactive carbon was not taken into consideration (Colacci et al. 1987).

After B6C3F1 mice were given a single oral dose of radioactively labelled 1,1,2,2-tetrachloroethane of 150 mg/kg body weight, ^{14}C became irreversibly bound to the DNA in the hepatocytes of the treated animals. The HPLC analysis and comparisons with chromatograms of mice treated with "^{14}C-formate" demonstrated an association between radioactivity and the purine bases of DNA. These findings are regarded as stronger evidence for the metabolic incorporation of radioactive carbon than for the formation of DNA adducts (HCN 2006; US EPA 2010).

A UDS test in B6C3F1 mice yielded negative results. The animals were treated with a single gavage dose: the males with doses of 50 to 1000 mg/kg body weight, the females with doses of 50 or 200 mg/kg body weight. This was followed by the examination of the hepatocytes (Mirsalis et al. 1989).

An oral 14-week study in male and female B6C3F1 mice (see Section 5.2.2) included a micronucleus test with peripheral erythrocytes. The test was carried out at the end of the study with groups of 5 animals per sex and group. A dose-dependent increase in erythrocytes containing micronuclei was observed; this increase was statistically significant in the males of the two high dose groups (700 and 1360 mg/kg body weight and day) in comparison with the levels determined in the controls. The trend analysis was positive for both sexes. At doses of 300 mg/kg body weight and day and above, systemic toxicity was found in the females in the form of reduced body weight gains and, at the end of the study, in the form of reduced body weights. In the males, systemic toxicity was observed at doses of 370 mg/kg body weight and day and above in the form of delayed body weight gains. In 2 of 10 females, effects on the liver (hypertrophy of the hepatocytes) were noted even in the low dose group (see also Table 1; NTP 2004). The peripheral erythrocytes were not examined for cytotoxic effects.

A screening programme was carried out to investigate the induction of genotoxic effects by 1,1,2,2-tetrachloroethane (Inveresk Research International Limited 1980). The in vivo test battery included a chromosomal aberration test in male and female CD rats, a dominant lethal test in male CD rats and a sperm anomaly test in B6C3F1 mice. The tests were carried out in the mammals either after a single inhalation exposure (chromosomal aberrations) or exposure for 7 hours per day on 5 successive days (chromosomal aberrations, dominant lethal test, sperm anomalies). Concentrations of 0, 5 or 50 ml/m^3 were used. Signs of toxicity were not evident in the mice and rats. In female rats exposed for 7 hours to 50 ml/m^3, the increase in chromosomal aberrations (without gaps) in the bone marrow was statistically significant 6 hours after the end of treatment. The analysis was performed 6, 24 or 48 hours after the end of treatment. By contrast, no reactions were produced by the males or by the females treated with the low concentration. Chromosomal aberrations were not induced after repeated exposure over a period of 5 days. The groups treated with a single exposure were made up of 30 animals per sex, the groups treated with repeated exposures were made up of 10 animals per sex (Inveresk Research International Limited 1980). As only a maximum of 50 cells per animal were analysed, the mitotic index was not determined and the positive control (ethyl methanesulfonate) yielded positive results only 6 hours after the end of treatment, the chromosomal aberration test does not meet the requirements of the OECD Test Guideline that is used today. For the reasons listed above, the results of the chromosomal aberration test are not included in the evaluation.

The dominant lethal test yielded negative results. After exposure of the male rats for 5 days to concentrations of 0, 5 or 50 ml/m^3, the male rats were mated with 2 different untreated females each week for 9 consecutive weeks. The authors noted that the increased number of "early deaths" in all groups (including the control group) may have been caused by a viral infection (Inveresk Research International Limited 1980).

Tab. 4 Genotoxicity of 1,1,2,2-tetrachloroethane in vivo

Test system		Dose	Results	References
SLRL	Drosophila, ♂	(1) 7 hours, 0, 5 ml/m³ (2) 40 minutes, 0, 50 ml/m³	(1), (2): –, (2) all animals sedated after 1 hour	Inveresk Research International Limited 1980
SLRL	Drosophila, adult ♂	1500 mg/l, feed 800 mg/l, injection	–	NTP 2004; Woodruff et al. 1985
SMART (eye mosaic test)	Drosophila, larvae	17 hours 0, 500, 1000 ml/m³	–	Vogel and Nivard 1993
DNA binding, liver (bound radioactivity)	mouse, B6C3F1, not specified	single, 150 mg/kg body weight, gavage	+, see text for commentary	HCN 2006; US EPA 2010
DNA binding, liver, kidneys, lungs, stomach (bound radioactivity)	rat, Wistar, 6 ♂	single, 8.7 µmol/kg body weight (1.46 mg/kg body weight), intraperitoneal	+, RNA and protein binding: +, adducts not determined	Colacci et al. 1987
DNA binding, liver, kidneys, lungs, stomach (bound radioactivity)	mouse, BALB/c, 12 ♂	single, 8.7 µmol/kg body weight (1.46 mg/kg body weight), intraperitoneal	+, RNA and protein binding: +, adducts not determined	Colacci et al. 1987
UDS, liver	mouse, B6C3F1, 3 ♂, 3 ♀ per group	single, 0, 50, 200, 600, 1000 mg/kg body weight and day in corn oil, gavage	–	Mirsalis et al. 1989
CA, bone marrow	rat, CD, 30 ♂, 30 ♀ per group analysis 6, 24, 48 hours after the end of exposure	1 × 7 hours, 0, 5, 50 ml/m³	♂: –, ♀: – at 5 ml/m³, + at 50 ml/m³ (without gaps), invalid (see text)	Inveresk Research International Limited 1980
CA, bone marrow	rat, CD, 10 ♂, 10 ♀ per group	7 hours/day, 5 days, 0, 5, 50 ml/m³	–	Inveresk Research International Limited 1980
MN, peripheral erythrocytes	mouse, B6C3F1, 5 ♂, 5 ♀ per group	14 weeks, ♂: 0, 100, 200, 370, 700, 1360 mg/kg body weight and day, ♀: 0, 80, 160, 300, 600, 1400 mg/kg body weight and day, feed	♂: + at 700, 1360 mg/kg body weight and day, ♀: –, trend + for ♂ and ♀, no determination of polychromatic/normochromatic erythrocytes	NTP 2004
DLT	rat, CD, 10 ♂ per group	7 hours/day, 5 days, 0, 5, 50 ml/m³	–	Inveresk Research International Limited 1980

CA: structural chromosomal aberrations; DLT: dominant lethal test; MN: micronuclei; SCE: sister chromatid exchange; SLRL: X-chromosomal recessive lethal mutations; SMART: test for somatic mutations and recombination; UDS: DNA repair synthesis

Summary: Mitotic recombination was not observed in Drosophila melanogaster. The SLRL test yielded negative results. In vivo, 1,1,2,2-tetrachloroethane did not lead to an increase in UDS in the liver of mice. In mice given oral doses for 14 weeks, high toxic doses induced micronuclei in the peripheral erythrocytes in both male and female mice; however, this was statistically significant only in male mice. A dominant lethal test with inhalation exposure of male rats to 1,1,2,2-tetrachloroethane for 5 days did not detect clastogenic effects in the germ cells. Overall, the evidence suggests that 1,1,2,2-tetrachloroethane causes only slight clastogenic effects.

5.7 Carcinogenicity

5.7.1 Short-term studies

A cell transformation test with BALB/c-T3 cells yielded negative results for 1,1,2,2-tetrachloroethane (Milman et al. 1988).

In an initiation study, groups of 10 male Osborne Mendel rats underwent a partial hepatectomy and 24 hours later received a single gavage dose of 1,1,2,2-tetrachloroethane of 100 mg/kg body weight. Beginning 6 days after the partial hepatectomy, phenobarbital was administered in the diet for 7 weeks. The control animals were given corn oil or diethylnitrosamine (DEN) at the same dose level (30 mg/kg body weight) and then a control diet or diet with phenobarbital. 1,1,2,2-Tetrachloroethane was not found to have initiating effects (Milman et al. 1988).

In a promotion study, groups of 10 male Osborne Mendel rats underwent a partial hepatectomy and 24 hours later received DEN by intraperitoneal injection. After 6 days, the animals were given gavage doses of 1,1,2,2-tetrachloroethane of 100 mg/kg body weight on 5 days a week for 7 weeks. The increase in the number of gamma-glutamyl transferase-positive foci in the liver was statistically significant both with and without an initiator. This is regarded as evidence that 1,1,2,2-tetrachloroethane is a tumour promoter in the liver, also without prior initiation (Milman et al. 1988; Story et al. 1986).

Groups of 20 male strain A mice were given 1,1,2,2-tetrachloroethane in tricaprylin by intraperitoneal injection twice weekly for 3 to 9 weeks at dose levels of 80 (5 injections), 200 (18 injections) or 400 (16 injections) mg/kg body weight. Only 5 of the 20 animals of the high exposure group survived in comparison with 15 of the 20 animals of the control group. A statistically significant increase in the lung tumour incidence was not observed (Theiss et al. 1977).

5.7.2 Long-term studies

Groups of 50 male and 50 female Osborne Mendel rats were given gavage doses of 1,1,2,2-tetrachloroethane of 0, 62 or 108 mg/kg body weight and day (males) and 0, 43 or 76 mg/kg body weight and day (females) for 78 weeks. A statistically significant increase in the tumour incidence was not noted; 2 hepatocellular carcinomas and a neoplastic nodule were found in the 49 exposed male rats in comparison with no tumours in the 20 control animals. Additionally, groups of 50 male and 50 female B6C3F1 mice were given gavage doses of 1,1,2,2-tetrachloroethane of 142 or 284 mg/kg body weight and day for 78 weeks. A dose-dependent increase in hepatocellular carcinomas was observed in both the males and the females; the increase was statistically significant and markedly above the historical control incidence. Therefore, the authors concluded that the effect was clearly substance-induced (NCI 1978; see Table 5).

Tab. 5 Studies of carcinogenicity induced by 1,1,2,2-tetrachloroethane

Author:	NCI 1978
Substance:	1,1,2,2-tetrachloroethane (90% purity)
Species:	**rat**, Osborne Mendel, exposed animals: 50 ♂, 50 ♀; 20 control animals per group
Administration route:	gavage
Dose:	♂: 0, 62, 108 mg/kg body weight and day; ♀: 0, 43, 76 mg/kg body weight and day
Duration:	exposure on 5 days/week for 78 weeks; observation period: 32 weeks
Toxicity:	reduced body weight gains in both dose groups, mortality in 20% of the females (highest dose: 10 in the first 5 weeks (8 of these with pneumonia, 2 undocumented), hunched posture, reddened eyes, urine stains) (see Section 5.2.2)

Tab. 5 *(continued)*

		Dose [mg/kg body weight] ♂/♀		
		0 (corn oil)	**62/43**	**108/76**
surviving animals	♂	50%	50%	50%
	♀	70%	58%	40%
tumours and preneoplasms				
neoplastic liver nodules, hepatocellular carcinomas	♂	0/20	0/50	3/49 (6%)
pituitary gland (adenomas)	♂	5/14 (36%)	5/48 (10%)	5/48 (10%)
	♀	3/20 (15%)	11/49 (22%)	6/48 (13%)
mammary glands (fibroadenomas)	♀	9/20 (45%)	13/50 (26%)	11/50 (22%)
uterus (endometrial polyps originating from the interstitial connective tissue)	♀	0/20	8/50 (16%)	4/48 (8%)
Author:		NCI 1978		
Substance:		1,1,2,2-tetrachloroethane (90% purity)		
Species:		**mouse**, B6C3F1, exposed animals: 50 ♂, 50 ♀; 20 control animals per group		
Administration route:		gavage		
Dose:		♂ and ♀: 0, 142, 284 mg/kg body weight		
Duration:		exposure on 5 days/week for 78 weeks; observation period: 12 weeks		
Toxicity:		lesions on body, alopecia, ♀: 95% of the high dose group with a distended stomach (see Section 5.2.2)		
		Dose [mg/kg body weight]		
		0 (corn oil)	**142**	**284**
surviving animals (end of study)	♂	50%	50%	34% (33 died in weeks 69–70)
	♀	75%	74%	50%
tumours				
hepatocellular carcinoms[a)]	♂	1/18 (6%)	13/50 (26%)*	44/49 (90%)**
	♀	0/20	30/48 (63%)[b)]**	43/47 (92%)[c)]**

[a)] historical controls: NCI Bioassay Program ♂: 74/612 (12%), Hazleton Laboratories ♀: 8/560 (1%);
[b)] first tumour in week 84;
[c)] first tumour in week 52
*$p \le 0.05$; **$p \le 0.01$

6 Manifesto (MAK value/classification)

The most sensitive end point is the liver toxicity in humans and animals.

MAK value. The data available for inhalation exposure at the workplace are not used for the derivation of a MAK value because of the lack of a control group and limited documentation. The findings from animal studies with inhalation exposure are not reliable because of shortcomings in the procedure or documentation and because the results are not plausible when compared with those from better-quality oral studies that tested higher doses. A NOAEL of 20 mg/kg body weight and day was derived for rats from a study in which 1,1,2,2-tetrachloroethane was given to rats and mice in microcapsules with the feed for 14 weeks. At the next-higher dose of 40 mg/kg body weight and day, the relative liver weights were increased (by about 21% in the males) and sperm motility was reduced. The NOAEL for male mice was determined to be the lowest dose tested of 100 mg/kg body weight and day. In female mice, however, increased relative liver weights (9%) and minimal to slight hypertrophy of the hepatocytes were observed in 2 of 10 animals at the lowest dose tested of 80 mg/kg body weight. As these effects were observed only in female

mice and were very slight in severity, the NOAEL of 20 mg/kg body weight and day for rats can still be used for the derivation of a MAK value.

The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific toxicokinetic correction value for the rat (1:4), the oral absorption of 95% determined experimentally, the body weight (70 kg) and the respiratory volume (10 m^3) of the person and the 60% absorption by inhalation determined under experimental conditions. The NOAEL may be lower after long-term exposure (1:2). As the NOAEL was determined from an animal study (1:2), the concentrations calculated from this are 19.4 mg/m^3 and 2.8 ml/m^3, respectively. After applying the preferred value approach, a MAK value of 2 ml/m^3 is derived.

Very little information is available for irritation. Exposure to 13 ml/m^3 for 10 minutes was tolerated by 2 subjects without effects; the odour threshold was 3 ml/m^3. In a field study, workers who were exposed to 1,1,2,2-tetrachloroethane concentrations of 2 to 248 ml/m^3 in the first year, 1 to 124 ml/m^3 in the second year and 1 to 36 ml/m^3 in the third year were examined at intervals of 2 months. The workers spent only very short periods of time in high concentration areas (no other details) and wore face masks. Taking into consideration that this study did not report findings of irritation in addition to the results of the study with subjects, the substance is not expected to induce irritation at a concentration of 2 ml/m^3.

Peak limitation. The critical effects of the substance are systemic; therefore, the substance remains classified in Peak Limitation Category II. As the half-life of the substance in blood is not known, the excursion factor of 2 has been retained, which is the default excursion factor used when the critical effect is systemic. Exposure to the substance at a concentration of 4 ml/m^3, the permissible peak concentration in this category, is not expected to lead to sensory irritation (see above).

Prenatal toxicity. As none of the available developmental toxicity studies investigated teratogenicity, 1,1,2,2-tetrachloroethane has been classified in Pregnancy Risk Group D.

Carcinogenicity. Exposure of male Osborne Mendel rats to a 1,1,2,2-tetrachloroethane dose of 108 mg/kg body weight and day in the high dose group did not lead to a statistically significant increase in neoplastic nodules and hepatocellular carcinomas. In male and female B6C3F1 mice, the increase in the incidence of hepatocellular carcinomas was statistically significant at dose levels of 142 mg/kg body weight and day and above (NCI 1978). Carcinogenic effects were not induced in male rats at a dose of 62 mg/kg body weight. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the corresponding toxicokinetic species-specific correction value for the rat (1:4), the oral absorption determined under experimental conditions (95%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, the absorption by inhalation determined under experimental conditions (60%) and the extrapolation of the findings from animal studies to humans (1:2). The concentration at the workplace calculated from this is 86 mg/m^3 (12 ml/m^3; 62 mg/kg body weight/4 × 70 kg body weight/10 m^3 × 95%/60%/2).

In the more sensitive species the mouse, a dose without carcinogenic effects was not obtained. 1,1,2,2-Tetrachloroethane did not show relevant genotoxic potential. In a liver foci test in rats, the substance had a promoting effect, but not an initiating effect. Therefore, the primary mechanism is not genotoxic. As liver tumours were induced in rats and mice and the metabolite dichloroacetic acid is classified in Carcinogen Category 4, 1,1,2,2-tetrachloroethane has likewise been classified in Carcinogen Category 4.

Germ cell mutagenicity. The in vitro data for 1,1,2,2-tetrachloroethane did not provide any evidence of a marked mutagenic or clastogenic potential. Mitotic recombination and sex-linked recessive lethal mutations were not observed in vivo in Drosophila melanogaster. In mammals, 1,1,2,2-tetrachloroethane did not lead to an increase in unscheduled DNA synthesis in the liver of mice. In mice given oral doses of the substance for 14 weeks, high toxic doses induced micronuclei in the peripheral erythrocytes of male mice; this effect was statistically significant. Micronuclei were induced also in female mice; however, the increase was not statistically significant. A dominant lethal test with

inhalation exposure of male rats to 1,1,2,2-tetrachloroethane for 5 days did not determine clastogenic effects in germ cells. In vivo data for 1,1,2,2-tetrachloroethane demonstrate that the substance induces at most slight clastogenic effects. No studies were carried out to investigate mutagenic effects in vivo. Therefore, the substance has not been classified in a category for germ cell mutagens.

Absorption through the skin. The findings of the study of Tsuruta (1975) for undiluted 1,1,2,2-tetrachloroethane and the estimated values obtained by applying the model of Fiserova-Bergerova et al. (1990) for a saturated aqueous solution suggest that 967 to 1240 mg of the substance is absorbed under standard conditions. A total absorbed amount of 58 mg was calculated for a saturated aqueous solution using the IH SkinPerm model (Section 3.1.1). The amount absorbed after inhalation exposure at the level of the MAK value (respiratory volume: 10 m^3, absorption: 60%) is about 84 mg. These results show that absorption through the skin contributes markedly to the total body burden. 1,1,2,2-Tetrachloroethane therefore retains the "H" designation (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. No data for sensitizing effects in humans, findings from animal studies or in vitro studies have become available. Therefore, 1,1,2,2-tetrachloroethane continues not to be designated with an "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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