Chapter 5.7 Dichloromethane

General description

Physical and chemical properties

Dichloromethane, CH_2Cl_2 (DCM), also known as methylene chloride, is a halogenated aliphatic hydrocarbon compound. It is a colourless liquid with penetrating ether-like or mild sweet odour. It is moderately soluble in water (2 g/100 ml at 20 °C) and soluble in most organic solvents such as ethanol, ether, phenols, aldehydes and ketones. Its evaporation rate is 27.5 (reference liquid is butyl acetate = 1). DCM vapours are heavier than air. DCM is normally stable, non-flammable and non-explosive when mixed with air; temperatures above 100 °C should be avoided. A wide range of odour thresholds (530–2120 mg/m^3) have been reported, but detection occurs around 530 mg/m^3 and recognition around 810 mg/m^3. DCM is commercially available in high purity *(1)*.

Sources

DCM may be formed from natural sources, but these are not believed to contribute significantly to global release. The worldwide production of DCM in 1980 was estimated to be 570 000 tonnes, of which 270 000 tonnes were produced in western Europe. Current estimates are that world production is at a similar level to that in 1980 *(2)*. Production of paint stripper, pharmaceuticals and process solvent are the most important industrial areas of DCM use. Other important uses of DCM include foam blowing of polyurethane, metal degreasing, stripping and degreasing in the electronics industry, as a solvent in polycarbonate resin production, in photographic film base manufacturing, and numerous other cleaning and thinning uses. DCM is also occasionally used as an extractant for naturally occurring, heat-sensitive substances such as edible fats, caffeine, cocoa, spices and hops.

DCM is also used in consumer products such as paint strippers, with a DCM content of 70–75%, and in hair-spray aerosols containing DCM as a solvent and vapour pressure modifier up to 35% w/w. Other products, such as household cleaning products, room deodorants, and lubricating and degreasing products in aerosol form, may also contain DCM.

The diverse nature of its application implies that DCM can be released to the environment to a large extent. Entry to the environment may also occur during production, transportation and storage, as well as from waste disposal sites, industrial effluents and water treatment facilities.

Occurrence in air

It is estimated that nearly 80% of all DCM produced globally is released to the atmosphere, with potential for 100% release *(3)*. Mean atmospheric levels of DCM observed at 22 locations across Canada in 1991–1992 ranged from 0.5 µg/m^3 to 9.9 µg/m^3 *(4)*. In surveys involving 20 cities in the United States, the average levels of DCM varied from not detectable to 570 µg/m^3 *(5)*. The annual mean concentration at three sites in the San Francisco Bay area over a four-year period, based on two 24-hour samples taken each month, indicated a slight reduction in average levels from 3.1 µg/m^3 to 1.8 µg/m^3 over the period 1987–1990. Monthly

DCM values were generally highest in winter, declined to a minimum in April and increased in the autumn *(6,7)*. Mean background concentrations in rural areas are 0.07–0.29 μg/m^3 .

The arithmetic means of DCM measured in hazardous waste sites in New Jersey ranged from 0.35 μg/m^3 to 5.6 μg/m^3. At one site, a mean concentration of 40 μg/m^3 and peak levels of 190 μg/m^3 were found *(8)*. DCM was found in more than 75% of samples taken in the ambient air at a New Jersey sewage treatment plant, with a peak concentration of 2180 μg/m^3 *(9)*.

In general, the mean concentration of DCM in indoor air is higher than that in ambient air by a factor of about 3 *(10)*. Based on preliminary results, the mean concentration in indoor air in 757 homes across Canada was 16.3 μg/m^3 (maximum = 1690 μg/m^3) *(11)*. Mean levels of DCM in samples of indoor air in a small survey in Toronto were similar, ranging from 9.1 μg/m^3 to 26.9 μg/m^3 *(12)*. In a non-occupational indoor environment, the time-weighted average (TWA) in a room without ventilation varied between 460 μg/m^3 and 2980 μg/m^3 during the use of paint removers containing dichloromethane *(13)*.

Atmospheric fate process

It is assumed that the photochemical degradation induced by hydroxyl radicals is the fundamental process in the destruction of DCM in the environment. Photooxidation and photolysis of DCM at sea level are expected to be minimal, whereas conditions in the upper troposphere will allow photooxidation to occur as a result of photochemically generated hydroxyl radicals. The life-time of DCM in the atmosphere is 40–160 days *(2)*. These values depend on the concentration of hydroxyl radicals and the light intensity in the region *(14)*. Migration of DCM from the troposphere to the stratosphere was estimated to take place within 5–10 years. This implies that 2.0–2.5% enters the stratosphere. Based on global estimates, approximately 0.08% of DCM in the troposphere is washed out annually by precipitation *(15)*.

Conversion factors

1 ppm = 3.53 mg/m^3

1 mg/m^3 = 0.28 ppm (at 20 °C and 1013 hPa)

Routes of exposure

Air

Exposure of humans to DCM occurs primarily through air. Exposures are highest in occupational settings and near sources of emissions. Inhalation exposure is also high in industrialized urban areas. Hazardous waste sites may release DCM to air. There is potential for low-level exposure of the general population from indoor use of consumer products (paint removers, aerosols, electronics, pharmaceuticals) containing DCM.

Drinking-water

A wide sampling exercise involving 630 public community water supplies serving 6.9 million people in New Jersey showed a range of concentrations from 1.1 μg/l to 2.0 μg/l *(16)*. In a Canadian study, the mean concentrations ranged from 0.2 μg/l to 2.6 μg/l (with a detection limit of 0.05 μg/l) *(17)*. In two Canadian studies, the chlorination of water in drinking-water or sewage treatment plants showed inconclusive results; the earlier study showed a slight increase in DCM levels, while the later study showed similar levels before and after

chlorination *(18,19)*. In surface water in the United States, a median concentration of 0.1 µg/l was estimated *(20)*.

Soil
Data on levels of DCM in soil are restricted to contaminated sites. Levels of dichloromethane in sediment from Lake Pontchartrain, New Orleans, ranged from "not detectable" to 3.2 ng/g wet weight *(21)*.

Food
Levels in biota are not expected to be high, based on physical and chemical properties of DCM (e.g. log K_{ow}, the octanol/water partition coefficient = 1.25). Mean levels in tissue of oysters and clams were 4.5–27 ng/g wet weight *(21)*. Concentrations of DCM in table-ready foods have been monitored in the Total Diet Program of the US Food and Drug Administration. Levels in ready-to-eat cereals and butter were the highest (95 and 84 µg/kg respectively), followed by cheese (45 µg/kg), margarine (27 µg/kg), processed foods (34 µg/kg) and peanut butter (19 µg/kg) *(22)*. In decaffeinated instant coffee, DCM content ranged from <0.05 mg/kg to 0.91 mg/kg *(23)*.

Population groups at greater risk of exposure
It is evident that several occupational subgroups have above-average exposure risk. Highest occupational inhalation exposure levels (1750 mg/m^3 as an 8-hour TWA) occur among workers engaged in DCM manufacturing, paint remover formulation and polycarbonate resin production. The industry-wide 8-hour TWA exposure level is 79 mg/m^3 *(24)*. High exposure concentrations may develop rapidly in poorly ventilated areas. Typical exposures during the application of paint remover, the removal of the paint soaked in DCM and the disposal of spent paint remover range from 18 mg/m^3 to about 1770 mg/m^3 (8-hour TWA) *(25)*.

Among the general population, transitory high-level atmospheric and sometimes dermal exposures to DCM are commonly associated with the use of DCM-containing paint strippers, adhesives and aerosol products for hobby and household uses. The general widespread distribution of DCM throughout the atmosphere contributes additional exposures to the general population; these are usually classified as low level, but may become significant in the vicinity of DCM industrial and point-of-use areas. People with compromised cardiovascular function are considered to be more sensitive to DCM exposure.

Toxicokinetics

Absorption
The principal route of human exposure to DCM is inhalation. Absorption is rapid. At low levels of exposure, blood concentrations of DCM increase linearly with exposure level. At high concentration, however, saturation occurs. About 70–75% of inhaled DCM was absorbed in people exposed to 175–700 mg/m^3 for 7.5 hours on a single occasion *(26)*. The amount of DCM absorbed increased with duration of exposure and physical activity as a result of increased ventilation and cardiac output. Physical activity for 0.5 hour during exposure to 880 or 1760 mg/m^3 DCM doubled absorption but decreased retention from 55% to 40% because of a three-fold increase in ventilation rate *(27)*. DCM absorption was also directly related to obesity *(28)*.

Uptake via the digestive tract is rapid *(29)*. Serious poisoning can result from swallowing DCM *(30)*. DCM in liquid form can penetrate healthy skin.

Distribution

There is some evidence for the accumulation of DCM in human body fat. However, DCM appears to reach a steady state and washes out rapidly. In animal studies with ^{14}C-labelled DCM, a rapid reduction of the concentration in adipose tissue was found; liver, kidneys and lungs are the organs that show the highest radioactivity 48 hours after a single oral dose or following 6 hours of inhalation exposure *(31,32)*. The liver/blood and muscle/blood partition coefficients for DCM are both about 1, while the fat/blood coefficient is about 10 *(33)*. Dichloromethane crosses the placental barrier in rats and humans, and can also be found in the breast-milk of exposed women *(34)*.

Metabolism and elimination

Two pathways for biotransformation of DCM have been identified. The first is a cytochrome P-450 dependent metabolism and the second is a glutathione-*S*-transferase (GST) dependent process. The oxidative cytochrome P-450 pathway produces carbon monoxide and carbon dioxide via an unstable intermediary metabolite, formyl chloride. The glutathione pathway yields carbon dioxide following the formation of a postulated glutathione conjugate and formaldehyde. Neither formyl chloride nor the glutathione conjugate of DCM have been isolated or characterized, but their formation is consistent with the products formed and the enzymes and cofactors required. Assays of metabolic activity *in vitro* are based on carbon monoxide formation from the cytochrome P-450 route and formaldehyde formation from the glutathione-*S*-transferase pathway. The iso-enzymes responsible for DCM metabolism by these pathways are principally cytochrome P-450IIE1 *(35)* and the glutathione-*S*-transferase theta-class enzymes *(36)*. The oxidative metabolic route has high affinity but only low capacity for DCM, whereas the glutathione-dependent pathway has low affinity but high capacity *(37)*.

It has been shown in liver fractions *in vitro* that the mouse metabolizes DCM via glutathione at an approximately 10-fold higher rate than the rat. The *in vitro* conjugation of DCM with glutathione by cytosolic glutathione-*S*-transferase of human liver homogenate showed a 1.4 times lower activity than with rat liver cytosol *(38)*. Thus the metabolism of DCM correlates with the species difference with regard to carcinogenicity. The oxidative metabolic pathway is saturated *in vivo* at relatively low exposure concentrations, around 1750 mg/m^3, in all species studied including humans. This pathway was also saturated in mice at the highest dose (250 mg/kg body weight) in the drinking water carcinogenicity study carried out by the National Coffee Association *(39)*, at which no increase in tumours was observed. In a National Toxicology Program inhalation study *(40)*, mice exposed to 7100 and 14100 mg/m^3 dichloromethane had a high, dose-dependent tumour incidence in liver and lungs. Thus there is no correlation between oxidative metabolism and tumour incidence in oral and inhalation studies. It follows that the glutathione metabolic pathway, which has a low affinity but high capacity for DCM, probably represents the critical pathway for carcinogenic activity.

The biotransformation of DCM is dose-dependent. At higher doses, a relatively smaller proportion is metabolized and a larger proportion exhaled unchanged. Humans exposed by inhalation to 175, 350, 520 or 700 mg/m^3 for 7.5 hours exhaled 25–35% as carbon monoxide, while 5% was exhaled unchanged. After exposure, the carbon monoxide concentration in exhaled air drops much more slowly than the dichloromethane concentration. Carbon

monoxide concentration in exhaled air seems to be about halved during the first 4 hours after exposure to concentrations not higher than 700 mg/m^3 *(26)*.

Rats that inhaled ^{14}C-methylene chloride in concentrations of 175, 1750 or 5520 mg/m^3 for 6 hours excreted about 8% of the radioactivity in urine and 2% in faeces in the following 48 hours. None of this was unmetabolized DCM *(32)*. Excretion of DCM in urine is also negligible in humans. Once absorbed, DCM is rapidly cleared from the blood; 1 mg/l was detected in the 700-mg/m^3 exposure group after 16 hours *(26)*.

Biomarkers of exposure

Dichloromethane exposure may be monitored by its determination in the blood, breath or urine of exposed persons. Significant linear correlations were found between DCM concentrations in the breathing zone and DCM in urine, as well as carbon monoxide concentrations in alveolar air among non-smoking workers *(41)*. In a cohort of 14 furniture strippers exposed to DCM at concentrations of 53–1290 mg/m^3, post-exposure breath concentrations of DCM ranged from 8.1 mg/m^3 to 590 mg/m^3 *(42)*.

Carboxyhaemoglobin (COHb) levels rise during a period of DCM exposure. This depends on the concentration and duration of exposure, and the extent of concurrent carbon monoxide exposure. The relationships, however, are affected by physical activity. Although DCM does not accumulate following repeated exposure, the COHb levels will be cumulative if the periods between consecutive exposures are not sufficiently long to enable COHb levels to return to normal (the biological half-life of COHb is 13 hours). It is possible to monitor COHb levels in workers exposed to DCM, with the measurements being made either about 0–2 hours or 16 hours after the end of exposure. Post-exposure COHb levels 2 hours after exposure ceases are not expected to exceed 2–3%, and at 16 hours 1%, where non-smokers are exposed to less then 350 mg/m^3 DCM for 8 hours.

Since the relationship between alveolar carbon monoxide and COHb has not been well established for DCM-exposed workers, breath analysis for carbon monoxide cannot be considered as providing definitive quantitative information regarding DCM exposure. The biological exposure indices for DCM at the end of a working shift have been reported to be 5% COHb and a blood level of DCM of 1 mg/l.

Health effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects

The acute toxicity of DCM by inhalation and the oral route is low. The inhalation 6 hour-LC_{50} values for all species are between 40 000 and 52 000 mg/m^3. Acute inhalation studies showed that DCM produced effects on the central nervous system (CNS). Deep narcosis occurred in rats at 53 000 mg/m^3 after 30 minutes *(43)*. Alteration of somatosensory-evoked potentials was observed after a 1-hour exposure to dose levels of 17 700 mg/m^3 or higher *(44)*. Reversible changes in motor activity in mice were reported at exposure for 1 hour to concentrations > 2600 mg/m^3 *(45)*. Increased COHb levels were found at concentrations of 1770 mg/m^3 and higher in various strains of rat *(46)*. Intratracheal administration of 350 mg/kg DCM killed rats in a few seconds, emphasizing the hazard of breathing DCM *(47)*. Myocardial contractility was altered in Swiss mice following a single exposure to DCM *(48)*

and DCM sensitized the myocardium to arrhythmia development in response to catecholamines *(49)*. The reported cardiovascular effects are inconsistent. Prolonged exposure to high concentration of DCM (>17 700 mg/m^3) caused reversible CNS effects and body weight reduction in mice. DCM is moderately irritant to the skin *(50)* and causes slight irritation to the eyes.

Short-term studies showed that DCM altered liver structure and cytochrome enzyme activity. Lifetime exposure to DCM increased the incidence of haemosiderosis, cytomegaly and cytoplasmatic vacuolization *(40),* and fatty infiltration of the liver was also observed *(51)*.

Studies have demonstrated that DCM can cross the placental barrier, although it is not teratogenic in rats and mice at concentrations up to 16 250 mg/m^3. Small effects on either fetal or maternal body weights were reported at 4400 mg/m^3. Neither external malformations nor differences in delayed ossification or dilation of the renal pelvis were found *(52,53)*.

The lowest-observed-effect-level for non-neoplastic effects in adequately documented investigations following chronic exposure by ingestion is 50 mg/kg body weight/day in F344 rats, at which fully reversible cellular proliferation and partially reversible fatty changes in the liver were observed *(54)*.

Carcinogenic effects

Dichloromethane has been studied for carcinogenicity in several animal studies. DCM induced a dose-dependent, statistically significant increase in liver and lung adenomas and carcinomas in male and female B6C3F1 mice exposed by inhalation (6 hours/day, 5 days/week for 102 weeks) at concentrations of 7100 or 14 100 mg/m^3 *(40)*. These tumours were not increased in a study in which DCM was administered to the same strain of mice in drinking-water at up to 250 mg/kg *(55)*. Furthermore, there were no increases in either tumour type in rats or hamsters exposed to DCM by inhalation *(40,56,57)* or in rats given DCM in drinking-water *(54)*. DCM induced a statistically significant increase in benign mammary tumours (of a type not expected to progress into malignant tumours) in female rats exposed at 7100 or 14 100 mg/m^3. Male rats developed mammary gland fibroadenomas at 14 100 mg/m^3, but only at a marginally significant rate *(40)*. These tumours were not seen in mice or hamsters, or in rats exposed to lower concentrations of DCM. The development of these tumours appears to be linked to an indirect mechanism, probably the induction of high levels of prolactin. Furthermore, elevated levels of prolactin will lead to an increased level of progesterone and endogenous oestrogens. All these factors may cause tubular-alveolar growth of the mammary glands. As prolactin is not luteotropic in primates, it is unlikely that this mechanism of tumour development is relevant for humans. In one study *(58)*, there was an increased incidence of sarcomas of various types in the ventral mid-cervical area of the salivary gland of male Sprague-Dawley rats exposed to 3500 mg/m^3. This neoplastic response has not been reported at this site in any of the other studies.

The possible carcinogenetic mechanism of inhaled DCM in mouse lung is the marked lesion in the Clara cells. Green *(59)* observed that Clara cells damaged by exposure to 7100 or 14100 mg/m^3 DCM for 1 or 10 days no longer contained cytochrome P-450 iso-enzymes. Using microsomes prepared from whole-lung homogenates, the metabolism of DCM to carbon monoxide was reduced by 50%, suggesting that 50% of the cytochrome P-450 responsible for metabolizing DCM is found in the Clara cells, which comprise only 5% of the total cell types in the mouse lung. Assay of the glutathione-*S*-transferases with DCM

indicated that these enzymes were not affected either in Clara cells or whole-lung homogenates. On a whole-lung basis, the metabolism of DCM remained reduced by 50%. DNA–protein cross-links due to formaldehyde derived from dichloromethane were detected in the liver but not in the lungs of mice, nor in the liver or lungs of hamsters *(60,61)*. The failure to detect DNA–protein cross-links in mouse lungs might be attributed to their formation in Clara cells.

Analysing the experimental data on carcinogenicity of DCM showed a good interspecies and high intraspecies reproducibility, even though obtained from different sexes, as well as varying degrees of severity of prognosis and, in the case of rats, different strains. The fluctuation of the estimated carcinogenic potencies was lower in mice than in rats *(62)*. Using physiologically based pharmacokinetic models, a reasonable correlation was found between the calculated internal dose of glutathione metabolites of DCM and the tumour incidence in mice. These calculations also indicated much lower internal doses in rats and hamsters, a result that is consistent with the absence of a carcinogenic response in these species.

Mutagenic effects
Dichloromethane has been evaluated in a variety of gene mutation and chromosomal assays in prokaryotic and eukaryotic systems *in vitro* and *in vivo*. There is a clear evidence of mutagenicity in bacteria *(63)*. It has been suggested that the bacterial mutagenicity of DCM is mediated by glutathione conjugation *(64)*. The pathway of DCM metabolism utilizing glutathione produces formaldehyde via a postulated *S*-chloromethylglutathione conjugate (GSCH2Cl). Formaldehyde is known to cause DNA–protein cross-links, and GSCH2Cl may act as a monofunctional DNA alkylator by analogy with the glutathione conjugates of 1,2-dihaloalkanes, suggesting that GSCH2Cl is responsible for dichloromethane mutagenicity in *Salmonella (65)*. DNA damage in the form of single-strand breaks and DNA–protein cross-links were also detected in Chinese hamster ovary cells and in hepatocytes incubated in the presence of DCM and mouse liver fractions *(61,65)*.

Mutagenicity tests in some strains of yeast showed weakly positive responses. The results of gene mutation and unscheduled DNA synthesis assays in mammalian cells *in vivo* were uniformly negative. Chromosomal aberrations have been reported following exposure of a variety of cell types to high concentrations of DCM *in vitro (66)*. *In vivo*, there was no evidence of chromosomal damage in rat or mouse bone morrow *(67)*. Small increases in chromosomal damage were seen in lung cells and circulating lymphocytes of mice exposed to 26 240 mg/m^3 DCM *(68)*.

The genotoxicity of DCM was not adequately predicted by the conventional battery of short-term tests. The primary reason for the failure of the mammalian tests is linked to the remarkably high glutathione-*S*-transferase theta activity seen in mouse tissues, and the nuclear localization of that activity. This combination of high enzyme activity and nuclear localization, which is necessary for genetic activity, has not been found in any mammalian species tested. The glutathione-*S*-transferase activity in simple prokaryotic cells such as *Salmonella* is also in close proximity to the nucleus, since bacteria do not possess a nuclear membrane. Thus, in this respect mice and bacteria are similar: the highly unstable and reactive *S*-chloromethyl glutathione conjugate can be formed in close proximity to DNA, and hence there is a high probability of DNA alkylation occurring before the conjugates are hydrolysed. This view is consistent with that expressed by Thier et al.*(69)*. These findings suggest that genotoxicity may play a role in the carcinogenicity of DCM.

Interactions with other chemicals
The influence of aromatic hydrocarbons on the metabolism of dichloromethane to carbon monoxide in rats was studied by Pankow et al. *(70)*. The carboxyhaemoglobin level was significantly enhanced by prior administration of benzene, toluene and xylene. Following simultaneous administration of DCM and the aromatic solvent, COHb formation was inhibited. It seems that the stimulation or inhibition of COHb formation, caused by pretreatment or simultaneous administration of aromatic solvents, is due to the induction of cytochrome P-450 or to competition between DCM and the aromatic solvent for these iso-enzymes of cytochrome P-450.

Effects on humans

Toxicological effects
The primary adverse health effect associated with short-term exposure to DCM is impairment of CNS function. Case studies of DCM poisoning have demonstrated that exposure can be fatal. In two cases of lethal poisoning following acute inhalation of extremely high concentrations of
DCM, the concentrations of the solvent found in the blood at autopsy (572 and 601 mg/l) were compatible with those measured in the air a few hours after the discovery of the bodies (up to 593 000 mg/m^3). High but not lethal carboxyhaemoglobin levels (30%) were found in the blood collected at autopsy. Narcosis and respiratory depression due to the effect of DCM on the CNS were the most prominent symptoms *(71)*. No lethality data were found in the available literature following chronic exposure to DCM.

Slight erythema was found when DCM in aerosol-spray deodorant was used twice a day for 12 weeks by 75 men and women *(72)*. On direct contact, DCM caused a chemical burning sensation and pain *(73)*.

A cohort study of 1758 retired airline mechanics to examine long-term exposure to DCM, using a comprehensive battery of physiological and psychological tests, revealed no lasting effects on the CNS. Two groups, one consisting of eligible retirees having long-term exposure to DCM and another group having low probability of exposure to solvents, were compared. No statistically significant differences between the groups were detected, although subtle differences in attention and memory were identified *(74)*.

Exposure to even higher levels of DCM (average of 1676 mg/m^3 as an 8-hour TWA) for more than 10 years produced no differences in symptoms or adverse health effects, as judged by selected liver, cardiac and neurological parameters, in a population of employees compared to a similar but non-exposed group *(75)*.

Carcinogenic effects and mortality studies
A mortality investigation of a 1964–1970 cohort of 1013 hourly-paid men exposed to DCM, followed up to 1984, was updated by Hearne et al. with four additional years of observation through to 1988 *(76)*. Information from 4300 individual occupational assignments was abstracted from personnel records, and an index of career exposure was developed. The mortality of the cohort was compared to both the general male population of New York State and to male Kodak workers who were not exposed to DCM. Concomitant exposures were noted. Follow-up was essentially complete (99%). The principal confounding factor for carcinoma of the lung and ischaemic heart disease was cigarette smoking. Overall mortality

from 1964 to 1988 (N = 238) was significantly reduced compared to both control populations. There were non-significant deficits in observed/expected ratios for lung cancer, liver cancer and ischaemic heart disease. Death from other malignant neoplasms were lower than expected based on the two control populations. In another study, the relationship between birth weight and exposure to DCM emissions was examined; no significant adverse effects were found *(77)*.

In a study of mortality among 1271 workers exposed to DCM during the production of cellulose triacetate fibre, there was excess mortality for cancer of the buccal cavity and pharynx (observed/expected = 2/0.87), liver and biliary passages (observed/expected = 4/0.70) and melanoma (observed/expected =2/0.88). A deficit in mortality was observed, however, for cancers of the respiratory system, breast and pancreas *(78)*. The mortality studies in relevant cohorts showed an inconsistent pattern in the causes of death.

Interactions with other chemicals
Much of the data focuses on concurrent exposure to carbon monoxide, since DCM is metabolized to carbon monoxide. Because carbon monoxide generated from DCM is additive to exogenous environmental carbon monoxide, DCM exposures are of concern to workers, to smokers maintaining significant constant levels of COHb, and to others who may have increased sensitivity to carbon monoxide toxicity, including those with cardiovascular disease and respiratory dysfunction.

Evaluation of human health risks

Exposure evaluation

Mean outdoor concentrations of DCM are generally below 5 $\mu g/m^3$. Significantly higher concentrations (by at least one order of magnitude) may occur close to industrial emission sources. Indoor air concentrations are variable but tend to be about three times greater than outdoor values. Under certain circumstances, much higher values (up to 4000 $\mu g/m^3$) may be recorded indoors, particularly with use of paint stripping solutions. Exposures of the general population occur principally through use of DCM-containing consumer products. Exposure in outdoor air, water and food is low.

Health risk evaluation

The critical effects of DCM include effects on the CNS, the production of COHb and carcinogenicity. The impairment of behavioural or sensory responses may occur in humans following acute inhalation exposure at levels exceeding 1050 mg/m^3 (300 ppm) for short durations, and the effects are transient. The cytochrome P-450-related oxidative pathway resulting in carbon monoxide production is saturable, producing maximum blood COHb levels of $\leq$9 %. Nevertheless, these COHb levels are sufficiently high to induce acute effects on the CNS, and it thus appears that such effects are probably due to COHb production. DCM does not appear to cause serious effects in humans at those relatively high levels reported in occupational settings.

Although there is no convincing evidence of cancer incidence associated with occupational exposure, the available data have limitations and are considered inadequate to assess human carcinogenicity. In male and female mice and male and female rats, the National Toxicology Program's bioassays led to the conclusion of clear evidence of carcinogenicity in mice, clear

evidence in female rats and equivocal evidence in male rats. IARC has classified DCM as showing sufficient evidence of carcinogenicity in experimental animals (Group 2B).

The health risks of exposure to DCM have been considered in detail by an International Programme on Chemical Safety (IPCS) expert group. Given the data on interspecies differences in metabolism and comparative cancer risks, that group concluded that carcinogenicity was not the critical endpoint for risk assessment purposes. It is therefore concluded that the formation of COHb is a more direct indication of a toxic effect, that it can be monitored, and that it is therefore more suitable as a basis for the derivation of a guideline. Furthermore, it is unlikely that ambient air exposures represent a health concern with reference to any cancer endpoint, since concentrations of DCM in ambient air are orders of magnitude lower than levels associated with direct adverse effects on the CNS or on COHb production in humans.

The application of physiologically based pharmacokinetic models to the available animal data lead to small risk estimates *(79,80)*. These risk estimates are much lower than the recommended guideline value using COHb formation, and were therefore not employed in guideline derivation.

Guidelines

The selected biological endpoint of interest is the formation of COHb, which is measured in the blood of normal subjects at levels of 0.5–1.5% of total haemoglobin. In heavy smokers, the level of COHb may range up to 10%. Carbon monoxide from various sources may contribute to the formation of COHb. Since overall levels in many cases approach the recommended maximum of 3%, it is prudent to minimize any additional amounts of COHb contributed from DCM. It was thus concluded that no more than 0.1% additional COHb should be formed from DCM exposure. This corresponds to the analytical reproducibility of the method applied to measure COHb at the level of concern. This maximum allowable increase in COHb corresponds to a 24-hour exposure to DCM at a concentration of 3 mg/m^3. Consequently, a guideline value of 3 mg/m^3 is recommended. In addition, the weekly average concentration should not exceed one seventh (0.45 mg/m^3) of this 24-hour guideline, given the half-life of COHb.

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