Public Health England

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Toluene

Toxicological Overview

Key Points

Kinetics and metabolism

- toluene is readily absorbed following inhalation, ingestion and partially through the skin
- following absorption toluene is rapidly distributed throughout the body
- toluene is oxidised to benzoic acid which is conjugated with glycine
- toluene is predominantly excreted in the urine as the metabolite hippuric acid

Health effects of acute exposure

- acute inhalation or ingestion can cause systemic effects such as euphoria, excitation, hallucinations, dizziness, drowsiness, ataxia, slurred speech, tremor, respiratory depression, arrhythmias and convulsions
- coma and death can occur following substantial exposures
- local effects are observed following inhalation (irritation to nose, throat and respiratory tract), ingestion (oropharyngeal and gastric irritation), ocular (lacrimation) and dermal exposure (erythema and dryness)

Health effects of chronic exposure

- chronic inhalation of toluene may cause liver and kidney damage
- chronic low level occupational exposure may cause mild neurotoxicity
- the International Agency for Research on Cancer (IARC) classified toluene as a category 3 carcinogen, ie not classifiable as to the carcinogenicity to humans
- toluene is considered to be a possible reproductive toxin

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Summary of Health Effects

Local effects following inhalation of toluene include irritation to the eyes, nose, throat and respiratory tract. Acute inhalation can cause systemic effects such as euphoria, excitation, hallucinations, dizziness, drowsiness, ataxia, tremor, respiratory depression, cardiac effects and convulsions. Exposure to high concentrations can lead to coma and death. The predominant effects of chronic toluene inhalation are on the central nervous system (CNS) and kidney. Neurological effects may include behavioural and personality changes, muscle weakness, peripheral neuropathy, tremor and impairments of speech, hearing and vision. In some cases CNS damage is permanent.

Following acute ingestion of toluene, systemic effects as seen following inhalation may occur as well as oropharyngeal and gastric irritation with abdominal pain and vomiting. Chronic oral exposure to toluene has not been characterised in humans.

Following acute dermal exposure to toluene, local effects may include irritation, blistering, dryness and erythema. Necrotic skin burns can develop following prolonged contact with toluene. Chronic dermal exposure may cause skin irritation and contact dermatitis.

Local effects following acute ocular exposure to toluene include lacrimation and transient corneal damage. Chronic exposure may result in loss of visual acuity, optical neuropathy and nystagmus.

The International Agency for the Research on Cancer (IARC) concluded that toluene is not classifiable as to its carcinogenicity in humans (group 3).

Toluene is classified in the EU as a reproductive toxicant, category 2 (hazard statement H361: suspected of damaging the unborn child). It readily crosses the placental barrier. Studies into exposures in the workplace or by solvent abuse have shown associations with a number of adverse reproductive outcomes; however, the evidence is inconclusive.

Kinetics and Metabolism

Toluene is readily absorbed from the respiratory and gastrointestinal tracts and to some degree through the skin [1]. It is estimated that 40–60% of inhaled toluene is absorbed [2]. Oral absorption is complete but the rate is slower than pulmonary absorption [1]. Dermal absorption of toluene is relatively slow; the rate of absorption through forearm skin is in the range of 14–23 mg/cm^2 per hour [3].

When exposed during exercise, the amount of toluene in the alveolar air has been observed to be 1.4–2 times higher than in those exposed at rest [4].

Following absorption, toluene is rapidly distributed throughout the body. Human and animal inhalation studies have shown high toluene concentrations in adipose tissue, bone marrow, adrenals, highly vascular tissues (eg the kidney and liver), brain and blood [5].

Following inhalation or oral exposure to toluene, approximately 60–75% of absorbed toluene, is metabolised to benzoic acid [2, 6]. The liver is the primary site of toluene metabolism [5]. The initial step involves side chain oxidation to benzyl alcohol by cytochrome P450 enzymes. Benzyl alcohol is then further oxidised to benzoic acid by alcohol dehydrogenase and aldehyde dehydrogenase. Benzoic acid is subsequently conjugated with glycine to form hippuric acid [2]. Between 3 and 20% of absorbed toluene may be converted to benzoyl glucuronide [5]. Less than 1% of absorbed toluene undergoes ring hydroxylation to form o- and p-creosol, which is excreted in the urine as glucuronide or sulphate conjugates [2].

Following inhalation, toluene is predominantly excreted in the urine as the metabolite hippuric acid. Approximately 7–20% of absorbed toluene is eliminated in air unchanged. Toluene may also be excreted into breast milk [5]. Following a single acute exposure, toluene and its metabolites are almost completely eliminated within 24 hours [2, 6].

Toluene can cross the placenta and is found in the fetus at concentrations of approximately 75% of that present in the maternal blood [5].

Sources and Route of Human Exposure

The main route of exposure to toluene is by inhalation, ie vapour in ambient air, cigarette smoking, petrol stations and garages, solvent abuse and use of household agents [2, 5, 6]. Ingestion (contaminated food or water) and dermal exposure (use of fuels, solvents and cosmetics) are less common routes of exposure to toluene [2].

The majority of toluene released into the atmosphere is from inadvertent sources, eg vehicle emissions and spills. Toluene is also released into the environment during its transport, production, use and disposal [2]. Levels of toluene detected in rural and urban air averaged 1.3 and 10.8 µg/m^3, respectively [1]. Indoor air levels of toluene are generally higher (31.5 µg/m^3) than outdoor levels due to cigarette smoke and the use of household products (eg paints, adhesives and thinners) [1].

Toluene does not persist in the environment; it is rapidly volatilised or biodegraded [2]. In surface soils, 90% of toluene is expected to volatilise within 24 hours; when present at greater depths the contaminant will be more persistent [7].

Toluene has been detected in drinking water, well water and in raw water [2]. However, exposure to toluene in drinking water is minimal, except in situations where heavy contamination occurs [6].

Exposure to toluene can occur in the workplace. Shoemakers, printers and individuals who are involved in the production of toluene or toluene-containing products are at risk of exposure to considerably higher levels of toluene than the general population [2].

The deliberate inhalation of products containing toluene such as paint, paint thinners and adhesives can lead to exposure to very high toluene levels. Solvent abusers may be exposed to concentrations ranging from 3,750–37,500 mg/m^3 (10–10,000 ppm) [5].

Toluene is found widely in nail cosmetics as a solvent; however, the penetration of toluene through human nail tissue is considered to be negligible [3]. Due to the high volatility of toluene, inhalation is considered the predominant route of exposure in the application of such products [3]. Toluene levels of 3.75–15 mg/m^3 (1–4 ppm) and 0.98 mg/m^3 (0.26 ppm) have been measured in household and professional studio (ventilated) use of nail cosmetics, respectively [3].

Health Effects of Acute/Single Exposure

Human data

General toxicity

The main target organ of toluene-induced toxicity is the central nervous system (CNS). Toluene is also an irritant to the skin and mucous membranes.

Inhalation

The acute toxic effects following inhalation of toluene are summarised in the table. Toluene vapours are irritating to the eyes, nose, throat and respiratory tract. Respiratory complications such as acute bronchitis, bronchospasm, pneumonitis, asphyxia and pulmonary oedema may also occur [2, 8].

Table: Summary of toxic effects in humans following acute exposure to toluene by inhalation [2]

Dose (mg/m^3)	Signs and symptoms
188–375	Subjective complaints (very mild headache, fatigue and downiness)
750	Mild throat and eye irritation, headache, dizziness, sensation of intoxication (8-hour exposure)
1,500	Irritation of the eyes and throat, lacrimation, mental confusion, incoordination
1,875–2,250	Anorexia, staggering gate, nausea, nervousness, momentary loss of memory, significant reduction in reaction time
5,625	Extreme weakness
15,000	Rapid impairment of reaction time and coordination, exposures of 1 hour or longer may lead to narcosis and possibly death
37,500–112,500	Onset of narcosis within minutes; longer exposures may be lethal

CNS toxicity is the main acute effect following toluene exposure. The effect can be depressant or excitatory, with euphoria, hallucinations followed by ataxia, confusion, dizziness, drowsiness, slurred speech, blurred vision, tremors, respiratory depression, convulsions, coma and, in severe cases, death [1, 2, 8].

Cardiovascular effects including hypotension or hypertension, bradycardia, tachycardia, ventricular fibrillation, cardiac arrest and myocardial infarction have been reported in humans following acute inhalation of toluene [1, 8]. Exposure to toluene may cause sensitisation of the myocadium to adrenaline and sympathetic stimulation, which may result in cardiac arrhythmias and sudden death [9].

Other effects of acute exposure include rhabdomyolysis, hepatic and renal damage, severe metabolic acidosis, fluid and electrolyte disturbances, paraesthesiae and peripheral neuropathy [8].

Death following toluene abuse is caused by hypoxia during toluene narcosis or while inhaling the solvent from a plastic bag over the head [9]. Approximately 100 deaths a year are reported following solvent abuse in the UK; 25% of these are caused by adhesive solvents which are composed mainly of toluene [5].

Toluene levels in the range of 750–5,625 mg/m^3 in occupational settings have been reported to cause dose-related CNS depression. Exposure to very high concentrations of toluene (≥37,500 mg/m^3) during industrial accidents has resulted in CNS excitation followed by progressive impairment of consciousness, seizures and coma [2].

Ingestion

Ingestion of toluene can cause severe acute toxicity, as described in the inhalation toxicity section. Local effects following ingestion include oropharyngeal and gastric irritation with abdominal pain, vomiting and haematemesis [8, 10].

One case study reported abdominal pain, haemorrhagic gastritis and CNS depression following ingestion of a paint thinner containing toluene, although other studies did not reveal gastrointestinal effects even after oral exposure to a lethal dose of toluene [11]. Other effects reported following ingestion of toluene include bradycardia, necrosis of myocardial fibres, enlarged liver and acute tubular necrosis [1].

Death, probably due to severe CNS depression, has been reported to have occurred within 30 minutes of ingestion of approximately 60 mL (625 mg/kg) of toluene [12].

Dermal/ocular exposure

Toluene is lipid soluble, therefore it can cause irritation, blistering, dryness and erythema to the skin through a defatting action [8]. Prolonged exposure may lead to necrotic skin burns [8]. Extensive chemical burns have been reported following prolonged exposure to toluene-based paint [13]. Dermal exposure in the absence of significant exposure from other routes is unlikely to give rise to systemic toxicity [8].

Exposure to toluene vapours may cause irritation to the eyes at concentrations greater than 750 mg/m^3 and lacrimation at 1,500 mg/m^3 [2]. Corneal injury may occur as a result of exposure, although this is usually reversible [8].

Health Effects of Chronic/Repeated Exposure

Human data

Inhalation

Health effects from chronic exposure to toluene may resemble those of acute exposure. Renal tubular acidosis and CNS effects are the most prevalent [8].

Permanent CNS damage and progressive encephalopathy may develop as a result of long-term toluene abuse [8]. Related neurological effects include behavioural and personality changes, confusion, paranoid psychosis, hallucinations, memory loss and impairments of speech, hearing and vision [1, 2, 8]. Nystagmus, ataxia, muscle weakness, peripheral neuropathy and tremors may also present in such cases [8].

There is a significant body of evidence linking mild neurotoxicity with chronic low level occupational exposure to toluene [5]. Subtle neurological effects including headaches, dizziness, degradation of colour vision and neurological and psychomotor functioning have been reported in workers exposed to toluene concentrations ranging from 150–495 mg/m^3 [5].

Some occupational studies have reported increased serum concentrations of liver enzymes in workers exposed to toluene concentrations between 113 and 1,312 mg/m^3 (30 and 350 ppm) [1]. Other studies have not reported any adverse effects on the liver. Liver damage has been reported in solvent abusers [1].

Irritation to the upper respiratory tract and conjunctiva was reported in workers occupationally exposed to 750–3,000 mg/m^3 of toluene for several years [2].

Distal renal tubular acidosis is associated with abuse of toluene containing solvents. Muscle weakness, nausea and vomiting are common symptoms and are thought be due to an electrolyte imbalance caused by the renal acidosis [6]. Metabolic acidosis and tubular injury were recorded in a 22-year-old female who sniffed up 6 litres of toluene throughout the previous month [1]. Irreversible renal failure has been reported in a 20-year-old male who sniffed glue containing 16.5% toluene twice a week for 9 months [2].

Ingestion

There is currently no data available on the chronic effects of toluene ingestion in humans.

Dermal/ocular exposure

There is limited data on the effects of dermal exposure to toluene. Liquid toluene will remove natural lipids from the skin. Therefore, repeated or prolonged dermal exposure may cause dryness, fissures and contact dermatitis [2, 10].

Loss of visual acuity, optical neuropathy and nystagmus have been reported in a number of studies involving toluene abusers [2].

Genotoxicity

An unequivocal evaluation of the genotoxic effects of occupational exposure to toluene cannot be made due to the small number of individuals analysed and the inadequate information on the possible exposure to other chromosome damaging agents [1, 2].

There are discrepancies in the findings related to the genotoxic effects of toluene in humans. An increase in chromosome breaks was recorded in the lymphocytes of workers exposed to 340–4,388 mg/m^3 (104–1,170 ppm) of toluene [1]. Chromosomal aberration analysis of the lymphocytes of printers exposed to 114–328 mg/m^3 revealed a concentration-related increase in sister chromatid exchange [1]. A significant increase in the frequency of sister chromatid exchanges and chromatid breaks compared to unexposed controls was recorded in the lymphocytes of workers exposed to 750–1,125 mg/m^3 (200–300 ppm)of toluene [1].

In contrast, other similar studies have shown no association between chronic toluene exposure and an increased incidence of chromosome damage. No exposure differences were reported in DNA damage in leukocytes of factory workers exposed to factory air containing 96–412 mg/m^3 of toluene [1]. Chromosomal aberration analysis of workers exposed to 26–420 mg/m^3 did not reveal an increase incidence of chromosome damage in blood lymphocytes compared with controls [2].

Carcinogenicity

IARC considered eight studies: two were community-based and six were occupational exposure studies. Toluene was considered to be the predominant source of exposure in only two of the studies, those of Swedish rotogravure printers and US shoe manufacturers [14].

A cohort of 1,020 Swedish rotogravure printers exposed primarily to toluene for at least 3 months showed increased mortality and incidence ratios for respiratory tract, stomach and colorectal cancer. However, there was no significant correlation between increased risk and cumulative exposure [1, 14].

The second study involved a cohort of 7,814 shoe-manufacturing workers in the US. The workers were potentially exposed to solvents and solvent-based adhesives. It was thought that the workers were primarily exposed to toluene; however, other chemicals (eg acetone and hexane) were detected at high concentrations. Benzene may have been present as an impurity of toluene. The rates of lung cancer were significantly elevated, but smoking may have been a contributing factor. There was a slight increase in the risk of colon cancer but this was not significant [14].

Overall, IARC stated that “considering the multiple exposure circumstances in most studies and the weak consistency of findings, these results are not strong enough to conclude that there is an association”. IARC concluded that there was inadequate evidence in humans for the carcinogenicity of toluene and as such classified it as group 3 (Not classifiable as to its carcinogenicity to humans) [14].

Reproductive and developmental toxicity

The abuse of toluene by pregnant women through deliberate inhalation of products such as paint, paint thinners and adhesives has been associated with a number of adverse reproductive outcomes. The effects reported include premature delivery, congenital cranio-facial, limb, cardiac, renal and CNS malformations. In such reports the evidence of an association between prenatal exposures to toluene and developmental toxicity is limited by the potentially confounding effects of other agents (eg alcohol or tobacco smoke) to which the subject may have been exposed [15, 16].

Several occupational studies have reported the reproductive outcomes among women exposed to toluene. Six studies have reported an association with spontaneous abortion, three with reduced fertility and two with congenital malformations. The studies on spontaneous abortion provide the most convincing evidence for an association with toluene. However, the potential for bias and multiple chemical exposures suggests that the results from these studies should be interpreted cautiously [17].

High incidences of menstrual disturbances have been reported in women occupationally exposed to toluene and other solvents [10].

Overall, the current data does not provide convincing evidence that toluene causes reproductive effects in humans, as a number of studies reporting an increased incidence of spontaneous abortion have not been supported by animal data [1].

Little data has been found regarding the effects of toluene on human male reproduction. One single case report regarding a 28-year-old male who chronically abused toluene for 10 years suggests that chronic abuse of toluene may cause testicular atrophy and reduced spermatogenesis. The subject was thought to have died as a result of excess sniffing and was found to have degeneration of the spermatogonia and Sertoli cells and showed evidence of suppressed spermatogenesis [15].

In the EU toluene is classified as a reproductive toxicant, category 2; this requires use of the hazard statement code H361 (suspected of damaging the unborn child) [18].

Animal and in-vitro data

Inhalation

Neurological effects including hearing loss, reduced brain weights, changes in the concentrations of neurotransmitters, interrupted sleep cycles and deficits in neurobehavioral performance have been reported in animals chronically exposed to toluene [1, 2].

Rats exposed to 2,250 mg/m^3 (600 ppm) of toluene for 5 weeks showed signs of lung irritation and rats exposed to 9,375 and 18,750 mg/m^3 (2,500 and 5,000 ppm) developed pulmonary lesions [10]. Inflammation of the nasal mucosa and degeneration of the respiratory epithelium were reported in rats exposed to 2,250 or 4,500 mg/m^3 (600 and 1,200 ppm) for 6.5 hours a day, 5 days a week for 2 years. However, mice exposed to the same concentrations for 2 years did not display the same effects [1].

Increased liver weights and increased serum levels of liver enzymes have been reported in rats repeatedly exposed to toluene at doses greater than 1,125 mg/m^3 (300 ppm) for at least 6 hours a day [1].

Rats exposed to toluene at concentrations of 750–18,750 mg/m^3 for 7 hours a day, 5 days a week developed renal casts within the collecting tubules of the kidneys [2]. Necrosis of the kidney tubules and increase in kidney weights were recorded in rats exposed to 7,500 mg/m^3 (2,000 ppm) of toluene for 90 days [1].

Ingestion

Female rats administered toluene (560 mg/kg for up to 6 months) by intubation showed no signs of toxicity [2].

In a sub-chronic study rats and mice were administered toluene by gavage at doses of 0, 312, 625, 1,250, 2,500 or 5,000 mg/kg of bw per day for 5 days a week for 90 days [16]. All the rats and mice given 5,000 mg/kg died within the first week of the study and 40% of the mice receiving 2,500 mg/kg also died [16]. No adverse effects were observed in rats exposed to 312 mg/kg, or in mice exposed to doses less than 2,500 mg/kg. The group of rats receiving 2,500 mg/kg exhibited ataxia, hypoactivity, bradypnoea, hypothermia, piloerection, prostration, lacrimation, excess salivation and body tremors [16]. Increases in liver and kidney weights were noted in the rats exposed to doses greater than or equal to 625 mg/kg [16].

Dermal/ocular exposure

Slight to moderate skin irritation was observed on the ears and body of rabbits exposed (10– 20 repeated applications) to undiluted solvent for 2–4 weeks [2]. Guinea pigs exposed to toluene three times a day, for 3 days, developed redness of the skin and an increase in epidermal thickness [1].

Genotoxicity

Toluene consistently gave negative results in the Ames *Salmonella* assay. It was also negative in the mouse lymphoma assay and other in-vitro test systems [2]. In animals, there have been reports of DNA single-strand breaks and chromosomal aberrations when toluene was administered by injection. However, in-vivo studies have produced negative results [5]. It can be assumed that toluene does not have a mutagenic potential.

Carcinogenicity

There is no evidence suggesting carcinogenicity of toluene in experimental animals. A 2-year inhalation study in mice and rats did not report an increase in incidence of tumours. Repeated application of toluene to the skin of mice did not result in an increase in incidence of skin tumours [14].

Reproductive and developmental toxicity

In a two-generation reproduction study no adverse reproductive effects were reported in rats exposed to toluene by inhalation of 7,500 mg/m^3 (2,000 ppm) for 6 hours a day for up to 95 days). In a separate study a significant reduction in sperm count and weight of epididymides was recorded in male rats exposed to 7,500 mg/m^3 (2,000 ppm) for 6 hours a day for a total of 90 days. However, there were no significant changes in reproductive performance [1].

Toluene has been reported to be fetotoxic but not teratogenic [2]. Studies have shown that toluene can retard fetal growth and skeletal developmental and can alter the behavioural development of offspring [1,2]. In an inhalation study rats were exposed to 1,000 mg/m^3 for 8 hours a day on gestation days 1–21. There were no signs of maternal toxicity but there was a significant reduction in the fetal weight and a significant increase in retarded ossification in the offspring of the group exposed to toluene [2]. In a behavioural development inhalation study pregnant rats were exposed to 2,000 ppm (7,500 mg/m^3) of toluene for 60 minutes, three times a day on gestation days 12–17 [1]. The offspring of the exposed rats were assessed on postnatal days 1–20 and showed significant performance deficits in neurobehavioral tests of reflex development, muscle strength and motor coordination [1].

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