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.).

Scientific Committee members

Jürgen Angerer, Ulrike Bernauer, Claire Chambers, Qasim Chaudhry, Gisela Degen, Elsa Nielsen, Thomas Platzek, Suresh Chandra Rastogi, Vera Rogiers, Christophe Rousselle, Tore Sanner, Jan van Benthem, Jacqueline van Engelen, Maria Pilar Vinardell, Rosemary Waring, Ian R. White

Contact
European Commission
Health & Consumers
Directorate D: Health Systems and Products
Unit D3 - Risk Assessment
Office: B232 B-1049 Brussels
Sanco-SCCS-Secretariat@ec.europa.eu

ISSN 1831-4767 ISBN 978-92-79-30786-7

Doi:10.2772/93077 ND-AQ-12-036-EN-N

http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

ACKNOWLEDGMENTS

Prof. J. Angerer
Dr. U. Bernauer
Dr. C. Chambers
Prof. G. Degen
Dr. W. Lilienblum (associate scientific advisor)
Dr. E. Nielsen
Dr. S.C. Rastogi
Prof. V. Rogiers
Prof. T. Sanner (chairman)
Dr. J. van Engelen
Prof. R. Waring (rapporteur)
Dr. I.R. White

Keywords: SCCS, scientific opinion, dichloromethane, directive 76/768/ECC, CAS 75-09-2, EC 200-838-9

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on dichloromethane, 11 December 2012

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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

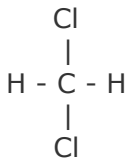
3.1.1.3 Trade names and abbreviations

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: CH_2Cl_2

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/m³	1 mg/m³ =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/cm³
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 LD_{50}-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 LC_{50} 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/m^3) 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/cm^2/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 (≥ 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/m^3 for 13 weeks (6 hours/day, 5 days/week). Effects on brain chemistry were observed in rats following exposure to ≥ 250 mg/m^3 (6 hours/day for 3 days).

Following intermittent exposure, histopathological changes were observed in the liver of rats at 3500 mg/m^3 (2 hours/day for 20 days) and in mice at 14 100 mg/m^3 (6 hours/day for 21 days); no effects were noted in the liver of rats following exposure to 880 mg/m^3 (5 hours/day for 28 days). After continuous exposure (for 100 days), slight cytoplasmatic vacuolisation in the liver of both rats and mice were seen at 88 mg/m^3.

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/m^3 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/m^3 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/m^3); 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/m^3 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/m^3) for 1.5-3 hours; effects on visual function were also observed after 95 minutes exposure to 290 ppm (1024 mg/m^3) while exposure to 672 ppm (2372 mg/m^3) 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/m^3 (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/m^3 (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

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 (OR1.2 (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 O_2 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 ~50ppm and reached half saturation at ~200ppm. 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 ~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 $^{14}CO_2$ 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 ~2% in faeces.

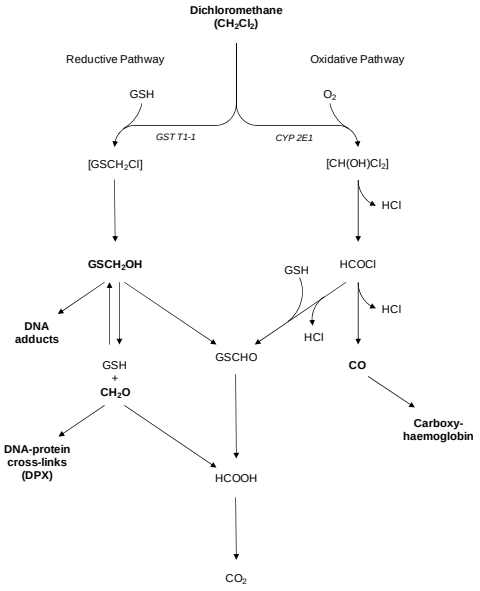


Figure 1: Metabolic pathways of dichloromethane. The oxidative pathway involving CYP2E1 predominates at low levels of dichloromethane. Formaldehyde, formed via the glutathione-S-transferase (GST) pathway, can form cross-links between protein and DNA.

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.

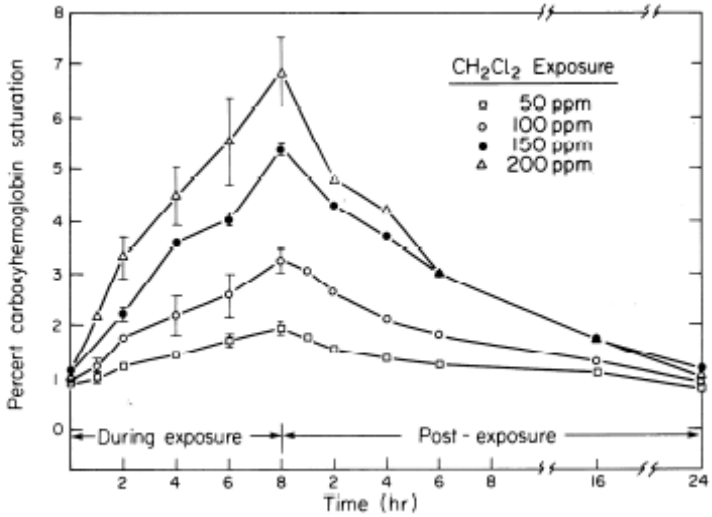


Figure 2: Time-course of the saturation of haemoglobin with carbon monoxide (% COHb) in volunteers exposed to different airborne levels of dichloromethane under resting conditions, according to Di Vincenzo and Kaplan (1981, ref. 25); means and SEM of 4-5 persons. Without exposure, a background COHb level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

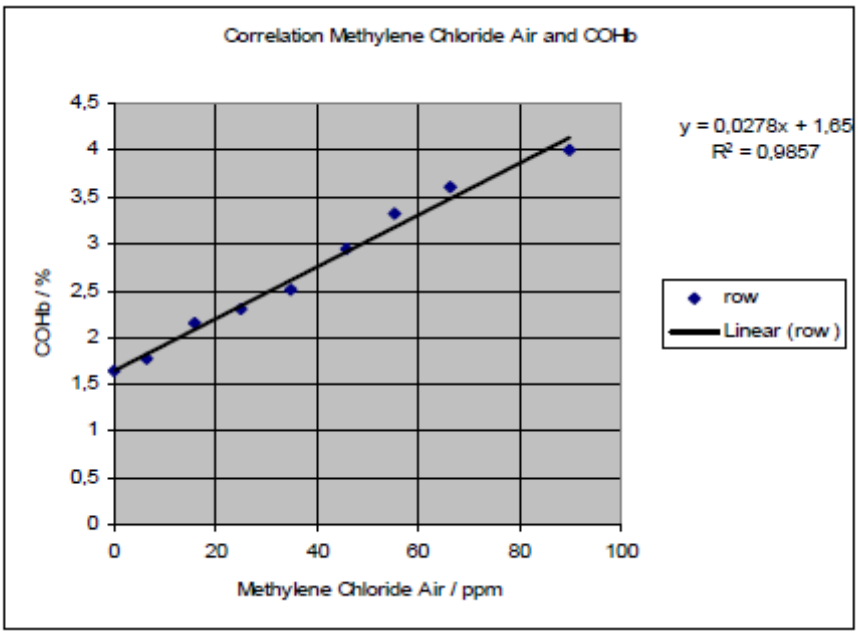


Figure 3: Correlation between airborne methylene chloride concentrations and COHb in non-smoking workers (reported subgroup means) after 8 h of exposure; data of Soden et al. (1996, ref 85)

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) 4.7x 10-7/(µg/m3)). 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 ~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 x 10-7 and 6.1 x 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 (AEGLs) 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 AEGLs (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 x 10-9 at the 95th percentile with a median at 9.33 x 10-10. The mean unit risk for a lifetime exposure to 1 µg/m3 dichloromethane (considering both lung and liver tumours) was estimated as 1.05 x 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 µg/m3 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 (*m*GSTT1-1) 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 *h*GST1 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, *h*GSTT1-1 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/m^3 (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 m^3.

Dutch studies (one of them quoted in the IPCS report (47)) found a peak exposure of 265 mg/m^3 (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/m^3, (average value 800 mg/m^3) (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/m^3 (average: 90 mg/m^3).

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/m^3 (100 ppm) of dichloromethane.

The IPCS report (47) quoted a measured consumer exposure of 106-265 mg/m^3 (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 m^3) with a low ventilation rate (2m^3/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/m^3 (62 ppm). It is furthermore assumed that consumers may use the hairspray twice a day, so they might be exposed to 219 mg/m^3 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/m^3 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/m^3 in European countries for sprays containing 35% dichloromethane: the European Chemicals Bureau (quoted in ref 69) calculated 30.6 mg/m^3 which is very similar to that used by the SCC (81). Simulation of heavy salon use gave a hairdresser exposure of 77.7 mg/m^3 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/m^3 (~200 ppm); the Norwegian Food Control Authority (69) used this value to derive an occupational setting NOAEL of 532 mg/m^3 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/m^3 after the tenth application within an hour of lacquer containing 25% dichloromethane in a room of 35 m^3.

5. Risk assessment

Cancer risks

[1] www.consexpo.nl

In the lifetime cancer risk characterisation, the ConsExpo exposure calculation of 219 mg/m^3 for twice a day for a total of 10 minutes can be used, representing an average exposure of 1.5 mg/m^3. 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 µg/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 x 10^{-5} which is considered tolerable.

Other risks

Formation of COHb

Experimental exposure of human volunteers to 100ppm (350 mg/m^3) 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/m^3) 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-1[2] values of 200, 230 and 290 ppm (710 mg/m^3, 810 and 1000 mg/m^3) 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 (~710mg/m^3) for 15 minutes based on possible short-term prenarcotic 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/m^3).

[2] AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) 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 mg/m^3 x h. TWA's in the experimental studies with exposure times of 30 or 60 min varied from 1300 to 3840 mg/m^3 x h. .

A TWA of 177 mg/m^3 x h has been deduced by SCOEL for short-term exposures at the work place (~710 mg/m^3 for 15 min) (82).
A TWA of 710 mg/m^3 x 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 mg/m^3 x 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 mg/m3 x 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

6. REFERENCES

1. Amsel J Soden KJ Sielken RL Jr. Valdez-Flora C 2001 Observed versus predicted carboxyhemoglobin levels in cellulose triacetate workers exposed to methylene chloride American J Industrial Medicine 40(2) 180-191
2. Anders MW Andersen ME Clewell HJ Gargas ML Guengerich FP Reitz RH 2010 Comment on MV Evans and JC Caldwell: evaluation of two different metabolic hypotheses for dichloromethane toxicity using physiologically based pharmacokinetic modelling of in vivo gas uptake data exposure in female B6C3F1 mice Toxicology and Applied Pharmacology 248(1) 63-4
3. Andersen ME, Clewell HJ, Gargas ML, MacNaughton MG, Reitz RH, Nolan RJ. 1991 Physiologically based pharmacokinetic modelling with dichloromethane, its metabolite carbon monoxide and blood carboxyhemoglobin in rats and humans Tox Appl Pharmacol 108 (1) 14-27
4. Andersen ME, Clewell HJ, Gargas ML, Smith FA, Reitz RH 1987 Physiologically based pharmacokinetics and the risk assessment process for methylene dichloride Toxicol Appl Pharmacol 24 243-61
5. Angelo MJ Pritchard AB Hawkins DR et al 1986a The pharmacokinetics of dichloromethane I. Disposition in B6C3F1 mice following intravenous and oral administration Food Chem Toxicol 24 963-974
6. Angelo MJ Pritchard AB Hawkins DR et al 1986b The pharmacokinetics of dichloromethane II Disposition in Fischer 344 rats following intravenous and oral administration Food Chem Toxicol 24 975-980
7. Anundi H Lind ML Friis L 1993 High exposure to organic solvents among graffiti removers Int Arch Occup Environ Health 65 247-251
8. Astrand I Ovrum P Carlsson A 1975 Exposure to methylene chloride I Its concentration in alveolar air and blood during rest and exercise and its metabolism Scand J Work Health Environ 1 78-94
9. ATSDR 2000 Toxicological profile for methylene chloride Agency for Toxic Substances and Disease Registry Division of Toxicology and Environmental Medicine Atlanta USA
10. ATSDR 2010 (Addendum to the Toxicological Profile for Methylene Chloride). Agency for Toxic Substances and Disease Registry Division of Toxicology and Environmental Medicine Atlanta USA
11. Barry KH Zhang Y Lan Q Zahm SH Holford TR Leaderer B Boyle P Hosgood HD Chanock S Yeager M Rothman N Zheng T 2011 Genetic variation in metabolic genes, occupational exposure and risk of non-Hodgkin lymphoma Am J Epidem 173 (4) 404-413
12. Blair A Hartge P Stewart PA McAdams M Lubin J 1998 Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow-up Occupat Env Med 55 161-171
13. Bos PMJ, Zeilmaker MJ, van Eijkeren JCH, 2006 Application of physiologically based pharmacokinetic modeling in setting Acute Exposure Guideline Levels for methylene chloride Toxicol Sci 91 576-85
14. Cabrera VJ Farmakiotis D Aggarwal V 2011 Methylene chloride intoxication treated with hyperbaric oxygen therapy Am J Med 124(5) e3-4
15. Cantor KP Stewart PA Brinton LA et al 1995 Occupational exposures and female breast cancer mortality in the USA J Occupational Env Med 37(3)336-348
16. Casanova M, Bell DA, Heck HD 1997 Dichloromethane metabolism to formaldehyde and reaction of formaldehyde with nucleic acids in hepatocytes of rodents and humans with and without glutathione S-transferase T1 and M1 genes Fundamental and Appied Toxicology 37 168-180
17. Chang YL Yang CC Deng JF Ger J Tsai WJ Wu ML Liaw HC Liaw SJ 1999 Diverse manifestations of oral methylene chloride poisoning: report of 6 cases J Toxicology – Clinical Toxicology 37(4) 497-504
18. Cherry N Venables H Waldron HA et al 1981 The acute behavioural effects of solvent exposure J Soc Occup Medicine 33 13-18

19. Cherry N Venables H Waldron HA 1983 The acute behavioural effects of solvent exposure J Soc Occup Med 33 13-18
20. Cocco P Dosemeci M Gomez MR et al 1999 A retrospective evaluation of exposure to dichloromethane by using a job-exposure matrix Med Lav 85 84-87
21. Cooper GS, Scott CS, Bale AS 2011 Insights from epidemiology into dichloromethane and cancer risk int J res Pub Health 8 (8) 3380-3398
22. David RM, Clewell HJ, Gentry PR, Covington TR, Morgott DA, Marino DJ 2006. Revised assessment of cancer risk to dichloromethane I. Application of probabilistic methods to cancer risk determinations Regul Toxicol Pharmacol 45 55-65
23. Dell LD, Mundt KA McDonald M, Tritschler JP, Mundt DJ 1999 Critical review of the epidemiology literature on the potential cancer risks of methylene chloride Int Arch Occup Env Health 72 (7) 429-42
24. Di Vincenzo GD Yanno FJ Astill BD 1972 Human and canine exposure to methylene chloride vapour Am Ind Hyg Assoc 33 125-135
25. Di Vincenzo GD and Kaplan CJ 1981 Uptake metabolism and elimination of methylene chloride vapor by humans Toxicol Appl Pharmacol 59 130-140
26. Dosemeci M Cocco P Gomez M et al 1994 Effects of three features of a job-exposure matrix on risk estimation Epidemiology 5 124-127
27. Dreisbach RH, Robertson WO 1987 Handbook of poisoning, prevention and treatment 12th edn Appleton and Lange Norwalk Connecticutt 589pp
28. Dumas S Parent ME Siemiatycki J Brissson J 2000 Rectal cancer and occupational risk factors: a hypothesis-generating, exposure-based case-control study Int J Cancer 87(6) 874-879
29. Ehler E Latta J Eichlerova A Mrklovsky M Urban P 2011 Exposure to iodomethane and dichloromethane associated with a confusional state Neurotoxicol 32 (3) 307-311
30. Ellenhorn MJ, Barceloux DG 1988. Medical toxicology – diagnosis and treatment of human poisoning. Elsevier Science Publishing New York
31. El-Masri HA, Bell DA, Portier CJ 1999 Effects of glutathione transferase theta polymorphism on the risk estimates of dichloromethane to humans Toxicology and Applied Pharmacology 158 (3) 221-30
32. Engstrom J and Bjurstrom R 1977 Exposure to methylene chloride: content in subcutaneous adipose tissue Scand J Work Environ Health 3 215-224
33. Evans MV and Caldwell JC 2010 Evaluation of two different metabolic hypotheses for dichloromethane toxicity using physiologically based pharmacokinetic modeling for in vivo inhalation gas uptake data exposure in female mice Toxicology and Applied Pharmacology 244(3) 280-290
34. Fechner G, Ortmann C, Du Chesne A, Kohler H 2001 Fatal intoxication due to excessive dichloromethane inhalation Forensic Science International 122 (1) 69-72
35. Gargas ML Clewell HJ Andersen ME 1986 Metabolism of inhaled dihalomethanes in vivo: differentiation of kinetic constants for two independent pathways Toxicol Applied Pharmacology 82 211-223
36. Gibbs GW Amsel J Soden K 1996 A cohort mortality study of cellulose triacetate–fiber workers exposed to methylene chloride J Occup Environ Med 38(7) 693-697
37. Goulle JP Lacroix C Vaz E Rouvier P Proust B 1999 Fatal case of dichloromethane poisoning J Analytical Toxicology 23(5) 380-383
38. Green T 1990 Species differences in carcinogenicity:the role of metabolism in human risk evaluation Teratogenesis,carcinogenesis and mutagenesis 10 103-113
39. Green T 1996 Methylene chloride induced mouse liver and lung tumours: an overview of the role of mechanistic studies in human safety assessment Human and Experimental Toxicology 16 (1) 3-13
40. Halogen Solvents Industry Alliance 2008 White Paper on Methylene Chloride
41. Hearne Ft Grosse F Pifer JW 1987 Methylene chloride mortality study. Dose response characterisation and animal model comparison J Occup Med 29(3) 217-228
42. Hearne FT and Pifer JW 1999 Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride J Occupational and Environmental Medicine 41 (12) 1154-69

43. Heineman EF Cocco P Gomez JR et al 1994 Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer Am J Ind Hyg Assoc 26 155 - 169
44. Hu Y Kabler SL Tennant AH Townsend AJ Kligerman AD 2006 Induction of DNA-protein crosslinks by dichloromethane in a V79 cell line transfected with the murine glutathione-S-transferase theta 1 gene Mutation Research 607 (2) 231-9
45. IARC 1999 Monographs on the evaluation of carcinogenic risks to humans Dichloromethane 71 Pt 1 251-315
46. Infante-Rivard C Siemiatycki J Lakhani R Nadon L 2005 Maternal exposure to occupational solvents and childhood leukaemia Env Health Perspect 113 (6) 787-92
47. IPCS 1996 International Programme for Chemical Safety Environmental Health Criteria Monograph 'Methylene Chloride' No. 164
48. Jonsson F Bois F Johanson G 2001 Physiologically based pharmacokinetic modeling of inhalation exposure of humans to dichloromethane during moderate to heavy exercise Toxicological Sciences 59 (2) 209-18
49. Jonsson F, Johanson G 2001 A Bayesian analysis of the influence of GSTT1 polymorphism on the cancer risk estimate for dichlormethane Toxicol Appl Pharmacol 174 99-112
50. Kernan GJ Ji BT Dosemeci M 1999 Occupational risk factors for pancreatic cancer: a case control study based on death certificates from 24 US states Am J Ind Med 36 260-270
51. Kim NY, Park SW, Suh JK 1996 Two fatal cases of dichloromethane or chloroform poisoning J Forensic Sci 41 (3) 527-9
52. Kim SN Seo JY Jung da W Lee MY Jung YS Kim YC 2007 Induction of hepatic CYP2E1 by a subtoxic dose of acetaminophen in rats: increase in dichloromethane metabolism and carboxyhemoglobin elevation Drug Metabolism and Disposition 35(10) 1754-1758
53. Kobayashi A, Ando A, Tagami N, Kitagawa M, Kawai E, Akioka M, Arai E, Nakatani T, Nakano S, Matsui Y, Matsumura M 2008 Severe optic neuropathy caused by dichloromethane inhalation J Ocular Pharm Therap 24 (6) 607-12
54. Kupczewska-Dobecka M Socko R 2008 Admissible concentration in biological material: an index of exposure to dichloromethane Medycyna Pracy 59(2) 187-95
55. Lanes SF Cohen A Rothman KJ 1990 Mortality update of cellulose fiber production workers Scand J Work Environ Health 16 247-251
56. Lash AA Becker CE So Y Shore M 1991 Neurotoxic effects of methylene chloride: are they long-lasting in humans? Brit J Indust Med 48 S 418-426
57. Lemasters GK Olsen DM Yiin JH Lockey JE et al 1999 Male reproductive effects of solvent and fuel exposure during aircraft maintenance Reproductive Toxicology 13(3) 155-166
58. McKenna MJ and Zempel JA 1981 The dose-dependent metabolism of [14C] methylene chloride following oral administration to rat Food Cosmet Toxicol 19 73-78
59. McKenna MJ Zempel JA Braun WH 1982 The pharmacokinetics of inhaled methylene chloride in rat Toxicol Applied Pharmacol 65 1-10
60. Manno M, Rugge M, Cocheo V, 1992. Double fatal inhalation of dichloromethane Human Exp Toxicol 196) 540-5
61. Marino DJ Clewell HJ Gentry PR Covington TR Hack CE David RM Morgott DA 2006 Revised assessment of cancer risk to dichloromethane: pt.1 Bayesian PBPK and dose response modelling in mice Regulatory Toxicology and Pharmacology 45(1) 44-54
62. Marino DJ Starr TB 2007 Probabilistic dose-response modelling: case study using dichloromethane PBPK model results Regulatory Toxicology and Pharmacology 49(3) 285-300
63. Mattsson JL Albee RR Eisenbrandt DL 1990 Neurotoxicological evaluation of rats after 13 weeks of inhalation exposure to dichloromethane or carbon monoxide Pharmacology Biochemistry and Behaviour 36 (3) 671-681
64. Moser VC Cheek BM MacPhail RC 1995 A multidisciplinary approach to toxicological screening III Neurobehavioural toxicity J Toxicol Environ Health 45 173 -210
65. Nakayama Y Kishida F Nakatsuka I Matsuo M 2005 Simulation of the toxicokinetics of trichloroethylene, methylene chloride, styrene and n-hexane by a

toxicokinetics/toxicodynamics model using experimental data Environmental Sciences 12(1) 21-32
66. Nitschke KD, Burek JD, Bell TJ, Kociba RJ, Rampy LW, McKenna MJ 1988a Methylene chloride: a 2-year inhalation toxicity and oncogenicity study in rats Fund. Appl Tox 11 (1) 48-59
67. Nitschke KD, Eisenbrandt DL, Lomax LG, Rao KS 1988b. Methylene chloride: two generation inhalation reproductive study in rats Fund Appl Tox 11(1) 60-7
68. Norman WC 1996 Flawed estimates of methylene chloride exposure Am J Ind Med 30 504-505
69. Norwegian Food Control Authority: letter to the European Commission, 9th April 2003
70. Ojajarvi A Partanen T Ahlbom A Boffeta P Hakulinen T Jourenkova N Kauppinen T Kogevinas M Vainio H 2001 Risk of pancreatic cancer in workers exposed to chlorinated hydrocarbon solvents and related compounds: a meta analysis Am J Epidemiol 153(9) 841-850
71. Olvera-Bello AE Estrada-Muniz E Elizondo G Vega L 2010 Susceptibility to the cytogenetic effects of dichloromethane is related to the glutathione S-transferase theta phenotype Toxicology Letters 199(3) 218-224
72. Ott MG Skory LK Holder BB 1983a Health evaluation of employees occupationally exposed to methylene chloride: clinical laboratory evaluation Scand J Work Environ Health 9(suppl1) 17-25
73. Ott MG Skory LK Holder BB 1983b Health evaluation of employees occupationally exposed to methylene chloride: mortality Scand J Work Environ Health 9(suppl1) 8-16
74. Ott MG Skory LK Holder BB 1983c Health evaluation of employees occupationally exposed to methylene chloride: 24-hour ECG monitoring Scand J Work Environ Health 9(suppl1) 26-30
75. Ott MG Skory LK Holder BB 1983d Health evaluation of employees occupationally exposed to methylene chloride: metabolism data Scand J Work Environ Health 9(suppl1) 31-38
76. Putz VR Johnson BL Setzer JV 1979 A comparative study of the effects of carbon monoxide and methylene chloride on human performance J Environ Pathol Toxicol 2 97-112
77. Raimondi S Paracchini V Autrup H et al 2006 Human genome epidemiology (HuGE) review. Meta and pooled analysis of GST-T1 and lung cancer: a HuGE-GSEC review Am J Epidemiol 164(11) 1027-1042
78. Rosenberg J, Hathaway G 1990 Methylene chloride toxicity: Case studies in Environmental medicine US Dept of Health and Human Services publication
79. Sakai T Morita Y Wakui C 2002 Biological monitoring of workers exposed to dichloromethane using head space gas chromatography Journal of Chromatography B Analytical Techniques in Biomedical and Life Sciences 778(1-2) 245-250
80. Savolainen H Kurppa K Pfaffli P 1981 Dose-related effects of dichloromethane on rat brain in short-term inhalation exposure Chem Biol Interract 34 315-322
81. SCC (1987) EU Scientific Committee (SCC) final opinion 11 April 1987 (paper XI/335/89-EN)
82. SCOEL 2009 Recommendation of the Scientific Committee on Occupational Exposure Limits for Methylene Dichloride (dichloromethane) SCOEL/SUM/130 European Commission
83. Sherratt PJ, Manson MM, Thomson AM, Hissink EAM, Neal GE, van Bladeren PJ, Green T, Hayes JD , 1998 Increased bioactivation of dihaloalkanes in rat liver due to induction of class theta GSTT-T1 Biochem J 335 619-630
84. Sherratt PJ, Williams S, Foster J, Kernohan N, Green T, Hayes JD 2002 Direct comparison of the nature of mouse and human GST T1-1 and the implications on dichloromethane carcinogenicity Tox Appl. Pharmacol 179 (2) 89-97
85. Soden KJ Marras G Amsel J 1996 Carboxyhemoglobin levels in methylene chloride-exposed employees J Occupational and Environmental Medicine 38 (4) 367-71
86. Soden KJ 1993 An evaluation of chronic methylene chloride exposure J Occup Med 35(3) 282-286

87. Starr TB Matanoski G Anders MW Andersen ME 2006 Workshop overview: reassessment of the cancer risk of dichloromethane in humans Toxicological Sciences 91 (1) 20-8.
88. Stewart RD, Dodd HC 1964 Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the human skin Am Ind Hyg Assoc J 25 439-446
89. Stewart RD Fischer TN Hosko MJ et al 1972 Experimental human exposure to methylene chloride Arch Env Health 25 342-348
90. Sweeney LM, Kirman CR, Morgott DA, Gargas ML 2004 Estimation of interindividual variation in oxidative metabolism of dichloromethane in human volunteers Toxicological Letters 154 201-16
91. Takeshita H, Mogi K, Yasusda T, Mori S, Nakashima Y, Nakajima T, Akuzawa H, Nakajo S, Hirota Y, Kishi K 2000 Postmortem absorption of dichloromethane: a case study and animal experiments Int J Legal Medicine 114 (1-2) 96-100
92. Taskinen H Lindbohm ML Hemminki K 1986 Spontaneous abortions among women working in the pharmaceutical industry Br J Ind Med 43 199-205
93. Their R, Wiebel FA, Hinkel A, Burger A, Bruning T, Morgenroth K, Senge T, Wilhelm M, Schulz TG 1998 Species differences in the glutathione transferase GSTT1-1 activity towards the model substrates methyl chloride and dichloromethane in liver and kidney Arch Toxicol 72 (10) 622-99.
94. Tomenson JA Bonner SM Heijne CG Farrar DG Cummings TF 1997 Mortality of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base. Occupational and Environmental Medicine 54(7) 470-476
95. Tsuruta H 1977 Percutaneous absorption of organic solvents Ind Med 15 (3-4) 131-139
96. Ursin C Hansen CM Van Dyk JW Jensen PO Christensen IJ Ebbehoej J 1995 Permeability of commercial solvents through living human skin Am Industr Hyg Assoc J 56(7) 651-660
97. US EPA 1994 US Environmental Protection Agency IRIS Record for Methylene Chloride Washington DC
98. Warbrick EV, Kilgour JD, Dearman RJ, Kimber I, Dugard PH 2003 Inhalation exposure to methylene chloride does not induce systemic immunotoxicity in rats J Tox Env Health pt A 66(13) 1207-19
99. Watanabe K, Liberman RG, Skipper PL, Tannenbaum SR, Guengerich FP 2007 Analysis of DNA adducts formed in vivo in rats and mice from 1,2-dibromoethane, 1,2-dichloromethane, dibromomethane and dichloromethane using HPLC/accelerator mass spectrometry and relevance to risk estimates Chem Res Tox 20 (11) 1594-600
100. Winneke G 1981 The neurotoxicity of dichloromethane Neurobehav Toxicol Teratol 3 391-395
101. Zamyslowska-Szmytke E and Sliwinska-Kowalska 2011 Vestibular and balance findings in nonsymptomatic workers exposed to styrene and dichloromethane Int J Audiol 50 (11) 815-822
102. Zarrabeitia MT, Ortega C, Altuzarra E, Martinez MA, Mazarrasa O, Calvet R 2001. Accidental dichloromethane fatality: a case report J Forensic Sci 46 (3) 726-7
103. Gamberale F, Annwall G, Hultengren M (1975) Exposure to methylene chloride. II: Psychological functions. Scand J Work Environm Hlth 1, 95
104. Soden KL et al (see ref 85)
105. Bos PMJ et al (see ref 13)
106 Peterson JE 1978 Modelling the uptake, metabolism and excretion of dichloromethane by man. Amer Industr Hyg Assoc J 39, 41-47.
107 European Chemicals Agency 2009 Guidance on information requirements and chemical safety assessment, Chapter R.15: Consumer exposure estimation: http://echa.europa.eu/documents/10162/13632/r15_update_version_2_rev00_en.pdf
108. Tukker A and Simons ILP 1999 Dichloromethane: Advantages and drawbacks of possible market restrictions in the EU. TNO Report STB – 99-53 Final

109 Slooff, W and Ros JPM 1988 Integrated Criteria Document Dichloromethane. National Institute for Public Health and Environment Protection, RIVM (Rijksintsituut voor Volksgezondheid en Milieuhygiene), the Netherlands. Report No. 758473009

110 Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, Dodd HC 1972 Carboxyhemoglobin elevation after exposure to dichloromethane. Science 176:295 296.

111 Iregren A (1996) Behavioral Methods and Organic Solvents: Questions and Consequences. Environ Health Perspect 104, Suppl 2, 361-366.

112 Allred EN, Bleecker ER, Chaitman BR, Dalims TE, Gotlieb SO, Hackney JD, Hayes D, Pagano M, & Selvester RH (1989) Acute effects of carbon monoxide exposure on individuals with coronary artery disease. Health Effects Institute, 98 pp (Research Report No. 25). (Citation by IPCS, 1996, ref. 47)

113 World Health Organization Regional Office for Europe Copenhagen (2000) Air Quality Guidelines for Europe, pp. 75-79. WHO Regional Publications, European Series, No. 91. Copenhagen. ISBN 1358 3.

114 National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee). Methylene chloride (CAS Reg. No. 75-09-2). Interim acute exposure guideline levels (AEGLs). Interim 1: 12/2008. http://www.epa.gov/oppt/aegl/pubs/methylene_chloride_interim_dec_2008_v1.pdf

115 Rozman KK & Doull J (2001) The Role of Time as a Quantifiable Variable of Toxicity and the Experimental Conditions When Haber's c x t Product Can Be Observed: Implications for Therapeutics. J Exp Ther 296 (3) 663-668.

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/m^3 ppm	Exposure interval	TWA mg/m^3 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

Type of study or conditions of exposure	Concentration mg/m³ ppm	Exposure interval	TWA mg/m³ 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 500 142 minimum value 800 239 mean value	5 min 5 min 5 min	133 41 67	Not applicable	109
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/m^3) 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