



Scientific Committee on Consumer Safety

SCCS

OPINION on

Dichloromethane

The SCCS adopted this opinion at its 17th plenary meeting
of 11 December 2012

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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1. BACKGROUND

Dichloromethane is a synonym of methylene chloride and has the CAS n° 75-09-2 and the EC n° 200-838-9. Dichloromethane has been restricted since 1976 and it is currently restricted in Annex III entry 7 of the cosmetics directive (76/768/EEC) to a concentration of up to 35% and furthermore, when the substance is mixed with 1,1,1-trichloroethane, the total concentration must not exceed 35%.

[The mixing with 1,1,1-trichloroethane is properly not relevant any longer as the latter is covered by Regulation 1005/2009 (EC) on ozone depleting substances].

From the first opinion it could be understood that dichloromethane was used as a propellant and originally this was reflected in the Directive under the heading "Conditions of use and warnings which must be printed in the label": "For preparations in aerosol dispensers. Do not spray on a naked flame or any incandescent material". This sentence was deleted by Directive 82/368/EEC.

In the Cosmetics Directive under the heading of "Other limitations and requirements" it is said: "0.2% as maximum impurity content". However, this statement seems to be ambiguous since it is not clear whether dichloromethane must not be present in other ingredients or in cosmetic products as an impurity in a concentration up to 0.2% or should the purity of dichloromethane be of a minimum of 99.8%.

The first scientific opinion on dichloromethane was delivered on the 30 June 1987 and a supplementary report by the scientific committee on cosmetology was delivered on the 11 April 1989, where the safety of use at the above mentioned concentrations was confirmed.

Dichloromethane is classified as a CMR substance, carcinogenic category 2 (CLP).

After a public call for scientific data the current submission has been compiled.

2. TERMS OF REFERENCE

1. *On the basis of the provided data the SCCS is asked to assess the risk to consumers when dichloromethane is used in cosmetic products under the current use conditions of max. 35% in cosmetic products*
2. *If this limit is considered safe, should the restriction of 35% be limited to its use as a propellant or can other uses as solvent up to 35% be accepted?*
3. *Can the SCCS assess whether the restriction on purity should be interpreted as purity criteria for the dichloromethane itself or should it be its presence as an impurity in cosmetic products that should be restricted to 0.2%?*
4. Does the SCCP have any further scientific concern with regard to its use in cosmetic products?

3. OPINION

After publication of the mandate for this assessment and during a public call for data, no indications were received that dichloromethane is presently used in cosmetic products on the European market. No comprehensive safety dossier has been submitted for this assessment, which consequently is based primarily on publicly available data and recent risk assessments performed by other bodies.

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Dichloromethane (IUPAC)

3.1.1.2. Chemical names

Methylene chloride
Methylene dichloride
Methylene bichloride

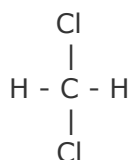
3.1.1.3 Trade names and abbreviations

| | |
|------------|---------|
| Solmethine | R-30 |
| Narkotil | DCM |
| Solaesthin | UN 1593 |
| Di-clo | MDC |
| Freon 30 | |

3.1.1.4 CAS /EC number

| | |
|------------|-----------|
| CAS: | 75-09-2 |
| EC: | 200-838-9 |
| UN No.: | 1593 |
| RTECS No.: | PA8050000 |

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

Formula: CH₂Cl₂

3.1.2 Physical form

Dichloromethane is a colourless, free-flowing non-flammable liquid with a penetrating, sweetish, ether-like odour. The odour threshold is 100-250 ppm. Highly volatile; spills will dry approximately 90-times faster than the equivalent volume of water at room temperature. The vapour is denser than air.

3.1.3 Molecular weight

Molecular weight: 84.93 g/mol

3.1.4 Impurities / accompanying contaminants

Traces of hydrochloric acid may occur in the presence of water.

3.1.5 Solubility

Water Solubility: Slightly soluble (13 g/L at 20 °C) (IPCS-INCHEM)
Soluble in alcohol and ether

3.1.6 Partition coefficient (Log P_{ow})

Log P_{ow}: 1.25

3.1.7 Additional physicochemical specifications

| | |
|--------------------------------|-----------------------------------------------------|
| Evaporation Rate: | 27.5 (n-butyl acetate = 1) |
| 1 ppm = 3.53 mg/m ³ | 1 mg/m ³ = 0.283 ppm at 20 °C (1013 hPa) |
| Melting point: | - 97 °C |
| Boiling point: | 40 °C |
| Flash point: | 556 °C |
| Vapour pressure: | 57.99 kPa at 25 °C |
| Density: | 1.33 g/cm ³ |
| Viscosity: | 0.393 mPa.s at 30 °C |

3.1.8. Stability

Stable under normal temperature conditions; decomposes on red-hot surfaces, in electric arcs or naked flames to give predominantly hydrochloric acid and a trace of phosgene gas.

3.1.9 Commercial Purity

Commercial grades of dichloromethane normally contain 0.005-0.02% of a stabiliser (methanol, ethanol, phenol, p-cresol, resorcinol, thymol, cyclohexane or *t*-butyl amine) to prevent formation of hydrochloric acid.

3.2 Function and uses

Dichloromethane is a saturated aliphatic halogenated hydrocarbon and was introduced over 60 years ago as a replacement for more flammable solvents. It does not occur naturally in the environment. However, its physical properties mean that it is a widely used industrial solvent with a worldwide production of several hundred thousand tonnes per annum.

The white paper on dichloromethane (DCM) by the Halogenated Solvents Industry Alliance in March 2008 (40) lists its uses as: paint removal (wood and metal); formulated product (adhesives, foam production, aerosols); pharmaceutical manufacture (solvent for reactions, re-crystallisations and extractions, carrier for tablet coatings); chemical processing (manufacture of polycarbonate resin and cellulose triacetate, solvent welding of plastics,

releasing agent from moulds); metal cleaning (degreasing agent both as a liquid and vapour); foam manufacture (as a blowing agent); various other solvent-related uses.

In hair spray formulations it acts as a solvent for active ingredients and as a propellant. In industrial processes it offers high purity and solvency and can be readily recycled by distillation from the final product.

3.3 Toxicological Evaluation – Animal data

As the abundant human data are much more relevant in order to assess the risk to consumers for the use of dichloromethane in cosmetic products, toxicity data from animal studies are only briefly summarised in this opinion and are based on the evaluations performed by the Scientific Committee on Occupational Exposure Limits (SCOEL) in 2009 (82) and the IPCS/WHO in 1996 (47) as well as by IARC in 1999 (45).

3.3.1. Acute Toxicity

3.3.1.1 Acute oral toxicity

The acute oral toxicity of dichloromethane is low with reported LD₅₀-values ranging from 1410 to 3000 mg/kg bw in rats, mice and dogs (47, 82).

3.3.1.2 Acute inhalation toxicity

The acute inhalation toxicity of dichloromethane is low with reported LC₅₀ values (6h) ranging from 11,380 ppm (40,200 mg/m³) to 15,810 ppm (55,870 mg/m³) in rats, mice and guinea pigs (47, 82).

Acute effects were primarily noted in the CNS and in the liver (several species). CNS disturbances were reported at concentrations above approximately 3900 ppm (14,000 mg/m³) with slight EEG (electroencephalographic) changes being reported in rats at concentrations above 1,700 mg/m³. Slight histological changes in the liver were observed at concentrations above approximately 17,700 mg/m³. Cardiac sensitisation to the effects of adrenaline was reported in mice exposed to 710,000 mg/m³ for 6 minutes. Cardiovascular effects have been reported in monkeys, dogs, and rabbits at concentrations above 35,300 mg/m³ for 1-5 minutes; however, the findings were inconsistent. Occasionally other organs were also affected, e.g., the kidney, and respiratory system (47, 82).

3.3.2 Irritation/corrosivity

Dichloromethane causes moderate skin irritation in rabbits and reversible irritation (moderate to severe changes) to the rabbit eye (47, 82).

3.3.3 Skin sensitisation

No data are available (47, 82).

3.3.4 Dermal/percutaneous absorption

Dichloromethane can be absorbed across the skin in man and animals. Studies on the permeability of rat and mouse skin to dichloromethane *in vitro* and *in vivo* (95) have shown transdermal fluxes ranging from 2.7-6.6 mg/cm²/h (the corresponding value in man is 2.4mg/cm²/h (96)).

3.3.5 Repeated dose toxicity

3.3.5.1 Repeated dose, inhalation toxicity

IPCS/WHO reviewed several inhalation studies. The results of the studies can be summarised as follows (47, 82):

Prolonged exposure to high concentrations of dichloromethane ($\geq 17\,700$ mg/m³, 6 hours/day, 5 days/week for 18/19 exposures) caused reversible CNS effects, slight eye irritation and mortality in several laboratory species. No evidence of irreversible neurological damage was observed in rats exposed for up to 7100 mg/m³ for 13 weeks (6 hours/day, 5 days/week). Effects on brain chemistry were observed in rats following exposure to ≥ 250 mg/m³ (6 hours/day for 3 days).

Following intermittent exposure, histopathological changes were observed in the liver of rats at 3500 mg/m³ (2 hours/day for 20 days) and in mice at 14100 mg/m³ (6 hours/day for 21 days); no effects were noted in the liver of rats following exposure to 880 mg/m³ (5 hours/day for 28 days). After continuous exposure (for 100 days), slight cytoplasmic vacuolisation in the liver of both rats and mice were seen at 88 mg/m³.

3.3.5.2 Repeated dose, oral toxicity

IPCS/WHO reviewed a few oral studies. The results of the studies can be summarised as follows (47, 82):

In rats, oral administration of dichloromethane in drinking water (125 mg/L for 13 weeks) did not result in any adverse effects (the concentration in drinking water was equivalent to 17.5 mg/kg bw/day assuming a rat body weight of 350 g and an intake of 0.049 litres water/day).

When dichloromethane was administered in the drinking water to rats and mice for 3 months, slightly decreased body weights and histopathological changes in liver were noted in both species from a concentration equivalent to approximately 607 and 226 mg/kg bw/day for rats and mice, respectively.

3.3.6 Mutagenicity/genotoxicity

IARC (45) and IPCS/WHO (47) reviewed numerous mutagenicity and genotoxicity tests performed on bacteria, fungi and cultured mammalian cells as well as a number of *in vivo* studies on mice and rats. The results of the studies with dichloromethane (methylene chloride) have been summarised by SCOEL as follows (82):

"Methylene chloride is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems. Methylene chloride induced sister chromatid exchanges, chromosome breakage and chromosome loss in vitro in human cells. In-vitro results in rodent cells were inconclusive or negative. Methylene chloride induced DNA single-strand breaks in mammalian cell cultures, but inconclusive or negative effects were reported for induction of gene mutations. It did not induce unscheduled DNA synthesis either in vivo in rodents or in human fibroblast cultures. It was genotoxic in fungi but not in Drosophila in the sex-linked recessive lethal assay."

Hu et al (44) using a Comet assay with V79 hamster cells transfected with mouse GST-T1 and treated with 2.5, 5.0 and 10 mM dichloromethane reported a dose dependent increase in DNA-protein cross links in transfected as opposed to parental cells.

Watanabe et al (99) administered dichloromethane by intraperitoneal injection to Fischer 344 rats (male) and B6C3F1 mice (male and female). DNA was isolated from livers and kidneys but none of the four known DNA adducts was detected.

3.3.7 Carcinogenicity

IARC (45) and IPCS/WHO (47) reviewed several inhalation studies performed on rats, mice and hamsters. The results of the studies can be summarised as follows (45, 47, 82):

Dichloromethane showed clear evidence of carcinogenicity in mice, causing both alveolar/bronchiolar neoplasms and hepatocellular neoplasms, following exposure to high concentrations (>7100 mg/m³ 6 hours/day, 5 days/week for 26 weeks and maintained for a further 78 weeks). Associated toxicity or hyperplasia in the target organs was not observed.

In rats, an increased incidence of benign mammary tumours has been reported for female rats (three studies) and for male rats (one study). In contrast, hamsters showed no evidence of carcinogenic effects related to exposure to dichloromethane (up to 12 400 mg/m³ 6 hours/day, 5 days/week for 2 years).

IARC (45) and IPCS/WHO (47) reviewed a few oral studies performed in rats and mice. No clear evidence of a carcinogenic effect was observed (up to 250 mg/kg bw/ day for 2 years in drinking water; or up to 500 mg/kg bw/day for 64 weeks by gavage in olive oil (45, 47, 82).

IARC (45) concluded that there is sufficient evidence in experimental animals for the carcinogenicity of dichloromethane. In the evaluation it was pointed out that mechanistic studies have established a link between glutathione S-transferase-mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice. The glutathione S-transferase responsible for the metabolism of dichloromethane is expressed to significantly greater extents in mouse tissues than in rat, hamster or human tissues and thus, the available data suggest a plausible mechanism for the development of liver and lung tumours occurring in mice which is assumed to be of less importance in rats and hamsters.

3.3.8 Reproductive toxicity

IPCS/WHO reviewed one two-generation study performed on rats and four developmental studies performed on rats and mice. The results of the studies can be summarised as follows (47, 82):

In the two-generation study, no evidence of adverse effects on reproductive parameters or neonatal survival/growth was found in either generation (inhalation exposure: up to 5300 mg/m³ 6 hours/day, 5 days/week for 17 weeks).

No teratogenic effects were reported in rats or mice (inhalation exposure: up to 16 250 mg/m³ for rats and up to 4400 mg/m³ for mice; oral exposure: up to 4% in their diet). An increased incidence of minor skeletal anomalies (dilated renal pelvis in rats, extra sternebrae in mice) was reported in one study (inhalation exposure: 4400 mg/m³ 7 hours/day on gestational days 6-15); maternal body weight was increased in mice and dams of both species had COHb levels of up to about 12% during exposure. No behavioural effects were noted in litters from rats (inhalation exposure: up to 16 250 mg/m³); foetal body weights were reduced and maternal COHb ranged from 7.1 to 10.1% during exposure.

3.3.9 Immunotoxicity

No effects on immune function or thymus weight were reported in rats (inhalation exposure: 17 700 mg/m³ 6 hours/day, 5 days/week for 28 days); a significant decrease in relative spleen weight was observed in females (98).

3.4 Toxicological Evaluation – Human data

3.4.1 Acute Toxicity

Table 1: Acute Toxicity parameters in humans, modified from reference 47

| ppm Dichloromethane | Effect | Time |
|---------------------|------------------------------------|--------|
| 100-280 | Odour threshold | |
| 300-800 | Psychomotor/sensory impaired | 40 min |
| 500-1000 | light-headedness | 1-2h |
| 2300 | Irritation, dizziness | 5 min |
| 2300 | Nausea | 30 min |
| Up to 5000 | Headache, fatigue, irritation | 10 min |
| 7200 | Paraesthesia, irritation | 8 min |
| 8000-20 000 | narcosis | 0.5-4h |
| > 50 000 | Immediate danger to life or health | |

3.4.1.1 Acute Oral toxicity

The adult fatal dose by ingestion or inhalation is ~ 25ml (27). When dichloromethane was ingested orally, CNS depression, tachypnoea and corrosive damage to the gastrointestinal tract were seen; the COHb level was elevated in 2 out of 6 cases (17).

3.4.1.2. Acute/chronic inhalation toxicity

Inhalation is the primary route of exposure where it can cause slight irritation to the upper respiratory tract with signs of mild depression of the central nervous system (CNS) such as dizziness, nausea, inability to concentrate and reduced coordination. Exposure to high concentrations may result in unconsciousness, pulmonary oedema, respiratory failure and death; hyperbaric oxygen therapy has been used to treat acute intoxication (14). However, when the health of groups of workers who have been regularly exposed to dichloromethane vapour for many years has been compared to similar unexposed groups, no significant differences have been observed (42).

In man, a steady state in blood and exhaled air is achieved rapidly after inhalation, usually after less than 1h with no substantial increase after 7.5 h. At 50-500 ppm net values of 52-75% are absorbed at steady state with lower values at higher concentrations and dichloromethane is then distributed to all tissues. For average sedentary non-smoking workers, the exposure of 200 ppm dichloromethane for 7.5 hours gave levels of 80 ppm in expired air and 0.18 mg/ml in blood with COHb levels of 6.8% (25, 30).

Neurotoxicity is the main effect of an acute inhalation dose of dichloromethane in humans. Experiments with volunteers have shown that neurobehavioral changes (impaired tracking, disturbed concentration) were seen after exposure to 250 ppm (882 mg/m³) for 1.5-3 hours; effects on visual function were also observed after 95 minutes exposure to 290 ppm (1024 mg/m³) while exposure to 672 ppm (2372 mg/m³) for 1 hour gave light-headedness as well as effects on visual function (76, 89, 100). Dependent on dichloromethane concentration and exposure time, carbon monoxide is formed by oxidative metabolism (for details see section 3.5.1). Carbon monoxide depresses CNS functions by forming an adduct with haemoglobin (carboxyhaemoglobin, COHb). COHb decreases the oxygen-carrying

capacity of the blood and CNS symptoms such as initial light-headedness and headache, then unconsciousness, would be expected. When visual flicker fusion frequency, auditory vigilance and psychomotor tasks were monitored in 38 women exposed to dichloromethane levels of 300-800 ppm for 4 hours in an exposure chamber, a depressed response to auditory vigilance and visual flicker fusion was seen at 300 ppm although this did not occur in volunteers exposed to 100 ppm CO for 5 hours (100). Putz et al. (76) exposed healthy volunteers to separate 4-hour exposures to 70 ppm CO and 200 ppm dichloromethane (the COHb level reached 5% in each case) and found that eye-hand coordination and auditory vigilance were impaired with both exposures. However, aside from effects mediated via COHb formation, dichloromethane itself can also have direct effects such as respiratory depression and narcosis since in some fatal industrial accidents, the COHb levels were within the normal range (102). Stewart et al. (89) reported that a 1-hour exposure to 868 or 986 ppm lead to light-headedness and difficulties in enunciation in volunteers; these effects were not observed after a 1-hour exposure to 514 ppm. Since the CNS effects disappeared within 5 minutes after cessation of exposure whereas the COHb level increased for at least an hour post-exposure the effects were attributed to the concentration of dichloromethane in the brain rather than to the formation of COHb (114).

An important issue are short-term exposures of consumers by use of hair sprays containing dichloromethane as a solvent (see Section 4). Short-term exposures of 30 min to dichloromethane concentrations of up to 2600 mg/m³ (around 750 ppm) had no effect on mental ability of healthy young male subjects when reaction time, short-term memory and numerical ability were tested whereas slight impairments of reaction time were observed at 3470 mg/m³ (around 1000 ppm) (103). Short-term exposures by dichloromethane in hair sprays and experimental exposures of volunteers are compared in Annex 1.

3.4.2 Irritation/corrosivity

Dichloromethane is corrosive to the eye and respiratory tract (102) Dichloromethane is classed as a moderate to severe irritant and can cause second and third degree burns if contact is prolonged e.g. if the liquid is trapped next to the skin by gloves or shoes. It should be noted that most commonly available types of glove provide only very limited protection against dichloromethane. Repeated low-level skin contact may result in dermatitis (redness and irritation) (47).

In humans, eye contact with dichloromethane vapour may cause mild to severe irritation depending on the concentration while the liquid may cause temporary damage to the cornea (47).

3.4.3 Dermal/percutaneous absorption

Dichloromethane can be absorbed through the skin in both humans and animals. Studies where dichloromethane was applied to human skin *in vitro* (96) show rapid absorption and skin exposure could potentially make a significant contribution to the total exposure to dichloromethane. Dermal absorption depends on type of skin and surface area and duration of exposure. Immersion of one thumb in 80 ml dichloromethane for 30 min produced a mean peak breath concentration of 3.1 ppm; by 2 h post exposure the mean value was 0.699 ppm (88). Due to its capacity for absorption by the dermal route, SCOEL has given dichloromethane a 'skin' notation (82).

3.4.4 Subchronic and chronic studies

There have been many studies of possible morbidity associated with exposure to dichloromethane in the workplace but most of these either do not include controls or are small scale or of environments where other solvents were in use at the same time. However, the data suggest that exposures of about 100 ppm over several years are not associated with any adverse effects (18, 19, 25) and that workplace exposure to dichloromethane at concentrations of up to 475 ppm has no significant effect on mortality. At higher levels in man, some neurotoxicity effects (memory and attention), eye and

respiratory tract irritation have been seen (29, 56, 64, 85, 86). There was a possibility of high-level deficits in the central part of the vestibular system in workers in the plastics industry but there was no relationship with exposure (101). Ott et al (72, 73, 74, 75) evaluated parameters of hepatic, haemopoietic and cardiac function in workers exposed to dichloromethane, with median Time Weighted Average (TWA) exposures from 60-475 ppm. Multiple regression analysis was used to control for parameters such as smoking status, age, sex and race. Increases in COHb were seen in all groups (increases of 0.7-2.1%/100 ppm increase in dichloromethane) but there were no changes in liver function. In a study (75) on exposure to dichloromethane (TWA 0-900 ppm), the results suggested a partial saturation of the enzyme systems metabolising the solvent and residual CO metabolism from the previous day in workers exposed at the highest levels. When continuous cardiac monitoring was evaluated in workers exposed to dichloromethane (60-475 ppm) in the workplace and with a history of heart disease, there were no differences in ECGs for workers and controls. Soden et al (85) studied the relationship between dichloromethane exposure, smoking and COHb levels. They noted that non-smokers had a maximum of 4.0% COHb at an average exposure of 90 ppm after shift while smokers had a corresponding maximum COHb level of 6.35% for exposures of 99 ppm and concluded that dichloromethane at this level did not give sufficient COHb to cause cardiac symptoms. Other workers have shown that the raised COHb levels from metabolism of dichloromethane are not linked with any increased risk of ischaemic heart disease (41, 42, 94). In a study with 56 exposed workers and 36 unexposed workers, Cherry et al (19) monitored exposure to dichloromethane (28-173 ppm) and blood levels and found some deterioration in mood with increased tiredness in workers at the highest concentrations. The level at which symptoms did not occur was ~100 ppm. The possibility that dichloromethane caused chronic CNS effects (impaired memory, and attention) was evaluated by Lash et al (56) who studied retired aircraft maintenance workers. The mean TWA in the work zone ranged from 82-236 ppm and averaged 225 ppm for painters and 100 ppm for mechanics. The evaluation included measurement of auditory response potential, grip strength, reaction times, short-term visual memory, attention and spatial ability. The final group sizes were very small (25 cases, 21 controls) so that the power to detect statistically significant differences was low; however, the exposed group had a slightly higher score on verbal memory tasks and a slightly lower score on the attention tasks and complex reaction time as compared with the controls.

3.4.5 Carcinogenicity, epidemiological studies

No consistent associations between exposure to dichloromethane and cancer at any particular site have been reported. There are many studies but most of these lack adequate controls, full information on the extent of exposure to dichloromethane, are from sites where use of dichloromethane was combined with that of other solvents and chemicals or have insufficient data on the subjects. The topic has been extensively reviewed (9, 10, 45, 82).

Two overlapping cohorts of employees were studied from a firm that manufactured photographic film support and used dichloromethane in the process (42). The first cohort contained 1311 men with a mean exposure of 39 ppm in an 8-hr time weighted average for 17 years. The median length of follow-up was 34 years from time of first exposure. Another cohort of 1913 men had 26 ppm (8-h time weighted exposure) for 24 years. The median length of follow-up from first exposure was 35 years. When compared with the general population, mortality was below expectation for all causes of death including ischaemic heart disease and cancers (including those of the lung), apart from possible weak associations with brain cancer and leukaemia.

Table 2: Summary of cohort studies and dichloromethane exposure

| Ref | Population data | Follow-up time | Inclusion criteria | Assessment | Cancers recorded |
|-----|---------------------|----------------|--------------------|---------------|------------------------|
| 55 | N=1271 (551M, 720F) | ~28 years | At least 3 | Work history/ | Liver SMR 2.98 (95%CI) |

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| Ref | Population data | Follow-up time | Inclusion criteria | Assessment | Cancers recorded |
|-----|---------------------------------------------------------------------|-------------------|------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| | Median exposure 140, 280, 475 ppm | | Months in preparation or extrusion areas | death certificate | 0.81-7.63), Lung SMR 0.80 (95%CI 0.43-1.37) |
| 36 | N=2909 (1931M, 978F) 50-100 ppm and 350-700 ppm, duration not given | ~17 years | Employed at least 3 months | Work history, air monitoring, death certificate | M, SMR~1.0 for lung cancer and leukaemia, F SMR ~1.0 for breast cancer and leukaemia |
| 94 | N=1473 M, mean 19 ppm Mean duration 9 years | Mean 27 years | Anytime employed | Work history, air monitoring death certificate | Brain cancer SMR 1.45 (95%CI 0.40-3.72) Lung cancer SMR 0.46 (95%CI 0.29-0.75) |
| 12 | N=14,066 (10461M, 3605F) exposure not reported | ~29 years | Employed at least 1 year | Work history/death certificate | M non-Hodgkin's lymphoma SMR~2.8(95%CI 0.68-7.8) F breast cancer SMR 2.6 (95% CI 1.0-6.3) |
| 42 | N=1311 M mean 39 ppm, 17 years N=1013 M mean 26 ppm, 24 years | 35 years 26 years | Employed at least 1 year | Work history/ death certificate | SMRs <1.0 for lung, liver, and pancreatic cancers Brain cancer SMR 2.16 (95%CI 0.79-4.69) leukaemia SMR 2.04 (95%CI 0.88-4.03) |

Heineman et al (43) carried out a detailed study on any association between astrocytic brain cancer and occupational exposure to chlorinated aliphatic hydrocarbons. The OR for the association between any exposure to dichloromethane and the risk of astrocytic brain cancer was 1.3 (95% CI 0.9-1.8) with a statistically significant trend ($p < 0.05$) with increasing probability of exposure to dichloromethane as compared with unexposed controls (OR = 2.4 (95% CI 1.0-5.9) for the high exposure group). This study has been criticised for the lack of direct exposure information (68) and for the apparent lack of correlation with animal studies although later results on another cohort of workers have also suggested an association between dichloromethane and CNS cancers (41). Cocco et al (20) have published results showing a weak association between dichloromethane exposure and CNS cancer (OR 1.2 (95% CI 1.1-1.3) although there were no exposure-related trends. In a case-control study of occupational exposures to dichloromethane and breast cancer mortality (15), there was little conclusive evidence of any association, nor was there a causal association between dichloromethane exposure and pancreatic cancer in a meta-analysis of studies reported over 30 years (50, 70). These reports all used cause of death data from death certificates and a job-exposure matrix to evaluate exposure intensity and probability; some, but not all, confounding factors were adjusted for. In a detailed study on renal cancer, with a relatively focused job exposure matrix, no association was found with dichloromethane exposure (26). Dumas et al (28) reported data from a case control study on rectal cancer; this had a large number of incident cases, specific job information and a clear diagnosis but had relatively low statistical power since a general population was used for controls. The OR for any exposure to dichloromethane was 1.2 (95% CI 0.5-2.8) and for substantial exposure was 3.8 (95% CI 1.1-12.2). Using data from structured telephone interviews, Infante-Rivard et al (46) examined the association between maternal occupational exposures to solvents, including dichloromethane, before and during pregnancy and risk of childhood acute lymphoblastic leukaemia and found a weak association (OR 1.34 (95% CI 0.54-3.34)) but no evidence for an increasing risk with increasing exposure levels.

Table 3: Summary of case-control studies of cancer risk and dichloromethane exposure

| Cancer type and reference | Population data | Exposure assessment | Number of other solvents or substances used | Results |
|----------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Brain (43) | 300 cases, 320 controls. Death certificates | Job exposure matrix | 6 | Increased risk with increased duration/intensity, no association with cumulative exposure |
| Breast (15) | 33,509 cases 117,794 controls. Death certificates | Job exposure matrix | 31 | Little evidence of association with exposure probability |
| Brain (20) | 12,980 cases, 51,920 controls. Death certificates | Job exposure matrix | 11 | Weak association overall (OR1.2) no trend with intensity or probability of exposure |
| Kidney (26) | 438 cases 687 controls, cancer registry and Medicare records | Job exposure matrix | 9 | No evidence of increased risk |
| Pancreas (50) | 63,037 cases 252,386 controls. Death certificates | Job exposure matrix | 11 chlorinated solvents and formaldehyde | Little evidence of associations with intensity or probability |
| Rectal (28) | 257 cases 1295 cancer controls 533 population controls. Histology | Job exposure matrix | 294 substances | Little evidence of association with any exposure apart from possible increased risk in small highly exposed group |
| Childhood acute lymphoblastic leukaemia (46) | 790 cases (age 0-14) with consultant diagnosis; 790 population controls | Information on all jobs held by mother before and during pregnancy | 21 substances and 6 mixtures | Possible association with high frequency/high concentration |

A number of studies have been described which have insufficient data on exposure to dichloromethane, include dichloromethane with other solvent exposure or have less accurate follow-up but nevertheless provide some information. The results of these studies were combined with others in a meta-analysis on 7300 subjects. The limited power to detect a risk of low-incidence cancers, including brain and leukaemia, the general lack of women workers and hence data on breast cancer incidence together with inadequate worker job histories make interpretation difficult but it has been suggested that the risks associated with dichloromethane exposure, if any, are small (23, 87). Cooper et al (21) have reviewed the available epidemiology literature, with five cohort studies and 13 case-control studies, and found that there was little indication of an increased risk of lung cancer with dichloromethane exposure but that odds ratios were slightly increased (1.5-2.2) for non-Hodgkin lymphoma.

The SCCS is of the opinion that although no major associations between dichloromethane exposure and cancer have been shown, the existing studies are too small and the exposure information insufficiently accurate to resolve the questions about dichloromethane exposure and cancer risk. On the other hand, although animal studies show that dichloromethane is carcinogenic in mice, the mechanisms involved are of much less relevance to humans (see section 3.6).

3.4.6 Reproductive toxicity

At low levels (less than 6 ppm) of dichloromethane some effects on sperm formation were reported but there were no clear correlations with dichloromethane exposure (57). In a case-controlled study on 44 women working with dichloromethane and other solvents, there was weak evidence that the risk of spontaneous abortion was increased with increased

exposure to dichloromethane but the significance of the finding is uncertain since the odds ratio was also raised for the other solvents used (92).

Reproductive toxicity has been studied in animals (67) and the SCCS is of the opinion that the epidemiological evidence does not suggest a significant risk of reproductive toxicity in humans.

3.4.7 Cardiac toxicity

ECG was used to monitor the cardiac function of 24 healthy workers chronically exposed to DCM at a range of 60-475 ppm. There was no evidence of any abnormalities and no evidence of ECG abnormalities in previously healthy subjects made unconscious by acute exposure. Theoretically, the conversion to COHb will reduce O₂ content of blood and might precipitate arrhythmias in individuals with pre-existing heart disease. However, COHb levels are ~5% in normal smokers and ~12% in heavy smokers and do not generally present a hazard. After exposure to 500 ppm dichloromethane, smokers had COHb levels of 15% but the authors concluded that this was non-hazardous in healthy individuals (78).

On the other hand, increases in COHb as low as 2% (Allred et al., 1989, ref. 112) have been shown to induce electrocardiographic changes in exercising patients with pre-existing coronary artery disease (cited by IPCS 1996, ref. 47). According to a WHO report (WHO 2000, ref. 113), "... in healthy subjects, endogenous production of carbon monoxide results in COHb levels of 0.4–0.7%. During pregnancy, elevated maternal COHb levels of 0.7–2.5%, mainly due to increased endogenous production, have been reported. The COHb levels in non-smoking general populations are usually 0.5–1.5%, owing to endogenous production and environmental exposures. To protect non-smoking, middle-aged and elderly population groups with documented or latent coronary artery disease from acute ischaemic heart attacks, and to protect the foetuses of non-smoking pregnant women from untoward hypoxic effects, a COHb level of 2.5% should not be exceeded. "

3.4.8 Case reports

A number of case reports are described in the literature. Typically, they involve an industrial accident where a worker is overcome by using solvents containing dichloromethane. Death appears to be due to asphyxiation (34) and COHb levels may be normal (102) suggesting that dichloromethane has a direct effect on the CNS, causing narcosis and respiratory depression (37). Blood levels of dichloromethane can be high in fatal cases; Takeshita et al (91) found 1660 mg/L in blood while other authors (51) found 252 mg/L in blood, and Manno et al (60) reported 572 mg/L in blood collected at autopsy which had high but not lethal levels of COHb (30%). Non-fatal cases can show CNS effects such as optic neuropathy, with decreased visual acuity, decreased critical flicker frequency and visual field narrowing (53).

3.5 Toxicokinetics

3.5.1 Metabolism, distribution and excretion of dichloromethane in man and animals

The major work on the toxicity of dichloromethane was conducted in the final thirty years of the 20th century. Two metabolic pathways were identified (18), an oxidative pathway mediated by cytochrome P450 2E1 (CYP 2E1) which produces carbon monoxide and can be modulated by ethanol and a second pathway mediated by conjugation with glutathione (GSH) via glutathione S-transferase (GST), the isoform GST T1-1 producing formaldehyde which typically forms cross-links between protein and DNA (DPX). It has been assumed that any genotoxicity/carcinogenicity of dichloromethane is entirely due to the GST pathway although some dichloromethane-induced DNA damage has been detected in human lung cultures without GSH metabolism (33). However, the relevance of this finding is unclear and has been disputed by other workers (2).

In man, dichloromethane is metabolised via the cytochrome P450 (CYP) linked pathway at low levels, CYP2E1 being the main isoform involved (Figure 1). Using physiologically based pharmacokinetic (PBPK) modelling (10,13,22,87), the rate equation for GST metabolism was shown to be first order, with metabolism increasing directly with the concentration of dichloromethane. In contrast, the CYP kinetics were non-linear and almost saturated above ~ 800 ppm exposure to dichloromethane; the interaction of the two pathways therefore resulted in an overall non-linear dose response. However, both CYP and GST metabolism were linear at concentrations of dichloromethane below 30ppm. At and below this dose level, the total exposure-response therefore approximated to linearity with no threshold and at least some GST metabolism at all exposures. In the model, CYP started to become non-linear and increasingly saturated above ~ 50 ppm and reached half saturation at ~ 200 ppm. Hence, as the dichloromethane concentration increased, the relative ratios of CYP/GST metabolism decreased and GST metabolism increased faster than that determined by a linear relationship. Nevertheless, in humans, GST metabolism remained quantitatively much less than that via CYP over the whole exposure range up to 2000 ppm; even at a CYP saturation of ~ 800 ppm, the ratio of CYP/GST metabolism was $\sim 18/1$.

As dichloromethane is volatile, it is eliminated through exhalation of the parent compound or after conversion via the CYP pathway to carbon monoxide and carbon dioxide; using ^{14}C -dichloromethane, both ^{14}CO and $^{14}\text{CO}_2$ were found in expired air (3, 4). Small amounts of metabolites can be found in urine and bile (5). Once exposure ceases, dichloromethane is rapidly eliminated from the body; in human studies, using exposure levels of 90, 100 or 210 ppm, the parent compound was almost completely removed from the blood stream and expired air by five hours post exposure (25). Urinary elimination of dichloromethane in humans is generally small; Di Vincenzo et al. (25) reported total urinary levels (parent compound) of ~ 65 -100 μg after inhalation exposure to 200 ppm dichloromethane for 2 hours. Despite these low levels, there was a direct correlation between dichloromethane exposure levels and urinary excretion of dichloromethane in human volunteers (54, 79). Animal studies using radiolabelled dichloromethane typically show 5-8% of the dose in urine and $\sim 2\%$ in faeces.

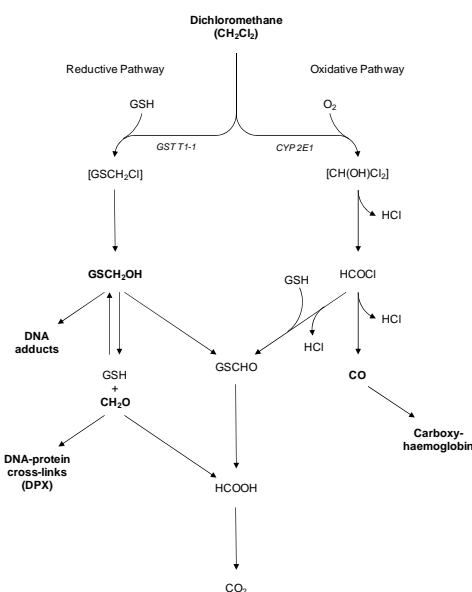


Figure 1: Metabolic pathways of dichloromethane. The oxidative pathway involving CYP2E1 predominates at low levels of dichloromethane. Formaldehyde, formed via the glutathione-S-transferase (GST) pathway, can form cross-links between protein and DNA.

In a study with human volunteers, there was a dose-related increase in carbon monoxide (CO) in expired air after inhalation exposure to 50-200 ppm dichloromethane, with CO accounting for ~25-35% of the original dose. Some of the CO formed by metabolism binds to the haemoglobin in blood to form COHb which can be readily monitored. In non-smoking workers, the levels of COHb in blood after exposure to dichloromethane were independent of exposure on previous days but dose and time dependent for same day exposures; COHb levels returned to normal within 24 hours after exposure to 200 ppm for 7.5 hours. In workers who also smoke, the COHb levels after dichloromethane exposure are higher than in non-smokers (because smoking leads to higher initial COHb levels in blood) and not dose-dependent (1, 25, 47, 82, 85).

Between 50 and 500 ppm dichloromethane and exposure times from 1.3 to 7.5 hrs, the increase of COHb concentration in blood can be assessed by an empirical equation. It was shown that COHb formation is proportional to both exposure time and concentration in a similar way (106). This is illustrated by the following figures (from SCOEL 2009, text adapted (ref. 82)):

Figure 2 shows monitoring data of COHb in human volunteers exposed to dichloromethane, as reported by Di Vincenzo and Kaplan (1981, ref. 25). This set of experimental data can be opposed to data in exposed workers by Soden et al. (1996; Figure 3). In this data set of group means the baseline COHb level of non-exposed persons (>1.5% COHb) appears relatively high, which is likely caused by an influence of unidentified smokers in this group. Considering this, the two data sets appear basically consistent with each other.

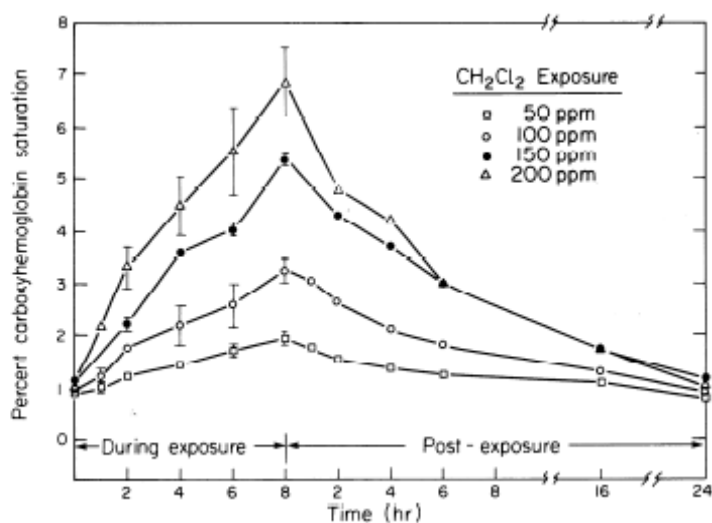


Figure 2: Time-course of the saturation of haemoglobin with carbon monoxide (% COHb) in volunteers exposed to different airborne levels of dichloromethane under resting conditions, according to Di Vincenzo and Kaplan (1981, ref. 25); means and SEM of 4-5 persons. Without exposure, a background COHb level of 1% was reported.

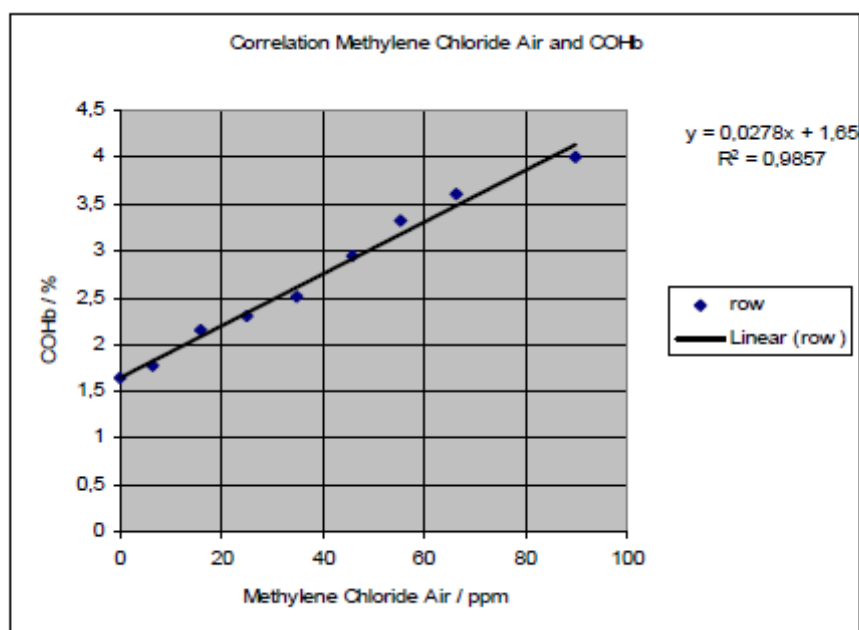


Figure 3: Correlation between airborne methylene chloride concentrations and COHb in non-smoking workers (reported subgroup means) after 8 h of exposure; data of Soden et al. (1996, ref 85)

Several studies in rats (5, 6, 58, 59) have shown that at lower dose levels, a greater percentage of the administered dichloromethane dose was metabolised by the CYP-related pathway and eliminated in expired air, showing that the CYP pathway may be saturated at higher levels (>250 ppm). In addition to saturation, this might also be due to the inhibition of CYP metabolism by the CO that is generated by this route since CO binds to CYP isoforms to give inactive products. Induction of CYP2E1 in rats increases COHb levels and dichloromethane metabolism (52).

3.5.2 Physiologically based pharmacokinetic (PBPK) models and assessment of carcinogenic risk

A number of PBPK models have been developed for representing dichloromethane absorption, distribution, metabolism and excretion (ADME) (61, 62). These aim to describe the biological behaviour of the compound and to predict parameters such as blood and tissue concentrations with kinetics of metabolism and excretion (65). They have been extensively used in setting regulatory limits.

Andersen et al (4) extended the rat model of earlier work (35) to include a lung compartment with lung metabolism and allometric scaling of animal CYP and GST pathway rate constants to man. The US EPA (97) modified this model, scaling for body surface area and body weight, to provide an estimate of human cancer risk (Inhalation Unit Risk (IUR) $4.7 \times 10^{-7}/(\mu\text{g}/\text{m}^3)$). Sweeney et al (906) modified the Andersen et al (4) human PBPK model to obtain a better fit between the model and their actual kinetics data. The results showed an approximate threefold range in individual maximal CYP metabolic activity and stimulated work incorporating individual variability of kinetic constants for both the CYP and GST pathways.

El-Masri et al (31) incorporated the effects of the GSTT-1 genetic polymorphism in a PBPK model of the risk distribution of dichloromethane in a human population and showed that the average and median cancer risks were $\sim 30\%$ lower when the incidence of the nul GSTT-1 polymorphism was included. Jonsson et al (48) merged *in vitro* metabolism data with inhalation data, a compartment for working muscle and a Markov Chain Monte Carlo (MCMC) simulation approach which quantitatively addressed the variability and uncertainty

in PBPK modelling. Their results indicated that the metabolic capacity of the CYP pathway in humans is larger than previously estimated and that the inter-individual variability of this pathway was smaller than the *in vitro* work had suggested. The predicted human cancer risks from dichloromethane exposure (up to 100 ppm) in this work were very similar to those obtained by El-Masri et al (31).

Further updating using Bayesian statistics on the PBPK and dose response modelling and fitting human toxicokinetic data (49) estimated the mean and median excess risks of exposure to 1 ppm dichloromethane as 7.8×10^{-7} and 6.1×10^{-7} respectively. Re-analysis by Sweeny et al (90) of earlier studies, adding a component for extrahepatic metabolism, suggested a relatively narrow range in human hepatic metabolism of dichloromethane. To derive acute exposure guideline levels (AEGs) which determined acute non-cancer risks of exposure, Bos et al (13) combined previous models then included an estimation of maximum COHb formation and CNS depression and extended the model to incorporate the saturation step in dichloromethane metabolism and considered the GSTT-1 polymorphism. These values have been used to set AEGs (10) (see also Annex I).

David et al (23) built on the basic PBPK model to provide a probabilistic human PBPK dichloromethane model and included components to recognise the higher dichloromethane metabolism at low concentrations, GST polymorphisms and all available human data. This was taken from four studies (8, 25, 32, 89) with humans exposed to dichloromethane with durations of 1-8 hours at concentrations ranging from 50-1000 ppm. On analysis, the distribution of CYP2E1 metabolism parameters was narrowed, reflecting a high degree of confidence in the population mean. Including the pharmacogenetic variation found in the human population where ~20% are non-conjugators with glutathione, the unit risk ranged from 0 to 2.70×10^{-9} at the 95th percentile with a median at 9.33×10^{-10} . The mean unit risk for a lifetime exposure to $1 \mu\text{g}/\text{m}^3$ dichloromethane (considering both lung and liver tumours) was estimated as 1.05×10^{-9} .

US EPA updated their hazard characterisation after inhalation of dichloromethane in 2011 (<http://www.epa.gov/iris/subst/0070.htm>). Their procedure to combine risks for liver and lung tumors using different dose metrics for the different tumours (i.e., liver-specific and lung-specific metabolism for liver and lung tumours, respectively) was used to derive the recommended inhalation unit risk of 1×10^{-8} per $\mu\text{g}/\text{m}^3$ based on what is assumed to be the most sensitive of the populations, the GST-T1+/+ group. This value will be used in the risk characterisation.

Despite all these refinements to the modelling method, there remain uncertainties since it is not clear that the kinetics of the CYP2E1 pathway are completely described by the Michaelis-Menten equation. The data for both animals and man suggest that another CYP isoform could be involved, one which has lower affinity than CYP2E1, or that the CYPs may have atypical kinetics with dual binding sites. The lack of clarity on the relative ratios of the activities of the CYP and GST pathways must affect estimation of cancer risks, although all methods of calculation show these to be small.

3.5.3 Effects of polymorphisms in human populations

Dichloromethane is metabolised by both GST-related pathways and also by CYP2E1 and possibly other CYP isoforms; the activities of these metabolic routes are not genetically linked. The prevalence of GST-T1^{-/-} non-conjugators is ~20% in a Caucasian population (higher values, ~50-65%, have been reported for Asian populations (77)) and they will have a greatly reduced risk for dichloromethane-induced cancer. Those most susceptible will be the individuals with the GST-T1^{+/+} genotype although the absolute increase in risk is estimated to be very small. *In vitro*, studies with human peripheral blood mononuclear cells have shown that dichloromethane (15-500 ppm for 72h) caused the greatest cytogenetic damage in cells with the highest GST-T1 activity, the frequency of sister chromatid exchange increasing from 60 ppm (71). GST-T1 is present in highest amounts in liver and kidney but the numerous cohort and case-control studies in human populations do not give any evidence for dichloromethane-induced tumours in these organs.

The oxidation of dichloromethane is due to CYP isoforms, particularly CYP2E1 which is known to be polymorphic, with a three to seven-fold variation in human populations. An association between exposure to dichloromethane and lymphoma risk in women with a specific CYP2E1 genotype was seen in an American population although the numbers involved were small (11). This variability has been incorporated into the PBPK modelling and may be further increased by dietary and environmental factors which can modulate activity.

The human foetus has relatively high activity of CYP2E1 in the brain, as compared with liver, and could therefore be susceptible to neurodevelopmental effects of CO generated by high chronic doses of dichloromethane. Results from animal studies (63, 67) do not indicate that dichloromethane is a reproductive or neurodevelopmental toxicant. However, the database on human neurodevelopmental toxicity of dichloromethane is insufficiently large to enable the assessment to be made.

3.6. Relevance of Carcinogenicity in Animals to Human Risk

Studies in rats and mice *in vivo* and in rat, mouse, hamster and humans *in vitro* have shown that the cytochrome P450 (CYP) pathway of metabolism is unlikely to be the basis for the carcinogenicity seen in the mouse (83, 84). The glutathione conjugation pathway occurs at very high rates in the mouse, in comparison to other species, both *in vivo* and *in vitro* and the carcinogenic effects of dichloromethane appear to be caused by the interaction of DNA with a glutathione conjugate produced by the theta class of glutathione S-transferases (GSTT1-1) (84); the generation of formaldehyde may also be involved as V79 cells transfected with the mouse enzyme (*mGSTT1-1*) and then incubated with dichloromethane (up to 10mM) formed the DNA-protein cross links (DPX) typically seen with formaldehyde (44). The mouse form of GSTT1-1 is more efficient in catalysing the conjugation of dichloromethane with GSH than the orthologous human enzyme and in addition the mouse expresses more GSTT1-1 in hepatic tissue. Histochemical analysis showed that GSTT1-1 was found in the nucleus of mouse liver cells (93) so that nuclear adducts could be formed more readily. The levels of GSTT1-1 are much lower in rats and hamsters than in mice (38, 39), consistent with the fact that dichloromethane does not cause lung or liver tumours in these species while the levels of this enzyme are lower still in humans. This is in agreement with the epidemiological finding that exposure to dichloromethane is not associated with an increased risk of lung cancer in humans (21). Further, in humans but not in other species, the *hGST1* gene is polymorphic, with ~20% of a European population having a complete deletion (*GSTT1*0*) which would be protective against formation of reactive metabolites (71). Also, again in humans but not in other species, *hGSTT1-1* is present in erythrocytes and would act as a 'metabolic sink' to remove reactive metabolites of dichloromethane. It therefore appears that several species-specific factors contribute to the higher susceptibility of mice.

4. Exposure

Measured exposure data for consumers

Quite a few measured exposure data were available. However, information on exposure conditions was not always reported.

The SCC opinion of 1987 (81) provided exposure data on use of hair sprays in the home as 261 mg/m³ (74 ppm) as a peak value after the second application in 10 minutes of a lacquer containing 35% dichloromethane in an unventilated room of 25 m³.

Dutch studies (one of them quoted in the IPCS report (47)) found a peak exposure of 265 mg/m³ (75 ppm) in home use while another, focusing on short-term exposure, used a hair spray around the head for about 10 seconds in a normally ventilated room. Six spray cans of four different brands were tested (concentration of dichloromethane not reported). During a period of 5 minutes after spraying, the concentrations near the mouth ranged from

500 to 1600 mg/m³, (average value 800 mg/m³) (109). When the spray was only used at the back and side of the head, the 5 minutes average concentrations ranged from 15 to 200 mg/m³ (average: 90 mg/m³).

The IPCS report (47) described a simulated exposure study where a hair spray (concentration of dichloromethane not reported) was used in absence of ventilation in a small room, resulting in a 10-minute time weighted average concentration of 353 mg/m³ (100 ppm) of dichloromethane.

The IPCS report (47) quoted a measured consumer exposure of 106-265 mg/m³ (10-minutes time weighted average) during salon use (actual concentration of dichloromethane in the product was not reported).

Estimates of exposure for consumers

Exposure for a consumer using a hair spray has also been calculated by using a consumer exposure model (ConsExpo, a model that is also described in the REACH guidance document for the assessment of consumer exposure under REACH, ref: 107). The scenario is described in the fact sheet 'Cosmetic Products'¹ and assumes use of a hair spray in a small room (bathroom, 10 m³) with a low ventilation rate (2m³/h) (module: evaporation model). Other assumptions are: the sprayed amount is 6.8 g, the hairspray contains 35% dichloromethane, the consumer is in the bathroom for 5 minutes, (all these assumptions are proposed as default values for this scenario, see ConsExpo fact sheet). The exposure was calculated to be in average 219 mg/m³ (62 ppm). It is furthermore assumed that consumers may use the hairspray twice a day, so they might be exposed to 219 mg/m³ for 5 minutes twice in a period of ~8h in each day.

The data sets are in agreement and result in average exposure levels of 200-350 mg/m³ during 5 to 10 minutes after application of hairspray, in a relatively small, poorly ventilated room. However, from a study in which concentrations were measured after spraying for 10 seconds around the head, it was demonstrated that the 5 minute average concentration measured in the breathing zone could be as high as 1600 mg/m³ (commercial hair spray containing dichloromethane, actual concentration not reported) (109). It should be noted that during spraying, peak exposure will even be much higher for a short period of time (seconds).

Occupational Exposure Values

Collecting data from several sources, the Norwegian Food Control Authority (69) reported TWA/8h values ranging from 3.5-67 mg/m³ in European countries for sprays containing 35% dichloromethane: the European Chemicals Bureau (quoted in ref 69) calculated 30.6 mg/m³ which is very similar to that used by the SCC (81). Simulation of heavy salon use gave a hairdresser exposure of 77.7 mg/m³ for an eight-hour TWA.

In a 2-year inhalation study in the rat (6h/day, 5d/week), Nitschke et al (66) found a NOEL of 710 mg/m³ (~200 ppm); the Norwegian Food Control Authority (69) used this value to derive an occupational setting NOAEL of 532 mg/m³ which is above the actual peak values found in hairdressing salons, since in hairdressers' salons, the SCC opinion (81) reported that the peak value was 435 mg/m³ after the tenth application within an hour of lacquer containing 25% dichloromethane in a room of 35 m³.

5. Risk assessment

Cancer risks

¹ www.consexpo.nl

In the lifetime cancer risk characterisation, the ConsExpo exposure calculation of 219 mg/m³ for twice a day for a total of 10 minutes can be used, representing an average exposure of 1.5 mg/m³. Moreover, it is assumed that a woman uses hairsprays for an average of 40 years. US EPA has recently updated their hazard characterisation in relation to lifetime cancer risk. They derived recommended inhalation unit risk of 1×10^{-8} per $\mu\text{g}/\text{m}^3$ based on what is assumed to be the most sensitive of the populations, the GST-T1+/- group. If this value is used in the risk characterisation, the lifetime cancer risk is calculated to be 0.8×10^{-5} which is considered tolerable.

Other risks

Formation of COHb

Experimental exposure of human volunteers to 100ppm (350 mg/m³) dichloromethane is known to result in an increase of about 3% COHb after 8h. Increases of COHb concentrations depending on exposure times from 0.5 up to 8 hours and on dichloromethane concentrations from less than 10 up to about 200 ppm have been demonstrated (Figures 2 and 3). However, there are no experimental data on formation of COHb from very short term exposure to dichloromethane such as use of hair sprays. Experimental human data combined with PBPK modelling suggest levels of less than 0.5% increase of COHb concentrations in blood for exposures up to 500 ppm (about 1760 mg/m³) for 10 min (Bos et al 2006, ref. 13). This is considered sufficiently below the recommended threshold of about 2.5% COHb for protecting nonsmoking, middle-aged and elderly population groups with documented or latent coronary artery disease from acute ischaemic heart attacks, and protecting the foetuses of non-smoking pregnant women from untoward hypoxic effects (WHO 2000).

CNS effects

Decreased performance of psychomotor tasks can be seen with exposure to dichloromethane and this appears to be largely due to the parent compound rather than its metabolism to CO with formation of COHb. Light-headedness and difficulties in enunciation were observed in volunteers exposed to 868 or 986 ppm for 1 hour and since the effects disappeared within 5 minutes post-exposure but the COHb level increased for at least an hour post-exposure the CNS effects were attributed to the concentration of dichloromethane in the brain rather than to the formation of COHb; the CNS effects were not observed after a 1-hour exposure to 514 ppm (Stewart et al. 1972, ref 89). AEGL-1² values of 200, 230 and 290 ppm (710 mg/m³, 810 and 1000 mg/m³) have been set for 60, 30 and 10 min of exposure, respectively. The AEGL-1 values were derived based on absence of the slight CNS effects (light-headedness and difficulties with enunciation in humans) observed in the Stewart et al. 1972 study (ref 89) by using a PBPK model to calculate the maximum concentration of dichloromethane in the brain (0.063 mM for an exposure concentration of 514 ppm) and application of an intraspecies assessment factor of 3 (ref. 114). Exposure of volunteers to 300 ppm dichloromethane for 4 hours gave depressed responses to auditory vigilance and visual flicker fusion which were not seen with exposure to 100 ppm CO for 5 hours (Winneke, 1974). Similarly, when volunteers were exposed to either 200 ppm dichloromethane or 70 ppm carbon monoxide for 4 hours, where the level of COHb reached 5% in both cases, auditory vigilance and co-ordination were more impaired by dichloromethane (Putz et al 1979). SCOEL has set a short term exposure limit (STEL) of 200 ppm ($\sim 710\text{mg}/\text{m}^3$) for 15 minutes based on possible short-term pre-narcotic effects. When shorter times of exposure occur (5 minutes), effects such as dizziness and irritation are found although not until levels are high; narcotic effects are seen at 2300 ppm (8165 mg/m³).

² AEGL-1 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

In industrial settings, no evidence of adverse effects on human health has been found when the exposure concentrations of dichloromethane in the workplace (8 hours, 5 days/week) have been ~ 100 ppm (350 mg/m^3) for several years.

However, for the risk assessment of the consumer (use in domestic settings, no adequate control of exposure conditions like ventilation, frequency, used amounts, more diverse population including children) the SCCS finds it not appropriate to use the occupational limits for risk assessment.

Short-term exposures by dichloromethane in hair sprays and experimental exposures of volunteers with and without neurobehavioral effects are compared in **Annex 1**. Based on time-weighted averages (TWA), values for different hair spraying assessments with exposure times of 5 to 10 min varied from 17 to $133 \text{ mg/m}^3 \times \text{h}$. TWA's in the experimental studies with exposure times of 30 or 60 min varied from 1300 to $3840 \text{ mg/m}^3 \times \text{h}$.

A TWA of $177 \text{ mg/m}^3 \times \text{h}$ has been deduced by SCOEL for short-term exposures at the work place ($\sim 710 \text{ mg/m}^3$ for 15 min) (82).

A TWA of $710 \text{ mg/m}^3 \times \text{h}$ can be deduced from the AEGL-1 value of 200 ppm (710 mg/m^3) for 60 min. Similarly, TWA's of 167 and $405 \text{ mg/m}^3 \times \text{h}$ can be deduced from the AEGL-1 values of 290 and 230 ppm (1000 and 810 mg/m^3) for 10 and 30 min, respectively.

From the comparison of the TWA values in Annex I it appears at first glance that a sufficient difference between worse case exposure by hair spraying and levels of no or first neurobehavioral effects may exist when comparing the lowest apparent short-term NOAEL (TWA) in the experimental studies and the highest TWA after hair spraying (1300 versus $131 \text{ mg/m}^3 \times \text{h}$).

However, these early experimental studies with apparently no or minor neurobehavioral effects should be considered with caution. It should be taken into account that Stewart et al. 1972 (ref. 89) and Gamberale et al. (1975, ref. 103) belong to the pioneers of investigating neurobehavioral effects of volatile solvents and that generally accepted test batteries for broad sets of neurobehavioral endpoints for testing effects of solvents have been developed later (Iregren 1996, ref. 111).

The approach of extrapolation over time by using Haber's rule as has been used for the derivation of the TWA values in Annex I and summarised above is associated with often unknown uncertainties (13). The conditions and prerequisites for the application of Haber's rule has been reviewed by Rozman and Doull (2001, ref 115).

Bos et al. (2006, ref. 13) showed that PBPK modelling is of great use to properly perform time extrapolations from 10 minutes to 8 hours in the setting of AEGLs for dichloromethane based on the appropriate dose metrics. The AEGL-1 value was based on absence of slight CNS effects (light-headedness and difficulties with enunciation in humans) for a 1-hour exposure to 514 ppm reported by Stewart et al. (1972, ref. 89). By using a human PBPK model a maximum concentration of dichloromethane in the brain of 0.063 mM was calculated from the 1-hour exposure to 514 ppm. An intraspecies assessment factor of 3 was considered sufficient since susceptibilities for gross CNS-depressing effects were considered not to vary by more than a factor of 2-3 resulting in a maximum target concentration of dichloromethane in the brain of 0.021 mM. The human PBPK model was then used to calculate the concentrations of dichloromethane in environmental air for exposures up to 8 hours that would result in a maximum brain concentration of 0.021 mM, i.e. the AEGL-1 values for different exposure durations. This approach was adopted by the NAC/AEGL Committee (114) as mentioned above.

The PBPK model used by Bos et al. (2006, ref. 13) was a combination of existing models that had been peer reviewed and used for specific risk assessments and extended with additional algorithms for the estimation of the maximum COHb levels. Both the COHb formation as well as the concentration of dichloromethane could be simulated within this model. The model, which was validated and verified with data obtained from volunteer studies, overestimated the blood concentration of dichloromethane and the COHb formation

by 50% at the most. The authors concluded that all the topics addressed in their paper could be adequately accounted for by the PBPK model.

In conclusion, due to the inadequate data on exposure by hair spraying and limited data on neurobehavioral and neurodevelopmental effects of dichloromethane after short-term exposure, dichloromethane in a concentration of up to 35% in hair sprays is not considered safe for the consumer.

4. CONCLUSION

1. *On the basis of the provided data the SCCS is asked to assess the risk to consumers when dichloromethane is used in cosmetic products under the current use conditions of maximum 35% in cosmetic products.*

The evidence does not suggest that dichloromethane shows cardiotoxicity or reproductive toxicity in man except at high levels. Although it is carcinogenic by inhalation in the mouse, factors have been identified which explain the higher susceptibility of mice compared to humans. Quantification of the risk to humans by toxicokinetic modelling and subsequent comparison of the toxicokinetics between mice and humans indicates that the cancer risk that dichloromethane may pose would be negligible.

Based on the available data on exposure by hair spraying and limited data on neurobehavioral and neurodevelopmental effects of dichloromethane after short-term exposure, dichloromethane in a concentration of up to 35% in hair sprays is not considered safe for the consumer.

2. *If this limit is considered safe, should the restriction of 35% be limited to its use as a propellant or can other uses as solvent up to 35% be accepted.*

Not applicable

3. *Can the SCCS assess whether the restriction on purity should be interpreted as purity criteria for the dichloromethane itself or should it be its presence as an impurity in cosmetic products that should be restricted to 0.2%?*

Not applicable

4. *Does the SCCP have any further scientific concern with regard to its use in cosmetic products?*

No information for other uses in cosmetic products is available to the SCCS.

5. MINORITY OPINION

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Annex 1**Short-term exposures to Dichloromethane (DCM) and possible neurobehavioral effects in humans in comparison to DCM exposures by hair spraying**

For the assessment of possible health risks by DCM emissions from hair spraying, available data on short-term exposures to DCM and early CNS effects were compared with exposure situations described in the literature and with calculations of exposure by modelling. According to Haber's rule, the product of concentration x exposure time (time-weighted average, TWA) can be used as a measure of the DCM exposure (and possible DCM effects) and for comparison of the different exposure situations experimentally conducted or modelled (13, 106).

| Type of study or conditions of exposure | Concentration mg/m³ ppm | Exposure interval | TWA mg/m³ x h | Effects reported or expected | Reference |
|---------------------------------------------------------------|-----------------------------------------------|--------------------------|-------------------------------------|-------------------------------------------------|--------------------------|
| Human volunteers | 3480 986 | 60 min | 3840 | Light-headedness, difficulties with enunciation | 89 (as cited by ref. 13) |
| Human volunteers | 1820 515 | 60 min | 1820 | None | 89 (as cited by ref. 13) |
| Resting male volunteers | 3470 1000 | 30 min | 1735 | Slight effects on reaction time | 103 |
| Resting male volunteers | 2600 750 | 30 min | 1300 | None | 103 |
| AEGL-1 value ¹⁾ derived by PBPK modelling | 710 200 | 60 min | 710 ¹⁾ | Light-headedness, difficulties with enunciation | 114 |
| AEGL-1 value ¹⁾ derived by PBPK modelling | 810 230 | 30 min | 405 ¹⁾ | Light-headedness, difficulties with enunciation | 114 |
| AEGL-1 value ¹⁾ derived by PBPK modelling | 1000 290 | 10 min | 167 ¹⁾ | Light-headedness, difficulties with enunciation | 114 |
| Short Term Exposure Limit (STEL) | 710 200 | 15 min | 177 | None (for adult healthy workers) | 82 |
| Home use of hair sprays | 265 75 | Ca. 5 min | 22 | Not reported | 47 |
| Simulated home use of hair sprays, small room, no ventilation | 353 100 | 10 min | 59 | Not reported | 47 |

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| Type of study or conditions of exposure | Concentration mg/m ³ ppm | Exposure interval | TWA mg/m ³ x h | Effects reported or expected | Reference |
|-------------------------------------------------------------|----------------------------------------|-------------------|------------------------------|------------------------------|----------------------------|
| Salon, hair spraying, simulation of consumer exposure | 106-265, 30-75 | 10 min | 17-44 | Not reported | 47 |
| Hair spraying, simulation of consumer exposure using 4 cans | 1600 453 maximum value | 5 min | 133 | Not applicable | 109 |
| | 500 142 minimum value | 5 min | 41 | | |
| | 800 239 mean value | 5 min | 67 | | |
| hair spraying, simulation by Cons-Expo calculation | 219 62 (average) | 5 min | 18 | Not applicable | 106 (see section 4) |

¹⁾ AEGL-1 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects.

However, the effects are not disabling and are transient and reversible upon cessation of exposure. Here, in the AEGL-1 values, an intraspecies assessment factor of 3 is already included taking into account that susceptibilities for CNS-depressing effects are considered not to vary by more than a factor of 2-3 between human individuals