CONTAMINANTS IN SOIL:

COLLATION OF TOXICOLOGICAL DATA AND INTAKE VALUES FOR HUMANS.

1,1,2,2-TETRACHLOROETHANE and 1,1,1,2-TETRACHLOROETHANE
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Statement of Use
This publication details the derivation of health criteria values for tetrachloroethanes. 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, tetrachloroethanes, 1,1,1,2-tetrachloroethane, 1,1,2,2-tetrachloroethane.

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1 Introduction

1.1 This report is one of a number of reports on the assessment of risks to human health from contaminants in soil. Key data and expert opinion are presented on the toxicology of 1,1,2,2- and 1,1,1,2-tetrachloroethane (tetrachloroethanes, PCAs) and their 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 tetrachloroethanes, 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 tetrachloroethanes.

1.3 The overall framework for this review and the associated underlying principles are set out in CLR9 Contaminants in Soils: Collation of Toxicological Data and Intake Values for Humans (Department for Environment, Food and Rural Affairs (Defra) and Environment Agency, 2002a). Reference to CLR9 is necessary to understand the concepts, terms and approach used in this report.

1.4 The computer model used for deriving the SGVs is described in CLR10 The Contaminated Land Exposure Assessment Model (CLEA): Technical Basis and Algorithms (Defra and Environment Agency, 2002b). SGVs for tetrachloroethanes will be published in SGV 14 Soil Guideline Values for 1,1,2,2-Tetrachloroethane and 1,1,1,2-Tetrachloroethane Contamination (Defra and Environment Agency, in preparation).

1.5 This report is based principally on the literature published up to June 2000. The report has been updated following a further review of key publications up to September 2002.
2 Identity

2.1 Tetrachloroethanes are compounds in which four hydrogen atoms of ethane have been replaced by chlorine. 1,1,2,2-Tetrachloroethane (CAS No 79-34-5), also known as acetylene tetrachloride or sym-tetrachloroethane, has two chlorine atoms on each of the two carbon atoms in the compound, and can be represented by the formula CHCl₂CHCl₂. The isomer 1,1,1,2-tetrachloroethane (CAS No 630-20-6), also known as uns-tetrachloroethane, has three chlorine atoms on one carbon atom and one on the other; this isomer can be represented by the formula CH₂ClCCl₃. In this report, the isomers will be abbreviated to 1,1,2,2-PCA and 1,1,1,2-PCA. The structures of the isomers are shown in Figure 2.1.

![Structures of Tetrachloroethane Isomers](Image)

**Figure 2.1 The Structure of Tetrachloroethane Isomers**

2.2 Both 1,1,1,2-PCA and 1,1,2,2-PCA are colourless, non-flammable liquids at room temperature and ambient pressure, with water solubilities of 1–3 g L⁻¹ at 20°C (IARC, 1999a,b). Both isomers are volatile, with vapour pressures of 665 Pa at 20°C for 1,1,2,2-tetrachloroethane and 1900 Pa at 25°C for 1,1,1,2-tetrachloroethane (IARC, 1999a,b).

2.3 The main use of 1,1,2,2-PCA has been as a starting material in the production of chlorinated ethenes. It has also been used as an industrial solvent, in paint removers, varnishes, lacquers and photographic film, and in some pesticide preparations (IARC, 1999a). It can be produced by the chlorination of ethene, but is primarily produced by the addition of chlorine to acetylene. Owing to its acknowledged toxicity and to changes in manufacturing processes, 1,1,2,2-PCA is no longer isolated as an end-product; it is immediately used to make trichloroethene or other chlorinated products (ATSDR, 1996). There are no known natural sources of 1,1,2,2-PCA (IPCS, 1998).

2.4 As a consequence of its usage as a chemical intermediate, 1,1,2,2-PCA has been found as an impurity in other halogenated hydrocarbons, in particular trichloroethene, 1,1,2-trichloroethane, dichloroethene and tetrachloroethene, and consequently may be released as airborne emissions or in waste water during their manufacture (ATSDR, 1996). 1,1,1,2-PCA has not been produced or used commercially in large quantities but may be formed incidentally during the manufacture of other chlorinated ethanes (IARC, 1999a).
Both 1,1,2,2-PCA and 1,1,1,2-PCA were among the 10 most prevalent chlorinated chemicals found in solvent wastes sent for incineration prior to 1980 in the USA (Travis et al, 1986). The vast majority of current releases to the environment are likely to be discharges into the air from manufacturing processes, although neither isomer is in the list of the 50 most significant volatile organic compounds emitted in the UK (DETR, 1998). Disposal to water and soil will mainly result in volatilisation to the atmosphere, where 1,1,2,2-PCA and 1,1,1,2-PCA are relatively stable, having estimated half-lives of 53 days to 2 years (ATSDR, 1996; IARC, 1999a; HSDB, 2003). Other transformation processes such as hydrolysis and anaerobic degradation also remove tetrachloroethanes; the major product of the pH-sensitive hydrolysis of 1,1,2,2-PCA is trichloroethene, while products of anaerobic biodegradation include trichloroethene, 1,2-dichloroethene and vinyl chloride (ATSDR, 1996).

Where studies have reported tetrachloroethane levels in ppm, a conversion factor of 1 ppm = 6.98 mg m\(^{-3}\) (IPCS, 1998) has been used to ensure consistency in units throughout this report.
3 Toxicity

3.1 The toxicity of 1,1,1,2-PCA and 1,1,2,2-PCA has been considered by the United States Environmental Protection Agency (USEPA, 1994, 1996), the International Programme on Chemical Safety (IPCS, 1998), the Agency for Toxic Substances and Disease Registry (ATSDR, 1996), the International Agency for Research on Cancer (IARC, 1979, 1986, 1999a,b), and by Luotamo and Riihimäki (1996) for the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group for Criteria Documentation of Health Risk from Chemicals (NEG). The material presented here is largely based upon these extensive reviews. Particular mention is made of those studies that have been used in the derivation of health criteria values.

3.2 Absorption. 1,1,2,2-PCA is well absorbed and rapidly metabolised following inhalation, ingestion and dermal exposure (IPCS, 1998). Following a single inhalation exposure, a human volunteer exhaled only 3% of the inhaled 1,1,2,2-PCA during the following hour (ATSDR, 1996). Limited studies with rats and mice have indicated that 1,1,2,2-PCA is largely absorbed after oral exposure. Unchanged PCA may also be exhaled after ingestion. Dermal uptake can be inferred from animal studies, but no quantitative data are available (ATSDR, 1996). There are few data on the absorption of 1,1,1,2-PCA. Inhalation and ingestion of this isomer by pregnant rats and rabbits resulted in high levels in fetuses, indicating absorption and transplacental passage. In mice given 1,1,1,2-PCA by subcutaneous injection, 21–62% of the dose was eliminated unchanged in exhaled air within 72 hours (IARC, 1986).

3.3 Distribution. Tissue binding studies in rodents with both isomers have indicated covalent binding to DNA, RNA and liver proteins, with greater binding by the symmetrical 1,1,2,2-PCA isomer. Liver studies suggest that the PCA isomer may be metabolically activated to acetylchlorides or free radicals, which may lead to toxicity following protein binding and lipid peroxidation (IARC, 1999a,b).

3.4 Metabolism and excretion. Metabolism of 1,1,2,2-PCA is believed to involve hydrolytic cleavage of the chlorine–carbon bonds via dichloroacetic acid and ultimately to glyoxylic acid (IPCS, 1998). Urinary metabolites identified within 24 hours of injecting 1,1,2,2-PCA into mice were dichloroacetic acid (27%), trichloroacetic acid (4%), trichloroethanol (10%), oxalic acid (10%) and glyoxylic acid (0.9%). Comparative inhalation, ingestion and injection studies in mice and rats with both isomers indicate that the main metabolic pathway for 1,1,1,2-PCA results in formation of trichloroethanol (17–49% of the dose) and trichloroacetic acid (1–7%), rather than dichloroacetic acid as for 1,1,2,2-PCA. Within 48 hours of exposure by inhalation or injection, rats excreted 20 times more trichloroacetic acid following 1,1,1,2-PCA exposure than after 1,1,2,2-PCA exposure (IARC, 1986).

3.5 Acute toxicity. 1,1,2,2-PCA can cause marked depression of the central nervous system (CNS) and subsequent respiratory failure following acute exposure to high doses. Both accidental and occupational acute exposure to PCA, especially in the
first half of the 20th century, resulted in a number of deaths. Effects of such exposure have included lowering of blood pressure, mucosal congestion of the oesophagus, nausea, loss of body weight, confusion and delirium, and particularly liver degeneration, as evidenced by jaundice and liver enlargement (ATSDR, 1996).

3.6 In short-term comparative toxicity studies with mice, Takeuchi (1966) concluded that 1,1,1,2-PCA was less toxic than 1,1,2,2-PCA. This was based on determining LD₅₀ values and observing the sleeping time after single injections of the compounds. The acute toxicity of 1,1,2,2-PCA in experimental animals is slight to moderate, with an LC₅₀ of about 6980 mg m⁻³ (4 hours inhalation) and oral and dermal LD₅₀ values of 250–1000 mg kg⁻¹ bw (milligrams per kilogram body weight) and 6360 mg kg⁻¹ bw respectively (IPCS, 1998).

3.7 Repeated toxicity. Lobo-Mendonça (1963) studied 380 workers in India exposed to 1,1,2,2,-PCA during the course of making bangles by dissolving cellulose acetate film in the solvent. The majority of workers were women, and more than one-third worked for one year or less before changing jobs. There was a high incidence of nervous complaints, with the major symptom being tremor. Fourteen per cent of workers exposed to air concentrations of 64 mg m⁻³ exhibited tremor, which rose to 50% in workers exposed to 460 mg m⁻³. A further study in penicillin works showed similar effects in workers exposed to 1,1,2,2-PCA at concentrations of 10–1700 mg m⁻³. With improvements to working conditions, most workers were reported to be free of symptoms when maximum levels were below 250 mg m⁻³ (IPCS, 1998).

3.8 In a 21-day study of renal toxicity in male F344/N rats (NTP, 1996), doses of 103 or 207 mg kg⁻¹ bw day⁻¹ (milligrams per kilogram body weight per day) of both PCA isomers were given by gavage. All rats receiving the higher dose of 1,1,2,2-PCA died by the end of the study. Hyaline droplet nephropathy was observed in the rats treated with the 1,1,1,2-PCA isomer, and replicative DNA synthesis was observed following treatment with both isomers.

3.9 Female Sprague-Dawley rats exposed by inhalation to 560 mL m⁻³ of 1,1,2,2-PCA for 5 or 6 hours per day, 5 days per week for 15 weeks had increased liver weight and signs of hyperplasia, granulation and vacuolation in the liver (Truffert et al., 1977). These effects were transient and reversible. This concentration was reported by ATSDR (1996) as 130 ppm (907 mg m⁻³) after conversion to a human equivalent dose (although information on the exposure level in the original paper was unclear; IPCS, 1998) and was used in deriving their recommendation for an intermediate exposure duration minimal risk level (MRL).

3.10 In a study by Shmuter (1977, cited by ATSDR, 1996 ), rabbits were exposed for 3 hours a day for 8 months to 10.5 mg m⁻³ of 1,1,2,2-PCA vapour (equivalent to a continuous exposure to 1.3 mg m⁻³, or 0.68 mg kg⁻¹ bw day⁻¹), and then inoculated with typhoid. When compared with unexposed controls, the specific antibodies were reduced in concentration and had an increased electrophoretic mobility. As other
immune function tests were not performed, these studies were not judged to be complete enough for consideration by the ATSDR (1996).

3.11 Rats treated by gavage with 3.2 or 8 mg kg\(^{-1}\) bw day\(^{-1}\) of 1,1,2,2-PCA for up to 17 weeks showed minor histological damage to the liver and kidney (Gohlke et al, 1977, cited by ATSDR, 1996). At the lower dosage rate, a high incidence of interstitial oedema was found in the testes, along with clumped sperm and partial necrosis and total atrophy of seminiferous tubules. The poor reporting and unusual design of the study, which included exposing the rats to high temperature (35°C), makes the evaluation of this study, and any comparison with other studies, problematical (ATSDR, 1996).

3.12 Long-term gavage studies in rats and mice at much higher dose levels of 1,1,2,2-PCA (NCI, 1978) failed to find any effects in the liver, kidney or reproductive organs of Osborne-Mendel rats, and only effects in the kidney in B6C3F1 mice at the highest dose studied (282 mg kg\(^{-1}\) bw day\(^{-1}\)). The gavage doses were 62 and 108 mg kg\(^{-1}\) bw day\(^{-1}\) for male rats, 43 and 76 mg kg\(^{-1}\) bw day\(^{-1}\) for female rats, and 142 and 282 mg kg\(^{-1}\) bw day\(^{-1}\) for mice of both sexes. This study did find a dose-related reversible decrease in body weight gain and increased mortality in rats, but not mice, given 1,1,2,2-PCA 5 days per week for 78 weeks. The body weights of female rats given 76 mg kg\(^{-1}\) bw day\(^{-1}\) were lower than the controls throughout most of the exposure period, but had recovered by the end of the study. Male rats treated with 108 mg kg\(^{-1}\) bw day\(^{-1}\), but not 62 mg kg\(^{-1}\) bw day\(^{-1}\), had a lower body weight than the controls at the end of the study. Respiratory effects were seen in all groups of rats, but not in the mice. Laboured respiration, wheezing and/or nasal discharge occurred in all groups during the first year of the study, increasing with time. The lower dose received by the female rats, 43 mg kg\(^{-1}\) bw day\(^{-1}\), was considered a “lowest observed adverse effect” level (LOAEL) by the ATSDR (1996). The carcinogenicity findings of this study are described in paragraph 4.2.

3.13 In a 103-week carcinogenicity study (NTP, 1983), 125 or 250 mg kg\(^{-1}\) bw day\(^{-1}\) 1,1,1,2-PCA was given for 5 days a week by gavage to groups of 50 male and 50 female mice and rats. No effect on body weight was observed in F344/N rats, but signs of CNS effects were seen at the higher dose in rats of both sexes. Male rats showed dose-related incidences of kidney mineralisation, and female rats demonstrated dose-related increases in hepatic clear-cell changes. The lower dose, of 125 mg kg\(^{-1}\) bw day\(^{-1}\) (89.3 mg kg\(^{-1}\) bw day\(^{-1}\), corrected for the dosing schedule of 5 days per week), was considered a LOAEL by the USEPA (1996). In this study, 27 male rats died from heat stress, and a further 15 females died from gavage error, which decreased the sensitivity of the study.

3.14 B6C3F1 mice fed 1,1,1,2-PCA at 250 or 500 mg kg\(^{-1}\) bw day\(^{-1}\), on the same schedule as above, only demonstrated effects at the higher dosage level. These effects included decreased body weight, CNS effects, and liver damage. The carcinogenicity aspects of this study are discussed in Section 4.
3.15 **Reproductive and developmental toxicity.** As noted in the reviews cited in paragraph 3.1, the reproductive and developmental toxicity of tetrachloroethane has not been adequately studied. Limited data for 1,1,2,2-PCA have been published, with reproductive and developmental effects only observed at levels associated with considerable decreases in body weight and other signs of maternal toxicity. No effects on reproductive organs were observed in the 78-week rat and mouse study described in paragraph 3.12 or in inhalation studies in rats (ATSDR, 1996; IPCS, 1998).
4 Carcinogenicity and genotoxicity

4.1 In a study of army workers exposed to tetrachloroethane by inhalation or dermal contact in clothing processing plants during World War II, Norman et al. (1981) reported a slight excess of deaths from genital cancers and leukaemia in comparison with similar unexposed workers used as controls. It was not stated which tetrachloroethane isomer or mixture of isomers was used in the processing plants, and the concentrations to which the workers were exposed were unknown. As the increased incidence was not statistically significant, and other confounding variables were present, the evidence is considered inconclusive as to whether tetrachloroethane causes cancer in humans.

4.2 In the long-term studies on 1,1,2,2-PCA conducted by the National Cancer Institute (NCI, 1978) described in paragraph 3.12, a statistically significant dose-related increase in liver cancers was observed in B6C3F1 mice of both sexes dosed by gavage at 142 and 282 mg kg\(^{-1}\) bw day\(^{-1}\) of 1,1,2,2-PCA, with the tumours appearing slightly earlier in the mice administered the higher dose. No statistically significant increase in tumours was observed in Osborne-Mendel rats. However, the authors concluded that, as the strain of rats used had a very low incidence of tumours when treated with carbon tetrachloride, the strain used may not have been sensitive enough to detect tumours caused by 1,1,2,2-PCA.

4.3 The long-term studies with 1,1,1,2-PCA described in paragraphs 3.13–3.14 (NTP, 1983) showed inconclusive results for carcinogenicity in F344/N rats. No statistically significant increases in tumour incidence were observed in female rats, and a dose-related trend in male rats was observed only for the combined incidence of neoplastic nodules and carcinomas of the liver. However, the authors concluded that carcinogenicity had not been demonstrated in rats. The accidental killing of 27 male and 15 female rats decreased the sensitivity of the study (USEPA, 1996).

4.4 A dose-related increase in liver carcinomas and adenomas was demonstrated in B6C3F1 female mice, while in male mice a statistically significant increase was demonstrated only for liver adenomas (USEPA, 1996).

4.5 In a rat liver foci assay for tumour-initiating activity, Osborne-Mendel rats were treated with 1,1,2,2-PCA following a partial hepatectomy. There was no increase in enzyme-altered foci and it was concluded that 1,1,2,2-PCA did not show initiating activity. In a tumour-promotion study, rats were treated with 1,1,2,2-PCA following an initial injection with the carcinogen, N-nitrosodiethylamine. Increased numbers of foci were observed after 8 weeks, indicating that 1,1,2,2-PCA showed tumour-promoting activity in this system (IARC, 1999a).

4.6 The USEPA (1994, 1996) classified both PCA isomers in Group C, “possible human carcinogens”, on the basis of the limited animal evidence. The International Agency for Research on Cancer (IARC, 1999a,b) considered both compounds to be “not
classifiable” as to their human carcinogenicity. This was because of the absence of epidemiological data relevant to carcinogenicity and only limited evidence in experimental animals for 1,1,1,2-PCA, and inadequate human data and only limited evidence in animals for 1,1,2,2-PCA.

4.7 As reported by Luotamo and Riihimäki (1996), five of six studies in which 1,1,1,2-PCA was tested with various strains of Salmonella typhimurium for forward and reverse mutations gave negative results, with and without metabolic activation. One study reported positive results with four strains without, but not with, activation. Mammalian in vitro tests gave positive results for sister chromatid exchange in Chinese hamster cells, and in the mouse lymphoma forward mutation assay, but 1,1,1,2-PCA did not induce DNA repair in rat hepatocytes. One in vivo study of mitotic recombination in Drosophila melanogaster gave negative results.

4.8 Many more in vitro studies have been carried out with the other isomer, 1,1,2,2-PCA, and again most studies with various strains of S. typhimurium gave negative results. Three out of eight studies gave some positive results, one with activation. In vitro mammalian cell studies have provided positive results for sister chromatid exchange in Chinese hamster cells, but negative results in tests for DNA repair with mouse and rat hepatocytes. Tests on unscheduled DNA synthesis and S-phase synthesis in primary hepatocytes from mice given one gavage dose of 1,1,2,2-PCA gave negative results. In vivo studies with D. melanogaster for induction of sex-linked recessive lethal mutations or mitotic recombination also proved negative.

4.9 It has been suggested that liver tumour induction in mice may not be relevant for human risk assessment, particularly with chemicals such as tetrachloroethane where there is limited evidence for genotoxicity. Mechanisms of action not relevant to humans may include the formation of rodent-specific carcinogenic metabolites or peroxisome proliferation. However, other proposed mechanisms associated with DNA and protein binding with subsequent damage, the formation of free radicals, or lipid peroxidation, may be relevant for human cancer risk assessment. The mechanism(s) by which tetrachloroethanes induce mouse liver tumours is unclear at present, and so firm conclusions on the importance of mouse liver tumour formation cannot be made (Luotamo and Riihimäki, 1996; IPCS, 1998).

4.10 The weight of evidence suggests that both isomers have no significant genotoxic potential. The carcinogenic profile (tumours in only one tissue of a single species – liver tumours in mice) is not that of a genotoxic carcinogen, there is no structural alert and there are negative results for all the significant in vitro and in vivo mutagenic assays. The only inconsistent data are those from the in vivo DNA binding studies.

4.11 On the basis of the present evidence, it is concluded that both 1,1,1,2-PCA and 1,1,2,2-PCA should be treated as non-genotoxic animal carcinogens, and it is therefore appropriate to derive tolerable daily intakes (TDIs). Reference should be
made to the discussion of carcinogens in CLR9 (Defra and Environment Agency, 2002a).
5 Derivation of tolerable daily intakes

The IPCS CICAD

5.1 The 1998 International Programme on Chemical Safety (IPCS) assessment of 1,1,2,2-PCA (Concise International Chemical Assessment Document (CICAD); IPCS, 1998) considered that the available data were inadequate to allow confident determination of a “no observed adverse effect” level (NOAEL) or LOAEL for liver toxicity.

5.2 Sample guidance values were proposed based upon the potency of 1,1,2,2-PCA for the induction of liver tumours in the NCI (1978) mouse gavage study described in paragraphs 3.12 and 4.2. Based on multi-stage modelling, the potency, expressed as the dose associated with a 5% increase in tumours (TD0.05), was calculated to range from 5.8 to 28 mg kg⁻¹ bw day⁻¹. Dividing the potency range by factors of 5000 or 50,000 gave intake values for ingestion of 1.2–5.6 or 0.12–0.56 µg kg⁻¹ bw day⁻¹. IPCS (assuming a linear dose–response effect below the TD0.05) noted that these values correspond to those considered by some agencies to represent "essentially negligible" risk (i.e. a lifetime cancer risk of 10⁻⁵ to 10⁻⁶) for a genotoxic carcinogen.

5.3 IPCS noted that, as available data indicated that 1,1,2,2-PCA "is, at most, weakly genotoxic, a smaller margin (e.g. 1000) might also be considered appropriate" when dividing the potency factor. This smaller margin is consistent with approaches to the evaluation of acceptable levels of exposure to non-genotoxic carcinogens in which an uncertainty factor of 1000 (consisting of factors of 10 each for inter- and intra-species variation and 10 for severity of effect (carcinogenicity)) may be applied to the NOAEL (approximated in this instance by the TD0.05). Applying this smaller margin of 1000 to the lowest value in the range (5.8 mg kg⁻¹ bw day⁻¹) results in a TDIoral of 5.8 µg kg⁻¹ bw day⁻¹.

5.4 The IPCS(1998) stated that “Although there may be substantial variations in toxicokinetics following exposure to 1,1,2,2-tetrachloroethane by different routes, available data are inadequate to quantitatively account for these differences in the derivation of guidance values.” The same value is therefore also to be used to derive a tolerable daily intake for exposure by the inhalation route, i.e. a TDIinh.

5.5 The IPCS has not considered 1,1,1,2-tetrachloroethane.

The WHO guidelines for air quality

5.6 The WHO Air Quality Guidelines (WHO, 2000) adopt the approach described in the CICAD (IPCS, 1998) and recommend a unit risk for 1,1,2,2-PCA of (0.6–3.0) × 10⁻⁶ (µg m⁻³)⁻¹ derived from the cancer potency values and guideline concentration range detailed in the CICAD and paragraph 5.2 above.
The recommendations of the USEPA

5.7 The USEPA has not recommended an oral reference dose (RfD)\(^1\) or inhalation reference concentration (RfC)\(^2\) for 1,1,2,2-PCA (USEPA, 1994). To protect against the potential carcinogenic risk of 1,1,2,2-PCA, the USEPA has derived unit risk factors, which are described below.

5.8 Using the results of the NCI mouse study (described in paragraphs 3.12 and 4.2) and application of the linearised multi-stage (LMS) model, the USEPA (1994) calculated an oral slope factor of 0.2 (mg kg\(^{-1}\) bw day\(^{-1}\))\(^{-1}\) (which is equivalent to a lifetime risk of 2.9 \times 10\(^{-6}\) for ingestion of 1 µg day\(^{-1}\) by a 70 kg adult), from which it derived a drinking-water unit risk of 5.8 \times 10\(^{-6}\) (µg L\(^{-1}\))\(^{-1}\) and an inhalation unit risk of 5.8 \times 10\(^{-5}\) (µg m\(^{-3}\))\(^{-1}\).

5.9 The USEPA (1996) has recommended an RfD for oral exposure to 1,1,1,2-PCA, based on the results of the NTP (1983) rat gavage studies described in paragraph 3.13. The RfD of 30 µg kg\(^{-1}\) bw day\(^{-1}\) was based upon a LOAEL of 89.3 mg kg\(^{-1}\) bw day\(^{-1}\) for kidney and liver effects. An uncertainty factor of 3000 was used, comprising factors of 10 each for extrapolating from a LOAEL to a NOAEL, and for inter- and intra-species variation, and an additional factor of 3 for lack of supporting reproductive and chronic toxicity studies. Low confidence was expressed for this derivation.

5.10 An RfC was not derived for 1,1,1,2-PCA, due to the lack of relevant data (USEPA, 1996).

5.11 Using the results of the 1983 NTP study (detailed in paragraphs 3.13 and 4.3), which demonstrated a dose-related increase in liver carcinomas and adenomas, and application of the LMS model, the USEPA (1996) calculated an oral slope factor of 0.026 (mg kg\(^{-1}\) bw day\(^{-1}\))\(^{-1}\) for 1,1,1,2-PCA. This corresponds to a drinking-water unit risk of 7.4 \times 10\(^{-7}\) (µg L\(^{-1}\))\(^{-1}\) (which is equivalent to a lifetime risk of 4.3 \times 10\(^{-7}\) for ingestion of 1 µg day\(^{-1}\) by a 70 kg adult), and an inhalation unit risk of 7.4 \times 10\(^{-6}\) for life-long inhalation of 1 µg m\(^{-3}\).

The recommendations of the ATSDR

5.12 The ATSDR (1996) has recommended an intermediate-duration (less than one year) minimal risk level (MRL) of 0.4 ppm (2.8 mg m\(^{-3}\)) for inhalation exposure to 1,1,2,2-PCA, based on the results of the single-dose level (unadjusted for exposure schedule), 15 week rat study by Truffert et al (1977) detailed in paragraph 3.9. An uncertainty factor of 300 was used, consisting of a factor of 10 each for inter- and

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

\(^2\) The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-carcinogenic effects during a lifetime.
intra-species variability, and a factor of 3 for use of a LOAEL as opposed to a NOAEL. This corresponds to a TDI$_{inh}$ of 0.8 mg kg$^{-1}$ bw day$^{-1}$ for a 70 kg adult breathing 20 m$^3$ of air per day. It should be noted that the ATSDR MRL is intended to be protective only against non-cancer risk.

5.13 Existing data were not considered suitable by the ATSDR for deriving an MRL for chronic (more than one year) inhalation exposure to 1,1,2,2-PCA.

5.14 A chronic-duration oral MRL for 1,1,2,2-PCA of 40 µg kg$^{-1}$ bw day$^{-1}$ was derived from the NCI (1978) study, using a LOAEL of 43 mg kg$^{-1}$ bw day$^{-1}$ for respiratory effects in female rats. An uncertainty factor of 1000 was used, consisting of a factor of 10 each for inter- and intra-species variability, and for the use of a LOAEL.

5.15 The toxicity of 1,1,1,2-PCA was not considered by the ATSDR.

Conclusions

5.16 The WHO recommendation is based upon a consideration of carcinogenicity due to its conclusion that the data for 1,1,2,2-PCA are inadequate to establish an adequate NOAEL or LOAEL for liver toxicity. A similar conclusion was reached by Luotamo and Riihimäki (1996) in their review of both isomers on behalf of the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group for Criteria Documentation of Health Risk from Chemicals (NEG). They recommended that any occupational exposure limits should be based on the carcinogenic effects of the compounds.

5.17 The toxicity of the two tetrachloroethane isomers has been inadequately studied, with most studies being old and of short duration (IPCS, 1998). As usage has been declining because of its acknowledged toxicity, there is little impetus to carry out further studies. The only long-term studies have been carcinogenicity studies, and the setting of a TDI based on the cancer data (and the assumption of a threshold) is therefore recommended.

5.18 As detailed in paragraph 5.3, IPCS suggested the application of an uncertainty factor of 1000 to the lower estimate of the dose associated with a 5% increase in tumours. As detailed in paragraph 5.3, this leads to the calculation of a TDI$^{oral}$ of 5.8 µg kg$^{-1}$ bw day$^{-1}$ for 1,1,2,2-PCA, which is the value recommended herein. This value should also be used for exposure by the inhalation route, that is, as the TDI$^{inh}$.

5.19 There is some evidence that 1,1,2,2-PCA may be more toxic than 1,1,1,2-PCA. The only direct experimental comparisons that have been made are short-term studies, which concluded that the symmetrical isomer (1,1,2,2-PCA) is the more toxic (paragraph 3.5). There is also some evidence that treatment with this isomer leads to more liver tumours in mice. It would seem prudent, however, to adopt the same TDI for 1,1,1,2-PCA as for 1,1,2,2-PCA, and this is recommended here.
6 Intake of tetrachloroethanes from food, water and air

6.1 Little information is available on environmental levels of tetrachloroethanes, and exposure of the general population is expected to be limited to contaminated water and atmospheric emissions.

6.2 Reviews by the ATSDR (1996) and the IPCS (1998) indicate that, in the majority of samples from surveys of air, water or food, tetrachloroethane was below the detection limit. Studies of 30 Canadian drinking-water treatment plants reported no levels of 1,1,2,2-PCA above the detection limit of 1 µg L⁻¹, nor has it been detected in three surveys of foodstuffs in Canada at detection limits of 1 µg L⁻¹ for liquids and 5–50 µg kg⁻¹ for solids.

6.3 Mean levels of 1,1,2,2-PCA in outdoor air in Canadian surveys were <0.1 to 0.25 µg m⁻³, and levels in residential indoor air in the USA and Canada have been reported to be less than 0.1 µg m⁻³ (IPCS, 1998). Using these values, the IPCS (1998) estimated the intake for the general population to be <0.006 to 0.01 µg kg⁻¹ bw day⁻¹ from outdoor air and <0.03 µg kg⁻¹ bw day⁻¹ from indoor air. For a 70 kg adult, this would represent a maximum intake of 2.1 µg day⁻¹. The IPCS noted that this is likely to be an overestimate, being based on mean values for detected concentrations, whereas 1,1,2,2-PCA was detected in only about 50% of samples.

6.4 Based on the values detailed above, the mean daily intake (MDI) for an adult is estimated to be less than 2 µg. For a six-year-old child, weighing 20 kg and inhaling 10 m³ of air per day (Defra and Environment Agency, 2002a), the MDI would be <1 µg, equivalent to less than 0.05 µg kg⁻¹ bw day⁻¹.
7 Other sources

7.1 Travis et al (1986) estimated the intakes of both isomers of tetrachloroethane resulting from the incineration of pesticide-related wastes. A risk assessment was carried out based upon the assumption of a 4400 kW rotary kiln incinerator located at three different sites in the USA. The maximum calculated intakes by inhalation for 1,1,1,2-PCA and 1,1,2,2-PCA were 0.6 and 0.2 $\mu$g yr$^{-1}$, respectively, for an adult. The maximum intakes by ingestion were 4 and 0.4 $\mu$g yr$^{-1}$, respectively. These estimates were based upon the composition of hazardous waste streams given by the USEPA in 1980, and a destruction and removal efficiency of 99.99%.
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 inhalation and oral MDI for a 70 kg adult is equivalent to 0.03 µg kg\(^{-1}\) bw day\(^{-1}\). Subtracting this value from the TDI\(_{oral/inh}\) of 5.8 µg kg\(^{-1}\) bw day\(^{-1}\) results in an adult TDSI of 5.8 µg kg\(^{-1}\) bw day\(^{-1}\) (rounded to 2SF). However, the TDSI for a child may be lower as a result of differences in dietary and inhalation intakes and body weight. For example, it is estimated that a 20 kg six-year-old child ingests 62% of the adult dietary intake and inhales 50% of the adult inhalation intake (Defra and Environment Agency, 2002a). Given that the MDI is based on inhalation only, the MDI for a 20 kg six-year-old child is equivalent to 0.05 µg kg\(^{-1}\) bw day\(^{-1}\). Subtracting this value from the TDI\(_{oral/inh}\) of 5.8 µg kg\(^{-1}\) bw day\(^{-1}\) results in a TDSI of 5.8 µg kg\(^{-1}\) bw day\(^{-1}\) (rounded to 2SF). The TDI and the MDI for 1,1,1,2-PCA and 1,1,2,2-PCA are given in Table 8.1; these figures apply to the oral and inhalation intakes from both isomers.

<table>
<thead>
<tr>
<th>TDI(_{oral/inh}) (µg kg(^{-1}) bw day(^{-1}))</th>
<th>Oral / Inhalation MDI (µg day(^{-1}))</th>
<th>Oral / Inhalation TDSI for an adult (µg kg(^{-1}) bw day(^{-1}))</th>
<th>Oral / Inhalation TDSI for a six-year-old child (µg kg(^{-1}) bw day(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8</td>
<td>2.0</td>
<td>5.8</td>
<td>5.8</td>
</tr>
</tbody>
</table>

8.3 No authoritative assessments of the health risks posed by dermal exposures to tetrachloroethanes were identified.
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