

**Department for Environment, Food and Rural  
Affairs and the Environment Agency**

**CONTAMINANTS IN SOIL:**

**COLLATION OF TOXICOLOGICAL DATA  
AND INTAKE VALUES FOR HUMANS.**

**TETRACHLOROETHENE**



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## **Statement of Use**

This publication details the derivation of health criteria values for tetrachloroethene. The report has been written for technical professionals who are familiar with the risks posed by land contamination to human health but who are not necessarily experts in risk assessment. It is expected to be of use to all parties involved with or interested in contamination, but in particular to those concerned with the assessment of land contamination.

## **Keywords**

Tolerable daily intake, tolerable daily soil intake, land contamination, risk assessment, human health, tetrachloroethene.

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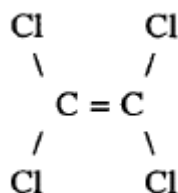


## 1 Introduction

- 1.1 This report is one of a number of reports on the assessment of risks to human health from contaminants in soil. Key data and expert opinion are presented on the toxicology of tetrachloroethene and its intake, by the general population, from background environmental exposure. It may be necessary to update this report in the future to incorporate new toxicological data as scientific knowledge advances.
- 1.2 The aim of this report is to set out authoritative health criteria values for tetrachloroethene, which have been established through a review of the scientific literature and a subsequent peer review process. The health criteria values that are presented herein will be used to derive Soil Guideline Values (SGVs) for tetrachloroethene.
- 1.3 The overall framework for this review and the associated underlying principles are set out in CLR9 *Contaminants in Soils: Collation of Toxicological Data and Intake Values for Humans* (Department for Environment, Food and Rural Affairs (Defra) and Environment Agency, 2002a). Reference to CLR9 is necessary to understand the concepts, terms and approach used in this report.
- 1.4 The computer model used for deriving the SGVs is described in CLR10 *The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms* (Defra and Environment Agency, 2002b). SGVs for tetrachloroethene will be published in *SGV 22 Guideline Values for Tetrachloroethene Contamination* (Defra and Environment Agency, in preparation).
- 1.5 This report is principally based on the literature published up to June 1999. The report has been updated following a further review of key publications up to April 2003.

## 2 Identity

- 2.1 Tetrachloroethene (CAS No 127-18-4) is also commonly known as tetrachloroethylene and perchloroethylene (or “perc”). It is a volatile (vapour pressure of approximately 1.9 kPa at 20°C), colourless, non-flammable liquid which has a chloroform-like odour and a low solubility in water (of 0.15 g L<sup>-1</sup>) (ECETOC, 1999). The structure of tetrachloroethene is shown in Figure 2.1.



**Figure 2.1 Structure of tetrachloroethene**

- 2.2 Tetrachloroethene is produced naturally by several temperate and subtropical marine macroalgae (Abrahamsson *et al*, 1995, in ATSDR, 1997). However, the majority is manufactured through oxyhydrochlorination, perchlorination and/or dehydrochlorination of hydrocarbons or chlorinated hydrocarbons (Fuller, 1976). The primary uses for tetrachloroethene are as a dry-cleaning agent and a degreasing solvent, and these result in large releases to the environment, particularly into the atmosphere. About 11,000 tonnes per year are emitted in the United Kingdom, and about 9600 tonnes of this is due to solvent usage (DETR, 1998).
- 2.3 Trace amounts of tetrachloroethene are found in water, aquatic organisms, marine sediments, air and food. Rapid degradation occurs in the environment, with no evidence of significant bioconcentration (ATSDR, 1997). Tetrachloroethene's slight aqueous solubility and density (greater than water) mean that some movement through the soil column and into groundwater may be expected to occur (Piet *et al*, 1981). However, the high vapour pressure indicates that volatilisation is the dominant removal process. Once in the atmosphere, photochemically produced hydroxyl radicals degrade it to phosgene and chloroacetyl chlorides, with a half-life of tetrachloroethene between 96 and 251 days (WHO, 1996).
- 2.4 In water, tetrachloroethene does not readily undergo hydrolysis or photolysis (WHO, 1996). Decomposition in water by dechlorination is accelerated by the presence of iron (Pearson and McConnell, 1975; McConnell *et al*, 1975). In soil, tetrachloroethene may undergo biodegradation in anaerobic conditions (WHO, 1996) by sequential reductive dechlorination to tetrachloroethane, dichloroethene, vinyl chloride and finally chloro(ethane) (Vogel and McCarty, 1985).
- 2.5 Where studies have reported tetrachloroethene levels in ppm, a conversion factor of 1 ppm = 6.78 mg m<sup>-3</sup> (WHO, 1996) has been used to ensure consistency in units throughout this report.

### 3 Toxicity

- 3.1 The toxicity of tetrachloroethene has been considered by the United States Environmental Protection Agency (USEPA, 1985, 1988), the Agency for Toxic Substances and Disease Registry (ATSDR, 1997), the International Agency for Research on Cancer (IARC, 1987, 1995), the International Programme on Chemical Safety (IPCS, 1984), World Health Organization (WHO, 1996, 2000), the Health and Safety Executive (Illing *et al*, 1987; HSE, 1997), and the European Centre for Ecotoxicity and Toxicology of Chemicals (ECETOC, 1999). This section (and Section 4) is largely based upon these reviews. Particular mention is made of those studies which have been used in deriving tolerable daily intakes (TDIs). In general, the primary reports have not been consulted.
- 3.2 **Absorption.** Inhalation studies in humans and rats have shown that tetrachloroethene is readily absorbed into the systemic circulation through the lungs (ATSDR, 1997). A 60% alveolar retention has been estimated in humans exposed for 4 hours to 480–960 mg m<sup>-3</sup> (Monster *et al*, 1979), with 50% absorption reported in male rats exposed for 3 hours to 340 mg m<sup>-3</sup> (Dallas *et al*, 1994a).
- 3.3 Exposure of the skin to vapour (3.5 hours to 4150 mg m<sup>-3</sup>) in human volunteers was found to result in dermal absorption of about 1% of that expected by the inhalation route (Riihimaki and Pfaffli, 1978). A 3-minute exposure of the forearm of six volunteers to tetrachloroethene resulted in an average dermal absorption rate of 0.68 mg cm<sup>-2</sup> min<sup>-1</sup> (Kezic *et al*, 2001; cited in Toxline, 2003). In mice, exposure to 1380 mg m<sup>-3</sup> of the vapour resulted in dermal absorption of 0.002 mg cm<sup>-2</sup> h<sup>-1</sup> (Tsuruta, 1975); exposure to the liquid resulted in an absorption of 0.24 mg cm<sup>-2</sup> h<sup>-1</sup> (Tsuruta, 1975).
- 3.4 In laboratory animals, tetrachloroethene was rapidly and “virtually completely absorbed” from the gastrointestinal tract (ATSDR, 1997).
- 3.5 **Distribution.** The distribution of tetrachloroethene in tissues is determined by its lipophilic nature (the fat/blood partition coefficient in humans is 125–160), which ensures that it is readily taken up by blood and fatty tissues (ATSDR, 1997). In volunteers exposed 7 h day<sup>-1</sup> to 690 mg m<sup>-3</sup> the increasing concentration of tetrachloroethene in the expired air over the 5-day experiment indicated an increase in body burden with repeated exposure (Stewart *et al*, 1970). The half-life of tetrachloroethene in the adipose tissue of humans is estimated to be 55 hours (ATSDR, 1997). High concentrations of tetrachloroethene were present in the liver, kidneys, brain and lungs of a dry-cleaner who was killed by an accidental high exposure (Levine *et al*, 1981).
- 3.6 Exposure of rats 6 h day<sup>-1</sup> for 4 days to 1380 mg m<sup>-3</sup> (Savolainen *et al*, 1977; cited in Toxline, 2003) or on a single 2-hour occasion to 3450 mg m<sup>-3</sup> (Dallas *et al*, 1994b) resulted in distribution primarily to the adipose tissue. Following oral administration to rats, the highest concentrations were found in the fat, liver, kidneys and brain (Dallas

*et al*, 1994b; Pegg *et al*, 1979). Tetrachloroethene has been shown to cross the placenta into the fetus of pregnant mice exposed by inhalation (Ghantous *et al*, 1986).

- 3.7 **Metabolism.** Tetrachloroethene is oxidised mainly in the liver by cytochrome P450-mediated pathways, principally to trichloroacetic acid, probably via an epoxide and trichloroacetyl chloride (ATSDR, 1997; ECETOC, 1999). The proportion of the absorbed dose that is biotransformed to trichloroacetic acid varies with species and is particularly high in the mouse, whereas it is formed in smaller amounts in rats (Odum *et al*, 1988). In humans, irrespective of the route of exposure, the extent of conversion to trichloroacetic acid is of the order of 1–3% (ATSDR, 1997). A wide range of  $V_{\max}$  values (a measure of metabolic rate) for total metabolism have been reported in humans ( $0.8\text{--}10.1 \mu\text{g kg}^{-1} \text{ bw min}^{-1}$ ) (micrograms per kilogram body weight per minute) and the equivalent ranges in rats and mice are 4.51–66.3 and 34.8–308 respectively (ATSDR, 1997). Other, lesser, metabolic pathways include one that involves the conjugation of tetrachloroethene with glutathione which results in the eventual formation of *N*-acetyl-*S*-1,2,2-trichlorovinyl-L-cysteine (IARC, 1995). Small amounts of this metabolite were found in the urine of four workers occupationally exposed to about  $350 \text{ mg m}^{-3}$  of tetrachloroethene (Birner *et al*, 1996).
- 3.8 Conversion to trichloroacetic acid is saturable in humans and the linear relationship with exposure only occurs at atmospheric concentrations below about  $690 \text{ mg m}^{-3}$  (Ohtsuki *et al*, 1983; Seiji *et al*, 1989; cited in ATSDR, 1997). Saturation of biotransformation has also been observed in both inhalation and gavage studies in rats and mice (Buben and O’Flaherty, 1985; Green *et al*, 1990; Schumann *et al*, 1980) although saturation occurs at higher doses in mice than in rats (IARC, 1995), as demonstrated by the relative metabolic capabilities. The amount of total metabolites in the urine of mice reached a plateau at gavage doses in excess of  $1 \text{ g kg}^{-1} \text{ bw day}^{-1}$  (NICNAS, 2001).
- 3.9 After saturation of metabolism via the oxidative pathway, conjugation with glutathione becomes more important. This metabolic pathway is more active in the rat than in the mouse and humans, and higher after gavage administration than after inhalation (Green *et al*, 1990).
- 3.10 **Excretion.** In humans, systemically absorbed tetrachloroethene is eliminated primarily unchanged via the lungs, with 40–70% being excreted in the first 24 hours after exposure, the remainder much more slowly (ECETOC, 1999). Trichloroacetic acid is eliminated in the urine with a half-life of 144 hours (WHO, 1996).
- 3.11 In rats exposed for 6 hours to  $70 \text{ mg m}^{-3}$ , the total excretion of non-volatile metabolites in the urine and faeces was about 25% of the absorbed dose. At an exposure of  $4070 \text{ mg m}^{-3}$ , only 9% of the absorbed dose was excreted in this form (Pegg *et al*, 1979). Mice excrete most of an absorbed inhaled dose as metabolites in the urine. After a 6-hour exposure of  $690 \text{ mg m}^{-3}$ , close to 90% of the absorbed material was excreted as non-volatile metabolites (Schumann *et al*, 1980). The main route of excretion of tetrachloroethene orally administered to rodents was as the unchanged compound in

the expired air; about 80–90% of a dose of around 500 mg kg<sup>-1</sup> bw and over 70% of a 1 mg kg<sup>-1</sup> bw dose was excreted in this manner (ATSDR, 1997).

- 3.12 **Acute toxicity.** Symptoms of toxicity in humans exposed to high concentrations of atmospheric tetrachloroethene include headache, drowsiness, dizziness, a reduced concentration and narcosis, with death resulting from depression of the respiratory centre or heart arrhythmia (ATSDR, 1997; ECETOC, 1999). Pathological examination of those who have died revealed changes to the liver, kidney, lung and brain (ECETOC, 1999). Recovery is believed to be complete in non-fatal cases (ECETOC, 1999). The first signs of mild reversible central nervous system toxicity occur in volunteers exposed for 1–7 hours to concentrations of around 0.7 g m<sup>-3</sup> (ECETOC, 1999). Central nervous system effects (inebriation, perceptual distortion and exhilaration) occurred in patients given 4.2–6 g orally (Haerer and Udelman, 1964).
- 3.13 Tetrachloroethene is of a low inhalation toxicity in rats and mice, and 4–6 hour exposures to in excess of 16 g m<sup>-3</sup> are necessary to produce deaths (ATSDR, 1997; IARC, 1995). Liver damage has been reported in rodents exposed to concentrations close to the lethal levels (ECETOC, 1999). In rats, oral LD<sub>50</sub> values of around 3–4 g kg<sup>-1</sup> bw have been reported, with the equivalent values in mice being markedly higher (in excess of 8 g kg<sup>-1</sup> bw) (ATSDR, 1997). The major toxic symptom was central nervous system depression (Hayes *et al*, 1986).
- 3.14 **Repeated toxicity.** Prolonged reaction times were recorded in 60 Italian women exposed for an average of 10 years to workroom atmospheres containing an average concentration of 102 mg m<sup>-3</sup> of tetrachloroethene. Exposure was assessed on the basis of both blood and air samples (Ferroni *et al*, 1992). An increase in subjective symptoms such as dizziness and forgetfulness has been reported in 56 Chinese workers exposed to around 140 mg m<sup>-3</sup> (Cai *et al*, 1991).
- 3.15 A subtle (sub-clinical) deterioration in colour vision was reported in 22 Italian dry-cleaners exposed to 50 mg m<sup>-3</sup> for 9 years (Cavalleri *et al*, 1994). The same research team noted that a poorer performance in tests of colour vision occurred in 19 workers exposed for 2 years to atmospheres that had an increasing burden of tetrachloroethene (from 12 mg m<sup>-3</sup> initially, up to 30 mg m<sup>-3</sup>), but not in 14 workers whose exposure over the same period had been reduced (from 20 mg m<sup>-3</sup> to 4.8 mg m<sup>-3</sup>) (Gobba *et al*, 1998; cited in Medline, 2003). No effect on colour vision was detected in 64 Japanese workers, working in atmospheres containing 75–105 mg m<sup>-3</sup>, screened using the same tests as the Italian investigators (Nakatsuka *et al*, 1992). Severe optic neuritis, presumed to have resulted from high (but uncertain) exposure to tetrachloroethene, was reported in an Italian dry-cleaner (Onofrj *et al*, 1998; cited in Medline, 2003).
- 3.16 A collaborative European study (Mutti *et al*, 1992) of 50 dry-cleaning workers with long-term exposure reported the possible onset of mild renal damage after exposure to a median concentration of 102 mg m<sup>-3</sup>. There were raised levels in the blood and urine of a number of markers of impaired kidney function.

- 3.17 There was no evidence of any change in liver function of 20 volunteers exposed 7.5 h day<sup>-1</sup> for 5 days to about 1 g m<sup>-3</sup> (Stewart *et al*, 1981). A biopsy of a woman exposed occupationally to tetrachloroethene fumes for 2.5 months did reveal liver damage (Meckler and Phelps, 1966). Ultrasound scans of the liver of workers exposed for at least 6 months to around 110 mg m<sup>-3</sup> were also more likely than unexposed controls to show “diffuse parenchymal changes” (Brodkin *et al*, 1995). Liver effects (obstructive jaundice and increased liver size) have been reported in an infant fed breast milk that contained 10 mg L<sup>-1</sup> of tetrachloroethene. The symptoms disappeared when breast feeding stopped (Bagnell and Ellenberger, 1977).
- 3.18 No convincing signs of neurotoxicity were detectable in rats exposed 6 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 13 weeks to atmospheres containing up to 5.5 g m<sup>-3</sup> of tetrachloroethene. The investigation included detailed examination of the function of the nervous system, and a microscopic examination of tissues of the central and peripheral nervous system (Mattsson *et al*, 1998; cited in Toxline, 2003). Doses of 50 mg kg<sup>-1</sup> bw day<sup>-1</sup>, administered by stomach tube for 8 weeks, reduced the locomotor activity of rats. There was an indication that a similar but less marked effect was also present in rats treated with 5 mg kg<sup>-1</sup> bw day<sup>-1</sup> (Chen *et al*, 2002). Very young mice given 5 mg kg<sup>-1</sup> bw day<sup>-1</sup> orally for 7 days were reported to have shown an increase in locomotion and rearing when they were examined about 6 weeks after treatment (Fredriksson *et al*, 1993).
- 3.19 In short- and long-term inhalation studies, mice were shown to be more susceptible than rats to kidney and liver toxicity. The 13-week experiments involved exposures (6 h day<sup>-1</sup>, 5 day week<sup>-1</sup>) of 0.68–10.9 g m<sup>-3</sup>, whereas in the 103-week studies the rats were exposed (again 6 h day<sup>-1</sup>, 5 day week<sup>-1</sup>) to 1.36 and 2.72 g m<sup>-3</sup> and the mice to 0.68 and 1.36 g m<sup>-3</sup> (NTP, 1986). Kidney pathology (renal karyomegaly and renal tubular hyperplasia) was induced in both species at both tested doses after 103 weeks. (The cancer findings are described in paragraph 4.6.) In the corresponding 13-week studies, the kidney was unaffected even at the maximum tested concentration of 10.9 g m<sup>-3</sup> in the rats, but kidney pathology was seen in mice exposed to 1.36 g m<sup>-3</sup> and above. Liver degeneration and necrosis were reported in the two groups of treated mice in the long-term study, but not in the treated rats. Liver injury was present in both species in the 13-week experiments from 2.72 g m<sup>-3</sup> and above, but the incidence was markedly higher in the mice than in the rats (NTP, 1986). There were clear signs of liver injury in mice exposed continuously for 30 days to atmospheres containing 520 mg m<sup>-3</sup> (Kjellstrand *et al*, 1984). Liver pathology was the main finding when guinea pigs were exposed to 1.4 g m<sup>-3</sup> for 6–8 months (Rowe *et al*, 1952).
- 3.20 Kidney damage (degenerative tubule and fatty changes and cloudy swelling) was observed in mice and rats of both sexes given about 465 mg kg<sup>-1</sup> bw day<sup>-1</sup> by stomach tube for 78 weeks (NCI, 1977).
- 3.21 Liver injury (including necrosis) occurred in male mice given tetrachloroethene by stomach tube 5 days per week for 6 weeks at doses of 200–2000 mg kg<sup>-1</sup> bw day<sup>-1</sup>. At 100 mg kg<sup>-1</sup> bw day<sup>-1</sup> there were increased liver triglyceride levels and liver weights. No signs of toxicity were seen at 20 mg kg<sup>-1</sup> bw day<sup>-1</sup> (which was equivalent to 14 mg

kg<sup>-1</sup> bw day<sup>-1</sup>, 7 day week<sup>-1</sup> exposure), although only the liver tissues were subjected to microscopic examination (Buben and O'Flaherty, 1985). Doses of 14, 400 and 1400 mg kg<sup>-1</sup> bw day<sup>-1</sup> were administered to male and female rats in drinking water for 90 days. Increases in liver and kidney weights and decreases in body weight of both sexes were observed at 400 and 1400 mg kg<sup>-1</sup> bw day<sup>-1</sup>. No effects were seen in either sex at 14 mg kg<sup>-1</sup> bw day<sup>-1</sup>. Tissues of the liver were not examined microscopically (Hayes *et al*, 1986). In 11-day studies involving administration by stomach tube, liver pathology, which was detectable in mice given 100 mg kg<sup>-1</sup> bw day<sup>-1</sup>, was not seen in rats that received doses of 1000 mg kg<sup>-1</sup> bw day<sup>-1</sup> (Schumann *et al*, 1980).

- 3.22 **Reproductive and developmental toxicity.** Several studies of dry-cleaning workers report an association between estimated tetrachloroethene exposure and a higher-than-expected risk of experiencing a spontaneous abortion (Ahlborg, 1990; Bosco *et al*, 1987; Kyyrönen *et al*, 1989; Lindbohm *et al*, 1990; Windham *et al*, 1991). A slightly protracted time to pregnancy has been seen in exposed workers (Sallmen *et al*, 1995) and in the wives of exposed male workers (Eskenazi *et al*, 1991a,b). One study has observed subtle changes in sperm shape associated with occupational exposure to tetrachloroethene (Eskenazi *et al*, 1991a).
- 3.23 In a 1993 assessment, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (DH, 1994) concluded that “the available epidemiological evidence, although based on studies that are methodologically weak, is consistent with the view that perchloroethylene may be a reproductive toxicant in humans”. As a result of this advice, the Health and Safety Executive (HSE) commissioned an investigation of the maternity histories of women currently or previously employed in dry-cleaning shops or laundry units.
- 3.24 Of the dry-cleaning workers included in this study (Doyle *et al*, 1997; cited in Toxline, 2003), a higher spontaneous abortion rate was seen in those described as “operators” than in those who were “non-operators” (17.1 vs 11.6%). Information was available on around 3110 women currently or previously employed in dry-cleaning or laundry establishments at the time of their pregnancy or in the three months before conception. In a 1997 evaluation COT agreed that there was an epidemiological association between the job category “dry-cleaning machine operators” and spontaneous abortion, but was of the opinion that there “is no evidence for a plausible biological mechanism by which tetrachloroethylene could cause this effect and that other factors could have contributed to the observed risk”. The COT therefore concluded that the increased risk of spontaneous abortion could not be specifically attributed to exposure to tetrachloroethene (DH, 1998).
- 3.25 Tetrachloroethene demonstrates low reproductive and developmental toxicity in laboratory animals. Decreased litter sizes and decreased pup survival during lactation were reported in a multigenerational rat study, but only at atmospheric concentrations (of up to 6.9 g m<sup>-3</sup>, 6 h day<sup>-1</sup>, 5 day week<sup>-1</sup>, for 11 weeks before mating) that were overtly neuro- and nephrotoxic in the parental generation. There were no statistically significant effects on reproduction at 2 g m<sup>-3</sup> (Tinston, 1995). An increased proportion

of abnormal sperm was seen in mice but not in rats exposed to  $3.5 \text{ g m}^{-3}$  for 5 days (Beliles *et al*, 1980).

- 3.26 Developmental toxicity studies in mice exposed by inhalation ( $7 \text{ h day}^{-1}$  on days 6–15 of pregnancy) have identified fetotoxicity (reduced fetal body weights and delayed ossification) at atmospheric concentrations of  $2 \text{ g m}^{-3}$ , which also produced signs of maternal toxicity. Lower exposures were not investigated (Schwetz *et al*, 1975). An increased fetal resorption rate was also reported in rats exposed  $7 \text{ h day}^{-1}$  on days 6–15 of pregnancy (Schwetz *et al*, 1975). No signs of embryotoxicity or fetotoxicity occurred in two strains of rat (including the strain tested by Schwetz *et al*) or rabbits exposed  $6\text{--}7 \text{ h day}^{-1}$  throughout pregnancy to  $3.4 \text{ g m}^{-3}$  (Hardin *et al*, 1981).
- 3.27 Treatment-related increases in embryo resorptions, malformations (small or no eyes) and post-natal deaths occurred in rats given a maternally toxic dose of  $900 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  by stomach tube on days 6–19 of pregnancy. Lower doses were not tested (Narotsky and Kavlock, 1995).
- 3.28 **Toxic mechanisms.** The effects on the central nervous system are thought to be the result of the interaction of tetrachloroethene with the tissues of the nervous system, although the details remain to be elucidated (ATSDR, 1997).
- 3.29 There is good experimental support for the view that the metabolite trichloroacetic acid is key to the production of the liver pathology, and therefore there are likely to be major quantitative species differences in the dose–response of the liver toxicity. The mouse’s higher conversions of tetrachloroethene to trichloroacetic acid are thought to explain the greater susceptibility of the mouse than the rat to liver injury. As the mechanism of liver damage is believed to involve initial peroxisome proliferation of the liver as an early and critical step, there is also the possibility of qualitative species differences. The liver of humans is known to be largely resistant to the peroxisome proliferating action of a range of other chemicals that are powerful proliferators in rodents (ATSDR, 1997).
- 3.30 Rats have a much higher potential than mice (and humans) for producing reactive intermediates from the glutathione conjugate of tetrachloroethene. The conjugate and its metabolic products may be important in the development of the kidney damage in rats (ATSDR, 1997). A particular type of kidney lesion,  $\alpha$ -2 $\mu$ -globulin nephropathy, is also seen in male rats treated with tetrachloroethene (ATSDR, 1997). On the basis of a large programme of mechanistic studies on a range of hydrocarbons that also commonly induce  $\alpha$ -2 $\mu$ -globulin nephropathy, it is accepted to be a response specific to the male rat that is not of relevance to humans.

## 4 Carcinogenicity and genotoxicity

- 4.1 An IARC Working Group, meeting in 1995, concluded that tetrachloroethene was “probably carcinogenic in humans” (Group 2A). In their opinion there was “sufficient” evidence of its carcinogenicity in experimental animals and some (“limited”) evidence in humans (IARC, 1995). Tetrachloroethene is classified as a Category 3 carcinogen under the EU Dangerous Substances Directive 67/548/EEC as amended (HSE, 2003). Category 3 carcinogens are substances that cause “concern for humans owing to possible carcinogenic effects, but in respect of which the available evidence is not adequate for making a satisfactory assessment”.
- 4.2 In reviewing five occupational cohort studies, the IARC Working Group concluded that “there is evidence for consistently positive associations between exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin’s lymphoma. These associations appear unlikely to be due to chance, although confounding cannot be excluded and the total numbers in the cohort studies combined are relatively small” (IARC, 1995). In 1996, the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) expressed the opinion that there was “no satisfactory epidemiological evidence to associate tetrachloroethylene exposure to cancer in the available cohort studies” (DH, 1997).
- 4.3 The two cohort studies reviewed by IARC that had examined oesophageal cancer (Blair *et al*, 1990; Ruder *et al*, 1994) had reported raised relative risks in those exposed to tetrachloroethene. Increased relative risks were reported in three cohorts for both cervical cancer (Blair *et al*, 1990; Anttila *et al*, 1995; Ruder *et al*, 1994) and non-Hodgkin’s lymphoma (Anttila *et al*, 1995; Blair *et al*, 1990; Spirtas *et al*, 1991). The COC in 1996 noted that the various analyses were based on very few cancer cases and did not include controls for multiple statistical tests (DH, 1997). In addition, the COC considered that the possibility of confounding, by alcohol drinking and smoking for oesophageal cancer, and virus infection for cervical cancer, had not been adequately addressed. Confident conclusions from the studies of non-Hodgkin’s lymphoma were not possible in the view of the COC because of the inadequacy of information on tetrachloroethene exposure (DH, 1997). An excess of deaths from cancer of the oesophagus and the cervix continued to be seen in an updated report on one of these cohorts, covering six more years of follow-up. The investigators noted that the excess risks at these sites were present both in a subgroup exposed only to tetrachloroethene, and among workers with the longer duration of tetrachloroethene exposure (Ruder *et al*, 2001).
- 4.4 The COC and IARC reviewed further studies on the links between tetrachloroethene exposure and cancer. According to the COC, “no convincing evidence of an association between exposure to tetrachloroethylene and cancer was documented in any of the case-control investigations”, and “no conclusions can be drawn from the investigations which alleged an association between tetrachloroethylene contamination

of drinking water and cancer” (DH, 1997). The IARC Working Group in 1995 had essentially the same view on these particular studies (IARC, 1995).

- 4.5 In a study of 8163 deaths of US workers formerly employed in laundrettes and dry-cleaners (Walker *et al*, 1997), there were some indications of an increase in the incidence of cancer of the oesophagus.
- 4.6 The main support for the cancer classifications of the EC and IARC is the clear evidence of cancer in tetrachloroethene-treated laboratory animals. In mice exposed 6 h day<sup>-1</sup>, 5 day week<sup>-1</sup> for 103 weeks to atmospheres containing 0.68 or 1.36 g m<sup>-3</sup>, there were increases in the incidence of malignant liver tumours in both sexes in both treatment groups. In the females, for example, liver cancer was present in 1 of the 48 controls, in 13 of the 50 mid-dose animals and in 36 of the 50 high-dose animals (NTP, 1986). The corresponding experiment in rats involved exposures of 1.36 and 2.72 g m<sup>-3</sup>. A small increase in kidney tumours was recorded in the males. Malignant kidney tumours, which are rarely seen in untreated rats, and did not develop in any of the 49 study controls, were found in 2 of the 50 high-dose males. Benign kidney tumours developed in 1 of the controls, in 3 of the 49 low-dose males and in 2 of the 50 high-dose males. An increase in the incidence of mononuclear leukaemia was also noted in the high-dose male and female rats, 74% and 58% respectively. These tumours are commonly seen in untreated rats, and were present in 56% of the male and 36% of the female controls (NTP, 1986).
- 4.7 In oral carcinogenicity studies, mice and rats were treated by stomach tube, 5 days a week, for 78 weeks (NCI, 1977). The mice were killed at week 90 and the rats at week 110. High incidences of liver cancer occurred in both groups of male and female mice at both tested doses, which were 386–536 and 772–1072 mg kg<sup>-1</sup> bw day<sup>-1</sup> respectively. For example, malignant liver tumours were found in 2 of the 20 untreated females, in 19 of the 48 mid-dose females and in 19 of the 48 high-dose females. There was no evidence of carcinogenicity in the rats, which received doses of about 470 and 950 mg kg<sup>-1</sup> bw day<sup>-1</sup>, although the low survival of both treated and control animals meant that this particular experiment would have had a low sensitivity. An earlier investigation found no evidence of carcinogenicity in two groups of 50 male and 50 female rats that received daily doses of 500 mg kg<sup>-1</sup> bw by stomach tube 4–5 times a week for 104 weeks (Maltoni and Cotti, 1986).
- 4.8 A substantial number of *in vitro* studies, including the standard Ames tests in *Salmonella typhimurium*, and investigations of mutations or chromosome damage in mammalian cells in culture, have in general given no evidence of genotoxic potential (ECETOC, 1999; IARC, 1995). No conclusive evidence of chromosome damage has been seen in the blood or bone marrow of a small group of exposed workers, of rats exposed by inhalation or of mice given intraperitoneal injections (ECETOC, 1999). Following intraperitoneal injection to mice, DNA strand breaks were detected in the liver and kidney, and there was some indication of DNA binding in the liver (ECETOC, 1999).

- 4.9 The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) in 1996 concluded that “the weight of evidence suggested that tetrachloroethylene was not an *in-vivo* genotoxin” (DH, 1997). They did suggest, however, that it “would be desirable to have an adequate *in-vivo* bone marrow micronucleus assay to provide additional reassurance”. Although no chromosomal damage (micronuclei) occurred in the bone marrow of mice given up to 2 g kg<sup>-1</sup> bw by intraperitoneal injection, there were indications of chromosome damage in the liver. At 1 and 2 g kg<sup>-1</sup> bw, a statistically significant dose-dependent increase in micronuclei in the liver cells was seen in the mice that had been subject to a partial hepatectomy (Murakami and Horikawa, 1995; cited in Toxline, 2003).
- 4.10 **Cancer mechanisms.** The possibility that tetrachloroethene may be carcinogenic to humans continues to be a topic of considerable research and debate. Studies on the mechanism of the liver tumours seen in mice have indicated that a critical factor is the conversion of tetrachloroethene to trichloroacetic acid. The metabolic pathway producing the trichloroacetic acid, which is saturated at atmospheric concentrations of 680 mg m<sup>-3</sup> in the rat, is far more active in the mouse (and may not be saturated until much higher concentrations). Humans are closer to the rat than to the mouse in their propensity to convert tetrachloroethene to trichloroacetic acid.
- 4.11 Trichloroacetic acid’s ability to induce peroxisome proliferation in the liver of the mouse may be the key to the liver tumour development. It is generally accepted that the liver of humans is very much less susceptible to peroxisome proliferation than is the liver of rodents (ECETOC, 1999). The UK COC subscribes to this view (DH, 1994). Not all Expert Groups are convinced, however, that peroxisome proliferation is the critical feature in tetrachloroethene’s induction of liver tumours. In their 1995 evaluation, the IARC Working Group noted for example that “a poor quantitative correlation was seen between peroxisome proliferation and tumour formation in the liver after administration of tetrachloroethylene by inhalation” (IARC, 1995).
- 4.12 The IARC Working Group was also concerned about the induction of leukaemia in rats, and mentioned this as an influence on their overall classification of tetrachloroethene into Group 2A. These treatment-related leukaemias did not have any direct impact on a WHO Working Group when they derived an air quality guideline for tetrachloroethene (WHO, 2000) at around the same time that the IARC experts were considering its cancer status. The significance for humans of this particular finding was said by the WHO Working Group to be “unclear owing to the lack of understanding of the mechanism underlying the formation of this cancer type, which has a high background incidence [in the laboratory animal under test]”. The UK COC in 1993 concluded that the form of leukaemia seen in the rats “had no predictive implications for humans” (DH, 1994).
- 4.13 A number of mechanisms have been proposed for the development of the kidney tumours in the male rats. There is experimental support for the view that the kidney pathology induced in rats is related to the rat’s propensity to conjugate tetrachloroethene in the liver. The resulting glutathione conjugate is metabolised further to what is proposed to be the proximate genotoxin, which may be responsible

for the attack on the DNA and the resulting tumour formation. The equivalent metabolic pathway in humans is likely to be only a very minor one. The tumours may also be a result of the long-term toxic injury to the kidney arising from the initial induction of  $\alpha$ -2 $\mu$ -globulin formation. This type of protein induction, and the pathological consequences to the kidney, which are also seen with a range of hydrocarbons, is accepted to be a problem only for the male rat. If  $\alpha$ -2 $\mu$ -globulin formation is critical in the kidney tumour development, the kidney carcinogenicity in rats would be of no relevance in humans (ECETOC, 1999). The COC has concluded that “the carcinogenic effects seen in the rat kidney were unlikely to occur in humans” (DH, 1994).

## 5 Derivation of tolerable daily intakes

### The recommendations of JECFA

- 5.1 At a 1979 meeting, the Joint FAO/WHO Expert Committee on Food Additives (WHO, 1980) considered a number of extraction solvents used in the food industry. The available data on tetrachloroethene were not sufficient for an evaluation, and a derivation of an acceptable daily intake (ADI) was not possible.

### The WHO guidelines for drinking water quality

- 5.2 As part of a four-year review programme starting in 1988, a WHO Task Group (WHO, 1996) recommended an oral tolerable daily intake (TDI) for tetrachloroethene of  $14 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . This was based on the dose–response of the liver pathology seen in the sub-chronic studies in mice (Buben and O’Flaherty, 1985) and rats (Hayes *et al*, 1986) (paragraph 3.21). The Task Group was aware that tetrachloroethene produces liver tumours in mice, and possibly kidney tumours and leukaemia in rats. “In view of the overall evidence for nongenotoxicity and evidence for a saturable metabolic pathway leading to kidney tumours in rats, it is appropriate to use a NOAEL [‘no observed adverse effect’ level] with a suitable uncertainty factor”. The chosen uncertainty factor was 1000, made up of constituent factors of 10 each for inter- and intra-species variation and 10 “for carcinogenic potential”, which was applied to the NOAEL for liver toxicity of  $14 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ . An additional uncertainty factor to reflect the short duration of the key studies was considered unnecessary “in view of the database [on tetrachloroethene] and considerations regarding the application of the dose via drinking-water in one of the two critical studies”.

### The WHO air quality guidelines

- 5.3 As part of a 1993–1997 assessment programme in Europe, an air quality guideline for tetrachloroethene of  $0.25 \text{ mg m}^{-3}$  was recommended by a WHO Working Group (WHO, 2000). The main health issues of concern were cancer and effects on the central nervous system, liver and kidneys. “Given the limitations of the weight of the epidemiological evidence, and the uncertainty of the relevance to humans of the induction of tumours in animals exposed to tetrachloroethylene”, the derivation of a guideline value was based on non-cancer toxicity rather than on carcinogenicity. Concern was nevertheless expressed about “a possible carcinogenic effect of tetrachloroethylene exposure in humans” and an in-depth risk evaluation was said to be required in the near future.
- 5.4 The chosen critical study involved the long-term exposure of dry-cleaning workers to tetrachloroethene, which suggested that mild effects on the kidney may have resulted from median concentrations of  $102 \text{ mg m}^{-3}$  (Mutti *et al*, 1992) (paragraph 3.16). This LOAEL (“lowest observed adverse effect” level) was divided by 4.2 to convert it from occupational to continuous exposure ( $168 \text{ vs } 40 \text{ h week}^{-1}$ ) and then an uncertainty factor of 100 was applied. The uncertainty factor was made up of two component

factors of 10, one for the use of a LOAEL (instead of a NOAEL), and the other to take account of inter-individual variations in susceptibility.

- 5.5 There was some uncertainty in the human LOAEL “because the effects observed at this level are not clear-cut, and because of fluctuations in exposure levels”. An alternative estimate of a guideline value was therefore derived from the laboratory animal data, in particular from the LOAEL of  $0.68 \text{ g m}^{-3}$  for liver and kidney toxicity seen in mice exposed for 103 weeks (paragraph 3.19). The application of an “appropriate” uncertainty factor of 1000 (not explained further, but presumably resulting from factors of 10 for inter-species and 10 for intra-species variations and for a LOAEL rather than a NOAEL) resulted in a guideline concentration of  $0.68 \text{ mg m}^{-3}$ . On the “basis of the overall health risk evaluation”, the value of  $0.25 \text{ mg m}^{-3}$  was recommended.

### **The recommendations of the USEPA**

- 5.6 A 1988 USEPA assessment (USEPA, 1988) resulted in an oral reference dose (RfD)<sup>1</sup> of  $10 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ , which was based upon the short-term studies of Buben and O’Flaherty (1985) in the mouse and of Hayes *et al* (1986) in the rat (paragraph 3.21). An uncertainty factor of 1000, made up of three constituent factors of 10 (for intra- and inter-species variability and for “extrapolation of a subchronic effect to its chronic equivalent”), was applied to the studies’ NOAELs of  $14 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  to produce (after rounding) the RfD (USEPA, 1988).
- 5.7 The USEPA has not derived a reference concentration (RfC) for the inhalation of tetrachloroethene (USEPA, 1988).
- 5.8 In 1986, the USEPA recommended a B2 (“probable human carcinogen”) classification for tetrachloroethene, based upon sufficient evidence of its carcinogenicity in laboratory animals and inadequate human evidence. Evaluations by their Science Advisory Board in 1987 and 1991 concluded that, although there was inadequate support for a B2 decision, the evidence “is stronger than for most other compounds classified as possible human carcinogens” (i.e. classification C). “In the spirit of the flexibility encouraged by the [1986 USEPA Cancer Risk Assessment] Guidelines, our best judgement places this compound on a continuum between these two categories” (ATSDR, 1997). The Board concluded that tetrachloroethene “is an example of a chemical for which there is no compelling evidence of human cancer risk, but for which reductions in unnecessary human exposure might well be prudent”.
- 5.9 The USEPA in a 1985 assessment used mouse data on liver cancer from the gavage study (NCI, 1977) (paragraph 4.7) to estimate a cancer risk for humans resulting from lifetime exposure to tetrachloroethene in water or air (USEPA, 1985). The theoretical risk associated with drinking  $2 \text{ L day}^{-1}$ , for a lifetime of 70 years, of water containing 1

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<sup>1</sup> The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable non-cancer risk of deleterious effects during a lifetime.

$\mu\text{g L}^{-1}$  was calculated to be  $1.5 \times 10^{-6}$  (i.e 1.5 extra cancers per million people exposed).

- 5.10 Using a pharmacokinetic model to minimise some of the uncertainty, the lifetime cancer risk associated with breathing air containing  $1 \mu\text{g m}^{-3}$  was estimated by the USEPA (1985) to be  $4.8 \times 10^{-7}$ .

### **The recommendations of the ATSDR**

- 5.11 The ATSDR (1997) has recommended a minimal risk level (MRL)<sup>2</sup> for chronic (> 1 year) inhalation exposure of 0.04 ppm ( $0.27 \text{ mg m}^{-3}$ ). This was based upon the observation of subtle neurological effects in workers (Ferroni *et al*, 1992) (paragraph 3.14). An overall uncertainty factor of 100, consisting of factors of 10 for use of a LOAEL and 10 to take account of inter-individual variations in susceptibility, was applied to a LOAEL that had been converted from an occupational to the equivalent continuous exposure (168 vs 40 h week<sup>-1</sup>).

- 5.12 Since the available long-term oral toxicity studies had “not focused on neurological effects, the principal effect of tetrachloroethylene in humans”, the ATSDR (1997) did not consider any studies to be suitable in setting an MRL for chronic oral exposure. Therefore no chronic oral MRL was recommended.

### **Conclusions**

- 5.13 The key features of tetrachloroethene’s hazard profile in laboratory animals are its carcinogenic potential in the liver, kidney (and possibly the blood), and toxicity to the liver and kidney. Observations in humans indicate that kidney toxicity is possibly of greater concern than liver toxicity. Neurotoxicity and reproductive toxicity have also been observed in humans. The epidemiology provides some, albeit limited, support for tetrachloroethene’s carcinogenicity.
- 5.14 The COC has concluded that “the available data were inadequate to draw any definite conclusions between exposure to [tetrachloroethene] and cancer in humans” (DH, 1997). All Expert Groups accept that tetrachloroethene produces liver tumours in mice exposed by inhalation or orally, and kidney tumours in rats exposed by inhalation. This clear evidence of carcinogenicity in the laboratory has encouraged a programme of work aimed at elucidating the mechanism of the kidney and liver tumours. Generally the results have been supportive of the view that the tumours are not likely to be of relevance to humans.
- 5.15 Doubts over the reproductive toxicity of tetrachloroethene also remain unresolved. A number of epidemiological studies indicate that female workers in the dry cleaning industry are at an increased risk of suffering a spontaneous abortion. Whether this is due to their exposure to tetrachloroethene is uncertain, and is not well supported by

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<sup>2</sup> An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specific duration of exposure.

the laboratory animal data, which have not demonstrated any developmental or reproductive toxicity at exposures that are not also overtly toxic to the mothers. There is a proposal within the European Union to label tetrachloroethene as a Category 2 (“may cause harm to the unborn child”) or Category 3 (“possible risk of harm to the unborn child”) reproductive toxin. An Expert Working Group was unable to agree between these two options and the Commission will now make a proposal (HSE, 2003).

- 5.16 Two Expert Groups have derived an oral TDI for tetrachloroethene. The WHO Task Group concerned with drinking water (WHO, 1996) and the USEPA (1988) both base their recommendations on the sub-chronic oral studies of Buben and O’Flaherty (1985) and Hayes *et al* (1986) that elucidated toxic potential to the liver. Although the same overall uncertainty factor of 1000 was applied, there was a different rationale for their choice of an additional factor of 10 beyond the usual two factors of 10 for intra- and inter-species variability. While the WHO Task Group believed it was needed to take account of the carcinogenic potential, the USEPA favoured its use to compensate for the use of sub-chronic studies to derive a safety limit pertinent to chronic exposure. The health criteria values derived by the two organisations are slightly different because of rounding by the USEPA. The WHO value of  $14 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  is recommended here as the  $\text{TDI}_{\text{oral}}$ .
- 5.17 Both a WHO Working Group (WHO, 2000) and the ATSDR (1997) based their recommendations for an inhalation guideline on studies of occupational exposure with the same LOAEL of  $102 \text{ mg m}^{-3}$ . In the opinion of the WHO, the critical study was that of Mutti *et al* (1992), which reported evidence of a mild effect on the kidney, while the ATSDR favoured the study of Ferroni *et al* (1992), which observed subtle signs of neurotoxicity in the exposed workforce. The same uncertainty factor of 100 was chosen. The resulting WHO guideline concentration of  $0.25 \text{ mg m}^{-3}$  is recommended as the basis of the inhalation TDI. A 70 kg adult inhales about  $20 \text{ m}^3$  of air a day, and the  $0.25 \text{ mg m}^{-3}$  concentration will therefore produce a  $\text{TDI}_{\text{inh}}$  of  $5 \text{ mg day}^{-1}$  or  $71 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ .

## 6 Intake of tetrachloroethene from food, water and air

- 6.1 The volatility of tetrachloroethene means that primary background exposure is expected to be via inhalation of ambient air. There may also be some dietary intake of tetrachloroethene in foodstuffs, given its moderate lipophilicity and potential to accumulate in fatty foods. In a study by Daft (1988), of 231 samples that were analysed, 93 contained measurable concentrations of tetrachloroethene; the highest concentration encountered was  $124 \mu\text{g kg}^{-1}$  and the mean was  $13 \mu\text{g kg}^{-1}$ . An estimate of dietary intake in Canada (CEPA, 1993) was between  $0.002$  and  $0.03 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  ( $0.14$ – $2.1 \mu\text{g day}^{-1}$ ). However, both studies are over 10 years old and use of chlorinated solvents has decreased significantly during the intervening period. Historic practices, such as the use of tetrachloroethene as a liquid fumigant and a grain protectant, no longer occur.
- 6.2 No “Total Diet Study” (TDS) of tetrachloroethene concentrations in food has been conducted by the Ministry of Agriculture, Fisheries and Food (MAFF) or the Food Standards Agency (FSA). In 1993, MAFF surveyed the tetrachloroethene content in 69 samples of butter and lard from shops immediately adjacent to dry-cleaners (MAFF, 1993). The average concentration found was  $40 \mu\text{g kg}^{-1}$ , with a maximum of  $763 \mu\text{g kg}^{-1}$ . Samples of foodstuffs from shops remote from dry-cleaning establishments did not usually contain detectable concentrations of tetrachloroethene. Advice from the FSA suggests that, given the low intake from UK foods in which the highest concentrations would be expected, the dietary intake from food would be negligible.
- 6.3 In December 2003, the tetrachloroethene drinking-water standard of  $10 \mu\text{g L}^{-1}$  for England and Wales<sup>3</sup> was effectively reduced as a result of transposition of the European Council Directive 98/83/EC, introducing a drinking-water standard<sup>4</sup> of  $10 \mu\text{g L}^{-1}$  for both tetrachloroethene and trichloroethene. Reported drinking-water concentrations from 10 UK drinking-water companies<sup>5</sup> for 2000–2003 varied between below the limit of detection (usually  $\leq 0.3 \mu\text{g L}^{-1}$  in 2000 and  $0.1 \mu\text{g L}^{-1}$  by 2002) up to<sup>6</sup>  $29.5 \mu\text{g L}^{-1}$ . Means for individual sampling points were up to  $4.2 \mu\text{g L}^{-1}$ , although the majority of the data supplied indicated that mean concentrations for individual sampling points rarely exceed  $1 \mu\text{g L}^{-1}$ . If it is conservatively assumed that the mean concentration in drinking water is  $4.2 \mu\text{g L}^{-1}$  and that an adult drinks 2 L a day, the adult mean daily intake from drinking water should be no more than  $8.4 \mu\text{g day}^{-1}$ . This is taken as the adult oral MDI.

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<sup>3</sup> Water Supply (Water Quality) Regulations 1989, SI 1147.

<sup>4</sup> Water Supply (Water Quality) Regulations 2000, SI 3184.

<sup>5</sup> Anglian, Bristol, Severn Trent, South East, South Staffordshire, South West, United Utilities, Welsh, Wessex and Yorkshire water companies – personal communication.

<sup>6</sup> Found in one sample only. When resampled, these levels were not found.

- 6.4 IPCS (1984) reports that average concentrations in air in 14 German cities varied between 1.7 and 6.1  $\mu\text{g m}^{-3}$ . A later study of concentrations in Hamburg (Bruckmann *et al*, 1988) cited levels varying between 1.8 and 70.8  $\mu\text{g m}^{-3}$  (the higher concentrations being close to dry-cleaning establishments). A survey of three industrialised areas of the USA found concentrations between 0.24 and 9.0  $\mu\text{g m}^{-3}$  (Hartwell *et al*, 1987). In the absence of any recent UK data, it will be assumed that concentrations in ambient urban air would not usually exceed 10  $\mu\text{g m}^{-3}$ . This equates to an intake of 200  $\mu\text{g day}^{-1}$  for an adult breathing 20  $\text{m}^3$  per day.
- 6.5 A US survey of indoor air concentrations in an office building, a school and an old peoples' home found median levels varying between 1.7 and 4.8  $\mu\text{g m}^{-3}$  (Hartwell *et al*, 1985). The major source of indoor air exposure was considered to be recently dry-cleaned clothes. There is insufficient information on indoor air concentrations of tetrachloroethene to include exposure from indoor air in the calculation of the inhalation MDI.

## 7 Other sources

- 7.1 People living near to dry-cleaning establishments or landfill sites may be exposed to higher levels than the rest of the general population elsewhere (IPCS, 1984; ATSDR, 1997).
- 7.2 Fisher *et al* (1997) simulated the transfer of a number of volatile contaminants to breast milk from occupationally exposed mothers. They found that moderate transfer of tetrachloroethene was likely to occur but would decrease with increased time between exposure and feeding. The preferential excretion pathway was by exhalation (99% or greater).

## 8 Conclusions

- 8.1 The tolerable daily soil intake (TDSI) is defined as the difference between the tolerable daily intake (TDI) and the mean daily intake (MDI) (i.e.  $TDSI = TDI - MDI$ ). The only exception to this is when the MDI is close to, or exceeds, the TDI, in which case the TDSI is set at 20% of the TDI. "Close to" is defined as greater than or equal to 80% of the TDI (Defra and Environment Agency, 2002a). TDSI values are rounded to two significant figures (2SF).
- 8.2 The oral MDI for a 70 kg adult is equivalent to  $0.12 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . Subtracting this value from the  $TDI_{\text{oral}}$  of  $14 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  results in an adult oral TDSI of  $14 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  (rounded to 2SF). However the, the TDSI for a child may be lower as a result of differences in dietary intake and bodyweight. For example, it is estimated that a 20 kg six-year-old child ingests 62% of the adult dietary intake (Defra and Environment Agency, 2002a). Therefore the oral MDI for a 20 kg six-year-old child is equivalent to  $0.26 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . Subtracting this value from the  $TDI_{\text{oral}}$  of  $14 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  results in an oral TDSI of  $14 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  (rounded to 2SF). The  $TDI_{\text{oral}}$  and the oral MDI of tetrachloroethene are given in Table 8.1.

**Table 8.1  $TDI_{\text{oral}}$ , oral MDI and TDSI for an adult and a six-year-old child**

$TDI_{\text{oral}}$ ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	Oral MDI for an adult ( $\mu\text{g day}^{-1}$ )	Oral TDSI for an adult ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	Oral TDSI for a six-year-old child ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )
14	8.4	14	14

- 8.3 The inhalation MDI for a 70 kg adult is equivalent to  $2.9 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . Subtracting this value from the  $TDI_{\text{inh}}$  of  $71 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  results in an adult inhalation TDSI of  $68 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . However the TDSI for a child may be lower as a result of differences in inhalation intake and bodyweight. For example it is estimated that a 20 kg six-year-old child inhales 50% of the adult inhalation intake (Defra and Environment Agency, 2002a). Therefore the inhalation MDI for a 20 kg six-year-old child is equivalent to  $5 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . Subtracting this value from the  $TDI_{\text{inh}}$  of  $71 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  results in an inhalation TDSI of  $66 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . The  $TDI_{\text{inh}}$  and the inhalation MDI of tetrachloroethene are given in Table 8.2.

**Table 8.2  $TDI_{\text{inh}}$  inhalation MDI and TDSI for an adult and a six-year-old child**

$TDI_{\text{inh}}$ ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	Inhalation MDI for an adult ( $\mu\text{g day}^{-1}$ )	Inhalation TDSI for an adult ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	Inhalation TDSI for a six-year-old child ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )
71	200	68	66

- 8.4 No authoritative assessments of the health risks posed by dermal exposures to tetrachloroethene were identified.

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