APPENDIX F

PROVISIONAL C4SLS FOR CADMIUM

CONTENTS

1. INTRODUCTION 6

1.1 BACKGROUND INFORMATION ON CADMIUM 6

2. LOW LEVEL OF TOXICOLOGICAL CONCERN FOR CADMIUM 8

2.1 ORAL ROUTE 8

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 8

2.1.2 FLOWCHART ELEMENT 2: REVIEW THE SCIENTIFIC BASIS OF EACH HBGV. CHOOSE THE PIVOTAL STUDY 9

2.1.3 FLOWCHART ELEMENT 6: ARE THERE ADEQUATE DOSE-EFFECTS DATA FOR THE CHOSEN PIVOTAL STUDY – HUMAN DATA? 11

2.1.4 FLOWCHART ELEMENT 6b: PERFORM BMD MODELLING 12

2.1.5 FLOWCHART ELEMENT 4: DOES THE CRITICAL ENDPOINT EXHIBIT A THRESHOLD? 13

2.1.6 FLOWCHART ELEMENT 4b: DERIVE A CHEMICAL-SPECIFIC ASSESSMENT FACTOR USING SCIENTIFIC EVIDENCE 13

2.1.7 FLOWCHART ELEMENT 5b: CALCULATE THE LLTC FOR THRESHOLDED CHEMICALS 14

2.1.8 TOXICOKINETIC MODELLING TO TRANSLATE URINARY CADMIUM LEVELS TO ORAL INTAKES 14

2.1.9 FLOWCHART ELEMENT 7: ASSESS LLTC FOR CADMIUM 15

2.2 INHALATION ROUTE 16

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 16

2.2.2 FLOWCHART ELEMENT 2: REVIEW THE SCIENTIFIC BASIS OF EACH HBGV. CHOOSE THE PIVOTAL STUDY 17

2.2.3 FLOWCHART ELEMENT 6: ARE THERE ADEQUATE DOSE-EFFECTS DATA FOR THE CHOSEN PIVOTAL STUDY – HUMAN DATA? 18

2.2.4 FLOWCHART ELEMENT 6b: PERFORM BMD MODELLING 18

2.2.5 FLOWCHART ELEMENT 4: DOES THE CRITICAL ENDPOINT EXHIBIT A THRESHOLD? 20

2.2.6 FLOWCHART ELEMENT 4b: DERIVE A CHEMICAL-SPECIFIC ASSESSMENT FACTOR USING SCIENTIFIC EVIDENCE 20

2.2.7 FLOWCHART ELEMENT 5b: CALCULATE THE LLTC FOR THRESHOLDED CHEMICALS 20

2.2.8 FLOWCHART ELEMENT 7: ASSESS LLTC FOR CADMIUM 20

2.3 DERMAL ROUTE 21

2.4 CARCINOGENICITY OF CADMIUM 21

2.5 OTHER CONSIDERATIONS: LIFETIME AVERAGING 21

3. EXPOSURE MODELLING FOR CADMIUM 23

3.1 DETERMINISTIC MODELLING 23

3.2 PROBABILISTIC MODELLING 25
4. POSSIBLE C4SLs FOR CADMIUM 28
4.1 PROVISIONAL C4SLS 28
4.2 QUANTITATIVE APPRAISAL OF UNCERTAINTY 29
4.2.1 RESIDENTIAL (WITH CONSUMPTION OF HOMEGROWN PRODUCE) LAND-USE 30
4.2.2 RESIDENTIAL (WITHOUT CONSUMPTION OF HOMEGROWN PRODUCE) LAND-USE 32
4.2.3 ALLOTMENTS LAND-USE 33
4.2.4 COMMERCIAL LAND-USE 34
4.3 QUALITATIVE APPRAISAL OF UNCERTAINTY 36
4.3.1 TOXICOLOGICAL ASSESSMENT 37
4.3.2 EXPOSURE MODELLING 38
4.4 OTHER CONSIDERATIONS 41
4.5 SUMMARY AND CONCLUSIONS 43
5. REFERENCES 46

APPENDICES

Appendix F1 - Human Toxicological Data Sheet for Cadmium

Appendix F2 - Reference List of Publications used by EFSA (2009) For Benchmark Dose Modelling Of β2 Microglobulin

Appendix F3 - Reference List of Publications used by ATSDR(2012) for benchmark dose modelling of renal effects

FIGURES

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

Figure 2.2: Outline of stepwise process in deriving an intake value for cadmium

Figure 2.3: Cumulative population distribution of daily cadmium exposure considering different percentiles to calculate AF

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

Figure 2.5: Correlation of urinary cadmium concentrations and age

Figure 4.1: Reverse cumulative frequency graph of oral and dermal ADE combined for alternative values of pC4SL for cadmium for residential (with consumption of homegrown produce) land-use

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

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

Figure 4.4: Reverse cumulative frequency graph of oral and dermal ADE combined for alternative values of pC4SLs for cadmium for allotments land-use

Figure 4.5: Probability of exposure exceeding LLTCoral with alternative values of pC4SLs for cadmium for allotments land-use

Figure 4.6: Reverse cumulative frequency graph of ADE for oral/dermal exposure for alternative values of pC4SL for cadmium for commercial land-use

Figure 4.7: Reverse cumulative frequency graph of ADE for inhalation exposure for alternative values of pC4SL for cadmium for commercial land-use

Figure 4.8: Probability of exposure exceeding LLTC with alternative values of pC4SLs for cadmium for commercial land-use

Figure 4.9: Key for symbols used to express judgements about the magnitude of potential over- or under-estimation of the LLTC and exposure in Tables 4.3 and 4.4 respectively.

Figure 4.10: Probability of exposure exceeding LLTC for cadmium for allotments land-use with alternative values for produce consumption rate.

Figure 4.11: Kriged concentrations of soil pH in uppermost 15 cm of soil (Emmett *et al*. 2010).

TABLES

Table 2.1: BMD and BMDL modelling for the total and sub-populations

Table 2.2: The choice of BMD values that could act as PODs in the derivation of a toxicology-based LLTC for C4SL determination

Table 2.3: Adjustment factor (AF), reference point (RF) and tolerable daily intake (TDI) as presented by EFSA

Table 2.4: Estimates of the UCD_{10} and cadmium intake from environmental exposure dose-response studies

Table 3.1: Contaminant specific parameter values used for derivation of provisional C4SLs for cadmium

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

Table 3.3: Parameters modelled probabilistically for cadmium

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

Table 4.1: Provisional C4SLs and SGVs

Table 4.2: Relative contributions of exposure pathways to overall exposure

Table 4.3: Qualitative appraisal of key residual uncertainties in toxicology evaluation

Table 4.4: Qualitative appraisal of key residual uncertainties in exposure modelling not captured by probabilistic modelling

Table 4.5: pC4SLs for cadmium

1. INTRODUCTION

This appendix presents provisional Category 4 Screening Levels (pC4SLs) for cadmium based on the methodology described in Section 5 of the main report. Section 1.1 provides brief background information on cadmium, 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 (eg, Defra).

1.1 BACKGROUND INFORMATION ON CADMIUM

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

- In its elemental form, cadmium is a silver-white coloured, lustrous metal that can be easily cut by a knife at room temperature. Cadmium metal will slowly oxidise in moist air to form cadmium oxide, which is a greenish-yellow, brown through red to black crystalline solid or powder.
- Cadmium has a relatively low crustal abundance, although it does occur ubiquitously in rocks and soils. It is found rarely in its elemental form, with greenockite (CdS), octavite (CdSe), and monteponite (CdO) being its principal minerals. Cadmium is often found in association with zinc-bearing and zinc-bearing lead ores, which are the main source of cadmium production.
- Cadmium has a similar chemistry to zinc with a strong affinity for sulphur. Its compounds almost exclusively involve the +2 oxidation state and may be highly coloured. Cadmium forms simple salts with oxygen, sulphur and many common anions including chloride, nitrate and carbonate. In aqueous solution, cadmium often forms simple hydrated hxdroxyl ions such as $[Cd(OH)(H_2O)_x]^+$ it also has an appreciable coordination chemistry with ligands including halides, hydroxides, cyanides and nitrate, although the range is much less extensive than for other transition metals. Organocadmium compounds are rather reactive and unstable to both air and water, though they have been used to prepare ketones from acid chlorides.
- The primary commercial source of cadmium is as a by-product from the processing of zinc ores including sphalerite and smithsonite. Historically, cadmium metal was recovered from the smelting of zinc ores by fractional distillation under reducing conditions to increase its purity. The current practice in most European countries involves the electrolytic treatment of cadmium sulphate solution collected during the production of zinc. Between 2000 and 2002, about 1,100 tonnes per year of cadmium was produced by European countries with a further 1,700 tonnes per year imported from outside the European Union.
- A small but important proportion of cadmium, primarily from batteries, is recycled. Cadmium oxide is an important industrial chemical, manufactured by the reaction of metal vapour with air. About 4,500 tonnes per year of cadmium oxide were produced across the European Union between 2000 and 2002.
- Cadmium metal, its alloys and compounds have been used in a variety of different industrial and consumer products, although most uses are now declining due to concerns about its toxicity. Currently, most cadmium is used in the production of nickel–cadmium batteries for industrial and commercial use although alternative products such as lithium ion batteries have eroded their market share in recent years. Cadmium is also still used as a semi-conductor and a photo-conductor in solar cells and other electronic devices. Cadmium has also been used in pigments for plastics, glass and ceramics, as a fungicide, in stabilisers for plastics including PVC, and in corrosion-resistant coatings on steel

and other non-ferrous metals; it has other minor applications for photography, photocopying, dyeing, calico printing, vacuum tube manufacture, galvanoplasty, lubricants, ice-nucleation agents, and in the manufacture of special mirrors.

- According to a mass balance analysis of production, imports and exports for the period 2000 to 2002, the European Union used around 2,300 tonnes of cadmium with some 80 per cent used to make Ni–Cd batteries, and the remaining 20 per cent used for pigments, stabilisers, and alloys/metal plating.

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

2. LOW LEVEL OF TOXICOLOGICAL CONCERN FOR CADMIUM

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 cadmium.

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 cadmium has also been completed, as shown in Appendix F1.

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 F1).

In 2009, the Environment Agency published a revised updated version of the TOX3 Toxicology Report for cadmium (Science report: SC050021/TOX3) (EA, 2009a). This was used as the start of the data search, and provides a thorough basis of the toxicology evaluation up to 2009. New information published between the years 2009-2012 was added to the data package.

The Environment Agency report (2009a) based the health criteria value (HCV) for cadmium on epidemiology data, from which a $BMDL_5$ for kidney toxicity was derived. This gave a HCV of 0.36 µg kg^{-1} bw day^{-1}.

There is a comparative wealth of toxicology information on cadmium. In 2013, the key cadmium toxicology evaluations come from three sources: the European Food Standards Authority evaluation (EFSA 2009a, 2009b, 2011a, 2011b), the World Health Organisation Joint Expert Committee on Foods Additives (JECFA) evaluation (JECFA, 2011) and the Toxicological Profile from the US Agency for Toxic Substances and Disease Registry (ATSDR) published in September 2012 (ATSDR 2012).

The EFSA (2009, 2011) evaluation focuses on the oral route of exposure to cadmium and covers a comprehensive meta-analysis and benchmark dose (BMD) modelling approach of 35 human epidemiology studies on the effects of cadmium on kidney and bone.

The JECFA (2011) evaluation also focuses on the oral route of exposure, uses the same dataset as the EFSA evaluation, but has included slightly different assumptions and interpretations in the modelling of the data that have been discussed in detail in EFSA (2011b). The main difference is the selection of a 'breakpoint' mean value of 5.4µg Cd g^{-1} creatinine in the JECFA evaluation vs BMD modelling and selection of a $BMDL_5$ of 4 µg Cd g^{-1} creatinine in the EFSA evaluation.

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

These reviews provide the best evidence that renal 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 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 renal effects overlap with the dose-response effects for bone-effects and cancer risk. Therefore, in setting the LLTC for cadmium, ALL three endpoints must be borne in mind (e.g. see Figure 2.1 below). 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. As described below, the 'choice' of LLTC for cadmium (based on the renal effects curve) also brings into consideration the evaluations for bone effects.

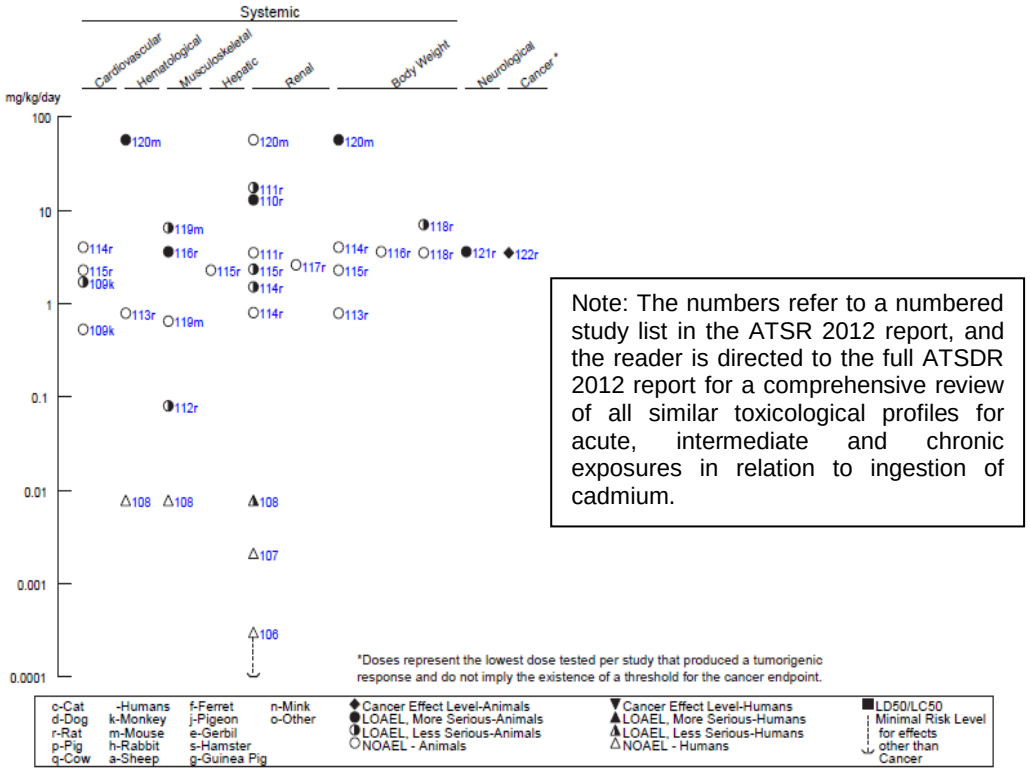


Figure 2.1: Example of all chronic (>365 days) animal and human study evaluations that lead to different adverse toxicological responses following oral exposure (ATSDR 2012)

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

2a) Animal Toxicology Data

Not applicable as none of the animal data were used in the HBGV evaluations of the oral toxicity of cadmium.

2b) Human Toxicology/Epidemiology Data

There are extensive human epidemiological studies for the most sensitive adverse health effects of renal toxicity and bone toxicity from cadmium exposure. All oral

HBGVs are based upon human data except the outdated USEPA evaluation from 1994.

The scientific basis of the existing minimal risk health criteria value (HCV) (EA 2009a) is the human epidemiology work described in EFSA (2009a, 2009b). EFSA (2009 and 2011) recommended using a $BMDL_5$ of 4 µg Cd g^{-1} creatinine as a point of departure (POD), which represents the 95th lower confidence limit of a benchmark response (BMR) of 5% incidence of exceeding the 300 µg β2 microglobulin (β2M) g^{-1} creatinine level in the total population. For the purposes of the EA minimal risk evaluation, this $BMDL_5$ was used (EA 2009a).

In terms of the chemical specific adjustment factor (CSAF), EFSA selected the 95th percentile, seeing as the data are based on heterogeneous human studies and there is a need to account for human interindividual variations in kinetics and responses in varying β2M levels. Therefore they used the corresponding adjustment factor (AF) of 3.9 (EFSA 2011). These data were also selected for derivation of the minimum risk HCV for oral exposure by EA in 2009. This led to a urinary cadmium excretion of 1 µg g^{-1} creatinine that represents the internal dose that indicates that 95% of the European population would not exceed the cut off limit of 300 µg g^{-1} creatinine for β2M in urine (EFSA 2009b). Kinetic modelling was used to translate this dose into an intake (see Figure 2.2 below) and an HBGV of 0.36 µg kg^{-1} bw day^{-1} was determined.

The EA also selected 0.36 µg kg^{-1} bw day^{-1} as the current minimal risk HCV (EA 2009a).

The JECFA (2011) evaluation used the same body of data as EFSA (2009) (see Appendix F2) but there were differences in the modelling parameters chosen and in some aspects of the toxicokinetic modelling (as described in full in EFSA 2011b). A 'breakpoint', where it was determined that there was no increase in β2M, was defined at 5.4 µg Cd g^{-1} creatinine. In their evaluation, using kinetic modelling to translate this into a daily intake, the lower bound of the 5th population percentile dietary cadmium exposure that equates to the breakpoint was estimated to be 0.8 µg kg^{-1} bw day^{-1} or about 25 µg kg^{-1} bw per month, which is the current JECFA PTMI.

The recent ATSDR evaluation in 2012 used a different dataset of 7 studies (see Appendix F3) to the JECFA & EFSA dataset of 35 studies (see Appendix F2) and a different range of biomarkers, including α1-microglobulin (α1M) and N-acetyl-β-D-glucosaminidase (NAG), which are more sensitive biomarkers than β2M. The ATSDR evaluation yields the lowest oral HBGV (0.1 µg kg^{-1} bw day^{-1}) of all those derived to date.

The work by EFSA has been endorsed by the UK COT and is a scientifically valid and widely accepted approach using β2M as a good marker of renal effects. It provides a more precautionary assessment than JECFA from the same dataset. It forms the current basis of minimal risk in the context of contaminated land risk assessment (EA 2009). The more recent ATSDR work has not yet been reviewed by the UK COT. It is also arguable as to whether increasingly lower levels of low molecular weight proteins changes that can be measured actually lead to adverse biological responses that constitute 'significant harm'. Therefore, the ATSDR approach is considered to be highly conservative.

It would be advised here, that to redefine minimal risk using the most sensitive ATSDR approach would be too highly precautionary in the context of contaminated land risk assessment, and that the current use of the $BMDL_5$ from the EFSA (2009) evaluation is a suitable value to use as a starting point for deriving LLTCs.

GO TO FLOWCHART ELEMENT 6

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

Not applicable.

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

Yes	No	Not applicable
X		

The quantitative data from the EFSA (2009) evaluation on renal effects will act as the chosen starting point of a quantitative evaluation to derive an $LLTC_{oral}$. As stated, above however, it should be noted how the dose-response for renal effects, overlaps with the dose-response for bone effects and approximated cancer risk (see Appendix F1).

The EFSA evaluation noted 35 epidemiology studies with good quantitative data (listed in Appendix F2) containing 165 paired data sets covering the renal effects of cadmium exposure in humans. Hence there are adequate data on which to perform dose-response modelling. This was carried out by EFSA (2009b) who carried out a meta-analysis on all available data, bringing all of the quantitative data from the 35 studies into a single analysis.

There are several steps in calculating the estimated intake that could lead to nephrotoxicity following cadmium exposure (Figure 2.2), namely:

- Concentration effect modelling that relates the cadmium in urine (expressed in terms of g Cd g^{-1} creatinine) with levels of renal biomarkers in urine such as low molecular weight proteins (β2M) or intracellular enzymes (NAG).
- Toxicokinetic modelling that relates urinary cadmium concentrations (g Cd g^{-1} creatinine) to intake (in mg kg^{-1} day^{-1}) from oral, inhalation or dermal routes of exposure.

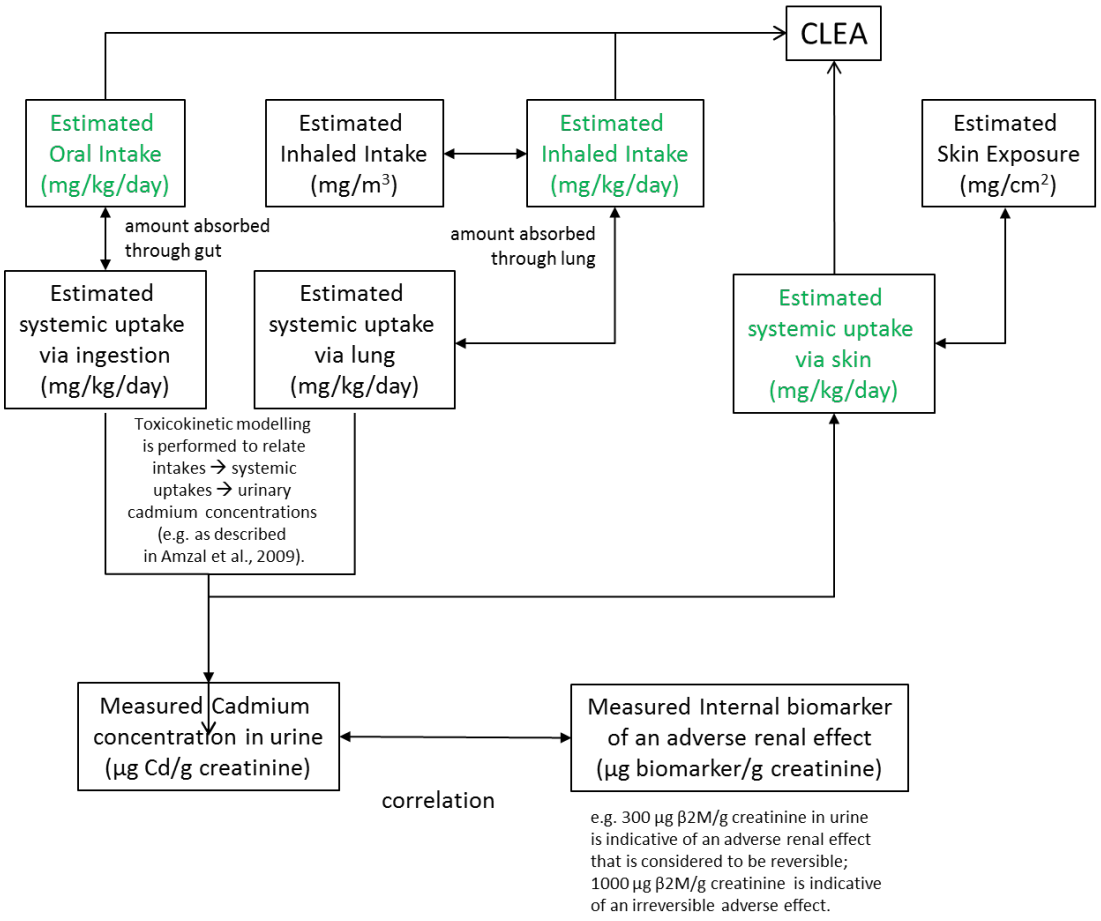


Figure 2.2: Outline of stepwise process in deriving an intake value for cadmium

GO TO FLOWCHART ELEMENT 6b

2.1.4 FLOWCHART ELEMENT 6b: PERFORM BMD MODELLING

Given there are good quantitative data on human populations for the most sensitive renal effects, a so-called 'hybrid' BMD modelling approach (Budtz-Jorgensen *et al.*, 2001; Crump, 2002; Suwazono *et al.*, 2006; Sand *et al.*, 2008) was performed by EFSA on the combined dataset for urinary β2M levels vs urinary levels of cadmium, chosen as the most appropriate and widely accepted internal biomarker of adverse renal effects (EFSA 2009b; Bernard, 2004).

The objective of their meta-analysis was to derive a BMD and its 95% lower confidence limit (BMDL) for humans using cut off points relevant to clinical changes in the kidney. Therefore modelling was performed for both cut off thresholds, namely 300 and 1000 µg β2M g^{-1} creatinine.

The BMD evaluation was carried out for the whole population and for subjects of the age of 50 and above, excluding worker sub-groups and adjusting for ethnicity to account for differences between Caucasians and Asians. The BMD and BMDL were calculated for both groups (Table 2.1) and for both clinical cut off values.

Table 2.1: BMD and BMDL modelling for the total and sub-populations

	Total population		**Caucasians only**		**Over 50, non occupationally exposed**	
U β2M >300 µg g^{-1} creatinine	**BMR 5**	**BMR 10**	**BMR 5**	**BMR 10**	**BMR 5**	**BMR 10**
BMD	4.09	4.72	4.65	5.32	5.25	5.73
BMDL	3.68	4.32	3.84	4.53	6.33	5.46
U β2M >1000 µg g^{-1} creatinine	**BMR 5**	**BMR 10**	**BMR 5**	**BMR 10**	**BMR 5**	**BMR 10**
BMD	5.83	6.4	6.8	7.32	6.33	6.77
BMDL	5.39	5.99	5.95	6.51	5.46	5.94

From available evidence (Bernard, 2004), EFSA considered that a level of 300 µg β2M g^{-1} creatinine was a threshold for reversible adverse renal effects and that a level of 1000 µg β2M g^{-1} creatinine was a threshold for irreversible adverse renal effects. For the purposes of setting an LLTC, the lower, more precautionary cut off for reversible adverse renal effects of 300 µg β2M g^{-1} creatinine is recommended.

This is a choice made in the interests of precaution for the derivation of a screening number given a small CSAF applied to the POD. Also, the values of cadmium in urine relating to the irreversible effects of β2M >1000 µg Cd g^{-1} creatinine are not much higher, being in the range of 5-7 µg Cd g^{-1} creatinine.

At this point, for LLTC derivation, one could choose either the BMD central tendency values or the BMDL, for a BMR_5 or BMR_{10} as the POD.

A $BMDL_5$ was chosen as the minimal risk value by EA (2009) based on the EFSA opinion (2009a) which describes a $BMDL_5$ of 4 µg Cd g^{-1} creatinine as being chosen. However from the BMD modeling shown in Table 2.1, this value was an approximation, hence a BMD_{10} or $BMDL_{10}$ would be more appropriate to reflect low concern. The $BMDL_{10}$ can be described as the lower 95th percentile cadmium dose at which there is a 10% increased incidence of the 300 µg β2M /g creatinine level being exceeded.

A summary of all of the evaluations is presented in Table 2.2.

Table 2.2: The choice of BMD values that could act as PODs in the derivation of a toxicology-based LLTC for C4SL determination

Possible PODs (µg Cd /g creatinine)	
4.09	BMD_{05}
3.68	$BMDL_{05}$
4.72	BMD_{10}
4.32	$BMDL_{10}$

We propose here, for the purposes of LLTC derivation, using a $BMDL_{10}$ of 4.3 µg Cd g^{-1} creatinine as evaluated by EFSA (2009) using meta-analysis data from 35 studies (Appendix F2) for β2-microglobulin in the general population.

In this case, there is only one pragmatic option to propose for the cadmium oral LLTC. The previously cited $BMDL_{05}$ of 4 µg Cd g^{-1} creatinine (reported by EFSA and used as the minimal risk POD as the basis of the HCV) is arguably so close to the BMD_{05} (4.09 µg Cd g^{-1} creatinine), that the latter value is also in the minimal risk region. The next useful reported BMR is for a 10% increased incidence of a response; the $BMDL_{10}$ and BMD_{10} are 4.3 and 4.7 µg Cd g^{-1} creatinine, respectively. Values higher than this BMD value start to approach the irreversible effects range (ie overlap on the dose responses for the 1000 µg β2M g^{-1} creatinine, which is essentially a different effects curve). If the BMD_{10} is chosen it would lead to a value >0.5 µg kg^{-1} day^{-1} where bone effects start to be seen, and this is not advisable to overlap onto another effects curve.

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

Yes	No	Not applicable
X		

As can be seen from Figure 2.1, the most sensitive effect for cadmium is renal toxicity, although other effects have been seen at higher doses. For this most sensitive renal effect (nephrotoxicity), there is a dose of cadmium in urine that leads to no significant change above background β 2M levels (see BMD curve in HTDS section IV), and hence a threshold for toxicity is observed. Similarly, there are thresholds for dose-response effects in bone (osteotoxicity); bone effects occur at doses of a similar magnitude as seen for renal effects. Cancer effects are seen at much higher doses in animals.

Therefore the critical effect is considered to exhibit a threshold, and a CSAF should be derived if appropriate data are available.

GO TO FLOWCHART ELEMENT 4b

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

In the BMD modelling approach used by EFSA (2009b), different CSAFs (also called adjustment factors) were proposed by EFSA. These were used to account for the fact that the BMDs are likely to be greater when derived from population data than when individual data are used. Therefore, the CSAF can account for interindividual differences in the population, and are dependent on the choice of percentile for the BMD. This is described in full in EFSA (2011b).

In basic terms the CSAF used by EFSA (2009b and 2011b) was based on an approach described in WHO (2005), where the ratio of the 95th percentile of the BMD to a central value (median BMD) of the respective population values was proposed:

$$AF = \frac{xthPercentile}{Median}$$

If different percentiles are chosen for the LLTC (and WHO 2005 explicitly states that the choice of percentile is a 'policy' decision depending on the severity of effect, robustness of data, nature of data distribution and risk management considerations), then the AF changes accordingly (Table 2.3).

For the minimal risk position EFSA selected a 95th percentile as the data are based on heterogeneous human studies that have a lower grade of evidence than animal studies, and due to β2M being a measure of kidney damage. They used the corresponding AF of 3.9 (EFSA 2011). These data were also selected for minimum risk by EA in 2009.

EFSA stated that other percentiles could be selected by applying different assumptions in relation to the association of the variability's between doses and effects (EFSA 2011), but the accompanying AFs must be used (Table 2.3).

Table 2.3: Adjustment factor (AF), reference point (RP) and tolerable daily intake (TDI) as presented by EFSA (2011b).

	PERCENTILES					
	99.5	**95.0**	**90.0**	**85.0**	**75.0**	**67.5**
AF	8.5	3.90	2.90	2.40	1.80	1.50
RP (µg Cd per g creatine)[1]	0.5	1.00	1.50	2.00	2.50	3.00
TDI µg kg^{-1} bw day^{-1}	0.18	0.36	0.54	0.73	0.91	1.09

We propose here, for the purposes of LLTC derivation and in the context of using a $BMDL_{10}$, using a corresponding CSAF of 2.9 for the 90th percentile of the population, which leads to the description of a low level of risk that is suitable for the context of setting an LLTC.

GO TO FLOWCHART ELEMENT 5b

2.1.7 FLOWCHART ELEMENT 5b: CALCULATE THE LLTC FOR THRESHOLDED CHEMICALS

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

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

It is proposed that the $BMDL_{10}$ of 4.3 µg Cd g^{-1} creatinine for the lower cut off threshold of 300µg β2M acts as the POD for the $LLTC_{oral}$. [N.B. Values higher than this lead to an LLTC that begins to overlap with doses that could lead to bone effects].

From Table 2.3 in Section 2.1.6 above, using the 90th percentile to protect 90% of the population and in conjunction with the $BMDL_{10}$, the CSAF is 2.9.

Therefore the $LLTC_{oral}$ is 4.3/2.9 = 1.5 µg Cd g^{-1} creatinine.

2.1.8 TOXICOKINETIC MODELLING TO TRANSLATE URINARY CADMIUM LEVELS TO ORAL INTAKES

As the quantitative information for cadmium is based on an internal biomarker concentration of β2M related to cadmium concentrations in urine, toxicokinetic modelling approaches are required to estimate the oral intake dose that would lead to

concentrations of cadmium in urine following oral absorption and clearance in the body (see Figure 2.3 below). The toxicokinetic modelling performed in relation to the interpretations by EFSA was published in Amzal *et al.*, 2009. Cadmium exhibits low absorption through the gut (<10%) but once in systemic circulation it is known to be very biopersistent in the body (mean half-life of 11.6 +/- 3 years cited in Amzal *et al*. 2009) and toxicokinetic models also consider this behaviour. The calculations of oral intake doses leading to cadmium levels in urine has been based on assumptions of dietary intakes as outlined in EFSA (2011b).

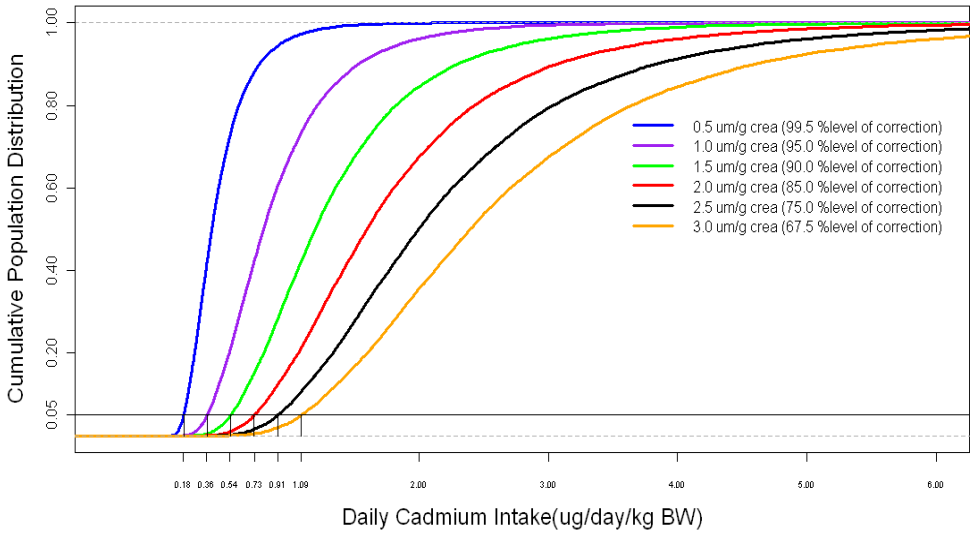


Figure 2.3: Reproduced from EFSA (2011b) Cumulative population distribution of daily cadmium exposure considering different percentiles to calculate AF. NB. Units are ug/g/creatinine.

Figure 2.3, taken from EFSA (2011b), illustrates the relationship between the expected percentages of the human population with urinary cadmium concentrations exceeding a threshold (y axis) versus intake in µg kg^{-1} bw day^{-1} (x-axis) for varying threshold levels of urinary cadmium (0.5-3 µg g^{-1} creatine). For example, one can see from the green curve that an oral intake of 0.54 µg kg^{-1} bw day^{-1} to the population would lead to 5% of the population having a urinary cadmium level of at least 1.5 ug g^{-1} creatinine.

Using toxicokinetic modelling to estimate an oral intake over a lifetime that would lead to the proposed LLTC of 1.5 µg Cd g^{-1} creatinine level (see Figure 2.3 above), this equates to an LLTC of 0.54 µg kg^{-1} bw day^{-1}.

GO TO FLOWCHART ELEMENT 7

2.1.9 FLOWCHART ELEMENT 7: ASSESS LLTC FOR CADMIUM

Based upon a scientific evaluation of renal effects in humans, an oral LLTC of 0.54 µg kg^{-1} bw day^{-1} is proposed, based on a $BMDL_{10}$ as the POD and a CSM of 2.9 (converted using toxicokinetic modelling). This value is:

a) at a 10% additional risk of exceeding the cut off of 300 µg β2M in the population, indicative of reversible kidney effects.

b) at the minimal risk level for bone effects (0.5 µg kg^{-1} day^{-1} calculated by ATSDR 2012) – this is an important level not to significantly exceed, as above this level the effects on bone development and growth start to become a real consideration in the risk assessment, and the concept of lifetime averaging does not apply to the target population of children.

c) still expected to be protective of carcinogenicity effects

d) at a similar level to current high end dietary intakes in adults and is lower than high end intakes in children and vegetarians (see HTDS section III).

In this case, there is only one pragmatic option to propose for the cadmium oral LLTC. The cited $BMDL_{05}$ of 4 μg Cd g^{-1} creatinine (reported by EFSA and used as the minimal risk POD as the basis of the HCV) is arguably so close to the BMD_{05} (4.09 μg Cd g^{-1} creatinine), that the latter value is also in the minimal risk region. The next useful reported BMR is for a 10% increased incidence of a response; the $BMDL_{10}$ and BMD_{10} are 4.3 and 4.7 μg Cd g^{-1} creatinine, respectively. If the BMD_{10} is chosen it would lead to a value >0.5 μg kg^{-1} day^{-1} where bone effects start to be seen, and this is not advisable to overlap onto another effects curve.

Therefore the $LLTC_{oral}$ of 0.54 μg kg bw^{-1} day^{-1} 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 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

In 2009, the Environment Agency published a revised updated version of the TOX3 Toxicology Report for cadmium (Science report: SC050021/TOX3) (EA, 2009a). This was used as the start of the data search, and new information published between the years 2009-2012 was added to the data package.

There is a comparative wealth of toxicology information on cadmium. The latest is a key new data package in the form of the Toxicological Profile from the US ATSDR published in September 2012 (ATSDR 2012) to consider that was not included in the EA TOX3 review for cadmium (EA 2009a). The document covers a full and comprehensive review of the primary literature on the toxicology of cadmium 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.

The USEPA's 1999 draft review of cadmium is still open to external review but has not yet been published as final on the IRIS website (and is therefore marked as amber in section I(B) of the HTDS as it cannot yet be cited formally). If this were to be finalised in the near future, the resulting value could be the lowest of all HBGVs. However, there are significant confounders in the work by Thun *et al.* 1985 and Stayner *et al.,* 1992, involving background tobacco smoke and concomitant arsenic inhalation.

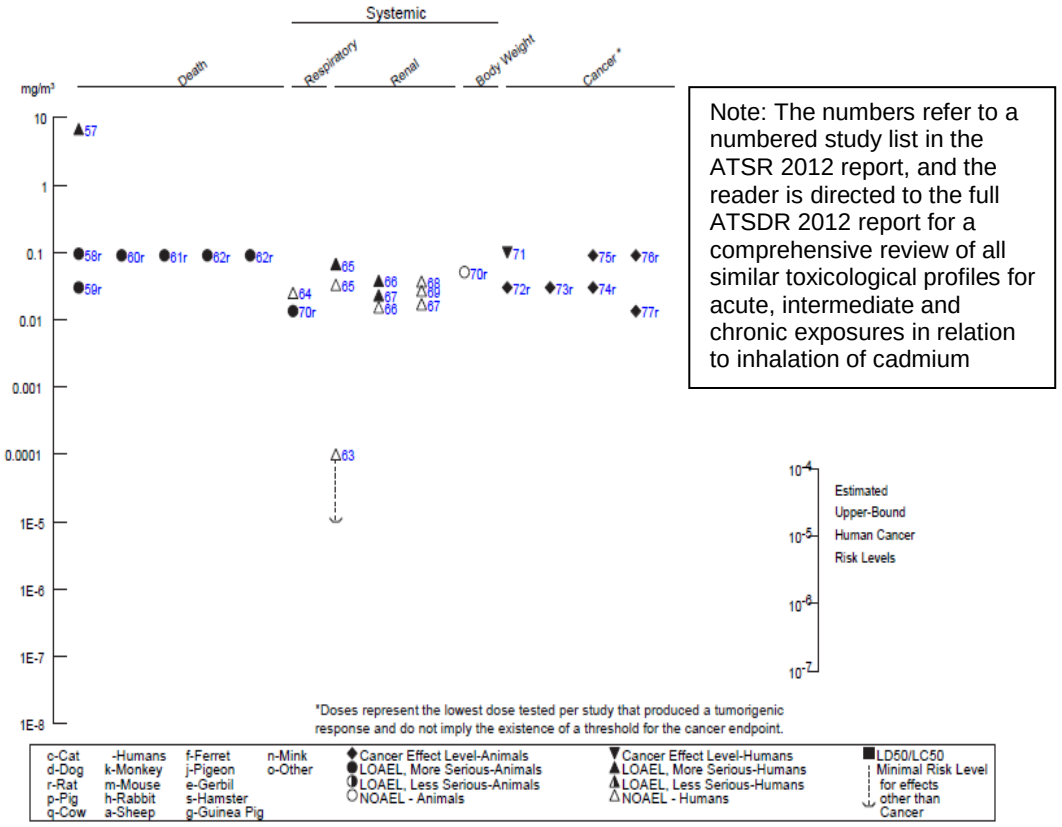


Figure 2.4: Example of all chronic (>365 days) animal and human study evaluations that lead to different adverse toxicological responses following inhalation exposure (ATSDR 2012)

These reviews provide the best evidence that renal effects and lung cancer are equally sensitive of all toxicological effects by the inhalation route although quantitative data on the renal endpoint are most conducive to dose-response modelling.

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

As above. flowchart element 2 requires a suitably qualified individual who sufficiently understands the nature of toxicological data to identify the scientific basis of all existing HCVs for the inhalation route. Again, three possible options are provided for the type of pivotal study that could be chosen at this point, i.e. in the form of: 1) animal toxicology data; 2) human toxicology/epidemiology data; and 3) an evidence-informed policy choice (i.e. based on an existing guideline from another regime, with or without a toxicological rationale).

2a) Animal Toxicology Data

Not applicable as none of the animal data were used in the HBGV evaluations of the inhalation toxicity of cadmium.

2b) Human Epidemiology Data

The scientific basis of the existing minimal risk inhalation HCV (EA 2009) is the human kidney toxicity data (LOAEL) from Thun *et al.* (1991) converted to continuous lifetime exposure for the general population (as per the approach by the EC working Group (2000). Although suitable to derive a minimum risk level in 2009, these data from Thun *et al*. 1991 are now not considered the most appropriate dataset on which to perform BMD modeling, as a more recent comprehensive meta-analysis has been carried out that better forms the basis of a toxicology evaluation of inhalation exposure on cadmium.

A recent meta-analysis of 11 human epidemiology studies performed between 1990-2006 (see Appendix F3), was carried out by ATSDR in 2012.. This was based upon an accepted hybrid BMD modelling/toxicokinetics approach for the inhalation route using all available good quality human epidemiology data, rather than a single study. The work by ATSDR (2012) leads to a chronic inhalation minimal risk level (MRL) for kidney toxicity (2.83 ng/kg bw day^{-1}) that is higher than any previous evaluation from single studies alone (see Appendix F1).

The USEPA has previously set limits for lung cancer. The official limit on the Integrated Risk Information System (IRIS) derived in 1994 was based on data published by Thun *et al.,* in 1985 and the draft 'unofficial' 1999 limit was based on a follow up study by Stayner *et al.* in 1992. These will be referred to, and excess lifetime cancer risks (ELCRs) compared with the outcome of the quantitative evaluation for renal toxicity, in order to assure that the LLTC is also protective of lung cancer. It should be noted that these estimates from EPA are considered worst case values due to the confounders of tobacco smoking and concomitant arsenic exposure causing cancers that are not necessarily due to cadmium exposure. But these numbers can act as a conservative guide for a 'cross-check' cancer evaluation.

CHOICE OF THE PIVOTAL STUDY: Of all of the available data for the inhalation route, the ATSDR 2012 evaluation is the most comprehensive and scientifically appropriate to use for LLTC derivation. The analysis makes the best use of all available data. It is, however, a highly precautionary approach, as discussed above for the oral route, the dataset used and modelling leads to stringent values through the evaluation of all sensitive low molecular weight protein markers.

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		

In the ATSDR (2012) meta-analysis for cadmium, there are 11 epidemiology studies (the same studies as used for the ATSDR (2012) evaluation of the oral route plus 3 additional studies from occupational exposures with good quantitative data (Chen *et al*. 2006a, 2006b; Järup and Elinder 1994; Roels *et al.* 1993)) listed in Appendix F3 covering the renal effects of cadmium inhalation exposure in humans. Hence there are adequate dose effects data for BMD modelling. As with the approaches described for the oral route, the studies relate the dose of cadmium in urine to biomarkers in urine, as markers of renal effects. This evaluation was based upon all available good quality human epidemiology data, rather than a single study and is a generic analysis including, from a toxicokinetic modelling perspective, using both oral and inhalation routes combined.

GO TO FLOWCHART ELEMENT 6b

2.2.4 FLOWCHART ELEMENT 6b: PERFORM BMD MODELLING

In 2012, ATSDR carried out the meta-analysis to examine the relationship between urinary cadmium and the prevalence of elevated biomarkers of renal function in urine. They implemented individual dose response curves from each of the 11 epidemiology studies mentioned in Appendix F3, to calculate estimates of the internal dose of cadmium that correlated to the probability of a 10% excess risk of low molecular

weight proteinuria (urinary cadmium dose, UCD_{10}). This urinary dose was expressed as μg /g creatinine. Data presented by ATSDR are shown in Table 2.4.

The most sensitive of all data comes from the European data ((Buchet *et al*., (1990); Suwazono *et al.,* (2006) and Jarup *et al.*, (2000)) (Table 2.4), which were also reviewed in the EU Risk Assessment Report (EC 2007) as well as by ATSDR (2012).

Table 2.4: Estimates of the UCD_{10} and cadmium intake from environmental exposure dose-response studies (taken from ATSDR 2012)

	Urinary cadmium dose (UCD_{10})[a] (μg Cd g^{-1} creatinine)	**Cadmium intake[b] (μg /kg bw day^{-1})**	
		Females	**Males**
Europe (n=4)[c]			
Mean	1.34	0.97	2.24
Median	-	-	-
95% CI	0.50, 2.18	0.33, 1.75	0.70, 3.94
All (n=11)			
Mean	4.99	4.37	9.58
Median	4.20	3.63	7.99
95% CI	1.44, 6.60	1/06, 5.86	2.45, 12.8

[a]Estimates of urinary cadmium level corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (UCD_{10})
[b]UCD was transformed into estimates of chronic cadmium intake that would result in the UCD at age 55 using a modification (Choudhury *et al*., 2001; Diamond *et al*.,. 2003) of the Kjellstrom and Nordberg (1978) model
[c]Dose-response function data from Buchet *et al*.,(1990), Suwazono *et al*.,(2006) and Jarup *et al*., (2000); dose response data from males and females in the Buchet *et al*., (1990) study were treated separately.

Based on European data, the lowest UCD_{10} of 1.34 μg Cd g^{-1} creatinine was derived, and the corresponding 95% lower confidence limit ($UCDL_{10}$) of 0.5 μg Cd g^{-1} creatinine is the proposed POD for the LLTC, which corresponds to a 10% increased prevalence of low molecular weight proteinurea in the meta-analysis.

As the quantitative information for cadmium is derived from a range of different (some highly sensitive) internal biomarker concentrations (β2M, α1-microglobulin, retinol-binding protein, NAG), the POD in this analysis is lower than for the EFSA and JECFA analyses[1]. As the marker concentrations are related to cadmium concentrations in urine, toxicokinetic modelling approaches are required to estimate the inhalation intake dose in mg kg^{-1} bw day^{-1} that would lead to concentrations of cadmium in urine. The toxicokinetic modelling performed in relation to the interpretations by ATSDR was using the approaches in both the ICRP Human Respiratory Tract Model (ICRP, 1994) and Kjellström and Nordberg (1978). Concomitant exposure to cadmium in the diet and cadmium inhaled from air were taken into account together in the toxicokinetic modelling. Cadmium exhibits low absorption into the body but once in systemic circulation it is known to be very biopersistent in the body (mean half-life of 11.6 +/- 3 years cited in Amzal *et al*., (2009)) and toxicokinetic models also consider this behaviour. This means that cadmium can accumulate over a lifetime and this has already been factored into the modelling.

We propose here, for the purposes of LLTC derivation, using a POD = $UCDL_{10}$ of 0.5 μg Cd g^{-1} creatinine as evaluated by ATSDR (2012) using meta-analysis data from 11 studies and targeted for the most sensitive LMWP biomarkers in the most sensitive

[1] This is a highly sensitive dataset, and yields a point of departure (0.5 μg Cd g^{-1} creatinine as a threshold of low molecular weight proteinurea) that is significantly lower than the point of departure derived by EFSA and JECFA (4 μg Cd g^{-1} creatinine or 5.4 μg Cd g^{-1} creatinine, respectively) from a larger dataset of 35 studies but for β2 microglobulin only).

European population. This is consistent with the choice of a 10% increased incidence of effect level as used for the oral POD.

GO TO FLOWCHART ELEMENT 4

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

Yes	No	Not applicable
X		

The critical endpoint of renal toxicity does exhibit a threshold for toxicity effects, hence it is appropriate to derive a CSAF.

GO TO FLOWCHART ELEMENT 4b

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

An overall CSAF of 9 is proposed as described by ATSDR in 2012. This is made up of a factor of 3 for human variability to account for the possible increased sensitivity of diabetics (Åkesson *et al*., 2005; Buchet *et al*. 1990). To account for the lack of adequate human data that could be used to compare the relative sensitivities of the respiratory tract and kidneys a factor of 3 is also proposed i.e. this factor is to ensure that the effects derived from the renal effects also cover the respiratory effects seen at a similar dose (see Figure 2.4).

The assessment factor is larger here (9) than it was for the oral LLTC (2.9) as the uncertainties for the inhalation route are greater. For this route, there are comparable but unquantifiable sensitivities to respiratory effects and a less robust underpinning dataset with a smaller human population, than was the case for the oral route.

2.2.7 FLOWCHART ELEMENT 5b: CALCULATE THE LLTC FOR THRESHOLDED CHEMICALS

As discussed above, it is proposed that a $UCDL_{10}$ of 0.5 µg Cd g^{-1} creatinine (equivalent to a $BMDL_{10}$ i.e. the cadmium dose at which there is a 10% increased incidence of low molecular weight proteinurea) acts as the POD for the derivation of the LLTC inhalation. This is based on the ATSDR (2012) evaluation.

Using toxicokinetic modelling performed in ATSDR (2012), specifically incorporating the inhalation pathway, an atmospheric concentration of 100 ng Cd m^{-3} (and assuming a background dietary intake of 0.3 µg kg bw^{-1} day^{-1} from various sources) would lead to a urinary cadmium concentration of 0.5 µg Cd g^{-1} creatinine. The POD as an equivalent concentration in air, is therefore 100 ng Cd m^{-3}.

A CSAF of 9 is proposed, as described above, to account for uncertainty.

Therefore, the $LLTC_{inhal}$ is 100/9 = 11.1 ng m^3 (rounded down to 10 ng m^3). For a 70 kg adult breathing 20 m^3 air per day, this yields an $LLTC_{inhal}$ as a daily intake of 0.0029 µg.kg$(bw)^{-1}$.day^{-1}.

GO TO FLOWCHART ELEMENT 7

2.2.8 FLOWCHART ELEMENT 7: ASSESS LLTC FOR CADMIUM

Based upon a scientific evaluation of renal effects data in humans, it is proposed that the inhalation LLTC is an intake value of 2.9 ng kg bw^{-1} day^{-1}. This value:

a) is the highest value of all authoritative HBGVs for the inhalation route.

b) is 2-fold higher than the current EA minimal risk value published in 2009, based on the Thun *et al*., 1991 paper.

c) describes a 10% increased incidence of low molecular weight proteinurea in a European population.

d) is significantly lower than the oral LLTC for the same effects (N.B. this is not a reflection of a higher absorption of cadmium through the lung, but that aspects of cadmium intake from the background diet are already included in the toxicokinetic modeling to determine an air intake that would lead to a urine cadmium concentration. Therefore, for the inhalation route, background dietary sources should not be included in the exposure calculations of the risk characterization.

e) is still expected to be protective of carcinogenicity effects; the USEPA 1994 calculated an ELCR of 1 in 100,000 for an air intake of 6 ng m^{-3} from Thun *et al*., (1985) In this context, the value of 10 ng m^{-3} for the LLTC represents an ELCR of 1 in 60,000, which is considered sufficiently protective.

f) is at a similar level to current adult intakes of cadmium from ambient air (see HTDS section III)

Therefore this $LLTC_{inhal}$ is considered to be a pragmatic level for setting a C4SL, and is considered suitably protective of all health effects in the general population.

2.3 DERMAL ROUTE

There are no specific toxicity data, HBGVs or authoritative evaluations on the dermal route of exposure. Hence, the oral LLTC should be used in assessing the dermal route.

2.4 CARCINOGENICITY OF CADMIUM

Cadmium is also classified by International Agency for Research on Cancer (IARC) as a Group 1 human carcinogen. There are not sufficient quantitative data to perform BMD modelling of this effect but from limited quantitative evidence it appears the dose that would be required to cause carcinogenicity is higher and therefore carcinogenicity is less sensitive than renal effects. There is also mechanistic evidence that genotoxicity and carcinogenicity are likely to be caused by indirect thresholded mechanisms (oxidative damage and metabolic interference) rather than non-thresholded direct DNA reactivity. Also, it is not clear whether carcinogenicity in epidemiology is confounded by tobacco smoking and concomitant exposures to arsenic. Quantitative evaluations for renal effects are also considered to protect against the carcinogenic potential of cadmium.

2.5 OTHER CONSIDERATIONS: LIFETIME AVERAGING

Cadmium accumulates in the body over time. The BMD modelling performed using epidemiology and toxicokinetic data to derive a tolerable daily intake, has accounted for the fact that a certain daily oral dose from dietary sources over a lifetime could accumulate into a cadmium concentration in urine in later years (>50 years) (Figure 2.5). For this reason, the derivation of the SGVs for cadmium averaged daily exposure over the lifetime of the receptor for comparison with the HCV (EA, 2009a). This approach has also been adopted here for the derivation of the pC4SLs.

Given that lifetime averaging has been used, it is not considered appropriate to make age specific adjustments to the inhalation LLTC.

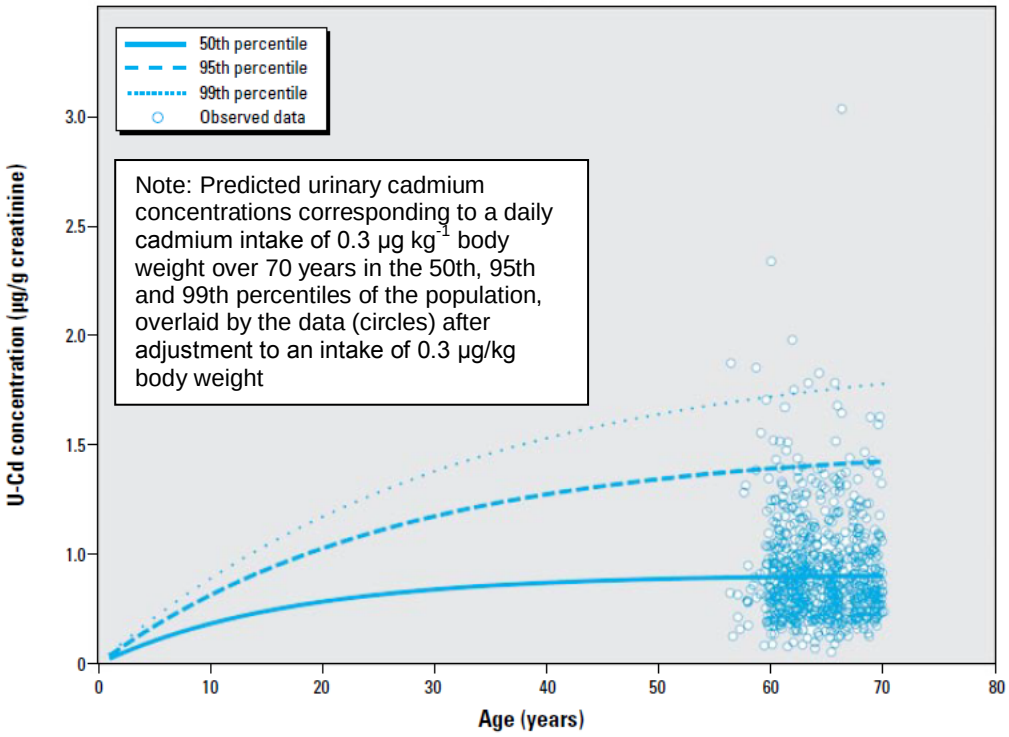


Figure 2.5: Correlation of urinary cadmium concentrations and age (taken from Amzal *et al.* 2009).

3. EXPOSURE MODELLING FOR CADMIUM

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

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

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

3.1 DETERMINISTIC MODELLING

Deterministic modelling uses a single value for each parameter input and derives one estimate of ADE for each exposure pathway. ADEs are then summed for some or all exposure pathways for comparison with the LLTC. The pathways considered in the summation are dependent on the critical toxicological effects that the LLTC is based on. In the case of cadmium, oral, dermal and inhalation exposures contribute to the same systemic effects on the kidney and bone and therefore the sum of the oral and dermal exposures have been compared with the $LLTC_{oral}$ and the sum of the inhalation exposure has been compared with $LLTC_{inhal}$.

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 the LLTCs are both based on systemic effects the former approach has been taken to determine the pC4SLs for cadmium.

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 cadmium from green vegetables and root vegetables for both the residential and allotments scenarios. Therefore, in accordance with the "top two" approach (see Section 3.5.5.3 of the main text for further details), 90^{th} percentile consumption rates have been used for these two produce types and mean consumption rates have been used for the remaining produce types. For the POS land-uses the assumptions and parameter values are described in Section 3.6 of the main report. Note that the pC4SLs have been derived assuming a sandy loam soil type (i.e. as used for deriving SGVs).

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

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

Parameter	Units	Value	Source/Justification
Dermal absorption fraction	-	0.001	EA, 2009c
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	0.052	Empirical factors recommended by EA from collation and review of literature values of for cadmium from literature (EA, 2009d). Values shown are geometrical mean values of the data.
Soil-to-plant concentration factor (root vegetables)		0.029	
Soil-to-plant concentration factor (tuber vegetables)		0.031	
Soil-to-plant concentration factor (herbaceous fruit)		0.016	
Soil-to-plant concentration factor (shrub fruit)		0.0031	
Soil-to-plant concentration factor (tree fruit)		0.0014	
Soil-to-dust transport factor (g g-1 DW)	-	0.5	EA, 2009c
Relative bioavailability soil	-	1	Conservative assumption made that bioavailability of cadmium in soil and dust is the same as bioavailability of cadmium 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 cadmium are discussed below.

Soil to plant concentration factors

The Environment Agency undertook a review of the scientific literature on the plant uptake of cadmium by fruit and vegetables based on findings from literature searches conducted during September and October 2008 (EA, 2009d). As part of this review they collated soil to plant concentration factors (CFs) from available studies. These were calculated from the ratio of concentration of the contaminant in the plant (mg^{-1} kg^{-1} fresh weight [FW]) to the concentration of the contaminant in soil (mg^{-1} kg^{-1} fresh weight [DW]). The summary statistics for the collated concentration factors are shown in Table 3.2.

Note that it is widely reported that soil pH and soil organic matter content are important properties affecting the uptake of cadmium into plants, however, the Environment Agency report that it is difficult to quantify this effect for individual plants and broadly defined produce groups (Environment Agency, 2009d). For this reason, the Environment Agency proposed the use of fixed CFs for cadmium, but noted that the empirical datasets used were largely for soils with pH ranging from 6 to 8.

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

Produce Category	Soil-to-plant concentration factors (mg kg^{-1} FW per mg kg^{-1} DW)				
	GM [1]	Minimum	Maximum	SD [2]	N [3]
Green vegetables	5.20E-02	1.10E-03	4.40E+00	7.20E-01	200
Root vegetables	2.90E-02	5.40E-04	3.30E-01	7.60E-02	77
Tuber vegetables	3.10E-02	5.00E-03	1.10E-01	3.10E-02	12
Herbaceous fruit	1.60E-02	7.70E-04	1.00E+00	2.00E-01	29
Shrub fruit	3.10E-03	1.70E-03	5.60E-03	1.90E-03	4
Tree fruit	1.40E-03	3.20E-04	3.20E-02	9.30E-03	11

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

NA: Not applicable because only one value is available

The Environment Agency recommended the use of the geomean of the concentration factors for each produce type, for the derivation of SGVs for cadmium.

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). For the derivation of the pC4SL, this is conservatively assumed to be 100% for both the oral and inhalation routes of exposure.

The bioavailability of cadmium via oral exposure is typically low with absorption via food expected to be less than 5% (EA, 2009a). Absorption via inhalation may be higher, e.g. 10 to 50% (EA, 2009a). The epidemiology studies used as the basis for LLTCs mostly involve intakes in food matrices (for oral exposure) or inhaled air (for inhalation exposure) and bioavailability has been accounted for in the toxicokinetic modelling used in the derivation of the LLTC. The RBA for cadmium in soil relative to food is not known but can be expected to vary with soil type and organic matter. However, it is unlikely to be greater than that in food. Given the lack of data and the fact that oral bioavailability was likely to be low, it is considered reasonable to assume an RBA_{oral} of 100%. Furthermore, for residential (with consumption of homegrown produce) and allotments land-uses, the principle pathway for exposure to cadmium from soils is predicted to be from ingestion of homegrown produce (see Table 4.2), where the RBA is 100%. The bioavailability from inhalation exposure may be higher relative to oral but again it is reasonable to assume that the bioavailability of inhaled soil derived dust is similar to that from the inhalation epidemiology studies.

3.2 PROBABILISTIC MODELLING

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

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 95^{th} percentile) selected for each parameter have been chosen to best represent the data on which the PDF is based. The PDF type and associated attributes for contaminant specific parameters are summarised in

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

Table 3.3: Parameters modelled probabilistically for cadmium

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

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

Parameter	Units	Basis of PDF	PDF attributes
Soil-to-plant concentration factor (green vegetables)	mg g^{-1} FW plant over mg g^{-1} DW soil	Log normal distribution assumed based on geomean and SD from Environment Agency, SGV supplementary report (2009). Values truncated at 2.5 and 97.5 %iles.	Log normal (gm 5.2e-2, SD [ln CFs] 2.17)
Soil-to-plant concentration factor (root vegetables)			Log normal (gm 2.9e-2, SD [ln CFs] 1.28)
Soil-to-plant concentration factor (tuber vegetables)			Log normal (gm 3.1e-2, SD [ln CFs] 0.78)
Soil-to-plant concentration factor (herbaceous fruit)			Log normal (gm 1.6e-2, SD [ln CFs] 2.12)
Soil-to-plant concentration factor (shrub fruit)			Log normal (gm 3.1e-3, SD [ln CFs] 0.71)
Soil-to-plant concentration factor (tree fruit)			Log normal (gm 1.4e-3, SD [ln CFs] 1.78)
Soil to dust transport factor	g g^{-1} DW	Triangular distribution based on ranges reported by Oomen & Lijzen (2004). They report range in literature values from 0.08 to 0.8, with 0.5 being most likely value. Max value multiplied by a factor of 2 to account for possibility of enrichment.	Triangular (min 0.08, mode 0.5, median 0.69, max 1.6)

4. PROVISIONAL C4SLs FOR CADMIUM

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

Table 4.1: Provisional C4SLs and SGVs

Exposure parameters	HCV or LLTC µg kg^{-1}(bw) day^{-1}		pC4SL (mg.kg^{-1}) [3]					
			Residential		Allot-ments	Commercial	POS_{resi}	POS_{park}
	Oral	Inhal	With home grown prod.	Without home grown prod.				
SGV	0.36	1.4E-3	10	84 [2]	1.8	230	-	-
pC4SL with exposure changes only [1]	0.36	1.4E-3	14	87	2.4	220	120	560
pC4SL with LLTCs but exposure parameters as SR3	0.54	2.9E-3	17	150	3.0	420	-	-
pC4SL with changes in exposure [1] and LLTCs	0.54	2.9E-3	22	150	3.9	410	220	880

1. Exposure parameters as described in Section 3
2. Derived using CLEA model but omitting consumption of homegrown produce pathways
3. Note that both SGVs and pC4SLs assume lifetime averaging

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

Table 4.2: Relative contributions of exposure pathways to overall exposure

Exposure pathway	Relative contribution to total exposure (%)					
	Residential		Allot-ments	Comm-ercial	POS_{resi}	POS_{park}
	With home grown prod.	Without home grown prod.				
direct soil & dust ingestion	6	50	0.4	50	50	52
sum of consumption of homegrown produce and attached soil	46	0	53	0	0	0
dermal contact (indoor)	4E-03	0.03	0	0.03	0.05	0
dermal contact (outdoor)	0.01	0.10	4E-03	0.05	0.06	0.4
inhalation of dust (indoor)	0.02	0.2	0	0.3	0.3	0
inhalation of dust (outdoor)	1E-05	7E-05	2E-04	2E-03	5E-04	0.02
inhalation of vapour (indoor)	0	0	0	0	0	0
inhalation of vapour (outdoor)	0	0	0	0	0	0
oral background	47	50	46	50	50	47
inhalation background	0.02	0.09	2E-04	0.08	0.09	0.02

4.2 QUANTITATIVE APPRAISAL OF UNCERTAINTY

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

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

- Reverse cumulative frequency (RCFs), i.e. graphs of the reverse cumulative frequency versus ADE for alternative pC4SL. 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 PDFs used to conduct the probabilistic modelling. Residual uncertainty in the underlying PDFs and remaining parameters modelled as set deterministic values (such as soil ingestion rate) are discussed in Section 4.3.

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

Figure 4.1 shows the RCFs of oral and dermal exposure combined for three alternative values of pC4SLs using alternative sets of exposure parameters. These are:

1. pC4SL = 14 mg/kg. This is the derived pC4SL using the proposed LLTC but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 22 mg/kg. This is the derived pC4SL using the proposed LLTC as above with proposed modifications to exposure modelling parameters (see Section 4); and
3. pC4SL = 60 mg/kg. 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 (soil ingestion rate reduced to 80 $mg.d^{-1}$ for AC1 to 12 and 40 $mg.d^{-1}$ for AC13 to 18, homegrown fraction halved for all produce types, mean consumption rates used for all produce types and dust loading factor reduced to 25 $ug.m^{-3}$).

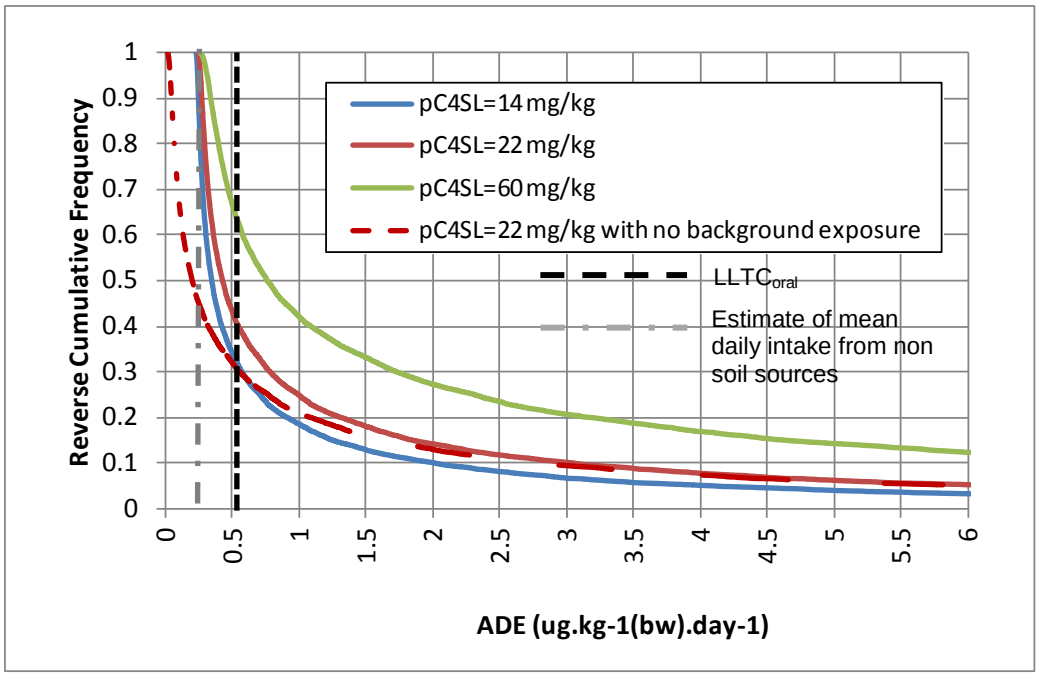


Figure 4.1: Reverse cumulative frequency graph of oral and dermal ADE combined for alternative values of pC4SLs for cadmium for residential (with consumption of homegrown produce) land-use

The coloured curves on Figure 4.1 show the RCFs for the alternative pC4SLs. These curves show that there is a high probability of exposure exceeding a low ADE value but a low probability of exposure exceeding a high value. Figure 4.1 also shows the $LLTC_{oral}$ (as a black dashed line) along with estimates of average background exposure from non soil sources for comparison with the RCFs of average daily exposure.

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

Figure 4.1 can be used to estimate the probability that exposure to a random individual within the critical receptor group would exceed the $LLTC_{oral}$ by reading off the probability from the y axis where the RCF curve intersects the LLTC vertical dashed line. Thus, the probability that exposure would exceed the LLTC is 32% for a

soil concentration of 14 mg/kg, increasing to 40% and 62% for soil concentrations of 22 and 60 mg/kg, respectively. For comparison purposes, the probabilities of exposure exceeding a value of ten times the LLTC (5.4 μg kg^{-1} bw day^{-1}) are significantly lower, ranging from 4 to 13% for the alternative pC4SL. As discussed in Section 4.3, a generally conservative approach has been adopted for the probabilistic modelling and it is likely that the true probabilities of exceedence are significantly lower.

The large range in exposures for the residential scenario indicated by Figure 4.1 is principally due to the large range in possible values for the soil to plant concentration factors, homegrown fraction and consumption rate. For families who grow a large quantity of fruit and vegetables in their garden for home consumption and where the nature of the soils is such that soil to plant concentration factors are high, exposure could be more than order of magnitude above median exposure.

Figure 4.1 also shows the reverse cumulative probability excluding oral background exposure for the pC4SL of 22 mg/kg. This shows that the median exposure from soils at this concentration is approximately equivalent to the mean daily intake for oral background exposure.

Figure 4.2 presents the probability of exceedence graphs for residential (with consumption of homegrown produce) land-use. This graph shows two curves: the probability that exposure from soil via the oral and dermal routes exceeds the $LLTC_{oral}$ and the probability that exposure from soil via the inhalation route exceeds the $LLTC_{inhal}$. As with Figure 4.1 this graph can be used to estimate the probability that exposure to a random individual in the critical receptor group exceeds the LLTC for alternative pC4SL, but has the added advantage that the relationship between probability of exceedence and soil concentration can be seen more easily.

Figure 4.2 shows that the probability of total exposure exceeding the $LLTC_{oral}$ is far greater than the probability of inhalation exposure exceeding the $LLTC_{inhal}$. This is because inhalation is a relatively unimportant exposure pathway for cadmium (see Table 4.2). For the three alternative pC4SLs of 14, 22 and 60 $mg.kg^{-1}$, the probability of inhalation exposure exceeding the $LLTC_{inhal}$ is negligible.

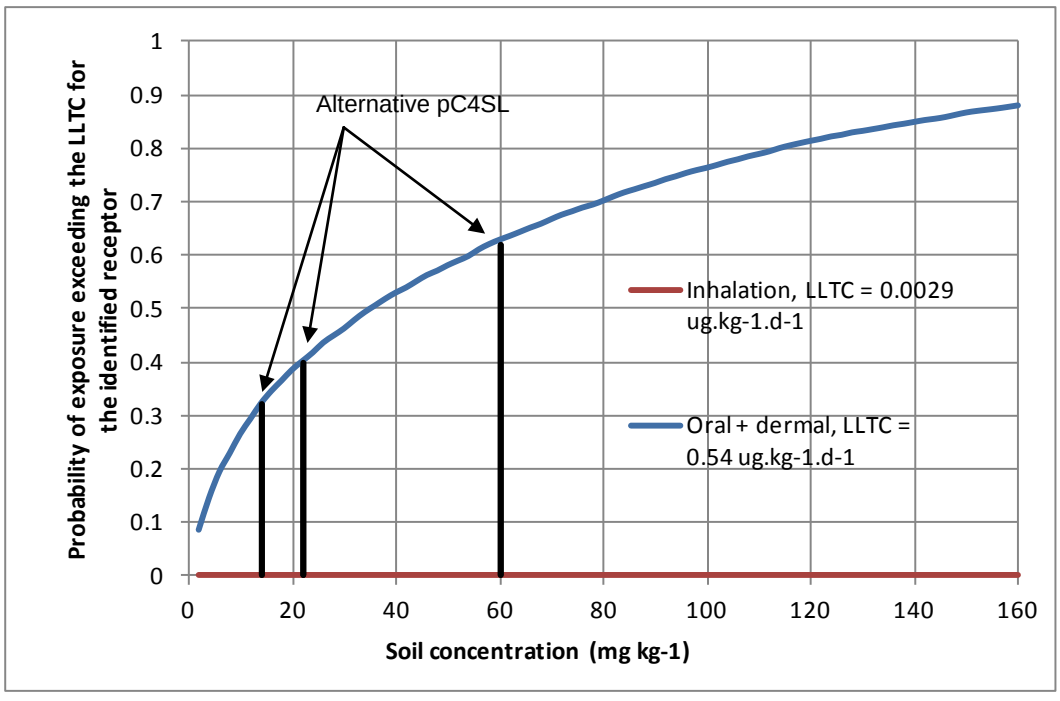


Figure 4.2: Probability of exposure exceeding LLTC with alternative values of pC4SLs for cadmium for residential (with consumption of homegrown produce) land-use.

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

Figure 4.3 shows the probability of exceedence graph for the residential (without consumption of homegrown produce) land-use for three alternative values of pC4SLs using alternative sets of exposure parameters. These are:

1. pC4SL = 146 mg kg^{-1}. This is the derived pC4SL using the proposed LLTC but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 149 mg kg^{-1}. This is the pC4SL derived using LLTC as above but with the proposed modifications to exposure modelling parameters described in Section 4; and
3. pC4SL = 200 mg kg^{-1}. This is the pC4SL derived as above, but with additional modifications to exposure modelling parameters that had been proposed in the draft interim methodology document produced in advance of the first Stakeholder Workshop. These additional modifications are soil ingestion rate reduced to 80 mg d^{-1} and dust loading factor reduced to 25 μg $.m^{-3}$.

The predicted probabilities of exceedence of the LLTC are significantly lower than those for the residential (with consumption of homegrown produce) land-use. The predicted probabilities of exceedence are 1.1%, 1.2% and 2.1% for the pC4SLs of 146, 149 and 200 mg/kg, respectively.

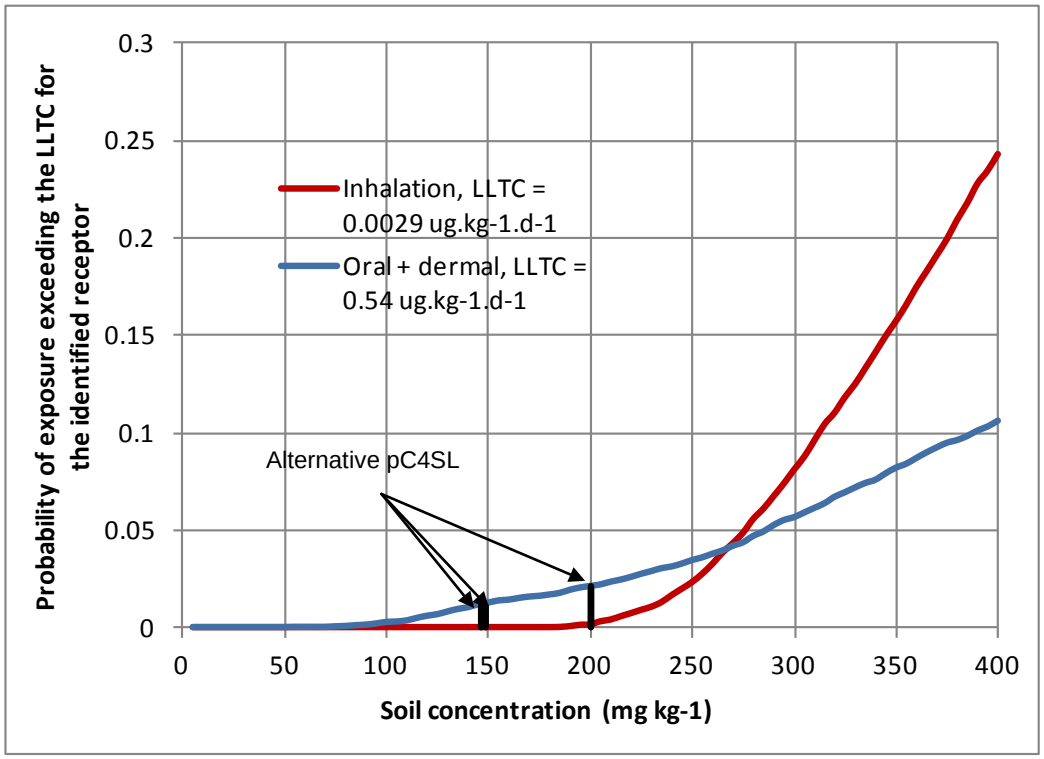


Figure 4.3: Probability of exposure exceeding LLTC with alternative values of pC4SLs for cadmium for residential (without consumption of homegrown produce) land-use

4.2.3 ALLOTMENTS LAND-USE

Figure 4.4 shows the RCFs of oral and dermal exposure combined for three alternative values of pC4SLs using alternative sets of exposure parameters. As with the residential land-use, inhalation exposure from soils is negligible compared to background and so RCFs are not shown for inhalation exposure. The three alternative pC4SLs considered are:

1. pC4SL = 2.4 mg/kg. This is the derived pC4SL using the proposed LLTC but making no changes to the exposure parameters from the CLEA SR3 report;
2. pC4SL = 3.9 mg/kg. This is the derived pC4SL using the proposed LLTC with the proposed modifications to the exposure modelling parameters (see Section 4).
3. pC4SL = 6.3 mg/kg. 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 $mg.d^{-1}$ for AC1 to 12 and 40 $mg.d^{-1}$ for AC13 to 18, exposure frequency outdoors for children halved and mean consumption rates used for all produce types.

Figure 4.4 also shows the $LLTC_{oral}$ for comparison with the RCFs of average daily exposure. This shows that the probability that exposure to a random individual from the critical receptor group would exceed the $LLTC_{oral}$ is 37% for a soil concentration of 2.4 mg kg^{-1}, increasing to 47% and 57% for concentrations of 3.9 and 6.3 mg kg^{-1}, respectively.

The probabilities of exposure exceeding a value of ten times the LLTC (0.54 μg kg^{-1} bw day^{-1}) are significantly lower, ranging from 5 to 11% for the alternative pC4SL. 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.

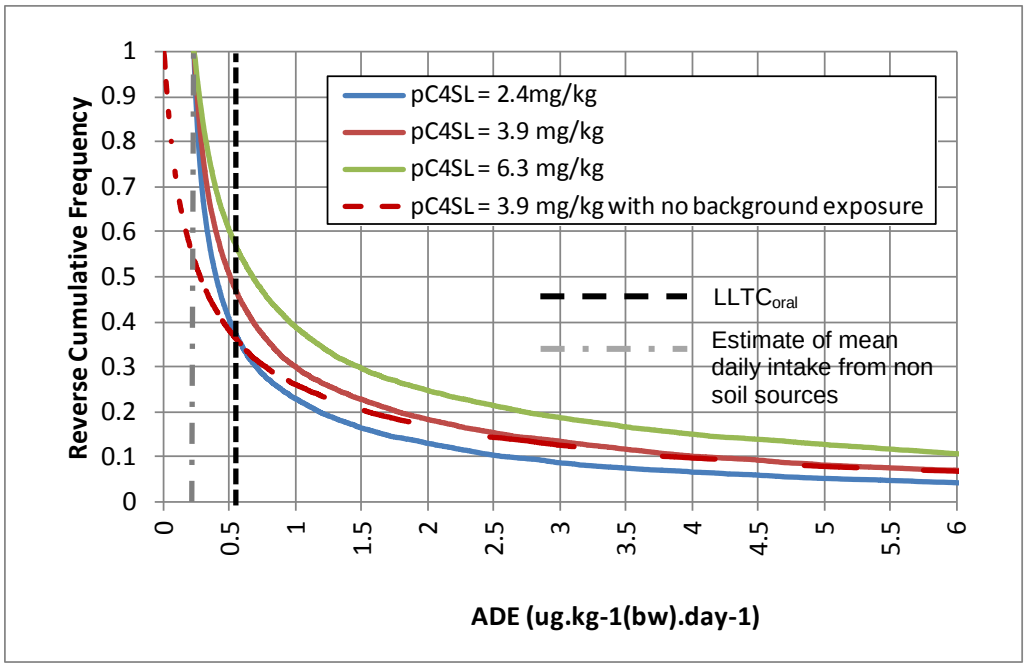


Figure 4.4: Reverse cumulative frequency graph of oral and dermal ADE combined for alternative values of pC4SLs for cadmium for allotments land-use

The large range in exposures for the allotments scenario indicated by Figure 4.4 is due to the large range in possible values for the soil to plant concentration factors, homegrown fraction and consumption rate. For families with allotments who consume

a large amount of fruit and vegetables and are mostly self-sufficient in these produce types and where the nature of the soils is such that soil to plant concentration factors are high, exposure could be more than order of magnitude above median exposure.

Figure 4.4 also shows estimated background exposure from non soil sources (the grey dotted line) and the predicted RCF for the pC4SL of 3.9 mg/kg excluding background exposure (the red dotted curve). Comparison of this RCF with background exposure shows that the median exposure from soils at this soil concentration is expected to be close to the mean daily intake for oral background exposure.

Figure 4.5 shows the relationship between the probability of exceedence of the $LLTC_{oral}$ versus soil concentration and confirms the probabilities of exceedence described above.

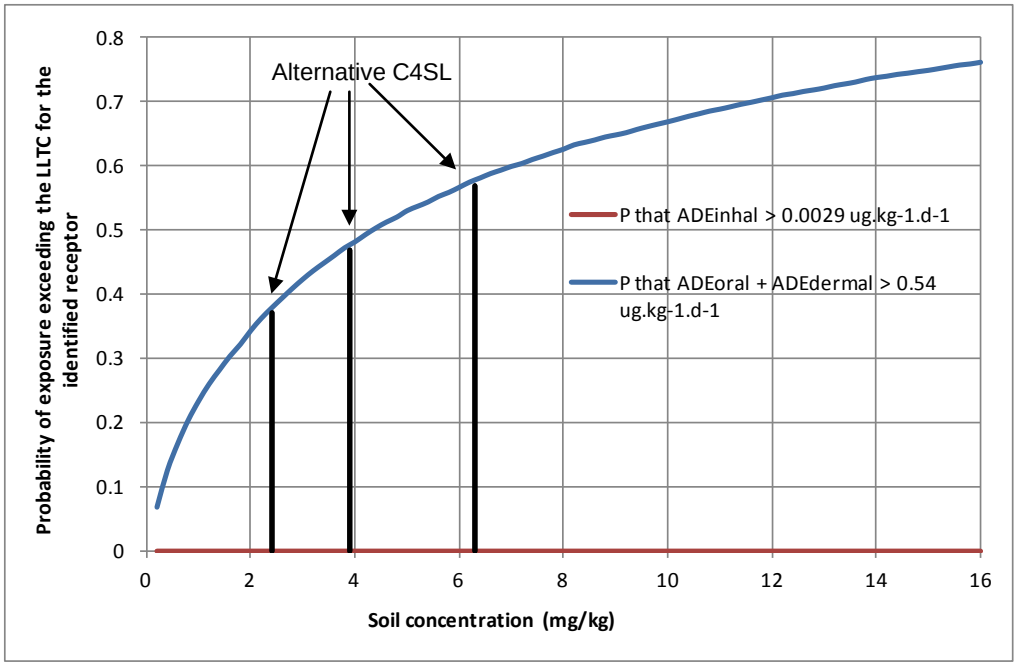


Figure 4.5: Probability of exposure exceeding $LLTC_{oral}$ with alternative values of pC4SLs for cadmium for allotments land-use

4.2.4 COMMERCIAL LAND-USE

Figures 4.6 and 4.7 show the RCFs of oral/dermal and inhalation exposure, respectively, for two alternative values of pC4SLs using alternative sets of exposure parameters. These are:

1. pC4SL = 410 mg kg^{-1}. This is the derived pC4SL using the proposed LLTC with the proposed modifications to exposure modelling parameters described in Section 3.5.7 of the main report; and
2. pC4SL = 570 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 $\mu g .m^{-3}$.

Unlike the residential and allotments scenarios only two sets of exposure parameters have been tested. This is because there is no difference between the pC4SL with the proposed exposure parameter changes described in Section 3.5.7 of the main report and the pC4SL using the SR3 parameters. The only difference in exposure

parameters for commercial land-use is a slight reduction in adult inhalation rate and this has no effect on the pC4SL for cadmium for this land-use.

Figures 4.6 and 4.7 also show the relevant LLTC and estimates of average background exposure from non-soil sources for comparison with the RCFs of average daily exposure. Figure 4.8 shows the relationship between the probability of exceedence of the relevant LLTCs for oral/dermal and inhalation exposure and soil concentration.

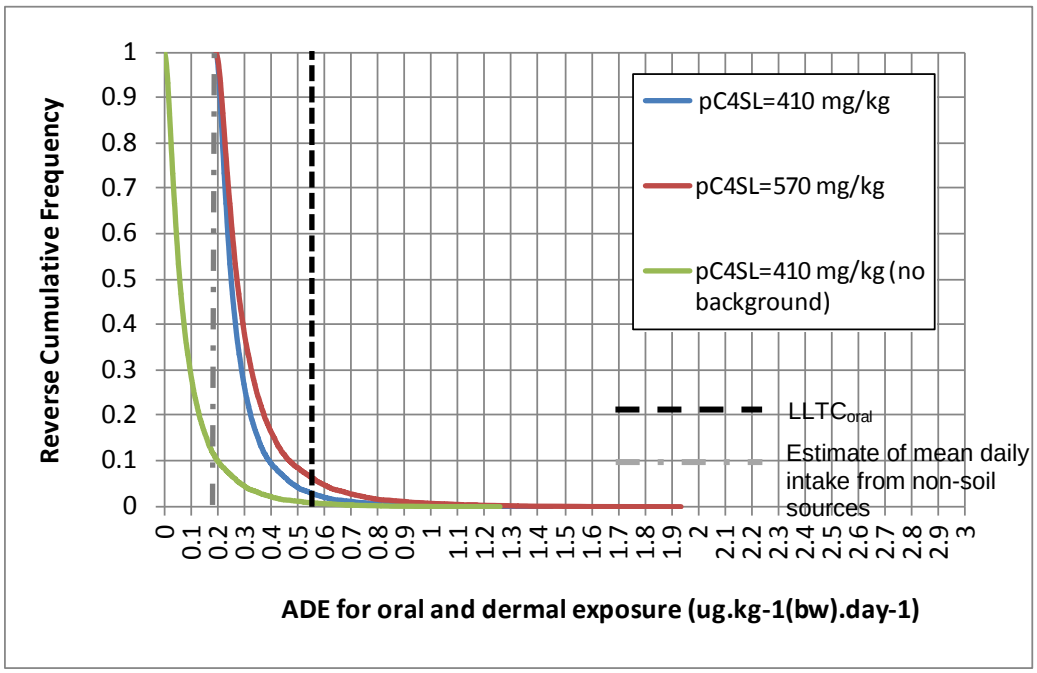


Figure 4.6: Reverse cumulative frequency graph of ADE for oral/dermal exposure for alternative values of pC4SLs for cadmium for commercial land-use

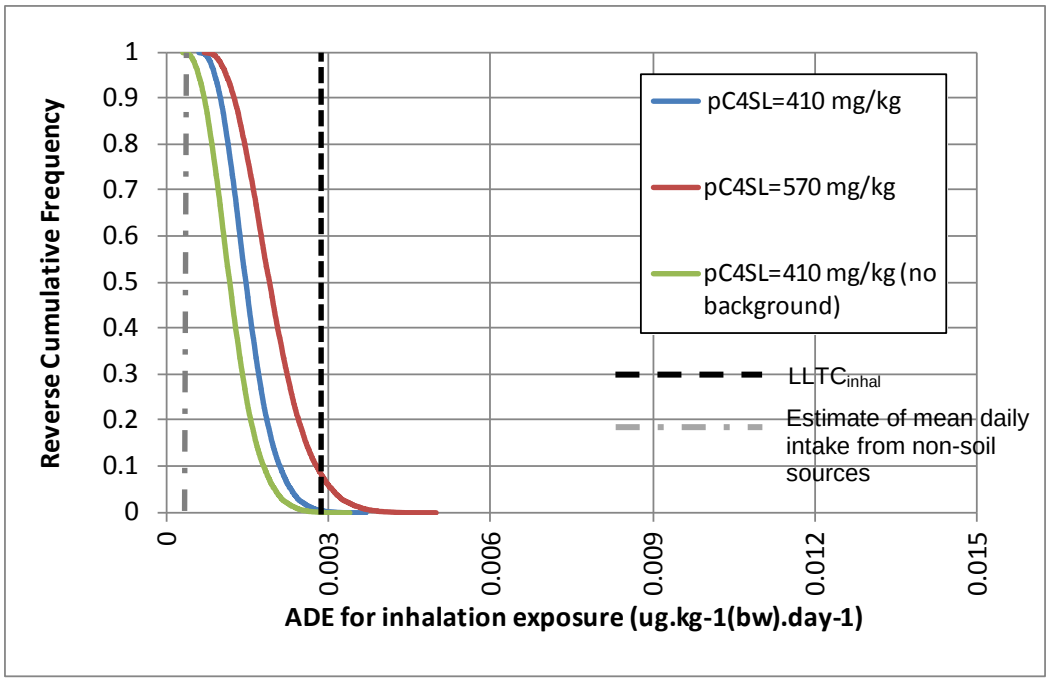


Figure 4.7: Reverse cumulative frequency graph of ADE for inhalation exposure for alternative values of pC4SLs for cadmium for commercial land-use

Figures 4.6 and 4.8 show that the probability that oral/dermal exposure to a random individual from the critical receptor group would exceed the $LLTC_{oral}$ is 3% for a soil

concentration of 410 mg kg^{-1}, increasing to 6% for a soil concentration of 570 mg kg^{-1}. Figures 4.7 and 4.8 show that the probability that inhalation exposure to a random individual from the critical receptor group would exceed the $LLTC_{inhal}$ is 0.5% for a soil concentration of 410 mg kg^{-1}, increasing to 8.5% for a soil concentration of 570 mg kg^{-1}. As discussed in Section 4.3, a generally conservative approach has been adopted for the probabilistic modelling and it is possible that the true probabilities of exceedence are significantly lower.

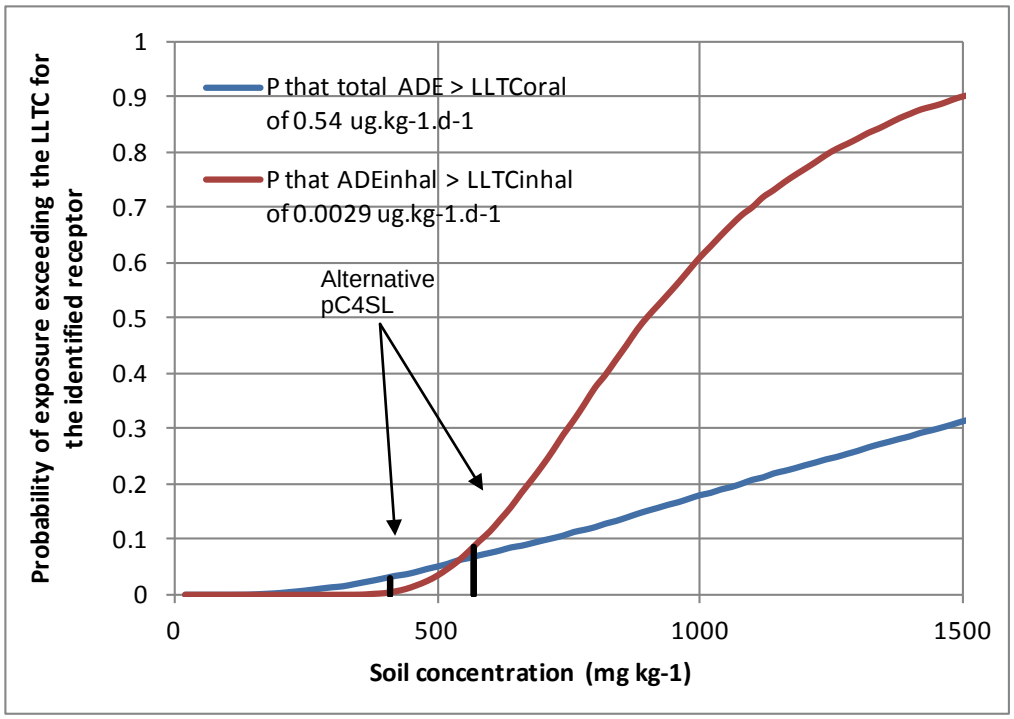


Figure 4.8: Probability of exposure exceeding LLTCs with alternative values of pC4SLs for cadmium for commercial land-use

As can be seen from Figure 4.6 there is a 10% probability that oral/dermal exposure exceeds typical background oral exposure, i.e. background exposure is likely to be greater than exposure from soils at the alternative pC4SLs shown. Figure 4.7 shows that inhalation exposure from soils is predicted to be greater than average background inhalation exposure from non soil sources, i.e. soil at the pC4SL could be the main contributor to inhalation exposure of cadmium for the commercial land-use scenario. However, as discussed in Section 4.3, the CLEA inhalation exposure estimates are likely to be highly conservative and thus actual exposure from soil may be significantly less than that predicted.

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 uncertainty in the LLTCs and uncertainty in the 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 cadmium in the environment.

A qualitative appraisal of these residual uncertainties has therefore been conducted, using an “uncertainty table” approach, as described in Section 5.1.2 of the main report. Tables 4.3 and 4.4 describe the key residual uncertainties and their impact on toxicity and exposure estimates for the exposure modelling of these pathways, respectively. The residual uncertainties are listed in the left hand column of the table, whilst the right hand column contains a subjective evaluation of the impact of each

uncertainty on the estimated LLTCs and exposures, using plus (+) and minus (-) symbols.

The number of symbols indicates the approximate magnitude of the over- or under-estimation, based on the scale, shown in Figure 4.9. A dot (●) represents a 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 overestimation of exposure and hence overestimation of risk, while a + for the LLTC implies overestimation of the LLTC which results in underestimation of risk.

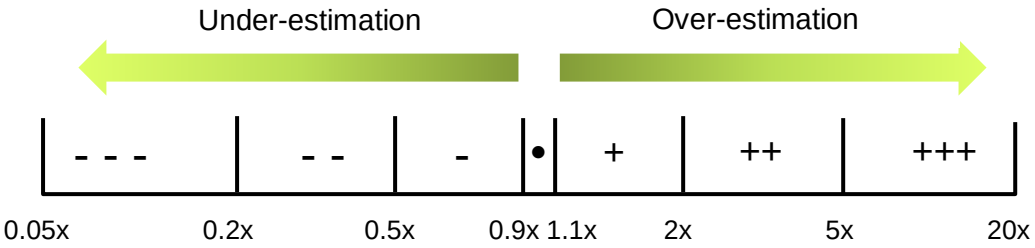


Figure 4.9: Key for symbols used to express judgements about the magnitude of potential over- or under-estimation of the LLTC and exposure in Tables 4.3 and 4.4 respectively.

Finally, at the foot of the table, a subjective evaluation is given of the overall impact of the combined uncertainties, using the same symbols. 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), with equal weight being given to over- and under-estimates.

4.3.1 TOXICOLOGICAL ASSESSMENT

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

Table 4.3: Qualitative appraisal of key residual uncertainties in toxicology evaluation (see Figure 4.9 for key to symbols)

Source of Uncertainty	Evaluation of uncertainty
ORAL LLTC	
Choice of biomarker: there is evidence that β2M is a sensitive and representative marker of adverse renal effects (Bernard, 2004). Hence, this choice of marker in the EFSA evaluation is considered the most appropriate. The level of 300 µg β2M/g creatinine is a conservative lower estimate of a marker of reversible renal effects, which may not be adverse.	●/-
Interspecies uncertainties: As the evaluation uses human data there are no uncertainties around extrapolations between animals and humans	●
Human intake variability: this factor in the analysis has been covered in the toxicokinetic modelling aspects of the derivation (Amzal et al 2009). Intraindividual intake variability was set at 25% in the model.	●
Age differences: From Amzal *et al.*, 2009 –'The assumption of constant cadmium intake per kilogram of body weight over a lifetime could be challenged, especially for younger ages. However, considering the estimated half-life (~ 12 years) and the age range of our study population (> 50 years of age), even large variations of intake before 20 years of age	●

Source of Uncertainty	Evaluation of uncertainty
are expected to have limited impact on the cadmium burden at older ages. Based on the model estimates, thus, a variation of 50% in cadmium intake until 15 years of age would, based on our model estimates, result in < 3% difference in the cadmium burden at 50 years of age.'	
Gender differences: the TK modelling was done for data on 650 women aged >50years only, and there is evidence that absorption of cadmium is higher in women than men (Vahter *et al.*, 2007). Hence, for the general population including males, the LLTC would be conservative and overestimate renal effects.	**-/●**
Mean data vs individual data: the modelling uses group means rather than data from individuals in the final analysis. It is possible that the mean data under- or over-estimates the intake in some individuals.	**-/+**
Potential for non-linearity of toxicokinetics: linearity has been assumed in the Nordberg-Kjelstrom model.	**-/+**
Modulation of effects from co-exposures to other dietary factors (e.g. zinc, manganese, vitamin D, selenium): In humans, cadmium toxicity can be modulated by other factors in the diet. Dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects following cadmium exposure (Kjellström 1986c). Iron deficiency has been shown to increase gastrointestinal absorption of cadmium in humans, while oral zinc supplementation has been demonstrated to decrease the oral absorption of cadmium (Flanagan *et al.* 1978). On balance, evidence of effects from dietary components can both increase and/or decrease Cd toxicity.	●
Susceptibility of diabetics: There is some evidence to suggest that diabetics may be more susceptible to the toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990; Haswell-Elkins et al. 2008). No analysis or assessment factor has been used to account for diabetics as a potential subpopulation.	**+**
Overall evaluation of uncertainty for $LLTC_{oral}$: based on the above, the uncertainties affecting the LLTC are mostly fairly limited (within a factor of two) with more tending to underestimation (conservative) than overestimation. The proposed $LLTC_{oral}$ is therefore considered a reasonable basis for setting the C4SL.	
INHALATION LLTC	
Choice of biomarker: In the ATSDR 2012 evaluation the most sensitive of biomarkers are evaluated, and it is not necessarily proven definitively that adverse effects would arise in the kidney at the low levels of biomarkers chosen. It is therefore considered likely that the $LLTC_{inhal}$ is conservative (an underestimate).	**-**
Susceptibility of diabetics has already been taken into account in the CSAF.	●
Non-linearity of toxicokinetics: linearity has been assumed in the Nordberg-Kjelstrom model.	**-/+**
Overall evaluation of uncertainty for $LLTC_{inhal}$: based on the above, the uncertainties affecting the LLTCs are mostly fairly limited (within a factor of two) with more tending to underestimation (conservative) than overestimation. The proposed $LLTC_{inhal}$ is therefore considered a reasonable basis for setting the C4SL.	

Note that the implications of the overall uncertainty on the pC4SLs can be considered by looking at the RCF graphs in Section 4.2: over- and under-estimation of the LLTC would imply the black dashed lines should be further left or right (respectively).

4.3.2 EXPOSURE MODELLING

As shown in Table 4.2, the principle exposure pathway for cadmium for the residential and allotments land-use is consumption of homegrown produce. The key uncertainties in estimating exposure for these pathways are described in Table 4.4.

Table 4.4: Qualitative appraisal of key residual uncertainties in exposure modelling not captured by probabilistic modelling (see Figure 4.9 for key to symbols)

Source of Uncertainty	Evaluation of uncertainty
RESIDENTIAL & ALLOTMENTS LAND-USES	
Soil to plant concentration factors. The soil to plant concentration factor (CF) PDFs are based on empirical measurements of the concentration of cadmium in fruit and vegetables and the soil they have been grown in. Empirical datasets used were largely for soils with pH ranging from 6 to 8. As discussed in Section 4.1, soil pH exerts a strong control on plant uptake of cadmium. For soils with a low pH (5 or less), plant uptake may be significantly under-estimated, whilst for soils with high pH (9 or above), plant uptake may be significantly over-estimated. However, given that most soils where produce is grown will have a pH in the range of 6 to 8, the impact of this uncertainty is reduced. A possible under/over estimation of exposure of x 0.1 to x 10 has been assigned to this parameter.	pH 6-8 **-/+** Other pH **---/+++**
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 PDFs for fraction of consumed produce that is grown (1) on a residential property and (2) on an allotments are based on data from the 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 RESIDENTIAL AND ALLOTMENTS LAND-USES: Based on the above it is considered that the estimates of total exposure predicted by the probabilistic modelling are likely to be conservative, particularly at specific locations.	
COMMERCIAL LAND-USE	
Soil and dust ingestion rate. The PDF used is based on the mean and 95th percentile soil ingestion rates for children estimated by Stanek, *et al*. (2012) from a meta-analysis of the key soil ingestion studies conducted in the USA. Average soil and dust ingestion by children is expected to be twice that of adults (USEPA, 2011) and therefore the assumed PDF is likely to result in an over-estimation of exposure to adults. Furthermore, the majority of commercial properties have limited exposed soils and this will limit the potential for soil and dust ingestion. For these reasons, the exposure estimates from soil and dust ingestion for the commercial land-use are likely to be over-estimates, possibly by as much as a factor of 10x.	**+ / +++**
Relative bioavailability (RBA). The CLEA modelling (deterministic and probabilistic) is based on the assumption of 100% RBA. The $LLTC_{oral}$ is based on dietary intake studies and it is possible that the bioavailability of cadmium in soil is less than via dietary exposure. Thus the exposure estimates using CLEA may be over-estimate uptake by a factor of 2x.	**● / +**
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	**+++**

Source of Uncertainty	Evaluation of uncertainty
outdoor soil contributes significantly to indoor dust in the majority of cases. 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 on the pC4SLs can be considered by looking at the RCF graphs in Section 4.2: over-and underestimation of the exposure would imply that the true RCF would be further to the left or right, respectively.

The uncertainty in the key exposure parameters for the residential (with consumption of homegrown produce) and allotments land-uses for cadmium, namely the soil to plant concentration factors, consumption rates and homegrown fraction have been further assessed by re-conducting the probabilistic modelling using alternative PDFs for these parameters for the allotments land-use, as described below:

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

Figure 4.10 shows the effects of using the alternative PDFs on the probability of exceedence graphs. As can be seen, use of the soil to plant concentration factors from the Devon and Cornwall crop surveys reduces the probability of exceeding the LLTC from 47% to 11% for the pC4SL of 3.9 mg/kg. Removing the correlation between homegrown fraction and consumption rate reduces the probability of exceedence from 47% to 34% for this pC4SL. Modelling the homegrown fraction as a uniform value of 1 results in the probability of exceedence increasing from 47% to 82%.

This sensitivity analysis shows that uncertainty in the PDFs creates considerable uncertainty in the estimates of probability of exceedence. However, in combination with the qualitative assessment of uncertainty presented in Table 4.4, it is considered likely that the probabilities of exceedence shown on Figures 4.2, 4.3, 4.5 and 4.8 are over-estimates.

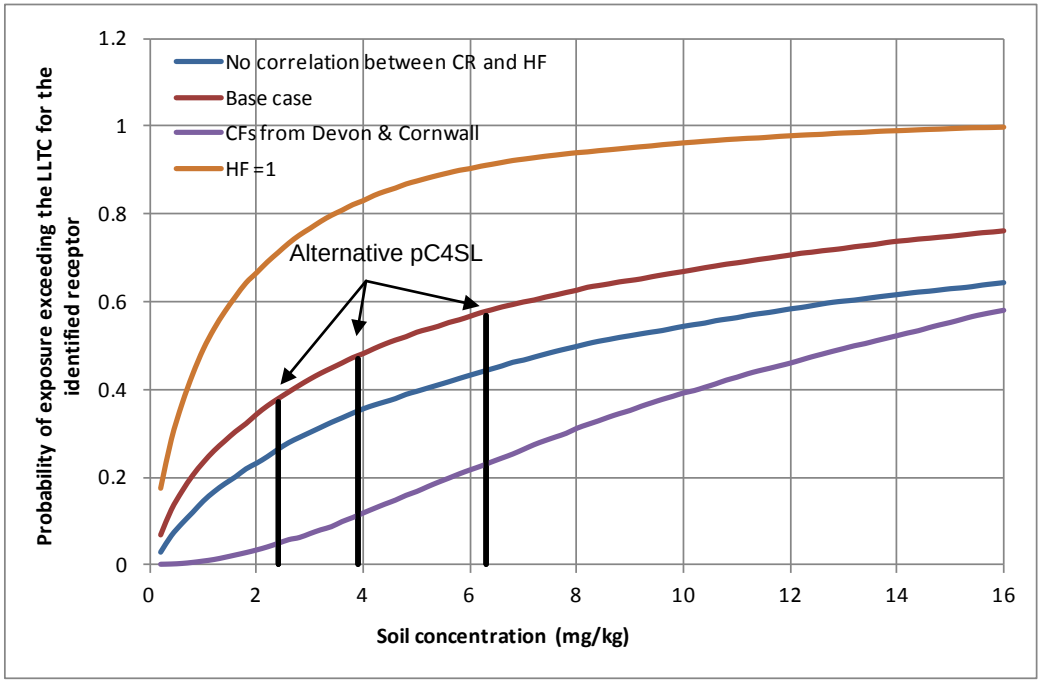


Figure 4.10: Probability of exposure exceeding the LLTCs for cadmium for allotments land-use with alternative values for produce consumption rate.

4.4 OTHER CONSIDERATIONS

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

- Median exposure from soils with concentrations of cadmium at the various pC4SLs for the residential and allotments land-uses are generally equal to background exposure. This is to be expected as the LLTCs are very close to the estimated mean daily intakes from non soil sources;

- The British Geological Survey (BGS) derived normal background concentrations (NBCs) for cadmium, which correspond to the upper confidence limit of the 95th percentile concentrations, for England and Wales. In England the reported NBCs range between 1 to 2.9 mg/kg for all domains other than 'mineral group 1' which has an NBC of 17 mg/kg (Defra, 2012). In Wales the reported NBCs range between 1 to 6.2 mg/kg for all domains (Defra, 2013). The pC4SLs for residential land-use are similar to the NBC for mineral group 1 in England and significantly above the NBCs for remaining domains. The pC4SLs for allotments land-use is below the NBC for mineral group 1 in England and close to the remaining NBCs for cadmium. The pC4SLs for commercial and public open space land-uses are significantly above the NBCs;

- The pC4SLs for allotments are close to the limit for cadmium in sludge amended soil of 3 mg/kg as defined under Schedule 2 of "The Sludge (Use in Agriculture) Regulations 1989";

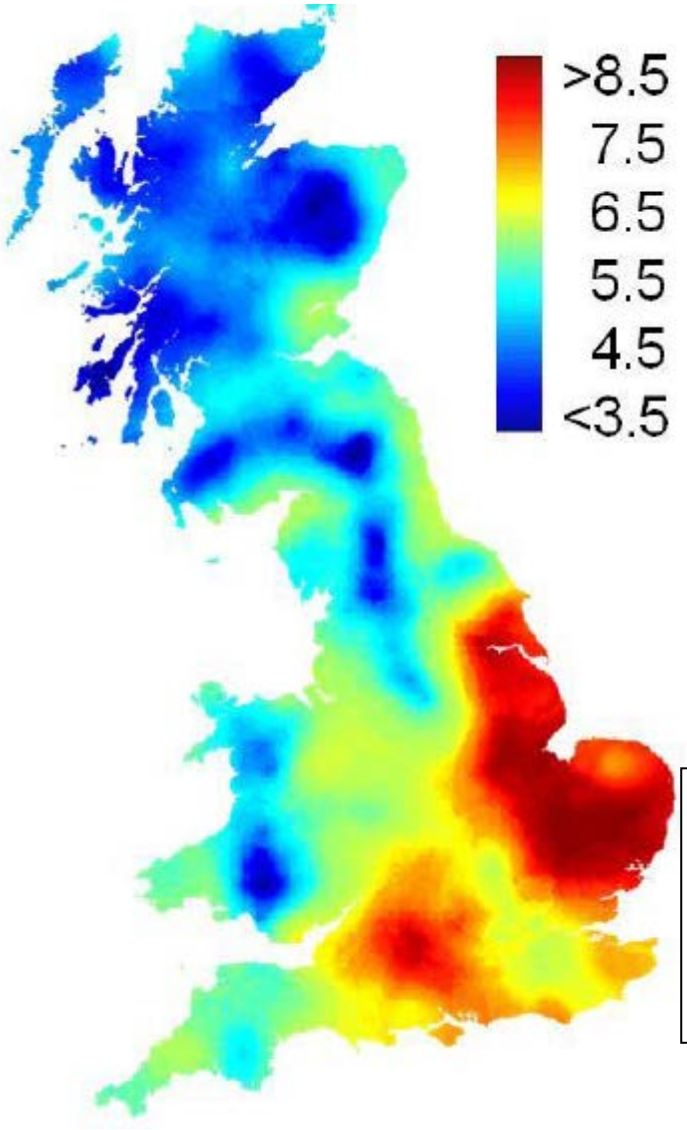
- Since cadmium is thought to be carcinogenic (although this might be via threshold mechanisms, as described above), it might be prudent to apply the "As Low as Reasonably Practicable" (ALARP) principle in relation to its remediation at specific sites (see EA, 2009a; 2009b for details). The principle 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.

- The consumption of homegrown produce is the principle pathway for residential (with consumption of homegrown produce) and allotments land-uses for cadmium. The soil to plant concentration factors are key parameters for estimating exposure from this pathway. The values for these parameters are based on the geomean from empirical estimates from soils that generally had a pH of 6 to 8. Soil to plant concentration factors may be significantly higher for low pH soils and therefore care should be adopted if applying the pC4SLs outside this range and especially at values less than 5, such as occurs in parts of Northern England, Scotland and West Wales (Figure 4.11).

- The relatively high variability in consumption rates, homegrown fraction and soil to plant concentration factors means that exposure may vary by more than an order of magnitude between individuals for the residential and allotments land-uses. The probabilistic modelling has shown that at the pC4SLs there may be individuals with exposures in excess of ten times the LLTCoral, particularly for the allotments land-use. Whilst such exceedences are likely to result in increases in the B2M biomarker for kidney effects, the actual health impacts of such exceedences are difficult to quantify.

- Epidemiological evidence from Shipham in England provides a line of evidence that significant exceedences of the LLTC may not result in measurable health effects. Shipham in the UK is reported to have high levels of cadmium in surface garden soils, ranging up to 360 $mg.kg^{-1}$. Many epidemiological studies have been carried out on populations living in the area. Early studies reported raised blood-cadmium levels in residents (Carruthers and Smith, 1979), and a small excess of hypertension, cerebrovascular, and genitourinary disease compared to control villages, although the influence of cadmium to such disease patterns was thought to be slight (Inskip *et al*., 1982; Carruthers and Smith, 1979). Latter studies concluded that there was no clear evidence of health effects from possible exposure to cadmium in Shipham despite the extremely high concentrations of cadmium in the soil (Elliott *et al*., 2000). Moreover, all-cause mortality rates in Shipham was similar to the control group and well below national average (Inskip *et al*., 1982).



Acknowledgement: Countryside Survey data owned by NERC – Centre for Ecology & Hydrology

Figure 4.11: Kriged concentrations of soil pH in uppermost 15 cm of soil (Emmett *et al*. 2010).

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 cadmium. These soil concentrations are the pC4SLs.

A range of pC4SLs have been derived 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 cadmium

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)	14	17	22
Residential (without consumption of homegrown produce)	87	150	150
Allotments	2.4	3.0	3.9
Commercial	220	420	410
POS_{resi}	120	NA	220
POS_{park}	560	NA	880

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.

The probabilistic modelling has indicated that the greatest uncertainty within the exposure modelling is associated with the consumption of homegrown produce pathway, stemming partly from the large degree of variability in produce consumption rates and the fraction consumed that is homegrown. Furthermore, there is a high degree of uncertainty in the soil to plant concentration factors used for modelling the plant uptake of cadmium.

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

As a final step within the C4SL derivation process, other relevant considerations are identified, which should have a bearing on any final choice of numbers. For cadmium, these take the form of recently published background levels in soil, estimates of background human exposure levels, severity of toxicological effect where the LLTC is exceeded and a review of epidemiological evidence of health impacts from cadmium 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 cadmium 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, 2009d) should be referred to for important caveats and supporting information regarding their use. Furthermore, the LLTCs have been derived using similar methods to those outlined in the Environment Agency’s HCV document (EA, 2009c), and the reader is referred to that document for the same reasons.

As described in the main report, the final C4SLs can be used in a similar manner to that described for SGVs in the Environment Agency’s “Using Soil Guideline Values”

document (EA, 2009e). Although they are unlikely to represent a “significant possibility of significant harm” (SPOSH), the likelihood of an exceedance of a C4SL being representative of SPOSH may be greater than if the default CLEA settings and toxicological criteria equivalent to minimal risk had been used in their derivation.

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APPENDIX F1

HUMAN TOXICOLOGICAL DATA SHEET FOR CADMIUM

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

Chemical: **Cadmium**

Human Health Hazard Profile - Key References

Authoratative bodies	Website	Checked (Y/N)	References
EA	http://www.environment-agency.gov.uk/	Y	EA Science report: SC050021 / TOX 3
FSA	http://www.food.gov.uk/	Y	MEASUREMENT OF THE CONCENTRATIONS OF METALS AND OTHER ELEMENTS FROM THE 2006 UK TOTAL DIET STUDY (January 2009) http://www.food.gov.uk/multimedia/pdfs/fsis0109metals.pdf : and See COT reference below.
HPA	http://www.hpa.org.uk/	Y	HPA compendium of chemical hazards. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1198504591766 : Cadmium Toxicological overview. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947375856
COC	http://www.iacoc.org.uk/	Y	No specific statement
COM	http://www.iacom.org.uk/	Y	No specific comments
COT	http://cot.food.gov.uk/	Y	COT Statement on the 2006 UK Total Diet Study of Metals and Other Elements. http://cot.food.gov.uk/pdfs/cotstatementtds200808.pdf
EU REACH	http://echa.europa.eu/information-on-chemicals/registered-substances	Y	EC, 2007. European Union Risk Assessment Report. Cadmium metal. Part II Human Health. 3rd Priority List, Volume 74. EUR 22767 EN. EU JRC Summary Risk Assessment Report 2008. http://echa.europa.eu/documents/10162/6434698/orats_summary_cadmium_en.pdf
EFSA	http://www.efsa.europa.eu/	Y	**(1)** Cadmium in food. Scientific Opinion of the Panel on Contaminants in the Food Chain (Question No EFSA-Q-2007-138) Adopted on 30 January 2009. EFSA Journal (2009) 980, 1-139. **(2)** TECHNICAL REPORT OF EFSA Meta-analysis of Dose-Effect Relationship of Cadmium for Benchmark Dose Evaluation.Prepared by the Assessment Methodology Unit. EFSA Scientific Report (2009) 254, 41-62. **(3)** SCIENTIFIC OPINION. Statement on tolerable weekly intake for cadmium. EFSA Panel on Contaminants in the Food Chain (CONTAM), EFSA Journal 2011;9(2):1975. **(4)** SCIENTIFIC REPORT OF EFSA Comparison of the Approaches Taken by EFSA and JECFA to Establish a HBGV for Cadmium, EFSA Journal 2011;9(2):2006.
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WHO	http://www.who.int/en/	Y	Cadmium in Drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/03.04/80/Rev/1. http://www.who.int/water_sanitation_health/dwq/chemicals/cadmium.pdf
RIVM	http://www.rivm.nl/English	Y	RIVM, 2001. Re-evaluation of human-toxicological maximum permissible risk levels. Chapter 1.3 Cadmium. RIVM Report 711701 025. Bilthoven, The Netherlands: National Institute for Public Health and the Environment. Available at: http://www.rivm.nl/bibliotheek/rapporten/711701025.html
ATDSR	http://www.atsdr.cdc.gov/	Y	TOXICOLOGICAL PROFILE FOR CADMIUM. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry, September 2012. http://www.atsdr.cdc.gov/toxprofiles/index.asp
USEPA	http://www.epa.gov/	Y	Latest IRIS record from 1994
Health Canada	http://www.hc-sc.gc.ca/index-eng.php	Y	PRIORITY SUBSTANCES LIST ASSESSMENT REPORT CADMIUM AND ITS COMPOUNDS, Government of Canada, Environment Canada, Health Canada, 1994, ISBN 0-662-22046-3. Drinking water standards http://wvlc.uwaterloo.ca/biology447/New_Pages_2011/WaterRegulations_CompoundFiles/cadmium.pdf
CSTEE	http://ec.europa.eu/health/scientific_committees/all_opinions/index_en.htm	Y	Opinion on: Position Paper on Ambient Air Pollution by Cadmium Compounds - Final Version, October 2000. Opinion expressed at the 24th CSTEE plenary meeting, Brussels, 12 June 2001.
EU working groups	http://ec.europa.eu/environment/air/pdf/pp_as_cd_ni.pdf	Y	EC 2000 Position paper: AMBIENT AIR POLLUTION BY As, Cd AND Ni COMPOUNDS. ISBN 92-894-2054-5. Luxembourg.

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

Chemical: **Cadmium**

I) Human Health Hazard Profile - Toxicological Evidence

Type of Evidence	POD type	POD value	Units	Species	Study Type	Classifications/Comments/Study Quality	Reference
1. Toxicokinetics							
Oral						Cadmium absorption after oral exposure in humans is relatively low (3–5 %) but cadmium is efficiently retained in the kidney and liver in the human body, with a very long biological half-life ranging from 10 to 30 years.	**EFSA 2009**
Inhalation							
Dermal							
2. Acute Toxicity							
Oral	LD50	72 to 300	mg CdO/kg	Rodent		**Classified R25: acutely toxic by the oral route**	
	NOEL	3	mg/one exposure	Human			**EU RAR 2008**
	Lethal dose	350 to 8,900	mg/one exposure	Human			**EU RAR 2008**
Inhalation	LOAEL	0.5	mg/m3 CdO	Rodent		**Classified R23: acutely toxic by the inhalation route**	**EU RAR 2008**
		1	mg/m3 Cd/8hr	Human		**Immediately dangerous to life**	**EU RAR 2008**
	Lethal dose	5	mg/m3 Cd/8hr	Human		**Lethal**	**EU RAR 2008**
Dermal						**No data**	
3. Irritation/Corrosivity							
Dermal						**No data**	
Eye						**No data**	
4. Sensitisation							
Dermal						**No data**	
Respiratory						**No data**	
5. Repeat-dose Toxicity						**Classified as T; R 48/23/25**	
Oral						Adverse bone and kidney effects	**Summarised best in ATSDR 2012 & EU RAR 2008 & EFSA 2009.**
	BMDLsd1						
	BMDL5						
Inhalation	NOAEL	0.025	mg CdO/m3	Rodent	13 week		
	NOAEL	0.01	mg Cd/m3	Hamster	16 month		
Dermal							
6. Genetic Toxicology						**Equivocal: positive observed genotoxicity attributed to thresholded cellular events, not direct DNA damage. Classification as Cat 3 Mutagen; Xn; R68.**	
In vitro							
In vivo							
7. Carcinogenicity						**IARC have classified Cd as a Class I human carcinogen (based on lung cancer). EU May 2002 Carc.cat 2 (T; R49, i.e. may cause cancer by inhalation) classification.**	
Oral						**No data**	
Inhalation						**Lung carcinogen: No quantitative animal data of sufficient quality for derivation of HBGVs**	**Takenaka et al. (1983) ; Oldiges et al. (1989); Glaser et al., 1990**
Dermal						**No data**	
8. Reproduction						EU category 3 (substances which cause concern for humans owing to possible developmental toxic effects) and to label the compounds with R63 (possible risk of harm to the unborn child)	EU RAR 2008
Oral	**LOAEL**	1	mg/kg/day	Rodent			EU RAR 2008
Inhalation	**NOAEL**	0.1	mg/m3	Rodent			EU RAR 2008
Developmental							
Teratogenicity						No data	
9. Human epidemiology data							
Oral	**Intake from BMDL5**	1.4	µg/kg/day	Human	Meta analysis of renal toxicity from Cd via the oral route from 35 epidemiology studies.	BMDL 5 = 4 µg Cd/g creatinine	EFSA 2009

Inhalation	Intake from BMDL5	0.029	µg/kg/day	Human	Meta analysis of renal toxicity from Cd via the inhalation route from selected epidemiology studies.	UCDL10 = 0.5 µg Cd/g creatinine; 0.1 µg/m^3	Thun et al., 1985; Stayner et al., 1992
Dermal						No data	

Most Sensitive Health Effect: **Renal effects, Bone effects, Lung cancer.**

Key

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

A) Oral Route	HBGVoral	Unit	UF used	PoD	Endpoint	Pivotal data used & Comments	Reference
US EPA 1994 RfD (food)	1	µg kg^{-1} bw day^{-1}	10	NOAEL; 10 µg kg^{-1} bw day^{-1}	Kidney Toxicity	USEPA 1994. Assumptions in modelling gut absorptions re food vs water (in order to achieve a no adverse effect concentration of 200 µg cadmium g^{-1} in the renal cortex) give rise to different RfDs for food and water intakes. (see below). UF of 10 used for human variability.	EPA IRIS Record 1994
WHO/JECFA 2011 PTMI	0.83	µg kg^{-1} bw day^{-1}	3.9	$BMDL_5$; 5.4 µg g^{-1} creatinine	Kidney Toxicity	Based on the provisional tolerable monthly intake, 25 µg kg^{-1} bw $month^{-1}$ (2011). Different models have been used on the same datasets as the EFSA evaluation . (see EFSA Journal 2011 reference). In the JECFA report a breakpoint of 5.24 (CI: 4.94 - 5.57) µg cadmium/g creatinine was used as a point of departure.	JECFA WHO 2011 Technical Report Series No. 960
EU RAR 2008	0.66	µg kg^{-1} bw day^{-1}	3	LOAEL; 2 µg g^{-1} creatinine	Kidney Toxicity & bone toxicity	Based on the body of all epidemiology data for repeat dose effects and data in Jarup et al 2000 (OSCAR study). UF of 3 used to convert the LOAEL to NOAEL, as kidney effects were thought to be benign non adverse effects. No other UFs used for interindividual differences as these were already included in the LOAEL derived from a general population.	EU JRC Summary Risk Assessment Report 2008.
US ATSDR 2012 Intermediate MRL	0.5	µg kg^{-1} bw day^{-1}	100	BMDLsd1: 0.05 mg Cd/kg/day	Bone toxicity	BMDLsd1 = 1 standard deviation from control). Default interspecies and intraspecies UFs of 10 x10 applied.	Appendix A in ATSDR September 2012
US EPA 1994 RfD (water)	0.5	µg kg^{-1} bw day^{-1}	10	NOAEL; 5 µg kg^{-1} bw day^{-1}	Kidney Toxicity	USEPA 1994. Assumptions in modelling gut absorptions re food vs water (in order to achieve a no adverse effect concentration of 200 mg cadmium g^{-1} in the renal cortex) give rise to different RfDs for food and water intakes. (see above). UF of 10 used for human variability.	EPA IRIS Record 1994
RIVM 2001 Maximum Permissible Risk Level (TDI)	0.5	µg kg^{-1} bw day^{-1}	2	UCD = 2.5 µg g^{-1} creatinine; 1 µg kg^{-1} day^{-1}	Kidney Toxicity	Kidney effects seen at 2.5 µg Cd g^{-1} creatinine, reached after intake over 40-50 yrs of daily exposure to 1 µg kg^{-1} bw day^{-1}. UF of 2 used to account for population effects over a longer 60-70 year lifespan.	
EFSA 2009 & 2011 TDI	0.36	µg kg^{-1} bw day^{-1}	3.9	$BMDL_5$; 4 µg g^{-1} creatinine	Kidney Toxicity	Tolerable weekly intake 2.5 µg kg^{-1} bw $week^{-1}$. Re-Adopted 18.01.11. Based on a $BMDL_5$ divided by a CSAF of 3.9 to account for interindividual variation, giving 1 µg Cd g^{-1} creatinine being the dose that would not cause a level of beta-microglobulin greater than 300 µg g^{-1} creatinine, this being the chosen marker of adverse renal toxicity.	EFSA Journal (2009) 980, 1-139.
CLEA 2009 Minimal Risk HCV	**0.36**	µg kg^{-1} bw day^{-1}	N/A	N/A	Kidney Toxicity	Intake value based upon the EFSA Opinion 2009 above i.e. PTWI of 2.5 µg kg^{-1} bw day^{-1}.	EA Report SC050021/Tox 3
US ATSDR 2012 Chronic MRL	0.1	µg kg^{-1} bw day^{-1}	3	$UCDL_{10}$=0.5 µg g^{-1} creatinine; 0.33 µg/kg/day	Kidney Toxicity	Based upon a meta analysis of 7 human epidemiological datasets in (Buchet et al. 1990; Järup et al. 2000; Jin et al. 2004c; Kobayashi et al. 2006; Shimizu et al. 2006; Suwazono et al. 2006; Wu et al. 2001). POD is a urinary cadmium dose (lower 95% confidence limit) yielding a 10% increased incidence (UCDL10) of low molecular weight proteinurea = 0.5 µg g^{-1} creatinine, which was converted using a kinetic model to 0.33 µg/kg bw/day. UF of 3 used for human variability. NB. Studies using a cut-off value for β2-microglobulin of ≥1,000 µg/g creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β2-microglobulin levels of 1,000–10,000 µg/g creatinine were indicative of irreversible tubular proteinuria. N.B. The lowest value was from the European dataset (Buchet et al. (1990), Suwazono et al. (2006), and Järup et al. (2000)) and yields the $UCDL_{10}$ cited as the chronic MRL.	Appendix A in ATSDR September 2012

Comment: NB. EFSA 2009/2011 have performed a meta analysis of 35 studies and focused on β2 microglobulin as the marker of renal toxicity, ATSDR in 2012 have drawn upon three European studies and used α1 microglobulin as a more sensitive marker. COT have endorsed the use of the approach in EFSA 2009.

Current UK oral HCV

CLEA HCV	0.36	µg kg-1 bw day-1	N/A	N/A	Kidney Toxicity	Intake value based upon the EFSA Opinion 2009 above i.e. PTWI of 2.5 mg kg-1 bw day-1.

B) Inhalation Route	HBGVinh	ng kg^{-1} bw day^{-1}	HBGVinh	ng m^{-3}	UF used	PoD	Endpoint	Pivotal Study used & Comments	Reference
ATSDR 2012 Chronic MRL	*2.86*	*ng kg^{-1} bw day^{-1}*	10	ng m^{-3}	9	$UCDL_{10}$; 0.5 µg g^{-1} creatinine	Kidney Toxicity	2012 meta analysis of epidemiology studies as per chronic oral MRL plus additional studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). POD is a urinary cadmium dose lower 95% confidence limit yielding a 10% increased incidence (UCDL10) of low molecular weight proteinurea. The ICRP 1994 and Kjellström-Nordberg pharmacokinetic (1978) models were used to simulate the urinary cadmium levels that correspond to a given inhalation exposure. Background dietary intake was already factored into the model yielding a tolerable atmospheric conc of 0.1 µg m^{-3}. UF of 3 for increased susceptibility of diabetics and a modifying factor of 3 was used to account for a lack of adequate human data that could be used to compare the relative sensitivities of the respiratory tract and kidneys. Conversion for 70kg adult and 20m^3 per day air intake.	Appendix A in ATSDR September 2012
CSTEE 2001 Limit value	*1.86*	*ng kg^{-1} bw day^{-1}*	6.5	ng m^{-3}	100	LOAEC; 650 ng m^{-3}	Kidney Toxicity	Buchet et al. (1990) and Järup et al. (2000) studies, accounting for all exposure routes, based on atmospheric level that produces urinary excretion of 2.7 µg per 24 hrs. UF of 10 to account for using a LOAEL and 10 for human variability.	Opinion expressed at the 24th CSTEE plenary meeting, Brussels, 12 June 2001
US EPA 1994 'Official' Limit value	*1.71*	*ng kg^{-1} bw day^{-1}*	6	ng m^{-3}		Inhalation unit risk; 1.8 x 10^{-3} per µg m^{-3}	Lung Cancer	Based on human lung cancer data from Thun et al 1985, USEPA derived a limit value posing an ELCR of 1 in 100,000.	US EPA IRIS Record 1994
EC Working Group 2000 Limit value	*1.43*	*ng kg^{-1} bw day^{-1}*	5	ng m^{-3}	50	LOAEL; 270 ng m^{-3}	Kidney Toxicity	Kidney tox data (LOAEL) from Thun et al 1991 converted to continuous lifetime exposure for the general population. The occupational LOAEL is extrapolated from 8 hours to 24 hours, from 225 working days to 365 days and distributed over an average human lifetime of 75 years. The overall conversion factor is 0.0027 (8/24 x 225/365 x 1/75). Consequently , by applying this factor, the LOAEL (occupational) of 100 µg/m^3 x years can be converted to a LOAEL (continuous) of 270 ng/m^3 = 270 ng m^{-3}. UF of 5 for conversion of LOAEL to NOAEL, and 10 for interindividual differences used to derive a limit value. Comparing with the WHO AQG and EPA ELCR, a limit value of 5 ng m^{-3} gives an ELCR of 1 in 100,000, which is protecitve of cancer effects as well as renal toxicity.	
WHO 2000	*1.43*	*ng kg^{-1} bw day^{-1}*	5	ng m^{-3}			Kidney toxicity	Air quality guideline driven by the need to prevent increases in cadmium levels in the kidney. Reference made to US EPA cancer risk estimate but this is not given significant weight, due to likely confounders in human cancer data. Limit value of 5 ng m^{-3} set in the range of current ambient levels "to prevent any further increase of cadmium in agricultural soils likely to increase the dietary intake of future generations".	WHO Air Quality Guidelines 2000
CLEA 2009 HCV	**1.43**	ng kg^{-1} bw day^{-1}	5	ng m^{-3}	50	LOAEL; 270 ng m^{-3}	Kidney Toxicity	Based on the EC working group 2000 derivation of the limit value. LOAEL from occupational exposure (Thun et al 1991) was converted to continuous exposure of 270 ng m^{-3}. UF of 5 for LOAEL to NOAEL conversion and 10 for interindividual variation.	EA Report SC050021/Tox 3
US EPA 1999 DRAFT limit value under external review	*0.60*	ng kg^{-1} bw day^{-1}	2	ng m^{-3}		Inhalation Unit Risk: 4.4x10^{-3} per ug/m^3	Lung cancer	Based on human lung cancer in Stayner et al., 1992 (Follow up of Thun et al 1985). DRAFT limit value in ng/m^3 posing a ELCR of 1 in 100000. It should be noted that these data "may be confounded at least in part by exposure to other known lung carcinogens such as arsenic and cigarette smoke".	EPA Toxicological Review 1999 - DRAFT NOT TO BE CITED AS OFFICIAL EPA VIEW

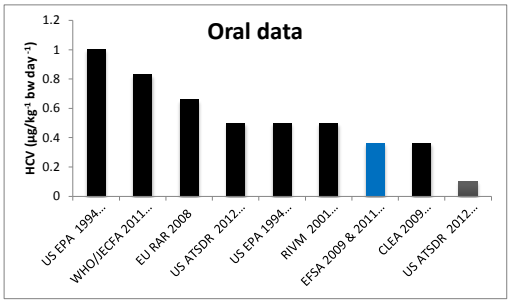
Current UK inhalation HCV

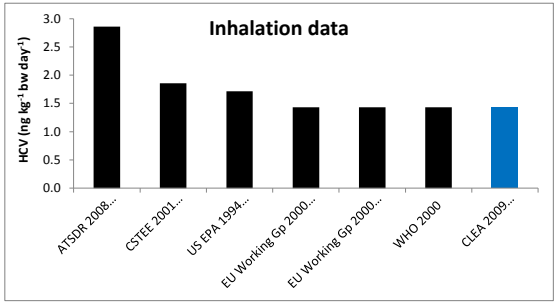
CLEA HCV	1.43	ng kg-1 bw day-1	5.005	ng m-3	50	LOAEL; 270 ng m-3	Kidney Toxicity	Based on the EC working group 2000 derivation of the limit value. LOAEL from occupational exposure (Thun et al 1991) was converted to continuous exposure of 270 ng m-3. UF of 5 for LOAEL to NOAEL conversion and 10 for interindividual variation.

C) Dermal Route	HBGVderm	Units	UF used	POD	Endpoint	Pivotal Study used & Comments	Reference
No evidence of specific toxicity via the dermal route. Use Oral HCV and an estimate of skin absorption.							

COT/COC Opinion: NB. The EFSA Oral PTWI of 2.5 µg Cd kg-1 bw was endorsed by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) when it assessed UK dietary cadmium intake in 2009, though COT noted it considered the TWI to be conservative (COT, 2009).

Positioning of UK Minimal Risk HCV vs other HBGV from authoritative bodies





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

	Pathways	Units	Adults	Children	Refs
Food (average)	Oral	µg kg^{-1} bw day^{-1}	0.27-0.43	0.36-0.49	EFSA 2009
Food (high)	Oral	µg kg^{-1} bw day^{-1}	0.36-0.55	0.78	EFSA 2009
Food vegetarians	Oral	µg kg^{-1} bw day^{-1}	0.78	-	EFSA 2009
Water	Oral	µg kg^{-1} bw day^{-1}	0.0057	0.01	EA 2009
House dust	Oral	µg kg^{-1} bw day^{-1}	0.076	0.607	EFSA 2009
Air	Inhalation	µg kg^{-1} bw day^{-1}	0.0024	0.0033	EFSA 2009
Smoking	Inhalation	µg kg^{-1} bw day^{-1}	0.35-0.70	-	EFSA 2009
MDI	Oral	µg kg^{-1} bw day^{-1}	0.19	0.5	EA 2009
MDI	Inhalation	µg kg^{-1} bw day^{-1}	0.0003	0.0007	EA 2009

Comment: N.B. Average daily dietary intake is at or above the 'minimum risk' value of 0.36 µg kg-1 bw day-1

IV) LLTC derivation

A) ORAL

Choice of Pivotal Data	Dosing vehicle	Doses	Units	Species	Study Type	Comments	Reference
Cadmium kidney toxicity as indicated by elevated levels of β2-microglobin (β2M) in urine. Approach taken by EFSA in 2009.	N/A	N/A	µg β2M/g creatinine	Human	Meta analysis of 165 paired datasets from 35 human epidemiology studies	A non-standard 'Hybrid' approach was taken in the BMD modelling of a comprehensive statistical analysis of data from 35 epidemiology studies studies. The 'dose' is expressed as an internal biomarker concentration of cadmium in urine that is associated with a level of β2-microglubulin protein per g of creatinine in urine. β2-microglubulin is a biomarker of kidney toxicity. Toxicokinetic models are then used to translate the internal exposure dose (in mg/kg bw/day) that would lead to a level of cadmium in urine.	EFSA Journal (2009) 980, 1-139. EFSA Scientific Report (2009) 254, 41-62.

BMD Modelling (if relevant)

Model used S-shaped Hill model _ Full details in EFSA Techical Report 2009

Cut off = 300 µg β2 microglobulin/g creatinine (threshold for reversible adverse renal effects)

	Total population		Caucasions only (more sensitive than Asian), adjusted for gender		Focus population: >mean age 50yrs adjusted for ethnicity, occupational data	
	BMD5	BMD10	BMD5	BMD10	BMD5	BMD10
BMD modelling (value) (µg Cd/g creatinine)	4.09	4.72	4.65	5.32	5.25	5.73
	BMDL5	BMDL10	BMDL5	BMDL10	BMDL5	BMDL10
BMDL modelling (value) (µg Cd/g creatinine)	3.68	4.32	3.84	4.53	4.45	4.97

Cut off = 1000 µg β2 microglobulin/g creatinine (threshold for irreversible adverse renal effects)

	Total population		Caucasions only (more sensitive)		Focus population: >mean age 50yrs adjusted for ethnicity, occupational data	
	BMD5	BMD10	BMD5	BMD10	BMD5	BMD10
BMD modelling (value) (µg Cd/g creatinine)	5.83	6.4	6.8	7.31	6.33	6.77
	BMDL5	BMDL10	BMDL5	BMDL10	BMDL5	BMDL10
BMDL modelling (value) (µg Cd/g creatinine)	5.39	5.99	5.95	6.51	5.46	5.94

Basis for Minimal risk = Nominal $BMDL_5$ of 4 µg Cd /g creatinine (chosen 5% increased prevalence of exceeding the cut off of 300 µg β2 microglobulin/g creatinine)
CSAF of 3.9 (see Table 1 in EFSA 2011) applied to a minimal risk HBGV: 4/3.9 = 1 µg Cd /g creatinine

Conversion of biomarker modelling to an intake dose in mg/kg bw/day

Toxicokinetic modelling **Described in full in Amzal et al., 2009**

Comments: BMD5 or BMD10 = the benchmark dose at which there is a 5% or 10% increased prevalence of exceeding the cut off.
The CSAF used is dependent upon the choice of percentage point (see table 1 in EFSA Journal 2011 reference). NB. In this hybrid approach, a BMD5 = a 10% incidence, a BMDL10 = a 15% incidence (10% extra risk above background)

Figure 1 Shape of the dose-effect curve from the meta-analysis of data on β2-microglobulin concentration in urine vs cadmium concentration in urine. (Figure 15 in EFSA 2009a)

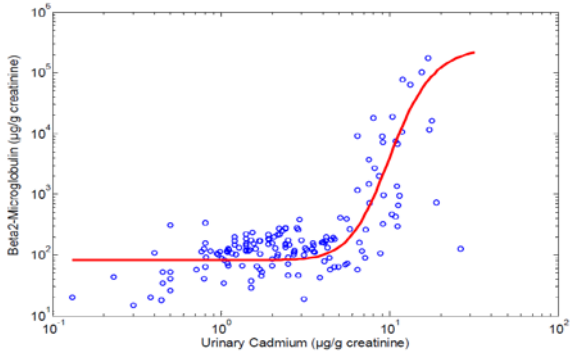


Figure 2 = Figure 20 from EFSA (2009b)

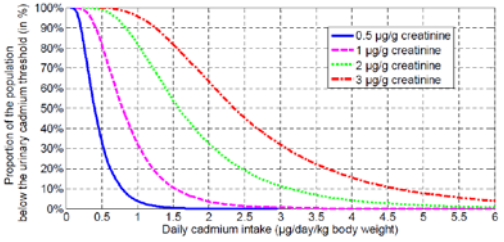
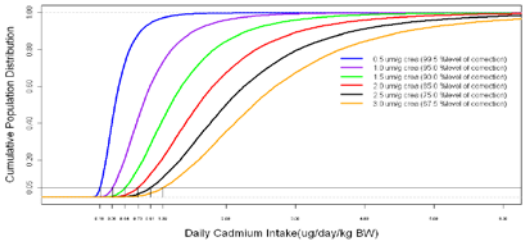


Figure 3 = Figure 2 from EFSA 2011b)



Point of Departure for ORAL LLTC:	Value	Units
Type of PoD	BMDL10	µg Cd/g creatinine
Description of PoD	exceeding the cut off of 300 µg β2	
Value selected	4.3	µg Cd/g creatinine

Chemical Specific Adjustment Factor to account for uncertainties in the data		
	Range	Selected value
Intraspecies	1 - 10	2.9
Interspecies	1 - 10	1
Quality of study	1 - 10	1
Severity of Effect	1 - 50	1

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

CSAF = 2.9 **(for thresholded chemical)**

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

ELCR =

Lifetime averaging to be applied in CLEA Yes

Oral LLTC calculation:

			Units
LLTC (Thresholded chemical)		1.5	µg Cd/g creatinine
	equates to	0.54	µg Cd kg^{-1} bw day^{-1}
LLTC (Non Thresholded chemical)			
LLTC (Human carcinogen)		Classified as IARC Class I human carcinogen; No quantitative data but considered thresholded from mechanism of action evidence.	

Comments: The BMD approach taken in EFSA 2009 is pivotal to informing the quantitative risk assessment decision of deriving an LLTC value around the endpoint of renal effects. The LLTC of 0.5 µg Cd kg^{-1} bw day^{-1} is equal to the ATSDR Intermediate MRL set for bone effects.

B) INHALATION							
Choice of Pivotal Data	**Dosing vehicle**	**Doses**	**Units**	**Species**	**Study Type**	**Comments**	**Reference**
Cadmium kidney toxicity as indicated by elevated levels of low molecular weight proteins in urine. Approach taken by ATSDR 2012.				Human	Meta Analysis of 11 Human epidemiology studies as described in ATSDR September 2012	NB. Most sensitive data was drawn from European cohorts.	ATSDR 2012 Toxicological review

BMD Modelling (if relevant)

Software used SPSS (version 12.0.1; SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA) for analyses. Hybrid approach; Maximum likelihood approach to fit the dose–response curve to the data (Crump 1995)

Effect for BMD modelling = cut off of N-acetyl-β-D-glucosaminidase 3.6 µg/g creatinine, renal tubule effects marker.

BMD modelling (value) (µg Cd/g creatinine)	BMR1	BMR5	BMR10	BMR15	BMR20
Adverse response incidence		10%	15%		
Urinary cadmium dose (UCD)		0.64	1.08		
UCDL		0.5	0.83		

Comments: The cutoff for adverse effects was defined as the 95th percentile, obtained by the model at no Cd exposure (U-Cd = 0) in the population under study, rather than as the 95th percentile of the effect marker in an apparently low-exposed "reference" population, with little information on the overall comparability. The obtained critical U-Cd levels then corresponds to an adverse response of 10% (5% additional probability of adverse response; BMR = 5%) or 15% (10% additional probability of adverse response; BMR = 10%).

Conversion of biomarker modelling to an intake dose in mg/kg bw/day

Toxicokinetic modelling **Described in ATSDR 2012**

Point of Departure for INHALATION LLTC:	**Value**	**Units**
Type of PoD	UCDL10	
Description of PoD	10 % increased prevalence of exceeding the cut off of 3.6 µg NAG /g creatinine	
Value selected	0.5	µg Cd/g creatinine

Chemical Specific Adjustment Factor to account for uncertainties in the data		
	Range	**Selected value**
Intraspecies	1 - 10	3
Interspecies	1 - 10	1
Quality of study	1 - 10	3
Severity of Effect	1 - 50	1

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

INHALATION LLTC calculation:

		Units
LLTC (Thresholded chemical)	0.17	µg Cd/g creatinine
equates to	10	ng/m^3
equates to	2.86	ng/kg bw/day

LLTC (Non Thresholded chemical)

LLTC (Human carcinogen) Classified as a human lung carcinogen. ELCR = 1 in 60000 based upon EPA 1994

NB. Cancer studies confounded by co-exposures to tobacco smoke and arsenic.

Human Toxicological Data Sheet - Cadmium

May 2013

CSAF =	9	**(for thresholded chemical)**
CSM =		**(for non-thresholded chemical)**
ELCR at LLTC	1 in 60000	based upon US EPA 1994 risk estimates using Thun et al 1985
	1 in 20000	based upon DRAFT US EPA 1999 risk estimates using Stayner et al.1992
Lifetime averaging to be applied in CLEA	No	

Physiological conversion factors		
	Value	**Units**
Body weight	70	kg
Inhalation rate	20	m^3

APPENDIX F2

REFERENCE LIST OF PUBLICATIONS USED by EFSA (2009) FOR BENCHMARK DOSE MODELLING OF β2 MICROGLOBULIN

AOSHIMA K, FAN J, CAI Y, KATOH T, TERANISHI H AND KASUYA M, 2003. Assessment of bone metabolism in cadmium-induced renal tubular dysfunction by measurements of biochemical markers. *Toxicol Lett* 136 (3), 183-192.

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KARAKAYA A, SUZEN S, VURAL N AND OFLAZ G, 1993. Evaluation of the biological threshold value of urinary cadmium concentration in a group of workers. *Bull Environ Contam Toxicol* 51 (4), 483-489.

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KIM S, KWON HJ, CHEONG HK, CHOI K, JANG JY, JEONG WC, KIM DS, YU S, KIM YW, LEE KY, YANG SO, JHUNG IJ, YANG WH AND HONG YC, 2008. Investigation on health effects of an abandoned metal mine. *J Korean Med Sci* 23 (3), 452-458.

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APPENDIX F3

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