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Category 4 Screening Levels: Vinyl Chloride

CL:AIRE

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This and other documents in this Category 4 Screening Levels (C4SLs) Phase 2 project have been developed for the Soil and Groundwater Technology Association (SAGTA – www.sagta.org.uk) by the following:

- 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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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
CSAF	Chemical-Specific assessment factor
CSM	Chemical Specific Margin
Defra	Department for Environment, Food and Rural Affairs
DWI	Drinking Water Inspectorate
DWS	Drinking Water Standard
ECHA	European Chemicals Agency
ELCR	Excess Lifetime Cancer Risk
HBGV	Health Based Guidance Value
HCV	Health Criteria Value
HED	Human Equivalent Dose
HPA	Health Protection Agency
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
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
SAGTA	Soil and Groundwater Technology Association
SCOEL	Scientific Committee on Occupational Exposure Limits
SOM	Soil Organic Matter
SR	Science Report
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency
VC	Vinyl Chloride
WHO	World Health Organization

1. INTRODUCTION

This report presents Category 4 Screening Levels (C4SLs) for vinyl chloride based on the methodology described in Section 5 of CL:AIRE (2014a) “SP1010 – Development of Category 4 Screening Levels for Assessment of Land Affected by Contamination”. Section 1.1 provides brief background information on vinyl chloride, 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 VINYL CHLORIDE

Vinyl chloride (also known as chloroethene, chloroethylene, and VC) (CAS No. 75-01-4) has the chemical formula C_2H_3Cl and is present as a colourless gas at room temperature and pressure. It is not reported to be naturally occurring. It is manufactured by the chlorination of ethene and can form through degradation of other chlorinated hydrocarbons in the environment (Defra and Environment Agency, 2004).

2. DERIVATION OF LOW LEVEL OF TOXICOLOGICAL CONCERN FOR VINYL CHLORIDE

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 the SP1010 report (CL:AIRE, 2014a) and reproduced below as Figure 2.1. The remainder of this section demonstrates the application of this framework to vinyl chloride. 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).

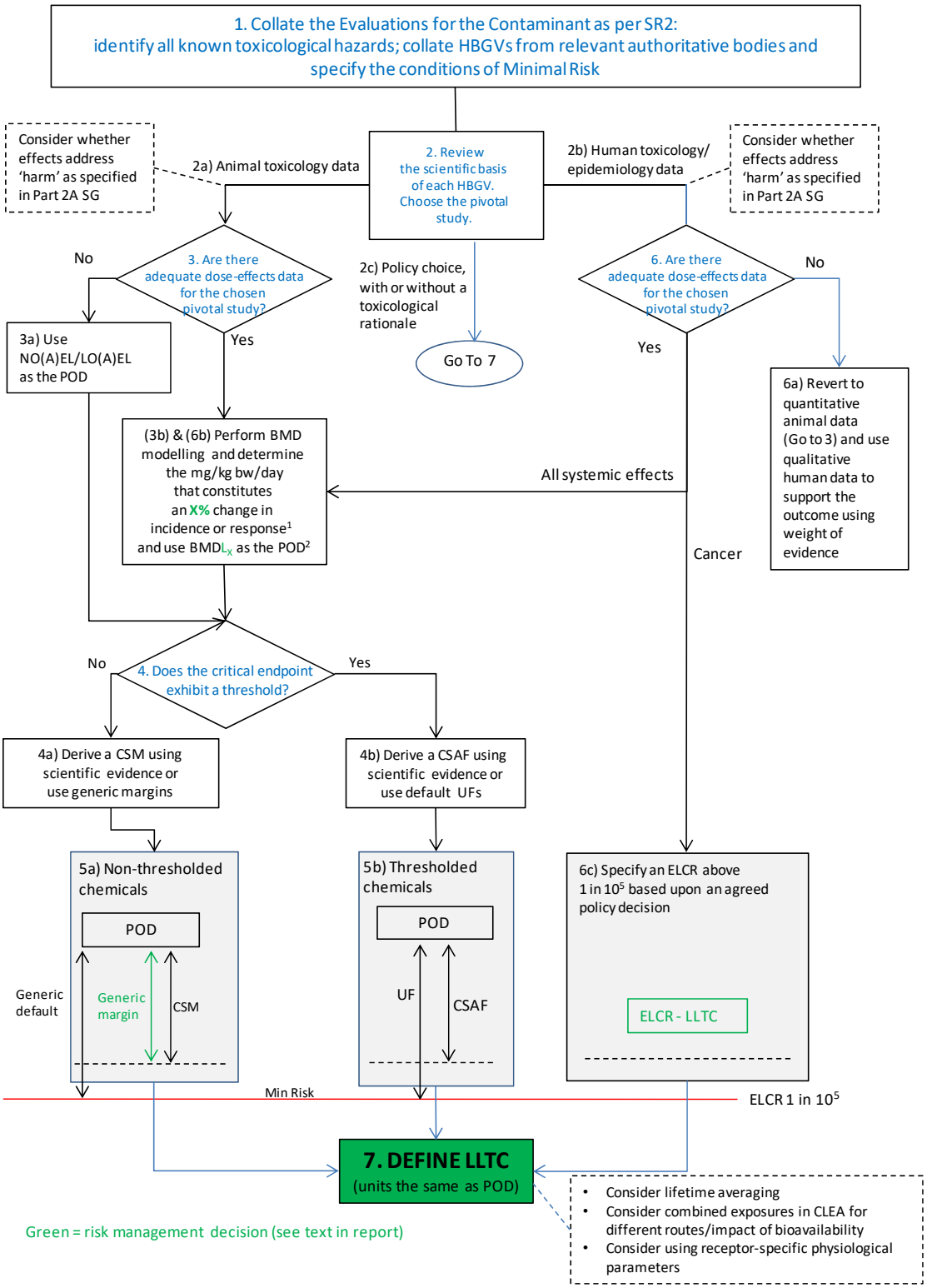

Figure 2.1: A framework for evaluating chemical-specific toxicology data for the purposes of LLTC derivation (reproduced from Figure 2.2 of SP1010 (CLAIRE, 2014a).

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 cancers of the liver, including angiosarcoma of the liver, and hepatocellular carcinoma, are some of the sensitive[1] toxicological effects following exposure to vinyl chloride by the oral route.

Vinyl chloride also exerts threshold effects with the liver being the primary target for non-cancer effects in animals and humans. Hepatotoxicity effects include liver necrosis, liver cell polymorphism and hepatic cysts as well as alterations in liver function US EPA (2000).

As a result, a threshold and non-threshold $LLTC_{oral}$ will be derived for vinyl chloride to ensure the C4SL is suitably protective for both effects.

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

Non-threshold effects

The critical toxic endpoint selected from the toxicity studies available is liver cancer including angiosarcoma of the liver and hepatocellular carcinoma. Based on all the data available, the Feron *et al.* (1981) study has been selected as the pivotal study for cancer effects.

In a lifetime dietary study, 60–80 Wistar rats per sex per dose were administered vinyl chloride (ingested doses of 0, 1.8, 5.6 or 17 mg kg^{-1} bw day^{-1}, which were converted to bioavailable doses of 0, 1.7, 5.0, or 14.1 mg kg^{-1} bw day^{-1}) for 7 days per week for 135 weeks (males) and 144 weeks (females).

Histological assessment indicated a dose-dependent statistically significant increase in hepatotoxicity in both male and female rats. Liver effects included clear cell, basophilic, and eosinophilic foci, neoplastic nodules, hepatocellular carcinoma and angiosarcoma. Tumours were observed at all doses. Hepatocellular tumours and neoplastic nodules were observed at low doses, angiosarcomas were seen at high doses whereas a mixture of angiosarcoma and hepatocellular carcinoma was observed at mid and high doses (US EPA, 2000). Incidence of liver tumours (as either neoplastic liver nodules, hepatocellular carcinoma and/or angiosarcoma) in females were reported as 2/57, 28/58, 49/59 and 56/57 (US EPA, 2000). Females were selected as the basis for HBGV derivation as the incidence

[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.

of liver tumour-bearing animals was greater than in males, giving a more conservative estimate.

Neoplastic nodules (observed at the low doses), while not malignant, have the potential to progress to malignancy. Although inclusion of neoplastic nodules may represent a conservative approach, low body weights were noted by Feron *et al.* (1981), due to restriction of food intake to four hours per day, which is likely to have decreased tumorigenesis.

US EPA (2000) considered the Feron *et al.* (1981) study to be well conducted, to use an adequate number of rats, and to be supported by results of a follow-up study by Til *et al.* (1991), as well as studies reported by Maltoni *et al.* (1981) and a further study in 1984 (cited by US EPA, 2000). Feron *et al.* (1981) is used by several regulatory authorities as the pivotal study for derivation of their HBGVs (US EPA, 2000; WHO, 2017; RIVM, 2001; Health Canada, 2013).

Threshold effects

The critical non-carcinogenic endpoints are hepatic cysts and liver cell polymorphism. Based on all the data available, the Til *et al.* study (Til *et al*. 1983, 1991) has been selected as the pivotal study. The work of Til *et al*. (1983, 1991) is an extension of Feron *et al.* (1981), conducted using lower doses of vinyl chloride.

In the lifetime feeding study, groups of 50 or 100 male and female Wistar rats were administered vinyl chloride (0, 0.46, 4.6, or 46 ppm, which were converted to 0, 0.014, 0.13 and 1.3 mg kg^{-1} bw day^{-1}) in the diet for 149 weeks.

Histopathological examination indicated increased incidences of numerous non-neoplastic lesions including liver cell polymorphism, hepatic cysts and liver necrosis. Of these, liver cell polymorphism was observed in males and hepatic cysts were seen in females, both at low doses, and hence were deemed the critical non-carcinogenic, thresholded effects.

US EPA (2000) attributed high confidence to the Til *et al.* study (1983, 1991) because it used adequate numbers of animals, was well controlled, and provided detailed reporting of histological effects. In addition, critical effects namely liver alterations and histopathology, are corroborated by other long-term studies including oral studies (Feron *et al*., 1981). Health Council of the Netherlands (2017) attributed a Klimisch score of 2 to the study deeming it a well conducted study.

Several regulatory authorities cited Til *et al. (1983, 1991)* as the pivotal study for derivation of their non-cancer HBGV (US EPA, 2000; RIVM, 2001; ATSDR, 2006; Health Canada, 2013).

GO TO FLOWCHART ELEMENT 3.

2b) Human Toxicology/Epidemiology Data

Ingestion of vinyl chloride is unlikely as it is a gas at room temperature (HPA, 2008) and inhalation is the primary route of human exposure. ATSDR (2006) was unable to locate any human/epidemiological oral studies for lethal, cancer or systemic adverse effects.

Human toxicological or epidemiological data are not applicable to the derivation of an $LLTC_{oral}$ for vinyl chloride.

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

For the $LLTC_{oral}$, a policy-based decision to use the UK Drinking Water Standard (DWS) of 0.5 µg L^{-1} as the basis of the LLTC could be adopted. This standard is based on a 'practical achievable limit' for vinyl chloride in drinking water. The value refers to the residual vinyl chloride monomer concentration in the water as calculated according to plastic pipework specifications of the maximum release from the corresponding vinyl chloride polymer in contact with the water. This principle, used in the derivation of the C4SL for arsenic (CL:AIRE, 2014b) applies only when soil would otherwise be disproportionately affected when compared to other media (in this case drinking water).

If the scientific-based LLTC is lower than a LLTC calculated from a regulatory standard i.e. the UK DWS, then the latter should be adopted.

The DWS (0.5 µg L^{-1}) corresponds to an intake of 0.0143 µg kg^{-1} bw day^{-1} for a 70 kg adult drinking 2 L water per day, 0.0376 µg kg^{-1} bw day^{-1} for a 13.3 kg child[2] drinking 1 L water per day and 0.0238 µg kg^{-1} bw day^{-1} for a 21 kg[3] child drinking 1 L water per day.

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

Yes	No	Not applicable
X (Non-Threshold)	X (Threshold)	

The data from Feron *et al.* (1981) on combined liver tumours (angiosarcoma, hepatocellular carcinoma, and neoplastic nodules) and Til *et al.* (1983, 1991) on liver cysts and liver cell polymorphism are considered to be the pivotal studies for non-threshold and threshold effects, respectively. Such studies could form the basis of the $LLTC_{oral}$. It is noted that various authoritative bodies used physiologically based pharmacokinetic (PBPK) modelling to calculate human equivalent dose (HED) from the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) in their evaluations in order to consider the toxicological effects from the toxic vinyl chloride metabolite. Other authoritative bodies including the US EPA and Health Canada have used PBPK rat and human models for vinyl chloride in the derivation of HBGV. However, PBPK models introduce considerable complexity and potential uncertainty. The HED derived from the NOAEL of 0.13 mg kg^{-1} bw day^{-1}, as reported, would be a slightly more conservative starting point (0.09 mg kg^{-1} bw day^{-1}) for the derivation of the oral LLTC. But it has not been within the scope of this project to review the appropriateness of the PBPK models used for vinyl chloride and therefore the NOAEL has been used.

GO TO FLOWCHART ELEMENT 3a/b

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

For the thresholded effects, US EPA stated that they used the data from the Til *et al.* (1983, 1991) study to calculate a Benchmark Dose (BMD_{10}) using internal dose metrics (mg metabolite L^{-1} liver) using PBPK modelling but concluded that due to the limitations in the data (only one non-zero datapoint, wide dose spacings) and variable outputs from the BMD models, the BMD approach was not appropriate (US EPA, 2000).

Therefore, for the purposes of deriving an $LLTC_{oral}$ for thresholded effects, a NOAEL of 0.13 mg kg^{-1} day^{-1} is proposed as the point of departure (POD), based on liver cell polymorphism in male rats, increased incidence of hepatic cysts in female rats, and increased mortality, observed by Til *et al.* (1991). This approach and the approach used to derive the $LLTC_{oral}$ for non-thresholded effects were further evaluated to ensure the most conservative LLTC is selected.

2.1.5 FLOWCHART ELEMENT 3b: Perform Benchmark Dose modelling

For the non-thresholded effects, there are good quantitative data available from the Feron *et al.* (1981) study. Such data have been used in BMD modelling to determine the non-threshold $LLTC_{oral}$. Due to uncertainties in the use of the HED, BMD modelling was

[2] Average body weight of a 0 to 6 year old child assumed for calculation of C4SL for residential, allotments and public open space (park) land-uses (CL:ARE, 2014a)

[3] Average body weight of a 3 to 9 year old child assumed for calculation of C4SL for public open space (residential) land-use (CL:ARE, 2014a)

undertaken on combined liver tumours from Feron *et al.* (1981) data using the animal external dose as the dose metric.

The US EPA Benchmark Dose Software (BMDS) version 2.7 was used to fit dichotomous models to incidence data for combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female Wistar rats exposed to vinyl chloride as reported by US EPA (2000), determined from Feron *et al.* (1981).

The dose-response models used to fit the data included:

- Gamma model
- Logistic model
- LogLogistic model
- LogProbit model
- Multistage model
- Multistage-Cancer model
- Probit model
- Weibull model
- Quantal-Linear model

The BMD_{10} and the corresponding 95th lower confidence limit ($BMDL_{10}$) were calculated associated with a benchmark response (BMR) of 10% extra risk of the effect occurring[4]. For the derivation of the LLTC, the BMD_{10} value could be selected as the POD.

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 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' (US EPA 2012).

Data from BMD modelling for non-thresholded effects are presented in Table 2.1 and the BMD modelling output from BMDS is shown in Figure 2.2.

Table 2.1: BMD_{10} and $BMDL_{10}$ calculations from the best fitting models for non-thresholded endpoints

Endpoint	Species/sex	Model	AIC	BMD_{10} (mg kg^{-1} bw day^{-1})	$BMDL_{10}$ (mg kg^{-1} bw day^{-1})
Angiosarcoma, hepatocellular carcinoma and neoplastic nodules	*Female Wistar rats*	*Multi-stage cancer; gamma; Weibull; Quantal linear*	*166.07*	*0.311*	*0.256*

[4] The BMD_{10} associated with a BMR of 10% was recommended by Defra (2014) for animal carcinogenicity data.

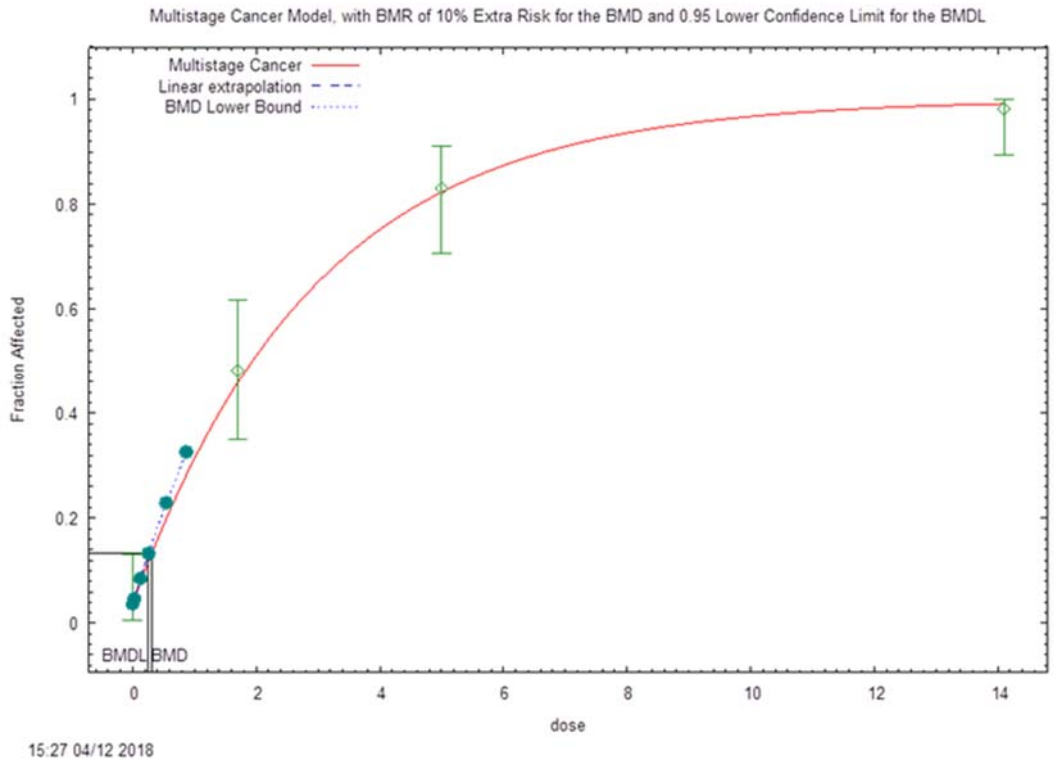

Figure 2.2: Multistage cancer model of combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female Wistar rats.

Overall, for the purposes of deriving an $LLTC_{oral}$ for non-thresholded effects, a BMD_{10} of 0.311 mg kg^{-1} bw day^{-1} is proposed as the POD, based on combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female Wistar rats.

This approach and the approach used to derive the $LLTC_{oral}$ for thresholded effects were further evaluated in order to ensure that the most conservative LLTC is selected.

GO TO FLOWCHART ELEMENT 4a/b

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

Yes	No	Not applicable
X	X	

Vinyl chloride exhibits non-thresholded and thresholded endpoints, namely combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) and liver cell polymorphism and hepatic cysts, respectively. Both threshold and non-threshold effects are evaluated in order to derive the most appropriate LLTC in accordance with the framework.

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

For the purpose of deriving an $LLTC_{oral}$ for vinyl chloride for the adult receptor, a generic margin of 5,000 is proposed in conjunction with the calculated BMD_{10}. This relates to a notional 'low' risk level of 1 in 50,000 as described in SP1010 (CL:AIRE, 2014a).

For the child receptor, an additional uncertainty factor (UF) of two is applied to account for the sensitivity of very young children. Health Canada (2013) state evidence from animal studies could indicate very young children may be more sensitive to the carcinogenic effects of vinyl chloride. It is suggested this is due to increased DNA adduct formation and liver tumour incidence observed in animals under five weeks of age exposed to vinyl chloride, compared with animals exposed after maturity. Although early-life data in humans are lacking, many of the factors likely to be responsible for early-life sensitivity in animals are also considered relevant to humans. These factors include rapid cell division during early life and dosimetric considerations (such as increased water intake per unit body weight and more rapid blood flow to liver). A second growth peak for the liver may occur around the age of six, indicating that children this age may also be sensitive to vinyl chloride. Consequently, in addition to the generic margin of 5,000, an UF of two (to give a chemical specific margin (CSM) of 10,000) is applied to the POD to derive the LLTC for the child receptor to protect young children from lifetime exposure to vinyl chloride. A similar approach is adopted by the US EPA (2000).

2.1.8 FLOWCHART ELEMENT 4b: Derive a chemical-specific assessment factor (CSAF) using scientific evidence or use default UFs

Most authoritative bodies used PBPK modelling and HED and hence the toxicokinetic element of the UF had been accounted for. Therefore, the total UF used by authoritative bodies is not appropriate for use when deriving the LLTC for threshold effects.

RIVM (2001) used a factor of 10 for both inter and intraspecies variability to give a total UF of 100 since its HBGV is based on the administered doses from the Til *et al.* study (1983, 1991) and not those calculated using PBPK modelling. If PBPK modelling is used to derive a HED, then using a UF to account for intraspecies differences is not necessary. No further UFs were used by authoritative bodies, e.g. due to a lack of a NOAEL or database inadequacies, because adequate chronic, developmental, and multigenerational reproductive studies exist.

For the derivation of an $LLTC_{oral}$, the default UFs are proposed as per the following:

- Intraspecies variability: 10 (to account for toxicokinetic and toxicodynamic variability within the human population); and
- Interspecies variability: 10 (to account for toxicokinetic and toxicodynamic variability between humans and rats).

Therefore, a CSAF of 100 is proposed.

GO TO FLOWCHART ELEMENT 5a/5b

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

For non-thresholded effects, the LLTC is calculated by dividing the POD by the generic margin or CSM:

POD/margin or CSM = LLTC (units as per POD)

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

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

Table 2.2 presents the choices of POD, choices of margin and the resultant LLTCs.

Table 2.2: Proposed choices of $LLTC_{oral}$ values using different PODs and/or CSMs for different receptors and land uses

	POD	Value ($mg\ kg^{-1}\ bw\ day^{-1}$)	CSM /CSAF	LLTC ($\mu g\ kg^{-1}\ bw\ day^{-1}$)
LLTC (non-threshold) ADULT (commercial land use)	BMD_{10}	0.311	5,000	0.0622
LLTC (non-threshold) CHILD (POS residential)	BMD_{10}	0.311	10,000	0.0311
LLTC (non-threshold) CHILD (residential, allotment and POS park)	UK DWS	0.0376* (based on DWS of 0.5 $\mu g\ L^{-1}$)	NA	0.0376
LLTC (threshold) ADULT and CHILD	NOAEL	0.13	100	1.3

*based on a 13.3 kg child drinking 1 L of water per day

GO TO FLOWCHART ELEMENT 7

2.1.10 FLOWCHART ELEMENT 7: Assess LLTC for vinyl chloride

Based upon a scientific evaluation of a dietary study in female Wistar rats (Feron *et al.,* 1981), **an $LLTC_{oral}$ of 0.0622 $\mu g\ kg^{-1}\ bw\ day^{-1}$** for adults is proposed, based on a BMD_{10} of 0.311 mg kg^{-1} bw day^{-1} and a margin of 5,000. For children, two LLTCs are proposed. For residential, allotments and Public Open Space (POS) parks, **an $LLTC_{oral}$ of 0.0376 $\mu g\ kg^{-1}\ bw\ day^{-1}$** is proposed based on the UK DWS. For POS residential, **an $LLTC_{oral}$ of 0.0311 $\mu g\ kg^{-1}\ bw\ day^{-1}$** is proposed, based on a BMD_{10} of 0.311 mg kg^{-1} bw day^{-1} and a margin of 10,000.

The adult value is four fold higher than the current Environment Agency minimal risk value of **0.014 $\mu g\ kg^{-1}\ bw\ day^{-1}$** (Defra and Environment Agency, 2004) that is based on an excess lifetime cancer risk (ELCR) of 1 in 100,000. The child values are two to three fold higher than the current Environment Agency minimal risk value.

Therefore, these LLTC are considered to be pragmatic levels for setting a C4SL, and are suitably protective of all health effects including cancer in the general population.

Toxicological effects from vinyl chloride are systemic and therefore a combined inhalation and oral C4SL should be derived in accordance with SR2 (Environment Agency, 2009a).

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 inhalation HBGVs from authoritative bodies provides the best evidence that liver angiosarcoma is the most sensitive toxicological effect following exposure to vinyl chloride by the inhalation route. Few threshold effects were reported with the exception of hepatic centrilobular hypertrophy, although this was only reported in short term studies so deemed not appropriate as a basis of the LLTC.

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 studies investigating adverse effects of vinyl chloride via the inhalation route as reviewed by US EPA (2000), RIVM (2001, 2009) and ATSDR (2006), human epidemiological data have been used as the pivotal study to derive the inhalation LLTC for vinyl chloride.

2b) Human Toxicology/Epidemiology Data

Inhalation is the primary route of human exposure to vinyl chloride, with occupational exposure being the main source (HPA, 2008). The risks estimated from epidemiological studies are the most relevant for human exposures.

The critical toxic endpoint selected from the toxicity studies available is cancer including haemangiosarcoma, hepatocellular carcinoma and angiosarcoma. Based on all the data available, a US occupational study, as reviewed by WHO (2000), has been used as the pivotal study for cancer effects.

The WHO (2000) air quality guideline is based on the 1978 US Equitable Environmental Health occupational study. The study identified 10,173 workers employed for one or more years across 37 vinyl chloride and PVC (polyvinyl chloride) production plants. The average duration of employment was 8.7 years and a weighted exposure of 650 ppm (converted by WHO to 1,665 mg m^{-3}) was estimated. From a total population at risk of 12,000, the unit exposure lifetime risk from an average exposure of 9 years was calculated as 0.75×10^{-5} per mg m^{-3}. Using linear dose-response relationships to convert from occupational to lifetime exposure, the continuous lifetime risk of haemangiosarcoma was estimated as 4.7×10^{-4} per mg m^{-3}, which equates to a 10^{-6} risk at 0.0021 mg m^{-3}. Assuming the number of cancers in other sites equals that of haemangiosarcomas, the ELCR of 1 in 1,000,000 for all cancers occurs as a result of continuous lifetime exposure to 0.001 mg m^{-3}. An ELCR of 1 in 100,000 is equivalent to 0.010 mg m^{-3}, which equates to 2.86 µg kg^{-1} bw day^{-1} assuming a 70 kg adult inhales 20 m^3 day^{-1}.

In comparison, using four different epidemiological studies, including the WHO (2000) evaluation, and three studies that carried out PBPK modelling, Scientific Committee on Occupational Exposure Limits (SCOEL) (2004) nominated the risk of angiosarcoma to be 2.1×10^{-3} following lifetime exposure to 1 ppm (2.59 mg m^{-3}). Therefore 4.76×10^{-3} ppm vinyl chloride (0.012 mg m^{-3}) is equivalent to an ELCR of 1 in 100,000. Similarly, the Health Council of the Netherlands (2017) used occupational data from a European cohort study and estimated that lifetime exposure to 0.0203 mg m^{-3} equates to an ELCR of 1 in 100,000 for angiosarcoma.

The concentrations associated with an ELCR of 1 in 100,000 provided by SCOEL (2004) (0.012 mg m^{-3}) and the Health Council of the Netherlands (2017) (0.0203 mg m^{-3}) are similar to, but less conservative, than that selected by WHO (2000) (0.010 mg m^{-3}).

GO TO FLOWCHART ELEMENT 6

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

There is no UK air quality standard for vinyl chloride and so this is not applicable to the derivation of an inhalation LLTC for vinyl chloride.

2.2.3 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

2.2.4 FLOWCHART ELEMENT 6c: Specify an ELCR above 1 in 100,000

Most authoritative bodies have based their HBGV on an ELCR of 1 in 100,000. For the purposes of deriving a LLTC, it is proposed that a concentration that equates to an ELCR of 1 in 50,000 (as per the C4SL framework) is used and is based on the WHO evaluation (WHO, 2000) (Table 2.3).

On the basis that WHO (2000) estimated that continuous lifetime inhalation exposure to 0.010 mg m^{-3} vinyl chloride would equate to an ELCR of 1 in 100,000 and assuming linear extrapolation, continuous lifetime exposure to 0.020 mg m^{-3} vinyl chloride would equate to an ELCR of 1 in 50,000. This converts to a dose of 5.71 µg kg^{-1} bw day^{-1} assuming a 70 kg adult inhales 20 m^3 day^{-1}.

Due to early life sensitivity of children to vinyl chloride, no child-specific LLTC values have been derived. Therefore, the adult LLTC value is proposed for all land uses. Note that child specific LLTCs would have been higher and therefore the adoption of the adult LLTC for all age groups is conservative.

Table 2.3: Inhalation LLTC value

	ELCR	Air Concentration (mg m^{-3})	LLTC (µg kg^{-1} bw day^{-1})
LLTC (all land-uses and receptors)	1 in 50,000	0.020	5.71

GO TO FLOWCHART ELEMENT 7

2.2.5 FLOWCHART ELEMENT 7: Assess LLTC for vinyl chloride

Based upon a scientific evaluation of occupational vinyl chloride exposure in workers WHO, (2000), the following inhalation LLTC is proposed:

LLTC of 5.71 µg kg^{-1} bw day^{-1} for adults; children aged 0-6 years of age and children aged 3-9 years of age

This LLTC is based on an ELCR of 1 in 50,000 at an air concentration of 0.020 mg m^{-3} adjusted for adult physiological factors.

The LLTC value:

a) is 19 fold higher that the current Defra and Environment Agency minimal risk Health Criteria Value (HCV) of **0.3 µg kg^{-1} bw day^{-1}** (Defra and Environment Agency, 2004), although it should be noted this is based on an ELCR of 1 in 1,000,000 as it predates SR2 (Environment Agency, 2009a) which defines 'minimal' risk as normally being 1 in 100,000. The proposed $LLTC_{inhal}$ is two fold higher than if the previous HCV (Defra and Environment Agency, 2004) were defined based on an ELCR of 1 in 100,000.

b) describes a 1 in 50,000 ELCR.

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.

Toxicological effects from vinyl chloride are systemic and therefore a combined inhalation and oral C4SL should be derived in accordance with SR2 (Environment Agency, 2009a).

2.3 DERMAL ROUTE

The gaseous nature of vinyl chloride precludes carrying out conventional skin sensitisation studies in animals (ECHA, 2018).

No data were found on the acute, chronic or cancer effects via the dermal route (ATSDR, 2006).

In the absence of dermal toxicity data and in accordance with SR2 (Environment Agency, 2009a), dermal exposure will be compared against the $LLTC_{oral}$ for the purposes of the derivation of the C4SL for vinyl chloride.

2.4 MEAN DAILY INTAKE

The recommendations from the above toxicology review have identified that non-threshold effects are the most sensitive for both oral and inhalation routes in deriving the LLTC values for vinyl chloride. Therefore, the Mean Daily Intake (MDI) for exposure from non-soil sources is not included in the exposure modelling as discussed in Section 3. For information purposes, a review of MDI data from food, air and drinking water sources is discussed in section 4.2 below.

3. EXPOSURE MODELLING FOR VINYL CHLORIDE

As described in C4SL SP1010 report (CL:AIRE, 2014a), 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 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 vinyl chloride, the critical effects for the LLTC via both oral and inhalation routes of exposure are systemic and the former approach has been taken to determine the C4SLs for vinyl chloride.

The assumptions and non-contaminant specific parameter values used for the derivation of the C4SLs are presented in the C4SL SP1010 report (CL:AIRE 2014a) and the SR3 report (Environment Agency, 2009b).

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

Table 3.1: Contaminant specific parameter values used for derivation of C4SLs for vinyl chloride

Parameter	Units	Value	Source/Justification
Air-water partition coefficient	dimensionless	0.747	SR7 (Environment Agency, 2008)
Diffusion coefficient in air	$m^2 s^{-1}$	1.11×10^{-05}	SR7 (Environment Agency, 2008)
Diffusion coefficient in water	$m^2 s^{-1}$	8.34×10^{-10}	SR7 (Environment Agency, 2008)
Relative molecular mass	g mol^{-1}	62.5	SR7 (Environment Agency, 2008)
Vapour pressure	Pa	220,000	SR7 (Environment Agency, 2008)
Water solubility	mg L^{-1}	2,760	SR7 (Environment Agency, 2008)
Log Koc	Log $cm^3 g^{-1}$	1.22	SR7 (Environment Agency, 2008)
Log Kow	dimensionless	1.38	SR7 (Environment Agency, 2008)
Dermal absorption fraction	dimensionless	0.1	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 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 vinyl chloride in soil and dust is the same as bioavailability of vinyl chloride 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 vinyl chloride are discussed briefly below.

Soil to dust transport factor

The soil to dust transport factor should be contaminant specific but where contaminant specific data are not available in the SR3 report (Environment Agency, 2009b) recommends a default value of 0.5, 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 used to calculate the C4SL.

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 vinyl chloride has been modelled using the default method for organic chemicals within the CLEA software.

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

4. C4SLs FOR VINYL CHLORIDE

4.1 C4SLS

The C4SLs for vinyl chloride 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 vinyl chloride

Land-use	C4SLs ($mg.kg^{-1}$)		
	SOM Content		
	1.0%	2.5%	6.0%
Residential with consumption of homegrown produce	0.0064	0.010	0.017
Residential without consumption of homegrown produce	0.015	0.019	0.029
Allotments	0.0017	0.0031	0.0058
Commercial	1.1	1.4	2.2
Public Open Space (residential)	7.8	7.8	7.8
Public Open Space (park)	18	19	19

The ADE:HCV 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	0.43	0.57
Residential without consumption of homegrown produce	0.01	0.99
Allotments	1.00	0.00
Commercial	0.02	0.98
Public Open Space (residential)	1.00	0.00
Public Open Space (park)	0.95	0.05

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	0.00	0.00	0.03	0.02	79.30	10.14
Sum of consumption of homegrown produce and attached soil	0.49	-	99.74	-	-	-
Dermal contact (indoor)	0.00	0.00	-	0.00	2.40	-
Dermal contact (outdoor)	0.00	0.00	0.02	0.00	2.81	1.00
Inhalation of dust (indoor)	0.00	0.00	-	0.00	0.28	-
Inhalation of dust (outdoor)	0.00	0.00	0.00	0.00	0.00	0.00
Inhalation of vapour (indoor)	99.51	100	-	99.97	-	-
Inhalation of vapour (outdoor)	0.00	0.00	0.21	0.01	15.21	88.85

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

- Consumption of homegrown produce and indoor inhalation of vapours for residential with homegrown produce land-use;
- Indoor inhalation of vapours for residential without homegrown produce and commercial land-uses;
- Consumption of homegrown produce for allotments land-use; and
- Ingestion of soil and soil derived dust for the POS_{resi} and POS_{park} land-uses[5].

4.2 OTHER CONSIDERATIONS

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

- Vinyl chloride is produced synthetically via the chlorination of ethene primarily as a precursor for PVC manufacture. There are no known naturally occurring sources of vinyl chloride in the environment, although it is known to occur as a degradation product of other synthetic chlorinated hydrocarbons under anaerobic conditions in the environment. Reactions include the reductive dehalogenation of trichloroethene to dichloroethene and vinyl chloride in the presence of microbes and appropriate environmental conditions (Defra and Environment Agency, 2004 and ATSDR, 2006). The presence of vinyl chloride may therefore indicate the presence of other chlorinated solvents, the risk from which should also be considered.

[5] Note that although vapour inhalation outdoors is the principal contributor to total exposure, the $LLTC_{oral}$ is significantly lower than the inhalation LLTC and therefore oral exposure drives risk

- Table 4.3 above shows that within the residential and commercial exposure scenarios (where the inhalation of vapour in indoor air pathway is operational) exposure to vinyl chloride 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 vinyl chloride 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.
- Typical currently reported commercial laboratory limits of detection (LODs) for vinyl chloride 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 C4SL presented in Table 4.1 are within or close to this range of LODs. When applying the C4SLs for vinyl chloride 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.
- Given the low values of the derived C4SL for allotment and residential land-use scenarios, appropriate volatile organic compound (VOC) soil sample collection methodologies are required to minimise uncertainty inherent in data collection and ensure that data are representative of soil conditions.
- No data were available in the literature for background concentrations of vinyl chloride in UK soils or USA soils (Defra and Environment Agency, 2004 and ATSDR, 2006). Vinyl chloride is not expected to occur above typical laboratory LODs in soil away from a source of chlorinated solvents (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 VOCs only 1% had a concentration of vinyl chloride above the LOD (5 to 10 μg kg^{-1}), with the majority of the detected concentrations being in the range of 10 to 1,000 μg kg^{-1}.
- Intake of vinyl chloride from non-soil sources (food, water and air) has been considered as follows:
    - No reports of UK measurements of vinyl chloride in drinking water were identified although the UK DWS is at 0.5 μg L^{-1} and therefore background exposure should be less than 1 μg L^{-1} for an adult consuming 2 litres of drinking water per day (Defra and Environment Agency, 2004).
    - Negligible concentrations are likely to be present in food due to changes to food packaging (Defra and Environment Agency, 2004 and ATSDR, 2006).
    - A mean daily intake of 23.4 μg day^{-1} of vinyl chloride in air was estimated from a maximum USA urban air concentration (omitting data from near industrial sites) of 1.17 μg m^{-3} (ATSDR, 2016) multiplied by an assumed adult respiration rate of 20 m^3 day^{-1}. Although the data are not UK-based, the value is within the range quoted by WHO (2000). The maximum air concentration recorded (including data from near industrial sites) was 6.16 μg m^{-3}. By way of comparison the predicted indoor air concentrations at the C4SLs for residential land-uses are in the region of 3 to 9 μg m^{-3}. The predicted indoor air concentrations at the C4SLs for commercial land-use are in the region of 100 μg m^{-3}.
- Since vinyl chloride 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.

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APPENDIX A
HUMAN TOXICOLOGICAL DATA SHEET FOR VINYL CHLORIDE

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

Chemical: **Vinyl chloride**

Human Health Hazard Profile - References

Authoritative bodies	Website	Checked (Y/N)	References
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Committee on Carcinogenicity	http://www.iacoc.org.uk/	Y	COT COM COC Annual Report 1997. https://cot.food.gov.uk/sites/default/files/cot/cotcomcoc1997.pdf
Committee on Mutagenicity	http://www.iacom.org.uk/	Y	COT COM COC Annual Report 2006 https://cot.food.gov.uk/sites/default/files/cot/cotannualrep2006.pdf
Committee on Toxicity	http://cot.food.gov.uk/	Y	COT Second Statement on Landfill Sites 2010 https://cot.food.gov.uk/sites/default/files/cot/cotstatementlandfill201001.pdf
ECHA REACH - is there a dossier?	http://echa.europa.eu/information-on-chemicals	Y	CLP Regulation Harmonised Classification and Labelling: https://echa.europa.eu/substance-information/-/substanceinfo/100.000.756
			REACH Registration Dossier: https://echa.europa.eu/registration-dossier/-/registered-dossier/16163/7/5/1 (viewed 14/02/18)
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	JEFCA 1984 http://www.inchem.org/documents/jecfa/jecmono/v19je16.htm
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US EPA	http://www.epa.gov/	Y	US EPA, 2000. Toxicological Review of Vinyl Chloride. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1001tr.pdf
			US EPA, 2000. IRIS Chemical Assessment Summary. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1001_summary.pdf
US National Toxicology Program	http://ntp.niehs.nih.gov/	Y	NTP, 2014. Report on Carcinogens, Fourteenth Edition. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/vinylhalides.pdf
Health Canada	http://www.hc-sc.gc.ca/index-eng.php	Y	Health Canada, 2013. Guidelines for Canadian Drinking Water Quality. https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-vinyl-chloride.html
Australia NICNAS	http://www.nicnas.gov.au/	Y	-
Risk Assessment Information System	http://rais.ornl.gov	Y	-
Other scientific reviews	Check for key reviews on pubmed	Y	PubMed and Web of Science checked 05/02/18, no relevant reviews >2005 found.
Other key sources:			
IPCS INCHEM OECD	http://www.inchem.org/	Y	OECD, 2001. Screening Information Data Set. http://www.inchem.org/documents/sids/sids/vinylchl.pdf
IARC	http://monographs.iarc.fr/	Y	IARC, 2012. http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-31.pdf
EC SCOEL	http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en	Y	SCOEL, 2004. http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en
Health Council of the Netherlands	https://www.gezondheidsraad.nl/en/home	Y	Health Council of the Netherlands, 2013. VCM. Health-based calculated occupational cancer risk values. https://www.gezondheidsraad.nl/sites/default/files/201701vinyl_chloride_monomer.pdf

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

Chemical: **Vinyl chloride**

I) Human Health Hazard Profile - Toxicological Evidence

Most sensitive health effects:

Sensitive endpoints	Other information	Source of evidence
Carcinogenicity	*non-neoplastic diffuse epithelial hyperplasia*	*NTP 2008*
Carcinogenicity	**Liver tumours (including angiosarcoma, hepatocellular carcinoma)**	**US EPA 2000**
Hepatotoxicity	**Liver cell polymorphism, liver necrosis, liver cysts**	**US EPA 2000**
Reprotoxicity	**Testicular changes**	**ATSDR 2006**

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
EXAMPLE: Draft USEPA 2010 RfD	*0.9*	*µg/kg bw/day*	*100*	*BMDL10*	*0.09*	*mg/kg bw/day*	*Epithelial hyperplasia*	*Based on epithelial hyperplasia in female mice (NTP 2008). NTP classified focal epithelial hyperplasia as a preneoplastic lesion so diffuse epithelial hyperplasia may also represent a preneoplastic lesion. However, although this lesion may progress to cancer (adenoma), EPA considered this to be a non-cancer endpoint because definitive data on the progression of this lesion does not exist. UF of 100 was applied (10 for inter and intraspecies differences; 1 to account for database deficiences).*
US EPA 2000 ***Drinking water unit risk***	0.0069	µg/kg bw/day	NA	ELCR	1 in 100,000	NA	Liver tumours (sum of angiosarcoma, hepatocellular carcinoma and neoplastic nodules)	US EPA calculated 0.48 µg/L in drinking water was associated with a 10-5 risk assuming exposure from adulthood, and 0.24 µg/L for exposure from birth, both using linearised multistage modelling (LMS) on data on total liver angiosarcoma, hepatocellular carcinoma, and neoplastic nodules in female Wistar rats following oral exposure via the diet in a lifetime study (Feron et al 1981). The human exposure dose (HED) was estimated using PBPK modelling and corrected for the bioavailable dose. The HBGV was calculated using the exposure from birth and adjusted using an adult weighing 70 kg drinking 2 L/day.
WHO 2017 DWG 4th Edition (Addendum) ***Drinking water guideline***	0.0086	µg/kg bw/day	NA	ELCR	1 in 100,000	NA	Liver tumours (sum of AS, HCC, neoplastic nodules)	A slope factor was derived from dose response data of increased incidences of liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) from an oral dietary study in rats (Feron et al 1981). A PBPK model was used to calculate HEDs and linear low-dose extrapolation was performed to calculate 0.3 µg/L in drinking water being associated with upper-bound excess risk of liver tumours of ELCR of 10−5 for lifetime exposure. The HBGV was calculated based on an adult weighing 70 kg drinking 2 L/day. Principal references WHO (2004) and IPCS (1999).
Health Canada 2013 ***Maximum Acceptable Concentration***	0.011	µg/kg bw/day	NA	ELCR	1 in 100,000	NA	Liver tumours (sum of AS, HCC, neoplastic nodules)	Using Feron et al. (1981) data from a dietary study in rats, Health Canada determined the concentration of VC in drinking water associated with an ELCR of 10−6 and 10−5 in adult humans as 0.08 and 0.8 µg/L, respectively, by applying BMD modelling and bespoke PBPK to data on combined liver tumours in female rats. Adjusting by a factor of 2 to account for early life sensitivity, ELCRs of 10−6 and 10−5 for early life exposure are associated with 0.04 and 0.4 µg/L, respectively. The HBGV was calculated based on a adult weighing 70 kg drinking 2 L/day. As the cancer risk assessment results in a more conservative value, Health Canada deemed it the most appropriate approach for developing the MAC, and will be protective for carcinogenic and non carcinogenic effects.
RIVM 2001 and 2009 ***Maximum Permissable Risk (MPR) value***	0.06	µg/kg bw/day	NA	ELCR	1 in 100,000	NA	Liver tumours (sum of AS, HCC, neoplastic nodules)	Using data from Feron et al (1981) and Til et al (1983, 1991), an ELCR of 10-4 is equivalent to 0.6 µg/kg bw/day was calculated using linear non-threshold extrapolation modelling on data on total liver tumours in female rats during a dietary study. 0.06 µg/kg bw/day is associated with an ELCR of 10-5
RIVM 2001 and 2009 ***Maximum Permissable Risk (MPR) value***	1.3	µg/kg bw/day	100	NOAEL	0.13	mg/kg bw/day	Liver cell polymorphism	A NOAEL of 0.13 mg/kg bw/day was based on liver cell polymorphism in rats administered VC in the diet during a lifetime feeding study (Til et al 1983, 1991). The TDI of 1.3 µg/kg bw/day was calculated by applying an UF of 100 to the NOAEL.
US EPA 2000 ***RfD***	3	µg/kg bw/day	30	NOAEL	0.09	mg/kg bw/day	Liver cell polymorphism	A NOAEL of 0.13 mg/kg bw/day (absorbed not ingested dose) was based on liver cell polymorphism (non carcinogenic effect) in rats administered VC in the diet during a lifetime feeding study (Til et al 1983, 1991). The NOAEL(HED) of 0.09 mg/kg-day was calculated using PBPK modelling (to convert from administered animal dose to human equivalent dose). The RfD of 3 µg/kg bw/day was calculated using UF of 30 (10 to protect sensitive human subpopulations and 3 for animal-to-human extrapolation). A modifying factor of 1 for database insufficiences was selected as adequate repeat dose, generational and multigenerational studies exist.

ATSDR 2006 ***Chronic MRL***	3	µg/kg bw/day	30	NOAEL	0.09	mg/kg bw/day	Liver cell polymorphism	ATSDR calculated a chronic-duration oral MRL from a NOAEL of 0.17mg/kg bw/day based on liver cell polymorphism in female rats during a chronic rat feeding study (Til et al 1983, 1991). Note: an average oral intake of combined sexes was used for NOAEL rather than the estimated absorbed dose 0.13 mg/kg/day used by EPA (2000)). The critical endpoint liver cell polymorphism was not considered a precursor to carcinogenicity hence is a threshold effect. A NOAEL(HED) of 0.09 mg/kg/day was estimated using PBPK modelling and the MRL of 3 µg/kg bw/day was calculated by applying an UF = 30 (3 for species extrapolation with a dosimetric adjustment and 10 for human variability) to the NOAEL (HED).
Health Canada 2013 ***Maximum Acceptable Concentration***	**8.96**	µg/kg bw/day	25	NOAEL	0.224	mg/kg bw/day	Liver cell polymorphism	A NOAEL of 0.13 mg/kg bw/day was based on liver cell polymorphism in female rats (Til et al 1983, 1991). The internal dose of 2.85 mg/l was calculated and used to determine the HED of 0.224 mg/kg bw/day human external dose using PBPK modelling, which was used to derive a TDI of 9 µg/kg bw/day (rounded up from 8.96), calculated by applying an UF of 25 (2.5 to account for interspecies toxicodynamic variability and 10 for intraspecies variability) to the HED. As the cancer risk assessment results in a more conservative value, Health Canada deemed it the most appropriate approach for developing the MAC, and will be protective for carcinogenic and non carcinogenic effects.

COT/COC Opinion

COM (2006) considers vinyl chloride genotoxic: See https://cot.food.gov.uk/sites/default/files/cot/cotannualrep2006.pdf
COC (1997) considers vinyl chloride a known human carcinogen: See https://cot.food.gov.uk/sites/default/files/cot/cotcomcoc1997.pdf

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 and EA TOX 18 2004	**0.014**	**µg/kg(bw)/day**	**NA**	**ELCR**	**1 in 100,000**	**NA**	**Cancer**	**Based on WHO 1996 drinking water guideline of 0.5 µg/L that is equivalent to an ELCR of 1 in 100,000 for angiosarcomas using data from a feeding study in rats by Til et al 1983, 1991. DEFRA and EA state: ELCR calculated using LMS; WHO 1996 estimated ELCR 10-5 equivalent to 20 µg per person per day; an additional correction factor of 2 was applied to account for risk from other cancers meaning exposure from 10µg/day represented an ELCR of 10-5. Assuming a daily intake 2 L drinking water the DWG is 5µg/L, or 0.014µg/kg bw/day for a 70 kg adult.**

B) Inhalation Route

Authoritative body (date) and HBGV type	Converted HBGVinh	Unit	HBGVinh	Unit	UF used	POD	POD value	Unit	Endpoint	Pivotal Study used & Comments
EXAMPLE: ATSDR 2010 MRL	*1.43*	*ng/kg bw/day*	*5*	*ng/m^3*	*100*	*NOAEL*	*0.5*	*µg/m^3*	*Nasal toxicity*	**For chromium aerosols and mists. Based on occupational data from workers exposed to chromic acid (Lindberg & Hedenstierna 1983). LOAEL of 2 µg m-3 adjusted for continuous exposure (0.5 µg m-3), and UF of 10 used for interspecies variation and 10 for extrapolating from a LOAEL.**
RIVM 2001 ***MPR***	0.103	µg/kg bw/day	0.00036	mg/m^3	NA	ELCR	1 in 100,000	NA	Liver angiosarcomas, angiomas, hepatomas and neoplastic nodules	The MPR is based on data from a rat inhalation study in which rats were exposed to VC 4 hrs/day, 5 days/week for 52 weeks (Maltoni et al (1981, 1984)). Using such data the concentration in air correlating to an ELCR of 10-4 was calculated to be 3.6 µg/m3 using linear non-threshold extrapolation model. 0.36 µg/m3 would correlate to an ELCR of 10-5. The air concentration was coverted to a HBGV assuming a 70 kg adult inhales 20 m3/day. A non carcinogenic HBGV based on testicular changes was 56 µg/m^3 (16 µg/kg bw/day) so the carcinogenic endpoint is also protective against non carcinogenic effects.
US EPA ***Unit risk estimate***	0.657	µg/kg bw/day	0.0023	mg/m^3	NA	ELCR	1 in 100,000	NA	Liver angiosarcomas, angiomas, hepatomas, and neoplastic nodules	US EPA used data from an inhalation study in female Sprague-Dawley rats (Maltoni et al (1981, 1984)). HECs were calculated using PBPK modelling, based on the metabolites formed in the liver. A unit risk estimate of 4.4 E-6 per 1 µg/m3 was calculated, using a linearised multustage model, for continuous, lifetime exposure during adulthood, and 8.8 E-6 per 1 µg/m3 if continuous lifetime exposure was from birth. Therefore 2.3 µg/m3 VC in air correlates to an ELCR of 10-5. The HBGV was calculated assuming a 70 kg adult inhales 20 m^3/day.
WHO 2000 ***Air Quality Guideline***	2.86	µg/kg bw/day	0.010	mg/m^3	NA	ELCR	1 in 100,000	NA	Cancer	WHO air quality guideline is based on a 1978 US occupational exposure study in which 10173 workers were employed in a VC and PVC production plant. Using linear dose-response relationships to convert from occupational to lifetime exposure, the continuous lifetime risk of haemangiosarcoma was 4.7 x 10-4 per mg/m3, which equates to a 10-6 risk at 2.1 µg/m3. Assuming the number of cancers in other sites equals that of haemangiosarcomas, the ELCR 10-6 for all cancers occurs as a result of continuous lifetime exposure to 1.0 µg/m^3. An ELCR of 10-5 is equivalent to 10 µg/m^3. The HBGV is calculated assuming a 70 kg adult inhales 20 m^3/day.
SCOEL 2004 ***Occupational Exposure Limit***	3.52	µg/kg bw/day	0.012	mg/m^3	NA	ELCR	1 in 100,000	NA	Angiosarcoma	SCOEL calculated risk estimations based on epidemiology and in vivo experimental data, using low dose linear extrapolation. Based on epidemiological data in which liver angiosarcomas were the critical effect, WHO (2000) and Clewell *et al* (1995) derived continous lifetime exposure risks of 2.59 x 10^{-3} and 1.8 x 10^{-3} following exposure to 1ppm VC, respectively. SCOEL also considered evaluations by Clewell et al (1995), Reitz et al (1996) and US EPA (2000) based on experimental data. The lifetime risk from 1 ppm VC was 3x10-3, 1.5x10-3, and 11.4x10-3 ppm, respecitvely, based on liver angiosarcomas, hepatomas and neoplastic nodules in rats during an inhalation study (Maltoni et al, 1971, 1984), calculated using linearised multistage modelling. SCOEL nominated an epidemiologically based risk of 0.3 x 10^{-3} following exposure to 1 ppm over a working lifetime, equivalent to a lifetime risk of 2.1 x 10^{-3} (where working time is 14 % or 1/7 of a lifetime calculated 8/24 x 240/365 x 45/70). The concentration correlating to an ELCR of 1 in 100,00 is 4.76x10^{-3} ppm VC. Converted using 1ppm = 2.59 mg/m^3 and assuming a 70 kg adult inhales 20 m^3/day. Risk estimates calculated by others (including US EPA (2000)) using experimental animal data (Maltoni *et al*) also evaluated by SCOEL and are of similar range 1.5-11.4 x 10^{-3} for 1ppm for lifetime exposure.

Health Council of the Netherlands 2017 ***Occupational health cancer risk values***	5.80	µg/kg bw/day	0.020	mg/m^3	NA	ELCR	1 in 100,000	NA	Angiosarcoma	Occupational data from European cohort study (Ward et al 2001) was used to estimate an excess ASL incidence of 4 per 100,000 following exposure to to 0.65 mg/m3 VC monomer (exposure between ages of 20-60). An equivalent ELCR of 1 in 100,000 for lifetime exposure, assuming working exposure is 12.5% of a lifetime (8/24 x 240/365 x 40/70 = 12.5% or 1/8), arises from exposure to 0.0203 mg/m^3 converted assuming a 70 kg adult inhales 20 m^3/day. BMD10 and risk estimates were also calculated from experimental data (Maltoni et al) for ASL in the rat. Animal risk estimates are slightly more conservative than epidemiologically derived risk estimates. Experimentally based estimates ranged from 0.001 to 0.1 mg/m^3 VCM for 4 per 100,000 (equivalent to 2.5x 10^{-4} to 0.025 mg/m^3 VCM at ELCR 1 in 100,000).
US EPA ***RfC***	23.8	µg/kg bw/day	0.083	mg/m^3	30	NOAEL	2.5	mg/m^3	Liver cell polymorphism	US EPA based their evaluation on a lifetime feeding study in rats (Til et al 1983, 1991) by carrying out route-to-route extrapolation, using liver cell polymorphism as non carcinogenic critical effect. The NOAEL of 0.13 mg/kg bw/day was converted to a NOAEL(HEC) of 2.5 mg/m3 calculated using PBPK modelling. An UF of 30 (10 for protection of sensitive human subpopulations and 3 for animal-to-human extrapolation) was applied to the NOAEL . The modifying factor for database insufficiencies was default of 1.
ATSDR ***Sub-chronic MRL***	24.7	µg/kg bw/day	0.086	mg/m^3	30	Other	2.59	mg/m^3	Hepatic centrilobular hypertrophy	ATSDR based their intermediate duration MRL on data from a 2 generation study in rats, exposed to 10, 100 or 1100 ppm for 6 hours/day for 10 premating and 3 week mating period (Thornton et al 2002). Using BMD modelling, the lower 95% confidence limit (LEC10) of a 10 % extra risk (EC10) of 5 ppm, based on liver hypertrophy, adjusted to 1 ppm to allow for intermittent exposure (6/24 hours) was selected as the POD. Using a PBPK model the HEC was estimated to be 1 ppm. The MRL of 0.03 ppm (2 sf) was calculated by applying an UF of 30 (3 for species extrapolation with a dosimetric adjustment and 10 for human variability) to the HED of 1ppm (1ppm/30 = 0.03333ppm) and converted using 1 ppm = 2.59 mg/m^3 to determine the $HBGV_{inh}$ of 0.086mg/m^3. No chronic MRL was calculated due to lack of appropriate chronic data.

COT/COC Opinion

COM (2006) considers vinyl chloride genotoxic https://cot.food.gov.uk/sites/default/files/cot/cotannualrep2006.pdf
COC (1997) considers vinyl chloride a known human carcinogen: https://cot.food.gov.uk/sites/default/files/cot/cotcomcoc1997.pdf
COT (2010) stated with regard to emisions from landfill sites: "*The project-specific HCV for chloroethene was 1 µg m^{-3}, which was the concentration estimated from occupational studies to present a 1 in 10^6 cancer risk, cited in the WHO Air Quality Guidelines for Europe [2000]. We agree that this is an appropriate reference concentration against which to assess the risk to public health from airborne concentrations of chloroethene*". See https://cot.food.gov.uk/sites/default/files/cot/cotstatementlandfill201001.pdf

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 and EA TOX 18 2004	**0.3**	**µg/kg(bw)/day**	**NA**	**ELCR**	**1 in 1,000,000**	**NA**	**Cancer**	**Using epidemiological occupational data WHO (2000) estimated 1 $µg/m^3$ vinyl chloride in ambient air would be equivalent to an ELCR of 10-6. Risk estimate calculated using linear extrapolation for risk from haemangiosarcomas and cancers at other sites. Converted using a 70 kg adult inhaling 20 m^3/day.**

C) Dermal Route

Authoritative body (date) and HBGV type	HBGV value	Unit	UF used	POD	POD value	Unit	Endpoint	Pivotal Study used & Comments
								No data

III) Current UK (WHO) regulatory values

	Value	Units	Refs
UK drinking water standard	0.5	µg/L	- England: The Water Supply (Water Quality) Regulations 2016 (S.I. 2016/614) - Wales: Water Supply (Water Quality) Regulations 2010 (S.I. 2010/994 (W.99)) and Water Supply (Water Quality) (Amendment) Regulations 2016 (S.I. 2016/410 (W.128)) (Wales) - Scotland: The Public Water Supplies (Scotland) Regulations 2014 (SSI No. 364)
WHO drinking water standard	0.3	µg/L	WHO (2017) (assumes ELCR 10-5)
UK air quality standard	-	-	N/A In addition there is no EU air quality standard for vinyl chloride
WHO air quality standard	1	$\mu g/m^3$	WHO (2000) (assumes ELCR 10-6)

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
NTP 2008	*Drinking water*	*0.38, 0.91, 2.4 or 5.9 (m/m); 0.38, 1.4, 3.1 or 8.7 (f/m)*	*mg/kg bw/day*	*Mouse*	*2 year drinking water study*	*Endpoints based on non-neoplasic epithelial hyperplasia in female mice via a threshold MOA (BMDL 0.09) or oral carcinoma in male mice mg kg (BMDL 1.2) (IPCS 2011) .*
Feron et al 1981 as assessed by all authoritative bodies	Diet *ad lib* (Gavage one dose only)	0, 1.7, 5.0, 17.1	mg/kg bw/day	Rat	Lifetime dietary study	Feron reported data in Wistar rats during a lifetime dietary study, in which 60–80 rats per sex per dose were administered VC (0, 1.7, 5.0, 14.1 mg/kg bw/day) via the diet 7 days per week for 135–144 weeks for males and females, respectively (Feron et al, 1981). Both non-carcinogenic and carcinogenic effects were noted. The critical carcinogenic endpoint is combined liver tumours (liver angiosarcoma, hepatocellular carcinoma, and neoplastic nodules) in females. A LOAEL of 1.7 mg/kg bw/day was determined based on angiosarcoma, hepatocellular carcinoma, and neoplastic nodules, and a BMD10 of 0.311 mg/kg bw/day calculated. It should be noted that US EPA did not regard data on combined liver tumours as being suitable for BMD modelling and all authoratative bodies considered the human equivalent dose to be the most appropriate dose metric due to VC being metabolised to a toxic metabolite in the liver. Although neoplastic nodules may not progress to malignancy, the use of this endpoint reduces the risk of underestimating the risk of cancer following VC exposure. Using combined liver tumours as the critical endpoint will also protect against lung adenoma. The critical non-carcinogenic endpoints are liver cysts, liver necrosis and liver cell polymorphism. A LOAEL of 1.7 mg/kg bw/day was determined in females based on liver cysts; NOAEL of 1.7 mg/kg bw/day based on liver necrosis in females; and a LOAEL of 17 mg/kg bw/day based on liver cell polymorphis in males. Data were also considered for BMD modelling. Only data for liver necrosis were suitable, giving a BMD of 1.8 mg/kg bw/day in females. Such data were not used as the PoD for the LLTC as data from Til showed effects occurred at lower doses, hence the PoD was lower and more conservative.
Til et al 1983, 1991 as assessed by all authoritative bodies	Diet *ad lib*	0, 0.014, 0.13, 1.3	mg/kg bw/day	Rat	Lifetime dietary study	The critical non-carcinogenic endpoint is liver cell polymorphism and hepatic cysts. Til reported liver cell polymorphism and hepatic cysts in female rats and increased mortality at 1.3 mg/kg bw/day, which was determined to be the LOAEL, the NOAEL being 0.13 mg/kg bw/day. Such effects are considered to be non-neoplastic events. Due to data limitations including having only one non zero datapoint in the dataset, wide dose spacings and a wide variability in models, BMD modelling is not appropriate for this endpoint. As with the data from Feron, most authoratative bodies converted teh external dose in rats to an internal dose in humans using PBPK modelling, which was considered to be the most apprpriate dose metric.

Selection of POD

POD for ORAL LLTC: non-threshold		
Are dose response data of adequate quality to derive a BMD	Yes	
Type of PoD	BMD	
Value selected	0.311	mg/kg bw/day
Type of PoD	LOAEL	
Value selected	1.70	mg/kg bw/day

POD for ORAL LLTC: threshold		
Type of PoD	NOAEL	
Value derived	0.13	mg/kg bw/day
Type of PoD		
Value derived		mg/kg bw/day

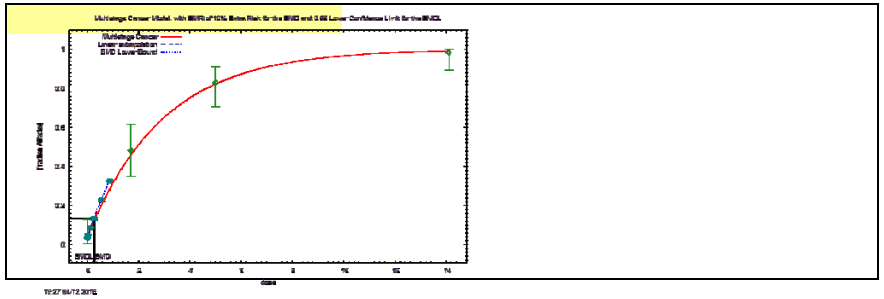
BMD Modelling (if answered 'Yes' to question above - see worksheet BMD modelling pivotal study)

Software used N/A

	BMD1	BMD5	BMD10	BMD15
BMD modelling (value) (mg/kg bw/day)			0.311	
	BMDL1	**BMDL5**	**BMDL10**	**BMDL15**
BMD modelling (value) (mg/kg bw/day)			0.256	

Comments:

BMD modelling carried out based on combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female rats. Multistage cancer, gamma, Weibull and Quantal-linear models all gave a BMD10 of 0.311 mg.kg bw/day. AIC value 166.07.



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	**Adult**	**Child**
	5000	10000
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 =	1 in 50000	1 in 50000

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 non threshold	Selected value threshold
Intraspecies	1 - 10	10	10
Interspecies	1 - 10	10	10
Quality of study	1 - 10	1	1
Use of LOAEL as POD	1-10	1	10
Total CSAF/CSM		100	1000

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

Oral LLTC calculation:

		Value	Units	Justification
LLTC (Thresholded chemical) using NOAEL		1.30	µg/kg bw/day	The NOAEL of 0.13 mg/kg bw/day based on liver cell polymorphism and hepatic cysts was used as a basis of the LLTC . An UF of 10 (for inter and intra species variation) was applied to the NOAEL to calculate the LLTC.
LLTC (Non Thresholded chemical) using BMD ***VALUE SELECTED FOR DERIVATION OF C4SL (ADULT)***		0.0622	µg/kg bw/day	The BMD10 of 0.311 mg/kg bw/day based on combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female rats was used as a basis of the LLTC. An UF of 5000 (default margin) was applied to the BMD10 to calculate the LLTC for adults.
LLTC (Non Thresholded chemical) using BMD ***VALUE SELECTED FOR DERIVATION OF C4SL (CHILD RESI/POS park/ALLOTMENT)***		0.0376	µg/kg bw/day	Based on the UK drinking water standard of 0.5 µg/L, converted to an intake value based on a 13.3 kg child drinking 1 L of water per day.
LLTC (Non Thresholded chemical) using BMD ***VALUE SELECTED FOR DERIVATION OF C4SL (CHILD POS resi)***		0.0311	µg/kg bw/day	The BMD10 of 0.311 mg/kg bw/day based on combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female rats was used as a basis of the LLTC. An UF of 10000 (default margin) was applied to the BMD10 to calculate the LLTC for children.

Sensitive Receptor	Early childhood

b) INHALATION

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments
Epidemiology study of lung cancer in workers in a chromate production (Gibb et al 2000)	*N/A*	*N/A*	*N/A*	*Human*	*Epidemiology study in chromate production workers*	*The ELCR for for lung cancer for 1, 0.1, 0.01 or 0.001 µg m-3 is equivalent to environmental exposure of 4 in 100, 4 in 1000, 4 in 10,000, or 4 in 100,000. Hence 1 in 100,000 would equate to 0.00025 mg m-3 (0.25 ng m-3).*
WHO Air Quality Guidelines 2000	**NA**	**NA**	**NA**	**Human**	**1978 US epidemiological study of workers employed in VC production plants**	**Risk estimates calculated using occupational data and a linear dose response with adjustments from workplace exposure to lifetime exposure. The ELCR 10-6 for cancer (including HCC and ASL) occurs as a result of continuous lifetime exposure to 1.0 µg/m^3. An ELCR of 10-5 is equivalent to 10 µg/m^3, and a 'low risk' ELCR of 1 in 50,000 equivalent to 20 µg/m^3. "POD Value selected" below has been converted assuming 70 kg adult breathing 20 m^3/day.**

Selection of POD

Published POD for INHALATION LLTC:		
Are dose response data of adequate quality to derive a BMD	No	
Type of PoD	ELCR	
Value selected	0.0057	mg/kg bw/day

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 **N/A**

	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?	No
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	5000
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 =	1 in 50000

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	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

Inhalation LLTC calculation:

	Value	Units	Justification
LLTC (Thresholded chemical) using NOAEL/LOAEL	NA	µg/kg bw/day	
LLTC (Thresholded chemical) using BMD	NA	µg/kg bw/day	
LLTC (Non Thresholded chemical) using NOAEL/LOAEL	NA	µg/kg bw/day	
LLTC (Non Thresholded chemical) using BMD	NA	µg/kg bw/day	
LLTC (Non Thresholded chemical) using ELCR ADULT RECEPTOR	**5.71**	µg/kg bw/day	Risk estimates calculated using occupational data and a linear dose response with adjustments from workplace exposure to lifetime exposure. The ELCR 10-6 for cancer (including HCC and ASL) occurs as a result of continuous lifetime exposure to 1.0 µg/m^3. An ELCR of 10-5 is equivalent to 10 µg/m^3, and a 'low risk' ELCR of 1 in 50,000 equivalent to 20 µg/m^3. This has been converted to equivalent dose assuming 70 kg adult breathes 20 m^3/day.
LLTC (Non Thresholded chemical) using ELCR CHILD RECEPTOR AGED 1-6	**5.71**	µg/kg bw/day	Risk estimates calculated using occupational data and a linear dose response with adjustments from workplace exposure to lifetime exposure. The ELCR 10-6 for cancer (including HCC and ASL) occurs as a result of continuous lifetime exposure to 1.0 µg/m^3. An ELCR of 10-5 is equivalent to 10 µg/m^3, and a 'low risk' ELCR of 1 in 50,000 equivalent to 20 µg/m^3. The adult value has been adopted to take into consideration early life sensitivity.
LLTC (Non Thresholded chemical) using ELCR CHILD RECEPTOR AGED 4-9	**5.71**	µg/kg bw/day	Risk estimates calculated using occupational data and a linear dose response with adjustments from workplace exposure to lifetime exposure. The ELCR 10-6 for cancer (including HCC and ASL) occurs as a result of continuous lifetime exposure to 1.0 µg/m^3. An ELCR of 10-5 is equivalent to 10 µg/m^3, and a 'low risk' ELCR of 1 in 50,000 equivalent to 20 µg/m^3. The adult value has been adopted to take into consideration early life sensitivity.

Sensitive Receptor	Early childhood

Any Additional Comments:
Vinyl chloride is a genotoxic IARC Group 1 carcinogen. Toxicological effects from vinyl chloride are systemic and therefore a combined inhalation and oral C4SL should be derived.

Two draft LLTCoral were proposed, both based on two lifetime studies in rats, in which threshold and non-threshold effects were observed. Combined liver tumours (angiosarcoma, hepatocellular carcinoma and neoplastic nodules) in female rats were selected as the critical carcinogenic effect, based on data from Feron. Liver cell polymorphism and liver cysts were selected as the critical non-carcinogenic effect, based on the data from Til. The final selected LLTCoral of 0.06 µg/kg bw/day is calculated for adults using BMD for carcinogenic effects and is highlighted in red text above. Due to the increased sensitivity of young children to VC, the LLTC value for a child (PPS resi) is calculated using an additional uncertainty factor of 2 resulting in a LLTC of 0.03 µg/kg bw/day, per the approach adopted by Health Canada (2013). The LLTC value for a child (resi/POS park/allotment) is calculated based on the UK drinking water standard of 0.5 ug/L, which was converted to the LLTC of 0.038 µg/kg bw/day based on a 13.3 kg child drinking 1 L of water per day.

The LLTCinhalation is based on occupational data and derived directly from the WHO AQO. An ELCR of 10-5 is equivalent to 10 µg/m3, therefore an ELCR 1 in 50,000 is equivalent to 20 µg/m3, or 5.7 µg/kg bw/day (assuming a 70 kg adult breathes 20 m3/day). If calculating child values using physiologial parameters the LLTCs are in fact higher than the adult value. Therefore in order to protect against early life sensitivity, the lower adult value is proposed for use for the child receptor.

IV A) BMD modelling

ARE DATA OF SUFFICIENT QUALITY YES

Toxicological data	Lifetime dietary study (Feron *et al* 1981, as reported in US EPA 2000)
Endpoint	Liver tumours (sum of angiosarcoma, hepatocellular carcinoma and neoplastic nodules)
Level of modelled response	BMD10
Chemical used in study	Vinyl chloride

Dose (mg/kg bw/day)	Species	Sex	n	Incidence of endpoint
0	Rat	Female	57	2
1.7	Rat	Female	58	28
5.0	Rat	Female	59	49
14.1	Rat	Female	57	56

Model Name	Maximum number of iterations	AIC	Chi squared value	p value	Accept	BMD	BMDL
Gamma	500	166.07	0.8	0.6708		0.31065	0.25555
Logistic	500	182.905	41.27	0		0.83451	0.68395
LogLogistic	500	167.904	0.44	0.5058		0.53837	0.26361
LogProbit	500	167.528	0.09	0.7597		0.52476	0.42685
Multistage	500	167.434	0	0.9704		0.27851	0.21388
Multistage-Cancer	500	166.07	0.8	0.6708		0.31065	0.25555
Probit	500	190.197	152.61	0		0.85481	0.71799
Weibull	500	166.07	0.8	0.6708		0.31065	0.25555
Quantal-Linear	500	166.07	0.8	0.6708		0.31065	0.25555

APPENDIX B
MEAN DAILY INTAKE DATA SHEET FOR VINYL CHLORIDE

Substance: **Vinyl Chloride (Chloroethene)**

MDI Oral			**Recommended adult oral MDI**	**Units**	**Justification:** Adult MDI for food from FSA (2014). 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	µg day-1			
Organisation/Source	**Date**	**Media**	**Value**	**Units**	**Description**	**Reference**	**Web link**
DWI	Jul-17	Tap water	-	µg L-1	No data for vinyl chloride	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	Jun-04	Tap water	<1	µg day-1	No data on concentrations in UK drinking water. But UK drinking water standard is 0.5 µg L-1 and so assuming adult consumes 2 L water per day, adult MDI will be less than 1 µg day-1	Defra and Environment Agency 2004. Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Vinyl Chloride.	http://webarchive.nationalarchives.gov.uk/20140328153902/http://www.environment-agency.gov.uk/static/documents/Research/vcm_old_approach_2029054.pdf
US ATSDR	Jul-06	Food	0		Daily exposure of <0.0004 ug/kg/day estimated for 1970s and 1980s (WHO 1999). Not likely to be applicable any more as changes to packaging have resulted in 'significant reduction in levels of VC in food'	ATSDR Toxicological Profile for Vinyl Chloride, July 2006	https://www.atsdr.cdc.gov/toxprofiles/tp20.pdf
DEFRA & Environment Agency	Jun-04	Food	0		Notes that VC concentrations have dropped significantly in food packaging and cites that ATSDR (1997) considers that there is essentially no migration of VC monomer into food and that inhalation is the most important route of exposure to the general population.	Defra and Environment Agency 2004. Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Vinyl Chloride.	http://webarchive.nationalarchives.gov.uk/20140328153902/http://www.environment-agency.gov.uk/static/documents/Research/vcm_old_approach_2029054.pdf

MDI Inhalation			**Recommended adult inhalation MDI**	**Units**	**Justification:** Vinyl chloride is not monitored by the Defra UK AIR Network. The IPCS (1999) value of 60 µg d-1 is based on actual measured concentrations, but the details behind the values are not reported. The more recent AQG (2000) quotes lower values (2 to 10 µg d-1) but these are based on dispersion modelling. More recent US and Canadian publications provide data from ambient air monitoring. The ATSDR (2016) maximum value (omitting industrial sites) of 1.17 µg m-3 is based on detailed monitoring, is considered suitably protective. Although the data is not UK-based, it is within the range quoted by WHO (2000). 1.17 µg m-3 is converted to 23.4 µg day-1 by multiplying by an assumed adult respiration rate of 20 m3.d-1.		
			23.4	**µg day-1**			
Organisation/Source	**Date**	**Media**	**Value**	**Units**	**Description**	**Reference**	**Web link**
DEFRA & Environment Agency Report	2004	Atmospheric Ambient Air	3	µg m-3	Cites IPCS (1999). Air concentration usually <3 µg m-3.	Defra and Environment Agency (2004). Contaminants in Soil: Collation of Toxicological Data and Intake Values for Humans. Vinyl Chloride.	http://webarchive.nationalarchives.gov.uk/20140328153902/http://www.environment-agency.gov.uk/static/documents/Research/vcm_old_approach_2029054.pdf
PHE Toxicological Overview	2008	Ambient air	2 to 10	µg day-1	Cites WHO AQG (2000). The majority of the population would inhale between 2 and 10 µg day-1.	PHE Toxicological Overview V1 2008.	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/338284/hpa_vinyl_chloride_toxicological_overview_v1.pdf
WHO Air Quality Guidelines	2000	Ambient air	0.1 to 0.5	µg m-3	Calculations based on dispersion models indicate 24-hour average concentrations of 0.1-0.5 µg m-3 exist as background across much of western Europe. In the vicinity of VC and PVC production facilities 24-hour concentrations can exceed 100 µg m-3 but are generally less than 10 µg m-3 >1 km from the plants (cited from RIVM 1984).	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
IPCS EHC	1999	Atmospheric Ambient Air	3	µg m-3	Atmospheric ambient air concentrations are usually <3 µg m-3. The source of the information is not cited. Other concentrations cited include air concentrations near VC/PVC production sites (100 µg m-3), waste disposal sites (8,000 µg m-3) and indoor air concentration in houses near landfill sites in the US (1,000 µg m-3).	IPCS (1999). Vinyl Chloride, Environmental Health Criteria 215.	http://www.inchem.org/documents/ehc/ehc/ehc215.htm
IARC	2012	Ambient air	3	µg m-3	Atmopsheric ambient air concentrations are usually <3 µg m-3. Cited from NTP (2005).	IARC (2012). Monograph Volume 100F.	http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F-31.pdf
US ATSDR	2016	Ambient air	0.0002 to 0.6	µg m-3	The mean concentration range of suburban and urban data points across the US in 2013 by the EPA's Air Quality System (AQS) was 0.000164 to 0.464754 ppbC. This was converted to ppb by dividing by 2 (a VC molecule has 2 carbons), and to mg.m-3 using a conversion of 1 ppm = 2.6 mg.m-3. i.e. 0.0002 to 0.6 µg.m-3. These concentrations are within the range of ambient air concentrations cited in the 2006 Toxiological Profie for Vinyl Chloride.	US ATSDR (2016). Toxicological Profile for Vinyl Choride, Addendum	https://www.atsdr.cdc.gov/toxprofiles/VinylChloride_addendum_508.pdf
US ATSDR	2016	Ambient air	1.17	µg m-3	Maximum of suburban and urban data points excluding sites affected by heavy industry. Maximum was 0.9 ppbC in New Castle, Delaware. This was converted to ppb by dividing by 2 (a VC molecule has 2 carbons), and to mg.m-3 using a conversion of 1 ppm = 2.6 mg.m-3 to 1.17 µg m-3.	US ATSDR (2016). Toxicological Profile for Vinyl Choride, Addendum	https://www.atsdr.cdc.gov/toxprofiles/VinylChloride_addendum_508.pdf
Health Canada	2013	Ambient air	<0.02 to 0.7	µg m-3	Discusses various Canadian and US studies from 2002 to 2009. The average ambient air concentrations from these studies ranged from <0.02 to 0.7 µg.m--3 with ~99% of samples below the MDL.	Health Canada (2013). Guidelines for Canadian Drinking Water Quality. Guideline Technical Document - Vinyl Chloride.	https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-vinyl-chloride.html
Health Canada	2013	Indoor air	<0.001 to 1.3	µg m-3	Mean indoor exposure concentratons ranged from <0.001 to 1.3 µg.m-3.	Health Canada (2013). Guidelines for Canadian Drinking Water Quality. Guideline Technical Document - Vinyl Chloride.	https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-vinyl-chloride.html