CC/2019/04

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Development of a framework for consideration of risk due to less than lifetime exposure

Introduction

1. The COC has previously considered the issue of less than lifetime (LTL) exposure to genotoxic and non-genotoxic carcinogens.

2. A set of principles that may be formulated into specific frameworks by individual Government departments and agencies was presented at the November 2018 meeting (CC/2018/08). The paper included an example flowchart for the risk assessment of retrospective and/or prospective LTL exposures. In addition, hypothetical case studies to illustrate the utility of the set of principles were also given, relating to arsenic exposure in water (retrospective) and formaldehyde in indoor air (prospective).

3. This paper contains amendments requested by members at the November 2018 meeting which it is hoped will form the basis for the derivation of a set of principles from the COC.

Questions for the Committee

4. Members are asked to comment on:

   i The structure and contents of the document,

   ii Whether to include the Annex case study examples in a COC opinion

   iii Whether this can be published as the COC opinion.

NCET at WRc/IEH-C under contract supporting the PHE COC Secretariat
March 2019

COC set of principles for consideration of risk due to less than lifetime exposure

1. Less than lifetime (LTL) exposure is broadly defined as 'any exposure that is not continuous daily exposure, for example, short-term, intermediate or intermittent, or a combination of these' (Felter et al., 2011).

2. Health-based guidance values (HBGVs) such as the acceptable daily intake (ADI) and tolerable daily intake (TDI) that are the amount of a chemical that people can be exposed to over a lifetime without appreciable risk to health, are based on standard animal toxicity studies with daily dosing regimens, often of chronic duration. The question that arises is how representative these are for human LTL exposure scenarios that may be intermittent or fluctuating in nature. Potentially sensitive sub-groups including infants and children have been highlighted as requiring particular consideration in terms of LTL exposures, due to their life-stage (Gerats et al., 2016), although data to allow comparison with adults for most effects are limited.

3. For UK Government departments and agencies, the need for guidance on LTL exposure falls into two broadly defined areas:

   a. Managing advice during and after an incident (i.e. retrospective risk assessment);

   b. Setting guidelines to protect health as a result of a specific exposure scenario (i.e. prospective risk assessment).

4. Chemical exposures that are shorter than a lifetime may result from planned activities or may be unplanned, such as in an incident scenario. Activities may be occupational or consumer related and may include environmental exposures via air, food, soil and water.

5. The following steps are designed as a set of principles to guide the risk assessment process for a specific LTL scenario, and assumes some level of expertise of the assessor. This document is not intended as guidance in the formal sense as users are encouraged to adapt the principles as needed in response to the available data and other case by case considerations. The steps are illustrated in Figure 1 (p. 9). Two case studies are included in Annex 1 to illustrate how the principles may be applied for retrospective and prospective risk assessment purposes.

Step 1 - What is the specific LTL scenario being assessed for risk?

Note: Current COC guidance to assist with the assessment of exposure to carcinogens (G01 and G04) is available.

Step 1A - Define the exposed population(s)

The aim of this step for retrospective risk assessments is to define who has been exposed to the carcinogen(s) of interest, and for prospective risk assessments, the population that is likely to be exposed. Consideration should be given to:

- the numbers of individuals exposed;
- particular life stages of exposed individuals (to encompass infant, toddler, child, adult). Some age groups may have greater susceptibility following exposure (*in utero*, pregnant women and the elderly) which may need to be taken into account during the assessment of risk in Step 3. *Note: if exposure of specific target groups can be ruled out, then they do not need to be included in the assessment*.

Step 1B - Define the exposure scenario

The aim of this step is to define the characteristics of the specific LTL exposure to a carcinogen that has or is likely to occur. Consideration should be given to:

- whether the exposure is ongoing or has ceased (retrospective only);
- is the exposure being assessed cumulative?
- whether there is a single or multiple route(s) of exposure;
- is there normally a background level of exposure from the source(s) being considered?
- are other background sources present (from water, food, air, consumer products etc.);
- is the substance under consideration produced endogenously and if so, how do endogenous levels compare with the exposure level?
- whether exposure(s) is continuous, fluctuating or intermittent, or peaks above ongoing background exposure;
- duration(s) of exposure(s);
- average and peak levels of exposure(s) (including consideration of how exposure(s) has been measured or estimated as an indication of accuracy);
- if environmental and/or physiological degradation of the parent chemical occurs, whether the degradation products are also carcinogenic and co-exposure(s) with the parent is possible / has been determined;
- whether, for inhalation exposure, levels of physical activity (low, medium, high) during the exposure period are known;
- whether calculation of body burden is appropriate (linked to accumulative properties of the particular chemical(s) and duration of exposure(s)).

Step 2 - What is the potential carcinogenic hazard(s) being assessed?

Note: Current COC guidance to assist with the hazard identification and characterisation of carcinogens (G01 and G03) is available.

Human and animal toxicological data and evaluations relating to the carcinogen(s) of interest should be collated to assist with the hazard identification process; this should include consideration of non-carcinogenic end points, as carcinogenesis may not be the most sensitive endpoint for to the scenario being considered. The aim of this step is to determine how the carcinogen of interest should be evaluated in Step 3 (Assessment of Risk).

Step 2A - Characterisation of the carcinogen(s) of concern - consideration of a non-genotoxic MOA.

Following evaluation of the available data, and confirmation that carcinogenesis is the most relevant endpoint for risk assessment, consideration should be given as to whether there is a biologically relevant MOA by which the chemical (and degradation product if appropriate) causes neoplasia. Of particular importance is whether the MOA exhibits a threshold and, in the evaluation of the genotoxic potential whether DNA reactivity is a key step in the MOA, i.e. whether the chemical is a genotoxic or non-genotoxic carcinogen.

Where the available data indicates that the carcinogen acts via a non-genotoxic MOA, consideration should be given to:

- have toxicokinetic properties been defined, including the potential for rapid metabolism or accumulation to occur;
- are dose-response relationships available for cancer and other toxicological end-points;
- whether cancer is the most applicable endpoint for the short-duration LTL exposure(s) being assessed (for example, would exposure levels that are protective of an endpoint early in the adverse outcome pathway such as irritation also protect against a later carcinogenic endpoint OR are there other adverse effects unrelated to carcinogenicity that should be protected for on a shorter-term basis);
- are the dose route, duration and intermittency of the studies used to generate hazard data, relevant to the LTL scenario being considered;
- the availability of suitable human data from occupational or epidemiology studies which can be used to derive a HBGV;
- has a dose-response relationship (in humans or animals) been defined for neoplastic outcomes on which a HBGV might be based;
- have cumulative exposure effects been assessed either in human or animal studies;

- potency of the carcinogen, particularly where tumour development (latency period) is known to be rapid;
- whether there is evidence for reversibility of pre-carcinogenic and carcinogenic changes following cessation of exposure.

Where the available data suggests a genotoxic MOA, the considerations outlined in Step 2B should be followed.

Step 2B - Characterisation of the carcinogen(s) of concern - consideration of a genotoxic MOA

Genotoxic carcinogens are assumed to have no threshold of effect. *NOTE: if there is no evidence relating to the MOA for a given carcinogen then it is assumed to have a non-threshold MOA - as per COC G01 and G03*.

Other important considerations that may have a particular impact on LTL exposures that should be taken into account during the assessment of risk in Step 3 include whether the MOA suggests:

- dose-rate-dependency;
- impairment of repair mechanisms; and
- targeting of particular life stages.

Considerations listed under Step 2A may also apply to genotoxic carcinogens if an endpoint other than carcinogenesis is identified as the predominant risk for the LTL scenario.

Step 3 - Assessment of risk

Combining findings from the exposure and hazard assessments needs to be carried out on a case-by-case basis and COC guidelines of risk characterisation methods (G06) are available. Other tools that may also support the risk assessment include the RISK21 software (Embry et al., 2014) and the threshold of toxicological concern (TTC) (EFSA, 2012). Separate guidance is available for the risk assessment of a mixture containing chemical carcinogens[1].

Commented [RB1]: To be updated to 2018/9 when new EFSA document is available

Step 3A - Risk assessment of non-genotoxic (threshold) carcinogens

COC guidance recommends that the risk assessment of non-genotoxic carcinogens be carried out through derivation of a HBGV where feasible, by application of appropriate uncertainty factors (UFs) to a point of departure (POD). The HBGV (e.g. acceptable daily intake (ADI) or tolerable daily intake (TDI)) reflects the dose that

[1] Statement on the risk assessment of the effects of combined exposures to chemical carcinogens. Available at: https://www.gov.uk/government/publications/risk-assessment-of-mixtures-of-chemicalcarcinogens.

one can be exposed to, **over a lifetime**, without adverse effects occurring. However, certain criteria need to be met:

- there is adequate evidence to support a threshold for carcinogenicity in that the compound and/or its metabolites are not DNA reactive; and
- there is adequate evaluation of the MOA for the tumours observed in animal studies and its applicability to humans.

Where data are not sufficient to establish a HBGV, an MOE approach can also be utilised based on the most appropriate POD. It should be noted that use of an HGBV based on long-term toxicity studies may be considered precautionary when applied to short duration LTL scenarios.

Step 3A-1 - Use or Calculate a HBGV

The preferred POD for derivation of a HBGV is the benchmark dose ($BMDL_{10}$), however this may not be available, and a no observed adverse effect level (NOAEL) can be used. Appropriate UFs (see 'Note on dealing with uncertainty' below) should be chosen to reflect differences in toxicokinetics and toxicodynamics between animals and humans and between humans, and default UFs applied may vary by individual Government departments and agencies. It may be appropriate to define a Chemical Specific Adjustment Factor (CSAF) which takes into account species differences or human variability in either toxicokinetics or toxicodynamics, allowing modification of the relevant 10-fold uncertainty factor (COT, 2007).

HBGVs developed by other agencies, national authorities from other countries or by international institutions should be considered, taking into account the applicability to the scenario, and the relevance of the UFs applied to the risk assessment.

Where no HBGV is available, an MOE approach may be appropriate, using a relevant POD and taking account of uncertainty as outlined below. In addition, where an MOE approach has been utilised by others, this should be considered for use.

Step 3A-2 - Estimate risk

Where the LTL exposure scenario being assessed indicates exposure to levels higher than the HBGV, qualitative estimations of risk need to be made using evidence from the collated exposure data (Step 1) and hazard data (Step 2). Uncertainties that are inherent in the estimate of risk should be clearly defined and the impact on the overall estimate understood (i.e. whether inclusion of uncertain data leads to an under or overestimate of risk; see 'Note on dealing with uncertainty' below).

If the MOE approach is utilised, a value judgement will be needed as to whether the magnitude of the MOE allows for sufficient uncertainty with respect to the available

toxicological database, and any differences between animals and humans. Judgement is therefore needed on a case-by-case basis.

Refinements to the risk assessment may be judged applicable where data allow (see 'Note on refining the risk assessment' below).

Step 3B - Risk assessment of genotoxic carcinogens

All exposures to genotoxic carcinogens should be managed according to the 'as low as reasonably practicable' (ALARP) principle. The MOE, described below, may assist with the evaluation of risks concerning *unavoidable* exposure to genotoxic chemical carcinogens.

Step 3B-1 - Calculate the MOE

The MOE is derived by dividing a POD (see COC guidance on points of departure and potency estimates, G05), preferably the $BMDL_{10}$, on the dose response curve by the estimated human exposure to the chemical. It should be noted that other levels of the BMD can be used (e.g. $BMDL_{05}$) which will be dependent on the best fit of the curve to the available data.

The use of Haber's rule to calculate an effect level is **not considered** appropriate by the COC due to its approach of assumed simple linearity.

Step 3B-2 - Estimate Risk

COC have proposed a banding system for MOE values *for neoplastic effects when calculated with $BMDL_{10}$ from a chronic animal study using tumour incidence as the effect of concern.* These are:

<10,000: may be a concern
10,000 – 1,000,000: unlikely to be a concern
≥1,000,000: highly unlikely to be a concern

Although these bandings are for lifetime exposure (i.e. worst case) they may be helpful indicators when considering individual LTL scenarios of shorter durations. Where MOEs are lower than the indicative bands, qualitative estimations of risk need to be made on a case-by-case basis, taking into account collated evidence from exposure (Step 1) and hazard data (Step 2). It is essential that inherent uncertainties in the estimate of risk are clearly defined and the impact on the overall estimate understood (i.e. whether inclusion of uncertain data leads to an under or overestimate of risk: see 'Note on dealing with uncertainty' below).

If other PODs are used (e.g. NOAEL; BMDL other than for a 10% response), or sources of data (e.g. human studies), the proposed bands are not applicable and expert judgement is required to consider the level of concern indicated by the MOE on a case-by-case basis (see for example, JECFA (2018)).

Note on dealing with uncertainty

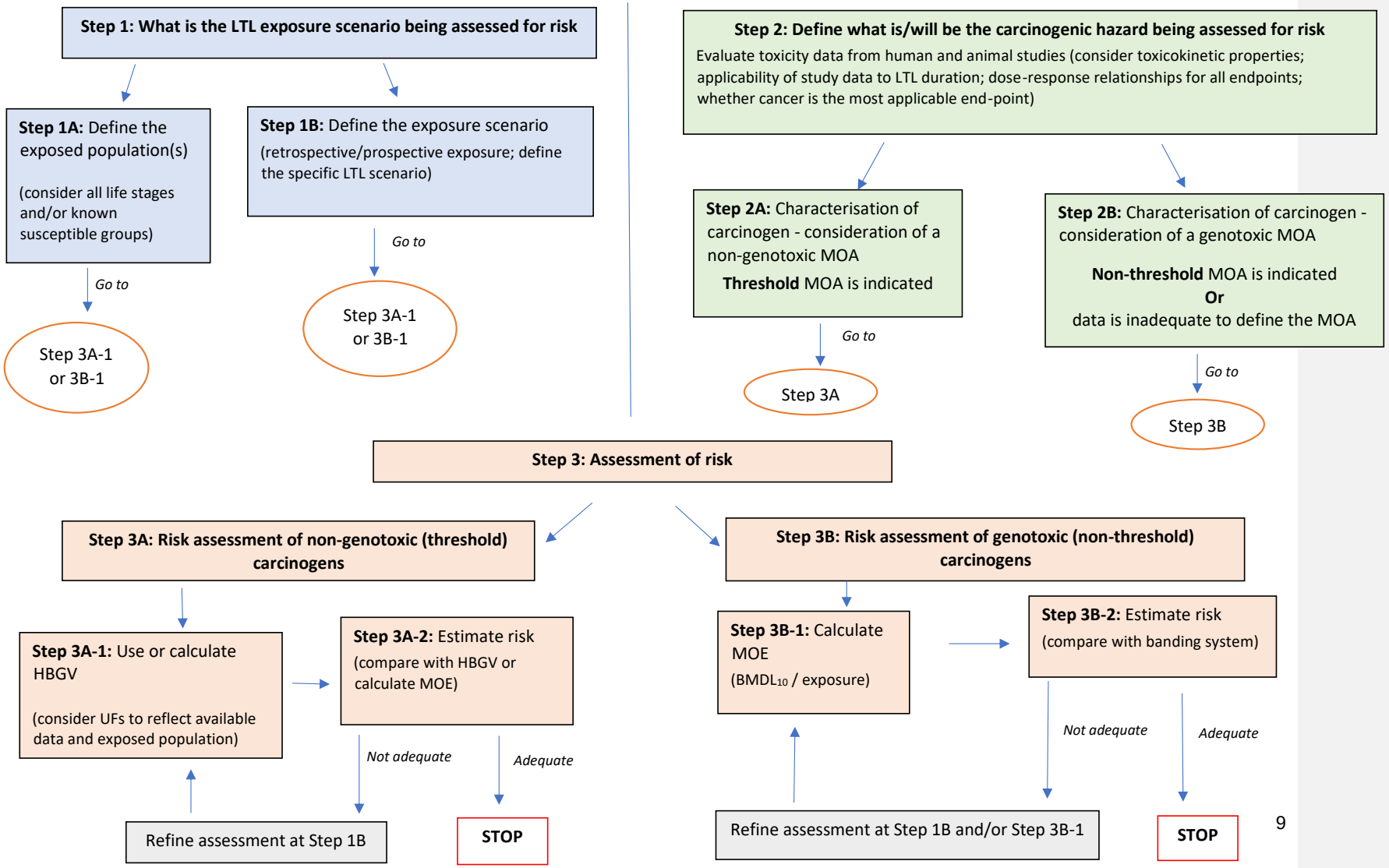
- Uncertainty is an inherent part of all steps within a risk assessment and, to aid transparency, should be identified, assessed, documented, and communicated.
- UF is a generic term used in the UK (also called assessment factor, safety factor and variability factor by other organisations) for the numerical factor applied to PODs from toxicity data to account for uncertainty in extrapolating animal data to derive HBGVs in humans.
- UFs are also used where there is evidence that humans or a human subpopulation have a greater (or lesser) sensitivity than the subjects of the critical study (animal or human) being used to derive a HBGV. If there is a known increased vulnerability (suspected or proved) of any specific sub-group of the exposed individuals to the chemical(s) of concern, then the application of additional UFs should be considered in the risk assessment process. If vulnerability is unknown, for susceptible populations a higher risk should be assumed and additional UFs employed.
- Approaches to the use of UFs and consideration of dealing with uncertainty within risk assessments is considered in the COC guidelines of risk characterisation methods (G06) and COT Working Group on Variability and Uncertainty in Toxicology (COT, 2007).
- Guidelines for performing an uncertainty analysis (qualitative or quantitative) are available from several organisations including: EFSA (2018); ECHA (2012); WHO (IPCS, 2008).

Note on refining the risk assessment

The use of default UFs that are generic and not chemical- or species-specific may result in HBGVs that are overly cautious, leading to an overestimate of potential risk. For non-genotoxic carcinogens, where an exceedance of the HBGV is seen, refinement of the assessment should be undertaken through consideration of:

- Whether a refined exposure assessment can be carried out (e.g. using non-standard assumptions of intakes);
- The contribution of the LTL exposure to chronic background exposure (e.g. in terms of body burden or cumulative exposure);
- Whether the results from a shorter-term study is a more appropriate basis for risk assessment of the scenario being considered.

Use of the Risk21 software may support refinement of the risk assessment by enabling visualisation of the uncertainty in the exposure and toxicity data.



Abbreviations/Glossary

ADI:	Acceptable daily intake
ALARP:	As low as reasonably practicable
BMDL:	Bench mark dose lower bound
CSAF:	Chemical specific adjustment factor
HBGV:	Health-based guidance value
JECFA:	Joint FAO/WHO Joint Expert Committee for Food Additives
LTL:	Less than lifetime exposure
MOA:	Mode of action
MOE:	Margin of exposure
NOAEL:	No observed adverse effect level
POD:	Point of departure
TDI:	Tolerable daily intake
TTC:	Threshold of toxicological concern
UF:	Uncertainty factor

References

ECHA (European Chemicals Agency) (2012) Chapter R19 of the "Guidance on Information Requirements and Chemical Safety Assessment". Available at: https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment [accessed August 2018].

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EFSA Scientific Committee (2012) Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). EFSA Journal 10(7), 2750 [103].

Embry, M.R., Bachman, A.N., Bell, D.R. et al. (2014) Risk assessment in the 21st century: Roadmap and matrix. Critical Reviews in Toxicology, 44:sup3, 6-16.

Felter, S.P., Conolly, R.B., Bercu, J.P. et al. (2011) A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. Critical Reviews in Toxicology. 41, 507–544.

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IPCS/WHO (2008) Uncertainty and data quality in exposure assessment. World Health Organization, Geneva, Switzerland.

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CC/2019/XX Annex 1

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Development of a framework (algorithm) for consideration of risk due to less than lifetime exposure

Hypothetical LTL exposure case studies

NCET at WRc/IEH-C under contract supporting the PHE COC Secretariat
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Retrospective LTL exposure case study

A family home has received elevated levels of arsenic in their drinking water at a concentration of 40 µg/L for 2 years (since moving in). Concentrations have now returned to within guideline levels (10 µg/L). The occupants comprise 2 adults aged 32 years and two children aged 6 and 1 year. All are in good health with no pre-existing health conditions. The 1 year old has been bottle fed throughout its life. Will there be an increased risk of cancer as a result of this exposure?

Step 1: Framing the question: what is the specific LTL scenario being assessed for risk?

Step 1A - Define the exposed population(s)		
Total number of individuals	4	As this is an exposure via drinking water, is it possible that other households may have been exposed?
Life stages of exposed population	Adult	No increased susceptibility expected (no pre-existing health condition).
	Child	Increased susceptibility may be anticipated due to life-stage – larger MOE may be considered in Step 3.
	Infant	Increased susceptibility may be anticipated due to life-stage - larger MOE may be considered in Step 3.
Step 1B – Define the exposure scenario		
Ongoing or ceased	Ceased	Remedial action to clean-up water supply has been implemented.
Single or multiple route(s)	Multiple	Oral intake through food and drinking water are main contributors to exposure for all occupants. Includes beverages and infant formula. Intake normally in the range of 20 – 300 µg/day of total arsenic (IARC, 2012). Higher levels in drinking water will mean that it will predominant over food as the source. Other exposures to drinking water sources may include washing/showering.
Characteristics	Continuous (assumed)	No details given regarding whether intermittent or continuous but as the source is drinking water in the home, assumed to be continuous

Duration	2 years	Known exceedance is 2 years.
Average and peak levels	No data	No data on average or peak levels of exposure given – assume an average of 40 µg/L. Measurement protocol should be assessed against standard sampling practices to verify levels are accurate.
Environmental degradation	No	Do not need to assess potential impact of co-exposure to parent and degradation products.
Is inhalation exposure a relevant route	No	Do not need to assess levels of physical activity during exposure.
Is accumulation possible	Yes	Consider whether calculation of body burden may be appropriate in Step 3.

Step 2: What is the potential hazard(s) being assessed?

The available evidence on the health effects of arsenic has been reviewed by several authoritative bodies (e.g. EFSA, 2009; WHO/JECFA, 2011; IARC, 2012; ECHA, 2017). Note that some key human carcinogenicity studies were not available for inclusion in the earlier document by EFSA (2009) and the IARC (2012) monograph. The information discussed below is taken from these documents.

Step 2A: Characterisation of the carcinogen(s) of concern – consideration of a non-genotoxic MOA.

Arsenic is a metalloid that occurs in a number of inorganic and organic forms and is found in the environment from natural occurrence and anthropogenic activity. It can exist in four oxidation states, namely: -3, 0, +3 and +5. In the environment, arsenic from all sources is predominately transported in water. The form and concentration will depend on the level of oxidation, the degree of biological activity, the type of water source and proximity to sources of arsenic. In drinking water, arsenic is predominately in the form As^{v} but As^{III} may also occur in reducing environments.

In humans, pentavalent and trivalent arsenicals are readily and nearly completely absorbed via the gastrointestinal tract. Following absorption, arsenic is widely distributed to almost all organs and crosses the placental barrier. Age-related accumulation can occur. Metabolism of pentavalent arsenic is achieved through reduction to trivalent arsenic, and subsequent methylation of the trivalent form. Inorganic arsenic is excreted as inorganic arsenate and arsenite and its methylated metabolites (monomethylarsonic acid [MMA^{v}] and dimethylarsinic acid [DMA^{v}]; the trivalent intermediates MMA^{III} and DMA^{III} are also formed during metabolism) in urine, within a few days. Arsenic is also excreted in human milk, although the levels are low.

Acute intoxication is characterised by abdominal pain, vomiting, diarrhoea, muscular pain, weakness and flushing of the skin. Continued exposure is associated with additional symptoms, within a month, including tingling sensation in the extremities, muscular cramping, a papular erythematous rash, palmoplantar hyperkeratosis, Mee's lines on fingernails and progressive deterioration in motor and sensory responses. The acute minimal lethal dose of arsenic in adults is estimated to be 70 to 200 mg or 1 mg/kg/day.

Extensive human study data is available that allows assessment of adverse effects following long-term exposure to inorganic arsenic via drinking water. WHO/JECFA (2011) identified the main adverse effects to be cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity and diabetes. Skin lesions were the most commonly reported symptom, appearing following a minimum of 5 years exposure. Cardiovascular effects were apparent following an average of 7 years exposure.

WHO/JECFA concluded that the greatest strength of evidence for a causal association between inorganic arsenic and **carcinogenic effects** in humans is for cancers of the skin, urinary bladder and lung; these were observed in studies in which levels of arsenic in drinking-water were relatively high (e.g. ≥100 µg/l). Most studies in experimental animals have not shown increased tumour incidences following chronic oral exposure to inorganic arsenic, however WHO/JECFA considered that experimental animals do not provide a good model for the carcinogenicity of arsenic. The use of data from animal studies for dose-response analysis was therefore not considered appropriate.

Although the currently available data indicates that arsenic acts via a non-genotoxic MOA, there is no definitive threshold mechanism on which to base a risk assessment. Following dose-response analysis using key epidemiology studies for each carcinogenic effect, WHO/JECFA calculated that the most sensitive carcinogenic endpoint following chronic (average of 11.5 years) oral exposure to arsenic was lung cancer. This was based on a prospective cohort study by Chen et al. (2010) in which 6888 participants aged 40 years and older (mean age (SD) 59.1 (11)) in north-eastern Taiwan, with measured arsenic concentrations in drinking water, were followed up for around 11 years. The mean duration of exposure was 42.0 (15.1) years with a mean exposure level of 117.2 (297.2) µg/L.

A $BMDL_{0.5}$ of between 3.0 – 5.0 µg/kg bw/day was calculated for the cohort based on a 0.5% increase in the incidence of lung cancer over background. WHO states that a range of assumptions were used to estimate exposure from drinking water and food for the Taiwan cohort which will lead to uncertainties around the calculated $BMDL_{0.5}$. In addition, the outcomes in the cohort may have been influenced by nutritional status (low protein intake) and other lifestyle factors and therefore, extrapolation of the $BMDL_{0.5}$ to other populations should be treated with caution.

Step 2B: Characterisation of the carcinogen(s) of concern - consideration of a genotoxic MOA.

Evidence from a wide range of studies has led to the conclusion that arsenic compounds do not react directly with DNA. There are a number of proposed mechanisms of carcinogenicity of inorganic arsenic, including oxidative damage, epigenetic effects and interference with DNA damage repair. These mechanisms could be assumed to have thresholds for effect but, the available data suggests the using the MOE approach is the most appropriate risk assessment approach rather than identification of a TDI (EFSA, 2009).

Step 3 - Assessment of risk

Step 3B-1 Calculate MOE

An appropriate POD is the lowest $BMDL_{0.5}$ of 3.0 µg/kg bw/day derived by WHO/JECFA (2011), based on lung cancer incidence in humans with chronic exposure (> 40 years) to arsenic via drinking water. As noted under step 2B this POD will be used with an MOE, instead of calculating a HBGV, therefore step 3B is used.

As study cohort members were aged 40 years and older, the duration of exposure is such that some members will have been exposed at early life stages (infancy and childhood). The cohort is therefore representative of the scenario under consideration.

Exposures for representative age groups exposed to contaminated drinking water can be calculated assuming, as a worst-case scenario, that the total intake of drinking water during the day comes from the contaminated source. Default values for weight and water consumption are used as follows to estimate intake of arsenic assuming a level of 40 µg/L:

- **Adult** with a body weight of 60 kg drinks 2 L of water per day giving an intake of **1.33 µg/kg bw/day. MOE = 2.3**
- **Child** with a body weight of 10 kg drinks 1 L of water per day giving an intake of **4 µg/kg bw/day. MOE = 0.75**
- **Infant** with a body weight of 5 kg drinks 0.75 L of water per day giving an intake of **6 µg/kg bw/day. MOE = 0.5**

Total intakes assuming arsenic levels at the current guideline of 10 µg/L can also be calculated as:

- **Adult** with a body weight of 60 kg drinks 2 L of water per day giving an intake of **0.33 µg/kg bw/day.**
- **Child** with a body weight of 10 kg drinks 1 L of water per day giving an intake of **1 µg/kg bw/day.**
- **Infant** with a body weight of 5 kg drinks 0.75 L of water per day giving an intake of **1.5 µg/kg bw/day**.

Step 3B-2 Estimate Risk

The exposure of adults to arsenic has been around 4 times higher for a 2-year period from the contaminated drinking water supply, than would be seen under guideline compliant levels. However, the elevated intake is below the range of $BMDL_{0.5}$ values, with an MOE of 2.3. In addition, exposure to elevated levels of arsenic has been over a very restricted period when compared to a lifetime of exposure to levels within guideline values. It can therefore be considered that an increased risk of developing lung cancer, as a consequence of the increased exposure to arsenic compared to water compliant with the regulatory limits, in adults is unlikely.

For a child, the exposure to arsenic has been 4 times higher for a 2-year period than would be seen under guideline compliant levels. An MOE of 0.75 is indicated based on the lowest $BMDL_{0.5}$ value, however the intake is within the range of $BMDL_{0.5}$ values. The default body weight used here to estimate intake is lower than would be expected for a 6 year old child, resulting in a more precautionary MOE. In addition, exposure to elevated levels of arsenic has been over a restricted period when compared to a lifetime of exposure to levels within guideline values. It can be considered that increased risk of developing lung cancer, as a consequence of the increased exposure to arsenic, is unlikely in a child.

Infant exposure to arsenic has been 4 times higher for a 1-year period than would be seen under guideline compliant levels, and above the $BMDL_{0.5}$ values, resulting in an MOE of 0.5. This suggests that the elevated levels of arsenic may pose a risk to health if exposure was ongoing as prolonged exposure may result in systemic and carcinogenic effects becoming apparent. However, the exposure estimates used in the calculation of the MOE are considered to be cautious in nature and so may overestimate risk. In addition, the levels of arsenic in the drinking water delivered to the household have had returned to guideline levels, meaning that continued exposure to higher levels is unlikely.

Assessment of increased susceptibility in adults, children and infants

ECHA (2017) report that there are no known studies that address the increased vulnerability of any specific human subpopulation to arsenic. It is noted that arsenic toxicity may be influenced by the rate and extent of its methylation in the liver, which may vary among individuals. However, the basis of this variation and the extent to which it impacts on arsenic toxicity has not been established. Smoking is considered to act synergistically with arsenic in the development of lung cancer and has been controlled for in the epidemiology study used to identify the POD.

Areas of uncertainty in the risk assessment

- The estimates of exposure are based on the assumption that all drinking water was obtained from the contaminated source. This is unlikely to be the case, particularly for the adults and the child who would leave the home on a regular basis and may lead to an overestimate of exposure and risk.

- The exposure level and duration of exposure for the cohort from which the POD is identified was considerably higher and longer than the scenario being assessed and may overestimate the risk.

- Due to the large size of the cohort from which the POD is identified, it has been assumed that intra-individual variability, gender and age differences are reflected in the POD. However, there is some uncertainty around the extrapolation to other populations due to the potential impact of nutritional status and lifestyle factors on the study outcomes.

- Estimated exposure levels do not include the contribution of arsenic in food as, at the drinking water levels encountered, food would not be the predominant source. This may underestimate total risk.

Taking the inherent uncertainties of the risk assessment into account and consideration that no increased susceptibility of infants to arsenic has been reported in the literature, an increased risk of developing lung cancer as a consequence of the increased exposure to arsenic is considered unlikely in an infant.

Comments on the experience of using the framework

In the case of arsenic, application of the framework at Step 2 (What is the potential hazard being assessed?) leads to the conclusion that the substance acts via a non-genotoxic mode of action. Following the framework, this would lead to a risk assessment using Step 3A through the derivation of a HBGV. However, the available data and other evaluations carried out by authoritative bodies suggest that the MOE approach (Step 3B) is the most appropriate one for arsenic, i.e. it is treated as a genotoxic carcinogen. This approach was therefore adopted in the case study. It should be noted however, that in this case study, it was only possible to deviate from the framework because arsenic is a data-rich compound whereas 'real-life' applications for many other substances known or suspected to be cancer-causing, may not have information regarding carcinogenic MoA.

Abbreviations/Glossary

BMDL:	Bench mark dose lower bound
HBGV:	Health-based guidance value
MOA:	Mode of action
MOE:	Margin of exposure
POD:	Point of departure
UF:	Uncertainty factor

References

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Prospective LTL exposure case study

A family will be exposed to elevated levels of formaldehyde of 0.2 mg/m^3 (i.e. twice the WHO indoor air quality guideline value) for up to 1 year due to off-gassing from carpets and furniture. The family is comprised of 2 adults aged 32 years, 1 child aged 6 years and 1 infant aged 1 year. All are in good health with no pre-existing health conditions. Will there be an increased risk of cancer as a result of this exposure?

Step 1: Framing the question: what is the specific LTL scenario being assessed for risk?

Step 1A - Define the exposed population(s)		
Total number of individuals	4	Exposure contained in-house.
Life stages of exposed population	Adult	No increased susceptibility expected (no pre-existing health condition).
	Child	Increased susceptibility may be anticipated due to life-stage - larger MOE may be considered in Step 3.
	Infant	Increased susceptibility may be anticipated due to life-stage - larger MOE may be considered in Step 3.
Step 1B – Define the exposure scenario		
Ongoing or ceased	Ongoing	Declining levels over time (highest levels are released within approximately 7 days).
Single or multiple routes	Multiple	Formaldehyde is produced endogenously and is present as a background exposure in indoor and outdoor air; in treated drinking water, bottled drinking water, surface water, and groundwater; on land and in the soil; and in numerous types of food.
Characteristics	Continuous	
Duration	1 year	
Average and peak levels	No data	No data as prospective assessment.
Environmental degradation	Yes	Broken down in indoor air by moisture and sunlight to CO_2.

Is inhalation exposure a relevant route	Yes	Levels of physical activity during exposure not considered relevant for this scenario.
Is accumulation possible	No	

Step 2 – What is the potential hazard(s) being assessed?

The available evidence on the health effects of formaldehyde has been reviewed by several authoritative bodies (e.g. WHO, 2010; IARC, 2012; SCOEL 2015) and the data reported below is taken from these sources.

Step 2A: Characterisation of the carcinogen(s) of concern – consideration of a non-genotoxic MOA.

Formaldehyde is a colourless gas which is flammable and highly reactive at room temperature. In ambient air it is rapidly photo-oxidised, with a half-life of approximately 1 hr. Formaldehyde is ubiquitous in the environment, being formed by natural sources and anthropogenic activities. It is also extensively produced industrially and used in the manufacture of resins, as a disinfectant and fixative or as a preservative in consumer products. These form indirect sources of formaldehyde in indoor air. Secondary formation is also possible through the oxidation of volatile organic compounds (VOCs) and the reaction of ozone and alkenes. Formaldehyde is also endogenously produced as an essential metabolic intermediate in all cells.

The absorption of formaldehyde following inhalation and oral exposure is rapid and extensive. Inhaled formaldehyde gas is rapidly metabolised to formate in the upper respiratory tract, however as much as 40% of inhaled formaldehyde may be removed by mucus flow. Dermal absorption is considered to be minimal. Formaldehyde is an essential metabolic intermediate in all cells and is also produced endogenously. Formaldehyde reacts instantaneously with primary and secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Reactivity with DNA, RNA and proteins can also occur forming reversible adducts or irreversible DNA-Protein cross-links (DPX). Absorbed formaldehyde and metabolites are rapidly removed by the mucosal blood supply and distributed throughout the body. Formate is incorporated into normal metabolic pathways or undergoes further oxidation to carbon dioxide, with exhalation via the lungs.

Key acute and short-term effects of exposure to formaldehyde include odour (which may cause discomfort) and sensory irritation to the eyes and upper airways. The average absolute odour threshold is estimated to be 0.125 mg/m^3, the threshold for eye irritation has been reported as 0.68 mg/m^3 and for subjective sensory irritation, 0.38 mg/m^3. Adult lung function remains unaltered at exposure levels below 1 mg/m^3. Other reported effects include asthma, allergy and eczema, however the evidence for these is currently not conclusive.

A no observed effect level (NOEL) for nasal irritation of 0.38 mg/m^3 has been reported in mice and in rats RD_{50} values (short-term exposure concentrations leading to a 50% reduction in respiratory rate) between 12.5 and 37.5 mg/m^3 have been determined. It should be noted that mice are markedly more sensitive to sensory irritation from formaldehyde than rats.

Long-term inhalation exposure to formaldehyde is associated with squamous cell carcinoma of the nasal cavity in rats at concentrations ≥7.5 mg/m^3, with a non-linear, bi-phasic concentration-response relationship seen. In humans, nasopharyngeal cancer is associated with long-term inhalation at high levels of exposure, with mean exposure levels above 1.25 mg/m^3 and peak exposures >5 mg/m^3. The development of squamous cell carcinoma is considered to be due the genotoxic effects of DPX together with cytolethality-regenerative cellular proliferation.

A causal association between long-term inhalation of high levels of formaldehyde and myeloid leukaemia has been reported. The 8-hr time-weighted average (TWA) associated with this effect was 0.125 – 0.25 mg/m^3, the average intensity between 1.9 and 2.25 mg/m^3 and peak exposure around 10 – 13 mg/m^3. Carcinogenicity studies in rats, mice and hamsters do not show consistent findings for the development of lymphohaematopoetic malignancies following exposure to formaldehyde.

A key mechanism for the development of nasal malignancies is cell damage mediated by formaldehyde, leading to increased cell proliferation. In rat nasal mucosa, increasing cell proliferation has been reported at concentrations ≥2.5 mg/m^3 formaldehyde following exposure of Fischer 344 rats for 6 hr/day, 5 days/week for 6 to 24 months. A NOAEL of 1.25 mg/m^3 was identified from this study.

IARC have classified formaldehyde as '*carcinogenic to humans'* (Group 1). There is *sufficient* evidence from experimental animals for upper airway carcinogenicity and *sufficient* epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans and may cause myeloid leukaemia. Any potential association between inhaled formaldehyde and cancer in humans is limited to high and prolonged exposures.

Step 2B: Consideration of the MOA of the carcinogen(s) of concern – consideration of a genotoxic MOA.

There is a comprehensive dataset to show that formaldehyde is genotoxic and mutagenic, with a predominately clastogenic mode of action. Formaldehyde induces mutagenic and genotoxic effects in proliferating cells of directly exposed cell lines however it is unclear whether these cytogenic effects also occur as a result of systemic exposure.

For indoor air exposures, the effects of formaldehyde are anticipated to be limited to the site of contact, generally the nasal and upper airways. As the prevention of cell proliferation in these cells will also protect against the development of nasal cancers,

it is appropriate to base the risk assessment on this thresholded effect with an appropriately defined POD (NOAEL), thus step 3A will be used for this assessment.

Step 3: Assessment of Risk

Step 3A-1 Use or calculate HBGV

An appropriate POD is the NOAEL of 1.25 mg/m^{3,} based on increasing cell proliferation in rat nasal mucosa, following inhalation exposure to formaldehyde. Uncertainty factors (UF) are required as follows:

- Interspecies - as the effect is local and specific to formaldehyde exposure an UF of 3 is applied.
- Inter-individual variation – as sensitivity differences between different populations are not apparent an UF of 2 is applied.

A proposed HBGV of 0.21 mg/m^3 is therefore derived to allow estimation of risk (Step 3A-2).

Step 3A-2 Estimate Risk

Using the derived HBGV, an anticipated exposure of 0.2 mg/m^3 gives an MOE of 1.05. This suggests that there will be no increased risk to members of the household following exposure to formaldehyde at twice the WHO indoor air quality guideline value of 0.1 mg/m^3.

Assessment of increased susceptibility in adults, children and infants

There is no evidence that potentially susceptible groups, including the elderly, asthmatics and children, show an increased sensitivity to formaldehyde exposure. In general, the elderly are less sensitive to sensory irritation which declines after the age of 60 years. As children practice greater oronasal breathing and have a higher respiration rate when compared to adults, they are not considered to be at a greater risk. This has been shown using fluid dynamic nasal modelling which indicated that adsorption rates per unit surface area of the nasal cavity are equal in adults and children.

Areas of uncertainty in the risk assessment

- The use of a HBGV based on preventing the local effect of cell proliferation assumes that any carcinogenic effects are a direct result of this preliminary step in the MOA of formaldehyde.

- The risk assessment assumes a continuous level of exposure; however off-gassing from new furniture and carpets will rapidly decline over a short period of time (days) resulting in lower levels of formaldehyde than predicted. This will lead to an overestimation of the risk.

- Natural ventilation within the home, the opening of windows in response to odour detection by the occupants (odour has a lower threshold than for irritancy) and time spent away from the home will also reduce exposure levels. This will lead to an overestimation of modelled exposure and thus risk.

Comments on the experience of using the framework

In the case of formaldehyde, application of the framework at Step 2 (What is the potential hazard being assessed?) leads to the conclusion that the substance acts via a genotoxic mode of action. Following the framework, this would lead to risk assessment using Step 3B through calculation of the MOE. However, available data on the MoA indicates that nasal cancers can be prevented through preventing cell proliferation in nasal epithelial cells following exposure to formaldehyde. As this is a threshold effect it was most appropriate to consider formaldehyde as a non-genotoxic carcinogen and assess using step 3A. It should be noted though that it was only possible to deviate from the framework because formaldehyde is a data-rich compound and 'real-life' applications for other substances may not have information regarding carcinogenic MoA.

Abbreviations/Glossary

DPX:	DNA-protein crosslinks.
HBGV:	Health-based guidance value
MOA:	Mode of action
MOE:	Margin of exposure
NOAEL:	No observed adverse effect level
NOEL:	No observed effect level
POD:	Point of departure
RD_{50}:	Short-term exposure concentration leading to a 50% reduction in respiratory rate
TWA:	Time weighted average
UF:	Uncertainty factor
VOC:	Volatile organic compound

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