

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

**CONTAMINANTS IN SOIL:**

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

**TRICHLOROETHENE**

## **Publishing Organisation**

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## **Statement of Use**

This publication details the derivation of health criteria values for trichloroethene. 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**

Index Dose, land contamination, risk assessment, human health, trichloroethene.

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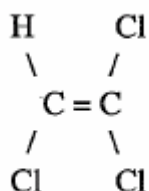
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## 1 Introduction

- 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 trichloroethene 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 trichloroethene 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 trichloroethene.
- 1.3 The overall framework for this review and the associated underlying principles are set out in CLR9 *Contaminants in Soil: 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 trichloroethene will be published in SGV 23 *Guideline Values for Trichloroethene Contamination* (Defra and Environment Agency, in preparation).
- 1.5 This report is primarily based upon the literature up to September 2002. The report has been updated to include the finalised opinions expressed within the EU risk assessment report, published in February 2004 (EU, 2004).

## 2 Identity

- 2.1 Trichloroethene (CAS No 79-01-6) is also commonly known as trichloroethylene. It is a volatile liquid (vapour pressure of 8.6 kPa at 20°C) that is slightly soluble in water (about 1.1 g L<sup>-1</sup> at 20°C) and has a log octanol/water partition coefficient of 2.29 (EU, 2004). The structure of trichloroethene is shown in Figure 2.1.



**Figure 2.1 The structure of trichloroethene**

- 2.2 Although trichloroethene is produced naturally by several temperate and subtropical marine macroalgae (Abrahamsson *et al*, 1995), the impact of this source on global emissions is not known. The majority of manufactured trichloroethene is produced through the chlorination or oxychlorination of ethylene or 1,2-dichloroethene (Nielson and Howe, 1992). The primary use is in industrial solvents for vapour degreasing and cold cleaning of fabricated metal parts. As a general solvent or as a component of solvent blends, it is found in adhesives, lubricants, paints, varnishes, paint strippers and pesticides, as well as in cold metal cleaners. It is also an extraction solvent in the textile manufacturing industry and a chemical intermediate (EU, 2004). In the past, trichloroethene has been used as a grain fumigant, an extraction solvent in the food industry, and as both an anaesthetic and an analgesic in obstetrics.
- 2.3 The volatilisation of trichloroethene from soil surfaces is an important abiotic fate pathway. However, because trichloroethene is denser than water, it is more likely to move downward through the subsurface until lower-permeability features impede its progress (Russell *et al*, 1992), resulting in groundwater contamination (Cowfer and Magistro, 1985).
- 2.4 Trichloroethene is not readily biodegradable (EU, 2004), although rates may increase in the presence of certain substrates. Under anaerobic conditions, it may be slowly biodegraded by reductive dechlorination to 1,1-dichloroethene and vinyl chloride. These metabolites may pose additional toxicity concerns, but several studies have shown that reductive dechlorination may continue to produce ethene and ethane (EU, 2004). The extent and rate of degradation will depend upon the strength of the reducing environment. Aerobic biodegradation only occurs under oxidative conditions (Hoekstra *et al*, 1998), such as those occurring in the soil surface layer, and does not produce toxic metabolites (Fan and Scow, 1993).

### 3 Toxicity

- 3.1 Comprehensive reviews of the toxicity of trichloroethene have been published by the European Union (EU, 2004), the Health and Safety Executive (HSE, 1982), the World Health Organization (WHO, 1987, 1996), the International Programme on Chemical Safety (IPCS, 1985), the United States Environmental Protection Agency (USEPA, 1985, 2001), the Agency for Toxic Substances and Disease Registry (ATSDR, 1997) and the International Agency for Research on Cancer (IARC, 1995). This section is largely based on these reviews. Particular mention is made of those studies that have been used for the derivation of health criteria values or cancer risk estimates. In general, the primary literature has not been consulted. To ensure consistency in units throughout this report where the cited source has described trichloroethene levels in ppm, a conversion factor of 1 ppm = 5.46 mg m<sup>-3</sup> (WHO, 2000) has been used.
- 3.2 **Absorption.** No data on the absorption of trichloroethene in humans after oral exposure have been identified. However, a ready absorption from the gastrointestinal tract would be expected because trichloroethene is a small, non-polar and highly lipophilic molecule. Trichloroethene has been shown to be rapidly (within 10 minutes) and completely absorbed in fasting rats, but less quickly in non-fasted animals (D'Souza *et al*, 1985). There are other rodent data that indicate almost complete absorption in non-fasting animals within 24 hours (ATSDR, 1997).
- 3.3 Human studies of the uptake of inhaled trichloroethene indicate that 28–80% of the exposed amount is taken up from the lung (EU, 2004). The blood/air partition coefficient in humans is about 10 at 37°C (IPCS, 1985).
- 3.4 Fairly rapid dermal absorption when undiluted trichloroethene is applied to the skin is evident in both humans and animals (ATSDR, 1997). In guinea pigs, dermal absorption did not significantly vary across a concentration range of 0.02 to 100 µg L<sup>-1</sup>: the permeability coefficient was about 0.2 ml cm<sup>-2</sup> h<sup>-1</sup> (Bogen *et al*, 1992).
- 3.5 **Distribution.** Trichloroethene is distributed to all tissues and crosses both the blood–brain barrier and the placenta. Tissue equilibrium is achieved after about 3 h of continuous exposure. Considerable amounts are stored in the lipid tissues (IPCS, 1985).
- 3.6 **Metabolism and excretion.** Both inhaled and ingested doses of trichloroethene are metabolised extensively in humans. Although the liver is the main site, there is evidence for some metabolism also in the lungs and possibly the kidneys. Trichloroethanol, its glucuronide and trichloroacetic acid are the major urinary metabolites, and chloral hydrate is a transient metabolite in the blood. The major metabolic pathway in all species involves initial conversion in the liver to an epoxide (EU, 2004). A considerably higher proportion of the absorbed material is exhaled unchanged at high exposures (IPCS, 1985). There is evidence to show that metabolism is saturable at much lower exposures in rats than in mice (EU, 2004).

- 3.7 **Acute toxicity.** In humans, the characteristic toxic sign from single exposure is depression of the central nervous system (CNS). In a study of 288 workers with acute intoxication from trichloroethene, effects on the CNS predominated. Symptoms indicative of mild hepatotoxicity were seen in only five of those affected, and renal effects in none (McCarthy and Jones, 1983). Effects on heart rhythm have been seen occasionally during trichloroethene-induced anaesthesia and in acute poisonings (EU, 2004).
- 3.8 A low acute toxicity has been demonstrated in laboratory animals, with oral LD<sub>50</sub> values in rodents ranging from 2.9 to 4.9 g kg<sup>-1</sup> bw (grams per kilogram body weight). For 4 h inhalation exposures, LC<sub>50</sub> values in rodents are of the order of 46–65 g m<sup>-3</sup> (EU, 2004). The main sign of toxicity irrespective of route was CNS depression. Mild liver injury and effects on the heart were also sometimes reported.
- 3.9 **Repeated inhalation toxicity.** The main effects reported in occupationally exposed individuals involve the CNS, usually subjective complaints and signs indicating impairment of psychomotor function. Adverse health effects (principally relating to the CNS) were reported in the majority of occupational studies when the urinary concentration of trichloroacetic acid was above 50 mg L<sup>-1</sup> (IPCS, 1985), which corresponds to a time-weighted average concentration of trichloroethene in air of about 135 mg m<sup>-3</sup>. The European Union risk assessment, whilst accepting CNS effects to be a key end-point in humans exposed by inhalation, noted that there were dose–response uncertainties but concluded that 270 mg m<sup>-3</sup> was a “no observed adverse effect” level (NOAEL) for “functional CNS disturbance” (EU, 2004). The USEPA takes a more conservative approach (and therefore a more liberal definition of a treatment-related effect on the nervous system). In a draft risk assessment, occupational studies (for example, Rasmussen *et al*, 1993; Ruijten *et al*, 1991) were said to report CNS symptoms at exposures in the range of 38–86 mg m<sup>-3</sup> (USEPA, 2004).
- 3.10 A few sub-chronic inhalation studies of neurobehavioural effects have been carried out. Rats exposed for 6 weeks or less exhibited decreased wakefulness time at about 270 mg m<sup>-3</sup> (Arito *et al*, 1994), and reduced social and exploratory behaviour at 500 mg m<sup>-3</sup> (Silverman and Williams, 1975). A detailed pathological examination of the nervous system revealed no abnormalities when rats were exposed for 13 weeks (7 h per day, 5 days per week) to 4370 mg m<sup>-3</sup>. The mild effects on nervous system function that were seen at this concentration were not present in the 12 males and 12 females exposed to 1365 mg m<sup>-3</sup> (Dow, 1993).
- 3.11 There are some reports of human liver toxicity. Controlled trichloroethene anaesthesia has generally been found to produce only minimal effects on the liver, as indicated by increased serum levels of the enzyme glutamic oxaloacetic transaminase. In contrast, liver effects, indicated by blood and urine indices of liver function, and enlarged livers have been reported in a number of studies of people occupationally exposed to trichloroethene (at unspecified levels) (ATSDR, 1997).

- 3.12 Increased relative liver weights and minor (often reversible) changes in histology or serum enzyme levels have sometimes been reported in inhalation studies in rodents exposed to high atmospheric concentrations of trichloroethene (EU, 2004). In mice, the “lowest observed adverse effect” level (LOAEL) was about  $200 \text{ mg m}^{-3}$  for a 30–120 day period of continuous exposure (Kjellstrand *et al*, 1983a,b). At equivalent exposures, liver weight increases were markedly higher in the mouse than in the rat (Kjellstrand *et al*, 1983a,b). The EU assessment described these lower-dose findings as adaptive changes rather than toxicological effects, and concluded that  $1090 \text{ mg m}^{-3}$  was a NOAEL for liver toxicity by the inhalation route (EU, 2004). Trichloroethene-induced liver toxicity appears to be enhanced by alcohol (Okino *et al*, 1991), which suggests that the oxidative metabolism of trichloroethene may be an important feature of its toxic potential.
- 3.13 Trichloroethene anaesthesia has not been found to produce renal effects. Minor changes in blood and urine indicators of kidney function have been reported in some occupational studies, but again the exposure conditions that may have been responsible were not specified (ATSDR, 1997).
- 3.14 Trichloroethene-induced kidney toxicity is seen in repeated inhalation studies in laboratory animals (EU, 2004). Indirect (biochemical) indications of kidney injury were present in rats exposed continuously to  $4320 \text{ mg m}^{-3}$  for 12 weeks (Arai *et al*, 1988). In long-term studies, there was a treatment-related increase in kidney pathology in male rats exposed for 2 years to  $1620$  or  $3240 \text{ mg m}^{-3}$  (7 hours per day, 5 days per week), but not in female rats exposed to  $3240 \text{ mg m}^{-3}$  for 2 years or in male or female mice exposed to  $3240 \text{ mg m}^{-3}$  for 78 weeks. The kidneys of the male rats were not affected by repeated exposures to  $540 \text{ mg m}^{-3}$  (7 hours per day, 5 days per week for 2 years) (Maltoni *et al*, 1986).
- 3.15 Indications of hormonal modulation (an increase in the blood of the male steroid hormone dehydroepiandrosterone and a decrease in sex hormone-binding globulin) have been reported in workers exposed to around  $60 \text{ mg m}^{-3}$  (Chia *et al*, 1997; Goh *et al*, 1998). Reduced testosterone levels occurred in rats exposed for 12 weeks to around  $2000 \text{ mg m}^{-3}$  (Kumar *et al*, 2000).
- 3.16 **Repeated oral toxicity.** There have been several attempts to find associations between the consumption of drinking water contaminated with trichloroethene and adverse effects in the exposed populations. CNS effects have been claimed. Limitations of these studies include exposure to other contaminants in the drinking water, and the results must be considered inconclusive (EU, 2004).
- 3.17 The liver is a target organ for trichloroethene in rodents treated orally. The most frequently reported effects are increased liver weights, which generally occur in mice after a few weeks’ treatment with around  $500 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  (milligrams per kilogram body weight per day) (Elcombe *et al*, 1985; Merrick *et al*, 1989; Stott *et al*, 1982). Liver weights were unaffected in mice given a daily dose of  $18 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  in the drinking water for 6 months (Tucker *et al*, 1982), but were increased in rats at the lowest

tested dose of 100 mg kg<sup>-1</sup> bw day<sup>-1</sup> administered by gavage, 5 days per week for 6 weeks (Buben and O'Flaherty, 1985) and at 50 mg kg<sup>-1</sup> bw day<sup>-1</sup> given by gavage for 14 days (Berman et al, 1995). Histopathological effects including necrosis (Goel et al, 1992; Melnick et al, 1987; Merrick et al, 1989) and cell hypertrophy (Elcombe et al, 1985; NTP, 1985; Stott et al, 1982) are seen at higher doses. Increased serum levels of liver enzymes have also been reported (Buben and O'Flaherty, 1985; Merrick et al, 1989). No evidence of liver pathology was detected in long-term oral studies in which rats and mice received daily doses of 500 mg kg<sup>-1</sup> bw (NTP, 1988, 1990).

- 3.18 Kidney toxicity also occurs in orally treated rodents, and according to an EU risk assessment is the most sensitive toxicity end-point arising from repeated oral administration (EU, 2004). In rat bioassays with cancer as the main end-point of interest, lifetime exposures to 500 mg kg<sup>-1</sup> bw day<sup>-1</sup> (NTP, 1988) and 250 mg kg<sup>-1</sup> bw day<sup>-1</sup> (Maltoni et al, 1986) produced kidney pathology (cytomegaly and meganucleocytosis respectively). In the Maltoni study, it was possible to establish a NOAEL of 50 mg kg<sup>-1</sup> bw day<sup>-1</sup>.
- 3.19 **Reproductive and developmental toxicity.** There is no convincing evidence that trichloroethene is a reproductive toxicant in humans. Studies of the fertility of occupationally exposed individuals either show insignificant effects or the results are inconsistent and difficult to interpret (CCTR, 2002). Reductions in testes weight, sperm count and motility, and serum testosterone levels were reported in rats exposed for 4 h daily to 2030 mg m<sup>-3</sup> for 12–24 weeks (Kumar et al, 2000, 2001). When mated with untreated females, the males exhibited a reduced fertility (Kumar et al, 2000). The effects of long-term oral administration on fertility and reproductive performance have been extensively investigated in rats and mice. Trichloroethene was shown to have some influences on reproduction only at exposure levels that produce general toxicity. NOAELs for reproductive effects were 350 mg kg<sup>-1</sup> bw day<sup>-1</sup> in mice and 75 mg kg<sup>-1</sup> bw day<sup>-1</sup> in rats (EU, 2004).
- 3.20 Inhalation studies in laboratory animals mainly indicate that the embryo and fetus are not especially sensitive to trichloroethene. There was no evidence of developmental toxicity when rabbits and rats were exposed repeatedly throughout pregnancy to 2730 mg m<sup>-3</sup> (NIOSH, 1980) or when mice and rats were exposed on days 6 to 15 of pregnancy to 1640 mg m<sup>-3</sup> (Schwetz et al, 1975). In a third study in rats, exposure throughout pregnancy to 9825 mg m<sup>-3</sup> was also without adverse effect (Dorfmueller et al, 1979). Litter losses were reported in another investigation in which rats were exposed to 550 mg m<sup>-3</sup> for 4 h day<sup>-1</sup> on days 8 to 21 of pregnancy (Healy et al, 1982); the results of this particular experiment were discounted by EU risk assessors because they were inconsistent with the other studies that involved higher exposures (EU, 2004).
- 3.21 Developmental effects were seen in a rat gavage study. An increase in eye defects (reduced or absent ocular bulge) was reported at doses of 475 mg kg<sup>-1</sup> bw day<sup>-1</sup> and above. These doses were also maternally toxic. The trichloroethene was administered on days 6–15 of pregnancy (Narotsky and Kavlock, 1995; Narotsky et al, 1995). Small increases in the incidence of cardiac malformations were also detected in rat pups from

mothers exposed to 0.2 and 129 mg kg<sup>-1</sup> bw day<sup>-1</sup> in their drinking water prior to and throughout pregnancy. No maternal effects were observed (Dawson *et al*, 1993; Johnson *et al*, 1998). The significance of the small increases over background is unclear in view of the lack of any obvious dose–response.

- 3.22 A research team has published several reports that note subtle changes in the behaviour, brain metabolism and brain morphology of the offspring of female rats that have received doses of 30–110 mg kg<sup>-1</sup> bw day<sup>-1</sup> in the drinking water throughout pregnancy (Isaacson and Taylor, 1989; Noland-Gerbec *et al*, 1986; Taylor *et al*, 1985). Reservations about the study reports and the biological significance of the observed changes meant that the EU assessors were unable “to draw clear conclusions about the relevance of these findings to human health without corroborative evidence from elsewhere”.

## 4 Carcinogenicity and genotoxicity

- 4.1 On the basis of “limited” evidence of carcinogenicity in humans, and “sufficient” evidence in laboratory animals, an IARC Working Group in 1995 assigned trichloroethene to Group 2A (“probably carcinogenic to humans”) (IARC, 1995).
- 4.2 In 1996 the Department of Health’s Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (the COC) noted that the limitations and uncertainties in both the human and animal data meant that there were considerable difficulties in reaching an overall conclusion as to the carcinogenicity of trichloroethene. However, the Committee concluded that trichloroethene should be regarded as a potential human carcinogen (DH, 1998).
- 4.3 Under EU regulations on classification and labelling, trichloroethene is described as a Category 2 carcinogen. “There is sufficient evidence to provide a strong presumption that human exposure ... may result in the development of cancer” (EU, 2004).
- 4.4 The main evidence for the IARC (1995) view that there is some evidence of carcinogenicity in humans was provided by three industrial cohorts from Sweden (Axelson *et al*, 1978, 1994), from Finland (Anttila *et al*, 1995) and from the USA (Spirtas *et al*, 1991). These consistently showed higher-than-expected incidence rates for cancer of the liver and biliary tract (a relative risk of about 1.8 from the three studies combined, based on 23 observed cases) and also for non-Hodgkin’s lymphoma (a relative risk of about 1.4 from the three studies combined, based on 27 observed cases). A weak association between trichloroethene occupational exposure and non-Hodgkin’s lymphoma has been reported in another US cohort (Boice *et al*, 1999), and was still present in an updated examination of the cohort of Spirtas *et al* (Blair *et al*, 1998). The EU Specialised Experts in the Fields of Carcinogenicity, Mutagenicity and Reprotoxicity cited the epidemiological data on non-Hodgkin’s lymphoma as part of the reason for their classification of trichloroethene as a Category 2 carcinogen (EU, 2004).
- 4.5 There was a slightly raised prostate cancer risk in both the Finnish and the Swedish cohorts and in the US study of Blair *et al*. The Finnish workers also experienced a higher-than-expected cervical cancer risk.
- 4.6 A significantly increased incidence of kidney cancer has been seen among workers exposed to trichloroethene in two studies in Germany. In a retrospective cohort study, seven cases were diagnosed in a workforce of 169 where less than one would have been expected (Henschler *et al*, 1995). A study comparing kidney cancer patients with hospital controls found that the 58 cancer patients were over 10 times more likely than the controls to have a history of occupational exposure to trichloroethene (odds ratio 10.8, 95% confidence limits 3.36–34.75) (Vamvakas *et al*, 1998). Whilst accepting that a causal association between trichloroethene exposure and kidney cancer had not been established in humans, the EU Specialised Experts noted that the epidemiological suspicions of an action on the kidney were another influence on their choice of the Category 2 carcinogen classification (EU, 2004).

- 4.7 The incidence of various cancers in populations exposed to drinking water contaminated with trichloroethene has been studied by a number of investigators (IARC, 1995). The interpretation of these studies is complicated by several methodological problems. A weak association between contamination and the incidence of leukaemia was found in two of the studies (Cohn *et al*, 1994; Lagakos *et al*, 1986), but it must be noted that no association was found in the cohort studies of trichloroethene-exposed workers. Two studies (Cohn *et al*, 1994; Vartiainen *et al*, 1993) suggested a marginal increase in the occurrence of non-Hodgkin's lymphoma in areas with contaminated water supplies.
- 4.8 There is convincing evidence of trichloroethene's carcinogenic potential in rodents treated orally. Significant and dose-related increases in the incidences of benign and malignant liver tumours were found in mice given trichloroethene by stomach tube. Clear indication of the liver carcinogenicity was present in both sexes at the lowest tested doses of around  $1 \text{ g kg}^{-1} \text{ bw day}^{-1}$  (NCI, 1976; NTP, 1990). Most of the oral rat studies were inconclusive because of poor survival rates or too short a dosing period. In two rat strains (NTP, 1988, 1990) there was a small but statistically significant increase in kidney tumours in males given  $500\text{--}1000 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  by stomach tube. In a third strain (NTP, 1988), an increased incidence in testicular tumours was reported (a control incidence of interstitial cell tumours of the testes of around 35% was increased to 64% and 82% in the males receiving 500 and  $1000 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  respectively).
- 4.9 Inhalation studies have also found trichloroethene to be carcinogenic in both the mouse and rat. Of the four strains of mice tested, three showed increased incidences of lung tumours (Fukuda *et al*, 1983; Maltoni *et al*, 1986, 1988), one an increased incidence of liver tumours (Maltoni *et al*, 1986, 1988), and one an increased incidence of lymphomas (Henschler *et al*, 1980). The lowest exposure producing lung tumours in mice was  $810 \text{ mg m}^{-3}$  (7 hours per day, 5 days per week for 104 weeks). The liver tumours developed at  $3240 \text{ mg m}^{-3}$  (7 hours per day, 5 days per week for 78 weeks). The lymphomas were present in mice exposed to  $540 \text{ mg m}^{-3}$  (6 hours per day, 5 days per week for 78 weeks). In rats, an increase in interstitial testicular tumours was seen throughout the tested exposure range. A 5% incidence in the controls was increased to 15%, 28% and 27% at 540, 1620 and  $3240 \text{ mg m}^{-3}$  respectively (7 hours per day, 5 days per week for 104 weeks). A low incidence of kidney tumours, a tumour type not previously recorded in untreated male rats of this strain at the study laboratory, was detected in the males exposed to  $3240 \text{ mg m}^{-3}$  (Maltoni *et al*, 1986, 1988).
- 4.10 Trichloroethene, in the presence of an exogenous metabolising system (S9), was weakly but convincingly mutagenic in both *Salmonella typhimurium* (Crebelli *et al*, 1985) and mouse lymphoma cells in culture (NTP, 1990) The mutagenicity of glutathione metabolites has also been demonstrated in *Salmonella* (EU, 2004). Investigations of chromosome aberrations, sister chromatid exchange and unscheduled DNA synthesis in mammalian cells in culture have given inconsistent results (EU, 2004).

- 4.11 Increases in chromosome damage (in the form of micronuclei) occurred in the bone marrow cells of male rats exposed for 6 h to atmospheres containing 27, 2730 or 27,300 mg m<sup>-3</sup> of trichloroethene (Kligerman *et al*, 1994), but were not present in rats exposed for up to four consecutive days (6 h day<sup>-1</sup>) to 2730 mg m<sup>-3</sup> (Kligerman *et al*, 1994). Corresponding studies in male mice found no treatment-related effects with either single or repeated exposures (Kligerman *et al*, 1994). Oral studies showed that micronuclei were increased in the kidney of rats given 525 mg kg<sup>-1</sup> bw (Robbiano *et al*, 1998) and in the blood of mice given 375–3000 mg kg<sup>-1</sup> bw (Duprat and Gradiski, 1980). There was no evidence of any similar increase in the blood cells of male mice that had received three consecutive daily intraperitoneal injections of up to 2.5 g kg<sup>-1</sup> bw (Shelby *et al*, 1993). Chromosome aberrations were not induced in the bone marrow of rats exposed to either single or five consecutive daily 7 h exposures to 2730 mg m<sup>-3</sup> (NIOSH, 1980). No increases in unscheduled DNA synthesis (an indicator of DNA damage) were detected in the liver of rats and mice given up to 1 g kg<sup>-1</sup> bw orally on three consecutive days (Mirsalis *et al*, 1989). Although DNA damage (in the form of single strand breaks) did occur in the liver of rats and mice given high single oral doses (close to LD<sub>50</sub> values) (Nelson and Bull, 1988), a Comet assay found no evidence of kidney damage in rats exposed for 6 h day<sup>-1</sup> for 5 days to 10,920 mg m<sup>-3</sup> (CTL, 1998). There was no treatment-related increase in mutations in the lung, liver and bone marrow of male transgenic mice (Muta mice) exposed for 6 h day<sup>-1</sup> for 12 days to 16,380 mg m<sup>-3</sup> (Douglas *et al*, 1999). Equivocal indications of mutagenicity have been reported in two spot tests involving single intraperitoneal injections of 140–350 mg kg<sup>-1</sup> bw to pregnant mice (Fahrig, 1977; Schiestl *et al*, 1997). A 24 h exposure to 2460 mg m<sup>-3</sup> did not induce dominant lethal mutations in male mice (Slacik-Erben *et al*, 1980). Mutations in tumour suppressor genes were detected in the kidney cancers of patients with a history of trichloroethene exposure (Brauch *et al*, 1999; Brüning *et al*, 1997).
- 4.12 The EU Specialised Experts Group concluded in 2000 that the weight of evidence supported “the assumption that trichloroethene exerts genotoxic activity and can interact with DNA, inducing changes relevant to mutagenicity in somatic cells of mammals *in vivo*” (EU, 2004). Under current EU regulations, trichloroethene is classified as a Category 3 mutagen (“substances which cause concern for humans owing to possible mutagenic effects”) (EU, 2004). The UK Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment, in an earlier opinion, had considered that, although the *in vivo* data were in general reassuring, there remained conflicting results in the bone marrow assays (DH, 1998). The Committee requested a bone marrow micronucleus test in rats exposed by inhalation to resolve these uncertainties.

## 5 Derivation of Index Doses

### The recommendations of JECFA

- 5.1 A 1979 attempt of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) to establish a TDI for trichloroethene, a possible food contaminant, was unsuccessful because of the inadequacy of the toxicity database (WHO, 1980).

### The WHO guidelines for drinking-water quality

- 5.2 WHO Review Groups meeting in 1990 and 1991 recommended a provisional drinking-water quality guideline for trichloroethene of  $70 \mu\text{g L}^{-1}$  (WHO, 1993, 1996).
- 5.3 The key study, a six-week treatment of mice by gavage (Buben and O'Flaherty, 1985), demonstrated a LOAEL of  $100 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  for "minor effects on relative liver weight" (paragraph 3.17). Allowance for 5 days per week dosing, and the use of an overall uncertainty factor of 3000, produced a TDI of  $23.8 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . The 3000 figure was the product of factors of 10 each for inter- and intra-species variation, 10 for limited evidence of carcinogenicity, and 3 to take account both of the short duration of the study and the use of a LOAEL instead of a NOAEL.

### The WHO guidelines on air quality

- 5.4 A WHO Working Group in 1986 recommended an air quality guideline of  $1 \text{ mg m}^{-3}$  (24 h average) for trichloroethene. This was derived from occupational studies reporting effects on the CNS system (paragraph 3.9). It was the view of the Working Group that the data did not permit the derivation of a NOAEL. As the signs of toxicity began to appear when the urinary level of trichloroacetic acid exceeded  $50 \text{ mg L}^{-1}$ , this was taken to be the LOAEL, which corresponds to a concentration of trichloroethene in air of about  $135 \text{ mg m}^{-3}$ . An uncertainty factor of 100 was applied (to take account of a change from occupational to environmental exposure, the variability and validity of the findings around the LOAEL, and the fact that it was a LOAEL and not a NOAEL) to arrive (after rounding) at the guideline value (WHO, 1987).
- 5.5 In 1995, a WHO Working Group considered that the main health effects of concern were cancer and liver toxicity, as well as toxicity to the CNS. The dose-response relationships for the non-carcinogenic effects were thought to be "insufficiently known", making it difficult to assess the health risk of long-term exposure to low levels of trichloroethene. On cancer, "because the available evidence indicates that trichloroethene is genotoxic and carcinogenic, no safe level can be recommended". The human cancer data were inconclusive. Although epidemiological studies had reported associations between exposure and increased risks of cancer of the liver and biliary tract and non-Hodgkin's lymphomas, confounding could not be ruled out. However, as the relevance to humans of the increases in lung cancer seen in mice and testes tumours seen in rats could not be excluded, these inhalation studies were judged to be the best available basis for risk assessment. Using the treatment-related increase in

testes tumours reported in rats in the study of Maltoni *et al* (1986, 1988) (paragraph 4.9), and applying the linearised multi-stage model, the Working Group estimated a unit cancer risk of  $4.3 \times 10^{-7}$  per  $\mu\text{g m}^{-3}$ . The ambient air concentrations corresponding to an excess lifetime cancer risk of 1:10,000, 1:100,000 and 1:1,000,000 were estimated to be 230, 23 and  $2.3 \mu\text{g m}^{-3}$  respectively (WHO, 2000).

### The recommendations of the EU

- 5.6 At a meeting of the Specialised Experts in the Fields of Carcinogenicity, Mutagenicity and Reprotoxicity held in 2000, a Category 2 classification for carcinogenicity (“substances which should be regarded as if they are carcinogenic to humans”) was agreed for trichloroethene. This was based on evidence in one animal species, kidney tumours in rats, supported by epidemiological data showing an association between exposure and kidney tumours and non-Hodgkin’s lymphoma. As the epidemiological data were not suitable for quantitative risk assessment, a cancer risk assessment undertaken as part of the EU exercise used the dose–response of the lymphomas seen in an inhalation study in mice (Henschler *et al*, 1980) (paragraph 4.9). The  $\text{TD}_{25}$ , the estimated systemic lifetime dose that would produce a 25% tumour yield in an exposed group of animals (assuming no tumours in the controls), was  $130 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ . The corresponding estimation of the systemic  $\text{TD}_{25}$  based on the kidney tumours developing in rats exposed by inhalation in the study of Maltoni *et al* (1986, 1988) was  $5607 \text{ mg kg}^{-1} \text{ bw day}^{-1}$  (EU, 2004).

### The recommendations of the USEPA

- 5.7 The USEPA in 1987 gave trichloroethene a cancer classification of B2 (probable human carcinogen), and derived a numerical estimate of cancer risk from animal studies (USEPA, 1987). The Science Advisory Board for the USEPA subsequently concluded that the weight of evidence was not strong enough for an unequivocal B2 ranking. The current Integrated Risk Information System (IRIS) file of the USEPA states that the earlier carcinogenicity assessment has been withdrawn, and that a new one is in preparation (USEPA, 2004).
- 5.8 The USEPA has published a draft health risk assessment (USEPA, 2001) which is “for review purposes only and does not constitute Agency policy”. According to the draft, trichloroethene is associated with neurotoxicity, immunotoxicity, developmental toxicity, liver and kidney toxicity, endocrine effects and several forms of cancer. Based on liver, kidney and developmental effects, the  $\text{RfD}^1$  was estimated to be  $0.3 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . The lowest tested or estimated doses producing liver effects in mice (Buben and O’Flaherty, 1985) and rats (Berman *et al*, 1995), and a NOAEL reported in mice (Tucker *et al*, 1982) (paragraph 3.17) were described as the “points of departure” of the risk assessment process. The “human-equivalent dose”, where adverse liver effects were beginning to be observed “in two species after subchronic dosing”, was  $1 \text{ mg kg}^{-1} \text{ bw}$

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

day<sup>-1</sup> (the conversion of the rodent doses to the human equivalent dose was based on pharmacokinetic modelling and the assumption that the blood levels of trichloroacetic acid were the critical measure of exposure in the development of liver toxicity). Application of an uncertainty factor of 3000, the default maximum allowable “in the face of substantial uncertainty”, to take account of the use of sub-chronic studies as a model of lifetime exposure, background exposure to trichloroethene, and intra- and interspecies variations, produced the RfD.

- 5.9 The equivalent inhalation limit (RfC)<sup>2</sup> was 40 µg m<sup>-3</sup>, based on CNS, liver and endocrine effects. The “point of departure” was the 38 mg m<sup>-3</sup> exposures that produced CNS toxicity in two occupational studies (Rasmussen *et al*, 1993; Ruitjen *et al*, 1991). A total uncertainty factor of 1000 was applied, consisting of factors of 10 in going from healthy workers to the general population, 10 for the use of a sub-chronic study to derive a lifetime safety limit, and 10 for using a LOAEL rather than a NOAEL.
- 5.10 As regards cancer hazard, the conclusion was that trichloroethene was “highly likely to produce cancer in humans”. “Epidemiological studies, considered as a whole, have associated [trichloroethene] with excess risks of kidney cancer, liver cancer, lympho-haematopoietic cancer, cervical cancer and prostate cancer”. Several cancer risk assessments were developed, using both epidemiology and animal data. Based on the number of liver or kidney cancers or cases of non-Hodgkin’s lymphoma seen in Finnish workers (Anttila *et al*, 1995), it was estimated that exposures between 1.4 × 10<sup>-7</sup> and 1.4 × 10<sup>-5</sup> mg kg<sup>-1</sup> bw day<sup>-1</sup> would present an excess lifetime cancer risk of 1:1000,000. The various mechanism-based models or linear and non-linear extrapolations applied to the mouse data on liver cancer indicated that doses in the range of 0.5 × 10<sup>-5</sup> to 1.25 × 10<sup>-3</sup> mg kg<sup>-1</sup> bw day<sup>-1</sup> would pose a lifetime cancer risk of 1:1000,000. The corresponding dose estimated from rat data on kidney cancer was 3.3 × 10<sup>-3</sup> mg kg<sup>-1</sup> bw day<sup>-1</sup>. The USEPA considered that the testes tumours seen in rats probably resulted from a mechanism involving hormonal disturbance, and as such the cancer dose–response was likely to exhibit a threshold. A dose of 8 × 10<sup>-4</sup> mg kg<sup>-1</sup> bw day<sup>-1</sup> was estimated to pose a “minimal risk” of testes cancer.

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

- 5.11 In a 1997 review, the ATSDR considered that there were insufficient data for the derivation of a sub-chronic or chronic oral minimum risk level (MRL), or for a chronic inhalation MRL (ATSDR, 1997). An MRL is defined as an estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse non-cancerous effects over a specified duration of exposure.
- 5.12 An inhalation MRL relevant to human exposure of up to one year (an intermediate MRL) was derived from the six-week rat study of Arito *et al* (1994) (paragraph 3.10). A LOAEL

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<sup>2</sup> The reference concentration (RfC) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC addresses non-cancer effects only.

(adjusted for the exposure regime) of  $230 \text{ mg m}^{-3}$  was reported for decreased wakefulness during exposure, and decreased post-exposure heart rate and slow wave sleep. The ATSDR used an uncertainty factor of 300 (3 for intra-species variability, 10 for inter-species variability and 10 for the use of a LOAEL) to arrive at an intermediate MRL (rounded) of  $0.5 \text{ mg m}^{-3}$ .

## Conclusions

- 5.13 The carcinogenic potential of trichloroethene dominates the more recent hazard and risk assessments. An extensive testing programme in laboratory animals has shown that trichloroethene may be able to induce cancers of the liver, lungs and lymphatic system in mice and cancer of the kidneys and testes in rats. Evidence of its activity has been generated by both oral and inhalation studies in rodents. Epidemiological studies provide some support for the view that it is carcinogenic in the human kidney, liver and lympho-haematopoietic system.
- 5.14 Research into the mechanisms of cancer development in laboratory animals has as yet produced few confident conclusions on the relevance of the animal data to humans. Uncertainty is also a feature of the genotoxicity status of trichloroethene. Although *in vitro* studies have generated strong evidence of a wide range of genotoxic activity, the more established protocols examining genotoxicity *in vivo* have generally produced negative results. Nevertheless, there were sufficient indications of activity in non-standard protocols to encourage the EU genotoxicity experts to classify trichloroethene as a Category 3 mutagen. Though there is experimental support for the view that genotoxic mechanisms may not play a key role in certain of the tumours seen in rodents exposed to trichloroethene (in particular, the mouse lung and liver cancers), this is not yet the case for other tumours seen in rats and mice. Until there is evidence to the contrary, it would be prudent therefore to assume a critical genotoxic step in the route to tumours, and the absence of a dose threshold. In this context, inhalation and oral Index Doses, rather than tolerable daily intake (TDI) values, are indicated.
- 5.15 Estimations of the cancer risks posed by inhalation exposure to trichloroethene have been undertaken by a WHO Working Group (using the rat data of Maltoni *et al*, 1986, 1988) and within the EU Existing Substances Programme (where the mouse data of Henschler *et al* (1980) were favoured). The critical EU calculation was that the systemic  $\text{TD}_{25}$  for the lymphomas seen in mice was  $130 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ . On the assumption that the cancer potency of trichloroethene is the same in humans and mice, a lifetime cancer risk of 1:100,000 in humans would be produced by a dose of  $5.2 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . The WHO Working Group applied a low-dose extrapolation from the dose-response of the testes tumours seen in rats. This led to the conclusion that an atmospheric concentration of  $23 \text{ } \mu\text{g m}^{-3}$  would pose a lifetime cancer risk to man of 1:100,000 (assuming man demonstrates the same susceptibility as does the rat). This atmospheric concentration would generate (assuming a 70 kg person, an inhalation of  $20 \text{ m}^3$  of air a day and a 100% pulmonary absorption) a systemic dose of  $460 \text{ } \mu\text{g}$  or  $6.6 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ .

- 5.16 In an early USEPA assessment (USEPA, 1989), a linearised multi-stage model applied to the NTP data on liver cancer in mice (NTP, 1985) indicated that an oral exposure of about  $1 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  would be associated with a lifetime cancer risk of 1:100,000. The more recent USEPA review (USEPA, 2001) proposes a range of risk estimations arising from various mathematical manipulations of the epidemiological data on liver and kidney cancers, and on non-Hodgkin's lymphoma, and of the oral data on liver cancer in mice, and testes and kidney tumours in rats, but comes to no definitive conclusion. For an excess lifetime cancer risk of 1:100,000, the USEPA estimates range from 0.0014 to  $33 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ .
- 5.17 Using different assessment approaches and choices of key study, the EU and WHO estimates of the inhalation exposures that would pose 1 in 100,000 lifetime cancer risks lead to very similar results, 5.2 and  $6.6 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  respectively, values that are also within the range of risks generated by a broad suite of analyses being explored by the USEPA. The EU value of  $5.2 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  is adopted here as the basis of an inhalation Index Dose.
- 5.18 There are no recent finalised expert reviews of the cancer risks from the ingestion of trichloroethene. The EU Risk Assessment Report (EU, 2004) concludes that "there are no significant differences in routes of elimination following oral or inhalation dosing, therefore it is likely that metabolism will be the same for each route of exposure", and that "for the purposes of risk assessment 100% absorption by all routes of exposure will be assumed". For the present purposes, it is assumed that the overall risk of cancer from ingestion is the same as that from inhalation, and therefore the inhalation Index Dose is adopted also as the oral Index Dose. Although there is a wide variation in health criteria values proposed by Expert Groups, this oral ID of  $5.2 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  lies between the oral TDI (for all effects, including cancer) of  $23.8 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ , derived by WHO (1993, 1996), and the RfD (for effects other than cancer) of  $0.3 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ , suggested in the USEPA draft risk assessment which has not yet been ratified (USEPA, 2001).

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

- 6.1 The volatility of trichloroethene means that the primary background exposure would be expected to be via inhalation of ambient air. However, trichloroethene is moderately lipophilic and therefore may accumulate within fatty foods. Few measurements of trichloroethene in the UK environment appear to have been reported, and trichloroethene concentrations were not reported in any of the Total Diet Studies (TDS) conducted by the Ministry of Agriculture, Fisheries and Food (MAFF) or the Food Standards Agency (FSA).
- 6.2 McConnell *et al* (1975) measured the concentrations of chlorinated hydrocarbons in a variety of foodstuffs and reported an average concentration of trichloroethene of a few (0.02 to 19) micrograms per kilogram. However, these data are old, and present concentrations are likely to be lower as a result of a reduction in use. For example, trichloroethene is no longer used as a grain fumigant or for cleaning food processing equipment, and levels in water used to process food have decreased significantly over recent years. Historically these were the main sources of trichloroethene in food (ATSDR, 1997). The assumption of low concentrations in food is supported by a MAFF study (MAFF, 1993), which did not detect trichloroethene in any of the butter and lard samples analysed. If present at significant concentrations, trichloroethene would be expected to be detectable in fatty foods. Advice from the FSA suggests that, given the low concentrations found in butter and lard, intakes from food would be negligible.
- 6.3 Until December 2003, the drinking-water limit for trichloroethene for England and Wales was 30  $\mu\text{g L}^{-1}$ . The current limit is 10  $\mu\text{g L}^{-1}$ , for the sum of the concentrations of trichloroethene and tetrachloroethene. Measurements from a number of water companies<sup>3</sup> were made available to the Environment Agency for this study. These data preceded the tightening of the regulatory limit. Individual concentrations of trichloroethene varied from below the limit of detection up to 14  $\mu\text{g L}^{-1}$ ; mean concentrations for individual sampling points varied from below the limit of detection up to 6.2  $\mu\text{g L}^{-1}$ . The data indicate that mean concentrations will not exceed 1  $\mu\text{g L}^{-1}$ . However, given the consistently high concentrations for some sampling points, it will be assumed that mean concentrations in drinking water are not likely to exceed 5  $\mu\text{g L}^{-1}$ . For an adult drinking 2 L per day, this would equate to an intake of 10  $\mu\text{g day}^{-1}$ . This can be taken as the adult oral mean daily intake (MDI).
- 6.4 The WHO Air Quality Guidelines (WHO, 2000) state that mean concentrations for European cities vary between 0.8 and 18.5  $\mu\text{g m}^{-3}$ . Typical concentrations given for urban areas of Germany are 5–15  $\mu\text{g m}^{-3}$  (it is noted that urban air concentrations in US studies tend to be lower, in the region of 2.5  $\mu\text{g m}^{-3}$ , regardless of the date of the study). The WHO suggests that average concentrations for rural areas are less than 1  $\mu\text{g m}^{-3}$ , while those for urban areas are 10  $\mu\text{g m}^{-3}$ .

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<sup>3</sup> Anglian, Bristol, Severn Trent, South East, South Staffordshire, South West, United Utilities, Welsh, Wessex and Yorkshire water companies (Personal Communication).

6.5 Volatilisation of trichloroethene from water may be an important source of trichloroethene in indoor air (WHO, 2000). Other sources may include products such as typewriter correction fluids, paint removers, adhesives and spot removers (ATSDR, 1997). WHO (2000) cites USEPA data for indoor air concentrations, with a median air concentration of  $0.68 \mu\text{g m}^{-3}$  and a mean of  $7.36 \mu\text{g m}^{-3}$ . The WHO also reports measured concentrations in Western European countries of between  $0.76$  and  $1200 \mu\text{g m}^{-3}$ . Given this variation and the general WHO statement that indoor air concentrations are in the same range as urban concentrations (taken as  $10 \mu\text{g m}^{-3}$ ), explicit consideration of exposure to indoor air will not be included within the inhalation MDI. If the mean concentration to which the general population is exposed is taken to be  $10 \mu\text{g m}^{-3}$ , then the average daily intake from air for the adult breathing  $20 \text{ m}^3$  per day is  $200 \mu\text{g day}^{-1}$ .

## **7 Other sources**

- 7.1 The most significant use of trichloroethene is as a metal degreasant, and higher exposure would be expected in those involved in such operations or living in industrial areas or close to waste facilities (ATSDR, 1997).

## 8 Conclusions

- 8.1 The oral and inhalation Index Doses (that is,  $ID_{oral}$  and  $ID_{inh}$ ) for trichloroethene are both derived from the risk assessment of the EU Specialised Experts in the Fields of Carcinogenicity, Mutagenicity and Reprotoxicity. They are based on a mouse inhalation study, and are given in Table 8.1.

**Table 8.1 Index Doses for trichloroethene**

$ID_{oral}$ ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )	$ID_{inh}$ ( $\mu\text{g kg}^{-1} \text{ bw day}^{-1}$ )
5.2	5.2

- 8.2 The Index Dose represents a dose that poses a minimal risk level from possible exposure from a particular source, with the additional requirement that exposure needs to be reduced to as low a level as reasonably practicable (Defra and Environment Agency, 2002a). Therefore, background exposure to trichloroethene is not considered, and the Index Dose itself is the toxicological assessment parameter used for deriving Soil Guideline Values.

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