ARBETE OCH HÄLSA

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Arbete och Hälsa 1992:27

NEG and DECOS Basis for an Occupational Standard

Methyl Chloride

Per Lundberg

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NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

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ISBN 91-7045-179-6
ISSN 0346-7821

Preface

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DECOS) of the Dutch Directorate-General of Labour and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities both in the Netherlands and in the Nordic Countries.

This document on health effects of methyl chloride was prepared by Dr P. Lundberg from the National Institute of Occupational Health in Solna, Sweden, and has been reviewed by the Dutch Expert Committee as well as by the Nordic Expert Group.

J. J. Kolk
Chairman
Dutch Expert Committee

P Lundberg
Chairman
Nordic Expert Group

Contents

1. Physical and Chemical Data

Systematic name	Chloromethane
Synonyms	Methyl chloride, Monochloromethane
CAS no	74-87-3
Formula	CH_3Cl
Mol. wt	50.49
Boiling-point	-24.2° C
Melting-point	-97.1° C
Density (20 °C)	0.9159
Vapour pressure (22 °C)	506.5 kPa
Flash-point	-45.5° C
Conversion factors (25 °C; 101.3 kPa)	1 ppm = 2.07 mg/m^3
	1 mg/m^3 = 0.48 ppm

At room temperature methyl chloride is a colourless gas with ethereal odour and sweet taste. The odour threshold in humans has been reported to be 10 ppm (21 mg/m^3) (73). It is slightly soluble in water (303 ml/100 ml at 20° C); soluble in ethanol, diethyl ether, acetone, chloroform, benzene, carbon tetrachloride and glacial acetic acid. Methyl chloride decomposes in water with a half-time of 4.66 h at 100° C. It reacts with active metals (aluminum, magnesium, potassium, sodium, zinc).

Methyl chloride is marketed as a liquefied gas under pressure, generally in 99.5 - 99.95 % purity. Impurities may include water, hydrochloric acid, dimethyl ether, methanol, acetone, ethyl chloride and vinyl chloride. (2).

2. Production, Use and Occurrence

2.1. Production and Use

In the most common production method of methyl chloride, equimolar portions of vaporized methanol and hydrogen chloride are reacted at approximately 350° C over a suitable catalyst. In a lesser used procedure methane is chlorinated (2).

Methyl chloride was in the 1920s and 1930s used primarily as a refrigerant (2). The current principal use of methyl chloride is in the production of methyl silicone polymers and resins, and in the manufacture of tetramethyl lead antiknock compounds for gasoline. To a lesser extent it is used as a chemical intermediate and as a solvent. Methyl cellulose, used as paint thickener, is produced by the etherification of cellulose with methyl chloride. It is used as a blowing agent of polystyrene foams. (2).

Methyl chloride has also been used as an intermediate in the production of plastics, pharmaceuticals, herbicides, dyes, disinfectants, methyl ethers and dichloromethane. To a limited extent it has been used as a local anaesthetic (2).

2.2. Occurrence

The principal sources of methyl chloride in the atmosphere are formation in the oceans by seaweeds and marine microorganisms and by the combustion of organic matter (16, 41). Methyl chloride is produced (synthesized) by a variety of marine organisms and the oceans are believed to release 1000 - 8000 million kg per year. Combustion processes are estimated to release 150-600 million kg per year and industrial emissions were estimated to contribute only about 20 million kg in 1980 (16).

Average levels of methyl chloride in air at urban sites in the US ranged from 0.7 ppb to 3.0 ppb (1.4 - 6.2 µg/m^3) and the background concentration at surface level from natural sources was estimated to be 0.65 ppb (1.3 µg/m^3) (68). In sea-water methyl chloride concentrations ranging from 0.01 to 0.05 µg/l have been reported (16).

Tobacco smoke contains 150-840 µg methyl chloride per cigarette (85).

Workplace concentrations have been measured in four US chemical plants (12). Three of the plants produced methyl chloride. The personal 8 h time-weighted average concentrations in the three plants ranged from 8.9 to 12.4 ppm (18.4 - 25.7 mg/m^3), from <0.2 to 7.5 ppm (<0.4 - 15.5 mg/m^3) and from < 0.1 to 12.7 ppm (<0.2 - 26.3 mg/m^3) respectively. In the fourth plant where methyl chloride was used as a blowing agent in the production of polystyrene foam, the personal exposures ranged from 2.98 to 21.4 ppm (6.2 - 44.3 mg/m^3) (12).

The 8 h average exposures of six workers in a Dutch methyl chloride production plant were calculated to be from 30 to 90 ppm methyl chloride (62-186 mg/m^3) during one working week (14). The ambient concentration was measured by continous monitoring from twelve sampling points in the area and personal 8 h averages were calculated according to previous experience.

Methyl chloride vapours were not detected during polystyrene foam cutting procedures. This might, however, be attributed to the duration of the foam cutting procedure (13).

2.3. Measurements of methyl chloride in air

According to the method recommended by NIOSH (48, 53) methyl chloride is adsorbed on activated charcoal. The analyte is desorbed in methylene chloride (dichloromethane) and determined by gas chromatography (GC) with flame-ionization detection (FID). The method is suitable in the range of 122-455 mg/m^3 with a sample size of 0.5 to 1.5 l.

The use of carbon disulfide at dry ice temperature for desorbing the analyte has also been described as well as thermal desorption (67). Later a thermally-desorbable diffusional dosimeter for monitoring methyl chloride in the workplace has been described (21). Very low concentrations (6 - 100 ng/m^3) of methyl chloride (in ambient air) can be analyzed by the use of photoionization, flame ionization and electron capture detectors in series (64).

Exposure to methyl chloride can as well be monitored in air by direct-reading infrared analyser, at minimum detectable concentrations of 0.8 - 3.1 mg/m^3 (19).

3. Kinetics

3.1. Uptake and distribution

Uptake of methyl chloride by the respiratory passages is demonstrated in experiments where volunteers were exposed to 10 ppm (20.6 mg/m^3) or 50 ppm (103 mg/m^3) for 6 h. During the first hour of the exposure the methyl chloride concentration in blood reached a plateau proportional to the exposure concentrations. (50). The partition coefficient (K_D) for blood/air is 0.8 (46).

Steady-state levels in blood of methyl chloride were rapidly reached in dogs and rats exposed to 50 and 1000 ppm (103 and 2060 mg/m^3). In rats exposed by inhalation to ^{14}C-methyl chloride for 6 h, radioactivity was highest in liver and kidneys and lower in testes. The doses were 50 to 1000 ppm (103 and 2060 mg/m^3) and rats were killed immediately after the 6 h exposures (37).

At the end of a 6 h exposure of rats by inhalation to 500 or 1500 ppm (1030 or 3090 mg/m^3) ^{14}C-methyl chloride, up to 20 % of the total radioactivity was incorporated into tissue proteins, lipids and nucleic acids. An accumulation of radioactivity was seen in lipid, RNA, DNA, and protein isolated from lung, liver, kidney, testes, brain, muscle and intestine (36).

3.2. Biotransformation and excretion

After inhalation as a single breath of ^{38}Cl-methyl chloride by volunteers, 29 % of the inhaled radioactivity was excreted in expired air within one hour (46).

When six volunteers were exposed for 6 h on two days separated by two weeks to 10 or 50 ppm (20.6 or 103 mg/m^3) of methyl chloride the concentration in blood and expired air was proportional to the exposure concentration. The concentration in two of the volunteers was two to three times higher than in the others. A five-fold difference in the rate constant for methyl chloride metabolism was calculated between the two groups (50).

In human erythrocytes methyl chloride is enzymatically conjugated with glutathione. In the human population there are two groups. Approximately 60 % show a significant enzymatic activity in the cytoplasm and 40 % show no measurable activity. No conversion of methyl chloride was found in erythrocyte cytoplasm of rats, mice,bovines, sheep or rhesus monkeys. (54, 55).

The methyl group of methyl chloride is metabolized via S-methylcysteine to formate. Elevated formate levels were found in blood and urine of rats exposed to methyl chloride by inhalation and treated with folate-dependent formate metabolism inhibitors. Formaldehyde has also been detected in rat liver microsomes incubated with methyl chloride and NADPH (35).

The total metabolic clearance of methyl chloride in rats was reported to be 0.20 and 3.3 nmol/min/g bw after exposure to 50 and 1000 ppm (103 and 2060 mg/m^3) respectively (39).

In rats, biphasic elimination kinetics were observed following inhalation of methyl chloride (3). Urinary metabolites in rats exposed by inhalation were reported to be S-methylthioacetic acid sulphoxide, N-acetyl-S-methylcysteine and N-(methylthioacetyl) glycine (37).

Methyl-S-methylglutathione and methyl-S-metylcysteine were found in homogenates of liver, brain and kidney from rat and guinea-pig after incubation with methyl chloride (58).

3.3. Biological monitoring

In persons occupationally exposed to methyl chloride (up to 90 ppm; 185 mg/m^3) urinary levels of thioether and S-methylcysteine were measured and compared to non-exposed persons. No significant increases in thioether levels were detectable. Increased excretion of urinary S-methylcysteine was reported in exposed persons. However, when following a group of workers during a seven-day shift it was revealed that two of six exposed workers hardly excreted any S-methylcysteine (14).

By measuring methyl chloride in blood and breath after exposure, two groups could be distinguished. The majority had concentrations in blood and expired air that were two to six times lower than in the minority (57, 74).

With the existence of two populations, a majority of "converters" with a lower body burden of methyl chloride and a minority of poor "converters" with a high methyl chloride body burden, it is difficult to perform biological monitoring of methyl chloride (45).

4. General Toxicology

Methyl chloride poisonings have occurred both in industry and as a consequence of leakages from domestic refrigerators. (6, 18, 20, 23, 24, 33, 40, 42, 43, 44, 62, 65, 72, 75). Some of these cases have been fatal. The symptoms associated with fatal poisoning include nausea, vomiting and abdominal pain, followed by headache, mental confusion, loss of balance and, eventually, consciousness.

Mortality from all causes was lower than expected according to mortality study of employees at a butyl rubber manufacturing plant. The cohort consisted of 852 male process workers who had worked at least 1 month during the period from 1943 through 1978. Data on exposure levels are not presented. A total of 179 deaths occurred during the study period, while 246 were expected based on age-specific mortality rates of US white males. This finding is, according to the authors (28), consistent with the "healthy worker effect". The results do not indicate an increased risk of death due to diseases of the nervous system or diseases of the digestive system.

According to RTECS (63) the LC_{50} value for methyl chloride in mice is 3146 ppm (6512 mg/m^3) for 7 h exposure. In an abstract (78), 6 h LC_{50} value of 2250 ppm (4600 mg/m^3) was reported for male mice and 8500 ppm (17500 mg/m^3) for female mice. The LC_{50} value (50 min) in rats is reported to be 152000 mg/m^3 (63).

In dogs exposed to 15000 ppm (31000 mg/m^3) methyl chloride the average survival time was 6 h (51). When guinea-pigs were exposed for 6 h to 3000 ppm (6200 mg/m^3) methyl chloride most animals died (70). The minimal lethal concentration of methyl chloride for guinea-pigs exposed for 72 hours is reported

to be approximately 75 ppm (155 mg/m^3), where 9 of 18 exposed animals died, (77). These data indicate that there is a species difference.

In guinea-pigs, mice, dogs, monkeys, rabbits or rats exposed to 300 ppm (620 mg/m^3) for six hours daily six days a week no apparent symptoms were seen after 64 weeks of exposure (70).

In mice the cerebellar toxicity and the renal toxicity (see chapter 5) induced by methyl chloride was decreased by pretreatments of the animals with BSO (L-buthionine-S,R-sulfoximine). BSO acts inhibitory on ∂-glutamylcysteine synthetase thereby inhibiting the synthesis of glutathione (GSH). This inhibition results in a substantial reduction in the cumulative amount of methylchloride-GSH conjugate formed as a result of exposure to methyl chloride (11).

5. Effects on Organ Systems

5.1. Effects on skin and mucous membranes

According to Patty (76) irritation of the skin and eyes has not been a significant problem but freezing due to evaporation could cause frostbite.

5.2. Effects on the respiratory tract

Clinically, pulmonary edema in animals was noted frequently and appeared to be a direct result of the irritation due to inhalation of 300 ppm (620 mg/m^3) methyl chloride or more for six hours a day, six days a week (15).

5.3. Effects on the liver

In the most severe cases of human methyl chloride intoxication impairment of liver function was seen according to the laevulose tolerance test. (33).

There was no evidence of liver dysfunction in animals exposed to 300 ppm (620 mg/m^3) methyl chloride or more for six hours a day six days a week (69). Histopathologically, a fairly constant but low to moderate amount of fatty metamorphosis of the liver was seen in the smaller species of animals studied (15).

When mice exposed to 500, 1000 or 2000 ppm (1035, 2070 or 4140 mg/m^3) methyl chloride for 6 hours per day for up to 12 days, severe hepatic lesions were confined to male mice in the highest dose group. The changes were not seen in rats exposed to 5000 ppm (10350 mg/m^3) methyl chloride (47).

As reported in an abstract (52) hepatocellular degeneration and necrosis was seen in mice exposed to 997 ppm (2064 mg/m^3) methyl chloride 6 h/day, 5 days/week for 24 months.

Hepatocellular cloudy swelling was observed in male rats exposed to 7500 ppm (15525 mg/m^3) methyl chloride 6 h/day for 2 days or 5000 ppm (10350 mg/m^3) 6 h/day for 5 days (10). Increased alanine aminotransferase activity in serum was detected in male mice 18 hours after a 6 h exposure to 1500 ppm (3100 mg/m^3) methyl chloride. Liver toxicity was inhibited when the animals were depleted of glutathione (GSH) prior to methyl chloride exposure (11).

5.4. Effects on the kidneys

In a severe case of human methyl chloride poisoning albumin and red cells in the urine and a raised blood-urea suggested some renal damage (33).

There was no evidence on renal dysfunction in animals exposed to 300 ppm (620 mg/m^3) methyl chloride or more for 6 h/day 6 days a week (69). The only morphologic changes that appeared to be a direct result of inhalation of methyl chloride were variable degrees of necrosis of the convoluted tubules in mice and rats, renal changes associated with hemoglobinuria in mice and occasional dogs, and a fairly constant but low to moderate amount of fatty metamorphosis of the kidneys in the smaller species of animals studied (15).

Tubular degeneration was present in mice exposed to 2000 ppm (4140 mg/m^3) for 6 h/day for up to 12 days. Tubular bosophilia, presumed to be regeneration, confined mainly to mice exposed to 1000 ppm (2070 mg/m^3). In rats exposed to 2000, 3500 or 5000 ppm (4140, 7250 or 10350 mg/m^3) degeneration of proximal convoluted tubules was observed with a clear exposure-concentration related response (47).

As reported in an abstract (52) renal cortical microcysts were seen in male mice exposed to 51 ppm (105.6 mg/m^3) methyl chloride 6 h/day 5 days/week for 24 months.

Degeneration of renal proximal convoluted tubules was observed in male rats exposed to 7500 ppm (15525 mg/m^3) methyl chloride 6 h/day for 2 days or 5000 ppm (10350 mg/m^3) 6 h/day for 5 days (10). Toxicity to kidney after exposure to 1500 ppm (3100 mg/m^3) methyl chloride 6 h/day, 2 days/week for two weeks was inhibited by glutathione depletion prior to methyl chloride exposure. The inhibition was measured by incorporation of [^{3}H]thymidine into renal DNA, an indicator of cell regeneration after cortical necrosis (11).

5.5. Gastrointestinal effects

In a report of 15 cases gastrointestinal complaints occurred in 12 of the cases. It was assumed that concentrations in excess of 500 ppm (1030 mg/m^3) would be required to produce these symptoms (23). The air level of methyl chloride was measured to be above 200 ppm (415 mg/m^3) in a report where the cases experienced nausea and vomiting (40).

5.6. Cardiovascular effects

When beagle dogs were exposed to 15000 ppm (31000 mg/m^3) methyl chloride severe circulatory disturbances appeared. They were mainly characterized by vaso-dilation after a latent period of about three hours. The dogs died after about six hours (51).

Exposure of pregnant mice to methyl chloride has caused heart malformations in fetuses (see chapter 9).

5.7. Hematological effects

There was no evidence of a primary effect upon the formed elements of the blood in animals exposed to 300 ppm (620 mg/m^3) or more for six hours a day six days a week (69).

5.8. Effects on the nervous system

In a report of 15 cases exposed to methyl chloride from leaking refrigerators, dizziness, weakness, muscular incoordination, sleep disturbances and mental confusion were reported by most of the cases. It was assumed that concentrations in excess of 500 ppm (1030 mg/m^3) would be required to produce those symptoms (23). The same type of symptoms are reported in another case report (33), where ataxia was found to persist for at least eight months and depression for four weeks. In a report, where the cases experienced fatigue, tremor and unsteadiness of gait, the air levels of methyl chloride were measured to be above 200 ppm (414 mg/m^3) (40).

A follow-up study of a patient 18 months after methyl chloride poisoning showed her still to have a marked intention tremor. She also had frequent headaches, insomnia and nervousness, symptoms that had not been present before the poisoning (24). In a study 13 years after methyl chloride poisoning neurological examination revealed neurological signs in five of ten patients, such as peripheral neuropathy in 2, tremor in 3, paralysis of accommodation in 2. Two of the original 15 patients developed severe depression and committed suicide within 2 years (20).

Headache, disturbance in balance, confusion, dizziness, numbness, staggering gait and disorientation occurred in workers after prolonged exposure to 265 to up to 300 ppm (550 to 620 mg/m^3) methyl chloride (65).

In a study with human subjects males were given single or repeated exposures to 0, 20, 100 or 150 ppm (0, 41, 207 or 310.5 mg/m^3) methyl chloride and females to 0 or 100 ppm (0 or 207 mg/m^3). Exposure were 1, 3 or 7.5 h/day for 5 days. Using a wide battery of behavioural and neurological tests no significant decrements were found (76).

In an experimental study where volunteers exposed for 3 h to 100 or 200 ppm (207 or 414 mg/m^3) methyl chloride were tested for eye-hand coordination, mental alertness and time discrimination. At 200 ppm (414 mg/m^3) a marginally significant impairment in task performance was observed (56, 57). A group of 122 workers currently exposed to approximately 35 ppm (72.5 mg/m^3) (range 8.5 to 58.7 ppm) methyl chloride for in excess of two years had significantly poorer performance on test of vigilance (light flash monitoring), menthal arithmetic, rail balancing, strength (dynamometer) and finger tremor than 49 unexposed controls. No relationship between exposure and test results was established (5, 59).

In animals a number of symptoms of methyl chloride poisoning are common to several species. Prominent among these are hyperactive reflexes, disturbances in ability to correct position and extreme spasticity. An exception is the behaviour of monkeys which is characterized by epileptiform convulsions and periods of unconsciousness (71).

Staggering atactic movement of the head, ataxia and paresis of the hind legs occurred in guinea-pigs exposed to 20000 ppm (41400 mg/m^3) methyl chloride 10 min per day 6 days a week up to 70 days. Necroses in the cerebellar cortex (in Stratum granulosum) were observed (34).

Focal degeneration of the cerebellar internal granular layer was found in female mice exposed to 1000 or 2000 ppm (2070 or 4140 mg/m^3) methyl chloride for 6 hours per day up to 12 days. The same type of degeneration, although more moderate, was seen in rats exposed to 5000 ppm (10350 mg/m^3) methyl chloride (47).

As reported in an abstract (52) cerebellar granular cell layer degeneration and atrophy was seen in mice exposed to 997 ppm (2064 mg/m^3) methyl chloride 6 h/day, 5 days/week for 24 months. Cerebellar granular cell layer degeneration was also observed in female mice exposed continously (22 h/day) to 100 ppm (207 mg/m^3) methyl chloride for 11 days or intermittently (5.5 h/day) to 400 ppm (828 mg/m^3) for 11 days. No effects were observed in mice exposed continously to 50 ppm (103.5 mg/m^3) or intermittently to 150 ppm (310.5 mg/m^3) methyl chloride (38). Focal and diffuse malacia of the cerebellar inner granular layer was found in female mice exposed to 1500 ppm (3105 mg/m^3) methyl chloride 6 h/day, 5 days/week for 2 weeks (31).

Male mice were protected by glutathione depletion from central nervous system toxicity caused by exposure to 1500 ppm (3105 mg/m^3) methyl chloride 6 h/day, 5 days/week for 2 weeks, as assessed by microscopic examination of the granule cell layer of the cerebellum (11).

5.9. Effects on other organs

Effects on the reproductive organs, see chapter 9.

Blurred vision were reported by all 15 patients in a case report. It was assumed that concentration in excess of 500 ppm (1030 mg/m^3) would be required to produce this symptom (23). Effects on the vision were reported already in 1914 as a result of exposure to methyl chloride (18). In another report of seven cases, eye symptoms were common. They were usually delayed for 24 hours and might persist for as long as two months (33). In a report where the cases experienced blurred vision the air levels of methyl chloride were measured to be above 200 ppm (414 mg/m^3) (40).

Blurry vision and diplopia is reported to occur in workers after prolonged exposure to levels of methyl chloride of up to 300 ppm (621 mg/m^3) in two cases and of 265 ppm (550 mg/m^3) in four cases. No evidence of methyl chloride intoxication was seen when the levels ranged from 15 to 195 ppm (31 to 400 mg/m^3) (65).

Vacuolar degeneration in adrenal cortex was observed in male rats exposed to 7500 ppm (15525 mg/m^3) methyl chloride 6 h/day for 2 days or 5000 ppm (10350 mg/m^3) for 5 days (10).

6. Immunotoxicity and allergy

As reported in an abstract (52) splenic lymphoid depletion and atrophy was seen in male mice exposed to 997 ppm (2064 mg/m^3) methyl chloride 6 h/day, 5 days/week for 24 months.

7. Mutagenicity and Genotoxicity

Methyl chloride at a concentration of 0.5-20.7 % in air was mutagenic to Salmonella typhimurium TA 1535 both in the presence and absence of a metabolic system (S9) (4). After exposure of S. typhimurium TM 677 to 5-30 % methyl chloride for three hours a dose-dependent increase in the number of 8-azaguanine-resistant mutants was found (17).

Following treatment of TK6 human lymphoblasts no increase in the incidence of DNA damage was found. Dose-dependent increases in the numbers of trifluorothymidine-resistant mutants were observed after exposure to 1-5 % methyl chloride for 3 h. After three hours exposure to 0.3-3 % methyl chloride a dose-dependent increase in the numbers of sister chromatid exchanges was seen (17).

Concentrations of 1-10 % methyl chloride in vitro induced unscheduled DNA synthesis in rat hepatocytes and pachytene spermatocytes but not in tracheal epithelial cells. Inhalation exposure to methyl chloride in vivo, 3000-3500 ppm (6200-7245 mg/m^3) 6 h/day for 5 days, failed to induce DNA repair in these cell types. In vivo exposure to 15000 ppm (31050 mg/m^3) for 3 h caused a marginal increase in unscheduled DNA repair in hepatocytes but failed to do so in epithelial cells and spermatocytes (84).

Inhalation of 300 ppm (6200 mg/m^3) methyl chloride for 6 h per day on five consecutive days induced epididymal inflammation and gave a positive response in the dominant lethal mutation test in sperm of Fischer 344 rats (8). The authors suggest that the dominant lethal mutations are a consequence of the induction of inflammation of the epididymis.

In male mice exposed for 8 h to 1000 ppm (2070 mg/m^3) methyl chloride DNA-protein cross-links and single-strand breaks were induced in renal tissue. The DNA-protein cross-links were removed at a fast rate whereas single strand breaks appeared to accumulate. However, 48 h after exposure neither of these lesions were detectable in the mouse kidney.The lesions were ascribed to the action of formaldehyde, a biotransformation product of methyl chloride (61). Neither in female mouse renal tissue nor in hepatic tissue (both sexes) were these lesions detectable (60).

Transformation of Syrian hamster embryo cells by SA7 adenovirus was enhanced after exposure to 3-50 parts per thousand (6.2-103.5 g/m^3) methyl chloride in sealed chambers for 30 h (25).

8. Carcinogenicity

A cohort study has been conducted of 852 male workers employed for at least one month between 1943 and 1978 in a butyl rubber manufacturing plant using methyl chloride (28). Among white men there was a total of 19 deaths from cancer. The expected number based on standardized mortality rates was 28.8. Among non-white male men the observed number om cancer deaths was 11 (17.5 expected). Further analysis, by time of first employment, duration of employment and level of exposure to methyl chloride, provided no indication of a dose-response relationship for all cancers taken together. The small number of deaths provides an insufficient basis for assessing cancer risk.

In an abstract (52) a two-year inhalation study on mice and rats is reported. Male and female B6C3F1 mice were exposed to 0, 51, 224 or 997 ppm (0, 106, 464 or 2064 mg/m^3) methyl chloride for 6 h per day on five days per week. An increase in the incidence of renal cortical adenomas and adenocarcinomas and cortical tubular cysts in males receiving the highest dose was reported. Renal cortical adenomas were also seen in males exposed to 224 ppm (464 mg/m^3). Male and female Fischer 344 rats were exposed according to the same protocol. No increase in tumour incidence was reported in the treated rats. The study is inadequately reported. The final report is not published but cited by NIOSH (49). A statistical significant increase in both malignant and nonmalignant renal tumours occurred in male mice at the highest exposure level. The tumours included cortical adenomas and adenocarcinomas, papillary cystadenomas and cystadenocarcinomas plus tubular cystadenomas (49).

9. Reproductive and Teratogenic Effects

In a case report on methyl chloride intoxication from a leaking refrigerator a 30-year-old female was 7 months pregnant. The woman was found in a comatose state and the seven-months-old fetus was spontaneously delivered (24).

Rats exposed to 2000-5000 ppm (4100-10300 mg/m^3) methyl chloride for up to nine days developed lesions in the seminiferous tubules and the epididymis (47). In several other studies testicular and epididymal damage have been reported in rats following exposure to methyl chloride by inhalation at levels of 1500 ppm (3100 mg/m^3) or higher for 6 h per day on five days or more (7, 22, 82, 83). At 1000 ppm (2070 mg/m^3) the exposed rats did not differ in this respect from the control rats (82, 83). Exposure of rats to methyl chloride by inhalation of 1500 ppm (3100 mg/m^3) for 6 h per day on five days per week for ten weeks and thereafter for 6 h per day on seven days per week for a further two weeks resulted in severe atrophy of the seminiferous tubules in all animals (10/10) and in epididymal granulomas in 3/10 animals. No litter resulted from breeding of males exposed to 1500 ppm (3100 mg/m^3). Fewer litters were born to females bred to males similarly exposed to 475 ppm (980 mg/m^3) methyl chloride. No such effect was observed following exposures to 150 ppm (310 mg/m^3) (22).

Groups of male rats were exposed to 1000 or 3000 ppm (2070 or 6200 mg/m^3) methyl chloride 6 h/day for 5 days and were bred to females weekly for up to 8

weeks. The females were killed 12 h post mating. Fertilization rates in the 1000 ppm (2070 mg/m^3) group were not significantly depressed. The percentage of fertilized ova in the 3000 ppm (6200 mg/m^3) group was significantly decreased, ranging from 3 to 72 % (81).

In a teratology study groups of 25 pregnant rats were exposed by inhalation to 0, 100, 500 or 1500 ppm (0, 207, 1035 or 3100 mg/m^3) methyl chloride for 6 h per day on gestation days 7-19. Fetal body weights and skeletal maturity were reduced following exposure to 1500 ppm (3100 mg/m^3). No exposure-related skeletal or visceral abnormality was seen (80).

Groups of pregnant mice were exposed to 0, 100, 500 or 1500 ppm (0, 207, 1035 or 3100 mg/m^3) methyl chloride for 6 h per day on gestation days 6-17. After six to nine days of treatment signs of neurotoxicity were observed in the highest dose-group and treatment was stopped. No fetal skeletal abnormality was detected but a low, significant incidence of heart defects was seen in the 500 ppm (1035 mg/m^3) group (80). In order to examine further these cardiac defects, groups of 74-77 pregnant mice were exposed by inhalation to 0, 250, 500 or 750 ppm (0, 515, 1035 or 1550 mg/m^3) methyl chloride for 6 h per day on gestation days 6-17. The incidence of cardiac defects was 0.7 % of the fetuses in control litters, 1.3 % at 250 ppm (515 mg/m^3), 2.5 % at 500 ppm (1035 mg/m^3) and 4.3 % at 750 ppm (1550 mg/m^3), significant at the two higher exposures (79). The mechanism of this seemingly unique alteration in the fetal mouse heart induced by methyl chloride is unclear (32).

10. Relation between Exposure, Effect and Response

10.1. Observations in man

In most of the cases where poisoning has been reported there are no information on the actual concentration of methyl chloride. However, in a report where gastrointestinal complaints, dizziness, muscular incordination, mental confusion and blurred vision were reported, the concentration of methyl chloride is said to be more than 500 ppm (1030 mg/m^3) (23). In another case report the same types of symptoms and effects were described after exposure to 200 ppm (414 mg/m^3) (40).

Effects on the nervous system and blurred vision are reported in six cases occupationally exposed to 265-300 ppm (550-620 mg/m^3) for two to three weeks, but no evidence of methyl chloride intoxication has been seen in a survey of 141 plants where the levels of methyl chloride ranged from 15 to 195 ppm (31 to 400 mg/m^3) (65). In a later study (5) significantly poorer psychomotor performance than in controls was demonstrated in some tests after more than 2 years occupational exposure to a mean concentration of about 35 ppm (72.5 mg/m^3) methyl chloride. However, no relationship was established between exposure and the test results (59).

According to Patty´s Industrial Hygiene and Toxicology (76) no significant decrements in behavioural and neurological tests were seen after exposure to 150 ppm (310.5 mg/m^3) 7.5 h/day for 5 days. On the other hand, marginally significant impairment in task performance was reported in persons

experimentally exposed to 200 ppm (414 mg/m^3) methyl chloride for 3 hours (56, 57).

10.2. Observations in animals

Data from animal studies are presented in Table I.

Table I. Effects on animals exposed to methyl chloride by inhalation.

Exposure ppm	Time	Animal	Effects	Ref
73430	50 min	rats	LC_{50}	(63)
20000	10 min/d, 6 d/w 70 d	guinea pigs	ataxia, paresis, necroses in cerebellar cortex	(34)
15000	6 h	dogs	average survival time	(51)
15000	3 h	dogs	severe circulatory disturbances	(51)
8500	6h	female mice	LC_{50}	(78)
7500	6h/d, 2d	male rats	vacuolar degeneration in adrenal cortex, renal tubular degeneration, hepatocellular cloudy swelling	(10)
5000	6h/d, 5d	male rats	hepatocellular cloudy swelling, renal tubular degeneration, vacuolar degeneration in adrenal cortex	(10)
5000	6h/d, 12d	rats	renal tubular degeneration, focal neuronal degeneration in , cerebellum, no hepatic lesions	(47)
3146	7h	mice	LC_{50}	(63)
3000	6h/d, 5d	male rats	significant decrease of fertilized ova in females bred to exposed males	(81)
3000	6h	guinea pigs	most animals died	(70)
2250	6h	male mice	LC_{50}	(78
2000	6h/d, 12 d	male mice	severe hepatic lesions, renal tubular degeneration	(47)
2000	6h/d, 12 d	rats	renal tubular degeneration	(47)
1500	6h	male mice	increased alanine amino-transferase activity in serum 18 h after exposure	(11)
1500	6h/d, 5d/w 2w	female mice	focal malasia in cerebellum	(31)
1500	6h/d, 5d/w 10 w	male rats	testicular and epididymal damage, no litter from breeding	(22)
1500	6h/d gest d 7-19	female rats	reduced fetal body weights and skeletal maturity	(80)
1000	8h	male mice	increased single strand breaks and DNA-protein cross-links	(61)
1000	6h/d, 12 d	female mice	focal neuronal degeneration in cerebellum	(47)
1000	6h/d, 5d/w 10 w	male rats	no testicular or epididymal damage	(83)
997	6h/d, 5d/w	mice	hepatocellular degeneration and	(52)

Exposure ppm	Time	Animal	Effects	Ref
	24 mo		necrosis, focal neuronal degeneration in cerebellum, increased incidenceof renal carcinomas	
997	6h/d, 5d/w 24 mo	rats	no increased tumour incidence	(52)
500	6h/d gest d 6-17	female mice	heart defects in fetuses	(79)
475	6h/d, 5d/w 10 w	male rats	decreased number of litter after breeding with unexposed females	(22)
400	5.5h/d, 11 d	female mice	focal neuronal degeneration in cerebellum	(38)
300	6h/d, 6d/w 64 w	mice rats	fatty metamorphosis of the liver and kidneys	(15)
300	6h/d, 6d/w 64 w	mice, rats, guinea pigs, dogs, monkeys rabbits	no apparent effects	(70)
224	6h/d, 5d/w 24 mo	male mice	renal cortical adenomas	(52)
150	5.5 h/d, 11d	female mice	no focal neuronal degeneration in cerebellum	(38)
150	6h/d, 5d/w 10 w	male rats	no effect on number of litter	(22)
100	22h/d, 11d	female mice	focal neuronal degeneration in cerebellum	(38)
≈75	72h	guinea pigs	minimal lethal concentration	(77)
50	22h/d, 11 d	female mice	no focal neuronal degeneration in cerebellum	(38)

11. Evaluations by other (inter)national bodies

In their series of monographs the IARC has evaluated methyl chloride (29). Based on the amount of data the task group concluded that there is inadequate evidence for the carcinogenicity of methyl chloride to experimental animals and to humans. In the overall assessment of data from short-term tests they concluded that there is sufficient evidence for genetic activity. In the overall evaluation (30) methyl chloride was placed in group 3 as being not classifiable as to the carcinogenicity to humans.

US NIOSH has evaluated monohalomethanes, including methyl chloride, with respect to carcinogenicity and teratogenicity (49). Based on an unpublished 2-year inhalation study on mice NIOSH recommends that methyl chloride be considered as potential occupational carcinogen. In the study there was a statistically

significant increase in both malignant and nonmalignant renal tumours in male mice exposed to 1000 ppm (2070 mg/m^3) methyl chloride (49).

Based mainly on the studies by Wolkowsky-Tyl et al (79, 80) on teratogenic effects, US NIOSH recommends that methyl chloride be considered a potential occupational teratogen (49).

In the documentation of the threshold limit values (1) ACGIH concludes that while the current human exposure data indicate no adverse irreversible effects to body organ systems at 100-200 ppm (207-414 mg/m^3) the margin may be small with respect to neurotoxic effects. A time-weighted value of 50 ppm (≈ 105 mg/m^3) is recommended. There is no indication on when this evaluation was made but it was probably in the end of the 1970ies.

In 1974 the German MAK-committee presented a documentation of German (West) exposure limit value of 50 ppm (105 mg/m^3). The value is based on an unpublished study from the industry and on animal data. Effects on the liver, kidneys and brain after long-term exposure to 100 ppm (207 mg/m^3) methyl chloride should be taken into consideration (26). In 1984 a reevaluation was performed by the MAK-committee (27). Methyl chloride was then placed in group III B as a suspect carcinogen. The classification was based on a carcinogenicity study (49, 52) where there was a significant increase of renal tumours in mice.

12. Needs for Further Research

There are still some unsolved problems concerning the biotransformation and the toxicokinetics of methyl chloride in humans, as well as species differences. A better understanding of the mechanisms that separates humans into two groups with apparent different biotransformation is desirable. This might as well lead to suitable methods of biological monitoring. Further studies on the mutagenic/genotoxic properties of methyl chloride would be relevant, e.g. formation of DNA-adducts.

There is a lack of epidemiological studies on workers exposed to methyl chloride. Especially studies designed to evaluate carcinogenic and/or teratogenic effects would be beneficial.

Also, experimental and epidemiological studies on behavioural effects especially in the low-dose region might be illuminative to the question of no-effect level for behavioural and neurotoxic effects. Studies to reveal the mechanism of blurred vision due to exposure to methyl chloride are as well needed.

13. Discussion and Evaluation

In the general population there exist obviously two groups who differ metabolically. One group "converters" excretes S-methyl-cysteine after exposure to methyl chloride, the other does not. One group "non-converters" has higher

concentrations of methyl chloride in blood and expired air than the other. The toxicological significance of this phenomenon is not yet known.

Acute effects of exposure to fairly high concentrations (more than 1000 mg/m^3) give rise to human intoxication. Typical symptoms are gastrointestinal complaints, dizziness, muscular incordination, mental confusion, blurred vision and eventually unconsciousness and death.

Effects on the nervous system, including behavioural effects and blurred vision, has been demonstrated in persons occupationally exposed to methyl chloride. The exposure levels were then usually higher than 500 mg/m^3. However, impairment in behavioural tests was demonstrated in some persons occupationally exposed to about 75 mg/m^3 methyl chloride for more than two years. Experimentally, impaired task performance was shown in persons exposed for 3 hours to about 400 mg/m^3.

Also in animal experiments the effects seen at the lowest exposure concentration are effects of the nervous system measured as focal neuronal degeneration in the cerebellum. This has been seen in female mice exposed continously (22h/day) for 11 days to 207 mg/m^3. In long-term studies (24 months) effects on the kidneys as cortical adenomas were observed in male mice after exposure to about 450 mg/m^3 6h/day, 5 days/week.

Methyl chloride is mutagenic to bacteria and induces sister chromatid exchanges in vitro in human lymphoblasts. Methyl chloride also induces unscheduled DNA-synthesis in rat hepatocytes in vitro. In vivo exposure to high concentrations of methyl chloride (31000 mg/m^3) for 3 h induced a slight increase in unscheduled DNA-sythesis in rat hepatocytes, but not in other tested cell types. Exposure for 8 h to 2000 mg/m^3 induced single strand breaks in renal tissue DNA in male mice but not in female mice.

In one epidemiological study mortality from all causes, including cancer, was lower than expected. The small number of cancer deaths provides, however, an insufficient basis for assessing cancer risk. Furthermore, the finding is consistent with the "healthy worker effect". In an animal cancer study tumours occurred in male mice exposed to 2064 mg/m^3. No increase in tumour incidence was reported in treated female mice nor in rats (both sexes).

Dominant lethal mutations in rat sperms were observed after exposure to 6200 mg/m^3 for 6 h/day during five days. Exposure to 3100 mg/m^3 of methyl chloride has induced testicular and epididymal damage in rats and no litter resulted from breeding of exposed males to unexposed females. When males had been exposed to 1000 mg/m^3 fewer litters were born. The authors conclude that the preimplantation loss caused by exposure to methyl chloride is due to failure of fertilization and not to a genotoxic effect. It is likely to result from effects on sperms located in the testes at the time of exposure. The only effects seen in a teratology study where rats were exposed to 3100 mg/m^3 during gestation were reduced total body weight and skeletal maturity. Fetal heart defects have been seen when mice were exposed to 515 mg/m^3 or higher during gestation. The mechanism is, however, at present unclear.

Based on human and animal data the critical effect of exposure to methyl chloride is the effect on the central nervous system. Methyl chloride has mutagenic and genotoxic properties. Data on carcinogenicity as well as on

teratogenicity are so far inadequate for an evaluation of a carcinogenic or teratogenic risk.

14. Summary

14.1. Summary in English

Lundberg P. NEG and DECOS Basis for an Occupational Health Standard. Methyl chloride. Arbete och Hälsa 1992:27, pp 1-23.

The literature on methyl chloride has been reviewed in order to establish a scientific basis for occupational health standards.

There seem to exist two different groups of humans as for the biotransformation of methyl chloride. The toxicological relevance of this is not understood. Acute effects of high exposures to methyl chloride are dizziness, muscular incordination, mental confusion, blurred vision and eventually unconsciousness and death. Effects on the nervous system, behavioural effects and blurred vision have been demonstrated in occupationally exposed persons. The critical effect is, based on human and animal data, the effect on the central nervous system. Methyl chloride has mutagenic properties. Data on carcinogenicity and teratogenicity are so far inadequate.

Key words: behavioural effects, blurred vision, carcinogenicity, methyl chloride, mutagenicity, neurotoxicity, occapational exposure limit, teratogenicity.

14.2. Summary in Swedish

Lundberg P. NEG and DECOS Basis for an Occupational Health Standard. Methyl Chloride. Arbete och Hälsa 1992:27, sid 1-23.

En genomgång av litteraturen av metylklorid har gjorts med avsikt att få fram ett veenskapligt underlag för ett hygieniskt gränsvärde.

Det tycks finnas två grupper av människor när det gäller metylklorids biotransformation. Den toxikologiska betydelsen av detta är inte klarlagd. Akuta effekter vid exponering för höga doser metylklorid är svindel, bristande muskelkoordination, mental förvirring, dimsyn och slutligen medvetslöshet och död. Effekter på nervsystemet, beteendeeffekter och dimsyn har påvisats hos yrkesexponerade personer. Den kritiska effekten, baserad på human- och djurdata, är effekter på centrala nervsystemet. Metylklorid har mutagena egenskaper. Carcinogenicitetsdata och teratogenicitetsdata är än så länge otillräckliga.

Nyckelord: beteendeeffekter, carcinogenicitet, dimsyn, hygieniskt gränsvärde, metylklorid, mutagenicitet, neurotoxicitet, teratogenicitet.

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Appendix

Occupational exposure limits in some countries

Country	mg/m^3	ppm	year	note	ref
Denmark	105	50	1988		2
Finland	105	50	1987		7
	160	75		STEL	
Germany (West)	105	50	1990	C[a], T	4
Iceland	105	50	1978		8
Netherlands	105	50	1989		5
Norway	50	25	1989	C	6
Sweden	100	50	1990		3
	200	100		STEL	
USA (ACGIH)	103	50	1990		1
	207	100		STEL	
(OSHA)	105	50	1990		1
	205	100		STEL	

C = Carcinogen
C[a] = Suspected carcinogen
STEL = Short-term exposure limit
T = Probably teratogenic

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Sent for publication June 10, 1992