

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

CONTAMINANTS IN SOIL:

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

1,1,1-TRICHLOROETHANE

Publishing Organisation

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Website: www.environment-agency.gov.uk

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June 2004

ISBN 1 844 32185 1

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Statement of Use

This publication details the derivation of health criteria values for 1,1,1-trichloroethane. 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, 1,1,1-trichloroethane.

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Acknowledgement

The first draft of this document was written by RPS Group plc. It was updated and substantially revised by Toxicology Advice & Consulting Ltd. WS Atkins Consultants Ltd updated sections 6 and 7 on the background intake of 1,1,1-trichloroethane from food, water and air. SLR Consulting Ltd provided assistance in the management and delivery of this document. The Department for Environment, Food and Rural Affairs and the Environment Agency greatly acknowledge the valuable inputs from various independent experts and government agencies and departments, particularly the Department of Health and Food Standards Agency.

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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. It presents key data and expert opinion on the toxicology of 1,1,1-trichloroethane 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 1,1,1-trichloroethane, which have been established through a review of the scientific literature and a subsequent peer review process. The health criteria values presented herein will be used to derive Soil Guideline Values (SGVs) for 1,1,1-trichloroethane.
- 1.3 The overall framework for this review and 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 approaches used in this report.
- 1.4 The computer model used for deriving the Soil Guideline Values is described in CLR10 *The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms* (Defra and Environment Agency, 2002b). SGVs for 1,1,1-trichloroethane will be published in *SGV 24 Guideline Values for 1,1,1-Trichloroethane 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 May 2003.

2 Identity

- 2.1 1,1,1-Trichloroethane (CAS No 71-55-6), also known as methyl chloroform, is a colourless, volatile liquid, with a vapour pressure of 13.3 kPa at 20°C (IPCS, 1992). It is slightly soluble in water, with an aqueous solubility of 1.33 g L⁻¹ at 25°C (Banerjee *et al* 1980, cited in CHEMFATE, 1995), but miscible in a number of organic solvents (IPCS, 1992).

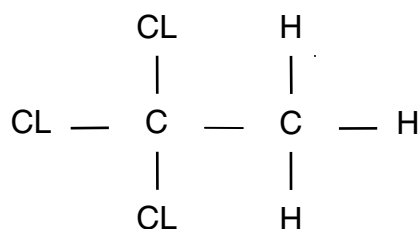


Fig 2.1 Molecular structure of 1,1,1 -Trichloroethane

- 2.2 Technical and industrial grades usually contain 3–8% of stabilisers, mainly to prevent the generation of hydrochloric acid and to avoid the corrosion of metals. The most frequently used stabilisers include 2-butanol, 1,4-dioxane, 1,3-dioxolane, butylene oxide, diisopropylamine, isobutyl alcohol, methyl ethyl ketone, *N*-methyl pyrrole, nitroethane, nitromethane and toluene. The trichloroethane structural isomer, 1,1,2-trichloroethane, may also be present as an impurity (IPCS, 1992).
- 2.3 1,1,1-Trichloroethane is used in the cleaning/degreasing of metals and plastics, and in the production of vinylidene chloride. As a solvent, it is present in a wide range of formulations, including adhesives, paints, varnishes and inks, and is used in textile processing. It is used also as a coolant and lubricant in metal cutting oils, as a developer in printed circuit boards, and as a solvent or additive in aerosols (IPCS, 1992).
- 2.4 No natural sources of this chlorinated hydrocarbon have been identified. It has some ozone-depleting potential, and there are various regulatory initiatives to phase out non-essential uses (IARC, 1999). The major releases into the environment, mainly directly into the atmosphere, come from its production and industrial use and road transport emissions. Relatively small amounts are released to water or soil from industrial discharges, in leachate from landfills and other contaminated sites, and from accidental spills (IARC, 1999; IPCS, 1992).
- 2.5 1,1,1-Trichloroethane is mobile in soil and may be released to the atmosphere through volatilisation, to surface water through runoff, and to groundwater as a result of leaching. In addition to volatilisation, 1,1,1-trichloroethane is also subject to abiotic removal from soil by hydrolysis or dehydrohalogenation, forming acetic acid and 1,1-dichloroethene respectively (Aronson and Howard, 1997). Both aerobic and anaerobic biodegradation occur in soils, but are reported to be very slow (IPCS, 1992), with a half-life of several years reported at many contaminated sites (Aronson and Howard, 1997). However,

biologically mediated degradation rates are reported to be at least an order of magnitude higher than abiotic degradation mechanisms (Klecka *et al*, 1990).

- 2.6 To ensure consistency throughout this report, where the cited source has given 1,1,1-trichloroethane levels in ppm, a conversion factor of 1 ppm = 5.4 mg m⁻³ (WHO, 1996) has been used.

3 Toxicity

- 3.1 Reviews of the literature on the toxicity of 1,1,1-trichloroethane have been published by the World Health Organization (WHO, 1996, 2003), the International Programme on Chemical Safety (IPCS, 1992), the International Agency for Research on Cancer (IARC, 1999), the Agency for Toxic Substances and Disease Registry (ATSDR, 1995) and the US Environmental Protection Agency (USEPA, 1996). This section (and Section 4) is largely based on these reviews, and in general the primary literature has not been consulted. Particular mention is made of those studies which have been used in deriving health criteria values.
- 3.2 **Absorption.** After 4 hours of continuous exposure to 378 or 756 mg m⁻³, a steady-state lung retention of 30% was observed in volunteers (Humbert and Fernandez, 1977; Monster *et al*, 1979). Upon first exposure (before steady-state levels are approached in the blood and tissues), there is a higher degree of pulmonary absorption, up to 95% (IARC, 1999). No data regarding the absorption of ingested 1,1,1-trichloroethane by humans have been found (ATSDR, 1995), but laboratory animal experiments indicate that it is rapidly and completely absorbed by the gastrointestinal tract (ATSDR, 1995).
- 3.3 1,1,1-Trichloroethane vapour is absorbed through human skin, but this is substantially less important than the inhalation route. It has been estimated that the exposure of the whole unclothed body to an atmospheric concentration of 3240 mg m⁻³ for 3.5 hours would deliver a systemic dose through the skin equivalent to that produced via the lungs from a similar period of exposure to an atmosphere containing only 3.2 mg m⁻³ (Riihimäki and Pfaffli, 1978). The rate of permeation of 1,1,1-trichloroethane through the skin of volunteers (arising from a 3-minute dermal exposure) was about 7.5 µg cm⁻² min⁻¹ (Kezic *et al*, 2001, cited in Toxline). Skin absorptions of a similar order have been seen in mice (Tsuruta, 1975) and guinea pigs (Jakobson *et al*, 1982).
- 3.4 **Distribution.** Laboratory animal studies show that 1,1,1-trichloroethane, after absorption into blood, is rapidly distributed throughout the body, with the highest concentrations occurring in lipid-rich tissues (e.g. fat and brain) and highly vascular tissues (e.g. liver and kidney) (ATSDR, 1995). In volunteers, 60–80% was eliminated from the blood within 2 hours of exposure (Monster *et al*, 1979). Transfer to the fetus has been demonstrated in inhalation studies in mice (Danielsson *et al*, 1986; Shimada, 1988).
- 3.5 **Metabolism.** Less than 10% of the absorbed dose is metabolised irrespective of the route of exposure. An inhalation study in volunteers indicated that less than 6% of the absorbed 1,1,1-trichloroethane was metabolised following a 4-hour exposure to around 378–756 mg m⁻³ (Monster *et al*, 1979). The metabolic pathways likely to be initially most involved are the cytochrome P450 mixed function oxidases, which are particularly abundant in the liver (ATSDR, 1995). The major metabolites identified are trichloroethanol, trichloroethanol glucuronide, trichloroacetic acid and carbon dioxide (ATSDR, 1995). There are some quantitative species differences in the toxicokinetics of 1,1,1-trichloroethane, with a higher rate and greater extent of metabolism being seen in the mouse than in the rat or human (ATSDR, 1995; IARC, 1999). In both rats and mice,

metabolism was a dose-dependent, saturable process that represented a minor route of elimination (Schumann *et al*, 1982a,b). Repeated exposure did not alter metabolic fate in rats and mice (Schumann *et al*, 1982a).

- 3.6 **Excretion.** Most (60 to >91%) of the absorbed 1,1,1-trichloroethane is excreted unchanged in exhaled air (ATSDR, 1995). In humans exposed for 4 hours to 378–756 mg m⁻³, metabolites are excreted mainly in the urine, although small amounts of trichloroethanol have also been detected in the expired air (Monster *et al*, 1979). Trichloroethanol glucuronide was the main urinary metabolite and its excretion was complete by day 8. Trichloroacetic acid's excretion was complete by day 12 (Humbert and Fernandez, 1977).
- 3.7 Rodents exposed by inhalation to radio-labelled 1,1,1-trichloroethane for 6 hours excreted more than 96% of the administered dose during the first 24 hours, mainly in the expired air (Schumann *et al*, 1982a). Almost all (>99%) of an intraperitoneal dose administered to rats was excreted unchanged in the expired air. Less than 1% was excreted as urinary metabolites (Hake *et al*, 1960).
- 3.8 **Acute toxicity.** In humans, high oral and inhalation doses produce nausea, vomiting and diarrhoea (ATSDR, 1995). The central nervous system (CNS) is the critical target receptor following high levels of inhalation exposure. Many human fatalities have been reported following inhalation, and death occurs through depression of the CNS or cardiac arrhythmia (ATSDR, 1995).
- 3.9 A reduced performance in psychomotor tests was seen in volunteers exposed to 950 mg m⁻³ for 3.5 hours (although their attention and concentration actually improved) (Mackay *et al*, 1987). Slight sedative effects were detectable in volunteers exposed for 4 hours to 1080 mg m⁻³ (Muttray *et al*, 2000, cited in Medline). Exposures above 2700 mg m⁻³ can cause dizziness, light-headedness and uncoordination (WHO, 1996). Estimated lethal concentrations are of the order of 32,000 to 108,000 mg m⁻³ (Droz *et al*, 1989). Mild degrees of liver pathology have occasionally been seen in the autopsies of the victims of fatal intoxications (Caplan *et al*, 1976; Hall and Hine, 1966), and small changes in kidney function have been recorded in those recovering from the neurotoxicity posed by high atmospheric concentrations (HSDB, 2003). Cardiovascular side-effects were seen when 1,1,1-trichloroethane was used as an anaesthetic to induce unconsciousness through brief exposures to 54,000 mg m⁻³ (IPCS, 1992).
- 3.10 A low acute toxicity has been demonstrated in several laboratory animal species, with oral LD₅₀ values exceeding 5700 mg kg⁻¹ bw (milligrams per kilogram body weight) (Torkelson *et al*, 1958). The equivalent inhalation values (for 6–7 hour exposures) are in excess of 50,000 mg m⁻³ (ATSDR, 1995). As in humans, the CNS is the main target of inhalation exposures (ATSDR, 1995).
- 3.11 **Repeated toxicity.** Short-term memory loss, decreased attention and concentration span, and peripheral neuropathy are amongst the nervous system effects of long-term occupational exposure to moderate or high concentrations of 1,1,1-trichloroethane

- (HSDB, 2003). However, there were no indications of neurotoxicity in 22 female factory workers exposed to 1,1,1-trichloroethane for an average period of about 7 years. A battery of psychometric tests and measurements of nerve conduction velocity identified no significant differences between the three exposed groups, working in atmospheres containing about 600, 800 and 1400 mg m⁻³ respectively, and a control group of seven unexposed women from the same factory (Maroni *et al*, 1977).
- 3.12 An investigation of 10 clinical cases of fatty liver disease found that four of the affected patients had been occupationally exposed to 1,1,1-trichloroethane. No good-quality quantitative information was available on exposure (Hodgson *et al*, 1989). Other case reports, again without exposure data, describe liver damage after 4 years occupational exposure to 1,1,1-trichloroethane (Cohen and Frank, 1994).
- 3.13 A study of 151 matched pairs of workers at two US plants gave no evidence that exposures, generally of around 270–1350 mg m⁻³ for 1–5 years, had any adverse effect on liver or kidney function, or produced any cardiovascular disturbances. One of each pair worked at a plant where there was daily exposure to 1,1,1-trichloroethane, whereas the other member of each matched pair worked at a plant that used only non-chlorinated solvents (Kramer *et al*, 1978). Tests of liver function were also normal in 28 workers exposed to high (and neurotoxic) levels of 1,1,1-trichloroethane for 10 years (Kelafant *et al*, 1994).
- 3.14 Biochemical effects on the central nervous system were seen in gerbils continuously exposed to 1134 or 5400 mg m⁻³ for 3 months (Rosengren *et al*, 1985). Brain weights were reduced. Four months after exposure had ceased, there was a significant increase in the level of glial fibrillary acid (GFA) protein in the sensorimotor cerebral cortex. No similar changes were present at 378 mg m⁻³. The same research team (Karlsson *et al*, 1987) also found decreases in DNA concentrations in several brain regions of gerbils that had been exposed to 378 mg m⁻³, the only concentration in which this end-point was examined. ATSDR assessors were of the view that the increase in GFA protein was an indirect indicator of brain injury; the significance of the reduced levels of DNA was described as “uncertain” (ATSDR, 1995). Commenting on the two papers, the IPCS (1992) noted that “if these findings are validated and confirmed, this may be of significant concern”.
- 3.15 There was some indication of a mild action on the nervous system (which resulted in a persistent decreased forelimb grip) in rats exposed repeatedly to 10,800 mg m⁻³ which was not seen in rats exposed to 3400 mg m⁻³. The treatment regime involved 6 h daily exposure, 5 day week⁻¹ for 13 weeks. Examination of tissues of the nervous system revealed no abnormalities (Mattsson *et al*, 1993). A pathological examination of the brain detected no abnormality in mice and rats exposed 6 h day⁻¹, 5 day week⁻¹ for 2 years to atmospheres containing 8100 mg m⁻³ (Quast *et al*, 1988).
- 3.16 Exposure of male mice to 5400 mg m⁻³ continuously for 14 weeks resulted in an increase in liver weight and some liver pathology (hepatocyte necrosis). Electron microscopy showed extensive cytoplasmic changes. There was little evidence of liver

abnormality at the lowest tested dose concentration of 1365 mg m⁻³ (McNutt *et al*, 1975). Mild liver pathology was reported in rats and mice exposed 6 h day⁻¹, 5 day week⁻¹ for 90 days to 10,800 mg m⁻³. The liver was normal in those exposed to 5400 mg m⁻³ (Calhoun *et al*, 1981). Repeated exposure of female guinea pigs to 5400 mg m⁻³ (3–180 min day⁻¹, 5 day week⁻¹ for 3 months) produced mild liver changes (and some lung irritation). Lower concentrations were not examined (Torkelson *et al*, 1958). The liver was unaffected in guinea pigs exposed to 3510 mg m⁻³, 7 h day⁻¹, 5 day week⁻¹ for 93 days (Adams *et al*, 1950).

- 3.17 There was a major reduction in body weight gain in dogs and rabbits exposed continuously for 90 days to atmospheres containing 2050 mg m⁻³. Growth was unaffected at 750 mg m⁻³ (Prendergast *et al*, 1967).
- 3.18 In a comprehensive rodent study (NTP, 2000), involving the microscopic examination of tissues from a wide range of organs, no clear signs of toxicity were detected in groups of 10 male and 10 female rats and mice given encapsulated 1,1,1-trichloroethane in their diet at 10,000 ppm for 13 weeks. The rats would have received doses of about 600–650 mg kg⁻¹ bw day⁻¹ and the mice around 1770–2820 mg kg⁻¹ bw day⁻¹ (NTP, 2000). At higher doses, treatment-related pathological changes were limited to the kidney of the male rats and were consistent with hyaline droplet nephropathy (a response that is generally thought to have no relevance to humans). The female rats given the highest dose (of 5000 mg kg⁻¹ bw day⁻¹) had reduced liver weights. Reduced weight gain occurred in the mice at doses of 3500 mg kg⁻¹ bw day⁻¹ and above (NTP, 2000). A more limited study (Bruckner *et al*, 1985, 2001, cited in Medline) noted an absence of toxicity in rats given 500 mg kg⁻¹ bw day⁻¹ by stomach tube, 5 times a week for up to 12 weeks; some induction of the liver enzymes was detectable at this dose level. Reduced body weight, effects on the CNS and deaths occurred at doses of 2500 mg kg⁻¹ bw day⁻¹ and above. At 5000 mg kg⁻¹ bw day⁻¹ indirect signs of liver injury (raised enzyme levels in the blood) were also present. There were decreases in both survival and body weight gain at the lowest tested doses in rat and mouse studies (NCI, 1977) involving treatment by stomach tube, 5 day week⁻¹ for 78 weeks; these were 750 mg kg⁻¹ bw day⁻¹ in the rats and 2800 mg kg⁻¹ bw day⁻¹ in the mice.
- 3.19 **Reproductive and developmental toxicity.** Several epidemiological studies have explored the relationship between 1,1,1-trichloroethane exposure and an adverse pregnancy outcome (spontaneous abortion or congenital malformations). They provided no clear evidence of any reproductive or developmental toxic potential, although none of the investigations would have had any great statistical power with respect to 1,1,1-trichloroethane (ATSDR, 1995). A preliminary study provides some indication of a reduced fertility in 12 male workers subjected to “intermediate/high” exposure to 1,1,1-trichloroethane (no absolute exposures reported) (Sallmén *et al*, 1998).
- 3.20 There was a slightly reduced sperm concentration in mice and rats given 80,000 ppm in the diet (producing a dose of about 5000 mg kg⁻¹ bw day⁻¹ in rats and 15,000 mg kg⁻¹ bw day⁻¹ in mice). Sperm counts were not affected at dietary concentrations of 40,000 ppm (NTP, 2000). Fertility was normal in a two-generation study in which mice received

up to 1000 mg kg⁻¹ bw day⁻¹ in their drinking water (Lane *et al*, 1982). Guinea pigs exposed to about 27,000 mg m⁻³ (7 h day⁻¹, 5 day week⁻¹ for 45 days) suffered varying degrees of testicular degeneration (the reproductive consequences were not examined) (Adams *et al*, 1950). No toxic effects were reported in guinea pigs exposed 7 h day⁻¹ for 30 days to 16,200 mg m⁻³ (Adams *et al*, 1950).

- 3.21 In a two-generation study, mice were given 1,1,1-trichloroethane in their drinking water to produce dose levels of 100, 300, or 1000 mg kg⁻¹ bw day⁻¹. There were no dose-dependent effects on either gestation or the survival of the offspring (Lane *et al*, 1982). An examination of the behaviour of the offspring of female rats that had been administered up to 750 mg kg⁻¹ bw day⁻¹ by stomach tube on day 6 of pregnancy to day 10 of lactation revealed no abnormalities (Dow, 1993).
- 3.22 Fetotoxicity (decreased fetal weight and a reduced degree of bone ossification) was observed when rats were exposed 4 h day⁻¹ on days 6–15 of pregnancy to a maternally toxic concentration of 32,000 mg m⁻³. No effects were detected at 16,200 mg m⁻³ (BRRC, 1987a). Mild fetotoxicity of a similar type was also reported in female rats exposed to 11,300 mg m⁻³. Only a single concentration was tested and the females, which were exposed 6 h day⁻¹, 5 day week⁻¹ for 2 weeks prior to mating, and 6 h day⁻¹ throughout pregnancy, exhibited no signs of toxicity (York *et al*, 1982). Developmental toxicity was not present in rats and mice exposed 7 h day⁻¹ on days 6–15 of pregnancy to 4700 mg m⁻³ (Leong *et al*, 1975). Signs of nervous system toxicity were recorded in the offspring of mice that had been exposed 17 h day⁻¹ from days 12 to 17 of pregnancy to 10,900 mg m⁻³ (Jones *et al*, 1996), and in the offspring of rats exposed to 37,800 mg m⁻³, 1 h day⁻¹ for 3 days during the last week of pregnancy (Coleman *et al*, 1999, cited in Medline). A mild fetotoxic action was seen when rabbits were exposed (6 h day⁻¹) to 32,000 mg m⁻³ on pregnancy days 6–18. The exposure reduced maternal body weight gain (BRRC, 1987b).

4 Carcinogenicity and genotoxicity

- 4.1 Neither the IARC (IARC, 1999) nor USEPA assessors in 1990 (USEPA, 1996) were able to evaluate the carcinogenicity of 1,1,1-trichloroethane to humans and it was assigned to Group 3 (“not classifiable as to its carcinogenicity”) and D (“not classifiable as to human carcinogenicity”) respectively.
- 4.2 The IARC (1999) noted that there was a slightly higher than expected number of overall cancers in a group of workers exposed to 1,1,1-trichloroethane. Seventeen cancers were recorded in this subset of the larger cohort, a number that was not statistically significantly higher than the number likely to develop in an equivalent unexposed general population (standardized incidence ratio 1.6; 95% confidence limits 0.9–2.5). As for specific cancer types, there were higher risks of cancer of the CNS and multiple myeloma in those exposed to 1,1,1-trichloroethane, although again these were not statistically significant increases and were based on very small numbers of cases, three and two respectively (Anttila *et al*, 1995).
- 4.3 In a study in which associations were sought between past occupational exposure to various chemicals and the incidence of a broad range of cancers, there was no excess risk for most of the types of cancer examined (including that of the CNS and multiple myeloma) and exposure to 1,1,1-trichloroethane (Siemiatycki, 1991). Excess rates were observed for lung cancer (based on the seven lung cancer cases who were exposed to any level of 1,1,1-trichloroethane) and kidney cancer in the whole population (based on four kidney cancer cases similarly exposed).
- 4.4 No evidence of carcinogenicity was present in groups of 50 male and 50 female rats and mice given technical-grade 1,1,1-trichloroethane by stomach tube 5 day week⁻¹ for 78 weeks (NCI, 1977). The rats received 750 or 1500 mg kg⁻¹ bw day⁻¹ and were observed for an additional 32 weeks, and the mice were given 2800 or 5600 mg kg⁻¹ bw day⁻¹ and were killed after an additional 12 weeks without treatment. There were no clear differences in the incidence of tumours in the treated groups compared with the respective controls (of 20 animals of each sex). The experiment had a limited power to detect carcinogenic potential because of the large number of early deaths in all groups. High mortality was also a problem when rats were given 375 or 750 mg kg⁻¹ bw day⁻¹ and mice were given 1500 or 3000 mg kg⁻¹ bw day⁻¹ by stomach tube, 5 times a week, for 103 weeks (NTP, 1983). There was a significant dose–response trend and increased incidence of liver cancer in male and high-dose female mice. The study was conducted under the auspices of the National Toxicology Program of the USA, and the investigators judged the study to be inadequate for an assessment of carcinogenicity, a verdict shared by the IARC (IARC, 1979).
- 4.5 An increased incidence of leukaemias developed in rats given technical grade 1,1,1-trichloroethane by stomach tube at 500 mg kg⁻¹ bw, 4 or 5 days a week for 104 weeks. The experiment lasted 141 weeks (Maltoni *et al*, 1986). Thirteen of the 80 treated rats developed leukaemias, compared with four in the 100 controls receiving the gavage

medium. The treated animals lived longer than the controls. The IPCS (1992) noted that the study was performed under a “non-standard protocol” and the published report “gave no statistical evaluation and [was] therefore, considered inadequate”. The IARC (1999) also considered that the study was “inadequate for evaluation”.

- 4.6 In a chronic inhalation study, groups of 50 male and 50 female rats and mice were exposed to technical-grade 1,1,1-trichloroethane, 6 h day⁻¹, 5 day week⁻¹ for 2 years. In none of the treated groups, which were exposed to 820, 2730 or 8190 mg m⁻³, did the tumour incidence differ significantly from that in the controls (Quast *et al*, 1988). There was also no evidence of carcinogenicity when rats were exposed to 4780 and 9560 mg m⁻³, 6 h day⁻¹, 5 day week⁻¹ for 12 months. The initial group sizes were 96 animals per sex, and the survivors were killed 6 months after the end of treatment (Rampy *et al*, 1977).
- 4.7 Confident overall verdicts on the genotoxic potential of 1,1,1-trichloroethane are probably premature. In mammalian cells in culture, 1,1,1-trichloroethane has produced equivocal and inconsistent results for the major end-points, with reports of chromosome damage in the absence of metabolic activation, but not in its presence (Galloway *et al*, 1987), and inconclusive indications of mutagenicity in the presence of metabolic activation (Myhr and Caspary, 1988; Tennant *et al*, 1986). There are a number of reports of mutagenicity in strains TA100 and TA1535 of *Salmonella typhimurium* (Ames tests). This mutagenic potential in bacteria has been seen in both the presence and absence of exogenous metabolic activation (IARC, 1999). Confident conclusions on the weight of evidence of 1,1,1-trichloroethane’s genotoxicity *in vitro* are undermined by the difficulties introduced by the specification of the tested material. It is likely that some of the studies would have involved the testing of 1,1,1-trichloroethane containing stabilisers, some of which (for example, butylene oxide) are unequivocally mutagenic.
- 4.8 There were low but detectable levels of covalent binding of 1,1,1-trichloroethane to the DNA of the liver, kidney, lung and stomach of mice and rats treated by intraperitoneal injection (Turina *et al*, 1986). An “equivocal” increase in chromosome damage (micronuclei) was seen in the peripheral blood cells of male mice given 1,1,1-trichloroethane in the diet for 13 weeks at doses of 1770 mg kg⁻¹ bw day⁻¹ and above. No similar increase was present in the females (NTP, 2000). In mice, intraperitoneal injection induced neither chromosome damage (micronuclei) in the bone marrow (Gocke *et al*, 1981; Salamone *et al*, 1981; Tsuchimoto and Matter, 1981) nor changes in sperm morphology (Topham, 1980). No evidence of dominant lethal mutations was seen in mice given high doses in the drinking water (Lane *et al*, 1982).

5 Derivation of tolerable daily intakes

The recommendations of JECFA

5.1 The Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed 1,1,1-trichloroethane as a food additive at their twenty-third and twenty-fifth meetings (WHO, 1980, 1981). The available data were considered inadequate for an evaluation of this solvent and no acceptable daily intake (ADI) was established.

The WHO guidelines for drinking-water quality

5.2 Based on the findings of a Working Group risk assessment completed in 1992, the WHO (1993, 1996) concluded that the oral studies then available were inadequate for the derivation of an oral tolerable daily intake (TDI) for 1,1,1-trichloroethane. As an interim measure, a provisional TDI of $0.58 \text{ mg kg}^{-1} \text{ bw}$ was proposed. This was based on the results of a 14-week inhalation study in mice (paragraph 3.16) and an assumption that the toxicity of a given systemic dose would be the same irrespective of whether that dose resulted from either the inhalation or oral route. The “no observed adverse effect” level (NOAEL) of 1365 mg m^{-3} was equivalent to an absorbed dose of $580 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ (assuming an average mouse body weight of 30 g, a breathing rate of $0.043 \text{ m}^3 \text{ day}^{-1}$ and a pulmonary absorption of 30%). The TDI was generated by the application of an uncertainty factor of 1000 (10 each for inter- and intra-species variation and 10 for a short duration study).

5.3 The WHO (1996) “strongly recommended that an adequate oral toxicity study be conducted to provide more acceptable data for the derivation of a guideline value”. Information on an NTP gavage study (paragraph 3.18) has subsequently become available, which has allowed a WHO reassessment (presently available in draft as WHO, 2003). An overall uncertainty factor of 1000, comprising factors of 10 each for inter- and intra-species variation, and 10 for the use of a short-term study to derive a limit for chronic exposure, was applied to the NOAEL of $600 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, to produce a TDI of $0.6 \text{ mg kg}^{-1} \text{ bw}$.

The WHO air quality guidelines

5.4 The WHO has not recommended an air quality guideline for 1,1,1-trichloroethane (WHO, 1987, 2000).

The recommendations of the USEPA

5.5 In its current Integrated Risk Information System (IRIS) file, the USEPA (1996) makes no recommendation for either a reference dose (RfD)¹ for chronic oral exposure, or a

¹ An 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 non-cancer effects during a lifetime.

reference concentration (RfC)² for chronic inhalation exposure. An earlier recommended value for an RfD was withdrawn in 1991. No quantitative cancer assessments have been undertaken because USEPA considered the data insufficient to assess whether or not 1,1,1-trichloroethane is a carcinogen.

- 5.6 In their drinking-water regulations and health advisories (USEPA, 2002), the USEPA recommends a maximum contaminant level (MCL) of 0.2 mg L⁻¹. This MCL dates from a health advisory of 1987 and was based on an RfD (0.035 mg kg⁻¹ bw day⁻¹) that was subsequently withdrawn.

The recommendations of the ATSDR

- 5.7 The ATSDR (1995) has not proposed any oral minimal risk levels (MRLs)³ for 1,1,1-trichloroethane due to the lack of suitable studies.
- 5.8 No chronic inhalation MRL was recommended because of the absence of a study of the appropriate duration that would allow an evaluation of “subtle neurological effects”. An MRL relevant for up to one year of human inhalation exposure (an “intermediate inhalation MRL”) was derived from the 3-month study by Rosengren *et al* (1985) (paragraph 3.14) in which the end-point was the occurrence of biochemical effects in several regions of the gerbil brain. The NOAEL was judged to be 378 mg m⁻³, and the ATSDR used an uncertainty factor of 100 (for inter- and intra-species variations) to arrive, after rounding, at an MRL of 4 mg m⁻³.

Conclusions

- 5.9 The main toxicological target of inhaled 1,1,1-trichloroethane in humans is the central nervous system. Amongst the non-lethal effects documented in volunteers and patients who had been exposed to single exposures were uncoordination and anaesthesia. There is also evidence that a mild degree of liver toxicity may arise from high acute exposure and in some occupational contexts.
- 5.10 A mild neurotoxic and hepatotoxic action has been seen in laboratory animals exposed either orally or by inhalation. The kidney lesions that developed in male rats treated orally are not thought to be relevant to humans. There are reports of fetotoxicity in rodents, but these are linked to high inhalation exposures, exposures that are usually also maternally toxic. As well as signs of mild general fetotoxicity, adverse effects have been detected in the nervous system of the offspring of rodents exposed during pregnancy. There is no convincing evidence of any genotoxic or carcinogenic potential in humans or other species. At present, therefore, it would seem reasonable to assume

² An RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime.

³ An MRL is 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.

that there is a dose threshold for the onset of any 1,1,1-trichloroethane-induced adverse effects, and the objective is to derive TDIs.

- 5.11 Only one Expert Group, the WHO in development of drinking-water guidelines, has derived an oral health criteria value for 1,1,1-trichloroethane. Data from a 14-week inhalation study in mice, and an assumption of a similar systemic toxicity irrespective of the route of exposure, were the basis of an initial provisional TDI of $0.58 \text{ mg kg}^{-1} \text{ bw day}^{-1}$. A draft document published as part of the current revision of the WHO guidelines recommends a TDI of $0.6 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ on the basis of a 13-week oral study in rats. Given the similarity of the two TDIs, the rounded value of $0.6 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ is recommended here as the TDI_{oral} .
- 5.12 The ATSDR is the only Expert Group that has proposed a health criteria value for the inhalation route. An intermediate MRL of 4 mg m^{-3} was recommended based on an inhalation study in gerbils (Rosengren *et al*, 1985). The lowest tested concentration of 378 mg m^{-3} was described as a NOAEL, and the application of an uncertainty factor of 100 generated an MRL applicable to one year of human exposure. The study of Rosengren *et al* has as its end-point biochemical effects rather than directly observed changes in behaviour. The effects are suggestive of an action on the brain of some kind, and neurotoxicity is generally regarded as the critical effect of exposure to 1,1,1-trichloroethane. Nevertheless there is an uncertainty over the true relevance of the findings to man.
- 5.13 The limited human data on neurotoxicity of 1,1,1-trichloroethane do not suggest a potent neurotoxic action. Volunteer studies indicate only mild and reversible effects on the nervous system at concentrations of around 1000 mg m^{-3} . Insights from the rat and mouse studies on neurotoxicity also point to a low potency. Unlike the gerbil studies, the rat and mouse experiments provide more conventional insights into neurotoxic potential, that is, changes in behaviour and pathology of tissues of the nervous system. All other things being equal, these should be a more reliable guide to the equivalent end-point in humans.
- 5.14 In deriving a provisional oral TDI, the WHO (1993, 1996) guidelines for drinking-water quality made the assumption that the toxicity of a given systemic dose of 1,1,1-trichloroethane would be the same irrespective of whether that dose resulted from either the inhalation or oral route. As the WHO (1993, 1996) drinking-water quality guideline was derived from the findings of a mouse inhalation study, it is proposed to use this same study as the basis of an inhalation limit. The WHO described the lowest tested concentration of 1365 mg m^{-3} in the 14-week mouse study as a NOAEL, leading to a systemic dose in the mice of $580 \text{ mg kg}^{-1} \text{ bw day}^{-1}$. Application of an uncertainty factor of 1000 (10 each for inter- and intra-species variations and 10 for the use of a sub-chronic study) and rounding results in a recommended inhalation TDI equal to the oral TDI of $0.6 \text{ mg kg}^{-1} \text{ bw day}^{-1}$.

6 Intake of 1,1,1-trichloroethane from food, water and air

- 6.1 1,1,1-Trichloroethane is a volatile organic contaminant. The principal source of exposure is therefore expected to be from ambient air. The IPCS (1992) reports that a German study estimated that 89% of the total exposure came from air. 1,1,1-Trichloroethane also has significant lipophilicity and might therefore be expected to accumulate within foods with a high fat content. In the past it has also been used as a fumigant (Daft, 1991; IPCS, 1992). However, current intakes of 1,1,1-trichloroethane are not likely to be of significance, as it is no longer used as a fumigant for food crops. The Montreal Protocol of 1990 and its subsequent amendments set a phase-out date of 1996 for the production of 1,1,1-trichloroethane by developed countries of 1996. It has not been produced⁴ in the UK since 1995 (Defra, 2001).
- 6.2 Trichloroethane has not been analysed in the Total Diet Studies conducted by MAFF (1994) and more recently by the Food Standards Agency (FSA). Apart from some work by Pearson and his co-workers in the 1970s (Pearson and McConnell, 1975), there are few published measurements of 1,1,1-trichloroethane in food, drinking water or air in the UK. Some results from a number of countries are summarised in the IPCS review (IPCS, 1992). Daft (1991) analysed 549 food items in the USA and found trichloroethane in 200 out of 849 total findings. The “average concentration found” was 22 ng g⁻¹. A study of the national mean daily intake in Germany (Düszeln *et al*, 1982) reported that 10% (3.6 µg day⁻¹) of the mean daily intake from all sources originated from foodstuffs.
- 6.3 However, since these studies were conducted, the use of 1,1,1-trichloroethane as a fumigant has ceased, as has its production. Following consultation with the FSA, it has therefore been decided to assume that concentrations in food are negligible.
- 6.4 The Environment Agency obtained information from English and Welsh water companies on concentrations of chlorinated solvents in drinking water. However, none of the companies that provided data⁵ measured concentrations of 1,1,1-trichloroethane. IPCS (1992) provides a review of various studies of drinking-water concentrations. In a review of measurements in drinking water from a number of countries, Pearson (1982) gave a value of 0.1 µg L⁻¹ as a typical level. A mean concentration of 0.02 µg L⁻¹ in drinking water has been reported in Germany (Düszeln *et al*, 1982). In surveys in three states in the USA, Wallace *et al* (1986) found very low concentrations, with mean values of 0.03 to 0.6 µg L⁻¹; in another US study cited by IPCS (1992), concentrations ranging from 0.4 to 17 µg L⁻¹ were found in areas near 1,1,1-trichloroethane production plants. In the absence of recent data, it will be assumed that the average concentration of 1,1,1-trichloroethane in UK drinking water is about 0.1 µg L⁻¹. For an adult consuming 2 litres of water per day (Defra and Environment Agency, 2002a), the mean daily intake from

⁴ Production is defined by the Montreal Protocol as “production minus the amount used as feedstock or process agent in the production of other chemicals”.

⁵ Anglian, Bristol, Severn Trent, South East Water, South Staffordshire Water, SW Water, Southern Water, United Utilities, Welsh Water, Wessex and Yorkshire Water

water is about 0.2 µg.

- 6.5 The mean daily intake from food and water is therefore probably not more than about 0.2 µg day⁻¹.
- 6.6 The most recent UK measurements of 1,1,1-trichloroethane in ambient air are those recorded by Pearson and McConnell (1975). Levels in suburban areas of Liverpool and Manchester of 0.54–32.4 µg m⁻³ were recorded. The median (16.5 µg m⁻³) of the range for Liverpool and Manchester has been used to estimate an inhalation MDI. The median has been used, rather than the upper end, because the IPCS quotes estimates of 2.7 to 5.4 µg m⁻³ for “polluted” areas and a measurement of 8.6 µg m⁻³ for urban New Jersey. Even so, the concentration appears high; this is possibly because of the industries prevalent in Manchester and Liverpool. It is likely that the choice of these levels is conservative, as they were measured well before the cessation of 1,1,1-trichloroethane production. However, while releases by the waste industry have steadily declined, the chemical industries in the UK were still releasing over 6 tonnes to air in 2000 (Environment Agency, 2003). Thus in the absence of any more recent measurements, the assumption of 16.5 µg m⁻³ will be retained. Assuming an inhalation rate of 20 m³ day⁻¹, the inhalation MDI would be approximately 330 µg day⁻¹.
- 6.7 In a study by Wallace *et al* (1986), the median concentration of 1,1,1-trichloroethane within the home was 17 µg m⁻³ (a range from 0.16–333,000 µg m⁻³ was recorded). This study was published in 1986, and there has been little or no research since the phasing out of 1,1,1-trichloroethane. Given the similarity of the median indoor air concentration and the outdoor air concentration noted above, exposure to indoor air concentrations is not included in calculating the inhalation MDI.
- 6.8 The conservative estimates of the inhalation MDI may be expected to decrease as usage of 1,1,1-trichloroethane decreases.

7 Other sources

- 7.1 Occupational exposure may occur in the production of trichloroethane, in the dry-cleaning industry or in the degreasing of metals and electronic components (IPCS, 1992). 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 trichloroethane was likely to occur but would decrease with increased time between exposure and feeding. The preferential excretion pathway was by exhalation (99% or greater).
- 7.2 Trichloroethane is used as a solvent in both aerosol and non-aerosol products. Cosmetic aerosols and fabric protectors may be significant sources of indoor exposure to trichloroethane (IPCS, 1992).

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 $0.003 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{oral} of $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an adult oral TDSI of approximately $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ (rounded to 2SF). However, the TDSI for a child may be lower as a result of differences in dietary intake and body weight. 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 $0.006 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{oral} of $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an oral TDSI of approximately $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ (rounded to 2SF). The TDI_{oral} and the oral MDI of 1,1,1-trichloroethane are given in Table 8.1.

Table 8.1 TDI_{oral} and oral MDI and TDSI for an adult and a six-year-old child

TDI_{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 ($\mu\text{g kg}^{-1} \text{ bw day}^{-1}$)
600	0.2	600	600

- 8.3 The inhalation MDI for a 70 kg adult is equivalent to $4.7 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{inh} of $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an adult inhalation TDSI of approximately $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. However, the TDSI for a child may be lower as a result of differences in inhalation intake and body weight. 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 $8.25 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{inh} of $600 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an inhalation TDSI of approximately $590 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. The TDI_{inh} and the inhalation MDI of 1,1,1-trichloroethane are given in Table 8.2.

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

TDI_{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 ($\mu\text{g kg}^{-1} \text{ bw day}^{-1}$)
600	330	600	590

- 8.4 No authoritative assessments of the health risks posed by dermal exposures to 1,1,1-trichloroethane were identified.

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