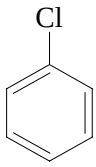
Recommendation of the Scientific Committee on Occupational Exposure Limits for Monochlorobenzene

8 hour TWA	:	5 ppm (23 mg/m^3)
STEL (15 mins)	:	15 ppm (70 mg/m^3)
Additional classification	:	-

Substance:

Monochlorobenzene



Synonyms	:	Benzene chloride; chlorobenzene; phenyl chloride		
EINECS N°	:	203-628-5		
EEC N°	:	602-033-00-1	Classification :	R10 Xn; R20
CAS N°	:	108-90-7		
MWt	:	112.56		

Conversion factor (20°C, 101 kPa) : 4.68 mg/m^3 = 1 ppm

Occurrence/use:

Monochlorobenzene is a colourless liquid with a mild aromatic odour. It has a MPt of -45°C, a BPt of 132°C and a vapour pressure of 1.14 kPa at 20°C. It has a vapour density of 3.88 times that of air and is explosive in the range 1.3 - 7.1% in air. The odour threshold is about 0.21 ppm (0.98 mg/m^3).

Monochlorobenzene has no natural sources but it bioaccumulates in fish, aquatic invertebrates and algae. It is produced by chlorination of benzene and has been used in the synthesis of organochlorine pesticides, including DDT, as well as phenol, picric acid and dyes. It is now used primarily as a degreasing solvent, as a chemical intermediate in the synthesis of nitrochlorobenzenes, in the dry cleaning industry and in the manufacture of resins, dyes, perfumes and pesticides. The production rate in the EEC is in excess of 100,000 tonnes per annum, but is decreasing.

Health Significance:

Monochlorobenzene may be absorbed by inhalation, ingestion or skin penetration. Quantitative data on skin penetration are not available.

The critical systemic effects on liver and kidneys as well as the haematological effects are considered to result from epoxide formation. At similar low exposure concentrations as they occur under workplace conditions, internal exposure to the rapidly metabolized chlorobenzene is not considered to differ between mice, rats, and humans because the ratio of uptake by inhalation to liver perfusion is almost equal among the different species (Csanady and Filser 2001). Considering the next metabolic step, the inactivation of the epoxide by epoxide-hydrolase, it has been demonstrated, that this process is generally faster in humans than in rodents (Lorenz et al. 1984, Guenthner and Luo 2001) with the consequence that the epoxide burden in humans is lower than in rodents at comparable exposure concentrations of the parent compound (chlorobenzene). Therefore it should be expected that humans are less sensitive than rodents to the toxic effects of chlorobenzene mediated via the formation of its epoxide. However, the resulting chlorobenzene-dihydrodiol is further metabolized to 4-chlorocatechol (e.g. Knecht and Woitowitz 2000). The toxicological consequences of its formation are unknown. Since catechols are reactive and their rate of formation in humans may be higher than in rodents, application of an appropriate interspecies scaling factors for setting an OEL is justified.

Exposure of human volunteers to monochlorobenzene resulted in various complaints of CNS or irritation symptoms at 60 ppm (282 mg/m^3) for 7h, with no effects at 12 ppm (55 mg/m^3) (Ogata *et al*, 1991). Well-reported studies on occupational exposure are not available.

Monochlorobenzene has a low acute toxicity in animals with CNS effects occurring at high concentrations.

The subacute, subchronic and chronic toxicity of monochlorobenzene is characterized by haematological effects, and effects on liver and kidneys. Repeated exposure of mice to 21 ppm (100 mg/m^3), 7h/d for 3 months resulted in decreased total leukocyte and neutrophil counts and increased lymphocyte counts (Zub, 1978). The authors suggested that these results indicate bone marrow damage. Increased liver weights and focal liver and kidney lesions were observed in a study, reported in abstract form, in which rats were exposed to 75 ppm (350 mg/m^3), 7h/d, 5d/w for 24 weeks (Dilley and Lewis, 1978). Skinner *et al* (1977) reported tubular degeneration in the kidneys of rats exposed to 75 ppm (350 mg/m^3) and decreased liver and kidney weights at 250 ppm (1170 mg/m^3) for 24 weeks.

Knapp *et al* (1979) reported, in meeting abstract form, an oral subchronic study in male and female beagle dogs which were given monochlorobenzene by capsule at doses of 0, 27.25, 54.5 or 272.5 mg/kg bw/day, 5 days/week, for 93 days. In the high dose group, 4 of 8 dogs died and a series of treatment-related biochemical and haematological

changes were observed as well as histopathological changes [not further specified] in the kidneys, gastrointestinal mucosa and haematopoietic tissues. In the abstract, it was stated that there were no consistent signs of chlorobenzene-induced toxicity at the mid and low dose levels (Knapp *et al*, 1979). However, according to the unpublished report, cited by the USEPA (EPA, 1988; Anonymus, 1988) monochlorobenzene-related hepatotoxicity was also seen in the mid dose group. The low dose (27.25 mg/kg bw/day) appeared to be a NOAEL.

A NOAEL of 60 mg/kg/day for liver, kidney and haematological effects, was established in a 2-year gavage study in rats and mice (NTP, 1985; Kluwe *et al*,1985).

Monochlorobenzene may be absorbed by inhalation and, ingestion or skin penetration. Quantitative data on skin penetration are not available. Dermal application of 2 ml monochlorobenzene/kg body weight (2212 mg/kg) on the shaved back of 5 rabbits for 24 hours under occlusive condition was not lethal (Kinkead and Leahy 1987). This indicate that dermal absorption plays a less important role.

Monochlorobenzene was not genotoxic in several *in vitro* assays (Litton Bionetics, 1976; Valencia, 1982; Brusick, 1986 abstract), but appeared positive (in a dose-related manner) in an *in vitro* gene mutation assay with mouse lymphoma L5178Y-cells in the presence and absence of metabolic activation (McGregor *et al*, 1988). In the NTP study (NTP, 1985), the only type of tumour found to occur at a statistically significantly increased incidence in monochlorobenzene-treated animals was benign neoplastic liver nodule in male rats of the high-dose group (120 mg/kg/day). The increased incidence was significant by dose-related trend tests, and pair-wise comparisons between the vehicle (corn oil) controls (2/50) but not the untreated controls (4/50) and the high-dose animals (8/49). The only hepatocellular carcinomas found, occurred in two untreated male controls. The committee did not consider these findings indicative of carcinogenic potential of monochlorobenzene.

In a two-generation inhalation reproduction study in rats, exposure to monochlorobenzene at levels of 50, 150, or 450 ppm (6 hr/day; 7 days/week) did not have any adverse effects on reproductive performance or fertility in males and females (Nair et al, 1987). Increased relative liver weights, hepatocellular hypertrophy and renal histopathological changes (tubular dilatation, interstitial nephritis, foci of epithelial regeneration) were observed among F_o and F_1 generation males exposed to 150 or 450 ppm. At 50 ppm (statistically significantly) increased relative liver weights were found in F_1 generation males. Since no other treatment-related effects were seen at this exposure level, the committee regarded 50 ppm as a “Lowest-Observed-Adverse-Effect-Level” (LOAEL).

Recommendation:

Weighing the total body of data obtained in genotoxicity and carcinogenicity studies of monochlorobenzene (one positive *in vitro* gene mutation test and several negative *in vitro* genotoxicity assays, and one negative long-term mouse and one negative long-term rat carcinogenicity study), the committee concludes that occupational exposure to

monochlorobenzene under normal conditions is of no health concern with respect to potential genotoxic or carcinogenic effects.

The committee has selected the LOAEL of 50 ppm obtained in the two-generation rat inhalation reproduction study (Nair et al. 1987) as the starting point for deriving an occupational exposure limit. Applying an uncertainty factor of 10 to allow for intra- and interspecies variation and for the absence of a NOAEL in the selected two-generation rat study, the committee recommends an occupatinal exposure limit for monochlorobenzene of 5 ppm (23 mg/m^3) as a TWA over 8-hours. The committee emphasizes that the proposed value is considered ~~to~~ protective for workers against potential haematotoxic effects as found in mice after prolonged inhalational exposure to 21 ppm (100 mg/m^3) monochlorobenzene (Zub, 1978), and also against sensory irritation as seen in human volunteers exposed to 60 ppm (282 mg/m^3) with no effects at 12 ppm (55 mg/m^3) (Ogata *et al*, 1991).

A STEL (15 mins) of 15 ppm (70 mg/m^3) is proposed to limit peaks in exposure which could result in irritation.

No “skin” notation is considered to be necessary, since acute dermal application of monochlorobenzene in a dose of more than 2000 mg/kg body weight was not lethal to rabbits.

At the levels recommended, no measurement difficulties are foreseen.

Key Bibliography:

Brusick, D.J. (1986). Genotoxicity of hexachlorobenzene and other chlorinated benzenes. IARC Sci. Publ. 40(77), 393-397 (abstract).

Csanady GA, Filser JG: The relevance of physical activity for the kinetics of inhaled gaseous substances. Arch Toxicol. 74, 663-672, 2001.

Dilley, J.V. and Lewis, T.R, (1978). Toxic evaluation of inhaled chlorobenzene. Toxicol. Appl. Pharmacol. 45, 327 (abstract, NIOSH report 210-76-0126).

Guenthner TM, Luo G: Investigation of the role of the 2',3'-epoxidation pathway in the bioactivation and genotoxicity of dietary allybenzene analogs. Toxicology. 160, 47-58, 2001.

Jongerius, O. and Jongeneelen, F.J (1992). Criteria document for an occupational exposure limit for chlorobenzene.

Kluwe, W.M., Dill, G., Persing, R. and Peters, A. (1985). Toxic responses to acute, subchronic and chronic oral administrations of monochlorobenzene to rodents. J. Toxicol. Environ. Health. 15, 745-767.

Kinkead ER, Leahy HF (1987) Evaluation of the acute toxicity of selected groundwater contaminants. Harry G. Armstrong Aerospace Med Res Lab (technical report) AAMRL-TR (US), ISS AAMRL-TR-87-021

Litton-Bionetics (1976). Mutagenicity evaluation of monochlorobenzene. Report No. 75-231 to Rohm and Haas, Bristol.

Nair, R.S., Barter, J.A., Schroeder, R.E., Knezevich, A. and Stack, C.R. (1987). A two-generation reproduction study with monochlorobenzene vapour in rats. Fund. Appl. Toxicol. 9 678-686.

NTP (1985). Toxicology and carcinogenesis studies of chlorobenzene (CAS 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). US Dept of Health and Human Services. NTP, technical report series no 261.

Ogata, M., Taguchi, T., Hirato, N., Shimada, Y. and Nakae, S. (1991). Quantitation of urinary chlorobenzene metabolites by HPLC: concentrations of 4-chlorocatechol and chlorophenols in urine and of chlorobenzene in biological specimens of subjects exposed to chlorobenzene. Int. Arch. Occup. Environ. Health 63, 121-128.

Skinner, W.A., Newell, G.W., Dilley, J.V. (1977). Toxic evaluation of inhaled chlorobenzene. Final Report prepared for the Division of Biochemical and Behavioural Sciences, NIOSH, Cincinnati, Ohio.

Valencia, R. (1982). Drosophila sex-linked recessive lethal test on monochlorobenzene. Report from the University of Wisconsin, Madison, WI to Bioassay System Corporation, Woburn.

Zub, M. (1978). Reactivity of the white blood cell system to toxic actions of benzene and its derivatives. Acta Biol. Cracoviensia 21, 163-217.