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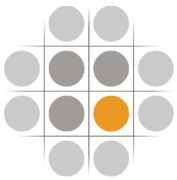

Category 4 Screening Levels: Trichloroethene (TCE)

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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CONTENTS

APPENDICES

ABBREVIATIONS

ADE	Average Daily Exposure
AIC	Akaike Information Criteria
ALARP	As Low As Reasonably Practicable
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMDL	Lower Confidence Limit of BMD
BMDS	Benchmark Dose Software
BMR	Benchmark Response
C4SL	Category Four Screening Level
CAS	Chemical Abstracts Service
CL:AIRE	Contaminated Land: Applications in Real Environments
CLEA	Contaminated Land Exposure Assessment
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
IC	Intra-Litter Correlation
IRIS	Integrated Risk Information System
IUR	Inhalation Unit Risk
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
LOD	Limit of Detection
LSC	Litter-Specific Covariates
MDI	Mean Daily Intake
MRL	Minimal Risk Level
NCTR	National Center for Toxicological Research
NHL	Non-Hodgkin Lymphoma
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
RfD	Reference Dose
SAGTA	Soil and Groundwater Technology Association
SOM	Soil Organic Matter
SR	Science Report
TCE	Trichloroethene
TOX	Toxicology
UF	Uncertainty Factor
UK	United Kingdom
USEPA	United States Environmental Protection Agency
VOC	Volatile Organic Compound
WHO	World Health Organization

1. INTRODUCTION

This report presents Category 4 Screening Levels (C4SLs) for trichloroethene (TCE) 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". Section 1.1 provides brief background information on TCE, 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 BRIEF OVERVIEW OF TCE

Trichloroethene, trichloroethylene, TCE or 'Trike' (CAS No. 79-01-06) has the chemical formula C_2HCl_3 and is present as a clear, colourless, watery, non-flammable liquid at room temperature. It slowly decomposes to hydrochloric acid in the presence of moisture and light (Environment Agency, 2008).

Although TCE is produced naturally by several temperate and subtropical marine macroalgae, the impact of this source on global emissions is not known. The majority of manufactured TCE is produced through the chlorination or oxychlorination of ethylene or 1,2-dichloroethene (Defra and Environment Agency, 2004).

TCE is a widely used industrial chemical and has historically been used for the degreasing of metal parts in manufacturing industry. It is currently used as a feedstock for production of refrigerants, as an industrial solvent for extraction, waterless drying and finishing, and as a general-purpose solvent in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners. TCE is released into the environment during the course of its manufacture, formulation and use.

Breakdown of TCE in the environment is via isomers of dichloroethene and vinyl chloride. Breakdown is expected to be slow in soil with most TCE removed through evaporation to air (ATSDR, 2019).

2. DERIVATION OF LOW LEVEL OF TOXICOLOGICAL CONCERN FOR TCE

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 TCE. 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).

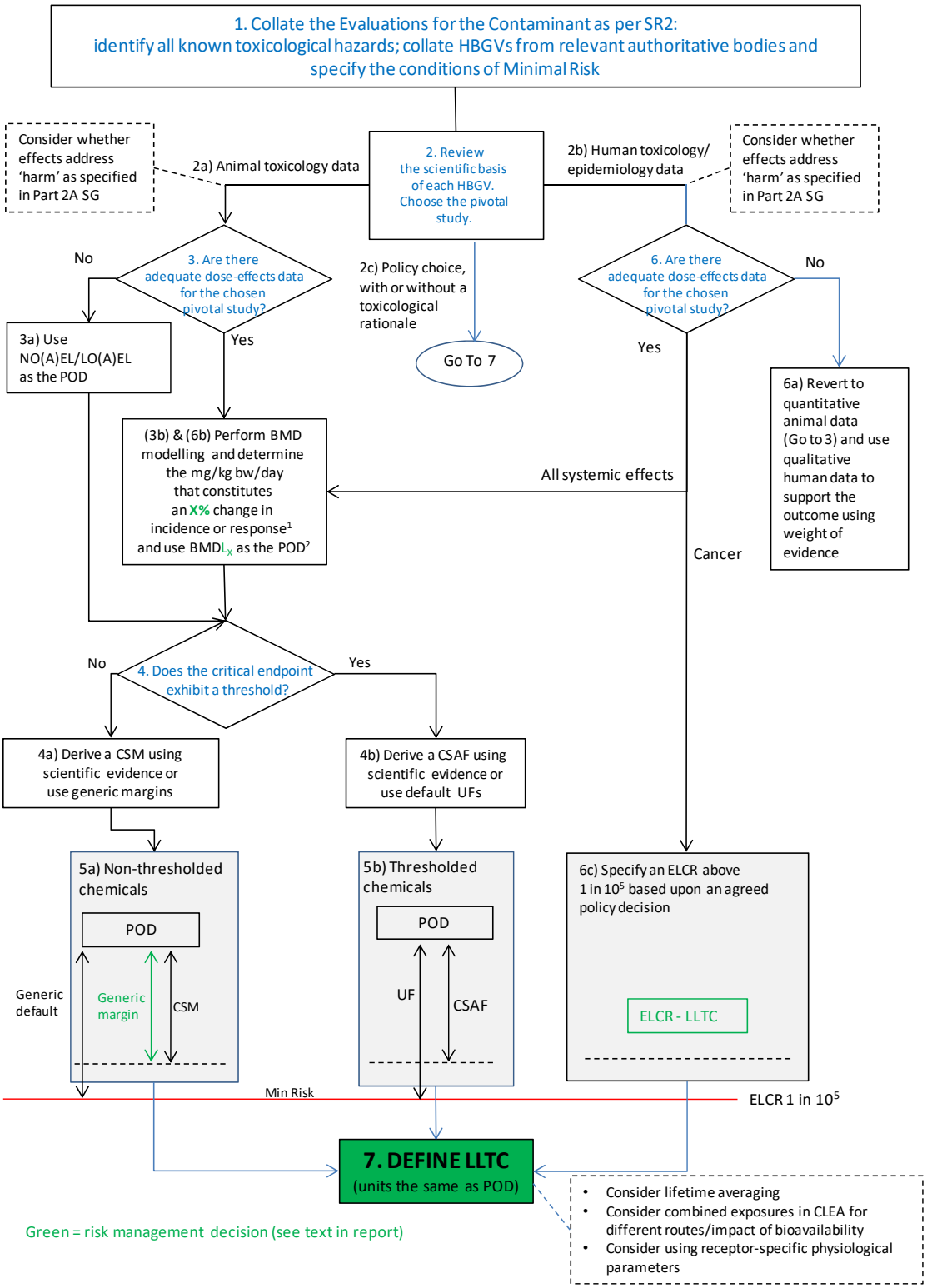

Figure 2.1: A framework for evaluating chemical-specific toxicology data for the purposes of LLTC derivation (reproduced from Figure 2.2 of SP1010 (CL:AIRE, 2014)).

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. This review indicates that kidney cancer, Non-Hodgkin Lymphoma (NHL) and liver cancer, decreased thymus weight, delayed type hypersensitivity and foetal heart malformations are the most sensitive[1] toxicological effects by 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).

2a) Animal Toxicology Data

A range of toxic endpoints are seen in animal studies for TCE, including cancer, immune system effects, decreased thymus weight and foetal heart malformations. All of these study data yield points of departure and guidance values of a similar magnitude.

Based on all the data available, the Johnson *et al*. (2003) study on foetal heart malformations is the most robust study and has been selected as the pivotal study. This study has also been selected as the most sensitive and relevant toxicological basis (from animal data) in authoritative guideline derivations by the United States Environmental Protection Agency (USEPA, 2011) and the US Agency for Toxic Substances and Disease Registry (ATSDR, 2019). It should be noted that these authoritative bodies both used a physiologically based pharmacokinetic (PBPK) model to extrapolate data from animals to humans and characterise human toxicokinetic variability in the quantitative derivation of HBGVs[2]. However, PBPK models introduce considerable complexity and potential uncertainty and it has not been within the scope of this project to review the appropriateness of the PBPK models used for TCE. PBPK modelling has therefore not been used in deriving the LLTC in this report. However, it is noted that if PBPK modelling were to be used, it would result in a higher LLTC.

In Johnson *et al.* (2003) groups of pregnant Sprague-Dawley rats (n = 9-13 per TCE exposure level; n = 55 in control groups) were administered TCE via drinking water. Rat dams were exposed throughout gestation (gestation days 1-22) at 0, 0.0025, 0.25, 1.5 and 1,100 ppm (estimated doses of 0.00045, 0.048, 0.218, and 129 mg kg^{-1} bw day^{-1}, respectively). Note that there was a large difference between the top dose (129 mg kg^{-1} bw day^{-1}) and the next lowest dose (0.218 mg kg^{-1} bw day^{-1}). At termination (gestation day 22), dams and foetuses were examined for gross abnormalities and foetuses were weighed, measured for crown-rump length and sexed. Foetal hearts and great vessels were examined for gross malformations and prepared for histopathological evaluations.

Maternal toxicity was not observed in any of the exposure groups. The study authors reported no statistically significant differences between controls and TCE-treated groups,

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[1] 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 evaluation of minimal/tolerable risk as described in SR2.

[2] USEPA derived a Reference Dose (RfD) and ATSDR derived a Minimal Risk Level (MRL)

except for the observed congenital heart malformations in the higher dose groups (1.5 and 1,100 ppm). Incidences of foetuses with heart abnormalities in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/144 (0%), 5/110 (4.5%), 9/181 (5.0%) (p = 0.044), and 11/105 (10.48%) (p = 0.001), respectively. The study authors also reported results on a per-litter basis (number of litters with at least one foetus that exhibited a cardiac malformation per number of litters). Nine of 55 control litters had one or more foetuses with a cardiac malformation; incidences in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/12 (0%), 4/9 (44%), 5/13 (38%), and 6/9 (67%), respectively. See Table 2.1 below.

Table 2.1: Types of heart malformations per 100 foetuses

Type of defect/100 fetuses	Control	TCE dose group			
		1,100 ppm	1.5 ppm	250 ppb	2.5 ppb
Abnormal looping	0.33		1		
Coronary artery/sinus				1.82	
Aortic hypoplasia			0.55		
Pulmonary artery hypoplasia			0.55		
Atrial septal defect	1.16	6.67	2.21	0.91	
Mitral valve defect	0.17			0.91	
Tricuspid valve defect				0.91	
Ventricular septal defect					
Perimembranous (subaortic)	0.33	2.86	1.66		
Muscular	0.33	0.95	0.55		
Atriventricular septal defect	0.17	0.95			
Pulmonary valve defect					
Aortic valve defects		1.9		0.91	
Fetuses with abnormal hearts (n)	13	11	9	5	0
Total fetuses (n)	606	105	181	110	144
Litters with fetuses with abnormal hearts/litter (n)	9/55	6/9	5/13	4/9	0/12
Litter with fetuses with abnormal hearts/number litters (%)	16.4	66.7	38.5	44.4	0.0

Source: Johnson *et al.* (2003) Table 2, p290.

The no observed adverse effect level (NOAEL) from this study is 0.0025 ppm (0.00045 mg kg^{-1} bw day^{-1}) and the lowest observed adverse effect level (LOAEL) is 0.25 ppm (0.048 mg kg^{-1} bw day^{-1}). The data were suitable for benchmark dose modelling (see Section 2.1.5), but the USEPA only performed this at the lower doses, due to the large dose spacing to the top dose yielding a poor model fit.

GO TO FLOWCHART ELEMENT 3

2b) Human Toxicology/Epidemiology Data

Although there are human epidemiological studies investigating the adverse cancer-related effects of TCE in Charbotel *et al.* (2006) as reviewed by USEPA (2011), all data in humans are for the inhalation route. In using inhalation data here, it is a requirement that some type of PBPK model must be used to extrapolate the data from the inhalation route to the oral route. This was done by the USEPA (2011) in the derivation of an oral RfD. A description of the PBPK model used is provided in Appendix A of the USEPA 2011 evaluation and also in Chiu *et al.* 2014. However, a UK authority has not reviewed the quality of this model. Given the uncertainties and current unknowns in the PBPK modelling aspects of the USEPA (2011) evaluation, animal toxicology data (Johnson *et al.* 2003) via the oral route have been used as the pivotal study to derive the oral LLTC for TCE, as per the C4SL framework. However, if PBPK modelling were to be used, it would result in a lower LLTC.

GO TO FLOWCHART ELEMENT 6

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

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

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 Johnson *et al.* (2003) study on foetal heart malformations will be considered as the pivotal study from which to derive an $LLTC_{oral}$.

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]

This is the approach taken here: the LLTC is based on an animal study via the oral route, being mindful of the weight of evidence from human data (and considering the PBPK extrapolations performed but not relying on them), that the derivation will be sufficiently protective of all endpoints, including cancer.

2.1.4 Flowchart element 3a: Use NOAEL/LOAEL as PoD

Not applicable - A BMD_1 has been derived in USEPA (2011) using the Johnson *et al*. (2003) data (see below).

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

There are good quantitative data available from the Johnson *et al.* (2003) study that authoritative bodies have used to carry out BMD modelling.

The USEPA in their 2011 evaluation used the USEPA Benchmark Dose Software (BMDS) (dated 2 August 2008) to fit a range of models to incidence data for foetal heart malformations (in pups) in terms of applied dose. They used nested dichotomous models for developmental effects in rodent studies to account for possible litter effects, such as litter-specific covariates (LSC) or intra-litter correlation (IC). The available nested models in BMDS are the nested log-logistic model, the Rai-VanRyzin models, and the National Center for Toxicological Research (NCTR) model.

From the Johnson *et al.* (2003) data, the BMD_1 and the corresponding 95th lower confidence limit ($BMDL_1$) were calculated associated with a benchmark response (BMR) of 1% extra risk of the effect occurring[3]. For the derivation of the LLTC, the BMD_1 value (rather than the BMD_{10}) is selected as the POD as the observed effects are potentially fatal, and a level of precaution is warranted.

To assess the acceptability of the different models, various criteria were evaluated. In general, model fit was assessed by a chi-square goodness of fit test (*i.e.* models with $p<0.1$ failed the goodness of fit criterion) and the Akaike Information Criteria (AIC) value. Smaller

[3] A 95th lower confidence limit is used to take into account the inherent uncertainty in the pivotal toxicity study and to ensure (with 95% confidence) that the selected BMR is not exceeded whereas the BMD_{10} value represents central tendency values. Here a precautionary 1% incidence rate is used to reflect the severity of effect of congenital heart malformations.

AIC values indicate a better fit of data. Of the models exhibiting adequate fit, the model with the lowest AIC value was selected as the best fit model as long as the BMDL calculated from all models were 'sufficiently close' (USEPA, 2011).

The results of the BMD modelling for foetal heart malformations using the nested log-linear model are presented in Table 2.2 and Figure 2.2 below. The USEPA report that the Rai-VanRyzin model gave essentially the same results but they opted to use the results from the nested log-linear model as the basis of their POD. They do not present results from the NCTR model.

Table 2.2: BMD_1 and $BMDL_1$ calculations from the nested log-logistic for foetal heart malformations (Reproduced from the USEPA 2011 evaluation Appendices Table F-6, Page F 10)

Model	LSC?[a]	IC?	AIC	Pval	BMR	BMD	BMDL
NLOG	Y	Y	246.877	NA (df = 0)	0.01	0.252433	0.03776
NLOG	Y	N	251.203	0.0112	0.01	0.238776	0.039285
NLOG	N	N	248.853	0.0098	0.01	0.057807	0.028977
NLOG	N	Y	243.815	0.0128	0.1	0.71114	0.227675
NLOG	N	Y	243.815	0.0128	0.05	0.336856	0.107846
NLOG[b]	**N**	**Y**	**243.815**	**0.0128**	**0.01**	**0.064649**	**0.020698**

[a]LSC analyzed was female weight gain during pregnancy.
[b]Indicates model selected (Rai-VanRyzin model fits are essentially the same).

NLOG = "nested log-logistic" model

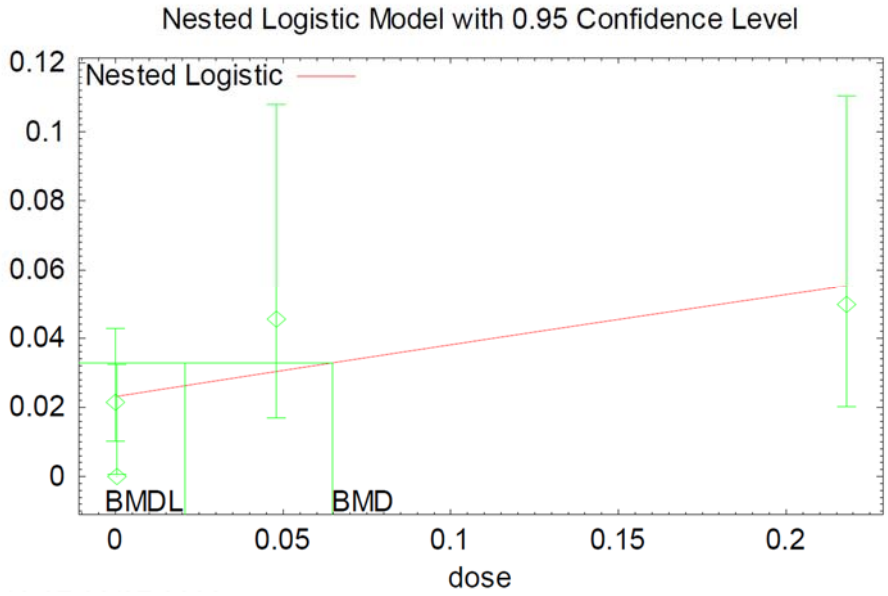

Figure 2.2 BMD modelling of Johnson *et al.* (2003) using nested log-logistic model, with applied dose, without the high-dose group, using BMR of 0.01 extra risk

The nested log-linear model which included IC but excluded LSC gave the lowest AIC and was selected by the USEPA as the basis of their POD. The BMD_1 for this model was calculated to be 0.0646 mg kg^{-1} bw day^{-1} and the $BMDL_1$ was 0.0207 mg kg^{-1} bw day^{-1}. For the purposes of deriving an LLTC, a BMD_1 of 0.0646 mg kg^{-1} bw day^{-1} is proposed, based on the sensitive effect of foetal heart malformations in rats in Johnson *et al.* (2003).

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

It is reasonable to assume that the effect of foetal cardiac malformations is a threshold systemic effect and that a default uncertainty factor of 100 to cover intraspecies (10x) and interspecies (10x) variability, can be applied to the precautionary BMD_1.

GO TO FLOWCHART ELEMENT 5a

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

Not applicable.

GO TO FLOWCHART ELEMENT 5b

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

For thresholded chemicals, the POD is divided by the default Uncertainty Factor (UF):

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

Therefore, for this evaluation:

$BMD_1/100$ = LLTC

0.0646(mg kg^{-1} bw day^{-1})/100 = 0.000646 mg kg^{-1} bw day^{-1} = 0.646 µg kg^{-1} bw day^{-1}

GO TO FLOWCHART ELEMENT 7

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

Based upon a scientific evaluation of foetal heart malformations in Sprague-Dawley rats, an oral LLTC of **0.646 µg kg^{-1} bw day^{-1}** is proposed, based on a BMD_1 of 0.0646 mg kg^{-1} bw day^{-1} as the POD from USEPA modelling of Johnson *et al.* (2003) data and an uncertainty factor of 100. This LLTC value is:

a) Comparable but slightly higher than the current minimal risk USEPA chronic oral RfD[4] of 0.5 µg kg^{-1} bw day^{-1} (also based on Johnson *et al*. (2003) data)

b) An order of magnitude lower than the Defra and Environment Agency (2004) minimal risk Index Dose of 5.2 µg kg^{-1} bw day^{-1}, which was based on extrapolation from outdated inhalation data.

[4] The USEPA define the RfD as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

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 all inhalation HBGVs from authoritative bodies provides the best evidence that kidney cancer, NHL & liver cancer, foetal heart malformations and decreased thymus weight are the most sensitive[5] toxicological effects by the inhalation route.

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

Although there are animal toxicology studies investigating the adverse effects of TCE via the inhalation route, as reviewed by ATSDR (2019) and USEPA (2011), the human epidemiology data in Charbotel *et al.* (2006) are selected as the most relevant pivotal study on kidney cancer to act as a main basis in deriving the inhalation LLTC for TCE on human data. All data in rodents corroborate cancer as a key effect for TCE exposure via inhalation.

GO TO FLOWCHART ELEMENT 3.

2b) Human Toxicology/Epidemiology Data

Overall, the critical toxic endpoints selected from the toxicity studies available are kidney cancer, NHL and liver cancer. Based on all the data available, the Charbotel *et al.* (2006) study has been selected as the pivotal study for kidney cancer, as it is the most sensitive epidemiological study performed to date that is relevant to the general population.

Human epidemiology data are based upon 87 cases from the Arve Valley region in France with 316 controls. Telephone interviews were performed with case or control participants or, if deceased, with next-of-kin. Semi quantitative TCE exposure was assigned to subjects using a task/TCE-Exposure Matrix, which was designed using information obtained from questionnaires and routine atmospheric monitoring of workshops or biological monitoring of workers carried out since the 1960s.

The study by Charbotel *et al.* (2006) produced data on kidney cancer as the most sensitive effect. This evidence was considered by the USEPA to be of good quality, as they were based on good quality human data with well-reasoned exposure estimates from defined scenarios. From the analysis of Charbotel alone, the lifetime unit risk is calculated at 1×10^{-6} per $\mu g.m^{-3}$ TCE in air (see conclusion of Section 5.2.2.1 on page 5-146 of USEPA 2011 report).

However, the USEPA also considered multi-organ cancers that could be a realistic risk from TCE exposure and a meta-analysis was performed in the context of deriving a protective risk estimate for observed liver cancers and NHL using a number of epidemiological studies. The data used and the meta-analysis performed are described in Sections B and C of the Appendices to the USEPA 2011 evaluation. The USEPA concluded

[5] 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 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.

that the unit risk factor for all three cancer types (kidney, liver and NHL) should be 4.1 x 10^{-6} per µg.m^{-3} TCE in air (see Section 5.2.2.2 of USEPA 2011 report). This was then adjusted to a unit risk of 4.8 per µg.m^{-3} TCE in air to account for early-life susceptibility (see Section 5.2.3.3.1 of USEPA 2011 report). The LLTC is based on the meta-analysis for all cancers.

GO TO FLOWCHART ELEMENT 6

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

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

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?

Not applicable.

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

2.2.4 Flowchart element 3a: Use NOAEL/LOAEL as PoD

Not applicable - A Lifetime Cancer Unit Risk from human data has been used (Go to ELEMENT 6c).

2.2.5 FLOWCHART ELEMENT 3b: Perform BMD modelling

Not applicable.

GO TO FLOWCHART ELEMENT 4a/b

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

Yes	No	Not applicable
	X	

An assumption of low-dose linearity is applied in the modelling of cancer risk, assumptive of a mutagenic mode of action.

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

Not applicable.

GO TO FLOWCHART ELEMENT 5b

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

Not applicable.

2.2.10 FLOWCHART ELEMENT 6: Are there adequate dose-effects data for the chosen pivotal study – human data?

Yes	No	Not applicable
X		

GO TO FLOWCHART ELEMENT 6c

2.2.11 FLOWCHART ELEMENT 6a: Revert to quantitative animal data (Go to 3) and use qualitative human data to support the outcome using weight of evidences POD

There is sufficient quantitative human epidemiological data presented by USEPA (2011) on which to derive the LLTC.

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

No BMD modelling has been performed. Instead, a meta-analysis of human epidemiology data for cancer effects, was performed by the USEPA (2011) and used to determine excess lifetime cancer risk (ELCR) (see section 2.2.13).

2.2.13 FLOWCHART ELEMENT 6c: Specify an ELCR above 1 in 10^5

Calculations of lifetime cancer unit risk were described in the USEPA (2011) evaluation (Table 5-48, Page 5-159) using a meta-analysis of a range of studies, with data on kidney cancer from Charbotel *et al.* (2006) as the main basis. This was a complicated derivation as described in full in sections B and C of the Appendices to the USEPA (2011) evaluation.

TCE is linked to a range of cancers in humans by inhalation exposure. In Charbotel *et al.* (2006) data are available for kidney cancer (renal cell cancer). Liver cancer and NHL have also been linked to TCE exposure. Risk estimates have been calculated in USEPA (2011) to cover all three types of cancer in a meta-analysis, with consideration of increased early life susceptibility and exposures over a lifetime. Based on continuous exposure to 1 $\mu g.m^{-3}$ from birth to age 70, the estimated total lifetime risk was calculated to be 4.8×10^{-6}, which corresponds to a lifetime unit risk estimate of 4.8×10^{-6} per $\mu g.m^{-3}$. The risk-specific air concentrations at risk levels of 10^{-6}, 10^{-5}, and 10^{-4} are 0.21 (*i.e.* 1 divided by 4.8), 2.1, and 21 $\mu g.m^{-3}$, respectively.

For a 2 in 10^{-5} or 1 in 50,000 ELCR, the associated air concentration is 4.2 $\mu g.m^{-3}$. For a 70 kg adult breathing 20 $m^3.day^{-1}$: (4.2x20)/70 = 1.20 $\mu g\ kg^{-1}$ bw day^{-1} as summarised in Table 2.3.

Table 2.3: Proposed inhalation LLTC

	ELCR	Air concentration ($\mu g\ m^{-3}$)	LLTC ($\mu g\ kg^{-1}$ bw day^{-1})
LLTC (non-threshold)	1 in 50,000	4.2	1.20

GO TO FLOWCHART ELEMENT 7

2.2.14 FLOWCHART ELEMENT 7: Assess $LLTC_{inh}$ for TCE

Based upon a scientific evaluation of human kidney cancer risks in Charbotel *et al.* (2006) together with a meta-analysis of a range of epidemiology studies as described in sections

B and C of the appendices of the USEPA (2011) TCE monograph, an inhalation LLTC of **1.20 µg kg^{-1} bw day^{-1}** is proposed, based on an Inhalation Total Unit Risk of $4.8x10^{-6}$ per µg m^{-3}, and an ELCR of 1 in 50,000.[6] This LLTC value is:

a) 5 times lower than the withdrawn Defra Index Dose of 5.2 µg kg^{-1} bw day^{-1}

b) Comparable to the USEPA Integrated Risk Information System (IRIS) inhalation unit risk (IUR) value of 0.57 µg kg^{-1} bw day^{-1} for a 1 in 100,000 ELCR but set at a higher ELCR of 1 in 50,000 as per the SP1010 C4SL policy companion document (Defra, 2014).

Therefore this LLTC is considered to be a pragmatic level for setting a C4SL and is suitably protective of all health effects including cancer in the general population.

Note that although the LLTC is based on an air concentration for the cancer endpoint, due to the broad spectrum of other potential systemic adverse health effects that could arise (but are not evidenced) from inhalation exposure to TCE, it is uncertain as to whether a receptor specific LLTC would be protective of all effects and hence has not been derived in this instance.

2.3 DERMAL ROUTE

There is no evidence to suggest that TCE induces local effects on the skin.

2.4 MEAN DAILY INTAKE

The oral LLTC recommended for TCE is based on threshold effects whilst the inhalation LLTC is based on non-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 LLTC but not for comparison with the inhalation LLTC.

Following discussion with the Steering Group, given that both the oral and inhalation LLTC are based on different systemic effects (threshold and non-threshold), the precautionary decision was made to base the C4SL on comparison of total exposure (oral, dermal and inhalation) with each LLTC and to then use the minimum of the CLEA derived assessment criteria as the C4SL (rather than combining the values). As the oral LLTC is based on non-threshold effects this includes oral and inhalation background exposure from non-soil sources.

Note that SR3 (Environment Agency, 2009b) recommends that inhalation background is not subtracted from the oral HCV where the inhalation HCV is based on non-threshold effects (and vice versa). However, the Steering Group considered that the SR3 document was based on tolerable and minimal risk where the non-threshold HCV (index dose) is likely to be based on the most sensitive endpoint. The LLTCs are based on higher levels of risk so there is the potential for overlapping toxicological effects data. Therefore, it would be important to ensure that the LLTCs are suitably protective of all endpoints. As such, both oral and inhalation MDI data are required for inclusion in the exposure calculation for comparison with the oral LLTC.

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 TCE are shown in Table 2.4 below. The Oral MDI is based upon the mean of the 99th percentile concentrations of TCE and tetrachloroethene measured in tap water reported by the Drinking Water Inspectorate for water companies in England and Wales for the year 2016 (DWI, 2017)[7]. Exposure to TCE via food is assumed to be negligible (Defra and Environment Agency, 2004).

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[6] For the purposes of deriving an LLTC, when using human data, an ELCR of 1 in 50,000 has been selected, as per DEFRA policy recommendation specifically in the context of C4SL derivation, as a generic margin representative of low risk (DEFRA, 2014).

[7] Note that the DWI only present concentrations for the sum of TCE and tetrachloroethene. They do not present concentrations for TCE alone.

There are limited published data on the concentrations of TCE in ambient outdoor and indoor air. WHO (2010) concluded that the ambient outdoor and indoor air concentrations of TCE in European and North American countries is generally less than 1 $\mu g.m^{-3}$. This is generally supported by TCE air concentrations reported by IARC (2014) and Health Canada (2005). ATSDR (2019) report yearly percentile concentrations from ambient air monitoring from locations across the US for years 1998 to 2018. These data show a declining trend in ambient air concentrations reflecting the reduction in TCE usage. The reported 95th percentile concentrations ranged from 0.14 to 0.16 parts per billion (ppb) (0.76 to 0.87 $\mu g\ m^{-3}$) for years 2010 to 2014 and 0.0099 to 0.023 ppb (0.054 to 0.13 $\mu g\ m^{-3}$) for years 2015 to 2018. For the purposes of deriving the C4SLs for TCE, the adult MDI is based on an assumed background air concentration of 1 $\mu g.m^{-3}$. This is multiplied by an assumed adult respiration rate of 20 $m^3\ day^{-1}$ to give the adult MDI of 20 $\mu g.day^{-1}$.

Table 2.4: Adult mean daily intake values for input to CLEA

Adult Mean Daily Intake	Value ($\mu g\ day^{-1}$)
Oral MDI	1.54
Inhalation MDI	20

3. EXPOSURE MODELLING FOR TCE

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, 2009 a & b), 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 TCE, the $LLTC_{inhal}$ is based on meta-analysis of a range of human epidemiology studies, with kidney cancer as the main basis (which is a non-threshold effect). The $LLTC_{oral}$ is based upon a scientific evaluation of foetal heart malformations observed in animal studies (rats) administered via drinking water which is a threshold effect. Both effects are systemic but, as discussed in Section 2.4, as the LLTCs are based on different end points, in order to remain appropriately precautionary, the Steering Group decided that all routes of exposure should be compared against both the $LLTC_{oral}$ and $LLTC_{inhal}$ with each end point considered separately. C4SLs have therefore not been integrated and are based on the lowest assessment criteria derived

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 TCE are shown in Table 3.1.

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

Parameter	Units	Value	Source/Justification
Air-water partition coefficient	dimensionless	$1.87x10^{-1}$	CLEA SR7, Environment Agency, 2008
Diffusion coefficient in air	$m^2 s^{-1}$	$7.91 x10^{-6}$	CLEA SR7, Environment Agency, 2008
Diffusion coefficient in water	$m^2 s^{-1}$	$6.23 x10^{-10}$	CLEA SR7, Environment Agency, 2008
Relative molecular mass	g mol^{-1}	131.39	CLEA SR7, Environment Agency, 2008
Vapour pressure	Pa	$4.58 x10^{3}$	CLEA SR7, Environment Agency, 2008
Water solubility	mg L^{-1}	$1.37 x10^{3}$	CLEA SR7, Environment Agency, 2008
Log Koc	Log $cm^3 g^{-1}$	2.15	CLEA SR7, Environment Agency, 2008
Log Kow	dimensionless	2.53	CLEA SR7, Environment Agency, 2008
Dermal absorption fraction	dimensionless	$1 x10^{-1}$	CLEA SR3, Environment Agency, 2009b
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	modelled	SR3 (Environment Agency, 2009b)
Soil-to-plant concentration factor (root vegetables)		modelled	
Soil-to-plant concentration factor (tuber vegetables)		modelled	
Soil-to-plant concentration factor (herbaceous fruit)		not considered	
Soil-to-plant concentration factor (shrub fruit)		not considered	
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, 2009b
Sub-surface soil to indoor air correction factor	dimensionless	1	Environment Agency, 2009b
Relative bioavailability soil	-	1	Conservative assumption made that bioavailability of TCE in soil and dust is the same as bioavailability of TCE 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 TCE 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 recommends a default value of 0.5 for derivation of the SGV (Environment Agency, 2009b), 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 TCE.

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 TCE has been modelled using the method for organic chemicals within the CLEA software.

CLEA predicts the greatest exposure to TCE from tree fruit and root vegetables for both the residential and allotments scenarios (via consumption of homegrown produce pathways). 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 TCE and it is considered appropriately conservative to assume an RBA of 100% for the derivation of C4SLs.

4. C4SLs FOR TCE

4.1 C4SLS

The C4SLs for TCE 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 TCE

Land-use	C4SLs (mg.kg^{-1})		
	SOM Content		
	1.0%	2.5%	6.0%
Residential with consumption of homegrown produce	0.0093	0.020	0.043
Residential without consumption of homegrown produce	0.0097	0.020	0.045
Allotments	0.032	0.072	0.16
Commercial	0.73	1.5	3.4
Public Open Space (residential)	76	78	79
Public Open Space (park)	41	54	69

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[8] 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. It should be noted that for TCE, all routes of exposure are compared against the oral LLTC and the C4SL is not integrated.

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	1.0	0.27
Residential without consumption of homegrown produce	1.0	0.27
Allotments	1.0	0.27
Commercial	1.0	0.28
Public Open Space (residential)	1.0	0.27
Public Open Space (park)	1.0	0.27

NB: ADE:HCV ratios presented for soil with concentrations equal to the derived C4SLs for 6% SOM

[8] "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	0.05	0.05	0.05	0.24	45.28	18.53
Sum of consumption of homegrown produce and attached soil	1.98	0.00	49.86	0.00	0.00	0.00
Dermal contact (indoor)	0.00	0.00	0.00	0.02	1.37	0.00
Dermal contact (outdoor)	0.00	0.00	0.03	0.02	1.61	1.83
Inhalation of dust (indoor)	0.00	0.00	0.00	0.00	0.16	0.00
Inhalation of dust (outdoor)	0.00	0.00	0.00	0.00	0.00	0.00
Inhalation of vapour (indoor)	47.97	49.95	0.00	52.06	0.00	0.00
Inhalation of vapour (outdoor)	0.00	0.00	0.06	0.03	1.59	29.63
Oral background	3.34	3.34	3.34	3.41	3.52	3.34
Inhalation background	46.66	46.66	46.66	44.23	46.48	46.66

Based on the information in Tables 4.2 and 4.3, the principal risk driving pathways for TCE 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.

It is noted that inhalation background exposure from non-soil sources accounts for approximately half of total exposure for all land-uses.

4.2 OTHER CONSIDERATIONS

Other considerations that were relevant when setting the C4SLs for TCE include the following:

- Since TCE is a known human carcinogen , it might be necessary to apply the “As Low as Reasonably Practicable” (ALARP) principle in relation to its remediation at specific sites (see Environment Agency, 2009a; 2009b for details). The principle of ALARP automatically applies to the regulation and management of non-threshold chemicals in the UK. It is important to note that ALARP remains the overriding principle even when a margin of exposure or minimal risk level or LLTC suggests there is a minimal/low concern for human health. What is considered practicable is a remediation/risk management decision and could be lower or higher than the scientific values derived.
- As critical health effects resulting from oral exposure to TCE are foetal malformations, consideration has been given to adopting pregnant women as an alternative critical receptor. Sensitivity analysis has been carried out which

demonstrates that C4SLs calculated based on the standard critical receptors are suitably protective of this receptor group[9].

- Intake of TCE from non-soil sources (food, water and air) has been considered as follows:
    - According to the 2004 CLEA TOX report for TCE (Defra and Environment Agency, 2004), exposure to TCE via food is assumed to be negligible.
    - The UK Drinking Water Inspectorate reports 99th percentile concentrations of sum of TCE 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 a 70 kg adult drinks 2 L of water per day, this equates to a daily intake of 0.022 µg kg^{-1} bw day^{-1}, which is approximately 3% 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.
    - WHO (2000, cited in Defra and Environment Agency, 2004) estimate the average air concentration of TCE to be 1 µg.m^{-3} in rural areas and 10 µg.m^{-3} in urban areas. More recent data from ATSDR (2019) and WHO (2010) indicate that typical ambient levels of TCE in indoor and outdoor air are less than 1 µg.m^{-3}. For a 70 kg adult breathing 20 m^3 of air per day this equates to an average daily intake of 0.286 µg kg^{-1} bw day^{-1} which is approximately 25% 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 TCE concentrations indicated by the POS_{resi} and POS_{park} C4SLs may be necessary.
- Typical reported commercial laboratory limits of detection (LODs) for TCE in soils (analysed using gas chromatography with mass spectrometry [GC-MS]) range from 1 to 10 µg kg^{-1}. It is noted that some of the C4SLs presented in Table 4.1 are within or close to this range of LODs. When applying the C4SLs for TCE assessors should be aware that measurement uncertainty (e.g. loss of volatiles during sampling and analytical uncertainty/reproducibility) can be significant, particularly where soil concentrations are close to LOD and could potentially be of a greater magnitude than the value of the C4SL.
- The British Geological Survey has not derived normal background concentrations for TCE (Defra, 2012). Although it occurs naturally, produced by temperate and subtropical marine macroalgae, TCE is not expected to occur above typical laboratory LODs in soil away from a source (such as metal part fabrication plant) and background soil concentrations are therefore expected to be negligible. This is supported by soils analytical data from two main commercial laboratories in the UK: Out of a total of approximately 19,000 soil samples analysed for volatile organic compounds (VOCs) only 5% had a concentration of TCE above the LOD (5 to 9 µg kg^{-1}), with the majority of detected concentrations being in the range of 10 to 500 µg kg^{-1}.
- 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 TCE 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 TCE and subsequent transport. Where exposure to soil vapour forms the critical pathway then further

[9] Residential, allotment and public open space exposure scenarios were modelled using a young adult female (age classes 15 and 16) as an alternative critical receptor. C4SLs calculated on this basis for all exposure scenarios were higher than for the 0 to 6 year old child.

consideration could be given to supporting the assessment in this area, for example, through obtaining site specific empirical data for soil vapour concentrations. The reader is referred to CIRIA (2009) and SoBRA (2018) for further guidance on this.

5. REFERENCES

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APPENDIX A
HUMAN TOXICOLOGICAL DATA SHEET FOR TCE

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

Chemical: **Trichloroethene**

Human Health Hazard Profile - References

Authoritative bodies	Website	Checked (Y/N)	References
Environment Agency	http://www.environment-agency.gov.uk/	Y	Defra, 2004. Collation of toxicological data and intake values for humans. Trichloroethene. Tox 24
Foods Standards Agency	http://www.food.gov.uk/	Y	-
Public Health England	https://www.gov.uk/government/organisations/public-health-england	Y	PHE, 2017. Trichloroethylene. Incident Management. PHE publications gateway number 2014790
Committee on Carcinogenicity	http://www.iacoc.org.uk/	Y	-
Committee on Mutagenicity	http://www.iacom.org.uk/	Y	-
Committee on Toxicity	http://cot.food.gov.uk/	Y	-
ECHA REACH - is there a dossier?	http://echa.europa.eu/information-on-chemicals	Y	ECHA, 2014. Trichloroethylene - Carcinogenicity dose-response analysis. ECHA project SR13. Final report
EFSA - is there an opinion?	http://www.efsa.europa.eu/	Y	-
JECFA	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/?	Y	WHO, 1983. Trichloroethylene, 1,1,2. Toxicological Evaluation of Certain Food Additives and Contaminants (WHO Food Additives Series 18)
WHO	http://www.who.int/en/	Y	WHO, 1983. Trichloroethylene, 1,1,2. Toxicological Evaluation of Certain Food Additives and Contaminants (WHO Food Additives Series 18)
WHO IPCS	http://www.who.int/ipcs/en/	Y	-
WHO EHC	http://www.who.int/ipcs/publications/ehc/en/	Y	WHO, 1985. Environmental Health Criteria 50. Trichloroethylene.
RIVM	http://www.rivm.nl/English	Y	RIVM, 2003. Trichloroethylene. Evaluation of the effects on reproduction, recommendation for classification. No. 2003/09OSH
US ATDSR	http://www.atsdr.cdc.gov/	Y	ATSDR, 2019. Toxicological profile for trichloroethylene.
US EPA	http://www.epa.gov/	Y	US EPA, 2011. Toxicological Review of Trichloroethylene. EPA/635/R-09/011F
US National Toxicology Program	http://ntp.niehs.nih.gov/	Y	-
Health Canada	http://www.hc-sc.gc.ca/index-eng.php	Y	Government of Canada, 1993. Trichloroethylene. Priority Substances List. Assessment Report
Australia NICNAS	http://www.nicnas.gov.au/	Y	NICNAS, 2000. Trichloroethylene. Priority Existing Chemical Assessment Report. No. 8
Risk Assessment Information System	http://rais.ornl.gov	Y	-
Other scientific reviews	**Check for key reviews on pubmed**	Y	CSTEE, 2001. Opinion on the results of the Risk Assessment of Trichloroethylene
	Human Toxicological Data Sheet - Chemical		Minnesota Department of Health, 2015. Toxicological Summary for: Trichloroethylene (TCE).
			California Environmental Protection Agency, 2009. Public Health Goals for Chemicals in Drinking Water.

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

Chemical: **Trichloroethene**

I) Human Health Hazard Profile - Toxicological Evidence

Most sensitive health effects:

Sensitive endpoints	Other information	Source of evidence
Nephrotoxicity	Kidney toxicity	Haag Gronlund et al 1995
Developmental toxicity	Decreased thymus weight	Kell et al 2009
Developmental toxicity	**Fetal heart malformations**	Johnson et al 2003
Immunotoxicity	Delayed type hypersensitivity	Peden-Adams et al 2006
Carcinogenicity	Kidney Cancer	Charbotel et al 2006
Carcinogenicity	**Kidney cancer, Non-Hodgkin Lymphona (NHL) and liver cancer (combined meta analysis)**	USEPA 2011, ATSDR 2019

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
ECHA Cancer Review for the purposes of REACH SVHC Authorisations 2014 (route to route)	23	µg/kg bw/day		ELCR	1 in 100,000		kidney cancer	As based on route to route extrapolation from an AGS 2008 German non-linear modelling evaluation using German worker studies (inhalation route), reviewed by Larsen & Giovalle 2014 and used by RAC (Committee of Risk Assessment) in their 22nd meeting to determine dose response relationships for authorisations. Extrapolations made to general population for chronic exposure. This report does not include any assessment of non-cancer effects for TCE. An oral slope factor of 4.32e-4 per mg/kg/d was derived. A dose that would give ELCR of 1 in 100,000 = (1/100,000)/4.32e-4 = 0.023 mg/kg/d = 23 ug/kg/d.
Public Health Goal for TCE in Drinking Water. Caifornia EPA 2009 (old study)	1.69	µg/kg bw/day		ELCR	1 in 100,000		cancer	An updated Public Health Goal (PHG) of 1.7 parts per billion (ppb) (1.7 ug/L) was established in 2009 for trichloroethylene (TCE) in drinking water, based on cancer effects and an ELCR of 1 in 1,000,000. This was calcuated from an oral cancer slope factor of 0.0059 per mg/kg/d and assuming an adult weighing 70kg drinks an equivalent of 7 .1L water per day (to account for the possibility of other routes of exposure) (70 kg x 10-6 / (0.0059 per mg/kg/d x 7.1 L eq/d) = 0.0017 mg/L). Cancer slope factor (CSF) was the geometric mean CSF from studies by NCI (1976) (liver tumours in female mice fed by gavage) and Maltoni et al (1986) (liver tumours in female mice, inhalation). For an ELCR of 1 in 100,000, the CF equates to a dose of 1.69 ug/kg/d ((1/100,000/0.0059) = 0.00169 mg/kg/d)
USEPA IRIS evaluation 2011 (developmental)(Also adopted by ATSDR 2019 as chronic ORAL MRL)	0.51	µg/kg bw/day	10	BMDL	0.0051	mg/kg/day (HED99, BMDL01)	fetal heart malformations	Johnson et al (2003) cardiac malformations in Sprague-Dawley rat foetuses whose mothers were exposed to TCE in drinking water from gestation days 1 to 22. UF of 10 applied (3.16 as PBPK model used for interspecies extrapolation, 3.16 as PBPK model used to characterise human toxicokinetic variability).
USEPA IRIS evaluation 2011 (developmental) (oral study)	0.48	µg/kg bw/day	100	LOAEL	0.048	mg/kg/day (HED99, LOAEL)	decreased thymus weight	Keil et al. decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water. Increased serum levels of IgG and selected autoantibodies at 1.4ppm dose. UF of 100 applied (10 as POD is LOAEL for adverse effect, 3.16 as PBPK model used for interspecies extrapolation, 3.16 as PBPK model used to characterise human toxicokinetic variability). No BMD modelling due to inadequate data fit. Low to moderate confidence in the quantitative data.
USEPA IRIS evaluation 2011 (immunotox) (oral study)	0.37	µg/kg bw/day	1000	LOAEL	0.37	mg/kg/day	decreased PFC response, increased delayed-type hypersensitivity	Peden-Adams et al. 2006 decreased plaque forming cell (PFC) response (at 3 and 8 weeks of age), increased delayed-type hypersensitivity (at 8 weeks of age) in pups exposed from gestation day 0 until 3 or 8 weeks of age through drinking water (placental and lactational transfer, and pup ingestion). UF of 1,000 applied (10 because POD is a LOAEL for multiple adverse effects, 10 for interspecies extrapolation because PBPK model was not used, 10 for human variability brcause PBPK model was not used). No BMD modelling due to inadequate data fit. Low to moderate confidence in quantitative data.
UK Drinking Water Standard 2016	0.286	µg/kg bw/day					cancer	Drinking water standard for sum of TCE and PCE is 10 µg/L; for a 70kg adult drinking 2L per day = (10 x 2)/70 = 0.286 µg/kg/day. NO explanation found of the basis for this value.

USEPA IRIS Oral Slope Factor. 2011 (route to route, cancer)	0.2	µg/kg bw/day		ELCR	1 in 100,000		kidney cancer, adjusted for additional NHL and liver cancer	US EPA 2011 linear evaluation. Human kidney cancer risks (Charbotel et al. 2006) French worker study, adjusted for potential risk for NHL and liver cancer. PBPK model uncertainties. Supported by oral slope factor estimates from multiple rodent bioasseys. From Charbotel cancer risk model, route-to-route extrapolation performed to yield an Oral Slope Factor of 0.05 per mg/kg/day, HBGV here calculated using 1 in 100,000 ELCR as per Defra policy for contam land.
USEPA IRIS Oral Total Unit Risk. 2011 (route to route meta-analysis cancer)	0.143	µg/kg bw/day		ELCR	1 in 100,000		kidney cancer, NHL and liver cancer	US EPA 2011 linear evaluation. Human kidney cancer risks (Charbotel et al. 2006) French worker study, adjusted for potential risk for NHL and liver cancer. PBPK model uncertainties. Supported by oral slope factor estimates from multiple rodent bioasseys. Oral Total Unit Risk for lifetime exposure taking account of presumed increased early life susceptibility to kidney tumours for TCE (See Table 5-49 Page 5-162 in EPA 2011) is of 2x10-6 per µg/L TCE in water. This considers early life susceptibility but is a non-standard bespoke approach to cancer evaluation. It does however, lead to the lowest value. HBGV= (1/100,000)/2x10-6 = 5 µg/L. For a 70kg adult drinking 2L per day: (5 x 2)/70 = 0.143 ug/kg/d.

COT/COC Opinion	Can not identify a COT/COC opinion for TCE. No search results on gov.uk. TCE is detailed within 1996 annual report (pages 39, 71) but this document is not freely available online. A reference value has not been generated for TCE by a UK or EU authoritative body in relation to chronic long term exposures and general public protection goals, i.e. considering new data since the EA Tox report in 2004.

Current UK oral HCV

Authoritative body (date) and HBGV type	HBGV value	Unit	UF used	PoD	POD value	Unit	Endpoint	Pivotal data used & Comments
DEFRA TOX 24 (2004) WITHDRAWN	5.2	µg/kg bw/day (Index Dose)	25,000	Other	130	mg/kg bw/d	Lymphomas	Mouse inhalation study (Henschler et al. 1980, within EU Existing Substances Programme. TD25 for lymphomas seen in mice was 130 mg/kg bw/day. Cancer potency of TCE is the same in humans as in mice. ELCR of 1 in 100,000. Significant new data has been generated since 2004.

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
OEHHA Chronic Toxicity Summary (no date in document) (inhalation study)	171	µg/kg bw/day	600	µg/m3	100	LOAEL	11.4	ppm	neurotoxicological effects	Based on neurotoxicological effects in workers (drowsiness, fatigue, headache) and eye irritation. Vandervort and Polnkoff (1973). Discontinuous occupational inhalation exposure to 19 workers and 9 controls for 8 hours a day (10m3/day inhalation rate), 5 days a week. Uncertainty factor of 100 used (10 for use of LOAEL, 1 for subchronic study, 1 for interspecies, 10 for intraspecies). HBGV converted from 600µg/m3 (0.1 ppm).
ECHA Cancer Review for the purposes of REACH SVHC Authorisations 2014 (inhalation study)	44	µg/kg bw/day	312.5	µg/m3		ELCR	1 in 100,000		kidney cancer	As based on AGS 2008 German non-linear modelling evaluation using german worker studies (inhalation exposed), reviewed by Larsen & Giovalle 2014 and used by RAC in their 22nd meeting to determine dose response relationships for authorisations. Extrapolations made to general population for chronic exposure. This report does not include any assessment of non-cancer effects for TCE. HBGV = (1/100,000) divided by inhalation slope factor of 6.4e-5 per mg/m3 = 0.154 mg/m3. For a 70kg adult breathing 20 m3/d: (0.154x20)/70 = 0.044 mg/kg/d.
USEPA IRIS Inhalation Unit Risk. 2011 (cancer) (inhalation studies)	0.71	µg/kg bw/day	2.5	µg/m3		ELCR	1 in 100,000		kidney cancer, NHL and liver cancer	Human kidney cancer risks (Charbotel et al. 2006), adjusted for potential risk for NHL and liver cancer. Supported by multiple rodent bioasseys. HBGV based on Inhalation Unit Risk (4x10-06 per µg/m3) and ELCR of 1 in 100,000 (1/100,000/4e-6 = 2.5 ug/m3). For a 70kg adult breathing 20 m3/d: (2.5x20)/70 = 0.71 ug/kg/d.
ATSDR Tox profile. June 2019. Inhalation MRL (route to route)	0.6	µg/kg bw/day	2.1	µg/m3	10	BMDL	0.021	mg/m3 (HEC99, BMDL01)	foetal heart malformations	MRL (0.57 µg/kg bw/day) based on two candidate chronic RfC; Keil et al. 2009 and Johnson et al. 2003 (both in EPA, 2011). Johnson et al. cardiac malformations in Sprague-Dawley rat fetuses whose mothers were exposed to TCE in drinking water from gestation days 1 to 22. HEC99 BM10 (the HEC99,BMDL01 is the route-to-route extrapolated 99th percentile [due to human toxicokinetic uncertainty and variability])of 0.021 mg/m3 calcuated from this study. UF of 10 applied (3.16 as PBPK model used for interspecies extrapolation, 3.16 as PBPK model used to characterise human toxicokinetic variability)to derive RfC = 2.1 ug/m3
USEPA IRIS Inhalation Unit Risk. 2011 (meta-analysis cancer) (inhalation studies)	**0.6**	µg/kg bw/day	2.1	µg/m3		ELCR	1 in 100,000		kidney cancer, NHL and liver cancer	A meta analysis using human kidney cancer (renal cell cancer(RCC)) risks (Charbotel et al. 2006), adjusted for potential risk for NHL and liver cancer (using other human epidemiology studies). HBGV based on Inhalation Total Unit Risk of 4.8x10-06 per µg/m3 taking account of presumed increased early life susceptability to kidney tumours for TCE (see page 5-159 Table 5-48 in US EPA 2011) and ELCR of 1 in 100,000 (1/100,000/4.8e-6 = 2.1 ug/m3). For a 70kg adult breathing 20 m3/d: (2.1x20)/70 = 0.6 ug/kg/d.
US EPA 2011 RfC (route to route)	0.57	µg/kg bw/day	2	µg/m3					foetal heart malformations + decreased thymus weight	Based on PBPK modellng approaches in US EPA 2011. the RfC is 0.0004 ppm (0.4 ppb or 2 µg/m3) based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations (rats) and decreased thymus weight (mice). This RfC value is further supported by route-to-route extrapolated results from an oral study of toxic nephropathy (rats).
ATSDR Tox profile. June 2019. Inhalation MRL (route to route)	0.54	µg/kg bw/day	1.9	µg/m3	100	LOAEL	0.19	mg/m3 (HEC99, LOAEL)	decreased thymus weight	MRL (0.57 µg/kg bw/day) based on two candidate chronic RfC; Keil et al. 2009 and Johnson et al. 2003 (both in EPA, 2011). Keil et al. decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water. Increased serum levels of IgG and selected autoantibodies at 1.4ppm dose. UF of 100 applied (10 as POD is LOAEL for adverse effect, 3.16 as PBPK model used for interspecies extrapolation, 3.16 as PBPK model used to characterise human toxicokinetic variability). No BMD modelling due to inadequate data fit. RfC for Keil et al. 2009 = 0.033ppm/100UF = 0.00033ppm = 1.9 ug/m3

COT/COC Opinion

Can not identify a COT/COC opinion for TCE. No search results on gov.uk. TCE is detailed within 1996 annual report (pages 39, 71) but this document is not freely available online. A reference value has not been generated for TCE by a UK or EU authoritative body in relation to chronic long term exposures and general public protection goals, i.e. considering new data since the EA Tox report in 2004.

Current UK inhalation HCV

Authoratative body (date) and HBGV type	HBGV value	Unit	UF used	PoD	POD value	Unit	Endpoint	Pivotal data used & Comments
DEFRA TOX 24 (2004) WITHDRAWN	5.2	µg/kg bw/day (Index Dose)	25,000	Other	130	mg/kg bw/d	Lymphomas	Mouse inhalation study (Henschler et al. 1980, within EU Existing Substances Programme. TD25 for lymphomas seen in mice was 130 mg/kg bw/day. Cancer potency of TCE is the same in humans as in mice. ELCR of 1 in 100,000

C) Dermal Route

Authoratative body (date) and HBGV type	HBGV value	Unit	UF used	POD	POD value	Unit	Endpoint	Pivotal Study used & Comments
None identified								

III) Current UK (WHO) regulatory values

	Value	Units	Refs
UK drinking water standard	10	µg/l	Water Supply (Water Quality) Regulations 2016. Table B, Part 1. Total concentration of TCE and PCE to be screened against this standard.
WHO drinking water standard	20	µg/l	Guidelines for Drinking-water Quality. Fourth Edition incorporating the first addendum (2017). Based on TDI of 7.5 ug/kg bw/d, based on NOAEL of 0.75 mg/kg bw/d for mild hepatic effects in a 1 year feeding study in dogs, with UF of 100 (inter and intra-species variation)
UK air quality standard			None
WHO air quality standard			None
ECHA			No threshold values identified for long term/chronic exposures

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
Johnson et al 2003	Water	0, 0.00045, 0.048, 0.218, and 129	mg/kg/day	Rat	Oral drinking water study	BMD1 calculated without PBPK modelling an internal dose. cardiac malformations in Sprague-Dawley rat fetuses whose mothers were exposed to TCE in drinking water from gestation days 1 to 22.

Selection of POD

Published POD for ORAL LLTC:		
Are dose response data of adequate quality to derive a BMD	Yes	
Type of PoD	BMD	
Value selected	0.0646	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)	0.0646			
	BMDL1	BMDL5	BMDL10	BMDL15
BMD modelling (value) (mg/kg bw/day)	0.0207			

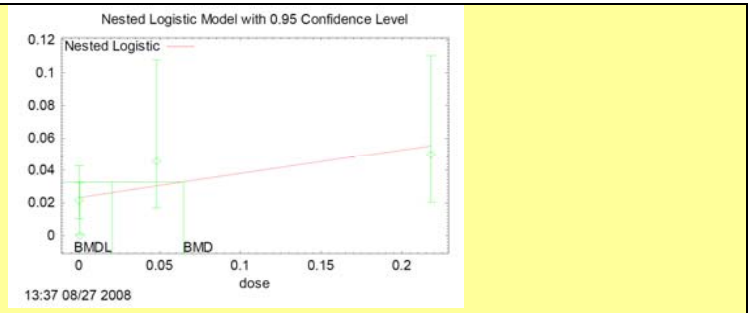
Comments: *Table F6 and Figure F2 from US EPA 2011 Appendices report.*

Table F-6. Results of nested log-logistic model for fetal cardiac anomalies from Johnson et al. (2003) without the high-dose group, on the basis of applied dose (mg/kg/day in drinking water)

Model	LSC?[a]	IC?	AIC	Pval	BMR	BMD	BMDL
NLOG	Y	Y	246.877	NA (df = 0)	0.01	0.252433	0.03776
NLOG	Y	N	251.203	0.0112	0.01	0.238776	0.039285
NLOG	N	N	248.853	0.0098	0.01	0.057807	0.028977
NLOG	N	Y	243.815	0.0128	0.1	0.71114	0.227675
NLOG	N	Y	243.815	0.0128	0.05	0.336856	0.107846
NLOG[b]	**N**	**Y**	**243.815**	**0.0128**	**0.01**	**0.064649**	**0.020698**

[a]LSC analyzed was female weight gain during pregnancy.
[b]Indicates model selected (Rai-VanRyzin model fits are essentially the same).

NLOG = "nested log-logistic" model



Addressing uncertainty

Thresholded effects?	Yes
If yes - use generic UF of 100 or (if data allow) calculate CSAF	100
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
Quality of study	1 - 10	1
Use of LOAEL as POD	1-10	1
Total CSAF/CSM		100

Lifetime averaging to be applied in CLEA (Yes/No)	No

Oral LLTC calculation:

	Value	Units	Justification
LLTC (Thresholded chemical) using NOAEL/LOAEL		µg/kg bw/day	
LLTC (Thresholded chemical) using BMD	0.646	µg/kg bw/day	BMD1 for fetal heart malformations from Johnson et al (2003) divided by a CSF of 100 (10 for interspecies x 10 for intraspecies)
LLTC (Non Thresholded chemical) using ELCR		µg/kg bw/day	
		µg/kg bw/day	

Delete as appropriate

Sensitive Receptor	Child, but also the developing fetus in pregnant woman. (consider time windows of exposure for foetal heart malformations)

b) INHALATION

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments
US EPA 2011 evaluation	N/A	N/A		Human	Meta analysis (all NHL, liver and kidney cancer data)	Human kidney cancer risks (Charbotel et al. 2006), adjusted for potential risk for NHL and liver cancer. Supported by multiple rodent bioasseys. HBGV based on Inhalation Total Unit Risk of 4.8x10-06 per µg/m3 taking account of presumed increased early life susceptability to kidney tumours for TCE (see page 5-159 Table 5-48 in US EPA 2011) and ELCR of 1 in 100,000 (1/100,000/4.8e-6 = 2.0 ug/m3). For a 70kg adult breathing 20 m3/d: (2.0x20)/70 = 0.57 ug/kg/d.

Selection of POD

Published POD for INHALATION LLTC:		
Are dose response data of adequate quality to derive a BMD	Yes	
Type of PoD	ELCR	
Value selected	0.6	ug/kg/day

Derived POD for INHALATION LLTC: (from data below)		
Type of PoD	BMDL	
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:

Example: Multistage model used for cancer effects.
Gamma etc used for non-cancer effects (diffuse epithelial hyperplasia)

Thresholded (non-cancer) effects?	No
If yes - use generic UF of 100 or (if data allow) calculate CSAF	
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 BMD10 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 =	1 in 50,000

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	
Interspecies	1 - 10	
Quality of study	1 - 10	
Use of LOAEL as POD	1-10	
Total CSAF/CSM		

Lifetime averaging to be applied in CLEA (Yes/No)	

Inhalation LLTC calculation:

	Value	Units	Justification
LLTC (Thresholded chemical) using NOAEL/LOAEL		µg/kg bw/day	
LLTC (Thresholded chemical) using BMD		µg/kg bw/day	
LLTC (Non Thresholded chemical) using ELCR	**1.20**	µg/kg bw/day	Based on USEPA 2011 evaluation that lifetime inhalation of 2.1 ug/m3 TCE in air would result in an ELCR of 1 in 100,000. Therefore, 4.2 ug/m3 would result in an ELCR of 1 in 50,000. 4.2 ug/m3 x assumed adult respiration volume of 20 m3/d and divided by adult body weight of 70 kg results in an LLTC of 1.20 ug/kg/d
LLTC (Non Thresholded chemical) using BMD		µg/kg bw/day	

Delete as appropriate

Sensitive Receptor	Child and Pregnant woman/developing foetus (consider time windows of exposure for FHM (oral LLTC))

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 2011 evaluation, which ATSDR have followed also in their evaluation. We have selected the same pivotal studies (Johnson et al 2003 (oral rodent data) and Charbotel et al 2006) (human inhalation study and meta analysis of kidney, NHL and liver cancer) as the basis of our LLTCs. and followed the principles of the C4SL framework to select appropriate margins of safety. Note, if PBPK modelling extrapolations are accepted as per EPA evaluation, without UK review, the LLTCs for both oral and inhalation would be lower than the values selected here.

APPENDIX B
MEAN DAILY INTAKE DATA SHEET FOR TCE

Substance: **Trichloroethene**

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 acros 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 TCE concentrations in food was negligible, based on MAFF 1993 study	Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Trichloroethene. Science Report TOX24.	http://webarchive.nationalarchives.gov.uk/20140328111046/http://www.environment-agency.gov.uk/research/planning/64002.aspx

MDI Inhalation			**Recommended adult inhalation MDI**	**Units**	**Justification: Trichloroethene is not monitored by the Defra UK AIR Network. WHO Indoor AQG (2010) provides more up to date data for indoor and outdoor concentrations than was available in Defra and EA (2004) and concludes that the ambient outdoor and indoor air concentrations of TCE in European and North American countries is generally <1 µg m-3.** WHO (2000) and WHO (2010) suggest that indoor air concentrations are in the same range as urban outdoor air concentration. Therefore, <1 µg m-3is considered suitably protective for the combined indoor and outdoor MDI. The concentrations reported by IARC (2014), ATSDR (2019) and Health Canada (2005) support this. 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 WHO (2000). A general average urban concentration of 10 µg m-3 based on data from European cities. Considered indoor exposure via groundwater volatilisation to be important but within the quoted range.	Defra and Environment Agency (2004). Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Trichloroethene	http://webarchive.nationalarchives.gov.uk/20140328153902/http://www.environment-agency.gov.uk/static/documents/Research/tce_old_approach_2029069.pdf
PHE Toxicological Overview	2008	Urban/Industrial Ambient Air	0.3 to 30	µg m-3	Cites EU RAR (2004). The range in urban and industrial air was 0.3 to 30 µg m-3.	PHE Toxicological Overview V1 2008.	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/341375/hpa_trichloroethylene_toxicological_overview_v1.pdf
WHO Air Quality Guidelines	2000	Urban Ambient Air	<10	µg m-3	Average ambient air concentrations in urban areas in European cities.	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 Air Quality Guidelines	2000	Rural Ambient Air	<1	µg m-3	Average ambient air concentrations in rural areas in European cities is <1 µg m-3.	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 Air Quality Guidelines	2000	Ambient Air	18.5	µg m-3	Maximum recorded mean concentration in European cities.	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 Air Quality Guidelines	2000	Ambient Air	0.8	µg m-3	Minimum recorded mean concentration in European cities.	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	<1	µg m-3	WHO reviewed the available studies and concluded that ambient outdoor and indoor air concentrations of TCE were generally less than 1 µg m-3 for European and North American countries. Data for Oxford recorded a median indoor residential concentration of 2.1 µg m-3 and an outdoor median concentration of 2.5 µg m-3. The available studies suggest that non-residential indoor concentration of TCE reflect outdoor ambient concentrations via infiltration from outdoors.	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
IARC	2014	Urban Ambient Air	0.08 to 0.43	µg m-3	Measurements of TCE in ambient air in the US indicate a downward trend in concentrations from 1980s to late 1990s. The mean concentrations and ranges in ambient air at urban sites across the US, Europe, Canada and Japan recorded in the past 15 years were provided with no measurements specifically from the UK. From the data where means were provided, and excluding industrial and gas well sites, the means ranged from 0.08 to 0.43 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
IARC	2014	Indoor Air	0.06 to 0.7	µg m-3	The range of mean indoor air concentrations, excluding one study near to a contaminated site was 0.06 to 0.7 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
US ATSDR	2019	Ambient Air	0.0541 to 0.874	µg m-3	The 95th percentile concentration in outdoor air in the US between 2010 and 2018 was between 0.0099 and 0.16 ppb. Using the conversion of 1 ppm = 5.46 µg.m-3 this equates to a range of between 0.0541 and 0.874 µg.m-3.	ATSDR (2019). Toxicological profile for trichloroethylene.	https://www.atsdr.cdc.gov/ToxProfiles/tp19.pdf
Health Canada	2005	Indoor Air	1.4	µg m-3	The most recent Canadian data for outdoor air concentrations was from the 1980s and 1990s and was considered too old to be relevant when more recent data sources for ambient air were available. A mean indoor air concentration of 1.4 µg.m-3 was measured in 1991.	Health Canada (2005). Guidelines for Canadian Drinking Water Quality: Supporting Documentation - Trichloroethylene	https://www.canada.ca/content/dam/canada/health-canada/migration/healthy-canadians/publications/healthy-living-vie-saine/water-trichloroethylene-eau/alt/water-trichloroethylene-eau-eng.pdf