The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

2-Chloroethanol

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

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Keywords

2-chloroethanol; toxicity; irritation; maximum workplace concentration; MAK value; peak limitation; developmental toxicity; skin absorption

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated 2-chloroethanol [107-07-3], considering all toxicological endpoints. Available publications are described in detail. The critical effect is high systemic toxicity with a steep dose-response relationship. The NOAELs are 45, 15, and 45 mg/kg body weight and day in rats, dogs, and monkeys, respectively, after oral administration, and 100 and about 200 mg/kg body weight and day in rats and mice, respectively, after dermal administration. Taking both oral and dermal studies in animals into consideration, a MAK value of 2 ml/m^3 is derived, which also protects from irritation. As the critical effect is systemic, Peak Limitation Category II is confirmed. The excursion factor of 1 is retained because of the steep dose-response relationship. The NOAELs for developmental toxicity are 50 and 227 mg/kg body weight and day for mice after gavage or drinking water administration, respectively, and 60 and 36 mg/kg body weight and day for mice and rabbits, respectively, after intravenous administration. The margins between the calculated concentrations at the workplace without effects and the MAK value are sufficiently high. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and the classification of 2-chloroethanol in Pregnancy Risk Group C is retained. 2-Chloroethanol is not regarded as genotoxic in vivo. The substance was not carcinogenic in dermal carcinogenicity studies in mice and rats. The substance is not a contact sensitizer in humans and mice. The low dermal LD_{50} values, the estimated dermal absorption of 25% and the reports of poisoning incidents at the workplace after dermal exposure point to a significant contribution of skin contact to systemic toxicity. Therefore, the designation with an "H" is retained.

Citation Note:
Hartwig A, MAK Commission. 2-Chloroethanol. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2022 Jun;7(2):Doc027. https://doi.org/10.34865/mb10707e7_2ad

Manuscript completed:
21 Mar 2018

Publication date:
29 Jun 2022

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MAK value (2018)	**2 ml/m³ (ppm) ≙ 6.7 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 1**
Absorption through the skin (1961)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1989)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
CAS number	107-07-3
Vapour pressure at 25 °C	9.57 hPa (NLM 2020)
log K_{OW}	0.03 (NLM 2020)
1 ml/m³ (ppm) ≙ 3.345 mg/m³	**1 mg/m³ ≙ 0.298 ml/m³ (ppm)**

Documentation for 2-chloroethanol was published in 1983 (Henschler 1993), followed by a supplement on peak limitation in 2002 (Greim 2002, 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, Section Ib and Ic). A blood:air partition coefficient of 2788 is calculated for 2-chloroethanol according to the formula of Buist et al. (2012). This supplement reviews whether the MAK value for 2-chloroethanol needs to be amended as a result of the higher respiratory volume at the workplace. In addition, germ cell mutagenicity is evaluated.

1 Toxic Effects and Mode of Action

In rabbits, 2-chloroethanol induced mild irritation of the skin and severe, irreversible eye irritation. Irritation of the respiratory tract is therefore assumed.

2-Chloroethanol was found to be severely toxic after single inhalation, oral and dermal exposures. The target organs are the liver, kidneys and pancreas in rats and mice and, in addition, the thyroid gland, heart and lungs in rats. Oral exposure of rats to 67.5 mg/kg body weight caused severe systemic toxicity, which was associated with an increased number of moribund animals; after dermal exposure for 13 weeks, initial effects on the pancreas were found at 125 mg/kg body weight and day and above, and increased mortality occurred at 250 mg/kg body weight and day and above. In a 2-year study with dermal application, increased mortality and congestion, inflammation and haemorrhage in the lungs were observed in male and female mice at 15 mg/animal (630 mg/kg body weight and day in week 1 and 411 mg/kg body weight and day in week 100). A steep dose–response relationship was observed for the substance particularly after administration by gavage.

In a prenatal toxicity study in CD-1 mice given gavage doses from days 6 to 16 of gestation, 2-chloroethanol led to reduced foetal weights with a concurrent reduction in maternal body weight gains at 100 mg/kg body weight and day and above. After intravenous injection of 2-chloroethanol, the most sensitive period for the induction of developmental toxicity in CD-1 mice was the period from days 8 to 10 of gestation. At 120 mg/kg body weight, an increased number of

resorptions per litter and a higher percentage of foetal malformations were observed concurrently with pronounced maternal toxicity in the form of increased mortality.

With the addition of a metabolic activation system 2-chloroethanol was mutagenic in bacteria; its mutagenic potential was much weaker without the addition of a metabolic activation system. In mammalian cells, without the addition of a metabolic activation system 2-chloroethanol was not mutagenic in the $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells and caused very weak mutagenicity with metabolic activation. 2-Chloroethanol is not regarded as genotoxic in vivo.

In carcinogenicity studies with dermal exposure of F344 rats and Swiss CD-1 mice, 2-chloroethanol was not carcinogenic; however, the maximum tolerated dose (MTD) was not reached.

2-Chloroethanol did not have sensitizing effects on the skin of mice.

2 Mechanism of Action

2-Chloroethanol caused cardiovascular effects such as cardiac arrest and vasorelaxation in humans. An isolated rat atrium model demonstrated that the metabolite 2-chloroacetaldehyde rather than 2-chloroethanol caused these effects as a result of the over-expression of the neuronal nitrogen monoxide synthase in the atria (Chen et al. 2011).

Glutathione (GSH) conjugation acts as a detoxification mechanism for 2-chloroethanol. As long as glutathione is available in the liver, the conjugation of 2-chloroacetaldehyde and 2-chloroacetic acid catalysed by GSH *S*-transferases takes place. When rats were given a single gavage dose of 2-chloroethanol of 0.68 mmol/kg body weight (55 mg/kg body weight), GSH levels were depleted to about 18% of the levels in the control animals after 2 hours (Johnson 1965).

The depletion of GSH to 30% of the initial value by diethyl maleate prior to the intraperitoneal injection of 2-chloroethanol at a dose level of 0.9 mmol/kg body weight (72 mg/kg body weight) intensified the acute hepatotoxicity in mice; 2 of 4 animals died. Without GSH depletion, none of 3 animals died at this dose level; likewise, none of 5 animals died after a single intraperitoneal injection of 2-chloroethanol of 1.2 mmol/kg body weight (97 mg/kg body weight) (Storer and Conolly 1985). With GSH depletion, increased hepatotoxicity leading to mortality was observed after a single intraperitoneal injection of 2-chloroethanol at a dose level of 72 mg/kg body weight. Detoxification by GSH conjugation is assumed to be efficient up to a dose corresponding to more than half of the intraperitoneal LD_{50} value for 2-chloroethanol of 98 to 134 mg/kg body weight.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

In male Wistar rats, single gavage doses of ^{14}C-2-chloroethanol of 5 or 50 mg/kg body weight led to rapid elimination of the radioactivity, mainly with the urine. After exposure to 5 mg/kg body weight, 77.2% was excreted with the urine, 1.7% with the faeces and 1.0% as carbon dioxide in the exhaled air; overall, 2.8% was excreted via these routes over the following 3 days, and the total radioactivity in the urine was 79.6% up to day 4 after exposure. At the high dose, the percentage of the substance excreted within 24 hours was 79.5% with the urine, 3.8% with the faeces and 1.7% as carbon dioxide in the exhaled air. The highest levels of radioactivity were determined in the liver, kidneys and blood 1 to 2 hours after exposure. These concentrations had decreased by half after 4 hours. After 4 days, 0.4% of the dose remained in the liver and 3% in the rest of the body. After exposure to 5 mg/kg body weight, the radioactivity in the urine consisted of 45% thiodiacetic acid and 45% thionyldiacetic acid. At the high dose, the corresponding values were 70% and 20%. Neither unchanged 2-chloroethanol nor 2-chloroacetic acid, *S*-carboxymethylcysteine or sulfonyldiacetic acid were found in the urine. Likewise, there was no evidence of beta-hydroxyethyl derivatives. However, *N*-acetyl-*S*-(2-hydroxyethyl)cysteine was observed with 2-chloroacetaldehyde and vinyl chloride (Grunow and

Altmann 1982; Henschler 1993). The study ended on day 4 after exposure. As only about 2% of the low dose and 3.8% of the high dose was excreted with the faeces, oral absorption is almost complete.

There are no quantitative in vivo or in vitro data available for the absorption of 2-chloroethanol through the skin.

However, dermal absorption can be estimated from the LOAEL (lowest observed adverse effect level) for mortality after subchronic oral and dermal exposures. The comparison of the mortality after a single dermal exposure (LD_{50} about 400 mg/kg body weight; NTP 1985) with that after dermal exposure for 14 days (LD_{50} > 400 mg/kg body weight; NTP 1985) shows that mortality depends more on the daily dose level than on the duration of exposure. Using the LOAELs for mortality from subchronic studies in rats of 67.5 mg/kg body weight after oral exposure (7 days/week; Oser et al. 1975) and 250 mg/kg body weight after dermal exposure (5 days/week; NTP 1985) and the experimentally determined 100% oral absorption as the basis for comparison, absorption through the skin is estimated to be about 25%.

After intravenous injection of 2-chloroethanol at a dose level of 46 mg/kg body weight, the elimination half-life was 40.8 minutes in the blood of beagle dogs. Clearance from the whole body was 10.3 ml/kg body weight and minute (ECB 2000).

3.2 Metabolism

Figure 1 shows the postulated metabolism of 2-chloroethanol in rats (Grunow and Altmann 1982).

In rats, 2-chloroethanol is oxidized to 2-chloroacetaldehyde in the liver by means of alcohol dehydrogenase and subsequently to 2-chloroacetic acid by means of aldehyde dehydrogenase. 2-Chloroacetaldehyde and 2-chloroacetic acid may form glutathione conjugates. 2-Chloroethanol itself does not react with glutathione in vitro, not even in the presence of GSH *S*-transferase. Carbon dioxide may form from 2-chloroacetic acid. On the basis of the glutathione conjugates, thiodiacetic acid may be formed by the hydrolysis and subsequent deamination and decarboxylation of the intermediate *S*-carboxymethylcysteine. Thionyldiacetic acid, the other metabolite, is formed by the oxidation of thiodiacetic acid (Grunow and Altmann 1982).

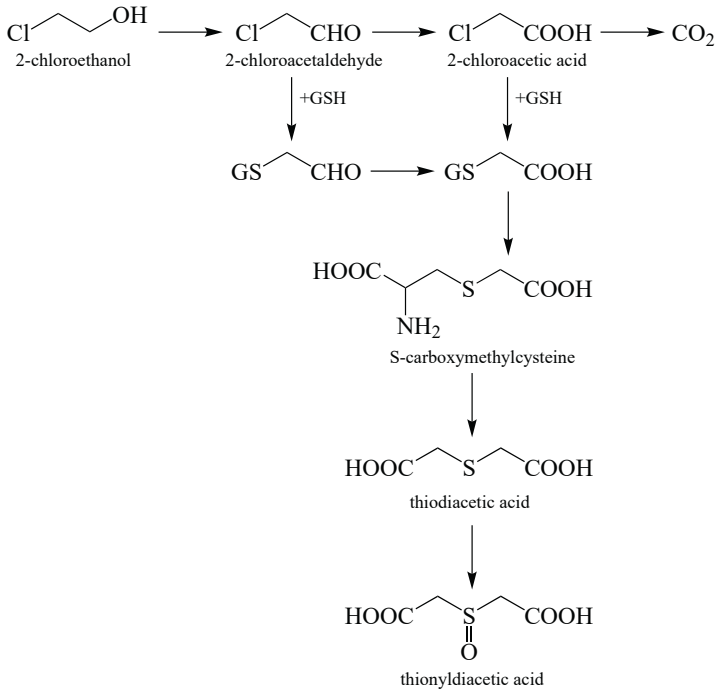

Fig. 1 Metabolism of 2-chloroethanol in rats (Grunow and Altmann 1982)

4 Effects in Humans

4.1 Single exposures

Signs of toxicity were observed in humans after oral, dermal and inhalation exposure (Henschler 1993). Other solvents were occasionally also involved and mortality occurred in some cases. Exposure to airborne concentrations of 300 to 500 ml/m^3 for about 2 hours led to death by cardiovascular failure and pulmonary oedema within 24 hours. Initial signs of toxicity included headaches, dizziness, a burning sensation in the eyes, nausea, vomiting, and numbness of the fingers and hands; confusion, dyspnoea, loss of consciousness, and circulatory collapse were observed later. Autopsy revealed general hyperaemia of the organs, oedema in the brain, pulmonary oedema, fatty infiltration of the liver, fatty degeneration of the myocardium, and cloudy swelling of the kidneys. The lethal dose for humans after percutaneous absorption is estimated to be less than 5 ml (ECB 2000).

On an agricultural farm in California, USA, 6 male workers were given the job of treating empty potato sacks with 2-chloroethanol to enhance the germination of potatoes. All 6 were exposed to the substance via inhalation and through the skin. Nausea, vomiting and dizziness, a burning sensation in the nose, eye irritation, diminished vision, numbness of the hands and fingers, and low blood pressure were observed. One worker died and the others recovered within hours or days. Laboratory tests were carried out under similar exposure conditions to determine the exposure concentration. These revealed maximum concentrations of 3300 ml/m^3, which decreased to about 400 to 500 ml/m^3 within 30 minutes and subsequently remained constant for 140 hours. Field studies in storage rooms yielded concentrations of about 50 to 1000 ml/m^3. Regular ventilation reduced the concentrations from about 200 to about 10 ml/m^3. The 2-chloroethanol concentrations in the air were determined by means of Volhard titration. The highest concentration levels expected 1 day after the treatment of the empty potato sacks were about 400 or 500 ml/m^3. This corresponds to the concentration level at which the 6 workers were probably exposed (Bush et al. 1949; Henschler 1993).

4.2 Repeated exposure

In a plant in England, a technical failure lasting for an unknown period of time led to the exposure of the workers (number of exposed persons not reported) to a vaporous mixture containing an average 2-chloroethanol concentration of 18 ml/m^3 and 1,2-dichloroethane (concentration not reported). Altogether 9 persons (4 men and 5 women) reported symptoms of the digestive system (nausea, abdominal pain and repeated vomiting), the nervous system (headaches, dizziness, problems of coordination, confusion and mild narcotic effects), the cardiovascular system (low blood pressure), the urinary system (slight, reversible albuminuria and polyuria), the respiratory system (coughing) and the skin (erythema on the arms and, in severe cases, the trunk). No deaths occurred. Recovery was complete and rapid in all but one exposed person (no other details). The authors concluded that the symptoms were caused mainly by 2-chloroethanol because the narcotic effects were only very mild (1,2-dichloroethane has narcotic effects). Irritation of the skin, eyes or mucous membranes was not observed; only one male worker had a dry cough. When the 2-chloroethanol concentrations were subsequently determined in 7 work areas of this plant at 4 different times between November 1941 and July 1942, concentrations of 2 to 49 ml/m^3 (average: 21 ml/m^3), 5 to 25 ml/m^3 (14 ml/m^3), 5 to 20 ml/m^3 (11 ml/m^3) and 0 to 5 ml/m^3 (4 ml/m^3) were obtained, whereas the 1,2-dichloroethane concentrations were 2 to 152 ml/m^3 (70 ml/m^3), 12 to 143 ml/m^3 (63 ml/m^3), 12 to 84 ml/m^3 (55 ml/m^3) and 12 to 48 ml/m^3 (36 ml/m^3) (Goldblatt and Chiesman 1944; Henschler 1993). The method of analysis was not reported. As only 1 of the 9 workers affected had a dry cough and no other effects of irritation were observed at a 2-chloroethanol concentration of 18 ml/m^3, this observation is regarded as a sign of very slight irritation or a lack of irritation up to a 2-chloroethanol concentration of 18 ml/m^3.

A retrospective cohort study was carried out in 61 workers of a 2-chloroethanol plant and 60 workers without contact with toxic substances who served as controls. The average exposure concentration was 4 mg/m^3, and the average duration of exposure was 11 years. The incidences of neurasthenia and anorexia and the blood cholesterol levels were statistically significantly increased in the workers exposed to 2-chloroethanol compared with those in the controls

(ECHA 2018). The effects were caused by the exposure peaks or possible exposure to more than one substance. The original study was published in Chinese (Yu et al. 1997).

4.3 Local effects on skin and mucous membranes

Visual disturbances and haemorrhage of the conjunctivae were reported in workers exposed to 2-chloroethanol (no other details; NCBI 2020).

A volunteer study did not reveal irritant effects on the skin of 11 of 12 test persons after semi-occlusive application of aqueous solutions containing 0.05% to 1.1% 2-chloroethanol for 1 to 8 hours. Erythema and mild oedema were observed in one volunteer at 0.05% and above (ECB 2000).

4.4 Allergenic effects

There are no data available.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

4.7.1 Case–control studies

A nested case–control study that investigated 29 139 workers from 2 chemical manufacturing facilities and a research and development centre in the United States reported 52 cases of non-Hodgkin's lymphomas, 20 cases of multiple myelomas, 39 cases of non-lymphocytic leukaemia and 18 cases of lymphocytic leukaemia in the period between 1940 and 1978. The control persons were selected from the total group of workers according to a group-matched incidence density sampling design. Exposure odds ratios (ORs) were calculated for 111 work areas and 21 specific chemicals and chemical groups that were associated with non-Hodgkin's lymphomas, multiple myelomas and non-lymphocytic and lymphocytic leukaemia. There was a significant trend between the duration of exposure and the incidence of non-lymphocytic leukaemia in 3 of 4 cases in the group employed for 5 or more years in the chlorohydrin unit (no specific data regarding which chemicals the workers were exposed to) (OR = 3.1; 95% CI: 0.9–11.1). However, the study did not include a case history of the workers. It was difficult to evaluate the level of exposure to 2-chloroethanol because the 5 workers with non-lymphocytic leukaemia had contact not only with 2-chloroethanol, but also with ethylene oxide and dichloroethyl ether. In addition, 4 workers were exposed to ethylene dichloride. Positive associations were observed between the duration of exposure to the individual substances and the incidences of non-lymphocytic leukaemia (see below), but the ORs were increased only in the workers of the chlorohydrin unit who had been employed for more than 5 years: 16.1 (3 cases). The ORs for non-lymphocytic leukaemia after exposure for fewer than 5 years were 2.2 (2 cases) for 2-chloroethanol, 2.1 (3 cases) for ethylene oxide, 1.3 (2 cases) for dichloroethyl ether and 0.5 (1 case) for ethylene dichloride. The corresponding values for exposures lasting for more than 5 years were 3.3 (3 cases), 2.5 (4 cases), 4.0 (3 cases) and 7.1 (4 cases) (confidence intervals not reported). The sub-categories for tumours other than non-lymphocytic leukaemia were not included in the table (Ott et al. 1989). The exposure concentrations were not determined.

It is not possible to evaluate the carcinogenic potential of 2-chloroethanol in humans on the basis of this study because the exposure concentration was not reported, the workers were exposed to more than one substance and the number of cases was small.

4.7.2 Cohort studies

Workers of a plant in West Virginia that produced 2-chloroethanol were followed up for mortality from 1940 to the end of 1988. These follow-up investigations were carried out to verify the increased incidence of cancer in the cohort of 278 male workers from this unit, which produced primarily 2-chloroethanol from 1925 to 1957. Ethylene dichloride (1,2-dichloroethane) and bis(2-chloroethyl) ether were formed as by-products of 2-chloroethanol production. The mean length of employment was 5.9 years and the mean duration until the follow-up investigation was 36.5 years. Standardized mortality ratios (SMRs) were calculated based on comparisons with the white male population of the United States. The SMR for pancreatic cancer was 492 (95% CI: 158–1140) based on 8 observed deaths (1.6 expected deaths). There were no additional deaths from leukaemia, but the 3-fold to 4-fold increase in the risk of lymphatic tumours persisted because new cases of non-Hodgkin's lymphomas (no other details) and a death from multiple myelomas were observed. The SMR for lymphatic and haematopoietic tumours was 294 (95% CI: 127–580; 8 observed cases compared with 2.7 expected cases). The risk for the total number of cancers, for all lymphatic and haematopoietic tumours and for leukaemia increased with an increase in the length of employment in this unit. However, most of the cases involved workers who had been employed in this unit during the 1930s when exposure was monitored to an even lower extent. In view of the probable exposure, the known toxicity of the chemicals and data from animal studies, the authors assumed that these cancers were most likely caused by high levels of exposure to 1,2-dichloroethane, perhaps in combination with other chlorinated hydrocarbons (Benson and Teta 1993). It is not possible to establish a causal relationship between the occurrence of the tumours and the exposure to 2-chloroethanol because the workers were exposed to more than one substance.

Another cohort study was carried out in 1361 male workers at 3 different plants (Texas, Louisiana and Michigan) of a company that produced 2-chloroethanol and propylene chlorohydrin. The persons had worked in 2-chloroethanol and propylene chlorohydrin production for a minimum of 30 days in the period from 1940 to 1992. These production units were located within factories that produced also ethylene oxide and propylene oxide. A total of 300 deaths were observed up to the end of 1992. The SMR for malignant neoplasms was 94 (95% CI: 74–118). There was 1 death from pancreatic cancer, compared with 4.0 expected cases (SMR: 25; 95% CI: 1–140), and 10 deaths from lymphatic and haematopoietic tumours, compared with 7.7 expected cases (SMR: 129; 95% CI: 62–238). Additional analyses that included the location, production process, duration of employment and the 25-year latency period yielded no significant results. The authors noted that only an additional follow-up investigation after 5 to 10 years would ensure latency periods comparable to those in the study of Benson and Teta (1993) (Olsen et al. 1997).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Rats were exposed to an atmosphere enriched at 40 °C with aqueous 12.5%, 25% or 50% 2-chloroethanol solutions. All animals were dead after 150 minutes. In another study, the exposure of rats for 1 hour to 7.5 ml/m^3 was lethal; the inhalation of 2 ml/m^3 induced paralysis in some animals (no other details; Ambrose 1950 in Henschler 1993). The concentrations were only calculated, but not determined. The results of the study are inconsistent with those of all other acute inhalation studies in animals (see below) and humans; therefore, the concentrations were presumably miscalculated.

In a study similar to OECD Test Guideline 403, a 4-hour LC_{50} value between 16 and 62 ml/m³ was obtained in male and female Sherman rats (Carpenter et al. 1949 in Henschler 1993).

LC_{50} values of 117 and 918 ml/m³ were reported for mice and guinea pigs, respectively (no other details; NTP 1985).

Whole-body exposure of rats to saturated 2-chloroethanol vapour led to the death of the animals after 10 minutes. Mice died after 6.5 minutes after exposure to almost saturated 2-chloroethanol vapour (no other details; ECHA 2018).

5.1.2 Oral administration

Oral LD_{50} values between 60 and 150 mg/kg body weight are available for rats, mice, guinea pigs and rabbits (Henschler 1993).

5.1.3 Dermal application

2-Chloroethanol doses of 38 to 2957 (males) and 55 to 3713 mg/kg body weight (females) were applied once dermally (in 80% ethanol in water) to the shaved skin of groups of 2 to 9 male and female F344/N rats. The controls were treated with the vehicle alone. Within 4 hours, all males died at 473 mg/kg body weight and above and all females died at 1853 mg/kg body weight and above. A dermal LD_{50} value of about 416 mg/kg body weight was calculated for female rats. An LD_{50} value between 331 and 473 mg/kg body weight was estimated for male rats. No data were reported for the effects (NTP 1985).

2-Chloroethanol was applied once dermally to the skin of groups of 5 male and 5 female Swiss CD-1 mice in doses of 92 to 1411 mg/kg body weight and above (males) and 109 to 1875 mg/kg body weight and above (females). The controls were treated with the vehicle alone. After exposure to 1411 mg/kg body weight, 3 of 5 males died, and after exposure to 1875 mg/kg body weight, 2 of 5 females died. All males died at dose levels above 1411 mg/kg body weight (no other details) and all females died at dose levels above 1875 mg/kg body weight. All deaths occurred within 2 days after exposure. Necropsy did not reveal any unusual findings. A dermal LD_{50} value was not reported (NTP 1985).

Dermal LD_{50} values between 68 mg/kg body weight (Lawrence et al. 1971 in Henschler 1993) and 470 mg/kg body weight (Smyth and Carpenter 1945 in Henschler 1993) were reported for rats, rabbits and guinea pigs.

2-Chloroethanol was applied to the skin of guinea pigs at different concentration levels. An amount of 100 µl of the concentrated substance (about 320 mg/kg body weight) led to the death of all 20 test animals, 250 µl of a 35% solution (about 280 mg/kg body weight) was lethal in 50% of the animals, and 250 µl of a 10% solution (about 80 mg/kg body weight) led to the death of only 1 of 20 animals. A dermal LD_{50} value of 260 mg/kg body weight was estimated (no other details; ECHA 2018).

5.1.4 Subcutaneous and intraperitoneal injection

A subcutaneous LD_{50} value of 72 mg/kg body weight was reported for rats (Mason et al. 1971 in Henschler 1993).

None of 5 B6C3F1 mice died after single intraperitoneal injections of up to 1.2 mmol/kg body weight (97 mg/kg body weight). The alanine aminotransferase and L-iditol dehydrogenase (iditol: (2S,3R,4R,5S)-hexane-1,2,3,4,5,6-hexol) activities in the serum and the relative liver weights were increased at this dose level compared with the corresponding values in the controls. Pre-treatment with a single intraperitoneal diethyl maleate dose of 3.0 mmol/kg body weight to induce GSH depletion before the injection of a 2-chloroethanol dose of 0.9 mmol/kg body weight (72 mg/kg body weight) led to the death of 2 of 4 animals. No deaths were observed without pre-treatment (Storer and Conolly 1985).

After intraperitoneal injection, the LD_{50} values were 120 mg/kg body weight for male and female mice (strain not reported), 98 mg/kg body weight for male Swiss Webster mice and 134 mg/kg body weight for male ICR mice (ECHA 2018).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The studies that investigated the effects of 2-chloroethanol after repeated inhalation exposure are shown in Table 1. These studies were not carried out according to valid test guidelines. It is not possible to derive a NOAEC (no observed adverse effect concentration).

Tab. 1 Studies of the effects of 2-chloroethanol after repeated inhalation exposure of rats, guinea pigs and cats

Species, strain, number per group	Exposure	Findings	References
rat, 3, no other details	**3 or 11 days**, 900 ml/m³ (3000 mg/m³), 15 minutes/day, no other details	all animals died by the end of the study	Goldblatt and Chiesman 1944; Henschler 1993
rat, no other details	**4 months**, 1, 10 mg/m³ (0.3, 3 ml/m³), 2-week recovery period, no other details	**0.3 ml/m³ and above**: blood: lecithin and cholesterol ↑ (sign of a disturbance of the liver lipid metabolism); after the 2-week recovery period: effects reversible at 1 mg/m³; no other details; brief original study in Russian	ECB 2000
rat, 15 ♀, no other details	**4 months**, 0, 1, 10 mg/m³ (0.3, 3 ml/m³), 5 days/week, 2-week recovery period, no other details	**concentration not reported**: body weight gains ↓, central nervous symptoms, serum: beta-globulins ↓, albumin–globulin coefficient ↑, relative liver weights ↑, urine: decrease in excretion of hippuric acid after treatment with sodium benzoate; **3 ml/m³**: dystrophic changes of parenchymatous organs including the liver; no other details; brief 3-page original study in Russian	ECB 2000
guinea pig, 1, no other details	**4 days**, 670 ml/m³ (2200 mg/m³), 3 or 4 hours/day, no other details	animal died	Koelsch 1927 in Henschler 1993
cat, 1, no other details	**2 or 4 days**, 750 (4 × 3 hours), 1370 (2 × 5.5 hours) ml/m³ (2500, 4500 mg/m³), no other details	animal died	Koelsch 1927 in Henschler 1993

5.2.2 Oral administration

The studies that investigated repeated oral administration of 2-chloroethanol are shown in Table 2.

Tab. 2 Effects of 2-chloroethanol after repeated oral exposure of rats, dogs and monkeys

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 5 ♂	**60 days**, 0, 500 mg/l drinking water (about 0, 45 mg/kg body weight and day[a]), purity: 99%	**45 mg/kg body weight**: body weight gains ↓, serum: LDH, AST and ALT activities, IgA and IgG concentrations ↑, liver: cytosolic fraction: ADH activity ↓, lungs: lymphocytic infiltration around small veins and consisting of polymorphous populations of lymphocytes (4/5, possibly infection); increase in relative weights of kidneys, brain, testes; no unusual findings in the histopathological examination: liver, heart, spleen, brain, kidneys, pancreas, thymus, testes, intestines, skeletal muscle, lymph nodes, salivary glands; clinical findings not reported	Kaphalia et al. 1996
rat, strain not reported, 6–7 ♂	**53 days**; or **93 days**, then 43 days without exposure, then **136 days** of exposure, 0, 240 mg/l drinking water (24 mg/kg body weight and day), purity: no data	**24 mg/kg body weight**: no effects on body weight gains; infection of the animals during the study	ECHA 2018
rat, FDRL, 25 ♂, 25 ♀	**12 weeks**, 0, 30, 45, 67.5 mg/kg body weight and day, gavage, 7 days/week, initially diet for 6 weeks: gavage for 12 weeks because the substance was not stable in the diet, 7 days/week, purity: commercial product of Eastman Kodak Company, Rochester, NY	**45 mg/kg body weight**: **NOAEL for systemic effects**; **67.5 mg/kg body weight**: feed consumption ↓, laboured breathing, mortality ↑ (as animals were moribund, they were sacrificed within the first 3 weeks, 17 ♂ and 19 ♀), body weight gains ↓, feed consumption ↓, moribund animals: histopathological changes in the heart (myocarditis in ♂ and ♀, no other details), thyroid gland (decrease in colloid in 1 ♂ and 4 ♀, congestion in 4 ♂), liver (fatty degeneration in 1 ♂ and 5 ♀), lungs (congestive changes in ♂ and ♀, no other details); no unusual findings in: behaviour, organ weights, gross pathological or histopathological examinations (surviving animals) and in the remaining examinations; no clinical findings during administration with the diet; examinations carried out: haemoglobin, haematocrit, leukocyte count, prothrombin time, blood: urea nitrogen, glucose, serum: AST, AP; urinalysis (no other details); organ weights of liver, kidneys, heart, gonads, adrenal glands, thyroid gland, pituitary gland; histopathological examination of 26 organs/tissues from 10 animals of the highest dose group, 10 animals of the control group and from the animals that died or were moribund and of the liver and kidneys from representative animals of the lowest dose group	Carson and Oser 1969; Henschler 1993; Oser et al. 1975
rat, strain not reported, 5 ♂	**220 days**, 0%, 0.01%, 0.02%, 0.04%, 0.08%, 0.12%, 0.16%, 0.24%, 0.32%, 0.64%, 1.28% in the diet (about 0, 5, 10, 20, 40, 60, 80, 120, 160, 320, 640 mg/kg body weight and day[a]); purity: no data	**40 mg/kg body weight**: no effects; **60 mg/kg body weight and above**: body weights ↓; **80 mg/kg body weight and above**: feed consumption ↓; **120 mg/kg body weight and above**: mortality ↑; **160 mg/kg body weight and above**: all animals died; no unusual findings in the histopathological examination of the surviving animals	Ambrose 1950 in Henschler 1993

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
dog, beagle, 4 ♂, 4 ♀	**15 weeks**, 0, 600, 900, 1350 mg/kg diet (0, 15, 22.5, 33.8 mg/kg body weight and day), because of vomiting: dose reduction to a maximum of 18–20 mg/kg body weight and day, purity: commercial product (see above)	**15 mg/kg body weight**: **NOAEL for systemic effects**; **22.5 mg/kg body weight and above**: vomiting, squatting position; no deaths; variations in haemoglobin and haematocrit levels not dependent on the dose; no unusual findings in: organ weights, gross-pathological or histopathological examinations; no unusual findings in the mucosa of the stomach in spite of vomiting; examinations carried out: see study in rats, this table	Carson and Oser 1969; Henschler 1993; Oser et al. 1975
monkey, Macaca mulatta, 2 ♂, 2 ♀	**12 weeks**, 0, 30, 45, 62.5 mg/kg body weight and day, orally by syringe, 7 days/week, purity: commercial product (see above)	**45 mg/kg body weight**: **NOAEL for systemic effects**; **62.5 mg/kg body weight**: body weight gains ↓, no deaths; no unusual findings in: behaviour; no dose-dependent findings in organ weights, gross-pathological or histopathological examinations; examinations carried out: see study in rats, this table	Carson and Oser 1969; Henschler 1993; Oser et al. 1975

[a)] conversion factor: 0.09 for data from subchronic studies and 0.05 for chronic studies according to EFSA (2012)
ADH: alcohol dehydrogenase; ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; Ig: immunoglobulin; LDH: lactate dehydrogenase; NOAEL: no observed adverse effect level

Rat

A 60-day drinking water study in Sprague Dawley rats, in which only one dose was tested of 45 mg/kg body weight, reported reduced body weight gains, reduced alcohol dehydrogenase activity and lymphocytic infiltration in the lungs. The animals may have had an infection (Kaphalia et al. 1996), but this was not examined. Another drinking water study in rats was carried out also with only one dose. In addition, the animals had an infection (ECHA 2018). Therefore, the two studies have not been included in the evaluation.

Gavage doses of 67.5 mg/kg body weight and day given to FDRL rats for 12 weeks led to increased mortality within the first 3 weeks (17 males and 19 females were moribund and were therefore sacrificed) and to decreases in body weight gains and feed consumption. The animals were first given 2-chloroethanol with the diet for 6 weeks. However, as the test substance was not stable, it was then administered by gavage. A high incidence of subacute myocarditis was found in the males and females that died. In addition, a decrease in colloid, congestion in the thyroid gland, fatty degeneration of the liver and a high incidence of congestive changes in the lungs were observed in a few of the animals that died. No unusual or dose-dependent findings were obtained at the two lower doses of 30 and 45 mg/kg body weight and day or in the surviving animals of the high dose group (Carson and Oser 1969; Henschler 1993; Oser et al. 1975). A NOAEL for systemic toxicity of 45 mg/kg body weight and day was derived (Carson and Oser 1969). The scope of the examinations carried out in the study of Oser et al. (1975) was sufficient. However, as the methods and results were described only briefly, the study is of only limited suitability for the evaluation.

In another study in rats with a restricted scope of examinations and insufficient documentation, body weight gains were reduced at about 60 mg/kg body weight and day and above. The dose of 40 mg/kg body weight and day did not induce any effects (Ambrose 1950 in Henschler 1993).

Dog

In a study in beagle dogs with administration via the diet, vomiting was observed at 22.5 mg/kg body weight and day and above; therefore, the doses were reduced. Subsequently, the highest dose tested was 18 to 20 mg/kg body weight and day. No other unusual findings were obtained. None of the animals died (Carson and Oser 1969; Henschler 1993; Oser et al. 1975). The NOAEL for systemic effects was 15 mg/kg body weight and day.

Monkey

In a study with exposure of Macaca mulatta monkeys to doses of 0, 30, 45 or 62.5 mg/kg body weight and day, body weight gains were reduced at the highest dose tested. None of the animals died. No other unusual findings were observed in this study (Carson and Oser 1969; Henschler 1993; Oser et al. 1975). The NOAEL for systemic effects was 45 mg/kg body weight and day (Carson and Oser 1969).

5.2.3 Dermal application

The studies that investigated repeated dermal application of 2-chloroethanol are shown in Table 3.

Tab. 3 Effects of 2-chloroethanol after repeated dermal exposure of rats and mice

Species, strain, number per group	Exposure	Findings	References
rat, F344/N, 5 ♂, 5 ♀	**14 days**, 0, 20, 30, 40, 60, 80 mg/animal and day, ♂: 0, 114, 172, 226, 339, 442 mg/kg body weight and day; ♀: 0, 147, 222, 313, 451, 611 mg/kg body weight and day, dermal application to the shaved skin, 7 days/week, vehicle: 80% ethanol in water, purity: 99%	**442 mg/kg body weight**: ♂: 1/5 died; **451 mg/kg body weight**: ♀: 2/5 died; **611 mg/kg body weight**: ♀: no deaths; no unusual changes: body weights, body weight gains, necropsy; no skin irritation; no histopathological examinations	NTP 1985
rat, F344/N, 10 ♂, 10 ♀	**13 weeks**, similar to OECD Test Guideline 411; 0, 62, 125, 250, 500, 1000 mg/kg body weight and day, dermal application to the shaved skin, 5 days/week, vehicle: 80% ethanol in water, purity: 99%	**62 mg/kg body weight**: ♀: **NOAEL for systemic effects**; **125 mg/kg body weight and above**: ♀: pancreas: vacuolar changes of acinar cells; **125 mg/kg body weight**: ♂: **NOAEL for systemic effects**; **250 mg/kg body weight**: ♂: 1/10 died, ♀: 3/10 died; **250 mg/kg body weight and above**: ♂/♀: lungs: congestion; ♂: pancreas: vacuolar changes of acinar cells; **500 mg/kg body weight**: ♂: 8/10 died, ♀: 8/10 died; **1000 mg/kg body weight**: all animals died; no unusual changes: body weights, body weight gains; no skin irritation	NTP 1985
rat, F344/N, 50 ♂, 50 ♀	**103 weeks**, 0, 50, 100 mg/kg body weight and day, dermal application to the shaved skin, 5 days/week, vehicle: 70% ethanol in water, purity: 99%	**100 mg/kg body weight**: **NOAEL for systemic effects**; no unusual changes: body weights, survival, necropsy, histopathological examination of about 43 organs/tissues; no skin irritation; see Section 5.7.2	NTP 1985

Tab. 3 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mouse, Swiss Webster, 5 ♂, 5 ♀	**14 days**, 0, 2.5, 5, 10, 20, 30, 45, 60 mg/animal and day, ♂: 0, 92, 174, 377, 741, 1095, 1411, 2182 mg/kg body weight and day; ♀: 0, 109, 225, 435, 847, 1376, 1875, 2703 mg/kg body weight and day, dermal application to the shaved skin, 7 days/week, vehicle: 80% ethanol in water, purity: 99%	**1411 mg/kg body weight**: ♂: 3/5 died; body weights ↓; **1875 mg/kg body weight**: ♀: 3/5 died; **2182 mg/kg body weight**: ♂: all died; **2703 mg/kg body weight**: ♀: all died; no unusual changes at necropsy; no skin irritation; no histopathological examinations carried out	NTP 1985
mouse, Swiss CD-1, 10 ♂, 10 ♀	**13 weeks**, similar to OECD Test Guideline 411; 0, 5, 10, 20, 30, 45 mg/animal and day, ♂: 0, 192, 385, 769, 1154, 1731 mg/kg body weight and day; ♀: 0, 227, 455, 909, 1304, 1957 mg/kg body weight and day, dermal application to the shaved skin, 5 days/week, vehicle: 80% ethanol in water, purity: 99%	**385 mg/kg body weight:** ♂: **NOAEL for systemic effects**; **455 mg/kg body weight**: ♀: **NOAEL for systemic effects**; **769 mg/kg body weight**: ♂: 1/10 died; kidneys: acute nephrosis (1/9); **909 mg/kg body weight**: ♀: 3/10 died; **1154 mg/kg body weight**: ♂: all animals died; kidneys: acute nephrosis (1/1), liver: fatty degeneration of hepatocellular cells (1/1); **1304 mg/kg body weight**: ♀: 9/10 died; kidneys: acute nephrosis (1/3), pancreas: necrosis of acinar cells (2/3), liver: fatty degeneration of hepatocellular cells (2/3); **1731 mg/kg body weight**: ♂: all animals died; **1957 mg/kg body weight**: ♀: 9/10 died; no unusual changes: body weights, body weight gains; no skin irritation	NTP 1985
mouse, Swiss CD-1, 50 ♂, 50 ♀	**104 weeks**, 0, 7.5, 15 mg/animal and day, 0, 253, 630 mg/kg body weight and day in week 1, 0, 188, 411 mg/kg body weight in week 100, 2 control groups: vehicle control and untreated; once/day, dermal application to the shaved skin, 5 days/week, vehicle: 70% ethanol in water, purity: 99%	**253/188 mg/kg body weight**: **NOAEL for systemic effects**; **630/411 mg/kg body weight**: mortality ↑; ♂: 7/50 died within the first 3 days, all with inflammation at the treatment sites, 5 of them: ulceration at the treatment sites, 5 of them: lungs: congestion, inflammation, haemorrhage; see Section 5.7.2	NTP 1985

NOAEL: no observed adverse effect level

Rat

The dermal exposure of male and female F344/N rats to 2-chloroethanol for 14 days did not cause skin irritation at the application site up to the highest doses tested of 442 and 611 mg/kg body weight and day, respectively. One male animal died at 442 mg/kg body weight and day, and one female died at 451 mg/kg body weight and day. Histopathological examinations were not carried out (NTP 1985).

After dermal exposure of F344/N rats to 2-chloroethanol for 13 weeks, an increased incidence of vacuolar changes of the pancreatic acinar cells was observed in the females at 125 mg/kg body weight and day and above. The same changes in the pancreas were observed in the males at 250 mg/kg body weight and above; in addition, congestion of the lungs and increased mortality were found. The NOAEL for systemic effects was 62 mg/kg body weight and day for females and 125 mg/kg body weight and day for males. Skin irritation was not observed up to the highest dose tested of 1000 mg/kg body weight and day (NTP 1985).

A carcinogenicity study with dermal exposure for 103 weeks did not report unusual systemic or local findings up to the highest dose tested of 100 mg/kg body weight and day. The MTD was not reached. The NOAEL for systemic effects was 100 mg/kg body weight and day, which was the highest dose tested (NTP 1985; see Section 5.7.2).

Mouse

The dermal exposure of Swiss Webster mice to 2-chloroethanol for 14 days led to increased mortality in males and females at 1095 and 1376 mg/kg body weight and day and above, respectively. Skin irritation was not observed in either the male or female animals up to the highest dose tested of 1411 or 1875 mg/kg body weight and day. Histopathological examinations were not carried out (NTP 1985).

In a dermal study carried out in Swiss CD-1 mice for 13 weeks, mortality was increased in the males and females at 769 and 909 mg/kg body weight and day and above, respectively. In addition, effects on the kidneys were found at 769 and 1154 mg/kg body weight and day, and effects on the liver were observed in the males at 1154 mg/kg body weight and day. At 1304 mg/kg body weight and day, effects on the kidneys, liver and pancreas were found in the females. The NOAEL for systemic effects was 385 mg/kg body weight and day for males and 455 mg/kg body weight and day for females. Skin irritation was not observed (NTP 1985).

A carcinogenicity study with dermal exposure of Swiss CD-1 mice for 104 weeks yielded increased mortality in the males at the highest dose tested of 630/411 mg/kg body weight and day. In the animals that died, inflammation (7/7 animals) and ulceration (5/7 animals) were observed at the application site and congestion, inflammation and haemorrhage were found in the lungs (5/7 animals). The NOAEL for systemic effects was 253 or 188 mg/kg body weight and day (NTP 1985; see Section 5.7.2).

Rabbit

In rabbits, the repeated dermal application of 0.5 ml 2-chloroethanol on 4 consecutive days led to the death of some of the test animals (no other details; Ambrose 1950 in Henschler 1993).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

The report of a study that used a method similar to OECD Test Guideline 404 did not include information either about the solvent used with 2-chloroethanol or about the volume applied, which does not conform to the test guideline. Test patches (2.5 by 2.5 cm) with the test substance were applied semi-occlusively to the shaved skin of 2 male Vienna White rabbits for 1, 5 or 15 minutes. The animals died within 24 hours after application. Mild erythema, which was the maximum local effect, was observed 15 minutes after application. Additional experiments demonstrated that rabbits do not survive after dermal application for 20 hours (ECHA 2018).

A study that used a method similar to OECD Test Guideline 404 did not conform to the test guideline in the following respects: occlusive application, volume of substance applied only 0.2 ml, exposure period of 2 hours, no readings taken after 1 hour, no data for oedema, findings only after 24 and 72 hours reported. In the study, the shaved skin of 6 New Zealand White rabbits per group (sex not reported) was exposed to the undiluted substance and to concentrations of 1%, 10% or 20%. The effects were evaluated after 24 and 72 hours by means of the Draize method. The undiluted substance caused mild erythema after 24 hours, which was reversible. No effects were induced by the diluted substance (ECHA 2018).

Another study that used a method similar to OECD Test Guideline 404 did not conform to the test guideline in the following respects: exposure periods of 24 and 48 hours, occlusive application, readings taken only at the end of exposure and a volume of substance applied of only 0.2 ml. In addition, documentation was limited. No signs of irri-

tation were found on the skin of New Zealand White rabbits after application of the undiluted test substance for 24 or 48 hours (ECHA 2018).

Summary: 2-Chloroethanol induced mild skin irritation in rabbits.

5.3.2 Eyes

In a study of eye irritation from 1973 that used a method similar to OECD Test Guideline 405, 60 mg undiluted 2-chloroethanol was instilled into the conjunctival sac of the right eye of 2 male Vienna White rabbits. Physiological saline alone was instilled into the other eye. The eyes were examined after 24, 48 and 72 hours. The irritation scores for the conjunctivae, chemosis and cornea of the 2 animals were 1 (conjunctivae, maximum: 3), 2.33 (chemosis, maximum: 4) and 2.33 and 2.67 (cornea, maximum: 4). None of the effects were reversible within 8 days except for chemosis in 1 animal. In addition, in deviation from Test Guideline 405, only 50 µl was used instead of 100 µl; this is a limitation of the study. The documentation was also limited, and a different system of evaluation was used (ECHA 2018).

In another study similar to OECD Test Guideline 405 that was carried out with undiluted 2-chloroethanol in 6 rabbits (strain not reported), the eyes were evaluated according to Draize. Mean irritation scores for effects on the iris of 1.8, 2.0 and 1.8 (maximum: 2) were recorded after 24, 48 and 72 hours, respectively. The effects on the cornea were only mild; the irritation index was 0.8 (maximum: 4) after 24 hours and subsequently returned to 0. After 24, 48 and 72 hours, the irritation scores for effects on the conjunctivae were 1.1, 2 and 2 (maximum: 3), respectively, and those for chemosis were 2.1, 2.3 and 1.6 (maximum: 4), respectively. At a dilution of 1:2, the test substance no longer induced opacity of the cornea. Mild irritation was still observed at a dilution of 1:5, and no effects were found at a dilution of 1:10. 2-Chloroethanol thus caused severe irritation of the eyes, and the effects on the iris were the main effects. In deviation from the OECD Test Guideline, details of the method were not reported; however, the study was carried out according to Federal Register Section 191.12. In addition, there is no information about the reversibility of the effects with the exception of the reversibility of conjunctival redness (ECHA 2018).

Three other studies that were included in the REACH dossier as supporting studies likewise reported irritant effects on the rabbit eye (ECHA 2018).

Summary: 2-Chloroethanol caused severe, irreversible eye irritation in rabbits.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

A local lymph node assay carried out with 2.5%, 5% and 10% 2-chloroethanol in acetone/olive oil (4:1) yielded stimulation indices of 1.2, 1.0 and 1.6, respectively, and thus negative results at these concentrations (Ashby et al. 1995).

Likewise, a modified maximization test with 2 groups of only 5 Hartley guinea pigs yielded negative results (no other details); however, this study has not been included in the evaluation because of the methodological inadequacies and the very poor documentation. Induction consisted of intradermal injections of 5% or 10% 2-chloroethanol, and both topical induction and the challenge treatment seem to have been carried out with the same concentration. Cottonseed oil was probably used as the vehicle. It was not reported whether the animals were treated with sodium lauryl sulfate before the topical induction (Lawrence et al. 1971 in Henschler 1993).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Fertility studies carried out according to valid test guidelines are not available.

When male T-stock mice were given 2-chloroethanol by intraperitoneal injection, fertility was not impaired up to the highest dose tested of 60 mg/kg body weight and day (Sheu et al. 1983).

Three male rats were given 2-chloroethanol by gavage for 8 days at a dose level of 30 mg. After the rats were mated with 1 untreated female, 13 implantations were observed in 1 pregnant animal on day 9 or 10 of gestation. One mating was not successful and there are no data for the third male. According to the authors, the substance does not reduce fertility (Ericsson and Youngdale 1970). The study cannot be used to evaluate fertility because of the lack of sufficient data.

The dermal long-term carcinogenicity studies did not report effects on the reproductive organs after 103-week exposure of F344/N rats up to the highest dose tested of 100 mg/kg body weight and day and after 104-week exposure of Swiss CD-1 mice up to the highest dose tested of 630/411 mg/kg body weight and day (NTP 1985; see Section 5.2.3).

5.5.2 Developmental toxicity

The studies that investigated the prenatal developmental toxicity of 2-chloroethanol are shown in Table 4.

Tab. 4 Studies with prenatal exposure to 2-chloroethanol

Species	Exposure	Findings	References
oral administration			
mouse, CD-1, 10–12 ♀	**GD 6–16**, 0, 50, 100, 150 mg/kg body weight and day, gavage, vehicle: water, purity: 99%, examination: GD 17	**50 mg/kg body weight**: **NOAEL developmental and maternal toxicity**; **50 mg/kg body weight**: foetuses: relative liver weights ↓ (by 6.2%); **100 mg/kg body weight and above**: dams: body weight gains ↓; foetuses: body weights ↓, absolute and relative liver weights ↓ (100 mg/kg body weight: absolute weights by 19.5%; relative weights by 8.7%); **150 mg/kg body weight**: dams: mortality: 75%, the remaining 25%: not pregnant; limited number of animals	Courtney et al. 1982
mouse, CD-1, 3–4 ♀, 227 mg/kg body weight: 13 ♀	**GD 6–16**, 0, 16, 43, 77, 227 mg/kg body weight and day, drinking water, vehicle: water, purity: 99%, examination: GD 17	**227 mg/kg body weight**: **NOAEL developmental and maternal toxicity**; no toxic effects up to the highest dose, no increase in frequency of malformations; small number of animals	Courtney et al. 1982
rat, Long Evans, 34 ♀ control animals, no other details	**GD 6–15**, 0%, 0.02%–24% of the oral LD_{50}, gavage, vehicle: no data, purity: no data, examination: no data	dose-dependent increase in malformations and embryolethality (no other details); abstract only	Mankes et al. 1985

Tab. 4 *(continued)*

Species	Exposure	Findings	References
intravenous injection			
mouse, CD-1, 5–25 ♀	**range-finding study**, **GD 6–8**, 0, 30, 60, 90, 120, 130, 140, 150, 180, 210 mg/kg body weight and day, vehicle: 5% dextrose, purity: pure substance of Eastman Kodak, examination: GD 17	**120 mg/kg body weight and above**: dams: mortality ↑ (16% and more, 120 mg/kg body weight: 4/26), weight losses, lethargy, vaginal haemorrhages, tremor, convulsions; **130 mg/kg body weight and above**: foetuses: number and percentage of live foetuses per litter ↓; **150 mg/kg body weight and above**: dams: 100% mortality	NIEHS 1983 a
mouse, CD-1, 34–54 ♀, 4 replicates per treatment period	**GD 4–6, GD 6–8, GD 8–10 or GD 10–12**, 0 (vehicle control), 60, 120 mg/kg body weight and day, vehicle: 5% dextrose, purity: pure substance of Eastman Kodak, examination: GD 17, mostly like OECD Test Guideline 414, according to OECD Test Guideline: GD 5–15	**GD 4–6**: **120 mg/kg body weight**: dams: no mortality, body weight gains ↓, occasional hyperactivity, resorptions/litter ↑; foetuses: body weights/litter ↓; no statistically significant change in percentage of malformations or variations compared with that in the controls; **GD 6–8**: **120 mg/kg body weight**: dams: mortality (4/50, 8%), body weight gains ↓, body weight losses, resorptions/litter ↑; foetuses: body weights/litter ↓; no statistically significant change in percentage of malformations or variations compared with that in the controls; **GD 8–10**: **60 mg/kg body weight**: **NOAEL developmental and maternal toxicity**; **60 mg/kg body weight**: foetuses: body weights/litter ↓ (by 5%, but number of foetuses per litter: 12, controls: 11.5, which might explain reduced body weights); **120 mg/kg body weight**: dams: mortality (7/57; 12.3%), body weight gains ↓, body weight losses, gravid uterus weights ↓, resorptions/litter ↑; foetuses: percentage of malformed foetuses ↑ (2.3%, controls: 0.2%; statistical analysis: incidence statistically significant only in replicate 3 with high mortality: 7/15; 46.7%); **GD 10–12**: **120 mg/kg body weight**: dams: mortality (10/64; 15.6%), body weight gains ↓, body weight losses, piloerection, gravid uterus weights ↓, resorptions/litter ↑; foetuses: number of dead foetuses/litter ↓, body weights/litter ↓; no statistically significant change in percentage of malformations or variations compared with that in the controls	LaBorde et al. 1982; NIEHS 1983 a
rabbit, New Zealand White, 4–5 ♀	**range-finding study**, **GD 6–14**, 0, 10, 20, 30, 40 mg/kg body weight and day, intravenous, vehicle: 5% dextrose, purity: pure substance of Eastman Kodak, examination: GD 30	**30 mg/kg body weight and above**: dams: local irritation at the injection site, number of implantations/litter ↓ (not in the main study, therefore more an incidental finding); **40 mg/kg body weight**: dams: mortality (1/4), local irritation at the injection site	NIEHS 1983 b

Tab. 4 *(continued)*

Species	Exposure	Findings	References
rabbit, New Zealand White, 15–21 ♀	**GD 6–14**, 0 (vehicle controls and untreated controls), 9, 18, 36 mg/kg body weight and day, intravenous, vehicle: 5% dextrose, purity: pure substance of Eastman Kodak, examination: GD 30, mostly like OECD Test Guideline 414, according to OECD Test Guideline: GD 6–16	**36 mg/kg body weight**: **NOAEL developmental and maternal toxicity** dams: mortality: 0 (vehicle control): 1/23 (4.3%), 9 mg/kg body weight: 1/19 (5.2%), 18 mg/kg body weight: 3/22 (13.6%), 36 mg/kg body weight: 3/20 (15.0%); no unusual findings: dams: body weights, body weight gains, gravid uterus weights; foetuses: implantation sites/litter, percentage of resorbed, dead, not live (dead and resorbed), affected (not live and malformed) foetuses per litter, litter size, mean body weights, body weights/litter, sex ratio, percentage of malformed foetuses/litter, percentage of foetuses with 1 or more malformations/litter, external, visceral and skeletal variations and malformations	LaBorde et al. 1982; NIEHS 1983 b

GD: gestation day; NOAEL: no observed adverse effect level

Oral administration

In a prenatal developmental toxicity study in **CD-1 mice** that were given gavage doses of 2-chloroethanol from days 6 to 16 of gestation, maternal body weights were decreased and, at the same time, the body weights and absolute and relative liver weights of the foetuses were reduced at 100 mg/kg body weight and day and above (Courtney et al. 1982). The NOAEL for developmental and maternal toxicity was 50 mg/kg body weight and day. However, at 10 to 12 animals, only a small number of animals were tested.

The same research group examined exposure of **CD-1 mice** via the drinking water from days 6 to 16 of gestation. Toxic effects were not observed either in the dams or in the foetuses up to the highest dose tested of 227 mg/kg body weight and day (Courtney et al. 1982). The number of animals was small.

Dose-dependent increases in the incidences of malformations and embryolethality were found in a study in **Long Evans rats** with gavage administration of 0.02% to 24% of the oral LD_{50}; the study is available only as an abstract (no other details, Mankes et al. 1985). The study has not been included in the evaluation because of the inadequate description.

Intravenous injection

In a range-finding study for the developmental toxicity study in **CD-1 mice** given intravenous injections of 2-chloroethanol from days 6 to 8 of gestation, increased mortality of 16% and higher was observed in the dams at 120 mg/kg body weight and day and above. The percentage of live foetuses per litter was reduced at the next-higher dose of 130 mg/kg body weight and day and above (NIEHS 1983 a).

In the main study in **CD-1 mice** with intravenous injection in various phases of gestation, the period from days 8 to 10 of gestation was the most sensitive period for the induction of developmental toxicity caused by 2-chloroethanol. At 60 mg/kg body weight and day, the foetal weights were reduced by 5% per litter without maternal toxicity; the number of live foetuses per litter was 12 in this dose group and 11.5 in the control group, which might explain the reduced foetal body weights. At the highest dose tested of 120 mg/kg body weight and day, 7 of 57 dams (12.3%) died, body weight gains were reduced and the number of resorptions per litter was increased. In this dose group, the increase in the percentage of malformed foetuses of 2.3% was statistically significant compared with that of 0.2% in the control group. At 120 mg/kg body weight and day, external malformations were observed in 2 of 408 foetuses tested (2 of 36 tested litters), visceral malformations were found in 1 of 362 (1 of 32 tested litters) and skeletal malformations were observed in 4 of 362 (3 of 32 tested litters). However, only 1 external malformation was found in 1 of 623 tested foetuses (1 of 54 tested litters) in the control group. A statistical analysis of the 4 replicates of this period of gestation demonstrated that the incidences were statistically significant only in replicate 3 with a high level of mortality in the dams (7/15;

46.7%). The incidence of malformations or variations was not increased in any other period of gestation tested up to the high dose of 120 mg/kg body weight and day (LaBorde et al. 1982; NIEHS 1983 a). In this study, administration was not continuous in the period from days 5 to 15 of gestation, as recommended by the OECD Test Guideline. Instead, the animals were treated for several short periods during gestation. However, organogenesis (up to day 12 of gestation) was completely covered by the 4 tested periods of gestation, and the most sensitive period for the induction of developmental toxicity from days 8 to 10 of gestation was included. The NOAEL for developmental and maternal toxicity during this period was 60 mg/kg body weight and day.

In a range-finding study for a prenatal developmental toxicity study in **New Zealand White rabbits** with intravenous injection from days 6 to 14 of gestation, the number of implantations was reduced at 30 mg/kg body weight and day and above. As the effect was not observed in the main study that followed, it seems to be an incidental finding (NIEHS 1983 b).

In the main study in **New Zealand White rabbits** with intravenous injection from days 6 to 14 of gestation, no unusual findings were observed either in the dams or in the foetuses up to the highest dose tested of 36 mg/kg body weight and day (LaBorde et al. 1982; NIEHS 1983 b). For the most part, the study was carried out using a method similar to the one described in the OECD Test Guideline. However, the period of administration covered only days 6 to 14 of gestation instead of days 6 to 16 of gestation. The NOAEL for developmental and maternal toxicity was thus 36 mg/kg body weight and day. The actual NAEL (no adverse effect level) may be higher.

5.6 Genotoxicity

5.6.1 In vitro

The numerous in vitro studies of the genotoxicity of 2-chloroethanol are shown in Table 5.

Tab. 5 In vitro studies of the genotoxicity of 2-chloroethanol

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m. a.	+m. a.		
rec assay	Bacillus subtilis	up to 1 mM, vehicle: DMSO, purity: no data, commercially available	no data	–	n. t.		Elmore et al. 1976
SOS response	Escherichia coli prophage lambda	728–93 234 µM, vehicle: cell medium, purity: no data, commercially available	+ 23 308 µM and above	+	+	–m. a.: + at 2914 µM and above; +m. a.: + at 728 µM and above	DeMarini and Brooks 1992
gene mutation (fluctuation test)	Klebsiella pneumoniae	0, 1.5, 15, 150 mM, vehicle: no data, purity: no data	no data	+	n. t.	no data for effect level	Henschler 1993; Voogd and Vet 1969
gene mutation (fluctuation test)	Klebsiella pneumoniae	0, 2, 5, 10, 20, 50, 100, 200 mM, vehicle: no data, purity: no data, commercially available	200 mM	+	n. t.	–m. a.: + at 5 mM and above	Henschler 1993; Knaap et al. 1982
gene mutation	Salmonella typhimurium TA1530, TA1535, TA1538	5, 10, 15, 17.5, 20 µl/plate, substances on impregnated sterile paper, purity: no data				no negative controls	Henschler 1993; Rosenkranz and Wlodkowski 1974

Tab. 5 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m. a.	+m. a.		
	Salmonella typhimurium TA1530		no data	+	n. t.	+ no data for effect level	
	Salmonella typhimurium TA1535		no data	+	n. t.	+ no data for effect level	
	Salmonella typhimurium TA1538		no data	–	n. t.		
gene mutation (plate incorporation)	Salmonella typhimurium TA1530, TA1535, G-46, TA1538	0, 0.4, 4, 40 µmol/ml, vehicle: no data, highest commercially available purity				TA1530 most sensitive, results for the other strains not listed in tables	Henschler 1993; Malaveille et al. 1975
	Salmonella typhimurium TA1530		–	+	+	–m. a.: + at 40 µmol/ml: 6-fold increase in revertants; +m. a.: + at 4 µmol/ml: 13-fold increase in revertants	
	Salmonella typhimurium TA1535		–	–	–		
	Salmonella typhimurium G-46		–	–	–		
	Salmonella typhimurium TA1538		–	–	–		
gene mutation (pre-incubation)	Salmonella typhimurium TA1535	experiment 1: 0, 0.1, 0.5, 1.5 mM, experiment 2: 0, 1, 10, 100, 500, 1000 mM, vehicle: water, purity: no data, commercially available substance	1000 mM: survival: 72%	+	n. t.	–m. a.: + at 1000 mM: 2-fold increase in revertants	Henschler 1993; Rannug et al. 1976
gene mutation (plate incorporation)	Salmonella typhimurium TA98, TA100, TA1535, TA1537	0, 5–300 µmol/plate, vehicle: water, purity: 99.5%					Henschler 1993; Pfeiffer and Dunkelberg 1980
	Salmonella typhimurium TA98		–	–	n. t.		
	Salmonella typhimurium TA100		–	(+)	n. t.	–m. a.: (+) at 300 µmol/plate: 1.5-fold increase in revertants	
	Salmonella typhimurium TA1535		–	+	n. t.	–m. a.: + at 300 µmol/plate: 2-fold increase in revertants; TA1535 more sensitive than TA100, number of revertants taken from a graph	

Tab. 5 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m. a.	+m. a.		
	Salmonella typhimurium TA1537		–	–	n. t.		
gene mutation (plate incorporation)	Salmonella typhimurium TA100	0, 1, 10, 100 µmol/plate, vehicle: no data, purity: 99%	–	+	+	–m. a.: + at 100 µmol/plate; +m. a.: + at 100 µmol/plate	Stolzenberg and Hine 1980
gene mutation (plate incorporation)	Salmonella typhimurium TA1530	0, 1.1, 10.8, 108 µmol/plate, vehicle: no data, purity: no data, commercially available	–	+	+	–m. a.: + at 108 µmol/plate: 5-fold increase in revertants; +m. a.: + at 108 µmol/plate: 10-fold increase in revertants	Bartsch et al. 1975
gene mutation (plate incorporation)	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	up to 1 mM, vehicle: DMSO, purity: no data, commercially available					Elmore et al. 1976
	Salmonella typhimurium TA98		no data	–	n. t.		
	Salmonella typhimurium TA100		no data	–	n. t.		
	Salmonella typhimurium TA1535		no data	–	n. t.		
	Salmonella typhimurium TA1537		no data	–	n. t.		
	Salmonella typhimurium TA1538		no data	–	n. t.		
gene mutation (plate incorporation)	Salmonella typhimurium TA100, TA1535	0, 10, 20, 40 µl/plate, vehicle: no data, purity: no data, commercially available					Bignami et al. 1980
	Salmonella typhimurium TA100		–	–	(+)	number of revertants almost a 2-fold increase (taken from the graph)	
	Salmonella typhimurium TA1535		–	+	+	–m. a.: + at 20 µl/plate and above; +m. a.: + at 10 µl/plate and above	
	Streptomyces coelicolor	0, 4, 10, 20, 40, 60 µl/plate	60 µl/plate: survival: 80%	–	n. t.		
gene mutation (plate incorporation)	Salmonella typhimurium TA100, TA1535	up to 5000, vehicle: no data, highest commercially available purity					McCann et al. 1975

Tab. 5 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m. a.	+m. a.		
	Salmonella typhimurium TA100		–	+	+	–m. a.: number of revertant colonies, TA100: per µmole: 2-chloroethanol: 0.6; 2-chloroacetaldehyde: 746	
	Salmonella typhimurium TA1535		–	–	+	no data for effect level	
gene mutation (pre-incubation)	Salmonella typhimurium TA98, TA100, TA1535, TA1537	0, 100, 333, 1000, 3333, 10 000, vehicle: water, purity: 99%					Haworth et al. 1983
	TA98		–m. a.: – +m. a.: 3333 and above	–	–		
	TA100		–	+	–	–m. a.: + at 10 000: 2-fold increase	
	TA1535		–	–	+	+m. a. + at 3333 and above: 2-fold increase	
	TA1537		–m. a.: 1000 and above +m. a.: 3333 and above	–	–		
gene mutation (plate incorporation)	Salmonella typhimurium TA100, TA1535	0, 30, 100, 300, 1000 µmol/plate, vehicle: no data, purity: no data, commercially available					Nakamura et al. 1979
	TA100		+ at 1000 µmol/plate	–	–		
	TA1535		+ at 1000 µmol/plate	–	+	+m. a.: + at 300 µmol/plate and above	
gene mutation	Aspergillus nidulans	0, 12.5, 25, 50, 100 µl/plate, vehicle: no data, purity: no data, commercially available	–	+	n. t.	–m. a.: + at 100 µl/ml	Bignami et al. 1980
gene mutation	Schizosaccharomyces pombe	0, 3.12–50 µM, vehicle: water, purity: about 94%	no data	–	–		Henschler 1993; Loprieno et al. 1977
gene conversion	Saccharomyces cerevisiae	0, 10, 100 mM, vehicle: no data, purity: about 94%	no data	–	–		Henschler 1993; Loprieno et al. 1977
DNA synthesis inhibition	HeLa cells	concentration not reported, vehicle: no data, purity: no data	no data	–	–		Painter and Howard 1982

Tab. 5 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m.a.	+m.a.		
SCE	CHO cells	–m.a.: 0, 119, 396, 1200, 4000, 5000, 6000 µg/ml, +m.a.: 0, 40, 119, 396 µg/ml, vehicle: cell medium, purity: 99%	5000 µg/ml and above: delay in cell cycle progression	+	+	–m.a.: + at 1200 µg/ml and above; +m.a.: + at 119 µg/ml and above	Ivett et al. 1989
DNA strand breaks, alkaline elution	primary hepatocyte culture	0, 0.125, 0.25, 0.5 mM, 20-hour incubation, vehicle: no data, purity: no data, commercially available	0.5 mM: decrease in cell viability: < 30%	–	n.t.		Allavena et al. 1992
UDS	primary hepatocyte culture	0, 10, 100 mM, 20-hour incubation, vehicle: no data, purity: no data, commercially available	0.5 mM: decrease in cell viability: < 30%	–	n.t.		Allavena et al. 1992
CA	CHO cells	–m.a.: 0, > 5000 µg/ml, +m.a.: 0, 794, 980, 2000 µg/ml, vehicle: cell medium, purity: 99%	decrease in cell confluence: 980 µg/ml: 25%, 2000 µg/ml: 38%	+	+	–m.a.: + at > 5000 µg/ml; +m.a.: + at 980 µg/ml and above	Ivett et al. 1989
gene mutation, HPRT	L5178Y mouse lymphoma cells	0, 10, 100 mM, vehicle: no data, purity: no data, commercially available	survival at 100 mM: 64.9%	–	n.t.		Henschler 1993; Knaap et al. 1982
gene mutation, 8-azaguanine and ouabain resistance (g-strophantin)	V79 cells	up to 2100 µM, vehicle: DMSO, purity: no data, commercially available	–	–	n.t.		Huberman et al. 1975
gene mutation, $TK^{+/-}$	L5178Y mouse lymphoma cells similar to OECD Test Guideline 476	–m.a.,: experiment 1: 0, 313, 625, 1250, 2500, 5000 µg/ml; experiment 2: 0, 2000, 3000, 4000, 5000 µg/ml; +m.a.: experiment 1: 0, 20, 40, 80, 160, 320 µg/ml; experiment 2: 0, 40, 100, 160, 220, 280 µg/ml; vehicle: DMSO, incubation period: 4 hours, purity: substances obtained from NTP Chemical Repository	–m.a.: none up to 5000 µg/ml; +m.a.: 160 µg/ml and above; 220 µg/ml: RTG: < 10%	–	+	+m.a.: +: experiment 1: 80 µg/ml: mutation frequency: 98, controls: 47, borderline effect; experiment 2: 160 µg/ml and above	McGregor et al. 1988

[a)] unless otherwise specified

CA: chromosomal aberrations; DMSO: dimethyl sulfoxide; +/–m.a.: with/without the addition of a metabolic activation system; n.t.: not tested; HPRT: hypoxanthine-guanine phosphoribosyltransferase; RTG: relative total growth; SCE: sister chromatid exchange; TK: thymidine kinase; UDS: test for DNA repair synthesis

A rec assay in Bacillus subtilis yielded negative results up to the highest concentration tested of 1 mM 2-chloroethanol (Elmore et al. 1976). 2-Chloroethanol induced the SOS response in Escherichia coli (DeMarini and Brooks 1992). In 2 fluctuation tests with Klebsiella pneumoniae, the substance increased the mutation frequency without the addition of a metabolic activation system (Henschler 1993; Knaap et al. 1982; Voogd and Vet 1969).

Numerous tests for gene mutations in Salmonella typhimurium strains demonstrated that TA1535 (Bignami et al. 1980; Haworth et al. 1983; Henschler 1993; McCann et al. 1975; Nakamura et al. 1979; Pfeiffer and Dunkelberg 1980; Rannug et al. 1976; Rosenkranz and Wlodkowski 1974) and TA1530 (Bartsch et al. 1975; Henschler 1993; Malaveille et al. 1975; Rosenkranz and Wlodkowski 1974) were the most sensitive strains. Only a very weak mutagenic potential was observed in bacteria without the addition of a metabolic activation system. The mutagenic effect was many times greater after the addition of a metabolic activation system. A comparative study of 2-chloroethanol and 2-chloroacetaldehyde yielded 0.6 and 746 revertant colonies per µmole, respectively, without the addition of a metabolic activation system (McCann et al. 1975). This suggests that the main effect of 2-chloroethanol is indirect mutagenicity mediated by 2-chloroacetaldehyde. The Salmonella strains TA1530 and TA1535 are indicators of base-pair substitutions.

In various yeast strains, the incidence of gene mutations was increased (Bignami et al. 1980) and gene conversions were either not induced (Henschler 1993; Loprieno et al. 1977) or their incidence was not increased (Henschler 1993; Loprieno et al. 1977).

While DNA synthesis was not inhibited in HeLa cells (Painter and Howard 1982), the incidence of sister chromatid exchange was increased in CHO (Chinese hamster ovary) cells (Ivett et al. 1989).

2-Chloroethanol did not induce either DNA strand breaks or DNA repair synthesis in a primary hepatocyte culture (Allavena et al. 1992).

Chromosomal aberrations were induced in CHO cells (Ivett et al. 1989).

In several gene mutation tests in mammalian cells without the addition of a metabolic activation system, no evidence of mutagenic effects was found (Henschler 1993; Huberman et al. 1975; Knaap et al. 1982; McGregor et al. 1988). Experiment 1 of a $TK^{+/-}$ test with L5178Y mouse lymphoma cells and the addition of a metabolic activation system yielded a 2-fold increase in the mutation frequency at 80 µg/ml compared with the levels in the control group; this increase could not be reproduced in experiment 2. In experiment 2, the mutation frequency was increased more than twice only with concurrent cytotoxicity (McGregor et al. 1988). Therefore, the mutagenicity in L5178Y mouse lymphoma cells is regarded as a borderline effect.

5.6.2 In vivo

The in vivo studies that investigated the genotoxicity of 2-chloroethanol are shown in Table 6.

Tab. 6 In vivo genotoxicity studies with 2-chloroethanol

Test system		Dose	Results	References
somatic cells				
UDS, hepatocytes	rat, Sprague Dawley, 5 ♂	single or twice at an interval of 24 hours, 0, 45.5 mg/kg body weight and day, oral, vehicle: phosphate-buffered physiological saline, purity: no data, commercially available	–	Allavena et al. 1992
DNA strand breaks, alkaline elution, hepatocytes	rat, Sprague Dawley, 5 ♂	single or twice at an interval of 24 hours, 0, 45.5 mg/kg body weight and day, oral, vehicle: phosphate-buffered physiological saline, purity: no data, commercially available	–	Allavena et al. 1992
DNA strand breaks, alkaline elution, hepatocytes	mouse, B6C3F1, 4 or 5 ♂	single, 0, 0.9, 1.05, 1.20 mmol/kg body weight (0, 72, 85, 97 mg/kg body weight), intraperitoneal, vehicle: 0.85% NaCl, purity: no data, commercially available	–	Storer and Conolly 1985

Tab. 6 *(continued)*

Test system		Dose	Results	References
somatic cells				
MN, bone marrow	mouse, B6C3F1, 5 ♂	single, 0, 25, 50, 100 mg/kg body weight, intraperitoneal, vehicle: phosphate-buffered physiological saline, purity: no data, commercially available	–	Shelby et al. 1993
MN, polychromatic erythrocytes in the bone marrow and hepatocytes	rat, Sprague Dawley, 5 ♂	single with partial hepatectomy or twice at an interval of 24 hours without hepatectomy, 0, 45.5 mg/kg body weight and day, oral, vehicle: phosphate-buffered physiological saline, purity: no data, commercially available	–	Allavena et al. 1992
CA, bone marrow	rat, no other details	up to 3 months, 4 hours/day, 6 days/week, 0, 1, 10 mg/m^3, inhalation, purity: no data	questionably + no differentiation between chromatid and chromosome breaks, translocations and gaps, study does not comply with current standards	ECB 2000; Isakova et al. 1971
germ cells				
SLRL	Drosophila, 5 broods	injection into the abdomen, 0, 3, 15 mM, 0.2 µl/fly, vehicle: physiological saline, purity: no data, commercially available	–	Henschler 1993; Knaap et al. 1982
SLRL	Drosophila, 5 broods	0, 3 mM, in the diet, 24 hours, vehicle: no data, purity: no data, commercially available	–	Henschler 1993; Knaap et al. 1982
SLRL	Drosophila, 3 broods	inhalation, 4 hours, 400 ml/m^3, mortality: 20%, purity: 99%	–	Valencia et al. 1985
heritable translocations	mouse, T-stock, 50 ♂, controls: 25 ♂, number of offspring examined: 692, 576, 475 at 0, 30, 60 mg/kg body weight and day	5 weeks, 5 days/week, 0, 30, 60 mg/kg body weight and day, intraperitoneal, vehicle: distilled water, purity: no data	–	Sheu et al. 1983
dominant lethal mutations	mouse, ICR/Ha Swiss, 10 ♂	5 days, 0, 20, 65, 130 mg/kg body weight and day, gavage, vehicle: water, purity: no data, commercially available	–	Epstein et al. 1972

CA: chromosomal aberration test; MN: micronucleus test; SLRL: sex-linked recessive lethal test; UDS: test for DNA repair synthesis

Somatic cells

Numerous in vivo tests such as a UDS test in hepatocytes (Allavena et al. 1992), tests for DNA strand breaks in hepatocytes (Allavena et al. 1992; Storer and Conolly 1985) and micronucleus tests in bone marrow and hepatocytes (Allavena et al. 1992; Shelby et al. 1993) yielded no evidence of a genotoxic potential of 2-chloroethanol in vivo.

An increased incidence of chromosomal aberrations in the bone marrow of rats was observed in only one chromosomal aberration test after inhalation exposure to 2-chloroethanol. The number of chromosomal aberrations was statistically significantly increased, and the course of mitosis was delayed. The number of chromosomal aberrations was determined after 1, 15, 60 and 120 days of exposure. The highest increase was observed after 15 and 60 days of exposure (no other details; ECB 2000; Isakova et al. 1971). The original study was published in Russian together with an English summary. No differentiation was made between chromatid and chromosome breaks, translocations, and gaps. Gaps were probably included in the chromosomal aberrations. The study does not comply with current standards.

The 1983 documentation (Henschler 1993) included a study (Semenova et al. 1971 in Henschler 1993) that reported an increase in chromosomal aberrations after long-term inhalation exposure of rats to 2-chloroethanol. The original study in Russian is not available.

The pre-treatment of mice with a single intraperitoneal diethyl maleate dose of 3.0 mmol/kg body weight to induce glutathione depletion before the injection of a 2-chloroethanol dose of 0.9 mmol/kg body weight (72 mg/kg body weight) did not lead to an increase in the incidence of DNA strand breaks in the hepatocytes. Therefore, it is not very likely that the detoxification of 2-chloroacetaldehyde via glutathione conjugation contributes to the negative results obtained in the genotoxicity test (Storer and Conolly 1985).

Germ cells

Three tests with Drosophila for X-chromosomal recessive lethal mutations yielded negative results. The animals were treated by injection, via the diet or by inhalation (Henschler 1993; Knaap et al. 1982; Valencia et al. 1985).

The fertility of the parental animals was not impaired in a test for heritable translocations up to the highest dose tested of 60 mg/kg body weight and day. At 30 and 60 mg/kg body weight and day, 3 and 1 male offspring, respectively, were sterile. No reciprocal translocations were observed in any of the 3 offspring of the low dose group. However, 2 translocations independent of each other were found in 1 of the offspring of the high dose group, which is very unusual. There was no statistically significant difference between the frequency of translocations related to the number of tested animals of 2/475 (assuming that the 2 independent translocations were found in 2 different animals) and compared with that in the controls of 0/692 (Sheu et al. 1983). Clastogenic and aneugenic effects can be detected by the heritable translocation test.

A dominant lethal test in mice did not result in increases in either pre-implantation losses or post-implantation losses up to the highest dose tested of 130 mg/kg body weight and day (Epstein et al. 1972).

Summary

With the addition of a metabolic activation system 2-chloroethanol was mutagenic in bacteria (base-pair substitutions); its mutagenic potential was much weaker without the addition of a metabolic activation system. The results obtained in bacteria are probably evidence of an indirect effect that is mediated by the metabolic formation of 2-chloroacetaldehyde. In mammalian cells, 2-chloroethanol was not mutagenic in the $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells without the addition of a metabolic activation system and caused very weak mutagenicity with metabolic activation. The data obtained in vivo, such as the negative test results for DNA strand breaks or the induction of DNA repair, provide no evidence of mutagenicity. With the exception of one study, tests for clastogenicity in somatic cells in vivo yielded negative results. The original study, which was published in Russian with an English summary (Isakova et al. 1971), is available and its result is not consistent with any other in vivo test for clastogenicity. The tests in somatic cells, a heritable translocation test and a dominant lethal test in mice provided no evidence of a genotoxic (clastogenic or aneugenic) potential for 2-chloroethanol in vivo.

5.7 Carcinogenicity

5.7.1 In vitro

A transformation test in BALB/c-3T3 cells was carried out with 2-chloroethanol concentrations of 0, 725, 1530, 2979 or 5959 µg/ml. The culture medium was used as the solvent. Positive responses were obtained in 2 experiments at 725 µg/ml and above. The authors reported that the substance reacted with water; the cells were thus exposed additionally to oxidized and hydrolysed products. The substance was assessed as active in the transformation test (Matthews et al. 1993).

No increased incidence of cell transformations was observed in another transformation test in BALB/3T3 cells with 2-chloroethanol concentrations up to 5000 µg/ml. Growth was 67.5% at 5000 µg/ml (Kajiwara et al. 1997).

5.7.2 Long-term studies

The 1983 documentation described several studies with subcutaneous injection in rats and mice that did not report substance-induced increases in tumour incidences (Derse 1968 in Henschler 1993; Dunkelberg 1983; Homburger 1968 in Henschler 1993; Mason et al. 1971 in Henschler 1993). However, the studies are not suitable for an evaluation of the carcinogenic potential of 2-chloroethanol because a form of administration was used that is not relevant to exposure at the workplace.

In an oral study described in the 1983 documentation, 50 female Sprague Dawley rats were given gavage doses of 2-chloroethanol in salad oil of 2.5 or 10 mg/kg body weight twice a week for 150 weeks. Tumour incidences were not increased in the treated animals (Dunkelberg 1983; Henschler 1993). This study has not been included in the evaluation of carcinogenicity because treatment was very short with doses that were given only twice a week.

In carcinogenicity studies with dermal exposure of male and female animals, no substance-induced increases in tumour incidences were observed up to the highest doses tested of 100 mg/kg body weight and day (F344 rats) and 15 mg/animal (630 mg/kg body weight and day in week 1 and 411 mg/kg body weight and day in week 100) (Swiss CD-1 mice). However, the MTD was not reached in rats. The analysis of blood samples from untreated sentinel animals (test animals for the detection of latent pathogens in animal populations) yielded evidence of virus infections such as the Sendai virus in rats and mice and the mouse minute or mouse hepatitis virus (NTP 1985). As the MTD was not reached in male or female rats, the carcinogenicity of 2-chloroethanol in rats after dermal application cannot be definitively evaluated (see Table 7).

A mutated v-Ha-ras gene has been inserted in the germ cell line of the Tg AC mouse. This gene is regulated by a foetal zetaglobin promoter sequence. When 2-chloroethanol was applied to the shaved skin at a dose level of 20 mg 5 times a week, an increased incidence of skin papillomas was not observed (Tennant et al. 1995, 1996).

Tab. 7 Studies of the carcinogenicity of 2-chloroethanol

Author:	NTP 1985
Species:	**rat**, F344/N, 50 ♂, 50 ♀
Administration route:	dermal application to the shaved skin
Dose:	0, 50, 100 mg/kg body weight and day, purity: 99%, solvent: 70% ethanol in water, control group: solvent
Duration:	103 weeks, once/day, 5 days/week
Toxicity:	no unusual findings: survival or body weights, no further toxicity, MTD not reached

Tab. 7 *(continued)*

		dose (mg/kg body weight and day)		
		0	**50**	**100**
surviving animals at the end of the study	♂	33/50 (66%)	37/50 (74%)	36/50 (72%)
	♀	42/50 (84%)	39/50 (78%)	38/50 (76%)
tumours:				
no increased tumour incidences				

Author:	NTP 1985
Species:	**mouse**, Swiss CD-1, 50 ♂, 50 ♀
Administration route:	dermal application to the shaved skin
Dose:	0, 7.5, 15 mg/animal and day, according to the authors, corresponding to the doses: in week 1: 0, 253, 630 mg/kg body weight and day, in week 100: 0, 188, 411 mg/kg body weight and day, purity: 99%, solvent: 70% ethanol in water, 2 control groups: solvent, untreated
Duration:	104 weeks, once/day, 5 days/week
Toxicity:	630/411 mg/kg body weight: 7 ♂ died within the first 3 days, all with inflammation at the treatment site, 5: ulceration at the treatment site, 5: lungs: congestion, inflammation, haemorrhage

		dose (mg/kg body weight and day)		
		0	**253/188**	**630/411**
surviving animals at the end of the study	♂	26/50 (52%)	16/50 (32%)	12/50 (24%)
	♀	26/50 (52%)	20/50 (40%)	20/50 (40%)
tumours:				
253/188 mg/kg body weight: ♂: increases in the incidence of lymphomas and leukaemia (combined) and of alveolar/bronchiolar adenomas or carcinomas (combined), but not considered individually; no increases in the high dose group				

5.8 Other effects

2-Chloroethanol induced the uncoupling of oxidative phosphorylation in mitochondria isolated from rat livers. Maximum stimulation was observed at 600 mM (97.6%) (Bhat et al. 1991).

In male Sprague Dawley rats given a single 2-chloroethanol dose of 50 mg/kg body weight by gavage, 2-chloroethyl palmitate, 2-chloroethyl oleate and 2-chloroethyl stearate were formed in the microsomal fraction of the liver 5 days after administration. These substances were not quantified. The fatty acid conjugates may be retained in the body (Kaphalia and Ansari 1989).

DNA synthesis was not increased in two in vivo tests for replicative DNA synthesis in hepatocytes of F344 rats (Uno et al. 1994) and B6C3F1 mice (Miyagawa et al. 1995) after single doses of up to 35 mg/kg body weight (rat) and 40 mg/kg body weight (mouse), respectively.

6 Manifesto (MAK value/classification)

In rabbits, 2-chloroethanol induced mild irritation of the skin and severe, irreversible eye irritation. Irritation of the respiratory tract is therefore assumed.

The target organs after inhalation exposure, oral administration and dermal application were the liver, kidneys and pancreas in rats and mice and, in addition, the thyroid gland, heart and lungs in rats.

MAK value. No data are available from studies of exposed persons that can be used to derive a MAK value. None of the inhalation studies with animals were carried out according to valid test guidelines. A MAK value cannot be derived from these studies. Likewise, the oral studies have various weaknesses, such as limited reporting of the methods and results. Therefore, the MAK value has been derived on the basis of a combined evaluation of the oral and dermal studies.

The toxicokinetic extrapolation of the NOAELs derived from oral and dermal studies to concentrations in air yielded similar results (Table 8); however, for the intensification of the effects over time, a higher factor than 1:2 would have to be considered for the studies in dogs and monkeys because of their longer lifespans. The toxicokinetics after dermal exposure is similar to that after inhalation exposure because the substance is absorbed slowly and there is no first-pass effect. However, there is a pronounced first-pass effect after oral administration; this probably leads to the formation of the toxic metabolite 2-chloroacetaldehyde. A steep dose–response relationship was observed after administration by gavage; this is explained by the severe glutathione depletion induced following bolus injection. Therefore, administration by gavage is regarded as the worst case for the derivation of the MAK value. The NOAEL of 45 mg/kg body weight and day derived from the 12-week gavage study in rats (Oser et al. 1975) is regarded as sufficiently reliable as a result of the scope of examinations of the study.

Tab. 8 NOAELs in various species and their extrapolation to possible limit values

Species (references)	Exposure	NOAEL	LOAEL	End point	Concentration in air = possible limit value[a)]	
rat (Kaphalia et al. 1996)	drinking water, 60 days	15 mg/kg body weight (LOAEL/3)	45 mg/kg body weight (only 1 dose)	body weight gains ↓, ADH activity ↓, lungs: lymphocytic infiltration (infection?)	9 mg/m³	**2.7 ml/m³**
rat (Oser et al. 1975)	gavage, 12 weeks (+ diet for preceding 6 weeks, dose not known because the test substance was not stable in the diet)	45 mg/kg body weight	67.5 mg/kg body weight	mortality ↑ (animals sacrificed because moribund: 17/25 ♂ and 19/25 ♀), body weight gains ↓, feed consumption ↓, animals that died: histopathological changes in the heart, thyroid gland, liver, lungs	28 mg/m³	**8.5 ml/m³**
dog (Oser et al. 1975)	diet, 15 weeks	15 mg/kg body weight	22.5 mg/kg body weight	vomiting, squatting position	26 mg/m³	**7.9 ml/m³**
monkey (Oser et al. 1975)	oral by syringe, 12 weeks	45 mg/kg body weight	62.5 mg/kg body weight	body weight gains ↓	55 mg/m³	**16.7 ml/m³**
rat (NTP 1985)	dermal, 13 weeks, 5 days/week	62 mg/kg body weight	125 mg/kg body weight	pancreas: vacuolar changes of acinar cells	14 mg/m³	**4.2 ml/m³**
rat (NTP 1985)	dermal, 2 years, 5 days/week	100 mg/kg body weight		highest dose tested	22 mg/m³	**6.7 ml/m³**
mouse (NTP 1985)	dermal, 2 years, 5 days/week	about 200 mg/kg body weight	15 mg/animal, 630 mg/kg body weight in week 1/411 mg/kg body weight in week 100	mortality ↑ 38/50 ♂ and 30/50 ♀; controls: 24/50 ♂ and 24/50 ♀, lungs: congestion, inflammation, haemorrhage	25 mg/m³	**7.6 ml/m³**

LOAEL: lowest observed adverse effect level; NOAEL: no observed adverse effect level

[a)] considerations and assumptions: daily exposure of the animals in comparison with exposure for 5 days at the workplace (7:5; except in dermal studies), species-specific correction values (rat, dog, monkey, mouse: 1:4, 1:1.4, 1:2, 1:7), oral absorption (100%) because it was almost complete in rat studies, dermal absorption (25%) determined in a comparison of the LOAELs for mortality in rats in subchronic studies with oral administration (62.5 mg/kg body weight and day, 7 days/week) and dermal application (250 mg/kg body weight and day, 5 days/week), the body weight (70 kg) and the respiratory volume (10 m³) of the person, the assumed 100% absorption by inhalation, and intensification of the effects over time: 60-day and 12/13-week studies: 1:2, exception: no intensification of the effects over time in the dermal 13-week study in rats because of the lack of effects on the pancreas in the 2-year study; extrapolation from animals to humans: 1:2

As 2-chloroethanol induced mild skin irritation and severe, irreversible eye irritation in rabbits, irritation of the respiratory tract is assumed. Local irritation was not observed in workers exposed to 2-chloroethanol and 1,2-dichloroethane up to a 2-chloroethanol concentration of about 18 ml/m³ (Goldblatt and Chiesman 1944). A burning sensation in the nose and eye irritation were observed in workers only at markedly higher concentrations of about 400 to 500 ml/m³ (Bush et al. 1949). Therefore, local irritation is not expected to occur after exposure at the MAK value for 2-chloroethanol of 2 ml/m³.

Peak limitation. As systemic effects are critical, 2-chloroethanol remains classified in Peak Limitation Category II. The excursion factor of 1 has been retained on the basis of the steep dose–response relationship.

Prenatal toxicity. In 1989, 2-chloroethanol was classified in Pregnancy Risk Group C on the basis of the MAK value of 1 ml/m³ (3.3 mg/m³).

The studies relevant to the evaluation, their toxicokinetic extrapolation and the resulting margins to the MAK value of 2 ml/m³ (6.7 mg/m³) are shown in Table 9.

Tab. 9 NOAELs relevant to the evaluation derived from prenatal developmental toxicity studies in mice and rabbits, toxicokinetic extrapolation of the NOAELs to concentrations in air and the resulting margins to the MAK value of 2 ml/m³ (≙6.7 mg/m³)

References	Species, exposure	NOAEL: end point	Toxicokinetic extrapolation[a] (ml/m³) [mg/m³]	Margin to the MAK value
	oral			
Courtney et al. 1982	mouse, gavage	50 mg/kg body weight: developmental and maternal toxicity	15 [50]	8
		100 mg/kg body weight: dams: body weight gains ↓; foetuses: body weights ↓	30 [100]	15
Courtney et al. 1982	mouse, drinking water	227 mg/kg body weight: developmental and maternal toxicity, highest dose	68 [227]	34
	intravenous			
NIEHS 1983 a	mouse	most sensitive period: GD 8–10 60 mg/kg body weight: developmental and maternal toxicity	18 [60]	9
		120 mg/kg body weight: dams: mortality, body weight gains ↓, body weight losses, gravid uterus weights ↓, resorptions/litter ↑; foetuses: percentage of malformed foetuses ↑	36 [120]	18
NIEHS 1983 b	rabbit	36 mg/kg body weight: developmental and maternal toxicity, highest dose tested	31 [105]	16

NOAEL: no observed adverse effect level

[a] NOAEL × 1:7 (mouse) and 1:2.4 (rabbit) × 70 kg / 10 m³ × 1.0 (oral absorption or intravenous injection in animals) / 1.0 (absorption by inhalation in humans)
assumption: 100% oral absorption in mice because it is almost complete in rats (Grunow and Altmann 1982)

The 8-fold margin to the MAK value of 2 ml/m³ derived in the study in mice is regarded as sufficiently high because gavage is a form of bolus administration. Likewise, this margin to the MAK value of 2 ml/m³ is regarded as sufficiently high in the light of the steep dose–response relationship and because the 100% bioavailability after intravenous injection represents the worst case. Therefore, 2-chloroethanol remains classified in Pregnancy Risk Group C.

Carcinogenicity. 2-Chloroethanol was not carcinogenic in the only carcinogenicity study suitable for the evaluation. The study was carried out in Swiss CD-1 mice with dermal application of 15 mg/animal (630 mg/kg body weight and day in week 1 and 411 mg/kg body weight and day in week 100) (NTP 1985).

2-Chloroethanol was mutagenic in bacteria with the addition of a metabolic activation system and caused very weak mutagenicity in mammalian cells. In vivo, 2-chloroethanol is not regarded as genotoxic (see below Section "Germ cell mutagenicity").

The primary metabolite 2-chloroacetaldehyde is classified in Carcinogen Category 3 B (Greim 1999). The rate-limiting step is the oxidation of 2-chloroethanol to 2-chloroacetaldehyde by alcohol dehydrogenase. Only small amounts of 2-chloroacetaldehyde are formed; in vivo, they are probably detoxified relatively efficiently by binding to glutathione. For example, after a single intraperitoneal injection of a 2-chloroethanol dose of 72 mg/kg body weight, increased hepatotoxicity with mortality was observed with glutathione depletion, whereas it was not observed without glutathione depletion (see Section 2; Storer and Conolly 1985). Detoxification of 2-chloroacetaldehyde in vivo cannot be quantified on the basis of the available literature. However, 2-chloroacetaldehyde seems to be inactivated rapidly in vivo because 2-chloroethanol did not induce a significant increase in tumour incidences in carcinogenicity studies in rats or mice and was not genotoxic in vivo.

2-Chloroethanol has not been classified in any of the categories for carcinogens because the carcinogenicity study in mice yielded negative results and the substance was not genotoxic in vivo.

Germ cell mutagenicity. With the addition of a metabolic activation system 2-chloroethanol was mutagenic in bacteria (base-pair substitutions); its mutagenic potential was much weaker without the addition of a metabolic activation system. The results obtained in bacteria are probably evidence of an indirect effect that is mediated by the metabolic formation of 2-chloroacetaldehyde. In mammalian cells, 2-chloroethanol was not mutagenic in the $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells without the addition of a metabolic activation system and caused very weak mutagenicity with metabolic activation. The data obtained in vivo, such as the negative test results for DNA strand breaks or the induction of DNA repair, provide no evidence of mutagenicity. With the exception of one study, tests for clastogenicity in somatic cells in vivo yielded negative results. The original study, which was published in Russian with an English summary (Isakova et al. 1971), is available and its result is not consistent with any other in vivo test for clastogenicity. The tests in somatic cells, a heritable translocation test and a dominant lethal test in mice provided no evidence of a clastogenic or aneugenic potential for 2-chloroethanol in vivo. Therefore, 2-chloroethanol is not regarded as genotoxic in vivo. On the basis of these results, classification in one of the germ cell mutagen categories is not required.

Absorption through the skin. There are no quantitative in vivo or in vitro data available for the absorption of 2-chloroethanol through the skin. The relatively low LD_{50} values after a single dermal application indicate that skin contact poses a high risk. An estimate based on a comparison of the LOAELs for mortality from subchronic oral and dermal studies in rats yielded the dermal absorption of about 25% of the applied dose. In addition, reports of poisonings after dermal contact with 2-chloroethanol at the workplace support the assumption that absorption through the skin substantially contributes to the systemic toxicity of the substance. Therefore, 2-chloroethanol remains designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no positive findings in humans for sensitizing effects of 2-chloroethanol on the skin or respiratory tract, and a valid local lymph node assay in mice yielded negative results. Therefore, 2-chloroethanol is not designated with “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

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

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