Tetrachloroethene in drinking-water

Background document for development of
WHO Guidelines for drinking-water quality

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Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters ...”, including those related to the safety and management of drinking-water.

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International standards for drinking-water*. It was revised in 1963 and 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects, reviewing selected microorganisms, was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006, and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2017.

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

Since the first edition of the GDWQ, WHO has published information on health criteria and other information to support the GDWQ, describing the approaches used in deriving guideline values, and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks to human health from exposure to that chemical in drinking-water was prepared. The draft health criteria document was submitted to a number of scientific institutions and selected experts for peer review. The draft document was also released to the public domain for comment. Comments were carefully considered and addressed, as appropriate, taking into consideration the processes outlined in the *Policies and procedures used in updating the WHO guidelines for drinking-water quality* and the WHO Handbook for guideline development. The revised draft was submitted for final evaluation at expert consultations.

During preparation of background documents and at expert consultations, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents; the International Agency for Research on Cancer; the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues; and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO website and in the current edition of the GDWQ.
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of the World Health Organization (WHO) Guidelines for drinking-water quality (GDWQ) was led by
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The work of the following experts was crucial in the development of this document and others in the
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of the GDWQ, held on 28–30 March 2017 and 13–14 July 2018. The final version of the document
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Many individuals from various countries contributed to the development of the GDWQ. The efforts of
all who contributed to the preparation of this document are greatly appreciated.
# Acronyms and abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BMDL$_{10}$</td>
<td>lower 95% confidence limit on the benchmark dose for a 10% response</td>
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<tr>
<td>bw</td>
<td>body weight</td>
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<tr>
<td>CAS</td>
<td>Chemical Abstracts Service</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CYP</td>
<td>cytochrome P450</td>
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<tr>
<td>DCA</td>
<td>dichloroacetic acid</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
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<tr>
<td>GDWQ</td>
<td>Guidelines for drinking-water quality</td>
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<tr>
<td>GSH</td>
<td>glutathione</td>
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<tr>
<td>GST</td>
<td>glutathione-S-transferase</td>
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<tr>
<td>GV</td>
<td>guideline value</td>
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<tr>
<td>JISA</td>
<td>Japan Industrial Safety Association</td>
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<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
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<tr>
<td>NAcTCVC</td>
<td>N-acetyl-S-trichlorovinyl-L-cysteine</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
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<tr>
<td>NTP</td>
<td>National Toxicology Program</td>
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<tr>
<td>PBPK</td>
<td>physiologically based pharmacokinetic (modelling)</td>
</tr>
<tr>
<td>PCE</td>
<td>tetrachloroethene (perchloroethylene)</td>
</tr>
<tr>
<td>PPAR</td>
<td>peroxisome proliferator activated receptor</td>
</tr>
<tr>
<td>TCA</td>
<td>trichloroacetic acid</td>
</tr>
<tr>
<td>TCVC</td>
<td>S-trichlorovinyl-L-cysteine</td>
</tr>
<tr>
<td>TCVG</td>
<td>S-(1,1,2-trichlorovinyl) glutathione</td>
</tr>
<tr>
<td>TDI</td>
<td>tolerable daily intake</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>US EPA</td>
<td>United States Environmental Protection Agency</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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<tr>
<td>VOC</td>
<td>volatile organic compound</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
## Contents

**Executive summary**

1. **General description**
   - Identity
   - Physicochemical properties
   - Organoleptic properties
   - Major uses and sources

2. **Environmental levels and human exposure**
   - Water
   - Food
   - Air
   - Bioaccumulation
   - Occupational exposure
   - Estimated total exposure, biomonitoring studies and relative contribution of drinking-water

3. **Toxicokinetics and metabolism in animals and humans**
   - Absorption
   - Distribution
   - Metabolism
   - Elimination
   - Physiologically based pharmacokinetic modelling

4. **Effects on humans**
   - Acute exposure
   - Short-term exposure
   - Long-term exposure
     - Systemic effects
     - Neurological effects
     - Reproductive and developmental effects
     - Immunological effects
     - Genotoxicity and carcinogenicity

5. **Effects on experimental animals and in vitro test systems**
   - Acute exposure
   - Short-term exposure
Executive summary

Tetrachloroethene, also known as perchloroethylene (PCE), is primarily, if not exclusively, a groundwater contaminant, because it volatilizes to the atmosphere from surface waters. The primary cause of groundwater contamination is poor handling and disposal practices, which result in soil contamination; in vulnerable aquifers, soil contamination can result in groundwater contamination. Commercial utility of PCE is decreasing as a result of regulations in place limiting its use, such as in North America and Europe.

Both cancer and noncancer end-points were considered in the derivation of the guideline value (GV) for PCE in drinking-water. For noncancer end-points, the nervous system is more sensitive to PCE than other target organs, such as the liver, kidney or immune system. Effects in humans are observed at lower concentrations than in animals. Hepatocellular adenomas and carcinomas arising from a nonlinear, nonmutagenic mode of action in mice are the most relevant end-point for cancer risk assessment of PCE exposure, being consistently observed with significant dose-related trends. The GV for PCE in drinking-water derived considering cancer effects was higher than the GV derived for noncancer effects. As a result, the GV of 100 µg/L for noncancer effects is protective for both cancer and noncancer effects. This level is technologically achievable using available treatment methods.

PCE monitoring requirements in drinking-water regulations and standards should be limited to groundwater sources where a catchment risk assessment indicates the possibility of presence of PCE. Source control should be the primary mitigation measure; however, this is not feasible where there is historical contamination. Conventional water treatment is not effective in removing VOCs including PCE. Effective techniques include packed tower aeration and granular activated carbon. Advanced oxidation processes may also be effective, but this depends on physical and chemical properties of the water. Surface water sources do not need to be monitored or treated, since PCE volatilizes to the atmosphere.
Tetrachloroethene in drinking-water

1 General description

1.1 Identity
Tetrachloroethene is also known as perchloroethylene (PCE), ethylene tetrachloride, PERC, perchlorethylene, perchloethene, perchloroethylene, tetrachlorethene or 1,1,2,2-tetrachloroethylene.

CAS No.: 127-18-4

Molecular formula: C₂Cl₄

Chemical structure:

1.2 Physicochemical properties
Table 1.1. Physicochemical properties of tetrachloroethene

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>165.83</td>
</tr>
<tr>
<td>Boiling point</td>
<td>121 °C</td>
</tr>
<tr>
<td>Melting point</td>
<td>−22.3 °C</td>
</tr>
<tr>
<td>Density at 20 °C</td>
<td>1.623 g/mL</td>
</tr>
<tr>
<td>Vapour pressure at 20 °C</td>
<td>18.5 mmHg</td>
</tr>
</tbody>
</table>

Solubility
Water at 25 °C 206 mg/L
Organic solvents Soluble in alcohol, ether, benzene, chloroform, solvent hexane and most of the fixed and volatile oils

Partition coefficients
Log Kow 2.53–3.40
Log Koc 2.2–2.54

Henry’s law constant at 25°C 1.8 × 10⁻² atm-m³/mol

Note: Conversion factors: 1 ppm = 6.78 mg/m³; 1 mg/L = 147.4 ppm (ATSDR, 2019)
Source: ATSDR (2019)

1.3 Organoleptic properties
PCE is a clear, colourless, nonflammable liquid with an ether-like odour (Health Canada, 2015). The odour thresholds for PCE in water and air are 0.3 mg/L and 7 mg/m³, respectively (ATSDR, 2019).
1.4 Major uses and sources

PCE has mainly been used as a solvent in the dry-cleaning industry, as a degreasing solvent in metal industries, as a heat transfer medium, and as a chemical intermediate in the manufacture of fluorochemicals (IPCS, 1984; Condie 1985). PCE production reached its peak during the 1980s (Linak, Leder & Yoshida, 1992). Since then, its use has substantially decreased, especially in dry-cleaning and textile processing, as a result of regulations such as in North America and Europe (IARC, 2014). Currently, the major use currently of PCE is as a feedstock for producing fluorocarbons (IARC, 2014).

2 Environmental levels and human exposure

Because PCE is a volatile organic compound, most PCE that is released into the environment is found in the atmosphere, where its half-life is 70–251 days. Photochemically produced hydroxyl radicals degrade PCE to phosgene, chloroacetyl chlorides and other degradation products (ATSDR, 2019). The partitioning tendency of PCE in various environmental media has been estimated as follows: air, 99.7%; water, 0.3%; soil, <0.01%; sediment, <0.01% (Boutonnet et al., 1998).

In water, PCE does not readily undergo hydrolysis or photolysis but is biodegraded by microorganisms to dichloroethene, vinyl chloride and ethene. PCE can persist in waters where volatilization cannot occur. It volatilizes less readily from soil than from water and, with a soil adsorption coefficient of 72–534, is expected to be fairly mobile in soils. Degradation may occur in anaerobic soils.

2.1 Water

PCE frequently occurs as a contaminant of groundwater due to inappropriate disposal and release from dry-cleaning facilities, or from landfills in Canada and the United States, but it has been found also in drinking-water, surface water and rainwater supplies.

Leaking underground storage tanks and nearby dry-cleaners have resulted in significant levels of PCE reported in drinking-water in specific sites in the United States of America. For example, at the Marine Corps Base in North Carolina, PCE concentrations in drinking-water ranged from 2 to 400 µg/L (mean of 153 µg/L), and groundwater levels as high as 1580 µg/L were observed (IARC, 2014). In provincial Canadian water bodies between 1994 and 2007, average PCE levels ranged from 0 to 6.1 µg/L, and maximum detections ranged from 0 to 54 µg/L (Health Canada, 2015).

A survey of drinking-water in the USA in 1976–77 detected PCE in nine of 105 samples at levels ranging from 0.2 to 3.1 µg/L (mean 0.81 µg/L) (US EPA, 2012). In other surveys of drinking-water supplies in the USA, 3% of all public water supply systems that used well water contained PCE at concentrations of 0.5 µg/L or higher, whereas those that used surface water contained lower levels (US EPA, 1987). In England and Wales, where more than 11,000 drinking-water samples were analysed for PCE in 2003, mean and maximum concentrations were 0.32 µg/L and 8.7 µg/L, respectively (P Marsden, UK Drinking Water Inspectorate, personal communication, 28 August 2018). In approximately 30% of all wells tested in Japan in the past, PCE was found at concentrations ranging from 0.2 to 23 000 µg/L (ATSDR, 1993). More recently, PCE was detected at unspecified levels in 11% (130 of 1179) of drinking-water samples from domestic wells in the USA; the reporting limit was 2 µg/L (Rowe et al., 2007).
2.2 Food

Food is not considered to be a major PCE exposure pathway (Health Canada, 2015). Food surveys in the USA have estimated the average PCE concentrations in various food groups to be as follows: dairy, 6.6 µg/kg; meat, 12.3 µg/kg; cereal, 14.7 µg/kg; fruit, 0.8 µg/kg; vegetables, 0.4 µg/kg; fats and oils, 12.9 µg/kg; and sugar, 2.9 µg/kg. Because of the lipophilic nature of PCE, it may bind to lipid molecules in foods such as margarine and butter stored in areas where there is PCE in the air (US EPA, 2012; Health Canada, 2015). As a result, foods with a high fat content that are stored or sold near dry-cleaning facilities may contain considerably higher concentrations of PCE than other foods (Chutsch et al., 1990).

PCE concentrations in seafood in the United Kingdom ranged from 0.5 to 30 µg/kg (Pearson & McConnell, 1975; Dickson & Riley, 1976). In other foodstuffs, PCE concentrations ranged from almost undetectable (0.01 µg/kg) in orange juice to 13 µg/kg in butter (McConnell, Ferguson & Pearson, 1975).

As part of the Total Diet Study in the USA during 1996–2000, PCE was found in 41% (29 out of 70) of food items from different supermarkets or restaurants (Fleming-Jones & Smith, 2003). Food was sampled four times per year on a regional basis over a five-year period. Based on 20 samples of each food item, butter had the most frequent (n = 8 of 20 samples) and highest levels (102 µg/kg) of PCE detection. Beef frankfurters (n = 3; 2–60 µg/kg) had the second highest level of detection, and margarine (n = 6; 3–42 µg/kg) had the second most frequent detection. Potential sources of the contamination were not investigated (Fleming-Jones & Smith, 2003).

2.3 Air

Concentrations of PCE in city air in the United Kingdom range from less than 0.7 to 70 µg/m³ (Pearson & McConnell, 1975). In Munich, Germany, suburban and urban air concentrations were 4 and 6 µg/m³, respectively (Löchner, 1976). Surveys in the USA indicated concentrations of less than 0.01 µg/m³ in rural areas and up to 6.7 µg/m³ in urban areas (Lillian et al., 1975). Measurement data from remote North American sites indicate that background concentrations of PCE have decreased since 1995 by more than 5% per year (McCarthy, Hafner & Montzka, 2006). In more recent surveys, levels of 0.032–0.075 µg/m³ were measured in Antarctica, and differences were still measured between rural and urban areas in Italy (0.109–0.719 and 0.461–4.314 µg/m³, respectively) (Zocolillo, Amendola & Insogna, 2009). Levels up to 24 µg/m³ were measured in the USA above contaminated soil (Forand, Lewis-Michl & Gomez, 2012), but background PCE levels in outdoor air are typically <1 µg/m³ (0.15 ppb) for most locations (ATSDR, 2019).

Relatively high levels have been measured in indoor air. PCE concentrations in two inner-city schools in Minneapolis, USA, were 0.1–1.3 µg/m³; indoor air in homes contained the highest levels of PCE (1.9–2.8 µg/m³), followed by personal samples (i.e. individual exposures reflecting time spent indoors and outdoors), outdoor air, and indoor air in schools (Adgate et al., 2004). In New York, USA, residential indoor air levels up to a peak value of about 5000 µg/m³ (mean value 34 µg/m³) were detected in 2001–2003 where dry-cleaners used PCE in the same buildings (McDermott et al., 2005; New York State Department of Health, 2010). In France, concentrations up to 2900 µg/m³ have been recorded (Chiappini et al., 2009; Billionnet et al., 2011). Levels ranged from 0.6 to 124.2 µg/m³ (0.09–18.3 ppb) in homes in Paris that were in close proximity to dry-cleaning facilities or do-it-yourself activities (e.g. photographic development, silverware), or in homes lacking air vents that were built before 1945 (Roda et al., 2013).
Tetrachloroethene in drinking-water

In areas where PCE contaminates soil as a result of industrial activities, and/or improper handling or disposal, indoor air contamination can occur, mainly as a result of soil vapour intrusion. For example, PCE levels ranged from <0.13 to 1.50 µg/m³ in homes in San Antonio, Texas, USA, that sit atop an extensive, shallow plume of contaminated groundwater (Johnston & Gibson, 2014). PCE levels were 0.1–24 µg/m³ in indoor air of residents in the Village of Endicott, New York, USA, the site of an industrial 1,1,1-trichloroethane spill (Forand, Lewis-Michl & Gomez, 2012). PCE can also enter the indoor air of homes from sewer gas emissions coming up through the bathroom plumbing (Pennell et al., 2013).

2.4 Bioaccumulation

Bioconcentration factors for PCE are reported to range from 39 to 49, and the compound is extensively metabolized in animals. As a result, PCE is not expected to bioconcentrate in organisms or to biomagnify within terrestrial and aquatic food chains (US EPA, 2012).

2.5 Occupational exposure

Average personal exposure of 59 ppm for dry-cleaning workers was reported in the USA for 1936–2001, with a trend of decreasing levels during this period (Gold et al., 2008). In Nordic countries in the mid-1970s, median personal exposures for dry-cleaning workers were about 20 ppm, decreasing to about 3 ppm in 2000 (Lynge et al., 2011). However, high exposures (around 100 ppm in air) still occur in dry-cleaning facilities in Middle Eastern countries such as Egypt and the Islamic Republic of Iran (Azimi Pirsaarei et al., 2009; Emara et al., 2010; Rastkari, Yunesian & Ahmadkhaniha, 2011).

Among workers degreasing metal and plastics in the USA, the average exposure was reported to be around 95 ppm during 1944–2001 (Gold et al., 2008). Exposure levels decreased by two orders of magnitude during the 60 years since 1944 (IARC, 2014).

2.6 Estimated total exposure, biomonitoring studies and relative contribution of drinking-water

PCE can be absorbed following inhalation, oral and dermal exposure. Air, drinking-water, food and soil contamination are potential routes of exposure of concern; inhalation of contaminated air and ingestion of contaminated drinking-water seem to be the most relevant.

Because of the high variability of PCE concentrations in air (including indoors), it is difficult to estimate the exposure of the general population via inhalation. Based on a hypothetical air concentration of 4–6 µg/m³, estimated exposure would be about 80–120 µg/day for an adult with an air intake of 20 m³. To evaluate the contribution from drinking-water, if the concentration of PCE in the drinking-water is 0.5 µg/L, the average daily exposure would be 1 µg for an adult consuming 2 L of water per day – that is, around 0.8–1.25% of the total inhaled amount. Insufficient data are available on the levels of PCE in foods to allow determination of an average exposure, or the contribution of food to total exposure.

In Canada in the early 1990s, the total daily intake of PCE was estimated to range from 1.22 to 2.67 µg/kg body weight (bw) for each of the age groups in the general population. Drinking-water ingestion contributed only a minor amount – estimated at 0.002–0.06 µg/kg bw/day (<3%) – to the overall exposure. Estimated contributions of food were 0.12–0.65 µg/kg bw/day (7–28%). The highest contributor to exposure was air, which provided >1.22 µg/kg (>62%) of daily exposure, of which the majority (1.21–1.88 µg/kg/day) came from indoor air (Health Canada, 2015).
Tetrachloroethene in drinking-water

A number of biomonitoring studies in various countries, mostly in the 1990s, have measured PCE in expired air or in blood, or trichloroacetic acid (TCA; a metabolite of PCE), in urine, especially among workers in dry-cleaning and other industries. These studies have been reviewed by the International Agency for Research on Cancer (IARC, 2014) and the Agency for Toxic Substances and Disease Registry (ATSDR, 2019). Data are also available for the general population (IARC, 2014), showing that levels are higher in urban than in rural areas, especially for individuals living near a dry-cleaning facility (Brugnone et al. 1994; Schreiber et al., 2002; Storm et al., 2013).

As a result of the volatility and lipid solubility of PCE, incidental exposure could occur through bathing, showering or swimming in drinking-water. This indirect dermal or inhalation exposure through drinking-water can be estimated in terms of litre-equivalents per day (Leq/day) (Krishnan & Carrier, 2008). For example, an inhalation exposure of 1.7 Leq/day means that the daily exposure to PCE via inhalation is equivalent to a person drinking an extra 1.7 L of water per day. In Japan, the indoor-air exposure to PCE attributable to drinking-water was estimated to be 9.1 Leq/day (median value for Japanese lifestyle; Akiyama et al., 2018).

Overall, drinking-water is not a major source of exposure, unless in the vicinity of a contaminated site.

3 Toxicokinetics and metabolism in animals and humans

3.1 Absorption
Animal studies indicate that PCE is rapidly and almost completely absorbed following oral and inhalation exposure. Absorption of PCE vapour by the skin is minimal compared with inhalation, but topical exposure to liquid PCE can result in significant absorption (IARC, 2014; Health Canada, 2015). Concentrations of PCE reached near-steady-state levels in the blood of human volunteers after 2 hours of continuous inhalation (Stewart et al., 1961).

3.2 Distribution
Because of the high lipophilicity of PCE, its fat:blood partition coefficient in humans is 125–159, whereas the coefficients for other tissues are 5–6 (IARC, 2014). Therefore, once absorbed, PCE is mainly distributed to adipose tissue and other fatty tissues, including the liver, brain and kidney, in both humans and experimental animals (Health Canada, 2015).

PCE readily crosses the blood–brain barrier. It is also found in breast milk, and can cross the placenta and distribute to the fetus (US EPA, 2012; ATSDR, 2019).

3.3 Metabolism
Toxicity and carcinogenicity induced by PCE are mainly mediated by its metabolites (except for solvent effects that occur at extremely high exposures to the parent compound). The two pathways of PCE metabolism are oxidation by cytochrome P450 isozymes and glutathione (GSH) conjugation via glutathione-S-transferase (GST). Both pathways have been extensively reviewed elsewhere (US EPA, 2012; IARC, 2014; Health Canada, 2015; ATSDR, 2019). In summary, although PCE metabolites are qualitatively similar in humans, rats and mice, these three species differ quantitatively in the extent of metabolism and the predominant pathway; the exposure route and magnitude of the dose further contribute to these variabilities (ATSDR, 2019). Mice metabolize PCE more extensively than rats, and rats metabolize it more extensively than humans. Saturation of oxidative metabolism, mainly via CYP2E1 (although other isoforms can be involved), occurs at similar levels in rats and humans (at exposure
Tetrachloroethene in drinking-water

centrations of ~100 ppm), but oxidative metabolism does not become saturated in mice, which might explain the lack of renal toxicity in mice (Health Canada, 2015). Geometric mean $V_{\text{max}}$ values for PCE metabolism of 13, 144 and 710 nmol/minute/kg have been reported for humans, rats and mice, respectively (ATSDR, 2019). Regardless of the route of exposure, only 1–3% of the absorbed PCE is metabolized to its major metabolite, TCA, by humans. TCA is a putative toxic moiety for PCE-mediated liver toxicity in mice (Health Canada, 2015).

In humans, variability of PCE metabolism among individuals is reflected in a wide range of reported $V_{\text{max}}$ and $K_{\text{m}}$ values. These variations might result from genetic polymorphisms in the active metabolic enzymes in the studied populations (Lash et al., 2007; US EPA, 2012). Oxidative metabolism is postulated to occur mainly in the liver, and to a lesser extent in the lung and kidney (Chiu & Ginsberg, 2011). Although renal metabolism is relevant in rats (Cummings et al., 1999), its role is less clear in humans.

After saturation, the second metabolic pathway (involving conjugation with GSH) predominates, although this pathway can also operate before saturation. The GST pathway has been proposed to occur primarily in the liver and kidney (Chiu & Ginsberg, 2011). Hepatic enzymatic GSH conjugation of PCE forms $S$-(1,2,2-trichlorovinyl) glutathione (TCVG), which is stable. TCVG travels to the kidney and is biotransformed to $S$-(1,2,2-trichlorovinyl) cysteine (TCVC) by gamma-glutamyltransferase and dipeptidases (US EPA, 2012), mainly on the brush-border plasma membrane of the renal proximal tubular cell. This cysteine conjugate can be bioactivated to reactive metabolites, or detoxified and excreted into urine, depending on the enzyme involved.

The renal $N$-acetyl transferase can detoxify TCVC by catalysing its conversion to $N$-acetyl-$S$-(1,2,2-trichlorovinyl)-L-cysteine (NAcTCVC), which has been detected in human urine (Volkel et al., 1998). On the other hand, β-lyase can convert TCVC to a highly reactive 1,2,2-trichlorovinylthiol compound (TCVT) (Anders et al., 1988; Krause, Lash & Elfarra, 2003), and flavin monooxygenase-3 and CYP3A enzymes can lead to the production of the reactive metabolite TCV sulfoxide. Dichloroacetic acid (DCA), the major end-product of the GST pathway, can be formed from TCVT (US EPA, 2012). In addition, both TCVC and the sulfate can rearrange spontaneously to form a thiolketene, which is the ultimate reactive and toxic agent.

3.4 Elimination

PCE is eliminated from the body mainly via the lungs in exhaled air as unchanged parent compound; in humans, this accounts for 80–99% of the intake, regardless of the exposure route. Urinary excretion of metabolites (predominantly TCA) accounts for 1–3% of the initial intake (IARC, 2014; Health Canada, 2015; ATSDR, 2019). TCA excretion in humans is linearly related to inhaled PCE concentrations up to about 50 ppm, and then a plateau is observed. This finding indicates that the metabolism of PCE is saturable and that the concentration of urinary metabolites would not reflect the amount of exposure at a concentration above the saturation of metabolism (ATSDR, 2019).

In humans, the elimination half-lives of exhalation and urinary excretion are 65 hours and 144 hours, respectively (Stewart et al., 1970; IPCS, 1984; Health Canada, 2015).
3.5 Physiologically based pharmacokinetic modelling

Although a number of inhalation studies are available in occupationally exposed humans and in experimental animals, the database on ingestion of PCE in drinking-water is limited. Physiologically based pharmacokinetic (PBPK) modelling predicts that exhalation can account for 90–99% of initial intake via inhalation and 81–99% of initial intake via ingestion (Chiu & Ginsberg, 2011).

Considering the main features of PCE kinetics, as summarized above, a linear extrapolation from high-dose studies in rodents to low-dose human exposures is not appropriate, for the following reasons:

- PCE is rapidly and well absorbed by both the oral and inhalation routes of exposure (ATSDR, 2019).
- The metabolic pathways and kinetics of excretion for oral exposure are similar to those for inhalation exposure (ATSDR, 2019).
- Data for oral exposure indicate a pattern of effects similar to that for inhalation exposure.
- Differences in first-pass effect (affecting systemic bioavailability) between oral and inhalation exposures can be adequately accounted for by a PBPK model.
- Quantitative differences in metabolism between humans and rodents exist.
- Metabolite production is not linear because the oxidative pathway is saturated at the high doses at which the GST pathway starts to be active.

The use of PBPK modelling allows a route-to-route extrapolation, as well as estimation of the internal exposure.

PBPK models developed for PCE before 2000 generally did not include all relevant information about metabolism. However, more recent models consider generation of TCA via the oxidative pathway for rats (Chiu & Ginsberg, 2011), mice (Fisher et al., 2004; Sweeney et al., 2009; Chiu & Ginsberg, 2011) and humans (Covington et al., 2007; Chiu & Ginsberg, 2011), as well as GST-mediated metabolism (Sweeney et al., 2009; Chiu & Ginsberg, 2011). Whereas the United States Environmental Protection Agency (US EPA) used the Chiu and Ginsberg model (2011), Health Canada developed and validated its own model (Nong, 2013) based on previously published models. Use of this PBPK model allows more precise rodent-to-human and inhalation-to-ingestion extrapolation to directly compare laboratory data with human oral exposures.

4 Effects on humans

The effects of PCE on human health have been extensively reviewed by Health Canada (2105), US EPA (2012), ATSDR (2019) and IARC (2014). IARC (2014) mainly focused on carcinogenicity induced by PCE.

4.1 Acute exposure

PCE is both a potent anaesthetic agent and a cardiac epinephrine sensitizer. Human deaths have been reported after inhalation of high vapour concentrations, as a result of these two effects (excessive depression of the respiratory centre and/or fatal cardiac arrhythmia induced by epinephrine sensitization) (ATSDR, 2019). Postmortem blood concentrations of PCE in people who have died have ranged from 15 to 44 mg/L (ATSDR, 2019).
Tetrachloroethene in drinking-water

Oral doses of 4.2–6 g of PCE administered to patients to control parasitic worm infections caused central nervous system (CNS) effects, such as inebriation, perceptual distortion and exhilaration (Haerer & Udelman, 1964).

Respiratory irritation can be observed in workers exposed to PCE vapours at levels from around 216 ppm or 1464 mg/m³ (ATSDR, 2019). In general, studies do not seem to support liver and kidney effects after acute (or short-term) exposure, except in extreme cases of accidental overexposure.

4.2 Short-term exposure

It is not easy to distinguish the health effects in humans associated with short-term exposure to PCE from those related to chronic exposure, because most studies have primarily used occupational settings; only limited studies have looked at non-occupational exposure through contamination of drinking-water or indoor air.

4.3 Long-term exposure

4.3.1 Systemic effects

Studies of targets of toxicity from chronic exposure to PCE have largely focused on the inhalation route of exposure. Noncancer-related targets include the CNS, the kidney, the liver, the immune and haematological systems, and development and reproduction. In general, neurological effects were judged to be associated with lower PCE concentrations than other noncancer end-points of toxicity. Adverse effects on liver and kidney function were reported by some studies but not others (Health Canada, 2015; ATSDR, 2019).

4.3.2 Neurological effects

Studies investigating subjective neurological symptoms, and objective measures of neurophysiological, neurobehavioural and neuroendocrine effects of PCE exposure in workers and the general public have been critically reviewed elsewhere (Health Canada, 2015). Most occupationally exposed cohorts were dry-cleaners or other workers in dry-cleaning facilities, who are generally exposed via inhalation. General population cohorts include residents living near, or in the same building as, dry-cleaning facilities. One cohort of adults exposed both prenatally and until the age of 5 years to PCE in drinking-water pipes was also studied (Getz et al., 2012).

Effects on visual function – specifically, colour vision and contrast sensitivity – were the neurophysiological effects consistently observed in a number of cohorts (Cavalleri et al., 1994; Echeverria, White & Sampaio, 1995; Gobba et al., 1998; Storm et al., 2011; Getz et al., 2012). A dose–response relationship was seen in adults occupationally exposed by inhalation (Cavalleri et al., 1994; Gobba et al., 1998), with visual effects observed at mean PCE levels of 4.35–7.27 ppm (Cavalleri et al., 1994; Gobba et al., 1998). Although some other studies did not find such an effect, the weight of evidence suggests an association between occupational and environmental exposure to PCE and decrements in colour discrimination (Health Canada, 2015). These effects seem to be sustained over time, with poor recovery (Gobba et al., 1998; Getz et al., 2012).

In the cohort exposed via drinking-water, contrast sensitivity was decreased at the highest frequency in the high-exposure group (estimated concentrations of ≥40 μg/L) (Getz et al.,
Tetrachloroethene in drinking-water

2012). However, this effect was not consistently reported in other studies (Health Canada, 2015).

The weight of evidence from epidemiological studies investigating neurobehavioural and other neurobiological effects suggests that PCE exposure at elevated levels might be associated with adverse effects on attention, vigilance, executive function and short-term memory function, but not on visuomotor or visuospatial function (Health Canada, 2015).

4.3.3 Reproductive and developmental effects

Several developmental effects – such as eye, ear, CNS, chromosomal and oral cleft anomalies – were associated with exposure to PCE and other solvents in contaminated drinking-water supplies (Lagakos, Wessen & Zelen, 1986). In female dry-cleaning workers, inhalation exposure has been associated with reproductive effects, including menstrual disorders and spontaneous abortions (Kyyrönen et al., 1989; Zielhuis, Gijsen & Van Der Gulden, 1989).

4.3.4 Immunological effects

The limited data available suggest that immunological and associated haematological effects are possible following PCE exposure in humans. These effects include alterations in serum immunoglobulin E, circulating leukocytes, immunosuppression (host resistance), immunostimulation, autoimmunity, allergy and hypersensitivity, and other markers (US EPA, 2012; Health Canada, 2015).

4.3.5 Genotoxicity and carcinogenicity

A limited number of small cross-sectional studies have evaluated genotoxic and cytogenetic effects associated with exposure to PCE (IARC, 2014). No significant increase in the frequency of sister chromatid exchange in association with exposure to PCE was observed in a cross-sectional study of 27 dry-cleaning workers and 26 controls in Japan (Seiji et al., 1990). This confirms results of a previous study of 10 PCE-exposed degreasing workers compared with non-exposed workers in the same facility (Ikeda et al., 1980). In a cross-sectional study in the USA of 18 female PCE-exposed dry-cleaning workers compared with 18 laundry workers not exposed to PCE, frequencies of acentric chromosomal fragments and chromosomal translocations were not statistically significantly different between the two groups (Tucker et al., 2011).

The carcinogenicity of PCE has been extensively studied, especially in laundry and dry-cleaning workers, and in other occupational settings. The studies include both cohort and case-control studies. An increased incidence of cancer was reported in several cohort and proportionate mortality studies (Blair, Decoufle & Grauman, 1979; Katz & Jowett, 1981; Lynge & Thygesen, 1990; WHO, 2003), and increased risks of cancer in workers exposed to PCE were found in case-control studies (Lin & Kessler, 1981; Stemhagen et al., 1983). However, study limitations, such as concomitant exposures to other chemicals and small sample sizes, make it difficult to reach a definite conclusion for most studies.

The National Research Council concluded that evidence is suggestive for an association between PCE exposure and lymphoma, and limited but insufficient for other cancer types, including liver, kidney and bladder cancer (NRC, 2010). The US EPA concluded that PCE is likely to be carcinogenic in humans by all routes of exposure, based on sufficient evidence in animals, and suggestive evidence of a causal association between PCE exposure in humans and
Tetrachloroethene in drinking-water

bladder cancer, multiple myeloma and non-Hodgkin lymphoma. IARC (2014) classified PCE as probably carcinogenic to humans (Group 2A).

5 Effects on experimental animals and in vitro test systems

5.1 Acute exposure

No major differences were seen between rodent species or between the sexes in susceptibility to lethal effects of PCE following acute exposure. Oral median lethal dose (LD$_{50}$) values of 3835 and 3005 mg/kg bw were found for male and female rats, respectively. Acute effects are dominated by CNS depression (Hayes, Condie & Borzelleca, 1986).

A 4-hour inhalation median lethal concentration (LC$_{50}$) of 5200 ppm for female albino mice has been reported (Friberg, Kylin & Nyström, 1953). The highest nonlethal concentrations reported for 4-hour exposure to PCE were in the range 2000–2450 ppm in mice and rats (NTP, 1986); the lowest lethal concentrations reported for 4-hour exposures were 2613–3786 ppm in mice and rats (NTP, 1986).

5.2 Short-term exposure

Groups of male Swiss–Cox mice were given gavage doses of PCE in corn oil at 0, 20, 100, 1000 or 2000 mg/kg bw, 5 days per week, for 6 weeks (equivalent to 0, 14, 70, 700 or 1400 mg/kg bw/day). Mice treated with doses as low as 70 mg/kg bw/day exhibited significantly increased liver triglyceride levels and liver-to-body-weight ratios. At higher doses, hepatotoxic effects included decreased DNA content; increased serum alanine aminotransferase levels; decreased serum glucose-6-phosphatase levels; and hepatocellular necrosis, degeneration and polyploidy. The no-observed-adverse-effect level (NOAEL) was 14 mg/kg bw/day (Buben & O'Flaherty, 1985).

Sprague–Dawley rats (20 per sex per dose) were given PCE in drinking-water at doses of 14, 400 or 1400 mg/kg bw/day for 90 days. Males in the high-dose group and females in the mid- and high-dose groups had depressed body weights. Increased liver- and kidney-to-body-weight ratios (equivocal evidence of hepatotoxicity) were observed at the two highest doses (Hayes, Condie & Borzelleca, 1986).

There was moderate fatty degeneration of the liver in mice following a single (4-hour) or repeated exposure to air containing 1340 mg/m$^3$ of PCE. Exposure to this level for 4 hours per day, 6 days per week, for up to 8 weeks increased the severity of the lesions (Kylin, Sumegi & Yllner, 1965).

5.3 Long-term exposure

5.3.1 Systemic effects

Chronic (i.e. 2-year) PCE exposure in laboratory animals has been assessed following inhalation exposure in rats or mice (NTP, 1986; JISA, 1993) and gavage exposure in rats (NCI, 1977). The target organs were the liver and kidney. CNS effects are discussed in section 5.3.2 and immune system effects in section 5.3.4.

Hepatic effects were more prevalent in mice than in rats (Health Canada, 2015). Non-neoplastic hepatic lesions in mice included angiectasis, and central degeneration and/or necrosis in one or both sexes exposed to 250 ppm (JISA, 1993). No adverse hepatic effects were observed in rats
Tetrachloroethene in drinking-water

in two of the studies (NCI, 1977; NTP, 1986). In the third study, the NOAEL for hepatic effects was 50 ppm; increases in spongiosis hepatitis were seen at ≥200 ppm in males, and decreases in granulation were seen at ≥200 ppm in females that were dead or dying (JISA, 1993). The lowest-observed-adverse-effect level (LOAEL) for non-neoplastic liver effects, based on necrosis in male mice in the National Toxicology Program (NTP) (1986) study, was 100 ppm (Health Canada, 2015). Hepatocellular tumours observed in mouse studies are discussed in section 5.3.5.

Non-neoplastic effects were observed in the kidneys of rats and mice, with the majority of effects observed in the proximal tubule (Health Canada, 2015). Nuclear enlargement was seen in the proximal tubule in all rat and mouse exposure groups in the NTP (1986) study, and in male rats exposed to ≥200 ppm, female rats exposed to 600 ppm, and male and female mice exposed to 250 ppm (as well as low-dose males scheduled for dissection) in the Japan Industrial Safety Association (JISA) (1993) study. Other proximal tubule effects included atypical dilatation in all high-dose groups of mice (JISA, 1993); degeneration, necrosis and regeneration in epithelium, and inflammatory cell infiltration, fibrosis and focal mineralization in male and female rats (NCI, 1977); and hyperplasia in a small number of rats (NTP, 1986). Nephropathy was observed in the majority of male and female rats and mice exposed by gavage (NCI, 1977). Nephrosis occurred in female mice exposed by inhalation in the NTP (1986) study. Casts were also observed in the kidneys of exposed male mice and high-dose female mice in the NTP (1986) study. The NOAEL for renal effects in the JISA (1993) study was 50 ppm, with nuclear enlargement occurring at 250 ppm; the LOAEL in the NTP (1986) study was 100 ppm for the same effect. Renal tumours in male rats in the NTP (1986) study are discussed in section 5.3.5.

5.3.2 Neurological effects

As reviewed by Health Canada (2015), three chronic bioassays with PCE (NTP, 1986; JISA, 1993; NCI, 1977) examined brain tissues for gross and histological pathology, but did not investigate more subtle neurological effects. No adverse effects were noted in rats or mice in the National Cancer Institute study (NCI, 1977), although, as noted, only gross and histological pathological changes were investigated. Relative brain weights were increased in mice inhaling PCE at 250 ppm, and vitreous deposits in the brain were increased at 50 ppm but not at 250 ppm in the JISA (1993) study. The NTP (1986) study identified a significant positive dose-related trend in the increase in gliomas in male rats exposed to PCE at 200 and 400 ppm; however, the incidence of gliomas in each dose group was not higher than in the controls (NTP, 1986).

5.3.3 Reproductive and developmental effects

Only three available studies have addressed reproductive and/or developmental effects of PCE exposure via the oral route (Narotsky & Kavlock, 1995; Fredriksson et al., 1993; Guariglia et al., 2011). These three studies have limitations due to few doses tested and limited number of endpoints evaluated (Health Canada, 2015). Animal studies of reproductive and developmental effects have focused primarily on the inhalation route of exposure. Although some contrasting results have been obtained, the weight of evidence suggests that inhalation exposure during gestation that resulted in maternal toxicity in mice, rats and rabbits can affect survival of offspring (e.g. through pre- and post-implantation losses, and decreased litter sizes) and alter ossification (resulting in delayed skeletal development). Inhalation exposure through gestation or early in development has been linked to neurological effects in adulthood (Health Canada, 2015).
Enhanced allergic reactions were observed in mice exposed to PCE at doses as low as 2 μg/kg bw/day (Seo et al., 2012). Health Canada (2015) noted that the study involved passively sensitizing mice before exposure, which leads to difficulties in quantitative dose–response assessment. Combined with some study limitations, this led to exclusion of this study by Health Canada (2015) from further consideration in the noncancer risk assessment.

5.3.5 Genotoxicity and carcinogenicity

The genotoxicity of PCE has been extensively reviewed (US EPA, 2012; IARC, 2014). *Salmonella* reverse mutation assays of PCE, as well as other bacterial and yeast tests, have yielded largely negative results with or without hepatic metabolic activation. Micronucleus formation testing gave inconsistent results; no evidence of unscheduled DNA synthesis was observed in human lymphocytes or fibroblasts, or in rat or mouse hepatocytes (IARC, 2014). In the presence of rat liver GST, GSH and kidney microsomes (simulating the multistep bioactivation pathway of GSH conjugation), PCE gave positive results, indicating that its metabolite TCVG is genotoxic. Other metabolites – TCVC, NAcTCVC, PCE oxide and DCA – have not been adequately tested in standard assays to support clear conclusions about their genotoxic potential.

In vivo tests of PCE have given equivocal results. At most, there is modest evidence of genotoxic effects in rodent tumour tissues examined (including mouse liver and rat kidney) following exposure at tumorigenic doses of PCE (US EPA, 2012). However, no evidence is available about the potential contribution of PCE genotoxicity to other rodent tumour types (particularly mononuclear cell leukemia, and tumours of the testis and brain).

With respect to chronic bioassays, exposure by inhalation (6 hours per day, 5 days per week for 103 weeks) of F344/N rats to PCE at 0, 1360 or 2720 mg/m³ produced a small (but not statistically significant) increase in the combined incidence of renal tubular cell adenomas and adenocarcinomas in males but not in females. In both sexes, there was an increase in the incidence of mononuclear cell leukemias at both doses, but the incidence was also unusually high in concurrent, as compared with historical, controls (NTP, 1986).

Exposure by inhalation (6 hours per day, 5 days per week for 103 weeks) of groups of 49 or 50 male and female B6C3F1 mice (8–9 weeks of age) to PCE vapour (99.9% purity) at concentrations of 0, 100 or 200 ppm (0, 680 or 1360 mg/m³) resulted in an increase in hepatocellular carcinomas in both sexes (NTP, 1986). When PCE was administered by gavage in corn oil, there was an increase in the incidence of hepatocellular carcinomas in both male and female mice but not in Osborne–Mendel rats; however, survival was reduced in both species as a result of pneumonia, and carcinogenic impurities were present in the PCE administered (NCI, 1977).

When groups of 50 male and 50 female Crj:BDF1 mice (5 weeks of age) were exposed by inhalation (6 hours per day, 5 days per week for 103 weeks) to PCE vapour (99% purity) at concentrations of 0, 10, 50 or 250 ppm (0, 68, 340 or 1695 mg/m³), significant positive trends in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma and carcinoma (combined) were observed in both males and females. The incidences of hepatic neoplasms were significantly greater at the highest dose than in controls. The incidence of hepatic degeneration was also increased at the highest dose in males (incidence rates of 1/50, 1/50, 4/50 and 37/50 for the respective male dose groups) and in females
Tetrachloroethene in drinking-water

(incidence rates of 0/50, 1/50, 2/50 and 30/50 for the respective female dose groups). The incidence of splenic haemangiendothelioma and karyomegaly of renal tubular cells was also increased at the highest dose compared with controls in males (incidence rates of 0/50, 0/50, 6/50 and 38/50 for the respective male dose groups) and females (incidence rates of 0/50, 0/50, 1/50 and 49/50 for the respective female dose groups).

5.4 Mode of action

The mode of action of PCE has been extensively analysed (US EPA, 2012; IARC, 2014; Health Canada, 2015). Some neurotoxic and cardiotoxic effects due to exposure to very high levels of PCE by inhalation are probably associated with the narcoleptic and epinephrine effects of the parent compound. Other than these effects, toxicity and carcinogenicity induced by PCE are mainly mediated by its metabolites.

Hepatotoxic and related carcinogenic effects of PCE in mice appear to be due to TCA and DCA, which is formed in greater amounts by mice than by rats or humans (Schumann, Quast & Watanabe, 1980; WHO, 2003). The weight of evidence for PCE tends to suggest that a nonmutagenic threshold mode of action predominates for hepatocellular tumours (Health Canada, 2015).

The mode of action through which TCA and DCA elicit benign and malignant hepatocellular tumours induced by oral or inhalation exposure to PCE in multiple strains and both sexes of mice remains to be fully elucidated. All the mechanisms proposed involve a nonmutagenic mode of action. Indeed, key events from several simultaneous mechanisms may operate, including epigenetic effects such as DNA hypomethylation, cytotoxicity alterations in cell proliferation and apoptosis, disruption of gap-junctional intercellular communication, oxidative stress and receptor activation. These mechanisms may involve activation of peroxisome proliferator activated receptor-alpha (PPARα) (Health Canada, 2015).

Peroxisome proliferation is a plausible mechanism for induction of hepatocellular tumours by PCE. This has two important consequences. First, a threshold approach could be used for risk assessment. Second, the human relevance of hepatocellular tumours might be limited, since PPARα expression is ≥10-fold lower in humans than in rodents, and its activation in humans is not related to induction of liver cell proliferation and suppression of apoptosis.

However, some data gaps prevent the confident identification of peroxisome proliferation as a main mode of action (Health Canada, 2015).

It has been suggested that the induction of kidney tumours in male rats is the combined result of the formation of a highly reactive metabolite and cell damage produced by renal accumulation of hyaline droplets (Green, 1990; Olson, Johnson & Reidy, 1990).

PCE-induced carcinogenicity in the male rat kidney has been associated with GSH conjugation to form the genotoxic metabolites TCVG and NAcTCVC (IARC, 2014). It has also been associated with α2µ-globulin-associated nephropathy, cytotoxicity not associated with accumulation of α2µ-globulin, and peroxisome proliferation mediated by the receptor PPARα. Because none of these mechanisms alone can explain the renal carcinogenicity in rats, it is likely that several simultaneous mechanisms operate.

The mechanism by which PCE induces immunotoxicity, or by which the toxicity may ultimately lead to carcinogenesis, could not be identified from the available human and animal
Tetrachloroethene in drinking-water

studies. Therefore, it was not possible to assess the plausibility and relevance of immunotoxicity to humans (IARC, 2014; Health Canada, 2015).

The mechanism by which PCE induces neurotoxic effects has not been identified. Considering the number of molecular targets reported in the studies, it is likely that several mechanisms operate concurrently.

6 Overall database and quality of evidence

6.1 Summary of health effects

The highest exposure levels of PCE have been associated with occupational environments (dry-cleaning facilities and industries using metal-degreasing products). Although these occupational uses of PCE are decreasing in developed countries, they still occur in some countries. For the general population, the important routes of PCE exposure are inhalation of ambient or indoor air, and ingestion of contaminated drinking-water.

The nervous system is more sensitive to PCE than other target organs such as the liver, kidney or immune system. Human epidemiological studies (Cavalleri et al., 1994; Echeverria, White & Sampaio, 1995; Gobba et al., 1998; Schreiber et al., 2002; Storm et al., 2011), and controlled-exposure experiments in humans (Hake & Stewart, 1977; Altmann, Bottger & Wiegand, 1990) have identified CNS effects following acute, intermediate-duration and chronic inhalation exposures to PCE.

Acute inhalational exposure at doses >216 ppm has been associated with respiratory irritation (see section 4.1). Inhalation of high PCE vapour concentrations causes CNS depression, loss of consciousness, cardiac failure and death. Chronic inhalation exposure at levels >4.8 ppm (Cavalleri et al., 1994) has been associated with neurobehavioural effects and vision changes in humans.

Studies in animals also identify the liver, kidney and immune system as potential targets of toxicity and carcinogenicity induced by PCE metabolites.

Data on human carcinogenicity are often weak and sometimes inconsistent. The mode of action for elicitation of tumours in experimental animal has not been fully elucidated, although the weight of evidence supports a nonmutagenic MoA. Indeed, it has been considered likely that key events from several simultaneous mechanisms operate, including epigenetic effects such as DNA hypomethylation, cytotoxicity alterations in cell proliferation and apoptosis, disruption of gap-junctional intercellular communication, oxidative stress and receptor activation, mainly focusing on a hypothesized PPARα-activation mode of action. On this basis, the relevance for humans could not be completely assessed. The US EPA (2012) concluded that PCE is likely to be carcinogenic in humans by all routes of exposure, based on sufficient evidence in animals, and suggestive evidence of a causal association between PCE exposure in humans and bladder cancer, multiple myeloma and non-Hodgkin lymphoma. IARC (2014) classified PCE as probably carcinogenic to humans (Group 2A), based on limited evidence in humans and sufficient evidence in experimental animals.

Reproductive and developmental effects on experimental animals were observed in some studies (e.g. increased pre- and post-implantation losses, decreased litter sizes, delayed skeletal development). For humans, the available epidemiological evidence relating to exposure in occupational settings or from contaminated drinking-water is limited; studies suffer from a number of limitations – including lack of measurement of exposure levels, co-exposure to other
Tetrachloroethene in drinking-water

solvents, lack of control for potential confounders, and small numbers of subjects – and do not provide sufficient bases to draw conclusions.

6.2 Quality of evidence

Overall, PCE is a data-rich compound with many good-quality studies on kinetics and toxicity in humans and animals. Although the main focus of the evidence is on inhalation exposure, the availability of PBPK modelling allows extrapolation from the inhalation route to the oral route.

Evidence on neurotoxic effects is well established in humans and animals. Human data have been obtained in occupationally exposed individuals, and two studies have shown a clear dose–response relationship. Many studies consisted of a single exposure group or had poorly matched control groups. No study was available on the general population.

Mode of action for tumour induction in experimental animals has not been fully elucidated, with many mechanisms likely concurrently operating. Evidence on human carcinogenicity is often weak and sometimes inconsistent. However, all the mechanisms proposed for tumour formation (DNA hypomethylation, cytotoxicity that alters cell proliferation and apoptosis, disruption of gap-junctional intercellular communication, oxidative stress and PPARα-receptor activation) are associated with a nonlinear, nongenotoxic process.

Available epidemiological studies on reproductive or developmental effects in occupational settings or from contaminated drinking-water suffer from a number of limitations and could not be used to draw any firm conclusions.

7 Practical considerations

7.1 Analytical methods and achievability

PCE can be analysed together with trichloroethene by gas chromatography using ISO 10301:1997, which has a limit of quantification of 0.1 μg/L (ISO, 1997).

Four methods for measuring PCE in drinking-water have been approved by the US EPA, with generally lower detection limits (US EPA, 2002):

- Method 502.2, revision 2.1, which uses purge and trap capillary gas chromatography (GC) with photoionization detectors and electrolytic conductivity detectors in series, has a method detection limit (MDL) range of 0.02–0.05 μg/L.
- Method 524.2, revision 4.1, which uses purge and trap capillary GC with mass spectrometry (MS) detection, has an MDL range of 0.05–0.14 μg/L.
- Method 524.3, version 1.0, which measures volatile organic compounds (VOCs) in drinking-water using GC-MS, has a detection limit of 0.036 μg/L. The advantages of this method include optimization of the purge and trap parameters, an option for use of selected ion monitoring (SIM) and use of solid acid preservatives.
- Method 551.1, revision 1.0, which uses liquid–liquid extraction and GC with electron capture detectors, has MDLs of 0.002 μg/L and 0.008 μg/L when methyl tertiary-butyl ether or pentane, respectively, is used as the extraction solvent.

7.2 Source control

PCE is primarily, if not exclusively, a groundwater contaminant because it is lost to the atmosphere from surface waters. The primary cause of contamination is poor handling and
disposal practices, which result in soil contamination and, in vulnerable aquifers, subsequent water contamination. This may occur some distance from the source, but contaminants may be drawn into the source by pumping. Because PCE can persist in waters where volatilization cannot occur, source control should be the priority action. Control at the source, by improving handling and disposal practices, should be relatively cheap and straightforward. Source control will not be feasible where there is historical contamination, which may be the major source of contamination in many countries.

7.3 Treatment methods and performance

Treatment of surface water sources is not needed because PCE volatilizes to the atmosphere.

Conventional treatment is only 0–29% effective in removing VOCs such as PCE (Love et al., 1983; Robeck and Love, 1983). Granular activated carbon (GAC) adsorption and packed tower aeration (PTA) are effective in reducing PCE concentrations in drinking-water. The efficiency of removal depends on process design and operational conditions, such as hydraulic loading rate, air-to-water ratio and packing height. PTA and GAC treatment technologies have reduced an influent concentration of PCE of 30–500 µg/L to an effluent concentration of less than 1 µg/L (Love & Eilers, 1982; Chrobak, Kelleher & Suffet, 1985; Reijnen, Van der Laan & Van Paassen, 1985; Hand et al., 1988; AWWA, 1991; Lykins & Clark, 1994; Dyksen, Racsko & Cline, 1995). A combination of GAC and PTA decreased an influent concentration of 100 µg/L PCE to less than 1 µg/L using an air-to-water ratio of 90 and a packing height of 3.0 m (AWWA, 1991). Generally, diffused aeration is effective but achieves lower removal efficiencies than PTA systems (AWWA, 1991). Typical diffused aeration performance ranges from 73% to 95% removal of PCE (US EPA, 1984, 1991). A pilot-scale diffused aeration study reduced the influent concentration of PCE from 636 µg/L to less than 1 µg/L (Love & Eilers, 1982).

Advanced oxidation processes (AOPs) can reduce concentrations of PCE, but effectiveness is impacted by physical and chemical properties of the water, including turbidity (Health Canada, 2015). AOPs include the use of a combination of ultraviolet (UV) light, chemical oxidants and catalysts (e.g. ozone/hydrogen peroxide, ozone/UV, UV/hydrogen peroxide).

In pilot-scale studies, an in-line ozone/hydrogen peroxide process reduced an influent PCE concentration of 18.6 µg/L to an effluent concentration of 1 µg/L using an applied ozone dose of 6.0 mg/L, a hydrogen peroxide to ozone ratio of 0.5 and a contact time of 3 minutes (Dyksen et al., 1992). Other full-scale data demonstrated that an ozone/hydrogen peroxide process was effective in reducing an influent PCE concentration of 10 µg/L to less than 1 µg/L using an ozone dose of 4.7 mg/L and a hydrogen peroxide to ozone ratio of 0.57 (Karimi et al., 1997). Full-scale data demonstrated that a combined UV/hydrogen peroxide/ozone oxidation process was capable of reducing an influent PCE concentration of 7 µg/L to less than 1 µg/L (Zeff, 1991).

Full-scale studies have demonstrated that UV radiation and hydrogen peroxide oxidation treatments are effective in removing PCE. Medium-pressure UV lamps and hydrogen peroxide doses of 15–70 mg/L decreased influent PCE concentrations of 70–150 µg/L to less than 1 µg/L (Topudurti et al., 1998). Field-scale results, reported by Hirvonen et al. (1998), showed that low-pressure mercury lamps and hydrogen peroxide doses of 83–138 mg/L could reduce an influent PCE concentration of 76–139 µg/L to an effluent concentration of less than 0.5 µg/L.
At the residential (household) scale, point-of-use treatment devices are available that can remove VOCs such as PCE from drinking-water based on adsorption (activated carbon) technologies. These may be installed at the faucet (point of use) or at the location where water enters the home (point of entry). Point-of-entry systems are generally preferred for the removal of VOCs because they provide treated water for bathing and laundry as well as for cooking and drinking, thereby reducing potential VOC exposure through inhalation (Health Canada, 2015).

8 Conclusions

8.1 Derivation of the guideline value

8.1.1 Cancer effects

Hepatocellular adenomas and carcinomas are the most relevant end-point for cancer risk assessment, since they were observed in both sexes of mice in both chronic inhalation studies – JISA (1993) and NTP (1986) – with significant dose-related trends. The weight of evidence for PCE suggests that a nonlinear, nonmutagenic mode of action is predominant for hepatocellular tumours (Health Canada, 2015).

Key studies are the following:

- NTP (1986) observed significant positive trends in male mice for the incidence of hepatocellular adenoma, and in both sexes for hepatocellular carcinoma. Renal tubular adenomas and adenocarcinomas in male rats were also observed.
- JISA (1993) observed significant positive trends in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma and carcinoma (combined) in male and female mice. The incidence of splenic haemangioendothelioma and karyomegaly of renal tubular cells was also increased at the highest dose compared with controls.

Cancer dose–response modelling for PCE exposure considered the generation of oxidative metabolites in the liver as the most relevant dose metric for hepatocellular tumours, recognizing that the external dose point of departure from NTP (1986) gave slightly more conservative (lower dose) results (Health Canada, 2015).

Considering a threshold mode of action, a BMDL_{10} (the lower 95% confidence limit on the benchmark dose for a 10% response) of 1.7 mg/kg bw per day was derived (Health Canada, 2015).

To calculate the tolerable daily intake (TDI), the BMDL_{10} is divided by an uncertainty factor of 75, comprising the following:

- 2.5 for the remaining uncertainty associated with potential interspecies toxicodynamic differences, since toxicokinetic differences between mice and humans were accounted for within the PBPK model.
- 10 for intraspecies variability. The variability of PCE metabolism among humans is reflected by a wide range of reported $V_{max}$ and $K_m$ values. It has been suggested that these variations can be attributed to genetic polymorphisms in the active metabolic enzymes in the studied populations (Lash et al., 2007; US EPA, 2012).
- 3 for gravity of effects (the mode of action for carcinogenicity potential has not been fully elucidated). This is considered a conservative approach.
The TDI is calculated using the following equation:

TDI (carcinogenic end-point) = \( \frac{1.7 \text{ mg/kg bw/day}}{75} \) = 0.023 mg/kg bw/day

### 8.1.2 Noncancer effects

Neurotoxicity was observed in humans and experimental animal studies; effects in humans were observed at lower concentrations than in animals. The availability of studies in humans, supported by animal data, and the availability of PBPK modelling to extrapolate from the inhalation route of exposure to the oral route, distinguish the present point of departure from the previous guideline value (GV) for PCE (WHO, 2003). The previous point of departure was 14 mg/kg bw/day from two oral toxicity studies in laboratory animals: a 6-week gavage study in male mice, and a 90-day drinking-water study in male and female rats (Buben & O’Flaherty 1985; Hayes, Condie & Borzelleca, 1986).

Key studies are the following:

- Cavalleri et al. (1994) showed a significant decrease in colour vision (mainly blue–yellow range) in exposed workers.
- Echeverria, White & Sampaio (1995), using a standardized neurobehavioural battery, found changes in cognitive function (reaction time measures and cognitive changes) and visuospatial function. These results can be used to qualitatively support the key study, since the exposure assessment was not as robust as the one performed by Cavalleri et al. (1994).

An inhalation NOAEL of 4.8 ppm for colour confusion was identified from Cavalleri et al. (1994). A BMDL\(_{10}\) of 6.6 ppm can be estimated (Health Canada, 2015). The PBPK modelling validated by Health Canada (Nong, 2013) can be applied to this value to extrapolate from inhalation exposures to equivalent oral doses. In the modelling, the peak concentrations of PCE in the kidney were used as a proxy for brain values, since partition coefficients for PCE in brain are similar to those in kidney (Dallas et al., 1994), and the effect is very likely to be mediated by the parent compound. The external oral dose associated with the BMDL\(_{10}\) was 4.7 mg/kg bw/day.

As noted by US EPA (2012), the reference doses for noncancer effects other than neurotoxicity are within about 10-fold of the reference dose; therefore, multiple effects may occur at about the same levels of exposure at which PCE begins to induce neurotoxicity. These results also suggest that it is important to take into account effects from PCE other than neurotoxicity when assessing the cumulative effects of multiple exposures.

To calculate the TDI, the BMDL\(_{10}\) is divided by an uncertainty factor of 300, comprising:

- 10 for database deficiencies, considering the relatively old studies that are available, which suffer from some limitations, and also that the mode of action for carcinogenicity potential has not been fully elucidated;
- 10 for intraspecies variability; and
- 3 to extrapolate from an occupational study with intermittent exposure for 8.8 years – this is considered as a conservative approach.
The TDI is calculated using the following equation:

TDI for neurological effects = \( \frac{4.7 \text{ mg/kg bw/day}}{300} = 0.016 \text{ mg/kg bw/day} \)

### 8.1.3 Guideline value

Cancer and noncancer end-points were considered in the derivation of the GV for PCE in drinking-water.

The TDI for PCE in drinking-water derived considering cancer effects (assuming a nongenotoxic, threshold mode of action) was higher than the TDI derived for the noncancer end-points. The GV was therefore derived for noncancer effects, and it is protective for both cancer and noncancer end-points:

\[
\text{GV} = \frac{0.016 \text{ mg/kg bw/day} \times 60 \text{ kg bw} \times 0.2}{2 \text{ L/day}} = 96 \mu\text{g/L (rounded to 100 µg/L)}
\]

where:
- 0.016 mg/kg bw/day is the TDI for noncancer end-points;
- 60 kg is the average body weight of an adult;
- 0.2 is the fraction of the total daily intake that is allocated to drinking-water, as there is evidence of widespread presence of PCE in at least one of air, food, soil and consumer products (Health Canada, 2015); and
- 2 L is the daily volume of water consumed by an adult.

A higher allocation than the default factor of 0.2 (20%) to drinking-water could have been considered, since releases of PCE into the air and water have continued to show decreasing trends over the past few decades (US EPA, 2012; Health Canada, 2015); thus, human exposures to PCE are anticipated to continue to decline by all probable exposure routes. However, this was not considered necessary, as 100 µg/L PCE in drinking-water should be achievable.

### 8.2 Considerations in applying the guideline value

For certain population groups, such as dry-cleaning workers, the level of inhalation and dermal exposure is likely to be high compared with exposure through drinking-water.

In some parts of the world, there may be a need to adapt the GV by adjusting the allocation factor or considering the Leq/day corresponding to inhalation exposure from the domestic use of water to account for local conditions, including inhalational exposure from showering and bathing, and/or from living in poorly ventilated buildings. Consideration could also be given to overall exposure through the various environmental media, as described in section 8.1.

Requirements for monitoring PCE in drinking-water regulations and standards should be limited to groundwater sources where a catchment risk assessment indicates the possibility of presence of PCE, such as where there is evidence of current or past poor handling practices in degreasing and dry-cleaning industries. In some cases, this may include PCE drawn in from contamination elsewhere in the aquifer. Monitoring can be conducted at the treatment works. If concentrations are shown to be stable or effective treatment is in place, the frequency of monitoring can be quite low.
If monitoring data show elevated levels of PCE, it is suggested that a plan be developed and implemented to address these situations. Monitoring is not needed for surface water sources because PCE volatilizes to the atmosphere.
References


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