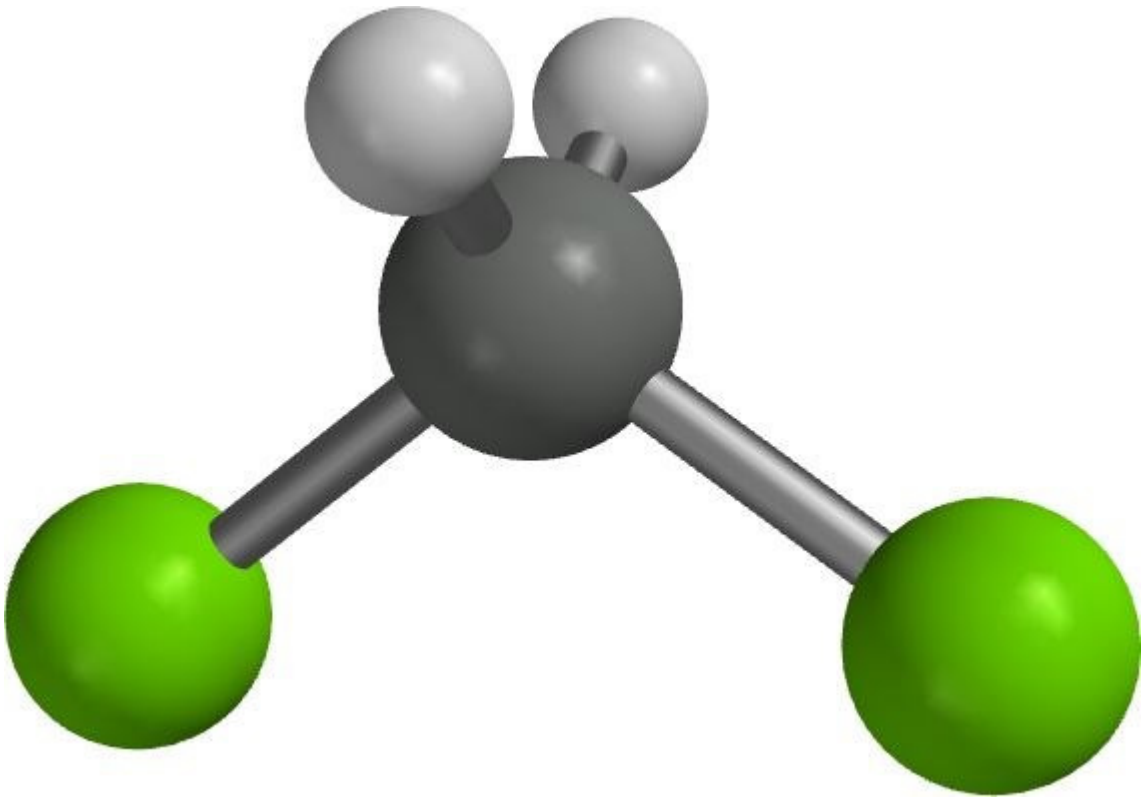
ecsa
european chlorinated solvents association

December 2015

Health Profile on Dichloromethane



eurochlor 17.

Executive Summary

The chlorinated solvent methylene chloride (also known as dichloromethane, often abbreviated as DCM) has been used in industry for over 80 years. Its unique combination of properties - low boiling point, high solvency power, relative inertness and almost non flammability - has led to its wide variety of solvent applications, such as paint and varnish removal, extraction and process solvent, aerosols (spray cans), and in electronics and metal cleaning, and as laboratory solvent; it is also used as a chemical feedstock (intermediate). It is the most widely-used of the chlorinated solvents, particularly for pharmaceuticals production.

Methylene chloride has been used extensively worldwide for many decades. During this time, the fatalities or serious injuries which have occurred have been due to massive over-exposure to vapours through a total disregard of good operating practices and risk management measures, or through deliberate misuse. When used with due care, methylene chloride poses no threat to human health or the environment. With sound operating practices that ensure exposure levels below mandatory levels, methylene chloride does not present a risk for human health or the environment.

Inhalation of solvent vapour is the most common route of exposure, when the solvent or its formulations are used in open systems or applications. In addition, vapours of methylene chloride are heavier than air and can accumulate in confined or poorly ventilated areas. As a result, proper risk management measures (ventilation or vapour extraction or respiratory protection) are essential in areas where the product is used in open applications. ECSA also strongly encourages use of state-of-the-art contained systems; to avoid the release of methylene chloride into the environment and exposure of man.

Methylene chloride does not deplete the ozone layer and its contribution to global warming, acid rain and tropospheric photochemical ozone creation is negligible, and it is not accumulating in living organisms or the environment.

As a volatile organic compound (VOC) with a boiling point of 40°C, emissions of methylene chloride from industrial installations are regulated in the EU under the Industrial Emissions Directive (2010/75/EU) (formerly by the Solvent Emissions Directive (1999/13/EC)), and other directives.

ECSA – European Chlorinated Solvent Association

Av. E. Van Nieuwenhuyse 4, box 2, B-1160 Brussels, Belgium

E-mail: ecsa@cefic.be

Web: www.chlorinated-solvents.eu

Introduction

Methylene chloride is a halogenated saturated aliphatic hydrocarbon. It is a colourless, highly volatile liquid, heavier than water, completely miscible with almost all other solvents but only sparingly soluble in water.

Chemical formula:	CH_2Cl_2
Molecular weight:	84.93 g/mol
CAS number:	75-09-2
EC number:	602-004-00-3

In Europe, methylene chloride is manufactured by (in brackets: production location):

Akzo Nobel Industrial Chemicals (Germany)
KEM ONE, formerly Arkema (France)
Olin Corporation (Blue Cube Assets Germany)
INOVYN (UK, France, Italy),

Uses

Methylene chloride's main uses are:

Process solvent: *in the industrial production of pharmaceuticals, agrochemicals, polycarbonate, cellulose triacetate, for the processing of cellulose acetate film & fibres, as extraction solvent in the food and pharmaceutical industry.*

Paint and varnish remover: *main component in paint stripping formulations in industrial installations. (Note: the use of DCM based paint strippers for consumers and professionals has been banned in the EU; only the UK has granted a derogation for trained and certified professionals).*

Metal cleaning: *for removing oils, grease and soils from metal parts in closed units, also referred to as vapour degreasing.*

Intermediate: *apart from the solvent uses, the substance is used as raw material (chemical intermediate) for the production of difluoromethane (HFC 32) that is used in refrigerant blends like R407c and R410a.*

Other uses: *in aerosol formulations for consumers, professional and industrial applications, (e.g. cleaning/degreasing products); in adhesives but also in adhesive removers; as co-blowing agent in soft polyurethane foam production; as a heat transfer / cooling fluid; as stripper of photo-resistant coatings in the production of printed circuit boards; and as laboratory solvent.*

Health Effects

Individuals are usually exposed to methylene chloride by inhalation of its vapour. Splashes of the liquid can also come into contact with the skin and eyes and can be ingested, usually by accident.

When inhaled, methylene chloride is rapidly absorbed from the lungs into the systemic circulation. It is also absorbed from the gastrointestinal tract (based on animal studies). Methylene chloride can be absorbed from the skin, however, due to its high volatility this route of exposure is of less significance than other routes of exposure under non-occlusive conditions. Once in the body, it is quite rapidly excreted, mostly unchanged *via* the lungs in the exhaled air. It can cross the blood-brain barrier and can be transferred across the placenta. Small amounts can be excreted in urine and breast milk.

When high levels of methylene chloride are absorbed, most of it is exhaled unchanged. The remainder is metabolised to carbon monoxide, carbon dioxide and inorganic chloride, whereby two routes of oxidative metabolism have been identified, one mediated by cytochrome P450 (predominantly in humans, rats and hamsters) and the other by glutathione-S-transferase T1 (GSTT1; especially in mice or only at high levels in other species).

The metabolic pathway of carbon monoxide includes the formation of carboxyhaemoglobin, which reduces the blood's ability to carry oxygen, and may exacerbate heart disease. However, this metabolic pathway becomes saturated in humans at a concentration of ca. 1800 mg/m^3, thus limiting the production of carbon monoxide and preventing excessive build-up of carboxyhaemoglobin. The second pathway, involving GSTT1 leads via formaldehyde and formate to carbon dioxide. This route only seems to be important at concentrations/doses above the saturation level of the oxidative pathway. In some species (e.g., the mouse) it is the major pathway at sufficiently high concentrations/doses. This species difference in GSTT1 metabolism correlates well with the observed species difference in carcinogenicity (see below).

Acute and short-term exposure

Methylene chloride shows acute toxicity via inhalation at high concentrations only; the 7-h LC50 value in mice was 49000 mg/m^3. The acute oral and dermal LD50 values exceeded 2000 mg/kg bw. Its acute toxicity is therefore considered to be low.

Splashes of liquid methylene chloride reaching the eyes can cause irritation that ceases when the eyes are rinsed.

As methylene chloride is a very volatile liquid, splashes on the skin will evaporate quickly thus absorption through the skin is very unlikely in these cases. However, immersion of skin parts (esp. hands and arms) in the liquid should be avoided, as the liquid can be absorbed by the skin. Repeated contact of the liquid with the skin also causes irritation, mainly due to its de-fatting properties. Prolonged contact may cause blistering.

Based on human data, methylene chloride vapours may be irritating to the respiratory tract at high concentrations. Based on human and animal data, it is not a skin sensitiser.

Repeated exposure

The NOAEC for immunotoxicity in rats was ≥ 17340 mg/m^3. Following chronic inhalation exposure, liver effects were observed in rodents and dogs; changes in renal tubules have only been observed in dogs. The 2-year inhalation NOAEC in rats was 695 mg/m^3 based on histopathological changes in the liver; the 2-year oral NOAEL in rats was 6 mg/kg bw/d based in increased haematological parameters and increased incidence of foci/areas of cellular alteration and fatty changes in the liver. A similar 2-year oral toxicity study in mice resulted in a NOAEL of 185 mg/kg bw/d based on histopathological liver changes.

Genotoxicity

Methylene chloride was found to be mutagenic in bacteria and not mutagenic in mammalian cells *in vitro*. It was found to be clastogenic *in vitro*. In general, methylene chloride did not induce chromosome aberrations, micronuclei or DNA damage in rats *in vivo* after oral or inhalation exposure. The increases in chromosomal damage (aberrations and micronuclei) seen only in B6C3F1 mice is thought to be related to this species high rate of metabolism of methylene chloride by the GSTT1 pathway. Methylene chloride tested negative for genotoxicity in standard *in vivo* studies in rats and mice. Overall, the data indicate that methylene chloride is not genotoxic *in vivo*.

Neurotoxicity

Following acute exposure, CNS effects were seen in several species at levels in excess of 14400 mg/m^3. Inhalation exposure of humans at 200 ppm (695 mg/m^3) for 4 h resulted in increased carboxyhaemoglobin levels and decreased tracking performance and a decline in response time in some neurotoxicity tests.

Following long term exposure, the results indicate no significant neurotoxic effects at concentrations of up to 2,000 ppm (6950 mg/m^3) for 90 days. Inhalation of high concentrations of methylene chloride (> 17000 mg/m^3) showed CNS depression in a broad range of species including rats and dogs. At concentrations below 7000 mg/m^3 methylene chloride did not induce neurological effects in rats. There is, therefore, no evidence that long-term exposure to methylene chloride causes irreversible CNS effects. From epidemiological studies it was concluded that chronic exposure to methylene chloride up to 475 ppm (1650 mg/m^3) did not result in effects on the CNS, nor did result in changes in cardiac and physiological parameters.

Reproductive and developmental toxicity

Several studies of potential reproductive and developmental effects of methylene chloride have been carried out in mice and rats. A No-Observed-Adverse-Effect-Concentration (NOAEC) of 5300 mg/m^3 for parental and reproduction toxicity was established from a 2-generation study in rats. The NOAEC for developmental toxicity in rats and mice was ≥ 4300 mg/m^3. The available data do not indicate that methylene chloride causes effects on fertility or induces developmental toxicity.

Carcinogenicity

Laboratory animal studies

Following lifetime inhalation exposure to high concentrations (2000 and 4000 ppm; 6950 and 13900 mg/m^3), methylene chloride is carcinogenic to mice, causing both lung and liver tumours. These tumours were not seen in rats or hamsters. In rats, in contrast, lifetime inhalation exposure to methylene chloride at 6950 and 13900 mg/m^3 resulted in increased incidences of mammary gland neoplasms. Mechanistic studies have shown that GSTT1-mediated metabolism of methylene chloride – producing reactive intermediates that are held responsible for the liver and lung tumour formation - is expressed to a greater extent in mouse tissues than in rat, hamster or human tissues, explaining the development of liver and lung tumours in mice. Mechanistic studies in rats demonstrating methylene chloride-induced elevation of serum prolactin provide evidence that mammary tumours found in rats are plausibly related to hyperprolactinaemia. As such there is some evidence from animal studies that methylene chloride may cause cancer, which is based either on a metabolism less relevant for humans or by a non genotoxic, threshold-mediated mode of action.

Epidemiology studies

In several epidemiological studies the mortality and cancer incidence patterns were investigated in large populations exposed to methylene chloride during its manufacture or use. These studies, where cohorts of industrial workers were compared with corresponding non-exposed populations, show no clear evidence for increased cancer risk due to exposure to relatively high concentrations of methylene chloride. Sporadic and weak associations were reported for cancers of the pancreas, liver, biliary passages, breast and brain. The exposure concentrations in the facilities under investigation regularly exceeded 100 ppm (348 mg/m^3) as daily time weighted averages and occasionally exceeded 500 ppm (1738 mg/m^3). The typical follow-up periods of these studies were between 20 and 50 years of observation.

In a recent evaluation by IARC in 2014, IARC classified methylene chloride as 'probably carcinogenic to humans (Group 2A)' on the basis of the limited evidence in humans (biliary-tract cancer and non-Hodgkin lymphoma) and on sufficient evidence of carcinogenicity in mice (lung and liver tumours). IARC considered that the specific metabolism observed in mice could also occur in humans. However, as indicated above, occupational studies have shown no strong or consistent findings for any site of cancer despite several studies of large occupational cohorts of workers potentially exposed to high concentrations of dichloromethane.

Moreover, methylene chloride is not genotoxic *in vivo*, and a detailed analysis of gene expression in mice has even shown that tumour responses could not be linked to effects expected for genotoxic carcinogens. Rather, this analysis showed that the response in mice may be due to increased levels of carboxyhaemoglobin and tissue carbon monoxide causing altered tissue oxygenation.

Environmental Effects

Air

The atmospheric half-life of methylene chloride is approximately 107 days. Once in the atmosphere, the most important removal process from the atmosphere is the reaction with hydroxyl radicals in the troposphere. Methylene chloride is photochemically oxidized by hydroxyl radicals abstracting H atoms.

In the stratosphere methylene chloride will rapidly degrade by photolysis and reaction with chlorine radicals.

Methylene chloride does not have ozone depletion potential (ODP ~ 0). The contribution of emitted DCM to acid rain and smog formation is negligible, and with a photochemical ozone creation potential (POCP) of 0.009 DCM is not a precursor of tropospheric ozone. Its contribution to global warming is also negligible due to its low global warming potential (GWP) of 8.7 (based on a 100 years horizon) in combination with its short lifetime.

Water

In the aquatic environment as well as in soil, methylene chloride is completely degraded via natural processes with final mineralisation to chloride ions and CO2. As a very volatile substance, DCM is mainly emitted from emissive uses (`open uses´) into the atmosphere or into waste waters, which are usually fed to municipal or industrial waste water treatment plants which eliminate DCM virtually completely. DCM is biodegradable in all environmental compartments (readily biodegradable after OECD Guideline 301 D), and thus does not persist or accumulate in living organisms or the environment.

Generally, discharge of the substance and formulations to waste water should be prevented and recovered as much as possible. Waste waters containing DCM above certain levels need to be treated by industrial or municipal sewage treatment plants, to keep emissions to natural waters below the limits set by legislation.

Soil

Emissions from/to soil are not considered to be relevant for methylene chloride.

PNECs derived under REACH

Compartment	PNEC
Freshwater	0.31 mg/L
Marine water	0.031 mg/L
Intermittent releases to water	0.27 mg/L
Sediments (freshwater)	2.57 mg/kg sediment dw
Sediments (marine water)	0.26 mg/kg sediment dw
Sewage treatment plant	25.9 mg/L
Soil	0.33 mg/kg soil dw
Air	n.a
Secondary poisoning	n.a.

Occupational Exposure Limits

In Europe, the Scientific Committee on Occupational Exposure Limits (SCOEL) published the following recommendation in 2009:

8 hour OEL (TWA):	100 ppm (353 mg/m^3)
15 min STEL (TWA):	200 ppm (706 mg/m^3)
Biological Limit Values:	CO: 4% COHb DCM: 0.3 mg/L in urine and 1 mg/L in blood

Note: In individual EU countries differing OELs and BLVs have been set, which are relevant for national work safety / occupational hygiene.

DNELs for Workers and General Population derived under REACH

Workers

DNEL inhalation long term, systemic effects:	100 ppm (353 mg/m^3)
DNEL inhalation short term, systemic effects:	200 ppm (706 mg/m^3)
DNEL dermal long term, systemic effects:	12 mg/kg/day

General Population

DNEL inhalation long term, systemic effects:	25 ppm (88.3 mg/m^3)
DNEL inhalation short term, systemic effects:	100 ppm (353 mg/m^3)
DNEL dermal long term, systemic effects:	5.82 mg/kg bw/day
DNEL oral long term, systemic effects:	0.06 mg/kg bw/day

Classification & Labelling

Below information is meant as a summary. Full information on Classification & Labelling (including precautionary statements) of the substance is to be found on the ECHA webpage of registered substances.

a) Regulation EC 1272/2008:

- Classification:
  - o Carcinogenicity Cat 2: H351 Suspected of causing cancer.

- Labelling:
  - o Signal word: Warning
  - o Pictogram: GHS08 (health hazard)
  - o Hazard Phrase H351 Suspected of causing cancer.

b) Self-classification by the REACH consortium after GHS criteria (Regulation EC 1272/2008):

- Classification
  - o Skin corrosion / irritation Cat 2: H315 Causes skin irritation
  - o Serious eye damage/eye irritation Cat 2: H319 Causes serious eye irritation
  - o Carcinogenicity Cat 2: H351 Suspected of causing cancer. Route of exposure: Inhalation
  - o Specific target organ toxicity - single exposure Cat 3:
    H336 May cause drowsiness or dizziness
    Affected organs: central nervous system
    Route of exposure: Inhalation

- Labelling:

o Signal word:	Warning
o Pictograms:	GHS07 (exclamation mark)
	GHS08 (health hazard)
o Hazard Phrase	H315 Causes skin irritation
	H319 Causes serious eye irritation
	H351 Suspected of causing cancer. Route of exposure: Inhala tion
	H336 May cause drowsiness or dizziness.
	Affected organs: central nervous system.
	Route of exposure: Inhalation

o Precautionary Phrases (restricted set for packaging label)

P201: Obtain special instructions before use.

P261: Avoid breathing vapours/spray.

P281: Use personal protective equipment as required.

P312: Call a POISON CENTER or doctor/physician if you feel unwell.

P501: Dispose of contents/container to [permitted disposal plant]

Regulation & Voluntary Industry Action

As a highly volatile organic compound (VOC) with a boiling point of 40°C, emissions of methylene chloride from industrial installations are regulated in the EU under the Industrial Emissions Directive (2010/75/EU) (formerly by the Solvent Emissions Directive (1999/13/EC)), and other directives. ECSA welcomes the implementation of this directive, with its goals of reducing workplace exposures and emissions from industrial installations. Modern equipment allows more efficient use of chlorinated solvents, and will continue to contribute to the sustainability of this class of products.

In 2010 ECSA members jointly registered methylene chloride under REACH (Regulation EC 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals). An excerpt of the registration dossier can be consulted via the ECHA website on registered substances.

ECSA released in 2011 an online toolbox freely accessible via the ECSA website to provide users of chlorinated solvents with information about the safe & sustainable use of these products. The recommendations do take into account REACH as well as other European legislation or voluntary industry commitments. The content of the toolbox is based on the REACH Chemical Safety Assessment (CSA) of the substances; however, it includes recommendations based on experience of ECSA members that go beyond the given legal framework of the CSA.

Revision Date: December 2015