***SP1010 - Development of Category 4 Screening Levels for Assessment of Land Affected by Contamination (C4SLs)***

***Final Draft Project Report***

***Peer review comments: Professor Alan R Boobis, Director of Toxicology Unit, Imperial College, 19 July 2013***

**General comments**

Given the policy requirements and context, this appears to be a reasonable approach to the development of Category 4 Screening Levels (C4SLs) but there are some presentational issues.

The approach relies to a considerable extent of previous authoritative evaluations of the substance under consideration, for example by JECFA or EFSA. This seems a sound approach, avoiding undue resource utilisation and helping to ensure a degree of harmonisation.

The level of protection is less well defined than in conventional risk assessments, albeit it is not very well defined even then. Different approaches have been used to select the POD for derivation of a LLTC. These vary from use of the BMD rather than the BMDL, choice of a higher BMDL than the lowest value available from acceptable models, and use of a BMR above the normal default. Whilst this variation in approach is often of necessity, because of the nature of the information available, it could lead to presentational difficulties.

The approach to threshold and non-threshold effects varies. In one, the "relaxation" of conservatism is such that the LLTC derived is of low, but not minimal, concern whilst in the other the derivation of LLTC values is as for conventional HBGVs, and the "relaxation" of conservatism is in what is considered an "acceptable" margin compared to estimated human exposure.

The final choice of C4SLs includes non-science, policy issues, such as cost of remediation and socio-economic factors. These should be better separated from the scientific factors used in the assessment of C4SLs, otherwise risk assessment and risk management considerations are not easily distinguishable.

Probabilistic approaches have been used effectively to explore exceedences of the average daily exposure at the LLTC and the soil concentration at the provisional C4SL. However, this takes account only of variables in estimating exposure, and not in estimating toxicity. Whilst this is acknowledged in the report, given the above, it does lead to significant uncertainty on the toxicity side as to the level of protection being achieved. This may well not be consistent for substance to substance, given the variation in approaches adopted.

**Specific comments**

Four of the examples are metals or metalloids.

Presumably definition of contaminated land is quantitative, as all of the contaminants will be present in all land at some level. Hence, term "contaminated land" could be misunderstood.

4.21d – This is entirely policy and needs to be distinguished from some of the other reasons for assigning cat 4.

The approach is highly subjective, which levels of risk are not minimal but still low enough to be considered acceptable.

Use of a tiered approach is appropriate and to be supported.

1.3 – Development of C4SLs: Whether to modify tox, exposure or both should depend on where the greatest uncertainty lies.

It is not clear why a new parameter, the C4SL, is required to replace the SGV in these assessments. Would an alternative have been to use the SGVs and interpret the MOE appropriately? Indeed this is done for compound with no threshold in their dose-response relationship.

The difficulty with the LLTC concept is that it represents an undefined risk level. The HCVs represent negligible risk, whilst the MOE for genotoxic carcinogens provides a nominal low risk level that has been agreed as a matter of policy. How can a level (the LLTC), which is defined as above minimal, still be suitably protective of health? Whilst it might be possible to define levels of substances with good human data, what will be done about substances where this is not the case? There are some presentational difficulties here.

Table 2.1: It would appear that potential effects on health from contaminated land are judged to a different standard from exposure to such contaminants from other sources, such as food.

2.2, line 601, line 731: It is an assumption that there is no dose below which effects occur for so called non-threshold compounds. There will certainly be doses below which no effect can be observed, for example due to methodological limitations and study power.

Page 16, line 622: Is no consideration given to the human relevance of the endpoint, as is done in other risk assessments?

Line 624: Choice of the highest NOAEL from several studies depends on careful consideration of relevant studies, and factors such as dose-spacing and consistency between studies.

Line 629: It is almost certain that the true no effect level is different from the NOAEL.

Line 631: What is meant by a true "LOAEL"? By definition this is the lowest dose at which there is a statistically significant difference from the controls. Hence, it is an operational parameter and does not have a "true" value.

Line 717: Inter-species difference might be due more to difference in toxicokinetics than toxicodynamics, but it is probably not accurate to say "largely" due to such differences.

Line 770: The exposure used to calculate the MOE for a genotoxic carcinogen should be chosen carefully, and adequately justified.

Line 815: The factors justifying the use of the additional 100-fold factor for deriving a MOE have not yet been generally agreed.

Line 822: Where does the suggestion that a MOE of 5000 might be considered of low concern come from?

Line 826: In general, the MOE approach does not lead to a HBGV in any circumstances.

Line 830: Is the TDI a regulatory standard? Is it not the associated exposure value, for example the maximum concentration in food or water, that is the regulatory standard?

Line 847: A closer analogy for JECFA would be with the provisional maximum tolerable daily intake (PMTDI).

Line 872: The implication that the NOAEL is a threshold dose should be avoided if possible. In general, the NOAEL and the BMDL10 for a threshold effect determined in a typical guideline study are numerically similar. It is the application of conservative uncertainty factors to the NAOEL that results in a human guidance value that is considered to be of negligible risk (as explained earlier in the report).

Line 893: Assuming a linear dose-response relationship from the POD and the human exposure level associated with the specified excess risk. In general, the argument for preferring the MOE approach is that it avoids the need to specify what is considered an acceptable excess risk.

Line 942: FQPA requires an additional factor of 10 for infants and children unless there are data suggesting that this is not necessary. Hence, it is a default first step in the derivation of a HBGV for a pesticide.

Line 953: Nevertheless, for a number of compounds, including pesticides, the pivotal POD will have been selected from amongst those that include PODs for developmental and reproductive effects.

Line 992: The COC has commented on the US EPA document on life stage sensitivity to carcinogens (July 2006; http://www.iacoc.org.uk/meetings/Minutes13.07.2006.htm).

Line 1003: Is this consistent with the assumption regarding children's susceptibility by other department and agencies in the UK?

Line 1056: Alternatively, a scientific approach could be used in interpreting the margin of exposure relative to the HCV, without specifically deriving a new value. The advantage of this would be that the margin between a value considered to be of negligible (threshold) or defined (non-threshold) concern (the HCV) would then be transparent.

Page 26, box 3a: The implication here is that it would be possible to use NOELs or LOELs. Should there not be some consideration of adversity, particularly given the definitions of harm used earlier (Table 2.1).

Page 26, box 5a: Why is the exposure level obtained using a CSM the same as that when using a generic margin?

Page 26, box 5b: The line for using CSAFs on the POD indicates that the resulting level will be higher than when using a default. Of course, this may not always be the case.

Line 1093: Where it is stated that a POD should be determined from the pivotal study for the endpoint and exposure route, does this mean identification of the POD that was used as the basis of the relevant HBGV or something more than this?

Line 1127: It should be noted that OECD TG No. 443 serves a similar purpose to that of OECD TG No. 416, and allows the same biological systems and processes to be evaluated.

Line 1163: Option 2c is not clear. According to the figure, the starting point is a HBGV, which presumably was derived from a POD. Hence, the instance cited would not apply.

Line 1218: This does not seem entirely logical, given that numerically the BMDL10 (or 5) is similar to the NOAEL in many studies conducted using acceptable guidelines, e.g. OECD. Hence, use of the LOAEL for a substance where a BMD cannot be calculated, will lead to an inconsistent risk level compared with that for compounds where a BMDL can be calculated.

Line 1244: What is meant by substances that need "special consideration"?

Line 1257: This introduces a dual approach to assessing soil values. One involves deriving a toxicological value taking into account pragmatic considerations such that, whilst of low concern, it is not of minimal concern. The other is to interpret the toxicological value using a different margin from that associated with a low level of concern. This could be very confusing in interpreting LLTCs, as this would require detailed information on their derivation. In the interests of transparency, this is not ideal as the LLTC values will be available to the community at large independent of their derivation.

Line 1257: Could some justification for the value of 5000 be provided?

Line 1271: See comments above re additional sources of uncertainty. The consequence is that there is currently insufficient information to judge whether information on any of these factors would justify modifying the 100-fold factor. For example, if information on interindividual differences in cell cycle control and DNA repair were available, how would this be used to adjust the value? Perhaps the report should acknowledge the current status and indicate areas of possible refinement in the future.

Page 31, Table 2.3: It should be noted that this table does not cover all of the factors that would have to be considered in interpreting the margin of exposure for a genotoxic carcinogen.

Line 1297: This was a urinary cadmium concentration associated with a low level of concern.

Line 1305: Perhaps reference could also be made here to Table 2.3.

Line 1335: Is the input of an epidemiologist needed at this stage?

Line 1361: Does this include carcinogens known to have a mode of action that does not involve genotoxicity?

Line 1358: If the BMD and the ELCR are derived from the same human population data to determine the same risk level, it is unclear how one would be more or less reliable than the other.

Page 34, Table 2.4: Is the difference in recommendation for use of BMD in deriving HCVs and LLTCs more one of time, in that the HCV guidance was written some time earlier. Presumably there is no scientific distinction in preference.

Again, there needs to be some clarity on the use of NOELs and LOELs, as opposed to NOAELs and LOAELs.

ELCR: There is some confusion between the table and the text. In line 1360, mention is made of an ELCR of 1 in 100,000 but the table refers to ELCRs of 1 in 1,000 – 1 in 5,000. This is also the first time mention is made of use of a range of values for this estimate.

Page 36, Table 3.1: Why is there no allowance of consumption of fruit and vegetables in the commercial scenario, yet there is for ingestion of dust derived from soil indoors? Is this because this would be covered in the residential scenario?

Line 1515: Does this mean that similar susceptibility is assumed from 0 – 12 months of age?

Line 1803: This is quite a strong statement and there is some uncertainty about the value to use for AT, at least.

Line 2033: It is not clear why it would be assumed that children would have greater regular contact with soils in an allotment than in a garden (cf line 2073 & 2103).

Line 2090: Would an adult not be exposed for at least part of almost every day to indoor dust?

Line 2095: Why a different number of days for dermal exposure than for general exposure frequency in the commercial scenario (cf line 2089)?

Line 2120: Is there any danger of double counting with the assumptions used, i.e. that a child spends more than 365 days either at home or the allotment?

Line 2169: It seems intuitive that soil contact will occur more than once per day. Is this accounted for by the assumption that the soil remains adherent after a single contact and that absorption occurs continuously from first contact until washing?

Line 2282: Is it worth noting that potency varies inversely with HCV?

Line 2399: The logic here seems reasonable. In this case particle size is simply a determinant of systemic exposure.

Line 2673: What are the default home-grown fractions used in CLEA?

Line 2720: Should this parameter be contaminant conc. in indoor air (mg $m^{-3}$)?

Line 2735: Is it not possible for a volatile substance like benzene to disperse into air directly from soil, rather than via water?

Line 2844: It should be noted that soil will not necessarily be the only source of volatiles in indoor air.

Line 3075: Presumably there is some uncertainty on the use of activity profiles based on measurements made over 15 years ago.

Line 3340 et seq: This approach to background exposure can be used when the HCV is calculated using similar considerations as for other HBGVs. However, when the LLTC is calculated on the basis of a different acceptable risk, will this not introduce some complications as the background will be held to different exposure standards? For example presumably it could lead to inconsistencies in assessments when the proportion of background to soil-derived exposure varies for different compounds, or even different scenarios.

Line 3413: Given the above, this would seem the most reasonable way to use background exposure in such assessments.

Line 3422: The reverse is also a possibility. For example, EFSA will add soil-derived and other exposures to that from food when determining whether the TDI for a contaminant is exceeded.

Line 3437: There may need to be discussion with those involved in the risk assessment of other media before reaching a final conclusion on this.

Page 84, Figure 5.3 – Formatting of x-axis labels (wrapping).

Page 85, Table 5.3: Soil and ingestion rate – "this uncertainty is unlikely to result in more than a factor of two over or underestimation in exposure.", yet the symbols indicate from negligible to 2-fold overestimation.

Relative bioavailability – "may over-estimate oral exposure from ingestion of soils by a factor of 2x or more" is not entirely consistent with the symbols used.

Line 3700: Does this include Runcorn (HCBD) and Shipham (Cd)?

Line 3712: This introduces policy considerations distinct from scientific issues into the decision. It might be helpful if a clearer distinction could be made between the strictly scientific aspects of the assessment and the policy-related aspects. This would help when such assessments are being evaluated by third parties.

Line 3725: It is difficult to see how level of precaution can be used when socio-economic considerations also need to be taken into account. The concern is that one might argue that the level of precaution is the one that meets the policy needs of the authority making the decision.

Page 87, Table 5.4: Despite stakeholder feedback that the BMD was preferred over the BMDL, the methodology proposes use of the BMDL. This decision is not addressed specifically in the report.

Line 3862 & line 3865: Text repeated.

Line 3871: Here, the derivation of LLTCs is based on the BMD. On line 3383, the BMDL10 is recommended.

Line 3892: There are a few endpoints where the toxicology supports the use of a higher BMR, as this is associated with no adverse effect, for example inhibition of acetyl cholinesterase activity.

Line 4244: It is always possible to predict potential additive effects by using the hazard index or equivalent. Perhaps what is meant here is that reliable prediction is not possible due to the limited amount of toxicity data available.

Fig A.1: What do the blue arrows signify?

Figure A.1, et seq: Why are there two entries for some parameters, but not for all?

**Appendices C-H**

What search strategy/search terms were used to retrieve information from the published literature for the respective substances discussed in the appendices?

Human Toxicology Data Sheets: What is meant by the grey shading of some boxes, and an entry of "no data" in column 7? There are data on some of the blank entries, such as local effects of benzene in humans and on its pharmacokinetics and on the genotoxicity of B[a]P..

The amount of information provided on the results of the benchmark dose modelling in the appendices is not consistent. For example, for benzo[a]pyene, detailed information is given on fitting of all of the models whereas for chromium (VI) only summary data are provided.

Were constraints, as recommended by EFSA, used on any of the models?

The criteria used for model acceptance differ from those recommended by EFSA.

If the requirement to involve an expert in toxicology is to be stated explicitly for each of case studies, should the name of the individual and their expertise not be provided?

**Appendix C: Arsenic**

Line 312: EA have established a policy-based HCV of 0.3 µg/kg.

Line 320: According to line 287, JECFA had concluded that model fit was poor for data on skin lesions.

Page 10, table 2.1: Under WHO/JECFA it is stated that BMR = 5%, yet for Rahman the designation for BMD and BMDL is 0.5 (e.g. $BMD_{0.5}$).

Table 2.2: Again, whereas the text above WHO/JECFA indicated a BMR of 0.5%, data for BMD/$BMDL_1$ are also shown for Chen et al.

Line 370: Were the skin lesions modelled from Ashan et al strictly cancer? In the paper, the lesions were described as premalignant.

Page 12, Table 2.4: Why is there no value for the BMDL for skin lesions in this table, whilst BMDLs are provided for the other two endpoints (and there are some values for acceptable model fits in Table 2.1). It should be noted that the BMDL for lung cancer using the data of Chen at al was the lowest of those obtained.

In general the rationale for the choice of BMD/BMDLs to include in this table is not clear. JECFA discounted all data on skin as not being reliable. However, in Table 2.4, data from Ashan et al are included, yet not form Xia et al. For bladder cancer, why not repeat the pattern of values for BMD/BMDL as for lung cancer in this table (e.g. $BMD_{0.5\ (average)}$)?

Line 387: There is some uncertainty as to whether arsenic is a non-threshold carcinogen at all sites, such as bladder.

(Line 401: Typo – "species" omitted?)

Line 401: The choice of a factor of 1 for interindividual variability, whilst reasonable, should be explicitly justified.

Page 13, table 2.5: Despite suggesting a factor of 100 for calculation of a CSM in line 400, this is not one of the values used in the table.

Line 424: Should this be "$\mu g\ kg^{-1}$ bw $day^{-1}$"?

Line 426: Why would a policy based HCV be ignored in this discussion? Presumably there were good policy reasons for this decision, and if it is considered adequately protective, would this not suffice for an LLTC?

Line 443: Intake is used in a slightly different way here, in that it was used to estimate the dose, for dose-response assessment, rather than exposure, since it was not the exposure in the target population but in the population in whom the response was determined, which ware not necessarily the same.

Line 454: It is not obvious from line 423 that aspects of risk management have been invoked, which could lead to potential confusion.

Line 536: Use (by EPAQS) of a factor of 10 to extrapolate from 40-years of exposure to lifetime exposure seems very conservative.

Page 16, flowchart element 6: Presumably this is not applicable, as unit risks were provided from previous evaluations (relative risks at different exposure levels are available and presumably could have been modelled).

Line 589: The statement that this value "is suitably protective of all health effects in the general adult population" appears to contradict the statement on lines 584-5.

Line 592: On line 472 it is assumed that for oral exposure, in the absence of evidence, it should be assumed that a child is the critical receptor. Here, the inference would appear to be somewhat different. This may simply be a matter of wording, but there is potential ambiguity.

Line 604: The discussion here does not relate to the dermal route of exposure, any more than lung cancer by the oral route relates to exposure by inhalation. There is no consideration of the effects of exposure by the dermal route. If there is no relevant exposure by this route, this should be stated. If there is, there should be explicit consideration of the risk following dermal exposure.

Line 645: Given that arsenic can cause lung cancer following oral exposure, is it certain that all cancer following inhalation is due to local effects, although it is still reasonable to compare exposure by inhalation with the $LLTC_{inhal}$.

Line 815: Why was probabilistic modelling not used with the POS scenarios?

Line 923 and line 953: Almost all of the information has already been provided. Could the text be condensed, either by providing a table for the various scenarios or just stating the differences in the third option?

Page 33, Table 4.3: As indicated above these is some uncertainty about the mode of action for arsenic carcinogenicity. This would impact on the assumption of linearity in the dose-response relationship.

Under linearity of response the uncertainty is rated +/-. However, it seems more likely that the response would be sub-linear than supra-linear at human exposure levels.

**Appendix D: Benzene**

Page 6, line 184: This is potentially misleading. It is not the use of animal data that the COC does not favour but low dose extrapolation. Elsewhere in COC/G06 it is clear that often it will be necessary to use animal data to undertake the risk assessment of genotoxic carcinogens.

Page 7, line 198: What is meant here by the "most sensitive" of effects. If based on the POD, it is not just the most sensitive effect, but also the nature of the effect that has to be considered, as different assumptions are used for genotoxic carcinogens and most other endpoints, resulting in very different HBGVs for the same POD.

Page 7, line 216: It would be helpful if this could be elaborated. What was the basis for the choice of such a suitably qualified individual?

Page 8, line 260: "…drinking water in the first…". Missing word?

Page 9, line 311: This seems somewhat contradictory ("greater weight being given to the previous human epidemiology data") with the text on page 8, line 267 ("epidemiology data are not the basis of the current standard").

Page 10, line 341: The phrase "suitably protective" is obviously context dependent here, as a risk value of 1 in 50,000 would not be considered suitable elsewhere.

Page 12, line 414: It seems somewhat anomalous that an NOAEL would be identified in an observational study of leukaemia for a genotoxic compound assumed to have no threshold in producing cancer.

Page 12, line 415: The reason for requiring a factor to convert to continuous exposure should be provided in the document (i.e. what was the nature of exposure in the Wong study).

Page 12, line 438: Higher than which health based values? Are these the oral equivalent values provided in section 2.2.4?

Page 13, line 471: Was any consideration given to using the same ELCR for the oral LLTC, to ensure consistency and to avoid disproportionately targeting oral exposure versus inhalation exposure?

Page 13, line 481: It might be helpful if the document were more specific about the nature of the uncertainty in deriving the WHO drinking water guideline.

Page 14, Table 2.3: Although it is possible to calculate receptor-specific LLTCs for inhalation, does the relative level of protection still not require consideration of the same data as used to calculate the WHO guideline value for water, and hence will be subject to some of the same uncertainties?

Page 14, line 496: This could be interpreted as rather dismissive of a potential risk from a genotoxic carcinogen. Perhaps it could be explained that it is route-specific toxicity that cannot be determined but that exposure by the dermal route is not ignored in the assessment.

Page 26, table 4.3: It is notable that the only significant uncertainty associate with the toxicological information is essentially the choice of ELCR. However, it is likely that there are other toxicological uncertainties. For example, the choice of POD, which varied in the various model fitting exercises, the reliability of the epidemiological estimates, the nature of the dose-response at exposure levels of concern.

**Appendix E: Benzeno[*a*]pyrene**

Page 7, line 276: From the appendix, it appears that $P<0.05$ was used as a criterion for model rejection, rather than $P<0.1$ (which is acceptable, but there needs to be consistency in the document).

Page 9, line 289: EFSA and JECFA have recommended that model averaging is the preferred approach to obtain a POD when using BMD modelling. If this is not possible, selection of the lowest plausible BMDL (e.g. statistically acceptable and visually a reasonable fit to the data) is recommended.

Page 10, line 296: The fact that a compound is a genotoxic carcinogen does not necessarily mean that there is no threshold. Rather, in the absence of robust evidence to the contrary it is assumed that there is no threshold.

Page 10, lines 315-316: Whilst not disagreeing that a factor of 10 is appropriate here, the justification provided does not appear to support this. Some clarification of the logic would help.

Page 10, line 21: Why would the fact that B[a]P is a multi-site carcinogen in itself imply the need for a factor of 10? A factor of 10 would be necessary when using the BMDL10 only if it is assumed that the dose-response is linear (regardless of whether there is a threshold). How does the use of good study design offset the need for a full factor of 100?

Page 10, line 337: There is a conflation of two issues here. One is the scientifically justified extrapolation factor to use with the POD from a rodent carcinogenicity study and the other is the appropriate factor to provide a notional cancer risk level.

Page 11, line 356: The discussion in the document prior to this was based on the use of the BMDL10 as POD. Some clear justification for switching to the BMD10 here should be provided.

Page 11, line 365: The basis for this statement is not entirely obvious from the preceding text.

Page 12, line 422: Was there not some concern of the Committee on Carcinogenicity on the appropriateness of the surrogate approach using B[a]P because of the presence of varying concentrations of more potent PAHs, such as dibenzo[a,l]pyrene?

Page 13, line 469: Whilst there might be pragmatic reasons for basing the LLTCs on different risk levels (1 in 50,000 for oral exposure and 1 in 10,000 for inhalational exposure) it is difficult to understand how both can be described as "suitably protective of all health effects in the general population".

Page 14, line 508: What is meant by acute toxicity here?

Page 14, line 520: Strictly speaking is it not the potency corrected doses that are additive, rather than the effects?

Page 15, line 526: If the TEF approach for PAHs was based on interaction with the Ah receptor, presumably a threshold approach would be used in their risk assessment. Did the Committee on Carcinogenicity not discuss the possible use of relative potency factors for the genotoxicity of PAHs, similar to those used by the USEPA?

Page 15, line 540: Is the inability to use the TEF approach for high potency PAHs because the data are not available or because of their high potency? The text is somewhat ambiguous in this respect.

Page 15, line 558: Although considerable amounts of data are available on B[a]P as noted elsewhere in the document, there are still notable data gaps.

Page 16, line 584: If B[a]P is not representative of the DB[a,l]P then presumably it will not be representative of the soil PAHs overall.

Page 16, line 586: How much uncertainty does this introduce into the assessment (the lack of data on DB[a,l]P and the assumption that B[a]P is an adequate surrogate PAH)?

Page 18, line 647: The level of precaution provided is relative only to the pC4SL which is defined as appropriate, but about which there is some uncertainty based on the assumptions used (see above). Hence, the results of such an analysis could be misinterpreted if presented in terms of level of protection or something similar.

Page 18, line 667: Comparison of total combined exposure with just one of the LLTC values introduces additional uncertainty as it is possible that some of the carcinogenic effects of exposure by the inhalation route will be missed (42 ng/kg bw/day compared with 0.3 ng/kg bw/day). Hence, the greater the proportion of total exposure due to inhalation, the greater the potential difference. If the inhalation LLTC value is used (as inferred from line 677) then the lower the proportion due to inhalation the greater the potential difference.

Page 33, Interspecies differences: It is not clear that a reduction in the inter-species factor to 5 is well justified. There are many other possible sources of variation between species in their response to B[a]P than those mentioned.

Page 34, Intraspecies uncertainties: Enzymes other than P450 may vary, such as GSTs, with an impact on outcome. Other processes could also vary amongst the population, such as DNA repair. Hence, even if good data were available on variability of P450 this would not help very much in determining the degree of uncertainty here.

Page 34, Adequacy of the database: What was the inadequacy in the database that led to the use of an additional factor of 2?

Page 34, Choice of BMR: Why was a value of 20% chosen for the comparison? Why not 5% or 40%?

Page 34, Overall evaluation: The normal factor used for inter-species differences is 10, whereas a factor of 5 was used here. Why, then is it concluded that assessment is more likely to be conservative. This could be worded more clearly.

Page 34, ELCR modelling: The uncertainty estimate suggests that the true relationship for the dose-response curve could be just as much supra-linear as sub-linear.

Page 36, Exposure frequency outdoors: The text indicates that exposure is more likely an over-estimate than an under-estimate, but the range of uncertainty is symmetric.

Page 36, Soil to plant concentration factors: The range of uncertainty does not match with the text at the end of the description of sources of uncertainty here.

**Appendix F: Cadmium**

Page 7, line 276: It is not readily apparent from figure 2.1, that the dose-response curves for renal and cancer effects overlap.

Page 10, line 317: The basis for the choice of chemical specific adjustment factor is not easy to follow form the explanation given here.

Page 15, line 554: The basis for the conclusion that the LLTC would be protective of carcinogenic effects has not been provided up to this point in the document.

Page 15, line 553: It would be helpful if the BMDL10 for effects on the bone could be provided, enabling the protection provided by the proposed LLTC to be judged more clearly.

Page 19, footnote: What is meant by a highly sensitive dataset?

Page 20, line 725: Why was an additional factor of 3 not necessary to protect diabetics in the derivation of the oral LLTC?

Page 21, line 760: This reads as if the highest HBGV is considered the most precautionary. Perhaps this needs to be reworded.

Page 21, line 704: As the dose-response for cancer is often assumed to be without a threshold whilst that for the others endpoints is considered to exhibit a threshold, it is not consistent to

suggest that the dose causing cancer is higher than that for other effects. Perhaps the evidence that cancer exhibits a threshold with Cd should be presented first.

Page 22, figure 2.5: Is this a correlation or a prediction (legend)?

Page 38, Modulation of effects from co-exposure: "On balance, evidence of effects from dietary components can both increase and/or decrease Cd toxicity". Should this not be reflected in the uncertainty estimate, perhaps -/+.

Inhalation LLTC, Susceptibility of diabetics: Is the difference in sensitivity of diabetics from the population studied known with confidence, or is there some uncertainty over this?

Page 41, line 1393: Given the implications of such a suggestion, a more robust scientific evaluation of the mode of action for carcinogenicity would seem warranted before recommending ALARP.

**Appendix G: Chromium (VI)**

Page 9, line 257: This statement is somewhat at odds with the risk estimates for cancer given in the next paragraph.

Page 11 et seq: Presumably the doses been corrected for the molecular weight of the salt used in the studies in experimental animals? This should be stated.

Page 14, line 215: How is this table to be interpreted? If it is not known whether there is a threshold, perhaps this could be footnoted, with no entry in the table.

Page 15, line 443: "…a factor of 50 is … to account for the good quality of this study" seems to be worded somewhat strangely. If the study was of good quality why use such a large factor. Of course this is not what is meant, but it could be read this way.

Page 17, line 497: The conservatism of the LLTC has been reduced from that of a "normal" exposure value for a non-threshold carcinogen by using both an MOE of 5000 and the BMD10 rather than the BMDL10. This introduces a difference of approx. 4-fold. The choice of BMD10 over the BMDL10 has not been discussed for Cr (VI).

Page 20, table 2.4: It might be helpful to indicate where the air concentration for an ELCR of 1 in 100,000 comes from (presumably the EPAQS evaluation)?

Page 35, Choice of data and endpoint: There is no evidence that exposure of humans to chromium can cause intestinal neoplasia. Hence, this is a source of additional uncertainty here.

**Appendix H: Lead**

Page 7, line 209: EFSA is the European Food Safety Authority.

Page 12, line 294: Visual inspection of the data set clearly indicates that a linear fit to the data is not appropriate. Hence, the logic of choosing a BMD based on an inappropriate model is not clear. A better (and more consistent) choice might be the BMD of 1.8.

Page 16, line 552: In general renal function has to deteriorate to some extent before notable changes in GFR are observed. Hence, there is little margin for consideration of severity here.

Page 41, Renal effects – confounders: Did Navas-Acien et al. not correct for Cd and smoking as confounders?