

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

CONTAMINANTS IN SOIL:

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

CARBON TETRACHLORIDE

Publishing Organisation

Environment Agency, Rio House, Waterside Drive, Aztec West, Almondsbury, Bristol, BS32 4UD

Tel: 01454 624400 Fax: 01454 624409 Website: www.environment-agency.gov.uk

© Environment Agency 2005

February 2005

ISBN 1 844 32161 4

Product code: SCHO0904BIEY-E-P

All rights reserved. No part of this document may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior permission of the Environment Agency.

Officers, servants or agents of the Environment Agency and the Department for Environment, Food and Rural Affairs accept no liability whatsoever for any loss or damage arising from the interpretation or use of the information, or reliance upon views contained herein.

Dissemination Status

Internal: Released to Regions

External: Released to Public Domain

Statement of Use

This publication details the derivation of health criteria values for carbon tetrachloride. 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, carbon tetrachloride.

Environment Agency Contact

Albania Grosso, Principal Human Health Scientist, Ecosystems & Human Health Science Group, Environment Agency, Evenlode House, Howbery Park, Wallingford, Oxon, OX10 8BD

Acknowledgment

This document was initially written by RPS Group plc and has subsequently been updated by Toxicology Advice & Consulting Ltd. SLR Consulting Ltd assisted 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 departments and agencies, particularly Food Standards Agency and Health Protection Agency.

Contents

1	Introduction	1
2	Identity	2
3	Toxicity	3
4	Carcinogenicity and genotoxicity	7
5	Derivation of tolerable daily intakes	9
	The IPCS Environmental Health Criteria Document	9
	The WHO guidelines for drinking-water quality	10
	The recommendations of the USEPA	10
	The recommendations of the ATSDR	11
	Conclusions	11
6	Intake of carbon tetrachloride from food, water and air	13
7	Other sources	15
8	Conclusions	16
	References	17

1 Introduction

- 1.1 This report is one of a number on the assessment of risks to human health from contaminants in soil. Key data and expert opinion are presented on the toxicology of carbon tetrachloride 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 carbon tetrachloride through a review of the scientific literature and a subsequent peer review process. The health criteria values presented will be used to derive Soil Guideline Values (SGVs) for carbon tetrachloride.
- 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 may be necessary to understand the concepts, terms and approach 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 carbon tetrachloride will be published in SGV 20 *Soil Guideline Values for Carbon Tetrachloride Contamination* (Defra and Environment Agency, in preparation).
- 1.5 This report is primarily based upon literature published before December 2002.

2 Identity

- 2.1 Carbon tetrachloride (CAS No 56-23-5), also known as tetrachloromethane, is a colourless, volatile liquid with the formula CCl_4 . Carbon tetrachloride has a characteristic sweet odour (HSDB, 2003) and has an aqueous solubility of 0.793 g L^{-1} at 25°C (Horvath, 1982). The structure of carbon tetrachloride is shown in Figure 2.1.

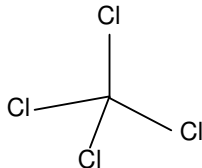


Figure 2.1 Structure of carbon tetrachloride

- 2.2 Carbon tetrachloride has been detected in volcanic gases (Isidorov *et al*, 1990). However, global atmospheric levels have been attributed to anthropogenic sources alone (Singh *et al*, 1976). Carbon tetrachloride is produced through the chlorination of methane, the hydrochlorination of methanol, the chlorination of hydrocarbons such as propylene, and the chlorination of carbon disulphide. Depending upon reaction conditions, the first three processes enable the manufacture of other products, such as tetrachloroethene.
- 2.3 The major use of carbon tetrachloride is in the manufacture of chlorofluorocarbons, primarily for use as refrigerants, propellants, foam-blowing agents and solvents, and in the production of other chlorinated hydrocarbons (IPCS, 1999). It has also been used as a grain fumigant, pesticide, solvent for oils and fats, metal degreaser, fire extinguisher and flame retardant, and in the production of paint, ink, plastics, semiconductors and petrol additives. It was previously also widely used as a cleaning agent (IPCS, 1999).
- 2.4 Since 1990 the production of carbon tetrachloride has decreased (IPCS, 1999). The Montreal Protocol of 1990 and its subsequent amendments established the phase-out by 1996 of production and use of carbon tetrachloride and of chlorofluorocarbons (CFCs) by major manufacturing countries (IPCS, 1999). As a result of this, all of the uses identified in paragraph 2.3 have tended to be phased out with the drop in production (ATSDR, 1994).
- 2.5 In soil most carbon tetrachloride is expected to evaporate rapidly due to its high vapour pressure (IPCS, 1999), and most environmental carbon tetrachloride is found in the atmosphere, with eventual diffusion into the stratosphere (IPCS, 1999). Carbon tetrachloride is reported to be resistant to aerobic biodegradation (McCarty, 1997; de Best *et al*, 1998). However, under anaerobic conditions, complete dechlorination can occur and this is dependent upon the prevailing environmental conditions (de Best *et al*, 1998). Reported dissipation half-lives range from 4 days (mean adjusted value for field/*in-situ* data set) to 187 days (for iron-reducing conditions) (Aronson and Howard, 1997).

3 Toxicity

- 3.1 This section is based mainly on reviews of the toxicity of carbon tetrachloride that have been published by the US Agency for Toxic Substances and Disease Registry (ATSDR, 1994), the UK Health and Safety Executive (HSE) (Standing and Cartledge, 1992), the International Agency for Research on Cancer (IARC, 1999), the US Environmental Protection Agency (USEPA, 1989, 1991), the World Health Organization (WHO, 2004) and the International Programme on Chemical Safety (IPCS, 1999). In general, the primary literature has not been consulted. Particular mention is made of those studies which have been used in deriving tolerable daily intakes (TDIs). To ensure consistency in units throughout this report, where the cited reference has described carbon tetrachloride levels in ppm, a conversion factor of 1 ppm = 6.4 mg m⁻³ (IPCS, 1999) has been used.
- 3.2 **Absorption.** Carbon tetrachloride is well absorbed following oral, dermal or inhalation exposure (IPCS, 1999). The gastrointestinal absorption of carbon tetrachloride is reported to be at least 85% in several animal studies. Absorption was extensive and rapid following dosing in water or other aqueous vehicles, and slower and less extensive when carbon tetrachloride was administered in corn oil (ATSDR, 1994). In a study in humans, 60% of inhaled carbon tetrachloride was absorbed (Lehmann and Schmidt-Kehl, 1936). Male Sprague-Dawley rats exposed to 6410 mg m⁻³ of carbon tetrachloride for 2 hours absorbed an amount equivalent to a systemic dose of 179 mg kg⁻¹ bw (milligrams per kilogram body weight) or about 54% of inhaled dose (Sanzgiri *et al*, 1995, 1997).
- 3.3 The ATSDR (1994) considers carbon tetrachloride to be less readily absorbed through the skin than by ingestion or inhalation. Carbon tetrachloride liquid is well absorbed through the skin, but dermal absorption of the vapour is slow (IPCS, 1999). Carbon tetrachloride was rapidly exhaled by volunteers who immersed their thumbs in undiluted carbon tetrachloride. It was estimated that immersion of both hands for 30 minutes would result in an exposure equivalent to a 30-minute exposure to atmospheres containing 100 to 500 ppm (640 to 3200 mg m⁻³) (Stewart and Dodd, 1964). In studies with anaesthetised mice, the absorption rate was 8.25 µg min⁻¹ cm⁻² (Tsurata, 1975). Complete absorption of carbon tetrachloride from aqueous solutions was reported when solutions ranging from around 33 to 100% saturation were applied to the skin of rats (Morgan *et al*, 1991).
- 3.4 **Distribution.** Sanzgiri *et al* (1995, 1997) exposed male rats to carbon tetrachloride in air (2 hours at 6410 mg m⁻³) and administered the equivalent systemic dose of 179 mg kg⁻¹ bw both as an oral bolus and by constant gastric infusion over a 2-hour period. The concentrations of carbon tetrachloride were greatest in fatty tissues, with levels being highest after the oral bolus. In the liver, the maximum concentrations were 58 and 20 µg g⁻¹ after the bolus and inhalation, respectively, and 0.5 µg g⁻¹ after gastric infusion. The lower levels seen after gastric infusion were believed to reflect very rapid metabolic clearance of the relatively low amounts reaching the liver. The large amounts of carbon tetrachloride appearing in the portal blood following the bolus gavage apparently exceeded the capacity of first-pass liver and pulmonary elimination.

- 3.5 **Metabolism and excretion.** A substantial proportion (50% or more) of absorbed carbon tetrachloride is eliminated unchanged in exhaled breath (ATSDR, 1994; IPCS, 1999) and smaller proportions (1–8%) are excreted as metabolites in the urine and faeces (IPCS, 1999). A proportion of absorbed carbon tetrachloride undergoes metabolism by cytochrome P450-dependent dechlorination and subsequent free-radical reactions. Chloroform and carbon dioxide are exhaled metabolites (ATSDR, 1999).
- 3.6 **Acute toxicity.** In humans, characteristic clinical signs of acute exposure to carbon tetrachloride (independent of exposure route) are indigestion with nausea, vomiting and gastrointestinal pain. Severe liver damage results in a swollen and tender liver, jaundice, elevated hepatic enzyme levels and, in some cases, fibrosis or cirrhosis. Chronic alcohol ingestion induces cytochrome P450 activity, thus exacerbating carbon tetrachloride toxicity (ATSDR, 1994; IPCS, 1999).
- 3.7 In common with other volatile halocarbons, exposure by ingestion or inhalation can result in depression of the central nervous system. Headache, blurred vision, lethargy and disorientation are a result of its direct narcotic action. Renal injury is often found in humans, but to a lesser degree in exposed animals. In laboratory animals, carbon tetrachloride is a mild skin and eye irritant, and exhibits a low acute toxicity. Oral LD₅₀ values in rodents are in excess of 2.5 g kg⁻¹ bw, whereas for inhalation exposure, the LC₅₀ value in mice for a 6-hour exposure was about 45,000 mg m⁻³ (IPCS, 1999).
- 3.8 **Repeated inhalation toxicity.** In a cross-sectional human volunteer study, liver function was assessed in workers occupationally exposed to carbon tetrachloride at three UK plants. These workers had been exposed at levels close to the UK occupational exposure limit. Though this study has some deficiencies, there was no biochemical evidence of any carbon tetrachloride-related liver dysfunction in the “low exposure group”, composed of workers whose mean exposure was up to 1 ppm (6.4 mg m⁻³) (Tomenson *et al*, 1995).
- 3.9 Continuous exposure at 6.1 mg m⁻³ for 90 days caused no overt toxicity or histopathological effects in rats, guinea pigs, dogs, rabbits or monkeys, though growth was reduced in all species except rats. This concentration was considered a “no observed adverse effect” level (NOAEL) for rats. At 61 mg m⁻³ there was decreased weight gain, clinical signs of toxicity and liver cell damage in all species (Prendergast *et al*, 1967).
- 3.10 When rats, guinea pigs, rabbits and rhesus monkeys were exposed at 32, 63, 160, 320, 630, 1282 or 2520 mg m⁻³ for 7 h day⁻¹, 5 day week⁻¹ for 6 months, a NOAEL of 32 mg m⁻³ was established in rats. This is equivalent to a concentration of 6.7 mg m⁻³ (32 mg m⁻³ × 7/24 × 5/7) for continuous exposure (24 h day⁻¹ and 7 day week⁻¹). Effects on body weight and liver degeneration, with cirrhosis, were seen at 63 mg m⁻³ and above. Similar results were observed in guinea pigs. Rabbits and monkeys exhibited liver toxicity (e.g. fatty degeneration and cirrhosis) at 160 and 630 mg m⁻³ or more, respectively (Adams *et al*, 1952).
- 3.11 Following exposure at 0, 64, 192, 577, 1731 or 5192 mg m⁻³ for 6 h day⁻¹, 5 day week⁻¹ for 13 weeks, microscopic changes were seen in the liver of rats and mice at 64 mg m⁻³. In the rats, there were effects on the blood at 192 mg m⁻³ and above, kidney

damage at 1731 mg m^{-3} and reduced growth at 5192 mg m^{-3} . The mice showed reduced growth at 192 mg m^{-3} and above, more severe liver damage at “higher” (unspecified) exposure levels, and blood effects in the top dose group. A NOAEL was not established (Japan Bioassay Research Centre, 1998).

- 3.12 In 2-year inhalation studies involving exposure at 0, 32, 157 or 787 mg m^{-3} of carbon tetrachloride for 6 h day^{-1} , 5 day week^{-1} for 104 weeks, the lowest tested concentration of 32 mg m^{-3} was considered by the IPCS in the Environmental Health Criteria Document (IPCS, 1999) to be a “lowest observed adverse effect” level (LOAEL). In mice, no effects were seen in the females exposed at this concentration, but anomalous control data precluded any conclusion for the males. Growth, the blood and the histopathological appearance of the liver, kidneys and spleen were affected at higher exposure concentrations. In rats exposed at 32 mg m^{-3} , there were effects on the appearance of the spleen, nasal cavity and (possibly) liver. In addition, changes in urine composition (increased nitrate and protein content) were indicative of possible kidney toxicity, while various mild changes in serum biochemistry values indicated minimal hepatic injury. More pronounced changes in the blood, serum biochemistry and microscopic appearance of the liver and kidneys were reported in higher-dose groups. Correcting for the exposure schedule ($6/24 \times 5/7$), the LOAEL for continuous exposure was calculated to be 5.7 mg m^{-3} (Japan Bioassay Research Centre, 1998; Nagano *et al*, 1998).
- 3.13 **Repeated oral toxicity.** A NOAEL of $1 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ was established when rats were given carbon tetrachloride 5 day week^{-1} for 12 weeks, by gavage in a corn oil vehicle. At 10 and $33 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, serum liver enzyme levels were increased and liver damage (vacuolation and cirrhosis) was observed. The NOAEL was equivalent to $0.71 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ when adjusted for daily dosing (Bruckner *et al*, 1986).
- 3.14 A study where mice were gavaged with carbon tetrachloride in a corn oil vehicle on 5 day week^{-1} for 90 days generated a NOAEL of $1.2 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, equivalent to $0.9 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ for daily dosing. At higher dose levels ($12 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ and above), changes in the serum levels of liver enzymes were seen, together with histopathological evidence of liver tissue damage (fatty infiltration and necrosis) (Condie *et al*, 1986). This study demonstrated how toxicity can be influenced by choice of gavage vehicle. When the same doses were given in 1% Tween 60, the NOAEL was $12 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ (Condie *et al*, 1986).
- 3.15 **Reproductive and developmental toxicity.** IPCS (1999) did not identify any relevant data in humans. ATSDR (1994) mentions two studies of birth outcome in New Jersey and carbon tetrachloride in the drinking water. These hinted that detectable concentrations in the water may be associated with cleft lip or cleft palate and ventricular septal defects, but it was stressed that methodological limitations may have resulted in associations that were chance, missed, overestimated or underestimated.
- 3.16 The IPCS (1999) repeated the 1994 view of the ATSDR that “the available data suggest that the fetus is not preferentially sensitive to carbon tetrachloride, and effects of carbon tetrachloride on fetal development and post-natal survival are likely to be secondary to maternal toxicity”. This opinion was based on studies where rats were repeatedly

exposed to carbon tetrachloride by inhalation or gavage during pregnancy, and on a repeated oral study in pregnant mice (IPCS, 1999).

4 Carcinogenicity and genotoxicity

- 4.1 In 1998, an IARC Working Group placed carbon tetrachloride in Group 2B (“possibly carcinogenic to humans”). This opinion was based on inadequate evidence for carcinogenicity in humans and sufficient evidence in laboratory animals (IARC, 1999). The same combination of data (inadequate evidence in humans, sufficient evidence in rats, mice and hamsters) led the USEPA in 1991 to classify carbon tetrachloride as a Category 2B carcinogen – “probable human carcinogen” (USEPA, 1991). In the EU, carbon tetrachloride is classified as a Category 3 carcinogen – “a substance which causes concern for humans owing to possible carcinogenic effects, but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2” (HSC, 2002).
- 4.2 An association between occupational exposure to carbon tetrachloride and non-Hodgkin’s lymphoma has been suggested in two cohort investigations and an independent nested case-control study. However, these studies are all characterised by exposure to other chemicals and inadequate carbon tetrachloride exposure data (IARC, 1999; IPCS, 1999). A recent case-control study also found a slightly raised risk of developing non-Hodgkin’s lymphoma in workers exposed to carbon tetrachloride (McDuffie *et al*, 2001).
- 4.3 A number of animal studies have conclusively demonstrated that carbon tetrachloride is a carcinogen. Liver cell carcinomas have been observed in several strains of rats and mice and in hamsters. The effects have been reported after repeated dosing by inhalation, ingestion or injection. In all of the studies, chronic liver damage was observed, which might have played a critical role in development of the liver tumours (IARC, 1979, 1999; IPCS, 1999; and other reviews noted in paragraph 3.1). In a 2-year inhalation study, mice also developed tumours of the adrenal gland (IARC, 1999; IPCS, 1999). This inhalation study and some key oral studies are noted below.
- 4.4 Following treatment of Syrian golden hamsters with carbon tetrachloride weekly by gavage in corn oil, liver cell carcinomas were found in all 10 animals that survived more than 10 weeks after the last administration. The 30-week treatment period delivered the equivalent of 15–30 mg kg⁻¹ bw day⁻¹ (Della Porta *et al*, 1961).
- 4.5 Treatment of 73 mice with 46 gavage doses of 64 mg of carbon tetrachloride (in olive oil) over four months, with a further three months of observation, resulted in liver tumours in 54% of males and 27% of females, compared with 1% in the controls. During the active treatment period, the animals were receiving the equivalent of about 800 mg kg⁻¹ bw day⁻¹ (Edwards *et al*, 1942).
- 4.6 The United States National Cancer Institute (NCI, 1976) carried out 78-week gavage studies (using a corn oil vehicle) in rats and mice, with additional observation for 33 and 13 weeks respectively after cessation of treatment. The male rats received 47 or 94 mg kg⁻¹ bw and the female rats 80 or 160 mg kg⁻¹ bw on 5 days each week. Excessive mortality occurred in the high-dose groups, and there was a slight increase in the

incidence of liver carcinoma in male and female rats at both doses. The mice received 1250 or 2500 mg kg⁻¹ bw, 5 days per week, and 96–100% developed liver carcinomas.

- 4.7 Groups of 50 male and female rats and mice were exposed to air containing 0, 32, 157 or 787 mg m⁻³ of carbon tetrachloride for 6 h day⁻¹, 5 day week⁻¹ for 104 weeks in Japanese studies (Nagano *et al*, 1998). In the rats, the incidence of liver carcinomas was significantly increased at the highest exposure concentration (1, 0, 0 and 32 out of 50 males; 0, 0, 3 and 15 out of 50 females). Liver adenomas were also increased in both sexes exposed at the highest concentration. In the mice, liver carcinomas were significantly increased in the mid- and top-dose groups (17, 12, 44 and 47 out of 50 males; 2/50, 1/49, 33/50 and 48/49 in females). Liver adenomas were also increased (in mid- and top-dose males, and low- and mid-dose females). The incidence of adrenal gland tumours was increased in mid- and high-dose males and high-dose females (incidences were 0, 0, 16 and 31 out of 50 males; 0/50, 0/49, 0/50 and 22/49 females).
- 4.8 Carbon tetrachloride gave no evidence of mutagenic activity in a large number of studies with *Salmonella typhimurium* (Ames tests) both with and without an added metabolic activation fraction (S9), and did not cause chromosome damage *in vitro* in hamster ovary cells, rat liver cells or human lymphocytes. DNA damage and mutations have been reported in *Escherichia coli*. In genotoxicity studies carried out *in vivo*, carbon tetrachloride did not induce chromosome aberrations in the bone marrow of mice or liver of rats, micronuclei in the peripheral blood erythrocytes or bone marrow of mice, micronuclei or unscheduled DNA synthesis in the liver of rats, or (in four out of five studies) DNA damage in the liver of rats and mice. DNA binding has been reported in the liver of rats, mice and hamsters. The weight of evidence indicates that carbon tetrachloride does not have significant genotoxic potential. The IPCS has concluded that carbon tetrachloride's effects upon the genetic material in some assay systems are explicable in terms of damage to nuclear protein or to DNA damage induced as a secondary effect to general toxicity (IPCS, 1999).
- 4.9 The covalent binding of reactive carbon tetrachloride metabolites to cell macromolecules (e.g. microsomal and nuclear lipids, phospholipids, cholesterol and cholesterol esters) in the liver and kidney, and consequent lipid peroxidation, is believed to be the principal mechanism underlying carbon tetrachloride toxicity, liver cell proliferation and perhaps carcinogenicity, and differences in these processes may account for the differences in toxicity seen between species and in different strains (IPCS, 1999).
- 4.10 In summary, carbon tetrachloride has induced liver tumours in rats, mice and hamsters. In one study, mice exposed by inhalation also developed adrenal gland tumours. The weight of evidence indicates that carbon tetrachloride does not possess significant genotoxic potential and, therefore, it is reasonable to assume that non-genotoxic mechanisms are involved in induction of the observed tumours. In the case of the liver tumours, supporting evidence for such a mechanism is available, liver toxicity being seen at exposure concentrations lower than those which induced liver tumours. The consensus view is that liver tumours developed as a secondary consequence of repeated cytotoxicity and persistent regenerative cell replication.

5 Derivation of tolerable daily intakes

The IPCS Environmental Health Criteria Document

- 5.1 The IPCS (1999) used two 90-day studies to derive oral TDIs. To the adjusted NOAEL of $0.71 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ from the study of Bruckner *et al* (1986), an uncertainty factor of 500 was applied to arrive at a TDI of $1.42 \text{ } \mu\text{g kg}^{-1} \text{ bw}$. The overall uncertainty factor was composed of factors of 10 each for inter- and intra-species variability and 10 for use of a sub-chronic study, as well as a modifying factor of 0.5. The latter has the effect of reducing the overall uncertainty factor and was introduced because the key study used bolus dosing in corn oil, which is likely to overestimate toxicity in comparison with administration in the diet or drinking water (IPCS, 1999).
- 5.2 The same overall uncertainty factor of 500 was also applied to the NOAEL from the 90-day mouse study of Condie *et al* (1986) (paragraph 3.14), which generated a TDI of $1.72 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ ($1.2 \text{ mg kg}^{-1} \text{ bw day}^{-1} \times 5/7 \times 1/500$) (IPCS, 1999).
- 5.3 Three key studies in rats were used to estimate “inhalation TDIs” for humans. In this derivation it was assumed that humans inhale 20 m^3 air per day and that 40% of the inhaled carbon tetrachloride is absorbed. Use of the absorption factor means that the “inhalation TDIs” given by the IPCS in this Environmental Health Criteria Document are actually TDIs expressed in terms of the systemic dose (IPCS, 1999).
- 5.4 To the NOAEL of 6.1 mg m^{-3} (for continuous exposure) from the 90-day rat study of Prendergast *et al* (1967) (paragraph 3.9), an uncertainty factor of 1000 was applied. This consisted of factors of 10 each for inter- and intra-species variability and 10 for use of a sub-chronic study. A tolerable concentration of $6.1 \text{ } \mu\text{g m}^{-3}$ was the result from which IPCS calculated a TDI (actually a systemic uptake) of $0.85 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ (IPCS, 1999).
- 5.5 The same overall uncertainty factor was applied to the experimental NOAEL adjusted for exposure time (6.7 mg m^{-3}) found in the 6-month rat study of Adams *et al* (1952) (paragraph 3.10). This generated a tolerable concentration of $6.7 \text{ } \mu\text{g m}^{-3}$, from which IPCS calculated a TDI (actually a systemic uptake) of $0.92 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ (IPCS, 1999).
- 5.6 The third critical report was the 2-year rat study (Japan Bioassay Research Centre, 1998; Nagano *et al*, 1998) (paragraph 3.12). To the adjusted LOAEL of 5.7 mg m^{-3} , IPCS applied an overall uncertainty factor of 500, comprising two factors of 10 for inter- and intra-species variability, and a third factor of 5 for using a marginal effect LOAEL rather than a NOAEL. This resulted in a tolerable concentration of $11.4 \text{ } \mu\text{g m}^{-3}$, from which IPCS calculated a TDI (actually a systemic uptake) of $1.56 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ (IPCS, 1999).
- 5.7 In deriving the inhalation TDIs, the IPCS made no adjustments to compensate for the different respiratory rates of rats and humans. This is a conservative approach because the same atmospheric concentrations of carbon tetrachloride would produce significantly higher inhaled doses in the rats than in man. If account had been taken of these physiological differences, higher TDIs would have resulted.

- 5.8 IPCS did not recommend a preferred oral or inhalation TDI figure, because “the upper limit of human daily intake under prevailing conditions is estimated to be $0.2 \mu\text{g kg}^{-1}$ body weight, well below the lowest tolerable daily intake ($0.85 \mu\text{g kg}^{-1}$ body weight)”, leading to the conclusion that “the currently prevailing exposure of the general population to carbon tetrachloride from all sources is unlikely to cause excessive intake of the chemical” (IPCS, 1999).

The WHO guidelines for drinking-water quality

- 5.9 In the background document (WHO, 2004a) to the third edition of the Guidelines for Drinking-Water Quality (WHO, 2004b), the WHO adopted the 1999 IPCS oral TDI of $1.4 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$, derived from the study of Bruckner *et al* (1986). Allocating 10% of this TDI to drinking-water and assuming a 60 kg adult drinking two litres of water per day, a guideline value of $4 \mu\text{g L}^{-1}$ was recommended.

The recommendations of the USEPA

- 5.10 The USEPA in 1991 used a linearised multi-stage model and tumour data from four oral studies (Della Porta *et al*, 1961; Edwards *et al*, 1942; NCI, 1976) to derive a risk estimate oral slope factor of 0.13 per $\text{mg kg}^{-1} \text{ bw day}^{-1}$ dose. In other words, an excess cancer risk of 1 in 100,000 would be associated with a lifetime ingestion of $4.5 \mu\text{g day}^{-1}$ (for a 60 kg adult). As all of the studies were deficient in some respect, USEPA used the geometric mean of the risk estimates from the individual studies (USEPA, 1991).
- 5.11 As no inhalation carcinogenicity studies were available in 1991, the same four oral studies and modelling method were used to calculate that an excess cancer risk of 1 in 100,000 would be associated with lifetime exposure at $0.7 \mu\text{g m}^{-3}$ of air. Assumptions of 20 m^3 per day air intake and 40% absorption from the lungs were made in deriving this estimate (USEPA, 1991).
- 5.12 Using the study of Bruckner *et al* (1986), the USEPA in 1991 also derived a reference dose (RfD¹) for chronic oral exposure of $0.7 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. The uncertainty factor of 1000 consisted of factors of 10 each for inter- and intra-species variability and 10 for extrapolation from the sub-chronic duration of the study to chronic exposure (USEPA, 1991).
- 5.13 The USEPA has not made any recommendation on the corresponding reference concentration (RfC) for chronic exposure to carbon tetrachloride by inhalation for non-carcinogenic effects (USEPA, 1991).

¹ A USEPA Reference Dose (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 non-cancer deleterious effects during a lifetime.

The recommendations of the ATSDR

- 5.14 The ATSDR (1994) set an oral minimal risk level (MRL²) for intermediate duration (oral exposure of less than one year) of $7 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ based upon the study by Bruckner *et al* (1986). This was derived by applying an uncertainty factor of 100 for inter- and intra-species variation to the study NOAEL of $1 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, adjusted to $0.7 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ to account for the dosing frequency (5 day week^{-1}). Inadequate chronic oral data prevented ATSDR from setting a chronic oral MRL (ATSDR, 1994).
- 5.15 Based upon the inhalation study of Adams *et al* (1952), an MRL for intermediate-duration inhalation exposure was set at 0.05 ppm ($320 \mu\text{g m}^{-3}$). It appears that an uncertainty factor of 100 for inter- and intra-species variation was applied to the observed study NOAEL (5 ppm) without adjusting for exposure time (7 h day^{-1} , 5 day week^{-1}). Inadequate chronic inhalation data prevented ATSDR from setting a chronic MRL for inhalation exposure (ATSDR, 1994).

Conclusions

- 5.16 Though carbon tetrachloride has induced liver tumours in rats and mice, the absence of any real evidence of genotoxic character, and the fact that liver toxicity is induced at exposure concentrations lower than those inducing tumours, supports the view (see paragraph 4.10) that the liver tumours develop as a secondary consequence of repeated cytotoxicity and persistent regenerative cell replication. On this basis, it is possible to derive a TDI and a tolerable concentration for human exposure to carbon tetrachloride.
- 5.17 The authoritative bodies cited above used the 90-day rat study of Bruckner *et al* (1986) (paragraph 3.13) as the basis for deriving a TDI for the ingestion of carbon tetrachloride. The IPCS (1999) applied an uncertainty factor of 500 to the adjusted NOAEL of $0.71 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ from this study to arrive at a TDI of $1.42 \mu\text{g kg}^{-1} \text{ bw}$. The overall uncertainty factor was composed of factors of 10 each for inter- and intra-species variability and 10 for use of a sub-chronic study, as well as a modifying factor of 0.5. The latter has the effect of reducing the overall uncertainty factor and was introduced because the study used bolus dosing in corn oil and it was thought that administration in the diet or drinking water would be likely to invoke a lower degree of toxicity (IPCS, 1999). High bolus doses are more likely to saturate normal metabolic pathways, an effect described at systemic exposures of $179 \text{ mg kg}^{-1} \text{ bw}$ in the studies of Sanzgiri *et al* (1995, 1997) (paragraph 3.4).
- 5.18 In a similar manner, IPCS used the 90-day mouse study of Condie *et al* (1986) (paragraph 3.14) to generate a TDI of $1.72 \mu\text{g kg}^{-1} \text{ bw}$ ($1.2 \text{ mg kg}^{-1} \text{ bw day}^{-1} \times 5/7 \times 1/500$) (IPCS, 1999), a figure that is in good agreement with that derived from the Bruckner *et al* (1986) rat study.
- 5.19 The WHO drinking-water guideline (WHO, 2004) is based on the TDI of $1.4 \mu\text{g kg}^{-1} \text{ bw}$ derived by IPCS (1999).
- 5.20 Therefore $1.42 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$, as derived by IPCS, is recommended as the oral TDI.

² An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.

5.21 The IPCS (1999) used three inhalation studies to derive tolerable concentrations for inhalation. The 2-year study by Nagano *et al* (1998) (paragraph 3.12) produced the lowest LOAEL (5.7 mg m^{-3} after adjustment for intermittent exposure). IPCS applied an overall uncertainty factor of 500, comprising two factors of 10 for inter- and intra-species variability, and a third factor of 5 for using a marginal effect LOAEL rather than a NOAEL. This resulted in a tolerable concentration of $11.4 \text{ } \mu\text{g m}^{-3}$, which is equivalent to an inhaled dose of $228 \text{ } \mu\text{g day}^{-1}$ or $3.26 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ (assuming $20 \text{ m}^3 \text{ day}^{-1}$ air inhalation volume and 70 kg body weight). IPCS used a 40% absorption factor to calculate a TDI (actually a systemic uptake) of $1.56 \text{ } \mu\text{g kg}^{-1} \text{ bw}$, based on an inhalation volume of 22 m^3 per day and a body weight of 60 kg (IPCS, 1999). However, the inhaled dose rather than the estimated systemic uptake is the relevant figure for comparison with exposures for use in the CLEA model, and so the figure of $3.26 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ as a TDI_{inh} is recommended here.

6 Intake of carbon tetrachloride from food, water and air

- 6.1 Carbon tetrachloride is highly volatile, and thus the major exposure for the general population is expected to be via ambient air (IPCS, 1999). However, it is also water-soluble and moderately lipophilic, and hence can accumulate in foods with a high fat content, potentially giving rise to oral exposure from food.
- 6.2 In the past, carbon tetrachloride was used as a fumigant, especially for cereals, resulting in food contamination. A food survey, undertaken in the USA in the late 1980s (Daft, 1991), analysed over 500 food items for the presence of carbon tetrachloride. Approximately 8% of food items contained carbon tetrachloride above the limit of detection, with an “average concentration found” of $31 \mu\text{g kg}^{-1}$. However, current intakes of carbon tetrachloride from food are likely to be substantially lower, as carbon tetrachloride has not been used as a fumigant for food in the UK, or in most of the countries from which we import food in significant quantities, for a number of years. The Montreal Protocol of 1990 and its subsequent amendments set a phase-out date of 1996 for the production of carbon tetrachloride by developed countries (UNEP, 2001). It has not been produced³ in the UK since 1995, or anywhere else in the world since 1999. Global consumption for 1999 was reported⁴ to be 100 tonnes (Defra, 2002).
- 6.3 MAFF (1993) did not detect any carbon tetrachloride in samples of butter and lard. These are foods with a high fat content and would be expected to contain carbon tetrachloride if present in the environment. A US study (Heikes, 1987) conducted before the US ban on the use of carbon tetrachloride as a fumigant found measurable concentrations of up to 6 ppb in butter samples. Other studies from Germany and Japan, cited by the IPCS (1999), were also conducted before the ban on the use of carbon tetrachloride as a fumigant and the cessation of production. Concentrations in food are considered to be negligible and have not been considered in derivation of the oral MDI.
- 6.4 The maximum permitted concentration of carbon tetrachloride in UK drinking water of $3 \mu\text{g L}^{-1}$ was introduced in 1989⁵. For the purposes of this report, however, the Environment Agency requested information from 10 English and Welsh water companies⁶ on concentrations of carbon tetrachloride between 2000 and 2002. A range of $0\text{--}2 \mu\text{g L}^{-1}$ was recorded. The mean concentrations for all sampling points surveyed for 2002 were approximately $0.1 \mu\text{g L}^{-1}$ or less. For an adult drinking 2 L of water per day, this is equivalent to a daily intake from drinking water of $0.2 \mu\text{g}$.
- 6.5 Combining the intakes from food and water would give an adult oral mean daily intake (MDI) of $0.2 \mu\text{g day}^{-1}$.

³ Production is defined by the Montreal Protocol as “production minus the amount used as feedstock or process agent in the production of other chemicals”.

⁴ Reporting is to the United Nations Environment Programme by countries party to the Montreal Protocol.

⁵ The Water Supply (Water Quality) Regulations 1989.

⁶ Information on carbon tetrachloride was supplied by Anglian, Bristol, Severn Trent, South East Water, South Staffordshire Water, SW Water, Southern Water, United Utilities, Wessex and Yorkshire Water.

- 6.6 Atmospheric concentrations for carbon tetrachloride are typically in the range 0.5–1 $\mu\text{g m}^{-3}$ (ATSDR, 1994; IPCS, 1999). Mean concentrations for urban and industrial areas were 2–3 $\mu\text{g m}^{-3}$, and substantially higher levels have been recorded near production facilities (IPCS, 1999). It is likely that there has been some decline since the phasing out of carbon tetrachloride production. However, although releases by the waste industry have steadily declined, the chemical industries in the UK were still releasing 15,000 kg to air in 2001 (Environment Agency, 2003). Therefore, an outdoor air concentration of 2.5 $\mu\text{g m}^{-3}$ has been assumed in calculating the inhalation MDI, reflecting concentrations in urban and industrial areas. For an adult breathing 20 m^3 daily, this will result in an inhalation MDI of 50 $\mu\text{g day}^{-1}$.
- 6.7 The IPCS cites a US study by Wallace (1986) which found that the average concentration of carbon tetrachloride within homes was 1 $\mu\text{g m}^{-3}$. This study was published in 1986; there has been little or no research since the phasing out of carbon tetrachloride. In view of this and the likely level of conservatism already present in the inhalation MDI, exposure to indoor air concentrations is not included.

7 Other sources

- 7.1 Occupational exposure to carbon tetrachloride can occur to workers involved in its production or in processes that use it as a feedstock, as described in Section 2. The drop in production of carbon tetrachloride as a result of the Montreal Protocol is expected to continue to reduce occupational exposure. Exposure may also occur as a result of emissions as a by-product of other industrial processes, such as wood pulp bleaching (IPCS, 1999).
- 7.2 Fisher *et al* (1997) simulated the transfer of a number of volatile contaminants to breast milk from occupationally exposed mothers. They found that moderate transfer of carbon tetrachloride was likely to occur but would decrease with increased time between exposure and feeding. The preferential excretion pathway was by exhalation (99% or greater).

8 Conclusions

- 8.1 The tolerable daily soil intake (TDSI) is defined as the difference between the tolerable daily intake (TDI) and the mean daily intake (MDI) (i.e. $TDSI = TDI - MDI$). The only exception to this is when the MDI is close to, or exceeds, the TDI, in which case the TDSI is set at 20% of the TDI. "Close to" is defined as greater than or equal to 80% of the TDI (Defra and Environment Agency, 2002a). TDSI values are rounded to two significant figures (2SF).
- 8.2 The oral MDI for a 70 kg adult is equivalent to $0.003 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{oral} of $1.42 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an adult oral TDSI of approximately $1.4 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ (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 $1.42 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an oral TDSI of approximately $1.4 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ (rounded to 2SF). The TDI_{oral} and the oral MDI of carbon tetrachloride 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 ($\mu\text{g kg}^{-1} \text{ bw day}^{-1}$)
1.42	0.2	1.4	1.4

- 8.3 The inhalation MDI for a 70 kg adult is equivalent to $0.71 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{inh} of $3.26 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an adult inhalation TDSI of approximately $2.5 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. The TDSI for a child, however, 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 $1.25 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. Subtracting this value from the TDI_{inh} of $3.26 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ results in an inhalation TDSI of approximately $2.0 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$. The TDI_{inh} and the inhalation MDI of carbon tetrachloride 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 ($\mu\text{g kg}^{-1} \text{ bw day}^{-1}$)
3.26	50	2.5	2.0

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

References

Adams EM, Spencer HC, Rowe VK, McCollister DD and Irish DD (1952) Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. *Archives of Industrial Hygiene and Occupational Health* **6** 50–66.

Aronson D and Howard P (1997) *Anaerobic Biodegradation of Organic Chemicals in Groundwater: A Summary of Field and Laboratory Studies*, Syracuse Research Corporation. Prepared for American Petroleum Institute.

ATSDR (1994) Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Carbon Tetrachloride*, US Department of Human Health and Services, Atlanta, GA.

Bruckner JV, MacKenzie WF, Muralidhara S, Luthra R, Kyle GM and Acosta D (1986) Oral toxicity of carbon tetrachloride: acute, subacute and subchronic studies in rats. *Fundamental and Applied Toxicology* **6** 16–34.

Condie LW, Laurie RD, Mills T, Robinson M and Bercz JP (1986) Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. *Fundamental and Applied Toxicology* **7** 199–206.

Daft JL (1991) Fumigants and related chemicals in foods: review of residue findings, contamination sources, and analytical methods. *The Science of the Total Environment* **100** 501–518.

de Best JH, Salminen E, Doddema HJ, Janssen DB and Harder W (1998) Transformation of carbon tetrachloride under sulfate reducing conditions. *Biodegradation* **8** 429–436.

Defra (2002) *Digest of Environmental Statistics*. Accessed [May 2003] online from <http://www.defra.gov.uk/environment/statistics/des/index.htm>

Defra and Environment Agency (2002a) *Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans*, R&D Publication CLR9.

Defra and Environment Agency (2002b) *The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms*, R&D Publication CLR10.

Defra and Environment Agency (in preparation) *Soil Guideline Values for Carbon Tetrachloride Contamination*, R&D Publication SGV 20.

Della Porta G, Terracini B and Shubik P (1961) Induction with carbon tetrachloride of liver cell carcinomas in hamsters. *Journal of the National Cancer Institute* **26** 855–863.

Edwards J, Heston WE and Dalton AJ (1942) Induction of the carbon tetrachloride hepatoma in strain L mice. *Journal of the National Cancer Institute* **3** 297–301.

Environment Agency (2003) *Pollution Inventory – Industry Sector Summary Spreadsheet*. Accessed [May 2003] online from www.environment-agency.gov.uk/pi

Fisher J, Mahle D, Bankston L, Greene R and Gearhart J (1997) Lactational transfer of volatile chemicals in breast milk. *American Industrial Hygiene Association Journal* **58** 425–431.

Heikes DL (1987) Purge and trap method for determination of volatile halocarbons and carbon disulfide in table-ready foods. *Journal – Association of Official Analytical Chemists*. **20** (2) 215–226.

Horvath AL (1982) *Halogenated Hydrocarbons: Solubility–Miscibility with Water*, Marcel Dekker, New York, pp. 889.

Accessed [May 2003] from SRC online database at: <http://esc.syrres.com/efdb/Chemfate.htm>

HSC (2002) *Approved Classification And Labelling Guide*, 5th edn, Chemicals (Hazard Information and Packaging for Supply) Regulations 2002, CHIP 3, Guidance on Regulations, HSE Publication L131.

HSDB (2003) *Hazardous Substances Data Bank*. Accessed [May 2003] from online database at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

IARC (1979) International Agency for Research on Cancer. *Some Halogenated Hydrocarbons*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans and their Supplements, vol. 20, International Agency for Research on Cancer, Lyon.

IARC (1999) International Agency for Research on Cancer. *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans and their Supplements, vol. 71, International Agency for Research on Cancer, Lyon.

IPCS (1999) *Carbon Tetrachloride*, Environmental Health Criteria Document No 208. WHO, Geneva.

Isidorov VA, Zenkerich IG and Ioffe BV (1990) Volatile organic compounds in sulfataric gases. *Journal of Atmospheric Chemistry* **10** 329-340 (Cited in IPCS, 1999).

Japan Bioassay Research Centre (1998) *Thirteen-Week and Two-Year Inhalation Studies on F-344 Rats and B6C3F₁ Mice (Studies Nos 0020, 0021, 0043 and 0044)*, Japan Industrial Safety and Health Association, Japan Bioassay Research Centre, Kanagawa, Unpublished report (cited in IPCS, 1999).

Lehmann KB and Schmidt-Kehl L (1936) The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. *Arch Hyg* **116** 131–268 (in German). (Cited in IPCS, 1999 and ATSDR, 1994).

MAFF (1993) Ministry of Agriculture, Fisheries and Food. *Tetrachloroethylene in Butter and Lard*, Food Surveillance Information Sheet No 5, Ministry of Agriculture, Fisheries and Food, London.

McCarty PL (1997) Biotic and abiotic transformations of chlorinated solvents in groundwater. *Proc. Symp. on Natural Attenuation of Chlorinated Organics in Groundwater*, EPA/540/R-97/504, USEPA ORD, Washington, DC.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF and Choi NW (2001) Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer and Epidemiology Biomarkers and Prevention* **10** 1155–1163.

Morgan DL, Cooper SW, Carlock DL, Sykora JJ, Sutton B, Mattie DR and McDougal JN (1991) Dermal absorption of neat and aqueous volatile organic chemicals in the Fisher 344 rat. *Environmental Research* **55** 51–63.

Nagano K, Nishizawa T, Yamamoto S and Matsushima T (1998) Inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice. In *Advances in the Prevention of Occupational Respiratory Diseases*, eds Chiyotani K *et al*, Amsterdam, Elsevier (cited in IARC, 1999).

NCI (1976). National Cancer Institute. *Report on Carcinogenesis Bioassay of Chloroform*, 1 March 1976, National Cancer Institute, Bethesda, MD. (cited in ATSDR, 1994 and USEPA 1989, 1991).

Prendergast JA, Jones RA, Jenkins LJ and Siegel J (1967) Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane and 1,1-dichloroethylene. *Toxicology and Applied Pharmacology* **10** 270–289.

Sanzgiri UY, Kim HJ, Muralidhara S, Dallas CE and Bruckner JV (1995) Effect of route and pattern of exposure on the pharmacokinetic and acute hepatotoxicity of carbon tetrachloride. *Toxicology and Applied Pharmacology* **134** 148–154.

Sanzgiri UY, Srivatsan V, Muralidhara S, Dallas CE and Bruckner JV (1997) Uptake, distribution and elimination of carbon tetrachloride in rat tissues following inhalation and ingestion exposure. *Toxicology and Applied Pharmacology* **143** 120–129.

Singh HB, Fowler DP, and Peyton TO (1976) Atmospheric carbon tetrachloride: another man-made pollutant. *Science* **192** 1231-1234 (Cited in IPCS, 1999).

Standing P and Cartledge GD (1992) [Health and Safety Executive]. *Toxicity Review 23*, Part 1, *Carbon Tetrachloride*, HSE Books, Sudbury.

Stewart RD and Dodd HC (1964) Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride and 1,1,1-trichloroethane through the skin. *American Industrial Hygiene Association Journal* **25** 439–446.

Tomenson JA, Baron CE, O'Sullivan JJ, Edwards JC, Stonard MD, Walker RJ and Fearnley DM (1995) Hepatic function in workers occupationally exposed to carbon tetrachloride. *Occupational and Environmental Medicine* **52** 508–514.

Tsurata H (1975) Percutaneous absorption of organic solvents. 1) Comparative study of the in vivo percutaneous absorption of chlorinated solvents in mice. *Industrial Health* **13** 227–236.

UNEP (2001) United Nations Environment Programme. The Ozone Secretariat. *Summary of Control Measures Under the Montreal Protocol (Updated January 2001)*.

Accessed [May 2003] online from <http://www.unep.org/ozone/>

USEPA (1989) United States Environmental Protection Agency. *Updated Health Effects Assessment for Carbon Tetrachloride*, EPA/600/8-89/088, Environmental Criteria and Assessment Office, Cincinnati.

USEPA (1991) US Environmental Protection Agency. *Integrated Risk Information System (IRIS), Carbon Tetrachloride (CASRN 56-23-5)*.

Accessed [November 2002] online at <http://www.epa.gov/iris/subst/0020.htm>

Wallace (1986) Personal exposures, indoor and outdoor air concentrations and exhaled breath concentrations of selected volatile organic compounds measured for 600 residents of New Jersey, North Dakota, North Carolina and California. *Toxicology and Environmental Chemistry* **12** 215–236.

WHO (2004a) Carbon Tetrachloride in Drinking-water. Background document for development of WHO *Guidelines for Drinking-water Quality*. World Health Organization, Geneva.

Accessed [February 2005] online at:

http://www.who.int/water_sanitation_health/dwq/chemicals/en/carbontetrachloride.pdf

WHO (2004b) *Guidelines for Drinking-Water Quality*, 3rd edn, World Health Organization, Geneva.

Accessed [January 2005] online at: http://www.who.int/water_sanitation_health/dwq/gdwq3/en/