APPENDIX C

PROVISIONAL C4SLS FOR

ARSENIC

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APPENDICES

FIGURES

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1. INTRODUCTION

This appendix presents provisional Category 4 Screening Levels (pC4SLs) for arsenic based on the methodology described in Section 5 of the main report. Section 1.1 provides brief background information on arsenic, while Section 2 summarises the toxicological review from which Low Levels of Toxicological Concern (LLTCs) are identified (Steps 1 and 2 of the methodology). Section 3 presents the exposure modelling aspects for the generic land-uses under consideration (Step 3), while Section 4 presents the remaining steps of the methodology (Steps 4 to 7). The pC4SLs presented herein can be used for the setting of final C4SLs by relevant authorities (e.g., Defra).

1.1 BACKGROUND INFORMATION ON ARSENIC

The following background information on arsenic is provided in the Environment Agency's Soil Guideline Value (SGV) report (Environment Agency, 2009a):

- In its elemental form, arsenic occurs in two forms under ambient conditions – a steel grey coloured brittle metallic solid or a dark grey amorphous solid. Although it is commonly described as a heavy metal, arsenic is a metalloid with a complex chemistry similar to phosphorous.
- Arsenic occurs naturally in the environment although rarely in its elemental form. Over 200 arsenic-containing minerals have been identified, with approximately 60 per cent being arsenates, 20 per cent sulphides and sulphosalts, and the remaining 20 per cent including arsenides, arsenites and oxides. The most commonly occurring form is arsenopyrite, an iron arsenic sulphide associated with many types of mineral deposits and especially those including sulphide mineralisation.
- Arsenic forms organic and inorganic compounds with the most common valence states being -3, +3 or +5. Arsenic trioxide is a white crystalline solid at room temperature. It is produced commercially as a by-product of the smelting of non-ferrous ores including copper and lead. Most arsenic trioxide is subsequently converted to arsenic acid, which forms arsenate salts.
- Due to its known toxicity, use of arsenic in many applications has either been banned or phased out. Most arsenic is currently used to produce copper chrome arsenate (CCA), a wood preservative and pesticide. In 2003, the UK was reported to be the largest consumer of CCA in the European Union at 15,000 tonnes per year and the location of three of the four manufacturing plants. As a result of an EU directive, use of CCA is now restricted in the UK to specified formulations and timber uses. High purity arsenic is also used in the manufacture of gallium arsenide semi-conductors, which are used in telecommunication systems, solar cells and space research.
- Historically, inorganic arsenic compounds including calcium arsenate, lead arsenate and sodium arsenite have been used as pesticides. In particular, lead arsenate has been used for pest control in fruit orchards.
- Arsenic and its inorganic compounds have also been used as a decolouriser in the manufacture of glass, in various metallurgical processes including the production of alloys, in veterinary and human medicines, and lead–acid batteries.

Further background information on arsenic, relevant to land contamination risk assessment, can be found in the above-referenced document.

2. LOW LEVEL OF TOXICOLOGICAL CONCERN FOR ARSENIC

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 main report. The remainder of this section demonstrates the application of this framework to arsenic.

As indicated in Figure 2.2 in the main report, the first task of the toxicological framework is to perform a review of existing health based guidance value (HBGV) evaluations for all routes of exposure. A checklist of information from authoritative bodies has been collated, as per the process in SR2, although pertinent primary literature in peer reviewed journals has also been searched and included, if relevant (although it should be noted that, as described in the main report, reviews by authoritative international and national bodies are preferred to the open scientific literature, for the purpose of LLTC derivation). A "Human Toxicological Data Sheet (HTDS)" for arsenic has also been completed, as shown in Appendix C1.

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

All oral HBGVs from authoritative bodies, together with a brief description of how they were derived, are given in descending order in Section II of the HTDS (see Appendix C1).

In 2009, the Environment Agency published a revised updated version of the Toxicology Report for arsenic (Science report: SC050021/TOX1) (EA, 2009b). This was used as the start of the data search, and provides a thorough basis of the toxicology evaluation up to 2009. New information published between the years 2009-2012 was added to the data package.

The Environment Agency report (2009b) recommended an evidence-informed 'policy based' health criteria value (HCV) of 0.3 µg kg^{-1} bw day^{-1} which is equivalent to an intake based on the WHO drinking water standard of 10 µg L^{-1}. WHO regard this as a 'practical quantification limit'. The UK drinking water standard is also set at the level of 10 µg L^{-1} (UK Drinking Water Standard, 2007). The evidence-informed policy-based decision for the HCV was taken at a cross-government department level as this deviates from a minimal risk value but is consistent with the position that the soil guideline value should not be targeted disproportionately to the values applied in other regimes e.g. drinking water standards.

In 2013, recent arsenic toxicology evaluations come from three sources: the World Health Organisation Joint Expert Committee on Foods Additives (JECFA) evaluation (WHO/JECFA, 2011a, 2011b), the European Food Standards Authority evaluation (EFSA 2009) and International Agency on the Research on Cancer (IARC 2012). The latter created a list of available human studies for arsenic in their monograph of 2012. Arsenic is a well-established non-thresholded genotoxic carcinogen; IARC have classified inorganic arsenic as a known human carcinogen (IARC Monograph, 2012). There are also many non-cancer systemic effects that have been reported as occurring from chronic arsenic exposure in the recent toxicology review (IARC, 2012). For the purposes of HBGV development, all quantitative data comes from human cancer epidemiology studies, and cancer as the key sensitive endpoint where there are good quantitative data shall be the focus of this review for developing an LLTC.

WHO/JECFA (2011a, 2011b) published a re-evaluation of the health evidence for arsenic, although they did not produce a new guideline value. EFSA (2009) published an Opinion by the CONTAM panel. They concluded that the 1988 JECFA PTWI was no longer appropriate and re-appraised the available data (as available up to 2009) to

derive BMD values for skin lesions, lung cancer and bladder cancer. Again, no guideline value has been derived, as EFSA recommend following a margin of exposure approach to risk assessment.

It is important to recognise, that the IARC monograph does not include the two key references on which WHO/JECFA based their evaluation in 2011 for lung and bladder cancer; namely Chen *et al.* (2010a and 2010b). As these references were also not available for the EFSA evaluation in 2009, this has led to different choices of pivotal studies selected by WHO/JECFA in 2011 and EFSA in 2009.

It should be noted that there is also a comprehensive review initiated by USEPA in 2013, and ongoing via a process of public consultation, due for completion in 2015, where the full range of effects will be covered.

2.1.2 FLOWCHART ELEMENT 2: REVIEW THE SCIENTIFIC BASIS OF EACH HBGV. CHOOSE THE PIVOTAL STUDY

Flowchart element 2 requires a suitably qualified individual who sufficiently understands the nature of toxicological data to review the scientific basis of all existing HBGVs and choose the pivotal toxicology study for the LLTC calculation for the oral route. 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) an evidence-informed policy choice (i.e. based on an existing guideline from another regime, with or without a toxicological rationale).

2a) Animal Toxicology Data

Not applicable as animal data have not been the focus in any evaluations of the toxicity of arsenic.

There are however many animal toxicology studies investigating the carcinogenicity of arsenic, which have been reviewed in the IARC Monograph (2012). It is not useful to include these studies here, as there is a wealth of human study data which has been evaluated for the purposes of setting environmental HBGV and takes precedence.

2b) Human Toxicology/Epidemiology Data

All existing HBGVs and human health evaluations deriving BMDs have been performed using human epidemiology data.

Until 2009, all evaluations used the data from the 1960's Taiwanese studies on skin lesions in populations drinking arsenic contaminated water (Tseng *et al*., 1968, 1977). These studies have largely been discounted by authoritative bodies in preference for using data from subsequent, better controlled epidemiology studies.

The previous provisional tolerable weekly intake (PTWI) of 15 µg kg^{-1} bw (equivalent to 2.1 µg kg^{-1} bw day^{-1}) derived by JECFA in 1988, was withdrawn in 2010, as subsequent data had shown effects (skin lesions, lung cancer and bladder cancer) could occur at lower intakes. The subsequent evaluations by WHO/JECFA (2011a and 2011b) have yielded BMD values for lung cancer and bladder cancer as the most sensitive quantifiable endpoints.

EFSA (2009) also concluded that the JECFA PTWI was no longer appropriate and re-appraised the available data up to 2009 to derive BMD values for skin lesions, lung cancer and bladder cancer as the most sensitive endpoints.

The US ATSDR (2007) chronic oral MRL is still available in the public domain and is 0.3 µg kg^{-1} bw day^{-1}. This value is considered to be scientifically out of date, however, as it uses data from Taiwanese data (Tseng *et al*., 1968, 1977) on skin lesions in populations drinking arsenic contaminated water, which has been superseded by better controlled epidemiology study data on a range of cancer effects (see below).

Similarly, the USEPA's 1994 oral RfD of 0.3 µg kg^{-1} bw day^{-1} is also based upon the Taiwanese skin lesion data (Tseng *et al*., 1968, 1977) and EPA have recently begun a major review of the health effects of arsenic, which is due for completion in 2015 (a toxicology review was published in February 2010 to inform the review (USEPA 2010)).

From these reviews for arsenic, the three most sensitive cancer effects of concern are skin lesions, lung cancer (from oral exposure) and bladder cancer, with potential for overlapping dose-effect responses. Sources of data on the pivotal studies, as chosen by each authoritative body for the quantitative evaluations of all three health effects of concern are presented from both the WHO/JECFA (2011) and EFSA (2009) evaluations:

WHO/JECFA (2011)

i) Skin lesions – three studies were evaluated: Ahsan *et al*., (2006) and Rahman *et al*., (2006) and Xia *et al*., (2009)

ii) Lung cancer – Chen *et al*., 2010a

iii) Bladder cancer – Chen *et al*., 2010b

EFSA (2009)

i) Skin lesions – two separate quantitative evaluations were performed using data from Ahsan *et al*. (2006) and Xia *et al*., (2009).

ii) Lung cancer – Ferreccio *et al*., (2000)

iii) Bladder cancer – Chiou *et al*., (2001)

For skin lesions, data were evaluated by WHO/JECFA and EFSA, but all studies were excluded from the final quantitative analysis by WHO/JECFA, as it was concluded that model fit was poor and all of the studies were confounded by factors other than arsenic exposure (e.g. smoking and sun exposure) that could not be evaluated. WHO/JECFA also considered the study by Xia *et al*., (2009) but it was discounted from modelling on the basis that concise diagnostic criteria were not available for the identification of skin lesions. Therefore the focus in WHO/JECFA (2011) was on the lung cancer and bladder cancer studies only.

In terms of lung cancer, at the time when EFSA carried out their evaluation in 2009, the Chen *et al*., (2010a) study (subsequently used by JECFA) was not available. Therefore the most appropriate study for lung cancer (by the oral route) at the time was the study by Ferreccio *et al*., (2000). WHO/JECFA (2011) did not choose the Ferreccio study as the pivotal study, due to potential selection bias in hospital based controls. Instead they favoured the new data from a general Taiwanese population (6888 subjects, 40 years or older, followed over 11 years) (Chen *et al.,* 2010a).

When considering bladder cancer, as the Chen *et al*., (2010b) study was not available, EFSA considered the most appropriate study for bladder cancer at the time was the study by Chiou *et al*., (2001). In contrast, WHO/JECFA (2011) favoured the new data from a general Taiwanese population (6888 subjects, 40 years or older, followed over 12 years) (Chen *et al*., 2010b).

Data from the WHO/JECFA evaluation are considered to be the most appropriate, on the basis that it is the most recent authoritative evaluation which includes the most robust data with better model fit.

GO TO FLOWCHART ELEMENT 6

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

As stated above, in the Environment Agency report (2009b) a cross-government department evidence-informed policy decision was taken, by setting the oral HCV at an equivalent intake of 0.3 µg kg^{-1} bw day^{-1} that would be achieved (in a 70 kg adult drinking 2 L water per day) at the UK drinking water standard of 10 µg L^{-1}. This standard is based on a 'practical achievable limit' for arsenic in drinking water, hence, this HCV is not a minimal risk value per se.

2.1.3 FLOWCHART ELEMENT 6: ARE THERE ADEQUATE DOSE-EFFECTS DATA FOR THE CHOSEN PIVOTAL STUDY – HUMAN DATA?

Yes	No	Not applicable
X		

All pivotal studies describing the critical effects i.e. skin lesions, lung cancer and bladder cancer had available datasets conducive to BMD modelling.

2.1.4 FLOWCHART ELEMENT 6b: PERFORM BMD MODELLING

Data on the BMD modelling for the three key health effects of arsenic exposure are presented below.

i) Skin lesions

Table 2.1: BMD modelling of skin lesion data from oral exposure to arsenic in drinking water

BMR = 0.5% (Rahman *et al.* 2006) and 5% (Ahsan *et al*. 2006) increased incidence of skin lesions					
WHO/JECFA 2011*			**BMD_5 (µg kg^{-1} bw day^{-1})**	**$BMDL_5$ (µg kg^{-1} bw day^{-1})**	**Model fit p value**
Ahsan *et al*., 2006			3.2-12.1	2.8-11.2	0.5-0.7 (50µg/d) 0.01 (400µg/d)
			$BMD_{0.5}$ (µg kg^{-1} bw day^{-1})	**$BMDL_{0.5}$ (µg kg^{-1} bw day^{-1})**	**Model fit p value**
Rahman *et al*., 2006			5.4	6.0	0.04
BMR = 1 or 5% increased incidence of skin lesions					
EFSA 2009**	**BMD_1 (µg kg^{-1} bw day^{-1})**	**$BMDL_1$ (µg kg^{-1} bw day^{-1})**	**BMD_5 (µg kg^{-1} bw day^{-1})**	**$BMDL_5$ (µg kg^{-1} bw day^{-1})**	**Model fit p value**
Ahsan *et al*., 2006	2.4-6.0	2.2-5.7	8.4-16.2	7.4-14.5	0.01
Xia *et al*., 2009	0.94-3.7	0.93	2.0-5.4	1.8-5.1	0.25

*Ranges are given due to differences in calculating arsenic intakes from diet and water assumed in the analysis: in this case 50-400 µg day^{-1} in diet, 3-5 litres of water consumption and a body weight of 55kg.

**Ranges are given due to differences in arsenic intakes in diet and water assumed in the analysis: in this case 50-200 µg day^{-1} in diet and 3-5 litres of water consumption and a body weight of 55kg.

N.B. WHO/JECFA 2011 discounted all skin lesion data from the analysis due to poor model fits, presence of confounders (eg smoking and sun exposure) in the data, and lack of clarity regarding accurate diagnostics in the Xia *et al*., 2009 study.

ii) Lung cancer

The BMD data for the lung cancer endpoint are presented in Table 2.2.

Table 2.2: BMD modelling of lung cancer data from oral exposure to arsenic in drinking water

BMR = 0.5% increased incidence of lung cancer					
WHO/JECFA 2011*	**$BMD_{0.5}$ (µg kg^{-1} bw day^{-1})**	**$BMDL_{0.5}$ (µg kg^{-1} bw day^{-1})**	**BMD_1** (µg kg^{-1} bw day^{-1})**	**$BMDL_1$ (µg kg^{-1} bw day^{-1})**	**Quantal linear Model fit p value**
Chen *et al.*, 2010a	4.5-7.3	3.0-5.0	9.1	NA	0.89
BMR = 1% increased incidence of lung cancer					
EFSA 2009***			**BMD_1 (µg kg^{-1} bw day^{-1})**	**$BMDL_1$ (µg kg^{-1} bw day^{-1})**	**Model fit**
Ferreccio *et al*., 2000			0.39-0.78	0.34-0.69	Not reported

*Ranges are given due to differences in calculating arsenic intakes from diet and water assumed in the analysis: in this case 50-200 µg day^{-1} in diet, 2-4 litres of water consumption and a body weight of 55kg for a Taiwan population average.

** Approximate average value from quantal linear model. BMR_1 = BMD of 500 µg day^{-1}, divided by 55kg.

***Ranges are given due to differences in arsenic intakes in diet and water assumed in the analysis: in this case 10-20 µg day^{-1} in diet and 1-2 litres of water consumption and a body weight of 70kg for a Chilean population average.

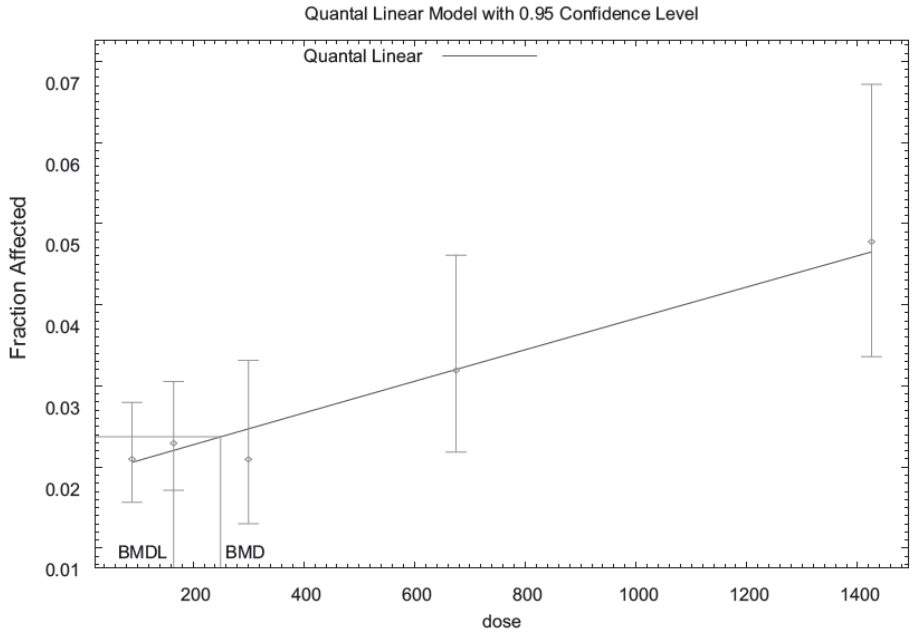

Figure 2.1: Quantal linear model of the lung cancer data in Chen *et al*., (2010a).

Reproduced from WHO/JECFA (2011a). Dose is in µg day^{-1}, 95% confidence limits on the data are shown. The marked BMD is for $BMD_{0.5}$, a 0.5% increased incidence in lung cancer.

iii) Bladder cancer

The BMD data for the bladder cancer endpoint are presented in Table 2.3.

Table 2.3: BMD modelling of bladder cancer data from oral exposure to arsenic in drinking water

BMR = 0.5% and 1% increased incidence of bladder cancer					
WHO 2011*	**$BMD_{0.5}$ (µg kg^{-1} bw day^{-1})**	**$BMDL_{0.5}$ (µg kg^{-1} bw day^{-1})**	**BMD_1** ** **(µg kg^{-1} bw day^{-1})**	**$BMDL_1$ (µg kg^{-1} bw day^{-1})**	**Quantal linear Model fit p value**
Chen *et al.*, 2010b	7.9-13.9	5.2-11.4	16	NA	0.96
BMR = 1% increased incidence of bladder cancer					
EFSA 2009***			**BMD_1 (µg kg^{-1} bw day^{-1})**	**$BMDL_1$ (µg kg^{-1} bw day^{-1})**	**Model fit**
Chiou *et al.*, 2001			7.9-15.4	3.2-7.5	Not reported

*Ranges are given as minimum and maximum values from modelling of the data; all models gave high p values of 0.96.

** Approximate average value from log-logistic model. BMR1% = BMD of 880 µg day^{-1}. Divided by 55kg.

***Ranges are given due to differences in arsenic intakes in diet and water assumed in the analysis: in this case 50-200 µg day^{-1} in diet and 3-5 litres of water consumption and a body weight of 55kg for a Taiwanese population average.

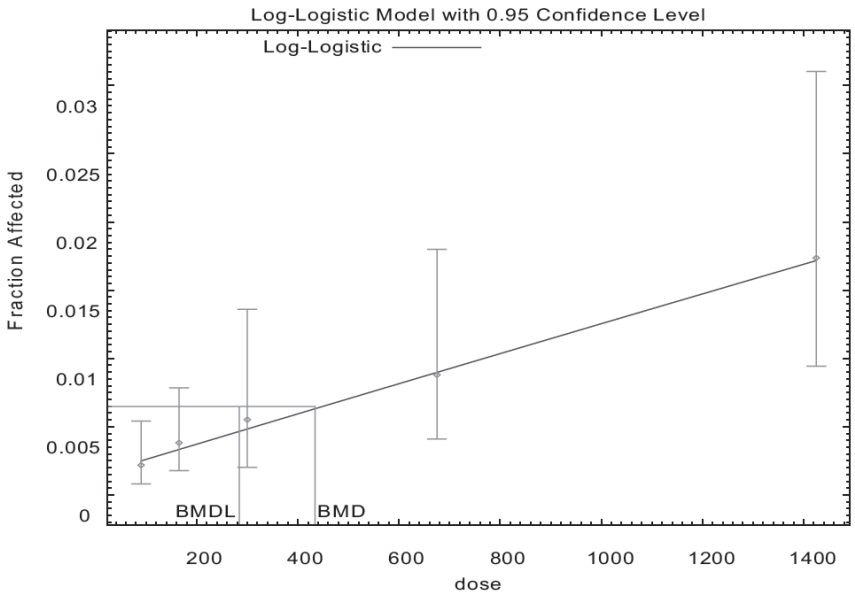

Figure 2.2: Log Logistic model of the bladder cancer data in Chen *et al.*, (2010b).

Reproduced from WHO/JECFA (2011a). Dose is in µg/day, 95% confidence limits on the data are shown. The marked BMD is for $BMD_{0.5}$, a 0.5% increased incidence in bladder cancer

A summary of the BMDs for the three cancer effects as derived in the WHO/JECFA (2011) evaluation is presented in Table 2.4.

Table 2.4: The choice of BMD values that could act as PODs in the derivation of a toxicology-based LLTC for C4SL determination

Possible BMDs		Effect	Reference
3.2*	BMD_5	Skin lesions	Ahsan *et al.*, 2006
3.0	$BMDL_{0.5}$	Lung cancer	Chen *et al.*, 2010a
4.5	$BMD_{0.5}$ (lowest)	Lung cancer	Chen *et al.*, 2010a
5.9	$BMD_{0.5}$ (average)	Lung cancer	Chen *et al.*, 2010a
9.1	BMD_1 (average)	Lung cancer	Chen *et al.*, 2010a
5.2	$BMDL_{0.5}$(lowest)	Bladder cancer	Chen *et al.*, 2010b
7.9	$BMD_{0.5}$ (lowest)	Bladder cancer	Chen *et al.*, 2010b

*This value for skin lesions is included here for completeness and comparison but given the reservations by WHO/JECFA and EFSA on the robustness of the data on skin lesions has been downweighted in favour of using the data on lung cancer and bladder cancer.

In the WHO/JECFA evaluation (2011), the best quality data and best model fit comes from data on lung cancer (Chen *et al*., 2010a) whereas the most sensitive data comes from effects on both lung cancer and bladder cancer (Chen *et al*., 2010b). Given the data for lung cancer yields slightly lower numbers, it is proposed that this endpoint data forms a scientific basis of the $LLTC_{oral}$ derivation.

GO TO FLOWCHART ELEMENT 4

2.1.5 FLOWCHART ELEMENT 4: DOES THE CRITICAL ENDPOINT EXHIBIT A THRESHOLD?

Yes	No	Not applicable
	X	

Arsenic is a well-established non-thresholded genotoxic carcinogen; IARC have classified inorganic arsenic as a known human carcinogen (IARC Monograph, 2012).

GO TO FLOWCHART ELEMENT 4a

2.1.6 FLOWCHART ELEMENT 4a: DEFINE A SUITABLE CHEMICAL-SPECIFIC MARGIN

The data for lung and bladder cancer endpoints allowed a BMD for a low BMR incidence of effects to be calculated (0.5% increased incidence). Therefore, a chosen margin could be lower here than would typically be used for higher BMR values.

The choice of margin to use is a risk management decision, depending upon the degree of precaution one wishes to take in representing the uncertainties. As a guide one can equate the BMR and choice of margin to a notional ELCR that would be represented by combining these choices (see Table 2.5 below).

Alternatively, a CSM of 100 may be calculated to account for the uncertainty in the carcinogenic processes, with an uncertainty in this case of 1 for inter- and intra-species variability.

GO TO FLOWCHART ELEMENT 5a

2.1.7 FLOWCHART ELEMENT 5a: CALCULATE THE LLTC FOR NON-THRESHOLDED CHEMICALS

For non-thresholded chemicals, the LLTC is calculated by dividing the POD by the CSM (or default margin)

POD/margin = LLTC (units as per POD)

In Table 2.5, options for the LLTCs using various PODs and margins of 10, 50 and 250 that relate to notional ELCRs of 1 in 2,000, 1 in 10,000 and 1 in 50,000, respectively, are presented.

Table 2.5: Proposed choices of oral LLTC values using different PODs based on lung cancer data from Chen *et al*. (2010a)

	POD	Value (µg kg^{-1} bw day^{-1})	Margin/ CSM	LLTC (µg kg^{-1} bw/day)	Notional ELCR
Proposed LLTC	$BMDL_{0.5}$ (lowest)	3	10	0.3	1 in 2,000
Alternative		3	50	0.06	1 in 10,000
		3	250	0.01	1 in 50,000
Alternative	$BMD_{0.5}$ (lowest)	4.5	10	0.45	1 in 2,000
Alternative		4.5	50	0.09	1 in 10,000
Alternative		4.5	250	0.02	1 in 50,000
Alternative	$BMD_{0.5}$ (average)	5.9	10	0.59	1 in 2,000
Alternative		5.9	50	0.2	1 in 10,000
Alternative		5.9	250	0.04	1 in 50,000
Current HCV for arsenic (EA 2009b)	Intake based upon WHO drinking water standard (10 µg/dL)(practical achievable limit)	Policy based		0.3	

GO TO FLOWCHART ELEMENT 7

2.1.8 FLOWCHART ELEMENT 7: ASSESS LLTC for ARSENIC

Deriving an LLTC by only applying 'generic criteria' (i.e. following suggestions in Section 5.4 of the main report) with no other considerations would lead to an LLTC at 0.02 µg kg^{-1} bw day^{-1} (i.e. using the $BMD_{0.5}$ of 0.45 µg kg^{-1} bw day^{-1} with a generic margin of 250 that would equate to an ELCR value of 1 in 50,000 – see Table 2.5). So as not to disproportionately target soil (and as per the derivation of the HCV discussed previously in section 2.1.1), the higher value of 0.3 µg kg^{-1} bw day^{-1} is recommended as the LLTC (which is equivalent to the HCV). However the associated ELCR of 1 in 2000 is above what could be considered as 'low concern' from the evidence.

For illustrative purposes, LLTCs (based on different choices of POD and margins) would result in similar orders of magnitude of notional ELCR.

For example all three numbers below relate to a notional ELCR of 1 in 2,000:

a) 0.3 µg kg^{-1} bw day^{-1}
   - lowest $BMDL_{0.5}$ with use of a CSM of 10
   - equivalent to the intake based on the UK drinking water standard (10 µg l^{-1})
   - equivalent to the HCV (EA 2009b)

b) 0.45 µg kg^{-1} bw day^{-1}
   - lowest $BMD_{0.5}$ with use of a CSM of 10

c) 0.59 µg kg^{-1} bw day^{-1}
   - average $BMD_{0.5}$ with use of a CSM of 10

The basis of the differences in numbers above, are:

- the choice of a BMDL vs a BMD at a BMR of 0.5% increased incidence of cancer (a vs b).
- the choice of whether to select the lowest value of the population distribution of dietary intakes (to cover all the population) or the average intake person in the population (b and c)

In recommending a single LLTC here in this report, aspects of risk management have been invoked (i.e. as the 'policy choice' route 2c on the framework in Figure 2.2. of the main report. The LLTC of 0.3 µg kg^{-1} bw day^{-1} is recommended to carry forward into the C4SL derivation, which is based upon the risk management/policy based measure of using the equivalent intake based upon the UK drinking water standard, so as not to disproportionately target soil. This value is also equivalent to the current EA 2009 HCV and given the scientific analysis it is recommended in this case not to go above that here for the purposes for C4SL derivation. Benchmarking this value against the toxicological data, this equates to a $BMDL_{0.5}$ with a margin of 10 applied. In this case, the notional ELCR of 1 in 2000 is above what could be considered as 'low concern'.

2.1.9 OTHER CONSIDERATIONS

Lifetime averaging should not be applied to arsenic, as there is a lack of evidence to determine whether children are more or less susceptible to the effects of arsenic than adults. Therefore assume a child as the critical receptor.

As the effects are systemic and can occur by all routes of exposure, then exposures should be combined in CLEA to derive the pC4SL.

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

As with the oral route, the EA report (Science report: SC050021/TOX1) has been used as the start of the data search, and new information published between the years 2009-2013 was added to the data package (EA, 2009a).

In 2009, the EA TOX1 report for arsenic recommended a value of 6.6 ng m^{-3} (equivalent to an intake of 0.002 µg kg^{-1} bw day^{-1} for a 70kg person breathing 20 m^3 of air per day) as the HCV for lung cancer effects from inhalation. This was based upon the WHO air quality guidelines for Europe (2000) recommendation that exposures of this magnitude would pose an excess lifetime cancer risk of about 1 in 100,000.

EPAQS derived a lower guideline value for ambient air arsenic of 3 ng m^{-3} using the same source of cancer effects data as used by WHO (2000) (EPAQS 2008).

For non-cancer effects, the WHO air quality guidelines (2000) reported cases of peripheral neuropathy in smelter workers, where exposure to arsenic dust at a

concentration of approximately 50 ng m^{-3} resulted in a decrease in peripheral nerve conduction velocities (Lagerkvist & Zetterlund,1994, cited in WHO, 2000).

In the CICAD 47 report for arsenic (2002), a guideline value of 50 ng m^{-3} air concentration was also derived for non-cancer effects, haemolysis, as observed in mice.

The EPA had previously calculated an RfC for inhalation in 1994. However, on the IRIS resource, this value is now withdrawn. An extensive review of arsenic toxicology and health effects has just begun in 2013, due to be completed in 2015.

2.2.2 FLOWCHART ELEMENT 2: REVIEW THE SCIENTIFIC BASIS OF EACH HBGV. CHOOSE THE PIVOTAL STUDY

As above, flowchart element 2 requires a suitably qualified individual who sufficiently understands the nature of toxicological data to identify the scientific basis of all existing HCVs for the inhalation route. Again, 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) an evidence-informed policy choice (i.e. based on an existing guideline from another regime, with or without a toxicological rationale).

2a) Animal Toxicology Data

The CICAD (2002) No. 47 report for arsenic includes a data evaluation from mouse studies (Hong *et al*., 1989; Rosenthal *et al*., 1989; Blair *et al*., 1990 a & b), for the observed critical non-cancer effects of haemolysis. These data are not key in the evaluation here, but can be used to provide a guide as to the next most sensitive endpoint after cancer via inhalation, which are effects on the cardiovascular system. The reported NOEC for haemolysis is 80 µg m^{-3} air concentration. The experimental NOAEL was for exposures of six hours per day, five days per week, and its continuous exposure equivalent (0.08 x 5/7 x 6/24) was divided by an uncertainty factor (UF) of 300 to generate an inhalation guidance value, after rounding, of 50 ng m^{-3}. An UF of 3 was used for interspecies differences, 10 for intraindividual differences and a composite factor of 10 for a short term study and database deficiencies.

2b) Human Toxicology/Epidemiology Data

The basis of the WHO (2000) air quality guideline and EA (2009b) HCV, was an evaluation of a set of three occupational studies (Tacoma study (Pinto *et al*., 1977); Montana study (Lee-Feldstein,1983) and Swedish Ronnskar study in Viren & Silvers (1994)), of workers exposed to arsenic by inhalation of dusts in smelters in the US and Sweden, and their incidence of lung cancer. These data act as the pivotal study data for this evaluation.

In 2008, EPAQS derived a guideline value by taking the mid-point of the exposure range from the Swedish (Ronnskar population) study (125 µg m^{-3} years) (Viren & Silvers, 1994) which converts to an average concentration of 3 µg m^{-3} over a 40 year working lifetime. If this concentration is considered as a LOAEL then (following the precedent set in the EPAQS report on polycyclic aromatic hydrocarbons) division by a factor of 10 giving a concentration of 0.3 µg m^{-3} (300 ng m^{-3}) provides a notional NOAEL. This was further divided by a factor of 10 to allow for the greater exposure duration of the general public and a further factor of 10 to allow for the presence of susceptible groups from within the general population. This led to a recommended guideline value of 3 ng m^{-3}, which is the lowest of all values derived.

GO TO FLOWCHART ELEMENT 6

2c) Policy only

Not applicable.

2.2.3 FLOWCHART ELEMENT 6: ARE THERE ADEQUATE DOSE-EFFECTS DATA FOR THE CHOSEN PIVOTAL STUDY – HUMAN DATA?

Yes	No	Not applicable
		X

The recommended evaluation to use in the derivation of an LLTC, is based upon the lung cancer risk estimates calculated by Viren & Silvers (1994) as evaluated in WHO (2000) and used as the basis of the Index Dose (ID) by the EA (2009b).

WHO (2000) stated 'When assuming a linear-dose relationship, a safe level for inhalation exposure cannot be recommended. At an air concentration of 1 µg m^{-3}, an estimate of lifetime risk is 1.5 x 10^{-3}. The ELCR is 1 in 10,000 or 1 in 100,000 at air concentrations of about 66 ng $m^{-3}$and 6.6 ng m^{-3}, respectively.

GO TO FLOWCHART ELEMENT 6c

2.2.4 FLOWCHART ELEMENT 6c. SPECIFY AN ELCR ABOVE 1 IN 10^5

Different LLTCs relating to different ELCRs are presented in Table 2.6. The HCV based upon a minimal risk of 1 in 100,000 is 1.9 ng kg^{-1} bw day^{-1}. Choosing an ELCR above this is a risk management choice based on the ELCR considered to be of low risk. Based on the scientific analysis, it is recommended not to go above an air concentration of 50 ng m^{-3}, as different effects of haemolysis start to occur at this level.

Table 2.6: Proposed choices of inhalation LLTC values (as target air concentrations) using different ELCRs. Conversion to an LLTC inhalation intake in ng kg^{-1} bw day^{-1} is performed assuming an adult body weight of 70kg and an air intake rate of 20m^3 per day.

	ELCR	Air concentration (ng m^{-3})	LLTC (ng kg^{-1} bw day^{-1})
Alternative – but exceeds the level where haemolysis is seen	1 in 10,000	66	18.9
Non cancer (haemolysis) effects HBGV (CICAD, 2002) Peripheral nephropathy in humans (WHO, 2000)	-	50	14.3
Proposed maximum LLTC	1 in 50,000	13.2	3.8
Alternative	1 in 75,000	9.8	2.8
HCV for arsenic (EA 2009b)	1 in 100,000	6.6	1.9

Conversion to an LLTC inhalation intake in ng kg^{-1} bw day^{-1} is performed assuming an adult body weight of 70kg and an air intake rate of 20m^3 per day.

GO TO FLOWCHART ELEMENT 7

2.2.5 FLOWCHART ELEMENT 7: ASSESS LLTC for ARSENIC

Based upon a scientific evaluation of carcinogenic data in humans, it is proposed that the inhalation LLTC is based on an ELCR of 1 in 50,000, which equates to 3.8 ng kg^{-1} bw day^{-1}. This is itself based on an air concentration of 13.2 ng m^{-3} and default physiological parameter values for the adult receptor (70 kg body weight and 20 m^3 air per day). This value:

a) is 2-fold higher than the minimal risk HCV (EA 2009b)

b) represents an ELCR of 1 in 50,000, which could be regarded as 'low risk', but it should be noted that this is a risk management decision

c) Is lower than the HBGV for non-cancer effects (haemolysis (mouse data) and peripheral nephropathy seen in humans)

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

2.2.6 CALCULATION OF A CHILD-SPECIFIC LLTC for ARSENIC

There is no evidence to suggest that the child is a more susceptible receptor than adults for arsenic toxicity. Inhalation LLTCs for other land use scenarios are derived based on receptor-specific physiological parameter values (i.e. for bodyweight and inhalation rate) and are detailed in Table 2.7, using the air target concentration of 13.2 ng m^{-3}.

Table 2.7: Proposed inhalation LLTCs for C4SL land use scenarios, considering child receptor specific physiological parameters

Land use	Critical receptor	Receptor age classes	Average bodyweight (kg)	Inhalation rate (m^3 day^{-1})	LLTC (ng kg^{-1} bw day^{-1})
Residential	Female child[2]	1-6	13.3	8.8	8.7
Allotments	Female child[2]	1-6	13.3	8.8	8.7
Commercial	Female worker[1]	17	70	20	3.8
POS-residential	Female child[2]	4-9	21	11	6.9
POS-park	Female child[2]	1-6	13.3	8.8	8.7

1. Default adult physiological parameter values for conversion of media concentrations to intake values detailed in EA, 2009c. 2. Values for other receptors are the average bodyweight and inhalation rate for the age class range taken from EA, 2009d.

2.3 DERMAL ROUTE

Effects of skin lesions in humans via the oral route contribute towards the basis of the LLTC oral value, which can also be used as a value in the evaluation of dermal exposure and skin absorption factored in appropriately.

Dermatitis, including hyperpigmentation and hyperkeratosis has been described in two workforces exposed via inhalation; in one the estimated lowest observed adverse effects level (LOAEL) was 80 µg/m^3 (Perry *et al.,* 1948), but in the other the NOAEL was ten-fold lower (Mohamed, 1998). It is expected that the inhalation LLTCs proposed in Table 2.7 will be protective of dermal effects via inhalation exposure.

3. EXPOSURE MODELLING FOR ARSENIC

As described in Step 4 of the framework (see Section 5.1 of the main report), the CLEA model has been used deterministically with the above LLTCs to derive provisional C4SLs for the following six land-uses:

- Residential with consumption of homegrown produce;
- Residential without consumption of homegrown produce;
- Allotments;
- Commercial;
- Public open space (POS):
    - The scenario of green 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 that there is negligible tracking back of soil (POS_{park}).

The CLEA model has then been used probabilistically to determine the probability that exposure of a random individual within the critical receptor group would exceed the LLTC values for a range of different soil concentrations (step 5). This probabilistic step helps to illustrate the level of precaution provided by each pC4SL and, if necessary, can be used to guide any modifications judged necessary. The approach and key assumptions for both types of exposure modelling are discussed in the following sections. The results of the modelling are presented in Section 4.

3.1 DETERMINISTIC MODELLING

Deterministic modelling uses a single value for each parameter input and derives one estimate of 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. In the case of arsenic, the $LLTC_{inhal}$ is based on carcinogenicity attributed solely to local pulmonary effects and therefore the ADE for inhalation routes of exposure are compared with the $LLTC_{inhal}$. As discussed in Section 2.2, the $LLTC_{oral}$ is based on systemic effects and therefore the total ADE for all routes of exposure (oral, dermal and inhalation) is compared with the $LLTC_{oral}$.

CLEA uses iteration to find the soil concentrations at which the summed ADEs equal the respective LLTC values and these are termed 'assessment criteria' (AC). As described in the CLEA SR2 and SR3 documents (EA, 2009 c & d), the AC are integrated by CLEA to determine an overall AC 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. Given that the $LLTC_{inhal}$ is based on localised effects the latter approach has been taken to determine the pC4SL. Note that the SGVs for arsenic are based on the oral AC only, on the basis that the ELCR associated with the oral HCV is orders of magnitude greater than that associated with the inhalation HCV. Adopting this alternative approach would, however, have no effect on the C4SLs as the oral AC are less than the inhalation AC for all the C4SL land-uses.

The assumptions and non-contaminant specific parameter values used for the derivation of the pC4SLs are presented in Section 3 of the main report. For residential, allotments and commercial land-uses the assumptions and parameter values are as those described in the SR3 report (EA, 2009d) with the exception of those summarised in Section 3.5.7 of the main report. Note that for consumption of homegrown produce, CLEA predicts the greatest exposure to arsenic from green vegetables and tree fruit for both the residential and allotments scenarios. Therefore, in accordance with the "top two" approach (see Section 3.5.5.3 of the main text for further details), 90^{th} percentile consumption rates have been used for these two

produce types and mean consumption rates have been used for the remaining produce types. For the POS land-uses the assumptions and parameter values are described in Section 3.6 of the main report. Note that the pC4SLs have been derived assuming a sandy loam soil type (i.e. as used for deriving SGVs).

Contaminant specific parameter values used for arsenic are shown in Table 3.1 and discussed further below.

Table 3.1: Contaminant specific parameter values used for derivation of pC4SLs for arsenic

Parameter	Units	Value	Source/Justification
Dermal absorption fraction	-	0.03	SR3 (EA, 2009b)
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	4.3 E-04	Geomeans of empirical soil to plant concentration factors derived from literature sources (EA, 2009c)
Soil-to-plant concentration factor (root vegetables)		4.0 E-04	
Soil-to-plant concentration factor (tuber vegetables)		2.3 E-04	
Soil-to-plant concentration factor (herbaceous fruit)		3.3 E-04	
Soil-to-plant concentration factor (shrub fruit)		2.0 E-04	
Soil-to-plant concentration factor (tree fruit)		1.1 E-03	
Soil-to-dust transport factor (g g^{-1} DW)	-	0.5	SR3 (EA, 2009b)
Relative bioavailability soil	-	1.0	Conservative assumption made that bioavailability of arsenic in soil and dust is the same as bioavailability of arsenic in critical toxicological studies used to derive the LLTC
Relative bioavailability dust	-	1.0	

Soil to plant concentration factors

The Environment Agency undertook a review of the scientific literature on the plant uptake of arsenic by fruit and vegetables based on findings from literature searches conducted in June 2007 (EA, 2009e). As part of this review they collated soil to plant concentration factors (CFs) from available studies. These were calculated from the ratio of concentration of the contaminant in the plant (mg^{-1} kg^{-1} fresh weight [FW]) to the concentration of the contaminant in soil (mg^{-1} kg^{-1} fresh weight [DW]). The summary statistics for the collated concentration factors are shown in Table 3.2.

Table 3.2: Summary statistics for soil to plant concentration factors for arsenic

Produce Category	Soil-to-plant concentration factors (mg kg^{-1} FW per mg kg^{-1} DW)				
	GM [1]	Minimum	Maximum	SD [2]	N [3]
Green vegetables	4.3×10^{-4}	1.6×10^{-5}	0.011	2.5×10^{-3}	46
Root vegetables	4.0×10^{-4}	6.0×10^{-5}	3.6×10^{-3}	1.0×10^{-3}	26
Tuber vegetables	2.3×10^{-4}	2.8×10^{-5}	1.8×10^{-3}	6.9×10^{-4}	6
Herbaceous fruit	3.3×10^{-4}	9.4×10^{-5}	2.6×10^{-3}	7.0×10^{-4}	12
Shrub fruit	2.0×10^{-4}	5.4×10^{-5}	9.1×10^{-4}	3.4×10^{-4}	6
Tree fruit	1.1×10^{-3}	7.1×10^{-4}	1.8×10^{-3}	7.6×10^{-4}	2

1. Geometric mean (GM) of data is reported as it is a more suitable representation of experimental ratios
2. Standard deviation (SD)
3. Number of studies (N)

The Environment Agency recommended the use of the geomean of the concentration factors for each produce type for derivation of SGV for arsenic.

Soil to dust transport factor

The soil to dust transport factor is an empirical measure of the tendency of a contaminant to concentrate in indoor dust from soil. It is used in the CLEA model to predict the concentration of contaminant in airborne respirable dust derived from soil (EA, 2009b). The soil to dust transport factor should be contaminant specific but where contaminant specific data are not available the EA recommend a default value of 0.5 for derivation of the SGV (EA, 2009c). This means that the concentration of contaminant in respirable dust is assumed to be 50% of the concentration of contaminant in outdoor soil.

Following a review of the literature, EA (2009e) concluded no data could be used to provide a generalised arsenic soil-to-dust transport factor. In the absence of a contaminant specific soil-to-dust transport factor, the default value of $0.5.g.g^{-1}$ DW was used for the derivation of the arsenic SGV (Environment Agency, 2009e). The same value ($0.5.g.g^{-1}$ DW) has been used for the derivation of the arsenic C4SL.

Relative bioavailability

The relative bioavailability (RBA) is the ratio of the bioavailability of the contaminant in soil to the bioavailability of the contaminant in the critical study used to derive the health criteria (i.e. the LLTCs in this context). For the derivation of the pC4SLs for arsenic, this is conservatively assumed to be 100% for both the oral and inhalation routes of exposure.

The proposed $LLTC_{oral}$ is based on a human epidemiological study involving a cohort exposed to arsenic via drinking water consumption. The bioavailability of arsenic from drinking water was not reported and it is an uncertain parameter as the exact gut uptake will depend on nutritional status. It is likely that the absorption of arsenic from drinking water in the human studies will be higher than the absorption of arsenic from ingested soil.

In-vitro bioaccessibility testing can be used to estimate the oral bioaccessibility as a surrogate for bioavailability of arsenic in soil. The Unified BARGE Method (UBM) is an in-vitro method that has been validated against in-vivo data for arsenic, antimony, cadmium and lead using juvenile swine (Denys *et al*., 2012). Appleton *et al*. (2012) used this method to measure the bioaccessible fraction of arsenic in 165 soil samples taken from urban areas in Glasgow, London, Northampton and Swansea and rural areas in Lincolnshire. The bioaccessible fraction in samples from Glasgow, London and Swansea ranged from 6 to 68%, with mean values of 22 to 30%. The bioaccessible fractions in samples from Northampton and Lincolnshire were lower, ranging from 2 to 15%, with mean values of 6 to 9%. The authors attribute the lower bioaccessibility in these areas to the dominance of ironstones in the parent material.

The results from Appleton *et al*. indicate that the bioavailability of arsenic from some UK soils is typically significantly below that associated with the critical toxicological study used to derive the $LLTC_{oral}$. Thus, for many parts of the UK, the assumption of 100% RBA is likely to be highly conservative. However, as demonstrated by Appleton *et al*., the bioaccessible fraction can vary widely from site to site. For this reason, adoption of a generic value of RBA of less than 100% is not considered appropriate for the derivation of pC4SLs for arsenic.

The proposed $LLTC_{inhal}$ is based on human epidemiological studies involving cohorts of smelter workers exposed to arsenic in dust. The bioavailability of arsenic via inhalation from these studies is not known but it is reasonable to assume that this would be similar to that from soil derived dust. Therefore the assumption of 100% RBA for inhalation exposure is considered appropriate for the derivation of pC4SLs for arsenic.

3.2 PROBABILISTIC MODELLING

The sensitivity analysis described in Section 3.4 of the main report helped to identify the key uncertain parameters contributing to the greatest uncertainty in the model results. The CLEA model has been used probabilistically, substituting the single deterministic values for these parameters with a probability density function and using Monte Carlo analysis to derive a distribution of possible ADE results for a given soil concentration. All other parameters in CLEA remain unchanged as deterministic single values. Although there is uncertainty in the remaining parameters, the sensitivity analysis demonstrated that this does not give rise to significant uncertainty in the CLEA model outputs and these remaining parameters have not therefore been modelled probabilistically. Key parameters modelled probabilistically together with an indication of where and how they are correlated are shown for the residential and allotments land-uses in Table 3.3.

Table 3.3: Parameters modelled probabilistically for arsenic

Parameter	Generic Land-use				Correlation
	Residential		Allot-ments	Comm-ercial	
	With home grown prod.	Without home grown prod.			
Body weight	✓	✓	✓	✓	Correlated between age classes, i.e. a heavy one year old is assumed to become a heavy six year old. Body weight is also correlated with inhalation rate, i.e. a child in the upper percentile body weight will also have an upper percentile inhalation rate
Soil ingestion rate	✓	✓	✓	✓	Correlated between age classes
Exposure Frequency skin contact outdoors	✓	✓	✓		Correlated between age classes
Soil to skin adherence factor outdoors	✓	✓	✓		Correlated between age classes
Maximum exposed skin fraction outdoors	✓	✓	✓		Correlated between age classes
Inhalation rate	✓	✓		✓	Correlated between age classes and with body weight
Dust loading factor	✓	✓		✓	Not correlated with other parameters
Soil to dust transport factor	✓	✓		✓	Not correlated with other parameters
Produce consumption rate	✓		✓		Correlated between age classes. Also, consumers of homegrown produce assumed to be within the upper quartile of consumers of fruit and vegetables
Homegrown fraction	✓		✓		Correlated between produce types, i.e. an individual who consumes potatoes, most of which are homegrown will also consume mostly homegrown root and green vegetables and fruit
Soil to plant concentration factors	✓		✓		Correlated between produce type, i.e. if a soil allows high plant uptake for potatoes, it will also allow high plant uptake for the remaining produce types

A probability density function (PDF) has been derived for each of these parameters. The type of distribution (e.g. normal, log normal, beta etc.) and associated attributes (e.g. mean, standard deviation or 95th percentile) selected for each parameter have been chosen to best represent the range of distribution families considered. The PDF type and associated attributes for contaminant specific parameters are summarised in

Table 3.4 below for contaminant specific parameters. The PDF types and attributes for the remaining parameters modelled probabilistically are summarised in Appendix B of the main report.

Table 3.4: PDF attributes for contaminant specific parameters for Monte Carlo analysis for arsenic

Parameter	Units	Basis of PDF	PDF attributes
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	Log normal distribution assumed based on geomean and SD from Environment Agency, SGV supplementary report (2009). Values truncated at 2.5 and 97.5 %iles.	Log normal (gm 4.3e-4, SD [ln CFs] 1.71)
Soil-to-plant concentration factor (root vegetables)			Log normal (gm 4.0e-4, SD [ln CFs] 1.26)
Soil-to-plant concentration factor (tuber vegetables)			Log normal (gm 2.30e-4, SD [ln CFs] 1.35)
Soil-to-plant concentration factor (herbaceous fruit)			Log normal (gm 3.3e-4, SD [ln CFs] 1.17)
Soil-to-plant concentration factor (shrub fruit)			Log normal (gm 2.0e-4, SD [ln CFs] 1.05)
Soil-to-plant concentration factor (tree fruit)			Log normal (gm 1.1e-3, SD [ln CFs] 0.61)
Soil to dust transport factor	g g^{-1} DW	Triangular distribution with min and max based on reported range in literature values from Oomen & Lijzen (2004). Most likely value = mid range of these values.	Triangular (min 0.08, mode 0.5, median 0.47, max 0.8)

4. PROVISIONAL C4SLs FOR ARSENIC

As described in the framework (see Section 5.1 of the main report), the setting of C4SLs involves an initial deterministic stage, whereby modified CLEA exposure modelling is combined with LLTCs to produce provisional C4SLs (pC4SLs) (Step 4), followed by quantitative (Step 5) and qualitative evaluations of uncertainty (Steps 6a and 6b), using probabilistic modelling and other methods, to examine their likely levels of precaution. Other considerations are also brought to bear, (Steps 6c and 6d), such that any final C4SLs (Step 7) can most closely match Defra's defined policy objectives.

4.1 PROVISIONAL C4SLs

The pC4SLs for arsenic derived from the deterministic CLEA modelling using the proposed LLTC values are presented in Table 4.1 below, along with arsenic's existing SGVs.

Table 4.1: Provisional C4SLs and SGVs

Exposure parameters	HCV or LLTC µg kg^{-1}(bw) day^{-1}		pC4SL (mg.kg^{-1})					
			Residential		Allot-ments	Comm-ercial	POS_{resi}	POS_{park}
	Oral	Inhal	With home grown prod.	Without home grown prod.				
SGV [1]	0.3	0.002	32	32	43	640	N/A	N/A
pC4SL with exposure changes only	0.3	0.002	37	40	49	640	79	170
pC4SL with LLTC but exposure parameters[2] as SR3	0.3	0.0038-0.0087[3]	32	35	43	640	N/A	N/A
pC4SL with changes in exposure [2] and LLTC	0.3	0.0038-0.0087[3]	37	40	49	640	79	170

1. Soil Guideline Value (EA, 2009a)
2. Parameters as described in Section 3
3. Note age specific adjustments used for residential and POS land-uses as shown in Table 3.9

N/A: Not applicable

The relative contribution of each exposure pathway to total ADE is shown for each land-use in Table 4.2.

Table 4.2: Relative contributions of exposure pathways to overall exposure

Exposure pathway	Relative contribution to total exposure (%)					
	Residential		Allot-ments	Comm-ercial	POS_{resi}	POS_{park}
	With home grown prod.	Without home grown prod.				
direct soil & dust ingestion	92	99	33	95	98	97
sum of consumption of homegrown produce and attached soil	7.0	0	62	0	0	0
dermal contact (indoor)	0.51	0.55	0	1.9	0.89	0
dermal contact (outdoor)	0.64	0.69	4.9	2.8	1.0	2.9
inhalation of dust (indoor)	0.20	0.22	0	0.64	0.16	0
inhalation of dust (outdoor)	1.6×10^{-4}	1.7×10^{-4}	0.013	4.4×10^{-3}	1.1×10^{-3}	0.025
inhalation of vapour (indoor)	0	0	0	0	0	0
inhalation of vapour (outdoor)	0	0	0	0	0	0
oral background	0	0	0	0	0	0
inhalation background	0	0	0	0	0	0

4.2 QUANTITATIVE APPRAISAL OF UNCERTAINTY

Monte Carlo probabilistic modelling has been conducted for the residential, allotments and commercial land-uses to estimate the possible distribution in ADE exposures for the critical receptor for a given soil concentration. This has been repeated for various soil concentrations to cover the range of pC4SLs presented in Table 4.1.

The results of this modelling are discussed in the following sections. The results are presented graphically as:

- Reverse cumulative frequency (RCFs), i.e. graphs of the reverse cumulative frequency versus ADE for alternative pC4SLs. The alternative pC4SLs have been derived using the deterministic CLEA model but making different choices for the exposure parameter values. These RCF graphs provide an indication of the probability of the ADE to a random individual within the critical receptor group exceeding the LLTC from a given soil concentration. As explained in Section 5.1 of the main report, this probability is one of the considerations that is relevant to deciding whether a pC4SL is appropriate. These graphs also show the potential magnitude of exposures above the LLTC, which is also a relevant consideration when setting the C4SL; and
- Probability of exceedence versus soil concentration graphs. These show how the probability of the ADE exceeding the LLTC varies with soil concentration.

It should be noted that the accuracy of these graphs is dependent on the accuracy of the underlying PDFs used to conduct the probabilistic modelling. Residual uncertainty in the underlying PDFs and remaining parameters modelled as set deterministic values (such as RBA) are discussed in Section 4.3.2.

4.2.1 RESIDENTIAL (WITH CONSUMPTION OF HOMEGROWN PRODUCE) LAND-USE

Figure 4.1 shows the RCFs of total exposure for three alternate values of pC4SLs using alternative sets of exposure parameters. These are:

1. pC4SL = 32 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.3 μg kg^{-1} bw day^{-1} and an age class adjusted $LLTC_{inhal}$ of 0.0087 μg kg^{-1} bw day^{-1} but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 37 mg kg^{-1}. This is the pC4SL derived using LLTCs as above but with the proposed modifications to exposure modelling parameters described in Section 3.5.7 of the main report; and
3. pC4SL = 48 mg kg^{-1}. This is the pC4SL derived as above, but with additional modifications to exposure modelling parameters that had been proposed in the draft interim methodology document produced in advance of the first Stakeholder Workshop. These additional modifications are soil ingestion rate reduced to 80 mg d^{-1}, mean consumption rate used for all produce types, homegrown fraction halved for all produce types and dust loading factor reduced to 25 μg.m^{-3}.

The coloured curves on Figure 4.1 show the RCFs for the alternative pC4SLs. These curves show that there is a high probability of exposure exceeding a low ADE value but a low probability of exposure exceeding a high value. Figure 4.1 also shows the $LLTC_{oral}$ (as a dashed line) along with the estimate of average background exposure from non-soil sources for comparison with the RCFs of average daily exposure. As discussed below, the probability of inhalation exposure exceeding the $LLTC_{inhal}$ is negligible and so RCFs are not presented for inhalation exposure in Figure 4.1.

Note that the probabilistic modelling for residential (with consumption of home-grown produce land-use) is based on the assumption that the property has a garden and the critical receptor consumes produce grown in that garden (albeit to varying degrees).

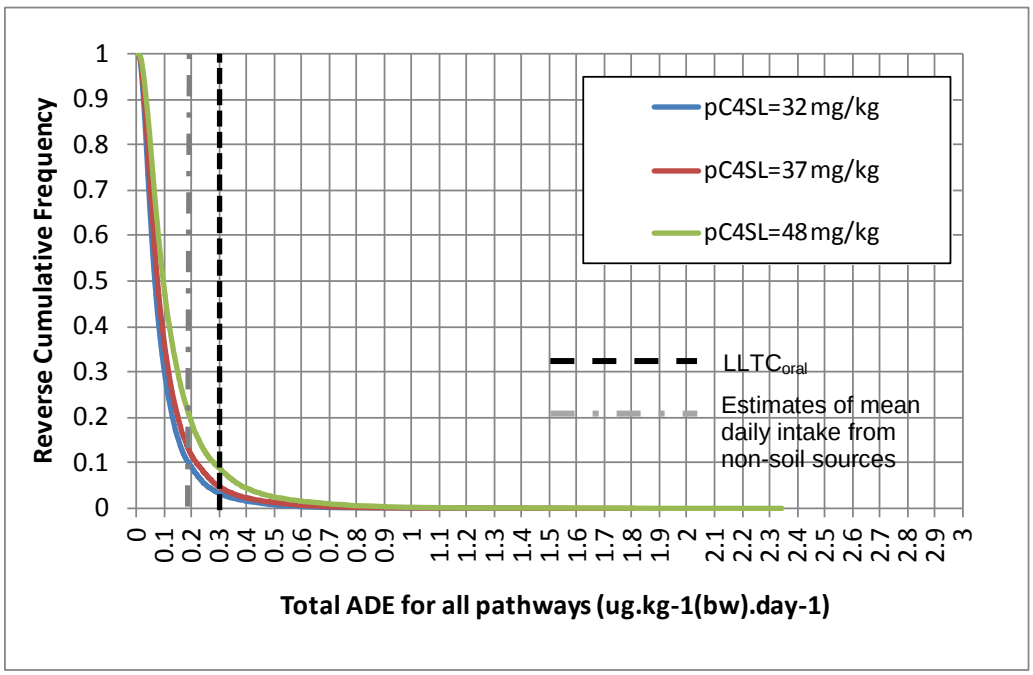

Figure 4.1: Reverse cumulative frequency graph of ADE for alternative values of pC4SL for arsenic for residential (with consumption of homegrown produce) land-use

Figure 4.1 can be used to estimate the probability that exposure to a random individual within the critical receptor group would exceed the $LLTC_{oral}$ by reading off the probability from the y axis where the RCF curve intersects the LLTC vertical dashed line. Thus, the probability that exposure would exceed the LLTC is 3% for a soil concentration of 32 mg kg^{-1}, increasing to 5% and 9% for soil concentrations of 37 and 48 mg kg^{-1}, respectively. As discussed in Section 4.3, a generally conservative approach has been adopted for the probabilistic modelling and it is possible that the true probabilities of exceedence are significantly lower.

Figure 4.1 can also be used to assess the relative importance of background exposure to exposure from soils. In the case of arsenic for residential (with consumption of homegrown produce) land-use there is only a 10% to 20% probability that exposure from soils would exceed background exposure from non-soil sources. This indicates that exposure from soils at the pC4SL is typically less than background exposure.

Figure 4.2 presents the probability of exceedence graphs for residential (with consumption of homegrown produce) land-use. This graph shows two curves: the probability that the total exposure from soil (i.e. from oral, dermal and inhalation routes) exceeds the $LLTC_{oral}$ and the probability that exposure from soil via the inhalation route alone exceeds the $LLTC_{inhal}$. As with Figure 4.1 this graph can be used to estimate the probability that exposure to a random individual in the critical receptor group exceeds the LLTCs for alternative pC4SLs, but has the added advantage that the relationship between probability of exceedence and soil concentration can be seen more easily.

Figure 4.2 shows that the probability of total exposure exceeding the $LLTC_{oral}$ is far greater than the probability of inhalation exposure exceeding the $LLTC_{inhal}$. This is because inhalation is a relatively unimportant exposure pathway for arsenic (see Table 4.2). For the three alternative pC4SLs of 32, 37 and 48 $mg.kg^{-1}$, the probability of inhalation exposure exceeding the $LLTC_{inhal}$ is negligible.

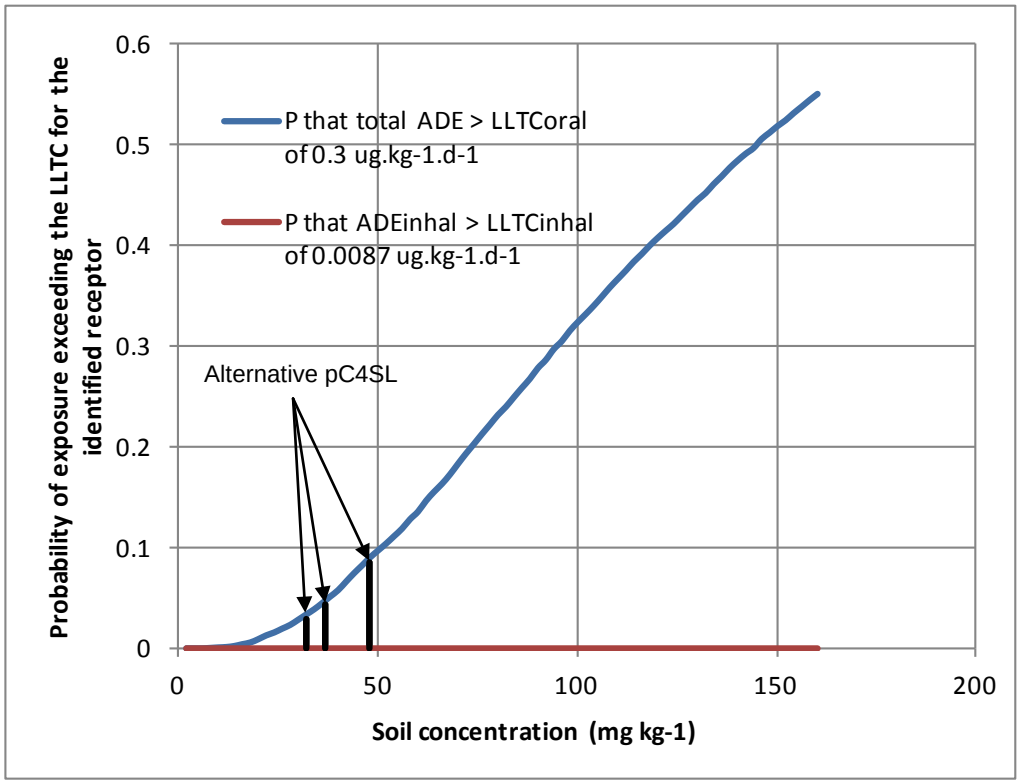

Figure 4.2: Probability of exposure exceeding the LLTC with alternative values of pC4SL for arsenic for residential (with consumption of homegrown produce) land-use

4.2.2 RESIDENTIAL (WITHOUT CONSUMPTION OF HOMEGROWN PRODUCE) LAND-USE

Figure 4.3 shows the probability of exceedence graph for the residential (without consumption of homegrown produce) land-use for three alternate values of pC4SL using alternative sets of exposure parameters. These are:

1. pC4SL = 32 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.3 μg kg^{-1} bw day^{-1} and an age class adjusted $LLTC_{inhal}$ of 0.0087 μg kg^{-1} bw day^{-1}

but making no changes to the exposure parameters from the CLEA SR3 report;

2. pC4SL = 40 mg kg^{-1}. This is the pC4SL derived using LLTCs as above but with the proposed modifications to exposure modelling parameters described in Section 3.5.7 of the main report; and
3. pC4SL = 50 mg kg^{-1}. This is the pC4SL derived as above, but with additional modifications to exposure modelling parameters that had been proposed in the draft interim methodology document produced in advance of the first Stakeholder Workshop. These additional modifications are soil ingestion rate reduced to 80 mg d^{-1} and dust loading factor reduced to 25 μg $.m^{-3}$.

The predicted probabilities of exceedence of the LLTCs are lower than those for the residential (with consumption of homegrown produce) land-use. The predicted probabilities of exceedence are 1%, 2% and 4% for the pC4SLs of 32, 40 and 50 $mg.kg^{-1}$, respectively.

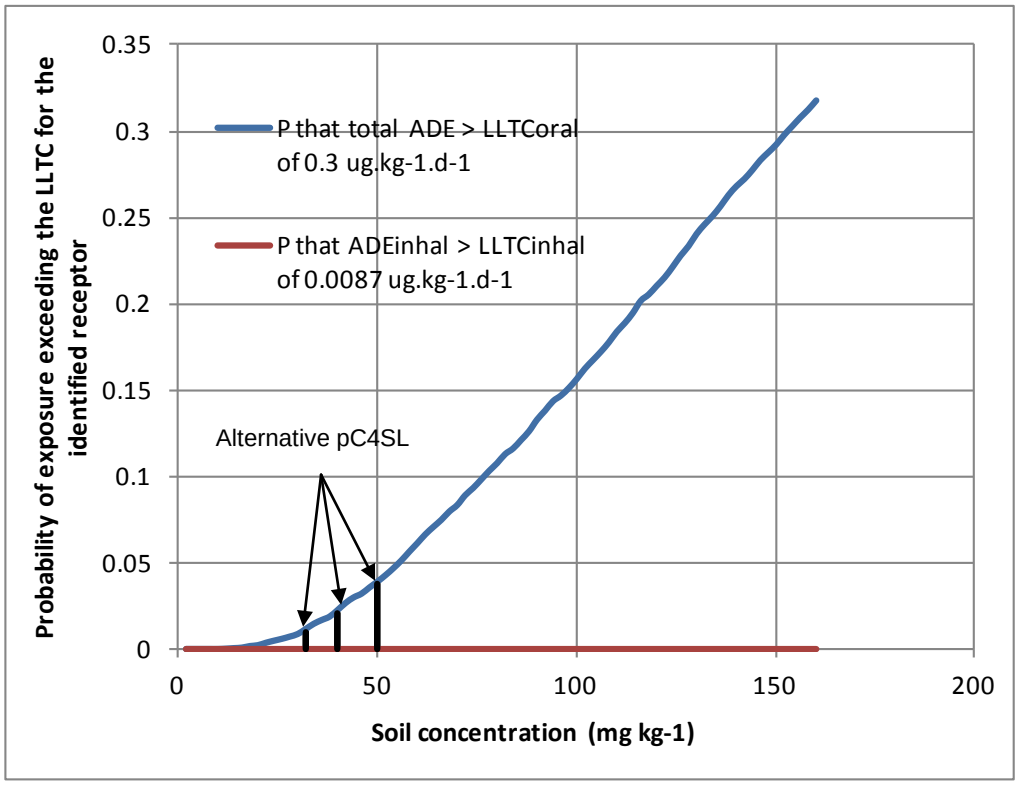

Figure 4.3: Probability of exposure exceeding the LLTCs with alternative values of pC4SL for arsenic for residential (without consumption of homegrown produce) land-use

4.2.3 ALLOTMENTS LAND-USE

Figure 4.4 shows the RCFs of total exposure for three alternate values of pC4SL using alternative sets of exposure parameters. These are:

1. pC4SL = 43 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.3 $ug.kg^{-1}(bw)day^{-1}$ and an age class adjusted $LLTC_{inhal}$ of 0.0087 μg kg^{-1} bw day^{-1} but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 49 mg kg^{-1}. This is the pC4SL derived using the LLTC as above with proposed modifications to exposure modelling parameters described in Section 3.5.7 of the main report; and
3. pC4SL = 88 mg kg^{-1}. This is the pC4SL derived as above, but with additional modifications to exposure modelling parameters that had been proposed in the draft interim methodology document produced in advance of the first Stakeholder Workshop. These additional modifications are soil ingestion rate

reduced to 80 mg.d^{-1}, mean consumption rate used for all produce types and exposure frequency outdoors for children halved.

Figure 4.4 also shows the $LLTC_{oral}$ and estimates of average background exposure from non-soil sources for comparison with the RCFs of average daily exposure. Figure 4.5 shows the relationship between the probability of exceedence of the LLTC and soil concentration. As for residential land-use, the probability of inhalation exposure exceeding the $LLTC_{inhal}$ for the range of alternative pC4SLs is negligible and so RCFs are not presented for inhalation exposure in Figure 4.4.

Figures 4.4 and 4.5 show that the probability that exposure to a random individual from the critical receptor group would exceed the LLTC is 32% for a soil concentration of 43 mg kg^{-1}, increasing to 37% and 61% for soil concentrations of 49 and 88 mg kg^{-1}, respectively. The probabilities of exposure exceeding a value of ten times the LLTC (i.e. 3 μg kg^{-1} bw day^{-1}) are significantly lower, ranging from 0.3 to 3% for the alternative pC4SLs (Figure 4.4). As discussed in Section 4.3, a generally conservative approach has been adopted for the probabilistic modelling and it is possible that the true probabilities of exceedence are significantly lower.

The large range in exposures for the allotments scenario indicated by Figure 4.4 is due to the large range in possible values for the soil to plant concentration factors, homegrown fraction and consumption rate. For families with allotments who consume a large amount of fruit and vegetables and are mostly self-sufficient in these produce types and where the nature of the soils is such that soil to plant concentration factors are high, exposure could be more than order of magnitude above median exposure.

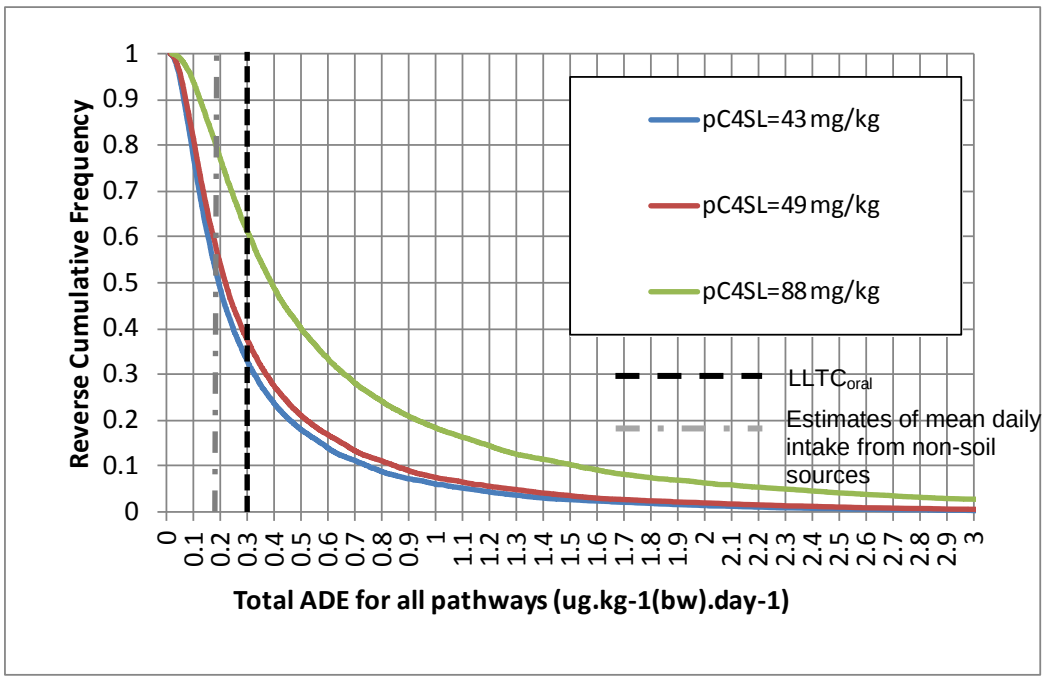

Figure 4.4: Reverse cumulative frequency graph of ADE for alternative values of pC4SL for arsenic for allotments land-use

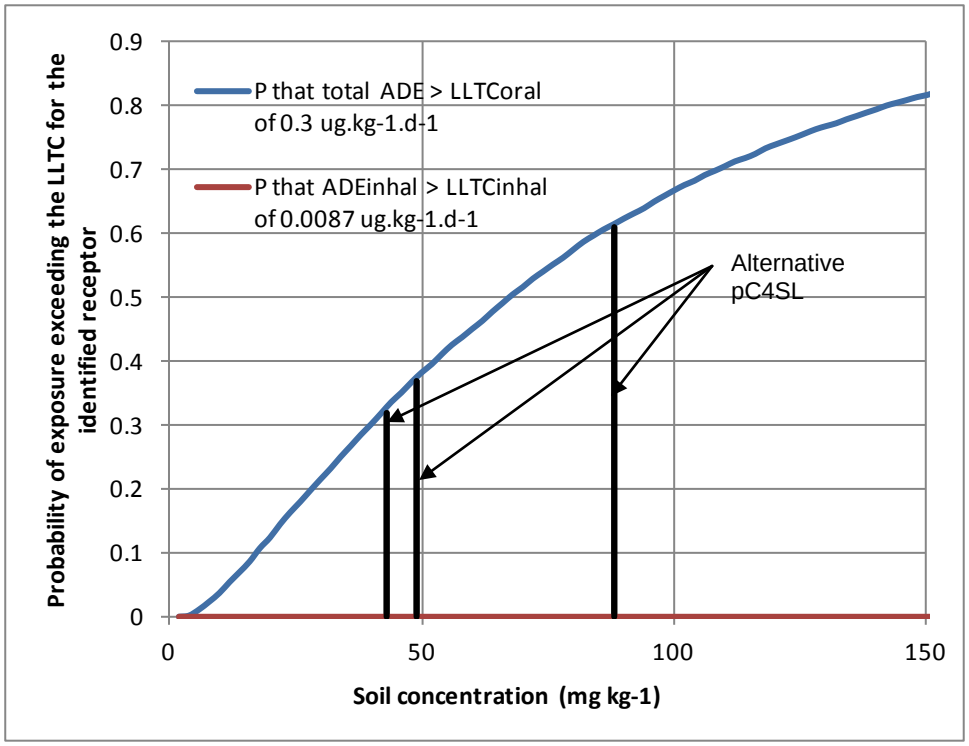

Figure 4.5: Probability of exposure exceeding the LLTC with alternative values of pC4SL for arsenic for allotments land-use

As can be seen from Figure 4.4 exposures from the three alternative pC4SLs are generally expected to exceed background exposure, i.e. exposure from soils is likely to be the main contributor of exposure to arsenic for the range of alternative pC4SLs presented.

4.2.4 COMMERCIAL LAND-USE

Figure 4.6 shows the RCFs of total exposure for two alternate values of pC4SL using alternative sets of exposure parameters. These are:

1. pC4SL = 635 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.3 $ug.kg^{-1}(bw)day^{-1}$ and an $LLTC_{inhal}$ of 0.002 μg kg^{-1} bw day^{-1} with the proposed modifications to exposure modelling parameters described in Section 3.5.7 of the main report; and
2. pC4SL = 785 mg kg^{-1}. This is the pC4SL derived as above, but with additional modifications to exposure modelling parameters that had been proposed in the draft interim methodology document produced in advance of the first Stakeholder Workshop. These additional modifications are soil ingestion rate reduced to 40 $mg.d^{-1}$ and dust loading factor reduced to 50 μg $.m^{-3}$.

Unlike the residential and allotments scenarios only two sets of exposure parameters have been tested. This is because there is no difference between the pC4SLs with the proposed exposure parameter changes described in Section 3.5.7 of the main report and pC4SLs using the SR3 parameters. The only difference in exposure parameters for commercial land-use is a slight reduction in adult inhalation rate and this has no effect on the pC4SLs for arsenic for this land-use.

Figure 4.6 also shows the $LLTC_{oral}$ and estimates of average background exposure from non-soil sources for comparison with the RCFs of average daily exposure. Figure 4.7 shows the relationship between the probability of exceedence of an LLTC and soil concentration. Although not negligible, the probabilities of inhalation exposure exceeding the $LLTC_{inhal}$ are lower than the probabilities of total exposure exceeding the $LLTC_{oral}$.

Figures 4.6 and 4.7 show that the probability that exposure to a random individual from the critical receptor group would exceed the $LLTC_{oral}$ is 11% for a soil concentration of 635 mg kg^{-1}, increasing to 16% for a soil concentration of 785 mg kg^{-1}. As discussed in Section 4.3, a generally conservative approach has been adopted for the probabilistic modelling and it is possible that the true probabilities of exceedence are significantly lower.

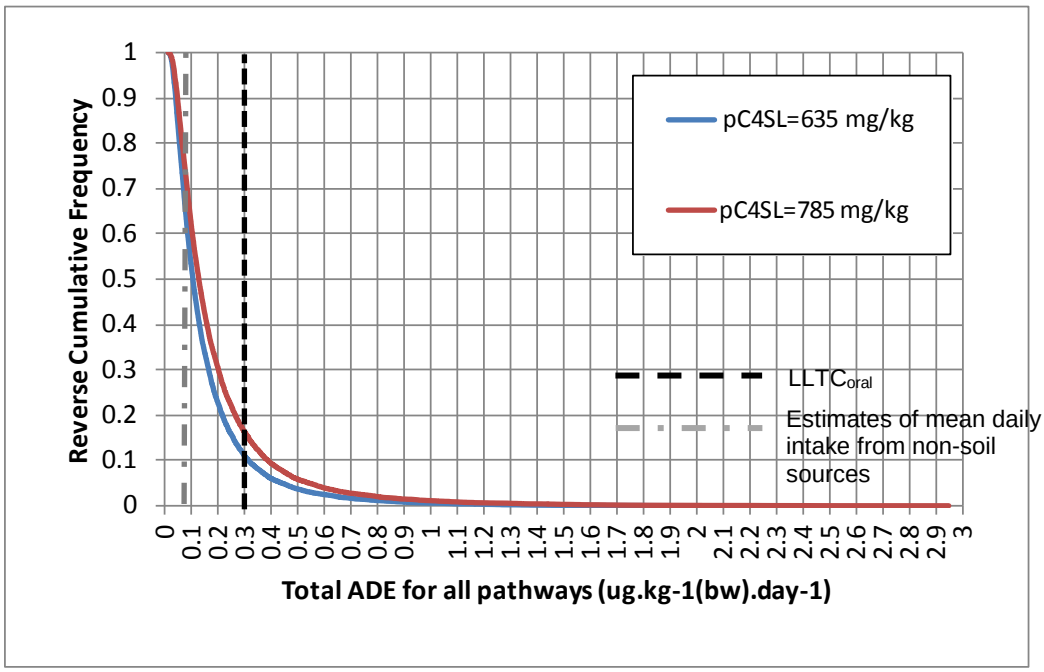

Figure 4.6: Reverse cumulative frequency graph of ADE for alternative values of pC4SL for arsenic for commercial land-use

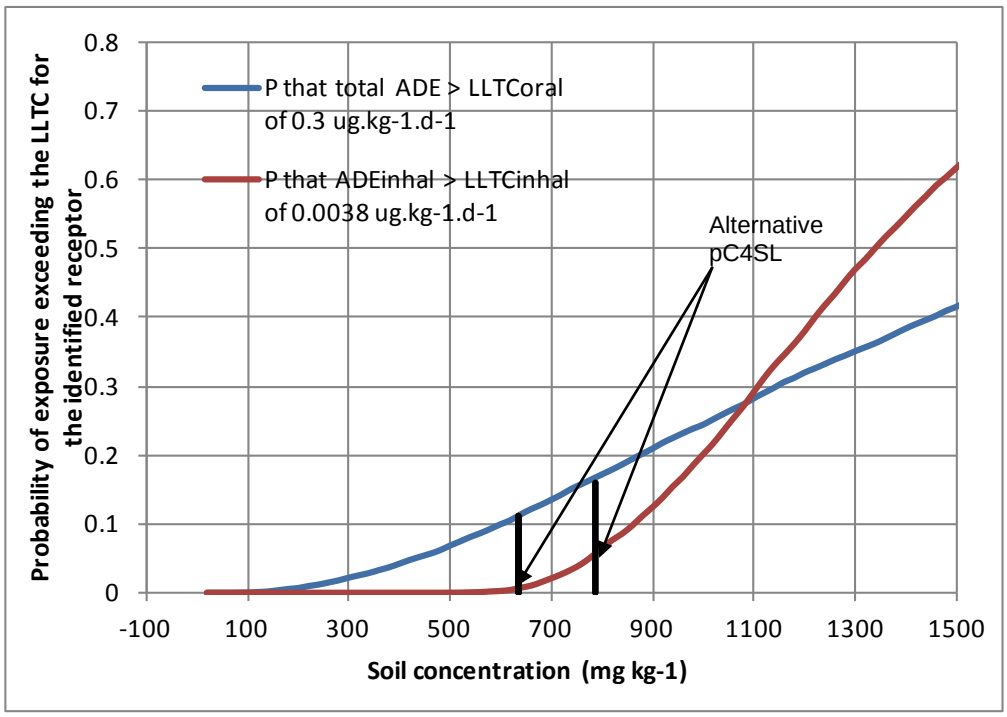

Figure 4.7: Probability of exposure exceeding an LLTC with alternative values of pC4SL for arsenic for commercial land-use

As can be seen from Figure 4.6 exposures from the two alternative pC4SLs are generally expected to exceed background exposure, i.e. exposure from soils is likely

to be the main contributor of exposure to arsenic for the range of alternative pC4SLs presented.

4.3 QUALITATIVE APPRAISAL OF UNCERTAINTY

As described previously, there are a number of uncertainties that have not been captured by the probabilistic modelling. These include identifiable uncertainty in the LLTCs and PDF attributes used for the probabilistic modelling, as well as unknown levels of uncertainty relating to aspects such as the assumed conceptual models, the representativeness of the algorithms embedded in CLEA and the behaviour of arsenic in the environment.

A qualitative appraisal of some of these residual uncertainties has been conducted using an "uncertainty table" approach, as described in Section 5.1.2 of the main report. Tables 4.3 and 4.4 describe the key residual uncertainties and their impact on toxicity and exposure estimates for the exposure modelling of these pathways, respectively. The residual uncertainties are listed in the left hand column of the table, whilst the right hand column contains a subjective evaluation of the impact of each uncertainty on the estimated LLTCs and exposures, using plus (+) and minus (-) symbols.

The number of symbols provides an estimate of the approximate magnitude of the over- or under-estimation, based on the scale, shown in Figure 4.8. A dot (●) represents an assumed negligible impact (< ±10 %), while symbols separated by a forward slash represent an uncertain impact (e.g. -/++ indicates between 0.5x underestimate and x5 overestimate). Note that the implications of the symbols differ between toxicity and exposure: a "+" for exposure implies an assumed overestimation of exposure, and hence a potential overestimation of risk, while a "+" for the LLTC implies an assumed overestimation of the LLTC which results in a potential underestimation of risk.

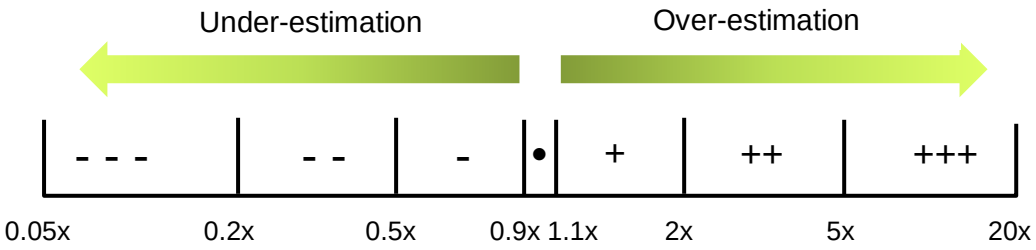

Figure 4.8 Key for symbols used to express judgements about the magnitude of potential over- or under-estimation of the LLTC and exposure in Tables 4.3 and 4.4 respectively.

Finally, at the foot of the table, a qualitative assessment is given of the overall impact of the identified uncertainties. The assessment of the overall impact is necessarily a subjective judgement, taking into account the evaluation of the individual uncertainties (as shown in the individual rows) and how they might combine (including potential dependencies between them where relevant). Importantly, further sources of unassessed (and potentially unknown) uncertainty may still remain in any risk-based modelling of this nature.

4.3.1 TOXICOLOGICAL ASSESSMENT

Table 4.3 describes the key residual uncertainties and their impact on the toxicology evaluation.

Table 4.3: Qualitative appraisal of key residual uncertainties in toxicology evaluation (see Figure 4.8 for key to symbols)

Source of Uncertainty	Evaluation of uncertainty
ORAL – lung cancer evaluation – using data in Chen *et al*., 2010a	
Choice of measure: ug/day measures are assumed from water sources containing measured high levels of arsenic (>100 mg/L water). A significant dose–response trend of lung cancer risk was associated with increasing arsenic drinking-water concentration over a period of 11.5 years.	●
Interspecies uncertainties: As the evaluation uses human data there are no uncertainties around extrapolations between animals and humans	●
Inter-individual variability in dietary intakes: different ranges of As in food intakes (50–200 µg of inorganic arsenic per day from food) and water volume consumed (2-4L) have been factored into the assessment. Underestimating the total dietary exposure in the study populations will lead to an overestimation of the risk. Here the lowest intake of the range has been used.	**-/●**
Inter-individual variability –selected population: The relevant populations in the study were located in north-eastern Taiwan, China. Their genetic background may be different from a UK population, which may be more or less sensitive to the effects of As. This is uncertain.	**-/+**
Age and gender differences: Not clear how this has been factored into the analysis. This is uncertain.	**-/+**
Modulation of effects from confounders: it is stated that smoking was accounted for as a confounder in the study. Details of how that has been done is not clear.	**-/**+
Overall, the study by Chen et al., 2010a is the best evaluation of lung carcinogenicity in a large human population exposed to As in drinking water. The relevancy of this study to deriving an LLTC for the general population is high, though there are aspects above that are uncertain, in general, conservative choices have been made in evaluating the science in Chen *et al*. In the case of As, a choice has been made to align the LLTC with the intake that equates to that from the UK drinking water guideline. As such, this is a pragmatic decision given the uncertainties in the data and that a conservative (lowest) estimate of intake has been taken in relation to the evaluation of the Chen data in deriving a $BMD_{0.5}$. The LLTC chosen using an evidence-informed policy choice route is likely to be at the less conservative end of the scientific evaluation, given that the margin on the BMD from the Chen study would be small at the intake chosen.	
INHALATION – lung cancer risk	
Interspecies uncertainties: As the evaluation uses human data there are no uncertainties around extrapolations between animals and humans	●
Inter-individual variability: The data are from US and Swedish populations. Age and gender – no known differences.	●
Linearity of response has been assumed	**-/+**
Translation of air concentration to an intake: child specific physiological parameters have been used. The ELCR data are from adult workers, so it is assumed that adults and children are equally susceptible to the cancer effects in the lung.	**-/+**
Modulation of effects from confounders: smoking, exposure to other carcinogenic substances in the smelter. It is not known as to whether these have been accounted for.	**-/+**
Measurement of air concentrations in workplace has been estimated rather than measured. It is not known as to what risk management measures were in place day to day.	**-/+**
Overall, this study has been performed in worker populations exposed to chronic daily doses of As in an occupational setting. The largest uncertainty is not knowing the exposure concentrations in more detail. ELCR values are also approximations to what would be a true risk estimate. Hence this value is uncertain. It may or may not be a precautionary estimate of risk.	

Note that the implications of the overall uncertainty for risk can be considered looking at the RCF graphs in Section 4.2: over- and under-estimation of the LLTC would imply the black dashed lines should be further left or right (respectively).

4.3.2 EXPOSURE MODELLING

As shown by Table 4.2, the principle exposure pathway for arsenic for the residential and commercial land-uses is incidental ingestion of soil and dust. The principle exposure pathways for arsenic for the allotments land-use is incidental ingestion of soil and dust and consumption of homegrown produce. The key uncertainties in estimating exposure for these pathways are described in Table 4.4.

Table 4.4: Qualitative appraisal of key residual uncertainties in exposure modelling not captured by probabilistic modelling (see Figure 4.8 for key to symbols)

Source of Uncertainty	Evaluation of uncertainty
RESIDENTIAL LAND-USE	
Soil and dust ingestion rate. The PDF used is based on the mean and 95th percentile soil ingestion rates estimated by Stanek, *et al*. (2012) from a meta-analysis of the key soil ingestion studies conducted in the USA. There is uncertainty over how the soil and dust ingestion rates derived from these studies relate to UK receptors and average annual conditions (i.e. winter and summer). It should also be recognised that the estimates for children do not just relate to soil and dust they ingest from their own property, but will also include soil and dust ingested outside the home, in the nursery/school, play park, car etc. There is also some uncertainty in the shape of the PDF, but this uncertainty is unlikely to result in more than a factor of two over or under-estimation in exposure. Overall, it is considered possible that the PDF is likely to over-estimate average annual ingestion of soils from UK residential properties by a factor of 2, although this could be much greater at specific locations.	● / +
Relative bioavailability (RBA). The CLEA modelling (deterministic and probabilistic) is based on the assumption of 100% RBA. As discussed in Section 4.1.2, based on in-vitro bioaccesibility testing on soils, the biovailability of arsenic in soils is typically less than 60% and depending on the source of the arsenic may be <10% in some cases. Thus the assumption of an RBA of 100% may over-estimate oral exposure from ingestion of soils by a factor of up to10x or more.	+ / +++
OVERALL EVALUATION OF UNCERTAINTY FOR RESIDENTIAL LAND-USE. Based on the above the probabilistic modelling is likely to have over- estimated exposure and as such can be considered conservative	
ALLOTMENTS LAND-USE	
Soil and dust ingestion rate. The PDF used for allotments is based on that used for residential. As discussed above there is uncertainty over how the soil and dust ingestion rates derived from the US studies relate to UK receptors and average annual conditions (i.e. winter and summer). There is added uncertainty on how they relate to an allotments scenario. Data from the Netherlands soil ingestion study indicate that children on campgrounds ingest approximately twice as much soil as children in day-care whilst the USEPA (2011) indicate that average daily ingestion of soil outdoors is equivalent to the average daily ingestion of soil indoors. There is also some uncertainty in the shape of the PDF, but this uncertainty is unlikely to result in more than a factor of two over or under-estimation in exposure. Overall, it is considered possible that the PDF over or under-estimates exposure for the allotments scenario by up to a factor of 2.	- / +
Relative bioavailability (RBA). The CLEA modelling (deterministic and probabilistic) is based on the assumption of 100% RBA. As discussed in Section 4.1.2, based on in-vitro bioaccesibility testing on soils, the biovailability of arsenic in soils is typically less than 60% and depending on the source of the arsenic may be <10% in some cases. Thus the assumption of an RBA of 100% may over-estimate oral exposure from ingestion of soils by a factor of up to10x or more. The bioavailability of arsenic in consumed produce may also be less than 100% but is unlikely to be as low as that from ingestion of soil and dust. Given that consumption of homegrown produce is	● / +

Source of Uncertainty	Evaluation of uncertainty
the principle exposure pathway for allotments, the oral bioavailability from soil and dust is less influential on estimates of oral exposure. Overall, it is considered possible that the assumption of 100% RBA for oral exposure over estimates exposure for the allotments scenario by up to a factor of 2.	
Exposure frequency outdoors. The exposure frequencies outdoors are based on children accompanying adults to the allotments for a percentage of time that the adult visits the allotments. The percentages are based on those in the SR3 report and appear to be relatively arbitrary but not unreasonable. The adult exposure frequency is based on a 1993 survey and may be weighted towards retired adults who regularly visit the allotment but rarely bring children. Thus the PDF for exposure frequencies is considered more likely to over- than under-estimate exposure.	**- / ++**
Soil to plant concentration factors. The soil to plant concentration factor (CF) PDFs are based on empirical measurements of the concentration of arsenic in fruit and vegetables and the soil they have been grown in. These empirical measurements have been obtained from studies in the UK and abroad from field and lab based studies. The use of all these data may lead to an over-estimation in the variability of soil to plant concentration factors and this could lead to both an over- and under-estimation of exposure. It is noted that geomean soil to plant concentration factors from a crop survey conducted in Devon and Cornwall are up to an order of magnitude below those assumed for the PDF. Thus it is considered more likely that the PDF tends towards an over-estimation than under-estimation of exposure.	**--/+++**
Produce consumption rates. PDFs for produce consumption rates are based on NDNS 2008-2011 survey data. It is considered likely that allotment holders and their families tend to be within the upper percentiles of consumers of fruit and vegetables. For the purposes of the probabilistic modelling the assumption was made that consumption rate is within the top quartile. This is likely to be a conservative assumption, as not all individuals who consume homegrown produce will be high level consumers for all produce types. Thus the PDF is considered likely to over- estimate exposure for families who have allotments, possibly by a factor of up to 2x.	**● / +**
Homegrown fraction. The PDF for fraction of consumed produce grown at the allotment is based on UK Expenditure and Food Survey 2004/5. It was beyond the scope of this project to re-assess the raw data from this survey and so the beta shaped PDF is based on information presented in SR3 and the former CLR10 report (EA, 2002). It is possible that PDF attributes over- or under-estimate exposure by a factor of up to 2.	**-/+**
OVERALL EVALUATION OF UNCERTAINTY FOR ALLOTMENTS LAND-USE: Based on the above the probabilistic modelling is more likely to over- than under-estimate exposure and as such can be considered conservative.	
COMMERCIAL LAND-USE	
Soil and dust ingestion rate. The PDF used is based on the mean and 95th percentile soil ingestion rates for children estimated by Stanek, *et al*. (2012) from a meta-analysis of the key soil ingestion studies conducted in the USA. Average soil and dust ingestion by children is expected to be twice that of adults (USEPA, 2011) and therefore the assumed PDF is likely to result in an over-estimation of exposure to adults. Furthermore, the majority of commercial properties have limited exposed soils and this will limit the potential for soil and dust ingestion. For these reasons, the exposure estimates from soil and dust ingestion for the commercial land-use are likely to be over-estimates, possibly by as much as a factor of 10x.	**+ / +++**
Relative bioavailability (RBA). The CLEA modelling (deterministic and probabilistic) is based on the assumption of 100% RBA. As discussed in Section 4.1.2, based on in-vitro bioaccesibility testing on soils, the biovailability of arsenic in soils is typically less than 60% and depending on the source of the arsenic may be <10% in some cases. Thus the assumption of an RBA of 100% may over-estimate oral exposure from ingestion of soils by a factor of up to10x or more.	**+ / +++**
OVERALL EVALUATION OF UNCERTAINTY FOR COMMERCIAL LAND-USE: Based on the above it is considered likely that the estimates of total exposure predicted by the probabilistic modelling are likely to be highly conservative.	

Note that the implications of the assessed levels of overall uncertainty for the C4SLs can be considered by looking at the RCF graphs: over-and underestimation of the exposure would imply that the RCF should be shifted to the left or right, respectively.

The overall impact of uncertainty on the estimates of probability of exceedence has been further assessed for the allotments land-use by re-conducting the probabilistic modelling using alternative PDFs for these parameters, as described below:

- Soil to plant concentration factors. The alternative PDF has been based on empirical estimates derived from crop surveys conducted in Devon and Cornwall (FSA, 2012).
- Consumption rates. As discussed in Table 4.4 it is possible that the assumption that all consumers of homegrown produce have overall consumption rates within the top quartile for each produce type may be overly conservative. An alternative PDF has been tested based on the assumption that consumers who eat homegrown produce do not eat more produce than consumers who do not eat homegrown produce i.e. there is no correlation between homegrown fraction and consumption rates.
- Homegrown fraction. Modelling the homegrown fraction as 100% in all cases results has been tested to model the allotment holders who are self sufficient.

Figure 4.9 shows the effects of using the alternative PDFs on the probability of exceedence graphs. As can be seen, use of the soil to plant concentration factors from the Devon and Cornwall crop surveys reduces the probability of exceeding the LLTC from 37% to 1.5% for the pC4SL of 49 $mg.kg^{-1}$. Removing the correlation between homegrown fraction and consumption rate reduces the probability of exceedence from 37% to 9% for this pC4SL. Modelling the homegrown fraction as 100% in all cases results in the probability of exceedence increasing from 37% to 74%.

This sensitivity analysis shows that uncertainty in the PDFs creates considerable uncertainty in the estimates of probability of exceedence. However, in combination with the qualitative assessment of uncertainty presented in Table 4.4, it is considered likely that the probabilities of exceedence shown on Figures 4.2, 4.3, 4.5 and 4.7 are significantly over-estimated. Thus, in the case of the allotments land-use, the probability of exceeding the LLTC at the pC4SL of 49 $mg.kg^{-1}$ is likely to be significantly less than 37%.

In summary, the above qualitative evaluation of uncertainty, together with the sensitivity analysis, has indicated that the overall distributions of estimated exposure derived by the probabilistic modelling are likely to be highly conservative.

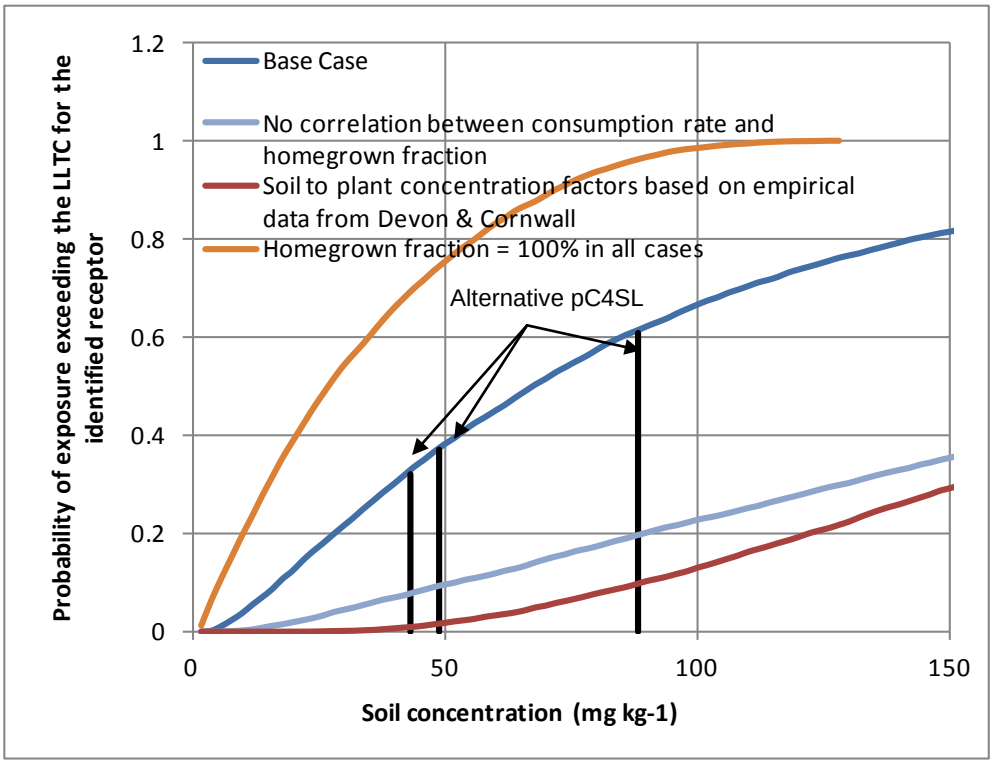

Figure 4.9: Probability of exposure exceeding the LLTC for arsenic for allotments land-use with alternative values for produce consumption rate.

4.4 OTHER CONSIDERATIONS

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

- As described above, average background exposure to arsenic from non-soil sources is typically greater than the modelled exposure from soil with arsenic concentrations at the various pC4SLs for the residential land-use. This should be considered in the light of para 4.21 (d) of the Part 2A Statutory Guidance (SG), which states that the following should be included within Category 4: Human Health:

  > *"Land where estimated levels of exposure to contaminants in soil are likely to form only a small proportion of what a receptor might be exposed to anyway through other sources of environmental exposure (e.g. in relation to average estimated national levels of exposure to substances commonly found in the environment, to which receptors are likely to be exposed in the normal course of their lives)."*

  This principle appeared to underpin the setting of the HCVs for arsenic (see above) "to avoid disproportionately targeting exposures from soil" (EA, 2009b).

- The British Geological Survey (BGS) derived normal background concentrations (NBCs) for arsenic, which correspond to the upper confidence limit of the 95th percentile concentrations, for England and Wales. In England the reported NBCs are 32 mg/kg for the "principal" domain, 290 mg/kg for the "mineralisation" domain and 220 mg/kg for the "ironstone" domain (Defra, 2012). In Wales, the reported NBCs are 36 mg/kg for the "principal" domain, 67 mg/kg for the "mineralisation" domain and 250 mg/kg for the "urban" domain (Defra, 2013). The pC4SLs for residential land-use shown in Table 4.1 are equal to, or slightly greater than, the NBCs for the "principal" domain,

while the allotments values are up to 50% higher. Those for public open space are above the "principal" domains and "mineralisation" domain in Wales but below the other domains. The pC4SLs for commercial land-use exceed the NBCs for all domains.

- Since arsenic is a known human carcinogen (see Section 2), it might be necessary to apply the "As Low as Reasonably Practicable" (ALARP) principle in relation to its remediation at specific sites (see EA, 2009c; 2009d 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.

- Based on a limited number of epidemiology studies, there is no clear causality between arsenic in soil and adverse health effects. However, lack of evidence does not mean a lack of effect, as this could be the result of limitations in risk assessment or epidemiological techniques (Kibble and Saunders 2001; Fera 2009).

4.5 SUMMARY AND CONCLUSIONS

Following the methodology described in Section 3 of the main report, deterministic exposure modelling with a modified version of CLEA has been used to estimate the soil concentration that could result in potential exposure to an individual receptor within the critical receptor group for each land-use equating to the LLTCs for arsenic. These soil concentrations are the pC4SLs.

A range of pC4SLs have been derived for arsenic, based on the following options:

Option 1: Use of minimal risk HCVs with changes to exposure parameters (as summarised in Section 3.5.7 of the main report);
Option 2: Use of LLTCs with no change to exposure parameters (i.e. as defined in SR3); and
Option 3: Use of LLTCs with changes to exposure parameters.

These are shown below:

Table 4.5: pC4SLs for Arsenic

Land-Use	pC4SL (mg/kg)		
	HCVs with suggested changes to exposure parameters	LLTCs with no change to exposure parameters	LLTCs with suggested changes to exposure parameters
Residential (with consumption of homegrown produce)	37	32	37
Residential (without consumption of homegrown produce)	40	35	40
Allotments	49	43	49
Commercial	640	640	640
POS_{resi}	79	NA	79
POS_{park}	170	NA	170

Quantitative probabilistic modelling has been conducted to better understand some of the uncertainty inherent within the exposure modelling aspects of the pC4SLs and the level of protection they may provide. The probabilistic modelling has focused on key exposure pathways and has helped to demonstrate the expected variability in exposures between individuals within the critical receptor group for a given soil concentration (and the probability that exposure to a random individual within the group would exceed the LLTC). Such modelling has not been carried out in relation to toxicological aspects, due to a lack of suitable data and approaches.

In addition to the probabilistic modelling, a qualitative analysis of uncertainty has been carried out to further elucidate the level of uncertainty within the pC4SLs. This has focused on other aspects of the exposure modelling, as well as the LLTC setting process.

As a final step within the C4SL derivation process, other relevant considerations are identified, which should have a bearing on any final choice of numbers. For arsenic, these take the form of recently published background levels in soil, estimates of background human exposure levels and a review of epidemiological evidence of health impacts from arsenic in UK soil.

As described in the main report, and at the request of the Steering Group, this appendix stops short of providing "final C4SLs" for arsenic since: 1) final C4SLs should be set by "relevant authorities" (eg, Defra); 2) the toxicological framework contained herein has recently been submitted for review by the Committee on Toxicity (COT, 2013), with comments pending; and 3) the whole document will also be the subject of peer review.

Since the above pC4SLs have been derived using a modified version of the CLEA model, the Environment Agency's SR3 document (EA, 2009d) should be referred to for important caveats and supporting information regarding their use. Furthermore, the LLTCs have been derived using similar methods to those outlined in the Environment Agency's HCV document (EA, 2009c), and the reader is referred to that document for the same reasons.

As is also described in the main report, final C4SLs can be used in a similar manner to that described for SGVs in the Environment Agency's "Using Soil Guideline Values" document (EA, 2009e). Although they are unlikely to represent a "significant possibility of significant harm" (SPOSH), the likelihood of an exceedance of a C4SL being representative of SPOSH may be greater than if the default CLEA settings and toxicological criteria equivalent to minimal risk had been used in their derivation. This is particularly so for arsenic, given that the SGV report states that the likelihood of an exceedance of the oral ID representing SPOSH is much greater than would be the case if the oral ID was based on minimal risk (EA, 2009a).

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APPENDIX C1

HUMAN TOXICOLOGICAL DATA SHEET FOR ARSENIC

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

Chemical: **Arsenic**

Human Health Hazard Profile - References

Authoratative bodies	Website	Checked (Y/N)	References
EA	http://www.environment-agency.gov.uk/	Y	EA 2009. Contaminants in soil: updated collation of toxicological data and intake values for humans Inorganic arsenic. Better Regulation Science Programme. Science report: SC050021/TOX 1.
FSA	http://www.food.gov.uk/	Y	No recent and relevant updates found
HPA	http://www.hpa.org.uk/	Y	Compendium of hazards for inorganic arsenic . http://www.hpa.org.uk/Topics/ChemicalsAndPoisons/CompendiumOfChemicalHazards/Arsenic/
COC	http://www.iacoc.org.uk/	Y	No recent and relevant updates found
COM	http://www.iacom.org.uk/	Y	No recent and relevant updates found
COT	http://cot.food.gov.uk/	Y	No recent and relevant updates found
EU REACH	http://echa.europa.eu/information-on-chemicals/registered-substances	Y	No recent and relevant updates found
EFSA	http://www.efsa.europa.eu/	Y	EFSA 2009, Scientific Opinion on Arsenic in Food. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal 2009; 7(10):1351
JECFA	http://www.who.int/foodsafety/chem/jecfa/publications/en/index.html	Y	http://apps.who.int/ipsc/database/evaluations/chemical.aspx?chemID=1863
WHO	http://www.who.int/en/	Y	http://whqlibdoc.who.int/trs/WHO_TRS_959_eng.pdf
			http://whqlibdoc.who.int/publications/2011/9789241660631_eng.pdf
RIVM	http://www.rivm.nl/English	Y	RIVM, 2001. Re-evaluation of human-toxicological maximum permissible risk levels. Chapter 1.1 Arsenic. RIVM report 711701 025. Bilthoven, The Netherlands: Dutch National Institute of Public Health and the Environment. Available at: http://www.rivm.nl/bibliotheek/rapporten/711701025.html
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USEPA	http://www.epa.gov/	Y	http://www.epa.gov/iris/subst/0278.htm
			Major review of all arsenic health effects is being performed by USEPA 2013-2015
Health Canada	http://www.hc-sc.gc.ca/index-eng.php	Y	Guidelines for Canadian drinking water http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/arsenic/arsenic-eng.pdf
Other references			

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

Chemical: **Arsenic**

Key

- Reliable data/approach
- Good data/approach but with reservations
- Not defensible/withdrawn

I) Human Health Hazard Profile - Toxicological Evidence

Type of Evidence	POD type	POD value	Units	Species	Study Type	Comments/Study Quality	Reference
1. Toxicokinetics							
Oral							
Inhalation							
Dermal							
2. Acute Toxicity							
Oral	Lethal dose	70-190	mg	human	poisoning incidents		EA 2008
Inhalation							
Dermal							
3. Irritation and Corrosivity							
Dermal							
Lung		0.1-1	mg/m3	human	occupational	Irritation of mucous membranes; laryngitis, bronchitis or rhinitis – effects minor or absent at exposure level.	ATSDR 1998
Eye							
4. Sensitisation							
Dermal							
Respiratory							
5. Repeat-dose Toxicity							
Oral							
Inhalation		50-500	µg/m3	human	occupational	cardiovascular - Smelter workers' exposure to arsenic dust – higher incidence of Raynaud's disease and increased constriction of	EA 2008
Dermal							
6. Genetic Toxicology							
In vitro		positive					
In vivo		positive				clastogenic	
7. Carcinogenicity							
Oral						IARC known human carcinogen. There is sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung, and skin.	IARC 2012 Monograph
Inhalation							
Dermal							
8. Reproduction							
Reproductive							
Developmental							
Teratogenicity							
Nervous system		50	µg/m3	human	occupational	Peripheral neuropathy in arsenic smelter workers	EA 2008
9. Human epidemiology data							
Oral							
Inhalation							
Dermal							

Most Sensitive Health Effect:

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

A) Oral Route	HBGVoral	Unit	UF used	PoD	Endpoint	Pivotal data used & Comments	Reference
WHO/JECFA 2011	None derived			BMDL0.5 = **3** µg kg^{-1} bw day^{-1}	Lung cancer and bladder cancer	The inorganic arsenic lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer (BMDL0.5) was determined from epidemiological studies to be 3.0 µg/kg bw per day (2–7 µg/kg bw per day based on the range of estimated total dietary exposure) using a range of assumptions to estimate total dietary exposure to inorganic arsenic from drinkingwater and food. Due to confounders in studies, data from studies on skin lesions not considered in the risk evaluation. Bladder cancer: Pivotal data from Chen et al., (2010a). Lung Cancer: Pivotal data from Chen et al., (2010b): Body weight of 55 kg used.	WHO/JECFA 2011. Tox monograph series 63
RIVM TDI	1	µg kg^{-1} bw day^{-1}	2	PTWI; 15 µg kg^{-1} bw $week^{-1}$	Cancer	Additional UF of 2 applied to the WITHDRAWN JECFA PTWI (= TDI of 2.1 µg kg^{-1} bw), to account for uncertainty in epidemiology	RIVM 2001
EFSA 2009 BMDL01	None derived			$BMDL_1$; **0.3**-8 µg kg^{-1} bw day^{-1}	Skin lesions, lung cancer & bladder cancer	2009 science based review. Benchmark dose accounting for 1% increased risk of lung cancer, bladder cancer or skin lesions (hyperkeratosis, hyperpigmentation, hypopigmentaiton). The most sensitive effect is lung cancer.	EFSA 2009
CLEA 2009 HCV	0.3	µg kg^{-1} bw day^{-1}				SC050021/Tox 1 Current published EA HCV recommendation. Policy based. Equivalent intake to the the UK, WHO & Health Canada drinking water standard of 10 µg L^{-1} WHO - "practical quantification limit". Health Canada - "maximum acceptable concentration".	EA 2009
US ATSDR ORAL CHRONIC MRL	0.3	µg kg^{-1} bw day^{-1}	3	NOAEL; 0.8 µg kg^{-1} bw day^{-1}	Skin cancer	Taiwan study, human NOAEL and applying an UF of 3 (human interindividual variability)	ATSDR 2007
US EPA Oral RfD 1998	0.3	µg kg^{-1} bw day^{-1}	3	NOAEL; 0.8 µg kg^{-1} bw day^{-1}	Skin cancer	**A major review for arsenic health effects has just begun - due for completion in 2015.** This value is still available on IRIS. RfD is based upon evaluation of Taiwan drinking water studies. Modelling an increased lifetime cancer risk: 1 in 100 000 ELCR from 0.2 µg/L in drinking water, for a 70 kg adult drinking 2L water per day = 0.006 µg/kg/day	http://www.epa.gov/iris/subst/0278.htm

COT view

May 2013

b) Inhalation Route	Converted HCVinh	µg kg^{-1} bw day^{-1}	HCVinh	ng m^{-3}	UF used	PoD	Endpoint	Pivotal Study used & Comments	Reference
RIVM 2001 TCA	*0.286*	µg kg^{-1} bw day^{-1}	1000	ng m^{-3}	10	LOAEC; 10 µg m^{-3}	Lung cancer	Based on occupational data from the 1999 draft ATSDR report. Later ATSDR reports did not derive an inhalation MRL as suitable studies showing dose-response relationships were not found. The UF of 10 used accounted for interindividual variability.	Baars et al 2001. RIVM
EC working group 2000 Limit value	*0.0286*	µg kg^{-1} bw day^{-1}	100	ng m^{-3}	100	LOAEL; 50 µg m^{-3}	Peripheral neuropathy	Based on occupational exposure converted to continuous exposure. UF of 10 for LOAEL to NOAEL and 10 for interindividual differences	**EC 2000**
CICAD 2002 Inhalation guidance value	*0.0143*	µg kg^{-1} bw day^{-1}	50	ng m^{-3}	300	NOAEC; 80 µg m^{-3}	Haemolysis	Based on inhalation studies in mouse. The experimental NOAEL was for exposures of six hours per day, five days per week, and its continuous exposure equivalent (0.08 x 5/7 x 6/24) was divided by an uncertainty factor (UF) of 300 to generate an inhalation guidance value, after rounding, of 50 ng m^{-3}. UF of 3 used for interspecies differences, 10 for interindividual differences and a composite factor of 10 for a short term study and database deficiences. Data from Hong et al., 1989; Rosenthal et al., 1989; Blair et al., 1990a,b .	**cited in http://www.inchem.org/documents/cicads/cicads/cicad47.htm**
US EPA 1994 RfC	*0.0143*	µg kg^{-1} bw day^{-1}	50	ng m^{-3}	300	NOAEC; 80 µg m^{-3}	Haemotoxicity	Based on inhalation studies in rodents. NOAEL converted to continuous equavalent. UF of 10 for sensitive populations, 3 for interspecies variations not captured by animal to human dose adjustment and 10 for less than chronic exposure and database deficiencies. US EPA IRIS record August 2012 has no RfC cited for inhalation.	IRIS record edited Aug 2012 No RfC
EC Working gp 2000 Limit value	*0.0037*	µg kg^{-1} bw day^{-1}	13	ng m^{-3}	100	LOAEL; 125-415 µg m^{-3} x year	Lung cancer	Based on Swedish and US workers. UF of 10 used to reduce cancer risks to a level that would be difficult to detect in a epidemiology study, then converted to continuous exposure. Another UF of 10 was then applied to protect sensitive groups.	**EC 2000**
WHO AQG 2000 Air conc	*0.002*	µg kg^{-1} bw day^{-1}	6.6	ng m^{-3}			Lung cancer	Air conc of 6.6 ng m^{-3} gives a ELCR of 1 in 100,000. The unit risk (of 1 mg m$^{-3)}$ is 1.5 x 10^{-3}. Based on average lung cancer risk from USA, Sweden and USEPA data.	**WHO 2000**
CLEA 2009 HCV	0.002	µg kg^{-1} bw day^{-1}	6.6	ng m^{-3}			Lung cancer	Based on WHO cancer risk assessment. Air conc of 6.6 ng m^{-3} gives a ELCR of 1 in 100,000. The unit risk (of 1 mg m^{-3}) is 1.5 x 10^{-3}. Based on average lung cancer risk from USA, Sweden and USEPA data.	EA 2009
EC Working gp 2000 Limit value	*0.0011*	µg kg^{-1} bw day^{-1}	4	ng m^{-3}	100	LOAEL; 125-415 µg m^{-3} x year	Lung cancer	Based on Swedish and US workers. UF of 10 used to reduce cancer risks to a level that would be difficult to detect in a epidemiology study, then converted to continuous exposure. Another UF of 10 was then applied to protect sensitive groups	**EC2000**
EPAQS 2008 GV	*0.0009*	µg kg^{-1} bw day^{-1}	3	ng m^{-3}	1000	LOAEL; 125 µg m^{-3} x year; annual conc 3 µg m^{-3}	Lung cancer	Based on Swedish and US workers. LOAEL based on on conc that was associated with a statistically significant increase in lung cancer risk. The mid-point range of all 3 studies was selected as the LOAEL. UF of 10 for conversion from LOAEL to NOAEL, 10 to allow for greater exposure duration of the public and 10 to protect susceptible groups were used.	

c) Dermal Route	HCVderm	HCV units			UF used			Pivotal Study used & Comments	Reference

COT/COC Opinion

Type text in here

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

EFSA: Estimated dietary ranges inorganic As (µg kg-1 bw day-1) 0.13-0.56 (mean); 0.37-1.22 (high 95 percentile). Refer to Table 23 for total As UK data (at EU mean level)]

MDI Units

	Pathways	Units	Adults	Children	Refs
Food (average)	Oral	µg kg^{-1} bw day^{-1}	0.13-0.56	0.74-1.39	EFSA 2009
Food (high)	Oral	µg kg^{-1} bw day^{-1}	0.37-1.22	1.47-2.66	EFSA 2009
Food infants	Oral	µg kg^{-1} bw day^{-1}	-	Breast fed; 0.04 Formula; 0.116 Rice based food; 1.63-1.76	EFSA 2009
Water	Oral	µg kg^{-1} bw day^{-1}	0.014	0.025	EA 2009
Air	Inhalation	µg kg^{-1} bw day^{-1}	0.001	-	EFSA 2009
Smoking	Inhalation	µg kg^{-1} bw day^{-1}	0.03	-	EFSA 2009
MDI	Oral	µg kg^{-1} bw day^{-1}	0.07	0.19	EA 2009
MDI	Inhalation	µg kg^{-1} bw day^{-1}	0.0002	0.0005	EA 2009

IV) LLTC derivation

A) ORAL

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments	Reference
EFSA 2009 (data provided for information & comparison)		**Drinking water**			**Human epidemiology studies**	**Most sensitive effects come from the lung cancer evaluation in Ferreccio et al., 2000. Skin lesions data are from Ahsan et al., 2006 and Xia et al., 2009. effects on bladder cancer from Chiou et 2001.**	**EFSA 2009**
WHO 2011		**Drinking water**			**Human epidemiology studies**	**MOST RECENT EVALUATION: Most sensitive effects are for lung cancer from Chen et al., 2010b. Next most sensitive: Effects on bladder cancer from Chen et al., 2010a.Skin lesions have been excluded from the evaluation due to confounders in the data (Taiwan studies, and poor fit of quantitative models).**	**WHO 2011 JECFA monograph**

BMD Modelling (if relevant)

Software used USEPA BMDS software v 2.1.1

EFSA 2009	Dermal 1	Dermal 2	Lung cancer	Bladder cancer
	BMD1	BMD1	BMD1	BMD1
BMD modelling (value) (μg kg^{-1} bw day^{-1})	2.4-6	0.94-3.7	0.39-0.78	7.9-15.4
	BMDL1	BMDL1	BMDL1	BMDL1
BMD modelling (value) (μg kg^{-1} bw day^{-1})	2.2-5.7	0.93-3.7	0.34-0.69	3.2-7.5

EFSA 2009	Dermal 1	Dermal 2	Lung cancer	Bladder cancer
	BMD5	BMD5	BMD5	BMD5
BMD modelling (value) (μg kg^{-1} bw day^{-1})	8.4-16.2	2.0-5.4	ND	ND
	BMDL5	BMDL5	BMDL5	BMDL5
BMD modelling (value) (μg kg^{-1} bw day^{-1})	7.4-14.5	1.8-5.1	ND	ND

EFSA 2009	Dermal 1	Dermal 2	Lung cancer	Bladder cancer
	BMD10	BMD10	BMD10	BMD10
BMD modelling (value) (μg kg^{-1} bw day^{-1})	16.8-30.1	8.1-15.6	ND	ND
	BMDL10	BMDL10	BMDL10	BMDL10
BMD modelling (value) (μg kg^{-1} bw day^{-1})	14.7-26.5	6.6-13.2	ND	ND

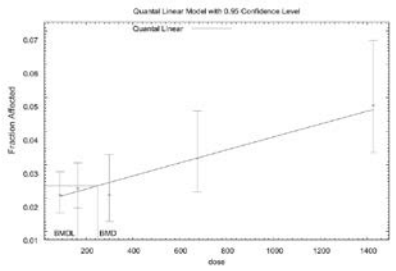
Comments:

Dermal 1: Data from skin lesions (Ahsan et al., 2006) Table A1 in EFSA 2009. Dermal 2: Data from skin lesions (Xia et al., 2009); Bladder cancer: data from Chiou et al., 2001). BMCLs in ug/L water are translated assuming 3-5L water, 50-200 μg/day food As and bw 55 kg. [e.g. (23x3)+50/55 = 2.2] Lung Cancer: data from Ferreccio et al., 2000; [BMCL translated assuming 1-2L water, 10-20 microgram As from food and 70kg bw. e.g. (14x1)+10/70 = 0.34.

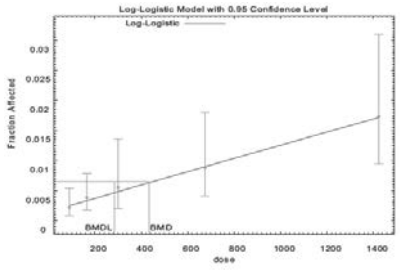
USEPA BMDS software v 2.1.1

WHO 2011	Lung cancer	Lung cancer	Bladder cancer	Bladder cancer
	BMD0.5	BMD1	BMD0.5	BMD1
BMD modelling (value) (μg kg^{-1} bw day^{-1})	4.5-7.3	9.1	7.9-13.9	16
	BMDL0.5	BMDL1	BMDL0.5	BMDL1
BMD modelling (value) (μg kg^{-1} bw day^{-1})	3.0-5.0		5.2-11.4	

Lung cancer model



Bladder cancer model



Dose units of microgram/day and body weight 55kg

Bladder cancer data: Chen et al., 2010a. Lung cancer: Chen et al., 2010b.

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OPTIONS	Value	Units	
Point of Departure for ORAL LLTC:			from WHO 2011 evaluation
Type of PoD	BMD various		
Value selected	3	µg kg^{-1} bw day^{-1}	BMDL0.5
	4.5	µg kg^{-1} bw day^{-1}	BMD0.5 (lowest)
	5.9	µg kg^{-1} bw day^{-1}	BMD0.5(average)

Chemical Specific Adjustment Factor to account for uncertainties in the data		
	Range	Selected value
Intraspecies	1 - 10	1
Interspecies	1 - 10	1
Other factors	1 - 100	100

Thresholded chemical? No
If yes - calculate CSAF
If no - calculate CSM

CSAF = **(for thresholded chemical)**

CSM = 10 **(for non-thresholded chemical)**
OPTIONS 50
250

ELCR = 10000-50000

Lifetime averaging to be applied in CLEA No

Oral LLTC calculation:

OPTIONS **Units**

LLTC (Non Thresholded chemical)			µg kg^{-1} bw day^{-1}
	POD value	CSM	
BMDL0.5	3	10	0.3
	3	50	0.06
	3	250	0.012
BMD0.5 (lowest)	4.5	10	0.45
	4.5	50	0.09
	4.5	250	0.018
BMD0.5(average)	5.9	10	0.59
	5.9	50	0.12
	5.9	250	0.024

HCV EA 2009 Minimal risk 0.3

B) INHALATION

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments	Reference
WHO Cancer risk assessment (2000) (Adopted by EA in 2009) Based on average lung cancer risk from USA, Sweden and USEPA data.				**Human**	**Epidemiology study data**	**Air conc of 6.6 ng m^{-3} gives a ELCR of 1 in 100,000. A 1in 50 000 ELCR = 13 ng m^{-3}**	

BMD Modelling (if relevant)

Software used

	BMD1	BMD5	BMD10	BMD15	BMD20
BMD modelling (value)					
	BMDL1	BMDL5	BMDL10	BMDL15	BMDL20
BMD modelling (value)					

Comments: Type comments in here

	Value	Units	Type of Value = NOAEL or BMD(L)?
Point of Departure for INHALATION LLTC:	13	ng m^{-3}	

Chemical Specific Adjustment Factor to account	
	Value
Intraspecies	1
Interspecies	1
Quality of study	1
Severity of Effect	1

Thresholded Yes or No

CSAF = NA **(for thresholded chemical)**

CSM = NA **(for non-thresholded chemical)**

ELCR = 1 in 50000

Lifetime averaging to be applied in CLEA No

NA = not applicable

INHALATION LLTC calculation:

		Units
LLTC (Thresholded chemical)	NA	
LLTC (Non Thresholded chemical)	NA	
LLTC (Human carcinogen)	0.0037	µg kg-1 bw day-1