14. Organic constituents

14.1 Carbon tetrachloride

14.1.1 General description

Identity

CAS no.: 056-23-5
Molecular formula: CCl₄

Physicochemical properties (1,2)

<table>
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<td>Water solubility</td>
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<tr>
<td>Log octanol-water partition coefficient</td>
<td>2.64</td>
</tr>
</tbody>
</table>

¹ Conversion factor in air: 1 ppm = 6.4 mg/m³

Organoleptic properties

The odour thresholds for carbon tetrachloride in water and air are 0.52 mg/litre and <64 mg/m³, respectively (3).

Major uses

Carbon tetrachloride is used mainly in the production of chlorofluorocarbon refrigerants, foam-blowing agents, and solvents. It is also used in the manufacture of paints and plastics, as a solvent in metal cleaning, and in fumigants (4).

Environmental fate

Most carbon tetrachloride released to the environment reaches the atmosphere, where it is uniformly distributed. It does not react with photochemically produced hydroxyl radicals in the troposphere but may undergo photolysis in the stratosphere. It has an estimated half-life of 50 years in the atmosphere (1, 5).

Carbon tetrachloride readily migrates from surface water to the atmosphere in a matter of days or weeks; however, levels in anaerobic groundwater may remain elevated for months or even years (5). Carbon tetrachloride is capable of being adsorbed onto organic matter in soils (1). Migration to groundwater is possible (6). Bioaccumulation has not been observed.

14.1.2 Analytical methods

Carbon tetrachloride in drinking-water is determined by purge and trap gas chromatography (7). It is usually detected by mass spectrometry, the detection limit being about 0.3 µg/litre (8).

14.1.3 Environmental levels and human exposure

Air
Most urban air concentrations of carbon tetrachloride are close to the background level of 0.8-0.9 µg/m³ found in the continental air mass. Outdoor concentrations as high as 3.7 µg/m³ have been reported near point sources. Indoor concentrations (1 µg/m³) tend to be higher than outdoor levels (1).

**Water**

Carbon tetrachloride was detected in the drinking-water of 30 of 945 cities in the USA at mean levels ranging from 0.3 to 0.7 µg/litre. Levels as high as 2-3 µg/litre have been measured (1). In Italy, carbon tetrachloride concentrations in drinking-water averaged 0.2 µg/litre (9). Carbon tetrachloride is an occasional contaminant of the chlorine used for drinking-water disinfection (1).

**Food**

Carbon tetrachloride has been detected in a variety of foodstuffs at levels ranging from 0.1 to 20 µg/kg (10). Foods often become contaminated when they are fumigated with it. However, carbon tetrachloride is now seldom used for this purpose.

**Estimated total exposure and relative contribution of drinking-water**

Although available data on concentrations in food are limited, the intake from air is expected to be much greater than that from food or drinking-water. At a typical carbon tetrachloride concentration of 1 µg/m³ in air, the daily exposure by inhalation is estimated to be about 20 µg for an adult with an air intake of 20 m³/day. At a typical concentration of 0.5 µg/litre in drinking-water, a daily exposure of 1 µg is estimated for an adult with an average consumption of 2 litres of water per day.

**14.1.4 Kinetics and metabolism in laboratory animals and humans**

Carbon tetrachloride is readily absorbed from the gastrointestinal tract, the respiratory tract, and the skin, the extent depending upon the administration vehicle (11-13). It appears to be distributed to all major organs following absorption (2), with highest concentrations being in fat.

Carbon tetrachloride is thought to be metabolized by the hepatic cytochrome P-450 enzymes with the production of the highly toxic trichloromethyl radical, which binds to macromolecules, initiating lipid peroxidation and destroying cell membranes (14). The resulting metabolites depend on the aerobic state of the tissue in which metabolism occurs (1) and include chloroform, hexachloroethane, and possibly phosgene (15, 16). The trichloromethyl radical can also combine with oxygen to form peroxy free radicals capable of binding to cellular molecules (17). Carbon tetrachloride and its metabolites are excreted primarily in exhaled air and to a lesser extent in the urine and faeces (2).

**14.1.5 Effects on laboratory animals and in vitro test systems**

**Acute exposure**

Oral LD₅₀ values ranging from 1000 to 12 800 mg/kg of body weight were reported in mice and rats (2).

**Short-term exposure**

Hepatotoxic effects (increased serum enzymes and histopathology) were observed in rats given carbon tetrachloride in corn oil by gavage at daily doses of 20 mg/kg of body weight and higher for 9 days. The same effects were observed in rats given oral daily doses of 10 mg/kg of body weight, 5 days per week for 12 weeks. No measurable adverse effects were observed in rats given 1 mg/kg of body weight per day for 12 weeks (18).

Hepatotoxicity (increased serum enzymes, increased organ weight, and pathological changes) was
observed in male and female CD-1 mice given carbon tetrachloride in corn oil by gavage at doses of 625, 1250, or 2500 mg/kg of body weight for 14 consecutive days. After 90 days, hepatotoxic effects were observed in animals that had ingested 12, 120, 540, or 1200 mg/kg of body weight (19).

Male and female CD-1 mice were given carbon tetrachloride at 0, 1.2, 12, or 120 mg/kg of body weight per day for 90 days (5 days per week) by gavage in corn oil or as an aqueous suspension in 1% polysorbate 60 (20). A significant increase in serum enzyme activity was detected at 12 and 120 mg/kg of body weight per day in the corn oil groups compared with the polysorbate 60 ones. Liver and liver-to-body weight ratios were significantly greater at 120 mg/kg of body weight per day. Hepatocellular changes (e.g. necrosis, fat) occurred at 12 and 120 mg/kg of body weight per day and were more frequently observed in the corn oil groups. Use of a corn oil vehicle yielded a NOAEL that was an order of magnitude lower than that obtained when the polysorbate 60 suspension was used (12 vs. 1.2 mg/kg of body weight per day).

**Long-term exposure**

Carbon tetrachloride at doses of 0, 80, or 200 mg/kg of diet (high dose equivalent to about 10-18 mg/kg of body weight per day) were fed to rats (18 per sex, strain not given) until sacrifice at 2 years (21). Although no adverse effects were observed, tissues were not examined microscopically, liver weights were not taken, and survival was below 50% at 21 months.

**Reproductive toxicity, embryotoxicity, and teratogenicity**

No reproductive effects were noted in rats fed diets containing carbon tetrachloride at 80 or 200 mg/kg for up to 2 years (22). Degeneration of testicular germinal epithelium has been reported in rats exposed to air concentrations of 1280 mg/m³ or above (23). An intraperitoneal dose of 2400 mg/kg of body weight resulted in adverse effects on testicular function in rats (24).

**Mutagenicity and related end-points**

In general, carbon tetrachloride is not mutagenic in bacterial test systems or cultured liver cells (2). However, weakly positive results were reported at cytotoxic levels in an alkaline elution-rat hepatocyte assay that measures DNA single-strand breaks. It has caused point mutations and gene recombination in a eukaryotic (yeast) test system (25). Carbon tetrachloride induced cell transformation in Syrian hamster embryo cells (26). In an in vivo-in vitro hepatocyte DNA repair assay, carbon tetrachloride did not induce unscheduled DNA synthesis in male or female B6C3F₁ mice (27), although significant increases in hepatic cell proliferation were observed. This effect was also produced by carbon tetrachloride in male Fischer 344 rats.

**Carcinogenicity**

In a number of studies, the development of liver tumours (primarily hepatomas and hepatocellular carcinomas) in several animal species, including hamsters, mice, and rats, has been reported following oral, subcutaneous, and inhalation exposure. In general, the first tumours appeared early, within 12-16 weeks in some experiments, and the incidence was high.

After inbred strain L mice were exposed to oral doses of 0.04 ml (approximately 64 mg) of carbon tetrachloride 2-3 times per week for 4 months, hepatomas developed in 47% of the treated animals, as compared with 1% of controls (28). In a study in which Syrian golden hamsters (10 per sex per group) were exposed to oral doses of carbon tetrachloride at 6.25-12.5 µl/day (approximately 10-20 mg/day) for 43 weeks, all animals that survived the treatment period (5 per sex) developed liver cell carcinomas (29).

Groups of B6C3F₁ mice (50 per sex) were given carbon tetrachloride at 0, 1250, or 2500 mg/kg of body weight five times per week for 78 weeks via corn oil gavage, and Osborne-Mendel rats were given 47 or 94 mg/kg of body weight (males) and 80 or 159 mg/kg of body weight (females) (30). The incidence of
hepatocellular carcinomas was markedly increased in treated mice (96-100%) but only slightly in rats (2-8%) as compared with controls (0-6%).

14.1.6 Effects on humans

Single oral doses of 2.5-15 ml (57-343 mg/kg of body weight) do not usually produce severe effect, although changes may occur in liver and kidney tissue, including fat accumulation in the liver and renal swelling. Some adults suffer adverse effects (including death) from the ingestion of as little as 1.5 ml (34 mg/kg of body weight). A dose of 0.18-0.92 ml (29-150 mg/kg of body weight) may be fatal in children. Alcohol consumption potentiates carbon tetrachloride-induced hepatic and renal effects in humans (1, 2).

Occupational exposure to 128-512 mg/m³ carbon tetrachloride for 2-3 months produced neurological effects (nausea, depression, dyspepsia, and narcosis) in workers. Hepatic and renal effects similar to those described for acute oral exposures have been reported after short-term exposures to 1280 mg/m³ (1).

Although an epidemiological study of workers in the rubber industry suggested an association between exposure to carbon tetrachloride and lymphosarcoma and lymphatic leukaemia, the authors stressed that the results should be interpreted cautiously because of multiple exposure, possible bias, and small sample size (31). The development of liver cancer in humans exposed to carbon tetrachloride fumes has been reported only in a few cases, and the data are insufficient to establish a causal relationship (1).

14.1.7 Guideline value

IARC has concluded that there is sufficient evidence that carbon tetrachloride is carcinogenic in laboratory animals to assign it to group 2B as a possible human carcinogen (4).

As there is unequivocal evidence that carbon tetrachloride is carcinogenic in several species, and as it metabolizes to give the highly toxic trichloromethyl radical, the linearized multistage model was chosen for calculating concentrations of carbon tetrachloride in drinking-water associated with lifetime excess cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$. Based on the geometric means of risk estimates for liver cancer from four bioassays in laboratory rodents, concentrations in drinking-water associated with lifetime excess cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$ are 600, 60, and 6 µg/litre, respectively.

Because carbon tetrachloride has not been shown to be genotoxic in most available studies, and because there is a possibility that it may act as a nongenotoxic carcinogen, a guideline value has been derived based on the division of a NOAEL by an uncertainty factor. The NOAEL in a 12-week oral gavage study in rats was 1 mg/kg of body weight per day (18). A TDI of 0.71 µg/kg of body weight (allowing for dosing for 5 days per week) was calculated by applying an uncertainty factor of 1000 (100 for intra- and interspecies variation, and 10 for evidence of possibly nongenotoxic carcinogenicity). No additional factor for the short duration of the study (12 weeks) was incorporated, as the compound was administered in corn oil in the critical study, and available data indicate that toxicity following administration in water may be an order of magnitude less. The guideline value based on 10% allocation to drinking-water is 2 µg/litre (rounded figure). This value is lower than the range of values associated with lifetime excess cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$ calculated by linear extrapolation.

References


19. Hayes JR, Condie LW Jr, Borzelleca JF. Acute, 14-day repeated dosing, and 90-day subchronic


14.2 Dichloromethane

14.2.1 General description

**Identity**

CAS no.: 75-09-2  
Molecular formula: CH₂Cl₂

Dichloromethane is also known as methylene chloride.

**Physicochemical properties** (1,2)
**Property** | **Value**
--- | ---
Melting point | -95.1 °C
Boiling point | 40 °C
Density | 1.3255 g/cm³ at 20 °C
Vapour pressure | 46.53 kPa at 20 °C
Water solubility | 20 000 mg/litre at 20 °C
Log octanol-water partition coefficient | 1.3

1 Conversion factor in air: 1 ppm = 3.53 mg/m³

**Organoleptic properties**

The odour thresholds for dichloromethane in air and water are 530-2120 mg/m³ and 9.1 mg/liter, respectively (3, 4).

**Major uses**

Dichloromethane is widely used as an organic solvent and is found in paints, insecticides, degreasing and cleaning fluids, and other products (2, 5, 6).

**Environmental fate**

Most dichloromethane released to water and soil will be vaporized. It can persist in air for up to 500 days, but is rapidly biodegraded in water. In soil, it undergoes only slight biodegradation and is highly mobile, being leached from subsurface soil into groundwater (5, 6).

**14.2.2 Analytical methods**

Purge-and-trap gas chromatography is routinely used for the determination of dichloromethane and other volatile organohalides in drinking-water (7). This method is suitable for use at concentrations of 1-1500 µg/litre, but there are difficulties at low concentrations because dichloromethane vapour readily penetrates tubing during the procedure. Mass spectrometry (detection limit 0.3 µg/litre) can be used to confirm the identity of the compound (8).

**14.2.3 Environmental levels and human exposure**

**Air**

Background levels in air are usually about 0.1 mg/m³; average concentrations in urban air range between 1 and 7 µg/m³ (2).

**Water**

Dichloromethane has been found in surface water samples at concentrations ranging from 0.1 to 743 µg/litre. Levels are usually higher in groundwater because volatilization is restricted; concentrations as high as 3600 µg/litre have been reported (5). Mean concentrations in drinking-water were less than 1 µg/litre.

**Food**

Food is not expected to be a significant source of exposure to dichloromethane, which is now rarely used in food-extraction processes (e.g. decaffeination of coffee); however, it is used as a post-harvest fumigant on some foods (e.g. strawberries and grains).
Estimated total exposure and relative contribution of drinking-water

Inhalation is the major route of environmental exposure (2), the estimated average daily intake from urban air being 33-307 µg (5). Exposure to dichloromethane through food and drinking-water is insignificant.

14.2.4 Kinetics and metabolism in laboratory animals and humans

Dichloromethane appears to be readily absorbed from the gastrointestinal tract (2, 9). Distribution in rats after oral administration was primarily to liver (10). The cytochrome P-450 and glutathione S-transferase systems can both metabolize dichloromethane to carbon monoxide or carbon dioxide (5, 11). Animal data indicate that dichloromethane is excreted primarily through the lungs, the excretion products depending on the dose (10).

14.2.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Dichloromethane has a low acute toxicity; LD₅₀ values of 2000 mg/kg of body weight for rats and mice have been reported (2, 12, 13). The primary effect associated with acute exposure is depression of the central nervous system.

Short-term exposure

Fischer 344 rats (20 per sex per group) were given dichloromethane in drinking-water for 90 days (0, 166, 420, or 1200 mg/kg of body weight per day in males, and 0, 209, 607, or 1469 mg/kg of body weight per day in females) (14). Centrilobular necrosis and granulomatous foci were noted in mid- and high-dose animals, and changes in some clinical chemistry parameters were noted in mid- and high-dose females. An increased incidence of hepatocyte vacuolization (lipid accumulation) was found in all dose groups. The LOAELs were 166 and 209 mg/kg of body weight per day for male and female rats, respectively.

In a study in which B6C3F₁ mice (20 per sex per group) received dichloromethane in drinking-water for 90 days at doses of 0, 226, 587, or 1911 mg/kg of body weight per day (males) and 0, 231, 586, or 2030 mg/kg of body weight per day (females), subtle centrilobular fatty changes in liver and slight decreases in body weight were seen in the mid- and high-dose groups. The NOAELs were 226 and 231 mg/kg of body weight per day for male and female mice, respectively (14).

Dichloromethane administered to Wistar rats in drinking-water at 125 mg/litre (17.5 mg/kg of body weight per day) (15) for 13 weeks did not affect behaviour, body weight, blood and urine chemistries, organ-to-body-weight ratios, or histopathology, except that the urine albumin test was often positive (2, 16).

Long-term exposure

Fischer 344 rats (85 per sex per group) received estimated mean doses of 6, 52, 125, or 235 mg/kg of body weight per day (males) and 6, 58, 136, or 263 mg/kg of body weight per day (females) for 104 weeks (17). Hepatic histological alterations (including an increased incidence of foci/areas of cellular alterations and fatty changes) were detected at 52 mg/kg of body weight per day and above. There were no other treatment-related effects (e.g. on survival, organ weight, gross pathology) at any dose tested. The NOAEL for hepatic effects was 6 mg/kg of body weight per day.

When given to B6C3F₁ mice for 104 weeks at estimated mean doses of 0, 61, 124, 177, or 234 mg/kg of body weight per day for males (100-200 per dose) and 0, 59, 118, 172, or 238 mg/kg of body weight per day for females (50-100 per dose), dichloromethane did not affect body weight, water consumption, survival, clinical signs, haematological parameters, or gross pathology in any dose group. The histological
alterations seen consisted of increased Oil Red O-positive material in both sexes at the highest dose tested. A NOAEL of 175 mg/kg of body weight per day (average for males and females) was identified (18).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

In a two-generation study in which Fischer 344 rats were exposed to dichloromethane via inhalation at levels up to 5.3 g/m³, no effects on fertility, litter size, neonatal growth and survival, or histopathology were observed (19). In a study in which mice and rats were exposed to dichloromethane at 4.4 or 15.9 g/m³ during gestation (2, 20, 21), fetal body weights were reduced in rats at 15.9 g/m³ (21), and minor skeletal variants (e.g. decreased incidence of lumbar spur in rats and increased incidence of a single extra sternal ossification centre in mice) were found at 4.4 g/m³ (20).

**Mutagenicity and related end-points**

Dichloromethane was positive in the *Salmonella typhimurium* assay with and without activation (22). Test results in cultured mammalian cells are usually negative, but dichloromethane has been shown to transform rat embryo cells and to enhance the viral transformation of Syrian hamster embryo cells (23, 24). No DNA alkylation was detected in rats and mice after inhalation of dichloromethane (25).

**Carcinogenicity**

Fischer 344 rats (85 per sex per group) received estimated mean doses of 6, 52, 125, or 235 mg/kg of body weight per day (males) and 6, 58, 136, or 263 mg/kg of body weight per day (females) in drinking-water for 104 weeks (17). Although the incidence of combined hepatocellular carcinomas and neoplastic nodules increased significantly in females in the groups receiving doses of 58 and 263 mg/kg of body weight per day (4/83, 6/85) as compared with controls (0/134), the number of tumours was similar to that for historical controls. No significant increase in liver tumours was evident in any of the male dose groups. The dose of 235 mg/kg of body weight per day was concluded to be borderline for carcinogenicity in Fischer 344 rats (6).

B6C3F₁ mice received dichloromethane in drinking-water for 104 weeks at estimated mean doses of 0, 61, 124, 177, or 234 mg/kg of body weight per day (males) and 0, 59, 118, 172, or 238 mg/kg of body weight per day (females) (18). There was a marginal increase in the incidence of combined hepatocellular adenomas/carcinomas in male mice in the groups receiving doses of 124, 177 and 234 mg/kg of body weight per day (30/100, 31/99, 35/125) as compared with controls (24/125) but the incidence rates were within the historical control range. Liver tumours were not observed in female mice. This study is regarded as providing suggestive but not conclusive evidence for the carcinogenicity of dichloromethane (6).

Groups of B6C3F₁ mice (50 per sex per dose) were exposed by inhalation to 0, 7.1 or 14.1 g/m³ dichloromethane for 102 weeks (26). The incidence of alveolar/bronchiolar carcinomas was increased in both dose groups in males (10/50, 28/50) and females (13/48, 29/48) as compared with controls (2/50 males, 1/50 females). The combined incidence of hepatocellular adenomas and hepatocellular carcinomas was increased in high-dose males (33/49 v. 22/50 and 24/49 for the control and low-dose group) and high-dose females (40/48 v. 3/50 and 16/48). This study was regarded as clear evidence of carcinogenicity in mice.
14.2.6 Effects on humans

Inhalation of a high concentration of dichloromethane has been associated with a variety of central nervous system effects, most notably narcosis. Acute exposure to levels of 1.06 g/m³ in air can impair sensory and motor function (2, 27). Epidemiological studies involving occupational exposure (2, 28-31) have failed to show a positive correlation between inhalation exposure and increased cancer incidence.

14.2.7 Guideline value

Dichloromethane is of low acute toxicity. An inhalation study in mice provided conclusive evidence of carcinogenicity, whereas a drinking-water study provided only suggestive evidence. IARC has placed dichloromethane in group 2B (possible human carcinogen) (32); however, the evidence suggests that it is not a genotoxic carcinogen and that genotoxic metabolites are not formed in relevant amounts in vivo.

A TDI of 6 µg/kg of body weight was calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 reflecting concern for carcinogenic potential) to a NOAEL of 6 mg/kg of body weight per day for hepatotoxic effects in a 2-year drinking-water study in rats (17). This gives a guideline value of 20 µg/litre (rounded figure), based on the allocation of 10% of the TDI to drinking-water. It should be noted that widespread exposure from other sources is possible.

References


14.3 1,1 Dichloroethane

### 14.3.1 General description

**Identity**

CAS no.: 75-34-3  
Molecular formula: C₂H₄Cl₂

**Physicochemical properties (1,2)**

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<td>Log octanol-water partition coefficient</td>
<td>61.7</td>
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1 Conversion factor in air: 1 ppm = 4.05 mg/m³

**Organoleptic properties**

1,1-Dichloroethane has an aromatic, ethereal and chloroform-like odour. Its odour threshold in air is 486 or 810 mg/m³ (2).

**Major uses**

The major use of 1,1-dichloroethane is as an intermediate in the production of 1,1,1-trichloroethane, vinyl chloride, and other chemicals (3). It is also used as a solvent in paint and varnish removers, as a degreaser and cleaning agent, and in ore flotation. It was formerly used as an anaesthetic.

**Environmental fate**

Most 1,1-dichloroethane released to the environment will be vaporized and enter the atmosphere, where photo-oxidation takes place; the estimated half-life is 44 days. Biodegradation is not expected to be
significant in aquatic systems (3).

14.3.2 Analytical methods

A purge-and-trap gas chromatographic procedure is used for the determination of 1,1-dichloroethane and other volatile organohalides in drinking-water (4). This method is applicable to the measurement of 1,1-dichloroethane over a concentration range of 0.02-1500 µg/litre. Mass spectrometry (detection limit 0.17 µg/litre) can be used to confirm the identity of the compound (5).

14.3.3 Environmental levels and human exposure

Air

1,1-Dichloroethane has been detected in urban air at concentrations ranging from 0.4 to 6.1 µg/m³. A median concentration of 0.22 µg/m³ was reported for urban, rural, and industrial sites across the United States. Concentrations in the vicinity of industrial sources ranged from 0.23 to 0.56 µg/m³, and a concentration of 22.5 µg/m³ was reported near a hazardous waste site. 1,1-Dichloroethane has also been detected in indoor air at a mean concentration of 12.8 µg/m³ (3).

Water

1,1-Dichloroethane was detected in 4.3% of 945 public water supplies in the USA at levels of up to 4.2 µg/litre. It was also detected in private wells used for drinking-water and in surface water and groundwater supplies, generally at levels below 10 µg/litre, although concentrations up to 400 µg/litre have been reported (3).

Estimated total exposure and relative contribution of drinking-water

Exposure to 1,1-dichloroethane may occur through drinking-water, but from the point of view of the general population the greatest exposure is usually from the inhalation of ambient air. Based on a median air level of 0.22 µg/m³, the average inhalation exposure to 1,1-dichloroethane is estimated at 4 µg/day (3).

14.3.4 Kinetics and metabolism in laboratory animals and humans

The detection of metabolites in the urine following oral exposure and its former use as an anaesthetic provide evidence for the absorption of 1,1-dichloroethane by the oral and inhalation routes (6). In general, chlorinated organic solvents are distributed throughout the body following absorption into the blood but preferentially to adipose tissue (7). Following intraperitoneal administration of 1,1-dichloroethane to rats, the compound was detected in liver, kidney, lung, and stomach tissues (8).

Following oral administration of 1,1-dichloroethane to mice and rats, 29% and 7% was metabolized, respectively (6), the major metabolite in both species being carbon dioxide. In vitro studies suggest that the primary route of biotransformation involves the hepatic microsomal cytochrome P-450 system, the major metabolite being ethanoic acid (9, 10). The metabolic capacity of the P-450 system may be exceeded with high oral doses (3). Absorbed 1,1-dichloroethane is excreted mainly in the urine and expired air (6, 7).

14.3.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Reported oral LD₅₀s in rats range from 0.7 to 14 g/kg of body weight (11, 12).
**Short-term exposure**

Groups of five male and five female Osborne-Mendel rats and B6C3F₁ mice received 1,1-dichloroethane in corn oil by gavage, 5 days per week for 6 weeks; this was followed by a 2-week observation period (13). Dose levels were 0, 562, 1000, 1780, 3160, or 5620 mg/kg of body weight per day for rats and 0, 1000, 1780, 3160, 5620, or 10 000 mg/kg of body weight per day for mice. Body weight was depressed in male rats at 562 and 1000 mg/kg of body weight per day and in female rats at 1780 and 3160 mg/kg of body weight per day. Two female rats in the group receiving 3160 mg/kg of body weight per day and two male and three female mice in that receiving 5620 mg/kg of body weight per day died.

Groups of 10 rats, 10 guinea pigs, four rabbits, and four cats were exposed to 2025 mg/m³ 1,1-dichloroethane by inhalation for 6 h per day, 5 days per week for 13 weeks (14). Because no effects were observed in these animals, the exposure concentration was increased to 4050 mg/m³ for an additional 10 by 13 weeks. Elevated blood urea nitrogen values were observed in cats only. At termination, histopathological examination revealed renal tubular dilation and degeneration.

**Long-term exposure**

Groups of Osborne-Mendel rats and B6C3F₁ mice were given 1,1-dichloroethane by gavage in corn oil, 5 days per week for 78 weeks, at time-weighted average doses of 382 or 764 mg/kg of body weight per day (male rats), 475 or 950 mg/kg of body weight per day (female rats), 1442 or 2885 mg/kg of body weight per day (male mice), and 1665 or 3331 mg/kg of body weight per day (female mice) (13). High mortality was seen in both treated and control animals; mortality in male rats and mice showed a significant dose-related trend. The increased mortality was thought to be related to pneumonia, which was observed in about 80% of the rats.

Male B6C3F₁ mice were given 1,1-dichloroethane in drinking-water at concentrations of 835 or 2500 mg/litre (high dose equivalent to about 540 mg/kg of body weight per day) for 52 weeks (15). No histopathological changes were observed in the liver, kidneys, or lungs.

**Reproductive toxicity, embryotoxicity, and teratogenicity**

1,1-Dichloroethane has been found to be embryotoxic but not teratogenic following inhalation exposure. Exposure of pregnant rats to 15.4 or 24.3 g/m³ 1,1-dichloroethane in air 7 h per day on days 6-15 of gestation did not affect the incidence of fetal resorptions or gross or soft tissue anomalies, although a significantly increased incidence of delayed ossification of the sternebrae, reflecting retarded fetal development, was observed in offspring of the rats exposed at 24.3 g/m³ (16).

**Mutagenicity and related end-points**

1,1-Dichloroethane was found to be mutagenic in several strains of *Salmonella typhimurium* with or without metabolic activation (17) but not in others (3, 18). It was not mutagenic in *Saccharomyces cerevisiae* strains with or without metabolic activation (3, 18). 1,1-Dichloroethane increased the frequency of DNA viral transformations in Syrian hamster embryo cells (19) but did not increase cell transformations in BALB/c-3T3 mouse cells (20). 1,1-Dichloroethane was positive in DNA binding assays in mouse and rat organs *in vivo*. Following intraperitoneal injection, it was reported to be covalently bound to macromolecules (DNA, RNA, proteins) in liver, lung, stomach, and kidney tissues of both species (8).

**Carcinogenicity**

Groups of Osborne-Mendel rats and B6C3F₁ mice were given 1,1-dichloroethane by gavage in corn oil, 5 days per week for 78 weeks, at time-weighted average doses of 382 or 764 mg/kg of body weight per day (male rats), 475 or 950 mg/kg of body weight per day (female rats), 1442 or 2885 mg/kg of body weight per day (male mice), and 1665 or 3331 mg/kg of body weight per day (female mice) (13). Marginally
significant dose-related increases in mammary adenocarcinomas and haemangiosarcomas in female rats and a nonsignificant increase in hepatocellular carcinomas in male mice were observed. A statistically significant increase in uterine endometrial stromal polyps (benign tumours) was also observed. Lymphomas of the cervical lymph nodes were reported in 2 of 47 female mice in the high-dose group but not in other groups. The authors concluded that high mortality in all the groups prevented the appearance of late-developing tumours. The results of this study suggest that 1,1-dichloroethane is carcinogenic in rats and mice, but the evidence is not considered conclusive.

1,1-Dichloroethane was administered in drinking-water to male B6C3F1 mice at concentrations of 835 or 2500 mg/litre (the latter is equivalent to about 540 mg/kg of body weight per day) for 52 weeks, either alone or following initiation with diethylnitrosamine (15). Lung and liver tumours were found in all groups, but neither the incidence nor the number of tumours per animal was increased as compared with controls in any treatment group. This was not a lifetime study, and there was a high incidence of spontaneous tumours in controls, so that its value is limited. The authors suggested that 1,1-dichloroethane may be more toxic by gavage than by drinking-water exposure.

14.3.6 Effects on humans

It can be assumed that inhalation exposures to high concentrations of 1,1-dichloroethane cause central nervous system depression, as the compound was used as an anaesthetic until its use was discontinued because of the occurrence of cardiac arrhythmias at concentrations required for anaesthesia (>100 000 mg/m³) (21).

14.3.7. Conclusions

The acute toxicity of 1,1-dichloroethane is relatively low, and only limited data on its toxicity are available from short- and long-term studies. There is limited in vitro evidence of genotoxicity. One carcinogenicity study by gavage in mice and rats provided no conclusive evidence of carcinogenicity, although there was some evidence for an increased incidence of mammary adenocarcinomas and haemangiosarcomas in treated animals (13).

In view of the very limited database on toxicity and carcinogenicity, it is concluded that no guideline value should be proposed.

References


chemistry and toxicology, 1985, 8:183-194.


14.4 1,2 Dichloroethane
14.4.1 General description

Identity

CAS no.: 107-06-2  
Molecular formula: C₂H₄Cl₂

1,2-Dichloroethane is also known as ethylene dichloride.

Physicochemical properties

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1 Conversion factor in air: 1 ppm = 4.05 mg/m³

Organoleptic properties

The odour thresholds for 1,2-dichloroethane in air and water are 356 mg/m³ and 7 mg/litre, respectively (2).

Major uses

The major use of 1,2-dichloroethane is in the production of vinyl chloride (1). It is also used as a solvent, in the synthesis of other chlorinated solvents, and as a lead scavenger in leaded petrol.

Environmental fate

Most 1,2-dichloroethane released to the environment volatilizes to the atmosphere, where it is photo-oxidized with a lifetime of up to 4 months. Biodegradation is not expected to be significant in aquatic systems (3). 1,2-Dichloroethane may persist for long periods in groundwater, where volatilization is restricted (1).

14.4.2 Analytical methods

A purge-and-trap gas chromatographic procedure is used for the determination of 1,2-dichloroethane and other volatile organohalides in drinking-water (4). This method is applicable to the measurement of 1,2-dichloroethane over a concentration range of 0.2-1500 µg/litre. Confirmatory analysis is by mass spectrometry, the detection limit being 0.3 µg/litre (5).

14.4.3 Environmental levels and human exposure

Air

1,2-Dichloroethane has been detected in urban air at concentrations ranging from 0.04 to 38 µg/m³ (6). Concentrations in the vicinity of industrial sources may be higher (1, 7).
### Water

1,2-Dichloroethane was detected in drinking-water in 26 of 80 cities in the USA at levels up to 6 µg/litre (8). It was not detected in the drinking-water of 100 cities in Germany, but was present at levels up to 61 µg/litre in tapwater in other areas of Europe (7).

### Food

1,2-Dichloroethane was detected in 11 of 17 spice samples at levels of 2-23 µg/g (9) and in milk products with added fruit at an average concentration of 0.8 µg/kg (7). There is no significant bioconcentration of 1,2-dichloroethane in fish (9).

### Estimated total exposure and relative contribution of drinking-water

The greatest exposure of the general population is usually from the inhalation of ambient air (3). Exposure from drinking-water may be important for about 5% of the population and may exceed exposure by inhalation in places where the water concentration is greater than 6 µg/litre (3). Volatilization of 1,2-dichloroethane from water during showering or other water uses and from consumer products (cleaning agents, wallpaper, and carpet glue) may also contribute to inhalation exposure.

### 14.4.4 Kinetics and metabolism in laboratory animals and humans

1,2-Dichloroethane is readily absorbed through the lungs, skin, and gastrointestinal tract by both humans and laboratory animals (1, 10-12). It appears to be readily distributed following oral or inhalation exposure, accumulating in the liver and kidneys (13). 1,2-Dichloroethane appears to cross the blood-brain barrier and the placenta (3), and it has been detected in human milk following occupational exposure (11).

1,2-Dichloroethane is readily metabolized following oral or inhalation exposure. The primary route of biotransformation appears to involve conjugation with glutathione in the liver to produce several urinary metabolites, including S-carboxymethylcysteine and thiodiacetic acid (3, 14, 15). Absorbed 1,2-dichloroethane is rapidly excreted, mainly in the urine and expired air (14, 15).

### 14.4.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

Reported oral LD₅₀s are 670 mg/kg of body weight for rats, 489 mg/kg of body weight for mice, and 860 mg/kg of body weight for rabbits (1, 16).

**Short-term exposure**

Mice exposed to 1,2-dichloroethane at 4.9 or 49 mg/kg of body weight per day for 14 days by gavage exhibited a significant depression of leukocyte counts at the higher dose, and a significant reduction in the number of antibody-forming cells and inhibition of cell-mediated immunity at both doses. No effects on other haematological parameters, body weights, or the hepatic, renal, or respiratory systems were observed. Mice exposed to 1,2-dichloroethane at time-weighted average doses of 3, 24, or 189 mg/kg of body weight per day for 90 days in drinking-water experienced no significant adverse effects on haematological, immunological, hepatic, renal, or respiratory parameters (17). Liver changes, including an increase in liver triglycerides and a 15% increase in fat accumulation in the liver, were observed in rats given 1,2-dichloroethane in the diet at 80 mg/kg of body weight per day for 5-7 weeks (12).

**Long-term exposure**

Significantly increased mortality was reported in groups of rats and mice exposed to 1,2-dichloroethane by
gavage in corn oil for 78 weeks at doses of 95 or 299 mg/kg of body weight per day, respectively (18). No treatment-related effects on growth or biochemical indices were observed in rats exposed to 1,2-dichloroethane at 250 or 500 mg/kg of diet (the higher dose is equivalent to about 26-35 mg/kg of body weight per day) for 2 years (12).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

In rats exposed to 1,2-dichloroethane at 250 or 500 mg/kg in the diet for 2 years, no effect was seen on male fertility or on reproductive activity in either sex (12). No reproductive effects, as measured by fertility, gestation, viability or lactation indices, pup survival, or weight gain, were found in a multigeneration reproduction study using male and female ICR Swiss mice that received 0, 5, 15, or 50 mg/kg of body weight per day in drinking-water (19). In a study in which male and female mice were exposed to 1,2-dichloroethane in drinking-water at doses of 0, 5, 15, or 50 mg/kg of body weight per day, no statistically significant developmental effects were observed, as indicated by incidence of fetal visceral or skeletal anomalies, were observed (19).

**Mutagenicity and related end-points**

1,2-Dichloroethane was mutagenic in several strains of *Salmonella typhimurium* and in *Escherichia coli* in some microsome assay test systems (1, 3, 20, 21) but not in others (3, 22). The mutagenic effects were enhanced by metabolic activation (3, 21). Sex-linked recessive lethals and somatic cell mutations were induced in *Drosophila melanogaster* (3, 23, 24). 1,2-Dichloroethane also induced mutations *in vitro* in human lymphoblasts and was positive in DNA-binding and DNA-damage assays in mice and rats *in vivo*. It did not induce micronucleus formation in mice (3).

**Carcinogenicity**

1,2-Dichloroethane administered by gavage 5 days per week for 78 weeks to Osborne-Mendel rats (time-weighted average doses of 47 or 95 mg/kg of body weight per day) and B6C3F₁ mice (time-weighted average doses of 97 or 195 mg/kg of body weight per day (males) and 149 or 299 mg/kg of body weight per day (females)) was reportedly carcinogenic to both species (1, 18). Statistically significant increases in the incidence of squamous cell carcinomas of the forestomach and haemangiosarcomas of the circulatory system were observed in male rats, and female rats showed a statistically significant increased incidence in adenocarcinoma of the mammary glands. Statistically significant increases in the incidence of mammary adenocarcinomas and endometrial stromal polyps or sarcomas were seen in female mice, and the incidence of alveolar/bronchiolar adenomas was increased in male and female mice.

In a bioassay in which 1,2-dichloroethane was administered in drinking-water to male B6C3F₁ mice at concentrations of 835 and 2500 mg/litre (the higher dose is equivalent to about 470 mg/kg of body weight per day) for 52 weeks, either alone or following initiation with diethylnitrosamine (25), no increase was seen in the incidence of tumours as compared with controls. However, this was not a lifetime study, and there was a high incidence of spontaneous tumours in the controls. In addition, 1,2-dichloroethane appears to be more toxic by gavage than by exposure to drinking-water (3, 17).

**14.4.6 Effects on humans**

Acute oral exposure to 1,2-dichloroethane is reported to cause central nervous system, hepatic, gastrointestinal, respiratory, renal, and cardiovascular effects in humans (1, 3, 26-28). Death following acute intoxication is most often attributed to cardiovascular or respiratory failure (3, 28). Repeated inhalation exposures in the workplace result in anorexia, nausea, vomiting, weakness and fatigue, nervousness, epigastric pain, and irritation of the respiratory tract and eyes (1, 29).
14.4.7 Guideline value

IARC has classified 1,2-dichloroethane in Group 2B (possible human carcinogen) (30). It has been shown to produce statistically significant increases in a number of types of tumour in laboratory animals, including the relatively rare haemangiosarcoma, and the balance of evidence indicates that it is potentially genotoxic. There are no suitable long-term studies on which to base a TDI.

On the basis of haemangiosarcomas observed in male rats in a 78-week gavage study (18), and applying the linearized multistage model, concentrations in drinking-water of 300, 30, and 3 µg/litre, corresponding to excess cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$, respectively, were calculated.

References


14.5 1,1,1-Trichloroethane

14.5.1 General description

Identity

CAS no.: 71-55-6
Molecular formula: C₃H₅Cl₃

Physicochemical properties (1,2)

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</table>

¹ Conversion factor in air: 1 ppm = 5.4 mg/m³

Organoletic properties

1,1,1-Trichloroethane has a chloroform-like odour.

Major uses

1,1,1-Trichloroethane is widely and increasingly used as a cleaning solvent for electrical equipment, motors, electronic instruments, and upholstery, as a solvent for adhesives, coatings, and textile dyes, as a coolant and lubricant in metal cutting oils, and as a component in inks and drain cleaners (1,2).

Environmental fate

1,1,1-Trichloroethane is found mainly in the atmosphere, where it has a half-life of approximately 2-6 years. It can be decomposed by photochemically produced hydroxyl radicals (1). In water, 1,1,1-trichloroethane is moderately soluble but can volatilize to air. It can be anaerobically dechlorinated by methane-producing bacteria to form 1,1-dichloroethane, and decomposed to give ethanoic acid and 1,1-dichloroethene by abiotic reactions, with a half-life of 200-300 days. 1,1,1-Trichloroethane is mobile in soils and readily migrates to groundwaters. Volatilization from surface soils is also likely. It does not bioaccumulate in animals (1).

14.5.2 Analytical methods

1,1,1-Trichloroethane in water is usually determined by a purge-and-trap gas chromatographic procedure (3). It can be detected by mass spectrometry, the detection limit being 0.3 µg/litre (4).
14.5.3 Environmental levels and human exposure

**Air**

The median concentration of 1,1,1-trichloroethane in air was 0.6 µg/m³ in rural and remote areas, 2.8 µg/m³ in urban and suburban areas, and 6.5 µg/m³ in source-dominated areas (5). Mean air levels in cities in the USA ranged from 0.001 to 60 µg/m³ for urban air and from 0.36 to 1.08 µg/m³ for rural air (1). Air concentrations are typically higher in the northern hemisphere (average 0.06-0.1 µg/m³) than in the southern hemisphere (average 0.02 µg/m³) (6).

**Water**

Tributaries of the Rhine contained 1,1,1-trichloroethane at levels of 0.05-2.2 µg/litre. Surface waters in Switzerland contained an average of 0.06 µg/litre. In Europe, groundwater levels were in the range 0.04-130 µg/litre (6).

In the USA, the mean level of 1,1,1-trichloroethane in drinking-water was 0.02-0.6 µg/litre; in well-water, the corresponding level was 9-24 µg/litre (1). A mean concentration of 0.3 µg/litre was reported for drinking-water in Italy (7). Surface water samples from 20 of 106 drinking-water systems analysed for 1,1,1-trichloroethane in the USA between 1977 and 1981 contained detectable levels of this compound (0.1-3.3 µg/litre, mean 0.6 µg/litre; detection limit 0.1 µg/litre). Of 316 groundwater systems tested, 15 contained 1,1,1-trichloroethane at levels ranging from the detection limit (0.5 µg/litre) to 142 µg/litre (mean 13 µg/litre) (8).

**Food**

Small amounts of 1,1,1-trichloroethane were found in various foodstuffs in the United Kingdom; it was present in meats, oils and fats, tea, and fruits and vegetables at levels ranging from 1 to 10 µg/kg (9). The highest levels of 1,1,1-trichloroethane found in a survey in the USA were in fatty foods (19 µg/kg) and margarine (45 µg/kg) (10).

**Estimated total exposure and relative contribution of drinking-water**

Exposures to 1,1,1-trichloroethane are highly variable and should be evaluated on an individual basis. If an air concentration of 5 µg/m³ is assumed, the daily intake would be 100 µg for an adult breathing 20 m³ of air per day. On the assumption of a 1,1,1-trichloroethane level of 0.6 µg/litre in drinking-water, the daily intake will be 1.2 µg for an adult consuming 2 litres of drinking-water per day. If the average concentration in food is 5 µg/kg, the intake will be 10 µg/day for an adult consuming 2 kg of food.

14.5.4 Kinetics and metabolism in laboratory animals and humans

1,1,1-Trichloroethane appears to be absorbed rapidly and completely from the lungs of human subjects (11). After 4 h of continuous exposure to 378 or 756 mg/m³, a steady-state lung retention of 30% was observed (12,13). The concentration of 1,1,1-trichloroethane in the expired air of humans after ingestion of 0.6 g/kg of body weight was equivalent to the expired air concentration following an inhalation exposure of 2700 mg/m³ (14).

After inhalation by humans, blood levels of 1,1,1-trichloroethane were highly correlated with alveolar air levels. Within 2 h of exposure, 60-80% was eliminated from the blood (12). One day after intraperitoneal administration of 1,1,1-trichloroethane at 700 mg/kg of body weight, rats retained 0.9% (as the parent compound) in the skin, 0.02% in the blood, 0.02% in the fat, and 0.1% in other sites (15).

1,1,1-Trichloroethane is metabolized to a very limited extent in mammals (12); the proportion is probably less than 6% in humans. Metabolites include trichloroethanol, trichloroethane glucuronide, and
trichloroethanoic acid. Less than 3% of a single intraperitoneal injection of 1,1,1-trichloroethane was metabolized by rats (15). The metabolic fate of inhaled 1,1,1-trichloroethane in rats and mice was not altered on repeated exposure (16).

1,1,1-Trichloroethane was detected in the expired air of human subjects exposed to oral doses (14). Metabolites were excreted primarily in urine; very small amounts of trichloroethanol (1%) were excreted by the lungs (12). Over 99% of intraperitoneally injected 1,1,1-trichloroethane was excreted by rats via the pulmonary route (98.7% unchanged); less than 1% was excreted via the urine, primarily as the trichloroethanol glucuronide (15). Rats and mice exposed via inhalation to radiolabelled 1,1,1-trichloroethane for 6 h excreted more than 96% of the administered radioactivity during the first 24 h, primarily via exhalation (16).

14.5.5 Effects on laboratory animals and in vitro test systems

Acute exposure

The acute oral LD₅₀ for 1,1,1-trichloroethane in several species ranged from 5.7 to 14.3 g/kg of body weight (17). A single oral dose of approximately 1.4 g/kg of body weight depressed the activities of hepatic cytochrome P-450 and epoxide hydratase in rats (18).

Short-term exposure

1,1,1-Trichloroethane at doses of 5 or 10 g/kg of body weight per day for 9 days produced fatalities, transient hyperexcitability, and protracted narcosis in rats. There were no observed adverse effects at 0.5 g/kg of body weight per day. When 1,1,1-trichloroethane was administered to rats by gavage five times a week for up to 12 weeks at doses of 0, 0.5, 2.5, or 5.0 g/kg of body weight, the animals given 2.5 or 5.0 g/kg of body weight exhibited reduced body weight gain and central nervous system effects. Although 35% of these rats died during the first 50 days of the experiment, only the group receiving 5.0 g/kg of body weight showed an increase in serum enzyme levels indicative of toxicity. No adverse effects were observed following ingestion of 0.5 g/kg of body weight for 12 weeks (19).

Male mice were exposed continuously to 1,1,1-trichloroethane by inhalation at levels of 1365 or 5460 mg/m³ for 14 weeks, while control mice were exposed to room air. Significant changes were observed in the centrilocublar hepatocytes of mice in the high-dose group, namely vesiculation of the rough endoplasmic reticulum with loss of attached polyribosomes and increased smooth endoplasmic reticulum, microbodies, and triglyceride droplets. The NOAEL is this study was 1365 mg/m³ (20).

Long-term exposure

Decreases in survival and body weight gain were noted in mice and rats given 1,1,1-trichloroethane by gavage in corn oil, 5 days per week for 78 weeks. The rats were given doses of 750 or 1500 mg/kg of body weight per day, and the mice 2800 or 5600 mg/kg of body weight per day (21).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a multigenerational study, no dose-dependent effects on fertility, gestation, or viability indices were seen in mice exposed to 1,1,1-trichloroethane in their drinking-water at dose levels of 100, 300, or 1000 mg/kg of body weight from premating to lactation (22).

Mutagenicity and related end-points

It was reported in several studies that 1,1,1-trichloroethane was not mutagenic in Salmonella typhimurium when tested with or without metabolic activation (7), but no attempt was made in the testing procedure to prevent volatilization of the test compound. 1,1,1-Trichloroethane was mutagenic in various strains of S.
typhimurium when tested with or without metabolic activation (1,23), but not in Saccharomyces cerevisiae or Schizosaccharomyces pombe (24). In several mammalian cell lines, exposure to 1,1,1-trichloroethane led to an increased frequency of transformed cells (1).

Carcinogenicity

Male and female rats (750 or 1500 mg/kg of body weight) and male and female mice (2800 or 5600 mg/kg of body weight) were given 1,1,1-trichloroethane in corn oil by gavage five times per week for 110 weeks (rats) and 78 weeks (mice). The incidence and types of tumours observed in treated animals were similar to those observed in controls. Because of the decreased survival time in both mice and rats, the authors concluded that this bioassay was not adequate to assess carcinogenicity in either species (2,21).

Rats (375 or 750 mg/kg of body weight) and mice (1500 or 3000 mg/kg of body weight) were given 1,1,1-trichloroethane in corn oil by gavage five times per week for 103 weeks. No treatment-related tumours were observed in male rats, and the study was inadequate for the evaluation of female rats because of the high mortality rate. Although there was a significant dose-response trend and increased incidence of hepatocellular carcinomas in male and high-dose female mice, the study was judged to be inadequate for assessment of carcinogenicity (25).

14.5.6 Effects on humans

Large oral doses of 1,1,1-trichloroethane have produced nausea, vomiting, and diarrhoea in humans. Acute inhalation exposures result in neurological effects (1). Impaired test performance occurs above 945 mg/m³, while dizziness, light-headedness, and incoordination can occur above 2.7 g/m³. Concentrations of 54 g/m³ result in general anaesthesia. Acute pulmonary congestion and oedema were often found in fatalities resulting from inhalation (26,27). Fatty vacuolization was also found in the liver of exposed subjects (26). High concentrations of 1,1,1-trichloroethane in air can produce respiratory failure and cardiac arrhythmia (1), while chronic exposure to low levels had no effect on parameters of serum and urine chemistry indicative of liver and kidney damage in humans (1).

14.5.7 Provisional guideline value

IARC has placed 1,1,1-trichloroethane in Group 3 (not classifiable as to its carcinogenicity to humans) (28). Available studies of oral administration were considered inadequate for calculation of a TDI. However, as there is an increasing need for guidance on this compound, a 14-week inhalation study in male mice was selected for use in calculating the guideline value (20). Based on a NOAEL of 1365 mg/m³, a TDI of 580 µg/kg of body weight was calculated from a total absorbed dose of 580 mg/kg of body weight per day (assuming an average mouse body weight of 30 g, breathing rate of 0.043 m³/day, and absorption of 30% of the air concentration), applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the short duration of the study). A provisional guideline value of 2000 µg/litre (rounded value) is proposed, if 10% of the TDI is allocated to drinking-water.

This value is provisional only because of the use of an inhalation rather than an oral study. It is strongly recommended that an adequate oral toxicity study be conducted to provide more acceptable data for the derivation of a guideline value.

References


### 14.6 Vinyl chloride

#### 14.6.1 General description

**Identity**

CAS no.: 75-01-4  
Molecular formula: C₂H₃Cl

The IUPAC name for vinyl chloride is chloroethene; it is also known as monochloroethylene.

**Physicochemical properties (1-3)**

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1 Conversion factor in air: 1 ppm = 2.6 mg/m³
**Organoleptic properties**

Vinyl chloride has a mild, sweetish odour at high concentrations. Odour thresholds in air range from 26-52 mg/m³ in sensitive individuals to 10 000 mg/m³ (3,4). An odour threshold of 3.4 mg/litre in water has been reported (5).

**Major uses**

Vinyl chloride is used primarily for the production of polyvinyl chloride (PVC). It is also used as a co-monomer with ethenyl ethanoate (vinyl acetate) or 1,1-dichloroethene (vinylidene chloride) and as a raw material in the manufacture of 1,1,1-trichloroethane and monochloracetaldehyde (4).

**Environmental fate**

In the atmosphere, vinyl chloride reacts with hydroxyl radicals and ozone, ultimately forming formaldehyde, carbon monoxide, hydrochloric acid, and formic acid; its half-life is about 20 h. It is stable in the absence of sunlight or oxygen but polymerizes when exposed to air, light, or heat (3).

Vinyl chloride released to surface water migrates to the atmosphere in a few hours or days. When released to the ground, it is not adsorbed onto soil but migrates readily to groundwater, where it may be degraded to carbon dioxide and chloride ion or may remain unchanged for several months or even years. Vinyl chloride has been reported to be a degradation product of trichloroethene and tetrachloroethene in groundwater (6).

**14.6.2 Analytical methods**

Vinyl chloride in drinking-water can be determined by purge-and-trap gas chromatography over the concentration range 0.06-1500 µg/litre. Mass spectrometry is used for confirmation (detection limit 0.3 µg/litre) (6).

**14.6.3 Environmental levels and human exposure**

**Air**

The background level of vinyl chloride in ambient air in western Europe is estimated to range from 0.1 to 0.5 µg/m³ (3). Concentrations are higher close to industrial production sources. Vinyl chloride has been found in the smoke of cigarettes (1.3-16 ng per cigarette) and small cigars (14-27 ng) (2).

**Water**

It was found in one survey that fewer than 2% of all groundwater-derived public water-supply systems contained vinyl chloride at levels of 1 µg/litre or higher. Those derived from surface water have also been found to contain vinyl chloride but at lower levels (6). The highest concentration of vinyl chloride detected in drinking-water in the USA was 10 µg/litre. In a five-city survey in that country, concentrations of vinyl chloride of up to 1.4 µg/litre were detected in drinking-water taken from distribution systems in which PVC pipe was used (7). Vinyl chloride has been detected only occasionally in samples of drinking-water from 100 cities in Germany. The highest level, 1.7 µg/litre, was ascribed to dissolution from PVC tubing (3).

**Food**

With the implementation of stringent manufacturing specifications for PVC, residual levels of vinyl chloride in food and drinks have decreased from 20 mg/kg in the mid-1970s to well below 10 µg/kg (4). In a survey of 50 food samples in the United Kingdom, it was detected in only five of them, the highest levels being
0.04 µg/kg in sunflower oil and 0.74 µg/kg in orange drink (4).

**Estimated total exposure and relative contribution from drinking-water**

If an ambient air concentration of 0.1-0.5 µg/m³ and a daily inhalation of 20 m³ of air are assumed, daily intake by the inhalation route would amount to 2-10 µg. Heavy smokers may inhale an additional 0.5 µg/day (2). At a concentration of 1-2 µg/litre in drinking-water, daily intake would be about 2-4 µg. Daily intake from food has been estimated to be about 0.02-0.025 µg (4). It appears that inhalation is the most important route of vinyl chloride intake, although drinking-water may contribute a substantial portion of daily intake where PVC piping with a high residual content of vinyl chloride monomer is used in the distribution network.

14.6.4 Kinetics and metabolism in laboratory animals and humans

Vinyl chloride is readily absorbed following oral administration or inhalation. Absorption through the skin is negligible (3). The highest concentrations of metabolites are found in the liver, kidneys, and spleen (2).

Vinyl chloride is metabolized via the microsomal mixed-function oxidase system, forming chloroethylene oxide, which can rearrange spontaneously to chloroacetaldehyde; both metabolites are highly reactive and mutagenic. Chloroacetaldehyde can be oxidized to chloroethanoic acid, and all three metabolites can be conjugated to glutathione or cysteine and excreted in the urine (3).

Vinyl chloride metabolism is dose-dependent and saturable. Low doses administered by gavage are metabolized and eliminated primarily in the urine, whereas with higher doses a substantial proportion is excreted unchanged via the lungs. Major urinary metabolites in rats include N-acetyl-S-2-hydroxyethyl cysteine and thiodiglycolic acid. These metabolites have also been found in the urine of humans following inhalation of vinyl chloride (3).

Vinyl chloride does not accumulate in the body to any significant extent. In rats, it is estimated to have a biological half-life of 20 min (2).

14.6.5 Effects on laboratory animals and *in vitro* test systems

**Acute exposure**

The acute toxicity of vinyl chloride is low, 2-hour LC₅₀s ranging from 295 g/m³ for mice to 595 g/m³ for guinea-pigs and rabbits (3).

**Short-term exposure**

Groups of 30 rats given vinyl chloride in soybean oil by gavage at 0, 30, 100, or 300 mg/kg of body weight, 6 days per week for 13 weeks, exhibited a dose-related increase in relative liver weight. A dose-related increase in adrenal gland weight (males only) was significant at the highest dose level. Histological changes in the liver and other organs were minimal. Hypertrophy of the endoplasmic reticulum was observed in hepatocytes of animals in the group given 300 mg/kg of body weight (8,9).

**Long-term exposure**

Groups of Wistar rats (60-80 per sex per dose) were fed diets containing PVC 7 days per week for 135-144 weeks (10). Oral exposure to vinyl chloride monomer during the period of feeding was 0, 1.7, 5.0, or 14.1 mg/kg of body weight per day. Another group of rats (80 per sex) received a 10% solution of vinyl chloride monomer in soybean oil by gavage, 5 days per week for 83 weeks, at a dose of approximately 300 mg/kg of body weight per day. There was a marked dose-related increase in mortality in the groups given 5.0 and 14.1 mg/kg of body weight per day. Rats in the groups given 14.1 and 300 mg/kg of body
weight per day exhibited a significant decrease in blood clotting time, slightly increased levels of α-fetoprotein in the blood serum, liver enlargement, and increased haematopoietic activity in the spleen. Liver-to-body-weight ratios were higher in the groups given 14.1 and 300 mg/kg of body weight per day than in controls, and the incidence of foci of cellular alteration was much higher in both of the treatment groups than in controls.

**Reproductive toxicity, embryotoxicity, and teratogenicity**

No significant effects on malformations or anomaly rates were seen following the inhalation exposure of mice, rats, or rabbits to vinyl chloride during different periods of pregnancy. The results of other experiments, however, have suggested that it may be embryotoxic in rats and mice (2,8).

**Mutagenicity and related end-points**

Vinyl chloride induced sister chromatid exchange in human lymphocytes in vitro, mutations in Chinese hamster cells, unscheduled DNA synthesis in rat hepatocytes, and transformation of BALB/c 3T3 cells. It also caused sex-linked recessive lethal mutations but not aneuploidy, heritable translocations, or dominant lethal mutations in Drosophila. It was mutagenic to plants including the yeast Schizosaccharomyces pombe, but not to other fungi. It induced gene conversion in yeast, caused DNA damage and mutation in bacteria and, with metabolic activation, bound covalently to isolated DNA (11).

Vinyl chloride induced chromosomal aberrations, sister chromatid exchange, and micronuclei in rodents exposed in vivo, but did not induce mutation in the mouse spot test or dominant lethal mutations in rats or mice. It alkylated DNA in several tissues of mice and rats exposed in vivo (11).

**Carcinogenicity**

There is sufficient evidence of the carcinogenicity of vinyl chloride to animals. When administered by inhalation, it induced angiosarcomas of the liver in rats, mice, and hamsters, Zymbal gland tumours in rats and hamsters, nephroblastomas in rats, pulmonary and mammary gland tumours in mice, and forestomach papillomas in hamsters. The minimum concentrations at which compound-related tumours were observed were 26, 130 and 1300 mg/m³ in rats, mice, and hamsters, respectively (4).

In the study in which groups of Wistar rats were fed vinyl chloride monomer in the diet for 135-144 weeks (0, 1.7, 5.0, or 14.1 mg/kg of body weight per day) or a 10% solution of vinyl chloride monomer in soybean oil by gavage, 5 days per week for 83 weeks (300 mg/kg of body weight per day), angiosarcomas of the liver were observed in the three highest dose groups and there was a dose-related increase in hepatocellular carcinomas. Angiosarcomas were present in the lungs in the two highest dose groups, and the incidence of adenomas of the mammary glands was twice as high in the test groups as in the controls (10).

In extended studies carried out in the same laboratory using the same methods but lower doses (12), hepatocellular carcinomas and angiosarcomas were found at the highest dose (1.7 mg/kg of body weight per day), although in smaller numbers. A statistically significant increase in the incidence of liver nodules (presumed to be hepatomas) was the only neoplastic response at levels below 1.7 mg/kg of body weight per day.

In another study, groups of Sprague-Dawley rats (40 per sex per dose) and groups of DS rats (75 per sex per dose) were given vinyl chloride monomer in olive oil at dose levels equivalent to 0, 3.3, 16.6, or 50 mg/kg of body weight (Sprague-Dawley) and 0, 0.03, 0.3, or 1 mg/kg of body weight (DS rats), 5 times a week for 52 or 59 weeks; the study was terminated at 136 weeks. In the study on Sprague-Dawley rats, there was a dose-related increase in angiosarcomas: 18 at 50 mg/kg of body weight, nine at 16.6 mg/kg of body weight, and one at 3.3 mg/kg of body weight. In the study on DS rats, four angiosarcomas were found at 1 mg/kg of body weight, two at 0.3 mg/kg of body weight, and none at 0.03 mg/kg of body weight.
Small numbers of other tumours were also found, including nephroblastomas, Zymbal gland carcinomas, and hepatomas (13).

In a study in which Wistar-derived rats (54 per sex per dose) were given vinyl chloride in drinking-water at concentrations of 0, 2.5, 25, or 250 mg/litre (equivalent to 0.12, 1.2, and 12 mg/kg of body weight per day for males, and 0.22, 2.2, and 22 mg/kg of body weight per day for females) for 101-152 weeks (Evans et al., unpublished, 1980, cited in references 4 and 8), malignant tumours occurred with greater frequency in the highest dose groups, the increase being more pronounced in females. Liver angiosarcomas occurred only in the highest dose groups. In addition, five males in the group given 250 mg/litre developed angiosarcoma in the spleen, and a single subcutaneous angiosarcoma was present in a male in the group given 25 mg/litre.

14.6.6 Effects on humans

Vinyl chloride is a narcotic agent, and loss of consciousness can occur at 25 g/m³. Effects of chronic inhalation exposure include Raynaud’s phenomenon, a painful vasospastic disorder of the hands, and pseudoscleroderma (2).

There is sufficient evidence of the carcinogenicity of vinyl chloride in humans from studies of industrial populations exposed to high concentrations via the inhalation route, and IARC has classified vinyl chloride in Group 1 (11). The causal association between vinyl chloride exposure and angiosarcoma of the liver is commonly accepted. There are conflicting opinions, however, regarding the relationship between vinyl chloride exposure and hepatocellular carcinoma, brain tumours, lung tumours, and malignancies of the lymphatic and haematopoietic tissues (4,11).

A number of cytogenetic studies have demonstrated an increased frequency of chromosomal aberrations in the peripheral lymphocytes of exposed workers, but negative studies have also been reported (4).

Although some studies suggest that paternal exposure to vinyl chloride may be associated with adverse reproductive outcomes, the available data cannot be considered conclusive, and no mechanism whereby the supposed reproductive effects could be produced is known (4).

14.6.7 Guideline value

There is sufficient evidence of the carcinogenicity of vinyl chloride in humans from industrial populations exposed to high concentrations via the inhalation route, and IARC has classified vinyl chloride in Group 1 (11). A causal association between vinyl chloride exposure and angiosarcoma of the liver is sufficiently proved, and some studies suggest that vinyl chloride is also associated with hepatocellular carcinoma, brain tumours, lung tumours, and malignancies of the lymphatic and haematopoietic tissues.

Animal data show vinyl chloride to be a multisite carcinogen. When administered orally or by inhalation to mice, rats, and hamsters it produced tumours in the mammary gland, lungs, Zymbal gland, and skin, as well as angiosarcomas of the liver and other sites.

Because there are no data on carcinogenic risk following oral exposure of humans to vinyl chloride, estimation of the risk of cancer in humans was based on animal carcinogenicity bioassays involving oral exposure. Using results from the rat bioassay, which yields the most protective value (12), and applying the linearized multistage model, the human lifetime exposure for a $10^{-5}$ excess risk of hepatic angiosarcoma was calculated to be 20 µg per day. It was also assumed that, in humans, the number of cancers at other sites may equal that of angiosarcoma of the liver, so that a correction (factor of 2) for cancers other than angiosarcoma is justified. Concentrations in drinking-water of 50, 5, and 0.5 µg/litre were calculated as being associated with excess risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$, respectively.
References


14.7 1,1-Dichloroethene

14.7.1 General description

Identity

CAS no.: 75-35-4
Molecular formula: C₂H₂Cl₂
1,1-Dichloroethene is also known as vinylidene chloride.

**Physicochemical properties**

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1 Conversion factor in air: 1 ppm = 4 mg/m³

**Organoleptic properties**

1,1-Dichloroethene has a mild, sweet odour. Its odour thresholds in air and water are 760 mg/m³ and 1.5 mg/litre, respectively.

**Major uses**

1,1-Dichloroethene is used mainly as a monomer in the production of polyvinylidene chloride co-polymers and as an intermediate in the synthesis of other organic chemicals, such as methyl chloroform and 1,1,1-trichloroethane.

**Environmental fate**

Most 1,1-dichloroethene released to the environment volatilizes to the atmosphere, where it is oxidized by hydroxyl radicals with a lifetime of about 1-3 days. Rapid photolysis is also expected to occur. Volatilization is the major removal mechanism in surface waters and soils, and anaerobic biotransformation to vinyl chloride is expected to be important in groundwater.

**14.7.2 Analytical methods**

The concentration of 1,1-dichloroethene is measured by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking-water. This method is applicable to the measurement of 1,1-dichloroethene over a concentration range of 0.03-1500 µg/litre. Mass spectrometry is used for confirmation (detection limit of 0.2 µg/litre).

**14.7.3 Environmental levels and human exposure**

**Air**

1,1-Dichloroethene has been detected in urban air at mean concentrations of 19.6-120 ng/m³. The median concentration in ambient air from all areas is less than 4 ng/m³. Concentrations in the vicinity of industrial plants or hazardous waste sites may be higher. It has also been detected in indoor air at an average concentration of 78.8 µg/m³.

**Water**

1,1-Dichloroethene was detected in 2.3% of 945 samples of finished drinking-water taken from groundwater sources in the USA at median concentrations of 0.28-1.2 µg/litre and in about 3% of public drinking-water supplies at concentrations ranging from 0.2 to 0.5 µg/litre. It was not detected in a survey of surface water in 105 cities.
Food

1,1-Dichloroethene residues have been reported in foodstuffs wrapped with co-polymer films at levels ranging from 0.005 to 0.1 mg/kg and in household food wraps at an average concentration of 8.8 mg/kg (5). Because of its high volatility, residual levels in food are expected to be low.

**Estimated total exposure and relative contribution of drinking-water**

Estimated average exposure from drinking-water in the USA is less than 0.01 µg/day; the maximum is about 1µg/day (10). At a mean concentration of 19.6-120 ng/m³ in urban air, the estimated average inhalation exposure is 0.4-2.5 µg/day (7). Food is not expected to be a significant exposure source.

**14.7.4 Kinetics and metabolism in laboratory animals and humans**

1,1-Dichloroethene is rapidly and almost completely absorbed from the gastrointestinal tract following administration by gavage (1,11,12). It is also readily absorbed from the lungs (13), and dermal absorption is expected to occur (5). It is rapidly distributed following oral or inhalation exposure, accumulating preferentially in the liver, kidneys, and lungs (1,11,12).

Biotransformation of 1,1-dichloroethene involves the cytochrome P-450 system and pathways that include the formation of 1,1-dichloroethylene oxide and chloroacetyl chloride and detoxification via conjugation with glutathione. The major metabolites include thiodiglycolic acid and N-acetyl-S-(2-carboxymethyl)cysteine (1,11,12,14). Mice metabolize more of an oral dose than rats (14), in which 1,1-dichloroethene metabolism may be a saturable process (12). Excretion occurs mainly via the urine and expired air (1,11,12,14).

**14.7.5 Effects on laboratory animals and in vitro test systems**

**Acute exposure**

Reported oral LD₅₀s for 1,1-dichloroethene are 1500 (15) and 1550 (14) mg/kg of body weight for rats and 194 and 217 mg/kg of body weight for female and male mice, respectively (14). Histopathological changes in the liver and kidneys (rats) and lungs (mice) were observed following administration of single oral doses of 200 mg/kg of body weight (16-18).

**Short-term exposure**

Increased cytoplasmic vacuolation of hepatocytes was observed in rats exposed to 1,1-dichloroethene in drinking-water at doses of 19.3 or 25.6 mg/kg of body weight per day in males and females, respectively, for 90 days (19). Beagle dogs given 1,1-dichloroethene in gelatin capsules at doses of 6.25, 12.5, or 25 mg/kg of body weight per day for 97 days experienced no adverse effects on hepatic, haematological, renal, or neurological end-points (1,20).

**Long-term exposure**

No treatment-related adverse effects were observed in Sprague-Dawley rats dosed with 1,1-dichloroethene at 0.5, 5, 10, or 20 mg/kg of body weight per day by gavage in corn oil for 1 year (1,21). Renal inflammation was observed in F344 rats receiving 5 mg/kg of body weight per day by gavage in corn oil for 2 years, but not in those receiving 1 mg/kg of body weight (22). In a study in which B6C3F₁ mice were dosed by gavage at 2 or 10 mg/kg of body weight per day, liver necrosis was reported in male mice at the higher dose but not in female mice (1,22).

Sprague-Dawley rats exposed to 1,1-dichloroethene in drinking-water for 2 years at doses of 7, 10, or 20 mg/kg of body weight per day (males) and 9, 14, or 30 mg/kg of body weight per day (females)
experienced no treatment-related effects on mortality, body or organ weights, or haematological, urinary, or clinical chemistry end-points (1,20). A statistically significant increase in the incidence of hepatic lesions (hepatocellular swelling and fatty changes) was observed in females at all dose levels and in males at the highest dose.

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Administration of 1,1-dichloroethene in drinking-water to rats at doses of up to 28 mg/kg of body weight per day for three generations produced no changes in reproductive outcome or neonatal development (1,23). No evidence of toxicity to the dams or offspring was observed in rats exposed to drinking-water containing 1,1-dichloroethene at 200 mg/litre on days 6-15 of gestation (24).

**Mutagenicity and related end-points**

1,1-Dichloroethene was mutagenic in several strains of *Salmonella typhimurium*, *Escherichia coli*, and *Saccharomyces cerevisiae* with metabolic activation but not without (1,25-28). It increased the frequency of chromosomal aberrations and sister chromatid exchanges in Chinese hamster CHL cells (29), and was also positive in host-mediated gene mutation and conversion assays in yeast (28). Negative results were reported in assays for dominant lethal mutations in mice and rats (30,31) and in a micronucleus test in mice (29).

**Carcinogenicity**

In a study in which F344/N rats and B6C3F1/N mice were administered 1,1-dichloroethene by gavage for 104 weeks at 1 or 5 mg/kg of body weight per day (rats) and 2 or 10 mg/kg of body weight per day (mice), the only significant effect was an increase in the incidence of lymphomas or leukaemias in female mice in the low-dose group (22). Similarly, in a study in which Sprague-Dawley rats received 1,1-dichloroethene in drinking-water at 7, 10, or 20 mg/kg of body weight per day (male) or 9, 14, or 30 mg/kg of body weight per day (female) for 2 years, a significant increase in the incidence of combined mammary gland fibroadenomas and adenofibromas was observed only in the low-dose females (1,20). Neither increase was considered to be treatment-related, because the effects were not seen in high-dose females or in male mice at either dose.

Swiss mice were exposed by inhalation to 1,1-dichloroethene 4 h per day, 4-5 days per week for 1 year at 40 or 100 mg/m³ (32). Carcinomas of the mammary gland were significantly increased in females at both doses, pulmonary adenomas were increased in males at 40 mg/m³ and in both sexes at 100 mg/m³, and renal adenocarcinomas were significantly increased in high-dose males.

**14.7.6 Effects on humans**

1,1-Dichloroethene reportedly induces central nervous system depression at high concentrations (16 g/m³ in air) (5). A possible association of 1,1-dichloroethene with liver and kidney toxicity following exposure to lower concentrations has also been suggested (5).

**14.7.7 Guideline value**

IARC has placed 1,1-dichloroethene in Group 3 (33). It was found to be genotoxic in a number of test systems *in vitro* but was not active in the dominant lethal assay *in vivo*. It induced kidney tumours in mice in one inhalation study but was not carcinogenic in other studies, including several in which it was given in drinking-water.

A TDI of 9 µg/kg of body weight per day was calculated from a LOAEL of 9 mg/kg of body weight per day in a 2-year drinking-water study in rats (20), using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a LOAEL in place of a NOAEL and the potential for
carcinogenicity). This gives a guideline value of 30µg/litre (rounded figure) for a 10% contribution to the TDI from drinking-water.

References


22. National Toxicology Program. *Carcinogenesis bioassay of vinylidene chloride in F344 rats and B6C3F1, mice (gavage study)*. Research Triangle Park, NC, US Department of Health and Human Services, 1982 (NTP-80-2; NIH Publication No. 82-1784).


14.8 1,2-Dichloroethene

14.8.1 General description

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Physicochemical properties (1,2)

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1 Conversion factor in air: 1 ppm = 3.97 mg/m³

Organoleptic properties

A mixture of 1,2-dichloroethene isomers has a pleasant odour (3). The odour thresholds for trans-1,2-dichloroethene in air and water are 68 mg/m³ and 0.26 mg/litre, respectively (4).

Major uses

1,2-Dichloroethene (cis/trans mixture) is used mainly as an intermediate in the synthesis of chlorinated solvents and compounds (5). It has also been used as an extraction solvent for organic materials.

Environmental fate

1,2-Dichloroethene is removed from the atmosphere mainly through reaction with photochemically generated hydroxyl radicals; the estimated half-lives for the cis- and trans-isomers are 8.3 and 3.6 days, respectively. Most 1,2-dichloroethene in surface water and surface soils is expected to be volatilized. The compound may be leached through subsurface soils to groundwater. Anaerobic biodegradation may remove both isomers from groundwater, the half-life then being 13-48 weeks (5).

14.8.2 Analytical methods

The concentrations of cis- or trans-1,2-dichloroethene are measured is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking-water (6). The method can differentiate between the cis- and trans-isomers at concentrations of 0.03-1500 µg/litre. Mass spectrometry is used for confirmation; the detection limit is 0.17 µg/litre (7).

14.8.3 Environmental levels and human exposure

Air

1,2-Dichloroethene has been detected in the air of urban and industrial areas at concentrations in the range 0.04-0.3 µg/m³ (mean) for the cis-isomer to 10.3 µg/m³ (maximum) for a mixture of isomers. Mean concentrations up to 32.2 µg/m³ have been measured in indoor air (5).
Water

1,2-Dichloroethene has been detected in industrial effluents, surface water, groundwater, and drinking-water supplies in the USA. It was detected in 16 of 466 randomly selected and 38 of 479 purposely selected drinking-water supplies derived from groundwater at levels of up to 2 and 120 µg/litre, respectively (5).

The cis-form of 1,2-dichloroethene is more frequently found as a water contaminant. The presence of these two isomers, which are metabolites of other unsaturated halogenated hydrocarbons in wastewater and anaerobic groundwater, may indicate the simultaneous presence of more toxic organochlorine chemicals, such as vinyl chloride. Accordingly, more intensive monitoring is necessary if they are found to be present.

Food

1,2-Dichloroethene was not detected in fish samples at 95 stations covered by the STORET database of the US Environmental Protection Agency, but was detected in fish tissue samples from Commencement Bay, WA, at mean levels of 0.04 mg/kg (5).

Estimated total exposure and relative contribution of drinking-water

Based on urban air levels of 0.04-0.3 µg/m³, the average inhalation exposure to 1,2-dichloroethene is about 1-6 µg/day (5). At a drinking-water concentration of 2 µg/litre, the daily intake by an adult would be about 4µg.

14.8.4 Kinetics and metabolism in laboratory animals and humans

As the cis- and trans-isomers of 1,2-dichloroethene are lipid-soluble compounds of low relative molecular mass, they would be expected to be readily absorbed by the oral or dermal routes (8). In humans, about 75% of inhaled trans-1,2-dichloroethene is absorbed through the lungs (9). 1,2-Dichloroethene may be preferentially distributed to adipose tissue (10). On the basis of distribution data for 1,1-dichloroethene, the highest concentrations might be expected to occur in liver and kidney (11).

The first step in the metabolism of both isomers of 1,2-dichloroethene appears to be the formation of the chloroethylene epoxide, which undergoes rearrangement to form dichloroacetaldehyde and possibly monochloroacetic acid (12,13). In vitro studies indicate that biotransformation involves the hepatic microsomal cytochrome P-450 system (14,15). The cis-isomer is metabolized at a faster rate than the trans-isomer (14). High doses may saturate the P-450 system and exceed its metabolic capacity (5). If excretion is similar to that of 1,1-dichloroethene, elimination would be expected to be relatively rapid, so that most of a single dose would be excreted in the urine within 24-72 h (15).

14.8.5 Effects on laboratory animals and in vitro test systems

Acute exposure

For a mixture of isomers, the reported oral LD₅₀ for rats is 770 mg/kg of body weight (16). Reported oral LD₅₀s for trans-1,2-dichloroethene are 1275 mg/kg of body weight for female rats, 7902 mg/kg of body weight for male rats, 2221 mg/kg of body weight for male mice, and 2391 mg/kg of body weight for female mice (17-19). Administration of single doses of cis-1,2-dichloroethene at 400 or 1500 mg/kg of body weight to rats caused significant elevations of liver alkaline phosphatase, whereas the same doses of trans-isomer did not (20).
**Short-term exposure**

trans-1,2-Dichloroethene was administered by gavage to male CD-1 mice for 14 days at doses of 0, 21, or 210 mg/kg of body weight per day (21). No changes in body or organ weights, serum alanine aminotransferase, or blood urea nitrogen were reported at any dose level. However, fibrinogen levels, prothrombin times, and lactate dehydrogenase levels were significantly decreased at the highest dose. In a similar study, the trans-isomer, administered by gavage at doses equal to 1% and 10% of the LD50 (22 or 222 mg/kg of body weight per day) to male mice for 14 days, caused no significant changes in body or organ weights, haematological or blood coagulation parameters, serum enzyme levels, or humoral immune response (18).

In a study on CD-1 mice (15-24 per sex per dose), male mice received trans-1,2-dichloroethene in doses of 17, 175, or 387 mg/kg of body weight per day and female mice received doses of 23, 224, or 452 mg/kg of body weight per day in drinking-water for 90 days (21). No changes in water consumption, body weight, or gross pathology were observed in any dose group. There were significant increases in serum alkaline phosphatase levels in male mice at the two highest doses, and liver glutathione concentrations were decreased at the highest dose. In females, thymus weight was significantly decreased at the two highest doses, and lung weight was depressed at the highest dose. A significant decrease in aniline hydroxylase activity was also observed in females exposed to the highest dose. In another phase of this study (22), no dose-dependent effects were observed either in cell-mediated immunity in either sex or in the humoral immune status of female mice. However, a significant decrease in spleen antibody-forming cells was noted at all dose levels in male mice. Female mice exposed to the highest dose demonstrated an enhanced spleen cell response to lipopolysaccharide at some, but not all, concentrations.

CD rats were exposed to trans-1,2-dichloroethene at doses of 402, 1314, or 3114 mg/kg of body weight per day (males) and 353, 1257, or 2809 mg/kg of body weight per day (females) in drinking-water for 90 days (19). No compound-related effects on water consumption, body weight, serum chemistry, or urinary parameters were observed, nor were any effects on gross or histological pathology noted. However, a significant dose-dependent decrease in kidney weight was observed at the two highest doses in females.

**Mutagenicity and related end-points**

*In vitro* investigations of the genotoxic potential of 1,2-dichloroethene yielded negative results for both isomers. 1,2-Dichloroethene was not found to be mutagenic in *Escherichia coli*, several strains of *Salmonella typhimurium*, or *Saccharomyces cerevisiae*, with or without metabolic activation (23-26). Neither isomer induced chromosomal aberrations or sister chromatid exchanges in Chinese hamster lung fibroblasts (27).

*In vivo* studies indicate that the cis-, and possibly the trans-, isomer may be genotoxic. The cis-isomer was found to be mutagenic in *S. typhimurium* and *S. cerevisiae* strains in two host-mediated assays in mice (23,24). Repeated intraperitoneal injections of cis-1,2-dichloroethene induced chromosomal aberrations in mouse bone marrow cells (24). The trans-isomer yielded negative results in these studies. However, an increase in the number of aneuploid V79 Chinese hamster cells was reported following treatment with the trans-isomer (28).

**14.8.6 Effects on humans**

Inhalation of high concentrations (38 g/m³ and above) of 1,2-dichloroethene in air causes central nervous system depression (17). Neurological effects, including nausea, drowsiness, fatigue, and vertigo, have been reported following exposure to lower levels (9). A burning sensation in the eyes was also reported. The trans-isomer is reportedly about twice as potent a central nervous system depressant as the cis-isomer (17), which has been used as an anaesthetic.

**14.8.7 Guideline value**
In a 3-month study in mice given the trans-isomer in drinking-water, there was an increase in serum alkaline phosphatase and reduced thymus and lung weights, as well as transient immunological effects, the toxicological significance of which is unclear. Only one rat toxicity study is available for the cis-isomer. There are limited data to suggest that both isomers may possess some genotoxic activity. There is no information on carcinogenicity.

Data on the toxicity of the trans-isomer in mice (21) were used to calculate a joint guideline value for both isomers because of the lack of adequate toxicity data for the cis-isomer and because data suggest that the mouse is a more sensitive species than the rat. Accordingly, the NOAEL of 17 mg/kg of body weight per day from the trans-isomer toxicity study was used with an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the short duration of the study) to derive a TDI of 17 µg/kg of body weight. This gives a guideline value of 50 µg/litre (rounded figure) for an allocation of 10% of the TDI to drinking-water.

References

9. Lehmann KB, Schmidt-Kehl L. [Study of the most important chlorohydrocarbons from the standpoint of industrial hygiene.] Archiv für Hygiene und Bakteriologie, 1936, 116:131-268 (in German).


14.9 Trichloroethene

14.9.1 General description

Identity
CAS no.: 79-01-6
Molecular formula: C₂HCl₃

Trichloroethene is also known as trichloroethylene.

**Physicochemical properties (1,2)**

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<tr>
<td>Water solubility</td>
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</tr>
</tbody>
</table>

1 Conversion factor in air: 1 ppm = 5.46 mg/m³

**Organoleptic properties**

The odour thresholds for trichloroethene in air and water are 546-1092 mg/m³ and 0.31 mg/litre, respectively (3,4).

**Major uses**

Trichloroethene is used mainly in dry cleaning, for the degreasing of fabricated metal parts, as a solvent for fats, waxes, resins, oils, rubber, paints, and varnishes, and as an inhalation analgesic and anaesthetic (1,5).

**Environmental fate**

Trichloroethene is readily released to the atmosphere, where it is highly reactive and does not persist for any significant length of time. In water, biodegradation occurs, possibly with some partitioning to sediment and suspended organic matter. Trichloroethene in anaerobic groundwater may be degraded to more toxic compounds, including vinyl chloride. It is highly mobile in soil and may be leached into groundwater supplies. Bioconcentration of trichloroethene in aquatic species is low to moderate (5).

14.9.2 Analytical methods

A purge-and-trap gas chromatographic procedure can be used to measure trichloroethene in drinking-water at concentrations of 0.01-1500 µg/litre (6). Mass spectrometry is used for confirmation (detection limit 0.2 µg/litre) (7).

14.9.3 Environmental levels and human exposure

**Air**

Mean concentrations of 0.16 µg/m³ and 2.5 µg/m³ have been detected in the atmosphere of rural and urban areas, respectively (5).

**Water**

Trichloroethene may be released directly into wastewater, deposited in water from the atmosphere, or formed as a by-product during water chlorination (5,8). In a survey of drinking-water in the USA it was found at a mean concentration of 2.1 µg/litre in 28 of 113 cities in 1976-77 (9). It was present in 24% of 158 nonrandom samples collected in a groundwater supply survey in the USA; median levels of 1 µg/litre
were reported and a maximum of 130 µg/litre was found in one sample (5).

**Food**

Trichloroethene has been found at concentrations of up to 10 µg/kg in meat, up to 5 µg/kg in fruits and vegetables, and up to 60 µg/kg in tea in the United Kingdom (1,10). It has also been detected in margarine samples in the USA at levels of 440-3600 µg/kg and in grain-based food at concentrations of up to 2.7 µg/kg (5).

**Estimated total exposure and relative contribution of drinking-water**

Because of its high vapour pressure, potential human exposure to trichloroethene is greatest from the inhalation of contaminated air. Exposure from drinking-water or food is not expected to pose a significant health risk, as it volatilizes rapidly from water and does not bioaccumulate to any significant extent.

14.9.4 Kinetics and metabolism in laboratory animals and humans

Analysis of human blood and breath following inhalation of 546 mg/m³ trichloroethene showed that peak levels were reached within 1 h of exposure (1,5). In rats, 72-85% of an orally administered dose was detected in expired air and 10-20% in urine (11), indicating that at least 80% of ingested trichloroethene is systemically absorbed. Transplacental diffusion has been demonstrated in humans following inhalation; the ratio of the concentrations in fetal and maternal blood ranged between 0.52 and 1.90 (12). Trichloroethene was widely distributed in rats given it by gavage (13), the highest concentration being in body fat.

Inhalation studies in humans show that 40-75% of the retained dose is metabolized (5). The principal urinary metabolites are trichloroacetaldehyde, trichloroethanol, trichloroacetic acid, and trichloroethanol glucuronide (14). An important metabolic intermediate is the reactive epoxide, trichloroethene oxide, which can alkylate nucleic acids and proteins (11). Trichloroethene is eliminated with a half-time of about 1.5 h (15). Metabolites are excreted more slowly; the biological half-life measured in human urine is about 50 h for trichloroethanol and 36-73 h for trichloroethanoic acid (16,17).

14.9.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

The acute oral LD₅₀ of trichloroethene in rats and mice are 4920 mg/kg of body weight and 2400 mg/kg of body weight, respectively (1,5,18).

**Short-term exposure**

In a study in which groups of 12B24 male Swiss-Cox mice received trichloroethene by gavage in corn oil, 5 days per week for 6 weeks, at doses of 0, 100, 200, 400, 800, 1600, 2400, or 3200 mg/kg of body weight per day, dose-related increases in hepatic DNA, relative liver weight, and hypertrophy of the liver were apparent at 100 mg/kg of body weight per day and above, and glucose-6-phosphate levels were decreased by 30-40% at 800 mg/kg of body weight per day and above. The LOAEL was 100 mg/kg of body weight per day (19).

Fischer 344/N rats and B6C3F₁ mice (10 per sex per dose) were given trichloroethene at doses of up to 2000 (male rats), 1000 (female rats), or 6000 (mice) mg/kg of body weight per day in corn oil by gavage, 5 days per week for 13 weeks. Survival in mice was greatly decreased at 3000 and 6000 mg/kg of body weight per day. Body weight was decreased in male rats at 2000 mg/kg of body weight per day and in male mice at 750 mg/kg of body weight per day and above. Mild to moderate cytomegaly and enlarged cell nuclei of the renal tubular epithelial cells in the inner cortex were observed in both sexes of both
species at 1000 and 2000 mg/kg of body weight per day (rats) and 3000 and 6000 mg/kg of body weight per day (mice) (20).

In rats exposed to air containing 300 mg/m$^3$ trichloroethene 5 days per week for 14 weeks, liver weights were elevated, possibly as the result of fatty accumulation. Haematological parameters, liver and renal function tests, blood glucose, and organ-to-body-weight ratios were the same as in controls (21).

**Long-term exposure**

The toxicity of trichloroethene (epichlorohydrin-free) was investigated in F344 rats and B6C3F$_1$ mice (50 per sex per dose) given 0, 500, or 1000 mg/kg of body weight per day (rats) and 0 or 1000 mg/kg of body weight per day (mice) in corn oil, 5 days per week for 103 weeks. Survival was reduced in male rats and mice but not in females. Toxic nephrosis, characterized as cytomegaly, occurred in rats at 500 and 1000 mg/kg of body weight per day and in mice at 1000 mg/kg of body weight per day. LOAELs of 500 mg/kg of body weight per day for rats and 1000 mg/kg of body weight per day for mice were identified (20).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

No statistically significant effects on sperm count, motility, or morphology were detected in male Long-Evans rats (10 per dose) intubated with 1, 10, 100, or 1000 mg of trichloroethene per kg of body weight per day, 5 days per week for 6 weeks. Copulatory behaviour was impaired at 100 mg/kg of body weight per day during the initial 4 weeks of exposure but returned to normal by week 5 (13).

A continuous-breeding fertility study was conducted in which male and female Fischer 344 rats were fed diets containing microencapsulated trichloroethene at dose levels of approximately 0, 75, 150, or 300 mg/kg of body weight per day from 7 days before mating to the birth of the F$_2$ generation. Although testicular and epididymal weights decreased in the F$_1$ generation, no histopathological changes were observed (22). In a similar study in CD-1 mice given up to 750 mg trichloroethene per kg of body weight per day, sperm motility was reduced by 45% in F$_0$ males and 18% in F$_1$ males. There were no treatment-related effects on mating, fertility, or reproductive performance in the F$_0$ or F$_1$ mice (23).

Mice and rats exposed to trichloroethene vapour at a concentration of 1600 mg/m$^3$ on days 6-15 of gestation for 7 h per day did not experience any teratogenic effects, although there was some evidence of haemorrhages in the cerebral ventricles and a few cases of undescended testicles (24).

**Mutagenicity and related end-points**

There are numerous studies of the genotoxicity of trichloroethene, but the evidence is conflicting, in part because of impurities in the test material and the presence of stabilizers that are themselves mutagenic. In a range of *in vitro* assays, the data indicate that it is either negative or only weakly positive (1,25). A dose-dependent increase in DNA single-strand breaks was observed in liver and kidney, but not lung, of male NMRI mice 1 h, but not 24 h, after intraperitoneal injection of 4-10 mmol of trichloroethene per kg of body weight (26).

**Carcinogenicity**

There was a significant increase in hepatocellular tumours in both sexes of B6C3F$_1$ mice given trichloroethene by gavage in corn oil (27). However, in a similar study in a strain of mice with a low background incidence of liver tumours, there was no evidence of increased tumour incidence (28). There was some indication of a small increase in renal tumours in male rats given 250 mg of trichloroethene per kg of body weight by gavage in corn oil, but these tumours are of doubtful significance for humans (1,29).

In an inhalation study, a dose-related increase in malignant lymphomas was reported in female HAN:NMRI mice exposed to 546 or 819 mg/m$^3$ trichloroethene vapour 6 h per day, 5 days per week for 18
months (30); this strain of mice has a high incidence of spontaneous lymphomas. An increased incidence of pulmonary adenocarcinomas was found in female ICR mice exposed to 820 or 2460 mg/m³ trichloroethene vapour as compared with controls, but no such increase was found in female Sprague-Dawley rats (31).

14.9.6 Effects on humans

Acute exposure to high concentrations of trichloroethene causes central nervous system depression (32). Exposure to 147 mg/m³ in air for 4 h caused drowsiness and mucous membrane irritation; at 442 mg/m³, it caused headaches. Drowsiness, lethargy, and nausea were observed within 5 min at 10.9 g/m³. Coma and respiratory depression may occur following prolonged exposure to levels above 10.9 g/m³ (5). Hepatic failure and subsequent death were reported following the use of trichloroethene as an anaesthetic, generally in patients with complicating transfusions (33). Oral exposure of humans to 15-25 ml (21-35 g) resulted in vomiting and abdominal pain, followed by transient unconsciousness (34).

Humans exposed occupationally to trichloroethene had an increase in serum aminotransferases, indicating damage to the liver parenchyma (35). Neurological abnormalities were associated with occupational exposure to 76-464 mg/m³ trichloroethene for between 1 month and 15 years, including decreased appetite, sleep disturbances, ataxia, vertigo, headache, and short-term memory loss (5).

14.9.7 Provisional guideline value

Trichloroethene has been classified by IARC in Group 3: not classifiable as to its carcinogenicity to humans (35). Although it induces lung and liver tumours in mice, there is no conclusive evidence that it causes cancer in other species. Trichloroethene is a weakly active mutagen in bacteria and yeast.

A TDI of 23.8 µg/kg of body weight has been calculated by applying an uncertainty factor of 3000 to a LOAEL of 100 mg/kg of body weight per day (normalized for 5 days per week exposure) for minor effects on relative liver weight in a 6-week study in mice (19). The uncertainty factor components are 100 for inter- and intraspecies variation, 10 for limited evidence of carcinogenicity, and an additional factor of 3 in view of the short duration of the study and the use of a LOAEL rather than a NOAEL. A provisional guideline value of 70 µg/litre (rounded figure) is derived by allocating 10% of the TDI to drinking-water.

References


23. National Toxicology Program. *Trichloroethylene: reproduction and fertility assessment in CD-1 mice*


### 14.10 Tetrachloroethene

#### 14.10.1 General description

**Identity**

CAS no.: 127-18-4  
Molecular formula: C₂Cl₄

Tetrachloroethene is also known as tetrachloroethylene and perchloroethylene.
**Physicochemical properties (1-3)**

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</table>

1 Conversion factor in air: 1 ppm = 6.78 mg/m³

**Organoleptic properties**

The odour thresholds for tetrachloroethene in water and air are 0.3 mg/litre and 7 mg/m³, respectively (3).

**Major uses**

Tetrachloroethene is used primarily as a solvent in the dry-cleaning industry. It is also used as a degreasing solvent in metal industries, as a heat transfer medium, and in the manufacture of fluorohydrocarbons (1,4).

**Environmental fate**

Most tetrachloroethene released to the environment is found in the atmosphere, where photochemically produced hydroxyl radicals degrade it to phosgene and chloroacetyl chlorides with a half-life of 96-251 days (3). In water, it does not readily undergo hydrolysis or photolysis but is biodegraded by microorganisms to dichloroethene, vinyl chloride, and ethene. Tetrachloroethene can persist in waters where volatilization cannot occur. It volatilizes less readily from soil than from water and, with a soil adsorption coefficient of 72-534, is expected to be fairly mobile in soils. Degradation may occur in anaerobic soils. It does not appear to bioaccumulate in animals or food-chains (3).

14.10.2 Analytical methods

A purge-and-trap gas chromatographic procedure is used for the determination of tetrachloroethene in drinking-water (5). Mass spectrometry or electron capture, flame-ionization, and halide-sensitive detectors may be used for detection, the detection limits ranging from 0.1 to 1.9 µg/litre in water (3,6).

14.10.3 Environmental levels and human exposure

**Air**

Concentrations of tetrachloroethene in city air in the United Kingdom range from less than 0.7 to 70 µg/m³ (7). In Munich, suburban and urban air concentrations were 4 and 6 µg/m³, respectively (8). Surveys in the USA indicated concentrations of less than 0.01 µg/m³ in rural areas and up to 6.7 µg/m³ in urban areas (9).

**Water**

A survey of drinking-water in the USA in 1976-77 detected tetrachloroethene in nine of 105 samples at levels ranging from 0.2 to 3.1 µg/litre (mean 0.81 µg/litre) (10). In other surveys of drinking-water supplies in the USA, it was found that 3% of all public water-supply systems that used well-water contained tetrachloroethene at concentrations of 0.5 µg/litre or higher, whereas those that used surface water contained lower levels (2). In the United Kingdom, it has been detected at levels of 0.4 µg/litre in municipal
waters (1,7) and, in Japan, in approximately 30% of all wells, at concentrations ranging from 0.2 to 23000 µg/litre (3). In Switzerland, tetrachloroethene concentrations as high as 954 µg/litre have been found in contaminated groundwater (11). Tetrachloroethene in anaerobic groundwater may degrade to more toxic compounds, including vinyl chloride (3).

Food

Tetrachloroethene concentrations in seafood in the United Kingdom ranged from 0.5 to 30 µg/kg (7,12). Those in other foodstuffs ranged from almost undetectable (0.01 µg/kg) in orange juice to 13 µg/kg in butter (13). Some foods (particularly those with a high fat content) stored or sold near dry-cleaning facilities may contain considerably higher concentrations (14).

Estimated total exposure and relative contribution of drinking-water

Based on a tetrachloroethene concentration in air of 6 µg/m³, estimated exposure would be about 120 µg/day for an adult with an air intake of 20 m³. If drinking-water contains 0.5 µg of tetrachloroethene per litre, the average daily exposure would be 1 µg for an adult consuming 2 litres of water per day. There are insufficient data on the levels of tetrachloroethene in foods to allow an average exposure to be determined.

14.10.4 Kinetics and metabolism in laboratory animals and humans

The results from animal studies indicate that tetrachloroethene is rapidly and completely absorbed from the gastrointestinal tract (3,15). It reached near-steady-state levels in the blood of human volunteers after 2 h of continuous inhalation (16). Rats given a gavage dose of radiolabelled tetrachloroethene contained radioactivity in the liver, kidney, and fat (15). Occupationally exposed subjects had whole-blood levels as high as 2500 µg/litre, as compared with 0.4 µg/litre in controls (17).

Metabolic products appear to be similar in humans and experimental animals (1,18,19). Tetrachloroethene is metabolized by a cytochrome P-450-mediated oxidation to tetrachloroethene oxide and trichloroacetyl chloride to form trichloroethanoic acid and trichloroethanol. In mice, trichloroethanoic acid is the major metabolite formed, whereas it is formed in relatively small amounts in rats (20). In humans, only 1.8% of the retained dose was converted into trichloroethanoic acid; 1.0% was converted into an unknown metabolite in 67 h (21).

Saturation of metabolism has been observed both in inhalation studies in rats (22) and in gavage studies in mice (23). After saturation of metabolism via the oxidative pathway, a second metabolic pathway through conjugation with glutathione to form a highly reactive trichlorovinylthiol compound has been shown to occur in rat kidney, activated by renal β-lyase enzyme. This metabolic pathway appears to be absent in humans (22) and to be significant only in male rats (24).

Tetrachloroethene is eliminated from the body primarily via the lungs; the half-life is about 65 h (1,25). Trichloroethanoic acid is eliminated via the urine with a half-life of 144 h (1,26).

14.10.5 Effects on laboratory animals and in vitro test systems

Acute exposure

LD₅₀ of 3835 and 3005 mg/kg of body weight were found for male and female rats to which single doses of tetrachloroethene were administered by gavage. Acute effects are dominated by central nervous system depression (27).
**Short-term exposure**

Groups of male Swiss-Cox mice were given oral doses of tetrachloroethene in corn oil at 0, 20, 100, 1000, or 2000 mg/kg of body weight, 5 days per week for 6 weeks (equivalent to 0, 14, 70, 700, or 1400 mg/kg of body weight per day). Mice treated with doses as low as 70 mg/kg of body weight per day exhibited significantly increased liver triglyceride levels and liver-to-body-weight ratios. At higher doses, hepatotoxic effects included decreased DNA content, increased serum alanine aminotransferase, decreased glucose-6-phosphatase serum levels, and hepatocellular necrosis, degeneration, and polyploidy. The NOAEL was 14 mg/kg of body weight per day (23).

Sprague-Dawley rats (20 per sex per dose) were given tetrachloroethene in drinking-water at doses of 14, 400, or 1400 mg/kg of body weight per day for 90 days. Males in the high-dose group and females in the mid- and high-dose groups exhibited depressed body weights. Increased liver- and kidney-to-body-weight ratios (equivocal evidence of hepatotoxicity) were also observed at the two highest doses (27).

There was moderate fatty degeneration of the liver in mice following a 4-h exposure to air containing 1340 mg of tetrachloroethene per m$^3$ (28). Exposure to this same level for 4 h per day, 6 days per week for up to 8 weeks increased the severity of the lesions (29).

**Long-term exposure**

Male and female Osborne-Mendel rats and B6C3F$_1$ mice were exposed to tetrachloroethene by corn oil gavage for 78 weeks at doses ranging from 471 to 1072 mg/kg of body weight per day. Increased mortality and nephropathy, as shown by degenerative tubule changes, fatty changes, and cloudy swelling, were observed in all treated animals (30).

Exposure of F344 rats to tetrachloroethene administered by inhalation at doses of 0, 1.36, or 2.72 g/m$^3$ for 103 weeks, 5 days per week, resulted in a significant reduction in survival, increased renal karyomegaly in both sexes, and renal tubular cell hyperplasia in males at both doses. Similar exposure of B6C3F$_1$ mice to 0, 1.36, or 2.72 g/m$^3$ resulted in reduced survival and increased renal nephrosis, tubular cell karyomegaly, and renal casts, as well as hepatic degeneration and necrosis (31).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Inhalation exposures to tetrachloroethene have resulted in maternal and fetal toxicity in mice, rats, and rabbits (3).

**Mutagenicity and related end-points**

Short-term studies indicate that tetrachloroethene induces single-strand DNA breaks in the mouse but does not cause chromosomal aberrations in rat bone marrow or human lymphocytes (1,30,32). In vitro assays in *Salmonella typhimurium*, *Escherichia coli*, and *Saccharomyces cerevisiae* were negative both with and without microsomal activation.

**Carcinogenicity**

The exposure by inhalation (6 h per day, 5 days per week for 103 weeks) of F344/N rats to 0, 1.36, or 2.72 g/m$^3$ tetrachloroethene produced a small (but not statistically significant) increase in the combined incidence of renal tubular-cell adenomas and adenocarcinomas in males but not in females. In both sexes, there was an increase in the incidence of mononuclear cell leukaemias at both doses, but the incidence was also unusually high in concurrent as compared with historical controls (31).

It has been suggested that the induction of kidney tumours in male rats is the combined result of the formation of a highly reactive metabolite and cell damage produced by renal accumulation of hyaline
The exposure by inhalation (6 h per day, 5 days per week for 103 weeks) of B6C3F1 mice at 0, 1.36, or 2.72 g/m³ resulted in an increase in hepatocellular carcinomas in both males and females (31). In an earlier bioassay, in which tetrachloroethene was administered by gavage in corn oil, there was an increase in the incidence of hepatocellular carcinomas in both male and female mice but not in Osborne-Mendel rats. In this experiment, survival was reduced in both species as a result of pneumonia, and impurities later shown to be carcinogenic were present in the tetrachloroethene (30).

Hepatotoxic and related carcinogenic effects of tetrachloroethene in mice appear to be due to trichloroethanoic acid, which is formed in greater amounts by mice than by rats or humans (19,35). In addition, mice are more sensitive than rats to trichloroethanoic acid, a peroxisome proliferator in mice (36).

14.10.6 Effects on humans

Oral doses of 4.2-6 g of tetrachloroethene administered to patients to control parasitic worm infections caused central nervous system effects, such as inebriation, perceptual distortion, and exhilaration (37). Several developmental effects, such as eye, ear, central nervous system, chromosomal, and oral cleft anomalies, were associated with exposure to tetrachloroethene and other solvents in contaminated drinking-water supplies (38). Inhalation exposures have been associated in female dry-cleaning workers with reproductive effects, including menstrual disorders and spontaneous abortions (39,40).

A few case reports and small-scale epidemiological and clinical studies involving a group of men occupationally exposed to tetrachloroethene at levels of 1890-2600 mg/m³ suggest an association between such exposure and serious central nervous system problems (1,41-43). However, workers were often simultaneously exposed to several solvents (44). Evidence for the carcinogenicity of tetrachloroethene was obtained by observing laundry and dry-cleaning workers, but was rated as inadequate by IARC (45). Although an increased incidence of cancer was reported in several cohort and proportionate mortality studies (1,46-48) and increased risks of cancer in workers exposed to tetrachloroethene were found in case-control studies (49,50), study limitations, such as concomitant exposures to other chemicals and small sample size, make it difficult to reach a definite conclusion.

14.10.7 Guideline value

IARC (45) has concluded that there is sufficient evidence of carcinogenicity in animals to classify tetrachloroethene in Group 2B: possible human carcinogen. It reportedly produces liver tumours in mice, with some evidence of mononuclear cell leukaemia in rats and kidney tumours in male rats. However, overall evidence indicates that this compound is not genotoxic.

In view of the overall evidence for nongenotoxicity and evidence for a saturable metabolic pathway leading to kidney tumours in rats, it is appropriate to use a NOAEL with a suitable uncertainty factor for calculation of the TDI. A 6-week gavage study in male mice and a 90-day drinking-water study in male and female rats both indicated a NOAEL for hepatotoxic effects of 14 mg/kg of body weight per day (23,27). A TDI of 14 µg/kg of body weight was calculated by applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for carcinogenic potential). In view of the database on tetrachloroethene and considerations regarding the application of the dose via drinking-water in one of the two critical studies, it was deemed unnecessary to include an additional uncertainty factor to reflect the length of the study. The guideline value is 40 µg/litre (rounded figure) for a drinking-water contribution of 10%.

References


35. Schumann AM, Quast JF, Watanabe PG. The pharmacokinetics and macromolecular interactions of


14.11 Benzene
14.11.1 General description

**Identity**

CAS no.: 71-43-2  
Molecular formula: C₆H₆

**Physicochemical properties (1,2)**¹

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¹ Conversion factor in air: 1 ppm = 3.2 mg/m³ at 20 °C and 101.3 kPa

**Organoleptic properties**

Benzene has a characteristic odour. Its odour threshold in water is 10 mg/litre (2).

**Major uses**

Benzene is used in the chemical industry for the production of styrene/ethylbenzene, cumene/phenol, and cyclohexane (1). Its use as a solvent has been greatly reduced in the last few years (3). Benzene is used as an additive in petrol to increase the octane number (2).

**Environmental fate**

In soil, benzene biodegrades under aerobic conditions only. In surface water, it rapidly volatilizes to the air, biodegrades with a half-life of a few days to weeks, or reacts with hydroxyl radicals with a half-life of several weeks to months. In air, it reacts with hydroxyl radicals, with a half-life of about 5 days (4).

14.11.2 Analytical methods

Benzene can be determined by a purge-and-trap gas chromatographic procedure with photoionization detection, a method which is applicable over a concentration range of 0.02-1500 µg/litre. Confirmation is by mass spectrometry (detection limit 0.2 µg/litre) (4).

14.11.3 Environmental levels and human exposure

**Air**

Rural background concentrations of benzene, which may originate from natural sources (forest fire and oil seeps), have been reported to range from 0.3 to 54 µg/m³. The general urban atmosphere reportedly contains 50 µg/m³. In several studies conducted since 1963, average concentrations in ambient air ranged from 5 to 112 µg/m³, mainly derived from vehicular emissions (1).

Exposure inside homes can occur from cigarette smoke or when houses are built on soil polluted with benzene. In one case, levels varying from 34 µg/m³ (in the living space) up to 230 µg/m³ (beneath the floor) were found. Benzene is found in the main stream (0.01-0.1 mg/cigarette) and in the side stream
(0.05-0.5 mg/cigarette) of cigarette smoke (3). In a study in three states of the USA, weighted median concentrations were 9.8-16 µg/m³ in indoor air and 0.4-7.2 µg/m³ in outdoor air (5).

**Water**

The major sources of benzene in water are atmospheric deposition, spills of petrol and other petroleum products, and chemical plant effluents. Levels of up to 179 µg/litre have been reported in chemical plant effluents (1). In seawater, levels were reported to be in the range 5-20 ng/litre (coastal area) and 5 ng/litre (central part) (3). Levels between 0.2 and 0.8 µg/litre were reported in the Rhine in 1976 (6). Levels of 0.03-0.3 mg/litre were found in groundwater contaminated by point emissions (7).

Benzene was detected in 50-60% of potable water samples taken at 30 treatment facilities across Canada; mean concentrations ranged from 1 to 3 µg/litre (maximum 48 µg/litre) (8). Federal drinking-water surveys in the USA estimated that approximately 1.3% of all groundwater systems contained benzene at concentrations greater than 0.5 µg/litre (highest level reported 80 µg/litre) (4).

**Food**

Benzene may occur in food naturally, through migration from metallic covering layers of packaging material, or through contamination from the environment. It has been reported in several foods (eggs: 500-1900 µg/kg; rum: 120 µg/kg; irradiated beef: 19 µg/kg; heat-treated or canned beef: 2 µg/kg), and has also been detected in such foodstuffs as haddock, cheese, cayenne pepper, pineapple, and black currants (9).

**Estimated total exposure and relative contribution of drinking-water**

Exposure to benzene may vary considerably. For nonsmokers, the estimated average daily intake is 200-450 µg/day. The estimated contribution from food is 180 µg/day but, as information on benzene levels in food is very scanty, this background level should be considered only as an approximate reference point. For smokers, the intake levels are increased by a factor of 2-3 (urban areas) or 2-6 (rural areas). The levels commonly found in drinking-water are minimal compared with the intake from food and air (3).

14.11.4 Kinetics and metabolism in laboratory animals and humans

Benzene is rapidly and efficiently (30-50%) absorbed following inhalation. Following ingestion, animal data suggest about 100% absorption from the gastrointestinal tract. Less than 1% is absorbed through the skin. After absorption, benzene is widely distributed throughout the body, independently of the route of administration. Levels fall rapidly once exposure stops. Following uptake, adipose tissues have been found to contain high levels of benzene metabolites.

The metabolism and elimination of absorbed benzene appear to follow similar pathways in laboratory animals and humans. Benzene is converted mainly to phenol by the mixed-function oxidase system, primarily in the liver, but also in bone marrow. A small amount of phenol is metabolized to hydroquinone and catechol, and an even smaller amount is transformed into phenylmercapturic or trans-muconic acid. Between 12% and 14% (up to 50% in laboratory animals) of the absorbed dose is excreted unchanged in expired air. The respiratory elimination of benzene in humans is triphasic. In the urine, a small part is excreted unchanged, the remainder being excreted as phenol conjugates (3,9-11).

14.11.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

Benzene has a low acute toxicity. The oral LD₅₀ in mice and rats is 1-10 g/kg of body weight; the 2.8-h LC₅₀ is 15-60 g/m³ (3).
**Long-term exposure**

Repeated exposure to low levels of benzene produces toxic effects principally in the blood and blood-forming tissues (3). Long-term exposure of mice to concentrations of 32-65 mg/m$^3$ results in inhibition of early differentiating blood cell elements (12).

In a study in which benzene was administered by gavage in corn oil 5 days per week for 103 weeks at doses of 0, 5, 100, or 200 mg/kg of body weight to F344/N rats or 0, 25, 50, or 100 mg/kg of body weight to B6C3F$_1$ mice, haematological effects, including lymphoid depletion of the splenic follicles (rats) and thymus (male rats), bone marrow haematopoietic hyperplasia (mice), lymphocytopenia, and associated leukocytopenia (rats and mice), were observed even at the lowest dose (13-15).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Benzene is not teratogenic even at maternally toxic doses. However, embryotoxicity/fetotoxicity was observed in rats and mice at levels as low as 65 mg/m$^3$ (9).

**Mutagenicity and related end-points**

Benzene was not mutagenic in several bacterial and yeast systems, in the sex-linked recessive lethal mutation assay with Drosophila melanogaster, or in the mouse lymphoma cell forward mutation assay. It can cause chromosome damage in plants and in mammalian somatic cells both in vitro and in vivo. Its clastogenic potential is partly due to its hydroxylated metabolites. Benzene and its metabolites may interfere with the formation of the mitotic spindle and perhaps do not interact directly with DNA. However, binding of benzene to nucleic acids has been reported (3,10,15).

**Carcinogenicity**

Benzene is carcinogenic in rats and mice after oral and inhalation exposure, producing malignant tumours at many sites. In a study by the National Toxicology Program, it was administered by gavage in corn oil 5 days per week for 103 weeks at doses of 0, 5, 100, or 200 mg/kg of body weight to F344/N rats and 0, 25, 50, or 100 mg/kg of body weight to B6C3F$_1$ mice. Compound-related non-neoplastic or neoplastic effects on the haematopoietic system, Zymbal gland, forestomach, and adrenal gland were seen in both sexes of both species. In addition, the oral cavity was affected in rats, and the lung, liver, hardenerian gland, preputial gland, ovary, and mammary gland in mice (13-15).

**14.11.6 Effects on humans**

Acute exposure of humans to high concentrations of benzene primarily affects the central nervous system. Acute exposure to 65 g/m$^3$ may cause death. Extensive haemorrhages have been observed in fatal cases (3).

Occupational exposure to more than 162 mg/m$^3$ results in toxic effects on the haematopoietic system, including pancytopenia. The white blood cells are the most sensitive (10).

There is considerable evidence that exposure to high benzene concentrations (≥325 mg/m$^3$) may eventually result in leukaemia, in many cases preceded by pancytopenia or aplastic anaemia. Both epidemiological studies (16,17) and several case-studies showed that exposure to benzene was correlated with the occurrence of leukaemia (particularly acute myeloid leukaemia). Cytogenetic effects in peripheral lymphocytes were observed in human subjects with benzene haemopathy (3,9,11,18).

**14.11.7 Guideline value**

Benzene is carcinogenic in mice and rats after both inhalation and oral exposure, producing malignant
tumours at many sites. It is considered to be a human carcinogen and is classified by IARC in Group 1 (18). Although it does not induce mutations or DNA damage in standard bacterial assay systems, it has been shown to cause chromosomal aberrations in a variety of species in vivo.

Because of the unequivocal evidence of the carcinogenicity of benzene in humans and laboratory animals and its documented chromosomal effects, quantitative risk extrapolation was used to estimate lifetime cancer risks. Based on a risk estimate using data on leukaemia from epidemiological studies involving inhalation exposure, it was calculated that a drinking-water concentration of 1 µg/litre was associated with an excess lifetime cancer risk of 10^{-6} (10 µg/litre is associated with an excess lifetime risk of 10^{-5} and 100 µg/litre with an excess lifetime risk of 10^{-4}) (15).

As data on the carcinogenic risk to humans following the ingestion of benzene are not available, risk estimates were also carried out on the basis of a 2-year gavage study in rats and mice (13). The robust linear extrapolation model was used, as there was a statistical lack of fit of some of the data with the linearized multistage model. The estimated range of concentrations in drinking-water corresponding to excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, based on leukaemia and lymphomas in female mice and oral cavity squamous cell carcinomas in male rats, are 100-800, 10-80, and 1-8 µg/litre, respectively. These estimates are similar to those derived from epidemiological data, which formed the basis for the previous guideline value of 10 µg/litre associated with a 10^{-5} excess lifetime cancer risk.

Guideline values corresponding to excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} are therefore 100, 10, and 1 µg/litre, respectively.

References


11. Ware GW, ed. USEPA Office of Drinking Water health advisories. Reviews of environmental


14.12 Toluene

14.12.1 General description

Identity

CAS no.: 105-88-3
Molecular formula: C₇H₈

The IUPAC name for toluene is methylbenzene.

Physicochemical properties (1,2)

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</table>

1 Conversion factor in air: 1 ppm = 3.75 mg/m³

Organolectic properties

Toluene has a sweet, pungent, benzene-like odour. The lowest concentrations reported to be perceptible to humans on inhalation range from 0.64 to 139 mg/m³ (3). The odour threshold in water is 0.024-0.17 mg/litre. The reported taste threshold ranges from 0.04 to 0.12 mg/litre (2,4,5).
Major uses

Toluene is used as a solvent, especially for paints, coatings, gums, oils, and resins, and as raw material in the production of benzene, phenol, and other organic solvents. Most toluene (in the form of benzene-toluene-xylene mixtures) is used in the blending of petrol.

Environmental fate

Toluene degrades readily in air. It is removed from the atmosphere mainly by reactions with atomic oxygen, peroxo- or hydroxyl radicals, and ozone. Its half-life in the atmosphere ranges between 13 h and 1 day (1,6).

When toluene is released to surface water, it volatilizes to air very rapidly, the half-life being about 5 h at 25 °C and increasing with the depth of the water column. Biodegradation and sorption are less important for the removal of toluene from surface waters. The extent to which it is biodegraded in soil ranges from 63% to 86% after 20 days (7).

The amount of toluene in environmental compartments can be estimated with the aid of models (8) when emission data are known. In the Netherlands, for example, the estimated percentages of total toluene in air, water, and soil are 98.6%, 0.8%, and 0.6%, respectively (6).

14.12.2 Analytical methods

A purge-and-trap gas chromatographic procedure with photoionization detection can be used for the determination of toluene in water over a concentration range of 0.02-1500 µg/litre (9). Confirmation is by mass spectrometry (10). Methods for the determination of toluene in air, soil, and other matrices have been reviewed and compiled by Fishbein & O’Neill (11).

14.12.3 Environmental levels and human exposure

Air

Mean atmospheric concentrations of toluene in urban areas around the world range from 2 to 200 µg/m³; concentrations are higher in areas with high traffic density. Lower levels (0.2-4 µg/m³) have been reported in rural areas. Indoor concentrations range from 17 to 1000 µg/m³ and are related to outdoor concentrations and to the presence of cigarette smoke (1,6).

Water

The concentration of toluene in rainwater in Germany has been reported to be 0.13-0.70 µg/litre (12). In the Netherlands, a median value of 0.04 µg/litre was found (6).

Toluene was found at concentrations of 1-5 µg/litre in water samples from a number of rivers in the USA (1). Concentrations of 0.8 µg/litre and 1.9 µg/litre have been reported in the Rhine in Germany and Switzerland, respectively (13). In coastal waters, levels of 0.01-1 µg/litre were found (14).

In groundwater contaminated by point emissions, toluene levels of 0.2-1.1 mg/litre were reported (15). The highest level reported in groundwater in the USA in 1983 was 1.4 µg/litre (2).

In approximately 1% of all groundwater-derived public drinking-water systems in the USA, toluene levels are above 0.5 µg/litre (2). In Canada, in a study of 30 water-treatment plants, drinking-water contained an average of 2 µg/litre (16). In a study of Ontario drinking-water, concentrations of up to 0.5 µg/litre were found (17). Toluene can be leached from synthetic coating materials commonly used to protect drinking-water storage tanks (18).
Food

Toluene concentrations of 1 mg/kg have been reported in fish (19). In cyclodextrin flavour complexes, residual concentrations can be in the range 2.7-10.2 mg/kg (20).

Estimated total exposure and relative contribution of drinking-water

Although information on the intake of toluene via food and drinking-water is limited, it can be expected that this intake will be low compared with that via air. Studies in the Netherlands suggest that the population is exposed to at least 30 µg/m³. If a mean ventilation volume of 20 m³/day and an absorption of 50% are assumed, the daily absorption ranges from 0.3 to 12 mg (6). Exposure is increased by traffic and cigarette smoking.

14.12.4 Kinetics and metabolism in laboratory animals and humans

In humans, toluene is probably absorbed completely from the gastrointestinal tract after oral uptake. The compound is rapidly distributed in animals, and tissue distribution is comparable after administration by inhalation and by mouth. After uptake, the compound is preferentially found in adipose tissue, followed in succession by the adrenal glands, kidneys, liver, and brain. It is rapidly converted into benzyl alcohol by the microsomal mixed-function oxidase system in the liver; then to benzoic acid, which is conjugated with either glycine or glucuronic acid and excreted in urine as hippuric acid or benzoyl glucuronide. Toluene is also metabolized to a small extent to o- and p-cresol. In the lungs, part of the resorbed toluene is excreted unchanged (3).

14.12.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Toluene has a low acute toxicity via the oral route; LD₅₀s in rats range from 2.6 to 7.5 g/kg of body weight.

Short-term exposure

In most short-term studies, toluene was administered by inhalation; liver enzyme induction, liver weight increase, and neurophysiological changes are the main effects seen in these studies (3). Few oral studies are available, and only one is of value for assessment purposes. This study was carried out in rats and mice with doses of 0, 312, 625, 1250, 2500, or 5000 mg/kg of body weight administered 5 days per week for 13 weeks. In rats, increased liver and kidney weights (without concomitant histopathological changes) were the most sensitive effects, occurring at doses of 625 mg/kg of body weight and above; the NOAEL in this study was 312 mg/kg of body weight. In mice, an increased relative liver weight was the most sensitive effect, being present at 312 mg/kg of body weight in females (21).

Long-term exposure

In the only adequate toxicity study, toluene was administered via the inhalation route in rats. In this study, the only significant difference between the treatment groups and the control group was a decrease in blood haematocrit (erythrocyte volume fraction), observed at 380 and 1100 mg/m³ but not at 110 mg/m³ (exposure 6 h per day, 5 days per week) (3).

Reproductive toxicity, embryotoxicity, and teratogenicity

Toluene has been tested for teratogenicity via the inhalation route (in rats, mice, and rabbits) and via the oral route (mice only). In the inhalation studies, embryotoxicity and fetotoxicity, but not teratogenicity, were observed at high dose levels (≥100 mg/m³). In one of the two oral studies, a significant increase in
embryonic deaths occurred at all dose levels (≥260 mg/kg of body weight); a teratogenic effect (increased incidence of cleft palate) was observed at the highest dose level (870 mg/kg of body weight) only (3,12).

**Mutagenicity and related end-points**

Toluene was found to be nongenotoxic in a number of in vitro systems (bacteria, yeasts, mammalian cells). In vivo studies on insects, rats, and mice have yielded conflicting results; chromosomal aberrations in rat bone marrow cells were observed in studies carried out in the former USSR but not in other countries, perhaps as a result of contamination with benzene in these studies. In mice, the induction of micronuclei in erythrocytes was observed, but not consistently. It has been concluded that toluene has not been demonstrated to be genotoxic (3,12).

**Carcinogenicity**

In an inhalation study in rats exposed to 110, 380, or 1100 mg/m³, 6 h per day, 5 days per week, no clear evidence for the carcinogenicity of toluene was found; the same results were found in several special carcinogenicity studies, all of which, however, were very limited in design (3). In an adequate inhalation carcinogenicity study carried out in rats and mice, no evidence for a carcinogenic effect was found (21). IARC concluded that there is inadequate evidence for the carcinogenicity of toluene in both experimental animals and humans and classified it in Group 3 (not classifiable as to its carcinogenicity to humans) (1).

14.12.6 Effects on humans

Virtually all the available data relate to exposure to toluene by inhalation. For acute exposure, the predominant effects were impairment of the central nervous system and irritation of mucous membranes. Fatigue and drowsiness were the most sensitive effects, being present at 375 mg/m³ and absent at 150 mg/m³. The toxic effects of toluene after long-term exposure are basically the same. There have been few controlled long-term studies via the oral and inhalation routes (3,12,22).

Studies designed to detect a possible increase in the frequency of chromosomal aberrations or sister chromatid exchanges in the peripheral lymphocytes of people occupationally exposed to toluene have yielded inconclusive results (1,3,12). Epidemiological studies on the occurrence of cancer as a consequence of exposure of human populations to toluene alone are not available (3).

14.12.7 Guideline value

The available evidence suggests that toluene should not be regarded as an initiating carcinogen; a TDI approach can therefore be used to derive the guideline value. The NOAEL from a 13-week gavage study in rats (21) was 312 mg/kg of body weight (administration 5 days per week); this dosage level had marginal effects in an identical study in mice. A TDI of 223 µg/kg of body weight can be derived using the LOAEL for marginal hepatotoxicity in mice of 312 mg/kg of body weight (equivalent to 223 mg/kg of body weight 7 days per week) and applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the short duration of the study and use of a LOAEL instead of a NOAEL). This TDI yields a guideline value of 700 µg/litre (rounded figure), allocating 10% of the TDI to drinking-water. It should be noted, however, that this value exceeds the lowest reported odour threshold in water of 24 µg/litre.

References


2. US Environmental Protection Agency. USEPA Office of Drinking Water health advisories. *Reviews of*
environmental contamination and toxicology, 1988, 106:189-203.


1983 (Publication No. PB84-100056).


14.13 Xylenes

14.13.1 General description

Identity

CAS no.: 1130-20-7
Molecular formula: C₈H₁₀

The IUPAC name for xylene is dimethylbenzene. There are three possible xylene isomers: 1,2-, 1,3-, and 1,4-dimethylbenzene; these will be referred to as o- (ortho), m- (meta), and p- (para) xylene. The xylenes are for the most part manufactured and marketed as a mixture of the isomers, which will here be called xylene.

Physicochemical properties (1,2)

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</table>

¹ Conversion factor in air: 1 ppm = 4.41 mg/m³

Organoleptic properties

The lowest xylene concentrations in air reported to be perceptible to humans range from 0.6 to 16 mg/m³ (3,4). The odour threshold for xylene isomers in water is 0.02-1.8 mg/litre (4,5). Concentrations of 0.3-1.0 mg/litre in water produce a detectable taste and odour (6).

Major uses

Xylene is used in the manufacture of insecticides and pharmaceuticals, as a component of detergents, and as a solvent for paints, inks, and adhesives. Xylene-containing petroleum distillates are used extensively and increasingly in blending petrol. The three isomers are used individually as starting materials in the manufacture of various chemicals (1,2).

Environmental fate

Releases of xylene to the environment are largely to air because of its volatility; the calculated distribution
of xylene is: air, 99.1%; water, 0.7%; soil, 0.1%; and sediment, 0.1% (7). Xylene degrades in air with a half-life of a few days. It is also readily biodegraded in soils and surface waters (2). Under aerobic conditions, it can be degraded in groundwater. Half-lives of from 24 to over 161 days have been reported (8,9). In anaerobic groundwater, no biotransformation is expected (10). When xylene is released to surface water, it volatilizes to air very rapidly.

14.13.2 Analytical methods

A purge-and-trap gas chromatographic procedure with photoionization detection can be used for the determination of xylene in water over a concentration range of 0.02-1500 µg/litre (11). Confirmation is by mass spectrometry (12). Methods for the determination of xylene in air, soil, and other matrices have been reviewed and compiled by Fishbein & O’Neill (13).

14.13.3 Environmental levels and human exposure

Air

Mean atmospheric concentrations of xylene in urban areas around the world range from 3 to 390 µg/m³ (1). Outdoor concentrations of 0.6-61 µg/m³ have been reported in the USA (1,14). Concentrations of 100 µg/m³ were found at cross-roads (1). Indoor air concentrations range from 5.2 to 29 µg/m³ and are higher (200 µg/m³) in the presence of cigarette smoke. The average ratio of indoor to outdoor air concentration is 1.2 for m-xylene and 4.0 for o-xylene (15).

Water

Xylene has been found at levels of 2-8 µg/litre in the surface water of Florida Bay (16). In the Netherlands section of the Rhine, the average xylene concentration in 1987 was 0.3 µg/litre (0.1 µg/litre for each isomer); the maximum value was 1.2 µg/litre. In the surface water of Lake Ijsselmeer, the average and maximum concentrations were 0.3 and 0.9 µg/litre, respectively (17).

In groundwater contaminated by point emissions, xylene levels of 0.3-5.4 mg/litre have been reported; levels in uncontaminated groundwater are low (<0.1 µg/litre) (18). The highest level in groundwater in the USA (1983) was 2.5 µg/litre (2). In the Netherlands, xylene was detected in 10.1% of 304 samples of groundwater used for potable water production; the maximum concentration found was 0.7 µg/litre (19).

Xylene levels in approximately 3% of all groundwater-derived public drinking-water systems and 6% of all surface-water-derived drinking-water systems in the USA were greater than 0.5 µg/litre, the maximum level being 5.2 µg/litre (2). In Canada, m-xylene was found in seven out of 30 potable water treatment plants at concentrations below 1 µg/litre (20). In Ontario, xylene was found in drinking-water at concentrations of less than 0.5 µg/litre (21). In drinking-water and tapwater in New Orleans, concentrations of 3-8 µg/litre were reported (16). Concentrations in drinking-water can be increased by the leaching of xylene from the synthetic coating materials commonly used to protect the tanks used for its storage (22).

Estimated total exposure and relative contribution of drinking-water

Because of the low levels of xylene reported in drinking-water, air is likely to be the major source of exposure. If a mean ventilation volume of 20 m³/day (75% indoor air; 25% outdoor air) and an absorption of 65% are assumed, the daily exposure can be estimated to range from 0.05 to 0.5 mg. This exposure will be increased when air is polluted with cigarette smoke.

14.13.4 Kinetics and metabolism in laboratory animals and humans

Data on absorption after ingestion are not available. Xylene isomers are readily absorbed after inhalation,
with retention percentages of 60-65% in humans. They are absorbed to some extent (exact percentages not known) via the skin; the few data available indicate rapid distribution of the compound after uptake. Xylenes can cross the placenta. They are stored in adipose tissue in both laboratory animals and humans. A small part (< 5%) of the absorbed amount is exhaled unchanged; the remainder is converted almost quantitatively to methyl benzoic acid, which is excreted in urine as methyl hippuric acid. Few data on rates of excretion are available; it is eliminated from subcutaneous fat in humans with a half-life ranging from 25 to 128 h (2,7,23).

14.13.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Xylene isomers have a low acute toxicity via the oral route; LD₅₀s in rats range from 3.6 to 5.8 g/kg of body weight (1).

Short-term exposure

Available short-term oral studies are of limited design. The toxicological significance of the ultrastructural liver changes observed in rats (24) at the only dose level tested (200 mg of o-xylene per kg of feed) is questionable given the absence of any histopathological signs in the livers of rats tested at much higher dose levels in oral studies carried out under the US National Toxicology Program (25). In addition, the results of the single-dose study are presented only for the group of methylated benzenes tested; the results observed with the individual compounds are not reported. In inhalation studies in rats, liver enzyme induction was observed at concentrations of 217 mg/m³ and above, 6 h per day (NOAEL not determined) (23,26).

Long-term exposure

A carcinogenicity study in rats and mice provided some relevant information on the toxic effects of xylenes after oral administration. In rats, 0, 250, or 500 mg/kg of body weight per day was administered by gavage in corn oil, 5 days per week for 103 weeks. Growth was decreased at 500 mg/kg of body weight per day; no compound-related histological lesions were observed. The NOAEL for rats was 250 mg/kg of body weight per day. In mice, the dose levels tested were 0, 500, and 1000 mg/kg of body weight per day. The only observed effect in this species was hyperactivity at 1000 mg/kg of body weight per day (25).

Reproductive toxicity, embryotoxicity, and teratogenicity

Both of the oral studies carried out in mice showed maternal toxicity with concurrent embryotoxicity and teratogenicity (increased incidence of cleft palate) at the higher dose levels tested (LOAEL 640 mg/kg of body weight; NOAEL 255 mg/kg of body weight) (27,28). Teratogenicity studies carried out in rats and mice by the inhalation route showed maternal toxicity at high dose levels but no teratogenicity (7,23).

Mutagenicity and related end-points

The mutagenic activity of xylenes was examined in bacteria and in mammalian cells (both in vitro and in vivo) with negative results. The significance of a weak positive effect observed with technical xylene in a Drosophila recessive lethal test is not clear, given the negative results in the same test system obtained with the individual components of the technical mixture (7,23,29).

Carcinogenicity

An oral carcinogenicity study in rats (0, 250, or 500 mg/kg of body weight per day administered by gavage in corn oil, 5 days per week for 103 weeks) and mice (0, 500, or 1000 mg/kg of body weight per day) did not show xylenes to be carcinogenic (25).
14.13.6. Effects on humans

No oral data are available. In acute inhalation studies, irritation of eyes and throat was observed at concentrations of 480 mg/m³ and above. After short-term exposure (6 h per day, 5 days per week), reaction time, manual coordination, body equilibrium, and electroencephalogram were affected at concentrations of 390 mg/m³ and above (NOAEL not determined). Controlled studies of longer duration are not available (7,23).

14.13.7. Guideline value

On the basis of the available evidence, xylenes should not be regarded as initiating carcinogens, so that a TDI approach may be used. A TDI of 179 µg/kg of body weight was derived using a NOAEL of 250 mg/kg of body weight per day based on decreased body weight in a 103-week gavage study in rats (25) with administration 5 days per week (equivalent to 179 mg/kg of body weight per day 7 days per week) and an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the limited toxicological end-point). This TDI yields a guideline value of 500 µg/litre (rounded figure), allocating 10% of the TDI to drinking-water. This value, however, exceeds the lowest reported odour threshold for xylenes in drinking-water of 20 µg/litre.

References


25. National Toxicology Program. Toxicology and carcinogenesis studies of xylenes (mixed) (60% m-xylene, 14% p-xylene, 9% o-xylene, 17% ethylbenzene) (CAS No. 1330-20-7) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC, 1986 (NTP Technical Report Series No. 327).


### 14.14 Ethylbenzene

#### 14.14.1 General description

**Identity**

CAS no.: 100-41-4  
Molecular formula: C₈H₁₀

**Physical and chemical properties (1)**

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</table>

1 Conversion factor in air: 1 ppm = 4.35 mg/m³

**Organoleptic properties**

Ethylbenzene has an aromatic odour. The odour threshold is in the range 0.27-0.4 mg/m³ in air (1,2) and 0.002-0.13 mg/litre in water (1,3). The taste threshold ranges from 0.072 to 0.2 mg/litre (2,3).

**Major uses**

Ethylbenzene is present in xylene mixtures at levels up to 15-20% (4). This mixture is used in the paint industry, in insecticide sprays, and in petrol blends. Ethylbenzene is used primarily in the production of styrene and acetophenone, as a solvent, and as a constituent of asphalt and naphtha.

**Environmental fate**

The primary source of ethylbenzene in the environment is the petroleum industry. Because of its high vapour pressure and low solubility, it will disperse into the atmosphere if released. More than 96% of ethylbenzene can be expected in the air compartment. It is phototransformed in the air by reaction with hydroxyl radicals; the half-life is approximately 1 day (5).

Biodegradation of ethylbenzene in soil under aerobic conditions with a half-life of 24.2 days has been reported. In activated sludge and water, it can be biodegraded under aerobic conditions (6).
14.14.2 Analytical methods

A purge-and-trap gas chromatographic procedure with photoionization detection can be used for the determination of ethylbenzene in water over a concentration range of 0.02-1500 µg/litre (7). Confirmation is by mass spectrometry (8). Methods for the determination of ethylbenzene in air, soil, and other matrices have been reviewed and compiled by Fishbein & O'Neill (9). Continuous monitoring of ethylbenzene and other volatile hydrocarbons is possible at the microgram per litre level (10).

14.14.3 Environmental levels and human exposure

Air

In Germany, average indoor and outdoor ethylbenzene concentrations of 13 µg/m³ were found (11). In Italy, mean indoor and outdoor air concentrations of 27 and 7.4 µg/m³ were reported (12).

The median daily concentrations of ethylbenzene in the urban air of nine major cities in the USA of 1.3-6.5 µg/m³ (13). In the Netherlands, mean and maximum values of 0.9-2.8 and 10.0-25.7 µg/m³, respectively, were reported (14).

Water

The maximum ethylbenzene concentration in the Besós river in Spain was 15 µg/litre and in the Llobregat river 1.9 µg/litre (15). Levels of 0.03-0.3 mg/litre were reported in groundwater contaminated by point emissions (16).

In a survey of groundwater supplies (17), it was found that approximately 0.6% of 945 such supplies contained ethylbenzene; the median concentration was 0.87 µg/litre. In the Netherlands, ethylbenzene was detected in 1% of 304 samples of groundwater (18); the maximum concentration was 0.4 µg/litre. Concentrations of up to 0.07 µg/litre were found in aquifers in the United Kingdom (19). In Canada, in a study of 30 water-treatment plants, concentrations in drinking-water were below 1 µg/litre (20).

In Los Angeles, USA, an ethylbenzene concentration of 9 ng/litre was found in rainwater (21).

Food

Ethylbenzene has been identified in volatiles of roasted hazelnuts. It can migrate from polystyrene food packaging into food. Concentrations of 2.5-21 µg/litre have been reported in milk and soup (5).

Estimated total exposure and relative contribution of drinking-water

Although there is little information concerning the intake of ethylbenzene via food and drinking-water, it is expected to be low compared with that via air. In the Netherlands, the estimated daily exposure is 40 µg (14), based on a ventilation volume of 20 m³/day.

14.14.4 Kinetics and metabolism in laboratory animals and humans

Ethylbenzene in liquid form is easily absorbed by humans via both the skin and the intestinal tract (exact absorption percentages not reported); the vapour is readily absorbed when inhaled (reported absorption percentage 64% for humans, 44% for rats). Both distribution and excretion are rapid. In humans, storage of ethylbenzene in fat has been reported, and the compound has been observed to pass the placental barrier. Biotransformation in humans is almost completely to mandelic acid and phenylglyoxalic acid, both these metabolites being excreted in urine. Metabolism in experimental animals differs from that in humans in that benzoic acid is the major metabolite together with mandelic acid. Urinary excretion of metabolites is almost complete within 24 h (1,5).
14.14.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Ethylbenzene has a low acute toxicity via the oral route; LD_{50}s in rats range from 3.5 to 4.7 g/kg of body weight (22).

Short-term exposure

In a short-term oral study in rats, effects on liver and kidneys were observed at 400 mg/kg of body weight and higher dose levels (administered 5 days per week for 6 months); there were no such effects at 136 mg/kg of body weight (23). Liver effects were also found in a number of inhalation studies; the LOAEL for this type of effect was 1305 mg/m^3, no effects being seen at 218 or 430 mg/m^3 (concentrations administered for 6 h per day, 5 days per week) (5,24,25).

Reproductive toxicity, embryotoxicity, and teratogenicity

In all the teratogenicity studies in rats and rabbits, dosing was via the inhalation route. No definite conclusions with regard to the observed effects (maternal toxicity, reduced fertility and, possibly, teratogenicity) can be drawn from the reports available (5,22).

Mutagenicity and related end-points

Studies were carried out in bacteria, yeasts, insects, mammalian cells (in vitro), and intact mammals; negative results were obtained in all test systems, showing ethylbenzene to be devoid of mutagenic activity (1,5,22).

14.14.6 Effects on humans

Relevant oral data are lacking. Data for the inhalation route are limited to acute studies considered insufficient as a basis for a guideline value (1,5,22).

14.14.7 Guideline value

No carcinogenicity data on ethylbenzene are available. The compound was shown to be nonmutagenic in a number of tests. Given these findings, a TDI approach may be applied.

The TDI is derived using a NOAEL of 136 mg/kg of body weight per day based on hepatotoxicity and nephrotoxicity observed in a limited 6-month study in rats (administration 5 days per week) (23); this dose level is equivalent to 97.1 mg/kg of body weight per day for dosing 7 days per week. After application of an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the limited database and short duration of the study), a TDI of 97.1 µg/kg of body weight results. This yields a guideline value of 300 µg/litre (rounded figure), allocating 10% of the TDI to drinking-water, which exceeds the lowest reported odour threshold in drinking-water (2.4 µg/litre).

References


14.15 Styrene

14.15.1 General description

Identity

CAS no: 100-42-5
Molecular formula: C₈H₈

The IUPAC name for styrene is phenylethene. It is also known as vinylbenzene, ethenylbenzene, and styrol.

Physicochemical properties (1-3)¹

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<th>Value</th>
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</thead>
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<tr>
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<tr>
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</tr>
</tbody>
</table>

¹ Conversion factor in air: 1 ppm = 4.2 mg/m³

Organoleptic properties

The average taste threshold reported for styrene in water at 40 °C is 0.12 mg/litre (4). Styrene has a sweet odour, and odour thresholds for solutions in water range from 0.02 to 2.6 mg/litre (5). An odour threshold for solutions in water at 60 °C of 0.0036 mg/litre has also been reported (4). The estimated odour threshold for styrene in air is 0.1 mg/m³ (6).
**Major uses**

Styrene is used for the production of plastics and resins \((1,6)\).

**Environmental fate**

Styrene in air is very reactive in the presence of hydroxyl radicals and ozone, having a half-life of about 2 h \((7)\). In air, it is oxidized to aldehydes, ketones, and benzoic acid. High relative molecular mass peroxides can also be formed \((6)\).

**14.15.2 Analytical methods**

The styrene content of water is determined by a purge-and-trap gas chromatographic procedure with photoionization detection, a method which is applicable over a concentration range of 0.05-1500 µg/litre. Confirmation is by mass spectrometry (detection limit 0.3 µg/litre) \((2,8)\).

**14.15.3 Environmental levels and human exposure**

**Air**

Concentrations of styrene far from a source are negligible because of its high reactivity with ozone and hydroxyl radicals. In Munich, styrene was detected in the open air in industrial areas at a mean concentration of 0.5-5.9 µg/m\(^3\). Near styrene production plants, concentrations were 0.3-3000 µg/m\(^3\). Indoor air concentrations of styrene may be significantly higher in homes of smokers than nonsmokers \((6)\). Reported median values for personal exposure are 1.3-1.9 µg/m\(^3\) for indoor air and 0.1-0.7 µg/m\(^3\) for outdoor air \((9)\).

**Water**

In 1985, styrene was detected in the Rhine at a maximum concentration of 0.1 µg/litre. In the Great Lakes (USA), it was detected at concentrations of 0.1-0.5 µg/litre. It was not detected in the raw water of groundwater pumping stations in Germany \((6)\), but has been found in finished drinking-water in the USA at concentrations of less than 1 µg/litre and in commercial, charcoal-filtered drinking-water in New Orleans, USA \((1)\).

**Food**

Styrene has been found in food packaged in polystyrene containers, especially yoghurt (2.5-34.6 µg/kg). In other milk products and honey, some tens of micrograms were found up to 120 days after packaging \((1)\). In east Australia, 146 food samples packaged in polystyrene, especially milk products, were analysed. About 85% of the yoghurt samples contained less than 50 µg/kg (maximum 100 µg/kg); the lowest concentrations were found in margarine (90% contained less than 10 µg/kg) \((10)\). In a study on 133 different types of foodstuffs packaged in styrene-based materials (100-500 mg/kg), the concentration in the foodstuffs ranged from less than 1 to 200 µg/kg. In meat products, styrene was present in the outermost layers and was not detected after cooking \((11)\).

**Estimated total exposure and relative contribution of drinking-water**

The population exposure level for styrene is estimated to be approximately 40 µg per person per day for nonsmokers in nonindustrial areas. This figure is based on the levels in the open air (2 µg/day), traffic (mean of 10-50 µg/day), and food (5 µg derived from the consumption of 500 g of milk products in styrene-based packages). The most important exposure is active smoking (500 µg/day). Passive smoking accounts for only a few micrograms per day. In industrial areas, the exposure via open air is 400 µg/day. Exposure via drinking-water is negligible \((6)\).
14.15.4 Kinetics and metabolism in laboratory animals and humans

After exposure by inhalation or administration by gavage, 60-90% of styrene is absorbed. Controlled laboratory studies in animals and humans have shown that uptake of styrene is rapid and that it is widely distributed to the whole body with a preference for lipids. Elimination from lipid depots is slower (half-life 2-4 days) than from other tissues. There is no tendency towards long-term accumulation.

Styrene is biotransformed mainly to styrene-7,8-oxide via the mixed function oxidase system. This occurs in the liver as well as in a number of other tissues and organs. The epoxide is further hydrolysed by the action of epoxide hydrolase to styrene glycol which, in turn, can be converted into mandelic acid, phenylglyoxylic acid, and hippuric acid, or conjugated to give glucuronic acid. Styrene-7,8-oxide can also be conjugated with glutathione to form mercapturic acid derivatives.

A small percentage of the dose absorbed is excreted unchanged in the expired air in both laboratory animals and humans after exposure via various routes. More than 90% of an oral dose is excreted rapidly as metabolites, mainly via the urine. In general, the metabolites in the urine of laboratory animals and humans are qualitatively the same, but the amounts are species-dependent. Major metabolites in humans are mandelic acid and phenylglyoxylic acid. Elimination of styrene and its metabolites can be described by a two-compartment kinetic model with an initial rapid phase and a slow terminal phase. At high exposure levels, elimination in animals appeared to be monophasic, suggesting a saturable metabolic pathway (2,5,12,13).

14.15.5 Effects on laboratory animals and in vitro test systems

Acute exposure

Styrene has a low acute toxicity. For the rat, the oral LD₅₀ is 5-8 g/kg of body weight, and the 4-h and 6-h LC₅₀s are 11 and 19 g/m³ of air, respectively (5,12). At lethal oral doses, rats became comatose before death. Autopsy revealed hepatic changes and incidental renal changes (5).

Short-term exposure

The NOAEL in a 6-month oral toxicity study in the rat was 133 mg/kg of body weight (14). In rats given dose levels above 200 mg/kg of body weight, enhanced activities of drug-metabolizing enzymes and decreased glutathione-S-transferase activity in the liver were seen (5). An increased sensitivity of dopamine receptors was found at 200 and 400 mg/kg of body weight, suggesting involvement of neurotransmitter function in the central nervous system effects caused by styrene (15). At dose levels above 400 mg/kg of body weight, decreased body weight gain, increased liver and kidney weights, significantly reduced glutathione concentrations in liver, kidneys, and brain, significantly enhanced liver enzyme activities, and histopathological changes in the liver were observed (5). At doses above 500 mg/kg of body weight, irritation of the oesophagus and stomach and hyperkeratosis of the forestomach were observed and deaths occurred. No haematological changes were observed in short-term oral studies in the rat (5). In a 19-month oral study in dogs, a dose-related increased incidence in Heinz bodies in erythrocytes was observed down to the lowest dose tested (200 mg/kg of body weight) (16).

Long-term exposure

In a study in which pregnant BDIV rats received a styrene dose of 1350 mg/kg of body weight in olive oil on day 17 of pregnancy and their offspring received 500 mg/kg of body weight in olive oil weekly from weaning for 120 weeks, congestion of lungs and kidneys and necrotic foci in liver parenchyma were seen in rats that died before 60 weeks. Rats dying after 80-90 weeks showed lesions of the forestomach (atrophy or local desquamation of epithelium, necrotic areas with inflammatory reactions of underlying tissues) and kidneys (hyperplasia of pelvis epithelium) (17).
In a study in which F344 rats were given styrene at 500, 1000, or 2000 mg/kg of body weight in corn oil, significantly increased mortality was seen in males at the highest dose level, probably due to hepatic necrosis. A dose-related growth depression in males was seen at all dose levels (18).

In a 2-year oral toxicity study, Charles River COBS CD (SD) rats received 0, 125, or 250 mg of styrene per litre of drinking-water. At 250 mg/litre, females showed a significantly lower terminal body weight than control females. No other treatment-related effects were seen. The parameters studied were clinical signs, mortality, growth, food and water intake, haemograms, clinical chemistry, urinalysis, gross necropsy, and histopathology. The NOAEL in this study was 125 mg/litre (corresponding to 7.7 mg/kg of body weight for males and 12 mg/kg of body weight for females) (19).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation reproductive study, Charles River COBS CD (SD) rats received 0, 125, or 250 mg of styrene per litre in drinking-water. No effect on reproductive parameters was observed (19). An oral teratogenicity study in rats did not reveal maternal toxicity, teratogenic effects, or embryotoxic effects at dose levels up to and including 300 mg/kg of body weight (20). In a study in which pregnant BDIV rats received styrene at 1350 mg/kg of body weight in olive oil on day 17 of pregnancy and their offspring received 500 mg/kg of body weight in olive oil weekly from weaning for 120 weeks, neonatal mortality in the test group was 10% compared with 2.5% in the control group (17).

Styrene was not teratogenic in studies on mice, rats, hamsters, and rabbits exposed by inhalation. Embryotoxic effects were seen at dose levels above 1050 mg/m³. Styrene-7,8-oxide caused embryotoxic but not teratogenic effects in rats and rabbits exposed to concentrations above 73.5 mg/m³ (5).

Mutagenicity and related end-points

Styrene is mutagenic in a variety of test systems but only with metabolic activation. It induces gene mutations in prokaryotic and eukaryotic microorganisms, *Drosophila*, and mammalian cells *in vitro*, as well as chromosomal abnormalities in mammalian cells *in vitro*. *In vivo* tests for chromosomal abnormalities gave contradictory results; positive results were observed mainly at high doses (3,5).

Styrene-7,8-oxide, the main reactive intermediate of styrene biotransformation, is a direct-acting mutagen that induces gene mutations in microorganisms, *Drosophila*, and mammalian cells *in vitro* as well as chromosomal abnormalities in mammalian cells *in vitro*. *In vivo* studies of chromosomal aberrations, DNA breaks, and sister chromatid exchange gave contradictory results (3,5).

Carcinogenicity

Oral carcinogenicity studies were carried out with two strains of mice already exposed *in utero*. In the first study, with O₂₀ mice, a significantly increased incidence of lung tumours (adenomas and adenocarcinomas) was observed in the test group. However, only one extremely high dose level (1350 mg/kg of body weight in olive oil) was used in this study, and dosing was terminated at 16 weeks of age because of high mortality. The experiment was terminated at 100 weeks when all animals had died (17). In the second study, with C57B1 mice, no significantly increased tumour incidences were observed in the test group. Only one dose level of 300 mg/kg of body weight was tested (17).

In an oral carcinogenicity study with B6C3F₁ mice, a significantly increased incidence of lung tumours (adenomas and carcinomas) was seen in males at the highest dose level only (300 mg/kg of body weight in corn oil). However, the control group was rather small (18).

In a study on *in utero* exposure, pregnant BDIV rats received styrene at 1350 mg/kg of body weight in olive oil on day 17 of pregnancy. Their offspring received 500 mg of styrene per kg of body weight in olive
oil weekly from weaning for 120 weeks. The incidence of tumours was not significantly increased (17). In a study with F344 rats dosed at 500, 1000, or 2000 mg/kg of body weight in corn oil, no significantly increased tumour incidences were observed (18). The same result was found both in a study, terminated after 140 weeks, in which Sprague-Dawley rats received 0, 50, or 250 mg of styrene per kg of body weight in olive oil, 4-5 days per week for 52 weeks (21), and in a study in which Charles River COBS CD (SD) rats received 0, 125, or 250 mg of styrene per litre in drinking-water (19).

In two long-term gavage studies in rats with styrene-7,8-oxide, significantly increased incidences of papillomas and carcinomas in the forestomach were observed. Dose levels were as high as 250 mg/kg of body weight (22,23).

14.15.6 Effects on humans

Short-term controlled studies in volunteers exposed by inhalation showed that styrene at concentrations above 210 mg/m$^3$ in air can cause irritation of the mucous membranes of the eyes, nose, and respiratory tract and depression of the central nervous system, as indicated by listlessness, drowsiness, incoordination, increased simple reaction times, and changes in visual evoked response and EEG amplitude (5,12).

In clinical studies in humans occupationally exposed for long periods, effects were generally observed at concentrations above 200 mg/m$^3$. Irritation of conjunctival and respiratory mucosa and prenarcotic symptoms were reported. Neurotoxicity involving the central as well as the peripheral nervous systems was seen in some cases. Effects were reported at dose levels of 100-200 mg/m$^3$. Some studies in workers suggested hepatotoxicity after long-term exposure to styrene, but no clear evidence for this effect could be found (3,5,12). In an extensive study in workers (24), 84 mg/m$^3$ caused only marginal effects. Because of the number of workers examined, the great number of parameters studied, and the absence of effects in other studies at concentrations below 100 mg/m$^3$, 84 mg/m$^3$ can be considered as the lowest observed marginal effect concentration in air for humans (5).

A few limited studies have reported on styrene-induced reproductive and teratogenic effects in occupationally exposed female workers. The results were contradictory, so that no definite conclusions could be drawn (3,5,12).

No chromosomal aberrations in peripheral lymphocytes could be detected in workers occupationally exposed to low concentrations of styrene, but significantly elevated frequencies of such chromosomal aberrations were observed in those occupationally exposed to much higher concentrations (5).

An association between the occurrence of leukaemia and lymphoma in humans and occupational exposure to styrene has been suggested. In the reinforced plastics industry, retrospective cohort mortality studies did not reveal any significantly increased mortality due to carcinogenicity. However, all the studies had serious defects, such as small or ill-defined cohorts and limited follow-up. In addition, mixed exposure to other compounds and/or past exposure to benzene had taken place (2,5,25).

14.15.7. Guideline value

On the basis of the available data, IARC classified styrene in Group 2B (25). It has been shown to be mutagenic in in vitro systems but only with metabolic activation. In vivo studies showed positive effects, but only at high doses. As the main metabolite, styrene-7,8-oxide, is a direct-acting mutagen, this compound is probably responsible for the positive effect of styrene after metabolic activation. Although carcinogenicity studies in mice and rats by various routes of administration did not provide evidence for the carcinogenicity of styrene, styrene-7,8-oxide was carcinogenic in long-term oral studies in rats. The available data therefore suggest that the carcinogenicity of styrene is due to the formation of the carcinogenic metabolite styrene-7,8-oxide as a consequence of the overloading of the detoxification mechanisms (e.g. glutathione conjugation and hydrolysis by epoxide hydrolase) after exposure to high
Based on the data given above, a TDI of 7.7 µg/kg of body weight can be derived from a NOAEL of 7.7 mg/kg of body weight per day for reduced body weight in the 2-year drinking-water study in rats (19), applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for carcinogenicity and genotoxicity of the reactive intermediate styrene-7,8-oxide). If 10% of the TDI is allocated to drinking-water, a guideline value of 20 µg/litre (rounded figure) can be calculated. It should be noted that the lowest observed odour threshold for styrene in water is also 20 µg/litre.

References


14. Polynuclear aromatic hydrocarbons

14.1 General description

Polynuclear aromatic hydrocarbons (PAHs) are a large group of substances with a molecular structure that includes two or more fused aromatic rings. Most of the available literature on PAHs is concerned with benzo[a]pyrene (BaP), on which this section will therefore be focused; information on other PAHs is included where appropriate.

Identity (1)

Benzo[a]pyrene (BaP)

CAS no.: 50-32-8
Molecular formula: C_{20}H_{12}
### Physicochemical properties

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### Major uses

PAHs have no industrial uses but are produced primarily as a result of the incomplete combustion of organic material (1). The principal natural sources are forest fires and volcanic eruptions (2), while anthropogenic sources include the incomplete combustion of fossil fuels, coke oven emissions, aluminium smelters, and vehicle exhausts (3, 4).

### Environmental fate

PAHs are microbially biodegraded in the surface layers of soil (5). Biodegradation is faster in the presence of oxygen (1); the rate also depends on redox conditions, nitrate levels, and the presence of organic soil constituents and chemicals toxic to the degrading microorganisms (5). Half-lives for microbial degradation range from 5 to 240 days (1).

Direct atmospheric input appears to be the major source of BaP in surface waters (6). In water, most PAHs are adsorbed onto sediments and suspended solids. Volatilization may be important over periods exceeding 1 month. Most PAHs are susceptible to aqueous photolysis under optimal conditions; they are biodegraded in water and taken up by aquatic organisms (1).

### 14.16.2 Analytical methods

Concentrations of BaP and other PAHs in water may be determined by gas chromatography in conjunction with mass spectrometry; the practical quantification limit is 0.01 µg/litre (Department of National Health and Welfare (Canada), unpublished data, 1988). High-pressure liquid chromatography with spectrofluorimetric detection (detection limit 0.1 ng/litre) can be used for the determination of BaP in drinking-water (7).

### 14.16.3 Environmental levels and human exposure

#### Air

Mean levels of BaP in air are generally less than 1 ng/m$^3$ (5, 8, 9), although levels as high as 37.3 ng/m$^3$ have been measured (10); the levels tend to be higher in winter than in summer (8, 9). The mean level of total PAHs in Canadian cities sampled from 1984 to 1986 was 100 ng/m$^3$ (8).

Concentrations of PAHs in indoor air are likely to vary considerably depending on indoor sources, such as woodstoves and tobacco smoke. Levels of BaP in indoor air in New Jersey ranged from 0.1 to 8.1 ng/m$^3$ (7).

#### Water

Water from 17 groundwater and 89 surface water systems was analysed for BaP, benzo[b]fluoranthene, and indeno [1, 2, 3-c,d] pyrene in 1976-77 in the USA; none of the systems sampled contained quantifiable levels of these PAHs (detection limits 0.03-0.1 µg/litre) (1).
The typical level of BaP in drinking-water in the USA is estimated to be 0.55 ng/litre (11). It was not detected (detection limit 1.0 µg/litre) in water from seven water-treatment plants in the area of Niagara Falls (12). The only PAH detected in treated drinking-water in Ontario (Canada) in surveys carried out in 1987 were benzo[k] fluoranthene (twice at 1 ng/litre), fluoranthene (20 and 30 ng/litre), and pyrene (twice at 40 ng/litre) (13). In 277 samples of municipal water supplies in the Atlantic provinces of Canada taken during 1985 and 1986, fluoranthene, benzo[b] fluoranthene, benzo[k] fluoranthene, BaP, indeno [1,2,3-c,d]pyrene, and benzo[g,h,i]perylene were detected in 58, 4, 1, 2, 0.4, and 0.7% of samples, respectively (detection limits 0.001-0.006 µg/litre; detected concentrations 0.001-0.024 µg/litre) (14-17).

Food

BaP may be present in foodstuffs as a result of the absorption and deposition of particulates during processing (e.g. of smoked foods and leafy vegetables), the pyrolysis of fats, and the incomplete combustion of charcoal (18-20). Typical concentrations in food products range from nondetectable (<0.01 µg/kg) to 44 µg/kg.

Estimated total exposure and relative contribution of drinking-water

Estimated daily intakes of total PAH in food range from 1.1 to 22.5 µg (11, 18); the corresponding figures for BaP range from 0.0014 to 1.6 µg (7, 11, 18, 21). Ranges for the estimated average daily intake of fluoranthene, benzo[k] fluoranthene, dibenzo[a,l]pyrene, 9,10-dimethylbenzanthracene, benzo[a]anthracene, benzo[b] fluoranthene, and dibenzo[a,h]anthracene in food by Canadians are 2.5-2.6, 0.026-0.030, 1.0-2.8, 0.046-0.12, 0.15-0.39, 0.082-0.12, and 0.061-0.10 µg/person, respectively (20, 22). Estimated daily intakes from water, food, and air are 20, 90-300, and 110 ng, respectively, for fluoranthene, and 0.4, 20-60, and 20 ng, respectively, for benzo[g,h,i]perylene (23, 24).

The mean total daily intake of BaP from air has been estimated to range from 0.025 µg/day (7) to 2.0 µg/day (1). The contribution of air to the daily intake is lower in rural areas than in urban areas (23, 24). Tobacco smoking is estimated to add a further 0.6 µg of BaP to daily intake (23, 24).

Daily intake of total PAHs from drinking-water is reported to be 0.027 µg (11). Daily intake of BaP in drinking-water is estimated to range from 0.1 to 1 ng (7, 11).

It would appear that food is the major and most variable source of daily exposure both to BaP and to PAHs in general; drinking-water makes only a minor contribution, probably no more than 1% of the total (1, 25).

14.16.4 Kinetics and metabolism in laboratory animals and humans

BaP is absorbed principally through the gastrointestinal tract and the lungs. Sprague-Dawley rats given BaP by duodenal infusion at 9.1-15.1 pmol/min absorbed approximately 40% of the dose from the duodenum (26). The rate of absorption of the different PAHs is influenced by their lipid solubilities (27) and by the content of polyunsaturated fatty acids in the diet (28). Absorbed BaP is rapidly distributed to the organs and tissues (29) and may be stored in mammary and adipose tissues (30). It crosses the placenta and is distributed in the developing fetus (31).

BaP is metabolized primarily in the liver, although significant metabolism can also occur in the tissues of the lung, gastrointestinal tract, placenta, skin, and kidney (32). It is metabolized in two steps, the first of which involves oxidation or hydroxylation via the cytochrome P-450-mediated mixed-function oxidase system, giving epoxides or phenols; the second step is detoxification of these metabolites to produce glucuronides, sulfates, or glutathione conjugates. Some of the epoxides may, however, be metabolized to dihydrodiols, which may undergo oxidation to diol-epoxides; these are thought to be responsible for carcino-genicity where this has been demonstrated. BaP metabolites are eliminated primarily in the
faeces; only small amounts are excreted in the urine as water-soluble conjugates (25).

14.16.5 Effects on laboratory animals and in vitro test systems

The health effect of primary concern is carcinogenicity; doses of at least an order of magnitude greater than those that result in neoplastic lesions are required to induce other effects.

Acute exposure

The oral LD$_{50}$s for various PAHs are reported to range between 490 and 18 000 mg/kg of body weight (33). Effects induced in animals following acute exposure include inflammation, hyperplasia, hyperkeratosis and ulceration of the skin, pneumonitis, damage to the haematopoietic and lymphoid systems, immunosuppression, adrenal necrosis, ovotoxicity, and antispermatic effects (11).

Short-term exposure

No treatment-related effects were observed in groups of CD-1 mice given anthracene by gavage at doses of 0, 250, 500, or 1000 mg/kg of body weight per day for at least 90 days. Male and female CD-1 mice given 0, 125, 250, or 500 mg of fluoranthene per kg of body weight per day for 13 weeks by gavage exhibited increased alanine aminotransferase levels, kidney and liver changes, and clinical and haematological changes at 250 mg/kg of body weight per day. In a study in which CD-1 mice were exposed to fluorene suspended in corn oil at 0, 125, 250, or 500 mg/kg of body weight per day by gavage for 13 weeks, a significant decrease in red blood cell count and packed cell volume was observed in females treated with 250 mg/kg of body weight per day and in males and females treated with 500 mg/kg of body weight per day; decreased haemoglobin concentrations and increased total serum bilirubin levels were also observed in the group given 500 mg/kg of body weight per day. Male and female CD-1 mice gavaged with pyrene in corn oil at 0, 75, 125, or 250 mg/kg of body weight per day for 13 weeks exhibited kidney effects (renal tubular pathology, decreased kidney weights) at 125 mg/kg of body weight per day (34).

Other reported effects after short-term exposure to various PAHs include: hepatic changes in rats dosed orally with 1 g of naphthalene per kg of body weight per day for 10 days; decreased spleen weight in females and lowered hepatic aryl hydrocarbon hydroxylase activity in both sexes at the highest dose in CD-1 mice given 5.3, 53, or 133 mg of naphthalene per kg of body weight per day for 90 days; loss of body weight and mild pathological changes in the liver and kidney in rats given oral doses of acenaphthene in olive oil at 2 g/kg of body weight per day for 32 days; and depression of body weight gain, elevated liver weight, and lowered spleen weight at the higher dose levels in rats fed diets containing 0.062-1.0% fluorene for 104 days (25).

Reproductive toxicity, embryotoxicity, and teratogenicity

In the offspring of pregnant CD-1 mice given oral doses of 0, 10, 40, or 160 mg of BaP per kg of body weight per day on days 7-16 of gestation, total sterility was noted in 97% of the two highest dose groups, whereas 20% of males and 34% of females exposed in utero to 10 mg/kg of body weight per day were infertile; fertility was reduced in the remaining animals in the lowest dose group (35).

Topical administration of BaP to pregnant mice on days 13 - 17 of gestation resulted in the appearance of a highly mutagenic dihydrodiol epoxide attached to the haemoglobin in the newborn (36). Transplacental carcinogenesis has been observed following subcutaneous administration of large doses (37). However, little BaP was transferred to the fetus following the oral administration to mice of a single dose of 12 mg/kg of body weight on days 11 - 18 of gestation (38).
Mutagenicity and related end-points

BaP was mutagenic in *Salmonella typhimurium* strain TA1538 after metabolic activation by a preparation of microsomal enzymes from a liver homogenate, fraction S9, obtained from rats (39); it has also induced mutations in cultured human lymphoblastoid cells (40). The diol-epoxide metabolites of BaP are considerably more mutagenic than the parent compound. Induction of sister chromatid exchanges in Chinese hamsters following intraperitoneal administration of BaP has been reported (41), and a correlation has been observed between sister chromatid exchange and the production of BaP metabolites in two variant mouse hepatoma cell lines (42).

Carcinogenicity

Many PAH-containing mixtures have been associated with an increased incidence of cancer, but the contribution of each of the individual components to the overall carcinogenic potency is difficult to assess (43). The relative carcinogenic potencies of various PAHs, based on bioassays by several routes of administration and related toxicological data, have been ranked in decreasing order as follows: dibenz[a,h]anthracene, BaP, anthanthrene, indeno[1,2,3-cd]pyrene, benzo[a]anthracene, benzo[b]fluoranthene, pyrene, benzo[k]fluoranthene, benzo[j]fluoranthene, cyclopentadieno[c,d]pyrene, benzo[g,h,i]perylene, chrysene, and benzo[e]pyrene (44). The Environmental Protection Agency in the USA has determined that acenaphthene, anthracene, fluoranthene, fluorene, and pyrene are not classifiable as to human carcinogenicity because of the absence of human data and the inadequacy of the data from animal bioassays (34).

BaP is one of the most potent PAH carcinogens; primary tumours have been produced, both at the site of administration and in other tissues, in mice, rats, hamsters, guinea-pigs, rabbits, ducks, and monkeys following intragastric, subcutaneous, dermal, or intratracheal administration. The target sites appear to be proliferating tissues such as the intestinal epithelia, bone marrow, lymphoid organs, and testes, which interact with the active metabolites of BaP (11). There appear to be interspecies differences in the formation of DNA adducts, as the binding of anti-BaP 7,8-dihydrodiol-9,10-epoxide to endometrial DNA has been determined to be greatest in humans, followed by hamsters, mice, and rats (45).

Groups of CFW mice of varying ages (23-73 per dose; number per sex not specified) were fed BaP in the diet at concentrations of 0.001, 0.01, 0.02, 0.03, 0.04, 0.045, 0.05, 0.10, or 0.25 mg/g of food for periods of 98-197 days. The control group consisted of 171 males and 289 females. There was a significant dose-related increase in stomach tumours, mostly squamous cell papillomas and some carcinomas, in the treated animals as compared with the controls. The incidence of gastric tumours was 0 in the controls, and 0, 0, 5, 0, 2.5, 10, 70, 82, and 90% in the treatment groups in order of increasing dietary concentration (46).

In an additional study conducted by the same authors, groups of 9-26 CFW mice were fed diets containing 0.25 mg of BaP per g for periods ranging from 1 to 30 days, then observed for up to 105 days. The incidence of gastric tumours in these groups was 0, 11, 10, 44, 30, and 100% for periods of administration of 1, 2, 4, 5, 7, and 30 days, respectively (46).

A total of 63 male CF1 mice given BaP by forced drinking (0.003% solution in 95% ethanol), 5 days per week for up to 22 months developed 11 oesophageal tumours (10 papillomas and one carcinoma) and 15 forestomach tumours (13 papillomas and two carcinomas), as compared with no oesophageal tumours and five forestomach tumours (all papillomas) in the 67 controls (47).

Groups of 160 female albino mice fed diets containing 4 mg of BaP per kg or 3 mg of 9,10-dimethylbenzantrachene per kg for 14 months had an incidence of gastric tumours of 8.1 and 28% and an incidence of mesenteric tumours of 0 and 69%, respectively (48).

14.16.6 Effects on humans
There have been few studies on the human health effects of PAHs. Human subjects skin-painted with BaP developed skin lesions (49, 50). Cases of accidental poisoning by naphthalene, resulting in death by acute haemolytic anaemia, have been reported (51).

14.16.7 Guideline value

Available toxicological data are sufficient to serve as a basis for the derivation of a guideline value only for BaP, one of the most potent carcinogens among the PAHs tested to date. IARC has classified BaP in Group 2A (probably carcinogenic to humans) (52). The guideline value is therefore derived on the basis of the lifetime cancer risk estimated by extrapolation of the tumour incidence data observed in the most appropriate carcinogenicity bioassay in animals.

The only study by the most appropriate route of administration (i.e. the oral route) in which there was an increase of stomach tumours associated with an increase in the ingested concentration of BaP was that in which CFW mice were fed BaP in the diet at concentrations of 0.001, 0.01, 0.02, 0.03, 0.04, 0.045, 0.05, 0.10, or 0.25 mg/g of food for periods ranging from 98 to 197 days (46). Because of the variable dosing patterns and age of the animals at sacrifice, data on tumour incidence from this study cannot be confidently extrapolated by means of the models currently employed in quantitative risk assessment (i.e. model-free or linearized multistage extrapolation, which was used in deriving the previous BaP guideline), as they assume constant exposure and sacrifice at the median point of the life span. However, the tumour incidence data have been extrapolated using the two-stage birth - death mutation model, which can incorporate the variable exposure and sacrifice patterns (53). With this model, the estimate of the upper bound on the low-dose risk was 0.46 (mg/kg of body weight per day)$^{-1}$ without correction for differences in body surface area, as BaP is an indirect-acting carcinogen, i.e. the carcinogenicity appears to be attributable to a metabolite rather than to BaP itself. The resulting estimated concentrations of BaP in drinking-water corresponding to excess lifetime cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$ for stomach tumours are 7, 0.7, and 0.07 µg/litre.

There are insufficient data available to derive drinking-water guidelines for other PAHs. However, the following recommendations are made for the PAH group:

- Because of the close association of PAHs with suspended solids, the application of treatment, when necessary, to achieve the recommended level of turbidity will ensure that PAH levels are reduced to a minimum.

- Contamination of water with PAHs should not occur during water treatment or distribution. Therefore, the use of coal-tar-based and similar materials for pipe linings and coatings on storage tanks should be discontinued. It is recognized that it may be impracticable to remove coal-tar linings from existing pipes. Research is needed on methods of minimizing the leaching of PAHs from such lining materials.

- To monitor PAH levels, the use of several specific compounds as indicators for the group as a whole is recommended. The choice of indicator compounds will vary for each individual situation. PAH levels should be monitored regularly in order to determine the background levels against which any changes can be assessed so that remedial action can be taken, if necessary.

- In situations where drinking-water is known to have been contaminated by PAHs, the specific compounds present and the source of the contamination should be identified, as the carcinogenic potential of PAH compounds varies.

References


34. US Environmental Protection Agency. *IRIS information on selected PAHs*. Cincinnati, OH, 1981.

35. Mackenzie KM, Angevine DM. Infertility in mice exposed *in utero* to benzo[a]pyrene. *Biology of


Risks to Humans, Suppl. 7).


14.17 Monochlorobenzene

### 14.17.1 General description

**Identity**

CAS no.: 108-90-7  
Molecular formula: C₆H₅Cl

**Physicochemical properties (1-3)†**

<table>
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<th>Value</th>
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<tr>
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<td>Vapour pressure</td>
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</tbody>
</table>

† Conversion factor in air: 1 ppm = 4.60 mg/m³

**Organoleptic properties**

Taste and odour thresholds of 10-20 µg/litre (4) and odour thresholds of 50, 40-120, and 100 µg/litre (2,5,6) have been reported for monochlorobenzene (MCB).

**Major uses**

MCB is used mainly as a solvent in pesticide formulations, as a degreasing agent, and as an intermediate in the synthesis of other halogenated organic compounds.

**Environmental fate**

The concentration of MCB released into water and onto land will decrease mainly because of volatilization into the atmosphere. In water, some biodegradation also occurs, proceeding more rapidly in fresh water than in estuarine and marine waters. The rate is also more rapid if there has been acclimatization of the degrading microorganisms. Some adsorption onto organic sediments occurs (3). MCB is relatively mobile in sandy soil and aquifer material and biodegrades slowly in these soils; it may therefore leach into groundwater (3). The octanol-water partition coefficient suggests that little or no bioconcentration of MCB will occur in aquatic species.

14.17.2 Analytical methods

A standard method for chlorobenzenes involves extraction with hexane followed by capillary column gas-liquid chromatography with electron-capture detection. The method is capable of achieving detection limits in tapwater and river water of about 0.1 µg/litre (7).
14.17.3 Environmental levels and human exposure

**Air**

Because MCB is volatile and is used extensively as a solvent, large quantities are released to air. However, atmospheric concentrations are usually very low, often much less than 4.6 µg/m³ (3, 8).

**Water**

MCB has been detected in wastewaters, surface and groundwaters, and drinking-water. In some Canadian potable water sources, mean concentrations were less than 1 µg/litre; the maximum value recorded was 5 µg/litre (9).

**Food**

Chlorobenzene has been found in edible freshwater and marine organisms, although levels are not significant. Human milk may be a source of exposure for infants; MCB was detected in five out of eight samples of human milk in a study in the USA (10).

*Estimated total exposure and relative contribution of drinking-water*

Despite the low levels of MCB in air, inhalation is probably the major route of environmental exposure.

14.17.4 Kinetics and metabolism in laboratory animals and humans

MCB appears to be readily absorbed via the oral and inhalation routes and accumulates mainly in fatty tissue (11,12). The major metabolites of MCB in mammals are \(p\)-chlorophenol mercapturic acid, 4-chlorocatechol, and \(p\)-chlorophenol. In humans, the main metabolite is 4-chlorocatechol (13). The major route of MCB excretion is the urine; little is excreted in the faeces or retained in the body.

14.17.5 Effects on laboratory animals and *in vitro* test systems

**Acute exposure**

MCB is of low acute toxicity to experimental animals via the oral and inhalation routes. Oral LD₅₀s in the grams per kilogram range have been reported for rodents. Major target organs of acute exposure are the liver and kidneys.

**Short-term exposure**

In a 13-week study, groups of 10 Fischer 344 rats and 10 B6C3F₁ hybrid mice of each sex received MCB in corn oil at 0, 60, 125, 250, 500, or 750 mg/kg of body weight by gavage, for 5 days per week. Effects were seen mainly in the liver, kidney, and haematopoietic system. A NOAEL of 125 mg/kg of body weight was identified in the study. The LOAEL was 250 mg/kg of body weight, which caused a slight decrease in spleen weight and lymphoid or myeloid depletion of the thymus, spleen, or bone marrow (14,15).

**Long-term exposure**

In a 2-year study, groups of 50 Fischer 344 rats and 50 B6C3F₁ mice of each sex received MCB in corn oil by gavage, 5 days per week for 103 weeks. The doses administered were 0, 60, or 120 mg/kg of body weight for female mice and rats of both sexes, and 0, 30, or 60 mg/kg of body weight for male mice. No evidence of MCB-related toxicity was reported. Although survival was reduced in male rats at 120 mg/kg of body weight and slightly reduced in male mice at 30 and 60 mg/kg of body weight, this was not thought to be compound-related, as body weight gains were unaffected and MCB-induced toxic lesions related to
death were not observed. A NOAEL of 60 mg/kg of body weight was therefore identified for male mice and one of 120 mg/kg of body weight for female mice and male and female rats (14,15).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Exposure of Fischer 344 rats and New Zealand white rabbits to 0, 75, 210, or 590 ppm MCB (0, 345, 966 or 2714 mg/m$^3$) via inhalation for 6 h per day during the major period of organogenesis did not cause embryotoxicity or teratogenicity in the rats (16). Fetal effects in rats were limited to slight delays in skeletal development, which occurred only at concentrations causing maternal toxicity (2714 mg/m$^3$). In rabbits, fetuses exhibited a low incidence of visceral malformations that were not dose-related. In a two-generation inhalation study, exposure levels of 50, 150, and 450 ppm (230, 690, and 2070 mg/m$^3$) did not have any adverse effects on reproductive performance or fertility in male and female rats (17).

**Mutagenicity and related end-points**

MCB was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without activation with rat or hamster liver S9 enzymes (18). In one study, the intraperitoneal injection of MCB in corn oil (up to 70% of the LD$_{50}$) to groups of five mice led to a dose-related increase in the formation of micronucleated polychromatic erythrocytes. The authors considered that the effects were due to the clastogenic activity of MCB (19). However, similar results have not been reported by other workers (20). MCB appears to bind covalently to DNA in liver, kidney, and lung of rats and mice following intraperitoneal injection (21), but the level of binding was considered to be low (20).

**Carcinogenicity**

In the 2-year study in which groups of 50 Fischer 344 rats and 50 B6C3F1 mice of each sex received MCB in corn oil by gavage, 5 days per week for 103 weeks, doses of 60 or 120 mg/kg of body weight caused slight (statistically significant at 120 mg/kg of body weight) increases in the frequency of neoplastic nodules of the liver in male rats (14,15). Increased incidences of hepatocellular carcinomas were not observed in male or female rats. No increased tumour incidences were observed in female rats or in male or female mice. Rare tumours observed in three exposed animals were not statistically significant; they included one renal tubular-cell adenocarcinoma in a high-dose (120 mg/kg of body weight) female rat and transitional cell papillomas of the bladder in two male rats, one in the low-dose group (60 mg/kg of body weight) and one in the high-dose group (120 mg/kg of body weight). The frequency of pituitary tumours was reduced in rats receiving MCB; the significance of this finding is not known. The study provided some not altogether convincing evidence of carcinogenicity in male Fischer 344 rats, but none in female Fischer 344 rats or in male or female B6C3F1 mice (14,15,20).

14.17.6 Effects on humans

MCB is toxic to humans; poisoning and occupational exposure caused central nervous system disturbances. In addition, subjects occupationally exposed to MCB for 2 years suffered from headaches, dizziness, and sleepiness (22).

14.17.7 Guideline value

Although there was a weak dose-related increase in neoplastic liver nodules in male rats, the weight of evidence suggests that MCB is not genotoxic; a TDI approach can therefore be adopted.

Based on the 2-year study with rats and mice in which a NOAEL of 60 mg/kg of body weight for neoplastic nodules was identified (14,15), a TDI of 85.7 µg/kg of body weight can be calculated by applying an uncertainty factor of 500 (100 for inter- and intraspecies variation and 5 for the limited evidence of carcinogenicity) to the NOAEL and allowing for dosing 5 days per week. This gives a guideline value of 300 µg/litre (rounded figure), based on an allocation of 10% of the TDI to drinking-water. However, this
value far exceeds the lowest reported taste and odour threshold in water of 10 µg/litre.

References


### 14.18 Dichlorobenzenes

#### 14.18.1 General description

**Identity**

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**Physicochemical properties (1-3)**

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* Conversion factor in air: 1 ppm = 6.01 mg/m³.

**Organoleptic properties**

The organoleptic thresholds for all three isomers are low. Odour thresholds of 2-10, 20, and 0.3-30 µg/litre have been reported for 1,2-DCB, 1,3-DCB, and 1,4-DCB, respectively (4,5). Taste thresholds of 1 and 6 µg/litre have been reported for 1,2-DCB and 1,4-DCB, respectively (4,6).

**Major uses**

The DCBs are widely used in industry and in domestic products such as odour-masking agents, dyestuffs, and pesticides. 1,2-DCB and 1,4-DCB are the most widely used (7).
Environmental fate

The DCBs are expected to be adsorbed moderately to tightly onto soils of high organic content and are not expected to leach appreciably into groundwater. In soils, they are biodegraded slowly under aerobic conditions; volatilization may be important in surface soils. In water, the major DCB-removal processes are likely to be adsorption onto sediments and bioaccumulation in aquatic organisms. Evaporation from surface water may also be important, but not aquatic hydrolysis, oxidation, or direct photolysis. DCBs may biodegrade in aerobic water after microbial adaptation. However, they are not expected to biodegrade under the anaerobic conditions that may exist in lake sediments or various groundwaters (2).

14.18.2 Analytical methods

A standard method for chlorobenzenes involves extraction with hexane followed by capillary-column gas-liquid chromatography with electron-capture detection (detection limit in tapwater and river water approximately 0.01 µg/litre) (8).

14.18.3 Environmental levels and human exposure

Air

The DCBs have been detected in the atmosphere at extremely low levels. In the USA, mean 1,2-DCB concentrations of 1.2, 0.3 and 0.01 µg/m³ have been measured in industrial, urban, and rural locations, respectively; the overall mean concentration was 0.54 µg/m³. Similarly, mean 1,3-DCB concentrations of 0.9, 0.5 and 0.04 µg/m³ have been reported for the same three locations, respectively; the overall mean concentration was 0.57 µg/m³. Mean 1,2-DCB and 1,4-DCB concentrations of 0.06-0.18 µg/m³ and 0.24-0.42 µg/m³ were detected in the ambient air of three New Jersey (USA) cities in 1981 (2).

Water

DCBs have been detected in wastewater, raw water, surface water, and drinking-water (2). Although all have been detected in drinking-water, 1,4-DCB is generally present in the greatest concentration. DCBs have been found in potable water sources before treatment at levels as high as 10 µg/litre and in drinking-water at 0.01-3 µg/litre (7). In a survey of the water supplies of three Canadian cities, total mean DCB concentrations ranged from 1.0 to 13 ng/litre, most of which was 1,4-DCB (9). In a study in the USA on the contamination of 685 groundwaters, 1,2-DCB, 1,3-DCB, and 1,4-DCB were detected in 20, 19, and 19 samples at maximum concentrations of 6800, 236, and 996 µg/litre, respectively (2).

Food

DCBs tend to accumulate in biological materials rich in lipids, such as fatty tissue and milk. Mean levels of 1,2-DCB, 1,3-DCB, and 1,4-DCB of 2.6, 0.14, and 5.5 µg/kg, respectively, have been measured in milk (2,10). Fish have also been shown to be a major source of DCBs; mean levels were 1, 0.3-3, and 1-4 µg/kg for 1,2-DCB, 1,3-DCB, and 1,4-DCB, respectively (2).

Estimated total exposure and relative contribution of drinking-water

General population exposure may occur through the inhalation of contaminated air, especially in areas where DCBs are manufactured, and from the ingestion of contaminated drinking-water and food, particularly contaminated fish.

14.18.4 Kinetics and metabolism in laboratory animals and humans

DCBs are almost completely absorbed from the gastrointestinal tract. Once absorbed, they are rapidly distributed, primarily to fat or adipose tissue because of their lipophilicity and to kidney, liver, and lungs.
They are metabolized mainly by oxidation in the liver to the respective dichlorophenols and their glucuronide and sulfate conjugates, although other minor metabolites have been detected. The metabolites are excreted mainly via the kidneys, and excretion is relatively slow. In rats, almost 100% of an oral dose of 1,4-DCB was excreted within 5 days, mostly in the urine (7).

14.18.5 Effects on laboratory animals and in vitro test systems

Acute exposure

The DCBs are of low acute oral toxicity in experimental animals. Oral LD_{50}s in rodents range from 500 to 3863 mg/kg of body weight. The major target organs are the liver and kidneys (7).

Short-term exposure

F344/N rats and B6C3F1 mice were given 1,2-DCB in corn oil at 0, 30, 60, 125, 250, or 500 mg/kg of body weight per day by gavage 5 days per week for 13 weeks. Decreased survival in male and female mice and female rats was seen at the highest dose level. Liver necrosis, hepatocellular degeneration, and depletion of lymphocytes were seen in the thymus and spleen of both sexes of rats and mice. At 250 mg/kg of body weight, necrosis of individual hepatocytes was observed in both sexes of rats and in male mice. Minimal hepatocellular necrosis was observed in a few rats at 125 mg/kg of body weight, but no hepatic alterations were observed in mice at this dose. A NOAEL of 125 mg/kg of body weight per day was identified (7).

Long-term exposure

In a 2-year gavage study, B6C3F1 female and male mice were given 0, 60, or 120 mg of 1,2-DCB per kg of body weight per day by gavage in corn oil, 5 days per week. The only evidence of toxicity was a dose-related trend towards tubular regeneration of the kidney in male mice, the incidence of which increased at the highest dose level. Otherwise, there was no evidence of non-neoplastic toxicity. NOAELs of 60 and 120 mg/kg of body weight were identified for male and female mice, respectively (7).

1,4-DCB was administered by gavage for 2 years, 5 days per week, to male and female Fischer 344 rats at dose levels of 0, 150, or 300, and 0, 300, or 600 mg/kg of body weight in corn oil. In males, reduced survival and body weight gain were observed at 300 mg/kg of body weight. Increased severity of nephropathy and hyperplasia of the parathyroid were observed at 150 mg/kg of body weight in males. In females, there was a dose-related increase in nephropathy at or above 300 mg/kg of body weight. LOAELs of 150 and 300 mg/kg of body weight per day were identified for male and female rats, respectively (7).

Reproductive toxicity, embryotoxicity, and teratogenicity

All three isomers were reported to be non-teratogenic when Sprague-Dawley rats were given oral doses of 50, 100, or 200 mg/kg of body weight per day on days 6-15 of gestation (11). In another study, CD rats were given 1,4-DCB by gavage at doses of 0, 250, 500, 750, or 1000 mg/kg of body weight per day on days 6-15 of gestation. Reduction of fetal weight was seen at the highest dose, and an increase in skeletal variations was observed at or above 750 mg/kg of body weight per day. A dose-related increase in extra ribs was observed at doses at or above 500 mg/kg of body weight per day. A LOAEL and a NOAEL of 500 and 250 mg/kg of body weight per day were identified, respectively (7).

Mutagenicity and related end-points

All three isomers were non-mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537, both in the presence and in the absence of metabolic activation. A number of other in vitro tests, such as those for the induction of chromosomal aberrations in Chinese hamster ovary cells, forward mutations in mouse lymphoma cells, and unscheduled DNA synthesis in human lymphocytes, have also
given negative results for 1,4-DCB. In all but one study, 1,4-DCB has not produced chromosome damage in bone marrow of mice when administered in vivo. Negative results have also been obtained for this isomer in an assay of DNA damage in liver of mice following oral exposure. Low-level covalent binding of 1,4-DCB to the liver, kidneys, and lungs of mice has been reported (7).

**Carcinogenicity**

In the 2-year gavage study in which B6C3F1 female and male mice were given 0, 60, or 120 mg of 1,2-DCB per kg of body weight in corn oil, 5 days per week, there was a dose-related trend in the incidence of malignant histiocytic lymphomas in both sexes; however, the authors concluded that there was no evidence for the carcinogenicity of 1,2-DCB in this study (7).

In the study in which 1,4-DCB was administered by gavage for 2 years, 5 days per week, to male and female Fischer 344 rats at dose levels of 0, 150, or 300, and 0, 300, or 600 mg/kg of body weight in corn oil, respectively, a dose-related increase in the incidence of tubular-cell adenocarcinomas of the kidney was observed in males only. A marginal increase in the incidence of mononuclear cell leukaemia was also noted in males when compared with the controls. It was concluded that the induction of kidney tumours in male rats was a species- and sex-specific response, probably a result of hyaline droplet formation. In the same study, 1,4-DCB increased the incidences of hepatocellular adenomas and carcinomas in mice dosed at 600 but not at 300 mg/kg of body weight (7).

**14.18.6 Effects on humans**

Data on the health effects of exposure to DCBs are restricted to case reports of accidental exposure to or misuse of DCB products. Reported acute effects following short-term exposure (all of which are reversible) include acute haemolytic anaemia, respiratory irritation, glomerulonephritis, and allergic response of the skin. Prolonged exposure to 1,4-DCB has caused granulomatosis, anaemia, disturbances of the reticuloendothelial system, central nervous system effects, and liver damage. In workers exposed to 1,4-DCB, probably in combination with other chemicals, there have been case reports of haematological disorders, including anaemia, splenomegaly, and gastrointestinal and central nervous system effects. Two cases of acute myeloblastic anaemia were reported in females exposed mainly to 1,2-DCB over 1 year (7).

**14.18.7 Guideline values**

**1,2-Dichlorobenzene**

IARC has placed 1,2-DCB in Group 3 (12). This isomer is of low acute toxicity by the oral route of exposure. Oral exposure to high doses affects mainly the liver and kidneys. The balance of evidence suggests that 1,2-DCB is not genotoxic, and there is no evidence for its carcinogenicity in rodents. Using the NOAEL of 60 mg/kg of body weight per day for tubular degeneration of the kidney, identified in a 2-year mouse gavage study with administration 5 days per week (7), and applying an uncertainty factor of 100 (for inter- and intraspecies variation), a TDI of 429 µg/kg of body weight can be calculated. An allocation of 10% of the TDI to drinking-water gives a guideline value of 1000 µg/litre (rounded figure). This value far exceeds the lowest reported taste threshold in water of 1 µg/litre.

**1,3-Dichlorobenzene**

There are insufficient toxicological data on this compound to permit a guideline value to be proposed, but it should be noted that it is rarely found in drinking-water.

**1,4-Dichlorobenzene**

1,4-DCB is of low acute toxicity, but there is evidence that it increases the incidence of renal tumours in
rats and hepatocellular adenomas and carcinomas in mice after long-term exposure. IARC has placed it in Group 2B (12).

1,4-DCB is not considered to be genotoxic, and the relevance for humans of the tumours observed in animals is doubtful. It is therefore valid to calculate a guideline value using the TDI approach. A TDI of 107 µg/kg of body weight has been calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the use of a LOAEL instead of a NOAEL and because the toxic end-point is carcinogenicity) to a LOAEL of 150 mg/kg of body weight per day for kidney effects observed in a 2-year rat gavage study (administration 5 days per week) (7). A guideline value of 300 µg/litre (rounded figure) is proposed, based on an allocation of 10% of the TDI to drinking-water. This value far exceeds the lowest reported odour threshold in water of 0.3 µg/litre.

References


14.19 Trichlorobenzenes

14.19.1 General description

Identity

<table>
<thead>
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<th>Molecular formula</th>
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<td>1,2,4-Trichlorobenzene</td>
<td>120-82-1</td>
<td>C₆H₃Cl₃</td>
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<tr>
<td>1,3,5-Trichlorobenzene</td>
<td>108-70-3</td>
<td>C₆H₃Cl₃</td>
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Physicochemical properties (1-4)

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<tr>
<td>Log octanol-water partition coefficient</td>
<td>4.04</td>
<td>4.02</td>
<td>4.49</td>
</tr>
<tr>
<td>Vapour pressure at 25 °C (kPa)</td>
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<td>0.04</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Organoleptic properties

Odour thresholds of 10, 5-30, and 50 µg/litre have been reported for 1,2,3-TCB, 1,2,4-TCB, and 1,3,5-TCB, respectively (5,6). A taste and odour threshold concentration of 30 µg/litre has been reported for 1,2,4-TCB (7).

Major uses

1,2,4-TCB is economically the most important isomer. Industrial-grade TCB, which consists of 93-98% 1,2,4-TCB and the remainder 1,2,3-TCB, is used as an intermediate in chemical synthesis, a solvent, a coolant, a lubricant, and a heat-transfer medium; it is also used in polyester dyeing, in termite-control preparations, and as an insecticide (8).

Environmental fate

The TCBs are expected to be adsorbed onto soils of high organic content, but not to leach appreciably into groundwater. They are not hydrolysed and are unlikely to biodegrade significantly. Some evaporation may occur from soil surfaces. In water, TCBs are likely to be adsorbed onto sediments and to bioconcentrate in aquatic organisms. Evaporation from water may be a significant removal process (3).

14.19.2 Analytical methods

A standard method for chlorobenzenes involves extraction with hexane followed by capillary column gasBliquid chromatography with electron-capture detection. Detection limits in tapwater and river water are about 0.1 µg/litre for TCBs (9).

14.19.3 Environmental levels and human exposure

Air

Levels are likely to be significant only in areas where TCBs are produced. Mean levels of 22-51 ng/m³ have been reported for three sites in California (10). An average of 181 ng/m³ was reported in areas where they are produced in the USA (3).
Water

TCBs have been detected in wastewater, surface and groundwater, and drinking-water (3). In a Canadian river, levels of 2, 7, and 2 µg/litre were reported for 1,2,3-TCB, 1,2,4-TCB, and 1,3,5-TCB, respectively (11). Tapwater concentrations were reported in the same study, the highest being for 1,2,4-TCB, for which the mean reported level was 2 ng/litre. The maximum value for all isomers found in a groundwater survey in the Netherlands was 1.2 µg/litre (12).

Food

TCBs tend to accumulate in biological materials rich in lipids, such as fatty tissue and milk; residues at levels of 0.1-4 mg/kg on a fat basis were found in the liver of cod from areas polluted by industrial effluents (13). Mean levels reported in human milk were 1, 1, and 5 µg/kg for 1,3,5-TCB, 1,2,4-TCB, and 1,2,3-TCB, respectively (14).

Estimated total exposure and relative contribution of drinking-water

General population exposure will occur mainly through the inhalation of contaminated air in areas where TCBs are manufactured and from the ingestion of contaminated food, especially fish.

14.19.4 Kinetics and metabolism in laboratory animals and humans

All three TCB isomers were readily absorbed following oral administration in rats. High concentrations of the parent compound were found in fat, skin, and liver, whereas high levels of metabolites were found in kidney and muscle (15). The major metabolic products are trichlorophenols (16). Species differences appear to exist in the metabolism of TCBs. Rats and rhesus monkeys given 1,2,4-TCB orally and intravenously excreted different urinary metabolites. Excretion was more rapid in rats than in monkeys; after 24 h, rats had excreted 84% of the oral dose in the urine and 11% in the faeces, as compared with 40% and <1%, respectively, in monkeys (17). There is also evidence that the TCBs are broad inducers of metabolizing enzymes (16).

14.19.5 Effects on laboratory animals and in vitro test systems

Acute exposure

TCBs are of low to moderate acute toxicity. Oral LD₅₀s in rodents range from 300 to 800 mg/kg of body weight. Major target organs of acute exposure are the liver and kidneys (16).

Short-term exposure

In a 13-week study, weanling Sprague-Dawley rats were fed diets containing TCB isomers at 1, 10, 100, or 1000 mg/kg. All three isomers at 1000 mg/kg caused increased relative liver and kidney weights and histological changes in the liver and thyroid of male rats. Males fed 1000 mg of 1,2,3-TCB per kg showed reduced weight gain; no other clinical signs of toxicity were observed. Only 1,2,4-TCB at 1000 mg/kg caused increases in hepatic aminopyrine methyl transferase and aniline hydroxylase activities in males and aminopyrine methyl transferase in females. The serum biochemical and haematological parameters measured were not affected. Only 1,3,5-TCB elicited moderate renal changes in male rats at 1000 mg/kg. Microscopic changes in females were milder than those in males. NOAELs were 100 mg/kg for all three isomers, equal to 7.8 mg/kg of body weight per day (1,2,4-TCB), 7.7 mg/kg of body weight per day (1,2,3-TCB), or 7.6 mg/kg of body weight per day (1,3,5-TCB) (18).

Long-term exposure

Relevant chronic studies via the oral route have not been carried out. In a 2-year dermal study, S1c:ddy
mice administered 0.03 ml of a 30% or 60% solution of 1,2,4-TCB twice a week showed signs of clinical toxicity, decreased survival, and keratinization of the epidermis (19). The main causes of death were respiratory infection, amyloidosis, and tumours.

**Reproductive toxicity, embryotoxicity, and teratogenicity**

No evidence of teratogenic effects was reported when Sprague-Dawley rats were given oral doses of 75, 150, or 300 mg/kg of body weight per day of 1,2,4-TCB or 150, 300, or 600 mg/kg of body weight per day of 1,2,3-TCB and 1,3,5-TCB on days 6-15 of gestation (20). Rats exposed to 0, 25, 100, or 400 mg/litre of 1,2,4-TCB in their drinking-water from the birth of the F0 generation to the weaning of the F2 generation did not show any effects on fertility (21).

**Mutagenicity and related end-points**

None of the isomers of TCB was mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with or without metabolic activation (22,23). All three caused dose-related increases in the formation of micronucleated polychromatic erythrocytes in mice injected with TCBs in corn oil at doses up to 70% of the LD50 (24). It was considered that the effects were due to the clastogenic activity of the TCBs; however, these results have not been confirmed by other workers (16).

**Carcinogenicity**

Relevant carcinogenicity studies via the oral route have not been carried out. In the 2-year dermal study in which S1c:ddy mice were given 0.03 ml of a 30% or 60% solution of 1,2,4-TCB twice a week (19), tumours occurred in both experimental and control groups, suggesting that they were spontaneous in origin and not due to the carcinogenic effects of this compound.

**14.19.6 Effects on humans**

TCBs are moderately toxic when ingested or inhaled. They produce irritation of the skin, eyes, and respiratory tract (8). There has been one report of aplastic anaemia in a woman chronically exposed to 1,2,4-TCB from washing work clothes (25).

**14.19.7 Guideline value**

The TCBs are of moderate acute toxicity. After short-term oral exposure, all three isomers show similar toxic effects, predominantly on the liver. Long-term toxicity and carcinogenicity studies via the oral route have not been carried out, but the data available suggest that all three isomers are non-genotoxic.

A TDI of 7.7 µg/kg of body weight was calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the short duration of the study) to the NOAEL of 7.7 mg/kg of body weight per day for liver toxicity identified in a 13-week rat study (18). The guideline value would be 20 µg/litre (rounded figure) for each isomer based on an allocation of 10% of the TDI to drinking-water; however, because of the similarity in the toxicity of the TCB isomers, the guideline value of 20 µg/litre is proposed for total TCBs. This value exceeds the lowest reported odour threshold in water of 5 µg/litre.

**References**


14.20 Di(2-ethylhexyl)adipate

14.20.1 General description

**Identity**

CAS no.: 103-23-1  
Molecular formula: C_{22}H_{42}O_{4}

This compound is also known as DEHA, bis(2-ethylhexyl)adipate (BEHA), and dioctyl adipate (DOA).

**Physicochemical properties (1-3)**

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</thead>
<tbody>
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</tbody>
</table>

**Major uses**

DEHA is used mainly as a plasticizer for synthetic resins such as polyvinyl chloride (PVC), but significant amounts are also used as a lubricant and for hydraulic fluids (1).

**Environmental fate**

Model experiments with activated sewage sludge systems have demonstrated the essentially complete biodegradation, measured as carbon dioxide evolution, of relatively high concentrations of DEHA in 35 days (3,4). Because of its low water solubility, DEHA released into the environment would be expected to partition to solids (biota, sediment, soil). Under ideal equilibrium conditions, it would partition mainly to the atmosphere and to terrestrial soil, and less than 1% of environmental DEHA would be found in the aquatic environment (3).
14.20.2 Analytical methods

DEHA in tapwater and surface water has been determined by gas chromatography with flame ionization detection or identification by mass spectrometry. In surface water, the detection limit is stated to be 0.2 µg/litre (3), although lower levels have been reported for both surface water (5) and drinking-water (6).

14.20.3 Environmental levels and human exposure

Water

DEHA was found at microgram per litre levels in two out of five samples of finished water from a waste-treatment plant in the USA (6). A survey of 23 major rivers and lakes in the USA showed that 7% of the samples contained DEHA at levels ranging from 0.25 to 1.0 µg/litre (3). Water samples from the Great Lakes contained a maximum level of 7.0 µg/litre (5). In Europe, DEHA has been identified as a trace-level contaminant of the Rhine (7). Finished drinking-water in five cities in the USA had levels of about 0.001-0.1 µg/litre (6,8,9).

Food

Food is the major source of exposure of the general population to DEHA because of its migration, particularly to fatty foods such as cheese and meat, from PVC films used for food packaging that have been plasticized with it. The estimated daily intake of DEHA through the diet in the United Kingdom is 16 mg (10); in the USA, it has been estimated to be as high as 20 mg (US Food and Drug Administration, personal communication, 1981).

Estimated total exposure and relative contribution of drinking-water

Air and drinking-water are insignificant sources of human exposure to DEHA compared with the intake via food.

14.20.4 Kinetics and metabolism in laboratory animals and humans

DEHA appears to be readily absorbed when given orally to rats and mice. It is widely distributed in the body; the highest levels have been reported in adipose tissue, liver, and kidney (11,12). Transplacental transport of DEHA has been noted (12).

DEHA is initially hydrolysed to mono(2-ethylhexyl)adipate (MEHA), adipic acid, and 2-ethylhexanol, which are excreted as such or further oxidized to several different compounds before being eliminated in the expired air, urine, and faeces of experimental animals. Major metabolites of DEHA are MEHA and its glucuronide (monkey), the glucuronide of 2-ethylhexanoic acid (mouse, rat), and adipic acid (mouse, rat). Single oral doses of DEHA seem to be completely excreted by rats, mice, and monkeys in 48 h (11,13).

14.20.5 Effects on laboratory animals and in vitro test systems

Acute exposure

The acute oral toxicity of DEHA is low. The oral LD$_{50}$ has been estimated to be 45 g/kg of body weight in male rats, 25 g/kg of body weight in female rats, 15 g/kg of body weight in male mice, and 25 g/kg of body weight in female mice (14).

Short-term exposure

Short-term (3-4 weeks) mouse and rat toxicity studies have demonstrated that high dietary levels of DEHA
(≥6000 mg/kg) induce liver toxicity, including increased liver weights, histopathological liver changes, and proliferation of liver peroxisomes, accompanied by increased activities of catalase and of enzymes involved in the oxidation of fatty acids as well as hypolipidaemia. DEHA-induced peroxisomal proliferation with accompanying biochemical events was found to be a dose-dependent phenomenon. A NOAEL of 100 mg/kg of body weight per day can be identified from these studies (15-17).

A 13-week toxicity study was conducted in F344 rats and B6C3F₁ mice at dietary concentrations of up to 25 000 mg of DEHA per kg. At 25 000 mg/kg, decreased weight gain was observed in both species and sexes. At 12 500 mg/kg, male and female rats as well as male mice showed slightly reduced body weight gain. At 6300 mg/kg, body weight gain was decreased in female mice and male rats. No compound-related increased mortality, histopathological changes, or reduction in feed consumption were observed (14).

**Long-term exposure**

In a 103-week study in which DEHA was administered to F344 rats and B6C3F₁ mice at dietary levels of 12 000 or 25 000 mg/kg, no dose-related effect on longevity was seen. A dose-related depression of growth rate was observed in mice. Except in the liver, where tumours developed, no histopathological changes were observed in the mouse. Growth rate was depressed in rats fed 25 000 mg of DEHA per kg. No DEHA-related histopathological changes were seen in rats (14).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

A fertility study was performed in which male and female Wistar rats were fed DEHA in the diet from 10 weeks before mating up to 36 days postpartum at levels of 300, 1800, or 12 000 mg/kg. At 12 000 mg/kg of diet, body weight gain was marginally reduced in females, and liver weights of both male and female parental animals were significantly increased. There were no effects on male or female fertility or on gestation length. At the highest dose level, total litter weights, body weight gain of pups, and mean litter size were reduced. No effect on pup survival was found at any treatment level. No treatment-related macroscopic abnormalities were found in the pups (18).

In a teratogenicity study, pregnant Wistar rats were fed DEHA in the diet at levels of 300, 1800, or 12 000 mg/kg, corresponding to daily doses of 28, 170, or 1080 mg/kg of body weight, on days 1-22 of gestation. Administration of 12 000 mg/kg resulted in slight maternal toxicity, expressed as a small reduction in body weight gain. There were no effects at any dietary level on fetal weight, litter weight, or number of intrauterine deaths. At the highest dose level, a small increase in pre-implantation loss as well as a minimal increase in post-implantation loss were noted. Incidences of major or minor external or visceral effects were low and were not increased by treatment with DEHA. However, two visceral variants (dilated and kinked ureter) were observed in increasing incidences in a dose-related manner at the two highest dose levels. Minor skeletal defects, indicating slightly poorer ossification, were also increased in a dose-related manner at the two highest dietary DEHA levels. No fetal effects were noted at 300 mg of DEHA per kg of diet. A NOAEL of 28 mg/kg of body weight can be identified from this study (19).

**Mutagenicity and related end-points**

A large number of short-term tests have failed to demonstrate any mutagenic activity of DEHA (20-23). One *in vitro* test with Chinese hamster ovary cells demonstrated some capacity to induce chromosomal aberrations in the absence of activation by a rat liver homogenate (S9 fraction). Studies of sister chromatid exchange in the same *in vitro* system were negative without activation and equivocal with it (24). Orally administered DEHA does not bind covalently to mouse liver DNA (25).

**Carcinogenicity**

In a 103-week carcinogenicity study, DEHA was administered to F344 rats and B6C3F₁ mice in the diet at
levels of 12 000 or 25 000 mg/kg, equivalent to a daily intake of 600 or 1250 mg/kg of body weight in rats and 1715 or 3570 mg/kg of body weight in mice. No increased tumour incidences were noted in rats. An increased number of hepatocellular carcinomas was found in female mice at both doses. Hepatocellular adenomas and carcinomas combined occurred in high-dose mice of both sexes and in low-dose female mice at incidences that were dose-related and significantly higher than those in control mice. The association of liver tumours in male mice with the administration of DEHA was not considered to be conclusive because the increased number of liver tumours in males reflected only an increase in adenomas in the high-dose group and because the time to observation of tumours was not significantly different in dosed and control males (14).

As DEHA fails to elicit mutagenic or genotoxic responses in available test systems and does not form adducts with DNA, it may be an epigenetic carcinogen for which a dose threshold exists, probably related to its ability to induce peroxisomal proliferation. Liver tumours are likely to occur only at doses causing proliferation of peroxisomes and, as there is a dose threshold for such proliferation, there is probably also a dose threshold for tumour development. The available information suggests that primates are less sensitive than rodents to chemically induced peroxisomal proliferation (26).

14.20.6 Guideline value

IARC has concluded that there is limited evidence that DEHA is carcinogenic in mice (1). It is not classifiable as to its carcinogenicity in humans (27).

Although DEHA is carcinogenic in mice, its toxicity profile and lack of mutagenicity support the use of a TDI approach to setting a guideline value for DEHA in drinking-water. A TDI of 280 µg/kg of body weight can be calculated by applying an uncertainty factor of 100 (for inter- and intraspecies variation) to the lowest observed NOAEL for DEHA of 28 mg/kg of body weight in a fetotoxicity study in rats (19). This gives a guideline value of 80 µg/litre (rounded figure), based on an allocation of 1% of the TDI to drinking-water.

References


25. von Däniken A et al. Investigation of the potential for binding of di(2-ethylhexyl)phthalate (DEHP) and di(2-ethylhexyl)adipate (DEHA) to liver DNA *in vivo*. *Toxicology and applied pharmacology*, 1984, 73:373-387.


14.21 Di(2-ethylhexyl)phthalate

14.21.1 General description

Identity

CAS no.: 117-81-7

Molecular formula: C_{24}H_{38}O_{4}

Di(2-ethylhexyl)phthalate (DEHP) is also known as 1,2-benzenedicarboxylic acid bis(2-ethylhexyl)ester, bis(2-ethylhexyl) phthalate, and dioctyl phthalate (DOP).

Physicochemical properties (1,2)\(^1\)

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</tbody>
</table>

\(^1\) Conversion factor in air: 1 ppm = 1.59 mg/m\(^3\)

Organoleptic properties

DEHP is odourless.

Major uses

DEHP is used primarily as a plasticizer in many flexible polyvinyl chloride products and in vinyl chloride co-polymer resins. It is also used as a replacement for polychlorinated biphenyls in dielectric fluids for small (low-voltage) electrical capacitors (1,2).
Environmental fate

DEHP is insoluble in water (23-340 µg/litre) (2,3). Because of the readiness with which it forms colloidal solutions, its “true” solubility in water is believed to be 25-50 µg/litre. DEHP has a very low volatilization rate. Photolysis in water is thought to be a very slow process (2). Hydrolysis half-lives of over 100 years at pH 8 and 30 °C have been found. DEHP biodegrades rapidly in water and sludges, especially under aerobic conditions; degradation of 40-90% in 10-35 days has been found. Biodegradation in sediment and water under anaerobic conditions is assumed to be very slow; however, the available information is contradictory (3).

14.21.2 Analytical methods

DEHP can be determined by gas chromatography with electron-capture detection; the method has a detection limit of 0.1 ng (4). The detection limit with flame ionization detection is 1 µg/litre. The identity of the compound can be confirmed by mass spectrometry with “single-ion” monitoring, especially when electron-capture detection is used (3,5).

14.21.3 Environmental levels and human exposure

It should be noted that some reported occurrences of DEHP in certain matrices have been found to result from contamination of the latter by plasticizer extracted from plastic tubing or other equipment (1,2).

Air

DEHP has been detected in ocean air at levels ranging from 0.4 ng/m³ over the Gulf of Mexico to 2.9 ng/m³ over the North Atlantic (1,2). Ambient air above the Great Lakes contains an average of 2 ng/m³ (range 0.5-5 ng/m³) (6). In the North Pacific, the average concentration in air was 1.4 ng/m³ (range 0.3-2.7 ng/m³) (3).

In city air, concentrations of phthalates in atmospheric particulate matter range from 5 to 132 ng/m³ (7,8), but a concentration of 300 ng/m³ has been reported in the vicinity of a municipal incinerator (9). Where DEHP is used inside houses, the concentration increases with temperature but decreases with humidity; after 4 months, the concentration will be about 0.05 mg/m³ (5).

Water

In Japan, DEHP was detected in 71 out of 111 samples of rainwater; average concentrations were in the range 0.6-3.2 µg/litre, the highest average value being found in an industrial town (5). In the North Pacific, the average concentration in rainwater was 55 ng/litre (range 5.3-213 ng/litre) (3).

DEHP has been detected in water from several rivers at levels of up to 5 µg/litre (1,2,5). In the Netherlands, sediments of the Rhine and the Meuse contained 1-70 and 1-17 mg/kg, respectively (1). The average concentration in water from the Rhine in 1986 was 0.3 µg/litre (range 0.1-0.7 µg/litre) and in suspended particulate matter 20 mg/kg (range 10-36 mg/kg) (10). In surface water near industrial areas, levels of up to 300 µg/litre were found (1,2).

In contaminated groundwater in the Netherlands, 20-45 µg of DEHP per litre was reported (11). A groundwater sample from New York State contained 170 µg/litre (12).

DEHP was detected in tapwater in two cities in the USA at an average level of 1 µg/litre and in Japan at levels in the range of 1.2-1.8 µg/litre. In “finished” drinking-water in two cities in the USA, average concentrations were 0.05-11 µg/litre; in several major eastern cities in the USA, average levels were below 1 µg/litre. The highest concentrations in drinking-water (up to 30 µg/litre) were reported in older surveys (1975) (1,2).
**Food**

Levels of DEHP below 1 mg/kg were detected in fish in different parts of the USA; most fish contained less than 0.2 mg/kg. In a sampling of a wide variety of foods, the highest levels were found in milk (31.4 mg/litre, fat basis) and cheese (35 mg/kg, fat basis). In a study of the migration of DEHP from plastic packaging films, it was found in tempura (frying) powder (0.11-68 mg/kg), instant cream soup (0.04-3.1 mg/kg), fried potato cake (0.05-9.1 mg/kg), and orange juice (0.05 mg/kg) (1,2).

Analysis of bottled beverages with polyvinyl chloride seals plasticized with DEHP demonstrated that very little migration occurs; all the concentrations reported were less than 0.1 mg/kg, the vast majority being below 0.02 mg/kg. Draught beer samples contained similar levels of DEHP (<0.01-0.04 mg/kg) (13).

**Estimated total exposure and relative contribution of drinking-water**

Exposure among individuals may vary considerably because of the wide variety of products into which DEHP is incorporated. The estimated average daily adult dose from the consumption of commodities highly likely to be contaminated (such as milk, cheese, margarine) is about 200 µg (14). Levels in community drinking-water are generally thought to be negligible, although there may be individual instances of high levels of contamination. Exposure from air is negligible compared with that associated with food (e.g. when the concentration in city air is 50 ng/m³, the daily exposure will be less than 1 µg).

Patients undergoing kidney dialysis may be exposed to high levels of DEHP; it is estimated that each patient will receive up to 90 mg per treatment (15). Exposure also occurs during the transfusion of stored whole blood. Concentrations will be low in frozen plasma. The Netherlands standard for the migration of DEHP from blood containers is 10 mg of DEHP per 100 ml of ethanol (16).

**14.21.4 Kinetics and metabolism in laboratory animals and humans**

In rats, DEHP is readily absorbed from the gastrointestinal tract after oral administration. It is hydrolysed to a large extent to mono(2-ethylhexyl)phthalate (MEHP) with release of 2-ethylhexanol (EH) before intestinal absorption (17). Absorption is lower in primates (including humans). In rats, over 90% was excreted in urine after dietary administration, whereas only 0.9% was excreted in urine by marmosets (2,18). In humans, 11-25% of an ingested dose was found in urine (2,19).

DEHP undergoes further modification after hydrolysis to the monoester. Several species (primates, including humans, and some rodent species) form glucuronide conjugates with the monoester, but rats appear unable to do so. In rats, the residual 2-ethylhexyl moiety is oxidized extensively (17). In mice and rats, urinary metabolites consist primarily of terminal oxidation products (diacids, ketoacids); in primates (monkeys, humans), they consist primarily of unoxidized or minimally oxidized products (MEHP, hydroxyacid) (18).

DEHP and its metabolites are extensively distributed throughout the body in rodents, the highest levels being found in the liver and adipose tissue. Little or no accumulation occurs in rats. Estimated half-lives for DEHP and its metabolites in rats are 3-5 days for fat and 1-2 days for other tissues (20).

**14.21.5 Effects on laboratory animals and in vitro test systems**

**Acute exposure**

DEHP has a low acute oral toxicity in animals; the oral LD₅₀ for mice and rats is over 20 g/kg of body weight (1).
**Short-term exposure**

Liver and testes appear to be the main target organs for DEHP toxicity. DEHP can cause functional hepatic damage, as reflected by morphological changes, alterations in energy-linked enzyme activity, and changes in lipid and carbohydrate metabolism. The most striking effect is proliferation of hepatic peroxisomes (21).

In short-term oral studies in rats with dosing periods ranging from 3 days to 9 months and dose levels ranging from 50 to 25 000 mg/kg of diet (2.5-2500 mg/kg of body weight per day), doses greater than 50 mg/kg of body weight per day caused a significant dose-related increase in liver weight, a decrease in serum triglyceride and cholesterol levels, and microscopic changes in the liver, namely perportal accumulation of fat and mild centrilobular loss of glycogen. An initial burst of DNA synthesis in the liver (indicative of liver hyperplasia) followed by a decrease in liver DNA content (indicative of liver hypertrophy) were observed. Changes to peroxisomes, mitochondria, and endoplasmic reticulum in the liver were seen. Significant increases in hepatic peroxisomal enzyme activities and in the number of peroxisomes in the liver were found (22-26). NOAELs for changes in liver weight were 25 mg/kg of body weight per day by gavage (23) and 500 mg/kg of diet (25 mg/kg of body weight per day) (22). Morton (22) found significantly decreased serum triglyceride levels at 50, 100, and 500 mg/kg of diet, whereas Barber et al. (25) did not find this effect at 1000 and 100 mg/kg of diet.

NOAELs for peroxisomal proliferation (based on changes in peroxisome-related enzyme activities or ultramicroscopic changes) were 25 mg/kg of body weight per day (LOAEL 100 mg/kg of body weight per day) in a 14-day gavage study in Sprague-Dawley rats (23), 50 mg/kg of diet (2.5 mg/kg of body weight per day) in a 7-day study in Sprague-Dawley rats (22) (LOAEL 100 mg/kg of diet or 5 mg/kg of body weight per day), and 100 mg/kg of diet (10 mg/kg of body weight per day) in a 3-week study in F344 rats (LOAEL 1000 mg/kg of diet or 100 mg/kg of body weight per day) (25). Marked species differences in the occurrence of peroxisomal proliferation exist, the available information suggesting that primates, including humans, are less sensitive to this effect than rodents (26).

Changes in the kidneys and thyroid in Wistar rats have also been observed. The effects on the thyroid (increased activity accompanied by a decrease of plasma T4) were observed at doses of 10 000 mg/kg of diet (1000 mg/kg of body weight per day) and higher (24).

**Long-term exposure**

In 2-year oral toxicity studies in rats, doses of 100-200 mg/kg of body weight and higher caused growth depression, liver and kidney enlargement, microscopic changes in the liver, and testicular atrophy. The NOAEL was 50-65 mg/kg of body weight (2,27,28). Increased activities of peroxisome-associated enzymes were found in another study even at the lowest dose level of 200 mg/kg of diet (10 mg/kg of body weight per day) (26).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Testicular effects, namely atrophy, tubular degeneration, and inhibition or cessation of spermatogenesis, were seen in mice, rats, guinea-pigs, and ferrets (29), supposedly caused by MEHP (2,30). In rats, testicular changes were seen at oral doses above 100 mg/kg of body weight per day (31).

In a reproduction study in mice, complete suppression of fertility in both sexes was seen at 0.3% DEHP in the diet (430 mg/kg of body weight per day). At 0.1% in the diet (140 mg/kg of body weight per day), significantly reduced fertility indices, again in both sexes, were observed, but no effects on fertility were seen at 0.01% in the diet (15 mg/kg of body weight per day) (26).

In mice, fetal mortality, fetal resorption, decreased fetal weight, neural tube effects, and skeletal disorders (exencephaly, spina bifida, open eyelid, exophthalmia, major vessel malformations, club-foot, and delayed
ossification) were seen in teratogenicity studies. The NOAEL for these effects was 0.025% in the diet (35 mg/kg of body weight per day) (32). The LOAELs were 0.05 mg/kg of body weight per day (33) and 0.05% in diet (70 mg/kg of body weight per day) (32). MEHP was more active than DEHP, which may, therefore, act as a result of conversion into MEHP. However, it was also hypothesized that 2-ethylhexanoic acid, the oxidation product of 2-ethylhexanol, was the proximate teratogen, as indicated in studies with rats (26).

Rats were less susceptible than mice to DEHP-related adverse effects on fetal development. At oral doses above 200 mg/kg of body weight per day, decreased fetal weights and an increased number of resorptions were observed (34,35). Teratogenic effects were not observed in F344 rats at dose levels of 0.5-2.0% in the diet (250-1000 mg/kg of body weight per day). Embryofetal toxicity was seen at levels of 1.0% in the diet and higher (≥500 mg/kg of body weight per day) (32).

**Mutagenicity and related end-points**

DEHP showed negative results in most short-term mutagenicity studies in vitro and in vivo (i.e. it did not induce gene mutations in bacterial systems, eukaryotic systems, or mammalian systems in vitro, or chromosomal aberrations or sister chromatid exchange in mammalian cells in vitro, or chromosomal aberrations in somatic or germ cells in vivo). No evidence was found for a covalent interaction of DEHP with DNA, the induction of single-strand breaks in DNA, or unscheduled DNA repair. However, DEHP induced aneuploidy in eukaryotic cells in vitro and cell transformations in mammalian cells in vivo and in vitro (20,36).

In general, MEHP and EH did not induce gene mutations in bacteria or mammalian cells in vitro. Contradictory results were reported for MEHP with respect to the induction of chromosomal aberrations and sister chromatid exchange in mammalian cells in vitro, but EH showed negative results in these test systems. In mammalian cells in vivo, MEHP and EH did not induce chromosomal aberrations (36).

**Carcinogenicity**

In a 2-year oral study in mice, increased incidences of hepatocellular carcinomas were seen in males and females at 3000 and 6000 mg/kg of diet. Rats given 6000 or 12 000 mg of DEHP per kg of diet for 2 years showed increased incidences of hepatocellular carcinomas and hepatic neoplastic nodules (2,37).

It has been suggested that the increased incidences of liver tumours in mice and rats in chronic bioassays are caused by the prolonged proliferation of hepatocellular peroxisomes and the enhanced production of the peroxisomal metabolic by-product, hydrogen peroxide. Primates, including humans, are far less sensitive to peroxisomal proliferation than mice and rats (38).

In in vivo studies with B6C3F1 mice, DEHP had no tumour-initiating activity in the liver but, in the same strain, showed promoting activity, also in the liver, as indicated by an increase in focal hepatocellular proliferative lesions, including hyperplastic foci and neoplasms. In rats, in vivo studies showed neither tumour-initiating or promoting activity, nor sequential syncarcinogenic activity in the liver (26).

**14.21.6 Effects on humans**

Two male volunteers dosed with 10 g of DEHP experienced mild gastric disturbances and moderate catharsis; a 5-g dose had no effect (1,2).

Dialysis patients receiving approximately 150 mg of DEHP intravenously per week were examined for liver changes. At 1 month, no morphological changes were observed by liver biopsy but, at 1 year, peroxisomes were reported to be “significantly higher in number” (20).

A high incidence of polyneuropathy was reported in studies on industrial workers exposed to different phthahlic acid esters, including DEHP (39), but this was not confirmed in another study (40). In a small
cohort study, eight deaths were observed among 221 workers exposed to DEHP for periods of 3 months to 24 years. One carcinoma of the pancreas and one bladder papilloma were reported. The study was considered to be inadequate to provide proof of a causal association (1,2).

Occupational exposure to 0.01-0.016 mg of DEHP per m³ over 10-34 years did not cause an increase in the frequency of chromosomal aberrations in blood leukocytes (1,2).

14.21.7 Guideline value

IARC has concluded that DEHP is possibly carcinogenic to humans (Group 2B) (41). Induction of liver tumours in rodents by DEHP was observed at high dietary dose levels. A relationship between the occurrence of hepatocellular carcinoma and prolonged induction of peroxisomal proliferation in the liver was suggested, although the mechanism of action is still unknown. On the basis of toxicity data in experimental animals, the induction of peroxisomal proliferation in the liver seems to be the most sensitive effect of DEHP, and the rat appears to be the most sensitive species. The available literature suggests that humans are less sensitive to chemically induced peroxisomal proliferation than rodents.

In 1988, JECFA evaluated DEHP and recommended that human exposure to this compound in food be reduced to the lowest level attainable. The Committee considered that this might be achieved by using alternative plasticizers or alternatives to plastic material containing DEHP (26).

In view of the absence of evidence for genotoxicity and the suggested relationship between the occurrence of hepatocellular carcinomas and prolonged proliferation of liver peroxisomes, a TDI was derived using the lowest observed NOAEL of 2.5 mg/kg of body weight per day based on peroxisomal proliferation in the liver in rats (22). Although the mechanism for hepatocellular tumour induction is not fully resolved, using a NOAEL derived from the species by far the most sensitive with respect to the particularly sensitive end-point of peroxisomal proliferation justifies the use of an uncertainty factor of 100 (for inter- and intraspecies variation). Consequently, the TDI is 25 µg/kg of body weight. This yields a guideline value of 8 µg/litre (rounded figure), allocating 1% of the TDI to drinking-water.

References


37. National Toxicology Program. *Carcinogenesis bioassay of di(2-ethylhexyl)phthalate (CAS no. 117-81-7) in F344 rats and B6C3F1 mice (feed study).* Research Triangle Park, NC, 1982.


14.22 Acrylamide
14.22.1 General description

Identity

CAS no.: 79-06-1
Molecular formula: C₃H₅NO

Physicochemical properties (1)

<table>
<thead>
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<th>Value</th>
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<td>Density</td>
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<td>Water solubility</td>
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<tr>
<td>Vapour pressure</td>
<td>0.009 kPa at 25 °C</td>
</tr>
</tbody>
</table>

Major uses

Most of the acrylamide produced is used as a chemical intermediate or as a monomer in the production of polyacrylamide. Both acrylamide and polyacrylamide are used mainly in the production of flocculants for the clarification of potable water and in the treatment of municipal and industrial effluents. They are also used as grouting agents in the construction of drinking-water reservoirs and wells (1).

Environmental fate

Acrylamide is highly mobile in aqueous environments and readily leachable in soil. As it has a higher mobility and lower rate of degradation in sandy soils than in clay soils (2), it may contaminate groundwater. However, its behaviour in subsurface soil, where most grouting takes place, has not been studied.

Acrylamide is susceptible to biodegradation in soil and surface water. Its concentration decreased from 20 to 1 µg/litre in 24 h in the effluent from a sludge dewatering process (3). One of the most important mechanisms for the removal of acrylamide from soils is enzyme-catalysed hydrolysis; nonbiological hydrolysis may be important in natural water. Volatilization is not an important removal process. As acrylamide is both highly soluble in water and degraded by microorganisms, it is not likely to bioconcentrate significantly (4).

14.22.2 Analytical methods

The methods used for measuring acrylamide include polarography, electron-capture gas chromatography, and high-performance liquid chromatography. A high-performance liquid chromatography/ultraviolet absorption detection procedure for the determination of acrylamide in water has a detection range of 0.2-100 µg/litre (5).

14.22.3 Environmental levels and human exposure

Air

Because of its low vapour pressure and high water solubility, acrylamide is not expected to be a common contaminant in air. Available monitoring data are insufficient to confirm this.
**Water**

The most important source of drinking-water contamination by acrylamide is the use of polyacrylamide floculants containing residual levels of acrylamide monomer. Generally, the maximum authorized dose of polymer is 1 mg/litre. At a monomer content of 0.05%, this corresponds to a maximum theoretical concentration of 0.5 µg/litre monomer in water (6). In practice, concentrations may be lower by a factor of 2-3. This applies to both the anionic and nonanionic polyacrylamides, but residual levels from cationic polyacrylamides may be higher.

Acrylamide was detected at levels of less than 5 µg/litre in both river water and tapwater in an area where polyacrylamides were used in the treatment of potable water. Samples from public drinking-water supply wells in West Virginia (USA) contained 0.024-0.041 µg of acrylamide per litre. In one study in the United Kingdom, tapwater levels in the low microgram per litre range were reported (5).

*Food*

No studies on the occurrence of acrylamide in foods were identified. However, polyacrylamide is used in the refining of sugar, and small amounts of acrylamide may remain in the final product.

**14.22.4 Kinetics and metabolism in laboratory animals and humans**

Acrylamide is readily absorbed by ingestion and inhalation, and through the skin (1), and is then widely distributed in body fluids. It can cross the placental barrier. The tissue distribution following intravenous injection of l-[14C]acrylamide (100 mg/kg of body weight) into male Porton strain rats was highest (up to 1360 µmol per g of tissue) in blood; progressively lower amounts were present in kidney, liver, brain, spinal cord, sciatic nerve, and plasma (7).

In rats, biotransformation of acrylamide occurs through glutathione conjugation and decarboxylation. At least four urinary metabolites have been found in rat urine; N-acetyl-S-(3-amino-3-oxypropyl)cysteine accounted for 48% of the oral dose, and unmetabolized acrylamide (2%) and three non-sulfur-containing metabolites (total 14%) were also present. Acrylamide and its metabolites are accumulated (protein-bound) in both nervous system tissues and blood, where it is bound to haemoglobin. Accumulation in the liver and kidney as well as in the male reproductive system has also been demonstrated (8).

The results of animal studies indicate that acrylamide is largely excreted as metabolites in urine and bile. Because of the enterohepatic circulation of biliary metabolites, faecal excretion is minimal. Two-thirds of the absorbed dose is excreted with a half-life of a few hours. However, protein-bound acrylamide or acrylamide metabolites in the blood, and possibly in the central nervous system, have a half-life of about 10 days. Acrylamide has been identified in rat milk during lactation (8).

There are no data indicating any major differences in acrylamide metabolism between humans and other mammals (1).

**14.22.5 Effects on laboratory animals and in vitro test systems**

**Acute exposure**

Oral LD50s for acrylamide were reported to range from 100 to 270 mg/kg of body weight in various strains of mice and rats. The dermal LD50 in rats was reported to be 400 mg/kg of body weight (9-12).

**Short-term exposure**

Studies have shown that acrylamide is a cumulative neurotoxin. Rats, cats, and dogs receiving 5-30 mg/kg of body weight per day in the diet exhibited weakness and ataxia in hind limbs for 14-21 days,
which progressed to paralysis with continued exposure (13,14). Other characteristic symptoms were testicular atrophy and degeneration of germinal epithelium (15).

**Long-term exposure**

Signs of acrylamide toxicity in animals exposed for longer periods of time (several months to 1 year) are generally the same as those in animals exposed for short times, but average daily doses as low as 1 mg/kg of body weight per day sometimes produce effects. When male and female F344 rats were exposed to 0, 0.05, 0.2, 1.5, or 20 mg/kg of body weight per day in drinking-water for 90 days, definite peripheral nerve and spinal cord lesions and testicular atrophy were observed in the group receiving 20 mg/kg of body weight per day; although 1.5 mg/kg of body weight per day caused no external signs of toxicity, histological evidence of neuropathy was noted. The NOAEL was 0.2 mg/kg of body weight per day (16).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Male Long-Evans rats exposed to acrylamide doses of up to 5.8 mg/kg of body weight per day for 10 weeks in their drinking-water experienced increased pre-implantation and post-implantation loss after mating (17). Another series of experiments carried out by the same authors suggested that acrylamide affected the spermatid-spermatozoa stages (18).

Acrylamide was administered to pregnant Porton rats either as a single intravenous dose (100 mg/kg of body weight) on day 9 of gestation or in the diet as a cumulative dose of either 200 or 400 mg/kg of body weight between days 0 and 20 of gestation. Apart from a slight decrease in the weight of individual fetuses from rats dosed with 400 mg/kg of body weight, no fetal abnormalities were seen, even at doses that induced neuropathy in the dams (19).

When fertilized chicken eggs were injected with 0.03-0.6 mg of acrylamide on days 5, 6, or 7 of incubation, embryonic mortality increased and leg deformities were observed in hatched chicks (20).

**Mutagenicity and related end-points**

Acrylamide does not cause mutations in bacterial test systems but does cause chromosome damage to mammalian cells both in vitro and in vivo (1,21,22).

**Carcinogenicity**

Recent results indicate that acrylamide may be a carcinogen. Male and female Fischer 344 rats were given 0, 0.01, 0.02, 0.5, or 2 mg/kg of body weight per day in drinking-water for 2 years. In male rats receiving doses of 0.5 and 2 mg/kg of body weight per day, there was an increase in the frequency of scrotal, thyroid, and adrenal tumours. In female rats receiving 2 mg/kg of body weight per day, there was an increased incidence of malignant tumours of the mammary gland, central nervous system, thyroid, and uterus (23).

Eight-week-old A/J male and female mice given oral doses of 6.3, 12.5, or 25.0 mg/kg of body weight three times per week for 3 weeks or intraperitoneal doses of 1, 3, 10, 30, or 60 mg/kg of body weight three times per week for 8 weeks showed a dose-dependent increased incidence of lung adenomas at 9 and 8 months of age, respectively (22).

**14.22.6 Effects on humans**

Subacute toxic effects were experienced by a family of five exposed through the ingestion and external use of well-water contaminated with 400 mg of acrylamide per litre as the result of a grouting operation (24). Symptoms of toxicity developed about a month later and included confusion, disorientation, memory
disturbances, hallucinations, and truncal ataxia. The family recovered fully within 4 months.

Many other cases of human exposure to acrylamide have been reported, generally the result of the dermal or inhalation exposure of workers in grouting operations or factories manufacturing acrylamide-based flocculants (25-28). Typical clinical symptoms were skin irritation, generalized fatigue, foot weakness, and sensory changes, which reflect dysfunction of either the central or peripheral nervous system.

14.22.7 Guideline value

In mutagenicity assays, acrylamide does not cause mutations in bacterial test systems but does cause chromosome damage to mammalian cells in vitro and in vivo. In a long-term carcinogenicity study in rats exposed via drinking-water, it induced tumours at various sites (23). IARC has placed acrylamide in Group 2B (29).

On the basis of the available information, it was concluded that acrylamide is a genotoxic carcinogen. Therefore, the risk evaluation was carried out using a non-threshold approach. On the basis of combined mammary, thyroid, and uterus tumours observed in female rats in a drinking-water study (23) and using the linearized multistage model, guideline values associated with excess lifetime cancer risks of $10^{-4}$, $10^{-5}$, and $10^{-6}$ are estimated to be 5, 0.5, and 0.05 µg/litre, respectively.

The most important source of drinking-water contamination by acrylamide is the use of polyacrylamide flocculants that contain residual acrylamide monomer. Although the practical quantification level for acrylamide is generally of the order of 1 µg/litre, concentrations in drinking-water can be controlled by product and dose specification.

References


10. Paulet G, Vidal. [On the toxicity of some acrylic and methacrylic esters, acrylamide and


14.23 Epichlorohydrin

14.23.1 General description

**Identity**

CAS no.: 106-89-8  
Molecular formula: C₃H₅ClO

Synonyms of epichlorohydrin (ECH) include 1-chloro-2,3-epoxypropane, 3-chloro-1,2-epoxypropane, 1-chloropropeneoxide, and 3-chloropropeneoxide.

**Physicochemical properties (1,2)**

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¹ Conversion factor in air: 1 ppm = 3.78 mg/m³

**Major uses**

ECH is used mainly for the manufacture of glycerol and unmodified epoxy resins, and to a lesser extent in the manufacture of elastomers, water-treatment resins, surfactants, ion exchange resins, plasticizers, dyestuffs, pharmaceutical products, oil emulsifiers, lubricants, and adhesives (3).

**Environmental fate**

ECH is released to the environment as a result of its manufacture, use, storage, transport, and disposal. Its half-lives in neutral, acidic, and alkaline solutions are 148, 79, and 62 h at room temperature, respectively. The rate of hydrolysis increases sevenfold when the temperature is raised to 40 °C (4).

14.23.2 Analytical methods

ECH in water can be determined by a purge-and-trap gas chromatographic/mass spectrometric procedure (GC-MS) (2), and by gas chromatography with flame-ionization (5) (detection limit 0.01 mg/litre) or electron-capture detection (6) (detection limit 0.05 µg/litre). A GC-MS method can also be used for the determination of ECH in ambient water and sediment (7) (detection limit 0.003 µg/litre).
14.23.3 Environmental levels and human exposure

**Air**

Data on ambient air levels of ECH are extremely limited and relate mainly to occupational exposure. At 100-200 m from a factory discharging ECH into the atmosphere in the former USSR, the airborne ECH concentration ranged from 0.5 to 1.2 mg/m³. At 400 m, five out of 29 samples had levels exceeding 0.2 mg/m³, whereas no ECH was detected at 600 m (3,8).

**Water**

ECH can enter drinking-water supplies through the use of flocculating agents containing it and through leaching from epoxy resin coatings on pipes. No ECH residue was found in water kept in containers coated with epoxy resins (detection limit 3 µg/litre) (9).

**Food**

Migration into food and drinking-water of ECH used as a cross-linking agent in packing materials and epoxy resin is possible but is expected to be low (3). No studies on its occurrence in food were identified. The compound has little potential for bioaccumulation in the food-chain (10).

14.23.4 Kinetics and metabolism in laboratory animals and humans

The pharmacokinetics of ECH have been reviewed by WHO (3) and the US Environmental Protection Agency (2). It is rapidly and extensively absorbed following oral administration and may be absorbed following both inhalation and dermal exposures (11).

Following oral administration of [14C]-ECH to rats, peak tissue levels were reached after 2 h in males and 2-8 h in females, depending on the tissue. The tissues containing the highest levels of radioactivity were the kidneys, liver, pancreas, spleen, and adrenal glands. ECH is rapidly removed from blood and is therefore not likely to accumulate during chronic exposures. Metabolites of ECH, however, are much more persistent and may therefore accumulate to a small extent during chronic exposures (11).

ECH has two electrophilic centres, C1 and C3, and may thus bind to cellular nucleophiles such as glutathione. This binding is catalysed by glutathione-S-epoxide transferase, resulting in a considerable increase in reaction rate. The major metabolites in urine were identified as N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine, formed by conjugation with glutathione, and α-chlorohydrin, accounting for about 36% and 4% of the administered dose, respectively (11,12).

Following oral administration and inhalation, ECH metabolites are rapidly excreted in the urine and expired air. Urinary excretion is approximately twice that in expired air. Only minor amounts (4%) are excreted in the faeces. Unmetabolized ECH has not been detected in any excreta (11).

14.23.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

ECH is a strong irritant and acutely toxic following oral, percutaneous, subcutaneous, or respiratory exposure. Death is due to effects on the central nervous system and the respiratory centre (13). Oral LD₅₀ were reported to range from 90 to 260 mg/kg of body weight in rats (2).

**Long-term exposure**

There was a gradual increase in mortality following the oral administration of ECH in water by gavage to
weanling Wistar rats of both sexes for 5 days per week for 2 years; clinical symptoms included dyspnoea, weight loss, a decrease in leukocytes, and hyperplasia in the forestomach at 2 and 10 mg/kg of body weight per day (14).

Lifetime inhalation of ECH by non-inbred male SD rats for 6 h per day, 5 days per week, caused weight loss, high mortality, severe inflammatory changes in the nasal cavity, lung congestion and pneumonia, tubular dilation, and dose-dependent tubular degeneration in the kidney at 38 and 114 mg/m³ (15).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

The sperm of rats that had received an oral dose of 25 or 50 mg of ECH per kg of body weight showed an increased percentage of abnormal sperm heads at the higher dose and a reduced number of sperm heads at the lower dose; no microscopic changes in the testes or changes in their weight were observed (16). When male rabbits and male and female rats were exposed for 6 h per day, 5 days per week, to ECH vapour at concentrations of 0, 19.7, 93.4, or 189.0 mg/m³ for 10 weeks, a dose-related transient infertility was induced at the two highest levels in male rats but not in female rats or male rabbits. Microscopic examination did not reveal any abnormalities in the reproductive organs. The sperm of the rabbits was investigated, but no adverse effects were found (17).

Female rats received oral doses of 0, 40, 80, or 160 mg of ECH per kg of body weight per day and female mice received 0, 80, 120, or 160 mg of ECH per kg of body weight per day in cottonseed oil between days 6 and 15 of pregnancy. Although the highest dose levels were toxic to the dams, no embryotoxic, fetotoxic, or teratogenic effects were observed (18). Similar negative results were obtained when female rats and rabbits inhaled vapours of ECH at concentrations of 0, 9.4, or 94.5 mg/m³ for 7 h per day between days 6 and 15 or 18 of pregnancy (19).

**Mutagenicity and related end-points**

ECH induced base-change-type mutations in *Salmonella typhimurium* and *Escherichia coli* in the absence of metabolic activation (20). It has been shown to cause chromosomal aberrations in mammalian cells *in vitro* (3) but was negative in the mouse micronucleus assay (21) and in the mouse dominant lethal assay (22).

**Carcinogenicity**

Male Wistar rats that received 18, 39, or 89 mg of ECH per kg of body weight per day in drinking-water for 81 weeks developed forestomach tumours characterized as squamous cell papillomas and carcinomas at the two highest doses and hyperplasia at all three doses (23). Similar findings were reported in a 104-week study in which Wistar rats were given 0, 2, or 10 mg of ECH per kg of body weight by gavage in distilled water (24). Male SD rats exposed for 30 days to ECH at 378 mg/m³ of air, 6 h per day, 5 days per week, developed squamous cell carcinomas in the nasal cavities during subsequent lifetime observation (15). In 100 rats, lifetime exposure to 113 mg/m³ yielded only one malignant squamous cell carcinoma of the nasal cavity and one nasal papilloma. Subcutaneous injection of EHC in ICR/Ha Swiss mice induced local sarcomas and adenocarcinomas (25).

**14.23.6 Effects on humans**

Acute toxic responses following dermal exposure are characterized by an initial redness and itching or burning sensation. With time, the redness intensifies and the tissue becomes swollen and blistered. The initial symptoms following inhalation are local irritation, burning of the eyes and throat, swelling of the face, nausea, vomiting, and severe headache (26).

In a case study, long-term effects due primarily to damage to the liver and kidneys were still present 2 years after exposure (26). In workers occupationally exposed to ECH, increased incidences of chromatid
and chromosomal breaks in peripheral lymphocytes and decreases in blood cell counts were observed (27).

An epidemiological study was undertaken on 863 workers with probable exposure to ECH at two chemical plants (28). All deaths due to cancer and leukaemia, and deaths from most other causes, were related to estimated levels of exposure to ECH. The most consistent relationship was between exposure level and heart disease.

The fertility status of 64 glycerol workers in the USA exposed to ECH, allyl chloride, and 1,3-dichloropropane was compared with that of a control group of 63 workers who had not handled chlorinated hydrocarbons for more than 5 years. No association was found between levels, duration, or intensity of exposure and sperm characteristics or hormone levels (29). A similar negative result for sperm count and hormone levels was obtained for a group of 128 workers from two plants compared with other chemical plant workers who had not been exposed to any chemical known to be toxic to the testes. In one of these plants, most of the employees were exposed to ECH concentrations below 3.8 mg/m³. The number of non-participating employees was high in both plants, namely 172 in total (30).

14.23.7 Provisional guideline value

The major toxic effects of ECH are local irritation and damage to the central nervous system. In rats, by the inhalation and oral routes, it induces squamous cell carcinomas in the nasal cavity and forestomach tumours, respectively. It has been shown to be genotoxic in vitro and in vivo. IARC has placed ECH in Group 2A (probably carcinogenic to humans) (31).

Although ECH is a genotoxic carcinogen, the use of the linearized multistage model for estimating cancer risk was considered inappropriate because tumours are seen only at the site of administration, where ECH is highly irritating. A TDI of 0.14 µg/kg of body weight was therefore calculated by applying an uncertainty factor of 10 000 (10 for the use of a LOAEL instead of a NOAEL, 100 for inter- and intraspecies variation, and 10 reflecting carcinogenicity) to a LOAEL of 2 mg/kg of body weight per day for forestomach hyperplasia in a 2-year study in rats by gavage (administration 5 days per week) (14). This gives a provisional guideline value of 0.4 µg/litre (rounded figure) based on an allocation of 10% of the TDI to drinking-water. A practical quantification level for ECH is of the order of 30 µg/litre, but concentrations in drinking-water can be controlled by specifying the ECH content of products coming into contact with water.

References


24. Van Esch GJ, Wester PW. Induction of preneoplastic lesions in the forestomach of rats after oral


27. Sram RJ, Zudova Z, Kuleshov NP. Cytogenetic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. Mutation research, 1980, 70:115-120.


14.24 Hexachlorobutadiene

14.24.1 General description

Identity

CAS no.: 87-68-3
Molecular formula: C₄Cl₆

Synonyms of hexachlorobutadiene (HCBD) include perchlorobutadiene, 1,3-hexachlorobutadiene, and 1,1,2,3,4,4-hexachloro-1,3-butadiene.

Physicochemical properties (1)

<table>
<thead>
<tr>
<th>Property</th>
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<td>Physical state</td>
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<td>Melting point</td>
<td>-19 to -22 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>210-220 °C</td>
</tr>
<tr>
<td>Density</td>
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</tr>
<tr>
<td>Vapour pressure</td>
<td>0.02 kPa at 20 °C</td>
</tr>
<tr>
<td>Log octanol-water partition coefficient</td>
<td>3.67</td>
</tr>
<tr>
<td>Water solubility</td>
<td>2.6 mg/litre</td>
</tr>
</tbody>
</table>

Organoleptic properties

The odour threshold for HCBD in air is 12.00 mg/m³ (2).
**Major uses**

HCBD is used as a solvent in chlorine gas production, an intermediate in the manufacture of rubber compounds, a lubricant, a gyroscopic fluid, a pesticide, and a fumigant in vineyards (1).

**Environmental fate**

HCBD may not volatilize rapidly from water because of its low vapour pressure. Adsorption onto soil particles in water is important.

14.24.2 Analytical methods

HCBD can be determined by means of gas chromatography; the minimum detection limit is 0.34 µg/litre. The purge-and-trap gas chromatography/mass spectrometry (GC-MS) technique has a minimum detection limit of 0.4 µg/litre. Closed-loop stripping analysis with GC-MS can detect HCBD at nanogram per litre levels (3).

14.24.3 Environmental levels and human exposure

**Air**

In a study of nine chemical plants, the highest levels of HCBD in air were found near those producing tetrachloroethene and trichloroethene (maximum 463 µg/m³) (1).

**Water**

In Europe, HCBD was detected in ambient water at 0.05-5 µg/litre, and in the USA at 0.9-1.9 µg/litre in Mississippi River water. It was also found in mud and soil at concentrations of up to 800 µg/kg in Louisiana (1). In the Rhine HCBD was found at concentrations of 0.1-5 µg/litre (1). HCBD was not detected in ambient water and mud in Japan (minimum detection limits: water 0.02 µg/litre; mud 2-200 µg/g) (4). It has been detected at 6.4 µg/litre in the effluent from a European chemical plant and at 0.27 µg/litre in European drinking-water (1).

**Food**

HCBD residues have been found at levels of 4 µg/kg in evaporated milk, 42 µg/kg in egg yolk, and 33 µg/kg in margarine. They were found in the United Kingdom at levels of 0.08 µg/kg in fresh milk, 2 µg/kg in butter, 0.2 µg/kg in cooking oil, 0.2 µg/kg in light ale, 0.8 µg/kg in tomatoes, and 3.7 µg/kg in black grapes (1).

14.24.4 Kinetics and metabolism in laboratory animals and humans

In rats, about 95% of the ingested dose of HCBD is absorbed (5); it was found in the blood, liver, and brain 3 h after a single injection and in the kidney, spleen, and mesentery after 6 h (6). When a mixture of chlorinated hydrocarbons, including HCBD, was administered orally to rats at doses of 2 or 4 mg/kg of body weight per day for up to 12 weeks, less than 7 mg of HCBD per kg of body weight accumulated in adipose tissue (7).

HCBD is metabolized in rats and mice via conjugation with glutathione (GSH), followed by biliary excretion of S-(1,2,3,4,4-pentachloro-1,3-butadienyl)-GSH (PCBD-GSH) (5,8,9). The GSH conjugate of HCBD is further metabolized in the gastrointestinal tract and kidney to a number of water-soluble metabolites that are excreted mainly in the urine (5,9). Experimental evidence suggests that the metabolism of PCBD-GSH involves, in part, degradation to PCBD-cysteine (PCBD-Cys), which is nephrotoxic via activation of the renal enzyme Cys conjugate β-lyase (5,9,10). PCBD-Cys is N-acetylated, presumably in a detoxification
reaction, to give the mercapturic acid, \(N\)-acetyl-PCBD-Cys (11).

After a single oral administration of \({}^{14}\text{C}\)-HCBD to rats, the principal route of excretion was in the bile; 17-20% of the initial dose was excreted on each of the first 2 days. Extensive enterohepatic circulation must have occurred, because faecal elimination amounted to only 5% of the total dose of radioactivity per day (5). In another study, 42-67% and 11-31% of the radioactivity were excreted in the faeces and urine by 72 h, respectively (9). Similar results were obtained in mice (67.5-76.7% in faeces, 6.6-7.6% in urine) (12).

14.24.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

Oral LD\(_{50}\)S were reported to be 200-400 and 504-667 mg/kg of body weight, in adult female and male rats, respectively (13).

**Short-term exposure**

Weanling Wistar rats given HCBD by gavage for 13 weeks at dose levels of 0, 0.4, 1, 2.5, 6.3, or 15.6 mg/kg of body weight per day exhibited an increase in relative kidney weight at the two highest doses and degeneration of the proximal renal tubules at and above 2.5 mg/kg of body weight per day (females) or 6.3 mg/kg of body weight per day (males). Increased cytoplasmic basophilia of hepatocytes associated with an increase in liver weight occurred in males at the two highest doses (14).

**Long-term exposure**

The kidney was the primary target organ in a study in which Sprague-Dawley rats were given HCBD by feed for 2 years at dose levels of 0, 0.2, 2, or 20 mg/kg of body weight per day. Effects included a treatment-related increase in relative and absolute kidney weights in males at 20 mg/kg of body weight per day, an increased incidence of multifocal or disseminated renal tubular epithelial hyperplasia in rats at 20 and possibly at 2 mg/kg of body weight per day, and focal adenomatous proliferation of renal tubular epithelial cells in some males at 20 mg/kg of body weight per day and some females at 20 and 2 mg/kg of body weight per day. No discernible ill effects attributable to treatment were found at 0.2 mg/kg of body weight per day, which was the NOAEL in this study (15).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

In a 148-day study in which groups of 10-17 male and 20-34 female adult rats per group were fed diets containing HCBD at doses of 0, 0.2, 2.0, or 20 mg/kg of body weight per day for 90 days prior to mating, 15 days during mating, and subsequently throughout gestation (22 days) and lactation (21 days), there were no treatment-related effects on pregnancy or neonatal survival. The body weights of 21-day-old weanlings in the highest dose group were slightly but significantly lower than those of controls. No toxic effects were observed in neonates at doses of 0.2 or 2.0 mg/kg of body weight per day (13).

When oral doses of 8.1 mg of HCBD per kg of body weight per day were given to pregnant rats throughout gestation, ultrastructural changes in neurocytes and higher levels of free radicals in the brain and spinal cord were seen in the offspring, which also had lower body weights and shorter crown-rump lengths than controls (16).

Pups of rats injected intraperitoneally with 10 mg of HCBD per kg of body weight per day on days 1-15 of gestation experienced three times as many soft tissue anomalies as controls, although no particular type of anomaly was predominant (17).
**Mutagenicity and related end-points**

Negative results have been reported in most (18,19) but not all (20) tests for the mutagenicity of HCBD in Ames test *Salmonella* strains. Metabolites and derivatives of HCBD were mutagenic to *Salmonella typhimurium* with metabolic activation (11,21), and some putative metabolites were mutagenic in this organism without such activation (8).

**Carcinogenicity**

Administration of HCBD in the diet at doses of 20 mg/kg of body weight per day for 2 years caused renal tubular adenomas and adenocarcinomas in SD rats. No renal tubular neoplasms were observed in rats ingesting 2.0 or 0.2 mg/kg of body weight per day. The authors concluded that HCBD-induced renal neoplasms developed only at doses higher than those causing discernible renal injury (15). Induction of lung adenomas was not observed in male strain A mice following intraperitoneal administration of HCBD (4 or 8 mg/kg of body weight) three times per week until a total of 52 or 96 mg had been administered (22). It did not act as an initiator in an initiation/promotion experiment in mouse skin, nor did it cause tumours in the skin or distant organs after repeated application to the skin (23).

14.24.6 Effects on humans

Farm workers exposed intermittently for 4 years to HCBD exhibited higher incidences of hypotension, myocardial dystrophy, nervous disorder, liver function disorders, and respiratory tract lesions (24).

14.24.7 Guideline value

Kidney tumours were observed in a long-term oral study in rats. HCBD has not been shown to be carcinogenic by other routes of exposure. IARC has placed HCBD in Group 3 (25). Both positive and negative results for HCBD have been obtained in bacterial assays for point mutation; however, several metabolites have given positive results.

On the basis of the available metabolic and toxicological information, it was considered that a TDI approach was most appropriate for derivation of a guideline value. A TDI of 0.2 µg/kg of body weight was therefore calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for limited evidence of carcinogenicity and the genotoxicity of some metabolites) to the NOAEL of 0.2 mg/kg of body weight per day for renal toxicity in a 2-year feeding study in rats (15). This gives a guideline value of 0.6 µg/litre, based on an allocation of 10% of the TDI to drinking-water. A practical quantification level for HCBD is of the order of 2 µg/litre, but concentrations in drinking-water can be controlled by specifying the HCBD content of products coming into contact with water.

**References**


14.25 Edetic acid

14.25.1 General description

**Identity**

CAS no.: 60-00-4  
Molecular formula: C_{10}H_{16}N_{2}O_{8}

Edetic acid (ethylenediaminetetraacetic acid) and its salts are commonly referred to as EDTA. The IUPAC name for EDTA is (1,2-ethanediyldinitrilo)tetraacetic-acid.

**Physicochemical properties** *(1)*

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<thead>
<tr>
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<th>Value</th>
</tr>
</thead>
<tbody>
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<td>Physical state</td>
<td>White crystalline solid</td>
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<td>Melting point</td>
<td>Decomposes at 240 °C</td>
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<tr>
<td>Water solubility</td>
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</table>

**Organoleptic properties**

EDTA has a slight salty taste *(1)*.

**Major uses**

EDTA is widely used in many industrial processes, in agriculture, in domestic products, including food additives, and in drugs for chelation therapy; calcium EDTA is the drug of choice in the treatment of lead poisoning in humans and domestic animals. EDTA is also used in laundry detergents, cosmetics, photochemicals, pharmaceuticals, galvanizing, water softening, electroplating, polymerization, textile treatments, and paper production.

**Environmental fate**

EDTA is only poorly degraded in the aquatic environment *(2)*. It is present in the environment in the form of metal complexes *(3)*. Although the mobilization of heavy metals by EDTA in water is a matter of some concern, it has been calculated that 40 µg of EDTA per litre - the maximum concentration observed in the Rhine and Meuse - would complex at most 4-15 µg of metals per litre. This would be likely to pose problems for drinking-water with regard to cadmium, but the effect on cadmium leaching would be limited because EDTA is primarily bound to other metals at these concentrations *(2)*.
14.25.2 Analytical methods

EDTA can be determined by potentiometric stripping analysis, which has been used to measure EDTA in a wide variety of wastewater and natural water samples; it has a detection limit of 1 µg/litre (4).

14.25.3 Environmental levels and human exposure

**Water**

EDTA is released to the aquatic environment in industrial emissions. It has been estimated that concentrations of 50-500 µg/litre are present in wastewaters (2).

Measured concentrations in natural waters have been reported to range from 10 to 70 µg/litre; the median value is 23 µg/litre (5). Annual average concentrations of EDTA in European surface waters ranged from 1 µg/litre to over 60 µg/litre; a concentration of 900 µg/litre was found in the Zerka river in Jordan (2).

**Food**

EDTA is used as a food additive in a range of products, including canned shrimps and prawns, canned mushrooms, and frozen chips. Maximum levels of EDTA in these products have been limited by the Codex Alimentarius Commission to 250, 200, and 100 mg/kg, respectively (6).

14.25.4 Kinetics and metabolism in laboratory animals and humans

Calcium disodium edetate is poorly absorbed from the gut; it is metabolically inert, and does not accumulate in the body (7, 8).

14.25.5 Effects on laboratory animals and *in vitro* test systems

**Long-term exposure**

The long-term toxicity of EDTA is complicated by its ability to chelate essential and toxic metals, both in water and in animals. Toxicity data are therefore equivocal and difficult to interpret.

In long-term feeding studies in rats and dogs, no evidence was found of interference with mineral metabolism in either species. Adverse effects on mineral metabolism and nephrotoxicity were seen only after parenteral administration of high doses (7, 8).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

The overall results of various studies indicate that EDTA and its salts have little or no propensity to teratogenicity in rats, when given orally (8-10).

**Carcinogenicity**

High doses of EDTA tested on animals in the USA were not carcinogenic (7, 8).

14.25.6 Effects on humans

The vast clinical experience of the use of EDTA in the treatment of metal poisoning has demonstrated its safety in humans.

Calcium disodium edetate as a food additive was evaluated toxicologically in 1973 by JECFA (7). An ADI of 0-2.5 mg/kg of body weight was allocated to this compound (equivalent to 0-1.9 mg/kg as the free acid).
However, JECFA recommended that no sodium edetate should remain in foods. There have been few new toxicological studies subsequent to this evaluation, and those that are available indicate that the apparent toxicological effects of EDTA have in fact been due to zinc deficiency as a consequence of complexation (9-11).

The view that the major problem for human health of oral exposure to EDTA is zinc complexation was reaffirmed by workers in the Netherlands in a recent review of EDTA toxicology (8); its possible effects on the metabolism of metal ions were not addressed in detail in the 1973 JECFA evaluation. It has also been suggested that EDTA may enter kidney cells and, by interfering with zinc metabolism, exacerbate the toxicity of cadmium (12). However, the very low absorption of EDTA from the gastrointestinal tract after oral intake would suggest that it will be the major site of any zinc complexation.

It has been concluded that the present levels of EDTA found in drinking-water do not present a significant risk to human health (2).

14.25.7 Provisional guideline value

JECFA proposed an ADI for calcium disodium edetate as a food additive of 2.5 mg/kg of body weight (equivalent to 1.9 mg/kg of body weight as the free acid) (7). However, JECFA recommended that no sodium edetate should remain in foods.

An extra uncertainty factor of 10 was introduced to reflect the fact that the JECFA ADI has not been considered since 1973 and concern over zinc complexation, giving a TDI of 190 µg/kg of body weight. In view of the possibility of zinc complexation a provisional guideline value was derived by assuming that a 10-kg child consumes 1 litre of water per day. The provisional guideline value is thus 200 µg/litre (rounded figure), allocating 10% of the TDI to drinking-water.

References

1. Dytlova NM et al. [Complexones.] Moscow, Medicina, 1970 (in Russian).


14.26 Nitrilotriacetic acid

14.26.1 General description

Identity

CAS no: 139-13-9
Molecular formula: C₆H₉NO₆

Physicochemical properties (1)

<table>
<thead>
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<tbody>
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<td>Melting point</td>
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<td>Water solubility</td>
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<tr>
<td>pH of saturated solution</td>
<td>2-3</td>
</tr>
</tbody>
</table>

Major uses

The trisodium salt of nitrilotriacetic acid (NTA) is used in laundry detergents as a “builder” to replace phosphates because of its ability to chelate calcium and magnesium ions (1). NTA is used extensively in the treatment of boiler water to prevent the accumulation of mineral scale and, to a lesser extent, in photography, textile manufacture, paper and cellulose production, and metal plating and cleaning operations. Its use as a therapeutic chelating agent for the treatment of manganese poisoning (2) and iron overloading has been suggested (3).

Environmental fate

NTA is degraded principally by microorganisms by carbon-nitrogen cleavage with the formation of such intermediates as iminodiacetate, glyoxylate, glycerate, glycine, and ammonia (4-6); the metabolic end-products are carbon dioxide, water, ammonia, and nitrate (7). NTA mobilizes heavy metals from aquatic sediments (8) and is present in water primarily in the form of metal complexes (9), most of which degrade rapidly. Under certain conditions, it is broken down by photochemical and chemical reactions (7).

The half-life for biodegradation of NTA in groundwater at 1-100 µg/litre is approximately 31 h (10). Concentrations of 5-50 mg/litre completely disappeared from river water containing acclimatized microorganisms in 2-6 days; concentrations below 5 mg/litre are expected to degrade within 1 day (11,12). Acclimatization of microorganisms in two lake waters resulted in the reduction of the disappearance time of up to 10 mg of NTA per litre from 6 and 11 days to 4 and 3 days, respectively (13). Sand-associated bacteria adapt more quickly to NTA and degrade it more actively than do plankton and algae (14).
14.26.2 Analytical methods

NTA concentrations in water may be determined by gas chromatography with a nitrogen-specific detector. This method is suitable for the detection of levels as low as 0.2 µg/litre (15).

14.26.3 Environmental levels and human exposure

**Water**

NTA has been detected in both raw and treated water. In a national survey of 70 Canadian municipalities, the mean concentrations of NTA in drinking-water and raw water samples were 2.82 µg/litre (range <0.2-30.4 µg/litre) and 3.9 µg/litre (range <0.2-33.5 µg/litre), respectively. Concentrations exceeded 10 µg/litre in only 14% of the locations (15). In a survey of tapwater in eight cities in New York State, 68% of the samples contained no detectable levels of NTA (detection limit 1 µg/litre); the remaining samples contained an average of 2.1 µg/litre (16). Mean concentrations in surface water ranged from 0.3 to 4.7 µg/litre in Germany (17) and from 1.0 to 12.0 µg/litre in Switzerland (18).

**Other routes of exposure**

No information on NTA concentrations in food or ambient air has been found. For a very small proportion of the population in households in which dishes are washed with detergents containing NTA, residues present on unrinsed dishes left to drip dry may be a source of exposure. Intake from this source may approximate 0.0025 mg/kg of body weight per day (0.15 mg for a 60-kg adult) (19).

**Estimated total exposure and relative contribution of drinking-water**

The daily intake of NTA in drinking-water can be calculated to be 5.64 µg, using the mean concentration in drinking-water reported in the Canadian national survey (2.82 µg/litre) (15) and assuming an average daily water consumption of 2 litres.

14.26.4 Kinetics and metabolism in laboratory animals and humans

Absorption of NTA from the gastrointestinal tract is rapid; however, there is considerable variation among species in the proportion of NTA eliminated in the urine. It does not appear to be metabolized by mammals: this conclusion is based on studies in mice, rats, dogs, and humans in which unchanged NTA is excreted in the urine (20-23).

NTA accumulates in bone because it forms complexes with divalent cations such as calcium; its turnover time in bone is similar to that of calcium (7). Deposition of NTA in the kidney has also been reported, although this may be an artefact associated with the retention of urine in the kidney rather than uptake by renal tissue (7).

14.26.5 Effects on laboratory animals and in vitro test systems

**Acute exposure**

NTA does not appear to be highly acutely toxic to mammals. Oral LD₅₀s in rats and mice of 1470 mg/kg of body weight and 3160 mg/kg of body weight, respectively, have been reported (24). The oral LD₅₀ of Na₃NTA·H₂O in rodents is about 2000 mg/kg of body weight (7). The oral LD₅₀s in rats for the metal complexes of NTA commonly found in drinking-water range from 810 mg/kg of body weight for CuNaNTA to over 22 500 mg/kg of body weight for NiNaNTA (7).
**Short-term exposure**

Results of short-term studies in which NTA was administered orally indicate that the kidney is the target organ and that damage is dose-dependent and rapidly induced. In two studies in which male Sprague-Dawley rats and Charles River CD rats consumed drinking-water containing between 0.01 and 0.1% Na₃NTA for 10 weeks, elevated blood glucose levels were observed at all dose levels. Six of the nine Sprague-Dawley rats in the high-dose group died by the fourth week; animals in this group showed marked vacuolization of renal tubules, and glycosuria was present in five rats. In a bioassay in which groups of weanling rats were fed diets containing 0, 2000, 7500, 10 000, or 20 000 mg of the trisodium salt per kg of diet for 90 days, hydronephrosis was observed in 63% of the animals in the group given 20 000 mg/kg; hydropic degeneration of the kidney tubular cells, tubular atrophy, and dilatation were reported in the groups given 7500 and 10 000 mg/kg; no adverse effects were observed at 2000 mg/kg. In a limited investigation in which two skeletally mature dogs were administered 2.5 mg of trisodium salt per kg of body weight per day in their drinking-water for 7 months, radial closure rates and the percentage of osteoid seams taking a fluorescent label were decreased, suggesting interference with the mineralization process.

**Long-term exposure**

Weanling Charles River CD rats (50 per sex per dose) were fed diets containing 0.03, 0.15, or 0.5% of the trisodium salt or 0.5% of the calcium chelate of NTA for 2 years. A dose-dependent increase in urinary zinc was reported in the groups receiving 0.15 and 0.5% Na₃NTA, accompanied by a dose-dependent increase in renal tubular cell toxicity. Mild nephrosis consisting of hydropic degeneration of tubular cells and the minor tubule was observed at 6 months at 0.15 and 0.5% Na₃NTA; its incidence and severity became more pronounced as the study continued. Renal effects at 0.5% for the trisodium salt and 0.5% for the calcium chelate were severe. The NOAEL for nephrosis or nephritis in rats was considered to be 0.03% for the trisodium salt, equivalent to 30 mg/kg of body weight per day in young rats and 15 mg/kg of body weight per day as they grew older (or 10 and 20 mg of NTA per kg of body weight per day, respectively). (19).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

NTA may be beneficial in neonatal development because it increases the bioavailability of essential elements.

NTA was not teratogenic or embryotoxic in studies with mice (0.2% NTA) (29), rats (0.1 or 0.5% trisodium salt) (30), or rabbits (250 mg of trisodium salt per kg of body weight) (30).

**Mutagenicity and related end-points**

The mutagenic and clastogenic potential of NTA has been investigated both in vivo and in vitro, but the results of the assays conducted to date have been largely negative (1,7,31,32). It enhances the induction of sister chromatid exchange in Chinese hamster cells by insoluble salts of some heavy metals (33,34), and some insoluble salts of chromium(VI) are mutagenic in the Salmonella microsome assay in the presence of NTA (35).

**Carcinogenicity**

There was no evidence of carcinogenicity in studies in which weanling Charles River CD rats were fed diets containing 0.03, 0.15, or 0.5% of the trisodium salt or 0.5% of the calcium chelate of NTA for 2 years (19), groups of 80 Swiss mice were given drinking-water containing 5 g of NTA per litre or 5 g of NTA plus 1 g of sodium nitrite per litre for 26 weeks (36), or groups of 15 male and 15 female MRC rats were exposed to the same levels for 84 weeks (37).
In an experiment in which groups of 24 male and 24 female Fischer 344 rats were fed diets containing 200, 2000, or 20 000 mg of Na₃NTA·H₂O per kg of diet for 2 years, a significant increase in primary neoplasms of the urinary tract was reported in both males and females in the highest dose group; in addition, five males and five females in this group developed metastatic transitional cell carcinomas, which appeared most frequently in the lung and often in the lymph nodes, pancreas, adrenal gland, and seminal vesicle (38).

In an 18-month study, Fischer 344 rats were fed diets containing 7500 or 15 000 mg of NTA per kg of diet or 7500 or 15 000 mg of Na₃NTA·H₂O per kg of diet, and B6C3F₁ mice were fed diets containing 7500 or 15 000 mg of NTA per kg of diet or 2500 or 5000 mg of Na₃NTA·H₂O per kg of diet. Several carcinogenic effects were observed in both rats and mice. In rats, these included a significant increase in the incidence of a variety of neoplastic lesions of the urinary tract in those exposed to 15 000 mg of NTA per kg of diet, a slight increase in the incidence of neoplasms of the urinary system in those exposed to 7500 and 15 000 mg/kg of the trisodium salt, a positive dose-response relationship for the incidence of tumours of the endocrine system, and a dose-related increase in the incidence of neoplastic nodules of the liver in female rats consuming NTA. In mice, effects included a statistically significant increase in tumours of the kidney, especially tubular-cell adenocarcinomas, in males ingesting 15 000 mg of NTA per kg and a dose-related increase in the incidence of tumours of the haematopoietic system in males consuming Na₃NTA·H₂O (38).

In a study in which male Sprague-Dawley albino rats were exposed to drinking-water containing 1000 mg of trisodium salt per litre for 2 years, the incidence of renal tumours, including renal adenomas and adenocarcinomas, was significantly increased in the exposed animals (39).

The induction of tumours is considered to be due to cytotoxicity resulting from the chelation of divalent cations such as zinc and calcium in the urinary tract, leading to the development of hyperplasia and neoplasia. It has been observed, for example, that only NTA doses that increase urinary calcium are associated with transitional epithelial cell tumours, leading to the hypothesis that uncomplexed NTA in urine extracts extracellular calcium from the transitional epithelial cells of the urinary tract faster than it can be replenished (7).

14.26.6 Effects on humans

There is little information on the toxicity of NTA in humans. On the basis of physical examination, blood chemistry analysis, and urinalysis, no adverse health effects were reported in a metabolism study in which volunteers ingested a single dose of 10 mg of NTA (23).

14.26.7 Guideline value

NTA is poorly absorbed in humans as compared with experimental animals and does not appear to be metabolized in mammals. It has not been shown to be teratogenic or genotoxic in the studies conducted to date but has induced urinary tract tumours in rats and mice at high doses (38,39). IARC has placed NTA in Group 2B (40).

The reported induction of tumours in rodents is considered to be due to cytotoxicity resulting from the chelation of divalent cations such as zinc and calcium in the urinary tract, leading to the development of hyperplasia and subsequently neoplasia. In general, neoplasms have occurred only following long-term ingestion of NTA at concentrations greater than 100 mg/kg of body weight per day, whereas nephrotoxicity occurs at a lower level, between 10 and 60 mg/kg of body weight per day (7).

Because NTA is nongenotoxic and induces tumours only after prolonged exposure to doses higher than those that produce nephrotoxicity, the guideline value is derived on the basis of a NOAEL for nephrotoxic effects but incorporating a larger uncertainty factor to account for the evidence of urinary tumour induction at high doses. A TDI of 10 µg/kg of body weight was calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for carcinogenic potential at high doses) to the NOAEL of
10 mg/kg of body weight per day for nephritis and nephrosis in a 2-year study in rats (19). In view of the higher absorption of NTA in rats than in humans, it should be noted that this TDI is probably conservative. Because there is no substantial exposure from other sources, 50% of the TDI was allocated to drinking-water, resulting in a guideline value of 200 µg/litre (rounded figure).

References


14.27 Organotins

14.27.1 General description

**Identity**

The organotins are a large class of compounds which differ in their properties and applications. They can be divided into four groups of general formula $R_4Sn$, $R_3SnX$, $R_2SnX_2$, and $RSnX_3$, where $R$ is usually an organic grouping and $X$ an anion, e.g. chloride, fluoride, oxide, or hydroxide.

**Major uses**

Of the various organotins, the disubstituted and trisubstituted compounds are the most widely used, the former being employed as stabilizers in plastics, including polyvinyl chloride (PVC) water pipes, and the latter in the preservation of materials (wood, stone, textiles), as fungicides, miticides, and disinfectants, as bactericides in cooling water, and in antifouling paints.

14.27.2 Analytical methods

Mono-, di-, and tributyltins can be determined by extraction followed by derivatization to form hexylbutyltins, which are measured by gas chromatography/mass spectrometry or gas chromatography with flame-photometric detection (GC-FPD). A detection limit of 2 ng/litre is reported (1). Similar detection limits are obtained when organotins are measured by preconcentration using a tropolene-loaded silica column, followed by ethylation, separation, and detection by capillary GC-FPD (2).

14.27.3 Environmental levels and human exposure

**Air**

Unknown quantities of organotins may be released into air from factories that produce polyurethane or PVC resins in which they are used as stabilizers.
**Water**

Tributyltins have been detected in raw water and sediment as a result of their use as antifouling agents (3,4); levels of up to 2.6, 0.3, and 0.08 µg/litre have been found in marinas, estuaries, and the open sea, respectively. There is evidence that organotin stabilizers leach into water from plastic pipes; a dibutyltin sulfide concentration of 100 µg/litre was reported after a plastic pipe had been in contact with static water (5).

**Food**

Tributyltin is thought to accumulate in aquatic food-chains incorporating crabs, mussels, or oysters (6,7). In addition, the use of organotin compounds as miticides in agriculture and as PVC stabilizers may result in their presence in food. Triphenyltin residues in various foodstuffs, such as potatoes, carrots, and sugar-beet, rarely exceed 0.1 mg/kg and can be considerably reduced by washing (8).

**14.27.4 Kinetics and metabolism in laboratory animals and humans**

The available data suggest that organotins are poorly absorbed (9); for example, it was reported that only 20% of dioctyltin dichloride was absorbed in rats (10). Organotins tend to be primarily distributed in the liver and kidney following oral administration in rodents (11,12). Low levels of dioctyltin dichloride have been found in the adrenal, pituitary, and thyroid glands (10).

It appears that alkyltins are metabolized by dealkylation (13). *In vitro*, tributyltin was metabolized to dibutyltin, hydroxybutyltins, butanol, and butene (14), whereas di-, tri, and tetraethyltin appeared to form ethene and ethane (15). Carbon dioxide and butene were detected as metabolites of both dibutyltin diethanoate and tributyltin ethanoate in mice *in vivo* (14).

After oral administration, it appears that the principal route of excretion of organotins is in the faeces (11). Bile is also a significant route for some compounds, such as tetraalkyltins (13). For others, significant amounts are expired as carbon dioxide (14).

**14.27.5 Effects on laboratory animals and in vitro test systems**

**Dialkyltins**

**Acute exposure**

Acute oral LD₅₀s of diocytltins in rodents range from 880 to 8500 mg/kg of body weight (16,17). The acute oral LD₅₀ of dibutyltin dichloride in rats has been reported to be 100 mg/kg of body weight (18).

**Short-term exposure**

Rats were fed diets containing diocytltin dichloride at 0, 50, or 150 mg/kg (equivalent to 0, 2.5, and 7.5 mg/kg of body weight) for 6 weeks. The principal effect was a reduction in thymus weight at both dose levels. Lymphocyte depletion was observed in the thymus and the thymus-dependent areas of the spleen and lymph nodes (19). A weekly oral dose of 500 mg/kg of body weight for 8 weeks reduced thymus weight and induced immunodeficiency in mice, whereas a dose of 100 mg/kg of body weight did not cause such effects (20).

Dibutyltin dichloride was fed to rats at 0, 10, 20, 40, or 80 mg/kg of diet (equivalent to 0, 0.5, 1, 2, or 4 mg/kg of body weight) for 90 days. Reduction in food intake, depressed growth, and mild anaemia were noted at the highest dose level, but no treatment-related effects were observed at lower doses (21). A reduction in thymus weight and immunocompetence was observed in rats fed diets containing diocytltin...
dichloride at 75 mg/kg (about 3.8 mg/kg of body weight per day) for 8 or 12 weeks (22).

**Mutagenicity and related end-points**

Dioctyltin dichloride gave negative results in the Ames test and in tests for the induction of unscheduled DNA synthesis in primary cultures of rat hepatocytes (23). No evidence of mutagenicity was found for dibutyltin diethanoate in the Ames test (24). Dibutyltin dichloride and dioctyltin dichloride have been reported to give positive results in mammalian cell mutation assays *in vitro* in the absence of metabolic activation (23,25), and dibutyltin sulfide increased the incidence of chromosomal aberrations in rat bone marrow cells *in vivo* (5).

**Carcinogenicity**

F344 rats and B6C3F1 mice were fed diets containing dibutyltin diethanoate at 66.5 or 133 mg/kg (rats) and 76 or 152 mg/kg (mice) for 78 weeks. Nonsignificant increased incidences of hepatocellular adenomas in female mice and both hepatocellular adenomas and carcinomas in male mice were noted (26).

Rats were fed a mixture of octyltin trichloride and dioctyltin dichloride in the diet at doses equivalent to approximately 0.3, 0.7, 2.3, or 6.0 mg/kg of body weight for 2 years. A highly significant increased frequency of primary tumours of the thymus, especially thymic lymphomas, was noted in females in the highest dose group. The females also showed an increased incidence of generalized malignant lymphomas, as did the males in the two higher dose groups, although there seemed to be an unusually low incidence of such tumours in the control groups. In animals treated at the lower dose levels, no increase in the incidence of primary thymic tumours or generalized malignant lymphomas was observed (27).

**Trimethyltins**

**Acute exposure**

An acute oral LD₅₀ of 12.6 mg/kg of body weight for trimethyltin chloride in rats has been reported (28).

**Short-term exposure**

Trimethyltin is a potent neurotoxicant in rodents (28,29). In a group of rats fed diets containing 15 mg of trimethyltin per kg (equivalent to 0.8 mg/kg of body weight per day) for 2 weeks, there were some deaths, relative thymus and spleen weights were decreased, and relative kidney, testes, and adrenal weights were increased. Pathological changes indicative of severe neurotoxicity were observed in the brain. At 5 mg/kg, there was growth retardation but no effects on organ weights or brain (30).

**Mutagenicity and related end-points**

Trimethyltin may have spindle-inhibiting properties. Human lymphocyte cultures treated with trimethyltin *in vitro* exhibited a reduction in average chromosome length (31).

**Triethyltins**

**Short-term exposure**

Triethyltin, like trimethyltin, is a potent neurotoxicant. Its effects tend to be more persistent than those of trimethyltin but can be reversible. The effects of triethyltin toxicity in rats are hind-limb weakness and cerebral oedema (32).
Rats fed diets containing 15 mg of triethyltin per kg (equivalent to 0.8 mg/kg of body weight per day) for 2 weeks exhibited growth retardation, a reduction in the relative weights of the thymus and spleen, and an increase in relative adrenal weight. At 50 mg/kg, 30% of animals died, and survivors exhibited brain oedema (30).

Groups of rats were fed diets containing triethyltin hydroxide at 0, 5, 10, or 20 mg/kg (equivalent to 0, 0.3, 0.5, and 1 mg/kg of body weight) for 90 days. All the rats given 20 mg/kg died during the experiment, as did 7 of 20 given 10 mg/kg. Brain weights were significantly increased in rats at 10 mg/kg, and the growth of animals was affected at 5 mg/kg. Interstitial oedema in the central nervous system was found in rats at all doses (33).

**Tributyltins**

**Acute exposure**

Acute oral LD₅₀s of 46-114, 117-122, 85-197, and 10-234 mg/kg of body weight have been reported in rodents for tributyltin ethanoate, chloride, fluoride, and oxide, respectively (34).

**Short-term exposure**

Reductions in food consumption, weight gain, and absolute thymus weight were reported in rats fed tributyltin oxide (TBTO) at 100 mg/kg in the diet (about 5 mg/kg of body weight per day) for 4 weeks. No effects were observed at 4 or 20 mg/kg (0.2 or 1 mg/kg of body weight per day) (35).

Wistar rats fed diets containing 0, 5, 20, 80, or 320 mg of TBTO per kg (0, 0.3, 1, 4, and 16 mg/kg of body weight per day) for 4 weeks exhibited decreased mean relative weight of the thymus at 20 (males only), 80, and 320 mg/kg of diet. The only effect noted at 5 mg/kg of diet was some histopathological change in the spleen, which became more severe with increasing dose. Histopathological changes in the thymus, mesenteric lymph nodes and liver, and haematological and clinical chemistry effects were also evident in the higher dose groups (36). Using the same dose levels, Vos et al. (37) found effects on a number of immunological parameters at both 20 and 80 mg/kg of diet.

TBTO was fed to rats in their diet for 13-14 weeks. At 20 mg/kg (about 1 mg/kg of body weight per day), there was a slight increase in blood coagulation time in males and a slight decrease in food consumption without growth retardation in females. At 100 mg/kg, there were reductions in the weight of the thymus, lymph nodes, and thyroid, but an increase in adrenal weight. The NOAEL in this study was reported to be 4 mg/kg (about 0.2 mg/kg of body weight per day) (35).

**Long-term exposure**

TBTO was fed to male and female Wister rats at 0, 0.5, 5, or 50 mg/kg in their diet for 106 weeks. At 50 mg/kg of diet, the ovaries, adrenals, spleen (females), heart (males), pituitary, liver, and kidneys were all increased in weight, but thyroid weight was decreased in females. Non-neoplastic alterations included a decrease in the cell weight of the thyroid follicles in all dose groups. In addition, vacuolation and pigmentation of the proximal tubular epithelium and nephrosis were enhanced at 50 mg/kg. On the basis of marginal effects at 5 mg/kg, a NOAEL of 0.5 mg of TBTO per kg can be established, equivalent to 0.025 mg/kg of body weight per day (38).

In a study in which weanling Wistar rats were fed diets containing 0, 0.5, 5, or 50 mg of TBTO per kg for up to 17 months, TBTO was found to alter both acquired and natural host resistance, particularly at the highest dose (39). In a similar experiment, Wistar rats given the same diets for 30 months exhibited changes, mostly at the highest dose level, that included a decrease in IgG and increase in IgM in females, a decrease in lymphocyte numbers, elevated adrenal weight, reductions in liver glycogen and spleen iron, and bile duct hyperplasia (40).
Adverse effects on thymus-dependent immunity and nonspecific resistance in rats were reported following exposure to TBTO for 17 months. A dose-related suppression of resistance to the nematode *Trichinella spiralis* was reported at 5 and 50 mg/kg of diet. A NOAEL of 0.5 mg/kg of diet (equivalent to 0.025 mg/kg of body weight) was identified (41).

**Reproductive toxicity, embryotoxicity, and teratogenicity**

Pregnant NMRI mice were given oral doses of 0, 1.2, 3.5, 5.8, 11.7, 23.4, or 35 mg of TBTO per kg of body weight per day on days 6-15 of gestation. At the highest dose, there was a significant increase in numbers of resorptions. A slight reduction in average fetal weight was noted at 23.4 mg/kg of body weight but was more pronounced at the highest dose. The frequency of cleft palate increased in a dose-dependent fashion, being statistically significant at 11.7 mg/kg of body weight. However, there was also evidence of maternal toxicity at this and higher dose levels (42).

Groups of pregnant Long-Evans rats were given oral doses of 0, 2.5, 5, 10, 12, or 16 mg of TBTO per kg of body weight per day on days 6-20 of gestation. Retarded fetal growth, a reduction in numbers of live births, and effects on postnatal growth and behaviour were observed at doses of 10 mg/kg of body weight per day and above. Maternal toxicity was also evident at these dose levels. At 12 mg/kg of body weight per day, two pups born dead exhibited cleft palate (43).

**Mutagenicity and related end-points**

TBTO gave negative results in bacterial and yeast mutagenicity tests. In mammalian cells *in vitro*, it gave negative results for induction of point mutations and sister chromatid exchange, but chromosomal aberrations were induced in Chinese hamster ovary cells in the presence of the S9 fraction of a rat liver homogenate. Mice given oral doses failed to show an increased incidence of micronuclei in bone marrow polychromatic erythrocytes (34,35,42).

**Carcinogenicity**

In a 106-week TBTO feeding study in rats, the incidence of benign tumours of the pituitary was significantly elevated at 0.5 and 50 mg/kg. At 50 mg/kg of diet (about 2.5 mg/kg of body weight per day), increases in phaeochromocytomas in the adrenal medulla and parathyroid adenomas were noted. There was also a low incidence of rare pancreatic adenocarcinomas. The incidence of tumours was not dose-related (34,38).

**Tricyclohexyltins**

**Acute exposure**

Acute oral LD$_{50}$s for tricyclohexyltin hydroxide in rodents range from 235 to 1070 mg/kg of body weight (44).

**Long-term exposure**

Groups of rats were fed diets containing tricyclohexyltin hydroxide at 0, 0.8, 3, 6, or 12 mg/kg of body weight per day for 2 years. At 12 mg/kg of body weight per day, there was reduced body weight gain and increased relative spleen and liver weights in females. Similar, but milder, effects were noted at 6 mg/kg of body weight per day, whereas no adverse effects were observed at 3 mg/kg of body weight per day. A NOAEL of 0.8 mg/kg of body weight per day was reported for dogs given the same doses for 2 years (8).
Reproductive toxicity, embryotoxicity, and teratogenicity

In a multigeneration study on rats, it was found that tricyclohexyltin hydroxide had no effects on reproduction at a dose of 4-6 mg/kg of body weight per day. Similarly, no evidence for teratogenicity was observed in rabbits receiving up to 3 mg/kg of body weight per day on days 8-16 of gestation (8).

Carcinogenicity

No evidence of carcinogenicity was found in a study of rats receiving tricyclohexyltin hydroxide at concentrations of up to 12 mg/kg of body weight per day for 2 years (8).

Triphenyltins

Acute exposure

Acute oral LD_{50}s of 81-491, 80-135, 1170, and 108-500 mg/kg of body weight have been reported in rodents for triphenyltin ethanoate, chloride, fluoride, and hydroxide, respectively (44).

Short-term exposure

Weanling rats fed a diet containing 25 mg of triphenyltin hydroxide per kg for 3 or 4 weeks exhibited suppression of cell-mediated immunity but not humoral immunity (45). A reduction in relative thymus weight was observed in rats fed triphenyltin chloride at 15 mg/kg in the diet for 2 weeks. Relative spleen weight was reduced at a dietary concentration of 50 mg/kg (30).

Rats were fed diets containing up to 50 mg/kg (about 2.5 mg/kg of body weight per day) of either triphenyltin ethanoate or triphenyltin hydroxide for 90 days. Guinea-pigs received similar diets but only three times per week. Growth in rats and guinea-pigs was affected at 25 and 5 mg/kg for triphenyltin ethanoate and 50 and 20 mg/kg for triphenyltin hydroxide, respectively. Guinea-pigs given 5-20 mg of triphenyltin acetate per kg exhibited lymphocytopenia and histological changes in the lymphopoietic system and spleen (33).

Long-term exposure

In 2-year studies, the dietary NOAEL for triphenyltin hydroxide in rats was approximately 2 mg/kg (0.1 mg/kg of body weight); for triphenyltin ethanoate in guinea-pigs, it was 5 mg/kg (0.3 mg/kg of body weight) (8).

Reproductive toxicity, embryotoxicity, and teratogenicity

Groups of pregnant rats were given oral doses of triphenyltin ethanoate of 0, 5, 10, or 15 mg/kg of body weight on days 6-15 of gestation. A reduction in the body weight gain of dams and an increase in post-implantation loss were apparent at the highest dose. A reduction in fetal skeletal ossification was observed in all treated groups, but there was no evidence of teratogenicity (46).

Mutagenicity and related end-points

Triphenyltin hydroxide gave negative results for mutagenicity in bacteria but was positive for the induction of point mutations in mammalian cells in vitro (46) and in an early mouse dominant lethal assay (48).

Carcinogenicity

Groups of Fischer 344 rats and B6C3F1 mice (50 per sex per dose) were fed triphenyltin hydroxide in their diet at 37.5 or 75 mg/kg for 78 weeks; they were then kept under observation for a further 26 weeks.
There appeared to be no increase in tumour incidence as compared with controls (49).

14.27.6 Effects on humans

There is evidence that trimethyltin is neurotoxic in humans. Mental confusion and generalized epileptic seizures were noted in two chemists who had been exposed to trimethyltin in a pilot plant manufacturing dimethyltin dichloride. Both subjects recovered and regained apparently normal health (50). Severe neurological damage was reported in some workers exposed over 3 days to a mixture of trimethyltin and dimethyltin dichloride (51).

A drug containing triethyltin as an impurity produced neurological symptoms in 209 patients, 110 of whom died. Most symptoms were indicative of raised intracranial pressure as a consequence of cerebral oedema, but some patients developed paraplegia. For those patients that survived, the paraplegia was largely irreversible, but other neurotoxic effects were not (52).

14.27.7 Guideline values

**Dialkyltins**

The disubstituted compounds that may leach from PVC water pipes for a short time after installation are primarily immunotoxins, although they appear to be of low general toxicity. The data available are insufficient to permit the proposal of guideline values for individual dialkyltins.

**Tributyltin oxide**

TBTO is not genotoxic. Although one carcinogenicity study was reported in which neoplastic changes were observed in endocrine organs, the significance of these changes is considered questionable. The most sensitive end-point appears to be immunotoxicity, with a lowest NOAEL of 0.025 mg/kg of body weight per day in a 17-month feeding study in rats related to the suppression of resistance to the nematode *Trichinella spiralis* (41). The significance to humans of this finding is not completely clear, but this NOAEL is consistent, within an order of magnitude, with other NOAELs for long-term toxicity.

A TDI of 0.25 µg/kg of body weight was calculated by applying an uncertainty factor of 100 (for inter- and intraspecies variation) to the NOAEL of 0.025 mg/kg of body weight per day. The guideline value for TBTO is 2 µg/litre (rounded figure) based on an allocation of 20% of the TDI to drinking-water.

The database on the toxicity of the other trisubstituted organotin compounds is either limited or rather old. It was therefore not considered appropriate to propose guideline values for these compounds.

References


38. Wester PW et al. Chronic toxicity and carcinogenicity of bis(tri-n-butyltin) oxide (TBTO) in the rat. *Food...*


