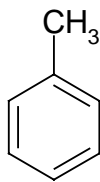


SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-88-3
Chemical Name	Toluene
Structural Formula	
<p style="text-align: center;">RECOMMENDATIONS</p> <p style="text-align: center;">The chemical is a candidate for further work.</p>	
<p style="text-align: center;">SUMMARY CONCLUSIONS OF THE SIAR</p> <p>Human Health</p> <p>Toluene is a toxicologically well-investigated chemical. Inhalation is the most important route of human exposure because of the high vapour pressure of the substance. Also absorption through the skin may however be of importance, because the substance passes the skin. Around 50 % is absorbed after inhalation. Adipose tissues may be a reservoir for toluene and concentrations in e.g. the brain are higher than in the blood. Toluene readily passes the placenta and is secreted into maternal milk. The half-life in human tissue may be up to three days. Toluene does not persist in the body. Around 20 % of absorbed toluene is eliminated via the expired air, whereas around 80 % is metabolised mainly in the liver by enzymatic oxidation and subsequent conjugation with glycine and glucuronic acid. It is excreted in the urine mainly as hippuric acid. Benzoylglucuronide may be formed and excreted at heavy exposure.</p> <p>Toluene has a low acute dermal, oral and inhalative toxicity, however it may cause sleepiness and dizziness, and general narcosis after inhalation of high concentrations. The chemical causes de-fatting and irritation of skin and some eye irritation, but does not cause skin sensitisation.</p> <p>A great number of repeated dose and chronic toxicity studies have been performed. An oral NOAEL of 625 mg/kg bw/day after 13 weeks of exposure has been observed in rats and mice. Neural cell death was observed in the rats in doses above the NOAEL. Lifetime inhalation exposure of rats caused degeneration of nasal epithelium and increased incidence of stomach ulcers with a NOAEC of 300 ppm and a LOAEC of 600 ppm. Other effects observed in laboratory animal inhalation studies include adaptive proliferation of the liver and long-lasting or irreversible ototoxicity, the latter being enhanced, when the animals were also exposed to certain other chemical agents or noise. A NOAEC of 700 ppm (2660 mg/m³) for hearing loss in rats has been established. Also for humans there is evidence that toluene may cause ototoxicity even though these studies do not allow establishment of a NOAEL or LOAEL. Long-term inhalative exposure has been shown to cause long lasting (> 6 months) effects on brain neurochemistry in rats and neuron loss in hippocampus, however these effects cannot readily be interpreted in functional terms. Several investigations on humans suggest that toluene, after inhalation of high concentrations may cause long-term effects on the brain / central nervous system, i.e. neuro-psychological effects. The evidence that toluene may cause or even the existence of "the organic solvent brain syndrome" is however disputed by some experts.</p> <p>Toluene has been tested for mutagenicity and other types of genotoxic effects in a multitude of <i>in vitro</i> and <i>in vivo</i> experiments and is evaluated as being non-mutagenic. The carcinogenicity of toluene has been investigated in two</p>	

inhalation studies in rats and mice respectively, and in a skin painting study in mice. The rat study was negative, non-malignant tumours were observed in the pituitary gland in the mice study, and malignant skin tumours occurred after skin application in mice at doses causing skin irritation. These effects were, however, not statistically significant. Toluene is evaluated as not carcinogenic.

Toluene did not affect rat fertility (NOAEC was 2000 ppm (7500 mg/kg/m³, 6h/day, 90 days)), but significantly decreased sperm count and epididymis weight. No human studies of the effects of toluene on sperm count are available, but limited human data fail to show clear indications of effects on fertility in men or menstrual function in women. Case studies of children born of women exposed to high toluene levels during pregnancy (via "sniffing") provide some evidence of human developmental toxicity (physical and neurological abnormalities). Two recent studies suggest an increased risk of spontaneous abortions associated with exposure to toluene at the workplace, one study gives an exposure level of 50-150 ppm, whereas the other study cannot be interpreted because of mixed exposure. The studies cannot be used to definitively establish a causal relationship between toluene exposure and late spontaneous abortions in humans, but suggest an increased risk. Rat inhalation studies provide strong evidence of developmental toxicity (lower birth weight and long-lasting developmental neurotoxicity) in the absence of maternal toxicity. The NOAEC for lower birth weight and delayed postnatal development is 600 ppm (2250 mg/kg/m³). A LOAEC for developmental neurotoxicity is 1200 ppm (4500 mg/kg/m³), whereas a NOAEC cannot be established.

The above-mentioned toxicological endpoints and their NOAELs and LOAELs, the severity of the effects seen, and the possible uncertainties concerning the effects have been taken into consideration in the evaluation of the various MOSes for the different types of human exposure situations considered in the risk characterisation.

Environment

Toluene is estimated to be stable to hydrolysis and photo-degradation in surface water. The photochemical oxidative degradation is measured to have a half-life of 1-2 days. Toluene is readily biodegradable, but simulation types of data suggest a decreased biodegradation at environmentally realistic low concentration in surface water: The half-life in Sewage Treatment Plants (STP) is estimated to be 0.0289 days (rate constant of 1hr⁻¹) and in surface water around 30 days. Only scarce data are available for degradation in soil, and the half-life is estimated to be 90 days under aerobic conditions according to "the realistic worst case" concept. Toluene has a low adsorption capacity with an estimated K_{oc} of 177 indicating a moderate to high mobility potential. The log K_{ow} 2.65 indicates a low bioaccumulation potential, which was confirmed in tests where BCF in two fish species were 13 and 90, respectively.

Toluene has been tested in a wide variety of aquatic species. Due to the nature of the substance (high volatility) only a few of the studies were considered valid. The acute toxicity to fish ranges from an LC₅₀ of 5.4 for Pink salmon to 26 mg/l for Fathead minnow. The lowest valid acute toxicity for *Daphnia magna* was 11.5 mg/l. Other crustaceans ranged from 3.5 mg/l for *Crangon franciscorum* to 33 mg/l for *Artemia salina*. For algae, the acute toxic EC₅₀ was not available in valid tests, but in two species (*Selenastrum capricornutum* and *Skeletonema costatum*) the NOECs were 10 mg/l. In absence of algae EC₅₀-values, the predicted values of 12.2 mg/l and 11mg/l were calculated using the QSAR-programmes ECOSAR and QTOXMIN, respectively. The long-term toxicity NOEC for fish ranged from 1.4 mg/l for *Oncorhynchus kisutch* to 4 mg/l for *Pimephales promelas*. The chronic NOEC for *Daphnia magna* ranged from 0.53 mg/l to 1.0 mg/l and for *Ceriodaphnia dubia* 0.74 mg/l. For the terrestrial compartment, the earthworm acute EC₅₀ was >150 but <280 mg/kg soil, NOEC values for mortality and cocoon production was ≤150 and <280 mg/kg, respectively, whereas a NOEC based on visual inspection was between 15 and 50 mg/kg soil. For plants, a yield decrease was observed in *Lactuca sativa* at 1000 mg/kg. For soil micro-organisms, NOEC for nitrification was <26 mg/kg soil dw. For micro-organisms in the STP, EC₅₀ for respiration was between 110 and 292 mg/l whereas EC₅₀ for nitrification was 84 mg/l. In regard to toxicity to green plants exposed via the air a NOEC of 60 mg/m³ after 14 days exposure has been observed.

An assessment factor of 10 was used to calculate a predicted no effect concentration (PNEC) for toluene in the aqueous environment since long-term data was present for fish, crustacea and algae: PNEC_{aqua} = 0.074 mg/l. For STP the most sensitive microbial process (nitrification) along with an assessment factor of 10 were used to derive the PNEC_{STP} = 8.4 mg/l. For the terrestrial environment, an assessment factor of 50 was used because of availability of two long-term tests on soil organisms: PNEC_{soil} = 0.3 mg/kg. Toluene may after reactions catalysed by light contribute to formation of ozone and other air pollutants in near surface atmosphere. Green plants, animals and humans seem roughly to be equally sensitive to the toxic effects of ozone.

Exposure

Toluene is a high production volume substance. In 1995, the production volume of toluene in EU was 2600 Ktonnes. Import and export volumes were imprecise, but the total EU consumption is estimated to be approximately 2800 Ktonnes (1995 value). Toluene occurs naturally and is present in crude oil. Most of the refinery streams containing toluene are used as a base or blending feedstock to produce motor gasoline. The commercial toluene is isolated from the refinery streams and is used as an intermediate in closed systems to manufacture other chemicals and as a solvent carrier in paints, thinners, adhesives, inks and pharmaceutical products and as an additive in cosmetic preparations. Toluene is used in a large number of industrial branches and consumer products.

Toluene may be released to the environment when substances containing toluene or preparations thereof are produced, distributed and handled. Besides the releases from use, distribution and handling of commercial toluene are the releases from natural sources (volcanoes, forest fires, etc.) and from the use and combustion of fuels. As these latter sources may well be of the same order or higher than releases from manufactured (isolated) toluene, they are likely to contribute as main sources for the observed background concentrations.

NATURE OF FURTHER WORK RECOMMENDED

In the context of the EU risk assessment programme, risk reduction measures are being considered for protection of human health and the environment. For human health, risk reduction is considered for consumers and for the workplace (production and use of toluene as well as of toluene containing products like glues, paints and other products). It is furthermore recommended that an in depth evaluation is performed under the appropriate EU Air Quality Directives regarding the contribution of toluene to the near ground atmospheric formation of ozone and other harmful air pollutants. For the environment, risk reduction is in the EU mainly considered for a number of downstream uses of toluene in relation to the aquatic and terrestrial environment.