The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

1,1-Dichloroethane

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

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

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

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

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

Keywords

1,1-dichloroethane; kidney; irritation; maximum workplace concentration; MAK value; toxicity; hazardous substance; carcinogenicity; developmental toxicity

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated 1,1-dichloroethane [75-34-3] considering all toxicological end points. The critical effect is kidney toxicity. Inhalation of 1000 ml/m^3 led to histopathologic injury to the kidneys, increased serum urea and creatinine after 3-month exposure of cats. A NOAEL of 500 mg/kg body weight and day for changes in the urinary excretion of acid phosphatase and N-acetylglucosaminidase was found in rats after 13-week oral exposure. Based on the NOAEC of 500 ml/m^3, the maximum concentration at the workplace (MAK value) has now been lowered to 50 ml/m^3 taking into account the increased respiratory volume at the workplace because the blood:air partition coefficient of 1,1-dichloroethane is > 5 (see List of MAK and BAT Values, Sections I b and I c). The same MAK value is obtained based on the oral NOAEL of 500 mg/kg body weight and day. As a systemic effect is critical, Peak Limitation Category II and the default excursion factor of 2 are retained. The margins between the MAK value and the NOAECs for developmental toxicity in rats 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-dichloroethane remains assigned to Pregnancy Risk Group C. 1,1-Dichloroethane is genotoxic in vitro but the findings are not quite consistent. A carcinogenicity study was performed, which is of limited validity because of high mortality. In female rats, a few haemangiosarcomas and mammary gland adenomas developed which are identical to the tumour types induced by 1,2-dichloroethane. Therefore, 1,1-dichloroethane is classified in Carcinogen Category 3B for suspected carcinogens. The substance is not regarded as a germ cell mutagen. Skin contact is suspected to contribute to systemic toxicity and the substance is designated with "H". Studies of the sensitization potential are not available.

Citation Note:
Hartwig A, MAK Commission. 1,1-Dichloroethane. MAK Value Documentation, supplement – Translation of the German version from 2020. MAK Collect Occup Health Saf. 2022 Mar;7(1):Doc007. https://doi.org/10.34865/mb7534e7_1ad

Manuscript completed:
12 Apr 2019

Publication date:
31 Mar 2022

MAK value (2019)	**50 ml/m³ (ppm) ≙ 210 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 2**
Absorption through the skin (2019)	**H**
Sensitization	**–**
Carcinogenicity (2019)	**Category 3 B**
Prenatal toxicity (2007)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	ethylidene chloride ethylidene dichloride
Chemical name	1,1-dichloroethane
CAS number	75-34-3
Density at 20 °C	1.175 g/cm³ (NCBI 2020)
Vapour pressure	243 hPa at 20 °C (IFA 2019) 302.6 hPa at 25 °C (NCBI 2020)
log K_{OW}	1.79 (NCBI 2020)
Solubility	5.06 g/l water (IFA 2019)
1 ml/m³ (ppm) ≙ 4.107 mg/m³	**1 mg/m³ ≙ 0.244 ml/m³ (ppm)**

For 1,1-dichloroethane, there is documentation from 1972 (Henschler 1972, available in German only), a supplement from 2001 for peak limitation (Greim 2001, available in German only), and a supplement from 2007 for prenatal toxicity (Greim 2007, 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 and vapour with a blood:air partition coefficient of < 5 (see List of MAK and BAT Values, Sections I b and I c). The mean blood:air partition coefficient of 1,1-dichloroethane is 5.17 according to the measurements by Meulenberg and Vijverberg (2000). This supplement evaluates whether the MAK value and the pregnancy risk group for 1,1-dichloroethane need to be re-assessed as a result of the higher respiratory volume at the workplace.

1,1-Dichloroethane is a colourless, oily liquid. The substance is used as a chemical intermediate in the production of vinyl chloride and 1,1,1-trichloroethane, as well as in the production of high-vacuum rubber and silicone oils; however, its use as a solvent is limited. Today, 1,1-dichloroethane is no longer used as an anaesthetic (NCBI 2020).

1 Toxic Effects and Mode of Action

High 1,1-dichloroethane concentrations have a narcotic effect in humans and animals.

1,1-Dichloroethane was toxic to the kidneys in cats after inhalation exposure to 1000 ml/m^3 for 3 months. In rats given an oral dose of 1,1-dichloroethane of 1000 mg/kg body weight for 13 weeks, changes in the urinary excretion of acid phosphatase and *N*-acetylglucosaminidase were observed.

1,1-Dichloroethane is moderately irritating to the skin and eyes of rabbits.

In a developmental toxicity study, an increase in delayed ossification of the sternebrae occurred in foetuses after exposure to 6000 ml/m^3.

Data for the genotoxicity of the substance are inconsistent. No mutagenicity or clastogenicity was demonstrated in a well-documented Salmonella mutagenicity test and in two tests with CHO cells (a cell line derived from Chinese hamster ovary) and lung fibroblasts for chromosomal aberrations. 1,1-Dichloroethane caused DNA repair in rat and mouse hepatocytes and sister chromatid exchanges in CHO cells.

In a carcinogenicity study with high mortality, haemangiosarcomas and mammary tumours were observed in female rats.

There are no data available for mutagenicity in germ cells and sensitizing effects of the substance.

2 Mechanism of Action

The occurrence of cardiac arrhythmias after the administration of 1,1-dichloroethane for anaesthetic purposes can be attributed to the enhanced effect of catecholamines when cardiac muscle activity is markedly reduced. This effect has been observed with other chloroalkanes at high concentrations and is thought to be responsible for mortality without further pathological abnormalities (Reinhardt et al. 1971).

The covalent binding index (CBI) for the binding of 1,1-dichloroethane to DNA from liver cells is 79 in rats and 65 in mice, indicating the substance to be a moderately weak initiator (Colacci et al. 1985). However, this study was unable to prove whether the formation of DNA adducts actually occurs.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

A male volunteer inhaled 5 mg ^{38}Cl-1,1-dichloroethane (in about 1.5 l air). After a 20-second period in which he held his breath, the radioactivity in the exhaled air was determined during the subsequent hour; 22% of the radioactivity was exhaled during this time (Morgan et al. 1970). As the steady state is not reached in the body during such a short period of exposure, the amount absorbed by inhalation cannot be calculated from this study.

1,1-Dichloroethane (purity 97%) was administered by gavage to male Osborne Mendel rats and B6C3F1 mice in corn oil at dose levels of 700 and 1800 mg/kg body weight and day, respectively, for 4 weeks. After a subsequent single ^{14}C-labelled dose of 1,1-dichloroethane, the substance was almost completely absorbed orally and exhaled predominantly either unchanged or in the form of CO_2. Overall, 2.3% of the administered dose was found in the excreta and the rest of the body in rats and 4% in mice. In the protein fraction of the liver homogenate, a higher level of radioactivity was found in mice than in rats (Mitoma et al. 1985).

For a saturated aqueous solution, calculations using the models of Fiserova-Bergerova et al. (1990) and IH SkinPerm (Tibaldi et al. 2014) yielded fluxes of 655 and 56 µg/cm^2 and hour, respectively. Assuming the exposure of 2000 cm^2 of skin (area of hands and forearms) for 1 hour, this would correspond to absorbed amounts of 1310 and 112 mg, respectively.

3.2 Metabolism

Rats and mice metabolized only a small part of an orally administered dose, the major fraction (86% in rats, 70% in mice) was exhaled in unchanged form. The main metabolite in rats and mice was CO_2 (5% and 25%, respectively). Possibly present metabolites in the excreta were not characterized (Mitoma et al. 1985).

In liver microsomes of Long Evans rats treated with and without phenobarbital, binding of 1,1-dichloroethane to cytochrome P450 (CYP) and increased NADPH oxidation were found. After 20-minute incubation of 1,1-dichloroethane with liver microsomes from rats treated with phenobarbital, an NADPH-generating system and ethylene diamine tetraacetate, acetic acid was identified as the main metabolite. In significantly smaller amounts (a maximum 0.1% of the amount of acetic acid formed), 2,2-dichloroethanol, monochloroacetic acid and dichloroacetic acid were found as further metabolites. The main metabolite of the structurally similar **1,2**-dichloroethane in this system was chloroacetaldehyde, which, however, could not be detected in the case of 1,1-dichloroethane. 15-Minute incubation in this system with 1,1-dichloroethane resulted in a 12% loss of CYP. The proposed metabolism is shown in Figure 1 (ATSDR 2015; McCall et al. 1983).

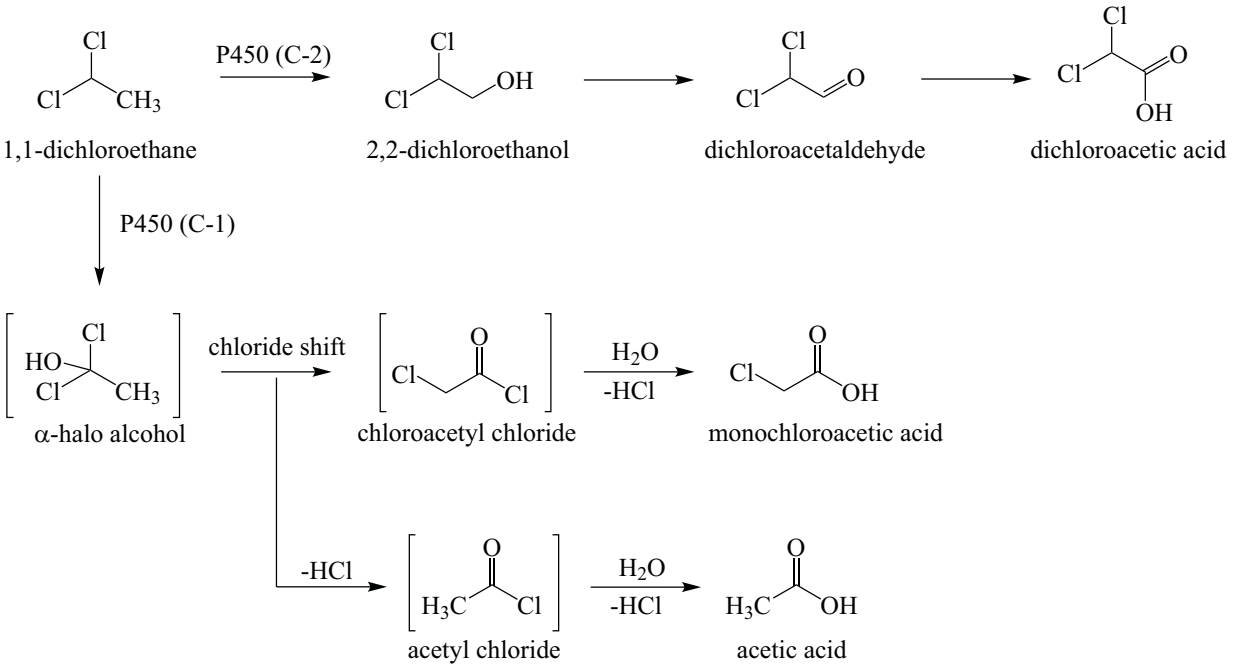

Fig. 1 Metabolism of 1,1-dichloroethane (according to ATSDR 2015)

Liver microsomes from Wistar rats or BALB/c mice treated with phenobarbital could effectively enhance the binding of 1,1-dichloroethane to DNA and proteins, whereas lung microsomes could do so only to a slight extent, and kidney and stomach microsomes could not. The simultaneous addition of glutathione (GSH) reduced the in vitro binding of ^{14}C-1,1-dichloroethane to calf thymus DNA, indicating that GSH plays a role in the metabolism of 1,1-dichloroethane (Section 5.6.1; Colacci et al. 1985).

Under anaerobic incubation conditions, measurements of the amount of NADPH consumed by liver microsomes of rats treated with phenobarbital showed that 1,1-dichloroethane was not metabolized at a detectable rate (Thompson et al. 1984).

A single oral dose of 1,1-dichloroethane of 4 g/kg body weight to male rats resulted in an increase in CYP2E1 and a decrease in CYP1A1 activity. After daily administration of 4 g/kg body weight, CYP2E1 activity decreased to 50% within

5 days and remained at this level in spite of further administration of 1,1-dichloroethane (Section 5.1.2; Muralidhara et al. 2001).

Intraperitoneal administration of 1,1-dichloroethane in mineral oil to 6 male CD-1 mice caused a dose-dependent increase in total CYP activity and in the isoform CYP2B1. The activities of the isoforms CYP1A1, CYP2E1 and CYP3A were only slightly increased (Paolini et al. 1992).

In isolated rat hepatocytes, 1,1-dichloroethane was found to cause only low numbers of radicals; these were detected only under hypoxic conditions using electron spin resonance (ESR) spectroscopy (Tomasi et al. 1984).

In the liver microsomes of male rats pretreated with phenobarbital, marked dechlorination (13.5%) was observed after 30 minutes following the addition of 1,1-dichloroethane in the presence of NADPH. Under the same conditions **1,2-**dichloroethane was hardly dechlorinated at all (< 0.5%) (Van Dyke and Wineman 1971). The results with 1,1-dichloroethane show that its metabolism does not proceed in the same way as that of the structurally similar 1,2-dichloroethane.

4 Effects in Humans

There are no data available for the effects of the substance on skin and mucous membranes, its allergenicity, reproductive toxicity, genotoxicity and carcinogenicity.

Single exposures

For dichloroethane (not specified which isomer), no concentration for a sensory irritant effect was given. The odour threshold is between 445 and 810 mg/m^3 (108.6 and 197.6 ml/m^3) (Ruth 1986).

1,1-Dichloroethane was formerly used for anaesthesia. The concentration required for this was 26 000 ml/m^3. At such a high concentration, cardiac arrhythmia occurred and its use as an anaesthetic was therefore discontinued (ATSDR 2015).

In the few cases of poisoning with dichloroethane (isomer not specified) that occurred, dizziness, nausea and vomiting were found in addition to the expected narcotic effect (no other details; Hamilton and Hardy 1974, pp. 277–291).

Repeated exposure

In a Bulgarian plant, 280 workers exposed to 1,1-dichloroethane and vinyl chloride were subjected to haematological and liver function tests. Vinyl chloride disease was diagnosed in one worker (Spasovski et al. 1984). The results of the publication in Bulgarian are available in English only as an abstract.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In male rats, the 4-hour LC_{50} was determined to be 13 000 ml/m^3 (ACGIH 2001).

After exposure to a 1,1-dichloroethane concentration of 14 350 ml/m^3 for 4 hours, 3 of 9 male rats died. The animals were unconscious after only 1 minute. Pathological examination revealed moderate kidney damage in some animals. Exposure to 7000 ml/m^3 for 6 to 7 hours resulted in unsteady gait, and the pathological examination revealed slight to moderate kidney and liver damage. None of these animals died or lost consciousness (no other details; Dow Chemical Company 1960).

Narcosis occurred in mice after exposure to concentrations of 8000 to 10 000 ml/m^3 for 2 hours (Henschler 1972).

Rats survived an 8-hour exposure to 4000 ml/m^3 and died after exposure to 16 000 ml/m^3 (Henschler 1972).

5.1.2 Oral administration

After the administration of single gavage doses of 1,1-dichloroethane of 0, 1, 2, 4, 8, 12 or 16 g/kg body weight (purity 99.99%) to groups of 8 male Sprague Dawley rats, an LD_{50} of 8.2 g/kg body weight (95% CI: 4.8–14.1 g/kg body weight) was determined. The animals displayed motor impairments and sedation at and above 2 g/kg body weight, which increased in a dose-dependent manner. No other treatment-related effects occurred. Enzyme levels in serum and urine, organ weights and tissue morphology were assessed. The authors suspected respiratory failure due to CNS depression as the cause of death (Muralidhara et al. 2001).

A single 1,1-dichloroethane dose of 2 g/kg body weight (as a 10% solution in corn oil) administered to 2 rats did not cause death; however, kidney damage was observed (no other details; Dow Chemical Company 1960).

In guinea pigs, all animals died after a single 1,1-dichloroethane dose of 1 g/kg body weight, while all animals survived the dose of 0.3 g/kg body weight (no other details; Dow Chemical Company 1960).

Preliminary tests for a metabolism study yielded maximum tolerable doses (MTD) of 700 mg 1,1-dichloroethane/kg body weight (purity < 97%, 3% dioxane) in rats and 1800 mg/kg body weight in mice (Mitoma et al. 1985).

5.1.3 Dermal application

Dermal exposure to a 1,1-dichloroethane dose of 2 ml/kg body weight for 24 hours did not cause any toxic effects in rabbits during a 14-day recovery period (ACGIH 2001).

5.1.4 Intraperitoneal injection

Intraperitoneal injection of 1000 mg 1,1-dichloroethane/kg body weight dissolved in corn oil caused tubular swelling but not necrosis in the kidneys of mice. After the injection of 2000 mg/kg body weight, the level of urinary protein was increased, and after 4000 mg/kg body weight, the urinary glucose concentration. At 4000 mg/kg body weight, 7 of the 10 animals died within 24 hours (Plaa and Larson 1965).

In guinea pigs, intraperitoneal injection of 1,1-dichloroethane at dose levels of 150, 300, 500 or 750 mg/kg body weight did not result in histological changes in the liver or a change in the activity of blood ornithine carbamyl transferase (DiVincenzo and Krasavage 1974).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a developmental toxicity study with pregnant Sprague Dawley rats exposed to 3800 ml/m^3 for 7 hours daily for 10 days, a statistically significant decrease in food consumption and body weights from gestation day 8 and day 13, respectively, were observed. Exposure to 6000 ml/m^3 led to a statistically significant increase in relative liver weights (by 23%) only in the Sprague Dawley rats that were not pregnant (n = 6) 6 days after the end of exposure, but not after exposure to 3800 ml/m^3 (n = 4) (Section 5.5.2; Schwetz et al. 1974 a).

Inhalation exposure to a 1,1-dichloroethane concentration of 500 ml/m^3 (purity 99%) for 6 hours daily, on 5 days per week, for 3 months, did not result in effects on body weight gains, blood parameters, urinary status, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum urea and serum creatinine in 5 male and 5 female rats and guinea pigs and 2 male and 2 female rabbits and cats. The same animals were exposed to 1000 ml/m^3 for a further 3 months. The time-weighted average concentration was thus 750 ml/m^3. While no adverse effects were observed in rats, guinea pigs and rabbits, kidney damage and delayed body weight gains occurred in cats. A progressive increase

in serum urea and serum creatinine as well as pathological changes in the kidneys were observed in the cats. Histologically, there were crystalline precipitates in the tubular lumina with obstruction, consecutive dilatation of the proximal segments and internal hydronephrosis. In addition, tubular degeneration, periglomerular fibrosis and tubular destruction had developed. One animal was withdrawn from the experiment after 23 weeks due to poor general condition (Henschler 1972; Hofmann et al. 1971). For the cats, a NOAEC (no observed adverse effect concentration) of 500 ml/m^3 was obtained from this study.

After exposure to 1,1-dichloroethane concentrations of 500 or 1000 ml/m^3 for 6 months, no haematological or histopathological effects were observed in rats, guinea pigs, rabbits and dogs. The animals were exposed for 7 hours daily, on 5 days per week (no other details; ACGIH 2001).

5.2.2 Oral administration

Gavage doses of 1,1-dichloroethane of 0, 1000, 2000 or 4000 mg/kg body weight (purity 99.99%) in corn oil to groups of 24 male Sprague Dawley rats for 10 consecutive days resulted in slight delays in body weight gains at 1000 mg/kg body weight and above, in addition to CNS depression. The relative liver weights were reduced in a statistically significant manner (by 11% to 19%) in all treated animals from the 5th dose. The relative kidney weights were unaffected, as were the activities of serum succinate dehydrogenase and ALT and the level of non-protein sulfhydryl (NPSH) in the liver. Renal NPSH levels were slightly increased in the animals given 2000 or 4000 mg/kg body weight. According to the authors, the slightly increased CYP levels were not treatment-related. Urinalysis as well as the histopathology of the examined organs liver, kidney, lung, brain, adrenal gland, spleen, testis and epididymis did not reveal abnormalities (Muralidhara et al. 2001).

In a study designed to determine possible effects on the proliferation of forestomach mucosa of known forestomach carcinogens, 1,1-dichloroethane was administered as a negative control. Gavage doses of 1,1-dichloroethane of 0, 350 or 700 mg/kg body weight administered on 5 days per week for 2 weeks to groups of 8 male F344 rats did not lead to a statistically significant increase in the proliferation of the forestomach mucosa (Ghanayem et al. 1986).

To determine the MTD for a carcinogenicity study, groups of 5 male and 5 female Osborne Mendel rats and of 5 male and 5 female B6C3F1 mice were given gavage doses of 1,1-dichloroethane in corn oil for 6 weeks. The recovery period was 2 weeks. The estimated MTD values were 900 mg/kg body weight for the rats and 3000 and 3600 mg/kg body weight for male and female mice, respectively (no other details; Weisburger 1977).

Groups of 15 male Sprague Dawley rats were given 1,1-dichloroethane doses of 0, 500, 1000, 2000 or 4000 mg/kg body weight in corn oil on 5 days per week for 13 weeks. At 2000 mg/kg body weight and above, CNS depression and a statistically significant decrease in body weights occurred. All animals in the 4000 mg/kg group were moribund at week 11. The dead and moribund animals displayed lung congestion as the only abnormal finding. No histological changes were observed in the tissues of liver, kidney, lung, brain, adrenal gland, stomach, testis, epididymis and spleen. No liver damage occurred and the relative liver weights were unaffected at weeks 11 and 13. Blood urea nitrogen and urinary protein and glucose levels were not significantly increased. At weeks 6 and 8, the excretion of urinary acid phosphatase (ACP) was increased in a statistically significant manner at 2000 mg/kg and 4000 mg/kg, and also at 1000 mg/kg after 8 weeks. However, a statistically significant decrease in the excretion of ACP occurred in all treated animals after 12 weeks without dose-dependency. Urinary excretion of *N*-acetylglucosaminidase was increased after 8 weeks in the animals treated with 1000, 2000 or 4000 mg/kg body weight. The kidney damage that occurred was judged by the authors to be slight. The total CYP levels in liver microsomes remained unaffected, but an increase in CYP2E1 activity was observed with a concomitant decrease in CYP1A1 activity. Pulmonary inflammation was increased at 1000 mg/kg body weight and above, but without dose-dependency (control 2/10; 500 mg/kg body weight 4/15; 1000 mg/kg body weight 10/15; 2000 mg/kg body weight 5/14; 4000 mg/kg body weight 3/7). The NOAEL (no observed adverse effect level) was given by the authors as 500 mg/kg body weight and day (Muralidhara et al. 2001). A NOAEL of 500 mg/kg body weight for the male rat can be derived from this study.

In an initiation–promotion study, male B6C3F1 mice received 4-week pre-treatment with 10 mg diethylnitrosamine (DENA)/l drinking water. Another group were given deionized water during the same period. The subsequent admin-

istration of 0, 835 or 2500 mg 1,1-dichloroethane/l drinking water (intake about 0, 1300 or 3800 mg 1,1-dichloroethane/kg body weight per week) led from week 40 onwards in the high dose group only in the animals pretreated with DENA to a slight, not statistically significant decrease in body weight gains (25 animals). Drinking water intake remained unaffected until week 52. Histopathological examination of the liver, lungs and kidneys did not reveal any abnormal findings (Section 5.7.2; Klaunig et al. 1986).

In a carcinogenicity study, groups of 50 male Osborne Mendel rats were given gavage doses of 1,1-dichloroethane (technical grade, purity 99%) of 0, 382 or 764 mg/kg body weight and day and groups of 50 female Osborne Mendel rats 0, 475 or 950 mg/kg body weight and day in corn oil for 78 weeks on 5 days per week, followed by an observation period of 33 weeks. The control groups without and with corn oil (vehicle) consisted of 20 animals. The doses are time-weighted averages, as continuous administration was not possible due to the high toxicity. Mortality was substance-related, but not dose-dependent. Only about 50% of the treated male and female rats were still alive after 62 and 70 weeks, respectively. At the end of the study, 30% and 40% of the untreated control animals, 5% and 20% of the animals given only corn oil, and 4% and 16% of the animals in the low dose group and 8% and 18% in the high dose group (males and females, respectively) were still alive. Pneumonia in about 80% of all rats and frequently observed kidney inflammation that was not substance-related were held responsible for the high mortality. The body weight gains of the treated animals and the vehicle control animals were slightly delayed. Due to high mortality, body weights fluctuated considerably during the 111 weeks. From week 20 onwards, hunched appearance and abdominal urine stains were observed in many animals; these effects were slightly increased in the treated animals compared with those in the control group. Except for mortality, no substance-related effects occurred other than the marginally increased tumour incidences described in Section 5.7.2 (NCI 1978).

In another carcinogenicity study, groups of 50 male B6C3F1 mice were given gavage doses of 1,1-dichloroethane (technical grade, purity 99%) of 0, 1442 or 2885 mg and groups of 50 female B6C3F1 mice 0, 1665 or 3331 mg/kg body weight and day in corn oil for 78 weeks on 5 days per week, followed by an observation period of 13 weeks. The control groups without and with corn oil consisted of 20 animals. The doses are time-weighted averages, as continuous administration was not possible due to the high toxicity. Mortality was increased in the high dose group. At the end of the study, of the male and female mice, 35% and 80% of the untreated control animals, 55% and 80% of the animals given only corn oil, 62% and 80% of the animals in the low dose group and 32% and 50% of the high dose group were still alive. Renal inflammation and amyloidosis in the kidneys and spleen, frequently observed only in the males, were probably not substance-related. The body weight gains of the treated animals were not delayed. Except for mortality, no substance-related effects occurred other than the marginally increased tumour incidences described in Section 5.7.2 (NCI 1978).

In a drinking water study, male and female ICR mice were given a mixture of various chlorinated alkanes and alkenes (1,1-dichloroethane, chloroform, 1,1-dichloroethene, 1,1,1-trichloroethane, trichloroethene and tetrachloroethene) for 16 to 18 months. The effects observed, such as liver damage, mammary tumours and inflammation of the ovaries, cannot be clearly attributed to 1,1-dichloroethane, since some of the other substances present in the mixture were used in significantly higher concentrations and, moreover, these substances are regarded as significantly more toxic (Wang et al. 2002).

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

Ten applications of the undiluted substance to the intact or scarified abdominal skin of presumably one rabbit resulted in weak redness (hyperaemia) after the first 6 applications and moderate redness after the following 4 applications. Slight swelling (oedema) and slight necrosis occurred after the fourth application. All effects had disappeared after 21 days. Ten applications to one ear of a rabbit did not cause irritation (no other details; Dow Chemical Company 1960).

The instillation of undiluted 1,1-dichloroethane into the eye of a rabbit caused moderate irritation of the conjunctiva with swelling, which had not completely subsided even after 1 week (no other details; Dow Chemical Company 1960).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no data available.

5.5.2 Developmental toxicity

In the prenatal developmental toxicity study with examination of the foetuses described in the supplement from 2007 (Greim 2007), similar to OECD Test Guideline 414, groups of 43, 16 and 19 Sprague Dawley rats were exposed whole-body from gestation days 6 to 15 to 1,1-dichloroethane (purity 99.7%) at concentrations of 0, 3800 or 6000 ml/m^3 for 7 hours daily. In the exposed dams, food consumption and body weight gains were reduced at concentrations of 3800 ml/m^3 and above. At 6000 ml/m^3, delayed ossification of the sternebrae occurred more frequently in the foetuses (Schwetz et al. 1974 a; method description: Schwetz et al. 1974 b). The NOAEC for developmental toxicity is thus 3800 ml/m^3, a NOAEC for maternal toxicity could not be derived. Teratogenicity was not observed (Greim 2007).

No other data are available.

In vitro

Using a whole embryo culture test system with embryos from day 9.5 of gestation, malformations in the form of rotations and heart defects were observed during morphogenesis after incubation with 1,1-dichloroethane for 2 days (no other details; Andrews et al. 2003). The results are available only as a summary.

5.6 Genotoxicity

5.6.1 In vitro

Table 1 shows the results of the in vitro genotoxicity tests. Metabolic activation was carried out using the microsomal fraction of rat liver treated with Aroclor 1254, unless otherwise stated.

The results of three bacterial mutagenicity tests with the Salmonella typhimurium strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 were negative in the presence and absence of metabolic activation (Nohmi et al. 1985; NTP 1986 c; Simmon et al. 1977; Zeiger et al. 1992). Cytotoxicity was recorded in one study at 10 000 µg/plate (Zeiger et al. 1992).

In a modified bacterial mutagenicity test with the Salmonella strains TA100, TA1535 (base pair exchange) and TA98 (frameshift) in the presence and absence of metabolic activation, mutagenic potential was reported for 1,1-dichloroethane (Milman et al. 1988; Mitoma et al. 1984; Riccio et al. 1983). Data specifying the concentrations used as well as the number of revertants were not given; thus, the result is only inadequately described.

In Aspergillus nidulans P1, a statistically significant increase in aneuploidy was observed at 0.2% (v:v) and above. However, the effect did not increase at the higher concentration of 0.3%. Mitotic crossing-over was not observed (Crebelli et al. 1988).

A DNA repair synthesis (UDS) assay with primary rat hepatocytes and primary mouse hepatocytes yielded positive results (Milman et al. 1988; Naylor Dana Institute 1983; Williams et al. 1989).

Liver microsomes from Wistar rats or BALB/c mice treated with phenobarbital enhanced in vitro binding of ^{14}C-1,1-dichloroethane to calf thymus DNA, microsomal RNA and proteins. Lung microsomes from both species induced only low-level binding to calf thymus DNA, while the level of binding to RNA and proteins was similar to that induced by liver microsomes. Kidney and stomach microsomes were ineffective in mediating 1,1-dichloroethane binding to calf thymus DNA (Colacci et al. 1985). However, this study did not prove whether DNA adducts were formed.

Tab. 1 Genotoxicity of 1,1-dichloroethane in vitro

End point	Test system	Concentration range	Effective concentration	Cytotoxicity	Results		References
					–m.a.	+m.a.	
gene mutation	Salmonella typhimurium TA97, TA98, TA100, TA102	no data		no data	–	–	Nohmi et al. 1985
gene mutation (modified, plates in desiccator)	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	0, 100 µl/ml		no data	not tested	–	Simmon et al. 1977
gene mutation	Salmonella typhimurium TA97, TA98, TA100, TA1535, TA1537	0, 100–10 000 µg/plate		10 000 µg/plate	–	–[a)]	NTP 1986 c; Zeiger et al. 1992
gene mutation (modified, plates in desiccator)	Salmonella typhimurium TA98, TA100, TA1535	no data	no data	yes	+	+	Milman et al. 1988; Mitoma et al. 1984; Riccio et al. 1983
gene mutation (plates in desiccator)	Salmonella typhimurium TA1537	no data		yes	–	–	Mitoma et al. 1984
gene mutation	Saccharomyces cerevisiae D7 (here: growth phase: cytochrome-P450 activity high = metabolically active)	no data		no data	–	–	Bronzetti et al. 1987
aneuploidy	Aspergillus nidulans P1	0, 0.1%–0.4%	0.2%	0.4%	(+)	not tested	Crebelli et al. 1988
mitotic crossing over	Aspergillus nidulans P1	0, 0.1%–0.4%		0.4%	–	not tested	Crebelli et al. 1988
covalent DNA-/RNA-/protein binding	liver microsome-mediated binding to calf thymus DNA or microsomal RNA or microsomal proteins from mice or rats treated with PB (100 mg/kg body weight, intraperitoneal)	2.5 µCi ^{14}C-1,1-dichloroethane			–	DNA +, 2.5-fold increase after PB administration RNA +, 2.5-fold increase after PB administration protein +, 2.5-fold increase after PB administration	Colacci et al. 1985

Tab. 1 *(continued)*

End point	Test system	Concentration range	Effective concentration	Cytotoxicity	Results		References
					–m.a.	+m.a.	
	lung, kidney, stomach microsome-mediated binding to calf thymus DNA or microsomal RNA or microsomal proteins from mice or rats treated with PB (100 mg/kg body weight, intraperitoneal)	2,5 µCi ^{14}C-1,1-dichloroethane			not tested	DNA – RNA – (+, lung) protein – (+, lung)	Colacci et al. 1985
	binding to calf thymus DNA, cytosolic enzymes from mice or rats treated with PB (100 mg/kg body weight, intraperitoneal)	2,5 µCi ^{14}C-1,1-dichloroethane			–	–	Colacci et al. 1985
DNA repair synthesis (UDS) test	primary rat hepatocytes	0, 0.00001%, 0.0001%, 0.001%, 0.01%, 0.1%, 1%	0.1%	not attained	+	not tested	Milman et al. 1988; Naylor Dana Institute 1983; Williams et al. 1989
DNA repair synthesis (UDS) test	primary mouse hepatocytes	0, 0.0001%, 0.001%, 0.01%, 0.1%, 1%	1%	not attained	(+)	not tested	Milman et al. 1988; Naylor Dana Institute 1983
SCE	CHO cells	0, 500–5000 µg/ml	500 µg/ml	not attained	+	+	NTP 1986 b
CA	CHO cells	0, 2500–5000 µg/ml		not attained	–	–	NTP 1986 a
CA	Chinese hamster lung fibroblasts	no data		no data	–	–	ATSDR 2015

[a] Activation with microsomal fractions from hamster and rat liver
CA: chromosomal aberration; PB: phenobarbital; SCE: sister chromatid exchange

5.6.2 In vivo

Groups of 3 male Swiss Webster mice were given single intraperitoneal doses of 1,1-dichloroethane of 0, 100, 200, 300, 400 or 500 mg/kg body weight. 1,1-Dichloroethane ("analytical grade", not further specified) was dissolved in ethanol, which was administered to the control animals. After 24 hours, the development of chromosomal aberrations and the formation of micronuclei in the bone marrow cells were investigated. A dose-dependent, statistically significant increase in the number of chromosomal aberrations (gaps and breaks) was observed, and a dose-dependent, statistically significant increase in micronuclei. The statistically significant decrease in the mitotic index at 300 mg/kg body weight and above indicates inhibition of cell growth caused by 1,1-dichloroethane (Patlolla et al. 2005). No positive control was included in the study and the number of animals used was too low. If the gaps are not taken into account, the increase in the frequency of chromosomal aberrations is not statistically significant. Furthermore, the PCE/NCE ratio was not reported and only 1000 instead of the 2000 cells per animal required in the guidelines were counted for the determination of micronuclei. Due to these shortcomings, the study is not suitable as proof of the genotoxicity of 1,1-dichloroethane.

A single intraperitoneal injection of 1,1-dichloroethane (99.7%, in corn oil) of 900 mg/kg body weight in male BALB/c mice did not result in DNA strand breaks (alkaline unwinding) in the liver 4 hours later (Taningher et al. 1991).

Four male Wistar rats and 12 male BALB/c mice were injected with a single intraperitoneal dose of ^{14}C-1,1-dichloroethane (127 µCi/kg body weight). After 22 hours, the liver, lungs, kidneys and stomach were removed and the content of ^{14}C in the DNA, RNA and proteins of these organs was examined. The ^{14}C content in RNA was higher than that in DNA in both species. The radioactivity was the highest by far in proteins. The CBI for binding to liver DNA was 79 in rats and 65 in mice, indicating a moderately weak initiator (Colacci et al. 1985). DNA adducts were not determined.

5.7 Carcinogenicity

5.7.1 Short-term studies

In a cell transformation assay without metabolic activation, a statistically significant increase in the incidence of transformations was not observed in BALB/c-3T3 embryonic cells at 1,1-dichloroethane concentrations of 4 to 250 µg/ml (purity 97% to 99%, no other details) (Arthur D. Little Inc 1983; Milman et al. 1988; Tu et al. 1985).

1,1-Dichloroethane (0–0.5 ml/chamber) enhanced the transformation of Syrian hamster embryonic cells by the SA7 adenovirus at and above 0.062 ml/chamber ($p < 0.01$) in a statistically significant manner which was not, however, dose-dependent (Hatch et al. 1983).

In an initiation–promotion study, 8 and 10 rats (no details as to whether Sprague Dawley or Fischer 344 rats) were given a single 1,1-dichloroethane dose of 7.33 mmol/kg body weight (about 725 mg/kg body weight) 12 and 18 hours after partial hepatectomy, respectively. Seven days after initiation, this was followed by the administration of phenobarbital for 10 weeks at a concentration of 500 mg/l drinking water. No increased incidences of γ-glutamyltranspeptidase-positive (GGT+) liver foci were found in the animals; there was thus no evidence of an initiating potential of 1,1-dichloroethane (Herren-Freund and Pereira 1986).

An initiation–promotion experiment did not reveal any increase in the incidences of GGT$^+$ liver foci after a single 1,1-dichloroethane dose of 700 mg/kg body weight (purity < 97%, containing 3% dioxane) in male Osborne Mendel rats 24 hours after partial hepatectomy followed by 7 weeks of dietary phenobarbital administration at a concentration of 0.05% (w/w). Thus, this study likewise provided no indication of an initiating potential (Milman et al. 1988; Story et al. 1986).

Male Osborne Mendel rats (10 animals per group) were given a single intraperitoneal dose of diethylnitrosamine of 30 mg/kg body weight for initiation after partial hepatectomy. After gavage doses of 1,1-dichloroethane of 700 mg/kg body weight (purity < 97%, containing 3% dioxane) on 5 days per week for 7 weeks, GGT$^+$ foci in the liver were increased in a statistically significant manner ($p < 0.05$). Without prior administration of the initiator, GGT$^+$ foci were increased, but without statistical significance. However, a high proportion of foci exhibited only weak GGT expression and also little histomorphological differentiation from the surrounding tissue. Considering only the clearly demarcated foci, no statistically significant tumour-promoting effect was seen (Milman et al. 1988; Story et al. 1986). The size of the foci was not reported in the study or considered in the evaluation. The morphology of the foci differed from those induced by phenobarbital.

In a drinking water study, male B6C3F1 mice received pre-treatment with 10 mg DENA/l for 4 weeks. Another group were given deionized water during the same period. The subsequent administration of 1,1-dichloroethane at dose levels of 0, 835 or 2500 mg/l drinking water (intake about 0, 1.3 or 3.8 g 1,1-dichloroethane/kg body weight per week) led to a slight, not statistically significant decrease in body weight gains from week 40 onwards in the high dose group, but only in the animals pretreated with DENA (25 animals). After 24 weeks (10 animals in each case), approximately 70% of all animals pretreated with DENA, including controls, developed liver tumours. After 52 weeks (25 animals in each case), liver tumours were observed in all animals pretreated with DENA, including controls. Approximately 80% of all animals pretreated with DENA, including controls, developed lung tumours after 52 weeks (Klaunig et al. 1986). Since all animals treated with DENA developed liver tumours, no statement can be made on the basis of this study as to whether 1,1-dichloroethane has a tumour-promoting potential.

5.7.2 Long-term studies

Groups of 50 male Osborne Mendel rats were given gavage doses of 1,1-dichloroethane (technical grade, purity 99%) of 0, 382 or 764 mg/kg body weight and day in corn oil and groups of 50 female Osborne Mendel rats 0, 475 or 950 mg/kg body weight and day on 5 days per week for 78 weeks, followed by an observation period of 33 weeks. The dose-levels given are time-weighted averages, as continuous administration was not possible due to the high toxicity. Control groups consisted of 20 males and 20 females either untreated or treated with corn oil from the current experiment and 20 vehicle control animals per sex from a parallel experiment (pooled with the current vehicle control). Very high mortality was observed in all groups (Section 5.2.2). The tumour incidences are shown in Table 2. In female rats, 1,1-dichloroethane caused a marginal but significant increase in mammary adenocarcinomas (statistically significant in the Cochran-Armitage trend test). However, compared with the pooled vehicle control, the increase was not statistically significant (Cochran-Armitage trend test). If only the animals that survived at least 52 weeks are taken into consideration, according to the Cochran-Armitage trend test, the increase in the incidence of mammary adenocarcinomas was statistically significant compared with that in the vehicle control group. Furthermore, haemangiosarcomas were observed in different tissues of the females (statistically significant in the Cochran-Armitage trend test). Calculations using Fisher's exact test did not yield statistically significant increases in tumour incidences. No haemangiosarcomas occurred in the untreated animals (20 males and 20 females) (NCI 1978). The high, early mortality, unrelated to the substance, prevented the observation of tumours that would have developed only after a longer period of treatment.

Groups of 50 male and 50 female B6C3F1 mice were given 1,1-dichloroethane (technical grade, purity 99%) by gavage at doses of 0, 1442 or 2885 mg/kg body weight and day (males) and 0, 1665 or 3331 mg/kg body weight and day (females) on 5 days per week for 78 weeks, followed by an observation period of 13 weeks. The control groups with and without treatment with corn oil consisted of 20 male and 20 female animals. In addition, a pooled vehicle control group of 79 animals each from this and other parallel studies was used. The doses were time-weighted averages, as continuous administration was not possible due to the high toxicity. The tumour incidences are shown in Table 2. The incidence of hepatocellular carcinomas in the males of both dose groups was increased, but not in a statistically significant manner. If only the animals that survived at least 52 weeks are taken into consideration, the increase in the incidence of hepatocellular carcinomas in the high-dose group was statistically significant compared with that in the pooled vehicle control group. Hepatocellular carcinomas were observed in 2 of 17 untreated male controls. In the males of the high dose group, there was also a statistically significant increase in the incidence of bronchiolar adenomas. No increased incidences of liver or lung tumours were observed in the females, but a statistically significant increase in benign endometrial polyps was seen in the high dose group (Section 5.2.2; NCI 1978).

Tab. 2 Studies of the carcinogenicity of 1,1-dichloroethane

Author		NCI 1978			
Substance:		1,1-dichloroethane (purity 99%) in corn oil			
Species:		**rats**, Osborne Mendel, 50 ♂ and 50 ♀, vehicle controls 20 ♂ and 20 ♀, pooled vehicle controls 39 ♀ (see text)			
Administration route:		oral, gavage			
Dose:		♂: 0, 382, 764 mg/kg body weight and day, ♀: 0, 475, 950 mg/kg body weight and day			
Duration:		78 weeks and 33 weeks observation period			
Toxicity:		initially high mortality			
		Dose (mg/kg body weight and day) ♂/♀			
		0	0 (pooled)	382/475	764/950
Survivors	♂	5%	no data	4%	8%
	♀	20%	no data	16%	18%
Tumours					
Haemangiosarcomas:	♀	0/19[#]	0/39[#]	0/50	4/50 (8%)

Tab. 2 *(continued)*

		Dose (mg/kg body weight and day) ♂/♀			
		0	0 (pooled)	382/475	764/950
Mammary gland:					
Adenocarcinomas	♀	0/19[#, a)]	1/39 (3%)	1/50 (2%)	5/50 (10%)
Fibroadenomas	♀	2/19 (11%)	5/39 (13%)	6/50 (12%)	6/50 (12%)
Author	NCI 1978				
Substance:	1,1-dichloroethane (purity 99%) in corn oil				
Species:	**mice**, B6C3F1, 50 ♂ and 50 ♀, untreated and vehicle controls 20 ♂ and 20 ♀, 79 pooled vehicle controls (see text)				
Administration route:	oral, gavage				
Dose:	♂: 0, 1442, 2885 mg/kg body weight and day, ♀: 0, 1665, 3331 mg/kg body weight and day				
Duration:	78 weeks and 13 weeks observation period				
Toxicity:	mortality ↑				
		Dose (mg/kg body weight and day) ♂/♀			
		0	0 (pooled)	1442/1665	2885/3331
Survivors	♂	55%	no data	62%	32%
	♀	80%	no data	80%	50%
Tumours and preneoplasms					
Liver:					
hepatocellular carcinomas (total)	♂	1/19 (5%)	6/79 (8%)	8/49 (16%)	8/47 (17%)
hepatocellular carcinomas (only for survival > 52 weeks)	♂	1/19 (5%) untreated: 2/17 (12%)	6/72 (8%)[#]	8/48 (17%)	8/32 (25%)*
Lungs:					
bronchiolar adenomas	♂	0/19	3/79 (4%)	1/49 (2%)	4/47 (9%)
Uterus:					
polyps, benign	♀	0/20[#]	0/79[#]	0/47	4/46 (9%)*

*$p \leq 0.05$, Fisher exact test compared with pooled vehicle control group; [#]$p \leq 0.05$, Cochran-Armitage trend test
[a)] also only for animals surviving for at least 52 weeks

6 Manifesto (MAK value/classification)

The critical effects are kidney damage in cats and, at high exposure concentrations, liver damage in rats and narcotic effects in humans and animals.

MAK value. After inhalation exposure to 1000 ml 1,1-dichloroethane/m^3 for 6 months, severe kidney damage occurred in cats with a NOAEC of 500 ml/m^3 after 3 months (Hofmann et al. 1971). Since both the treatment period and the concentration were increased in the study, it is not possible to distinguish whether it was the concentration or time period (or both) that led to the renal effects. In rats, mice and rabbits, there was no evidence of an amplification of the effects with time. Therefore, a factor of 2 for the time extrapolation is considered sufficient for the experiment with cats, although the ratio of study duration to lifetime is significantly lower than in rats and mice. Taking into account the extrapolation of the data from the animal experiment to humans (1:2) and a possible amplification of the effects with chronic exposure (1:2) as well as the increased respiratory volume (1:2), a value of 62.5 ml/m^3 can be derived from this study.

The 13-week experiment in rats (Muralidhara et al. 2001) revealed a NOAEL of 500 mg/kg body weight. At 1000 mg/kg body weight and day, transient changes in urinary excretion of acid phosphatase and *N*-acetylglucosaminidase occurred. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 500 mg/kg body weight to a concentration in workplace air: the species-specific correction value (1:4) for the rat, the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 875 mg/m^3. Taking into account the extrapolation of the data from the animal experiment to humans (1:2) and a possible amplification of the effects with chronic exposure (1:2), a concentration of 219 mg/m^3 can be derived from this study (≙ 53 ml/m^3).

From both studies, using the preferred value approach, a MAK value of 50 ml/m^3 is obtained.

Peak limitation. Due to systemic toxicity, 1,1-dichloroethane was assigned to Peak Limitation Category II in 2001. A substance-specific excursion factor could not be given due to lack of data, therefore an excursion factor of 2 was set for 1,1-dichloroethane (Greim 2001).

As there are still no data for the half-life, peak limitation with the default excursion factor 2 has been retained. Irritant and pre-narcotic effects are not to be expected at the short-term concentration of 100 ml/m^3 thus permitted.

Prenatal toxicity. In a prenatal developmental toxicity study with Sprague Dawley rats, delayed ossification of the sternebrae was observed in the foetuses at a concentration of 6000 ml/m^3 with concomitant maternal toxicity in the form of decreased body weight gains and feed intake. The NOAEC for developmental toxicity is 3800 ml/m^3. Taking the increased respiratory volume into account, the NAEC (no adverse effect concentration) is 1900 ml/m^3, which is 38 times the MAK value of 50 ml/m^3. As this margin is considered sufficiently wide and teratogenicity was not observed, assignment of the substance to Pregnancy Risk Group C is confirmed.

Carcinogenicity. The data for the genotoxicity of the substance are inconsistent. In valid studies, two positive results were obtained in indicator tests in vitro which provide evidence of genotoxicity in vitro: in a DNA repair synthesis test and a sister chromatid exchange assay. Further studies of genotoxicity with positive results cannot be evaluated due to insufficient presentation of the data. No mutagenicity or clastogenicity was demonstrated in a well-documented Salmonella mutagenicity test and in two tests for chromosomal aberrations.

Overall, the genotoxicity data demonstrate that the genotoxic potential of 1,1-dichloroethane is not the main effect compared with its toxicity.

No effects were observed in a cell transformation test and a 52-week drinking water study. Only a modified transformation test with viruses revealed increased transformations, but without dose-dependency. As to the carcinogenicity studies, no statement can be made regarding the late occurrence of increased tumour incidences due to the high mortality. However, the haemangiosarcomas and mammary tumours observed in the female rats suggest some evidence due to the comparability of the tumour types observed with 1,2-dichloroethane. 1,1-Dichloroethane has therefore been classified in Carcinogen Category 3 B.

Germ cell mutagenicity. In a well-documented Salmonella mutagenicity test, 1,1-dichloroethane was not mutagenic (NTP 1986 c; Zeiger et al. 1992). Two Salmonella mutagenicity tests in the desiccator yielded one positive result (Mitoma et al. 1984) and one negative result (Simmon et al. 1977). In both cases, however, no exact data were given, so that the effect strength, the attainment of cytotoxicity and the validity of the studies cannot be assessed. Therefore, 1,1-dichloroethane is regarded as not mutagenic. Valid in vivo studies are not available.

The available data do not justify classification in one of the categories for germ cell mutagens.

Absorption through the skin. For humans, a maximum dermal absorption of 1310 mg can be estimated from a model calculation (Section 3.1) for exposure to a saturated aqueous solution under standard conditions (2000 cm^2 of skin, exposure for 1 hour).

For exposure at the level of the MAK value, an amount of 2100 mg would be absorbed assuming 100% absorption by inhalation and a respiratory volume of 10 m^3. This means that absorption through the skin makes up more than 25%

of the systemically tolerable amount, and the substance has therefore been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are still no data available for the sensitizing effects of the substance in humans and no results from experimental studies in animals or in vitro studies. Therefore, 1,1-dichloroethane has not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways) due to lack of data.

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.

References

ACGIH (American Conference of Governmental Industrial Hygienists) (2001) 1,1-Dichloroethane. In: Documentation of TLVs and BEIs. Cincinnati, OH: ACGIH

Andrews J, Nichols H, Hunter E (2003) Developmental toxicity of mixtures of di- and tetrachloroethane and dichloropropane in embryo culture. Toxicologist 72: 247

Arthur D. Little Inc (1983) Cell transformation assays of 11 chlorinated hydrocarbon analogs (final Report) Icair Work Assignment No. 10. EPA Document No. 40-8324457, NTIS/OTS0509392. Alexandria, VA: NTIS. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0509392.xhtml, accessed 07 Feb 2019

ATSDR (Agency for Toxic Substances and Disease Registry) (2015) Toxicological profile for 1,1-dichloroethane. Atlanta, GA: ATSDR. https://www.atsdr.cdc.gov/ToxProfiles/tp133.pdf, accessed 06 Nov 2018

Bronzetti G, Galli A, Vellosi R, Rossi F, Morichetti E, Carratore RD (1987) Genetic activity of chlorinated ethanes. Eur J Cancer Clin Oncol 23: 1737–1738

Colacci A, Arfellini G, Mazzullo M, Prodi G, Grilli S (1985) Genotoxicity of 1,1-dichloroethane. Res Commun Chem Pathol Pharmacol 49(2): 243–254

Crebelli R, Benigni R, Franekic J, Conti G, Conti L, Carere A (1988) Induction of chromosome malsegregation by halogenated organic solvents in Aspergillus nidulans: unspecific or specific mechanism? Mutat Res 201(2): 401–411. https://doi.org/10.1016/0027-5107(88)90027-9

DiVincenzo GD, Krasavage WJ (1974) Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. Am Ind Hyg Assoc J 35(1): 21–29. https://doi.org/10.1080/0002889748507002

Dow Chemical Company (1960) Results of range finding toxicology tests on 1,1-dichloroethane. NTIS/OTS0515949. Alexandria, VA: NTIS. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0515949.xhtml, accessed 22 Sep 2020

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17(5): 617–635. https://doi.org/10.1002/ajim.4700170507

Ghanayem BI, Maronpot RR, Matthews HB (1986) Association of chemically induced forestomach cell proliferation and carcinogenesis. Cancer Lett 32(3): 271–278. https://doi.org/10.1016/0304-3835(86)90179-5

Greim H, editor (2001) 1,1-Dichlorethan. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 33rd issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb7534d0033

Greim H, editor (2007) 1,1-Dichlorethan. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 43rd issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb7534d0043

Hamilton A, Hardy HL (1974) Industrial toxicology, 3rd ed. Littleton, MA: Publishing Sciences Group

Hatch GG, Mamay PD, Ayer ML, Casto BC, Nesnow S (1983) Chemical enhancement of viral transformation in Syrian hamster embryo cells by gaseous and volatile chlorinated methanes and ethanes. Cancer Res 43(5): 1945–1950

Henschler D, editor (1972) 1,1-Dichlorethan. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 1st issue. Weinheim: VCH. Also available from https://doi.org/10.1002/3527600418.mb7534d0001

Herren-Freund SL, Pereira MA (1986) Carcinogenicity of by-products of disinfection in mouse and rat liver. Environ Health Perspect 69: 59–65. https://doi.org/10.1289/ehp.866959

Hofmann HT, Birnstiel H, Jobst P (1971) Zur Inhalationstoxicität von 1,1- und 1,2-Dichloräthan. Arch Toxikol 27(3): 248–265

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (2019) 1,1-Dichlorethan. GESTIS-Stoffdatenbank. https://gestis.dguv.de/data?name=030340, accessed 30 Jan 2019

Klaunig JE, Ruch RJ, Pereira MA (1986) Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. Environ Health Perspect 69: 89–95. https://doi.org/10.1289/ehp.866989

McCall SN, Jurgens P, Ivanetich KM (1983) Hepatic microsomal metabolism of the dichloroethanes. Biochem Pharmacol 32(2): 207–213. https://doi.org/10.1016/0006-2952(83)90545-2

Meulenberg CJ, Vijverberg HP (2000) Empirical relations predicting human and rat tissue:air partition coefficients of volatile organic compounds. Toxicol Appl Pharmacol 165(3): 206–216. https://doi.org/10.1006/taap.2000.8929

Milman HA, Story DL, Riccio ES, Sivak A, Tu AS, Williams GM, Tong C, Tyson CA (1988) Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann N Y Acad Sci 534: 521–530. https://doi.org/10.1111/j.1749-6632.1988.tb30143.x

Mitoma C, Tyson CA, Riccio ES (1984) Investigations of the species sensitivity and mechanism of carcinogenicity of halogenated hydrocarbons, final report EPA contract 68-01-5079. NTIS/OTS0509408. Alexandria, VA: NTIS. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0509408.xhtml, accessed 07 Nov 2018

Mitoma C, Steeger T, Jackson SE, Wheeler KP, Rogers JH, Milman HA (1985) Metabolic disposition study of chlorinated hydrocarbons in rats and mice. Drug Chem Toxicol 8(3): 183–194. https://doi.org/10.3109/01480548508999169

Morgan A, Black A, Belcher DR (1970) The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann Occup Hyg 13(4): 219–233. https://doi.org/10.1093/annhyg/13.4.219

Muralidhara S, Ramanathan R, Mehta SM, Lash LH, Acosta D, Bruckner JV (2001) Acute, subacute, and subchronic oral toxicity studies of 1,1-dichloroethane in rats: application to risk evaluation. Toxicol Sci 64(1): 135–145. https://doi.org/10.1093/toxsci/64.1.135

Naylor Dana Institute (1983) DNA repair tests of 11 chlorinated hydrocarbon analogs. EPA Document No. 40-8324292, NTIS/OTS0509403. Alexandria, VA: NTIS. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0509403.xhtml, accessed 07 Feb 2019

NCBI (National Center for Biotechnology Information) (2020) 1,1-Dichloroethane. PubChem compound summary for CID=6365. https://pubchem.ncbi.nlm.nih.gov/compound/6365, accessed 14 Sep 2020

NCI (National Cancer Institute) (1978) Bioassay of 1,1-dichloroethane for possible carcinogenicity. CAS No. 75-34-3. NCI-CG-TR-66. Bethesda, MD: NCI. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr066.pdf, accessed 30 Jan 2019

Nohmi T, Miyata R, Yoshikawa K, Ishidate M Jr (1985) [Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Bacterial mutagenicity tests]. Eisei Shikenjo Hokoku (103): 60–64

NTP (National Toxicology Program) (1986 a) Cytogenetic study of 1,1-dichloroethane in Chinese hamster ovary cell chromosome aberrations test. NTP Study No. 508873_CA. https://manticore.niehs.nih.gov/cebssearch/genetox/002-01022-0002-0000-9/, accessed 29 Jan 2019

NTP (National Toxicology Program) (1986 b) Cytogenetic study of 1,1-dichloroethane in Chinese hamster ovary cell sister chromatid exchange test. NTP Study No. 508873_SCE. https://manticore.niehs.nih.gov/cebssearch/genetox/002-01022-0001-0000-8/, accessed 29 Jan 2019

NTP (National Toxicology Program) (1986 c) Genetic toxicity evaluation of 1,1-dichloroethane in Salmonella/E. coli mutagenicity test or Ames test. Study 777132. Research Triangle Park, NC: NTP. https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.download&bin_id=12733&library_id=16140&fileIdsSelected=1de240ff65768bcc0165ee40dc3d08d2, accessed 29 Jan 2019

Paolini M, Mesirca R, Pozzetti L, Biagi GL, Cantelli-Forti G (1992) Selective induction of murine liver cytochrome P450 IIB1 by halogenated hydrocarbons. Toxicol Environ Chem 36(3–4): 235–249. https://doi.org/10.1080/02772249209357846

Patlolla BP, Patlolla AK, Tchounwou PB (2005) Cytogenetic effects of 1,1-dichloroethane in mice bone marrow cells. Int J Environ Res Public Health 2(1): 101–106. https://doi.org/10.3390/ijerph2005010101

Plaa GL, Larson RE (1965) Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. Toxicol Appl Pharmacol 7(1): 37–44. https://doi.org/10.1016/0041-008x(65)90072-4

Reinhardt CF, Azar A, Maxfield ME, Smith PE Jr, Mullin LS (1971) Cardiac arrhythmias and aerosol 'sniffing'. Arch Environ Health 22(2): 265–279. https://doi.org/10.1080/00039896.1971.10665840

Riccio E, Griffin A, Mortelmans K (1983) A comparative mutagenicity study of volatile halogenated hydrocarbons using different metabolic activation systems. Environ Mutagen 5(3): 472. https://doi.org/10.1002/em.2860050318

Ruth JH (1986) Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J 47(3): A142-151. https://doi.org/10.1080/15298668691389595

Schwetz BA, Leong BKJ, Gehring PJ (1974 a) Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol Appl Pharmacol 28(3): 452–464. https://doi.org/10.1016/0041-008x(74)90230-0

Schwetz BA, Leong BKJ, Gehring PJ (1974 b) Embryo- and fetotoxicity of inhaled chloroform in rats. Toxicol Appl Pharmacol 28(3): 442–451. https://doi.org/10.1016/0041-008x(74)90229-4

Simmon VF, Kauhanen K, Tardif RG (1977) Mutagenic activity of chemicals identified in drinking water. Dev Toxicol Environ Sci 2: 249–258

Spasovski M, Stanchev S, Nosko M, Zlatev Z, Popov T (1984) [Changes in the biochemical indices of workers exposed to vinyl chloride and dichloroethane]. Probl Khig 9: 50–58

Story DL, Meierhenry EF, Tyson CA, Milman HA (1986) Differences in rat liver enzyme-altered foci produced by chlorinated aliphatics and phenobarbital. Toxicol Ind Health 2(4): 351–362. https://doi.org/10.1177/074823378600200402

Taningher M, Parodi S, Grilli S, Colacci A, Mazzullo M, Bordone R, Santi L (1991) Lack of correlation between alkaline DNA fragmentation and DNA covalent binding induced by polychloroethanes after in vivo administration. Problems related to the assessment of a carcinogenic hazard. Cancer Detect Prev 15(1): 35–39

Thompson JA, Ho B, Mastovich SL (1984) Reductive metabolism of 1,1,1,2-tetrachloroethane and related chloroethanes by rat liver microsomes. Chem Biol Interact 51(3): 321–333. https://doi.org/10.1016/0009-2797(84)90157-1

Tibaldi R, ten Berge W, Drolet D (2014) Dermal absorption of chemicals: estimation by IH SkinPerm. J Occup Environ Hyg 11(1): 19–31. https://doi.org/10.1080/15459624.2013.831983

Tomasi A, Albano E, Bini A, Botti B, Slater TF, Vannini V (1984) Free radical intermediates under hypoxic conditions in the metabolism of halogenated carcinogens. Toxicol Pathol 12(3): 240–246. https://doi.org/10.1177/019262338401200306

Tu AS, Murray TA, Hatch KM, Sivak A, Milman HA (1985) In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett 28(1): 85–92. https://doi.org/10.1016/0304-3835(85)90096-5

Van Dyke RA, Wineman CG (1971) Enzymatic dechlorination. Dechlorination of chloroethanes and propanes in vitro. Biochem Pharmacol 20(2): 463–470. https://doi.org/10.1016/0006-2952(71)90082-7

Wang F-I, Kuo M-L, Shun C-T, Ma Y-C, Wang J-D, Ueng T-H (2002) Chronic toxicity of a mixture of chlorinated alkanes and alkenes in ICR mice. J Toxicol Environ Health A 65(3–4): 279–291. https://doi.org/10.1080/15287390252800864

Weisburger EK (1977) Carcinogenicity studies on halogenated hydrocarbons. Environ Health Perspect 21: 7–16. https://doi.org/10.1289/ehp.77217

Williams GM, Mori H, McQueen CA (1989) Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat Res 221(3): 263–286. https://doi.org/10.1016/0165-1110(89)90039-0

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen 19 Suppl 21: 2–141. https://doi.org/10.1002/em.2850190603