

Toluene in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A “final task force” meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

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The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
EU	European Union
GLP	Good Laboratory Practices
IUPAC	International Union of Pure and Applied Chemistry
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organisation for Economic Co-operation and Development
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	105-88-3
Molecular formula:	C ₇ H ₈

The IUPAC name for toluene is methylbenzene.

1.2 Physicochemical properties¹ (US EPA, 1988; IARC, 1990)

<i>Property</i>	<i>Value</i>
Physical state	Clear, colourless liquid
Melting point	-95 °C
Boiling point	110.6 °C
Vapour pressure	3.78 kPa at 25 °C
Density	0.8623 g/cm ³ at 15.6 °C
Water solubility	535 mg/litre
Log octanol–water partition coefficient	2.69

1.3 Organoleptic properties

Toluene has a sweet, pungent, benzene-like odour. The lowest concentrations reported to be perceptible to humans on inhalation range from 0.64 to 139 mg/m³ (Van der Heijden et al., 1988). The odour threshold in water is 0.024–0.17 mg/litre. The reported taste threshold ranges from 0.04 to 0.12 mg/litre (Alexander et al., 1982; US EPA, 1988; ATSDR, 1989).

1.4 Major uses

Toluene is used as a solvent, especially for paints, coatings, gums, oils and resins, and as raw material in the production of benzene, phenol and other organic solvents and in the production of polymers and rubbers. Most toluene (in the form of benzene–toluene–xylene mixtures) is used in the blending of petrol (petrol combustion is a major source of emissions), and it also occurs as a by-product of styrene manufacture.

1.5 Environmental fate

Toluene degrades readily in air. It is removed from the atmosphere mainly by reactions with atomic oxygen, peroxy or hydroxyl radicals and ozone. Its half-life in the atmosphere ranges between 13 h and 1 day (Slooff & Blokzijl, 1988; IARC, 1990).

When toluene is released to surface water, it rapidly volatilizes to air, the half-life being about 5 h at 25 °C and increasing with the depth of the water column.

¹ Conversion factor in air: 1 ppm = 3.75 mg/m³.

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Biodegradation and sorption are less important for the removal of toluene from surface waters. The extent to which toluene is biodegraded in soil ranges from 63% to 86% after 20 days (Wilson et al., 1983). In soil, degradation half-lives of 3 and 2 days at 5 mg of toluene per kg of soil and 12 and 9 days at 200 mg of toluene per kg of soil at 14% and 100% moisture content, respectively, have been reported (Davis & Madsen, 1996). Anaerobic degradation also occurs, with up to 49% of radiolabelled toluene (6 mg of toluene per kg of soil) being removed (77% of this transformed to carbon dioxide) in 2 weeks (Haag et al., 1991).

The amount of toluene in environmental compartments can be estimated with the aid of models (Mackay & Leinonen, 1975) when emission data are known. In the Netherlands, for example, the estimated percentages of total toluene in air, water and soil are 98.6%, 0.8% and 0.6%, respectively (Slooff & Blokzijl, 1988).

2. ANALYTICAL METHODS

A purge-and-trap gas chromatographic procedure with photoionization detection can be used for the determination of toluene in water over a concentration range of 0.02–1500 µg/litre (US EPA, 1985a). Confirmation is by mass spectrometry (US EPA, 1985b). Methods for the determination of toluene in air, soil and other matrices have been reviewed and compiled by Fishbein & O'Neill (1988).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Mean atmospheric concentrations of toluene in urban areas around the world range from 2 to 200 µg/m³; concentrations are higher in areas with high traffic density. Lower levels (0.2–4 µg/m³) have been reported in rural areas. Indoor concentrations range from 17 to 1000 µg/m³ and are related to outdoor concentrations and to the presence of cigarette smoke (Slooff & Blokzijl, 1988; IARC, 1990).

3.2 Water

The concentration of toluene in rainwater in Germany has been reported to be 0.13–0.70 µg/litre (IPCS, 1985). In the Netherlands, a median value of 0.04 µg/litre was found (Slooff & Blokzijl, 1988).

Toluene was found at concentrations of 1–5 µg/litre in water samples from a number of rivers in the USA (IARC, 1990). Concentrations of 0.8 µg/litre and 1.9 µg/litre have been reported in the Rhine in Germany and Switzerland, respectively (Merian & Zander, 1982). Concentrations in the Morava River in Slovakia range from a winter maximum of 0.58 µg/litre to a summer maximum of 3.49 µg/litre (Al-Rekabi et al., 1996); in Spain, levels as high as 22 µg/litre have been detected at the mouth of the Besos River (Gomez-Belinchon & Grimalt, 1991). In coastal waters, levels of 0.01–1 µg/litre have been found (Wakeham et al., 1985).

In groundwater contaminated by point emissions, toluene levels of 0.2–1.1 mg/litre were reported (Loch et al., 1989). The highest level reported in groundwater in the USA in 1983 was 1.4 µg/litre (US EPA, 1988).

In approximately 1% of all groundwater-derived public drinking-water systems in the USA, toluene levels are above 0.5 µg/litre (US EPA, 1988). In Canada, in a study of 30 water treatment plants, drinking-water contained an average of 2 µg/litre (Otson et al., 1982). In a study of Ontario drinking-water, concentrations of up to 0.5 µg/litre were found (Smillie et al., 1978). Toluene can be leached from synthetic coating materials commonly used to protect drinking-water storage tanks (Bruchet et al., 1988).

3.3 Food

Toluene concentrations of 1 mg/kg have been reported in fish (US EPA, 1983). In cyclodextrin flavour complexes, residual concentrations can be in the range 2.7–10.2 mg/kg (Gerloczy et al., 1983).

3.4 Estimated total exposure and relative contribution of drinking-water

Although information on the intake of toluene via food and drinking-water is limited, it can be expected that this intake will be low compared with that via air. Studies in the Netherlands suggest that the population is exposed to at least 30 µg/m³. If a mean ventilation volume of 20 m³/day and an absorption of 50% are assumed, the daily absorption ranges from 0.3 to 12 mg (Slooff & Blokzijl, 1988). Exposure is increased by traffic and cigarette smoking.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

In humans, toluene is probably absorbed completely from the gastrointestinal tract after oral uptake. The compound is rapidly distributed in animals, and tissue distribution is comparable after administration by inhalation and by mouth. After uptake, the compound is preferentially found in adipose tissue, followed in succession by the adrenal glands, kidneys, liver and brain. Toluene is rapidly converted into benzyl alcohol by the microsomal mixed-function oxidase system in the liver, then to benzoic acid, which is conjugated with either glycine or glucuronic acid and excreted in urine as hippuric acid or benzoyl glucuronide. Toluene is also metabolized to a small extent to *o*- and *p*-cresol. In the lungs, part of the resorbed toluene is excreted unchanged (Van der Heijden et al., 1988).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Toluene has a low acute toxicity via the oral route; LD₅₀s in rats range from 2.6 to 7.5 g/kg of body weight. Toluene is irritating to the skin in rabbits (Exxon, 1988). In a

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recent study in guinea-pigs, a 100% solution was irritating, but a 50% solution was not (NOTOX, 1996). This study went on to evaluate skin sensitization using the maximization test (EU guideline B6), and toluene was not a skin sensitizer. Direct toluene instillation into the eye of rabbits resulted in slight irritation (findings did not trigger classification) in a GLP OECD guideline 405 study (Exxon, 1995).

5.2 Short-term exposure

In most short-term studies, toluene was administered by inhalation; liver enzyme induction, liver weight increase and neurophysiological changes are the main effects seen in these studies (Van der Heijden et al., 1988). Few oral studies are available, and only one is of value for assessment purposes. This study was carried out in groups of 10 male and 10 female F344 rats and B6C3F1 mice with doses of 0, 312, 625, 1250, 2500 or 5000 mg/kg of body weight per day administered 5 days per week for 13 weeks (US NTP, 1990).

In rats, all animals treated with 5000 mg/kg of body weight per day died in the first week. Increased liver and kidney weights (without concomitant histopathological changes) were the most sensitive effects, occurring at doses of 625 mg/kg of body weight per day and above; however, neuropathological effects in the brain, consisting of neuronal cell necrosis in the dentate gyrus and Ammon's horn of the hippocampus, were seen at 1250 and 2500 mg/kg of body weight per day. The NOEL in this rat study was 312 mg/kg of body weight per day and the NOAEL was 625 mg/kg of body weight per day, based on increased absolute and relative kidney weights (without histopathology).

In mice, an increased relative liver weight was the most sensitive effect, being present in females at the lowest dose tested, 312 mg/kg of body weight per day; in the absence of histopathology, it is likely to reflect adaptive change (US NTP, 1990). High-dose animals showed clinical signs of neurotoxicity, and myocardial degeneration was detected in several mice.

A second study reports ototoxicity in male Sprague-Dawley rats treated by oral gavage with 1.0 ml of toluene per kg of body weight per day (as toluene has a density of 0.876, this is equivalent to 876 mg/kg of body weight per day) for 8 weeks (Sullivan et al., 1997). This treatment caused loss of hair cells in the inner ear, and a NOAEL could not be established. Numerous other studies by the inhalation route report cochlear lesions and hearing loss in rats (Campo et al., 1997; Lataye & Campo, 1997).

5.3 Long-term exposure

In the only adequate toxicity study, toluene was administered via the inhalation route in rats. In this study, the only significant difference between the treatment groups and the control group was a decrease in blood haematocrit (erythrocyte volume fraction), observed at 380 and 1100 mg/m³ but not at 110 mg/m³ (exposure 6 h per day, 5 days per week) (Van der Heijden et al., 1988).

5.4 Reproductive and developmental toxicity

Toluene has been tested for teratogenicity via the inhalation route (in rats, mice and rabbits) and via the oral route (mice only). In the inhalation studies, embryotoxicity and fetotoxicity, but not teratogenicity, were observed at high dose levels (≥ 100 mg/m³) (IPCS, 1985). In one of the two oral studies, described in an abstract, in which toluene was administered 3 times a day by gavage to CD-1 mice on days 6–15 of gestation at doses of 0.3, 0.5 or 1 ml/kg of body weight (equal to 780, 1300 or 2600 mg/kg of body weight per day), increased embryonic mortality was observed at all doses; reduced fetal weight was observed at the top two doses, and a teratogenic effect (increased incidence of cleft palate) was observed at the highest dose level (780 mg/kg of body weight per day) (Nawrot & Staples, 1979; US EPA, 1994). In a behavioural study, Kostas & Hotchin (1981) exposed Nylar mice to concentrations of 0, 16, 80 or 400 mg of toluene per litre in drinking-water pre- and postnatally. Although effects on rotorod performance were noted in all groups, there was an inverse dose–response. No other adverse effects were noted, but there were inadequacies in the study that render it inadequate for risk assessment purposes (US EPA, 1994). A regulatory standard inhalation exposure developmental toxicity study at concentrations up to 11 250 mg/m³ has been conducted and showed reduced fetal weights and delayed ossification, but no increase in malformations; the NOAECs were 5600 mg/m³ for maternal toxicity and 2800 mg/m³ for developmental toxicity (Huntingdon Research Centre, year unknown). In a study compliant with OECD test guideline 426 for developmental neurotoxicity, prenatal toluene exposure (6750 mg/m³ from day 7 to day 20 of gestation) resulted in adverse neurobehavioural development and learning (Hougaard et al., 1999). No oral exposure developmental toxicity studies were located. In a 15-week inhalation range-finding study in rats conducted by the US NTP (1990), there were no effects on sperm morphology or vaginal cytology (estrous cycles).

5.5 Mutagenicity and related end-points

Toluene was found to be non-genotoxic in a number of *in vitro* systems (bacteria, yeast, mammalian cells). *In vivo* studies on insects, rats and mice have yielded conflicting results; chromosomal aberrations in rat bone marrow cells were observed in some studies but not in others, possibly as a result of contamination with benzene. In mice, the induction of micronuclei in erythrocytes was observed, but not consistently. In more recent studies, toluene failed to induce sister chromatid exchange *in vitro* or *in vivo* in human lymphocytes (Richer et al., 1993) and did not induce micronuclei *in vitro* in human lymphocytes (Zarani et al., 1999). It has been concluded that toluene has not been demonstrated to be genotoxic (IPCS, 1985; Van der Heijden et al., 1988).

5.6 Carcinogenicity

In an inhalation study in rats exposed to 110, 380 or 1100 mg/m³, 6 h per day, 5 days per week, no clear evidence for the carcinogenicity of toluene was found; the same

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results were found in several special carcinogenicity studies, all of which, however, were very limited in design (Van der Heijden et al., 1988). In an adequate inhalation carcinogenicity study carried out in rats and mice, no evidence for a carcinogenic effect was found at dose levels up to 4500 mg/m³ (US NTP, 1990). In a dermal carcinogenicity study in male mice (pure toluene application at a dose of 50 µl twice per week), irritation occurred with a concomitant slight (statistically non-significant) increase in skin tumours (Broddle et al., 1996). A study of rotogravure printers exposed to toluene over the period 1925–1985 (measurements indicated toluene concentrations of 1700 mg/m³ throughout the 1940s and 1950s, falling to 110 mg/m³ in the mid-1980s) did not show any consistent increase in cancers (Svensson et al., 1990).

6. EFFECTS ON HUMANS

Virtually all the available data relate to exposure to toluene by inhalation. For acute exposure, the predominant effects were impairment of the central nervous system and irritation of mucous membranes. Fatigue and drowsiness were the most sensitive effects, being present at 375 mg/m³ and absent at 150 mg/m³. The toxic effects of toluene after long-term exposure are basically the same. There have been few controlled long-term studies via the oral and inhalation routes (Andersen et al., 1983; IPCS, 1985; Van der Heijden et al., 1988).

Studies designed to detect a possible increase in the frequency of chromosomal aberrations or sister chromatid exchanges in the peripheral lymphocytes of people occupationally exposed to toluene have yielded inconclusive results (IPCS, 1985; Van der Heijden et al., 1988; IARC, 1990); however, recent studies have failed to detect evidence of clastogenicity in human lymphocytes exposed *in vitro* or *in vivo* (Richer et al., 1993; Zarani et al., 1999). Epidemiological studies on the occurrence of cancer as a consequence of exposure of human populations to toluene alone are not available (Van der Heijden et al., 1988).

7. GUIDELINE VALUE

IARC (1990) concluded that there is inadequate evidence for the carcinogenicity of toluene in both experimental animals and humans and classified it in Group 3 (not classifiable as to its carcinogenicity to humans).

The evidence on the toxicity of toluene supports the use of a TDI approach to derive the guideline value. The NOEL from a 13-week gavage study in rats (US NTP, 1990) was 312 mg/kg of body weight per day (administration 5 days per week); this dosage level had marginal effects in an identical study in mice. A TDI of 223 µg/kg of body weight can be derived using the LOAEL for marginal hepatotoxicity in mice of 312 mg/kg of body weight per day (equivalent to 223 mg/kg of body weight per day for 7 days per week dosing) and applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the short duration of the study and use of a LOAEL instead of a NOAEL). This TDI yields a guideline value of 700 µg/litre (rounded

figure), allocating 10% of the TDI to drinking-water. It should be noted, however, that this value exceeds the lowest reported odour threshold in water of 24 µg/litre.

Aeration and air stripping are effective methods for toluene removal to concentrations well below the guideline value; toluene is also removed by granular activated carbon and by ultraviolet with hydrogen peroxide.

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