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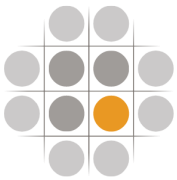

Category 4 Screening Levels: Tetrachloroethene (PCE)

CL:AIRE

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- C4SL Phase 2 Project Team – see page ii where the team members are listed.
- C4SL Phase 2 Steering Group – see page ii where the participants are listed.
- SAGTA secretary Doug Laidler for assistance in establishing the project and subsequent co-ordination.

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Foreword by Frank Evans, Chair of SAGTA

Looking back, the original Defra work from 2014 that developed the Category 4 Screening Levels (C4SL) was important in establishing the level at which risk from land contamination was considered to be acceptably low. It also provided a useful scientific framework for making this assessment of risk. I was also impressed by the delivery model used to create the Soil Generic Assessment Criteria in 2010 and in particular the strength that comes from the collective efforts of a group of experts and peers.

This report presents an output from a phase 2 project to develop a further set of C4SL. It is the result of a cross-industry collaboration brought together by seed funding from SAGTA, project management from CL:AIRE and a project team made up of a number of toxicologists and exposure modellers' who have given considerable time and expertise. This guidance document would not have been possible without everyone's collaborative working, determination, and enthusiasm. My deepest thanks go to them, and to the members of the Steering Group who have overseen the development of this guidance document.

I would also acknowledge the effort and commitment of Doug Laidler who was the long-standing secretary of SAGTA and who played an important role in initiating and coordinating the project. Sadly, Doug died in the autumn of 2019 and as with so many other matters in his life, was unable to see this work brought to conclusion. May he rest in peace.

Frank Evans
Chair of SAGTA

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Appendix B - Mean Daily Intake Data Sheet for Tetrachloroethene

ABBREVIATIONS

ADE	Average Daily Exposure
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
C4SL	Category Four Screening Level
CAS	Chemical Abstracts Service
CL:AIRE	Contaminated Land: Applications in Real Environments
CLEA	Contaminated Land Exposure Assessment
COC	Committee on Carcinogenicity
CSAF	Chemical Specific Adjustment Factor
Defra	Department of Food and Rural Affairs
DWI	Drinking Water Inspectorate
ELCR	Excess Lifetime Cancer Risk
HBGV	Health Based Guidance Value
HCV	Health Criteria Value
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LLTC	Low Levels of Toxicological Concern
$LLTC_{inhal}$	Low Levels of Toxicological Concern - Inhalation
$LLTC_{oral}$	Low Levels of Toxicological Concern - Oral
LOAEL	Lowest Observed Adverse Effect Level
MDI	Mean Daily Intake
MRL	Minimum Risk Level
NOAEL	No Observed Adverse Effect level
PBPK	Physiologically Based Pharmacokinetic
POD	Point of Departure
POS	Public Open Space
POS_{park}	Public Open Space - Park
POS_{resi}	Public Open Space – Residential
RBA	Relative Bioavailability
RfC	Reference Concentration
SoBRA	Society of Brownfield Risk Assessment
SOM	Soil Organic Matter
SR	Science Report
PCE	Tetrachloroethene
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

1. INTRODUCTION

This report presents Category 4 Screening Levels (C4SLs) for tetrachloroethene based on the methodology described in Section 5 of CL:AIRE (2014) "SP1010 – Development of Category 4 Screening Levels for Assessment of Land Affected by Contamination"[1]. Section 1.1 provides brief background information on tetrachloroethene, while Section 2 summarises the toxicological review from which Low Levels of Toxicological Concern (LLTCs) are identified. Section 3 presents the exposure modelling aspects for the generic land-uses under consideration, while Section 4 presents the C4SLs.

1.1 BACKGROUND TO TETRACHLOROETHENE

Tetrachloroethene (CAS No. 127-18-4), which is also commonly known as tetrachloroethylene, perchloroethylene, PCE or 'perc', has the chemical formula C_2Cl_4 and is present as a colourless and non-flammable liquid at room temperature, with a chloroform-like odour. It is a volatile compound (vapour pressure of approximately 1 kPa) and has a low solubility in water (225 mg L^{-1}) (Environment Agency, 2008). Once in the atmosphere, photochemically produced hydroxyl radicals degrade tetrachloroethene to phosgene and chloroacetyl chlorides (Defra and Environment Agency, 2004).

Although tetrachloroethene is produced naturally by several temperate and subtropical marine macroalgae, the majority is manufactured through oxyhydrochlorination, perchlorination and dehydrochlorination of hydrocarbons or chlorinated hydrocarbons (Defra and Environment Agency, 2004).

Tetrachloroethene is most commonly used as a dry-cleaning agent and a degreasing solvent. These uses result in large releases to the environment, particularly into the atmosphere in accordance with tetrachloroethene being a volatile compound (Defra and Environment Agency, 2004).

Tetrachloroethene can be broken down in the environment under a variety of conditions, most commonly by reductive dechlorination under anaerobic conditions which produces trichloroethene, dichloroethene, vinyl chloride and ethene as degradation daughter products. The presence of other contaminants (such as hydrocarbons) can increase biodegradation rates of tetrachloroethene in the environment. Breakdown of tetrachloroethene in surface soils where aerobic conditions prevail is expected to be slow, with most tetrachloroethene removed through evaporation to air (ATSDR, 2019).

[1] The reader is also referred to the Defra (2014) policy companion document for development of C4SLs.

2. DERIVATION OF LOW LEVEL OF TOXICOLOGICAL CONCERN FOR TETRACHLOROETHENE

A framework for evaluating chemical-specific toxicology data for the purposes of LLTC derivation is presented in the form of a flowchart in Figure 2.2 of SP1010 (CL:AIRE, 2014) and reproduced below as Figure 2.1. The remainder of this section demonstrates the application of this framework to tetrachloroethene. A proforma summarising the pertinent information referred to in this section is included as Appendix A.

As indicated in Figure 2.1, the first task is to perform a review of existing health based guidance values (HBGV) for all routes of exposure, collating information from authoritative bodies, as per the process in SR2 (Environment Agency, 2009a).

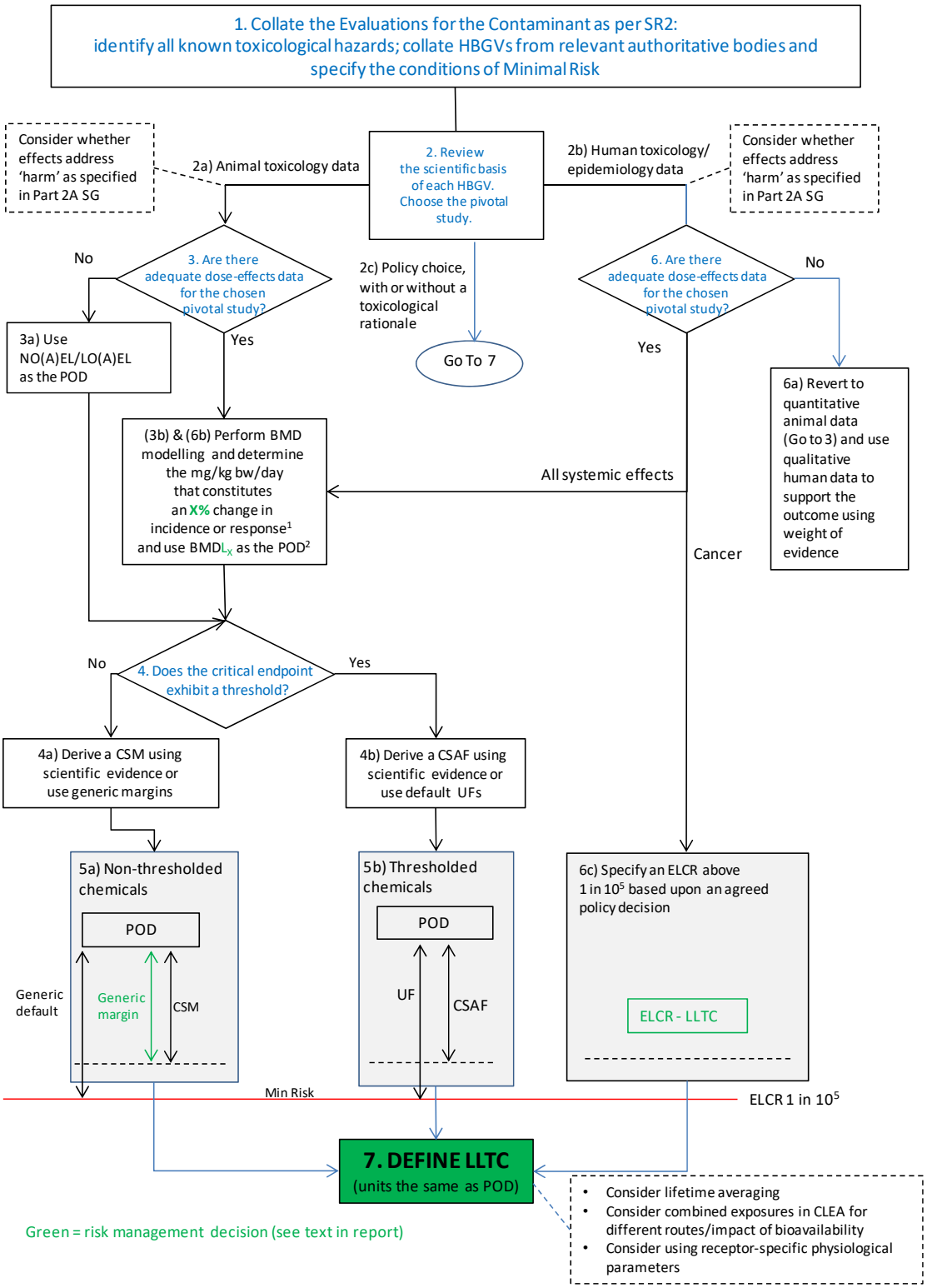

Figure 2.1: A framework for evaluating chemical-specific toxicology data for the purposes of LLTC derivation (reproduced from Figure 2.2 of SP1010 (CL:AIRE, 2014)).

2.1 ORAL ROUTE

2.1.1 FLOWCHART ELEMENT 1: Collate the evaluations for the contaminant as per SR2: identify all known toxicological hazards; collate HBGVs from relevant authoritative bodies and specify the conditions of minimal risk

A review of toxicological hazards and available HBGVs presented by authoritative bodies for the oral route of exposure has been undertaken and is provided in Appendix A. Many toxicological effects have been observed for tetrachloroethene, including a possibility for carcinogenic potential (COC, 1996 and IARC, 2014) although this has not been proven in humans through the oral route. Based on the available authoritative reviews, liver and kidney effects are the most sensitive[2] toxicological effects following exposure to tetrachloroethene by the oral route. Systemic neurotoxicological effects have been observed in humans following inhalation exposure and may also be a relevant sensitive effect for humans via the oral route.

2.1.2 FLOWCHART ELEMENT 2: Review the scientific basis of each HBGV. Choose the pivotal study

Three possible options are provided for the type of pivotal study that could be chosen at this point, *i.e.* in the form of: 1) animal toxicology data; 2) human toxicology/epidemiology data; and 3) a policy choice (*i.e.* based on an existing guideline from another regime, with or without a toxicological rationale). For tetrachloroethene, there were two animal toxicology studies (Hayes *et al*., 1986 and Buben and O'Flaherty, 1985) which provided adequate data on liver and kidney effects to form the basis of an LLTC derivation for the oral route of exposure.

2a) Animal Toxicology Data

The most sensitive and relevant toxic endpoints seen in the available animal studies are liver and kidney effects, although it should be recognised that tetrachloroethene is also a rodent carcinogen (IARC, 2014).

Studies by Hayes *et al.* (1986) and Buben and O'Flaherty (1985) were used as the basis for the WHO guidelines for drinking-water quality (WHO, 2003).

In Hayes *et al.* (1986) groups of Sprague-Dawley rats (20 per sex per dose) were administered tetrachloroethene via drinking water at doses of 14, 400, or 1400 mg kg^{-1} of body weight per day (mg kg^{-1} bw day^{-1}) for 90 days. The study authors reported depressed body weights in males in the high dose group and females in the mid- and high-dose groups. Increased liver- and kidney-to-body-weight ratios (equivocal evidence of hepatotoxicity) were also reported at the two highest doses.

In Buben and O'Flaherty (1985) groups of male Swiss-Cox mice were administered tetrachloroethene in corn oil via gavage at doses of 0, 20, 100, 1000, or 2000 mg kg^{-1} bw, 5 days per week for 6 weeks (equivalent to doses of 0, 14, 70, 700 and 1400 mg kg^{-1} bw day^{-1} for continuous exposure). The study authors reported significantly increased liver triglyceride levels and liver-to-body-weight ratios at doses as low as 70 mg kg^{-1} bw day^{-1}. Hepatotoxicity was observed at higher doses, including decreased deoxyribonucleic acid content, increased serum alanine aminotransferase, decreased glucose-6-phosphatase serum levels, and hepatocellular necrosis, degeneration and polyploidy.

The no observed adverse effect level (NOAEL) from both studies for hepatotoxic effects was 14 mg kg^{-1} bw day^{-1}.

GO TO FLOWCHART ELEMENT 3

[2] In defining minimal/tolerable risk, it is only necessary to focus on the most sensitive of all effects in defining the HBGV. In order to choose a point on the dose-response curve that is higher than minimal/tolerable risk, it is important to note that the dose-responses for the most sensitive effects may overlap with other effects. Therefore, in setting the LLTC, ALL endpoints must be borne in mind. This is an important principle in any of the toxicological evaluations where there are overlapping toxicological effects, and is an important departure from the principles of evaluation of minimal risk described in SR2.

2b) Human Toxicology/Epidemiology Data

Although there are human epidemiological studies investigating the adverse neurotoxicological effects of tetrachloroethene (Cavalleri *et al.*, 1994; Gobba *et al.*, 1998; Echeverria *et al.*, 1995), all data in humans is for the inhalation route of exposure, as discussed in Section 2.2.

In using inhalation data here, it necessitates that some type of physiologically based pharmacokinetic (PBPK) model is used to extrapolate human inhalation data to the oral route. Such modelling was undertaken by the Agency for Toxic Substances and Disease Registry (ATSDR, 2019), World Health Organization (WHO, 2006), United States Environmental Protection Agency (US EPA, 2012) and Health Canada (2015) in the derivation of their authoritative guideline values for the oral route of exposure.

Due to the uncertainties arising from the lack of an authoritative UK review of the PBPK modelling and its underpinning parameterisation it has not been involved in deriving metrics for this report.

GO TO FLOWCHART ELEMENT 6

2c) Policy choice, with or without a toxicological rationale

The UK drinking water standard for the sum of trichloroethene and tetrachloroethene is 10 µg L^{-1}. Assuming that the concentration of trichloroethene is zero, the maximum permitted concentration of tetrachloroethene in drinking water would be 10 µg L^{-1}, equivalent to an intake of 0.286 µg kg^{-1} bw day^{-1} for a 70 kg adult drinking 2 L of water per day. This is lower than the $LLTC_{oral}$ derived from toxicological data (see Section 2.1.9) and therefore does not affect the final choice of $LLTC_{oral}$.

GO TO FLOWCHART ELEMENT 7

2.1.3 FLOWCHART ELEMENT 3/6: Are there adequate dose-effects data for the chosen pivotal study to perform BMD modelling – animal data?

Yes	No	Not applicable
	X	

The data from the Hayes *et al.* (1986) study on rats and Buben and O'Flaherty (1985) study on mice have been considered as the pivotal studies from which to derive an $LLTC_{oral}$. These data were used in deriving the WHO guidelines for drinking-water quality (WHO, 2003).

It is considered a pragmatic and protective approach here to use the NOAEL, as other worldwide authorities have done. There are three dosing concentrations in the Hayes *et al.* (1986) study, with a clear NOAEL for the target organ (kidney and liver) effects observed. The raw study data is not available to perform benchmark dose (BMD) modelling.

GO TO FLOWCHART ELEMENT 3a/b or 6a/b/c

[Flowchart element 6a: Revert to quantitative animal data (3) and use human data to support the outcome using weight of evidence]

The oral LLTC is based on a NOAEL from an animal study via the oral route but is intended to be sufficiently protective of all endpoints, including cancer.

2.1.4 FLOWCHART ELEMENT 3a: Use NOAEL/LOAEL as PoD

It is considered appropriate to take the NOAEL of 14 mg kg^{-1} bw day^{-1} from the 90-day study reported by Hayes *et al.* (1986) as the point of departure (POD). This NOAEL is also equal to the NOAEL from the 6-week study by Buben and O'Flaherty (1985).

2.1.5 FLOWCHART ELEMENT 3b/6b: Perform BMD modelling

Not applicable to the derivation of an oral LLTC for tetrachloroethene.

GO TO FLOWCHART ELEMENT 4a/b

2.1.6 FLOWCHART ELEMENT 4: Does the critical endpoint exhibit a threshold?

Yes	No	Not applicable
X		

2.1.7 FLOWCHART ELEMENT 4a: Define a suitable chemical-specific margin

Not applicable.

GO TO FLOWCHART ELEMENT 5a

2.1.8 FLOWCHART ELEMENT 4b: Derive a chemical-specific assessment factor using scientific evidence

WHO applied an uncertainty factor (UF) of 1000 in the derivation of the drinking water quality guideline value for tetrachloroethene. This accounted for extrapolation from animals to humans (10), human variability (10) and carcinogenic potential (10) (WHO, 2003).

The previous toxicological report (Defra and Environment Agency, 2004) used the same study, same POD and the same UF for tetrachloroethene. The previous toxicological report commented that "an additional uncertainty factor to reflect the short duration of the key studies was considered unnecessary in view of the database [on tetrachloroethene] and considerations regarding the application of the dose via drinking-water in one of the two critical studies".

In the derivation of an LLTC, the same chemical specific adjustment factor (CSAF) of 1000 has been applied (100 for intra- and interspecies variation and 10 for the uncertainties regarding carcinogenic potential by the oral route and also to address potential gaps in the database on neurotoxicity).

GO TO FLOWCHART ELEMENT 5b

2.1.9 FLOWCHART ELEMENT 5a/b: Calculate the LLTC for non-thresholded / thresholded chemicals

For thresholded effects, the POD is divided by a default UF or CSAF:

POD/default UF or CSAF = LLTC (units as per POD)

Therefore, for this evaluation:

POD = 14 mg kg^{-1} bw day^{-1} = 14000 µg kg^{-1} bw day^{-1}

LLTC = POD/UF = 14000 / 1000 = 14 µg kg^{-1} bw day^{-1}

GO TO FLOWCHART ELEMENT 7

2.1.10 FLOWCHART ELEMENT 7: Assess $LLTC_{oral}$ for tetrachloroethene

Based upon a scientific evaluation of liver and kidney effects in rats and mice, an oral LLTC of **14 µg kg^{-1} bw day^{-1}** is proposed, based on a NOAEL of 14 mg kg^{-1} bw day^{-1} as the POD and a UF of 1000. In this instance it has not been possible to derive a value based on low level risk (as per C4SL framework) using the available toxicological data for oral exposure to tetrachloroethene. The proposed value is the same as the health criteria value (HCV) recommended by Defra and Environment Agency (2004) which was based on the same studies and assumptions. The proposed value is higher than the HBGVs derived more recently by US EPA (2012), ATSDR (2019), and Health Canada (2015), based on route-to-route extrapolation and PBPK modelling.

This LLTC is based on systemic toxicological effects.

2.2 INHALATION ROUTE

2.2.1 FLOWCHART ELEMENT 1: Collate the evaluations for the contaminant as per SR2: identify all known toxicological hazards; collate HBGVS from relevant authoritative bodies and specify the conditions of minimal risk

A review of toxicological hazards and available HBGVs presented by authoritative bodies for the inhalation route of exposure has been undertaken and is provided in Appendix A. This review indicates that neurotoxicity and kidney effects are the most sensitive[3] toxicological effects following exposure to tetrachloroethene by the inhalation route. There is limited evidence of human carcinogenicity via the inhalation route (IARC, 2014), and in agreement with authoritative bodies to date, the most sensitive effect by the inhalation route, neurotoxicity, has been selected as the pivotal proven effect.

2.2.2 FLOWCHART ELEMENT 2: Review the scientific basis of each HBGV. Choose the pivotal study

Three possible options are provided for the type of pivotal study that could be chosen at this point, *i.e.* in the form of: 1) animal toxicology data; 2) human toxicology/epidemiology data; and 3) a policy choice (*i.e.* based on an existing guideline from another regime, with or without a toxicological rationale).

2a) Animal Toxicology Data

A range of animal toxicology studies are available investigating the adverse effects of tetrachloroethene via the inhalation route, as reviewed by ATSDR (2019), WHO (2006), WHO (2010), US EPA (2012) and IARC (2014).

Tetrachloroethene and several of its metabolites have been evaluated for genotoxic potential (US EPA, 2012; IARC, 2014). Tetrachloroethene has been confirmed as a multi-site thresholded carcinogen in rodent studies (with brain, testicular, liver and kidney cancers, mononuclear cell leukaemia, and hemangiosarcomas reported) (US EPA, 2012). Several metabolites of tetrachloroethene are carcinogenic in mice, and it is thought that the hepatocarcinogenicity of the parent compound is mediated through the action of one or more of its metabolites. Many complex mechanisms have been postulated but none confirmed, and the relevance of rodent data to humans, given no evidence of genotoxicity/ carcinogenicity in humans, remains uncertain.

[3] In defining minimal/tolerable risk, it is only necessary to focus on the most sensitive of all effects in defining the HBGV. In order to choose a point on the dose-response curve that is higher than minimal/tolerable risk, it is important to note that the dose-responses for the most sensitive effects may overlap with other effects. Therefore, in setting the LLTC, ALL endpoints must be borne in mind. This is an important principle in any of the toxicological evaluations where there are overlapping toxicological effects data, and is an important departure from the principles of how SR2 and minimal risk evaluations are implemented more simply.

US EPA (2012) reviewed a range of endpoints, including two year cancer studies on mice and rats exposed to tetrachloroethene by inhalation from National Toxicology Program (1986) and Japan Industrial Safety Association (1993). Complex BMD modelling incorporating PBPK modelling were used in the EPA evaluation across a range of tumour types in rodents. The BMD modelling did not use specific metabolites, but rather the total liver oxidative metabolism of tetrachloroethene to best fit the dose-response curves. A range of candidate unit cancer risk values for a range of tumours seen in animals is provided in Table 5-19 of the US EPA IRIS Review (US EPA, 2012).

It is noted that other bodies such as WHO (2010) noted that "there is some uncertainty about the epidemiological evidence as well as the relevance of the animal carcinogenicity data to humans".

GO TO FLOWCHART ELEMENT 3.

2b) Human Toxicology/Epidemiology Data

Based on all the data available (including the animal data), the Cavalleri *et al.* (1994) study has been selected as the pivotal study for neurological effects as it is the most sensitive epidemiological study performed to date that is relevant to use in the general population context. Note that the LLTC derived from this study is intended to be sufficiently protective of all endpoints, including cancer.

The Cavalleri *et al.* (1994) study comprised an occupational inhalation exposure study of 35 tetrachloroethene-exposed workers (22 dry-cleaners and 13 ironers) matched with non-exposed workers which observed impairments in colour vision (acquired dyschromatopsia). It was supported by evidence from re-examination after two years in a follow up study by Gobba *et al.* (1998). No significant difference in colour vision was found in the ironers exposed to an estimated mean concentration of 4.8 parts per million (ppm). A significant decrease in colour vision did occur for the dry cleaners exposed to an estimated mean concentration of 7.3 ppm with an average of 106 months (8.8 years) exposure.

The Cavalleri *et al.* (1994) study was selected by ATSDR (2019) as covering the most sensitive effect of neurotoxicity and was supported by evidence from the follow up study after two years by Gobba *et al.* (1998). ATSDR selected the mean exposure concentration for dry-cleaners of 7.3 ppm as the lowest observed adverse effect level (LOAEL) and adjusted this to a continuous exposure LOAEL of 1.7 ppm (equivalent to 11.5 $mg.m^{-3}$, or 3.29 $mg\ kg^{-1}$ bw day^{-1} assuming a 70 kg adult breathes 20 $m^3.day^{-1}$) by multiplying by 8 hrs/24 hrs x 5 days/7 days. This POD is considered the most reliable for the inhalation HBGV, based upon clear data from an epidemiology study with appropriate application of UFs.

Note that the US EPA (2012) arrived at a slightly different POD from the same study as they used the average exposure concentration for all workers (ironers and dry-cleaners combined) of 6.2 ppm (despite ironers not showing a significant decrease in colour vision) and multiplied by a different conversion factor (5 days/7 days x 10 m^3/20 m^3) to derive a continuous exposure LOAEL of 2 ppm (15 mg m^{-3}).

GO TO FLOWCHART ELEMENT 6

2c) Policy choice, with or without a toxicological rationale

Not applicable to the derivation of an inhalation LLTC for tetrachloroethene.

GO TO FLOWCHART ELEMENT 7

2.2.3 FLOWCHART ELEMENT 3/6: Are there adequate dose-effects data for the chosen pivotal study to perform BMD modelling - animal data?

Yes	No	Not applicable
	X	

The data from the Cavalleri *et al.* (1994) human epidemiological study will be considered as the pivotal study from which to derive an $LLTC_{inhal}$. These data were used in deriving the ATSDR chronic-duration inhalation Minimal Risk Level (MRL) (ATSDR, 2019) and the US EPA reference concentration (RfC) (US EPA, 2012). The Cavalleri data are not suitable for BMD modelling.

GO TO FLOWCHART ELEMENT 3a/b or 6a/b/c

2.2.4 FLOWCHART ELEMENT 3a: Use NOAEL/LOAEL as POD

The LOAEL of 11.5 mg m^{-3} from the Cavalleri *et al.* (1994) occupational study as used by ATSDR (2019) has been selected as the POD. This can be converted to an equivalent dose of 3.29 mg kg^{-1} bw day^{-1} assuming a 70 kg adult breathes 20 m^3 day^{-1}.

2.2.5 FLOWCHART ELEMENT 3b: Perform BMD modelling

There are no adequate quantitative data available for BMD modelling from the Cavalleri *et al.* (1994) study, hence a LOAEL will be used as the POD.

GO TO FLOWCHART ELEMENT 4a/b

2.2.6 FLOWCHART ELEMENT 4: Does the critical endpoint exhibit a threshold?

Yes	No	Not applicable
X		

The endpoint has an apparent threshold in that the Cavalleri study indicated that a smaller number of workers exposed to a lower concentration of 4.8 ppm (equivalent to 32.6 mg m^{-3}) were unaffected.

2.2.7 FLOWCHART ELEMENT 4a: Define a suitable chemical-specific margin

Not applicable.

GO TO FLOWCHART ELEMENT 5a

2.2.8 FLOWCHART ELEMENT 4b: Derive a chemical-specific assessment factor using scientific evidence

ATSDR applied a UF of 300 in the derivation of the minimal risk HBGV for chronic inhalation exposure for the endpoint of impairment of colour vision (acquired dyschromatopsia) in an occupational inhalation exposure study. This accounted for human variability (10), extrapolation from a LOAEL (10) and database deficiencies (3) for inadequate information on low-dose immune system effects (ATSDR, 2019). It is noted that the US EPA (2012) applied a UF of 10 for database deficiencies (on neurological, developmental, and immunological effects) in deriving their RfC. However, the US EPA used a higher POD (the mid-point LOAEL between two studies (Cavalleri *et al*., 1994 and Echeverria *et al*., 1995) and their resultant RfC was the same as the ATSDR MRL.

In the derivation of an LLTC, the ATSDR UF of 300 has been applied (10 for human variability, 10 for extrapolation from a LOAEL and 3 for database deficiencies for

inadequate information on low-dose immune system effects) on account of the ATSDR review (2019) being more recent than the US EPA review (2012).

GO TO FLOWCHART ELEMENT 5b

2.2.9 FLOWCHART ELEMENT 5a/b: Calculate the LLTC for non-thresholded / thresholded chemicals

For thresholded chemicals, the POD is divided by a default UF or CSAF:

POD/default UF or CSAF = LLTC (units as per POD)

Therefore, for this evaluation:

POD/300 = LLTC

POD = 3.29 mg kg^{-1} bw day^{-1} = 3290 µg kg^{-1} bw day^{-1}

LLTC = POD/UF = 3290 / 300 = 11.0 µg kg^{-1} bw day^{-1}

GO TO FLOWCHART ELEMENT 7

2.2.10 FLOWCHART ELEMENT 7: Assess $LLTC_{inh}$ for tetrachloroethene

Based upon a scientific evaluation of neurotoxicity in humans following occupational exposure to tetrachloroethene (Cavalleri *et al*., 1994), an inhalation LLTC of **11.0 µg kg^{-1} bw day^{-1}** is proposed. This value is the same as the ATSDR (2019) MRL and US EPA (2012) RfC, both of which can be considered as tolerable risk levels (i.e. equivalent to HCVs). It has not been possible, in this instance, to derive a value based on low level risk (as per C4SL framework) using the available toxicological data for oral exposure to tetrachloroethene. This LLTC is considered to be a pragmatic level for setting a C4SL and is suitably protective of all health effects.

This LLTC is based on systemic toxicological effects.

2.3 DERMAL ROUTE

ATSDR (2019) could not locate any intermediate-duration or chronic-duration animal or human dermal exposure studies. They also reported that “the limited dermal exposure studies of tetrachloroethene in animals indicate that the compound can be absorbed following direct application, but the studies have clearly not identified any effects”.

In the absence of dermal toxicity data and in accordance with SR2 (Environment Agency, 2009a), dermal exposure will be compared against the oral LLTC for the purposes of the derivation of the C4SL for tetrachloroethene.

2.4 MEAN DAILY INTAKE

Both the oral and inhalation LLTCs recommended for tetrachloroethene are based on threshold effects. As such, in accordance with the C4SL SP1010 framework (CL:AIRE, 2014) and SR2 (Environment Agency, 2009a), the Mean Daily Intake (MDI) from non-soil sources is to be included in the exposure modelling for comparison with the oral and inhalation LLTCs.

Available oral and inhalation MDI data have been collated and reviewed and used to derive estimated adult MDIs for the oral and inhalation pathways (see Appendix B). The adult MDIs used to derive the C4SLs for tetrachloroethene are shown in Table 2.1 below.

The oral MDI is based upon the mean of the 99th percentile concentrations[4] of the sum of tetrachloroethene and trichloroethene measured in tap water reported by the Drinking Water Inspectorate for water companies in England and Wales for the year 2016 (DWI, 2017) which is 0.77 µg L^{-1}. This is converted to an adult oral MDI of 1.54 µg day^{-1} by multiplying by an assumed adult water consumption rate of 2 L day^{-1}. Exposure to tetrachloroethene via food is assumed to be negligible (Defra and Environment Agency, 2004).

Tetrachloroethene is not monitored by the Defra UK AIR Network. WHO (2000) concludes that concentrations of tetrachloroethene in urban ambient air are generally <5 µg m^{-3}. More recent data from WHO (2006 and 2010), IARC (2014), and Health Canada (2015) all support this, with reported ranges in these reviews largely <1 µg m^{-3}. ATSDR (2019) summarises results from comprehensive ambient air monitoring across the USA from 2010 to 2018. The 95th percentile concentrations for each of these years were <1 µg m^{-3}, with a maximum concentration of 4 µg m^{-3} recorded. These reviews also suggest that indoor air concentrations are in the same range as urban outdoor air concentrations. Therefore a value of 1 µg m^{-3} is considered suitably protective for the combined indoor and outdoor MDI. This is converted to an adult inhalation MDI of 20 µg day^{-1} by multiplying by an assumed adult respiration rate of 20 m^3 day^{-1}.

Table 2.1: Adult mean daily intake values for input to CLEA

Adult Mean Daily Intake	Value (µg day^{-1})
Oral MDI	1.54
Inhalation MDI	20

[4] Note that mean concentrations are not provided in DWI (2017). The mean of the reported 99th percentile concentrations is likely to be highly conservative estimate of MDI

3. EXPOSURE MODELLING FOR TETRACHLOROETHENE

As described in the C4SL SP1010 report (CL:AIRE, 2014), the CLEA model has been used deterministically with the above LLTCs to derive C4SLs for the following six land-uses for a sandy loam soil type:

- Residential with consumption of homegrown produce;
- Residential without consumption of homegrown produce;
- Allotments;
- Commercial;
- Public open space (POS):
    - The scenario of open space close to housing that includes tracking back of soil (POS_{resi}); and
    - A park-type scenario where the park is considered to be at a sufficient distance from the home that there is negligible tracking back of soil (POS_{park}).

3.1 CLEA PARAMETER INPUTS

CLEA derives an estimate of average daily exposure (ADE) for each exposure pathway. ADEs are then summed for some or all exposure pathways for comparison with the LLTC. The pathways considered in the summation are dependent on the critical toxicological effects that the LLTC is based on. CLEA uses iteration to find the soil concentrations at which the summed ADEs equal the respective LLTC values and these are termed 'assessment criteria'. As described in the CLEA SR2 and SR3 documents (Environment Agency, 2009a and 2009b), the assessment criteria are normally integrated by CLEA to determine an overall assessment criteria where the critical toxicological effects via both routes of exposure are systemic. Where the critical toxicological effect is localised for either the oral or inhalation routes of exposure, the assessment criteria are not integrated and the lowest of the two criteria is chosen as the overall assessment criteria.

In the case of tetrachloroethene, the $LLTC_{inhal}$ is based on scientific evaluation of an occupational exposure study of impairments of colour vision in 539 exposed workers in dry cleaners and ironers (Cavalleri *et al*., 1994). This is a threshold effect. The $LLTC_{oral}$ is based upon a scientific evaluation of liver and kidney toxicity observed in animal studies (rats and mice) administered via drinking water (Buben and O'Flaherty, 1985; Hayes *et al.,* 1986), which is a threshold effect. Both LLTC are based on thresholded systemic effects and therefore combined C4SL have been calculated combining the oral and inhalation pathways.

CLEA requires a number of contaminant and non-contaminant specific parameter values for modelling exposure. The description of these parameters is provided within the C4SL SP1010 report (CL:AIRE, 2014) and the SR3 report (Environment Agency, 2009b). Contaminant specific parameter values used for tetrachloroethene are shown in Table 3.1.

Table 3.1: Contaminant specific parameter values used for derivation of C4SLs for tetrachloroethene.

Parameter	Units	Value	Source/Justification
Air-water partition coefficient	dimensionless	3.16 x10^{-1}	CLEA SR7, Environment Agency, 2008
Diffusion coefficient in air	m^2 s^{-1}	7.10 x10^{-6}	CLEA SR7, Environment Agency, 2008
Diffusion coefficient in water	m^2 s^{-1}	5.61 x10^{-10}	CLEA SR7, Environment Agency, 2008
Relative molecular mass	g mol^{-1}	165.83	CLEA SR7, Environment Agency, 2008
Vapour pressure	Pa	1.01 x10^{3}	CLEA SR7, Environment Agency, 2008
Water solubility	mg L^{-1}	225	CLEA SR7, Environment Agency, 2008
Log Koc	Log cm^3 g^{-1}	2.43	CLEA SR7, Environment Agency, 2008
Log Kow	dimensionless	2.88	CLEA SR7, Environment Agency, 2008
Dermal absorption fraction	dimensionless	1 x10^{-1}	CLEA SR3, Environment Agency, 2009a
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	modelled	Environment Agency, 2009a (Note that CLEA does not model soil-to-plant concentration factors for organic substances for herbaceous or shrub fruit)
Soil-to-plant concentration factor (root vegetables)		modelled	
Soil-to-plant concentration factor (tuber vegetables)		modelled	
Soil-to-plant concentration factor (herbaceous fruit)		-	
Soil-to-plant concentration factor (shrub fruit)		-	
Soil-to-plant concentration factor (tree fruit)		Modelled	
Soil-to-dust transport factor	g g^{-1} DW	0.5	Default value from CLEA SR3, Environment Agency, 2009d
Sub-surface soil to indoor air correction factor	-	1	Environment Agency, 2009a
Relative bioavailability soil	-	1	Conservative assumption made that bioavailability of tetrachloroethene in soil and dust is the same as bioavailability of tetrachloroethene in critical toxicological studies used to derive the LLTC
Relative bioavailability dust	-	1	

The key contaminant specific parameter values used for derivation of the C4SLs for tetrachloroethene are discussed briefly below.

Soil to dust transport factor

The soil to dust transport factor should be ideally contaminant specific but where contaminant specific data are not available the Environment Agency (2009b) recommends a default value of 0.5 g g^{-1} DW, meaning that the concentration of contaminant in respirable dust is assumed to be 50% of the concentration of contaminant in outdoor soil. This default value has been assumed for tetrachloroethene.

Soil to plant concentration factors

No reliable information was found in the literature to support the use of contaminant specific plant uptake factors. Consequently, plant uptake for tetrachloroethene has been modelled using the method for organic chemicals within the CLEA software.

CLEA predicts the greatest exposure to tetrachloroethene from consumption of homegrown produce to be via green vegetables and root vegetables for both the residential and allotments scenarios. Therefore, in accordance with the "top two" approach, 90th percentile consumption rates have been used for these two produce types and mean consumption rates have been used for the remaining produce types.

Relative bioavailability

There are few data available on the relative bioavailability (RBA) of tetrachloroethene and it is considered appropriately conservative to assume an RBA of 100% for the derivation of C4SLs.

4. C4SLs FOR TETRACHLOROETHENE

4.1 C4SLS

The C4SLs for tetrachloroethene derived using a Soil Organic Matter (SOM) content of 1%, 2.5% and 6% are presented in Table 4.1 below.

Table 4.1: C4SLs for tetrachloroethene

Land-use	C4SLs (mg.kg^{-1})		
	SOM Content		
	1.0%	2.5%	6.0%
Residential with consumption of homegrown produce	0.31	0.70	1.6
Residential without consumption of homegrown produce	0.32	0.71	1.6
Allotments	2.0	4.8	11
Commercial	24	55	130
Public Open Space (residential)	3,200	3,300	3,400
Public Open Space (park)	1,400	1,900	2,500

N.B. These C4SLs are based on chronic risk only. For further discussion of acute risks and other factors that should be considered when using these C4SL see section 4.2 below.

The ADE:HCV[5] ratio at the C4SL (6% SOM) for both oral / dermal route and the inhalation routes of entry are shown in Table 4.2. The relative contribution of each exposure pathway contributing to the C4SL (6% SOM) is shown for each land-use in Table 4.3.

Table 4.2: ADE:HCV ratios at C4SLs derived at 6% SOM

Land-use	ADE:HCV Ratio Oral and dermal routes of entry	ADE:HCV Ratio inhalation route of entry
Residential with consumption of homegrown produce	0.02	0.98
Residential without consumption of homegrown produce	0.00	1.00
Allotments	1.00	0.00
Commercial	0.00	1.00
Public Open Space (residential)	0.96	0.04
Public Open Space (park)	0.35	0.65

[5] "ADE:HCV ratio" is the term used within the CLEA model, referring to the ratio between the average daily exposure and the health criteria value. Although an LLTC is used in place of the HCV the terminology has been retained, reflecting the CLEA output.

Table 4.3: Relative contributions of exposure pathways to overall exposure at 6% SOM

Exposure pathway	Relative contribution to total exposure (%)					
	Residential		Allotments	Commercial	POS_{resi}	POS_{park}
	With home grown produce	Without home grown produce				
Direct soil & dust ingestion	0.11	0.11	0.16	0.51	87.68	35.23
Sum of consumption of homegrown produce and attached soil	2.69	0.00	98.79	0.00	0.00	0.00
Dermal contact (indoor)	0.00	0.00	0.00	0.03	2.66	0.00
Dermal contact (outdoor)	0.00	0.00	0.08	0.05	3.11	3.48
Inhalation of dust (indoor)	0.00	0.00	0.00	0.00	0.31	0.00
Inhalation of dust (outdoor)	0.00	0.00	0.00	0.00	0.00	0.01
Inhalation of vapour (indoor)	85.58	88.76	0.00	96.55	0.00	0.00
Inhalation of vapour (outdoor)	0.00	0.00	0.18	0.06	2.77	50.90
Oral background	0.78	0.12	0.62	0.20	0.39	0.69
Inhalation background	10.84	11.00	0.18	2.59	3.08	9.68

Based on the information in Tables 4.2 and 4.3, the principal risk driving pathways for tetrachloroethene are expected to be:

- Consumption of homegrown produce for allotments;
- Indoor inhalation of vapours for residential with homegrown produce, residential without homegrown produce and commercial land uses;
- Ingestion of soil and soil derived dust for the POS_{resi} and POS_{park} land-uses; and,
- Outdoor inhalation of vapours for POS_{park} land-use.

4.2 OTHER CONSIDERATIONS

Other considerations that are relevant when setting the C4SLs for tetrachloroethene include the following:

- Intake of tetrachloroethene from non-soil sources (food, water and air) has been considered as follows:
  - According to the 2004 CLEA TOX report for tetrachloroethene (Defra and Environment Agency, 2004), concentrations in food remote from dry-cleaning establishments were negligible based on a 1997 study. It is noted that tetrachloroethene has the potential to accumulate in foods near dry-cleaning establishments and in contaminated soils (ATSDR, 2019).
  - The UK Drinking Water Inspectorate reports 99th percentile concentrations of the sum of trichloroethene and tetrachloroethene measured in tap water for all thirty water companies in England and Wales. The average of the reported 99th percentile concentrations for

2016 was 0.77 µg.L^{-1}. Assuming this is all tetrachloroethene and a 70 kg adult drinks 2 L of water per day, this equates to a daily tetrachloroethene intake of 0.022 µg kg^{-1} bw day^{-1}, which is 0.157% of the oral LLTC. Given that this background exposure is based on 99th percentile concentrations, background oral exposure is likely to be typically much less.

  - Tetrachloroethene is not monitored by the Defra UK AIR Network. Reviews undertaken by WHO (2006 and 2010), IARC (2014), Health Canada (2015) and ATSDR (2019) indicate that ambient air concentrations are typically <1 µg m^{-3}. The adult MDI is conservatively based on the assumption that the average ambient air concentration is 1 µg m^{-3}. For a 70 kg adult breathing 20 m^3 of air per day this equates to an average daily tetrachloroethene intake of 0.286 µg kg^{-1} bw day^{-1} which is approximately 2.6% of the inhalation LLTC.

- C4SLs have been derived on the basis of chronic exposure and risks to human health, and do not explicitly account for acute risks (e.g. due to one-off ingestion of a significant amount of soil by a young child). It is noted here that the C4SLs derived for POS_{resi} and POS_{park} are significantly higher than values for the residential land use where inhalation exposure (to indoor vapour) is the most important exposure pathway in deriving the C4SL. Therefore, further consideration of the possibility of acute risk due to ingestion of soil at the tetrachloroethene concentrations indicated by the POS_{resi} and POS_{park} C4SLs may be necessary. The reader is referred to the Society of Brownfield Risk Assessment (SoBRA) "Development of Acute Generic Assessment Criteria for Assessing Risks to Human Health from Contaminants in Soil" (SoBRA, 2019) for further guidance on this.
- It should also be noted that the C4SLs for POS land-uses exceed the CLEA calculated soil saturation concentrations of tetrachloroethene which are 424 mg kg^{-1} for 1% SOM, 951 mg kg^{-1} for 2.5% SOM and 2,180 mg kg^{-1} for 6% SOM. The soil saturation concentration is the theoretical concentration in soil above which free phase contamination may be present. The assessor should be aware that the C4SLs may not be sufficiently precautionary where free phase is present and as such, where free phase is suspected, should consider the risks from this (such as direct contact and vapour inhalation) separately.
- The British Geological Survey has not derived normal background concentrations for tetrachloroethene (Defra, 2012). Although it occurs naturally, produced by temperate and subtropical marine macroalgae, tetrachloroethene is not expected to occur above typical laboratory limits of detection in soil away from an anthropogenic source and background soil concentrations are therefore expected to be negligible.
- Table 4.3 above shows that within the residential and commercial exposure scenarios (where inhalation of vapour in indoor air pathways are operational) exposure to tetrachloroethene is primarily driven by, and is especially sensitive to, the vapour inhalation in indoor air pathway. In applying the C4SL the risk assessor should consider that generic modelling of this pathway is based on general assumptions and published data regarding vapour partitioning of tetrachloroethene and subsequent transport. Where exposure to soil vapour forms the critical pathway then a soil vapour assessment is recommended. The reader is referred to CIRIA (2009) and SoBRA (2018) for further guidance on this.
- The lowest derived C4SL in Table 4.1 of 0.31 mg kg^{-1} (310 µg kg^{-1}), which is for the residential with consumption of homegrown produce land-use, is above typical laboratory limits of detection for tetrachloroethene in soil which are typically circa 1 to 10 µg kg^{-1}.

5. REFERENCES

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APPENDIX A
HUMAN TOXICOLOGICAL DATA SHEET FOR TETRACHLOROETHENE

Human Toxicological Data Sheet for C4SL derivation: Reference checklist for sources of authoritative information

Chemical: **Tetrachloroethene**

Human Health Hazard Profile - References

Authoritative bodies	Website	Checked (Y/N)	References
Environment Agency	hhttps://www.gov.uk/government/organisations/environment-agency	Y	TOX report from 2004 cited
Foods Standards Agency	http://www.food.gov.uk/	Y	No relevant documents identified. Post Implementation Review: The Contaminants in Food (England) Regulations 2013 - relates to Brexit and refers to the presence of non-UK standards for tetrachloroethene in food.
Public Health England	https://www.gov.uk/government/organisations/public-health-england	Y	PHE 2016 Tetrachloroethylene Toxicological Overview
Committee on Carcinogenicity	https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemica	Y	None identified.
Committee on Mutagenicity	https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-che	Y	1996 Report of the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.
Committee on Toxicity	http://cot.food.gov.uk/	Y	COT statement on tetrachloroethylene and the reproductive health of workers in the dry-cleaning industry (November 1997) adds no data
ECHA REACH - is there a dossier?	http://echa.europa.eu/information-on-chemicals	Y	RAR does not include human health sections
EFSA - is there an opinion?	http://www.efsa.europa.eu/	Y	None identified
JECFA	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/?	Y	No threshold data identified
WHO	http://www.who.int/en/	Y	1. WHO 2010 Selected pollutants: WHO guideline for indoor air quality 2. WHO 2003 Tetrachloroethene in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality
WHO IPCS	http://www.who.int/ipcs/en/	Y	WHO CICAD (Concise International Chemical Assessment Document) 68 2006
WHO EHC	http://www.who.int/ipcs/publications/ehc/en/	Y	WHO CICAD (Concise International Chemical Assessment Document) 68 2006
RIVM	https://www.rivm.nl/en	Y	Latest toxicology report dated 2001 - Not reviewed as there are more up to date reviews
US ATDSR	http://www.atsdr.cdc.gov/	Y	ATSDR 2019 Toxicological Profile For Tetrachloroethylene
US EPA	http://www.epa.gov/	Y	1. USEPA 2012 - Toxicological Review of Tetrachloroethylene (Perchloroethylene) In Support of Summary Information on the Integrated Risk Information System 2. Office of Environmental Health Hazard Assessment (OEHHA) 2016 - Perchloroethylene Inhalation Cancer Potency Values SRP REVIEW DRAFT May2016
US National Toxicology Program	https://ntp.niehs.nih.gov/	Y	No report identified. Studies refereed to appear to have been included in other reports.
Health Canada	http://www.hc-sc.gc.ca/index-eng.php	Y	Health Canada 2015, Guidelines for Canadian Drinking Water Quality, Guideline Technical Document Tetrachloroethylene
Australia NICNAS	http://www.nicnas.gov.au/	Y	**NICNAS June 2001 Tetrachloroethylene - Priority Existing Chemical Assessment Report No. 15 - Not reviewed as there are more up to date reviews**
Risk Assessment Information System	http://rais.ornl.gov	Y	**Oak Ridge National Laboratory , 1993, Toxicity summary for terachloroethyelne - Not reviewed given the presence of more up to date assessments based on key data after this date**
International Agency for Research on Cancer	https://www.iarc.fr/	Y	IARC 2014 TRICHLOROETHYLENE, TETRACHLOROETHYLENE, AND SOME CHLORINATED AGENTS VOLUME 106
Other scientific reviews	**Check for key reviews on pubmed**		

Human Toxicological Data Sheet for C4SL derivation: Toxicological Evidence, HBGVs, MDIs and LLTC derivation

Chemical: **Tetrachloroethene**

I) Human Health Hazard Profile - Toxicological Evidence

Most sensitive health effects:

Sensitive endpoints	Other information	Source of evidence
	Multiple end effects to consider	
Neurotoxicity	Visual and autonomic disturbances - Colour vision loss/confusion index, vision effects and decision reaction time (most commonly cited)	Cavalleri et al. 1994, Gobba et al 1998 and Echeverria et al. 1995
Carcinogenicity	Multisite thresholded carcinogen (in rodents): brain, testicular, liver, kidney, mononuclear cell leukemia, hemangeosarcomas EPA (2012) - 'likely to be carcinogenic in humans' by all routes of exposure. NTP (2011) - reasonably anticipated to be a human carcinogen. ACGIH (2012) - A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans). IARC (2013) - category 2A carcinogen - probably carcinogenic to humans.	IARC 2014. Animal data from NTP 1986 and JISHA 1993
Hepatotoxicity	Liver effects	Hayes et al 1986
Nephrotoxicity	Early biomarkers of kidney effects in humans	Mutti et al 1992

II) Health Based Guidance Values (HBGVs) from Authoritative Bodies (in descending order of magnitude)

A) Oral route

Authoritative body (date) and HBGV type	HBGV value	Unit	UF used	PoD	POD value	Unit	Endpoint	Pivotal data used & Comments	Full Reference
ATSDR 2019 (Chronic oral MRL)	0.008	mg/kg bw/day	300	LOAEL	1.7 2.3	ppm mg/kg bw/d (HED)	Neurotoxicity (colour confusion)	Epidemiological: Based on impairments in colour vision (acquired dyschromatopsia) observed in an occupational **inhalation** exposure study (Cavalleri et al., 1994), supported by a follow up study (Gobba et al. 1998). Oral MRL was derived by **route to route extrapolation using PBPK** modelling (Chiu and Ginsberg, 2011) to convert the chronic-duration inhalation LOAEL of 1.7ppm (equivalent continuous exposure concentration derived from a LOAEL of 7.3ppm (106 month average)) to an oral dose LOAEL of 2.3mg/kg bw/day. UF of 300 was applied (10 for human variability; 10 for extrapolation from a LOAEL and 3 for database deficiencies). The same value was also adopted by ATSDR as the acute-duration and intermediate-duration oral MRLs.	ATSDR, 2019. Toxicological profile for tetrachlorethylene. June 2019.
WHO CICAD 2006 (oral TDI)	0.05	mg/kg bw/day	100	LOAEC	20	mg/m3	Neurological effects (perceptual speed and choice reaction times, attention (digit reproduction and digit symbol) and visual scanning and memory (cancellation)).	Epidemiological: Based on neurological effects observed in an **occupational inhalation exposure study** involving neuropsychological tests to 44 German dry cleaning workers (Seeber, 1989) with high tetrachloroethene exposure (mean exposure duration of 10.6 years), 57 workers with low exposure (mean exposure duration of 11.8 years) and 84 controls. Based on **route-to-route extrapolation using PBPK** modelling (Rao and Brown, 1993) to convert the equivalent continuous exposure concentration of 20 mg/m3 (derived from the mean LOAEC of 83 mg/m3) to an oral dose. A UF of 100 was applied (10 used for human variability and 10 for extrapolation from a LOAEC) to give a concentration of 0.2 mg/m3. PBPK modelling showed the equivalent oral dose to be 0.047 mg/kg bw/day which was rounded up to the TDI of 0.05 mg/kg/d. The database for derivation of a TDI for oral exposures to PCE was deemed inadequate.	WHO, 2006. Concise International Chemical Assessment Document 68 - Tetrachloroethene.
USEPA 2012 (oral RfD) non-cancer	0.006	mg/kg bw/day	1000	LOAEL	40 6	mg/m3 mg/kg bw/d (HED)	Neurotoxicity (Colour confusion) and Neurological effects (reaction times, attention loss and memory effects)	Epidemiological: Based on neurotoxicity observed in two **occupational chronic inhalation** studies which demonstrated color vision changes (Cavalleri et al., 1994) and cognitive and reaction time changes (Echeverria et al., 1995). Derived by **route-to-route extrapolation using PBPK modelling** (Chiu and Ginsberg, 2011) to derive the continuous oral dose that would result in the same tetrachloroethene in blood AUC as that following continuous inhalation exposure from the two studies. The inhalation LOAELs of 42 mg/m3 (Cavalleri et al., 1994) and 156 mg/m3 (Echeverria et al., 1995) were converted to time weighted average LOAELs of 15 and 56 mg/m3 respectively (corresponding to 2 and 8 ppm). Using PBPK oral HEDs were calculated of 2.6 mg/kg bw/day and 9.7 mg/kg bw/day, respectively. Midpoint values of TWA LOAEL 40 mg/m3 and oral HED of 6 mg/kg bw/day were chosen. A UF of 1,000 was applied (10 for human variability; 10 for extrapolation from a LOAEL; and 10 for database uncertainty).	USEPA, 2012.Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) In Support of Summary Information on the Integrated Risk Information System (IRIS). February 2012.

Health Canada 2015 (oral TDI)	0.0047	mg/kgbw/day	1000	BMDL10	6.6 4.7	ppm mg/kg bw/d (HED)	Neurotoxicity (colour confusion)	Epidemiological: Based on neurotoxicity observed in an **occupational chronic inhalation** study of ironing workers which demonstrated color confusion (Cavalleri et al., 1994). A NOAEL of 4.8ppm (32.6mg/m3) was derived and BMD modelling conducted to derive a BMD10 of 7.2ppm (48.8mg/m3) and a BMDL10 of 6.6ppm (44.8mg/m3), based on summary statisitics for colour confusion index scores. Given the volatility of tetrachloroethene, a **multiroute exposure** assessment was performed using **PBPK modelling** (adjusted Gearhart et al., 1993 model). The BMDL10 was converted to an external oral dose of 4.7mg/kgbw/day. Daily peak concentrations of tetrachlorethene in the brain (the kidney component of the PBPK model was used as a proxy for brain exposure) and blood were selected as the relevant dose metric. A UF of 1000 was applied (10 for intraspecies variability; 10 for database deficiency; and 10 to extrapolate from a less than lifetime exposure). Database deficiencies relate to studies showing effects at lower levels which could not be used for dose response and due to the healthy worker effect.	Health Canada, 2015. Guidelines for Canadian Drinking Water Quality. Guideline Technical Document. Tetrachloroethylene. January 2015.
WHO Drinking Water Guidelines 2003 (oral TDI)	0.014	mg/kg bw/day	1000	NOAEL	14	mg/kg bw/day	Kidney and liver effects	Based on a range of effects including kidney and liver effects observed in a 6-week **oral gavage study** in male mice (Buben and O'Flaherty, 1985) and a **90-day drinking-water study** (Hayes et al, 1986) in male and female rats both indicated a NOAEL for hepatotoxic effects of 14 mg/kg of body weight per day. A UF of 1,000 was applied (100 for intra- and interspecies variation and 10 for carcinogenic potential). A chemical specific assessment factor is used here, to account for the highly likely but uncertain carcinogenic potential in humans via the oral route.	WHO, 2003. Tetrachloroethene in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/03.04/23. See review of Hayes et al (1986) in ATSDR 2019.

COT/COC Opinion

COC 1996 - Following the 1995 IARC monograph in which it was concluded that tetrachloroethylene is a 'probable human carcinogen', the COC agreed the following conclusion: No conclusions can be drawn regarding the significance of in vitro mutagenicity experiments.
COM 1996 - reviewed the available in-vitro (in mammalian cells) and in-vivo genetic tox tests. Although there were deficiencies in the conduct and/or reporting of many of these studies, the weight of evidence suggested that tetrachloroethylene **was not an in-vivo genotoxin**.
COT 1997 - reviewed an occupational cohort study (HSE, 1994) showing that dry-cleaning machine operators potentially had an increased risk of spontaneous abortion compared with non-operators. COT were of the opinion, that there is no evidence for a plausible biological mechanism by which tetrachloroethylene could cause this effect and that other factors could have contributed to the observations. COT concluded, that the increased risk of spontaneous abortion could not be specifically attributed to exposure to tetrachloroethylene.

Current UK oral HCV

Authoritative body (date) and HBGV type	HBGV value	Unit	UF used	PoD	POD value	Unit	Endpoint	Pivotal data used & Comments	Full Reference
Defra & EA 2004 (oral HCV)	0.014	mg/kg bw/day	1000	NOAEL	14	mg/kg bw/day	liver pathology	Based on the assessment made in WHO 2003 Tetrachloroethene in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality	Department for Environment, Food and Rural Affairs (Defra) and Environment Agency (EA). Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Tetrachloroethylene, R&D Publications TOX 23, 2004. Environment Agency: Bristol.

B) Inhalation Route

Authoratative body (date) and HBGV type	Converted HBGVinh	Unit	HBGVinh	Unit	UF used	POD	POD value	Unit	Endpoint	Pivotal Study used & Comments	Full Reference
ATDSR 2019 (Inhalation chronic MRL)	0.011	mg/kg bw/day	0.006 0.038	ppm mg/m3	300	LOAEL	1.7 11.5	ppm mg/m3	Neurotoxicity (colour confusion)	Epidemiological: Based on impairments in colour vision (acquired dyschromatopsia) observed in an occupational **inhalation exposure study** (Cavalleri et al., 1994), supported by a follow up study (Gobba et al. 1998). A LOAEL of 7.3ppm (106 month average) was adjusted for continuous exposure (7.3 x 8/24 hours x 5/7 days) to derive a chronic-duration inhalation LOAEL of 1.7ppm (equivalent to 11.5 mg/m3 at atmospheric pressure of 1 atm and temperature of 25oC [1.7ppm x 165.83 g/mol/24.45 L/mol]. An UF of 300 was applied (10 for human variability; 10 for extrapolation from a LOAEL and 3 for database deficiencies for inadequate information on potential low-dose immune system effects). This yields an MRL of 0.006ppm, which is equivalent to 0.04 mg/m3 (11.5/300). This is equivalent in mg/kg bw/day of 0.04 mg/m3 x 20m3 air divided by 70kg bw = 0.011 mg/kg/day.	ATSDR, 2019. Toxicological profile for tetrachlorethylene. June 2019.
WHO CICAD 2006 (Inhalation TC - Tolerable concentration)	0.057	mg/kg bw/day	0.20	mg/m3	100	LOAEC	20	mg/m3	Neurological effects (perceptual speed and choice reaction times, attention (digit reproduction and digit symbol) and visual scanning and memory (cancellation)).	Epidemiological: Based on neurological effects observed in an occupational **inhalation exposure study** involving neuropsychological tests to 44 German dry cleaning workers (Seeber, 1989) with high tetrachloroethene exposure (mean exposure duration of 10.6 years), 57 workers with low exposure (mean exposure duration of 11.8 years) and 84 controls. Equivalent continuous exposure concentration of 20 mg/m3 (derived from the mean LOAEC of 83 mg/m3). A UF of 100 was applied (10 used for human variability and 10 for extrapolation from a LOAEC).	WHO, 2006. Concise International Chemical Assessment Document 68 - Tetrachloroethene.
USEPA 2012 (Inhalation RfC) non-cancer	0.011	mg/kg bw/day	0.040	mg/m3	1000	LOAEL	40	mg/m3	Neurotoxicity (Colour confusion) and Neurological effects (reaction times, attention loss and memory effects)	Epidemiological: Based on neurotoxicity observed in two occupational chronic inhalation studies which demonstrated color vision changes (Cavalleri et al., 1994) and cognitive and reaction time changes (Echeverria et al., 1995). The inhalation LOAELs of 42 mg/m3 (Cavalleri et al., 1994) and 156 mg/m3 (Echeverria et al., 1995) were converted to time weighted average LOAELs of 15 and 56 mg/m3 respectively (corresponding to 2 and 8 ppm). A UF of 1,000 was applied (10 for human variability; 10 for extrapolation from a LOAEL; and 10 for database uncertainty). The midpoint of the calculated range of TWA LOAELs (40 mg/m3) was chosen as the POD yielding an RfD (POD/1000) of 0.04 mg/m3. This is equivalent in mg/kg bw/day of 0.04 mg/m3 x 20m3 air divided by 70kg bw = 0.011 mg/kg/day.	USEPA, 2012.Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) In Support of Summary Information on the Integrated Risk Information System (IRIS). February 2012.
WHO 2010 (Air quality guideline) (and also cited in ATSDR 2019)	0.07	mg/kg bw/day	0.25	mg/m3	100	LOAEL	24.3	mg/m3	Effects in the kidney indicative of early renal disease (and supported by assessment of impaired neurobehavioural performance).	Based on impaired neurobehavioural performance and early renal changes. In a cross-sectional study, about 20 markers of early nephrotoxic effects were measured in workers in dry cleaning facilities (n = 50). The median exposure concentration was 102 mg/m3 (range, trace–580 mg/m3) (Mutti et al 1992). The LOAEL of 102mg/m3 was converted to continuous exposure (multiplying by 40/168) to give 24.3 mg/m3. A UF of 100 was applied (and uncertainty factors of 10 for intraspecies variation; and 10 for use of a LOAEL) were applied. In support, a study by Ferroni at al was cited from a test battery for neurological function, and found a LOAEL of 15ppm (102mg/m3). The chronic inhalation MRL of 0.24 mg/m3 was calculated from this concentration by expanding to continuous exposure (8/24 hours, 5/7 days) and dividing by an uncertainty factor of 100 (10 for use of a LOAEL; and 10 for human variability). On the basis of the overall health risk evaluation, the recommended guideline for year-long exposure is 0.25 mg/m3.	WHO, 2010. WHO guidelines for indoor air quality: selected pollutants.

COT/COC Opinion	See above.

Current UK inhalation HCV

Authoratative body (date) and HBGV type	HBGV value	Unit	UF used	PoD	POD value	Unit	Endpoint	Pivotal data used & Comments	Full Reference
Defra & EA 2004 (inhalation HCV)	0.071	mg/kg bw/day	100	LOAEL	25	mg/m3 (continuous exposure)	Mild kidney effects and neurotoxicity	Based on WHO 2000. Critical study was Mutti et al. The ATSDR 1997 (based on Ferroni et al 1992) was also cited as giving the same values. LOAEL of 102 mg/m3 divided by 4.2 (to convert from working to continuos exposure) and UF of 100 to give a guideline concentration of 0.25mg/m3.	Department for Environment, Food and Rural Affairs (Defra) and Environment Agency (EA). Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Tetrachloroethylene, R&D Publications TOX 23, 2004. Environment Agency: Bristol.

C) Dermal Route

Authoratative body (date) and HBGV type	HBGV value	Unit	UF used	POD	POD value	Unit	Endpoint	Pivotal Study used & Comments	Full Reference

III) Current UK (WHO) regulatory values

	Value	Units	Refs
UK drinking water standard	10	ug/l	Combined with trichloroethene. The Water Supply (Water Quality) Regulations 2016
WHO drinking water standard	40	ug/l	WHO 2003 Tetrachloroethene in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality
UK air quality standard	-	-	Not found
WHO air quality standard	0.25	mg/m3	WHO 2010 Selected pollutants: WHO guideline for indoor air quality

IV) Mean Daily Intakes from Other Sources (e.g. Diet)

	Pathways	Units	Adults	Children	Refs
Food (average)	Oral				
Food (average)	Oral				
Water	Oral				
Air	Inhalation				
Smoking	Inhalation				

V) LLTC derivation

A) ORAL

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments
Hayes et al., 1986	drinking water	14, 400, 1400	mg/kg bw/day	Rat	90-day subchronic study	There was evidence of liver and kidney toxicity at the two highest dose levels. The NOAEL was 14 mg/kg of body weight per day.
Buben and O'Flaherty, 1985	corn oil	14,70,700,1400	mg/kg bw/day	Mouse	6-week subchronic study	Hepatoxic effects observed in male mice were noted at dose levels of ≥ 70 mg/kg bw/day, indicating a NOAEL for hepatotoxic effects of 14 mg/kg bw/day.

Selection of POD

Published POD for ORAL LLTC:		
Are dose response data of adequate quality to derive a BMD	No	
Type of PoD	NOEL	
Value selected	14	mg/kg bw/day

Derived POD for ORAL LLTC: (from data below)		
Type of PoD		
Value derived		mg/kg bw/day
AIC value		
P value		

BMD Modelling (if answered 'Yes' to question above - see worksheet BMD modelling pivotal study)

Software used — **US EPA BMDS Version [to be specified]**

	BMD1	BMD5	BMD10	BMD15
BMD modelling (value) (mg/kg bw/day)				
	BMDL1	BMDL5	BMDL10	BMDL15
BMD modelling (value) (mg/kg bw/day)				

Present benchmark dose graph here

Comments:

Addressing uncertainty

Thresholded effects?	Yes
If yes - use generic UF of 100 or (if data allow) calculate CSAF	1000
If no : see below for non-thresholded effects	
If animal data are used as POD (NO(A)EL or BDM) use generic margin of 5000 or (if data allows) calculate CSM	
If human data are used to derive a BMD use the margin that relates to a notional risk of 1 in 50000 based on the BMR (using the table opposite). The same margin can also be applied to a NO(A)EL, but not to a LO(A)EL.	
ELCR =	

BMR	Margin	Corresponding ELCR estimate
0.50%	250	1 in 50000
1%	500	1 in 50000
5%	2500	1 in 50000
10%	5000	1 in 50000

Chemical Specific Adjustment Factor/Chemical Specific Margin to account for uncertainties in the data		
	Range	Selected value
Intraspecies	1 - 10	10
Interspecies	1 - 10	10
Sub-chronic to chronic	1-10	1
Database deficiencies	1-3	1
Quality of study	1 - 10	1
Use of LOAEL as POD	1-10	1
Allowance for carcinogenicity risk	1 - 10	10
Total CSAF/CSM		1000

Is the LLTC based on systemic or localised toxicological effects?	Systemic
Lifetime averaging to be applied in CLEA (Yes/No)	No

Oral LLTC calculation:

	Value	Units	Justification
LLTC (Thresholded chemical) using NOAEL/LOAEL	14.0	µg/kg bw/day	It is considered appropriate to take as the POD the NOEL of 14 mg/kg bw/day from the 90-day study reported by Hayes et al 1986. This NOAEL is also equal to the NOEL from the 6-week study by Buben et al, 1985. BMD modelling is unhelpful in this case. Many effects are observed for tetrachloroethene, including a possibility for carcinogenic potential though not proven by the oral route. There are also only 3 dosing concentrations in the Hayes et al study, with a clear NOEL but not enough quality of data to assess multiple end effects by BMD modelling. A CSAF of 1,000 was applied (100 for intra- and interspecies variation and 10 for carcinogenic potential).
LLTC (Thresholded chemical) using BMD		µg/kg bw/day	
LLTC (Non Thresholded chemical) using NOAEL/LOAEL		µg/kg bw/day	
LLTC (Non Thresholded chemical) using BMD		µg/kg bw/day	

Delete as appropriate

Sensitive Receptor	Child	

b) INHALATION

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments
Cavalleri et al., 1994	Respired air	4.8 - 7.3	ppm	Human	Occupational study in dry cleaners	Based on impairments in colour vision (acquired dyschromatopsia) in an occupational inhalation exposure study of in 35 tetrachloroethylene-exposed workers (22 dry-cleaners and 13 ironers) match with non-exposed workers (Cavalleri et al. (1994) with supporting evidence from re-examination after 2 years (and a follow-up study by Gobba et al. (1998)). A LOAEL of 7.3ppm (106 month average) was adjusted for continuous exposure to derive a chronic-duration inhalation LOAEL of 1.7ppm (equivalent to 11.5 mg/m3 or 3.29 mg/kg bw/d assuming a 70kg adult breathes 20m3/d). This study was selected by US ATSDR as covering the most sensitive effect of neurotoxicity and is the most reliable POD for the inhalation HBGV, based upon clear data from an epidemiology study with appropriate application of UFs. US EPA arrived at a similar HBGV, drawing upon both Cavalleri and Echeverria studies, which is supportive of te Cavalleri study for use in risk assessment here.

Selection of POD

Published POD for INHALATION LLTC:		
Are dose response data of adequate quality to derive a BMD	No	
Type of PoD	LOAEL	
Value selected	11.5	mg/m3

Derived POD for INHALATION LLTC: (from data below)		
Type of PoD		
Value derived		mg/kg bw/day
AIC value		
P value		

BMD Modelling (if answered 'Yes' to question above - see worksheet BMD modelleing pivotal study)

Software used US EPA BMDS 2.3.1

	BMD1	BMD5	BMD10	BMD15
BMD modelling (value) (mg/kg bw/day)				
	BMDL1	BMDL5	BMDL10	BMDL15
BMD modelling (value) (mg/kg bw/day)				

Present benchmark dose graph here

Comments:

Thresholded effects?	
If yes - use generic UF of 100 or (if data allow) calculate CSAF	300
If no : see below for non-thresholded effects	
If animal data are used as POD (NO(A)EL or BDM) use generic margin of 5000 or (if data allows) calculate CSM	
If human data are used to derive a BMD use the margin that relates to a notional risk of 1 in 50000 based on the BMR (using the table opposite). The same margin can also be applied to a NO(A)EL, but not to a LO(A)EL.	
ELCR =	

BMR	Margin	Corresopnding ELCR estimate
0.50%	250	1 in 50000
1%	500	1 in 50000
5%	2500	1 in 50000
10%	5000	1 in 50000

Chemical Specific Adjustment Factor/Chemical Specific Margin to account for uncertainties in the data		
	Range	Selected value
Intraspecies	1 - 10	10
Interspecies	1 - 10	1
Sub-chronic to chronic	1-10	1
Database deficiencies	1-3	1
Quality of study	1 - 10	3
Use of LOAEL as POD	1-10	10
Other	1 - 10	1
Total CSAF/CSM		300

Is the LLTC based on systemic or localised toxicological effects?	Systemic
Lifetime averaging to be applied in CLEA (Yes/No)	No

Inhalation LLTC calculation:

	Value	Units	Justification
LLTC (Thresholded chemical) using NOAEL/LOAEL	11.0	µg/kg bw/day	LOAEL of 11.5 mg/m3 from occupation study converted to equivalent dose of 3.3 mg/kg bw/d by multiplying by 20 m3/d and dividing by 70kg bw. This POD divided by UF of 300 (10 for human variability; 10 for extrapolation from a LOAEL and 3 for database deficiencies owing to inadequate information on low-dose immune system effects: ATSDR 2019 identified that the role of tetrachloroethene in respiratory sensitization, cancers of the immune system and inflammation in some tissues was unclear and warranted further study. Additionally , EPA 2012 noted that a study by Emara (2010) on Egyptian dry cleaning workers indicated some disturbance of blood immune parameters but the results were unclear because of variation between the control groups.
LLTC (Thresholded chemical) using BMD		µg/kg bw/day	
LLTC (Non Thresholded chemical) using NOAEL/LOAEL		µg/kg bw/day	
LLTC (Non Thresholded chemical) using BMD		µg/kg bw/day	

Delete as appropriate

Sensitive Receptor	Child	

Any Additional Comments: In this evaluation we have chosen not to use values where PBPK modelling has been used either to calculate a HED or for route to route extrapolation. This is because we cannot see the detail of the PBPK models and how they have been built, including the details of the input parameters used in the model. PBPK modelling derives from the US EPA 2012 evaluation, which ATSDR have followed also in their evaluation of 2019. We have therefore selected a different pivotal studies for the oral route (Hayes et al 1986) which is the only good quality 90-day study available by the relevant route, as the basis of our oral LLTC. We have followed the principles of the C4SL framework to select appropriate margins of safety. In this case a CSAF 1000 is used for the oral LLTC, aincluding an additional UF of 10 to account for uncertainties in oral carcinogencity potential in humans. Note, if PBPK modelling extrapolations were accepted as per EPA evaluation, without UK review, the LLTCs for the oral route would be lower than the value selected here. For the inhalation route, we agree with the US ATSDR approach using the Cavalleri data as the pivotal study, and a CSAF of 300. There is no evidence of human carcinogenicity, but from the evidence of BMC(L)10 calculations in rodents (see "Other relevant effects of note" worksheet), it is expected that the LLTCs proposed here will also be protective of cancer in humans. The most sensitive effect by the inhalation route is neurotoxicity and for the oral route, systemic toxicity (liver and kidney effects) is selected as the pivotal proven effect.

APPENDIX B
MEAN DAILY INTAKE DATA SHEET FOR TETRACHLOROETHENE

Substance: **Tetrachloroethene**

MDI Oral			**Recommended adult oral MDI**	**Units**	**Justification**: Estimated adult MDI from water. Background exposure from food assumed negligible. Adult MDI for water estimated from average 99th percentile concentration in tapwater in England and Wales from DWI (2016) multiplied by assumed adult water consumption rate of 2 L.d-1		
			1.54	ug day-1			
Organisation/Source	**Date**	**Media**	**Value**	**Units**	**Description**	**Reference**	**Web link**
DWI	Jul-17	Tap water	0.77	µg L-1	99th percentile concentrations of TCE + PCE measured in 2016 averaged across all 30 water companies in England & Wales	Data summary tables from Drinking Water Inspectorate annual report Drinking water 2016	http://www.dwi.gov.uk/about/annual-report/2016/index.html
Defra & Environment Agency	2004	Food	0	ug day-1	TOX report suggested PCE concs in food remote to dry-cleaning establishments was negligible, based on MAFF 1997 study	Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Tetrachloroethene. Science Report TOX23.	http://webarchive.nationalarchives.gov.uk/20140328111046/http://www.environment-agency.gov.uk/research/planning/64002.aspx

MDI Inhalation			**Recommended adult inhalation MDI**	**Units**	**Justification:** Tetrachloroethene is not monitored by the Defra UK AIR Network. The WHO AQG (2000) provides a more up to date review of the ambient concentrations of PCE than IPCS (1984) which was used in Defra and Enviroment Agency (2004). WHO AQG (2000) concludes that concentrations of PCE in urban ambient air are generally <5 µg m-3. More recent data from Oxford, UK (cited in WHO (2010)), WHO CICAD (2006), IARC (2014), ATDSR (2019) and Health Canada (2015) all support this, with ranges in these studies largely <1 µg m-3. These studies also suggest that indoor air concentrations are in the same range as urban outdoor air concentrations. Therefore a value of 1 µg m-3 is considered suitably protective for the combined indoor and outdoor MDI. 1 µg m-3 is converted to 20 µg day-1 by multiplying by an assumed adult respiration rate of 20 m3.d-1.		
			20	ug day-1			
Organisation/Source	**Date**	**Media**	**Value**	**Units**	**Description**	**Reference**	**Web link**
DEFRA & Environment Agency Report	2004	Urban Ambient Air	10	µg m-3	Cites IPCS (1983). A range of values, largely from German cities and US industrialised areas was reviewed, and the TOX report concluded that, in the absence of UK data, that ambient urban air concentrations would not usually exceed 10 µg m-3.	Defra and Environment Agency (2004). Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Tetrachloroethene	http://webarchive.nationalarchives.gov.uk/20140328153904/http://www.environment-agency.gov.uk/static/documents/Research/percold_2029065.pdf
PHE Toxicological Overview	2016	Urban Ambient Air	<5	µg m-3	Cites WHO AQG (2000). Urban concentrations are generally <5 µg m-3.	PHE Toxicological Overview No, 2014790, Feburary 2016.	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/500824/Tetrachloroethylene_TO_PHE_120216.pdf
WHO Air Quality Guidelines	2000	Urban Ambient Air	<5	µg m-3	Ambient air concentrations are generally less than 5 µg m-3 in urban areas and less than 1 µg m-3 in rural areas. Indoor concentrations may rise to >1 mg m-3 in close proximity to dry cleaning opereations.	WHO (2000) '*Air Quality Guidelines for Europe*' WHO Regional Publications, European Series, No. 91. Second edition	http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf?ua=1
WHO Indoor Air Quality Guidelines	2010	Indoor Air	0.16 to 8.7	µg m-3	WHO reviewed the available studies and concluded that indoor concentrations are generally well below 20 µg m-3 with median concentrations ranging from 0.16 to 8.7µg m-3. Data from Oxford recorded a median indoor residential concentration of 1.9 µg m-3.	WHO (2010) 'WHO Guidelines for Indoor Air Quality: Selected Pollutants' WHO Regional Office for Europe.	http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf?ua=1
WHO Indoor Air Quality Guidelines	2010	Ambient Air	<5	µg m-3	WHO reviewed the available studies and concluded that ambient air concentrations of PCE are generally <5 µg m-3. Data from Oxford (from before 1998) recorded an outdoor median concentration of 1.7 µg m-3.	WHO (2010) 'WHO Guidelines for Indoor Air Quality: Selected Pollutants' WHO Regional Office for Europe.	http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf?ua=1
WHO Background for Drinking Water	2003	Urban Ambient Air	<0.7 to 70	µg m-3	Cites Pearson et al 1975. Concentrations in city air in the UK range from <0.7 to 70 µg m-3.	WHO (2003). Tetrachloroethene in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/03.04/23.	https://www.who.int/water_sanitation_health/dwq/chemicals/tetrachloroethene.pdf
IPCS EHC	1984	Urban Ambient Air	1.7 to 6.1	ug m-3	Surveys of ambient air in 9 US cities recorded averages of between 1.98 and 3.99 µg m-3 (studies published 1974 to 1982), and German average concentrations were between 1.7 and 6.1 µg m-3 in the early 1980s.	IPCS (1984). Tetrachloroethylene, Environmental Health Criteria 31.	http://www.inchem.org/documents/ehc/ehc/ehc31.htm
IARC	2014	Urban Ambient Air	0.01 to 0.8	µg m-3	Provides mean concentrations and ranges for ambient air at largely urban sites across the US, Europe, Canada and Japan largely recorded in the past 15 years. No measurements were specifically from the UK. From the data where means were provided, these ranged from 0.01 to 0.8 µg m-3.	IARC (2014). Monograph Volume 106. Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents.	https://monographs.iarc.fr/wp-content/uploads/2018/06/mono106.pdf
WHO CICAD	2006	Ambient Air	<1 to 10	µg m-3	Cites EU RAR (2001). The majority of ambient concentrations are below 10 µg m-3 with most below 1 µg m-3.	WHO (2006). Concise International Chemical Assessment Document 68: Tetrachloroethene.	https://www.who.int/ipcs/publications/cicad/cicad68.pdf?ua=1
US ATSDR	2019	Ambient Air	<1	µg m-3	95th percentile concs of PCE in ambient air in the US for the period 2010 to 2018 were less than 0.1ppb (0.678 ug/m3)	ATSDR (2019). Toxicological Profile For Tetrachloroethylene.	https://www.atsdr.cdc.gov/ToxProfiles/tp18.pdf
Health Canada	2015	Outdoor Air	<1	ug m-3	A study of outdoor air in 11 Canadian cities (reported in Dann and Wang (1992)) ranged from 0.2 to 5 µg.m-3. Recent studies in three cities (2010 and 2012) recorded geometric mean outdoor concentrations of <1 µg.m-3.	Health Canada (2015). Guidelines for Canadian Drinking Water Quality: Supporting Documentation - Tetrachloroethylene	https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-tetrachloroethylene/guidelines-canadian-drinking-water-quality-guideline-technical-document-tetrachloroethylene-page-6.html#s5.3
Health Canada	2015	Indoor Air	<1	ug m-3	In a pilot study of indoor air in randomly selected Canadian homes (reported in Otson et al (1992)) the average concentration was 5.1 µg.m-3. Recent studies in three cities (2010 and 2012) recorded geometric mean indoor concentrations of <1 µg.m-3.	Health Canada (2015). Guidelines for Canadian Drinking Water Quality: Supporting Documentation - Tetrachloroethylene	https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-tetrachloroethylene/guidelines-canadian-drinking-water-quality-guideline-technical-document-tetrachloroethylene-page-6.html#s5.3