APPENDIX G
PROVISIONAL C4SLs FOR CHROMIUM (VI)

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1. INTRODUCTION

This appendix presents provisional Category 4 Screening Levels (pC4SLs) for chromium (VI) based on the methodology described in Section 5 of the main report. Section 1.1 provides brief background information on chromium (VI), 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 a relevant authority (e.g., Defra).

1.1 BACKGROUND INFORMATION ON CHROMIUM (VI)

The following background information on chromium (VI) has been obtained from the (now withdrawn) Environment Agency Soil Guideline Value (SGV) report (Defra and the Environment Agency, 2002a) and the HPA's "Compendium of Chemical Hazards" document (HPA, 2007):

- Chromium is a transition metal of Group VIB of the periodic table which occurs naturally in the environment in the form of chromite ore, which contains other metals such as iron. Naturally occurring chromium exists predominantly in its chromic (chromium III) form, while the chromate (chromium VI) state is rarely found in nature and is produced mainly from commercial and industrial processes.
- Large amounts of chromium (VI) are produced through a range of activities, including the production of chromates and bichromates, stainless steel, welding, chromium plating, ferrochrome alloys and chrome pigment production, material tanning, the combustion of coal and oil, cement works, and waste incineration. The global production of the major chromium (VI) compounds is estimated at about 1942 kT per year, with a proportion of this, estimated to be about 17.5 T year per year, being released into the environment.
- Environmental releases of chromium (VI) from any source are expected to be reduced via abiotic and biotic processes to chromium (III) in most situations and the impact of the chromium (VI) form is therefore likely to be limited to the area around a source. In biological systems, the oxidation of chromium (III) to chromium (VI) never occurs and in foodstuffs, chromium is generally considered to be present as chromium (III).
- Chromium (VI) is present in cement at levels which must not exceed 0.0002% (2 ppm) dry weight, on the basis of skin sensitisation risk (EU Directive, 2003/53/EC - implemented in the UK via the COSHH and CHIP regulations).

Further background information on chromium (VI), relevant to land contamination risk assessment, can be found in the above-referenced documents.

2. LOW LEVEL OF TOXICOLOGICAL CONCERN FOR CHROMIUM (VI)

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 chromium (VI).

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 chromium (VI) has also been completed, as shown in Appendix G1.

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 G1).

In 2002, the Environment Agency (EA) published the TOX4 report for chromium (Defra & EA 2002b). This has been used as the starting point of the data search. However, significant new data has been published on chromium in recent years and such data has been added to the data package.

In 2013, the main sources of data come from the draft International Programme on Chemical Safety (IPCS) Concise International Chemical Assessment Documents (CICAD) report (IPCS 2011), the draft US Environmental Protection Agency (USEPA) report (USEPA 2010) and the Agency for Toxic Substances and Disease Registry (ATSDR 2012).

All authoritative bodies carried out benchmark dose (BMD) modelling, using data from the pivotal oral carcinogenicity study carried out by the US National Toxicology Program (NTP) in rats and mice (NTP 2008).

WHO and USEPA also considered intestinal cancer in male mice to be a critical carcinogenic effect, again using the National Toxicology Programme (NTP) data as the pivotal study (IPCS 2011; USEPA 2010).

The ATSDR 2012 document covers a review of the primary literature based on the toxicology of chromium (VI) (Cr(VI)) by oral exposure (ATSDR 2012) and maps all quantitative toxicological responses seen in animal and humans. An example of the type of information provided in the ATSDR report is shown below in Figure 2.1.

This review provides the best evidence that gastrointestinal, hepatic and immunological effects are the most sensitive of all toxicological effects by the oral route. In defining minimal risk, it is only necessary to focus on the most sensitive of all effects in defining the HBGV. In order to choose a point on the dose-response curve that is higher than minimal risk, it is important to note that the dose-response effects for such effects overlap with the dose-response effects for cancer risk. Therefore, in setting the LLTC for chromium (VI), ALL endpoints must be borne in mind e.g. see Figure 2.1 below) – in this case carcinogenicity effects. This is an important principle in any of the toxicological evaluations where there are overlapping toxicological effects data, and is an important departure from the principles of how SR2 and minimal risk evaluations are implemented more simply.

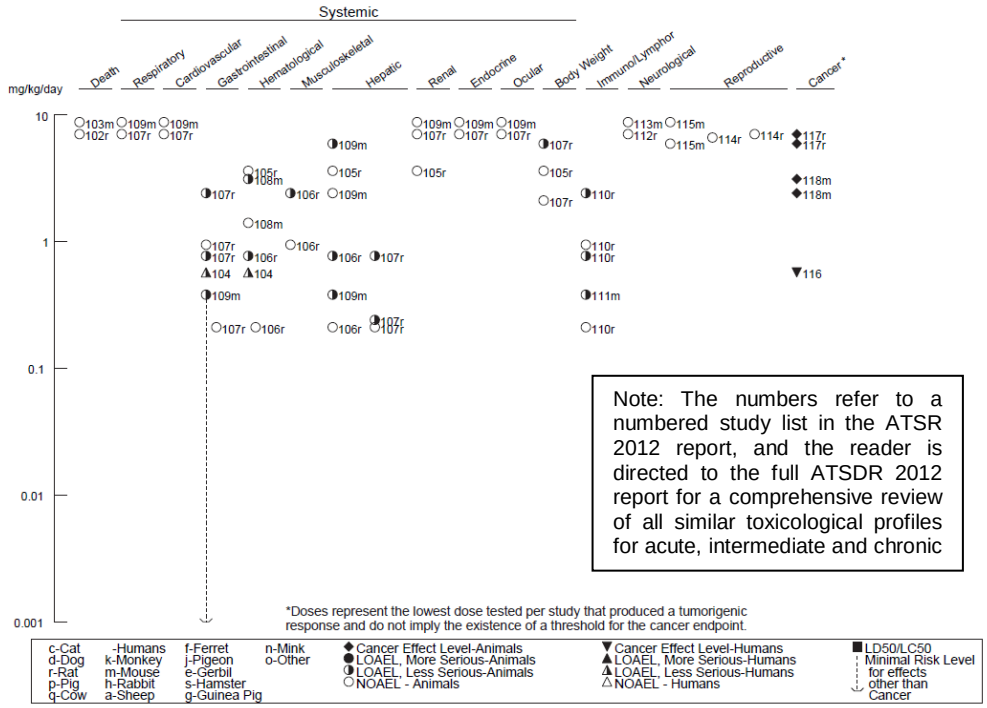


Figure 2.1: Example of all chronic (>365 days) animal and human study evaluations that lead to different adverse toxicological responses following oral exposure (ATSDR 2012)

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) a policy choice (i.e. based on an existing guideline from another regime, with or without a toxicological rationale).

2a) Animal Toxicology Data

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 for chromium (VI) (see Appendix G1).

The critical toxic endpoints selected from the toxicity studies are diffuse epithelial hyperplasia of the duodenum (small intestine) or carcinogenicity, including tumours of the intestine. Older evaluations carried out by RIVM and USEPA were based on an old drinking water study in rats by MacKenzie (1958), whereas later assessments by USEPA (2010), WHO (2011) and ATSDR (2012) were based on the NTP mouse study (NTP 2008).

The NTP study consisted of a 2-year drinking water study in male and female mice and rats administered sodium dichromate dihydrate. The study included multiple dose groups and assessed a comprehensive array of endpoints. Dose response modelling using USEPA BMD modelling software was conducted for histopathological changes in the duodenum (diffuse epithelial hyperplasia in male and female mice), liver (chronic liver inflammation in female rats and histiocytic cellular infiltration in mice), mesenteric lymph node (histiocytic cellular infiltration in male and female mice) and pancreas (cytoplasm cellular alteration of acinar epithelial cells in female mice). Carcinogenic endpoints were

also observed, including neoplasms of the small intestines in male and female mice, and squamous cell neoplasms of the oral cavity in male and female rats (NTP 2008).

WHO (IPCS), USEPA and ATSDR all considered the critical effect to be epithelial hyperplasia of the duodenum (an increase in cells of the gut lining appearing as a growth) in female mice. There was some debate surrounding whether this was a neoplastic (pre-cancerous) or non-neoplastic (non-cancerous) event. WHO and ATSDR considered the epithelial hyperplasia to be non-neoplastic (IPCS 2011; ATSDR 2012). The NTP classified focal epithelial hyperplasia as a pre-neoplastic lesion (i.e. could possibly lead to cancer) hence diffuse epithelial hyperplasia may be considered to be the same (NTP 2008). The USEPA stated that although this lesion may lead to cancer (adenoma), it was thought to be a non-cancer endpoint because definitive data on the progression of this lesion into an adenoma does not exist (USEPA 2010).

Overall the HBGVs proposed by all authoritative bodies (Appendix G1) using various studies range from 0.5 to 5 $\mu g\ kg^{-1}$ bw day^{-1} for Cr (VI). Lower range values (0.5-0.9 $\mu g\ kg^{-1}$ bw day^{-1}) come from more recent evaluations of NTP data. Various points of departure (POD) have been selected by different authoritative bodies. For thresholded effects, all authoritative bodies (WHO, USEPA and ATSDR) calculated the 95^{th} lower confidence limit of the benchmark dose ($BMDL_{10}$) using data from the NTP (2008) study. An UF of 100 was applied to all PODs to reflect inter- and intra-species differences. This gave a reference dose (RfD), tolerable daily intake (TDI) or minimal risk level (MRL) of 0.9 or 1 $\mu g\ kg^{-1}$ bw day^{-1} (depending on the rounding of the $BMDL_{10}$) (USEPA 2010; WHO, 2011; ATSDR 2012), respectively.

In terms of carcinogenic effects, the USEPA also calculated a $BMDL_{10}$ based on neoplasms of the small intestine in mice, from which cancer slope factors were calculated by dividing the BMR by the $BMDL_{10}$ and converting the slope factor value to human equivalents. A 70 year risk estimate for a constant average daily exposure to 0.1 $\mu g\ kg^{-1}$ bw day^{-1} is 8×10^{-3} (USEPA 2010). In contrast, WHO calculated an excess lifetime cancer risk that does not exceed 0.5×10^{-3} at a dose of 1 $\mu g\ kg^{-1}$ bw day^{-1} (the TDI calculated for non-cancer endpoints) (IPCS 2011).

In the UK, the current oral HCV published in 2002 was based on the USEPA RfD, derived from a maximum contaminant level (MCL) in drinking water of 100 $\mu g\ L^{-1}$. Using default physiological assumptions (a 70 kg adult drinking 2L water per day), the EA considered the MCL to be equivalent to an oral TDI of 3 $\mu g\ kg^{-1}$ bw day^{-1} for Cr(VI) (EA 2002). Moreover, as much of the chromium in soil is expected to be in the form Cr(III) rather than Cr(VI), EA stated that it was important to obtain information about the oxidation state of the chromium present in the soil sample and also recognised that assuming that all chromium in soil is Cr(VI) is conservative. Therefore, given that Cr(III) is most prevalent in soil which has a much lower toxicity, the EA considered the RfD dose derived by the USEPA as a TDI rather than an index dose, despite Cr (VI) being mutagenic (EA 2002b).

This value of 3 $\mu g\ kg^{-1}$ bw day^{-1} is the current minimal risk value available at present for UK contaminated land risk assessment. However, this EA (2002b) value does not account for the recent data now available from the NTP (2008) oral carcinogenicity study and reviewed by authoritative bodies (USEPA 2010; WHO 2011; ATSDR 2012;).

Based on the data available, the 2 year mouse NTP study (2008) has been selected as the pivotal study.

GO TO FLOWCHART ELEMENT 3.

2b) Human Toxicology/Epidemiology Data

Not applicable as no human epidemiology data were used in the evaluation of the oral toxicity of Cr (VI).

GO TO FLOWCHART ELEMENT 6

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

Not applicable.

2.1.3 FLOWCHART ELEMENT 3: ARE THERE ADEQUATE DOSE-EFFECTS DATA FOR THE CHOSEN PIVOTAL STUDY – ANIMAL DATA?

Yes	No	Not applicable
X		

The data from the NTP study (2008) on epithelial hyperplasia and intestinal tumours will be considered as the pivotal studies from which to derive an $LLTC_{oral}$. These data were used by USEPA 2010; WHO, 2011; ATSDR 2012 as described above.

The NTP study provides adequate data on which to carry out BMD modelling. The BMD modelling on diffuse epithelial hyperplasia was carried out by ATSDR in 2008, although this report has been superseded by the version published in 2012 (ATSDR 2012). Such BMD modelling was used and cited by USEPA in 2010 and WHO in the IPCS document (IPCS 2011). WHO and USEPA also carried out BMD modelling on the carcinogenicity data (USEPA 2010; IPCS, 2011).

GO TO FLOWCHART ELEMENT 3b

2.1.4 FLOWCHART ELEMENT 3b: PERFORM BMD MODELLING

As stated above, there are good quantitative data available from the NTP study (2008) that various authoritative bodies have used to carry out BMD modelling.

ATSDR used the USEPA Benchmark Dose Software (BMDS) version 1.4.1 to fit dichotomous models to incidence data for various endpoints in male and female rats and mice exposed to sodium dichromate hydrate in drinking water for 2 years (NTP 2008).

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

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

To assess the acceptability of the different models, various criteria were evaluated. In general, model fit was assessed by a chi-square goodness of fit test (i.e. models with $p<0.1$ failed the goodness of fit criterion) and the Akaike Information Criteria (AIC) value. Smaller AIC values indicate a better fit of data. Of the models exhibiting adequate fit, the model with the lowest AIC value was selected as the best fit model as long as the BMDL calculated from all models were 'sufficiently close' (USEPA 2012).

From the NTP data, the BMD_{10} and the corresponding 95^{th} lower confidence limit ($BMDL_{10}$) were calculated associated with a benchmark response (BMR) of 10 % extra risk of the effect occurring. Such a BMR is commonly used when information related to

what level of change is considered biologically significant is unavailable (USEPA 2010; ATSDR 2008). A 95th lower confidence limit is used to take into account the inherent uncertainty in the pivotal toxicity study and to ensure (with 95% confidence) that the selected BMR is not exceeded whereas the BMD_{10} value represents central tendency values. For the derivation of the LLTC, the BMD_{10} value could be selected as the POD.

ATSDR modelled incidence data for seven selected endpoints (chronic inflammation of the liver, diffuse epithelial hyperplasia of the duodenum, histiocytic cellular infiltration of the mesenteric lymph node and liver, cytoplasmic alteration of the pancreas) in female rats and male and female mice exposed to sodium dichromate hydrate in drinking water for 2 years (NTP 2008). Data from BMD modelling for thresholded effects are presented in Section IV of Appendix G1, Table 2.1 and Figure 2.2 below.

Table 2.1: BMD_{10} and $BMDL_{10}$ calculations from the best fitting models for several thresholded endpoints in mice and rats after exposure to sodium dichromate dihydrate in the NTP study (2008)

Endpoint	Species/ sex	Model	AIC	BMD_{10} (mg Cr(VI) kg^{-1} bw day^{-1})	$BMDL_{10}$ (mg Cr(VI) kg^{-1} bw day^{-1})
Liver: chronic inflammation	Rat/female	Log-logistic	312.57	0.22	0.14
Duodenum: diffuse epithelial hyperplasia	Mouse/male	1-degree polynomial multistage/quantal linear	166.34	0.16	0.13
Duodenum: diffuse epithelial hyperplasia	Mouse/ female	Gamma/ multistage/quantal linear/Weibull	126.06	0.12	0.09*
Liver: histiocytic cellular infiltration	Mouse/ female	Log-logistic	251.36	0.17	0.12
Pancreas: acinus, cytoplasmic alteration	Mouse/ female	Log-logistic	205.22	0.68	0.52

Presented by ATSDR 2012

No models fit the data on mesenteric lymph node: histiocytic cellular infiltration

* would be used for minimal risk calculations

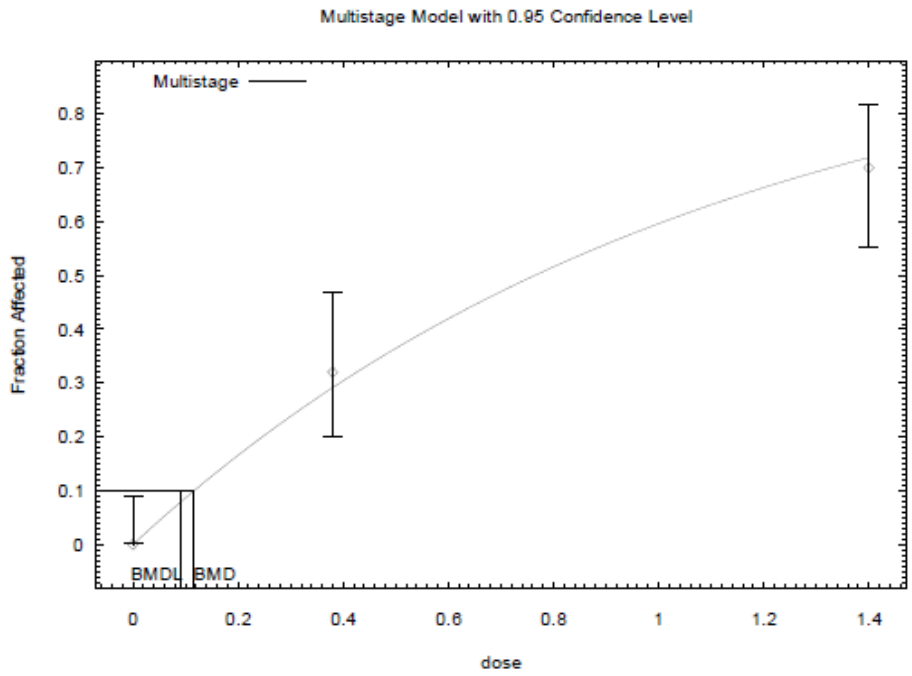


Figure 2.2: Reproduced from ATSDR (2012). Multistage model of diffuse epithelial hyperplasia in duodenum of female mice.

Dose is in mg Cr(VI) kg bw^{-1} day^{-1}, 95% confidence limits on the data are shown. The marked BMD is for BMD_{10}, a 10% extra risk of epithelial hyperplasia.

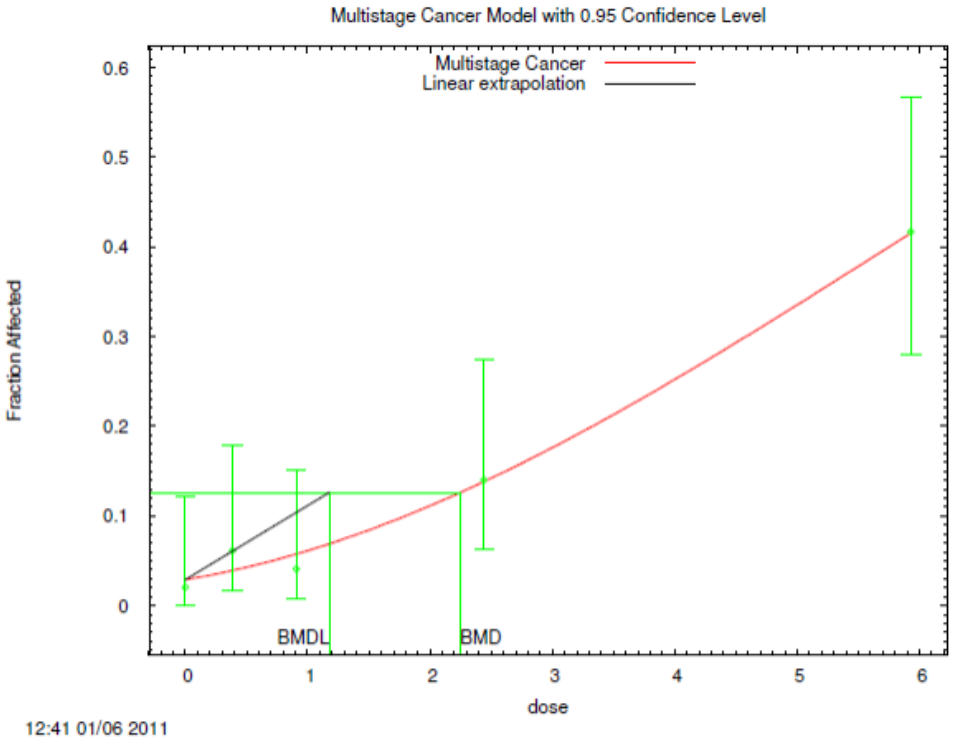
WHO and USEPA also carried out BMD modelling on tumour incidence data, also from the NTP study and fit the multistage model to the incidence of squamous cell papillomas and carcinoma of the oral mucosa and tongue in male and female rats, and adenomas and carcinomas of the small intestine in male and female mice (NTP 2008). Data from BMD modelling for carcinogenic effects are presented in Section IV of Appendix G1 and Table 2.2 below. Data from BMD modelling for carcinogenic effects are presented in Section IV of Appendix G1, Table 2.2 and Figure 2.3 below.

Table 2.2: BMD_{10} and $BMDL_{10}$ calculations from the multistage model for adenomas and carcinomas of the oral cavity and small intestine in male and female rats and mice after exposure to sodium dichromate dihydrate in the NTP study (2008)

Endpoint	Species/ sex	Model	AIC	BMD_{10} (mg Cr(VI) kg^{-1} bw day^{-1})	$BMDL_{10}$ (mg Cr(VI) kg^{-1} bw day^{-1})
Oral carcinoma	Rat/male	Multistage	40.3	5.8	4.3
Oral carcinoma or adenoma	Rat/male	Multistage	58.8	5.4	4.0
Oral carcinoma	Rat/female	Multistage	70.3	4.3	3.3
Oral carcinoma or adenoma	Rat/female	Multistage	93.3	4.6	3.4
Small intestine: carcinoma	Mouse/ male	Multistage	87.6	5.7	3.0
Small intestine: adenoma or carcinoma	Mouse/ male	Multistage	161.7	2.2	1.2*
Small intestine: carcinoma	Mouse/ female	Multistage	97.4	6.5	3.9
Small intestine: adenoma or carcinoma	Mouse/ female	Multistage	187.5	1.3	1.0*

Presented by USEPA 2010 and IPCS 2011

* would be used for minimal risk calculations



Dose is in mg Cr (VI)kg bw $^{-1}$ day^{-1}, 95% confidence limits on the data are shown. The marked BMD is for BMD_{10}, a 10% extra risk of intestinal tumours.

Figure: 2.3: Reproduced from IPCS (2011). Multistage model of intestinal tumours (adenomas and carcinomas (in male mice).

Based on the lowest $BMDL_{10}$ value, diffuse epithelial hyperplasia in female mice was selected by ATSDR in the draft 2008 toxicological profile report as the POD for the derivation of minimal risk HBGVs. This value was also selected in the draft IPCS document that cited the modelling carried out by ATSDR in 2008 and by USEPA (IPCS 2011, USEPA 2010).

For carcinogenic effects, the cancer slope factor was based on neoplasms in the small intestine of male and female mice as the mouse was deemed the most sensitive species as tumour incidences were significantly elevated at lower concentrations, hence were used as the basis of the cancer slope factor (USEPA 2010, IPCS 2011).

For the purposes of deriving an LLTC, a BMD_{10} of 2.2 mg kg^{-1} bw day^{-1} is proposed, based on small intestinal adenomas or carcinomas in male mice. Alternatively, a BMD of 0.12 mg kg^{-1} bw day^{-1} based on diffuse epithelial hyperplasia in female mice could be considered. However the former was selected as the POD due to the uncertainty surrounding whether diffuse epithelial hyperplasia represents a threshold or non-thresholded endpoint.

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

Yes	No	Not applicable
X	X	

Differing opinions exist surrounding whether diffuse epithelial hyperplasia exhibits a threshold

IARC concluded that there is sufficient evidence in humans for the carcinogenicity of Cr(VI) and classified it as group 1 – carcinogenic to humans (IARC 1990).

However, in terms of the most sensitive effect in female mice, namely epithelial hyperplasia, although it was generally accepted that this *may* represent a pre-neoplastic lesion that *may* progress to cancer (adenoma), EPA actually considered this to be a non-neoplastic endpoint as definitive data on the progression of this lesion to cancer does not exist. This decision is key to deciding upon the magnitude and type of uncertainty factor to use.

GO TO FLOWCHART ELEMENT 4a/4b

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

The default margin for establishing a "minimal risk" level for non-thresholded carcinogens from animal data using a $BMDL_{10}$ is 10,000. For derivation of a LLTC for genotoxic carcinogens, three alternative methods could be considered for deriving a CSM or generic margin:

a) Using scientific evidence on the specific uncertainties relating to the data from the pivotal study, a CSM may be derived by adjusting factors relating to :

- Intraspecies variability: Considerable variability existed in terms of absorption and elimination of Cr(VI) by human volunteers and may reflect interindividual differences that influence gastric reduction, such as the period of time between meals, gastric contents or different genetic capacities for Cr(VI) reduction (USEPA 2010). Therefore, to account for toxicokinetic as well as toxicodynamic variation, a default value of 10 is proposed.
- Interspecies variability: Species differences in the reduction of Cr(VI) has been reported. In humans, the K_m (the concentration of substrate that leads to half-maximal velocity) for Cr (VI) was three orders of magnitude lower than that for rats, although the V_{max} (the maximum initial velocity of the enzyme catalysed reaction under the given conditions) was similar. Humans have a greater gastric acid production than rodents and are expected to reduce more Cr(VI) to Cr(III), therefore have an increased ability to detoxify Cr(VI). Moreover, contrary to rats, in humans cytochrome P450 does not play a significant role in the reduction process, and other microsomal flavoproteins are responsible for reducing Cr (VI). WHO concluded that the metabolism of chromium (VI) in rodent systems may not readily be extrapolated to humans (IPCS 2011). Due to the large number of uncertainties in the toxicokinetics and toxicodynamics of Cr(VI) between animals and humans, and the fact that there are little data to quantitatively assess toxicokinetic and toxicodynamic differences between animals and humans, a default factor of 10 is proposed.
- Additional uncertainties: The two year drinking water study carried out in mice and rats by the NTP was a well carried out study, with the appropriate number of animals per dose group and adequate dose levels. Therefore a factor of 50 rather than the default of 100 is proposed to account for the good quality of this study.

Therefore a CSM of 5000 is proposed supported by the above scientific rationale.

b) Previously, a $BMDL_{10}$ divided by a default uncertainty factor of 10,000 has been equated to a risk level of 1 in 100,000 for genotoxic carcinogens (EA 2009), which has been defined as a minimal level of risk (Defra 2008). Therefore, a low level of risk could be defined as a notional cancer risk level of 1 in 50,000 (using $BMDL_{10}$ and a generic margin of 5000). It should be noted that this risk estimate is an approximation as it is derived in the context of animal data and not human data.

c) The choice of generic margin used to derive the LLTC could be communicated on a purely risk management basis. A margin of 5000-fold less than the POD could be

considered as an acceptable margin. The ideal situation is when the scientific information corroborates that this is a pragmatic margin.

In the context of setting the LLTC, a margin of 5000 is proposed, justified using the rationales at both a) and b) above.

GO TO FLOWCHART ELEMENT 5a

2.1.7 FLOWCHART ELEMENT 4b: DERIVE A CHEMICAL-SPECIFIC ASSESSMENT FACTOR USING SCIENTIFIC EVIDENCE

USEPA, WHO and ATSDR used an uncertainty factor of 100 in the derivation of the minimal risk HBGVs, for endpoints that they considered non-cancer lesions and thresholded. This accounted for extrapolation from animals to humans, and human variability (USEPA 2010; IPCS 2011; ATSDR 2012).

For the derivation of a LLTC, a CSAF may be derived by adjusting factors relating to:

- Intraspecies variability: As described above, the default value of 10 is proposed to account for this large human variability.
- Interspecies variability: As discussed above, due to the large number of uncertainties in the toxicokinetics of chromium (VI) between animals and humans, the default factor is 10 is proposed.

Therefore a CSAF of 100 is proposed.

GO TO FLOWCHART ELEMENT 5b

2.1.8 FLOWCHART ELEMENT 5a/b: CALCULATE THE LLTC FOR NON-THRESHOLDED / THRESHOLDED CHEMICALS

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

POD/margin = LLTC (units as per POD)

For thresholded chemicals, the POD is divided by a CSAF (or default UF);

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

Table 2.3 presents the choices of POD, choices of margin and the resultant LLTCs.

Table 2.3: Proposed choices of oral LLTC values using different PODs and/or CSMs

	POD	Value (mg kg^{-1} bw day^{-1})	CSM /CSAF	LLTC (µg Cr(VI) kg^{-1} bw day^{-1})
Alternative (non-threshold)	BMD_{10}	0.12**	5000	0.024
Alternative (non-threshold)	$BMDL_{10}$	1.2	10000*	0.12
Proposed LLTC (non-threshold)	**BMD_{10}**	**2.2**	**5000**	**0.44**
Alternative (threshold)	$BMDL_{10}$	0.09	100	0.90
Alternative (threshold)	BMD_{10}	0.12	100	1.20
Current HCV (total Cr)I (EA 2002)	NOAEL	2.5	900	3.00

*Default margin

** Diffuse epithelial hyperplasia is considered by USEPA, ATSDR and WHO as a thresholded endpoint, although it may progress to cancer. LLTCs are therefore presented for both thresholded and non-thresholded opinions.

GO TO FLOWCHART ELEMENT 7

2.1.9 FLOWCHART ELEMENT 7: ASSESS LLTC for CHROMIUM (VI)

Based upon a scientific evaluation of small intestine adenoma or carcinoma in male mice, an oral LLTC of **0.44 µg kg^{-1} bw day^{-1}** is proposed, based on a BMD_{10} as the POD and a CSM of 5000. This LLTC value:

a) is lower than the current (2002) EA minimal risk HCV of 3 µg kg^{-1} bw day^{-1} considered as a TDI (EA 2002)

b) is lower than the minimal risk values recently published (principally the ATSDR MRL value of 0.9 µg kg^{-1} bw day^{-1} (ATSDR 2012)

c) is protective against diffuse epithelial hyperplasia

d) is higher than the mean dietary intakes in adults and children from food and water

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

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 original EA 2002 Tox 4 report for chromium has been used as the start of the data search, with more recent information being included.

In 2013, as with the oral data, the main sources come from the draft IPCS CICAD report (IPCS 2011), ATSDR (ATSDR 2012) and EPAQS (EPAQS 2009). The USEPA have not assessed the toxicology of Cr(VI) via inhalation, stating that reassessment of the non-cancer and cancer health effects of hexavalent chromium associated with the inhalation route of exposure will be conducted at a later date (USEPA 2010).

EPAQS, ATSDR and WHO based their evaluations on lung cancer as the critical effect based on occupational data from a cohort of chromate workers in Baltimore, presented by Gibb *et al.* (2000). WHO also considered non-cancer effects following inhalation exposure to chromic acid/chromium trioxide or salts of Cr(VI) i.e. chromates and dichromates (Linberg and Hedenstierna 1983; Glaser *et al.* 1990). Nasal irritation was reported in workers exposed to chromic acid by Linberg and Hedenstierna (1983). Moreover, alterations of lactate dehydrogenase in bronchoalveolar lavage (BAL) fluid was reported, which is considered a sensitive indicator of lung toxicity, potentially reflecting chronic lung inflammation that may lead to pulmonary fibrosis (IPCS 2011).

The ATSDR document covers a review of the primary literature based on the toxicology of Cr(VI) by inhalation exposure (ATSDR 2012) and maps all quantitative toxicological responses seen in animal and humans. An example of the type of information provided in the ATSDR report is shown below in Figure 2.4.

This review provides the best evidence that respiratory and immunological effects are the most sensitive of all non-cancer effects by the inhalation route, although gastrointestinal and renal effects have been reported at only slightly higher concentrations.

In defining minimal risk, it is only necessary to focus on the most sensitive of all effects in defining the HCV. In order to choose a point on the dose-response curve that is higher than minimal risk, it is important to note that the dose-response effects for gastrointestinal and renal effects overlap with the dose-response effects for cancer risk. Therefore, in setting the LLTC for Cr(VI), ALL endpoints must be borne in mind.

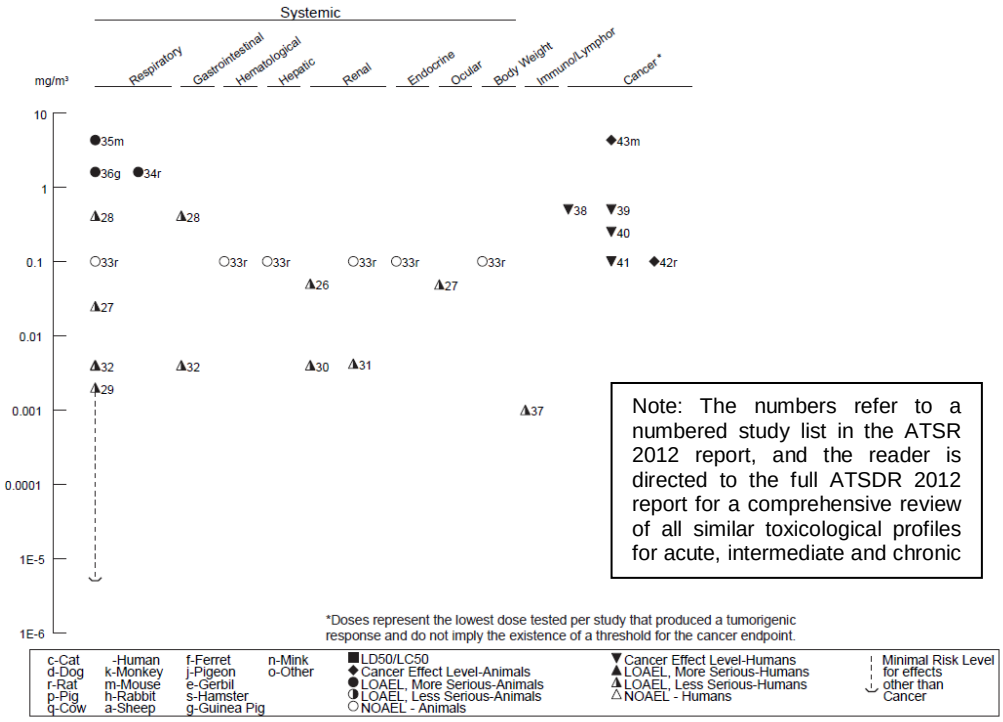


Figure 2.4. Example of all chronic (>365 days) animal and human study evaluations that lead to different adverse toxicological responses following inhalation exposure (ATSDR 2012)

These reviews provide the best evidence that respiratory and immunological effects as well as lung cancer are equally sensitive of all toxicological effects by the inhalation route although the expert group consensus recommends that lung cancer should be considered the most sensitive health effect following inhalation of Cr(VI).

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) a policy choice (i.e. based on an existing guideline from another regime, with or without a toxicological rationale).

2a) Animal Toxicology Data

WHO (2011) derived a tolerable concentration in air (TC) for chromates, based on the rat study by Glaser *et al.* (1990), using lactate dehydrogenase in BAL fluid as the critical effect. A lowest benchmark concentration ($BMCL_{10}$) of 16 μg Cr(VI) m^{-3} for changes in lactate dehydrogenase in BAL fluid was selected, then converted to BMC_{adj} of 10 μg m^{-3} (by multiplying the BMCL by a regional deposited dose ratio (RDDR[1]) of 0.60) was then divided by an UF of 300 to account for pharmacodynamics differences, inter-individual variability and use of a 90 day study. The resultant TC was 30 ng Cr(VI) m^{-3} (8.6 ng Cr(VI) kg^{-1} bw day^{-1}).

2b) Human Toxicology/Epidemiology Data

Expert group consensus recommends that lung cancer is the most sensitive health effect following inhalation of Cr(VI). Results from both in vitro and in vivo studies provide evidence that Cr(VI) is mutagenic, mediated through the generation of reactive intermediates and reactive oxygen species that react with DNA leading to DNA damage. In humans, data indicate the possibility of genotoxic effects (USEPA 2010; ATSDR 2012).

Expert Panel on Air Quality Standards (EPAQS) and WHO both used occupational data from chromate production workers in Baltimore (Gibb *et al*. 2000).

EPAQS derived a LOAEL of 0.35 μg m^{-3} based on lung cancer. This was converted to a notional NOAEL then divided by an overall uncertainty factor of 100 to account for a greater exposure duration for the public and to protect susceptible groups. Their guideline value of 0.35 ng m^{-3} for CrO_3 was expressed as Cr(VI) (by multiplying by 0.52) giving a HBGV for Cr(VI) of 0.2 ng m^{-3}. The guideline value of 0.2 ng Cr(VI) m^{-3} equates to an ELCR of 7 in 1,000,000 which is a similar value to other cancer risk estimates derived using unit risk methods (EPAQS 2009). WHO used data from the same chromate production workers (Gibb *et al*. 2000) that was remodeled by Park *et al*. (2004) who calculated the cumulative lifetime risk of lung cancer from environmental exposure to 1, 0.1, 0.01 and 0.001 μg Cr(VI) m^{-3} to be 4 in 100, 4 in 1000, 4 in 10,000 and 4 in 100,000 (IPCS 2011).

EPAQS also carried out a unit risk evaluation, again based on the data from chromate production workers (Park *et al*. 2004) to quantitatively estimate cancer risks. They estimated that the risk of lung cancer associated with lifetime exposures to 0.05, 0.5 and 5 ng m^{-3} CrO_3 to be 1 in 1,000,000, 1 in 100,000 and 1 in 10,000, respectively (EPAQS 2009). Converting this value to Cr(VI) results in a 1 in 100,000 ELCR being associated with 0.26 ng m^{-3} Cr(VI).

Non-cancer effects have been assessed by ATSDR (2012) and WHO (IPCS, 2011), although different data were considered as the pivotal study.

ATSDR and IPCS based their MRL derivation on occupational data exposed to chromic acid in the form of aerosols and mists (Linberg and Hedenstierna 1983). A LOAEL for nasal irritation was used as the POD, which was then adjusted for continuous exposure and an UF of 100 used to account for human variability and the use of a LOAEL. The

[1] The RDDR factors is used to adjust the inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration in a human

resultant MRL or TC was 5 ng Cr(VI) m^{-3} (1.43 ng Cr(VI) kg^{-1} bw day^{-1}) (ATSDR 2012; IPCS 2011).

WHO also derived a non-cancer HBGV based on the data from chromate production workers (Gibb *et al*. 2000). Nasal irritation seen at 10 μg m^{-3} was considered to be the critical effect, to which an UF of 300 was applied to account for human variability, LOAEL to NOAEL conversion and early onset of toxicological effects. The overall TC derived was 30 ng Cr(VI) m^{-3} (8.6 ng Cr(VI) kg^{-1} bw day^{-1}), the same as that derived from the rat study by Glaser *et al.* (1990) (IPCS 2011).

GO TO FLOWCHART ELEMENT 6

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

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

GO TO FLOWCHART ELEMENT 6c

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

Various authoritative bodies have based their HBGV indicating minimal risk on an ELCR of 1 in 100,000. For the purpose of deriving the LLTC, it is proposed that the dose that equates to an ELCR of 1 in 50,000 is used. Table 2.4 shows the resultant LLTCs.

Table 2.4: Proposed choices of inhalation LLTC values using different PODs and/or CSMs

	ELCR	Air concentration (ng m^{-3})	HCV/LLTC (ng kg^{-1} bw day^{-1})
Alternative**	1 in 100,000	0.26	0.074
Proposed LLTC	**1 in 50,000**	**0.52**	**0.15**
Current HCV for Cr(VI)	1 in 10,000	2.5	1*

*rounded up from 0.7 ng kg^{-1} bw day^{-1} **from EPAQS

GO TO FLOWCHART ELEMENT 7

2.2.5 FLOWCHART ELEMENT 7: ASSESS LLTC for CHROMIUM (VI)

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 **0.15 ng kg^{-1} bw day^{-1}.** This is based on an air concentration of 0.5 ng m^{-3} and default physiological

parameter values for the adult receptor (70 kg body weight and 20 m^3 air intake per day). This LLTC value:

a) is lower than the current EA minimal risk value of 1 ng kg^{-1} bw day^{-1} (EA 2002)

b) describes 1 in 50,000 lifetime cancer risk

c) is lower than the mean intakes in adults from ambient air

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 population.

2.2.6 CALCULATION OF A CHILD-SPECIFIC LLTC for CHROMIUM (VI)

There is no evidence to suggest that the child is particularly sensitive receptor for Cr (VI) toxicity. For the inhalation LLTC, it is suggested that a concentration of 0.52 ng m^{-3} Cr(VI) is used, which equates to 0.15 ng kg^{-1} bw day^{-1} based on default physiological parameter values for the adult receptor that would be considered in the commercial land use scenario. Inhalation LLTCs for other land use scenarios are derived based on receptor-specific (e.g. child) physiological parameter values (i.e. for bodyweight and inhalation rate, taken from EA 2009b) and are detailed in Table 2.5. The LLTC for a child would therefore be 0.34 ng kg^{-1} bw day^{-1}.

Table 2.5. Proposed chromium (VI) inhalation LLTCs for C4SL land use scenarios

Land use	Critical receptor	Receptor age classes	Average bodyweight (kg)	Inhalation rate (m^3 day^{-1})	LLTCinhal (ng Cr(VI) kg^{-1} bw day^{-1})
Residential	Female child	1-6	13.3	8.8	0.34
Allotments	Female child	1-6	13.3	8.8	0.34
Commercial	Female worker	17	70[2]	20[2]	0.15
POS-residential	Female child	4-9	21	11	0.27
POS-park	Female child	1-6	13.3	8.8	0.34

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

Substances containing chromium may cause skin sensitization in non-sensitised individuals or may induce a response in those already sensitized.

Data from patch testing indicate that applied mass loading of allergen on the skin are most useful for risk assessment purposes. A minimum elicitation threshold for 10 per cent of sensitised individuals ($MET_{10\%}$) of 0.089 µg Cr(VI) cm^{-2} was reported by Nethercott *et al.* (1994), which was supported by RIVM in 1999. Subsequently a lower $MET_{10\%}$ of 0.03 µg Cr(VI) cm^{-2} has been proposed by Hansen *et al*. (2003).

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

As allergic contact dermatitis following chromium (VI) is thought to occur in less than 1 per cent of the general population the $MET_{10\%}$ would be expected to be protective of health for greater than 99.9 per cent of the general population.

3. EXPOSURE MODELLING FOR CHROMIUM (VI)

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 open space close to housing that includes tracking back of soil (POS_{resi}); and
    - A park-type scenario where the park is considered to be at a sufficient distance from the home that there is negligible tracking back of soil (POS_{park}).

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 chromium (VI), 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 the $LLTC_{oral}$ is also based on localised effects and therefore the ADE for oral (and dermal) exposure 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 a & b), 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 both the $LLTC_{inhal}$ and $LLTC_{oral}$ are based on localised effects the latter approach has been taken to determine the pC4SLs for chromium (VI).

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 chromium (VI) from tuber vegetables and tree fruit for both the residential and allotments scenarios (via ingestion of soil attached to produce). Therefore, in accordance with the "top two" approach (see Section 3.5.5.3 of the main

text for further details), 90th 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).

CLEA requires a number of contaminant specific parameter values for modelling exposure. Contaminant specific parameter values used for chromium (VI) are shown in Table 3.1.

Table 3.1: Contaminant specific parameter values used for derivation of pC4SLs for chromium (VI)

Parameter	Units	Value	Source/Justification
Dermal absorption fraction	-	0.01	Highest observed sweat leachability for chromate in contaminated soils reported by Finley and Paustenbach (1997) with an additional factor of ten to account for potentially more soluble forms of chromate in other soils and wastes.
Water solubility,	mg L^{-1}	8.76×10^5 (25°C)	Aqueous solubility of sodium chromate; unhydrated and tetrahydrate forms (25°C). Lide (2008).
Soil–water partition coefficient,	$cm^3\ g^{-1}$	8.5	Kd value for loamy sand 'Windsor' soil from Montgomery (2007)
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	0	Chromium (VI) compounds are accumulated by plants but rapidly converted to chromium (III).
Soil-to-plant concentration factor (root vegetables)		0	
Soil-to-plant concentration factor (tuber vegetables)		0	
Soil-to-plant concentration factor (herbaceous fruit)		0	
Soil-to-plant concentration factor (shrub fruit)		0	
Soil-to-plant concentration factor (tree fruit)		0	
Soil-to-dust transport factor (g g-1 DW)	-	0.5	EA, 2009b
Relative bioavailability soil	-	1	Conservative assumption made that bioavailability of chromium (VI) in soil and dust is the same as bioavailability of chromium (VI) in critical toxicological studies used to derive the LLTC
Relative bioavailability dust	-	1	

The key contaminant specific parameter values used for derivation of the provisional C4SLs for chromium (VI) are discussed below.

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 and is important here due to the significance of this exposure pathway for chromium (VI). 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, 2009a). This means that the concentration of contaminant in respirable dust is assumed to be 50% of the concentration of contaminant in outdoor soil.

The CLEA default value of 0.5.$g.g^{-1}$ DW is used here for the derivation of the chromium (VI) pC4SLs. Falerious *et al*. (1992) measured airborne concentrations of chromium at

unpaved and partially paved commercial sites with significant chromium (VI) soil contamination. They reported indoor chromate levels to be similar to those found at reference sites (residential) without chromate soil contamination, and between a factor of two and four lower than ambient outdoor concentrations. This would suggest that the default soil to dust transport factor selected for derivation of the C4SL is likely conservative for the commercial land-use.

Soil to plant concentration factors

Evidence suggests that hexavalent chromium is rapidly converted to chromium (III) forms within root cells or within the xylem sap (Zayed *et al*., 1998; Kabata-Pendias and Pendias, 2001; Juneja and Prakash, 2005; Shanker *et al*., 2005; IPCS, 2009). EVM (2003) also stated that chromium "in foods or supplements are in the trivalent form". Soil to plant concentration factors are therefore set to zero within the CLEA model.

Cornelis *et al*. (2005) noted that the analytical speciation of chromium in food is only rarely carried out and that the lifetime of soluble chromates in food would be expected to be short (from minutes to a few hours) because of the reductive potential of organic materials. It is therefore considered reasonable to assume that the concentrations of hexavalent chromium in the edible fractions of fruit and vegetables are effectively zero, with the exception of entrained contaminated soil and dust particles.

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 LLTC). There is little data available on the RBA of chromium (VI) and it is considered appropriately conservative to assume an RBA of 100% for the derivation of C4SLs.

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 3.2.

Table 3.2: Parameters modelled probabilistically for chromium (VI)

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 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

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 3.3 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 3.3 PDF attributes for contaminant specific parameters for Monte Carlo analysis for chromium (VI)

Parameter	Units	Basis of PDF	PDF attributes
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 CHROMIUM (VI)

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 chromium (VI), derived from the deterministic CLEA modelling using the proposed LLTC values, are presented in Table 4.1 below, along with published generic assessment criteria (GACs).

Table 4.1: Provisional C4SLs and GACs

Exposure parameters	HCV or LLTC µg kg^{-1}(bw) day^{-1}		pC4SLs ($mg.kg^{-1}$)					
			Residential		Allot-ments	Commercial	POS_{resi}	POS_{park}
	Oral	Inhal	With home grown prod.	Without home grown prod.				
Current GAC (LQM; Nathanail *et al*., 2009))	1.0	1.0 x10^{-4}	4.3	N/A	2.1	35	N/A	N/A
pC4SL with exposure changes only [1]	1.0	1.0 x10^{-4}	6.1	6.1	120	33	7.7	220
pC4SL with LLTC but exposure parameters as SR3 [2,3]	0.44	1.5 x10^{-4} - 3.4 x10^{-4} [3]	14	14	170	52	N/A	N/A
pC4SL with changes in exposure and LLTC	0.44	1.5 x10^{-4} - 3.4 x10^{-4} [3]	21	21	170	49	21	250

1. Parameters as described in Section 3 (including assumed absence of plant uptake) and include non integration of assessment criteria
2. Chemical specific parameters as Section 3. Non contaminant specific parameters as SR3
3. Note age specific adjustments used for residential and POS land-uses as shown in Table 3.5

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.l	Without home grown prod.				
direct soil & dust ingestion	98	99	79	98	99	99
sum of consumption of homegrown produce and attached soil	0.89	0	18	0	0	0
dermal contact (indoor)	0.18	0.19	0	0.65	0.30	0
dermal contact (outdoor)	0.23	0.23	3.9	0.96	0.39	0.98
inhalation of dust (indoor)	0.22	0.22	0	0.66	0.34	0
inhalation of dust (outdoor)	0	0	0.03	0	0	0.030
inhalation of vapour (indoor)	0	0	0	0	0	0
inhalation of vapour (outdoor)	0	0	0	0	0	0

4.2 PROBABILITY OF EXCEEDING THE LLTC

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 are discussed in Section 4.3.

4.2.1 RESIDENTIAL LAND-USE

Table 4.1 shows that there is no difference between the pC4SLs for residential with and without consumption of homegrown produce land uses. This is because chromium (VI) is reduced to chromium (III) in plants and therefore the consumption of homegrown produce is not a contributing pathway for this contaminant (Section 4.1.2), although a minor

contribution of exposure is expected from ingestion of soil attached to vegetables (Table 4.2). The probabilistic modelling has been conducted for the residential with consumption of produce land-use but the results are equally applicable to the residential without consumption of homegrown produce land-use.

Figure 4.1 shows the RCFs of inhalation exposure (the key exposure route for chromium (VI)) for three alternate values of pC4SLs using alternative sets of exposure parameters. These are:

1. pC4SL = 14 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.44 μg kg^{-1} bw day^{-1} and an age class adjusted $LLTC_{inhal}$ of 3.4 x 10^{-4} μg kg^{-1} bw day^{-1} but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 21 mg kg^{-1}. This is the pC4SL derived using LLTC as above but with the proposed modifications to exposure modelling parameters described in Section 3.5.7 of the main report; and
3. pC4SL = 40 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 $LLTC_{inhal}$ (as a dashed line) along with estimate of average inhalation background exposure from non soil sources for comparison with the RCFs of average daily exposure. As discussed below, the probability of oral exposure exceeding the $LLTC_{oral}$ is negligible and so RCFs are not presented for oral and dermal exposure in Figure 4.1.

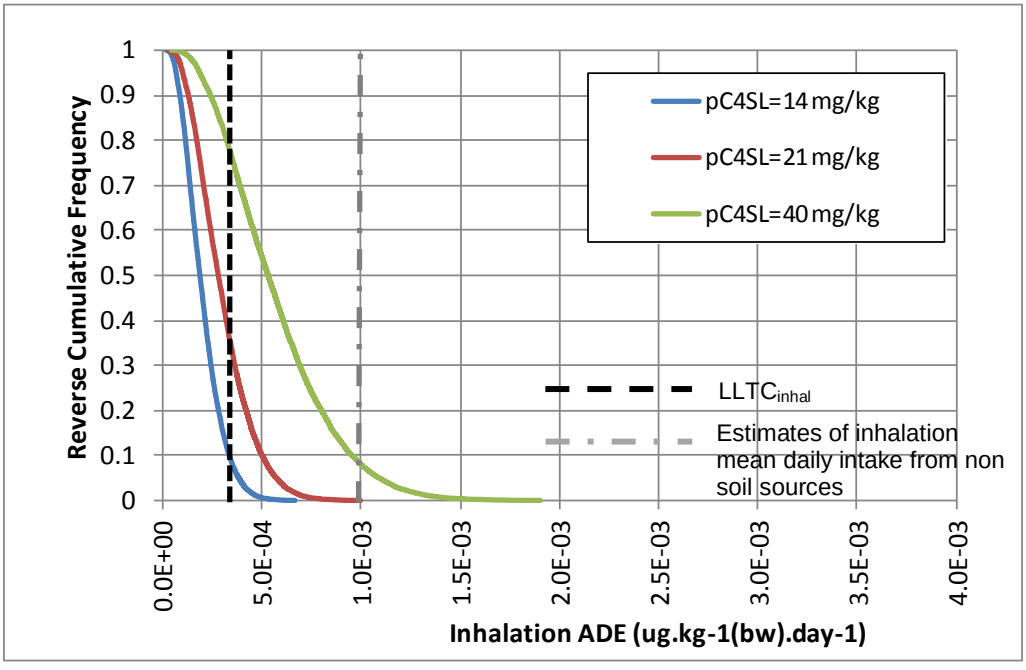


Figure 4.1: Reverse cumulative frequency graph of inhalation ADE for alternative values of pC4SL for chromium (VI) for residential (with consumption of homegrown produce) land-use

Figure 4.1 can be used to estimate the probability that exposure to a random individual within the critical receptor group would exceed the $LLTC_{inhal}$ 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 9% for a soil concentration of 14 mg kg^{-1}, increasing to 34% and 77% for soil concentrations of 21 and 40 mg kg^{-1}, respectively. The probability of inhalation exposure exceeding 10 times the LLTC (i.e. 3.4 x 10^{-3} ug.kg(bw)$^{-1}$.day^{-1}) is negligible. 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 chromium (VI) for residential land-use inhalation exposure from soils at the alternative pC4SL is expected to typically be significantly below background exposure from non soil sources (estimated from 2002-2011 mean UK air concentration of ~0.005 ug.m^{-3} (NPL, 2012) multiplied by assumed receptor respiration rate and based on the assumption that 25% of average concentrations of total chromium in air is in the form of hexavalent chromium).

Figure 4.2 presents the probability of exceedence graphs for residential land-use. This graph shows two curves: the probability that the oral and dermal exposure from soil exceeds the $LLTC_{oral}$ and the probability that exposure from soil via the inhalation route alone exceeds the $LLTC_{inhal}$. Like Figure 4.1, this graph can also 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 oral and dermal exposure exceeding the $LLTC_{oral}$ is negligible and that inhalation of chromium (VI) in dusts is the pathway of concern for residential land-use.

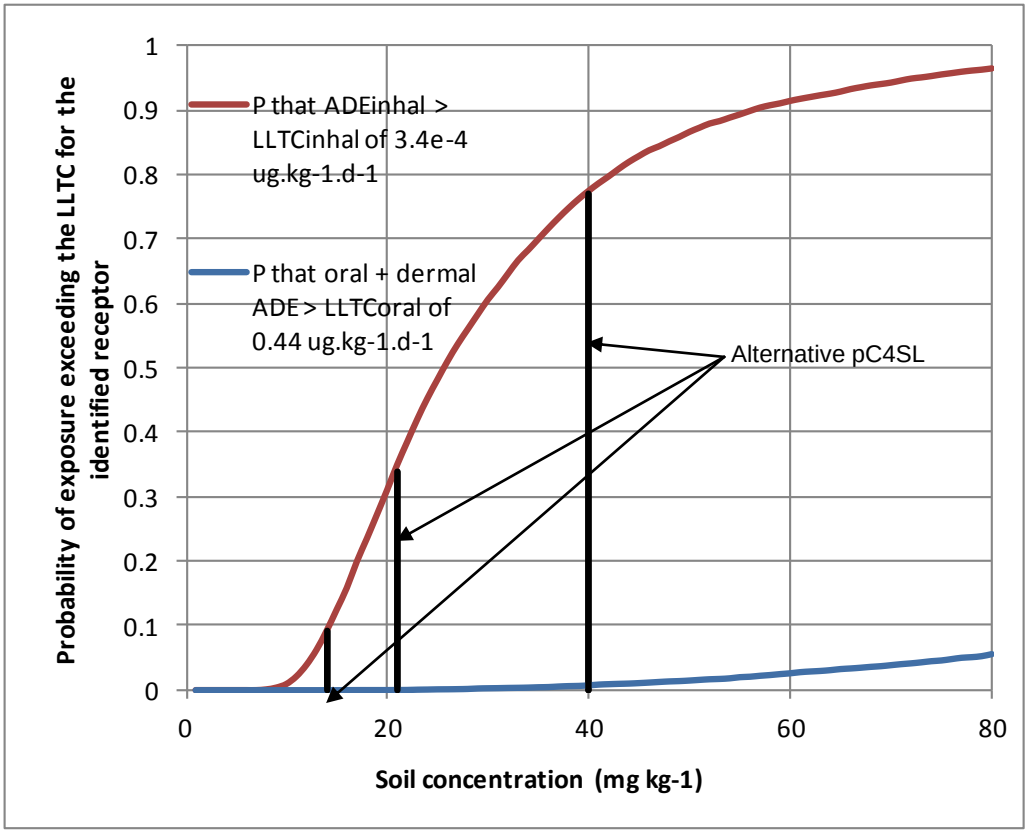


Figure 4.2: Probability of exposure exceeding the LLTCs with alternative values of pC4SL for chromium for residential (with consumption of homegrown produce) land-use

4.2.2 ALLOTMENTS LAND-USE

Figure 4.3 shows the RCFs of total exposure for three alternate values of pC4SL using alternative sets of exposure parameters. These are:

1. pC4SL = 170 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.44 μg kg^{-1} bw day^{-1} and an age class adjusted $LLTC_{inhal}$ of 3.4 x 10^{-4} μg kg^{-1} bw day^{-1} but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 170 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 (application of changes to exposure parameters makes a negligible difference due to the absence of the consumption of homegrown produce pathway due to the reduction of chromium (VI) to chromium (III)); and
3. pC4SL = 350 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 4.3 also shows the $LLTC_{oral}$ and estimate of average oral background exposure from non soil sources for comparison with the RCFs of average daily exposure. Figure 4.4 shows the relationship between the probability of exceedence of the LLTC and soil concentration. For allotments land-use, the probability of oral and dermal exposure exceeding the $LLTC_{oral}$ is greater than the probability of inhalation exposure exceeding the $LLTC_{inhal}$ and so RCFs are not presented for inhalation exposure in Figure 4.3.

Figures 4.3 and 4.4 show that the probability that exposure to a random individual from the critical receptor group would exceed the LLTC is 1% for a soil concentration of 170 mg kg^{-1}, increasing to 10 for a soil concentration of 350 mg kg^{-1}. The probability of oral/dermal exposure exceeding 10 times the LLTC (i.e. 4.4 $ug.kg(bw)^{-1}.day^{-1}$) is negligible. 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.

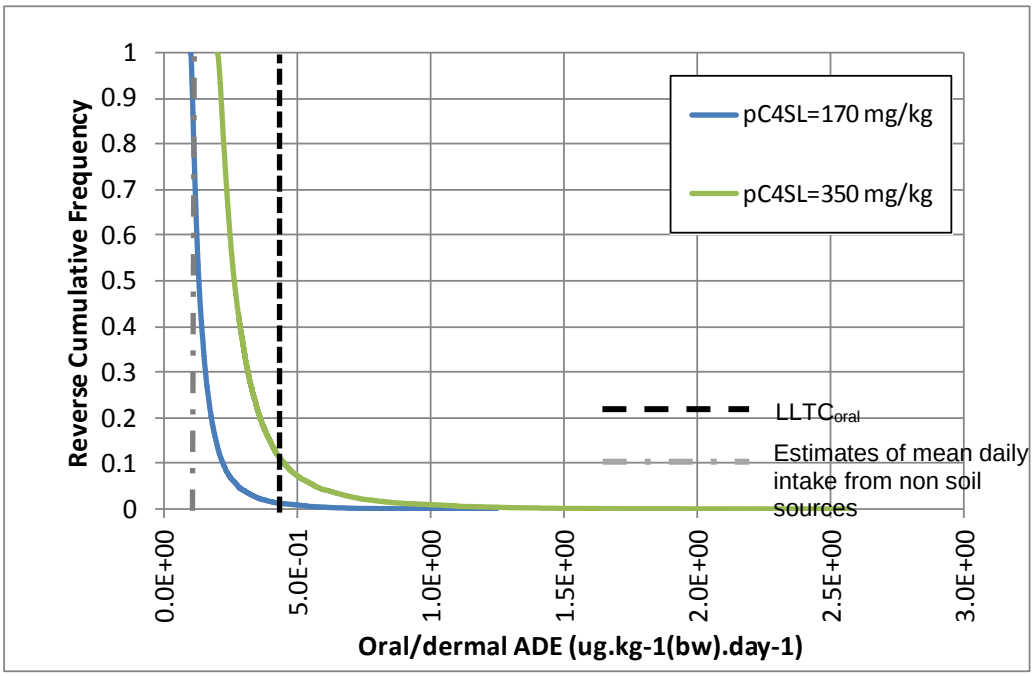


Figure 4.3: Reverse cumulative frequency graph of ADE for alternative values of pC4SL for chromium (VI) for allotments land-use

Figure 4.3 can also be used to assess the relative importance of background exposure to exposure from soils. In the case of chromium (VI) for allotments land-use inhalation exposure from soils at the alternative pC4SL is expected to typically be significantly below background exposure from non soil sources.

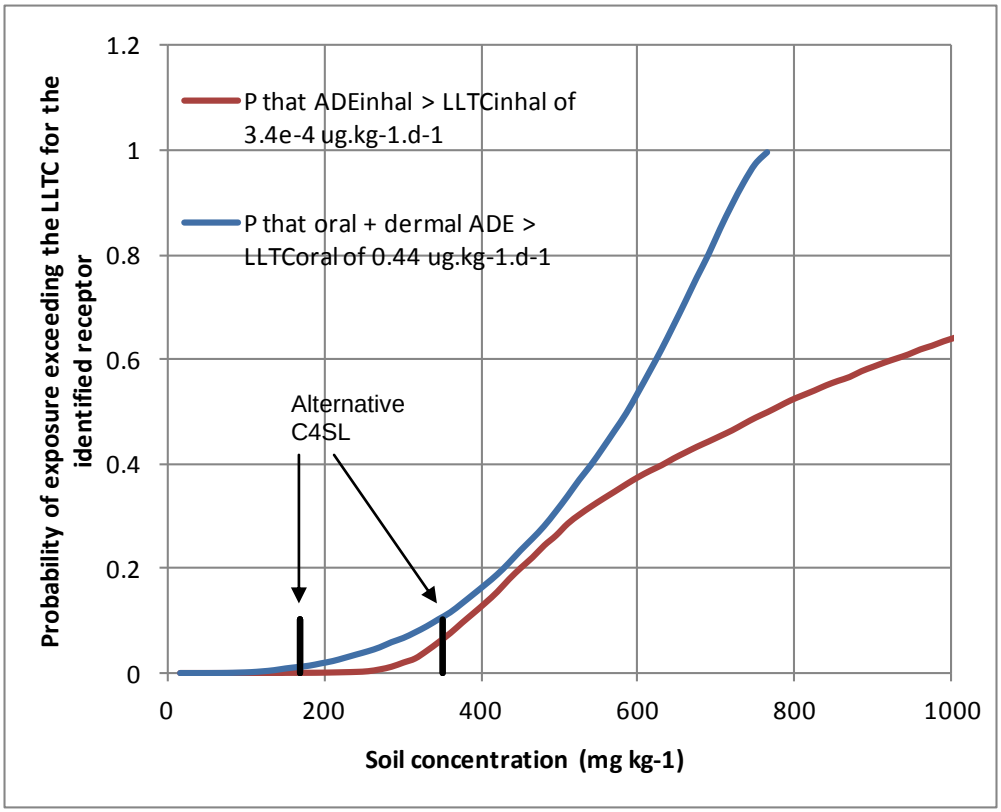


Figure 4.4: Probability of exposure exceeding the LLTC with alternative values of pC4SL for chromium (VI) for allotments land-use

4.2.3 COMMERCIAL LAND-USE

Figure 4.5 shows the RCFs of total exposure for three alternate values of pC4SL using alternative sets of exposure parameters. These are:

1. pC4SL = 52 mg kg^{-1}. This is the pC4SL derived using an $LLTC_{oral}$ of 0.44 μg kg^{-1} bw day^{-1} and an $LLTC_{inhal}$ of 1.5 x 10^{-4} 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 = 82 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}.

Figure 4.5 also shows the $LLTC_{inhal}$ and estimated average inhalation background exposure from non soil sources for comparison with the RCFs of average daily exposure. Figure 4.6 shows the relationship between the probability of exceedence of the LLTC and soil concentration. As for residential and allotments land-uses, the probabilities of oral exposure exceeding the $LLTC_{oral}$ are negligible.

Figures 4.5 and 4.6 show that the probability that inhalation exposure to a random individual from the critical receptor group would exceed the $LLTC_{inhal}$ is 47% for a soil

concentration of 52 mg kg^{-1}, decreasing to 40% for a soil concentration of 49 mg kg^{-1}. The probability of inhalation exposure exceeding the LLTC at a soil concentration of 82 $mg.kg^{-1}$ is 86%. The probability of inhalation exposure exceeding 10 times the LLTC (i.e. 1.5 x 10^{-3} $ug.kg(bw)^{-1}.day^{-1}$) is negligible. 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.

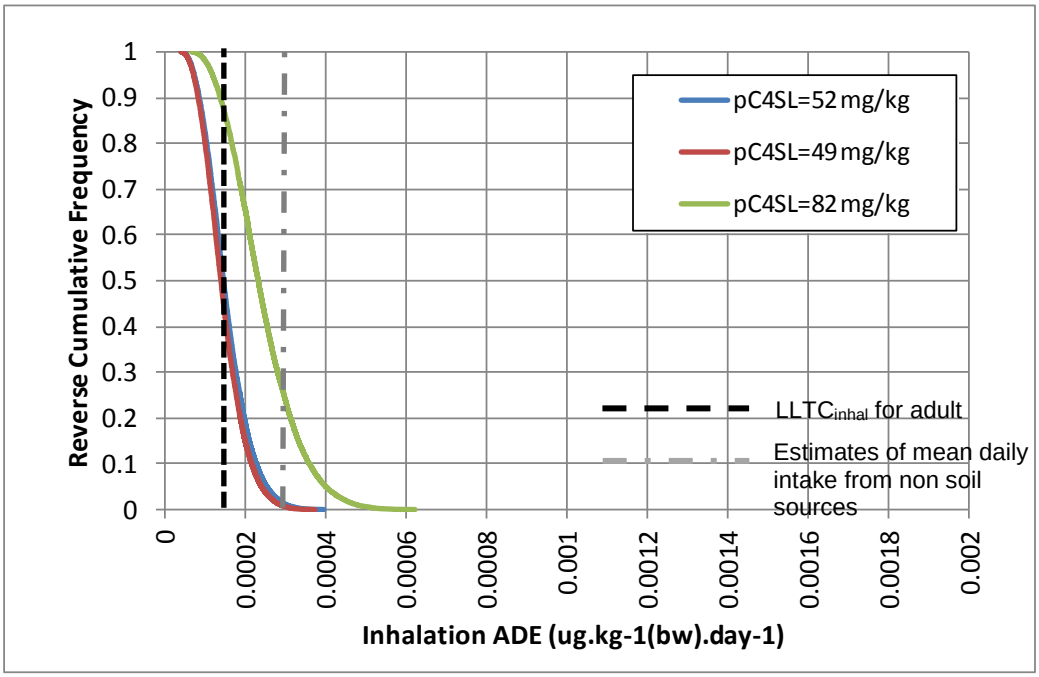


Figure 4.5: Reverse cumulative frequency graph of ADE for alternative values of pC4SL for chromium (VI) for commercial land-use

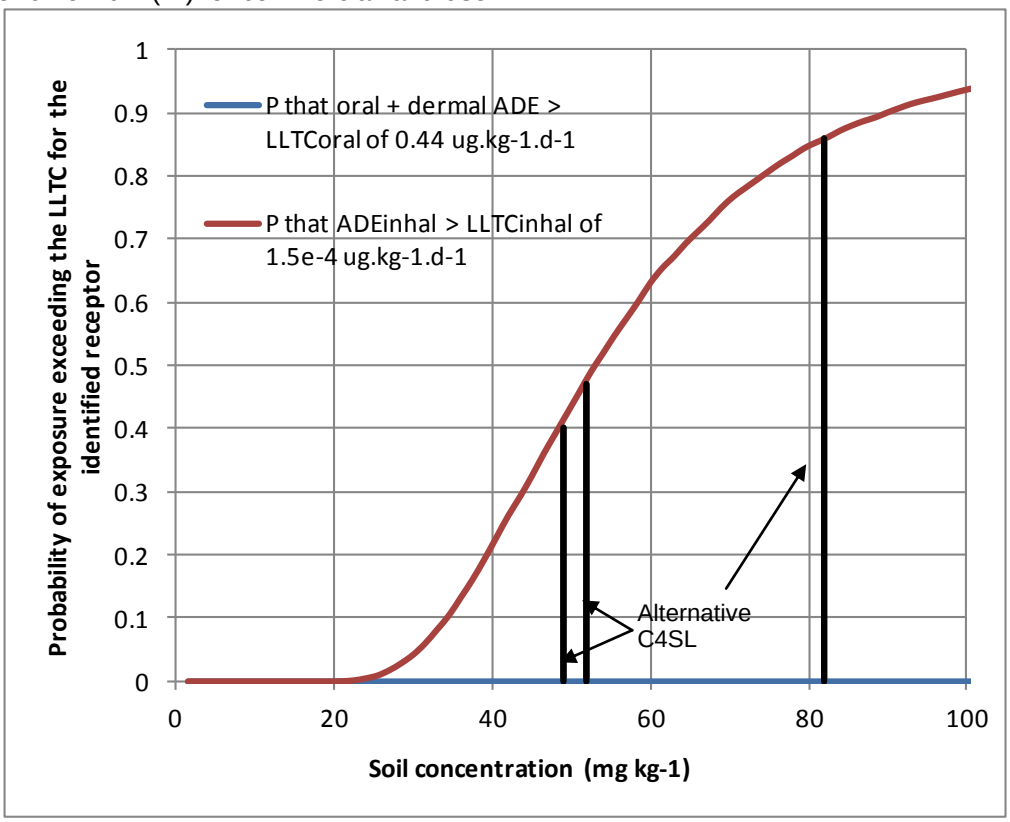


Figure 4.6: Probability of exposure exceeding the LLTC with alternative values of pC4SL for chromium (VI) for commercial land-use

Figure 4.5 can also be used to assess the relative importance of background exposure to exposure from soils. In the case of chromium (VI) for commercial land-use inhalation exposure from soils at the alternative pC4SLs is expected to typically be significantly below background exposure from non soil sources.

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 chromium (VI) 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 LLTC 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 4.7. 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.

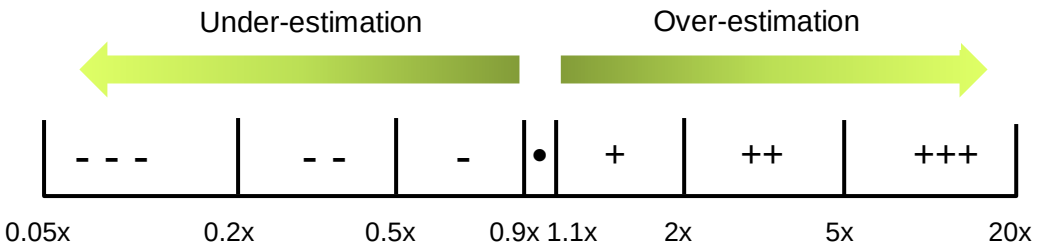


Figure 4.7: Key for symbols used to express judgements about the magnitude of potential over- or under-estimation of the LLTC and exposure in Tables 5.3 and 5.4 respectively.

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 the toxicology evaluation (see Figure 4.7 for key to symbols)

Source of Uncertainty	Evaluation of uncertainty
ORAL LLTC	
Choice of pivotal study: the NTP study in mice and rats was chosen as the pivotal study by ATSDR, WHO and USEPA. Extrapolation from animals to humans inevitably has some uncertainty that is accounted for by applying the appropriate UFs. There are an adequate number of high quality studies that have been carried out to investigate the oral toxicity of chromium (VI) hence reducing uncertainty over the quality of the data.	**-/+**
Choice of data and endpoint from pivotal study: in the critical study chromium (VI) was administered to mice and rats via drinking water for 2 years. Toxic effects were seen in the gastrointestinal tract, liver, and reproductive organs, the form being the most sensitive target organs. We chose to use data for neoplasms of the small intestine as the critical endpoint. The good quality data and reproducible toxic endpoint reduces uncertainty. The lack of evidence that exposure of humans to Cr(VI) causes neopasia adds additional uncertainty.	**-/+**
Interspecies uncertainties: the critical effect and the magnitude of a toxicological effect are extrapolated from animals to humans, introducing some uncertainty. Species differences in the reduction of chromium (VI) have been reported, humans reducing more chromium (VI) to Cr(III) than rats therefore have the ability to 'detoxify' Cr(VI) more efficiently. WHO concluded that the metabolism of chromium (VI) in rodent systems may not readily be extrapolated to humans. Therefore due to the large number of uncertainties in the toxicokinetics of chromium (VI) between animals and humans, the default factor is 10 is proposed. However, it remains possible that a lower factor could be used as humans detoxify Cr(VI) quicker, in which case the $LLTC_{oral}$ would be underestimated.	**-**
Intraspecies uncertainties: variability exists in terms of absorption and elimination of chromium (VI) in individuals and may reflect differences that influence gastric reduction, such as the period of time between meals, gastric contents or different genetic capacities for Cr(VI) reduction. Human variability may actually be high or lower than the default 10-fold UF, but data needed to show the potential differences are unavailable.	**-/+**
Choice of BMD model: the choice of the BMD model does not lead to significant uncertainties as the selected BMDL are within the range of the experimental data (USEPA 2010). Other models that were not used may fit the data better although the models that were used gave similar BMDL values.	**●**
Choice of BMD or BMDL: the choice of a BMD or BMDL has an influence on the $LLTC_{oral}$ value. The lower confidence limit tends to be conservative and may lead to over estimation of the actual level of risk (NHMRC 1999). In this study the BMDL value is only marginally lower than the BMD (1.2 and 2.2 mg kg^{-1} bw day^{-1}, respectively). We chose to use the BMD as the POD hence the $LLTC_{oral}$ of 0.44 μg kg^{-1} bw day^{-1} could be considered slightly overestimated.	**●/+**
Overall evaluation of uncertainty for $LLTC_{oral}$: Although the $LLTC_{oral}$ of 0.44 μg kg^{-1} bw d^{-1} is less conservative than other values examined, it still contains a number of conservative elements (tending to underestimate the LLTC). The largest uncertainty relates to intraspecies and intraspecies variability, for which the factor of 10 is widely accepted in regulatory risk assessment. Overall it is judged that the toxicological assessment is more likely to be conservative (underestimated LLTC, hence overestimating risk) than unconservative. Therefore the proposed $LLTC_{oral}$ is therefore considered a reasonable basis for setting the C4SL.	
INHALATION LLTC	
Choice of pivotal study: There are relatively few studies that have been carried out to assess the carcinogenicity of chromium (VI) via inhalation. In	**-/+**

Source of Uncertainty	Evaluation of uncertainty
the studies used by all authoritative bodies (Gibb *et al* 2000; Lindberg and Hedenstierna 1982), the exposure assessment introduces uncertainty. In addition, due to the lack of comparative data, the use of chromium (VI) salts adds additional uncertainty as the Cr(VI) salts may not be representative of all Cr(VI) compounds (USEPA 2010).	
Basis of LLTC: the $LLTC_{inhal}$ is based on an air concentration that would lead to an excess lifetime cancer risk 1 in 50,000 so is double the minimal risk value. A concentration that led to a ELCR of 1 in 10,000 could also be proposed implying that the $LLTC_{inhal}$ may be underestimated.	**-/+**
ELCR modelling: the linear relative rate Poisson regression model was used. Other models could increase or decrease the POD.	**-/+**
Overall evaluation of uncertainty for $LLTC_{inhal}$: the proposed $LLTC_{inhal}$ is based on the Air concentration that corresponds to a ELCR of 1 in 50,000. This is higher than the ELCR that would normally be associated with minimal risk (1 in 100,000) but given that the LLTC represents low risk it is considered a suitable basis for setting the C4SL.	

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).

The above qualitative evaluation of uncertainty has indicated that the LLTCs are likely to be conservative.

4.3.2 EXPOSURE MODELLING

As shown in Table 4.2, the principle exposure pathway for chromium (VI) for the residential and allotments land-use is direct ingestion of soil and soil-derived dust. However, the inhalation of indoor dust makes a very small contribution to total exposure but is the most significant risk driver for the residential and commercial land use scenarios because of the lower LLTC for inhalation health effects. For the allotments land–use there is also a significant contribution from ingestion of soil attached to food; consumption of homegrown produce itself is not considered as chromium (VI) is reduced to chromium (III) within plants. The probabilistic modelling has considered variation in soil ingestion rates and the dust loading and soil to dust transport factors which are the key parameters in assessing these exposure pathways. The remaining 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 4.7 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	● / +

Source of Uncertainty	Evaluation of uncertainty
locations.	
Relative bioavailability via inhalation exposure pathway. No information was identified on the bioavailability of chromium (VI) in soil relative to the form in the toxicological and epidemiological studies on which the LLTCinhal is based. The $LLTC_{inhal}$ is based on epidemiological studies of workers exposed to chromate salts and it is considered probable that chromium (VI) in soil would exist in a less bioavailable form.	● / +
Dust loading factor. The PDF assumes a triangular distribution with min, max and mode values based on PM10 estimates for commercial properties cited in the literature. There is limited data available on which to base the PDF but the exposure estimates are unlikely to be under- or over-estimates by more than a factor of x0.5 to x2	- / +
Soil-to-dust transport factor. The PDF assumes a triangular distribution with min, max and mode values based on soil to dust estimates for mostly residential properties cited in the literature. It is possible that the PDF attributes used result in a slight over- or under-estimation of exposure	- / +

OVERALL EVALUATION OF UNCERTAINTY FOR RESIDENTIAL LAND-USE: Based on the above it is considered that the estimates of total exposure predicted by the probabilistic modelling are likely to be moderately conservative, particularly at specific locations where chromium (VI) may be present in soil in a less available form.

ALLOTMENTS LAND-USE	
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 it is considered likely that the estimates of total exposure predicted by the probabilistic modelling are likely to be slightly conservative but variation in these parameters will not have a large influence as exposure to Cr(VI) will only occur via soil attached to produce.

COMMERCIAL LAND-USE	
Relative bioavailability via oral and inhalation exposure pathways. No information was identified on the bioavailability of chromium (VI) in soil relative to the form in the toxicological and epidemiological studies on which the LLTCs are based. However, it is considered unlikely that chromium (VI) in soil would exist in a more bioavailable form.	● / +
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	+ / ++

Source of Uncertainty	Evaluation of uncertainty
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.	
Dust loading factor. The PDF assumes a triangular distribution with min, max and mode values based on PM10 estimates for commercial properties cited in the literature. There is limited data available on which to base the PDF but the exposure estimates are unlikely to be under- or over-estimates by more than a factor of x0.5 to x2	**-/+**
Soil-to-dust transport factor. The PDF assumes a triangular distribution with min, max and mode values based on soil to dust estimates for mostly residential properties cited in the literature. The mode is based on the CLEA default of 0.5. This implies that 50% of the dust within the commercial property is derived from outdoor soil at the property. Most commercial properties have little exposed soil outdoors and it is therefore doubtful that outdoor soil contributes significantly to indoor dust in the majority of cases. This is confirmed by the work of Falerious *et al* (1992). The PDF is therefore likely to over-estimate inhalation exposure indoors by a factor of x10 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 likely to be highly conservative, particularly at specific locations.	

Note that the implications of the overall uncertainty for risk (and therefore C4SLs) can be considered by looking at the RCF graphs in Section 4.2: over-and underestimation of the exposure would imply that the RCF should be shifted to the left or right, respectively.

The above qualitative evaluation of uncertainty has indicated that the exposure estimates derived by the probabilistic modelling are likely to be over-estimates.

4.4 OTHER CONSIDERATIONS

Other considerations that are relevant when setting the C4SLs for chromium (VI) include the following:

- The British Geological Survey (BGS) has not derived normal background concentrations (NBCs) for hexavalent chromium. As indicated above, chromium (VI) is not expected to occur in soil away from a source.
- As indicated above, background chromium (VI) inhalation exposure is thought to be greater than both the $LLTC_{inhal}$ and the modelled inhalation exposure at the C4SLs. 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)."*

- Since chromium (VI) is a known human carcinogen (see above), it might be necessary to apply the "As Low as Reasonably Practicable" (ALARP) principle in relation to its remediation at specific sites (see EA, 2009a; 2009b for details). The principle of ALARP automatically applies to the regulation and management of non-threshold chemicals in the UK. It is important to note that ALARP remains the overriding principle even when a margin of exposure or minimal risk level or LLTC suggests there is a minimal/low concern for human health. What is

considered practicable is a remediation/risk management decision, and could be lower or higher than the scientific values derived.

- There are no known epidemiological studies directly linking chromium (VI) in soil with adverse health effects (Fera, 2009). The Fera report describes how extensive studies carried out in the late 1990s of an area near Glasgow contaminated by the former activities of a chromium-processing site found no relationship between cases of leukaemia / congenital malformations and distance of residence to the site (chromium (VI) concentrations were up to 450 mg/kg, 2-3 km away). The self-reported health of a group of individuals living in an area contaminated by chromium (chromium group) was also compared with that of a group living in an uncontaminated area (control group), with little difference being found in health scores between the two groups (although health scores for the chromium group were significantly worse across all dimensions for those who believed that chromium adversely affected health).
- As detailed in Section 6.3 of the main report, C4SLs have been derived on the basis of chronic exposure and risks to human health. They have not been specifically derived to be protective of acute risks (e.g. due to one-off ingestion of a significant amount of soil by a young child). It is noted here that the C4SLs derived for allotments and POS_{park} are significantly higher than values for the residential land use where inhalation exposure (to airborne dust) is the most important exposure pathway in deriving the C4SL. Therefore, further consideration of the possibility of acute risk due to ingestion of soil at the chromium (VI) concentrations indicated by the allotment and POS_{park} C4SLs may be necessary.
- Step 6c of the framework used to derive these C4SLs highlights the need to consider other factors such as thresholds for phytotoxicity, which may be an issue at the soil concentrations of chromium (VI) derived as C4SLs for allotments and POS_{park}. The derivation of phytotoxicity thresholds is beyond the remit of this project but the USEPA did not identify any suitable plant toxicity data for chromium in their derivation of ecological soil screening levels (USEPA, 2008).
- Section 2.4 noted that prolonged skin exposure to soluble chromate might result in allergic contact dermatitis in sensitised individuals. This effect is not explicitly considered in the derivation of the C4SLs and is addressed using the screening methodology proposed by Horowitz and Finley (1994).

Horowitz and Finley (1994) proposed a screening methodology for dermal contact allergens. It uses data from chemical skin patch tests, soil-to-skin adherence factors and knowledge of leaching potential from soil to derive a screening level soil concentration for health-based risk assessment. The equation below is based on their proposals:

$$GAC_{contact} = \frac{P}{AF} x \frac{1}{LF} x 1000000\ mg.kg^{-1}$$

where:

$GAC_{contact}$	= soil screening level for dermal contact with skin allergen (mg kg^{-1} DW)
P	= patch test threshold for no effect level following exposure to allergen (mg allergen cm^{-2} skin)
AF	= soil-to-skin adherence factor (mg soil cm^{-2} skin)
LF	= leaching factor from soil to sweat (mass fraction).

As detailed in Section 2.4, Hansen *et al*. (2003) concluded that a minimum elicitation threshold for 10 per cent of the sensitised individuals ($MET_{10\%}$) was 0.03 µg Cr(VI) cm^{-2} of skin and this value has been assumed for the patch test threshold (P). AF values of 0.1 mg cm^{-2} and 1 mg cm^{-2} are taken from the land use scenario defaults described for residential and allotment land uses in Section 3.5.3.3 of the main report. Finley and Paustenbach (1997) observed a maximum chromate leachability of 0.1 per cent from COPR contaminated soils using human sweat. An LF value of 0.01 has been assumed based on this study but with an additional uncertainty factor for more soluble chromate in other soils and wastes. The calculated $GAC_{contact}$ values for the residential/POS and allotment land use scenarios are 30,000 and 3,000 mg kg^{-1} DW, respectively. pC4SLs in

this report are therefore also considered to be protective of elicitation of contact dermatitis from hexavalent chromium in soil.

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 chromium (VI). These soil concentrations are the pC4SLs.

A range of pC4SLs have been derived for chromium (VI) 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 Chromium (VI)

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)	6.1	14	21
Residential (without consumption of homegrown produce)	6.1	14	21
Allotments	120	170	170
Commercial	33	52	49
POS_{resi}	7.7	NA	21
POS_{park}	220	NA	250

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 may have a bearing on the final choice of numbers. For chromium (VI), these take the form of ALARP considerations, a recognition that background soil concentrations away from sources are negligible, estimates of background human exposure levels and a review of epidemiological evidence of health impacts from

chromium (VI) 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 chromium (VI) since: 1) final C4SLs should be set by “relevant authorities” (e.g., 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, 2009a) 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, 2009b), and the reader is referred to that document for the same reasons.

As described in the main report, the finalised C4SLs can be used in a broadly similar manner to that described for SGVs in the Environment Agency’s “Using Soil Guideline Values” document (EA, 2009c). 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.

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APPENDIX G1

HUMAN TOXICOLOGICAL DATA SHEET FOR CHROMIUM (VI)