Contaminants in soil: updated collation of toxicological data and intake values for humans
Toluene

Better Regulation Science Programme
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Steve Killeen

Head of Science
Executive summary

This report, one of a number on the assessment of risks to human health from contaminants in soil, presents key data and expert opinions on the toxicology and intake of toluene. It provides an update to an earlier report by the Department for Environment, Food and Rural Affairs (Defra) and the Environment Agency published in March 2004.

The report is based on findings from a literature search made during August 2008. These findings, together with evaluations of national, European and international expert groups, are used to recommend Health Criteria Values (HCVs) and to estimate mean daily intakes (MDIs) for toluene in the UK.

Chemical overview

Toluene is a colourless, volatile liquid at ambient temperature and pressure. It is used in the manufacture of many organic chemicals and products. The major toluene releases into the environment are into the atmosphere, but small amounts are released in industrial wastewater and into soils through land disposal of sludges and petroleum wastes. Toluene is only slightly soluble in water, but is miscible with most organic solvents. Owing to its volatility, toluene is lost from soil and water by volatilisation. It can also be degraded in soil by a number of bacterial species.

Toluene is commonly encountered with the similar aromatic chemicals benzene, ethylbenzene and xylene, collectively termed BTEX.

Pharmacokinetics

Evidence from human studies indicates about 50% of inhaled toluene is absorbed into the bloodstream, while gastrointestinal absorption is nearly complete. Absorption through the skin is slow. Absorbed toluene is distributed rapidly throughout the body. It crosses the placenta and is found in the foetus at concentrations about 75% of that in the maternal blood.

Toluene metabolism is similar in humans and laboratory animals and is catalysed by a series of cytochrome P450 enzymes; thus the liver is expected to be the primary site of metabolism. The main route of excretion of absorbed toluene is in the urine. A smaller proportion is eliminated unchanged in expired air. Toluene is also secreted into breast milk.

Toxicity

The central nervous system (CNS) is the most sensitive target of chronic inhalation exposure of humans to toluene. Subtle signs of neurotoxicity are induced in workers by long-term occupational exposure to atmospheric toluene concentrations in the region of 150–495 mg m⁻³. There has been a suggestion that a mild neurotoxic effect also occurred in one study group at around 128 mg m⁻³, but in general no neurotoxic effects have been seen at such workplace exposures.

Repeated oral administration of high doses of toluene, five days per week for 13 weeks, produced overt nervous system toxicity in rats and mice, and brain, bladder, liver and kidney injury in rats. Increases in kidney and liver weight were recorded in rats repeatedly given 625 mg kg⁻¹ bw whereas liver weights were increased in mice repeatedly given 312 mg kg⁻¹ bw. Slight changes in brain biochemistry have been seen in mice receiving 5 mg kg⁻¹ bw day⁻¹ orally for four weeks.

High and maternally toxic inhalation exposures are probably toxic to the human foetus. There is a limited indication that occupational exposures of around 330 mg m⁻³ can
Contaminants in soil: updated collation of toxicological data and intake values for humans. Toluene

Increase the risk of miscarriage. Developmental toxicity has been reported in rats repeatedly exposed to toluene by inhalation to 3,750–4,500 mg m⁻³ in the absence of maternal toxicity.

There is no convincing indication that toluene is likely to be either genotoxic or carcinogenic in humans.

Health Criteria Values and risk assessment

Based on the CNS effects seen in workers exposed to toluene, an inhalation TDI (TDIinh) of 1,400 µg kg⁻¹ bw day⁻¹ (1.4 mg kg⁻¹ bw day⁻¹) is recommended here for the purpose of developing SGVs.

Toxicity data from repeated oral exposure are not available for humans. Based on the organ weight effects seen in 13-week experimental animal studies, an oral tolerable daily intake (TDIoral) of 223 µg kg⁻¹ bw day⁻¹ is recommended here.

No authoritative assessments of the health risks posed by dermal exposures to toluene were identified. In view of the slower absorption of toluene through the skin than via the gastrointestinal tract, and the absence of an indication of any notable first-pass detoxification metabolism following oral absorption, it is reasonable to assume that the oral HCV value can be used for a conservative rudimentary dermal risk assessment.

Both ingestion and inhalation of toluene can give rise to neurotoxicity. This should therefore be considered in a risk assessment of toluene.

Mean daily intakes from non-soil sources

Relative to the TDIinh, background inhalation exposure to toluene in ambient air is low; the inhalation mean daily intake (MDIinh), at 520 µg day⁻¹, occupies only a very small fraction of the TDIinh. Background oral exposure to toluene from its presence in food and water is also low, and the oral mean daily intake (MDIoral), at 10 µg day⁻¹, similarly occupies only a very small fraction of the TDIoral (see table below).

HCV and MDI values for toluene

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Oral</th>
<th>Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>µg day⁻¹</td>
<td>10</td>
<td>520</td>
</tr>
<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>0.14</td>
<td>7.4</td>
</tr>
<tr>
<td>MDI for 20-kg child</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>0.37 a</td>
<td>19.3 a</td>
</tr>
<tr>
<td>TDI</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>223</td>
<td>1,400</td>
</tr>
</tbody>
</table>


Summary of changes to HCV recommendations

The TDIinh of 1,400 µg kg⁻¹ bw day⁻¹ recommended here is much larger than the value (of 74 µg kg⁻¹ bw day⁻¹) recommended in the 2004 report. This is due to the availability of more extensive occupational data giving a greater level of insight and confidence into the understanding of the dose–response of inhaled toluene in humans.

The TDIoral of 223 µg kg⁻¹ bw day⁻¹ recommended here is essentially the same as previously recommended (200 µg kg⁻¹ bw day⁻¹) – the earlier figure was rounded to one significant figure.
Acknowledgements

This document was initially written by RPS Group plc and has subsequently been updated, in 2002 by the MRC Institute for Environment and Health and in 2008 by bibra. Entec UK Ltd provided assistance in the management and delivery of the initial document. The Environment Agency is also grateful for the valuable inputs from various government agencies and departments, particularly the Department of Health, Health Protection Agency and Food Standards Agency.
## Contents

1. **Introduction**  
1.1 Update to R&D Publication TOX 14  
1.2 Background  
1.3 Advice on using this report  

2. **Chemical overview**  

3. **Toxicity**  
3.1 Literature sources  
3.2 Pharmacokinetics  
3.3 Acute toxicity  
3.4 Repeated dose toxicity  
3.5 Reproductive and developmental toxicity  
3.6 Genotoxicity  
3.7 Carcinogenicity  
3.8 Summary  

4. **Derivation of Health Criteria Values**  
4.1 Joint WHO/FAO Expert Committee on Food Additives  
4.2 WHO guidelines for drinking-water quality  
4.3 WHO air quality guidelines for Europe  
4.4 EU Risk Assessment Report  
4.5 EU Indoor Exposure Limits  
4.6 United States Environmental Protection Agency  
4.7 US Agency for Toxic Substances and Disease Registry  
4.8 Dutch National Institute for Public Health and the Environment  
4.9 Discussion  

5. **Background intake**  
5.1 Food  
5.2 Water  
5.3 Air  
5.4 Other sources  
5.5 Mean daily intakes  

6. **Conclusions**  

References  
List of abbreviations
Appendix – Literature search

Tables
Table 2.1 Physical-chemical parameters for toluene (Environment Agency, 2008) 5
Table 6.1 HCV and MDI values for toluene 21

Figures
Figure 2.1 Structure of toluene 4
1 Introduction

1.1 Update to R&D Publication TOX 14

This report presents key data and expert opinion on the human toxicology and non-soil intakes of toluene. It updates and replaces R&D Publication TOX 14 published in March 2004 (Defra and Environment Agency, 2004a), taking into account:

- updates to the toxicological framework document which describes how the human toxicity of chemical soil contaminants is assessed (Environment Agency, 2009);
- further review of the scientific literature on the toxicology of toluene and the findings and opinion of national, European, and international expert groups up to August 2008 (see Appendix).

1.2 Background

The main purpose of this report is to provide technical guidance to regulators and their advisors in support of the statutory regimes addressing land contamination, particularly Part 2A of the Environmental Protection Act 1990 and development control under the Town and Country Planning Acts.

Part 2A defines the term contaminated land according to whether or not it poses a significant risk to human health and/or the environment.

In relation to health effects not attributable to radioactivity, it considers land to be contaminated land where it:

“...appears to the local authority in whose area the land is situated to be in such a condition by reason of substances in, on or under the land that (a) significant harm [to human health] is being caused or there is a significant possibility of such harm being caused.”

Statutory guidance (Defra, 2006) explains that significant harm to a person would include such health effects as death, disease, serious injury, genetic mutation, birth defects or the impairment of reproductive function. The definition of significant harm therefore encompasses a broad range of possible health outcomes from chemical exposure.

Land contamination is a material consideration within the planning regime. A planning authority has to consider the potential implications of contamination both when it is developing structure or local plans (or unitary development plans) and when it is considering applications for planning permission. Planning Policy Statement 23: Planning and Pollution Control (PPS 23) (ODPM, 2004) explains the relationship between planning and Part 2A. In the granting of planning permission for new development including permission to carry out remediation, PPS 23 states that remediation must remove unacceptable risk to human health and make the site suitable for its intended use. As a minimum, after carrying out a development and

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1 For the purpose of the Statutory Guidance, disease is taken to mean an unhealthy condition of the body or part of it and can include, for example, cancer, mental dysfunction, liver dysfunction or extensive skin ailments.
commencement of its use, the land should not be capable of being determined as *contaminated land* under Part 2A.

1.3 Advice on using this report

This report reviews the key toxicological literature and expert opinion on health effects arising from exposure to toluene. It has been prepared by the Environment Agency with the support of the Health Protection Agency (HPA) and the Food Standards Agency (FSA).

This report recommends one or more Health Criteria Values (HCVs) for use in assessing the risks to health from long-term human exposure to toluene in soil. HCVs are a critical part of the risk assessment process. They are used subsequently in the derivation of Soil Guideline Values (SGVs), which are scientifically-based generic assessment criteria (GAC) used to simplify the screening of land contamination (Defra and Environment Agency, 2004b). HCVs can also be used to derive site-specific assessment criteria for soil as part of any Detailed Quantitative Risk Assessment (DQRA).

The HCVs set out in this report represent levels of minimal or tolerable risk from long-term human exposure to chemicals in soil. They represent a baseline and health protective position to minimise risks of *significant harm*. They do not represent thresholds above which there is an *unacceptable intake* or a *significant possibility of significant harm* in the context of Part 2A, but they can be a useful starting point for such an assessment (Defra, 2008). Science alone cannot answer the question of whether or not a given possibility of *significant harm* is significant, since what is either significant or unacceptable is a matter of socio-political judgment and the law entrusts decisions on this to the enforcing authorities (Defra, 2008).

In the context of Part 2A, an assessor using the HCVs in this report can conclude that (Defra, 2008):

- human exposure at or below the HCV is unlikely to represent a *significant possibility of significant harm*;
- human exposure above the HCV might represent a *significant possibility of significant harm*, with the significance linked to the margin of exceedance, the duration and frequency of exposure, and other factors that the enforcing authority may wish to take into account.

The information presented in this report is intended for technical professionals familiar with assessment of the risks posed to human health by land contamination. It should be read in conjunction with Science Report SC050021/SR2 *Human Health Toxicological Assessment of Contaminants in Soil* (Environment Agency, 2009), which introduces and describes the terms and general technical approaches used in this review of toluene.

Although HCVs are an important quantitative tool for judging the health risks associated with a particular level of human exposure, they should not be used in isolation from the rest of the information presented in this report. Further understanding of the mechanisms of toxicity and the range of potential health effects are important to assessing the risks posed by toluene at any level of exposure, both individually and when combined with other chemicals present.

The remainder of this report is separated into the following sections.

Section 2 provides a short overview of the chemistry of toluene, its main uses and its behaviour in the environment with particular reference to soils.
Section 3 presents information obtained from the literature search on the toxicity of toluene (pharmacokinetics, acute toxicity, repeated dose toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity).

Section 4 sets out the HCVs derived by various expert groups worldwide.

Section 5 gives estimates of exposure to background levels of toluene in food and water, air and other sources.

Section 6 presents the conclusions drawn from the literature review including the recommendations for HCVs for toluene.
2 Chemical overview

Toluene (CAS No. 108-88-3) (Figure 2.1) is a colourless, volatile liquid at room temperature and ambient pressure. It is only slightly soluble in water, but is miscible with most organic solvents (ATSDR, 2000). Table 2.1 provides some standard physical-chemical property information for toluene.

Toluene’s vapour has an aromatic (benzene-like) odour, and forms explosive mixtures with air (IPCS, 1986). Technical grade toluene can contain benzene at levels of up to 0.02% w/w (EU-JRC, 2003).

![Structure of toluene](image)

Figure 2.1 Structure of toluene

Toluene is used as a feedstock for the manufacture of many organic chemicals (including benzene, xylene and phenol) and products such as detergents, pharmaceuticals and dyes (Nielsen and Howe, 1991). It is also added to petrol at an average concentration of 5–7% in order to improve octane ratings (ATSDR, 2000) – people filling their vehicles with petrol at garages and service stations experience short-term exposure to toluene via inhalation (ATSDR, 2000).

The major toluene releases into the environment arise from toluene production processes; the distribution, sale and use of petrol in, and subsequent emissions from, motor vehicles; and the use of toluene as a solvent (IPCS, 1986; ATSDR, 2000). Although almost all of this toluene is discharged directly into the atmosphere, small amounts are released in industrial wastewater and into soils through land disposal of sludges and petroleum wastes (ATSDR, 2000).

Toluene levels indoors are usually higher than those outdoors and arise from smoking, household products (e.g. paints, thinners and glues) and the infiltration of car emissions – sometimes from integral garages. Cigarette smoke is likely to contribute the major part of the daily uptake of toluene for a heavy smoker (see Section 5).

Owing to its volatility, the majority of toluene released to the environment will partition to air (ATSDR, 2000). Consequently, toluene is lost from soil and water by volatilisation. Toluene can also be degraded in soil by a number of bacterial species (ATSDR, 2000). It can also be rapidly broken down in the atmosphere, by reaction with hydroxyl radicals, depending upon atmospheric conditions (ATSDR, 2000).

Collectively termed BTEX, toluene is commonly encountered with the similar aromatic chemicals benzene, ethylbenzene and xylene.
Where studies have reported atmospheric toluene levels in ppm, a conversion factor of 1 ppm = 3.75 mg m\(^{-3}\) (IPCS, 1986) has been used to ensure consistency in units throughout this report.

Table 2.1  Physical-chemical parameters for toluene (Environment Agency, 2008)

<table>
<thead>
<tr>
<th>Chemical property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C(_6)H(_5)CH(_3)</td>
</tr>
<tr>
<td>Molecular weight (g mol(^{-1}))</td>
<td>92.14</td>
</tr>
<tr>
<td>Physical state at room temperature</td>
<td>Liquid</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>-95.0</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>110.7</td>
</tr>
<tr>
<td>Water solubility (mg L(^{-1}), at 25°C)</td>
<td>590</td>
</tr>
<tr>
<td>Octanol-water partition coefficient (log K(_{OW}))</td>
<td>2.73</td>
</tr>
<tr>
<td>Vapour pressure (Pa, at 10°C)</td>
<td>1,730</td>
</tr>
<tr>
<td>Henry’s law constant (Pa m(^{3}) mol(^{-1}), at 25°C)</td>
<td>660</td>
</tr>
</tbody>
</table>
3 **Toxicity**

3.1 **Literature sources**

Reviews of the literature on the toxicity of toluene have been carried out by:

- Health and Safety Executive (HSE, 1989)
- Health Protection Agency (HPA, 2007)
- International Programme on Chemical Safety (IPCS, 1986)
- International Agency for Research on Cancer (IARC, 1989, 1999)
- US Environmental Protection Agency (USEPA, 2005a, 2005b)
- US Agency for Toxic Substances and Disease Registry (ATSDR, 2000)

This section is largely based on these reviews. Those studies used in deriving HCVs receive particular mention in this report. In general the primary literature was not consulted.

3.2 **Pharmacokinetics**

3.2.1 **Absorption**

A number of investigations in humans have shown that at rest a three-hour exposure to toluene vapour will result in an uptake amounting to about 50% of the inhaled toluene (EU-JRC, 2003). The time to reach a steady state between the lung and the bloodstream has been variously reported to be from 13 minutes to two hours (ATSDR, 2000). The only study found on the uptake of toluene in humans after oral exposure indicated close to 100% absorption (Baelum *et al.*, 1993).

Laboratory animal studies indicate similar levels of absorption after ingestion and inhalation, although absorption is less rapid after ingestion (ATSDR, 2000). Evidence in mice suggests that toluene may be absorbed through the olfactory bulb (Ritchie *et al.*, 2001).

Toluene is absorbed slowly through the human skin. The rate of absorption of liquid toluene through forearm skin was reported to be in the range of 14 to 23 mg cm\(^{-2}\) hour\(^{-1}\) (Dutkiewicz and Tyras, 1968).

3.2.2 **Distribution**

Human and laboratory animal studies (mostly concerned with inhalation exposure) show that, after absorption, toluene is distributed rapidly throughout the body, with the highest concentrations occurring in lipid-rich tissues (e.g. adipose tissue, brain and bone marrow) and highly vascular tissues (e.g. liver and kidney).

Toluene passes across the placenta easily and is found in the foetus in concentrations of about 75% of that found in the mother's blood (EU-JRC, 2003).
3.2.3 Metabolism

Toluene metabolism is similar in humans and laboratory animals (IARC, 1999). Some 60–75% of absorbed toluene is metabolised in the liver to benzoic acid, which may conjugate with glycine to form hippuric acid (IPCS, 1986; HSE, 1989). A relatively small amount (variably reported as 3–20%) of absorbed toluene is converted to benzoyl glucuronide and even smaller amounts form cresols (ATSDR, 2000). Toluene metabolism is catalysed by a series of cytochrome P450 (CYP) isozymes; thus the liver, with its high concentration of CYP isozymes, is expected to be the primary site of toluene metabolism (ATSDR, 2000).

3.2.4 Excretion

The main route of excretion of absorbed toluene is in the urine – principally as hippuric acid, but also as benzoyl glucuronide and sulphate or glucuronide conjugates of cresols (IPCS, 1986; ATSDR, 2000). A smaller proportion (variably reported as 7–20%) is eliminated unchanged in expired air (ATSDR, 2000). Toluene is also secreted into breast milk (EU-JRC, 2003). Kinetic data indicate that most absorbed toluene is eliminated rapidly from the body and a smaller portion (that which enters adipose tissue) is eliminated more slowly (ATSDR, 2000). The elimination of toluene from adipose tissue is much faster in the rat than in humans (EU-JRC, 2003).

3.3 Acute toxicity

The toxicity of toluene after short-term inhalation exposure appears to be primarily limited to the central nervous system (CNS). Short-term human exposures to quantities of toluene sufficient to produce unconsciousness and possible brain damage do not, generally, harm other body organs. Of the approximately 100 cases of death from volatile solvent abuse per year reported in the UK, about 25% are caused by adhesive solvent, which is considered to be mainly toluene (Ramsey et al., 1989). It has been suggested that levels of 1,500–2,250 mg m$^{-3}$ are needed to achieve the euphoric effects sought by abusers and that actual levels experienced by abusers are likely to be up to 10 times higher than this (Bukowski, 2001) – USEPA (2005b) suggests levels of 1,000–10,000 ppm (3,750–37,500 mg m$^{-3}$) are typical.

In volunteers, exposure for seven hours to 281 mg m$^{-3}$ resulted in an impaired neuropsychological function, and caused headache and mucosal irritation (Echeverria et al., 1989). These adverse effects were not detected in 16 volunteers exposed for six hours to 150 mg m$^{-3}$ (Andersen et al., 1983).

For inhalation exposure in rats, the 4-hour LC$_{50}$ value was 28,100 mg m$^{-3}$ (BASF, 1980).

Only one study on the acute effects of oral exposure in humans was identified. A 51-year-old man died after ingesting about 60 mL of liquid toluene – approximately 625 mg kg$^{-1}$ bodyweight (bw). Although the probable cause of death was severe depression of the CNS, the autopsy also revealed damage to the heart, liver, lungs and kidney (Ameno et al., 1989).

The oral LD$_{50}$ in rats was 5,580 mg kg$^{-1}$ bw (Withey and Hall, 1975).

The LD$_{50}$ value for dermal toxicity in the rabbit was 12,400 mg kg$^{-1}$ bw (Smyth et al., 1969).
3.4 Repeated dose toxicity

3.4.1 Inhalation exposure

Toxicity to the CNS is the primary human health concern following medium- and long-term inhalation exposure to toluene. Chronic toluene abuse by, for example, glue sniffer, is associated with neurotoxic symptoms, narcosis, permanent damage to the nervous system and death (Ramsey et al., 1989). There is also some limited indication that long-term occupational exposure to toluene may lead to organic brain syndrome (EU-JRC, 2003) – a generic term referring to impaired mental function as a result of disease or damage to the brain.

There is a substantial body of evidence for a relationship between less severe neurological effects and toluene exposure in humans. USEPA (2005a) identified ten key studies of individuals that were chronically exposed to toluene but probably to no other solvent, and in which neurological endpoints were examined by accepted testing procedures and comparisons were made to unexposed control groups (Foo et al., 1990; Nakatsuka et al., 1992; Abbate et al., 1993; Murata et al., 1993; Vrca et al., 1995; Boey et al., 1997; Zavalic et al., 1998a; Eller et al., 1999; Cavalleri et al., 2000; Neubert et al., 2001). Various subtle neurological effects (such as headache, dizziness, impairment of colour vision, neurological and psychomotor functioning) were reported at 150–495 mg m\(^{-3}\). Four studies (Nakatsuka et al., 1992; Zavalic et al., 1998a; Eller et al., 1999; Neubert et al., 2001), in the view of USEPA (2005a), found no evidence of neurotoxicity in workers exposed to an average toluene concentration of 128 mg m\(^{-3}\).

In contrast, the opinion of ATSDR (2000) was that there were still indications of mild neurotoxicity, as indicated by deficits in colour vision, in Croatian workers exposed to a geometric mean concentration of approximately 128 mg m\(^{-3}\) (Zavalic et al., 1998a, 1998b). The increased colour confusion index in exposed workers was considered to be a less serious adverse effect (ATSDR, 2000).

The study by Foo et al. (1990, 1993) has been used by some expert groups (see Section 4.3 and 4.8) as the sole critical study in the derivation of HCVs. The study was a cross-sectional study of 30 female workers exposed for 5.7 ± 3.2 years (average ± SD) to a mean average toluene concentration of 88 ppm (332 mg m\(^{-3}\)) and 30 matched control females exposed for 2.5 ± 2.7 years to 13 ppm (49 mg m\(^{-3}\)). Statistically significant differences were seen between the two groups in six out of the battery of eight neurobehavioural tests the workers completed. Linear regression of individual test results and personal exposure concentrations also indicated performance was related to toluene exposure (USEPA, 2005b).

A 2005 meta-analysis of studies investigating the neurobehavioural effects of occupational exposure to toluene (Meyer-Baron, 2005) concluded that, while most of the pooled analyses showed a negative impact of toluene exposure (as assessed by neuropsychological tests), none showed a statistically significant effect at averaged exposure levels between 33 and 89 ppm (124 and 334 mg m\(^{-3}\)).

A 2006 study of Taiwanese workers (Chang et al., 2006) concluded that occupational noise-related hearing loss is exacerbated by concurrent exposure to toluene at concentrations of 33 ppm (124 mg m\(^{-3}\)). However, this was a small study and there was no investigation of the effects of toluene alone. Other studies – both of humans and experimental animals – have shown similar ototoxic effects, but the existing evidence does not allow characterisation of the dose–response in humans (Hoet and Lison, 2008).
There is some evidence for effects on other tissues or organs, including the peripheral nervous system, liver, kidney and haematopoietic system (ATSDR, 2000; Jacob et al., 2007). Toluene is also an irritant to the nose, throat and eyes (ATSDR, 2000); though in general the data suggest that these effects occur only at dose levels greater than the lowest-observed adverse effects levels (LOAELs) for CNS effects.

### 3.4.2 Oral exposure

There is a lack of human oral toxicity data for toluene. In a 13-week rat study, groups of 10 males and 10 females were given toluene by stomach tube for five days a week at dose levels of 0, 312, 625, 1,250, 2,500 or 5,000 mg kg\(^{-1}\) bw (equivalent to 0, 223, 446, 900, 1,800 or 3,600 mg kg\(^{-1}\) bw day\(^{-1}\)). All animals in the highest dose group died within the first week. Overt nervous system toxicity (prostration, hypoactivity, ataxia and body tremors), and damage to the brain, urinary bladder, liver (hepatocellular hypertrophy) and kidney (nephrosis and changes in the tubular epithelium) occurred in the higher dose groups.\(^2\) Brain abnormalities were present from 1,250 mg kg\(^{-1}\) bw. Increases in liver and kidney weight were seen at doses of 625 mg kg\(^{-1}\) bw and above. There was no evidence of treatment-related changes in the rats receiving 312 mg kg\(^{-1}\) bw (NTP, 1990).

High-dose overt toxicity to the nervous system was the main finding of the corresponding study in mice. Again groups of 10 males and 10 females received doses of 0, 312, 625, 1,250, 2,500 or 5,000 mg kg\(^{-1}\) bw, five days a week for 13 weeks. There were increases in (relative) liver weight in the females at all doses. Histological examination of tissues from a range of organs (including the brain, urinary bladder, liver and kidneys) revealed no treatment-related effects (NTP, 1990).

Alterations in the levels of biogenic amines were recorded in various regions of the brain of male mice given toluene in drinking-water for 28 days (Hsieh et al., 1990a, 1990b). Some effects were seen even in the five males receiving the lowest dose of 5 mg kg\(^{-1}\) bw day\(^{-1}\) and this was described as a “minimal LOAEL” by ATSDR (2000) (see Section 4.7). USEPA (2005b), in contrast, did not judge the study to be of any major importance in its assessment, simply noting that the biochemical changes have not been correlated with behavioural or neuropsychological effects. Other reports from the same research team (Hsieh et al., 1989, 1990c, 1991), which described suppressed immune responses in mice given toluene orally, were one of the reasons USEPA applied an additional Uncertainty Factor (UF) of 3 in its derivation of its oral Reference Dose (RfD) (see Section 4.6). None of the studies by the Hsieh team featured in the EU Risk Assessment Report (RAR) (EU-JRC, 2003).

### 3.5 Reproductive and developmental toxicity

Two studies have suggested an increased risk of miscarriage to be associated with exposure to toluene in the workplace (Ng et al., 1992; Taskinen et al., 1994), although this has not been supported by animal data (ATSDR, 2000). The estimated exposure of the women studied by Ng et al. (1992) was about 330 mg m\(^{-3}\) (range 190–560 mg m\(^{-3}\)). Overall, current data do not provide convincing evidence that adverse reproductive effects may occur following exposure to toluene (ATSDR, 2000).

\(^2\) The available information on the pathology of the liver and kidney of the treated animals is confused. USEPA (2005b), supposedly citing the full National Toxicology Program (NTP) report, describes injury to the liver (hepatocellular hypertrophy) and kidney (nephrosis and changes in the tubular epithelium). The EU Risk Assessment Report (EU-JRC, 2000) correctly notes that the NTP report does not mention any liver and kidney injury in the toluene-treated rats of the 13-week study. It must be assumed that the USEPA evaluators obtained more detailed information on the study findings from the NTP staff.
Case studies of pregnant women who had been exposed by inhalation to very high levels of toluene through habitual solvent abuse (glue sniffing) provide evidence of developmental toxicity such as premature delivery, congenital cranio-facial, limb, cardiac, renal and CNS malformation, although confounding factors such as alcohol and tobacco were not taken into account. The physical and neurological abnormalities seen in their infants resembled those seen in foetal alcohol syndrome (Donald et al., 1991; Bukowski, 2001; EU-JRC, 2003).

Rat inhalation studies provide strong evidence of developmental toxicity (lower birth weight and long-lasting developmental neurotoxicity) in the absence of maternal toxicity. The effective dose levels were 3,750 mg m$^{-3}$ or higher. The no-observed adverse effect level (NOAEL) for lower birth weight and delayed postnatal development was 2,250 mg m$^{-3}$ (Thiel and Chahoud, 1997). The LOAEL for developmental neurotoxicity was 4,500 mg m$^{-3}$; no NOAEL was determined (Hass et al., 1999). More limited studies in mice suggest a similar development toxic potential (EU-JRC, 2003).

Under EU regulations, toluene is classified as a Category 3 reproductive toxicant (substances which cause concern for humans owing to possible developmental effects) and has been assigned the risk phrase R63 (possible risk to unborn child) (HPA, 2007; ECSIS, 2008).

### 3.6 Genotoxicity

Well-conducted Ames tests using methodology suited to the testing of a volatile liquid have shown no evidence of mutagenic potential in *Salmonella typhimurium*. Furthermore, toluene at non-cytotoxic concentrations did not induce mutations, chromosomal damage (micronuclei) or DNA damage in mammalian cells in culture. In *in vivo* studies where benzene contamination can be excluded, toluene did not produce chromosomal damage in the bone marrow of rodents or DNA damage in the peripheral blood, bone marrow and liver of mice. Dominant lethal assays in mice have also failed to detect evidence of mutagenic potential. Although a few occupational studies have shown an increased incidence of chromatid breaks, micronuclei, and sister chromatid exchanges, the evidence was confounded by exposure to other organic chemicals and limited by small cohort size and a lack of historical monitoring data. “On balance, toluene can be considered to be non-genotoxic” (EU-JRC, 2003).

### 3.7 Carcinogenicity

An IARC Working Group in 1998 was aware of six cancer epidemiology studies related to occupational exposure to toluene, and two involving exposure of the general population. Considering the multiple chemical exposures that were a feature of most of the studies and the lack of inter-study consistency, the Working Group decided that these results “were not strong enough to conclude that there is any association [between cancer risk and toluene exposure]” (IARC, 1999).

Toluene has been tested for carcinogenicity by inhalation in mice and rats. In both species, groups of 60 males and 60 females were exposed for 6.5 hours per day five days per week for up to 103–104 weeks to 0, 2,260 or 4,520 mg m$^{-3}$ (NTP, 1990). An additional group of mice were similarly exposed to 450 mg m$^{-3}$. No treatment-related increase in the incidence of any tumour was observed in the rats. In the mice, adenomas of the pars intermedia in the pituitary gland (a very rare tumour type) were found in all toluene-exposed groups of females and in the highest dose group of males. A single adenoma was found in each of these groups (NTP, 1990). An earlier rat study had found no evidence of carcinogenicity (or any convincing signs of toxicity) in groups
of 120 males and 120 females exposed 6.5 hours per day, five days per week for up to 24 months to concentrations of 0, 112, 375 or 1,125 mg m$^{-3}$ (Gibson and Hardisty, 1983).

Toluene was administered by stomach tube, 4–5 days per week for 104 weeks at a single dose level of 500 mg kg$^{-1}$ bw in one study and at 800 mg kg$^{-1}$ bw in a separate study (Maltoni et al., 1983, 1985, 1997). Mammary cancers and haemolymphoreticular neoplasias and malignant tumours were increased in the 500 mg kg$^{-1}$ bw but not the 800 mg kg$^{-1}$ bw animals. A small but significant increase in oral cavity tumours was seen in 800 mg kg$^{-1}$ bw males only. The inadequacies of the resulting reports (including the data analysis) have been noted (IARC, 1989; EU-JRC, 2003; USEPA, 2005b) and the studies have been considered by expert groups as not relevant to an assessment of toluene’s carcinogenic potential.

An IARC Working Group in 1989 evaluated the results of eight skin-painting studies in mice in which toluene had been used as a vehicle control and concluded there was no evidence of skin carcinogenicity (IARC, 1989). A study published subsequently (Primate Research Centre, 1988; Brodell et al., 1996) was described in the EU RAR (EU-JRC, 2003). There was a possible treatment-related increase in skin tumours when pure toluene was applied to the skin of 50 male mice, twice a week, for life. Four of the mice developed malignant skin tumours at the test site (one fibrosarcoma and three squamous cell carcinoma) – an incidence on the borderline of statistical significance ($p=0.055$; Fisher Exact test). The dose regime also produced local irritation. The investigators described toluene as a “weak dermal carcinogen”.

The EU RAR noted some concern regarding the pituitary tumours seen in the NTP (1990) mouse study, but concluded that “the evidence [of toluene’s carcinogenicity] is not strong enough to fulfil the EU criteria for classification for carcinogenicity” (EU-JRC, 2003). The pituitary tumours did not warrant mention in the IARC (1999) summary of the animal study findings, and IARC classified toluene as Group 3 (“not classifiable as to its carcinogenicity to humans”) based on “inadequate evidence in humans” and “evidence suggesting a lack of carcinogenicity … in experimental animals” (IARC, 1999).

### 3.8 Summary

Toluene exhibits a low acute oral and inhalation toxicity in rodents and a low acute dermal toxicity in rabbits. In humans, mild effects on the nervous system were detected following seven-hour exposure to 281 mg m$^{-3}$, but were not seen in a different group of volunteers following six hours exposure to 150 mg m$^{-3}$.

The CNS is the most sensitive target of chronic inhalation exposure of humans to toluene. Subtle signs of neurotoxicity are induced by long-term exposure to atmospheric toluene concentrations in the workplace in the region of 150–495 mg m$^{-3}$. There has been a suggestion that a mild neurotoxic effect also occurred in one study group at around 128 mg m$^{-3}$, but in general no neurotoxic effects have been seen at such workplace exposures.

Repeated oral administration of high doses of toluene, five days per week for 13 weeks, produced overt nervous system toxicity in rats and mice, and brain, bladder, liver and kidney injury in rats. Increases in kidney and liver weight were recorded in rats repeatedly given 625 mg kg$^{-1}$ bw whereas liver weights were increased in mice repeatedly given 312 mg kg$^{-1}$ bw. Slight changes in brain biochemistry have been seen in mice receiving 5 mg kg$^{-1}$ bw day$^{-1}$ orally for four weeks.
High and maternally toxic inhalation exposures are probably toxic to the human foetus. There is some limited indication that occupational exposures of around 330 mg m$^{-3}$ can increase the spontaneous abortion risk. Developmental toxicity has been reported in rats repeatedly exposed to toluene by inhalation to 3750–4500 mg m$^{-3}$ in the absence of maternal toxicity.

There is no convincing indication that toluene is likely to be either genotoxic or carcinogenic in humans.
4 Derivation of Health Criteria Values

4.1 Joint WHO/FAO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered a number of extraction solvents at its 25th meeting (WHO, 1981). In view of toluene’s low toxicity, its rapid hepatic metabolism and clearance, and the failure of animal studies to demonstrate carcinogenicity, the Committee considered that “the residues of toluene occurring in foods, based on good manufacturing practice, would not pose any toxicological problems” (WHO, 1981).

4.2 WHO guidelines for drinking-water quality

A 1993 World Health Organization (WHO) assessment of the oral toxicity of toluene resulted in a tolerable daily intake (TDI) of 223 μg kg⁻¹ bw (WHO, 1993, 1996). The critical finding was “the marginal hepatotoxicity” (an increased relative liver weight) reported in mice given 312 mg kg⁻¹ bw by stomach tube, five days per week for 13 weeks (NTP, 1990). The TDI was generated by a conversion of the experimental LOAEL to its daily equivalent (of 223 mg kg⁻¹ bw day⁻¹) and then division by an UF of 1,000 (100 for inter- and intra-species variation, and 10 for the short duration of the study and the use of a LOAEL). Allocation of 10% of the TDI to drinking-water and the assumption that a 60-kg adult drinks two litres of water a day resulted (after rounding) in the drinking-water guideline value of 0.7 mg L⁻¹.

A WHO Final Task Force meeting in 2003 agreed that this earlier risk assessment was still valid. It was thus brought forward to be included in a 2006 revision of the drinking-water guidelines (WHO, 2006).

4.3 WHO air quality guidelines for Europe

In 1996, WHO recommended an air quality guideline for the general public of 0.26 mg m⁻³ (WHO, 2000). This was based on the lowest reported level of chronic occupational exposure to toluene to be associated with a decrease in neurobehavioral function, which was the 332 mg m⁻³ seen in Singaporean workers (Foo et al., 1990, 1993). Application of an UF of 300 (10 for intra-species variation, 10 for the use of a LOAEL, and 3 because of concerns about potential effects on the developing CNS) and a further factor of 4.2 to convert from occupational exposure (eight hours per day, five days per week) to continuous exposure (24 hours per day, seven days per week) resulted in the guideline value.

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3 The JECFA evaluation resulted in an “ADI not specified” designation. This means that, on the basis of the available data (toxicological, biochemical and other), the total daily intake of the substance arising from its use or uses at the levels necessary to achieve the desired effect, and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For this reason, the establishment of an acceptable daily intake (ADI) in mg kg⁻¹ bw is not deemed necessary.
4.4 EU Risk Assessment Report

Toluene has undergone an in-depth risk assessment at European Community level (EU-JRC, 2003). The objective was to estimate Margins of Safety (MOS) by comparing toxic effect levels with estimates of occupational and consumer exposure, and indirect human exposure via the environment. No HCVs were derived. The report was based on the key studies identified in a literature search undertaken in 2000 and was reviewed by the technical experts of the Member States in the same year.

A number of studies were identified as being critical in the risk characterisation. These included a seven-hour lowest-observed adverse effect concentration (LOAEC) of 281 mg m\(^{-3}\) for the acute effects on the nervous system of humans (Echeverria et al., 1989) and from laboratory animal studies, a no-observed adverse effect concentration (NOAEC) of 1,125 mg m\(^{-3}\) for long-term inhalation exposure from a two-year inhalation study in rats (Gibson and Hardisty, 1983) and a NOAEL of 625 mg kg\(^{-1}\) bw day\(^{-1}\) for repeated oral exposure arising from 13-week gavage studies in rats (NTP, 1990).

The EU RAR similarly considered the NOAEL for the 13-week mouse study (NTP, 1990) to be 625 mg kg\(^{-1}\) bw day\(^{-1}\). Although increases in liver and/or kidney weights were seen in the 13-week rodent studies at 625 mg kg\(^{-1}\) bw day\(^{-1}\) (for example, in the rat study, up to 46% increase in relative kidney weight and up to 78% increase in relative liver weight at 625 mg kg\(^{-1}\) bw day\(^{-1}\)) the EU RAR viewed these changes as “toxicologically non-significant signs of metabolic activity related to exposure”. [WHO (see Section 4.2) considered the NOAEL in the mouse study to be 312 mg kg\(^{-1}\) bw day\(^{-1}\) based on the increased relative liver weights seen at 625 mg kg\(^{-1}\) bw day\(^{-1}\), and USEPA (see Section 4.6) considered the critical point of departure to be 238 mg kg\(^{-1}\) bw day\(^{-1}\) based on the increased absolute kidney weights seen in the rat study.]

4.5 EU Indoor Exposure Limits

The EC also reviewed the toxicity of toluene as part of its INDEX project to set Exposure Limits (ELs) for priority chemicals found in indoor air (EU-JRC, 2005). The review produced a long-term EL of 0.3 mg m\(^{-3}\) for toluene based on the application of an UF of 100 (10 for use of a LOAEL and 10 for intraspecies variability) to the LOAEL of 30 mg m\(^{-3}\) for CNS effects (impairment of colour vision) identified in human occupational studies (Zavalic et al., 1998a, 1998b) after adjustment for continuous exposure.

4.6 United States Environmental Protection Agency

In 2005, the US Environmental Protection Agency (USEPA) noted that there was “a substantial body of evidence in humans indicating a relationship between neurological effects and toluene exposure at the lowest occupational exposure levels measured” and based its Reference Concentration for chronic inhalation exposure (RfC)\(^{4}\) on an overview of ten qualifying studies (Foo et al., 1990; Nakatsuka et al., 1992; Abbate et al., 1993; Murata et al., 1993; Vrca et al., 1995; Boey et al., 1997; Zavalic et al., 1998a; Eller et al., 1999; Cavalleri et al., 2000; Neubert et al., 2001). Qualifying criteria

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\(^{4}\) The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious, non-cancer health effects during a lifetime.
included no known co-exposure to other workplace solvents, a comparison to a defined control group, and accepted testing procedures for neurological end-points.

All of the studies reported LOAEL values and four also were said to describe NOAELs (Nakatsuka et al., 1992; Zavalic et al., 1998a; Eller et al., 1999; Neubert et al., 2001). The arithmetic mean of the four NOAEL values was 34 ppm (128 mg m⁻³). An adjustment was made to convert this occupational exposure to continuous conditions (it was assumed that a worker would inhale 10 m³ of air over an eight-hour shift and works five days per week, and that an adult inhales 20 m³ over a 24-hour period and would be exposed daily). The resulting value of 46 mg m⁻³ was then divided by an UF of 10 (to take account of potentially susceptible human sub-populations and life stages) to generate an RfC, after rounding, of 5 mg m⁻³ (USEPA, 2005a).

Also in 2005, USEPA recommended an RfD⁵ for chronic oral exposure of 0.08 mg kg⁻¹ bw day⁻¹ (USEPA, 2005a). This was derived from a benchmark dose (BMD) analysis of the increase in (absolute) kidney weights seen in male rats in a 13-week gavage study (NTP, 1990). An UF of 3,000 was applied to the BMDL⁶ of 238 mg kg⁻¹ bw day⁻¹ to generate (after rounding) the RfD. The overall UF comprised factors of 10 to take account of possible interspecies differences, 10 for possible interindividual variations in susceptibility in the human population, 10 for the use of a subchronic study to derive an HCV for chronic exposure, and 3 for database “insufficiencies”. These included only limited oral studies of neurotoxicity, a lack of a two-generation reproductive toxicity study by the oral route, and indications of immunotoxicity in mice treated orally.

4.7 US Agency for Toxic Substances and Disease Registry

In an assessment in 2000, the US Agency for Toxic Substances and Disease Registry (ATSDR) derived a chronic Minimal Risk Level (MRL)⁷ for inhalation exposure to toluene. This was based on a study of shoemakers who experienced colour vision impairment when exposed repeatedly to workplace atmospheres containing a geometric mean toluene concentration of 35 ppm (131 mg m⁻³) (Zavalic et al., 1998a, 1998b). Application of an UF of 100 (10 for the use of a LOAEL and 10 to account for human variability) and adjustment to continuous exposure from occupational exposure (multiplying by 5/7 × 8/24), gave, after rounding, the MRL of 0.08 ppm or 0.3 mg m⁻³ (ATSDR, 2000). [USEPA (2005a) described the lowest exposure group of Zavalic et al. (1998a) as a NOAEL.]

ATSDR considered that no suitable data were available (in 2000) for the derivation of a MRL for chronic oral exposure. An intermediate MRL applicable to human oral exposures of up to one year was derived based on the subtle biochemical changes (regional increases in monoamine neurotransmitters in the brain) observed in male mice exposed to toluene via drinking-water for four weeks (Hsieh et al., 1990a). These were present even at the lowest tested dose of 5 mg kg⁻¹ bw day⁻¹. This LOAEL was

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⁵ The oral RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious, non-cancer health effects during a lifetime.

⁶ The Benchmark Dose (BMD) was defined as the maximum likelihood estimate of the dose corresponding to a one standard deviation change from the control value. In this instance the standard deviation corresponded to a 9% increase in absolute kidney weight from controls. A BMDL is the statistical 95% lower confidence limit on the BMD. In this analysis, USEPA had converted the five day per week test doses in the NTP study to their seven-day equivalents (x 5/7).

⁷ An ATSDR MRL is an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.
4.8 Dutch National Institute for Public Health and the Environment

A 1999 assessment of toluene by the Dutch National Institute for Public Health and the Environment (RIVM) resulted in oral and inhalation HCVs taken from other published expert group deliberations. WHO’s TDI of 223 µg kg\(^{-1}\) bw (see Section 4.2) was recommended as the oral limit value. The then USEPA RfC of 0.4 mg m\(^{-3}\) was favoured as the Tolerable Concentration in Air (TCA).\(^8\) This was based on the mild behavioural effects seen in female workers exposed repeatedly over long periods to 332 mg m\(^{-3}\) (Foo et al., 1990). The LOAEL was adjusted to continuous exposure using a factor of 2.8.\(^9\) The application of an UF of 300 (10 each to account for intra-species variability and the use of a LOAEL, and an additional factor of 3 to account for “database deficiencies”) and rounding generated the RfC (and TCA) (RIVM, 2001). [USEPA updated its opinion on toluene in 2005; Foo et al. (1990) was then only one of ten studies that were used to provide a more confident view of the LOAEL in humans.]

4.9 Discussion

All the expert group derivations of chronic inhalation HCVs are based on occupational epidemiology, in particular the exposure estimates of the atmospheric concentrations responsible for mild neurological changes detected in the workforces. The WHO air quality guideline derived in 1996 and the RIVM TCA proposed in 1999 rely on the LOAEL of 332 mg m\(^{-3}\) reported in a single study of 30 exposed Singaporean women (Foo et al., 1990, 1993). In fact, the RIVM derivation was taken directly from that of the then USEPA RfC.

The RIVM TCA (and the then USEPA RfC) of 0.4 mg m\(^{-3}\) differed from the corresponding WHO value of 0.26 mg m\(^{-3}\) only because of the different factors used to convert the occupational LOAEL to its continuous exposure equivalent. WHO assumed a linear relationship in going from the eight hours of a work shift to the 24-hour exposure of the general population, whereas USEPA (and RIVM) assumed that the volume of air inhaled in the work shift would be equal to the volume of air inhaled in the other 16 hours of the day. Both derivations invoked the same overall UF of 300, which included a factor of 3 to take account of data base concerns/inadequacies. USEPA considered this was necessary because of a lack of laboratory animal data evaluating neurotoxicity and respiratory irritation; WHO’s concern was with potential effects of toluene on the developing CNS.

The chronic inhalation HCV set by ATSDR, an MRL of 0.3 mg m\(^{-3}\), arose from a 2000 assessment and was based on a study of Croatian workers (Zavalic et al., 1998a, 1998b), which was said to have found effects on colour vision in a group of 43 women and three men exposed to a geometric mean concentration of around 130 mg m\(^{-3}\). ATSDR used the same occupational-to-continuous dose conversion as WHO, and both

\(^8\) The TCA is the concentration of a substance in the atmosphere that any human individual can be exposed to continuously during a full lifetime without significant health risk.

\(^9\) This factor results from an assumption that a worker would inhale 10 m\(^3\) of air over an eight-hour shift and works five days per week, and that an adult inhales 20 m\(^3\) over a 24-hour period and would be exposed daily (20/10 x 7/5).
expert groups agreed on the use of UFs of 10 for interindividual variations in the human population and for the use of a LOAEL. The resulting approximate agreement on the inhalation HCV (0.3 mg m$^{-3}$ compared with 0.26 mg m$^{-3}$) – despite the differing LOAELs – was a consequence of the incorporation by WHO of the additional UF for database deficiencies (WHO, 1996). In 2005, the EU set its long-term EL of 0.3 mg m$^{-3}$ on the same basis as ATSDR’s inhalation MRL.

USEPA updated its review of toluene in 2005. The much broader range of epidemiological studies identified by USEPA enabled a better definition of the dose–response of toluene’s neurotoxic potential. Ten studies were chosen that provided useful insights into what was a reliable minimal LOAEL and four of these also reported NOAELs for neurotoxicity; two of the four post-dated the ATSDR 2000 assessment. The mean NOAEL from these four studies was, in the opinion of USEPA, 128 mg m$^{-3}$. The RfC of 5 mg m$^{-3}$ resulted from the application of an UF of 10 (to take account of possible inter-human variations in susceptibility to toluene’s toxicity) to the group NOAEL converted from occupational to continuous exposure. USEPA did not consider a need for a UF for database deficiencies.

Based on the default 70-kg adult inhaling 20 m$^{3}$ of air per day, the RfC is equivalent to an intake of 1.4 mg kg$^{-1}$ bw day$^{-1}$ (rounded to two significant figures), which is recommended here as the TDI$_{inh}$ for the purposes of deriving SGVs.

In the absence of oral toxicity data in humans, the expert group derivations of oral HCVs have relied on laboratory animal studies – in all but one case on the findings from 13-week gavage studies in rodents conducted by NTP (1990). WHO in 1993 (supported by RIVM in 1999) based its TDI of 223 µg kg$^{-1}$ bw on the increased liver weights seen in the mice given the lowest tested dose level. The “LOAEL” (though the increase in liver weight was not associated with histological evidence of liver damage at any of the higher dose levels) of 223 mg kg$^{-1}$ bw day$^{-1}$ was divided by an UF of 1,000, which included a factor of 10 to take account of both a subchronic study (in the derivation of a chronic safety limit) and the use of a “minimal” LOAEL.

USEPA favoured the corresponding rat study as the foundation of its 2005 derivation of an RfD of 80 µg kg$^{-1}$ bw day$^{-1}$. An organ weight increase was again chosen as the critical endpoint (in this case of the kidney) but the increase in weight at the lower doses was accompanied at higher doses with histological evidence of kidney damage. USEPA used a BMD analysis to calculate a BMDL and then divided it by an UF of 3,000. Compared with WHO’s use of a factor of 10 to take account of both the less-than-lifetime period of administration and a minimal LOAEL [or perhaps lowest-observed effect level (LOEL)], USEPA used a factor of 10 for the short duration of the study but also another factor of 3 for database “insufficiencies”.

ATSDR was the only expert group not to use the results of the NTP studies in the derivation of an oral HCV. Its intermediate oral MRL (for human exposures of up to one year) proposed in 2000 was based on subtle changes in brain biochemistry detected in male mice given 5 mg kg$^{-1}$ bw in the drinking-water for four weeks (Hsieh et al., 1990a). USEPA (2005b) noted that these biochemical changes have not been correlated with behavioural or neuropsychological effects. The EU RAR makes no mention of the study (or the other work from the same research group on immune effects in similarly treated mice). ATSDR applied an overall UF of 300, which included a component factor of 3 for the use of a minimal LOAEL, in deriving its (rounded) intermediate MRL of 20 µg kg$^{-1}$ bw day$^{-1}$.

The USEPA’s use of the rat renal weight data seems most justified since it was accompanied by histopathological effects at higher doses. However, USEPA’s application of an UF of 3,000 to a BMDL equivalent to only a 9% increase in absolute kidney weight in the derivation of its RfD is perhaps excessively precautionary. If an UF of 1,000 had been applied to the BMDL, the resulting HCV would have been 240
µg kg$^{-1}$ bw day$^{-1}$, i.e. very similar to the TDI reconfirmed by WHO in 2006. The WHO TDI of 223 µg kg$^{-1}$ bw day$^{-1}$ is therefore recommended here as the TDI$_{oral}$ for the purposes of deriving SGVs.
5 Background intake

5.1 Food

The 1993 UK Total Diet Study (MAFF, 1995) reported on toluene and other aromatic hydrocarbons. Samples of 20 food groups collected from ten locations in the UK were analysed. Each food group consisted of retail food products prepared as for consumption and combined in amounts reflecting their importance in the average UK diet. Toluene was present in most of the food group samples analysed. The average UK dietary intake of toluene was estimated to be about 7.7 µg day\(^{-1}\), with the largest contributions from milk (14% of total), milk products (13% of total) and beverages (12% of total).

5.2 Water

There is no regular reporting of the concentration of toluene in drinking-water in the UK. In 1976, toluene was found at all sites in a survey of 14 drinking-water sources in the UK conducted over a period of nine months. No actual concentrations were reported (Fielding et al., 1981), but it was implied that most levels were less than 1 µg L\(^{-1}\). In a survey of 32 UK public and private supply boreholes in the summer of 1983, toluene was found to be present in 19 of the ground waters sampled. The mean toluene level in the 19 positive samples was 0.046 µg L\(^{-1}\) and the average level over all 32 samples was 0.009 µg L\(^{-1}\). The maximum level found was 0.07 µg L\(^{-1}\) (Kenrick et al., 1985).

Few measurements from other countries appear to have been reported. In a Canadian survey, toluene was detected in drinking-water most frequently in the summer months, when about 20% of the measurements gave positive results. The average and maximum concentrations were 2 and 27 µg L\(^{-1}\) respectively (detection limit 1 µg L\(^{-1}\)) (Otsun et al., 1980). A brief summary of measurements in US drinking-water indicates that toluene is only detected occasionally, with concentrations around the limit of detection – ranging from about 0.5 to 3 µg L\(^{-1}\) (De Zuane, 1990). It seems unlikely, therefore, that average concentrations in UK drinking-water are any greater than about 1 µg L\(^{-1}\); that is, the mean daily intake is probably less than 2 µg for an adult consuming two litres of water per day.

5.3 Air

Over the period 1994–1996, the average annual concentrations of toluene in UK urban air ranged from about 1.3 to 4.8 µg m\(^{-3}\) (overall average: 2.2 µg m\(^{-3}\)). At a rural site the figure was about 0.6 µg m\(^{-3}\) (DETR, 1998). Indoor concentrations of toluene are generally higher than the corresponding outdoor ones.

No general surveys of toluene concentrations in dwellings in this (or any other) country appear to have been made, but some UK measurements indicate an indoor/outdoor concentration ratio of around 3 (Berry et al., 1996; Brown and Crump, 1998). Similarly, ATSDR (2000) reported mean outdoor (urban) and indoor concentrations for the USA of about 11 and 32 µg m\(^{-3}\) respectively from a 1988 USEPA study.

Assuming an occupancy factor for dwellings of 0.9 (i.e. on average, people spend 90% of their time indoors; Mann et al., 1997), an indoor/outdoor concentration ratio of 3 and
a mean outdoor concentration of 2.2 µg m\(^{-3}\), the mean personal exposure would be 6.2 µg m\(^{-3}\). This is equivalent to 124 µg day\(^{-1}\) based on the default 70-kg adult breathing 20 m\(^{3}\) of air per day (Environment Agency, 2009).

### 5.4 Other sources

Toluene is present in cigarette smoke. In a study carried out at the UK Laboratory of the Government Chemist (Darrall et al., 1998), the yields of toluene were measured in the mainstream smoke of 26 cigarette brands on the UK market and of smoke from hand-rolled tobacco; they ranged between 5 and 82 µg per cigarette, with an average of approximately 56 µg. For a person smoking 20 cigarettes a day, the intake of toluene would therefore be about 1,000 µg day\(^{-1}\), some eight times greater than the estimated MDI\(_{\text{inh}}\) for a non-smoking adult.

Petrol/gasoline contains 5–7% toluene and significant quantities may evaporate at filling stations. Mean atmospheric concentrations of toluene at self-service filling stations could be around 10 mg m\(^{-3}\) (range 0–63 mg m\(^{-3}\)) (EU-JRC, 2003). The adult daily dose (averaged over a week) arising from two 10-minute visits each week to a self-service station would be in the order of 396 µg or 5.7 µg kg\(^{-1}\) bw.

Background exposure may also be increased in the vicinity of some industrial sites. Processes that may release toluene to the atmosphere and wastewater include printing (where toluene is used as a solvent for inks and dyes), paint processing, leather tanning and the plastics industry (ATSDR, 2000). However, the largest source of toluene release is during the production, transport and use of petrol/gasoline (ATSDR, 2000).

### 5.5 Estimation of mean daily intakes

Based on data for food and water, the oral mean daily intake (MDI\(_{\text{oral}}\)) for an adult is estimated to be approximately 10 µg (7.7 µg day\(^{-1}\) from food and 2 µg day\(^{-1}\) from drinking-water).

Based on ambient atmospheric toluene level data and estimated inhalation exposure from vehicle refuelling at petrol stations, the inhalation mean daily intake (MDI\(_{\text{inh}}\)) for an adult is estimated to be approximately 520 µg (124 µg day\(^{-1}\) from ambient air and an additional 396 µg day\(^{-1}\) from exposure at petrol stations).
6 Conclusions

The CNS is the critical target of inhaled toluene. A range of subtle neurological effects has been observed in workers exposed for protracted periods to atmospheric concentrations in the workplace in the region of 150–495 mg m⁻³, while effects have not been apparent at around 128 mg m⁻³. An inhalation TDI (TDIₗᵢᵦₙ) of 1.4 mg kg⁻¹ bw day⁻¹ is recommended here for the purpose of developing SGVs.

No repeated oral toxicity data in humans have been identified. In 13-week oral studies, increases in kidney and liver weight were recorded in rats given 446 mg kg⁻¹ bw day⁻¹, whereas liver weights were increased in mice given 223 mg kg⁻¹ bw day⁻¹. An oral TDI (TDIₗₒᵦᵦ₉) of 223 µg kg⁻¹ bw day⁻¹ is recommended here for the purpose of developing SGVs.

No authoritative assessments of the health risks posed by dermal exposures to toluene were identified. In view of the slower absorption of toluene through the skin than via the gastrointestinal tract, and the absence of an indication of any notable first-pass detoxification metabolism following oral absorption, it would not seem unreasonable to assume that the oral HCV value could be used for a conservative rudimentary dermal risk assessment.

The MDIₗᵢᵦₙ and MDIₗₒᵦᵦ₉ are estimated to be 520 and 10 µg day⁻¹, respectively. Only a very small fraction of each TDI is therefore required to accommodate background exposure (see Table 6.1).

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<th>Parameter</th>
<th>Units</th>
<th>Oral</th>
<th>Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>µg day⁻¹</td>
<td>10</td>
<td>520</td>
</tr>
<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>0.14</td>
<td>7.4</td>
</tr>
<tr>
<td>MDI for 20-kg child</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>0.37 a</td>
<td>19.3 a</td>
</tr>
<tr>
<td>TDI</td>
<td>µg kg⁻¹ bw day⁻¹</td>
<td>223</td>
<td>1,400</td>
</tr>
</tbody>
</table>

* See Environment Agency (2009) for details of MDI conversion factors.

Neurotoxicity is a key feature of both oral and inhalation exposure to toluene. This should therefore be considered in a risk assessment of toluene where there is exposure via both routes.
References


BASF, 1980. *Bestimmung der akuten Inhalationstoxizität LC50 von Toluol min. 99.5% (Merck AG) als Dampf bei 4stundiger Exposition an Sprague-Dawley-Ratten* [cited in EU-JRC, 2003].


List of abbreviations

ADI acceptable daily intake
ATSDR Agency for Toxic Substances and Disease Registry [USA]
BMD benchmark dose
BMDL lower confidence limit of the benchmark dose
bw bodyweight
CNS central nervous system
CYP Cytochrome P450
Defra Department for Environment, Food and Rural Affairs [UK]
EL Exposure Limit [EU]
FAO Food and Agriculture Organization [United Nations]
FSA Food Standards Agency [UK]
HCV Health Criteria Value
HPA Health Protection Agency [UK]
HSE Health and Safety Executive [UK]
IARC International Agency for Research on Cancer
IPCS International Programme on Chemical Safety
JECFA Joint FAO/WHO Expert Committee on Food Additives
JRC Joint Research Centre [EU]
LOAEC lowest-observed adverse effect concentration
LOAEL lowest-observed adverse effect level
LOEL lowest-observed effect level
MDI mean daily intake
MOS margin of safety
MRL Minimal Risk Level
NOAEC no-observed adverse effect concentration
NOAEL no-observed adverse effect level
NTP National Toxicology Program [USA]
ppm parts per million
RAR Risk Assessment Report [EU]
RfC Reference Concentration
RfD Reference Dose
SD standard deviation
SGV  Soil Guideline Value
TDI  tolerable daily intake
UF  uncertainty factor
USEPA  United States Environmental Protection Agency
WHO  World Health Organization
Appendix – Literature search

The literature search that formed the basis of this update report was undertaken in February 2007, and repeated in August 2008, using a proprietary database – the TRACE database developed and managed by bibra toxicology advice & consulting. The database was searched for comprehensive reviews and evaluations of toluene, and for primary papers published since the most recent expert group evaluation (2004).

TRACE includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources (websites, official publications and evaluations by authoritative groups) including:

- UK government agency (Defra and the Environment Agency, FSA, HPA) and advisory committee (COT, COM, COC, ACAF, ACNFP and ACP) reports and evaluations
- EU Risk Assessment Reports
- EU expert committees (EU scientific committees, EFSA scientific panels)
- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- US government agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS and OEHHA)
- OECD SIDS dossiers/SIARS
- ECETOC, ACGIH, BG Chemie and DFG reports and monographs
- IUCLID data sets
- NICNAS Priority Existing Chemical Assessments
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