Recommendation from the Scientific Committee on

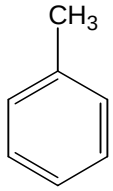
Occupational Exposure Limits

for Toluene

8-hour TWA	:	50 ppm (192 mg/m^3)
STEL (15 mins)	:	100 ppm (384 mg/m^3)
Additional classification	:	"skin"

Substance:

Toluene



Synonyms:	Methylbenzene, phenylmethane	
EINECS No:	203-625-9	
EEC No:	601-021-00-3;	Classification: F; R11 Xn; R20
CAS No:	108-88-3	
MWt:	92.13	

Conversion factor (20°C, 101kPa): 3.83 mg/m^3 = 1 ppm

Occurrence/use:

Toluene is a colourless flammable liquid with an unpleasant sour to burned aromatic odour. It has a melting-point of -95 °C, a boiling-point of 111 °C and a vapour pressure of 3.73 kPa at 25 °C. It has a vapour density 3.2 times that of air and is explosive over the range 1.2 to 7.1%. The odour threshold is about 5 ppm (18 mg/m^3).

The production rate of toluene in the European Union is in the order of 1 million tonnes per annum. It is used in many types of industry as a solvent for paints, lacquers, fats, resins and other applications. It is an additive in petrol and therefore occurs worldwide. Toluene often occurs together with other solvents. Occupational exposure levels reported recently are generally below 200 ppm (750 mg/m^3).

Health significance:

Experimental animal and human studies indicate that airborne toluene vapour is well absorbed from the respiratory tract following inhalation. There is also evidence for limited absorption of toluene vapour via the skin. Liquid toluene is well absorbed through the gastrointestinal tract and is absorbed through the skin to a limited extent.

Absorbed toluene is widely distributed but has a particular affinity for fat-rich tissues; toluene can also pass through the placenta to the fetus, and into breast milk. The major metabolic pathway for toluene is oxidation of the methyl group to benzoic acid, which is then conjugated mainly to glycine (forming hippuric acid) or to glucuronic acid, both of which are excreted in the urine; alternatively, a small proportion of toluene is oxidised on the phenyl ring, producing cresols. Excretion of toluene is relatively rapid, although there can be a gradual increase in the body burden of toluene with daily exposure during a working week (MAK Commission, 1993; Danish Draft ESR Assessment, 1998).

Urinary hippuric acid concentration has been used as a biological monitoring approach to assessing toluene exposure. However, hippuric acid also occurs in significant quantities in human urine from other sources such as food and normal metabolism, such that in Europe this parameter of biological monitoring cannot reliably detect occupational exposure to toluene when workplace airborne concentrations are below 100 ppm (383 mg/m^3) (Lauwerys, 1983). A number of alternative methods are available, including urinary o-cresol concentration which has been shown to correlate well with toluene exposure (Truchon *et al*., 1996).

Liquid toluene exhibits some irritancy towards the skin and eyes on direct contact, the severity of the effects depending on the duration of exposure. Airborne toluene vapour reportedly produces symptoms of eye and upper respiratory tract irritation in humans; the balance of evidence available for these effects suggests that the threshold for irritation lies at about 75-80 ppm (286-300 mg/m^3). Toluene does not possess sensitisation properties towards the skin or respiratory tract (Danish Draft ESR Assessment, 1998).

Single exposure to very high concentrations of airborne toluene, of the order of thousands of ppm over a period of several hours can produce pronounced central nervous system (CNS) depression, narcosis and even death. A single exposure of human volunteers to concentrations of 75-150 ppm (287-575 mg/m^3) for several hours has produced symptoms of CNS disturbance, such as dizziness, headache and fatigue, together with impairment of performance in neurobehavioural tests; a NOAEL of 40 ppm (153 mg/m^3) has been recorded in such studies (Andersen *et al*., 1983; Echeverria *et al*., 1989; Baelum *et al*., 1985).

In relation to the effects of repeated inhalation exposure, in standard animal studies no significant evidence of toxicity has been observed with repeated, prolonged periods of exposure to concentrations up to at least 300 ppm (1149 mg/m^3). Some irritation of the nasal epithelium has been seen in rats repeatedly exposed to 600 ppm toluene and at exposure levels above this (in the region of 1000 ppm - 3830 mg/m^3 - and above), the most notable toxic effect observed has been hearing loss, seen in rats (the only experimental species in which this has been investigated) and due to histopathological

damage to the cochlea. CNS excitation and/or depression and mortality has been produced in rodents with repeated exposures to 1500 ppm (5745 mg/m^3) and above (DFG 1996; Danish Draft ESR Assessment, 1998)

Behavioural toxicity

In general, there is a substantial number of studies available on the effects in humans of repeated exposure to toluene, both in workplace investigations and in volunteer studies; however, much of the earlier work is of little value in understanding the toxicity of toluene, as the workforces were also significantly exposed to other toxicants, including benzene contamination of the toluene. The principal focus of investigation has been to explore symptomatology and performance test results indicative of potential effects on the central nervous system. A number of such studies are available, exploring the effects of repeated 4-8 hour exposures to toluene concentrations in the range 60-80 ppm (230-306 mg/m^3); no effects on performance, relative to controls, were observed (Echeverria *et al*., 1989). In some but not all of these studies, the toluene-exposed subjects reported non-specific symptoms such as fatigue. At higher exposures, in the range 90-150 ppm (345-575 mg/m^3), decrements in performance test results and symptoms of dizziness, headache and mucous membrane irritation have been recorded in several studies (Stewart *et al*., 1975; Dick *et al*., 1984; Baelum *et al*., 1985; Echeverria *et al*., 1989; Foo *et al*., 1990 and 1993). Other studies that are available are difficult to interpret, in terms of discriminating between "effect" and "no-effect" levels, because of uncertainty about the relationship between the effects monitored, the levels of contemporary exposure measured and the levels of exposure previously encountered by the workers (Iregren, 1982; Ørbaek and Nise, 1989; Van Thriel et al. 2000).

Some studies using neurobehavioural methods are especially important for the discussion of the lowest observed effect level (LOAEL). Kempe *et al*. (1980) compared 24 printers exposed to toluene in a printing works with 18 control persons; tests took place during and after the shift on 3 consecutive days. The exposure level determined with personal samplers was 62 ppm (237 mg/m^3) averaged over the shift; measurements of the air concentrations close to the machines revealed 121 ppm (463 mg/m^3). The persons had been exposed for an average of 13 years. Reaction times, perception time determined with a tachistoscope and the results of a visual search test were not markedly changed. Fatigue, lack of concentration, exhaustion, discord were significantly increased in the printers at the end of shift. In the interpretation of the findings, it must also be taken into account that the printers were exposed to noise levels of about 90 dB.

Foo *et al*. (1990, 1993) compared 30/24 women/men exposed to average toluene concentrations, of 88/70 ppm (337/268 mg/m^3) (glue, electronic assembly) with 30/64 control persons. The tests took place during the working week. For persons exposed to higher concentrations, performance was significantly poorer in a visual search test, visual reproduction test, verbal memory test and manual dexterity test. In 6 of 8 tests the performance decreased with increased average workplace concentration. Both the duration of exposure and the level of occupational training (confounding factor affecting performance in psychological tests) were taken into account.

Iregren (1982) investigated 34 printers exposed for 3 to 30 years to toluene concentrations between 50 and 150 ppm (192 and 575 mg/m^3) and compared them with 34 non-exposed control persons. The printers were found to have longer reaction times.

Ørbaek and Nise (1989) studied 30 printers exposed on average for 29 years in parallel with 72 "healthy men" as control group. Current toluene concentrations were determined as 11 and 42 ppm (42 and 161 mg/m^3); in previous years the concentrations had been considerably higher. Tests carried out on Monday mornings revealed performance deficits in the exposed persons. However, no correlation with a cumulative exposure index or with the current average exposure was found. Fatigue, short-term memory problems, concentration difficulties and mood swings were more frequent in the printers.

Relevant experimental studies

Gamberale and Hultengren (1972) described the effects of exposing two groups of 6 persons by inhalation of toluene through a mouth-piece; the persons were exposed either first on 7 consecutive days to toluene concentrations which increased from 100 to 700 ppm (383 to 2681 mg/m^3), each concentration for 80 minutes, and then to normal air on 7 consecutive days or first to air and then to the toluene. Perception time and choice reaction time in a test with light signals were not significantly affected by the exposure. The simple reaction time, however, was longer after exposures to 300 ppm (1149 mg/m^3) or more and reached a maximum at 700 ppm (2681 mg/m^3). The authors concluded that simple psychological functions are affected more than complex CNS activities at low toluene concentrations (Iregren, 1982; Kempe *et al*., 1980). Similar results were obtained in studies which made use of other psychological tests (Hänninen *et al*., 1976; Lindstrøm, 1973; Sepplainen *et al*., 1978). In studies of printing works employees exposed to toluene concentrations between 50 ppm (192 mg/m^3) and 150 ppm (575 mg/m^3), deviations from the norm were not found at concentrations under 100 ml/ m^3 (Iregren, 1982). However, the interpretation of such data is made more difficult by the fact that the exposure data are often not known reliably and by variation in the interval after the end of exposure (Lindstrøm, 1973, 1981). Determination of the motor and sensory conduction velocities (MCV and SCV) revealed only slight increases which, taken as a whole, were not statistically significant (Seppäläinen *et al*., 1978).

Andersen *et al*. (1983) studied the effects of exposure of 16 volunteers under laboratory conditions for 6 hours to toluene concentrations of 10, 40 and 100 ppm (38, 153 and 383 mg/m^3) in a repeated exposure experiment. At 100 ml/ m^3, the effects on the results of tests for perceptiveness (Landolt ring test), manual dexterity and one other performance test were on the borderline of significance and the incidence of headaches, dizziness and feeling intoxicated was significantly increased. No adverse effects were detected at 10 ppm (38 mg/m^3), or at 40 ppm (153 mg/m^3).

Echeverria et al. (1989) exposed 42 volunteers under laboratory conditions for 6.5 hours with 3 days repeated exposures to a toluene concentration of 75 ppm (286 mg/m^3) or 150 ppm (572 mg/m^3). Each test person was tested at only one exposure concentration but with a very extensive test battery (70 minutes). Evaluation was based on differences in the results of tests before and after exposure. At 150 ppm (572 mg/m^3) performance

in the tests for short term memory of patterns, recollection of numbers, pattern recognition and manual dexterity was significantly reduced. The results obtained at 75 ppm (287 mg/m^3) and in the control group revealed in tendency a dose-effect relationship. Headaches and mucosal irritation also increased significantly with the dose. At 75 ppm (287 mg/m^3), performance was not different from that of the control group but the persons complained of more subjective symptoms.

Anselm-Olsen *et al*. (1985) examined the effects of repeated exposure of 16 volunteers under laboratory conditions to a toluene concentration of 80 ppm (300 mg/m^3) for 4 hours each time in a study of the effects of combined exposure to toluene and xylene under laboratory conditions. No effects were found on psychic performance parameters or on how the persons felt.

Iregren *et al*. (1986) examined the effects of repeated exposure of 12 volunteers to a toluene concentration of 80 ppm (300 mg/m^3) for 4.5 hours each time in a study of the effects of combined exposure to toluene and alcohol under laboratory conditions. No effects on psychic performance parameters were found. Headaches and mucosal irritation (summed values for various regions of mucous membrane) were considered to be more severe during exposures than under control conditions.

Baelum *et al*. (1985) examined 46 printers who were accustomed to toluene and 43 control persons during exposure to a toluene concentration of 100 ppm (383 mg/m^3) for 6.5 hours under laboratory conditions. The tests determined 31 performance parameters and numerous indicators of how the subjects felt; each test person was subjected only once to the toluene concentration and once to control conditions. Colour discrimination decreased during the exposure as did perceptiveness (Landolt rings) and manual dexterity. Irritation of the eyes, throat (less in the printers) and the nose, a feeling of intoxication and dizziness were increased during the exposure to toluene.

Dick *et al*. (1984) examined 30 persons exposed for 4 hours to a toluene concentration of 100 ppm (383 mg/m^3) and 18 control persons under laboratory conditions. During the first 2 hours of exposure, the scores in the visual vigilance test were decreased Stewart *et al*. (1975) obtained similar results during 7.5 hours exposure to 100 ppm (383 mg/ m^3).

Winneke (1982) examined 18 persons subjected under laboratory conditions to a toluene concentration of 100 ppm (383 mg/m^3) with repeated 3.5-hour exposures. Determination of the critical flicker fusion threshold, vigilance and various psychomotor parameters revealed no toluene-induced effects.

Other issues of concern

A principal area of general toxicity concern with respect to repeated exposure to toluene, which has been explored in two studies by one group, is effect on hearing. In groups of printing workers exposed to toluene (and other organic solvents) and to substantial noise levels, an association was apparent between toluene exposure and hearing loss (Morata *et al*., 1993; Morata *et al*., 1997). In the second of these studies, toluene exposure was estimated quantitatively from airborne toluene and urinary

hippuric acid measurements. Of the 124 workers studied, almost half were diagnosed as having hearing loss, and with daily workshift exposure to toluene (extrapolated from urine hippuric acid measurements) of 100 ppm (383 mg/m^3) the odds ratio for the development of hearing loss was calculated to be 4. However, there are several problems with the interpretation of these two studies including: inconsistent effects of exposure to noise alone between the two studies; absence of correlation of hearing loss with airborne toluene measurements; the questionable ability of the monitoring of urinary hippuric acid to identify toluene exposure below 100 ppm (383 mg/m^3). Overall, the findings of these studies, particularly the quantitative aspects, would require confirmation before they could be a reliable basis for the derivation of an occupational exposure limit (Heitmann and Bolt 1996). Specifically, it has to be excluded that workers showing effects of the combination of toluene and noise had been exposed to higher levels in the past, compared to more recent occupational hygiene conditions

In an extensive series of studies recently conducted, investigating a range of health aspects in German printing plant workers, 90% of all contemporary atmospheric measurements showed toluene concentrations of below 50 ppm. There were no indications of significant toluene-induced effects on symptomatology, neurobehavioural test performance or other health endpoints (data provided to SCOEL by Berufsgenossenschaft Druck und Papierverarbeitung, Wiesbaden).

Toluene is not genotoxic in standard *in vitro* tests for point mutation or chromosome damage in bacterial or mammalian cell systems (Bos *et al*, 1981; Litton Bionetics, 1978; Gerner-Schmidt & Friedrich, 1978). In genotoxicity studies *in vivo*, variable results have been reported including some apparently positive findings (Mohtashamipur *et al*., 1985; Litton Bionetics, 1981; Gad el Karim et al., 1984; Dobrokhotov & Enikeev, 1977; Lyapkalo, 1973; Hine Laboratories, 1978). However, against the background of no detectable genotoxic activity in vitro and the poor reporting and/or recognisably unreliable source of the claimed positive results, it is concluded that toluene is not genotoxic.

Toluene gave negative results in carcinogenicity studies in animals and there is no indication that it possesses carcinogenic potential (Gibson & Hardisty, 1983).

In relation to potential effects on reproduction, there are a considerable number of studies available in experimental animals. From these studies there is no evidence that toluene expresses effects on the gonads or on fertility. Numerous developmental toxicity studies have been conducted, the overall pattern of results indicating that toluene does not express teratogenicity. In relation to embryo/fetotoxicity, there are no indications that toluene expresses such activity in mice or rabbits. In rats, there is some evidence for a weak effect, but only at exposure levels beyond 400 ppm, (1532 mg/m^3), i.e. close to, or at, those producing maternal toxicity (HRC, 1992; Roberts *et al*., 1993). Using a questionnaire, Ng *et al*. (1992) reported an increased abortion rate in 105 pregnancies of 55 toluene-exposed women in Singapore. The average exposure was 88 ppm (337 mg/m^3) with a range of 50 to 150 ppm (192 to 576 mg/m^3). The abortion rate of the higher exposed group was 12.4% compared to the 2.9% in the lower exposed group and 4.5% in the non-exposed group. The authors excluded a number of confounders and indicated that the abortion rate in Singapore was in the region of 5 to

10%, also based on questionnaires. The authors considered their observations relevant but requested further studies for corroboration. Abortions have not been reported upon accidental high exposure or toluene abuse by pregnant women (Wilkins-Haug and Gabow (1991). Overall, it is concluded that an exposure limit of 50 ppm (192 mg/m^3) would also protect against potential fetotoxicity.

Recommendation:

The data from performance studies suggest that the first effects (LOAEL) are found at concentrations of about 75 ppm (237 mg/m^3); this applies for short-term effects (Echeverria *et al*., 1989) and long-term effects (Foo *et al*., 1990). Ørbaek and Nise (1989) reported about first effects at levels below 50 ppm (191 mg/m^3). However, the higher toluene concentrations to which those printers had been exposed in the long term had not been assessed individually. In this context, the absence of reproducible effects found in repeated performance tests with persons exposed long-term to higher concentrations (62 ppm - 237 mg/m^3) in spite of simultaneous noise exposure (Kempe *et al*., 1980) must be taken into account. The data available for subjective effects of toluene (effects on how the persons feel) suggest that the LOAEL is about 60 ppm (230 mg/m^3).

Overall, a great deal of human data is available, which produce no reliable evidence of effects at or below toluene concentrations of 50 ppm (192 mg/m^3). Therefore the SCOEL considers 50 ppm (192 mg/m^3) to be an appropriate level for the 8 hour TWA.

A STEL /15 min) of 100 ppm (384 mg/m^3) is proposed to limit peaks of exposure which could result in short-term neurobehavioural effects. This is based on the toxicokinetics of toluene, in conjunction with the experimental data by Iregren et al. (1986) on human neurobehaviour at 80 ppm toluene. According to Arlien-Søborg (1992) the steady-state level of toluene in blood is reached after ≈ 25 min of exposure. This means that a 15 min peak exposure of toluene, at the proposed STEL, would not lead to adverse health effects.

A "skin" notation is also recommended, as dermal absorption of liquid toluene could contribute substantially to the total body burden."

At the level recommended, no measurement difficulties are foreseen.

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