# Chapter 5.14 Toluene

## General description

### Physical and chemical properties

Toluene ($C_6H_5CH_3$) is a noncorrosive, volatile liquid with an aromatic odour. Its solubility in water is 535 mg/litre *(1)*. The odour threshold varies considerably; a geometric mean of 11 ppm has been estimated from published data *(2)*.

### Sources

Toluene production worldwide is estimated to be 10 million tonnes *(3)*. Production for 1994 in the USA alone has been estimated at more than 3 million tonnes *(3)*. It is produced from two principal sources: catalytic conversion of petroleum and aromatization of aliphatic hydrocarbons, and as a byproduct of the coke oven industry *(5)*. The bulk of production is in the form of a benzene-toluene-xylene mixture that is used in the backblending of petrol to enhance octane ratings. Crude toluene can contain as much as 24% benzene *(5)*. It has a number of industrial uses: as a solvent, carrier, or thinner in the paint, rubber, printing, cosmetic, adhesives and resin industries, as a starting material for the synthesis of other chemicals and as a constituent of fuels *(6)*. It is present in a variety of household products in which the average content is 12% *(5)*.

Emissions to the atmosphere result from point sources (e.g. production) and area sources (e.g. marketing and use of petrol). Annual emissions to the atmosphere in the USA have been estimated at 450 000 metric tonnes *(5)*. It is difficult to estimate emissions on a country-by-country basis because total use and source distribution vary widely. Since petrol use accounts for more than 90% of toluene production, it is the largest source of emissions *(7)*. Because of toluene's high volatility and low solubility in water, most toluene occurring in natural waters may be expected to be eventually released to the atmosphere. Nonoccupational uses of paints and thinners, together with tobacco smoke, represent the principal sources of toluene in indoor environments.

Toluene is believed to be the most prevalent hydrocarbon in the troposphere. Its dispersion is largely dependent upon meteorological conditions and its atmospheric reactivity. Reaction with hydroxyl radicals in the troposphere represents the principal mechanism by which toluene is removed *(8)*. In winter, the lifetime of toluene can be several months; in summer, several days. Together with other emitted pollutants associated with smog production, toluene may contribute significantly to the causation of smog.

### Occurrence in air

Toluene is widespread in the environmental owing to its use in a wide variety of commercial and household products *(7)*. Average concentrations can vary considerably *(9)*. Data collected in 1990 from 11 US cities indicated a mean concentration of 20 µg/m$^3$ (75 ppb) with a range of 0.23–750 µg/m$^3$ (0.9–2812 ppb) *(10)*; mean averaging time was not stated. Edgerton et al. *(11)* found that 24-hour average concentrations of toluene in ambient air in major US metropolitan centres ranged from 8 to 62 µg/m$^3$ (30–234 ppb). Vehicle exhaust was considered to be the dominant source given

 

the similarity of the exhaust profile of contaminants with the profile of the pollutants found in the cities studied. A screening study involving 14 US urban sites indicated an 24-hour average concentration of 17 μg/m$^3$ or 4.5 ppb *(12)*. Helmig and Arey *(13)* compared toluene concentrations in air from forested sites and urban sites in California. Two-hour sampling periods indicated that urban samples contained 7.1–9.6 μg/m$^3$ (1.9–2.5 ppb) while forested areas (ground level and canopy) contained 0.3–0.45 μg/m$^3$. Toluene had the highest measured concentration (mean = 64 μg/m$^3$ or 17 ppb) of several organic compounds in the urban air of Turin, Italy in 1991 *(14)*. Toluene levels of similar magnitude have been measured at sites in the USA, the United Kingdom and Australia. Mean concentrations (24-hour average) at six urban sites in Canada ranged from 5 to 44 μg/m$^3$ (0.9–11.7 ppb), respectively *(15)*; mean concentrations for individual samples ranged up to 145 μg/m$^3$. Mean concentrations at a rural site were 3.5 and 5.0 μg/m$^3$.

Toluene levels in indoor environments are expected to be significantly higher than outdoor levels in those situations involving nonoccupational use of paints and thinners, and also where tobacco smoke is present *(16)*. Lebret et al. *(17)* found an indoor:outdoor ratio of 8 in the Netherlands whereas Gilli et al. *(14)* found a ratio of 3 in Turin, Italy. For indoor air levels measured in several countries, Lebret et al. *(17)* reported the highest concentration of 2252 μg/m$^3$ (597 ppb) in the Netherlands in a residence, as well as the highest mean concentration (43 μg/m$^3$). Otson et al. *(18)* reported a mean concentration of 36 μg/m$^3$ (9.5 ppb) in Canadian residences. A lower limit for concentration in indoor air was reported as 0.25 ppb in US residences *(19)*. Otson et al. *(20)* detected toluene at 0.3 ppm (6-hour average) in office air.

**Conversion factors**

1 ppm (in air, 25 °C) = 3.76 mg/m$^3$
1 mg/m$^3$ = 0.266 ppm

**Analytical methods (in air)**

Air sampling is generally accomplished by adsorption on a sorbent such as Tenax followed by detection using gas chromatography/mass spectrometry *(13)* or flame ionization *(14)*. The method recommended by the US Environmental Protection Agency involves sorbent trapping followed by detection with gas chromatography and photoionization *(21)*.

## Routes of exposure

**Air**

Air pollution from motor vehicle exhaust is unquestionably a major source of exposure *(11)*. Occupational subpopulations involved in toluene production or use are likely to be exposed to considerably higher levels than the general population. In addition, air levels in the vicinity of industrial sources and petrol stations are likely to represent an additional burden to both workers and local residents *(22)*

*Smoking*

Toluene is a major component of tobacco smoke and concentrations can vary greatly. The concentration per cigarette in sidestream smoke is typically higher than in mainstream smoke. The amount of toluene in mainstream smoke from an unfiltered cigarette was estimated to range from 100 to 200 μg with a sidestream/mainstream smoke ratio of 1.3 *(23)*. Gilli et al. *(14)*(1994), using

 

samplers to adsorb toluene in the breathing zone of smokers and nonsmokers over a 24-hour period, found that active smokers were exposed to about four times the level for passive smokers. Cigarette smoking enhanced elimination of toluene and hippuric acid from the body. Smokers had significantly higher blood levels than nonsmokers *(24)* with the level affected more by the length of time since the last cigarette was smoked than by the extent of smoking.

In a study carried out in Germany in 1990–1991 with 113 persons selected at random over the country, the geometric mean of personal exposure to toluene was found to be 74 µg/m$^3$; the 95th percentile was 382 µg/m$^3$ *(25)*.

**Drinking-water**

Exposure via drinking-water is minor, except in cases of unusually heavy contamination *(4,26)*. Levels indicated by surveys in the USA are generally less than 10 µg/l *(26)*. Meek and Chan *(22)* estimated daily uptake via drinking-water in Canada at less than 0.12 µg/kg body weight (bw).

**Food**

Exposure via food is also considered to be insignificant. Meek and Chan *(22)* estimated a daily contribution from fish of 0.1–0.2 µg/kg bw.

**Relative significance of different routes of exposure**

Inhalation is the predominant route of exposure. Worst-case exposure values relevant to a discussion of health effects can be constructed from the information presented in Table 1.

## Toxicokinetics

**Absorption**

Absorption of toluene takes places primarily via the respiratory tract. The uptake rate is variable depending on exposure conditions and has been measured at between 0.16 and 1.6 mg/minute *(29–31)* The average percentage of toluene retained by the body after inhalation is estimated to be 36–85% *(29,31)*. Retention decreases with exposure time *(32)*. Physical activity increases total uptake and reduces retention compared to individuals at rest *(33)*.

Blood levels measured in rural, urban and chemical workers not occupationally exposed to toluene were less than 3 µg/litre *(24)*. The lowest levels were found in rural workers. Even lower blood levels have been reported by others *(34)*. Differences between levels measured in these studies may be based, in part, on differences in sampling and analysis procedures. Toluene was detected in most blood samples of nonoccupationally exposed individuals with a mean level of less than 1 ppb *(35)*. Mean blood levels in a nonoccupationally exposed population examined by Antoine et al. was 1.5 ppb *(36)*.

Studies with laboratory animals *(37–39)* and humans *(27)* indicate that percutaneous absorption is slow compared to pulmonary uptake. Relative to other solvents investigated, toluene penetration of rat skin was moderate; however, rat skin may be more permeable to solvents than human skin *(38)*. Experimental data from volunteers simulating skin contact under occupational conditions indicate that absorption is about 0.5 mg/cm$^2$ per hour *(27)*. Absorption from the gastrointestinal tract is considered to be complete.

**Table 1. Estimated toluene exposure levels in different types of exposure**

| Type of exposure | Observed range of concentration | Frequency of exposure | Total volume inhaled[a] or amount consumed | Inhalation or ingestion rate (mg/week) |
|---|---|---|---|---|
| **General population** | | | | |
| Inhalation: | | | | |
| urban areas[a] | 5–145 µg/m$^3$ | 168 hours/week | 140m$^3$ | 0.7–20 |
| rural and remote areas[a] | trace–5 µg/m$^3$ | 168 hours/week | 140m3 | trace–0.7 |
| areas near user sites[b] | trace–20 mg/m$^3$ | 168 hours/week | 140m3 | 2800 |
| indoor (non-industrial)[c] | trace–2.2 mg/m$^3$ | 168 hours/week | 140m$^3$ | 308 |
| Ingestion: | | | | |
| drinking-water[d] | trace–10 µg/litre | 2 litres/day | 14 litres | 0–0.3 |
| food (fish only)[b] | 0–1 mg/kg | 6.5 g/day | 4.5 g | 0–0.045 |
| **Occupational group** | | | | |
| Inhalation[e] | 376 mg/m$^3$ | 40 hours/week | 50 m$^3$ | 18 800 |
| Dermal[e] | 0.5 mg/cm$^2$/hour | 0–30 min/week | | 0–1.0 |
| **Cigarette smokers** | | | | |
| Inhalation: | | | | |
| mainstream[f] | 0.2 mg/cigarette | 20 cigarettes/day | 140 cigarettes | 28 |
| sidestream[f] | 0.3 mg/cigarette | | | |

[a] Dann et al. *(15)*.

[b] Meek & Chan *(22)*.

[c] Lebret et al. *(17)*.

[d] US Environmental Protection Agency*(26)*.

[e] Monster et al. *(27)*.

[f] US Environmental Protection Agency *(23)*. Toluene content may be higher or lower depending on tobacco type.

## Distribution

In inhalation experiments with laboratory animals, considerable amounts of toluene have been shown to be distributed to white adipose tissue, adrenals, skin, kidneys, liver, lung and brain *(9, 40)*. In mice, inhalation of toluene was shown to result in distribution to the fetuses *(41)*. Transplacental transfer to a human fetus has also been reported *(42)*.

The lowest brain levels of toluene in rats exposed to very high concentrations were found in the hippocampus and cerebral cortex while the highest concentrations were found in the brain stem regions *(43,44)*. Distribution was related to blood concentrations and brain lipid content.

## Metabolism and elimination

The major pathway of toluene metabolism in both humans and laboratory animals involves sidechain oxidation by sequential action of cytochrome P-450, alcohol dehydrogenase and aldehyde dehydrogenase leading to benzoic acid which, upon conjugation with glycine, results in hippuric acid, the major urinary metabolite. Minor metabolites include *ortho*- and *para*-cresol. A minor metabolite that is specific for toluene exposure is *S*-benzyl-*N*-acetyl-L-cysteine *(45)*. *In vitro* evidence

suggests that the rate of metabolism in humans is greater than that in rats *(46)*. Conversion of benzyl alcohol, the first intermediate, to benzaldehyde was primarily mediated by cytochrome P-450 rather than alcohol dehydrogenase. Ring hydroxylation in both humans and experimental animals leads to *ortho*- and *para*-, but not *meta*-cresol formation.

About 70–80% of an absorbed dose in humans is converted to benzoic acid *(5)*, while 7–20% is excreted as unchanged toluene in expired air *(31)*. An average elimination half-life in breath was reported at 25 minutes *(47)*

Metabolism of toluene is mediated by several isozymes that vary in expression according to diet, species, age, race and sex *(48,49)*. Of the two aldehyde dehydrogenase (ALDH) isozymes, ALDH2 was found to be lacking in about half the Japanese population *(49)*. This isozyme predominates at low liver levels of benzaldehyde and thus plays a more important role in metabolism than ALDH1. The influence of P-450 polymorphism on toluene metabolism is unclear *(49)*. Toluene concentrations in the workplace or in ambient air are so low as to not induce P-450 isoforms *(48)*.

The level at which exposure exceeds conjugation capacity has been estimated at 780 ppm during light work or 270 ppm during heavy work *(9)*. Conjugation capacity appears to be limited by the availability of glycine.

Several substances interfere with toluene biotransformation *(3)*. Co-administration of benzene to rats results in reduced excretion of hippuric acid. Ethanol is a competitive inhibitor of toluene metabolism *(50)*. However, no metabolic interactions between xylenes and toluene in humans were observed *(51,52)* although smoking inhibited the metabolism of both *(50)*. In contrast, Tardif et al. *(53)* reported mutual inhibition upon acute exposure of rats to both solvents.

The elimination of toluene from adipose tissue is prolonged according to the findings of Periago et al. *(54)*, who examined a worker population. The half-time for elimination from adipose tissue was reported to range between 0.5 and 2.7 days, depending on the amount of body fat. Elimination from bone marrow also is prolonged *(4,9)*.

**Biomarkers of exposure**

Urinary hippuric acid, a major metabolite of toluene, has long been considered a biomarker of exposure *(55,56)*. However, the weight of evidence suggests that its reliability is limited at low levels of exposure *(57)*, and is dependent upon specific exposure conditions *(58)* and specific genotypes for aldehyde dehydrogenase *(49)*. Excretion of hippuric acid has been correlated with the time-weighted average concentration (TWA) of toluene during the workshift *(59)*, but appears to be useful only as a rough measure of exposure prior to sampling. Hippuric acid correlates with toluene TWA at the end of a workshift *(27)* but not during the postexposure period *(58)*. The half-time ranges from 1 to 2 hours *(60)*.

In addition to a large interindividual variation in concentration *(61)*, hippuric acid also suffers from limited specificity since levels can be modified by benzoic acid or its precursors *(6)* and other chemicals, such as ethyl benzene and styrene *(62)*. Standardization with creatinine levels in urine has limited usefulness since there is a large interindividual variation in creatinine concentration, partly due to sex differences and smoking *(63)*.

*Ortho*-cresol, a minor metabolite of toluene, has also been considered as a possible surrogate of exposure. It constitutes only 0.1% of toluene metabolism and its background level is low *(64)*. However, it may not be specific *(45)*. Urinary levels have been correlated with TWA of toluene exposure *(58,65)*, but *o*-cresol has other limitations in its usefulness as a biomarker. Levels of *o*-cresol are influenced by smoking, sex differences, alcohol consumption, and physical activity, and measurement is more complicated than for hippuric acid *(65,66)*

Toluene in venous blood may be the most practical, reliable and sensitive predictor of exposure *(67,68)*, but levels are affected by smoking, exercise, alcohol ingestion and sex differences. The stability of toluene in blood must also be considered. Saker et al. *(69)* have shown that samples stored at 24 °C or below result in a 25% loss after one week. Mizunuma et al. *(70)* found blood toluene to be highly correlated to toluene in air at levels (< 1 ppm) where hippuric acid was no longer significant. Blood toluene levels determined on Monday mornings before work or near the end of the work week were found to be a suitable measure of exposure in the preceding week *(71)*. During this time period, blood levels are representative of concentrations in adipose tissue which, in turn, were shown to be linearly related to weekly exposure concentrations *(71)*. Foo et al. *(62)* found venous blood concentrations highly correlated to same-day TWA concentrations. Because blood toluene decreased rapidly after exposure, sampling immediately after exposure was recommended. Higher levels were recorded when sampling was done by finger prick and may suggest that dermal contact with toluene had taken place. Lowry *(60)* concluded that that a blood toluene level of 1 mg/litre is roughly equivalent to a toluene exposure of 100 ppm under moderate work activity.

Toluene in end-expired air may also be a useful monitor of exposure *(27,72)*. Monster et al. *(27)* found that toluene in end-expired air 8 hours after the end of exposure correlated best with a two-day TWA. However, Baelum *(66)*, in a study involving controlled exposures, found levels in alveolar air very sensitive to the sampling method and minor changes in sampling time. Exercise also alters toluene levels in alveolar air *(31)*. Given the rapid clearance from the lung and toluene's short half-time, sampling immediately after exposure likely probably only reflects recent exposure.

**Physiologically-based pharmacokinetic modelling**

Physiologically-based pharmacokinetic models that have incorporated toluene pharmacokinetics typically focus on the effects toluene has on the distribution and metabolism of other chemicals (e.g. benzene). A model patterned after that of Sato et al. *(73)* has been developed by Lapare et al. *(51)* which successfully modelled experimental exposures to toluene and *m*-xylene. The model incorporated different workloads and exposure scenarios. It was concluded that toluene concentration in expired air is a suitable measure of toluene exposure. Models have also been used to simulate metabolic interactions between toluene and benzene *(74)*.

## Health effects

**Effects in laboratory animals**

An extensive number of studies provide strong support for effects upon the central nervous system (CNS). Nearly all studies employed exposure concentrations or doses that far exceed the concentrations to which humans have been exposed in the workplace or in ambient air. To this

degree, these studies may relate best to the effects observed in toluene abusers. Recently, use of a "benchmark-dose" statistical approach applied to behavioural effects of toluene in rats suggests that CNS-associated effects in laboratory animals may occur at levels associated with indications of CNS impairment in humans *(75)*.

*Effects on the brain*

Studies in the rat and mouse have detected effects of toluene inhalation on brain constituents and morphological and biochemical parameters. High levels approaching 2000 ppm have caused ataxia, prostration and tremors in rats exposed for 7 days *(76)*. At the completion of this 26-week study, there were no treatment-related effects. Regional loss of cells in the hippocampus coupled with abnormal electrical activity in this region was observed when rats were exposed to a toluene concentration of 500 ppm for 8–16 hours/day for up to 5 weeks *(77)*; it was concluded that toluene causes irreversible effects in this area of the brain.

Alterations in catecholamine synthesis and utilization are consistent findings in a number of studies in rats. Neonatal exposure to 80 ppm (days 1–7) was found to cause persistent changes in catecholamine synthesis and release in specific brain regions that led to alterations in the response of adult rats to low level toluene exposure *(78)*; responses occurred in the absence of alterations in serum hormone levels and without histopathological changes under light microscopy. Toluene-induced conformational changes in dopamine and hydroxytryptamine receptors have been reported *(79)*. Alterations in dopamine metabolism in the substantia nigra *(80)*, and the striatum *(81)* have been observed upon acute exposure; these effects appear to be dose-related. Exposure of adult male rats to toluene at a concentration of 80 ppm for 4 weeks is associated with an increase in serum prolactin levels during postexposure *(82)*. It was suggested that prolactin levels may correlate with altered dopamine receptor functioning.

Inhaled toluene in rats has been detected in all brain regions, with the highest concentration in the brainstem, an area also found to be involved in neurological sequelae in toluene abusers *(43)*. Uptake was correlated with lipid content in each brain region. Enzyme activities and receptor binding was most affected in the brainstem of rats exposed subchronically and chronically *(83)*. Given the variety of brain-related changes caused by toluene, it is not surprising that deficits in neurobehavioural functioning and performance testing have been observed.

*Effects on neurobehavioural performance*

A variety of tests have been employed to test learned behaviour in rats *(84)*. Acute exposure of rats to toluene concentrations of up to 1000 ppm have not been shown to impair avoidance performance *(85)*. However, effects were found at repeated exposure to levels as low as 900 ppm *(86)*. Long-lasting impairment of operant behaviour was observed in rats exposed to 1000 ppm for 21 hours/day, 5 days/week, for 4 weeks *(87*). Impairment of spatial learning and memory accompanied by a persistent increase in dopamine-mediated locomotor activity was observed in rats exposed to 80 ppm for 6 hours/day, 5 days/week for 4 weeks *(88)*. Although spontaneous locomotor activity was not affected, apomorphine-induced locomotion and activity was increased by toluene exposure in this protocol *(82)*. Exposure of rats to 1000 ppm, 21 hours/day for up to 11 weeks caused disturbances in vestibulo-oculomotor function *(89)*.

 

*Effects on liver and kidney*

A variety of studies suggest that toluene is only minimally toxic to the liver and kidney. Exposure of rats to toluene at concentrations of 30 and 300 ppm for 6 hours/day, 5 days/week for four weeks produced only minimal histological changes and had no effect on AST, liver weight, or mixed function oxidases *(90)*; serum alkaline phosphatase was elevated at 300 ppm. There were no histopathological changes in the kidney. In a two-year inhalation study, rats or mice exposed to up to 1200 ppm toluene did not exhibit histopathological changes in liver or kidney. Renal tubule necrosis and dilation was elevated in exposed mice but there was no concentration–response trend *(91)*. Similar conclusions for rats exposed to up to 300 ppm were reported for another two-year study *(92)*. There were no clear effects upon liver enzymes in a 26-week inhalation toxicity study in rats *(76)*.

Even when toluene exposure conditions in mice (4000 ppm for 8 weeks, intermittently) approximated concentrations inhaled during toluene abuse, there was a lack of histopathological evidence of damage not only in the liver and kidney, but in brain as well *(93)*.

*Ototoxicity*

Information gained from animal studies supports the observations in humans that toluene can be ototoxic. Ototoxicity has been observed in rats when toluene was injected subcutaneously *(94)*, via gavage dosing *(95)* or by inhalation *(96)*. Li et al. *(97)* demonstrated that toluene exposure can aggravate auditory degeneration in genetically predisposed mice.

*Carcinogenic effects*

A chronic (106-week) bioassay of toluene in F344 rats reported no carcinogenic responses *(98)*. However, this study has been categorized as inadequate since the highest dose was below the median toxic dose and because of the high incidence of lesions and pathological changes in control animals *(99)*. A two-year inhalation bioassay conducted by the US National Toxicology Program in rats and mice revealed no carcinogenic responses at levels of up to 1200 ppm *(91)*.

*Mutagenic effects*

Toluene and its metabolites have not demonstrated genotoxicity in an extensive number of studies involving *Salmonella*/microsomal assays with and without metabolic activation published prior to 1984 *(3)*. More recent assays also found toluene and its metabolites to be without effect *(100)*.

*Developmental, reproductive and teratogenic effects*

Inhalation studies with mice and rats have shown that toluene has the potential to cause growth retardation and skeletal anomalies in the offspring of exposed dams. The potential for teratogenic effects appears limited.

In mice exposed to toluene at concentrations of 400–1000 ppm a significant increase in the number of fetuses with extra ribs was observed *(101–103)*. Reduction in fetal weight was observed in mice exposed to 133 ppm for 24 hours/day on gestation days 6 to 13 *(104)*. The offspring of rats exposed to 399 ppm showed decreased fetal weight and skeletal retardation. In addition irregular sternebrae and extra ribs were significantly increased when exposed during days 9–14 of gestation *(104)*.

Postnatal neurobehavioural and cognitive development has been shown to be affected by prenatal and postnatal exposures to toluene in rats *(105)* and mice *(106)*. In dams and weanling rats exposed to 100 or 500 ppm morphological examination of the brains of the pups revealed alterations of specific neuron populations in areas of the hippocampal region (*107)*.

Toluene had minimal effects on development of F1 offspring of rats exposed prior to mating, during mating, and during gestation and suckling for 6 hours/day, 7 days/week to toluene levels of 100, 500 and 2000 ppm *(108)*. There was no abnormal histopathology or effects on reproductive parameters.

There was no evidence of maternal toxicity, embryotoxicity, fetotoxicity or teratogenicity in artificially inseminated Himalayan rabbits exposed to toluene levels of 100 or 500 ppm during the period of organogenesis *(109)*.

Toluene was not found to adversely affect rat mature sperm or the spermatid stage when rats were given toluene at levels of one-quarter of the $LD_{50}$ intraperitoneally for 5 consecutive days *(110)*. However, degeneration of germinal cells and a significant decrease in testes weight have been reported in male Donryu rats *(9)*. There was no concentration–response relationship with respect to testes weight or histopathological findings in a two-year bioassay in which Fischer 344 rats and B6C3F1 mice were exposed to levels of up to 1200 ppm *(91)*.

*In vitro* studies with mouse gamete cells showed that toluene decreased sperm motility and inhibited *in vitro* fertilization and embryo survival *(111)*.

*Interactions with other chemicals*

A number of studies with laboratory animals have shown that toluene interferes with the metabolism and toxicity of several chemicals, including ethanol, benzene, xylene, hexane and styrene *(4,112,113)*. The effect of toluene on benzene metabolism and toxicity has been reviewed by Medinsky et al. *(114)*. Exposure of rats to a high concentration mixture of methanol and toluene for 28 days found little evidence of an interactive effect *(90)*

**Effects on humans**

Toxicity studies in humans have primarily involved evaluation of individuals exposed to toluene via inhalation in experimental or occupational settings or as a result of intentional abuse. Only those studies involving primarily toluene are described.

*Effects on the central nervous system*

An extensive database on human exposure to toluene indicates that dysfunction of the CNS is of primary concern. Deficits in neurobehavioural functioning have been viewed as precursors of more serious indications of CNS toxicity *(4,55)*. Their measurement is generally held to be more reliable than subjective symptoms, which may involve situational factors unrelated to a cause–effect relationship with exposure. Potential confounders such as age, alcohol, drugs and education need to be assessed to ensure correlations of toxicity with exposure.

Toluene abuse typically involves acute or chronic exposure to unknown, high levels. Cognitive dysfunction may be the most disabling and frequent feature of chronic toluene abuse *(115)*. Gradual resolution of some effects was found upon discontinuance of toluene abuse, although persistent neurological impairment was foreseen some individuals. The types of effects seen in abuse cases

 

include: cerebral, cerebellar and brainstem atrophy, ataxia, muscular incoordination, neuronal degeneration and personality disorders *(3)*. Magnetic resonance imaging or computerized tomography have been useful tools for examining affected areas of the brains of toluene abusers *(116)*.

Evidence of abnormal brainstem auditory evoked potential, considered to be an early indicator of CNS injury, has also been found in chronic toluene abusers *(117)*. Slow-wave abnormalities upon electroencephalography have been demonstrated in some case reports *(3)*. Workers exposed to high concentrations of toluene for extended periods of time have been reported to exhibit signs of mild chronic toxic encephalopathy *(118)*.

Studies of nonsmoking and nondrinking female workers chronically exposed to only toluene provide evidence of a concentration–response association in neurobehavioural aspects of CNS functioning. Duration of exposure was not a significant factor. Foo et al. *(119,120)* found that neurobehavioural test scores in 6/8 tests of psychomotor function were significantly lower in the group exposed to a TWA of 88 ppm (332 mg/m$^3$) toluene compared to controls from the same facilities who were exposed to a TWA of 13 ppm (49 mg/m$^3$). Controls were matched for age sex, and ethnicity. A no-observed-adverse-effect level was not identified. The lack of a duration–response relationship in this and other studies suggest that the controlled acute exposures of individuals to levels around 88 ppm may be considered relevant to the longer-term effects noted by Foo et al. *(119,120)*. Echeverria et al. *(121)* observed a concentration-dependent increase in the incidence of sleep and headache in individuals exposed to toluene levels of 75 ppm (283 mg/m$^3$), and 150 ppm (566 mg/m$^3$) for 7 hours as well as a decrease in several performance functions. In this study, individuals served as their own controls.

Abnormalities in visual evoked potential in printers exposed to a mean toluene concentration of 2000 mg/m$^3$ or 530 ppm (measured over a ten-year period) were suggested as evidence of subclinical CNS dysfunction *(122)*. Toluene exposure of workers was also suggested as a cause of altered visual evoked potential, although an exposure–response relationship was not demonstrated *(123)*.

*Effects on kidney and liver*

Distal renal tubular acidosis is a common finding in toluene abusers *(124)* and has even been found in infants born to mothers who abused toluene *(125)*. Symptoms include muscle weakness, nausea and vomiting and are believed to be the result of an electrolyte imbalance precipitated by the renal acidosis *(126)*. The role of toluene metabolism in distal renal tubule acidosis was evaluated by Carlisle et al. *(127)*. Recently, acute toluene abuse in a woman was observed to have resulted in muscle weakness of the lower extremities and complications of renal tubular injury with metabolic acidosis *(124)*. Damage was judged to have occurred in both the proximal and distal regions.

Toluene exposure has not been generally associated with liver toxicity *(4,9)*, although acute fatty liver was found in a woman with long-term toluene exposure who gave birth to a stillborn child *(128)*, and hepatic reticuloendothelial failure was observed in a male with a history of toluene exposure *(129)*.

*Developmental, reproductive and teratogenic effects*

Abuse of toluene by pregnant women through deliberate inhalation of products such as paint thinners, glues and paints has been associated with a number of developmental and congenital anomalies in infants *(130)*. In such reports it is difficult to determine the degree to which other substances may play a role in the development of adverse effects. Effects commonly noted postpartum include low birth weight, growth retardation, microencephaly, CNS dysfunction, renal tubule acidosis, and minor craniofacial and limb abnormalities. Perinatal death has also been reported.

Ng et al. *(131)* found that the incidence of spontaneous abortion was significantly higher for women occupationally exposed to toluene compared to controls in the same factory or women in a community control group. Among exposed women, the incidence of spontaneous abortion was significantly lower before employment compared to rates after employment and exposure to toluene. Lindbohm et al. *(132)* found an increased risk of spontaneous abortion in toluene-exposed shoe-leather workers compared to controls; statistical significance was not achieved owing to sample size limitations. There did not appear to be any association between menstrual function and toluene exposure when exposed workers were compared to factory controls *(133)*. Menstrual disorders in workers were reported, but the possible presence of other chemicals in the exposure environments and unmatched characteristics of the exposed and control groups make these findings difficult to interpret *(9)*. Possible exposure-related effects upon follicle stimulating hormone and testosterone *(134)*, but not serum prolactin levels *(135)*, have been observed in printers without overt effects of toluene.

*Carcinogenic potential*

There is no information from human studies that suggests that toluene has carcinogenic potential. Svensson et al. *(136)* examined a cohort of 1020 toluene-exposed workers who had been employed for a minimum period of three months during the period 1925–1985. There were no significant increases in tumours and no cumulative dose–response relationship in workers with an exposure period of at least five years and a latency period of 10 years. Exposure to benzene had taken place up to the 1960s. Toluene has been shown, however, to hyperphosphorylate rat liver p53, a tumour suppressor gene *(137)*. This observation may be of concern, since a reduced ability of p53 to suppress genetic errors may result in tumour formation.

*Genotoxicity*

An unequivocal evaluation of the genetic effects of occupational toluene exposure cannot be made because of the small numbers of individuals analysed and insufficient information on possible exposure to other chromosome-damaging agents *(3)*. Recent data indicate that toluene induces clastogenic effects in pokeweed-mitogen-stimulated peripheral blood lymphocytes of printers *(138)*. However, variations in exposure history preclude identification of an exposure–response relationship. Toluene exposure of printers was also highly correlated with an excess of chromatid breaks in peripheral lymphocytes compared to controls *(139)*, although concurrent exposure to printing dyes as a factor cannot be excluded. No effects on sister chromatid exchange, cell cycle delay or cell mortality were observed in peripheral blood lymphocytes in volunteers exposed for three consecutive days to 50 ppm *(140)*. Previously, Bauchinger et al. *(141)* found a significant increase in sister chromatid exchanges and chromosome aberrations in printers (smokers and nonsmokers relative to controls) exposed to toluene for more than 16 years. Even after two years of

exposure cessation a higher incidence of aberrations was observed in exposed individuals compared to controls *(142)*.

*Interactions with other chemicals*
Exposure of volunteers to toluene (50 ppm) and xylene (50 ppm) resulted in decrements in reaction time, one of a battery of psychomotor and cognitive tests administered *(143)*. Toluene alone did not result in deficits in any of the tests. Ethanol ingestion during exposure of volunteers to a toluene level of 300 mg/m$^3$ (80 ppm) for 4.5 hours was found not to alter the occurrence or severity of the subjective symptoms associated with toluene alone *(144)*.

## Evaluation of human health risks

### Exposure evaluation

Mean ambient air concentrations of toluene in rural areas are generally less than 5 µg/m$^3$, while urban air concentrations are in the range 5–150 µg/m$^3$. Close to industrial emission sources concentrations may be higher.

### Health risk evaluation

The acute and chronic effects of toluene on the CNS are the effects of most concern. Toluene may also cause developmental decrements and congenital anomalies in humans, and these effects are supported by findings of studies on animals, e.g. fetal development retardation, skeletal anomalies, low birth weights and developmental neurotoxicity. The potential effects of toluene on reproduction and hormonal imbalances in women, coupled with findings of hormonal imbalances in exposed males, are also of concern. Limited information suggests an association between occupational toluene exposure and spontaneous abortions. Both the human and animal data indicate that toluene is ototoxic at elevated exposures. Sensory effects have also been found. Toluene has minimal effects on the liver and kidney, except in cases of toluene abuse. There has been no indication that toluene is carcinogenic in bioassays conducted to date and the weight of available evidence indicates that it is not genotoxic.

The lowest level of chronic occupational toluene exposure unequivocally associated with neurobehavioural functional decrements is 322 mg/m$^3$ (88 ppm). CNS effects in humans are supported by findings in exposed animals. For example, rat pups exposed to either 100 or 500 ppm (1–28 days after birth), demonstrated histopathological changes in the hippocampus. Women occupationally exposed to toluene at an average concentration of 322 mg/m$^3$ (88 ppm) incurred higher spontaneous abortion rates and menstrual function disturbances. The interpretation of these observations was hampered, however, by confounding factors. Men occupationally exposed to toluene at 5–25 ppm have also been shown to exhibit hormonal changes.

With regard to short-term exposure, subjective effects have been reported at 100 ppm (6-hour exposure) while symptoms at lower levels cannot be ruled out. Numerous confounding factors, however, need to be considered.

Exposure data related to CNS endpoints were best characterized in certain occupational studies and these data have been employed in the derivation of the guideline. a no-observed-adverse-effect level for chronic effects of toluene has not been identified.

**Guidelines**

The lowest-observed-adverse-effect level for effects on the CNS from occupational studies, is approximately 332 mg/m$^3$ (88 ppm). A guideline value of 0.26 mg/m$^3$ is established from these data adjusting for continuous exposure (dividing by a factor of 4.2) and dividing by an uncertainty factor of 300 (10 for interindividual variation, 10 for use of a lowest-observed-adverse-effect level rather than a no-observed-adverse-effect level, and an additional factor of 3, given the potential effects on the developing CNS). This guideline value should be applied as a weekly average. This guideline value should also be protective for reproductive effects (spontaneous abortions).

The air quality guideline could also be based on the odour threshold. In this case, the peak concentrations of toluene in air should be kept below the odour detection threshold level of 1 mg/m$^3$ as a 30 minutes average.

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