Executive summary

Scope

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Exposure Safety (DECOS), a committee of the Health Council, proposes health-based recommended occupational exposure limits for chemical substances in the air at the workplace. These recommendations serve as a basis in setting legally binding occupational exposure limits by the minister.

In this report, the committee discusses the consequences of occupational exposure to methanol and recommends a health-based occupational exposure limit. The committee's conclusions are based on scientific papers published prior to April 2009.

Physical and chemical properties

At room temperature, methanol (CAS number 67-56-1) is a clear, colourless, volatile, flammable liquid. When pure, it has a mild alcoholic odour.

In 2008, global production of methanol amounted to ca. 50 million tonnes/year. About 75% served as a feedstock for the manufacture of chemicals such as formaldehyde, methyl tertiary butyl ether, tertiary amyl methyl ether, and acetic acid (12%), and about 10% is used for fuel applications.

Methanol occurs naturally in the human body; endogenous blood methanol concentrations can range from about 1-2.5 mg/L.

Monitoring

The US National Institute of Occupational Safety and Health (NIOSH) and Occupational Safety and Health Administration (OSHA) and the Working Group on Analytical Chemistry of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) of the German Research Foundation (Deutsche Forschungsgemeinschaft - DFG) described methods to determine concentrations of methanol in occupational air. These methods are based on gas chromatographic analysis with flame ionisation detection (GC-FID).

For the determination of methanol in urine and blood, GC-FID methods are described, amongst others, by the Working Group Analytical Chemistry of the MAK Commission of the DFG. This technique enables also the determination of methanol in exhaled breath.

Limit values

In the Netherlands, the current, legally binding, occupational exposure limit (OEL) for methanol is 260 mg/m^3 (200 ppm), as an 8-hour time-weighted average. This value is consistent with the Indicative Occupational Exposure Limit Value (IOELV) of the European Union. Also in countries such as Denmark, Germany, Sweden, the UK, and the USA, a limit value of 200 ppm (260 mg/m^3) is set or recommended.

In addition, in the Netherlands, there is a 15-minute Short-Term Exposure Limit (STEL) of 520 mg/m^3 (400 ppm), while in the afore-mentioned countries, the STEL ranges from 250 ppm (325-350 mg/m^3) in Denmark, Sweden, the UK, and the USA to 800 ppm (1080 mg/m^3) in Germany.

In almost every country, including the Netherlands, a skin notation (H) has been designated.

With respect to reproduction toxic effects, methanol is classified in the Netherlands in category 2 (‘substances which should be regarded as if the cause developmental toxicity in humans’). The German MAK-committee has classified methanol in Pregnancy risk group C (‘there is no reason to fear damage to the embryo or foetus when MAK an BAT values are observed’).

Kinetics and toxic mechanism of action

Inhaled methanol is absorbed for 60-85% through the, especially upper, respiratory tract, with not much difference between humans and animals. After dermal exposure, methanol rapidly diffuses through the skin. In a human volunteer study, a dermal penetration rate of 8.1 mg/cm^2/h has been established.

Results from toxicokinetic experiments and modeling indicate that blood methanol levels in rodents and primates increase linearly at 8-hour exposures up to ca. 1600 mg/m^3 (1200 ppm), At higher levels, blood methanol levels increase linearly in humans, but non-linearly in laboratory animals (most sharply in mice, less sharply in monkeys). At exposures to ca. 266 mg/m^3 (200 ppm), levels in rats and monkeys do not exceed endogenous levels.

Methanol distributes through the body uniformly to body water content. In the liver, methanol is metabolised through formaldehyde (in rodents by catalase; in primates by alcohol dehydrogenase) and formate to carbon dioxide. In rodents, the rate-limiting step in the metabolism of methanol is the oxidation of methanol to formate, while the oxidation of formate to carbon dioxide is rate limiting in primates. As a consequence, exposure to high concentrations or doses of methanol may cause accumulation of methanol in rodents and of formate in primates. In humans, accumulation of formate may occur at methanol doses >210 mg/kg bw.

By far the most of the methanol taken up and distributed is excreted as carbon dioxide and only minor amounts unchanged by the lungs and the kidneys. The methanol metabolites formaldehyde and formate are thought to bind to various endogenous molecules or enter a number of endogenous synthetic pathways. In humans, elimination half-lives of methanol in blood were 1.4-3 h and in urine and breath ca. 1.4 h.

The most suitable biological parameter for biological monitoring of persons exposed to methanol is the methanol concentration in urine.

Effects

Human data

Studies addressing acute effects of methanol in humans are limited to case reports in which subjects have ingested or inhaled unspecified high levels of methanol, often in combination with other chemicals. Such exposures can result in a transient depression of the central nervous system (CNS), which is thought to be a direct effect of methanol. After a latent period of several hours to two days, the CNS depression is often followed by metabolic acidosis, ocular toxicity (blindness), and mortality, which are formate effects. Minimal lethal oral doses are between 300 and 1000 mg/kg bw. Fatalities were reported at blood methanol levels of 1500-2000 mg/L, and CNS and ocular effects at levels above 200 and 500 mg/L, respectively.

In a number of controlled inhalation studies in which relatively small groups of healthy human volunteers were exposed at concentrations not exceeding 200 ppm (266 mg/m^3), for 75 to 240 minutes, no irritation or relevant neurophysiological or neurobehavioural effects were observed. No data on sensitising properties of methanol in humans were available.

There were hardly any epidemiological studies addressing occupational chronic exposure to methanol and adverse effects, including carcinogenicity and reproduction toxicity. In one US study, exposure for presumably about 3 years to a duplicator fluid containing 99% methanol at 15-minute average concentrations ranging from 365 to 3080 ppm (485-4096 mg/m^3), with 70% exceeding 800 ppm (1064 mg/m^3), induced eye irritation, dizziness, headaches, blurred vision, and nausea.

Animal data

Laboratory animal studies indicated that liquid methanol may cause moderate skin irritation, but no skin sensitisation. Concentrations >29% were irritating and corrosive to the eyes.

For rats and mice, LC_{50} values ranged between 79,000 and 130,340 mg/m^3 (59,200 and 98,000 ppm) (exposure duration: 2.25 to 8 hours). The dermal LD_{50} in rabbits was 17,000 mg/kg bw. In rats, no mortality was observed after occlusive application of 35,000 mg/kg bw; amounts of 45,000 mg/kg bw were lethal.

In repeated-dose toxicity studies, no systemic effects were observed in male and female monkeys at exposure to concentrations of 665 to 6650 mg/m^3 (500-5000 ppm), 6 hours/day, 5 days/week, for 4 weeks, and in female monkeys to concentrations of 266-2394 mg/m^3 (200-1800 ppm), 2.5 hours/day, for ca. 350 days (i.e., during pre-mating, mating, and gestation), or in rats exposed to concentrations of 665 to 6650 mg/m^3 (500-5000 ppm), 6 hours/day, 5 days/week, for 4 weeks, or to 13,300 mg/m^3 (10,000 ppm) for 6 weeks (only lungs examined).

Well-performed inhalation studies in which rats and mice were exposed to concentrations of 13 to 1330 mg/m^3 (10-1000 ppm), 19-20 hours/day, for 18-24 months, did not show evidence of neoplastic or non-neoplastic effects of methanol.

There is no convincing evidence that methanol is a genotoxic compound. The majority of mutagenicity tests in bacteria, yeasts, and mammalian cells, assays on chromosome aberrations and SCEs in mammalian cells, micronucleus tests in mammalian cells, and other tests on DNA or chromosome damage in bacteria and fungi were negative. *In vivo*, exposure by inhalation did not increase the frequency of micronuclei in peripheral blood or lung cells or of SCEs or chromosomal aberrations in lung cells of mice. Both positive and negative results were observed in tests in which methanol was orally or intraperitoneally administered to mice, but tests with higher doses and repeated dosing were negative. A mutation test in fruit flies (*D. melanogaster*) was negative. All four cell transformation assays were negative.

Reproduction toxicity studies were performed with monkeys, rats, and mice. No effects were seen in female monkeys exposed to methanol concentrations of 266-2394 mg/m^3 (200-1800 ppm), 2.5 hours/day, during pre-mating, mating, and gestation (ca. 350 days in total), and their offspring. A conclusive judgment of the results of the neurobehavioural tests performed in the monkey offspring was hampered because the changes were small, occurred in the presence of large variations among offspring, and were assessed in a low number of offspring. Exposure of pregnant rats to methanol concentrations of 13,300 and 26,600 mg/m^3 (10,000 and 20,000 ppm), 7 hours/day, on gestational days 1-19 and 7-15, respectively, caused decreased fetal weights and at 26,600 mg/m^3 also increased incidences of skeletal and visceral malformations. Also in mice, methanol induced developmental effects. Exposure to 2660 mg/m^3 (2000 ppm), 7 hours/day, on gestational days 6 through 15, caused increased incidences of cervical ribs at concentrations of 2660 mg/m^2 (2000 ppm) and above and of cleft palate and exencephaly at concentrations of 6650 mg/m^3 (5000 ppm) and above. The NOAELs for developmental effects were 6650 and 1330 mg/m^3 (5000, 1000 ppm) in rats and mice, respectively. No maternal toxicity was observed in the rodent studies.

Evaluation and recommendation

From the carcinogenicity data, the Subcommittee on the Classification of Carcinogenic Substances of DECOS concludes that methanol cannot be classified with respect to its carcinogenicity (comparable with EU class ‘not classifiable’). The subcommittee is further of the opinion that results from genotoxicity tests indicate that methanol is not likely to have a genotoxic potential.

Based on the lack of a genotoxic potential and negative results in inhalation carcinogenicity studies, DECOS is of the opinion that methanol is not likely to have a carcinogenic potential.

Based on the available data on reproduction toxic effects, the Subcommittee on the Classification of Reproduction Toxic Substances recommended classification of methanol in category 2 ('substances which should be regarded as if they cause developmental toxicity in humans').

Based on the methanol levels measured in the blood of mice and rats at the NOAELs (ca. 100 and 1000-2170 mg/L, respectively) and LOAELs (ca. 540 and 1840-2240 mg/L, respectively) of the reproduction toxicity studies, DECOS is of the opinion that methanol is not likely to induce reproduction toxic effects in occupationally exposed workers.

Since there were no human studies which allow to assess health effects following chronic exposure to methanol, the committee takes the chronic inhalation studies in rats and mice as starting points for deriving a health-based recommended occupational exposure limit (HBROEL). In these studies, no neoplastic or non-neoplastic effects were seen at exposure to methanol concentrations up to 1330 mg/m^3 (1000 ppm), 19-20 hours/day, 7 days/week, for 18-24 months.

Taking the NOAEL of 1330 mg/m^3 and applying an assessment factor of 10 for interspecies and intraspecies variation, the committee recommends a health-based occupational exposure limit of 133 mg/m^3 (100 ppm) for methanol. Moreover, the committee notes that the NOAEL was the highest concentration level tested and that exposure was almost continuous, and concludes that these aspects provide an additional margin of safety.

The committee is of the opinion that the HBROEL of 133 mg/m^3 (100 ppm) will also protect workers from acute neurotoxic/CNS effects.

Since dermal penetration may contribute significantly to the body burden, DECOS considers a skin notation warranted.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Safety of the Health Council recommends a health-based occupational exposure limit for methanol of 133 mg/m^3 (100 ppm), as an 8-hour time-weighted average. DECOS also recommends a skin notation.