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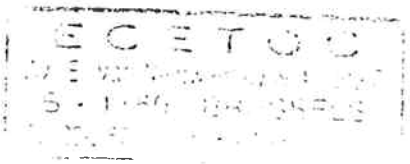

Environmental Health Criteria 164

METHYLENE CHLORIDE (SECOND EDITION)

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ENVIRONMENTAL HEALTH CRITERIA FOR METHYLENE CHLORIDE

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ENVIRONMENTAL HEALTH CRITERIA FOR METHYLENE CHLORIDE

1. SUMMARY

1.1 Identity, physical an chemical properties, and analytical methods

Methylene chloride (dichloromethane) is a clear, highly volatile, non-flammable liquid with a penetrating ether-like odour. Pure dry methylene chloride is a very stable compound. Methylene chloride hydrolyses slowly in the presence of moisture, producing small quantities of hydrogen chloride. Commercial methylene chloride is normally inhibited with small quantities of stabilisers to prevent acidification and corrosion.

Analytical methods are available for the determination of methylene chloride in biological media and environmental samples. All methods involve gaschromatography in combination with a suitable detector. In this way, very low detection limits have been reached (e.g. in food: 7 ng/sample; water: 0.01 µg/ℓ; air: 0.5 ppb; blood: 0.022 mg/ℓ).

1.2 Sources of human and environment exposure

World production of methylene chloride is estimated to be 570 kt/y. Most applications are based on the solvent capacity for grease, plastics and paint binding agents, in combination with its volatility and stability; it is also no-flammable. The worldwide usage pattern breaks down into aerosols (20-25%), paint remover (25%), process solvent in the pharmaceutical industry (35-40%), miscellaneous uses (e.g. polyurethane foam manufacturing) and metal cleaning (10-15%). The usage of methylene chloride shows some indication of a decrease, at least in Western Europe.

More than 99% of the atmospheric releases of methylene chloride result from its use as an end-product by various industries, and the use of paint removers and aerosol products at home.

1.3 Environmental transport, distribution and transformation

Due to its high volatility, most of the methylene chloride released to the environment will partition to the atmosphere, where it will degrade by reaction with photochemically produced hydroxy radicals with a half-life of 6 months.

Abiotic degradation in water is slow compared to evaporation. Methylene chloride has shown to disappear rapidly from soil and groundwater.

The aerobic and anaerobic degradation of methylene chloride has been proven by a variety of different test systems. Its complete biodegradation, especially by acclimated bacterial cultures under aerobic conditions, is rapid (e.g. 49-66% mineralisation in 50 h with acclimated municipal sludge). In bioreactors up to 10% degradation per h is achievable. There is no evidence that significant bioaccumulation or biomagnification of methylene chloride along the food chain will occur.

Methylene chloride is expected to have no significant impact on stratospheric ozone depletion. It will not contribute significantly to photochemical smog-formation.

1.4 Environmental levels and human exposure

Methylene chloride has been detected in ambient air of rural and remote areas, at concentrations of 0.07-0.29 $\mu g/m^3$. In suburban areas, the average concentration is < 2 $\mu g/m^3$ and in urban areas < 15 $\mu g/m^3$. In the vicinity of hazardous waste sites up to 43 $\mu g/m^3$ was found. Precipitation may also contain methylene chloride.

Methylene chloride enters the aquatic environment through waste water discharges from various industries, and methylene chloride has been found in surface water, ground water and sediments.

Exposure of members of the general public to methylene chloride will occur from its use in consumer products, such as paint removers, which can result in relatively high levels being found in indoor air. Occupational exposure during production arises primarily during filling and packaging (manufacturing is in closed systems). Because of its use in paint strippers, occupational exposure to methylene chloride occurs during formulation of paint-remover, original equipment manufacture, maintenance sector and commercial furniture refinishers. Methylene chloride is widely used as a process solvent in the manufacture of a variety of products, in particular in the industries mentioned above (section 1.2)

Biological monitoring of methylene chloride exposure can be based on measurement of the solvent itself in exhaled air or blood. However, as production of carbon monoxide with exposure for more than 3-4 h/day appears to be the limiting factor in regard to health risk, biological monitoring based upon either analysis of carbon monoxide in exhaled air or of CO-Hb in blood is to be preferred. However, this can only be applied in non-smoking subjects. Sampling should be done at about 0-2 h post-exposure, or after 16 h i.e. on the following morning.

Post-exposure CO-Hb levels at 2 h after exposure ceases are not expected to exceed 2-3%, and at 16 h 1%, in the case of an 8 h exposure to less than 350 mg/m^3 methylene chloride in non-smokers.

1.5 Kinetics and metabolism

Methylene chloride is rapidly absorbed though the alveoli of the lungs into the systemic circulation. It is also absorbed from the gastrointestinal tract and dermal exposure results in absorption but at a slower rate than the other exposures.

It is quite rapidly excreted, mostly via the lungs in the exhaled air. It can cross the blood-brain barrier, it can be transferred across the placenta, and small amounts can be excreted in urine or in milk.

At high concentrations, most of the absorbed methylene chloride is exhaled unchanged. The remainder is metabolised to carbon monoxide, carbon dioxide, and

inorganic chloride. Metabolism occurs by either or both of two pathways, whose relative contribution to the total metabolism is markedly dependent on the dose and on the animal species concerned.

One pathway involves oxidative metabolism mediated by cytochrome P-450 and leads to both carbon monoxide and carbon dioxide. This pathway appears to operate similarly in all rodents studied and in man. Whilst this is the predominant metabolic route at lower doses, saturation occurs at a relatively low dose (around 1800 mg/m^3). Increasing the dose above the saturation level does not lead to extra metabolism by this route.

The other pathway involves a glutathione transferase, and leads via formaldehyde and formate to carbon dioxide. This route seems only to become important at doses above the saturation level of the 'preferred' oxidative pathway. In some species (e.g. the mouse) it becomes the major metabolic pathway at sufficiently high doses. In contrast, in other species (e.g. hamster, man) it seems to be used very little at any dose.

Species difference in GST metabolism correlate well with the observed species difference in carcinogenicity. The extent of metabolism by this pathway in relevant species has been used as the basis for a kinetic model to describe the metabolic behaviour of methylene chloride in various species.

1.6 Effects on organisms in the environment

Algae and aerobic bacteria show no inhibition of growth below 500 mg/ℓ. Bacteria have been identified which are able to grow in the presence of methylene chloride at much higher concentrations including saturated water (Section 4.2.4.1). Anaerobic bacteria are more sensitive; growth inhibition has been observed at 1 mg/ℓ in anaerobic biological sludge.

In soil 10 mg/kg strongly decreased the ATP content of the biomass including fungi and aerobic bacteria, and induced transient inhibitionof enzyme activity. The no effect level was 0.1 mg/kg. In earthworms methylene chloride is moderately toxic (100-1000 μg/cm^2). In sediment no toxic effects were observed even at very high levels.

In higher plants no effects were found after exposure for 14 days to 100 mg/m^3.

Adult fish seem to be relatively insensitive to methylene chloride even after prolonged exposure (14-d LC_{50} > 200 mg/ℓ). The effect of methylene chloride on *Daphnia* is difficult to assess given the large variation in the outcome of the studies performed. The lowest reported EC_{50} was 12.5 mg/ℓ.

In the aquatic environment, fish and amphibian embryos have been shown to be the most sensitive with effects on hatching from 5.5 mg/ℓ.

1.7 Effects on laboratory mammals and *in vitro* test systems

1.7.1 Single exposure

The acute toxicity of methylene chloride by inhalation and oral administration is low. The inhalation 6h-LC_{50} values for all species are between 40,200 and 52,000 mg/m^3. Oral LD_{50} values of 1410 - 3000 mg/kg were recorded. Acute effects after methylene chloride administration by various routes of exposure are primarily associated with the central nervous system (CNS) and the liver and these occured at high doses. CNS disturbances were found of 14,100 mg/m^3 and higher with slight changes in EEG at 1770 mg/m^3. Slight histological changes in the liver were found of 17,700 mg/m^3 and higher. Occasionally other organs are affected such as the kidney or respiratory system. Cardiac sensitization to adrenaline-induced arrhythmias has been reported and cardiovascular effects were reported but the effects were inconsistent.

1.7.2 Short- and long-term exposure

Prolonged exposure to high concentrations of methylene chloride (≥ 17,700 mg/m^3) caused reversible CNS effects, slight eye irritation and mortality in several laboratory species. Body weight reduction was observed in rats at 3500 mg/m^3 and in mice from 17,700 mg/m^3. Slight effects on the liver were noted in dogs continuously exposed to 3500 mg/m^3 for up to 100 days. After intermittent exposure, effects on the liver were observed in rats at 3500 mg/m^3 and in mice at 14,100 mg/m^3.

Other target organs were the lungs and the kidneys. In mice, effects on the lungs were restricted to the Clara cells after exposure to 7100 mg/m^3 and higher for 10 days.

No evidence of irreversible neurological damage was seen in rats exposed by inhalation to concentrations up to 7100 mg/m^3 for 13 weeks.

Oral administration of methylene chloride to rats caused effects on the liver from about 200 mg/kg per day.

1.7.3 Skin and eye irritation

Methylene chloride is moderately irritant to the skin. Only corrosive effects could occur under hard conditions. Reversible irritating effects appeared when methylene chloride gets into the eyes.

1.7.4 Developmental and reproductive toxicity

Methylene chloride is not teratogenic in rats or mice at concentrations up to 16,250 mg/m^3. No evidence of an effect on the incidence of skeletal malformations or other developmental effects were observed in 3 animal studies. Small effects on either foetal or maternal body weights were reported at 4400 mg/m^3. A two-generation reproductive toxicity study in rats exposed to methylene chloride by inhalation at concentrations up to 1500 mg/m^3, 6 h/day, 5 days/week for 14 weeks did not show evidence of an

adverse effect on any reproductive parameter, neonatal survival or neonatal growth in either the F_0 or F_1 generation.

1.7.5 Mutagenicity and related end-points

Under appropriate exposure conditions, methylene chloride is mutagenic in prokaryotic microorganisms with or without metabolic acivation (*Salmonella* or *E. coli*). In eukaryotic systems it gives either negative or, in one case, weakly positive results. *In-vitro* gene mutation assays and tests for UDS in mammalian cells were uniformly negative. *In vitro* assays for chromosomal aberrations using different cell types gave positive results, whereas negative or equivocal results were obtained in tests for SCE induction.

The majority of the *in vivo* studies reported have provided no evidence of mutagenicity of methylene chloride (e.g. chromosome aberration assay, micronucleus test or UDS assay). A very marginal increase in frequencies of SCEs, chromosomal aberrations and micronuclei in mice has been reported following inhalation exposure to high concentrations of methylene chlrodie. The significance of these results is questionable due to methodological deficiencies in the statistical analysis.

There was no evidence of binding of methylene chloride to DNA or DNA damage in rats or mice given high doses of methylene chloride. These studies are potentially the most sensitive *in vivo* studies, the best of which are capable of detecting one alkylation in 10^6 nucleotides.

Within the limitations of the short-term tests currently available, there is no conclusive evidence that methylene chloride in genotoxic *in vivo*.

1.7.6 Chronic toxicity and carcinogenicity

Methylene chloride is carcinogenic in the mouse, causing both lung and liver tumours, following exposure to high concentrations (7100 and 14,100 mg/m^3) of methylene chloride. The incidence of both lung and liver tumours was increased in mice exposed to 7100 mg/m^3 methylene chloride for 26 weeks and maintained for a further 78 weeks. There was no substantial evidence of associated toxicity or hyperplasia in the target organs.

Syrian hamsters exposed to methylene chloride by inhalation at concentrations up to 12,400 mg/m^3 for 2 years showed no evidence of a carcinogenic effect related to exposure to methylene chloride.

Rats exposed to methylene chloride via various routes have shown increased incidences of tumours at certain sites. An excess of tumours in the region of the salivary gland was reported in female rats exposed to either 5300 or 12,400 mg/m^3 methylene chloride for 2 years. This excess was only evident when the tumours, which were all of mesenchymal origin, were grouped together for statistical analysis. As the tumours arose from a variety of different cells, the statistical approach adopted was inappropriate. Furthermore, it was reported that the rats in the study had been infected