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

Better Regulation Science Programme
Science report: SC050021
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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 xylene. It provides an update to an earlier report by the Department for Environment, Food and Rural Affairs (Defra) and the Environment Agency published in November 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 xylene in the UK.

Chemical overview

There are three structural isomers of xylene – ortho-, meta- and para-xylene. The common name ‘xylene’ generally refers to mixtures of the three isomers. Each isomer is a colourless, volatile liquid at ambient temperature and pressure.

Xylene is blended into petrol and used as a solvent in products such as paints, inks and coatings. The greatest contribution to the environmental release of xylene is anthropogenic emissions to the atmosphere. Xylene may enter water or soil from industrial discharges, in leachate from landfills and from accidental spillages. Xylene is slightly soluble in water, but may volatilise from soil into the atmosphere. It may also undergo microbial degradation.

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

Pharmacokinetics

In humans exposed to xylene in air, lung retentions of between 50–87% have been reported. Limited ingestion studies in humans suggest oral absorption is slightly lower; oral absorption appears to be greater in rats than in humans. Absorption through the skin can occur, but to a much lesser extent. Absorbed xylene is likely to be distributed primarily to lipid-rich tissues, but it does not significantly accumulate. ortho-Xylene has been shown to cross the placenta in rats.

Metabolism of each xylene isomer takes place primarily in the liver. Xylene is excreted principally in the urine – mainly as the metabolite methylhippuric acid – though some is released in exhaled air.

Toxicity

Occupational epidemiology studies reveal the central nervous system (CNS) to be the critical target of inhaled xylene. Mild neurotoxicity has been reported in workers exposed to atmospheric concentrations of around 60 mg m⁻³. In laboratory animals, concentrations of 435 mg m⁻³ have produced neurotoxicity.

Toxicity data from repeated oral exposure are not available for humans. In long-term experimental animal studies, xylene has caused mild neurotoxicity in mice at oral doses of 1,000 mg kg⁻¹ bw day⁻¹, but not at 500 mg kg⁻¹ bw day⁻¹. In a similar study in rats, no effects were seen at 250 mg kg⁻¹ bw day⁻¹; however, mild kidney toxicity has been seen in rat studies of shorter duration at 150 mg kg⁻¹ bw day⁻¹.

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¹ The common name ‘xylene’ refers in this report to the three structural isomers.
A wide range of screening tests indicate that the xylenes do not possess significant genotoxic potential and long-term oral studies of mixed xylenes have generated no evidence of carcinogenicity.

Studies in rats, mice and rabbits demonstrate xylene is able to produce foetotoxic effects. Several of the available studies were poorly designed or reported, but it would appear foetotoxic effects may occur at exposure levels that are not necessarily overtly toxic to the mother.

**Health Criteria Values and risk assessment**

Based on the neurotoxic effects seen in occupational studies, an inhalation tolerable daily intake (TDI\textsubscript{inh}) of 60 µg kg\textsuperscript{-1} bw day\textsuperscript{-1} is recommended here for the development of Soil Guideline Values (SGVs).

Based on the effects of xylene in orally exposed rats, and after accounting for the limitations of the data, the potential differences in susceptibility between rats and humans and variance in sensitivity within the human population, an oral tolerable daily intake (TDI\textsubscript{oral}) of 180 µg kg\textsuperscript{-1} bw day\textsuperscript{-1} is recommended here.

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

**Mean daily intakes from non-soil sources**

The adult inhalation mean daily intake (MDI\textsubscript{inh}) of xylene from its background presence in ambient air is estimated as 140 µg day\textsuperscript{-1}, which corresponds to a minor proportion of the TDI\textsubscript{inh}. Background oral exposure to xylene from its presence in food and water is low, and the adult oral mean daily intake (MDI\textsubscript{oral}), at 11 µg day\textsuperscript{-1}, occupies only a very small fraction of the TDI\textsubscript{oral} (see table below).

### HCV and MDI values for xylene

<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\textsuperscript{-1}</td>
<td>11</td>
<td>140</td>
</tr>
<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg\textsuperscript{-1} bw day\textsuperscript{-1}</td>
<td>0.16</td>
<td>2</td>
</tr>
<tr>
<td>MDI for 20-kg child</td>
<td>µg kg\textsuperscript{-1} bw day\textsuperscript{-1}</td>
<td>0.41 \textsuperscript{a}</td>
<td>5.2 \textsuperscript{a}</td>
</tr>
<tr>
<td>TDI</td>
<td>µg kg\textsuperscript{-1} bw day\textsuperscript{-1}</td>
<td>180</td>
<td>60</td>
</tr>
</tbody>
</table>

\textsuperscript{a} See Environment Agency (2009) for details of MDI conversion factors.

**Summary of changes to HCV recommendations**

The HCVs recommended herein are essentially the same as were recommended in 2004 – the previously recommended TDI\textsubscript{oral} of 179 µg kg\textsuperscript{-1} bw day\textsuperscript{-1} has been rounded to 180 µg kg\textsuperscript{-1} bw day\textsuperscript{-1} and additional evaluations and rounding underlie the change of TDI\textsubscript{inh} from 63 to 60 µg kg\textsuperscript{-1} bw day\textsuperscript{-1}. 
Acknowledgements

This document was initially written by RPS Group plc and has subsequently been updated, first by the MRC Institute for Environment and Health, then in 2003 by Toxicology Advice & Consulting Ltd, and in 2008 by bibra. SLR Consulting Ltd provided assistance in the management and delivery of the 2003 document. The Environment Agency is also grateful for the valuable inputs from various independent experts and government agencies and departments, particularly the Department of Health, Health Protection Agency and Food Standards Agency.
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1 Introduction

1.1 Update to R&D Publication TOX 19

This report presents key data and expert opinion on the human toxicology and non-soil intakes of xylene. It updates and replaces R&D Publication TOX 19 published in November 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 xylene 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 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 xylene. 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 xylene 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 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.

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 xylene.

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 xylene 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 xylene, 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 xylene (pharmacokinetics, acute toxicity, repeated dose toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity).

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

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

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

There are three structural isomers of xylene (see Figure 2.1). The common name ‘xylene’ (CASRN 1330-20-7) is in wide use and generally refers to mixtures of the three isomers. Each of the isomers, a dimethylbenzene, is a colourless liquid at normal room temperature. They are volatile, slightly soluble in water, but miscible with ethanol, diethyl ether and other organic solvents (IPCS, 1997). Table 2.1 lists some standard physical-chemical properties for each of the isomers.

![Figure 2.1 Structures of xylene isomers](image)

Although xylene is a natural constituent of petroleum, the majority of commercial xylene is manufactured. Commercial grades of “mixed xylenes” are mixtures of all three isomers; meta-xylene, typically present at 40–77% of the total, predominates, although up to 20% ethylbenzene may also be present (USEPA, 2003a). Mixed xylenes are produced in large quantities and the majority is blended into petrol. They are also used as a solvent in products such as paints, inks and coatings. Similarly the individual isomers are used as solvents and also as intermediates in the production of other industrial chemicals.

The greatest contribution to the environmental release of xylene is from man-made emissions to the atmosphere. In the UK, the major sources are solvent use, road transport, and petrol marketing and distribution (Crookes et al., 1993). Xylene may be released to water or soil from industrial discharges, in leachate from landfills, from contaminated sites and from accidental spillages. Human exposure may also occur from cigarette smoke.

Xylene in soil may be released to the atmosphere through volatilisation. It may also undergo microbial degradation, typically occurring more slowly under anaerobic conditions than aerobic conditions. ortho-Xylene is degraded more slowly than the meta- and para- isomers (IPCS, 1997).
Collectively termed BTEX, xylene is commonly encountered with the similar aromatic chemicals benzene, toluene and ethylbenzene.

Where a cited source has described atmospheric xylene levels in parts per million (ppm), a conversion factor of 1 ppm = 4.35 mg m$^{-3}$ (IPCS, 1997) has been used to ensure consistency in units throughout this report.

Table 2.1 Physical-chemical parameters for ortho-, meta- and para-xylene (Environment Agency, 2008)

<table>
<thead>
<tr>
<th>Chemical property</th>
<th>o-xylene</th>
<th>m-xylene</th>
<th>p-xylene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>$C_8H_{10}$</td>
<td>$C_8H_{10}$</td>
<td>$C_8H_{10}$</td>
</tr>
<tr>
<td>Molecular weight (g mol$^{-1}$)</td>
<td>106.17</td>
<td>106.17</td>
<td>106.17</td>
</tr>
<tr>
<td>Physical state at room temperature</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td>Melting point (ºC)</td>
<td>-25.2</td>
<td>-47.8</td>
<td>13.3</td>
</tr>
<tr>
<td>Boiling point (ºC)</td>
<td>144.6</td>
<td>139.4</td>
<td>138.4</td>
</tr>
<tr>
<td>Water solubility (mg L$^{-1}$, at 25ºC)</td>
<td>173</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Octanol-water partition coefficient (log $K_{OW}$)</td>
<td>3.12</td>
<td>3.20</td>
<td>3.15</td>
</tr>
<tr>
<td>Vapour pressure (Pa, at 10ºC)</td>
<td>385</td>
<td>495</td>
<td>475</td>
</tr>
<tr>
<td>Henry’s law constant (Pa m$^3$ mol$^{-1}$, at 25ºC)</td>
<td>551</td>
<td>730</td>
<td>669</td>
</tr>
</tbody>
</table>
3  

Toxicity

3.1  Literature sources

Major reviews of the literature on the toxicology of xylene have been published by:

- Health and Safety Executive (HSE, 1992)
- World Health Organization (WHO, 1996)
- International Programme on Chemical Safety (IPCS, 1997)
- International Agency for Research on Cancer (IARC, 1999)
- European Union (EU-JRC, 2005)
- US Environmental Protection Agency (USEPA, 2003a, 2003b)

This section is largely based on the major conclusions of these reviews. Particular mention is made of those studies used in deriving HCVs. In general, the primary literature was been consulted.

3.2  Pharmacokinetics

3.2.1  Absorption

In humans exposed to either individual isomers or mixed xylenes in the atmosphere, lung retentions of between 50 and 87% have been reported (USEPA, 2003b). Physical exertion can increase the fraction of xylene retained (ATSDR, 2007).

Limited studies in humans indicated that at least 34% of ortho-xylene and 53% of meta-xylene were absorbed orally (ATSDR, 2007). All isomers were well absorbed when administered orally to rats (Gut and Flek, 1981). The extent of oral absorption of meta-xylene in rats was high (74–96%), irrespective of whether the xylene was administered along with soil or alone (Turkall et al., 1992).

Absorption can also occur through the skin “but to a much lesser extent than the oral or inhalation routes” (ATSDR, 2007). The approximate dermal absorption of xylene arising from the immersion of the hands of volunteers in liquid meta-xylene was 2 µg cm⁻² min⁻¹ (Engström et al., 1977; Lauwerys et al., 1978). An in vitro system reported a similar level of absorption through human abdominal skin (about 3 µg cm⁻² min⁻¹) for a solution of the para-isomer (Fasano and McDougal, 2008). The dermal absorption of meta-xylene vapour in subjects exposed to about 2,600 mg m⁻³ of meta-xylene in the air was estimated to be about 0.01 µg cm⁻² min⁻¹ (Riihimäki and Pfäffli, 1978).

3.2.2  Distribution

The high olive oil/blood partition coefficients of all three isomers (Sato and Nakajima, 1979) suggest that xylenes absorbed into the blood are likely to be distributed primarily to lipid-rich tissues. Although it has been estimated that 4–10% of the systemically absorbed dose in humans is deposited in the adipose tissue (ATSDR, 2007), metabolic processes prevent significant accumulation in the human body (IPCS, 1997).
Inhalation studies in rats with meta-xylene confirmed the propensity of xylene and its metabolites to be found in fat and also reported an initial high intake into the kidney (Carlsson, 1981). In mice exposed to meta-xylene in the atmosphere, high levels of metabolites were detected in the blood, respiratory tract, liver, kidney and intestinal contents (Bergman, 1979, 1983). ortho-Xylene has been shown to cross the placenta of rats exposed by inhalation (Ungváry et al., 1980a).

### 3.2.3 Metabolism

All xylene isomers are primarily metabolised by microsomal enzymes in the liver to methylbenzyl alcohols, followed by further oxidation to the corresponding methylbenzoic acid. In humans, these are conjugated principally with glycine to form methylhippuric acids (IPCS, 1997; USEPA, 2003b). More than 90% of the systemically absorbed xylene (all isomers) following inhalation exposure in volunteers was metabolised to the methylhippuric acids (Sedivec and Flek, 1976; ATSDR, 2007). Aromatic hydroxylation of xylene to xylenol occurs to only a limited extent in humans (ATSDR, 2007).

In the rat, glycine conjugation was favoured in the metabolism of meta- or para-xylene, whereas glucuronide conjugation may predominate with the ortho isomer (IPCS, 1997).

### 3.2.4 Excretion

In human volunteer studies the main urinary metabolites are the methylhippuric acids (Sedivec and Flek, 1976; ATSDR, 2007). The excretion of these acids is rapid; a significant amount is detected in the urine within two hours of inhalation exposure (ATSDR, 2007). Only about 5% of the intake retained in the lungs of volunteers exposed to mixed xylene vapour was subsequently exhaled unchanged (Sedivec and Flek, 1976; Astrand et al., 1978).

Rats given an oral dose of meta-xylene excreted 9–22% unchanged in the expired air. About 50–59% of an administered dose was excreted in the urine within 12 hours. Approximately 70% of this was methylhippuric acid, 2–18% was xylenol, and 1% was unchanged xylene (Turkall et al., 1992).

The major route of excretion of radiolabelled meta-xylene applied to the skin of rats was in the expired air. If the dermal dose was adsorbed onto clay soil, urinary excretion matched that in air, whereas this changed pattern of excretion did not occur in the corresponding experiment using sandy soil (Skowronski et al., 1990).

### 3.3 Acute toxicity

#### 3.3.1 Humans

There are reports of poisoning following single very large inhaled or ingested doses of xylene by humans. Central nervous system (CNS) effects appear to be of most concern in accidental poisoning, but signs of impaired kidney and liver function, as well as gastrointestinal, respiratory and ocular irritation, have also been observed (ATSDR, 1995; EU-JRC, 2005).

In general, no reliable estimates of the doses producing serious toxicity can be made, but there is one report of death following acute inhalation exposure (Morley et al.,
One of three men died after breathing paint fumes for several hours (possibly 18 hours) containing an estimated concentration of about 40,000 mg m\(^{-3}\) of "xylene" (not further defined). Xylene made up over 90% of the paint solvent. Pathology of the lung, brain and liver was seen at autopsy. Cyanosis of the extremities and reversible neurological impairment were the main symptoms of toxicity in the two men who survived. In both men, there were increases in enzyme activity in the blood indicative of liver damage.

Single exposures to 3,045 mg m\(^{-3}\) can produce headache, nausea, vertigo and dizziness (HSE, 2002). A number of studies exposed volunteers for short periods (commonly four hours) to atmospheres containing measured concentrations of xylene – usually the \textit{meta} isomer, but sometimes \textit{para}-xylene or mixed xylenes (IPCS, 1997). Concentrations of around 435–870 mg m\(^{-3}\) were described by USEPA as being close to the threshold for reversible neurological changes and local irritation (USEPA, 2003a). A four-hour exposure to 300 mg m\(^{-3}\) of \textit{para}-xylene had no discernible influence on the CNS of 16 volunteers (Anshelm Olson \textit{et al.}, 1985), whereas feelings of intoxication, headache, nausea (and local irritation) were recorded in 56 volunteers exposed for two hours to 200 mg m\(^{-3}\) of \textit{meta}-xylene (Ernstgard \textit{et al.}, 2002).

### 3.3.2 Experimental animals

**Inhalation**

In rats, the individual isomers (and mixed xylene) exhibited low acute inhalation toxicity. LC\(_{50}\) values for a six-hour exposure to \textit{ortho}-, \textit{meta}- or \textit{para}-xylene were around 17,400–26,000 mg m\(^{-3}\) (Bonnet \textit{et al.}, 1979). A similar order of toxicity following acute inhalation exposure was observed in mice (Bonnet \textit{et al.}, 1979). Narcosis occurred in rats at exposures of around 8,700 mg m\(^{-3}\). Reduced respiratory rates were also reported and the cause of death of treated animals was respiratory failure. Pathological examinations of animals exposed to lethal concentrations generally found no systemic tissue injury (IPCS, 1997).

**Oral**

A low acute toxicity was indicated in rodents treated orally, with LD\(_{50}\) values well in excess of 2,000 mg kg\(^{-1}\) bodyweight (bw) (IPCS, 1997). Pathological abnormalities (congestion) in the liver, kidney and spleen (as well as symptoms involving the CNS) occurred in mice given lethal oral doses of mixed xylenes (NTP, 1986).

**Dermal**

In rabbits, the dermal LD\(_{50}\) for 24-hour covered contact with \textit{meta}-xylene was 12,200 mg kg\(^{-1}\) bw (Smyth \textit{et al.}, 1962).
3.4 Repeated dose toxicity

3.4.1 Humans

Occupational exposure to xylene mainly produces effects on the CNS. In a study in which xylene exposure was reasonably well defined (Uchida et al., 1993), an increase in subjective symptoms was reported in Chinese workers exposed for an average of seven years. The final test group of 175 workers (107 men, 68 women) was selected from a total group of 997 solvent-exposed workers on the basis that at least 70% of their solvent exposure was to xylenes (other solvent exposures included toluene and ethylbenzene, but no benzene) and they completed all the tests. The measured xylene levels showed that the workers were exposed to mixed xylenes in the factory at geometric mean concentrations of about 60 mg m\(^{-3}\) \(^4\) (arithmetic mean of about 91 mg m\(^{-3}\)). The control group comprised 241 non-exposed workers (116 men, 125 women) in the same factories or elsewhere.

The symptoms included anxiety, forgetfulness, floating sensation, an inability to concentrate and dizziness. There was also an increased prevalence of poor appetite, eye irritation and sore throat. A concentration-relationship was reported for eye irritation, sore throat and floating sensation (indicative of a CNS effect). The blood cell profile was normal and the serum biochemistry gave no evidence of any changes in liver and kidney function.

Workers exposed to mixtures of xylenes and other solvents have been shown to experience liver and kidney effects. However, the complexity of the exposure regimes means that it is impossible to attribute any of the observed effects conclusively to xylenes (IPCS, 1997; Jacob et al., 2007). Lung, cardiovascular and gastrointestinal effects from undetermined occupational exposures have also been reported (EU-JRC, 2005).

3.4.2 Experimental animals

Inhalation

The motor co-ordination and pain sensitivity of groups of 12 male rats were examined periodically during and at the end of a three-month period during which they had been exposed for six hours per day, five days per week to atmospheres containing 217 or 435 mg m\(^{-3}\) of meta-xylene (Korsak et al., 1994). Motor co-ordination impairment and an increase in pain sensitivity occurred at the higher exposure. Although the significant effects on pain sensitivity were also present at 217 mg m\(^{-3}\) this exposure was described by USEPA (2003a) as a no-observed adverse effect level (NOAEL); ATSDR (2007) considered this lowest tested concentration as a "minimal LOAEL [lowest-observed adverse effect level]".

Other studies have identified persistent neurological changes in rats exposed repeatedly to vapour concentrations ≥435 mg m\(^{-3}\) of either meta-xylene (Gralewicz et al., 1995; Gralewicz and Wiaderna, 2001) or mixed xylene (Pryor et al., 1987; Nylén and Hagman, 1994) and in gerbils exposed continuously to 700–1,400 mg m\(^{-3}\) of xylene (18% ortho-xylene, 70% meta-xylene, 12% para-xylene and <3% ethylbenzene) (Rosengren et al., 1986). In 13-week repeated inhalation studies in rats, an

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\(^4\) Variously cited as 60, 60.9 and 62 mg m\(^{-3}\) in expert group evaluations, probably due to differences in the conversion of data in ppm to units of mg m\(^{-3}\) and rounding.
atmospheric concentration of 3,915 mg m⁻³ of the *para*-isomer induced ototoxicity (impaired hearing), whereas no similar effect resulted from exposure to 7,830 mg m⁻³ of either the *ortho-* and *meta*-isomers (Gagnaire *et al.*, 2001).

A number of rat studies have found that, although repeated inhalation exposures to high concentrations of mixed xylenes or the individual isomers increased liver weights and induced the activity of liver enzymes, there was little evidence of any associated liver damage (e.g. Savolainen *et al.*, 1978; Patel *et al.*, 1979; Ungváry *et al.*, 1980b; Tátrai *et al.*, 1981; Wisniewska-Knypl *et al.*, 1989; Simmons *et al.*, 1991).

**Oral**

No clear target organ toxicity was reported in gavage studies in which rats received 0, 100, 200 or 800 mg kg⁻¹ bw day⁻¹ of either *meta*-xylene (Wolfe *et al.*, 1988a) or *para*-xylene (Wolfe *et al.*, 1988b) for 90 days. The pathological changes seen in the lung of some of the treated rats were ascribed to the aspiration of the test material. USEPA (2003a) concluded the NOAEL and LOAEL, respectively, to be 200 and 800 mg kg⁻¹ bw day⁻¹ in each study based on decreased bodyweight (*m*-xylene) and early mortality (*p*-xylene) likely due to aspiration of test material.

There were also no signs of tissue damage when a mixture of xylenes and ethylbenzene (60% *meta*-xylene, 13.6% *para*-xylene, 9.1% *ortho*-xylene, 17% ethylbenzene) was administered by stomach tube five days per week for 13 weeks at up to 1,000 mg kg⁻¹ bw to rats and 2,000 mg kg⁻¹ bw day⁻¹ to mice (NTP, 1986). The rats receiving the high dose showed decreased bodyweight gain; the NOAEL was concluded by USEPA (2003a) to be 500 mg kg⁻¹ bw. In the mice, transient signs of nervous system depression were seen at the high dose; the NOAEL was concluded by USEPA (2003a) to be 1,000 mg kg⁻¹ bw.

Comprehensive long-term studies have also been conducted in mice and rats given the same mixture of xylenes and ethylbenzene (60% *meta*-xylene, 13.6% *para*-xylene, 9.1% *ortho*-xylene, 17% ethylbenzene) by stomach tube (NTP, 1986). Doses of 500 or 1,000 mg kg⁻¹ bw were administered to mice, and 250 or 500 mg kg⁻¹ bw to rats, five days per week for 103 weeks. Microscopic examination of an extensive range of tissues identified no treatment-related lesions in any of the xylene-exposed animals. Mice given the higher dose of 1,000 mg kg⁻¹ bw day⁻¹ exhibited hyperactivity, a sign of CNS toxicity. There was a reduced survival rate and a small decrease in bodyweight gain in rats given the higher dose of 500 mg kg⁻¹ bw day⁻¹. Both a WHO Task Group (WHO, 1996) and USEPA evaluators (USEPA, 2003a) considered there was no conclusive evidence of toxicity in the rats given 250 mg kg⁻¹ bw day⁻¹ or the mice given 500 mg kg⁻¹ bw day⁻¹.

Although a number of oral studies in rodents have reported increases in liver weight and induction of liver enzyme activity, the liver tissue was generally normal on microscopic examination (ATSDR, 2007). In rats given 800 mg kg⁻¹ bw day⁻¹ of *meta*-xylene by stomach tube (five days per week) for 3.5 weeks, there were increases in the the enzyme alanine aminotransferase in the blood, which is indicative of liver damage (Elovaaara *et al.*, 1989). A similar result was seen in rats receiving 750 mg kg⁻¹ bw day⁻¹ of mixed xylene for 90 days (Condie *et al.*, 1988).

There is one report of kidney pathology in rats given a mixture of xylenes and ethylbenzene (17.6% *ortho*-xylene, 62.3% *meta*-xylene and *para*-xylene, 20% ethylbenzene) for 90 days by stomach tube (Condie *et al.*, 1988). The type of kidney abnormality present in the males throughout the tested dose range of 150–1,500 mg kg⁻¹ bw day⁻¹ (hyaline droplet formation) was similar to that induced in rats by a range of other hydrocarbons. This is generally accepted as being a male-rat-specific response that is of no relevance to humans. There was, however, a different type of
mild pathology of the kidney (minimal chronic nephropathy) seen in the females (at incidences of 1/10, 3/10, 6/10, 7/10 at doses of 0, 150, 750 and 1,500 mg kg\(^{-1}\) bw day\(^{-1}\) respectively). Expert groups have differed in how to view these findings: ATSDR (2007) considered the lowest tested dose to be a NOAEL, whereas RIVM (2001) considered that it was a LOAEL.

Hearing loss and ear abnormalities resulted from the repeated administration of 900 mg kg\(^{-1}\) bw day\(^{-1}\) of \textit{para}-xylene, five days per week for two weeks by stomach tube to rats. The same doses of either the \textit{ortho-} or the \textit{meta-}isomer were without ototoxic effect (Gagnaire and Langlais, 2005). Guinea pig studies of the same duration revealed no indication of ototoxicity from oral doses of either 900 mg kg\(^{-1}\) bw day\(^{-1}\) of the \textit{para}-isomer or 1,800 mg kg\(^{-1}\) bw day\(^{-1}\) of the \textit{meta}-isomer (Gagnaire \textit{et al.}, 2007).

3.5 Reproductive and developmental toxicity

3.5.1 Humans

Preliminary studies have reported an association between xylene exposure of pregnant workers and an increased risk of miscarriage (Taskinen \textit{et al.}, 1994), or producing a child with a congenital physical anomaly (Kucera, 1968; Holmberg and Nurminen, 1980). The reports involved only very small numbers of cases and, as the women were exposed to a number of other solvents as well as xylenes, it is not possible to conclude that the association with xylene is causal.

3.5.2 Experimental animals

\textit{Inhalation}

Reproduction was unaffected in rats exposed to atmospheres containing 2,200 mg m\(^{-3}\) of technical-grade xylene (44.2% \textit{meta}-xylene, 20.4% \textit{ortho}-xylene, 20.3% \textit{para}-xylene, 12.8% ethylbenzene, 2.4% toluene). Males and females were exposed for six hours per day, five days per week for 131 days prior to mating, and females continued to be exposed throughout pregnancy and until weaning of the offspring (Bio/Dynamics Inc., 1983). Fertility was also normal in male rats exposed for 18 hours daily for 61 days to 4,300 mg m\(^{-3}\) of "xylene solvent" (Nylén and Hagman, 1994).

In a study conducted according to current test guidelines, rats were exposed for six hours a day on days 6–20 of pregnancy to 435, 2,175, 4,350 and 8,700 mg m\(^{-3}\) of \textit{ortho-}, \textit{meta-}, \textit{para}-xylene or a mixture of xylenes and ethylbenzene (21.3% \textit{ortho}-xylene, 43.9% \textit{meta}-xylene, 19.4% \textit{para}-xylene and 15.3% ethylbenzene) (Saillenfait \textit{et al.}, 2003). There were no signs of either maternal or foetal toxicity in the rats exposed to 2,175 mg m\(^{-3}\) of the \textit{meta} or \textit{para} isomer. At higher exposures, foetotoxicity (retarded ossification, increases in skeletal variations or reduced foetal weight) and overt maternal toxicity (reduced weight gain) occurred. With \textit{ortho}-xylene and the mixed xylenes, mild foetotoxicity (reduced foetal weight) was clearly present at 2,175 mg m\(^{-3}\), a concentration that did not affect maternal bodyweight. Foetal weight was not statistically significantly reduced at 435 mg m\(^{-3}\).

Foetal toxicity (delayed development, extra ribs or foetal loss) resulted from the continuous exposure of rats to 3,000 mg m\(^{-3}\) of either \textit{ortho-}, \textit{meta-} or \textit{para}-xylene from day 7 to day 14 of pregnancy. These exposures were overtly toxic to the mothers.
There were subtle qualitative differences in the developmental toxicity of the three isomers (Ungváry et al., 1980a). Foetal and maternal toxicity were also evident at 1,500 mg m$^{-3}$. With para-xylene, it was claimed that the foetotoxicity (delayed ossification) was also present at the lowest concentration of 150 mg m$^{-3}$, a concentration at which there was no maternal toxicity. A review published by IPCS commented critically on the inadequacy of the description of the criteria for assessing ossification in this study (IPCS, 1997).

All three isomers have demonstrated foetotoxicity in mice (Ungváry and Tátrai, 1985). This limited report contained no information on whether the treatments with the individual isomers (exposure for 12 hours per day on days 6–15 of pregnancy to 500 mg m$^{-3}$) were also maternally toxic. The corresponding experiment with “xylene” (not defined further, but presumably a mixture of all three isomers), which used doses of 0, 500 and 1,000 mg m$^{-3}$, found signs of foetotoxicity at the high dose but not at the low dose (Ungváry and Tátrai, 1985).

Continuous exposure of rabbits to 1,000 mg m$^{-3}$ of mixed xylene or para-xylene on days 7–20 of pregnancy resulted in abortions as well as maternal deaths. At 500 mg m$^{-3}$ (the lowest dose), there was mild foetotoxicity (reduced foetal bodyweight in the females) but no overt signs of maternal toxicity (Ungváry and Tátrai, 1985).

There was some evidence of impaired neurological development (impaired performance in tests for cognitive function and reduced brain weights) in the offspring of rats exposed to 2,200 mg m$^{-3}$ mixed xylenes and ethylbenzene (19% ortho-xylene, 45% meta-xylene, 20% para-xylene, and 15% ethylbenzene) for six hours per day on days 7 to 20 of pregnancy. This was the only dose level tested and it did not induce any overt signs of toxicity in the mothers (Hass et al., 1995, 1997).

Earlier work from the same research team (Hass and Jakobsen, 1993), in which the offspring of 12 rats exposed to 870 mg m$^{-3}$ of mixed xylenes (six hours per day on gestation days 4–20) underwent tests for developmental milestones and rotarod tests for motor coordination and balance, had indicated a reduced motor performance. However, Hass et al. (1995) criticised their earlier methodology as the study investigators were not blind to the exposure status of the rats. With an improved protocol in their later study in which the higher concentration of 2,200 mg m$^{-3}$ was used (Hass et al., 1995), no significant evidence for an effect on rotarod performance was reported.

**Oral**

A brief abstract notes that there were abnormalities (cleft palate) in the offspring of mice that had received ortho-, meta- or para-xylene at high and maternally toxic oral doses (m-xylene at about 2,600 mg kg$^{-1}$ bw day$^{-1}$; o- and p-xylene also at about 2,000 mg kg$^{-1}$ bw day$^{-1}$; no similar effects were present at 774 mg kg$^{-1}$ bw day$^{-1}$) on either days 6–15 or 12–15 of pregnancy (Nawrot and Staples, 1980).

Cleft palate was the main foetal abnormality when a xylene and ethylbenzene mixture (60.2% meta-xylene, 9.1% ortho-xylene, 13.6% para-xylene and 17.0% ethyl benzene) was administered to mice by stomach tube on days 6–15 of pregnancy at doses of 2,000–3,000 mg kg$^{-1}$ bw day$^{-1}$. Foetotoxicity (including deaths) was also reported. No adverse effects were detected at 1,000 mg kg$^{-1}$ bw day$^{-1}$ (Marks et al., 1982).
3.6 Genotoxicity

The clear weight of evidence from a wide range of screening tests is that xylenes do not possess significant genotoxic potential. No indications of activity were seen in studies of chromosome effects in occupationally exposed groups, chromosome damage in the bone marrow of rats and mice, sperm abnormalities in rats, chromosome damage and gene mutations in mammalian cells in culture, and mutagenicity in Salmonella typhimurium (Ames tests) (USEPA, 2003a; ATSDR, 2007).

3.7 Carcinogenicity

An IARC Working Group reporting in 1999 concluded that the xylenes were "not classifiable" as regards their carcinogenicity to humans (Group 3) (IARC, 1999). A 2003 review of carcinogenicity by USEPA concluded that the "data are inadequate for an assessment of the carcinogenic potential of xylenes” (USEPA, 2003a).

3.7.1 Humans

There are a small number of reports describing associations between occupational exposure to xylene and increased risks of leukaemia, non-Hodgkin’s lymphoma and cancer of the rectum, colon or nervous system (USEPA, 2003a; Miligi et al., 2006; Vineis et al., 2007). The various limitations of the studies and the concurrent exposure of the workers to other solvents mean that it is not possible to draw conclusions from these studies about the carcinogenicity of xylenes.

3.7.2 Experimental animals

Long-term oral studies in rats and mice (NTP, 1986) (see Section 3.4) did not generate any evidence of carcinogenic potential for a mixture of xylenes and ethylbenzene (60% meta-xylene, 13.6% para-xylene, 9.1% ortho-xylene, 17.0% ethylbenzene). No treatment-related increases in the incidence of any tumour type were seen. The maximum tested doses administered by stomach tube were 1,000 mg kg$^{-1}$ bw day$^{-1}$ to the mice and 500 mg kg$^{-1}$ bw day$^{-1}$ to the rats. Initial group sizes were 50 animals of each sex and a comprehensive range of tissues were subjected to microscopic examination.

3.8 Summary

CNS toxicity is the most sensitive systemic indicator of inhalation exposure to xylene. CNS effects were reported from repeated occupational exposure to around 60 mg m$^{-3}$ of mixed xylenes, in volunteers exposed for two hours to 200 mg m$^{-3}$ of meta-xylene, and in laboratory animals repeatedly exposed to 435 mg m$^{-3}$ of meta-xylene or mixed xylenes.

Hearing loss occurred in rats exposed repeatedly to 3,915 mg m$^{-3}$ of the para-xylene but not in rats exposed similarly to 7,830 mg m$^{-3}$ of the meta- or ortho-isomer. Acute LC$_{50}$ values for six-hour exposures in rats were over 17,000 mg m$^{-3}$ for all isomers.

In long-term rodent studies in which mixed xylenes were administered by gavage, there were signs of mild neurotoxicity in mice at 1,000 mg kg$^{-1}$ bw day$^{-1}$ and reduced
bodyweight gain in rats at 500 mg kg\(^{-1}\) bw day\(^{-1}\). There were no signs of toxicity in mice given 500 mg kg\(^{-1}\) bw day\(^{-1}\) and in rats given 250 mg kg\(^{-1}\) bw day\(^{-1}\).

Other rat studies involving shorter term repeated administration by stomach tube reported mild kidney toxicity at doses of 150 mg kg\(^{-1}\) bw day\(^{-1}\) of mixed xylenes and some liver changes at doses of 750–800 mg kg\(^{-1}\) bw day\(^{-1}\) of the meta-isomer or mixed xylenes. Repeated oral doses of 900 mg kg\(^{-1}\) bw day\(^{-1}\) of para-xylene induced hearing loss in rats but not in guinea-pigs. The ortho- and meta-isomers given orally at 900 mg kg\(^{-1}\) bw day\(^{-1}\) had no impact on the hearing of rats. Acute oral LD\(_{50}\) values in rodents were in excess of 2,000 mg kg\(^{-1}\) bw.

A wide range of screening tests indicate that the xylenes do not possess significant genotoxic potential. Long-term oral studies of mixed xylenes generated no evidence of carcinogenicity.

Mild effects on the foetus were observed when pregnant rats were exposed repeatedly to 2,175 mg m\(^{-3}\) of either mixed xylene or ortho-xylene, an atmospheric concentration that did not produce overt signs of toxicity in the mothers. The foetal toxicity was not present at exposures of 435 mg m\(^{-3}\). In the same study, the para- and meta-isomers produced adverse effects on the foetus only at maternally toxic exposures. Limited reports describe foetotoxicity in mice exposed repeatedly to 500 mg m\(^{-3}\) of each isomer and in rabbits exposed repeatedly to 500 mg m\(^{-3}\) of mixed xylene or para-xylene. Foetal abnormalities were induced in mice dosed orally during pregnancy with a maternally toxic dose of 2,000–3,000 mg kg\(^{-1}\) bw day\(^{-1}\) of a xylene mixture.
4 Derivation of Health Criteria Values

4.1 WHO drinking-water guidelines

The World Health Organization (WHO) guideline value for drinking-water quality published in 1993 was based on a tolerable daily intake (TDI) of 179 µg kg\(^{-1}\) bw derived from a long-term study in which a mixture of xylenes and ethylbenzene was administered by stomach tube to rats (NTP, 1986). The only toxic effect confidently ascribed to treatment was the lower gain in bodyweight noted at 500 mg kg\(^{-1}\) bw day\(^{-1}\); growth was unaffected at 250 mg kg\(^{-1}\) bw day\(^{-1}\). This study NOAEL was adjusted to 179 mg kg\(^{-1}\) bw day\(^{-1}\) to reflect continuous exposure rather than the study exposure regime of five days per week. Application of an Uncertainty Factor (UF) of 1,000 (10 each for inter- and intra-species variation, and 10 for “the limited toxicological end-point”) produced the TDI of 179 µg kg\(^{-1}\) bw (WHO, 1993, 1996).

A WHO Final Task Force Meeting in 2003 agreed that the 1993 risk assessment could be brought forward to the 2006 edition of the drinking-water guidelines (WHO, 2006).

4.2 EU Scientific Committee on Food

The TDI of 179 µg kg\(^{-1}\) bw derived by WHO (see Section 4.1) was specifically cited and used – and therefore by implication endorsed – by the EU Scientific Committee on Food (SCF) in 1999 to judge the toxicological acceptability of the levels of xylenes in foods (SCF, 1999).

4.3 International Programme on Chemical Safety

A WHO International Programme on Chemical Safety (IPCS) Task Group in 1995 derived a number of guidance values\(^5\) for inhalation exposure to xylenes and published these in an Environmental Health Criteria (EHC) document (IPCS, 1997). The guidance value applicable to the general population was based on a finding of developmental neurotoxicity seen at the lowest tested concentration of 870 mg m\(^{-3}\) in a rat study (Hass and Jakobsen, 1993). Developmental neurotoxicity was described as the critical endpoint, as it is a serious effect that may be long lasting. The “lowest observed adverse effect” level (LOAEL) was divided by an UF of 1,000 (10 each for inter- and intra-species variations, and 10 for the use of a LOAEL instead of a NOAEL) to generate a guidance value of 0.87 mg m\(^{-3}\). An UF of 10 for the use of a LOAEL was regarded as justified because of evidence from other studies of less serious effects (either reduced foetal weight or delayed ossification) at lower exposure levels. IPCS did not seem to account for the difference between the experimental exposure regime (six hours per day) and the purpose of the guidance limit (applicable to 24-hour exposure).

\(^5\) A “guidance value” is an estimation of an exposure experienced over a lifetime that would be expected to be without appreciable health risk in the general population.
4.4 EU Indoor Exposure Limits

As part of the European Commission’s INDEX⁶ project, the Joint Research Centre (JRC) in collaboration with a steering committee of European experts in the area of indoor air pollution derived a chronic inhalation Exposure Limit (EL) for xylenes (EU-JRC, 2005). Their evaluation of the toxicological literature (identified by searches undertaken in 2004) indicated that, although differences in the toxicity of individual xylene isomers had been detected, no consistent pattern following inhalation exposure had been identified. It was decided that an EL for xylenes as a class could be based on a neurological endpoint and that this could be achieved from the results of the occupation study of Uchida et al. (1993). A neurological effect (“floating sensation”) and a range of other mild effects (eye irritation, sore throat and poor appetite) were reported at exposures of 62 mg m⁻³ in this study. This LOAEL was adjusted to 22 mg m⁻³ (a conversion from occupational to continuous exposure⁷) and then divided by a “total assessment factor” of 100 (10 for use of an LOAEL and 10 for human variability) to generate, after rounding, an EL of 0.2 mg m⁻³ (EU-JRC, 2005; Koistinen et al., 2008).

4.5 US Environmental Protection Agency

A 2003 reassessment of the toxicological status of xylene mixtures by the US Environmental Protection Agency (USEPA) resulted in the development of an inhalation Reference Concentration (RfC)⁸ (USEPA, 2003a). It was based on the neurological findings seen in rats exposed for six hours per day, five days per week for 13 weeks to meta-xylene in the atmosphere (Korsak et al., 1994). The study NOAEL of 217 mg m⁻³ was converted to its equivalent continuous exposure⁹ of 39 mg m⁻³ and then to its Human Equivalent Concentration (HEC),¹⁰ which was also 39 mg m⁻³. An overall UF of 300 was then applied to generate, after rounding, the RfC of 0.1 mg m⁻³. This UF of 300 arose from component factors of 3 for the interspecies extrapolation, 10 to take account of interindividual variations in sensitivity within the human population, 3 for the use of a subchronic study to derive a chronic safety limit, and 3 for uncertainties in the database, in particular a lack of a two-generation reproductive toxicity study.¹¹ An interspecies UF of 3 was thought to be sufficient because the toxicokinetic interspecies adjustment was considered to be accommodated in the conversion of the rat NOAEL to the NOAEL(HEC).

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⁶ Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU.

⁷ It was assumed that the men worked eight hours a day, five days a week. The workers were assumed to inhale 10 m³ of air over an eight-hour shift compared with the inhalation of 20 m³ by an adult in 24 hours, i.e. 62 x 10/20 x 5/7.

⁸ 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 effects during a lifetime. The RfC addresses non-cancer effects only.

⁹ 217 x 6/24 x 5/7.

¹⁰ The HEC is derived through the application of a factor reflecting the ratio of the rat to human blood/gas partition coefficients. If this ratio is greater than 1, the substance partitions into the blood more efficiently in rats than in humans. Where this occurs, as is the case with xlenes, USEPA defaults to an adjustment factor of 1 (i.e. it sets the human coefficient equal to that of the rat, thereby assuming that xlenes are more efficiently partitioned to human blood than they actually are).

¹¹ The uncertainty factors of “3” are also referred to as “√10” in the detailed Toxicological Review paper (USEPA, 2003b).
An oral Reference Dose (RfD)\textsuperscript{12} of 0.2 mg kg\textsuperscript{-1} bw day\textsuperscript{-1} was also developed in 2003 (USEPA, 2003a). The critical effects were considered to be the decreased bodyweight gain and higher mortality seen in rats given 500 mg kg\textsuperscript{-1} bw day\textsuperscript{-1} of mixed xylenes by stomach tube for two years (NTP, 1986). The NOAEL was 250 mg kg\textsuperscript{-1} bw day\textsuperscript{-1}. This dose was administered five days per week and the daily equivalent was calculated as 179 mg kg\textsuperscript{-1} bw day\textsuperscript{-1}. An UF of 1,000 was applied and the resulting value was rounded to give an RfD of 0.2 mg kg\textsuperscript{-1} bw day\textsuperscript{-1}. The UF was made up of components of 10 each for inter- and intra-species variations, and an additional 10 to take account of the limitations of the database (in particular a lack of oral neurotoxicity studies as well as multi-generation reproductive toxicity and developmental neurotoxicity studies). The factor for database limitations was higher in the derivation of the RfD than for the RfC because of the relative paucity of oral over inhalation data.

4.6 US Agency for Toxic Substances and Disease Registry

The US Agency for Toxic Substances and Disease Registry (ATSDR) 2007 Toxicological Profile for xylene noted that, although some studies had shown different orders of toxicity for the individual xylene isomers, there was no consistent pattern indicating that a particular isomer was the most potent for all endpoints. It was therefore proposed that “the most sensitive effect by mixed xylenes or any isomer” was used to derive minimal risk levels (MRLs) that were applicable to “mixed xylenes and all isomers” (ATSDR, 2007).

ATSDR (2007) considered the LOAEL of 14 ppm (60.9 mg m\textsuperscript{-3}) for “subjective respiratory and neurological effects” reported by workers in the Uchida et al. study (1993) to be the best foundation for a chronic inhalation MRL. “The rapid clearance of xylene from the body” was said to justify the direct use of this occupational LOAEL (rather than its continuous exposure equivalent) in the derivation of the MRL. An UF of 100 (comprising factors of 10 for the use of a LOAEL and 10 to take account of human variability) was applied, along with a modifying factor (MF) of 3 to account for the lack of any supporting studies on the chronic neurotoxicity of xylene. The division of the LOAEL by 300 and rounding generated the inhalation MRL of 0.05 ppm (0.22 mg m\textsuperscript{-3}) (ATSDR, 2007).

The NOAEL of 250 mg kg\textsuperscript{-1} bw day\textsuperscript{-1} reported in a two-year study in rats treated with mixed xylenes by gavage (NTP, 1986) was said to provide a “minimal basis” for the derivation of a chronic oral MRL. A slight decrease in bodyweight gain and an unexplained reduction in survival of males occurred at the LOAEL of 500 mg kg\textsuperscript{-1} bw day\textsuperscript{-1}. After adjustment of the experimental regime to continuous exposure (giving an adjusted NOAEL of 179 kg kg\textsuperscript{-1} bw day\textsuperscript{-1}), the application of an UF of 100 and a MF of 10 generated (after rounding) an oral MRL applicable to chronic human exposures of 0.2 mg kg\textsuperscript{-1} bw day\textsuperscript{-1}. The UF comprised constituent factors of 10 for extrapolation from laboratory animals to humans, and 10 to accommodate variability within the human population. The MF was invoked to take account both of the inadequacy of the key study (in particular its lack of testing for the subtle neurological effects that were the most sensitive endpoints in inhalation studies and acute oral studies) and the absence of developmental and multi-generational data (ATSDR, 2007).

\textsuperscript{12} The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD addresses non-cancer effects only.
4.7 Dutch National Institute for Public Health and the Environment

In its 1999 assessment, the Dutch National Institute for Public Health and the Environment (RIVM) noted that there was “limited justification” for individual isomer HCVs because the values that may result “probably reflect the differences in the data available for the different isomers rather than any real differences in toxicological properties”. A “pooled evaluation” of xylene isomers was therefore undertaken (RIVM, 2001).

A Tolerable Concentration in Air (TCA)\(^{13}\) of 0.87 mg m\(^{-3}\) was proposed. It was based on the application of an UF of 1,000 to the LOAEL reported in a developmental study in rats. Behavioural impairment was seen in the offspring of rats exposed during pregnancy to the lowest tested concentration of 870 mg m\(^{-3}\) (Hass and Jakobsen, 1993). The overall UF comprised factors of 10 each for interspecies and intraspecies differences, and a factor of 10 for the use of a LOAEL.

The mild chronic nephropathy seen in female rats given 150 mg kg\(^{-1}\) bw day\(^{-1}\) of mixed xylenes by gavage for 90 days (Condie et al., 1988) was the foundation of an oral TDI. The application of an UF of 1,000 to this LOAEL generated the oral TDI of 0.15 mg kg\(^{-1}\) bw. The component UFs were 10 for possible interspecies differences, 10 for intraspecies variations, and 10 for the limited duration of the pivotal study. As the toxic effects at this lowest tested dose were said by RIVM to be “marginal”, an extra factor for the use of an LOAEL was deemed to be unnecessary.

4.8 Japanese guidelines for indoor air quality

Public concern in Japan over “sick building syndrome” encouraged the Ministry of Health, Labour and Welfare to develop guidelines on indoor air pollutants. In 2000, a limit of 722 \(\mu g\) m\(^{-3}\) was proposed for xylene. It was based on the effects on the CNS recorded in humans occupationally exposed to 91 mg m\(^{-3}\).\(^{14}\) The application of UFs of 10 to convert the LOAEL to a NOAEL, and 3 to take account for the less-than-lifetime exposure of the experimental data-point generated the guideline value\(^{15}\) (Azuma et al., 2007).

4.9 Discussion

Most of the studies that have attempted to elucidate the dose–response of the toxicology of the xylenes have used various xylene mixtures (in some cases with other structurally similar chemicals present such as ethylbenzene). Consequently, the evaluations by authoritative bodies of TDIs or their equivalent have generally been expressed in terms of “xylene” and are currently considered applicable to all the isomers.

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\(^{13}\) 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.

\(^{14}\) The study is presumably that of Uchida et al. (1993), but unlike EC (2005) and ATSDR (2007), the Japanese assessment used the arithmetic mean exposure concentration of 91 mg m\(^{-3}\) rather than the geometric mean value.

\(^{15}\) No further details of the derivation are given in the available secondary source. It would seem that the occupational LOAEL was converted to its equivalent continuous exposure assuming a 40-hour working week (91 x 40/168).
The available database from which to select a health-based guideline value is poor and all the studies used by expert groups for this purpose have limitations. Six expert groups have developed chronic inhalation HCVs on the basis that the critical target of inhaled xylene is the CNS (some also citing ocular and respiratory irritancy as co-critical effects). However, they have used different studies as the basis for guideline derivation.

The chronic inhalation MRL of 0.05 ppm (0.22 mg m\(^{-3}\)) recommended in a 2007 ATSDR assessment is based on mild effects on the CNS reported by workers exposed for long periods to xylenes (Uchida et al., 1993). It arose from the division of the reported occupational LOAEL of 14 ppm (60.0 mg m\(^{-3}\)) by an UF of 100 (10 for the use of an LOAEL and 10 for interindividual differences in sensitivity) and an extra MF of 3 to compensate for database inadequacies – in particular a lack of studies on chronic neurotoxicity. This same epidemiological study is the foundation of an EL for xylenes derived as part of the 2005 INDEX project to recommend indoor exposure limits. The European derivation involved the conversion of the occupational LOAEL of 62 mg m\(^{-3}\) to its continuous equivalent of 22 mg m\(^{-3}\) – a step not considered necessary by ATSDR because of the “rapid clearance of xylene from the body”. Application of a “total assessment factor” of 100 (10 for the use of an LOAEL and 10 to take account of interindividual differences in sensitivity) to the adjusted LOAEL generated, after rounding, a chronic inhalation HCV (EL) of 0.2 mg m\(^{-3}\).

There is also a Japanese indoor air quality guideline for xylene. It was derived in 2000 and is also based on an occupational LOAEL [the secondary source does not identify the study or studies responsible, but the LOAEL is presumed to be that of Uchida et al. (1993) described as the arithmetic mean exposure concentration] and the conversion of this to continuous exposure, albeit by a marginally different methodology to that used in the EC INDEX project. The Japanese included an UF of 3 to take account of the less-than-lifetime exposure of the workers, a measure that did not feature in the European derivation. However, the absence of any UF to account for interindividual variations in susceptibility in the Japanese derivation resulted in the more liberal guideline value of 0.72 mg m\(^{-3}\) proposed by the Japanese. The normal interindividual default factor of 10 was applied in the INDEX project assessment.

In a 2003 assessment, USEPA was critical of the value of Uchida et al. (1993) because of the lack of any clear demonstration of a relationship between response and dose or duration, the problems introduced by co-exposure to other chemicals, and the inherent bias introduced by self-reporting of symptoms. USEPA preferred to derive an RfC from a 13-week inhalation experiment in rats which demonstrated meta-xylene’s neurological action (Korsak et al., 1994). USEPA considered the low dose of 217 mg m\(^{-3}\) to be a NOAEL (ATSDR in its 2007 report described it as a minimal LOAEL). The RfC of 0.1 mg m\(^{-3}\) recommended by USEPA was generated through the application of an UF of 300 to the continuous exposure equivalent of the “NOAEL”. Constituent UF\(s\) included 3 to take account of the use of a subchronic study and 3 to compensate for the inadequacies of the database.

A study reporting neurological impairment in the offspring of treated rats (Hass and Jakobsen, 1993) was the selected basis both of a 1995 IPCS evaluation (published as IPCS, 1997) and a 1999 RIVM assessment. Although the investigators themselves have acknowledged the limitations of the study methodology, the IPCS Task Group and RIVM considered that it provided evidence of developmental neurotoxicity at the lowest tested concentration of 870 mg m\(^{-3}\). Applying an UF of 1,000 (100 for inter- and intra-species extrapolation, and 10 for the use of a LOAEL) produced an inhalation HCV of 0.87 mg m\(^{-3}\) – a guidance value in IPCS terminology, and a RIVM TCA.

The Hass and Jakobsen (1993) study involved repeated six-hourly daily exposures to xylenes during pregnancy. No account was taken by either IPCS or RIVM in their derivation of inhalation HCV values of the difference between this experimental regime
and the 24-hour exposure of the human population to which the HCV is applicable. If this had been incorporated in the derivation, it would have resulted in a reduction of the guideline values from 0.87 mg m\(^{-3}\) to approximately 0.22 mg m\(^{-3}\). The more recent assessment undertaken under the EU INDEX initiative proposed a chronic inhalation HCV of 0.2 mg m\(^{-3}\) based on an occupational study (Uchida et al., 1993). An ATSDR assessment finalised in 2007 also used the findings of Uchida et al. (1993) to derive a chronic inhalation limit of 0.22 mg m\(^{-3}\), though the method by which ATSDR derived this value differed from that of the European experts.

An atmospheric concentration of (approximately) 0.2 mg m\(^{-3}\) would therefore seem a reasonable basis for proposing an inhalation TDI (TDI\(_{inh}\)) here. On the assumption that a 70-kg adult inhales 20 m\(^3\) of air a day, the recommended TDI\(_{inh}\) (after rounding) is 60 µg kg\(^{-1}\) bw day\(^{-1}\).

The evaluations of WHO task groups in 1993 and 2003, USEPA in 2003, and ATSDR in 2007 each agreed that the critical study for the derivation of a chronic oral guideline value for xylene was the two-year oral gavage study of mixed xylenes in rats (NTP, 1986). The reported NOAEL in this study was 250 mg kg\(^{-1}\) bw day\(^{-1}\). Application of an UF of 1,000, which included a factor of 10 for database inadequacies, to the daily equivalent of the five-day-a-week NOAEL was used to generate the relevant health-based guideline value. The difference in the final values for the oral HCV of 179 µg kg\(^{-1}\) bw day\(^{-1}\) from WHO and 200 µg kg\(^{-1}\) bw day\(^{-1}\) for the two US agencies is a result of rounding up to one significant figure.

In 1999, RIVM based its oral TDI of 150 µg kg\(^{-1}\) bw on the results of a 90-day gavage study of mixed xylenes in rats which were said to support a LOAEL of 150 mg kg\(^{-1}\) bw day\(^{-1}\) for mild kidney changes (Condie et al., 1988). RIVM applied an overall UF of 1,000 to the LOAEL, including a factor of 10 because of the use of a short-term study in the derivation of a chronic HCV. No uncertainty factor for the use of a LOAEL was considered necessary due to the very mild nature of the effect on the kidney.

In essence, there is agreement on the oral chronic HCVs that have confirmed expert group support, and the 180 µg kg\(^{-1}\) bw value (rounded to two significant figures) of WHO, endorsed by SCF, which lies in the centre of the range (150, 179 and 200 µg kg\(^{-1}\) bw day\(^{-1}\)) is recommended here as the TDI\(_{oral}\) for the purposes of deriving SGVs.
5 Background intake

5.1 Food

The most recently identified survey of xylenes and other aromatic hydrocarbons in the UK diet was that carried out in 1993 by the then Ministry of Agriculture, Fisheries and Food (MAFF, 1995). In this Total Diet Study, samples of 20 food groups collected from ten locations in the UK were analysed. Each group consisted of retail food products, prepared as for consumption and then combined in amounts reflecting their relative importance in the average UK diet. Xylene was detected in most samples of meat, fish and nuts, but were not generally detected (detection limit 2 µg kg\(^{-1}\)) in other food groups. The average UK dietary intake of xylenes (the three isomers combined) was estimated to be less than 5 µg per person per day, with an upper bound estimate (assuming that the chemical was present at the detection limit in any food group sample in which it was not detected) of around 10 µg day\(^{-1}\).

5.2 Water

No measured values of xylene in UK drinking-water have been identified, although all three isomers were detected (but not quantified) in 14 samples of UK drinking-water derived from rivers, lowland reservoirs and groundwater (Fielding et al., 1981). In British aquifers (uncontaminated sites thought to represent background levels), the ortho and meta isomers were detected in some samples at concentrations up to 0.02 µg L\(^{-1}\) (Kenrick et al., 1985).

Drinking-water levels in other countries have been reported by WHO (1996) and IPCS (1997). Mean concentrations of individual isomers were generally less than 1 µg L\(^{-1}\).

A concentration of 3 µg L\(^{-1}\) (all isomers combined) would result in a daily intake of 6 µg, assuming a daily water consumption of two litres for an adult.

5.3 Air

The UK Air Quality Archive provides data and statistics from the air quality monitoring networks operated on behalf of Defra and the devolved administrations. For 2006, the annual mean concentrations for meta- and para-xylene at five (four urban and one rural) sites ranged from 0.4 to 5 µg m\(^{-3}\), with maximum hourly levels of 17–109 µg m\(^{-3}\). For ortho-xylene, the annual means and maxima for the five sites were 0.2–2.5 and 6–30 µg m\(^{-3}\) respectively (Defra, 2007).

In 2002, the annual mean concentrations for meta- and para-xylene at five (rural and urban) sites ranged from 0 to 2 µg m\(^{-3}\) (rounded values), with annual maxima of 2–22 µg m\(^{-3}\); for ortho-xylene, the annual means and maxima for the five sites were 0–1 and 1–5 µg m\(^{-3}\) respectively (Defra, 2003). For the 2001 monitoring period, the annual mean concentration of xylenes (all isomers combined) for four (rural and urban) sites in the UK was about 2 µg m\(^{-3}\). Annual maxima at these sites ranged from around 4 to 33 µg m\(^{-3}\) (Defra, 2002).

Taken together, the annual mean data for 2006, 2002 and 2001 indicate that an overall mean concentration for xylenes in UK outdoor air would be about 2–3 µg m\(^{-3}\).
A few measurements of the concentration of xylenes in dwellings in the UK have been reported (Brown and Crump, 1998; Kim et al., 2001), while data from other countries are described by IPCS (1997), ATSDR (1995, 2007) and EU-JRC (2005). These suggest that indoor concentrations are usually higher – typically by a factor of between 1.5 and 3 – than those taken outdoors. Some US surveys provide data on personal air concentrations as well as indoor and outdoor concentrations. Outdoor concentrations were lower than indoor concentrations which, in turn, were lower than personal air samples. The concentration in personal air was typically two to three times higher than that in outside air (Wallace et al., 1988, 1991).

5.4 Other sources

General population exposure to xylene can occur through skin contact with the many consumer products containing it including cleaning solvents, insecticides, lacquers, paint thinners and removers, and pesticides (ATSDR, 2007). For example meta-xylene was detected in 33.3% of household cleaners and polishes and in 60.3% of paint-related products (Sack et al., 1992). Quantitative estimates of these exposures are, however, not available.

Cigarette smoke also contains xylenes. In a study carried out at the Laboratory of the Government Chemist, the yields of xylenes were measured in the mainstream smoke of 26 cigarette brands on the UK market and of smoke from hand-rolled tobacco (Darrall et al., 1998). The levels (all isomers combined) ranged between 1 and 25 µg per cigarette; the average value was about 12 µg. For a person smoking 20 cigarettes a day, the intake of xylenes would therefore be about 240 µg day⁻¹.

5.5 Estimation of mean daily intakes

The adult intake of xylenes from food and water combined is unlikely to be greater than about 20 µg. Assuming the average intakes from food and water are, respectively, 5 and 6 µg day⁻¹, the adult oral mean daily intake (MDIoral) is estimated to be 11 µg day⁻¹.

Using an occupancy factor for dwellings of 0.9 (Mann et al., 1997), an indoor/outdoor concentration ratio of 3 and a mean outdoor concentration of 2.5 µg m⁻³, the mean personal exposure concentration for people living in the UK is estimated at 7 µg m⁻³. Based on a 70-kg adult inhaling 20 m³ of air per day, this corresponds to an adult inhalation mean daily intake (MDIinh) of about 140 µg day⁻¹.

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16 Personal air is defined as air samples that were collected using a sampling vest worn by the participant with the pump and collecting cartridge close to the breathing zone.

17 Indoor (0.9 x 2.5 µg m⁻³ x 3) + Outdoor (0.1 x 2.5 µg m⁻³).
6 Conclusions

The CNS is the critical target of inhalation exposure to xylene. Occupational exposure to atmospheric concentrations of around 60 mg m\(^{-3}\) (during working hours) of mixed xylenes has produced signs of mild neurotoxicity and is the basis of the recommended TDI\(_{\text{inh}}\) of 60 µg kg\(^{-1}\) bw day\(^{-1}\).

Toxicity data from repeated oral exposure are not available for humans. Effects seen in long-term oral studies in rodents form the basis of the recommended TDI\(_{\text{oral}}\) of 180 µg kg\(^{-1}\) bw day\(^{-1}\).

Information on dermal toxicity and skin absorption is limited; however, the available data suggest dermal absorption occurs but to a much lesser extent than oral or pulmonary absorption.

The adult MDI\(_{\text{inh}}\) and MDI\(_{\text{oral}}\) are estimated to be 140 and 11 µg day\(^{-1}\), respectively. For inhalation, therefore, background exposure to xylene from ambient air occupies a minor proportion of the TDI\(_{\text{inh}}\) while, for the oral route, only a very small fraction of the TDI\(_{\text{oral}}\) is required to accommodate background exposure to xylene from food and water (see Table 6.1).

Table 6.1 HCV and MDI values for xylene

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Oral</th>
<th>Inhalation</th>
</tr>
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<tbody>
<tr>
<td>MDI</td>
<td>µg day(^{-1})</td>
<td>11</td>
<td>140</td>
</tr>
<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg(^{-1}) bw day(^{-1})</td>
<td>0.16</td>
<td>2</td>
</tr>
<tr>
<td>MDI for 20-kg child</td>
<td>µg kg(^{-1}) bw day(^{-1})</td>
<td>0.41 (^{a})</td>
<td>5.2 (^{a})</td>
</tr>
<tr>
<td>TDI</td>
<td>µg kg(^{-1}) bw day(^{-1})</td>
<td>180</td>
<td>60</td>
</tr>
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</table>

\(^{a}\) See Environment Agency (2009) for details of MDI conversion factors.

Neurotoxicity is a key feature of both oral and inhalation exposure to xylene. This should therefore be considered in a risk assessment of xylene.
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## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry [USA]</td>
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<tr>
<td>BTEX</td>
<td>benzene, toluene, ethylbenzene and xylene</td>
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<tr>
<td>bw</td>
<td>bodyweight</td>
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<tr>
<td>CASRN</td>
<td>Chemical Abstracts Service registry number</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>Defra</td>
<td>Department for Environment, Food and Rural Affairs [UK]</td>
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<tr>
<td>EHC</td>
<td>Environmental Health Criteria [monograph of IPCS]</td>
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<tr>
<td>EL</td>
<td>Exposure Limit</td>
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<tr>
<td>FSA</td>
<td>Food Standards Agency [UK]</td>
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<tr>
<td>HCV</td>
<td>Health Criteria Value</td>
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<tr>
<td>HEC</td>
<td>human equivalent concentration</td>
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<td>HPA</td>
<td>Health Protection Agency [UK]</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<tr>
<td>IPCS</td>
<td>International Programme on Chemical Safety</td>
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<tr>
<td>LOAEL</td>
<td>lowest-observed adverse effect level</td>
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<tr>
<td>MAFF</td>
<td>Ministry of Agriculture Fisheries and Food [UK]</td>
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<tr>
<td>MDI</td>
<td>mean daily intake</td>
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<tr>
<td>MF</td>
<td>modifying factor</td>
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<tr>
<td>MRL</td>
<td>minimal risk level</td>
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<tr>
<td>NOAEL</td>
<td>no-observed adverse effect level</td>
</tr>
<tr>
<td>NTP</td>
<td>National Toxicology Program [USA]</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>RfC</td>
<td>Reference Concentration</td>
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<tr>
<td>RfD</td>
<td>Reference Dose</td>
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<tr>
<td>SCF</td>
<td>Scientific Committee on Food [EU]</td>
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<tr>
<td>SGV</td>
<td>Soil Guideline Value</td>
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<tr>
<td>TCA</td>
<td>Tolerable Concentration in Air</td>
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<tr>
<td>TDI</td>
<td>tolerable daily intake</td>
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<tr>
<td>UF</td>
<td>uncertainty factor</td>
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<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
Appendix – Literature search

The literature searches that formed the basis of this update report were undertaken using a proprietary database – the TRACE database developed and managed by bibra toxicology advice & consulting. The database was searched in June 2007 and again in August 2008 for comprehensive reviews and evaluations of xylene using the CAS Registry Numbers of the three individual isomers and the mixture. A TRACE search was then undertaken to identify any critical toxicity reports in the primary literature published since 2004 which would not as yet have been subject to expert group evaluation or included in a comprehensive review.

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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