The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Pentachloroethane

MAK Value Documentation – Translation of the German version from 2020

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

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

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

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

Keywords

1,1,1,2,2-pentachloroethane; hepatocellular carcinoma; liver tumor promotor; alpha-2u-globulin; toxicity; MAK value; maximum workplace concentration; peak limitation; skin absorption

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated pentachloroethane [76-01-7] considering all toxicological end points. In a carcinogenicity study with pentachloroethane, male rats showed a non-significantly increased incidence of kidney tumours induced by the alpha-2u-globulin mechanism. This mechanism is specific to male rats and not relevant for humans. Pentachloroethane leads to hepatocellular carcinomas in B6C3F1 mice. As pentachloroethane is not considered to be genotoxic in vivo, these tumours are assumed to have been caused by tumour promotion. Although no corresponding studies are available, pentachloroethane is assumed to be a liver tumour promotor like the related compounds hexachloroethane and 1,1,2-trichloroethane for which this has been confirmed experimentally. B6C3F1 mice are known for a high incidence of spontaneously initiated liver cells and are therefore very susceptible for liver carcinogenesis via the stimulation of proliferation. Pentachloroethane may induce cytotoxic effects in the liver, probably arising from metabolically formed radicals. This effect is relevant also for humans and pentachloroethane is classified in Carcinogen Category 3B. Pentachloroethane is neither a mutagen in vitro nor a clastogen in vivo. In a 13-week toxicity study with rats, the body weight gain was reduced at 125 mg/kg body weight and day. Based on the NOAEL of 50 mg/kg body weight and day, a maximum concentration at the workplace (MAK value) of 2 ml/m^3 has been established. By analogy with the related compounds hexachloroethane and 1,1,2,2-tetrachloroethane, no irritation is expected at this concentration. As the critical effect is systemic, pentachloroethane has been assigned to Peak Limitation Category II. The default excursion factor of 2 has been set because the half-life is not known. There are no developmental toxicity studies of pentachloroethane and the substance has therefore been assigned to Pregnancy Risk Group D. Model calculations predict that pentachloroethane can be taken up via the skin in toxicologically relevant amounts and the substance is therefore designated with "H". There are no data that show that pentachloroethane is a skin or airway sensitizer.

Citation Note:
Hartwig A, MAK Commission. Pentachloroethane. MAK Value Documentation – Translation of the German version from 2020. MAK Collect Occup Health Saf. 2022 Dec;7(4):Doc074. https://doi.org/10.34865/mb7601e7_4or

Manuscript completed:
26 Mar 2019

Publication date:
19 Dec 2022

MAK value (2019)	**2 ml/m³ (ppm) ≙ 17 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 2**
Absorption through the skin (2019)	**H**
Sensitization	**–**
Carcinogenicity (2019)	**Category 3 B**
Prenatal toxicity (2019)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	ethane pentachloride pentalin
Chemical name	1,1,1,2,2-pentachloroethane
CAS number	76-01-7
Structural formula	CCl_3–$CHCl_2$
Molecular formula	C_2HCl_5
Molar mass	202.29 g/mol
Melting point	–29 °C (NLM 2019)
Boiling point	162 °C (NLM 2019)
Density at 20 °C	1.68 g/cm³ (IARC 1986)
Vapour pressure at 25 °C	4.7 hPa (NLM 2019)
log K_{OW}	3.22 (NLM 2019)
Solubility at 25 °C	0.49 g/l water (NLM 2019)
1 ml/m³ (ppm) ≙ 8.393 mg/m³	**1 mg/m³ ≙ 0.119 ml/m³ (ppm)**

Since 1991 it has been prohibited in Germany to place pentachloroethane or preparations containing the substance on the market for private use or for use in non-commercial premises (BMJV 1991). Pentachloroethane does not occur naturally and was a solvent used, for example, in cellulose plastics, natural gums and resins, for dry cleaning, as a drying agent for wood and for cleaning coal. There is no evidence that pentachloroethane is still used for these purposes. It may be formed as an intermediate in the synthesis of chlorinated ethylenes (IARC 1999).

1 Toxic Effects and Mode of Action

After gavage administration of pentachloroethane doses of 250 or 500 mg/kg body weight and day to male and female B6C3F1 mice for 40 to 103 weeks, high mortality and hepatocellular carcinomas were observed from week 30 onwards. Oral pentachloroethane doses of 75 or 150 mg/kg body weight and day administered to F344 rats over a period of 2 years caused diffuse inflammation of the kidneys, mineralization of the renal papillae and renal tumours in male rats due to an α_{2u}-globulin-mediated mechanism. Pentachloroethane increased mortality also in female rats without a specific mechanism or target organ being evident.

Pentachloroethane is not mutagenic in bacteria, but mutagenic in yeast and is clastogenic in mammalian cells. In vivo mutagenicity tests are not available. Clastogenic effects in vitro have not been confirmed in vivo.

Model calculations suggest high dermal absorption.

There are no studies of sensitization or developmental toxicity caused by the substance.

2 Mechanism of Action

The exact mechanism of action of the hepatocarcinogenicity of pentachloroethane is not known. Pentachloroethane increased replicative DNA synthesis in the hepatocytes of B6C3F1 mice 39 and 48 hours after the administration of 1000 mg/kg body weight, thus inducing cell proliferation (Miyagawa et al. 1995). Pentachloroethane has no relevant genotoxic potential, and the tumour-promoting activity has not been studied. The administration of single doses of pentachloroethane to mice markedly decreased the cytochrome P450 (CYP) content in the liver (see Section 3.2). However, the hepatotoxicity seems to affect mainly cytochrome P448 (no other details; Bronzetti et al. 1989). Intraperitoneal administration to male CD1 mice reduced the total CYP activity to about 50% of the control value and aminopyrine *N*-demethylase activity to 90% of the control value. Pentoxyresorufin *O*-dealkylase and ethoxyresorufin *O*-deethylase (CYP1A1) activities were increased to up to 330% and 520% of the control value, respectively (Paolini et al. 1992).

The toxic and carcinogenic effects could be due to the formation of radicals during reductive dechlorination. However, studies using rat liver microsomes or hepatocytes for reductive dechlorination with several chloroalkanes showed that the extent of dechlorination or radical formation did not correspond to the carcinogenic potency of chloroalkanes in mouse liver (Nastainczyk et al. 1982; Salmon et al. 1981, 1985; Thompson et al. 1984; Tomasi et al. 1984). Therefore, the contribution of radical formation to the hepatocarcinogenicity is unclear.

In NMRI mice, 2% to 16% of the pentachloroethane absorbed is metabolized to trichloroethylene and 3% to 9% to tetrachloroethylene. Both substances induced hepatocellular carcinomas also in B6C3F1 mice, but not in Osborne-Mendel rats (Greim 1998; Hartwig and MAK Commission 2019). Therefore, it is reasonable to assume that B6C3F1 mice (with the same quantitative metabolism as NMRI mice) may have been systemically exposed to 40 and 80 mg trichloroethylene/kg body weight and day and 23 and 46 mg tetrachloroethylene/kg body weight and day, respectively, when treated with 250 or 500 mg pentachloroethane/kg body weight and day. It is possible that these metabolites are responsible for the hepatocarcinogenicity, but there are insufficient data to support this. In the studies with trichloroethylene and tetrachloroethylene, the lowest effective doses were 1169 and 536 mg/kg body weight and day in the male animals and 869 and 368 mg/kg body weight and day in the female animals, respectively (NTP 1983).

Likewise, hexachloroethane, present as an impurity (4.2%) in the pentachloroethane used, induced an increased incidence of hepatocellular carcinomas in mice, but not in rats (NCI 1978). Mice given the low dose of pentachloroethane (250 mg/kg body weight and day) were exposed to 10.5 mg hexachloroethane/kg body weight and day, those given the high dose (500 mg/kg body weight and day) to 21 mg hexachloroethane/kg body weight and day. It is unlikely that this low dose alone is responsible for the hepatocellular carcinomas associated with exposure to pentachloroethane (NTP 1983). In the study with hexachloroethane, the lowest effective dose was 590 mg/kg body weight and day (NCI 1978).

A comparison of the studies with different chloroethanes showed that many of the substances led to an increased incidence of hepatocellular carcinomas in mice, but not in rats. In vitro mutagenicity tests with the corresponding substances yielded negative results. One reason for the induction of liver tumours in B6C3F1 mice but not in rats may be the high spontaneous incidence and cytotoxic mechanisms in the liver. The structurally similar substances 1,1,2-trichloroethane (Hartwig and MAK Commission 2022 b) and hexachloroethane (Hartwig and MAK Commission 2022 c) were found to have promoting effects in the rat liver foci assay which can be assumed also for pentachloroethane (see Section 5.7 and Hartwig and MAK Commission 2022 a, b). This assumption is supported by the following observation: in the control groups, the incidence of hepatocellular carcinomas in B6C3F1 mice was 187/904 (20.7%) in males and

30/996 (3.0%) in females compared with 0/270 (0%) in male and 1/270 (0.37%) in female Osborne-Mendel rats and 7/992 (0.7%) in male and 1/946 (0.1%) in female F344 rats (NTP 1983).

[U-^{14}C]-Pentachloroethane was administered intraperitoneally to male Wistar rats and male BALB/c mice. After 22 hours, covalent binding of the radioactivity to DNA, RNA and proteins of the liver, kidneys, lungs and stomach was examined. Binding was highest in the liver and higher in the lungs and liver in the mouse than in the rat. However, DNA-adducts were not determined (Turina et al. 1989).

In a carcinogenicity study with oral administration to rats, there were no statistically significant increases in tumour incidences, but a trend for increased benign and malignant tubular cell tumours of the kidneys (1/50, 2/49, 4/50), which was not statistically significant, was evident in the males; this was accompanied by dose-dependent renal toxicity. Responsible for this is an α_{2u}-globulin-mediated mechanism, as the protein was detected and pentachloroethane increases cell proliferation in the kidney (Goldsworthy et al. 1988).

After administration of other chloroalkanes, sensitization of the heart to adrenaline has been observed, in other words, cardiac arrhythmia may result from an increased effect of catecholamines when cardiac muscle activity is markedly increased. This effect has been held responsible for deaths without other pathological abnormalities (Reinhardt et al. 1971). Such deaths occurred also in the carcinogenicity study with pentachloroethane and mice.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There are no studies in humans.

To determine kinetic parameters, male F344 rats were exposed to pentachloroethane vapour at a concentration of 2895 mg/m^3 for 6 hours, and then placed in exhaled breath chambers. The maximum metabolic rate V_{max} was 9.2 mg/kg body weight and hour (45.5 µmol/kg body weight and hour) and the Michaelis-Menten constant was 0.9 mg/l (4.45 µM) (IARC 1999).

The calculated blood:air partition coefficient of pentachloroethane is 17 according to the formula of Buist et al. (2012) and 50.3 according to that of Meulenberg and Vijverberg (2000).

There are no studies available for the absorption of the substance through the skin.

For a saturated aqueous solution, using the model of Fiserova-Bergerova et al. (1990) and the algorithm of the IH SkinPerm model (Tibaldi et al. 2014), fluxes of 326 and 11.9 µg/cm^2 and hour, respectively, were calculated. Assuming the exposure of 2000 cm^2 of skin (area of hands and forearms) for 1 hour, this would correspond to absorbed amounts of 652 and 23.8 mg, respectively.

3.2 Metabolism

After subcutaneous injection of 1100 to 1800 mg pentachloroethane/kg body weight, in female NMRI mice 12% to 51% of the dose was exhaled unchanged over a 72-hour period, 2% to 16% as trichloroethylene and 3% to 9% as tetrachloroethylene. The major urinary metabolites were trichloroethanol (16%–32%) and trichloroacetic acid (9%–18%, presumably formed via chloral hydrate). The recovery was 87% (Figure 1; Yllner 1971).

The reductive metabolic pathway plays a greater role for pentachloroethane in vivo than for monochloroethane, dichloroethane, trichloroethane or tetrachloroethane (Loew et al. 1984).

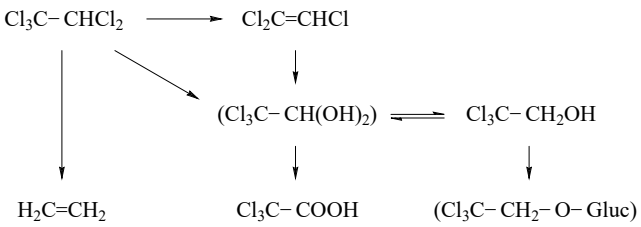

Fig. 1 Metabolism of pentachloroethane in mice. Metabolites given in parentheses were not isolated (according to Yllner 1971)

In in vitro studies using rabbit liver microsomes or a CYP system derived from them, 1.7% pentachloroethane was dechlorinated in the presence of NADPH and oxygen. However, without oxygen, 96% was metabolized to trichloroethylene and 4% to 1,1,2,2-tetrachloroethane (IARC 1999).

Dechlorination under anaerobic conditions was demonstrated also with rat liver microsomes (Nastainczyk et al. 1982; Salmon et al. 1985; Thompson et al. 1984).

Unlike with 1,1,2-trichloroethane, no metabolites containing sulfur were found, so it appears that conjugation with glutathione does not take place in the metabolic pathway of pentachloroethane (Loew et al. 1984).

Single intraperitoneal injections of 462.3 and 925.4 mg pentachloroethane/kg body weight in mice (about 35% and 70% of the LD_{50}, respectively) resulted in a statistically significant reduction in the CYP level (by 43% and 57%, respectively), pentoxyresorufin *O*-dealkylase activity (by 17% and 20%, respectively, CYP2B) and ethoxyresorufin *O*-deethylase activity (by 58% and 69%, respectively, CYP1A1) in hepatic microsomes examined 24 hours after dosing (Bronzetti et al. 1989).

4 Effects in Humans

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The lowest lethal concentration in rats was 4238 ml/m^3 (no other details; NTP 1983).

The lowest lethal concentration in mice was 35 000 mg/m^3 (≙ 4165 ml/m^3) in a static investigation lasting 2 hours (IARC 1999).

5.1.2 Oral administration

Groups of 5 male and 5 female F344 rats and B6C3F1 mice were given single gavage doses of pentachloroethane of 0, 10, 50, 100, 500 or 1000 mg/kg body weight in corn oil. No substance-related findings occurred and all animals survived (NTP 1983).

The LD_{50} in rats was 920 mg/kg body weight (no other details; NICNAS 2014).

A single gavage dose of pentachloroethane of 525 mg/kg body weight reduced CYP levels and epoxide hydrolase activity in rats (IARC 1999).

The lowest lethal oral doses in dogs were 0.5 ml/kg body weight (about 840 mg/kg body weight) and 1750 mg/kg body weight (no other details) (IARC 1986).

5.1.3 Dermal application

There are no studies available.

5.1.4 Subcutaneous and intravenous injection

A subcutaneous dose of 700 mg/kg body weight was lethal to rabbits (IARC 1986). In female NMRI mice, a subcutaneous injection of 1100 to 1800 mg/kg body weight did not result in deaths until 72 hours after administration (Yllner 1971).

The lowest lethal dose in dogs after intravenous injection was 100 mg/kg body weight (IARC 1986).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Rabbits were exposed to pentachloroethane concentrations of 2, 10 or 100 mg/m^3 for 3 hours daily, on 6 days a week for 8 to 10 months. Total antibody titers increased during typhoid immunization (no other details; IARC 1986; Shmuter 1972, 1977). Further statements cannot be inferred from the article, which is available in Russian only, as the methods and scope of the investigation were inadequately described.

5.2.2 Oral administration

Gavage administration of a pentachloroethane dose of 150 mg/kg body weight and day (purity 96%, 5 days/week) to male and female F344 rats for 10 days resulted in increased kidney α_{2u}-globulin concentrations of 25.9 mg/kg kidney wet weight in the males, compared with 9.1 ± 2.3 mg/kg kidney wet weight in the controls. The [^{3}H]thymidine labelling index increased particularly in the P_2 tubule segment of the kidney from 11.5% ± 0.7% in the control animals to 38.8% ± 3.9% in the exposed animals. The corresponding values for the P_1 and P_3 segments were 8.7% ± 0.6% and 8.5% ± 1.5%, respectively, in the control animals and 9.2% ± 1.6% for both segments in the exposed animals. In the female rats, the labelling index in the P_2 segment was 1.8% ± 0.7% in the control animals and 0.8% ± 0.2% in the exposed animals (Goldsworthy et al. 1988; IARC 1999).

Pentachloroethane was administered by gavage on 5 days a week for 2 years at dose levels of 0, 75 or 150 mg/kg body weight and day to F344 rats and for 40 to 103 weeks at dose levels of 0, 250 or 500 mg/kg body weight and day to B6C3F1 mice (see Table 1). In mice, high mortality and hepatocellular carcinomas occurred from week 31 onwards. In male rats, pentachloroethane caused diffuse inflammation of the kidneys and mineralization of the renal papilla, which was distinguishable from the usual age-related nephropathy, and a low incidence of malignant tubular cell tumours (1/50, 2/49, 4/50). The accumulation of α_{2u}-globulin was detected in the kidneys of male F344 rats. For pentachloroethane no specific spectrum of effects was found in both chronic and subacute studies, but it caused increased mortality, especially in mice (see Table 1). The causes discussed are the accumulation of the substance in the body and non-specific toxicity (NTP 1983).

In a 3-week study, male F344 rats were given equimolar doses of various halogenated ethane compounds (containing three or more chlorine atoms, four or more bromine atoms, or chlorine and fluorine atoms) daily by gavage for comparative characterization of renal toxicity. The doses selected were 0, 0.62 and 1.24 mmol/kg body weight and day. A female pentachloroethane control group was treated with 1.24 mmol/kg body weight and day, another with vehicle only. Histopathological examination included only the kidneys and liver. Treatment with pentachloroethane induced in the male rats pronounced nephropathy associated with the formation of hyaline droplets, increased kidney weights, increased urinary excretion of glucose, increased *N*-acetyl-β-*D*-glucosaminidase activity, and an increase in urinary aspartate aminotransferase that was not statistically significant. The proliferating cell nuclear antigen (PCNA) level

in the renal tubule cells was three times as high as that in the control animals, but was not dose-dependent. The weights of the right kidney were increased also in female rats, with no evidence of hyaline droplet formation. In male and female rats, urinary protein excretion, liver weights, and the incidence of cytoplasmic vacuolization in the liver were increased (NTP 1996).

Tab. 1 Effects of pentachloroethane after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rats, F344, 5 ♂, 5 ♀	**2** weeks, 0, 10, 50, 100, 500, 1000 mg/kg body weight and day in corn oil, daily, gavage	**100 mg/kg body weight**: **NOAEL**; **500 mg/kg body weight**: lethargy, mortality 3/5 (♂) and 3/5 (♀) between days 4 and 10, body weight gains ↓ by 29% (♂) and 40% (♀) in surviving animals; **1000 mg/kg body weight**: mortality 10/10 (6 on day 1, 4 on day 3); no treatment-related findings in the histopathological examination of the liver, lungs and spleen	NTP 1983
rats, F344, 5 ♂, 5 ♀	**3** weeks, 0, 0.62, 1.24 mmol/kg body weight and day (0, 125, 250 mg/kg body weight and day) in corn oil, daily, gavage, histopathology of the kidneys and liver	**125 mg/kg body weight and above**: ♂: hyaline droplet nephropathy, accumulation of α_{2u}-globulin in the kidneys, kidney weights ↑, urinary excretion of glucose, *N*-acetyl-β-*D*-glucosaminidase activity ↑; urinary aspartate aminotransferase ↑ (not significant), PCNA in renal tubular cells ↑, ♀: right kidney weights ↑, ♂ and ♀: liver weights ↑, vacuolization of hepatocytes ↑, urinary protein excretion ↑	NTP 1996
rats, F344, 10 ♂, 10 ♀	**13** weeks, 0, 5, 10, 50, 125, 250 mg/kg body weight and day in corn oil, 5 days/week, gavage	**50 mg/kg body weight**: **NOAEL**; **125 mg/kg body weight**: body weight gains ↓ by 8% (♂) and 8% (♀); body weights at end of study ↓ by 5% (♂) and 9% (♀); **250 mg/kg body weight**: body weight gains ↓ by 10% (♂) and 17% (♀), body weights at end of study ↓ by 5% (♂) and 9% (♀); no treatment-related findings in the histopathological examination	NTP 1983
rats, F344, 50 ♂, 50 ♀	**103** weeks, 0, 75, 150 mg/kg body weight and day, 5 days/week, gavage	**0 mg/kg body weight**: mortality 18% (♂) and 24% (♀), chronic inflammation of the kidneys (♂) 4/50 (8%); **75 mg/kg body weight**: mortality 34% (♂) and 28% (♀), chronic inflammation of the kidneys 14/49 (29%) (♂), mineralization of the renal papilla (♂), body weights ↓ by 4% (♂) and 8% (♀); **150 mg/kg body weight**: mortality ↑ (♂ 48%, ♀ 50%), body weights at end of study ↓ by 5% (♂) and 12% (♀), chronic inflammation of kidneys 33/50 (66%) (♂), mineralization of the renal papilla (♂); chronic inflammation of the kidneys characterized by interstitial fibrosis, interstitial accumulation of mononuclear inflammatory cells, severe tubular dilation in the pars recta (inner cortex) with some dilated tubules containing giant cells, hyalinization of the glomerulus	NTP 1983
mice, B6C3F1, 5 ♂, 5 ♀	**2** weeks, 0, 10, 50, 100, 500, 1000 mg/kg body weight and day in corn oil, daily, gavage	**50 mg/kg body weight and above**: body weight gains ↓ by 25%–50% (♀), not dose-dependent; **1000 mg/kg body weight**: mortality 1/5 (♀), body weight gains ↓ by 7% (♀); no treatment-related findings in the histopathological examination of the liver, lungs, spleen	NTP 1983

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mice, B6C3F1, 10 ♂, 10 ♀	**13** weeks, 0, 5, 10, 50, 100, 500 mg/kg body weight and day in corn oil, 5 days/week, gavage	**500 mg/kg body weight**: mortality 1/5 (♀), body weight gains ↓ by 8% (♀); no treatment-related findings in the histopathological examination	NTP 1983
mice, B6C3F1, 50 ♂, 50 ♀	**41–103** weeks, 0, 250, 500 mg/kg body weight and day, 5 days/week, gavage	**0 mg/kg body weight**: mortality at the end of the study 6/25 (24%) (♂) and 12/50 (24%) (♀); **250 mg/kg body weight**: mortality (♂) from week 31 onwards, mortality at the end of the study 28/50 (56%) (♂), mean body weights during weeks 42–104 ↓ by 30% (♂); mortality (♀) from week 53 onwards, mortality at the end of the study 41/50 (82%) (♀), mean body weights from week 70 onwards ↓ by about 10% (♀); **250 mg/kg body weight and above**: hepatocellular carcinomas (see Section 5.7); **500 mg/kg body weight**: mortality (♂) from week 18 onwards, week 41 mortality 42/50 (84%) (♂) – remaining 8 animals (**+ 25 controls**) also sacrificed at week 41, no body weight gains from week 12 onwards (♂); mortality (♀) from week 38, all (♀) had died by week 74, mean body weights ↓ from week 70 onwards by about 10% (♀)	NTP 1983

PCNA: Proliferating Cell Nuclear Antigen

5.2.3 Dermal application

There are no studies available.

5.3 Local effects on skin and mucous membranes

There are no studies available. According to safety data sheets, pentachloroethane is irritating to the eyes and respiratory tract, but studies of this end point have not been described (NTP 1983). In gavage studies, irritation of the forestomach of rats and mice was not reported. Irritant effects are therefore unlikely.

5.4 Allergenic effects

There are no studies available.

5.5 Reproductive and developmental toxicity

There are no studies available.

5.6 Genotoxicity

5.6.1 In vitro

In the Microscreen prophage-induction assay using lambda lysogen $WP2_S$ cells, pentachloroethane yielded positive results in the presence of a metabolic activation system at concentrations of 25.8 mM and above. Cytotoxicity was observed at 206.5 mM. Without the addition of metabolic activation, the test result was negative (DeMarini and Brooks 1992).

In yeasts that were in the stationary growth phase, the induction of point mutations and gene conversions was observed in the presence of a metabolic activation system; the incidences were low but statistically significant. Statistically significant, concentration-dependent results were obtained without the presence of a metabolic activation system when cells were in the logarithmic growth phase. In this phase, the level of CYP in yeast cells is high (Bronzetti et al. 1989).

Pentachloroethane was not mutagenic up to the toxic concentration of 333 µg/plate in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 in either the presence or absence of a metabolic activation system from the livers of male Sprague Dawley rats or male Syrian hamsters treated with Aroclor 1254 (Haworth et al. 1983; NTP 1981).

In Chinese hamster ovary cells, in the absence of a metabolic activation system, the concentration-dependent induction of sister chromatid exchange was observed at 100 to 160 µg pentachloroethane/ml. The concentration of 50 µg/ml was without effect; strong cytotoxicity occurred at 200 µg/ml and above. In the presence of a metabolic activation system from rat liver, a negative result was obtained (Galloway et al. 1987).

Up to the highest pentachloroethane concentration tested of 266 µg/ml, there was no increased incidence of chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of a rat liver metabolic activation system after 10.5 or 21 hours of incubation. Cytotoxicity occurred at the highest concentrations tested. The results for the positive controls mitomycin C and cyclophosphamide were positive in the test system (Galloway et al. 1987).

Structural chromosomal aberrations and polyploidy were induced in Chinese hamster lung fibroblasts in the absence of a metabolic activation system. After the addition of a metabolic activation system from rat liver, the result was negative (Matsuoka et al. 1996).

Positive results were induced in the $TK^{+/-}$ assay in L5178Y mouse lymphoma cells (McGregor et al. 1988; Sofuni et al. 1996) interpreted as clastogenic effects (Sofuni et al. 1996).

Tab. 2 Genotoxicity of pentachloroethane in vitro

End point	Test system	Concentration [µg/plate][a)]	Effective concentration[a)]	Cytotoxicity[a)]	Results		References
					–m.a.	+m.a.[b)]	
prophage induction	Escherichia coli WP2s (λ)	0.1–206 mM	25.8 mM	206 mM	–	+	DeMarini and Brooks 1992
gene conversion and reverse point mutation	Saccharomyces cerevisiae D7 gene conversion at trp locus	stationary growth phase: 2.5–10 mM logarithmic growth phase: 0.5–2.5 mM	stationary growth phase: ≥2.5 mM (+m.a.) logarithmic growth phase: ≥1 mM	higher toxicity in logarithmic growth phase than in stationary growth phase stationary growth phase: ≥2.5 mM logarithmic growth phase: ≥0.5 mM	stationary growth phase: – logarithmic growth phase: +	+	Bronzetti et al. 1989
	Saccharomyces cerevisiae D7 reverse point mutation at ilv locus	stationary growth phase: 2.5–10 mM logarithmic growth phase: 0.5–2.5 mM	stationary growth phase: at 7.5 mM (+m.a.) logarithmic growth phase: ≥1 mM (+m.a.)	stationary growth phase: ≥2.5 mM logarithmic growth phase: no data	stationary growth phase: – logarithmic growth phase: no data	stationary growth phase: + logarithmic growth phase: +	
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537	3–333	–	333	–	– [b), c)]	Haworth et al. 1983; NTP 1981

Tab. 2 *(continued)*

End point	Test system	Concentration [µg/plate][a]	Effective concentration[a]	Cytotoxicity[a]	Results		References
					–m.a.	+m.a.[b]	
SCE	CHO cells	–m.a.: 16.1–537 µg/ml +m.a.: 101–172 µg/ml	–m.a.: 100 µg/ml	–m.a.: 200 µg/ml +m.a.: 172 µg/ml	+	–	Galloway et al. 1987; NTP 1982 b
CA	CHO cells	–m.a.: 128.8–266 µg/ml +m.a.: 112.5–266 µg/ml	–	–m.a.: 225 µg/ml +m.a.: 193 µg/ml	–	–	Galloway et al. 1987; NTP 1982 a
structural CA	CHL cells	80–600 µg/ml	–m.a.: 600 µg/ml	–m.a.: 600 µg/ml	+	–	Matsuoka et al. 1996
polyploidy	CHL cells	80–600 µg/ml	–m.a.: 80 µg/ml	–m.a.: 600 µg/ml	+	–	Matsuoka et al. 1996
$TK^{+/-}$	mouse lymphoma cells L5178Y	6.25–200 µg/ml	70 µg/ml	200 µg/ml	+	not tested	McGregor et al. 1988
$TK^{+/-}$	mouse lymphoma cells L5178Y (microtiter method)	20–100 µg/ml	–m.a.: 80 µg/ml	no data	+	–	Sofuni et al. 1996

[a] unless otherwise indicated [µg/plate]
[b] metabolic activation from rat liver
[c] metabolic activation from hamster liver
CA: chromosomal aberration; CHL: cell line derived from Chinese hamster lung cells; CHO: cell line derived von Chinese hamster ovary cells; m.a.: metabolic activation system; SCE: sister chromatid exchange; TK: thymidine kinase

5.6.2 In vivo

A sex-linked recessive lethal test in Drosophila melanogaster yielded negative results after the administration of pentachloroethane in a concentration of 300 mg/l with the diet or the injection of 800 mg/l (Foureman et al. 1994).

Radiolabelled [^{14}C]-pentachloroethane (127 µCi/kg body weight = 1.75 mg/kg body weight) was administered intraperitoneally to 7 male Wistar rats and 12 male BALB/c mice. After 22 hours, covalent binding of the radioactivity to DNA, RNA and proteins of the liver, kidneys, lungs and stomach was found. Binding was highest in the liver and higher in the lungs and liver in the mouse than in the rat (Turina et al. 1989). However, the metabolic incorporation of ^{14}C into DNA as well as DNA adducts were not studied.

Pentachloroethane increased replicative DNA synthesis as a measure of cell proliferation in the hepatocytes of B6C3F1 mice 39 and 48 hours after the administration of 1000 mg/kg body weight (Miyagawa et al. 1995).

In 4 male B6C3F1 mice, the frequency of sister chromatid exchange in the bone marrow was not increased 23 hours after intraperitoneal injection of pentachloroethane doses of 0, 475, 950 or 1900 mg/kg body weight in corn oil (NTP 1987 b).

In male mice, the incidences of chromosomal aberrations in the bone marrow were not increased 17 hours after intraperitoneal injection of pentachloroethane doses of 0, 475, 950 or 1900 mg/kg body weight in corn oil. The groups consisted of 8 animals (NTP 1987 a). Also, 36 hours after intraperitoneal administration of pentachloroethane doses of 0, 325, 650 or 1300 mg/kg body weight in corn oil, the incidence of chromosomal aberrations in the bone marrow was not increased (NTP 1992).

In male B6C3F1 mice, the incidence of micronuclei in the bone marrow was not increased 24 hours after the last of three intraperitoneal injections of pentachloroethane doses of 39 to 2500 mg/kg body weight in corn oil up to the dose of 625 mg/kg body weight. The ratio of polychromatic erythrocytes to normochromatic erythrocytes remained unchanged. Higher doses could not be evaluated. The groups consisted of 5 animals (NTP 1995).

A micronucleus test with bone marrow cells from CD-1 mice yielded negative results after a single intraperitoneal injection of up to 2000 mg pentachloroethane/kg body weight (Crebelli et al. 1999).

5.6.3 Summary

Pentachloroethane is not mutagenic in bacteria but mutagenic in yeast. Positive results were observed in the $TK^{+/-}$ assay in mouse lymphoma cells probably due to clastogenicity. The substance induced SCE and chromosomal aberrations in mammalian cells only in the absence of a metabolic activation system; negative results were obtained after the addition of a metabolic activation system. After intraperitoneal administration, pentachloroethane is not clastogenic in mouse bone marrow. In mammals, no mutagenicity tests in vivo or germ cell tests are available.

5.7 Carcinogenicity

Pentachloroethane was administered to F344 rats for 2 years at dose levels of 0, 75 or 150 mg/kg body weight and day by gavage. No statistically significant increases in tumour incidences occurred. A trend for benign and malignant tubular cell tumours of the kidneys (1/50, 2/49, 4/50), which was not statistically significant, was observed in the males; this was accompanied by dose-dependent renal toxicity. There was a statistically significant negative trend for subcutaneous tissue fibromas in male rats and for pituitary gland adenomas in male and female animals. For further findings, see Section 5.2.2. The accumulation of α_{2u}-globulin in the kidneys of male F344 rats was observed. The tumours induced by this mechanism in the kidney of the male rat have no relevance to humans (NTP 1983). Pentachloroethane was not carcinogenic in the liver of F344 rats.

Long-term gavage administration of pentachloroethane at dose levels of 0, 250 or 500 mg/kg body weight and day resulted in increased mortality in B6C3F1 mice (see Table 3 and Section 5.2.2). In the males of the high dose group, 42 of 50 animals had died by week 41, and the eight remaining were killed and examined in week 41, as were 25 males from the control group. Only 22 of 50 animals (44%) in the low dose group were alive at the end of the study period. In the female mice, all high-dose animals had died by week 74 and only 9 of 50 (18%) in the low-dose group were alive at the end of the study. The incidence of hepatocellular carcinomas was increased in the treated male and female mice compared with that in the control animals. However, due to the increased mortality, the usual statistical analysis is only of limited applicability (NTP 1983). Pentachloroethane was hepatocarcinogenic in B6C3F1 mice.

A comparison of the studies with different chloroethanes showed that many of the substances led to an increased incidence of hepatocellular carcinomas in mice but not in rats. A common mechanism is suspected. This could be a tumour-promoting effect, since in vitro mutagenicity tests with the corresponding substances yielded negative results (see Section 2).

Conclusion: Pentachloroethane does not have any relevant genotoxic potential in vivo, and a tumour-promoting effect has not been investigated. However, since structurally related substances with the same activity profile such as hexachloroethane and 1,1,2-trichloroethane had a promoting but not an initiating effect in a liver foci assay in rats, the liver tumours in mice are most likely due to the promotion of spontaneously initiated cells in the liver. These are present in high numbers in B6C3F1 mice and result in relatively high spontaneous incidences of liver tumours in this mouse strain, which is sensitive to liver carcinogenesis, whereas rats are less sensitive as regards tumour-promotion in the liver due to the low spontaneous incidence.

Tab. 3 Study of the carcinogenicity of pentachloroethane in mice

Author:		NTP 1983		
Substance:		pentachloroethane (purity 95.5%, 4.2% hexachloroethane)		
Species:		**mouse**, B6C3F1, 50 ♂, 50 ♀		
Administration route:		gavage		
Dose:		0, 250, 500 mg/kg body weight and day		
Duration:		40–103 weeks, 5 days/week		
Toxicity:		increased mortality at 250 mg/kg body weight and above		
		Dose (mg/kg body weight and day)		
		0	**250**	**500**
Survivors	♂	19/25 (76%) week 103 (another 25 examined after week 41)	22/50 (44%) week 103	8/50 (16%) week 41 (= end of study)
	♀	38/50 (76%) week 103	9/50 (18%) week 103	0/50 (0%) week 74
Tumours				
liver:				
hepatocellular adenomas				
total	♂	10/48 (21%)	4/44 (9%)	7/45 (16%)
weeks 0–52	♂	5/25 (20%)	0/2 (0%)	7/45 (16%)
weeks 53–103	♂	0/4 (0%)	2/18 (11%)	–
end of study, week 104	♂	5/19 (26%)	2/24 (8%)	–
		P = 0.235N[a)]	P = 0.162N[b)]	P = 0.444N[b)]
total	♀	2/46 (4%)	8/42 (19%)	19/45 (42%)
adjusted[c)]	♀	5.4%	44.6%	60.9%
end of study, week 104	♀	2/37 (5%)	3/9 (33%)	–
statistical tests				
life table test	♀	P < 0.001[a)]	P < 0.001[b)]	P < 0.001[b)]
incidental tumour test	♀	P = 0.060[a)]	P = 0.023[b)]	[d)]
Fisher's exact test	♀	P < 0.001[e)]	P = 0.032[b)]	P < 0.001[b)]
hepatocellular carcinomas				
total	♂	4/48 (8%)	26/44 (59%)	7/45 (16%)
weeks 0–52	♂	0/25 (0%)	1/2 (50%)	7/45 (16%)
weeks 53–103	♂	0/4 (0%)	9/18 (50%)	–
end of study, week 104	♂	4/19 (21%)	16/24 (67%)	–
		P < 0.001[a)]	P < 0.001[b)]	P = 0.049[b)]
total	♀	1/46 (2%)	28/42 (67%)	13/45 (29%)
adjusted[c)]	♀	2.7%	84.6%	67.7%
end of study, week 104	♀	1/37 (3%)	5/9 (56%)	–
statistical tests				
life table test	♀	P < 0.001[a)]	P < 0.001[b)]	P < 0.001[b)]
incidental tumour test	♀	P = 0.005[a)]	P < 0.001[b)]	[d)]
Fisher's exact test	♀	P = 0.004[e)]	P < 0.001[b)]	P < 0.001[b)]

Tab. 3 *(continued)*

		Dose (mg/kg body weight and day)		
		0	**250**	**500**
hepatocellular adenomas and carcinomas				
total	♂	14/48 (29%)	30/44 (68%)	14/45 (31%)
weeks 0–52	♂	5/25 (20%)	1/2 (50%)	14/45 (31%)
weeks 53–103	♂	0/4 (0%)	11/18 (61%)	–
end of study, week 104	♂	9/19 (47%)	18/24 (75%)	–
		P = 0.026[a)]	P = 0.005[b)]	P = 0.237[b)]
total	♀	3/46 (7%)	36/42 (86%)	32/45 (71%)
adjusted[c)]	♀	8.1%	96.8%	93.6%
end of study, week 104	♀	3/37 (8%)	8/9 (89%)	–
statistical tests				
life table test	♀	P < 0.001[a)]	P < 0.001[b)]	P < 0.001[b)]
incidental tumour test	♀	P < 0.001[a)]	P < 0.001[b)]	[d)]
Fisher's exact test	♀	P < 0.001[e)]	P < 0.001[b)]	P < 0.001[b)]

[a)] trend test; "N" = negative trend
[b)] pairwise comparison with controls
[c)] estimated lifetime tumour incidence after adjustment for intercurrent mortality
[d)] no statistical evaluation possible due to high mortality
[e)] Cochran Armitage trend test

6 Manifesto (MAK value/classification)

No information is available for effects in humans.

Pentachloroethane caused hepatocellular carcinomas in B6C3F1 mice, in which the spontaneous incidence of this tumour is high. Increased mortality occurred in both rats and mice without specific toxicity.

MAK value. In a 13-week toxicity study in male and female F344 rats with gavage administration on 5 days per week, the body weight gains were reduced by 8% at 125 mg/kg body weight and day. The systemic NOAEL was 50 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the species-specific correction value for the rat (1:4), oral absorption of 95% as determined for hexachloroethane (Hartwig and MAK Commission 2022 c), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. As this value is derived from a NOAEL from experimental studies with animals (1:2) and a decrease in the NOAEL with chronic exposure cannot be excluded (1:2), a concentration of 20.8 mg/m^3 in the air is calculated. This corresponds to 2.5 ml/m^3, as pentachloroethane may be present also in vapour form at this concentration. Using the preferred value approach, a MAK value of 2 ml pentachloroethane/m^3 can be derived.

In safety data sheets, pentachloroethane is described as being an eye and respiratory tract irritant, but relevant studies are not described. Oral animal studies do not indicate a strong irritant potential, as no effects in the forestomach were reported even after 2 years of gavage administration. For the structurally similar chloroalkanes hexachloroethane and 1,1,2,2-tetrachloroethane, the NOAECs for irritant effects in the respiratory tract are 48 ml/m^3 (inhalation studies in animals; Hartwig and MAK Commission 2022 c) and about 13 ml/m^3 (human studies of limited usefulness; Hartwig and MAK Commission 2022 a). Because of its very similar molecular structure, pentachloroethane is not expected to be irritating with exposure at the MAK value of 2 ml/m^3.

Peak limitation. As the critical effect is systemic, the substance has been assigned to Peak Limitation Category II. The default excursion factor of 2 has been set because the half-life is not known. Irritant effects are not to be expected at the permissible short-term concentration of 4 ml/m^3 in view of the data for hexachloroethane and 1,1,2,2-tetrachloroethane (see above).

Prenatal toxicity. There are no developmental toxicity studies of pentachloroethane and the substance has therefore been assigned to Pregnancy Risk Group D.

Carcinogenicity. Administration of pentachloroethane by gavage did not result in a statistically significant increase in tumour incidences in rats. However, in the males, there was a not statistically significant trend for benign and malignant renal tubular cell tumours induced by the α_{2u}-globulin-mediated mechanism. Corresponding proteins have been detected in short-term experiments in male rats after exposure to pentachloroethane. This mechanism is not relevant for humans. There was a statistically significant increase in the incidence of hepatocellular carcinomas in B6C3F1 mice. Pentachloroethane was not found to have genotoxic potential in vivo. The structurally related substances hexachloroethane and 1,1,2-trichloroethane had promoting, but not initiating effects in a liver foci test in rats. Pentachloroethane has not been studied in this test system. Therefore, it can be assumed that the liver tumours in mice are most likely due to the promotion of spontaneously initiated cells in the liver. These are present in high numbers in B6C3F1 mice and result in relatively high spontaneous incidences of liver tumours in this strain of mice, which is sensitive for liver carcinogenesis. Pentachloroethane may induce cytotoxic effects in the liver and thus liver tumours, probably arising from metabolically formed radicals or oxidative metabolites. This effect is relevant also for humans. To summarize, in high concentrations pentachloroethane is suspected of having carcinogenic effects on the liver whereby genotoxicity is not the main effect. However, this carcinogenicity in mice has not been confirmed by studies in the rat. Therefore, pentachloroethane has been classified in Carcinogen Category 3 B.

Germ cell mutagenicity. Pentachloroethane is not mutagenic in vitro in bacteria but mutagenic in yeasts. Positive results were observed in mouse lymphoma cells in the TK$^{+/-}$ assay probably due to clastogenicity. The substance induced sister chromatid exchange and chromosomal aberrations in mammalian cells only in the absence of a metabolic activation system; after the addition of an activation system the results were negative. This suggests that in vivo mutagenicity does not occur or is not the main effect. The carcinogenicity studies confirmed this assumption (see above). After intraperitoneal administration, pentachloroethane was not clastogenic in the bone marrow of mice. Thus, the clastogenicity observed in in vitro test systems could not be demonstrated in vivo. Mutagenicity tests in vivo or tests on germ cells are not available. The substance has not been shown to reach the germ cells. Based on the available data, pentachloroethane has not been classified in one of the categories for germ cell mutagens.

Absorption through the skin. From a model calculation for humans (Section 3.1), a maximum dermally absorbed amount of 652 mg can be estimated following exposure to a saturated aqueous solution under standard conditions (2000 cm^2 of skin, exposure for 1 hour).

For humans a systemically tolerable concentration of 20.8 mg/m^3 can be calculated (see above). For 100% absorption by inhalation and a respiratory volume of 10 m^3, the systemically tolerable amount is 208 mg.

Thus, the amount dermally absorbed is above the systemically tolerable level and the substance has been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data for sensitizing effects in humans and no results from experimental studies in animals or in vitro studies. Pentachloroethane has therefore not been 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.

References

BMJV (Bundesministerium der Justiz and für Verbraucherschutz), editor (1991) Erste Verordnung zum Schutz des Verbrauchers vor bestimmten aliphatischen Chlorkohlenwasserstoffen (1. Chloraliphatenverordnung – 1. aCKW-V). Bundesgesetzblatt I (28): 1059

Bronzetti G, Morichetti E, Del Carratore R, Rosellini D, Paolini M, Cantelli-Forti G, Grilli S, Vellosi R (1989) Tetrachloroethane, pentachloroethane, and hexachloroethane: genetic and biochemical studies. Teratog Carcinog Mutagen 9(6): 349–357. https://doi.org/10.1002/tcm.1770090603

Buist HE, de Wit-Bos L, Bouwman T, Vaes WHJ (2012) Predicting blood:air partition coefficients using basic physicochemical properties. Regul Toxicol Pharmacol 62(1): 23–28. https://doi.org/10.1016/j.yrtph.2011.11.019

Crebelli R, Carere A, Leopardi P, Conti L, Fassio F, Raiteri F, Barone D, Ciliutti P, Cinelli S, Vericat JA (1999) Evaluation of 10 aliphatic halogenated hydrocarbons in the mouse bone marrow micronucleus test. Mutagenesis 14(2): 207–215. https://doi.org/10.1093/mutage/14.2.207

DeMarini DM, Brooks HG (1992) Induction of prophage lambda by chlorinated organics: detection of some single-species/single-site carcinogens. Environ Mol Mutagen 19(2): 98–111. https://doi.org/10.1002/em.2850190204

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

Foureman P, Mason JM, Valencia R, Zimmering S (1994) Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environ Mol Mutagen 23(3): 208–227. https://doi.org/10.1002/em.2850230310

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B, Zeiger E (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ Mol Mutagen 10 Suppl 10: 1–35. https://doi.org/10.1002/em.2850100502

Goldsworthy TL, Lyght O, Burnett VL, Popp JA (1988) Potential role of alpha-2μ-globulin, protein droplet accumulation, and cell replication in the renal carcinogenicity of rats exposed to trichloroethylene, perchloroethylene, and pentachloroethane. Toxicol Appl Pharmacol 96(2): 367–379. https://doi.org/10.1016/0041-008x(88)90095-6

Greim H, editor (1998) Trichloroethylene. MAK Value Documentation, 1986. In: Occupational Toxicants. Volume 10. Weinheim: Wiley-VCH. p. 201–244. Also available from https://doi.org/10.1002/3527600418.mb7901e0010

Hartwig A, MAK Commission (2019) Tetrachloroethylene. MAK Value Documentation, 2017. MAK Collect Occup Health Saf 4(4): 2168–2273. https://doi.org/10.1002/3527600418.mb12718e6319

Hartwig A, MAK Commission (2022 a) 1,1,2,2-Tetrachloroethane. MAK Value Documentation – Translation of the German version from 2020. MAK Collect Occup Health Saf 7(4): Doc075. https://doi.org/10.34865/mb7934e7_4ad

Hartwig A, MAK Commission (2022 b) 1,1,2-Trichloroethane. MAK Value Documentation – Translation of the German version from 2020. MAK Collect Occup Health Saf 7(4): Doc076. https://doi.org/10.34865/mb7900e7_4ad

Hartwig A, MAK Commission (2022 c) Hexachloroethane. MAK Value Documentation – Translation of the German version from 2020. MAK Collect Occup Health Saf 7(2): Doc031. https://doi.org/10.34865/mb6772e7_2ad

Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983) Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5 Suppl 1: 3–49. https://doi.org/10.1002/em.2860050703

IARC (International Agency for Research on Cancer) (1986) Pentachloroethane. In: Some halogenated hydrocarbons and pesticide exposures. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 41. Lyon: IARC Press. p. 99–111. https://publications.iarc.fr/_publications/media/download/1589/6cbc08eaf3b1969806bbb96f6aa5e5f4f5af4aa9.pdf, accessed 09 May 2018

IARC (International Agency for Research on Cancer) (1999) Pentachloroethane. In: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 71. Lyon: IARC Press. p. 1519–1523. https://publications.iarc.fr/_publications/media/download/2279/d7e4bcce9c42cec078b965c33b0298cf0a3aff3d.pdf, accessed 09 May 2018

Loew GH, Rebagliati M, Poulsen M (1984) Metabolism and relative carcinogenic potency of chloroethanes: a quantum chemical structure-activity study. Cancer Biochem Biophys 7(2): 109–132

Matsuoka A, Yamakage K, Kusakabe H, Wakuri S, Asakura M, Noguchi T, Sugiyama T, Shimada H, Nakayama S, Kasahara Y, Takahashi Y, Miura KF, Hatanaka M, Ishidate M Jr, Morita T, Watanabe K, Hara M, Odawara K, Tanaka N, Hayashi M, Sofuni T (1996) Re-evaluation

of chromosomal aberration induction on nine mouse lymphoma assay 'unique positive' NTP carcinogens. Mutat Res 369(3–4): 243–252. https://doi.org/10.1016/s0165-1218(96)90029-4

McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Riach C, Caspary WJ (1988) Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12(1): 85–154. https://doi.org/10.1002/em.2860120111

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

Miyagawa M, Takasawa H, Sugiyama A, Inoue Y, Murata T, Uno Y, Yoshikawa K (1995) The in vivo–in vitro replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mutat Res 343(2–3): 157–183. https://doi.org/10.1016/0165-1218(95)90082-9

Nastainczyk W, Ahr HJ, Ullrich V (1982) The reductive metabolism of halogenated alkanes by liver microsomal cytochrome P450. Biochem Pharmacol 31(3): 391–396. https://doi.org/10.1016/0006-2952(82)90187-3

NCI (National Cancer Institute) (1978) Bioassay of hexachloroethane for possible carcinogenicity, CAS No. 67-72-1. NCI-CG-TR 68. Bethesda, MD: NCI. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr068.pdf, accessed 13 Jun 2018

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2014) IMAP Single Assessment Report. Ethane, pentachloro-: human health tier II assessment. Sydney: Australian Government Department of Health. https://www.industrialchemicals.gov.au/sites/default/files/Ethane%2C%20pentachloro-_Human%20health%20tier%20II%20assessment.pdf, accessed 30 Nov 2020

NLM (National Library of Medicine) (2019) Pentachloroethane. ChemIDplus Data Bank. https://chem.nlm.nih.gov/chemidplus/rn/76-01-7, accessed 03 Jan 2019

NTP (National Toxicology Program) (1981) Genetic toxicity evaluation of pentachloroethane in Salmonella/E. coli mutagenicity test or Ames test. Study 926918. Research Triangle Park, NC: NTP. https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.download&bin_id=12960&library_id=16367&fileIdsSelected=1de240ff65768bcc0165ee417cfc0a19, accessed 28 Sep 2020

NTP (National Toxicology Program) (1982 a) Cytogenetic study of pentachloroethane in Chinese hamster ovary cell chromosome aberrations test. NTP Study ID 818137_CA. https://manticore.niehs.nih.gov/cebssearch/genetox/002-02642-0002-0000-8/, accessed 28 Sep 2020

NTP (National Toxicology Program) (1982 b) Cytogenetic study of pentachloroethane in Chinese hamster ovary cell sister chromatid exchange test. NTP Study ID 818137_SCE. https://manticore.niehs.nih.gov/cebssearch/genetox/002-02642-0001-0000-7/, accessed 28 Sep 2020

NTP (National Toxicology Program) (1983) Carcinogenesis bioassay of pentachloroethane (CAS No. 76-01-7) in F344/N rats and B6C3F1 mice (gavage study). TR 232. Research Triangle Park, NC: NTP. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr232.pdf, accessed 08 May 2018

NTP (National Toxicology Program) (1987 a) Cytogenetic study of pentachloroethane in rodent chromosome aberrations test. NTP Study ID 868606_CA. https://manticore.niehs.nih.gov/cebssearch/genetox/002-02642-0008-0000-4/, accessed 28 Sep 2020

NTP (National Toxicology Program) (1987 b) Cytogenetic study of pentachloroethane in rodent sister chromatid exchange test. NTP Study ID 868606_SCE. https://manticore.niehs.nih.gov/cebssearch/genetox/002-02642-0007-0000-3/, accessed 28 Sep 2020

NTP (National Toxicology Program) (1992) Cytogenetic study of pentachloroethane in rodent chromosome aberrations test. NTP Study ID 868606_CA. https://manticore.niehs.nih.gov/cebssearch/genetox/002-02642-0008-0000-4/, accessed 28 Sep 2020

NTP (National Toxicology Program) (1995) Genetic toxicity evaluation of pentachloroethane (76-01-7) in micronucleus study A48831 in B6C3F1 mice. Research Triangle Park, NC: NTP. https://tools.niehs.nih.gov/cebs3/views/index.cfm?action=main.download&bin_id=10264&library_id=13671&fileIdsSelected=1de240ff6604d3e201660c33ed33031b, accessed 08 May 2018

NTP (National Toxicology Program) (1996) NTP technical report on renal toxicity studies of selected halogenated ethanes administered by gavage to F344/N rats. Toxicity report series no. 45. Research Triangle Park, NC: NTP. https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox045.pdf, accessed 07 May 2018

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

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

Salmon AG, Jones RB, Mackrodt WC (1981) Microsomal dechlorination of chloroethanes: structure-reactivity relationships. Xenobiotica 11(11): 723–734. https://doi.org/10.3109/00498258109045876

Salmon AG, Nash JA, Walklin CM, Freedman RB (1985) Dechlorination of halocarbons by microsomes and vesicular reconstituted cytochrome P-450 systems under reductive conditions. Br J Ind Med 42(5): 305–311. https://doi.org/10.1136/oem.42.5.305

Shmuter LM (1972) [Effect of the chronic action of small concentrations of chlorinated hydrocarbons on the formation of different classes of immunoglobulins]. Gig Sanit 37(2): 36–40

Shmuter LM (1977) [Effect of chronic exposure to low concentrations of chlorinated hydrocarbons of the ethane series on the specific and nonspecific immunologic reactivity of experimental animals]. Gig Tr Prof Zabol (8): 38–43

Sofuni T, Honma M, Hayashi M, Shimada H, Tanaka N, Wakuri S, Awogi T, Yamamoto KI, Nishi Y, Nakadate M (1996) Detection of in vitro clastogens and spindle poisons by the mouse lymphoma assay using the microwell method: interim report of an international collaborative study. Mutagenesis 11(4): 349–355. https://doi.org/10.1093/mutage/11.4.349

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

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

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

Turina MP, Colacci A, Grilli S, Mazzullo M, Prodi G, Lattanzi G, Bonora B, Bartoli S, Guidotti L (1989) Metabolic activation and covalent binding to nucleic acids of pentachloroethane as short-term test of genotoxicity. Res Commun Chem Pathol Pharmacol 63(1): 81–91

Yllner S (1971) Metabolism of pentachloroethane in the mouse. Acta Pharmacol Toxicol (Copenh) 29(5): 481–489. https://doi.org/10.1111/j.1600-0773.1971.tb00622.x