MEMORANDUM:

A PRIMER FOR EVALUATING HUMAN HEALTH RISK AT CONTAMINATED SITES FOR CHRONIC AND LESS-THAN-CHRONIC EXPOSURES TO CHEMICALS (OCTOBER 2016)

1. INTRODUCTION

This memorandum was developed in support of the Government of Canada's Federal Contaminated Sites Action Plan (FCSAP). The program is designed to ensure improved and continuing federal environmental stewardship as it relates to contaminated sites located on federally-owned or operated properties or non-federal lands for which the federal government has accepted full responsibility. This memorandum highlights the fundamentals of Health Canada's current advice regarding the evaluation of cancer and non-cancer health risks from exposure to chemicals present at a contaminated site related to a) chronic (e.g. lifetime) and b) less-than-chronic (e.g.less-than-lifetime or short-duration) exposures. Other guidance documents on human health risk assessment (HHRA), prepared by the Contaminated Sites Division (CSD) of Health Canada (HC) in support of the FCSAP, are listed on the HC website (http://www.hc-sc.gc.ca/ewh-semt/contamsite/docs/index-eng.php), and may be obtained by contacting the Contaminated Sites Division at cs-sc@hc-sc.gc.ca.

Ecological health risks are evaluated separately from human health risks. Please refer to the FCSAP Ecological Risk Assessment Guidance (FCSAP 2010a, b; 2012a, b; 2013) and consult with Environment and Climate Change Canada (ECCC) and Fisheries and Oceans Canada (DFO) for further guidance.

1.1 Purpose

The main purpose of this memorandum is to provide additional guidance to custodians of federal contaminated sites where human access to the site is infrequent and/or for short periods of time. Short-duration exposure at contaminated sites may be associated with activities that occur over a relatively short period of time, such as seasonal activities (e.g. gardening and camping), certain occupational activities (e.g. construction and underground service installation, or rare site visits to remote locations). As a result of these short-duration exposure scenarios, health risks from short-duration exposure often need to be addressed at federal contaminated sites.

Health effects due to less-than-chronic (or less-than-lifetime) exposure may differ from effects resulting from chronic (or lifetime) exposure and thus evaluating these short-duration exposure risks may require different approaches. Health Canada's (2012) Preliminary Quantitative Risk Assessment (PQRA) and HC's (2010) Detailed Quantitative Risk Assessment (DQRA) guidance on human health risk assessment mainly address chronic or lifetime exposures. In addition, the *Interim Guidance on Human Health Risk Assessment for Short-Term Exposure to Carcinogens at Contaminated Sites* (HC, 2013) presents an updated cancer risk assessment approach that is applicable to both lifetime and less-than-lifetime exposures. However, the 2013 interim guidance is often mistaken as applicable to less-than-lifetime or short-duration exposures only.

This memorandum provides supplemental information related to evaluating potential for cancer and non-cancer health effects resulting from exposure to chemicals at contaminated sites under both chronic and less-than-chronic (single, repeated or intermittent) exposure scenarios. For other HHRA issues related to federal contaminated sites, please refer to relevant HC guidance documents.

1.2 Background

The significance of exposure to chemical contaminants is typically characterized by comparison with Toxicological Reference Values (TRVs) derived from epidemiological or toxicological studies with comparable exposure patterns (i.e. chronic exposure compared to a TRV derived from a chronic study; short-duration exposure compared to a TRV derived from a short-duration study). Application of a TRV originally developed for a different exposure duration or pattern than the site exposure of interest can introduce significant uncertainty in characterizing health risk.

Toxicological Reference Values for carcinogens are often based on the results of animal studies in which the animals were exposed on a daily basis throughout their adult lifespan. Exposures to people at a contaminated site may mirror this pattern of exposure, but more often, exposure occurs for only a portion of the lifetime (i.e. exposure will be less than 24 hours/day, 365 days/year, 80 years/lifetime) or may be intermittent. Exposure may occur *in utero* or during childhood, which are lifestages not represented in standard cancer bioassays. In the case of non-carcinogenic effects, most of the TRVs are for chronic exposure and are derived from studies involving long-duration exposure

of at least 6 months. An uncertainty factor is applied for those that are based on subchronic studies (i.e. more than 30 days and up to 10% of the life span, which is approximately 90 days for rodents) to extrapolate to chronic exposure. As with cancer risk, uncertainty in risk characterization of non-cancer effects arises when exposures to people are of a much shorter duration.

The current practice of characterizing health risks associated with short-duration exposures involves averaging a short period of exposure or several intermittent short-duration exposures over a longer duration *(*i.e. mathematically spreading out a short-duration dose over a longer period of non-exposure). It assumes toxicity to be linearly proportional to the magnitude and duration of exposure. For example, it assumes an exposure of 365 μg/kg bw-day for 1 day, 36.5 μg/kg bw-day for 10 days and 1 μg/kg bw-day for 365 days to be toxicologically equivalent, which could be untrue.

The following issues related to dose averaging (sometimes referred to as dose amortization) have been raised (HC, 2013).

- The potential for underestimating chronic health risks due to the practice of time averaging of exposures. This issue arises for both cancer and non-cancer risk assessments.
- The possibilities of acute/subchronic non-cancer effects due to elevated exposures that exceed chronic TRVs have not been considered.
- The variability in sensitivity among different lifestages may not have been fully considered. For example, specific lifestages such as prenatal, neonatal, childhood, adolescent, peri-menopausal and senior lifestages, and genetic predisposition are currently not included in standard adult animal bioassays used for deriving estimates of cancer potency.

2. NON-CARCINOGENIC EFFECTS

This section provides HC CSD's current guidance on approaches to assessment of risk associated with non-cancer effects from chronic and less-than-chronic exposures to chemicals at contaminated sites. It is suggested that the reader be familiar with general concepts and approach to human health risk assessment presented in HC (2010) *Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals (DQRA)*.

2.1 Chronic Exposure

For guidance on evaluation of non-cancer effects from chronic exposures, please refer to HC's (2010) *Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals (DQRA)*.

2.2 Less-Than-Chronic Exposure

Non-cancer effects from less-than-chronic exposures can be evaluated for the most critical receptors accessing a site. This evaluation includes consideration of the most sensitive (which is chemical-specific) and the most exposed relevant receptors/lifestages. For chemicals with non-carcinogenic effects (i.e. where the potential effects on human health is not cancer), a tiered approach to risk assessment is recommended requiring higher levels of toxicological expertise as one moves to higher tiered assessments.

The initial screening step to assess chemicals with non-carcinogenic effects involves comparing an unadjusted daily exposure (i.e. without dose averaging and using an exposure term of "1") to a chronic TRV (which is based on the most sensitive endpoint and lifestage, including developmental toxicity). For these substances, health effects are not anticipated if target risk levels are not exceeded. If target risk levels are exceeded, a more detailed evaluation (i.e. higher tiered assessment) is required to characterize the potential for health effects since the initial tier is a conservative screening approach, designed to eliminate those substances which do not need to be considered further. This tiered approach is desirable in order to minimize costs associated with HHRAs, and to ensure that appropriate attention is given to the substances which may be of concern and which may require additional work.

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Higher-tiered assessments compare exposure with short-duration TRVs developed for a similar (or longer) duration as the exposure scenario of interest. In the absence of short-duration TRVs, *de novo* TRVs of appropriate duration can be derived as per HC's DQRA guidance (2010). Alternatively, the assessment ends at the screening level (without dose averaging) using chronic TRVs. Higher-tiered assessments may consider dose averaging in defining the exposure estimates, provided that appropriate, scientifically based rationale is provided in the assessment report. Higher-tiered assessments may also involve physiologically-based-pharmacokinetic (PBPK) modelling, which is not typically conducted at contaminated site risk assessments with the exception of very large and complex sites. For example, when a multimedia DQRA that exceeds the target risk level is deemed overly conservative based on evidence from the scientific literature, the risk assessment can be further refined to reduce uncertainty. Like bioavailability testing, PBPK modelling is one of the potential tools that can be used to further reduce uncertainty.

It is important that any dose averaging conducted does not underestimate the potential for threshold effects. The HHRA practitioner should not mathematically spread out a daily short-duration exposure rate over a longer period and conclude that the unadjusted daily short-duration exposure rate is toxicologically equivalent to the adjusted daily exposure rate (which is lower in value) over the long period, without a sound basis for doing so. Instead, exposure should be averaged over the total actual exposure period (e.g. if a person is exposed continuously for 20 days, the total dose should be averaged over 20 days and not over a period longer than 20 days) and compared to the appropriate TRV.

When dose averaging is being considered, HC's DQRA guidance (2010) recommends that it be supported by appropriate scientific rationale on a chemical-specific basis (with supporting TRVs - acute, subchronic, chronic) to indicate why the approach is adequately protective of human health for the exposure period considered. Firstly, the TRV should match as closely as possible the duration of exposure at the site; the TRVs must be developed for the same (or longer) duration as the exposure of interest. Secondly, the anticipated effects of the dose-averaged exposure should remain biologically equivalent to the unadjusted exposure. In all cases, the risk assessor should provide an analysis of the relevant toxicological information in support of the TRVs applied or derived for assessment of short-duration exposures. Considerations should include:

- the mode of action of the chemical, for example:
    - if toxicity is primarily driven by contaminant concentration (c), or
    - if toxicity is primarily driven by time-integrated exposure (concentration or dose multiplied by time [c * t], or expressed as the area under the concentration-time curve), or
    - if toxicity is primarily driven by both the contaminant concentration and time-integrated exposure;
- the duration of effects (i.e. reversibility of the effect in between periods of exposure);
- the likelihood of exposure during a specific window of susceptibility or sensitive lifestage; and
- the whole-body elimination half-life of the chemical or its active metabolite(s).

For some chemicals, sufficient toxicokinetic and/or toxicodynamic data may not be available to satisfy the data requirements needed to adequately consider the chemical-specific feasibility of dose averaging. In such cases, an exposure term of "1" may be more appropriate.

Notwithstanding the phased approach above, an exposure term of "1" (i.e. no dose averaging) should be considered on a chemical-specific basis where developmental effects are concerned, as these effects may result from exposures during a particular "window of susceptibility". For instance, where a chemical may have teratogenic effects (e.g. structural birth defects in a developing fetus exposed for just a few days of gestation), the elevated exposure over a short time period require consideration to ensure that this exposure would not exceed a TRV for this endpoint, even for one day.

Sections 2.2.1 and 2.2.2 provide a brief description of the higher-tiered assessments that would be most applicable to Federal contaminated sites.

2.2.1 Single Exposure

Short-duration TRVs with comparable exposure periods can be used for short-duration exposures, but the TRVs must be developed for similar (or longer) duration as the exposure scenario of interest. These less-than-chronic duration TRVs can be obtained either from other regulatory agencies or derived based on literature values as per the HC's DQRA guidance (2010). If short-duration TRVs are not available, an analysis can be conducted based on relevant dose-response information from toxicity studies. It is also important to consider whether the short-duration exposure might elicit health effects at a later date, or earlier biological key events that might progress to these health effects.

2.2.2 Repeated and Intermittent Exposures

It is important to note that most TRVs intended for short-duration exposure are derived assuming one-time exposure and not repeated intermittent exposure events. Intermittent exposure can happen at contaminated sites where people access the site multiple times, but each time is only for a short period. Repeated exposures may result in different health effects than those from a single exposure, particularly if the substance can build up in the body over time. In order to evaluate the potential for threshold effects when exposures are intermittent, it is recommended that the HHRA identify a suitable duration TRV that addresses intermittent exposures or compares the intermittent exposure to a suitable longer-duration TRV. A suitable longer-duration TRV would be one that has been developed for duration equal to, or longer than, the combined exposure duration (i.e. sum of exposure episodes and non-exposure intervals). Dose averaging may not be appropriate, particularly if the chemicals (or their active metabolite[s]) have long elimination half-lives. In situations when dose averaging cannot be supported, the exposure scenario can be effectively treated as continuous, with daily exposure rate equal to the highest daily exposure rate among all exposure episodes. This type of risk assessment would require rationale from a toxicologist to support the TRV and anticipated exposure. As above, in a tiered approach, if the assumption of chronic exposure is sufficient for the purpose of the HHRA, then further assessment would not be required.

In certain cases, where the elimination half-life is relatively short compared to the intervals between exposure, if effects are reversible and recovery from these effects is rapid (i.e. recovery time shorter than the interval between exposures), it may be adequate just to apply a short-duration TRV to each discrete exposure period. Rationale should be provided in the HHRA, with references. The potential for biological effects associated with each exposure episode to accumulate during non-exposure periods may have an impact on the assessment. In these situations, though the chemical (or its active metabolite[s]) has been virtually eliminated before re-exposure occurs, biological changes will likely progress with repeated exposures to cause adverse effects. The use of short-duration TRVs for HHRA of repeated exposures should therefore be justified on a case-by-case basis, and should include a discussion of uncertainties and the potential for over- or under-estimation of risk.

The analysis to be conducted for intermittent exposure is illustrated in the following figure, which highlights that a short-duration TRV should be selected that is consistent with the (repeated or intermittent) discrete exposure episode.

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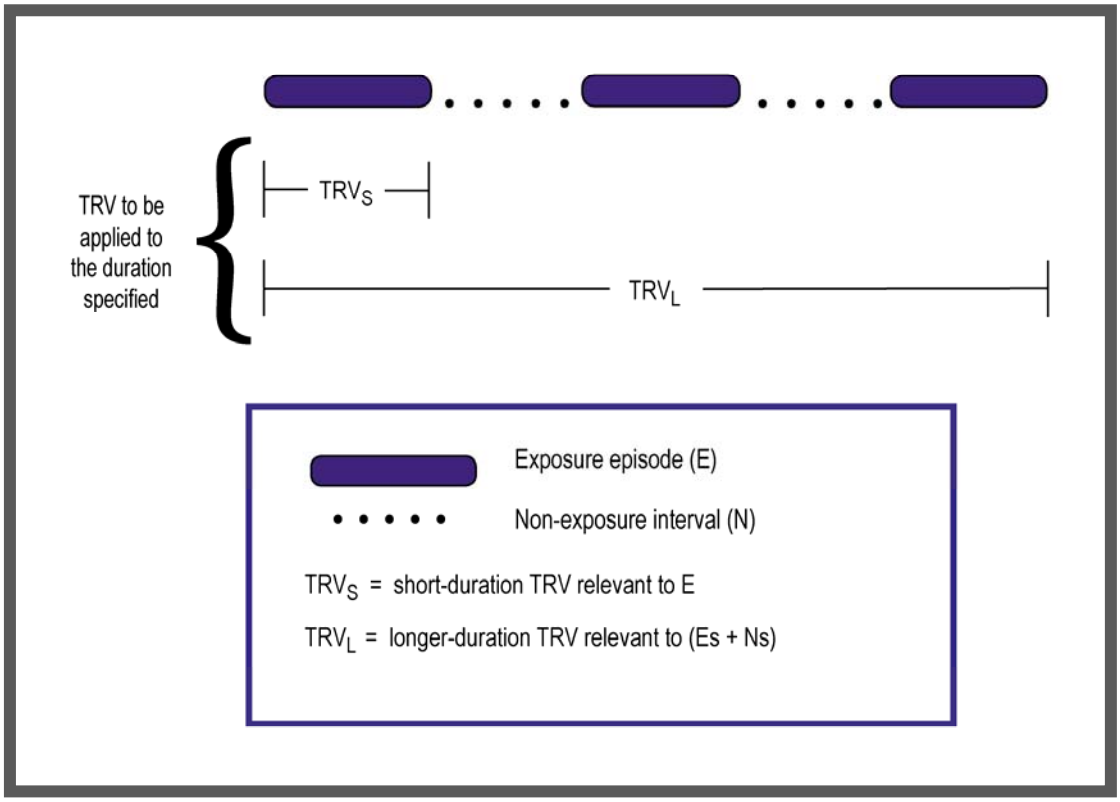
Figure 1: Analysis Required for the Selection of Appropriate TRVs for assessing non-carcinogenic effects associated with Intermittent Exposures



2.3 Examples of Short-Duration Exposure

The following examples illustrate assessment of non-cancer effects for short-duration exposures. Whether dose averaging is appropriate for non-carcinogenic effect needs to be determined on a chemical-specific basis because the mode of action, the duration of effects, and the whole-body elimination half-life of each chemical are different. The basic principles applied to dose averaging are summarized below.

- If the chemical (or active metabolite[s]) cannot be eliminated entirely before the next exposure, no dose averaging is supported.
- If the chemical is eliminated entirely but the effect persists beyond the non-exposure interval, the mode of action determines if dose averaging can be supported, as follows.
    - No dose averaging can be supported if toxicity is primarily driven by contaminant concentration (c).
    - Dose averaging may be appropriate if toxicity is primarily driven by time-integrated exposure (t) (i.e. c x t or area under the concentration-time curve).
    - Dose averaging may not be appropriate if toxicity is primarily driven by both the contaminant concentration and time-integrated exposure.

Whether there is a lifestage particularly sensitive to the action of the chemical is also chemical-specific and has to be factored in the consideration. All considerations need to be provided and fully referenced in the HHRA report.

A screening assessment is usually recommended at the outset comparing the exposure (without dose averaging) to an appropriate chronic TRV. A TRV based on developmental effects can be considered a chronic TRV. If the hazard quotient is above the desired value (refer to HC's DQRA guidance), then further assessment is required.

2.3.1 Scenario 1

5 days per week, 1 week per year, 35 years

This scenario involves an exposure episode of 5 days, which is not repeated until the following year. In this case, a short-duration TRV (≥ 5 days) with no dose averaging would apply. Additional assessment is needed if the chemical (or active metabolite[s]) cannot be eliminated entirely before the next exposure occurs (i.e. 1 year later) or the effect accumulates (and does not reverse) within the 1-year no-exposure interval. Generally, provided that elimination mechanisms are not saturated, approximately 97% of the chemical present in the body would have been eliminated (often considered "complete removal") after a period of five whole body elimination half-lives has elapsed since exposure ceases. Since this exposure is repeated for 35 years, the additional assessment would involve a chronic TRV. Whether dose averaging is appropriate will depend on the factors indicated in Section 2.2.2.

2.3.2 Scenario 2

1 day every 2 weeks, 26 weeks per year, 60 years

This scenario involves a 1-day exposure and no exposure until 2 weeks later. It is necessary to evaluate whether there is effect resulting from the 1-day exposure. Additional assessment is needed if the chemical (or active metabolite[s]) cannot be eliminated entirely before the next exposure occurs (i.e. 2 weeks later) or the effect accumulates (and does not reverse) within the 2-week non-exposure interval. Generally, a chemical can be considered completely eliminated from the body if the non-exposure interval is ≥ 5 x whole body elimination half-life. Since this exposure is repeated for 60 years, the additional assessment would involve a chronic TRV. Whether dose averaging is appropriate will depend on the factors indicated in Section 2.2.2.

3. CARCINOGENIC EFFECTS

This section summaries HC CSD's current guidance on approaches to assessment of cancer risk resulting from lifetime and less-than-lifetime exposures to chemical carcinogens at contaminated sites. These approaches (with supporting scientific analysis) are described in HC's *Interim Guidance on Human Health Risk Assessment for Short-Term Exposure to Carcinogens at Contaminated Sites* (HC 2013). For detailed guidance, equations, worked examples, and an analysis of dose-averaging issues in less-than-lifetime exposures for cancer effects, please refer to the HC (2013) document.

3.1 Lifetime Exposure

3.1.1 Non-threshold Carcinogenic Effects

The approach to cancer risk assessment varies according to the mode of action at the tumour site in question. Unless there is evidence to support a threshold mode of action, the current approach assumes a linear dose–response relationship at low doses (i.e. non-threshold). The incremental lifetime cancer risk (ILCR) is calculated as a product of the lifetime daily dose (or concentration) and TRV, expressed as cancer slope factor (or inhalation unit risk).

The US Environmental Protection Agency approach (US EPA 2005 a,b) has been adapted as the interim default recommendation for contaminated site risk assessments, which is discussed further in HC (2013). The ILCR can be estimated by summing the risk from each

discrete lifestage exposure period. The receptor who is exposed throughout all lifestages in a lifetime is often referred to as a "composite" receptor. This approach takes into consideration potential varying sensitivity of the different lifestages to the carcinogenic agent. Equation 1 summaries the recommended approach to cancer risk assessment.

Equation 1

$$ILCR = \sum_i (SF * ADAF_i * LADD_i)$$

Where:

ILCR	=	incremental lifetime cancer risk
SF	=	cancer slope factor for adults $(mg/kg\text{-}day)^{-1}$
$ADAF_i$	=	age-dependent adjustment factor for lifestage i
$LADD_i$	=	lifetime average daily dose (i.e. dose received during lifestage i averaged over a lifetime [mg/kg-day])

For non-threshold carcinogens acting through a mutagenic mode of action, it is recommended that age-dependent adjustment factors (ADAFs) be applied to the cancer slope factor (or inhalation unit risk) for adults with exposure averaged over a lifetime ($LADD_i$), to account for varying sensitivities of the age-specific exposure periods. In HC (2013), default ADAFs were developed by adjusting the US EPA's ADAFs to be consistent with the age groups recommended by CSD. These default factors can be applied when age-specific cancer slope factors (or inhalation unit risks) or chemical-specific data are not available. When the mode of action is unknown or the burden of proof for a threshold mode of action has not been met, CSD recommends a non-threshold approach to cancer risk estimation; in this case, default age-specific adjustment is not recommended (i.e. ADAF = 1 for all lifestages). However, for all carcinogenic effects, adjustments to the cancer slope factor can be made on a chemical-specific basis if supported by experimental data.

3.1.2 Threshold Carcinogenic Effects

When there are sufficient data to ascertain the mode of action at the tumour site in question and to conclude that the dose–response relationship is not linear at low doses, a threshold approach can be applied. For these threshold carcinogenic effects, the TRVs are expressed as tolerable daily intakes (TDIs) or tolerable concentrations (TCs), the intakes or concentrations to which it is believed that a person can be exposed daily over a lifetime without deleterious effects (for further information please consult HC's DQRA guidance [2010]). Polychlorinated dibenzo-p-dioxins (commonly known as dioxins) provide an example of chemicals that are associated with threshold carcinogenic effect(s) when exposures are high whereas lower, environmental concentrations are associated with threshold noncarcinogenic response(s). Human exposure is compared with these TRVs, where appropriate, to determine health risks.

3.2 Less-than-lifetime Exposure

3.2.1 Non-threshold Carcinogenic effects

The same risk equations (e.g. Equation 1) and ADAFs apply to estimation of cancer risk from less-than-lifetime exposure to a chemical that elicits non-threshold carcinogenic effect.

3.2.2 Threshold Carcinogenic Effects

The CSD recommends that dose averaging of short-duration exposure (i.e. intermittent, seasonal activities, occasional visits, or certain occupational activities) for threshold carcinogenic effects be performed in the same way as for substances with threshold non-carcinogenic effects in Section 2.2. The carcinogenic short-duration TRV should match the duration of exposure at the site as closely as possible; the

TRVs must be developed for the same (or longer) duration as the exposure of interest. In addition, the anticipated effects of the dose-averaged exposure should remain biologically equivalent to the unadjusted exposure.

3.2.3 Other (Noncarcinogenic) Considerations

It should be noted that short-duration exposure to carcinogenic agents may also elicit non-cancer health effects. For carcinogenic contaminants that may elicit both non-carcinogenic and carcinogenic health effects, the potential risk of non-carcinogenic effects need to be evaluated, in addition to risk from the carcinogenic endpoint. Please refer to Section 2.2 for basic principles related to assessment of the potential for non-cancer health effects from short-duration exposure.

3.3 Example of Short-Duration Exposure

Daily exposure for 4 months in a lifetime

This scenario involves exposure to a carcinogenic substance for a period of 4 months in a lifetime (e.g. during remediation of a contaminated site). HC (2013) provides further detail on the required assessment for this type of exposure scenario, but briefly, it is necessary to evaluate whether there is risk of developing cancer above the target ILCR resulting from the 4 month exposure. However, even if there is no increased risk above the target ILCR level, it is necessary to consider whether the short-duration exposure to the carcinogen might also have non-carcinogenic effects associated with the short-duration exposure. In this case, a short-duration TRV may be identified and additional assessment is needed.

4. REFERENCES

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