The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

1,1,1-Trichloroethane

MAK Value Documentation, supplement – Translation of the German version from 2019

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Keywords

1,1,1-trichloroethane; neurotoxicity; central nervous system; acute toxicity; MAK value; maximum workplace concentration; developmental toxicity; prenarcotic effects; peak limitation; toxicokinetics

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 1,1,1-trichloroethane [71-55-6]. Critical are pre-narcotic effects observed in male volunteers exposed at rest to 350 ml/m^3. The MAK value has now been lowered to 100 ml/m^3 taking into account the increased respiratory volume at the workplace because the blood:air partition coefficient of 1,1,1-trichlorethane is > 5 (see List of MAK and BAT Values, Sections Ib and Ic). As a systemic effect is critical, Peak Limitation Category II is retained. To avoid short-term pre-narcotic effects, the excursion factor of 1 is also retained. The differences between the MAK value and the NOAECs for developmental toxicity in rats, rabbits and mice are sufficient even taking into account the increased respiratory volume at the workplace. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and 1,1,1-trichloroethane remains assigned to Pregnancy Risk Group C. 1,1,1-Trichloroethane is neither carcinogenic in rats or mice nor a germ cell mutagen. The designation with "H" (for substances that can be absorbed via the skin in toxicologically relevant amounts) is retained. There are no data on the sensitizing potential in humans. 1,1,1-Trichloroethane is not a skin sensitizer in guinea pigs.

Citation Note:
Hartwig A, MAK Commission. 1,1,1-Trichloroethane. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2021 Dec;6(4):Doc084.
DOI: https://doi.org/10.34865/mb7155e6_4ad

Manuscript completed:
21 Mar 2018

Publication date:
30 Dec 2021

MAK value (2018)	**100 ml/m³ (ppm) ≙ 550 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 1**
Absorption through the skin (2001)	**H**
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (1986)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value (2018)	**275 µg/l blood**
CAS Number	71-55-6
Vapour pressure at 20 °C	133 hPa (DECOS 2012)
1 ml/m³ (ppm) ≙ 5.536 mg/m³	**1 mg/m³ ≙ 0.181 ml/m³ (ppm)**

Documentation for 1,1,1-trichloroethane was published in 1972 (Henschler 1972, available in German only), followed by supplements for prenatal toxicity (Henschler 1987, available in German only) and a re-evaluation (Greim 2001, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapours if their blood:air partition coefficient is < 5 (see List of MAK and BAT Values, Sections Ib and Ic). A blood:air partition coefficient of 6 was determined for 1,1,1-trichloroethane (Dills et al. 1994), whereas the calculated value was 5 (Greim 2001). This supplement reviews whether the MAK value and the pregnancy risk group for 1,1,1-trichloroethane need to be amended as a result of the higher respiratory volume at the workplace.

The documentation is based primarily on an evaluation by the Dutch Expert Committee on Occupational Standards (DECOS 2012) and on a BUA report (BUA 1995).

1,1,1-Trichloroethane is classified as ozone depleting and its use has been banned since 1996.

Toxicokinetics and Metabolism

After inhalation, volunteers exhaled about 90%, mice and rats about 95% of the absorbed amount of 1,1,1-trichloroethane in unchanged form. In humans, percutaneous absorption of gaseous 1,1,1-trichloroethane accounts for less than 1% of the amount absorbed compared with absorption by inhalation. The liquid substance is readily absorbed through the skin and contributes to the body burden (BUA 1995; Greim 2001).

After the exposure of 12 volunteers to 175 ml/m³, 1,1,1-trichloroethane reached steady state in the blood after 60 to 120 minutes. The blood concentration was 5 to 6 µmol/l, or about 1.6 mg/l, 20 minutes after the beginning of exposure and was thus about half of the maximum value of 12 µmol/l (Greim 2001; Mackay et al. 1987).

In volunteers exposed to a concentration of 200 ml/m³ for 3 hours, the first 10 minutes of which were spent exercising on a bicycle ergometer at a load of 100 W, a 1,1,1-trichloroethane concentration of 19.9 µmol/l blood was determined 15 minutes after the beginning of exposure. In another experiment, the concentration was increased to 400 ml/m³ for 10 minutes at the beginning of the 3-hour exposure period and then maintained at 135 ml/m³. The 1,1,1-trichloroethane

concentration in the blood was 34 µmol/l 15 minutes after the beginning of exposure and thus almost twice as high as after exposure to 200 ml/m^3. In this experiment, the exposure concentration of 400 ml/m^3 was reached by initially increasing the concentration from 135 to 400 ml/m^3 over a period of 5 minutes, followed by exposure to 400 ml/m^3 for 10 minutes while exercising on a bicycle ergometer and then reducing the exposure concentration from 400 to 135 ml/m^3 over a period of 5 minutes. After a break of 40 minutes, exposure continued according to the pattern described above. In this case, the concentration in the blood of 49.1 µmol/l at the exposure peak of 400 ml/m^3 was more than twice as high as that at 200 ml/m^3 of 21.5 µmol/l (Laine et al. 1996).

After exposure to a 1,1,1-trichloroethane concentration of 142 ml/m^3 while exercising on a bicycle ergometer at a load of 100 W, the respiratory minute volume was about 3 times as high (30 l/min) and the lung clearance was about 2.3 times as high than at rest (Monster et al. 1979). The respiratory minute volume is twice as high at the workplace than under resting conditions and absorption is thus about 1.5 times as high.

As equilibrium between the 1,1,1-trichloroethane concentrations in the blood and brain was very rapidly reached when mice were exposed to 500 to 14 000 ml/m^3 (Warren et al. 2000), rapid elimination from the brain is likely.

After the exposure of 6 volunteers to 35 or 350 ml/m^3 for 6 hours at rest, a tri-exponential decrease in the blood concentration of 1,1,1-trichloroethane was observed with half-lives of 44 minutes, 5.7 hours and 53 hours. About 5% to 6% of the amount of 1,1,1-trichloroethane taken up was excreted with the urine mainly as 2,2,2-trichloroethanol glucuronide and trichloroacetic acid (Greim 2001).

1,1,1-Trichloroethane is metabolized to trichloroethanol by cytochrome P450 in vivo and in vitro. After ^{14}C-1,1,1-trichloroethane was administered parenterally or by inhalation, $^{14}CO_2$ was identified in the exhaled air (ACGIH 2001).

In mice, intraperitoneal injection induced increased expression of the cytochrome P450 2B1 isoform in liver microsomes, whereas the total cytochrome P450 activity decreased (Paolini et al. 1992).

Effects in Humans

Single exposures

In a volunteer study using a cross-over design, 12 male students (non-smokers; no medication) were exposed to 1,1,1-trichloroethane concentrations of 20 (control persons) or 200 ml/m^3 at rest. The levels of interleukins IL-1β, IL-6 and IL-8 were significantly increased in nasal secretion at a concentration of 200 ml/m^3. The prostaglandin E_2 levels were not increased. Effects on mucociliary transport (transport duration of saccharine) or the ciliary beat frequency of the nasal epithelial cells were not observed. The volunteers did not report irritation of the mucosa, breathing difficulties or any pre-narcotic effects (Muttray et al. 1999). In this study, sensory irritation was not induced by the concentration of 200 ml/m^3. The release of IL-1β mediated by NF-κB was expected to lead to an increased formation of prostaglandin E_2; however, no such increase was observed. In addition, the parameters were determined only once after exposure; therefore, it was not possible to make a comparison of the levels before and after exposure.

The neurophysiological effects of this study were investigated by recording electroencephalograms (EEG) before (baseline reference) and at the end of each exposure with eyes open and closed and during a colour–word stress test. Spectral power was calculated by fast Fourier transformation. Subjective symptoms were assessed by means of a questionnaire. There was a slight increase in the score for tiredness during and after exposure to the concentration of 200 ml/m^3. The significant differences in the EEG that were described in some cases (δ band: 3 significant differences; α_1 band: 1 significant difference; α_2 band: 2 significant differences) were not adjusted for multiple comparisons; therefore, only the overall impression can be interpreted. The changes in the EEG and the increased score for tiredness observed after exposure to a 1,1,1-trichloroethane concentration of 200 ml/m^3 may be considered evidence of mild sedative effects (Muttray et al. 2000). Other indicators of neurotoxic effects were not observed at 200 ml/m^3. Therefore, there is no evidence that acute neurotoxic effects are caused by exposure to 200 ml/m^3.

In this study, no effects on olfactory performance were found using "Sniffin' Sticks" after 1 hour. The olfactory threshold for *n*-butyl alcohol was slightly increased after 4 hours (p = 0.04) (Muttray et al. 2004).

In a study using a cross-over design, the exposure of 9 male volunteers to 1,1,1-trichloroethane concentrations of 0, 200 or 135 ml/m³ with peaks of 400 ml/m³ (10 minutes, but increasing and decreasing over 20 minutes at the beginning and end of the exposure period) for 4 hours did not lead to any changes in the α, θ or δ bands in the EEG, in the visually evoked potentials or in the body sway test. Only the activities in the β2 band were significantly higher after exposure to 400 ml/m³ for 10 minutes at the beginning of exposure, but not at the end of exposure. However, this increased activity did not correlate with the 1,1,1-trichloroethane levels in the blood, which increased with the duration of exposure. The effects are thus not consistent. Substance-induced effects were not observed after continuous exposure to 200 ml/m³. In this study, the volunteers exercised on a bicycle ergometer (100 W) for 10 minutes at the beginning of exposure and after 3 hours (Greim 2001; Laine et al. 1996).

The results of the various volunteer studies are shown in Table 1 (Greim 2001; Muttray et al. 1999, 2000).

Tab. 1 Volunteer studies with exposure to 1,1,1-trichloroethane (Greim 2001)

Test persons	Exposure	Effects	References
12	20 (controls), 200 ml/m³, 4 hours	200 ml/m³: **LOEC** mild sedative effects, interleukins increased in nasal secretion	Muttray et al. 1999, 2000
6	400–500 ml/m³, 2 × 4 hours	mild dizziness during the first 20 minutes, no delayed reaction time	Salvini et al. 1971
12	0, 250, 350, 450, 550 ml/m³, exposure to increasing concentrations for 30 minutes in each case	250 ml/m³: **NOEC** 350 ml/m³ and above: perceptual speed reduced 450 ml/m³: simple and choice reaction times delayed	Gamberale and Hultengren 1973
9	0, 200, 400 ml/m³, 4 hours	200 ml/m³: **NOAEC** 400 ml/m³: cumulative reaction time delayed	Savolainen et al. 1981
12	0, 175, 350 ml/m³, 3.5 hours	175 ml/m³: **LOEC** simple reaction time delayed, choice reaction time delayed, mild effects	Mackay et al. 1987
9	0, 200 ml/m³, 135 ml/m³ with exposure peaks of 400 ml/m³ for 20 minutes at the beginning and end of exposure, 3 hours and 40 minutes with a 40-minute break, 2 × 10 minutes on a bicycle ergometer at 100 W	400 ml/m³: **NOAEC** increased activity in the β2 band in the EEG only at the beginning of exposure, not at the end of exposure, effects inconsistent	Laine et al. 1996

LOEC: lowest observed effect concentration; NOAEC: no observed adverse effect concentration; NOEC: no observed effect concentration

Summary: Single exposures to 1,1,1-trichloroethane delayed the reaction times by about 10%; this is a sign of pre-narcotic effects. The reaction times were delayed at concentrations of 175 ml/m³ (Mackay et al. 1987) and 450 ml/m³ (Gamberale and Hultengren 1973).

Repeated exposure

There are no new studies available.

Studies after repeated exposure to 1,1,1-trichloroethane are shown in Table 2 (BUA 1995; Greim 2001; Stewart et al. 1975).

Tab. 2 Studies with repeated exposure to 1,1,1-trichloroethane (BUA 1995; Greim 2001; Stewart et al. 1975)

Participants	Exposure, duration	Effects
10 ♂ volunteers	0, 100, 350, 500 ml/m³, 5 days, 1, 3 or 7.5 hours/day	350 ml/m³: NOAEC 500 ml/m³: changes in the EEG, no other effects (neurological and cognitive tests, lung function tests, blood examinations and urinalysis)
10 ♀ volunteers	0, 350 ml/m³, 5 days, 1, 3 or 7.5 hours/day	350 ml/m³: NOAEC (neurological and cognitive tests, lung function tests, blood examinations and urinalysis)
15 workers	1–46 ml/m³, 8-hour shift	beginning and end of shift: delayed reaction time (morning shift only)
151 workers	100–350 ml/m³, no data	no effects (examination only of the cardiovascular system and liver and kidney functions)
22 female workers	110–990 ml/m³, no data	negative results in behavioural tests, reaction time not determined
196 workers	22–294 mg/m³, about 4–53 ml/m³, 5 years, 8 hours, 5.5 days/week	no effects (test for perception of vibrations, differential blood count, urobilinogen and protein levels)

These studies reported only few effects, even after exposure to relatively high concentrations.

The pre-narcotic effects were investigated only in the study with the lowest exposure levels (1–46 ml/m³). The extension of reaction times was examined at the beginning and end of the shift. In the morning shift, reaction times were significantly delayed compared with those of the control persons both at the beginning and at the end of the shift, but not in the late shift or night shift (Cherry et al. 1983).

Local effects on skin and mucous membranes

Eye irritation was observed in volunteers after exposure to a 1,1,1-trichloroethane concentration of 450 ml/m³ for 30 minutes. Irritation of the throat was found in volunteers after exposure to 2000 ml/m³ and above for 75 minutes (Greim 2001).

A decrease in cell viability, an increased release of IL-1α and marked necrosis were observed in an in vitro test system with reconstituted human skin carried out according to OECD Test Guideline 431 (Tornier et al. 2006).

The substance caused irritation in an in vitro human skin model with keratinocytes (EpiDerm), whereas no irritation was observed in a human skin model with a functional stratum corneum (EPISKIN) (Fentem et al. 2001).

Reproductive and developmental toxicity

There are no new data available.

No conclusions can be drawn about possible toxic effects on reproduction from studies that investigated the relationship between the absorption of 1,1,1-trichloroethane and spontaneous abortions or prenatal developmental toxicity because the studies did not include important data or the persons were exposed to more than one substance (Greim 2001).

Carcinogenicity

Case–control studies and cohort studies that evaluated tumour incidences in workers or in the general population associated with the estimated exposure to 1,1,1-trichloroethane are shown in Table 3 (DECOS 2012).

Tab. 3 Human data for the carcinogenicity of 1,1,1-trichloroethane (DECOS 2012)

Group of persons	Exposure concentration	Exposure duration (years)	Follow-up study	Type of tumour	References
case–control studies					
181 cases 481 control persons	up to 60 000 ml/m³ × year	up to 45	–	multiple myelomas OR: 1.8[a)] (95% CI: 1.1–2.9) OR: 2.2[b)] (95% CI: 1.1–4.4)	Gold et al. 2011
300 cases 300 control persons	low to high exposure combined	2–20	–	astrocytoma OR: 1.8 (95% CI: 1.0–3.3), no concentration–effect relationship	DECOS 2012
5866 cases 252 386 control persons	–	–	–	oesophageal cancer mortality in Afro-Americans, high levels of exposure likely (n = 8) OR: 2.9 (95% CI: 1.2–7.5)	DECOS 2012
438 cases 687 control persons	–	–	–	renal cell cancer (n = 13) OR: 1.26 (95% CI: 0.6–2.8)	Dosemeci et al. 1999
3730 cases 533 control persons	–	–	–	lung cancer in French Canadians (n = 7) OR: 3.5 (95% CI: 1.0–12.0)	DECOS 2012
790 cases 790 control persons	maternal exposure 2 years before pregnancy and during pregnancy, no other details	–	–	acute lymphoblastic leukaemia in offspring OR: 7.55 (95% CI: 0.92–61.97)	Infante-Rivard et al. 2005
14 067 workers United States	–	–	–	oesophageal cancer: no increased risk	DECOS 2012
14 oesophageal cancer cases 56 control persons; 8 stomach cancer cases 32 control persons	–	–	–	oesophageal cancer and stomach cancer: no increased risk	DECOS 2012
cohort studies					
140 male and 131 female workers, Finland	–	0–8	8–17	tumours of the nervous system (n = 3) SIR: 6.1 (95% CI: 1.25–17.7), multiple myelomas (n = 2) SIR: 16 (95% CI: 1.9–57.7)	DECOS 2012
14 457 workers, United States (Hill Air Force Base)	–	> 1	> 1	multiple myelomas mortality (n = 2) SMR: 56.6 (95% CI: 6.9–204.5)	DECOS 2012

[a)] primary analysis
[b)] re-analysis
CI: confidence interval; OR: odds ratio; SIR: standardized incidence ratio; SMR: standardized mortality ratio

Case–control studies

The most recent study examined the relationship between the occurrence of multiple myelomas and exposure to various chlorinated solvents. The exposure to 1,1,1-trichloroethane was determined from occupational histories obtained in personal interviews in 181 cases and the data were compared with the exposure conditions of 481 population controls. Exposure to 1,1,1-trichloroethane was associated with an odds ratio (OR) of 1.8 (95% Cl: 1.1–2.9). Information bias may have occurred in this study. In addition, no trend was determined between the incidence and cumulative exposure (DECOS 2012; Gold et al. 2011).

The risk of developing a renal cell carcinoma after occupational exposure to chlorinated hydrocarbons was examined in a comparison between a group of persons affected in this way (n = 438) and a control group (n = 687). For 9 substances, a job exposure matrix was used to assess whether an increased tumour incidence was attributable to exposure to the individual substances. No significant increase in the risk of renal cell carcinomas was found for exposure to 1,1,1-trichloroethane (DECOS 2012; Dosemeci et al. 1999).

A population-based study examined the association between maternal exposure to solvents and the occurrence of acute lymphoblastic leukaemia in the offspring and yielded an OR of 7.55 (95% CI: 0.92–61.97) for 1,1,1-trichloroethane. The increase was not statistically significant. The study included 790 cases and 790 control persons, and the exposure concentrations at the workplaces of the mothers reported in questionnaires were determined. The exposure levels of the group of persons exposed to 1,1,1-trichloroethane were 7 times higher than the levels determined for the control persons. An exposure period of 2 years preceding conception was taken into account (DECOS 2012; Infante-Rivard et al. 2005).

Definite conclusions about 1,1,1-trichloroethane cannot be drawn from the other case–control studies shown in Table 3. Most of the studies do not provide data for the duration of exposure, the duration of employment, smoking habits or socio-economic status. In some studies, the female workers were exposed to other solvents (DECOS 2012).

Cohort studies

In two cohort studies, the increase in tumours of the nervous system (3 cases) and multiple myelomas (2 cases in each study) was statistically significant. However, no conclusions can be drawn for 1,1,1-trichloroethane because most of the workers were exposed to various solvents (DECOS 2012).

Therefore, the epidemiological studies yielded no evidence of carcinogenicity in humans after exposure to 1,1,1-trichloroethane.

Allergenic effects

There are no data available.

Animal Experiments and in vitro Studies

Acute toxicity

Oral administration

A gavage study found no hepatotoxic effects in Sprague Dawley rats after the administration of single 1,1,1-trichloroethane doses of 0, 500, 1000, 2000 or 4000 mg/kg body weight (Bruckner et al. 2001).

Subacute, subchronic and chronic toxicity

Inhalation

There are no new data available.

In four inhalation studies in rats and mice that were carried out over a period lasting from 90 days to 24 months, no effects of 1,1,1-trichloroethane were observed in the concentration range of 150 to 1750 ml/m^3. In another 2-year study, body weights were significantly reduced in the female rats after exposure to 1500 ml/m^3. Minimal effects on the olfactory epithelium and liver and reduced grip strength were observed only at 2000 ml/m^3 (Greim 2001).

Oral administration

Daily doses of 0, 500, 5000 or 10 000 mg/kg body weight given on 9 days did not lead to an increase in serum liver enzymes or histopathological changes in the liver of rats. Mortality was increased in the two high dose groups. Doses of 0 or 500 mg/kg body weight and day administered on 5 days a week for 13 weeks did not cause any apparent effects on the CNS, changes in body or organ weights, histopathological changes in the liver or changes in clinical or biochemical parameters. After the administration of 2500 or 5000 mg/kg body weight and day (5 days/week) for 10 weeks, many animals died from CNS depression (Bruckner et al. 2001). In this oral 13-week study, the NOAEL (no observed adverse effect level) for rats was 500 mg/kg body weight and day.

In a feeding study carried out in mice for 13 weeks, the NOAEL for mice was 10 000 mg/kg diet (about 3500 mg/kg body weight and day). Body weight gains were reduced at higher doses (Greim 2001).

Allergenic effects

A maximization test with non-stabilized 1,1,1-trichloroethane (purity: 99.99%) in groups of 10 female and 10 male Dunkin Hartley guinea pigs yielded negative results. Intradermal induction was carried out with a 10% formulation in corn oil, and the undiluted substance was used for topical induction. As the undiluted substance caused irritation in range-finding tests, sodium lauryl sulfate was not applied before the topical induction. Challenge treatment with a 50% formulation caused mild erythema in 2 of 20 animals after 24 hours and mild and moderate erythema in 2 animals and 1 animal, respectively, after 48 hours, but no reaction was observed in the 10 control animals in each case. It is not clear from the documentation whether corn oil or acetone was used as the vehicle for the challenge (ECHA 2018).

Reproductive and developmental toxicity

Fertility

A multi-generation study in ICR Swiss mice given drinking water with 1,1,1-trichloroethane concentrations of 0, 580, 1750 or 5800 mg/l (purity: 97%; 0, 100, 300 or 1000 mg/kg body weight and day) yielded no effects on fertility, gestation, survival of the pups or the lactation index (see Table 4; BUA 1995; Lane et al. 1982). However, the actual doses may have been lower because of the volatility of 1,1,1-trichloroethane (see Greim 2001).

A 1,1,1-trichloroethane dose of 80 000 mg/kg administered in microcapsules in the diet for 13 weeks reduced the epididymal sperm counts in mice and rats with concurrent general toxicity (NTP 2000).

Developmental toxicity

The studies with prenatal, perinatal and postnatal exposure to 1,1,1-trichloroethane are shown in Table 4.

Prenatal developmental toxicity

The inhalation of a 1,1,1-trichloroethane concentration of 875 ml/m^3 from days 6 to 15 of gestation for 7 hours a day did not induce any toxic effects on development or maternal toxicity in Sprague Dawley rats (Schwetz et al. 1975).

In Long Evans rats exposed by inhalation to a 1,1,1-trichloroethane concentration of 2100 ml/m^3 from days 6 to 20 of gestation or 2 weeks before mating up to day 20 of gestation for 6 hours a day, on 7 days a week, the body weights of the offspring were reduced by less than 5% and ossification was delayed only in the group exposed before mating up to day 20 of gestation (York et al. 1982). Therefore, a NOAEC for developmental and maternal toxicity of 2100 ml/m^3 was obtained in rats for treatment during gestation.

An inhalation study in which Sprague Dawley rats were exposed to 1,1,1-trichloroethane concentrations of 0, 1000, 3000 or 6000 ml/m^3 from day 6 of gestation to postnatal day 10 reported reduced body weights and an increased number of skeletal variations and non-ossified cervical centrum 6 in the offspring of the animals exposed to 6000 ml/m^3.

Maternal toxicity was observed at concentrations of 1000 ml/m^3 and above in the form of reduced body weights, feed consumption was reduced at 3000 ml/m^3 and above, and water consumption and hyperactivity increased in the dams at 6000 ml/m^3 and above (Halogenated Solvents Industry Alliance 1987 a).

In a study with Sprague Dawley rats given 1,1,1-trichloroethane concentrations of 0, 3, 10 or 30 mg/l in the drinking water, no developmental or maternally toxic effects were observed up to a concentration of 30 mg/l drinking water. A thorough examination of the heart was performed. No abnormalities of the ductus arteriosus or of the atria were found (NTP 1987 a; US EPA 2007). The concentrations of 2.7, 8.5 or 27.1 mg/l drinking water determined by the NTP (NTP 1987 a) were higher on average than the exposure concentrations found to induce effects on the heart in the study of Dapson et al. (1984) (see Section "Perinatal and postnatal developmental toxicity and neurobehavioural toxicity").

An inhalation study in which New Zealand White rabbits were exposed to 1,1,1-trichloroethane concentrations of 0, 1000, 3000 or 6000 ml/m^3 from days 6 to 18 of gestation reported a reduced number of implantations per litter and an increased incidence of skeletal variations (13th ribs) in the offspring of the animals exposed to 6000 ml/m^3. The NOAEC for prenatal developmental toxicity in rabbits was 3000 ml/m^3. Maternal toxicity was observed in the form of reduced body weights at 3000 ml/m^3 and above (Halogenated Solvents Industry Alliance 1987 b).

The inhalation of a 1,1,1-trichloroethane concentration of 875 ml/m^3 from days 6 to 15 of gestation for 7 hours a day did not induce any developmental or maternally toxic effects in Swiss Webster mice (Schwetz et al. 1975).

Perinatal and postnatal developmental toxicity and neurobehavioural toxicity

After exposure of rats to 2100 ml/m^3 by inhalation, no effects on postnatal development were observed in neurobehavioural toxicity tests (running wheel, open field and amphetamine challenge) and there were no gross changes (see Section "Prenatal developmental toxicity"; York et al. 1982).

Initial effects of developmental toxicity and neurobehavioural toxicity were found in rats after inhalation of 7000 ml/m^3 in the form of decreases in survival and in litter, body and brain weights and in the form of deficits in co-ordination, muscular strength, and locomotor activity of the offspring. The postnatal developmental landmarks (righting response, incisor eruption, pinnae detachment and eye opening) were not affected. At the same time, signs of neurotoxicity and reduced body weights were observed in the dams (Coleman et al. 1999).

Up to the highest dose tested of 750 mg/kg body weight and day in F344 rats, no effects were observed on postnatal developmental landmarks, the functional observational battery, learning and behaviour, brain weights and size, or neuropathology (postnatal days 28 and 68) (no other details; SCOEL 1995).

In an abstract, Dapson et al. (1984) reported effects on the heart of rats (persistent ductus arteriosus and right or left atrial hyperplasia or displacement) after doses of 10 mg/l in the drinking water. These effects were investigated in a study of the NTP using doses of 0, 3, 10 or 30 mg/l (George et al. 1989; NTP 1987 b). However, it was not possible to analyse the concentrations in the blood because the doses used led to concentrations below the limit of detection of 0.05 µg/ml (incorrect concentration of 0.2 µg/ml reported by Dapson et al. (1984), corrected by Dapson to 0.03 µg/ml in NTP (1987 b)). The NTP study did not report increases in malformations of the heart at the dose levels tested (up to 30 mg/l in the drinking water) with the exception of a few cases of persistent ductus arteriosus (3 in 2 litters; see Table 4). The NTP noted that functional closure of the ductus arteriosus in rats occurs in the first 1 to 3 hours after birth and that this constriction is reversible. At this time, the ductus is probably closed by prostaglandins or an increase in the oxygen pressure in the blood vessels and is not a sign of abnormal development. The second closure is complete by postnatal day 5 (George et al. 1989; NTP 1987 b, p. 53). Although the average concentrations of 2.5, 6.5 or 18.6 mg/l drinking water in the NTP study were higher than used in the study by Dapson et al. (1984), there was no evidence of abnormalities of the ductus arteriosus or the atria (US EPA 2007).

After exposure of CD mice by inhalation to 2000 ml/m^3 for 17 hours a day or to 8000 ml/m^3 for 3 hours a day from days 12 to 17 of gestation and subsequent cross-rearing, no unusual findings in developmental landmarks (postnatal day 14: reflexes, grip strength, co-ordination and geotaxis) were observed in the offspring of the treated mice. Decreases in body weights and feed consumption and signs of neurotoxicity were found in the dams (Jones et al. 1996).

A multi-generation study that included an examination of developmental toxicity reported no developmental or maternally toxic effects in Swiss Webster mice given doses of 1000 mg/kg body weight and day in the drinking water (Lane et al. 1982).

Tab. 4 Studies that investigated developmental toxicity and neurobehavioural toxicity after exposure to 1,1,1-trichloroethane

Species, number per group	Exposure	Findings	References
prenatal			
rat			
Sprague Dawley, 20–35 ♀	**GD 6–15,** 0, 875 ml/m³, inhalation, 7 hours/day, purity: 94.5%, 5.5% inhibitors and impurities, examination: GD 20	**875 ml/m³: NOAEC developmental and maternal toxicity,** dams: (slight) decrease in absolute liver weights, but not in relative liver weights	Schwetz et al. 1975
Long Evans, 13 ♀	**GD 6–20,** 0, 2100 ml/m³, inhalation, 6 hours/day, 7 days/week, purity: 95%, 5% inhibitors and impurities, half of the dams: examination on GD 20, (the other half: rearing of the pups, postnatal examination of behaviour, see below)	**2100 ml/m³: NOAEC developmental and maternal toxicity,** foetuses: body weights ↓ (< 5%)	York et al. 1982
Long Evans, 20 ♀	**2 weeks before mating up to GD 20,** 0, 2100 ml/m³, inhalation, 6 hours/day, 7 days/week, purity: 95%, 5% inhibitors and impurities, half of the dams: examination on GD 20, (the other half: rearing of the pups, postnatal examination of behaviour, see below)	**2100 ml/m³: NOAEC maternal toxicity,** foetuses: body weights ↓ (< 5%), skeletal and soft tissue variations, interpreted as signs of delayed ossification/development	York et al. 1982
Sprague Dawley, 24 ♀	**GD 6–PND 10,** 0, 1000, 3000, 6000 ml/m³, inhalation, 6 hours/day, 7 days/week, purity: 99.9%, examination: GD 21	**1000 ml/m³:** dams: body weight gains ↓ (GD 18 and 21, 0–21); **3000 ml/m³: NOAEC developmental toxicity,** dams: body weight gains ↓ (GD 6–9, 0–21), feed consumption ↓; **6000 ml/m³:** dams: body weight gains ↓ (GD 6–9, 15–18, 15–21, 18 and 21, 0–21), water consumption ↑, hyperactivity, foetuses: body weights ↓ (by 6% in ♀, by 4% in ♂ and overall); skeletal variations ↑ (on a litter basis; non-ossified cervical centrum 6)	Halogenated Solvents Industry Alliance 1987 a
Sprague Dawley, 20 ♀	**2 weeks before mating up to GD 20,** 0, 3, 10, 30 mg/l in the drinking water with 0.05% Tween 80 (♀: 0, 0.3, 0.9, 2.4 mg/kg body weight and day), purity: 99% examination: GD 20	**2.4 mg/kg body weight: NOAEL developmental and maternal toxicity,** especially no effects on the heart	NTP 1987 a
rabbit			
New Zealand White, 20–24 ♀	**GD 6–18,** 0, 1000, 3000, 6000 ml/m³, inhalation, 6 hours/day, 7 days/week, purity: 99.9%, examination: GD 29	**1000 ml/m³: NOAEC maternal toxicity; 3000 ml/m³: NOAEC developmental toxicity,** dams: body weight gains ↓; **6000 ml/m³:** dams: body weight gains ↓, foetuses: number of implantations/litter ↓, skeletal variations ↑ (on a litter basis; 13th rib)	Halogenated Solvents Industry Alliance 1987 b

Tab. 4 *(continued)*

Species, number per group	Exposure	Findings	References
mouse			
Swiss Webster, 30–40 ♀	**GD 6–15,** 0, 875 ml/m³, inhalation, 7 hours/day, purity: 94.5%, 5.5% inhibitors and impurities, examination: GD 20	**875 ml/m³: NOAEC developmental and maternal toxicity**	Schwetz et al. 1975
perinatal and postnatal			
rat			
Long Evans, 13 ♀	**GD 6–20,** 0, 2100 ml/m³, inhalation, 6 hours/day, 7 days/week, purity: 95%, 5% inhibitors and impurities, (half of the dams: examination on GD 20, see above), the other half: rearing of the pups (8 pups/litter), postnatal examination of behaviour (2 pups/sex and litter, 21 days, 40–110 days), gross changes examined at 12 months of age	**2100 ml/m³: NOAEC postnatal developmental toxicity, neurobehavioural toxicity and maternal toxicity,** no effects on body weights on PND 4 and thereafter, survival, neurobehavioural toxicity (running wheel, open field and amphetamine challenge), gross changes	York et al. 1982
Long Evans, 20 ♀	**2 weeks before mating up to GD 20,** 0, 2100 ml/m³, inhalation, 6 hours/day, 7 days/week, purity: technical product, (half of the dams: examination on GD 20, see above), the other half: rearing of the pups (8 pups/litter), postnatal examination of behaviour (2 pups/sex and litter, 21 days, 40–110 days), gross changes examined at 12 months of age	**2100 ml/m³: NOAEC postnatal developmental toxicity, neurobehavioural toxicity and maternal toxicity,** no effects on body weights on PND 4 and thereafter, survival, neurobehavioural toxicity (running wheel, open field and amphetamine challenge), gross changes	York et al. 1982
Sprague Dawley, 9–10 ♀ controls: 19 ♀	**GD 13–19,** 0, 7000 ml/m³, inhalation, 3 × 1 hour/day, purity: 99%, examination: PND 1–21 postnatal developmental landmarks, neurotoxicity/neurobehavioural toxicity	**7000 ml/m³: LOAEC,** dams: body weights ↓ (during exposure), salivation, lacrimation and unsteady gait, signs of neurotoxic effects on the hind limbs, ataxia, tremor, 2 total resorptions; prolonged gestation, offspring: resorptions/litter ↑, mortality ↑, number of live foetuses/litter ↓, litter weights ↓, body weights ↓ (PND 2–14); decrease in brain weights (absolute by 31% and relative by 25%) together with reduced body weights (by 13%), cerebellum weights reduced by 25%, deficits in co-ordination (negative geotaxis and inverted screen tests), reduced muscular strength, reduced spontaneous locomotor activity, no effects on postnatal developmental landmarks (PND 14–21: righting reflex, incisor eruption, pinnae detachment and eye opening)	Coleman et al. 1999
F344	**GD 6–PND 10,** 0, 75, 250, 750 mg/kg body weight and day, gavage	**750 mg/kg body weight: NOAEL developmental toxicity, neurobehavioural toxicity and maternal toxicity,** no effects on postnatal developmental landmarks, functional observational battery, learning and behaviour, brain weights and size, or neuropathology (PND 28 and 68)	SCOEL 1995; no other details

Tab. 4 *(continued)*

Species, number per group	Exposure	Findings	References
Sprague Dawley, 3 ♂, 9 ♀	**2 weeks before mating up to PND 21,** 0, 10 mg/l drinking water with 0.05% Tween 80 (allometric conversion of water and feed consumption: 1.4 mg/kg body weight and day; US EPA 2007), purity: 97%, 3% 1,4-dioxane	**1.4 mg/kg body weight:** parental animals: mean duration up to gestation ↑ (20.4 days (7–27 days) compared with 14.7 days (8–30 days) in the controls), but not of biological relevance according to the US EPA, offspring: 9% increase in mean absolute heart weights (not statistically significant), incidence of heart anomalies on a foetal basis ↑ (62% compared with 4% in the controls, only persistent ductus arteriosus: 29% compared with 0% in the controls, examined on PND 21–23), not evaluated on a litter basis	Dapson et al. 1984; no other details (abstract)
Sprague Dawley, > 30 ♀, > 30 ♂	**2 weeks before mating up to PND 21,** 0, 3, 10, 30 mg/l drinking water with 0.05% Tween 80 (♂: 0, 0.3, 0.9, 2.6 mg/kg body weight and day; ♀: 0, 0.3, 1.0, 3.0 mg/kg body weight and day (before mating up to gestation; 0, 0.3, 1.2, 3.5 mg/kg body weight and day (gestation); 0, 0.6, 2.0, 5.9 mg/kg body weight and day (lactation)), purity: 97%, 3% 1,4-dioxane, examination: PND 21, study to replicate the results of Dapson et al. (1984)	**0.3 mg/kg body weight:** offspring: PND 1: of the animals that died: ductus arteriosus: 6 from 4 litters compared with 0 in the controls; **0.9 mg/kg body weight:** offspring: persistent ductus arteriosus: 1 from 1 litter; **2.6 mg/kg body weight: NOAEL developmental toxicity including heart,** offspring: mortality increased (due to 1 litter), persistent ductus arteriosus: 3 from 2 litters, no effects on the heart or other malformations observed on GD 20 (see above NTP 1987 a) or PND 21 (unlike Dapson et al. (1984))	George et al. 1989; NTP 1987 b
mouse			
CD-1, 10 ♀	**GD 12–17,** 0, 2000 ml/m³, inhalation 17 hours/day, cross-rearing, purity: 99%, examination of the offspring: PND 1–14; and spontaneous locomotor activity, only ♂: PND 23–25	**2000 ml/m³:** dams: body weight gains and feed consumption ↓, unsteady gait, signs of neurotoxic effects on the hind limbs, offspring: no unusual findings in development (PND 14: reflexes, grip strength, co-ordination, geotaxis)	Jones et al. 1996
CD-1, 10 ♀	**GD 12–17,** 0, 8000 ml/m³, inhalation, 3 × 1 hour/day, cross-rearing, purity: 99%, examination of the offspring: PND 1–14; and spontaneous locomotor activity, only ♂: PND 23–25	**8000 ml/m³: NOAEC postnatal developmental toxicity,** dams: unsteady gait, signs of neurotoxic effects on the hind limbs, ataxia, tremor, offspring: no unusual findings for development (PND 21: reflexes, grip strength, co-ordination, geotaxis, PND 85: learning and memory)	Jones et al. 1996
ICR Swiss, no other details	**multi-generation study, 5 weeks before mating up to PND 21,** 0, 100, 300, 1000 mg/kg body weight and day, drinking water, purity: 97%, 3% 1,4-dioxane; controls: a) distilled water, b) 0.17 mg 1,4-dioxane/ml in 1% Emulphor in distilled water, examination for teratogenicity: skeletons of 2/3 of the foetuses examined; additionally dominant lethal test	**1000 mg/kg body weight: NOAEL developmental toxicity and maternal toxicity**	Lane et al. 1982

GD: gestation day; LOAEC: lowest observed adverse effect concentration; NOAEC/L: no observed adverse effect concentration/level; PND: postnatal day

Genotoxicity

In vitro

Negative results were obtained in several bacterial mutagenicity tests with the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and with Escherichia coli. However, weakly positive results were observed in enclosed systems with TA1535, TA100, TA104, TA98 and TA97 (DECOS 2012; Falck et al. 1985; Strubel and Grummt 1987). Evidence was found that the positive results obtained with technical products were due to their genotoxic stabilizers (BUA 1995). Studies of the mutagenicity in yeasts reported negative results. With one exception, DNA repair tests in prokaryotes and yeasts and tests for chromosome damage in yeasts yielded negative results both with and without the addition of metabolic activation (DECOS 2012; Norpoth et al. 1980). Negative results were obtained in a test for induction of the SOS response in Escherichia coli (SOS chromotest). An increase in DNA repair was observed in a test with primary mouse hepatocytes (UDS test), but not in 4 tests with rat hepatocytes or in a test with HeLa cells (Greim 2001; Legault et al. 1994).

A UDS test with primary rat hepatocytes yielded negative results without metabolic activation (DECOS 2012; Galloway et al. 1987).

A very low level of binding to DNA, RNA and proteins was observed with metabolic activation (Turina et al. 1986).

Negative results were obtained in two SCE tests in CHO cells and in a test in human lymphocytes. Another SCE test yielded a questionably positive result after metabolic activation (Galloway et al. 1987; Greim 2001).

Positive results were obtained in a chromosomal aberration test with CHO cells without metabolic activation, but not with metabolic activation (DECOS 2012; Galloway et al. 1987).

Exposure to 0.5 mM 1,1,1-trichloroethane and above induced micronuclei in the MCL-5 and h2E1 cell lines stably expressing cytochrome P450 and in the AHH-1 cell line natively expressing cytochrome P450. A cytotoxic concentration was reached at 2.5 mM 1,1,1-trichloroethane (Doherty et al. 1996).

Negative results were obtained in two $TK^{+/-}$ mutation tests with mouse lymphoma cells, and a questionably positive result was obtained in another test, all of which were carried out with the addition of metabolic activation (Greim 2001).

In vivo

No mutagenic effects were found in a Drosophila test for X-chromosomal recessive lethal mutations (SLRL test) (Greim 2001).

When male rats and mice were given intraperitoneal doses of 1,1,1-trichloroethane, weak binding to DNA, RNA and proteins was found in the lungs, liver, stomach and kidneys after metabolic activation. Binding to DNA and RNA in vivo was low compared with that of 1,1-dichloroethane and 1,1,2-trichloroethane (Turina et al. 1986).

There was no evidence of chromosomal aberrations in the bone marrow when rats were exposed to 1,1,1-trichloroethane concentrations of 0, 875 or 1750 ml/m^3 for 52 weeks (6 hours a day, 5 days a week). No clastogenic or aneugenic effects were observed in four micronucleus tests in polychromatic erythrocytes with doses up to 2000 mg/kg body weight (DECOS 2012; Gocke et al. 1981; Greim 2001). A micronucleus test was carried out in the peripheral blood cells of mice following a 13-week feeding study. A dose-dependent increase in the frequency of micronuclei in normochromatic erythrocytes to twice the control value was found for male animals. The results were negative in the female animals. The authors considered the results in male mice to be equivocal in spite of a positive trend test because the increase in the values in the individual dose groups was not statistically significant compared with the levels determined in the control group (Greim 2001; NTP 2000).

A dominant lethal test in mice with doses up to 1000 mg/kg body weight in the drinking water did not yield dose-dependent findings. Sperm head anomalies were not observed in mice given intraperitoneal injections of up to 2680 mg/

kg body weight (Greim 2001). However, changes in sperm morphology are not reliable indicators of mutations, and the relevance of the effects for germ cell mutagenicity is questionable (ICPEMC 1983; Salamone 1988; Wild 1984).

Summary

In vitro, most of the studies yielded negative results, with only a few isolated positive findings. Although this suggests clastogenic effects, these were not confirmed by the data obtained in vivo in chromosomal aberration, micronucleus or dominant lethal tests. 1,1,1-Trichloroethane continues to be classified as a non-genotoxic substance.

Carcinogenicity

Short-term studies

In vitro

In three cell transformation tests without metabolic activation, the increase in the frequency of transformations observed in BALB/c 3T3 embryo cells at 1,1,1-trichloroethane concentrations of 20 µg/ml and above and in Fischer rat embryo cells at 1,1,1-trichloroethane concentrations (purity: 99.9%) of 13.4 µg/ml and above was statistically significant (DECOS 2012; Price et al. 1978; Tu et al. 1985). As a technical product was used for the transformation tests with BALB/c 3T3 embryo cells (purity: 97–99%, no other details), the stabilizing additives butylene oxide and diethylene dioxide were probably partially responsible for the effects (ATSDR 2006; Tu et al. 1985). Only a slight increase was observed in SA7/Syrian hamster embryo cells (2.5-fold at the most) (Hatch et al. 1983).

Transformation tests with kidney cells of newborn hamsters reported a single positive result (6050 µg/ml, in the range of the LC_{50}), which the authors attributed to cytotoxic effects. Another research group obtained a negative result with the same test system at 100 µg/ml. In this study, the LC_{50} was also 100 µg/ml (BUA 1995; Greim 2001).

In vivo

An initiation study with single 1,1,1-trichloroethane doses of 9.9 mmol/kg body weight (MTD) given to male Osborne Mendel rats 24 hours after partial hepatectomy and subsequent administration of phenobarbital in the diet for 7 weeks at a concentration of 0.05% (w/w) yielded no increase in the incidences of γ-glutamyl transpeptidase-positive (GGT^+) liver foci (BUA 1995; Milman et al. 1988; Story et al. 1986).

In a promotion study with partial hepatectomy in male Osborne Mendel rats (10 animals per group) given gavage doses of 1,1,1-trichloroethane of 7.4 mmol/kg body weight (3/4 of the MTD) on 5 days a week for 7 weeks, no increase in the number of GGT^+ foci in the liver ($p < 0.05$) was observed either after initiation with a single intraperitoneal dose of diethylnitrosamine of 30 mg/kg body weight or without the addition of the initiator (BUA 1995; Milman et al. 1988; Story et al. 1986).

Therefore, the initiation-promotion study yielded no evidence of a carcinogenic potential.

Long-term studies

In an inhalation toxicity and carcinogenicity study in rats and mice, no increased tumour incidences were observed up to a concentration of 1500 ml/m^3. A technical product of 1,1,1-trichloroethane was used that contained 5% stabilizers (for example, butylene oxide, nitromethane and nitroethane). However, the MTD was not reached in mice or male rats (Greim 2001; Quast et al. 1988).

A study with oral doses of 0, 750 or 1500 mg/kg body weight in rats and doses of 0, 2000 or 4000 mg/kg body weight in mice is not regarded as valid because of the increased incidence of mortality of more than 50%. The tumour incidences observed were in the range of those of the control animals (Greim 2001; NCI 1977). In another carcinogenicity

study with oral doses of 500 mg/kg body weight and day in SD rats, the malignant tumours that occurred (leukaemia, lymphoblastic lymphosarcomas and immunoblastic lymphosarcomas in the lungs) could not be attributed solely to 1,1,1-trichloroethane because a technical product containing 0.47% butylene oxide for stabilization in addition to other constituents was used (Greim 2001; Maltoni et al. 1986).

Manifesto (MAK value/classification)

The critical effects of 1,1,1-trichloroethane are the pre-narcotic effects that were observed in humans.

MAK value. In the 2001 supplement (Greim 2001) a NOAEC of 200 ml/m^3 for pre-narcotic effects in humans was derived.

In the study of Mackay et al. (1987), in which volunteers were exposed for 3.5 hours at rest, the concentrations of 1,1,1-trichloroethane in the blood showed that the steady state was almost achieved after exposure for 2 to 3 hours. Therefore, an increase in effects is not expected after exposure for 8 hours. During physical exercise at 100 W (bicycle ergometer), the lung clearance of 1,1,1-trichloroethane was 2.3 times as high and the respiratory volume was about 3 times as high as the levels determined during exposure at rest (Monster et al. 1979). At a load of 50 W, which corresponds to the assumed respiratory volume at the workplace of 10 m^3 over a period of 8 hours (20 l/min), a 1.5-fold increase in absorption can be derived. As the previous MAK value was derived from volunteer studies at rest, the MAK value has been lowered to 100 ml/m^3 to take the increased respiratory volume at the workplace into account.

Peak limitation. As systemic effects are the critical effects, 1,1,1-trichloroethane remains classified in Peak Limitation Category II.

The excursion factor of 1 has been retained because of the short half-life in the blood of 44 minutes in the initial phase. Furthermore, as 1,1,1-trichloroethane passes easily into the brain, the marked concentration peaks in the blood typical of substances with short half-lives are likewise mirrored in the brain.

In the study of Laine et al. (1996), the concentration of 1,1,1-trichloroethane in the blood after 15 minutes was almost twice as high after 10-minute exposure to peaks of 400 ml/m^3 than after continuous exposure to 200 ml/m^3 without exposure peaks.

On the basis of a MAK value of 100 ml/m^3 and an excursion factor of 2, the peak concentration would correspond to the concentration in the blood of volunteers exposed to 300 ml/m^3 at rest (MAK value: 100 ml/m^3 × 2 for the excursion factor × 1.5 for the increased respiratory volume at the workplace while performing work at a load of 50 W). However, two studies revealed effects at a concentration of 350 ml/m^3 in the form of delayed choice reaction times (Mackay et al. 1987) and reduced perceptual speed, respectively (Gamberale and Hultengren 1973).

Prenatal toxicity. No conclusions can be drawn about possible toxic effects on reproduction from studies that investigated the relationship between the absorption of 1,1,1-trichloroethane and spontaneous abortions or prenatal developmental toxicity in humans because the studies did not include important data or the persons were exposed to more than one substance.

Studies investigated developmental and neurobehavioural toxicity in animals after inhalation and administration in the drinking water.

The NOAECs or NOAELs relevant to the evaluation, their toxicokinetic extrapolation or consideration of the increased respiratory volume at the workplace and the resulting margins to the MAK value of 100 ml/m^3 are shown in Table 5.

Tab. 5 NOAECs/NOAELs in rats and mice relevant to the evaluation, toxicokinetic extrapolation of the NOAELs to concentrations in air and resulting margins to the MAK value of 100 ml/m³

Species, exposure	NOAEC/NOAEL: end point	Toxicokinetic extrapolation[a] (in ml/m³)	Margin to the MAK value of 100 ml/m³	References
rat				
prenatal, inhalation	3000 ml/m³: developmental toxicity LOAEC: 6000 ml/m³	1500[b]	**15**	Halogenated Solvents Industry Alliance 1987 a
prenatal, inhalation	2100 ml/m³: postnatal developmental toxicity and neurobehavioural toxicity	1050[b]	**11**	York et al. 1982
prenatal, inhalation	7000 ml/m³: postnatal developmental toxicity LOAEC: 7000 ml/m³ for neurobehavioural toxicity	3500[b]	**35**	Coleman et al. 1999
prenatal and postnatal, drinking water	750 mg/kg body weight and day: postnatal developmental toxicity and neurobehavioural toxicity (highest dose tested)	1313[a]	**13**	SCOEL 1995
rabbit				
prenatal, inhalation	3000 ml/m³: developmental toxicity LOAEC: 6000 ml/m³	1500[b]	**15**	Halogenated Solvents Industry Alliance 1987 b
mouse				
prenatal, inhalation	875 ml/m³: developmental toxicity (only concentration tested)	438[b]	**4**	Schwetz et al. 1975
prenatal, inhalation	2000 ml/m³: postnatal developmental toxicity and neurobehavioural toxicity	1000[b]	**10**	Jones et al. 1996
generation study, prenatal and postnatal, drinking water	1000 mg/kg body weight and day: prenatal, perinatal and postnatal developmental toxicity (highest dose tested)	1400[a,c]	**14**	Lane et al. 1982

[a] toxicokinetic extrapolation from oral exposure to inhalation: (1:4; 1:7) × 1.0 (oral absorption in animals)/1.0 (absorption by inhalation in humans)
[b] taking into account the increased respiratory volume (1:2) at the workplace
[c] additional extrapolation of 7-day treatment in animals to 5-day exposure at the workplace

The margins between the MAK value and the NOAECs for prenatal, perinatal and postnatal developmental toxicity and neurobehavioural toxicity are sufficiently high, and 1,1,1-trichloroethane remains classified in Pregnancy Risk Group C.

Carcinogenicity. On the basis of the data published since the last documentation, the classification of 1,1,1-trichloroethane in one of the categories for carcinogens is not required.

Germ cell mutagenicity. The new data for genotoxicity in vitro or in vivo do not suggest a potential for germ cell mutagenicity. Therefore, 1,1,1-trichloroethane is not classified in any of the germ cell mutagen categories.

Absorption through the skin. Since 2001, 1,1,1-trichloroethane has been designated with an "H" on the basis of human data that demonstrate that liquid 1,1,1-trichloroethane is absorbed through the skin in toxicologically relevant amounts (Greim 2001). Therefore, the designation with "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) has been retained.

Sensitization. There are no findings in humans available for the sensitizing effects of 1,1,1-trichloroethane on the skin, but a maximization test in guinea pigs yielded negative results. There are no findings available for sensitizing effects on the respiratory tract. 1,1,1-Trichloroethane continues not to be designated with either "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 (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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