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Federal Contaminated Site Risk Assessment in Canada

Interim Guidance on Human Health Risk Assessment of Non-cancer Effects Resulting from Less-Than-Chronic Exposures at Federal Contaminated Sites

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

The Federal Contaminated Sites Action Plan (FCSAP) was established in 2005 as a 15-year horizontal program with funding of $4.54 billion from the Government of Canada. In 2019, the program was renewed for another 15 years, from 2020 until 2035. The primary objective of FCSAP is to reduce environmental and human health risks from known federal contaminated sites in Canada and their associated federal financial liabilities. To achieve this objective, FCSAP funds federal departments, agencies and Consolidated Crown corporations (collectively referred to as "custodians") to assess, remediate and risk manage the federal contaminated sites for which they are responsible. FCSAP also provides guidance, tools and resources to custodians to ensure that federal contaminated sites are managed in a scientifically sound and a nationally consistent manner. The Federal Approach to Contaminated Sites and the FCSAP Decision-Making Framework provide a 10-step roadmap that outlines the specific activities, requirements and key decisions to effectively address federal contaminated sites in Canada. The FCSAP Decision-Making Framework along with other FCSAP-related resources can be found on the FCSAP website.

This document, "*Federal Contaminated Site Risk Assessment in Canada: Interim Guidance on Human Health Risk Assessment of Non-Cancer Effects Resulting from Less-Than-Chronic Exposures at Federal Contaminated Sites",* was developed by Health Canada to provide information related to human health risk assessment (HHRA) of short-duration exposure at federal contaminated sites. It provides specific information to supplement other Health Canada guidance documents related to federal contaminated site risk assessment in Canada and is intended for use whenever people may be exposed to contamination from federal contaminated sites on a less-than-chronic or intermittent basis.

Guidance documents on human health risk assessment (HHRA) prepared by Health Canada (HC) in support of FCSAP may be obtained by contacting HC at cs-sc@hc-sc.gc.ca or from the website at: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/contaminated-sites.html. Any questions or comments should be directed to the email address.

As is common with national guidance, this document will not satisfy all requirements related to federal contaminated sites, custodial departments or risk assessors. New and updated information on various aspects of HHRA may result in revisions to this interim guidance document. Please consult HC at the email address above to confirm that the version of the document in your possession is the most recent.

At federal contaminated sites where persons are employed by the federal government, or working on federal property, the *Canada Labour Code* and the *Canada Occupational Health and Safety Regulations* apply. This supplemental guidance is not intended for the assessment of occupational exposure.

The work and opinions of various consultants, academics and governmental agencies were used to create this guidance. In particular, HC employees Angela Li-Muller, Asish Mohapatra, Nicole Somers, Sanya Petrovic and Bertrand Langlet are recognized for their contribution. This guidance document is adapted from information presented in Haber et al. (2016), published by Wiley.

ABBREVIATIONS AND ACRONYMS

ADI	acceptable daily intake
AOP	adverse outcome pathway
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BBDR	biologically-based dose-response
BMC	benchmark concentration
BMCL	statistical lower confidence limit on benchmark concentration
BMD	benchmark dose
BMDL	statistical lower confidence limit on benchmark dose
C_{max}	maximum (or peak) serum or tissue concentration of chemical
CalEPA	California Environmental Protection Agency
CCME	Canadian Council of Ministers of the Environment
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CO	carbon monoxide
COPC	contaminant of potential concern
DNEL	derived no-effect level
DQRA	detailed quantitative risk assessment
ECHA	European Chemicals Agency
EHMI	equivalent human monthly intakes
FCSAP	Federal Contaminated Sites Action Plan
HBV	health-based value
HHRA	human health risk assessment
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JECFA	Joint Expert Committee on Food Additives
K_{ow}	octanol:water partition coefficient
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
MDH	Minnesota Department of Health
MeHg	methylmercury
MOA	mode of action
MRL	minimal risk level
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PAL	provisional advisory level
PBPK	physiologically-based pharmacokinetic
PBTK	physiologically-based toxicokinetic
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-p-dioxins
PCDFs	polychlorinated dibenzofurans
PMRA	Pest Management Regulatory Agency
POD	point of departure (in derivation of a TRV)
PPRTV	provisional peer reviewed toxicity values

PQRA	preliminary quantitative risk assessment
(Q)SAR	quantitative structure-activity relationship
RAIS	Risk Assessment Information System
RCRA	Resource Conservation and Recovery Act
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfC	reference concentration
RfD	reference dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
ROS	reactive oxygen species
SSTL	site-specific target level
TC	tolerable concentration
TCEQ	Texas Commission on Environmental Quality
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TDI	tolerable daily intake
TEF	toxic equivalency factors
TLV	threshold limit value
TMI	tolerable monthly intake
TRV	toxicological reference value
TWI	tolerable weekly intake
UCLM	upper confidence limit of the mean
UF	uncertainty factor
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

GLOSSARY

Acute exposure: Defined in this guidance as exposure lasting for 24 hours or less (≤24 hours).

Adverse health effect: Defined by United States Environmental Protection Agency as a biochemical change, functional impairment, or pathological lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

Adverse outcome pathway (AOP): A sequence of events commencing with initial interaction(s) of a stressor with a biomolecule within an organism (i.e., molecular initiating event) that causes a perturbation in its biology, which can progress through a dependent series of intermediate key events and culminate in an adverse outcome. An individual AOP defines a single sequence of biological events leading from a single initiating event to a single adverse outcome.

Area under the curve (AUC): The area under the plot of concentration (usually in serum or plasma) versus time and is used in this document as a surrogate for the total absorbed dose or internal dose.

Biologically-based dose-response (BBDR) model: A type of model that describes biological processes at the cellular and molecular level linking target organ dose to an adverse effect.

Chronic exposure: Defined in this guidance as repeated exposures that last for 1 year or more, and up to a lifetime.

Contaminant of potential concern (COPC): Those chemicals for which the maximum on-site concentration exceeds appropriate human health-based environmental criteria; those chemicals for which the maximum on-site concentration exceeds local or regional background concentrations; or those chemicals for which no human health-based criteria or background data exist.

Continuous exposure: Uninterrupted exposure that could last for days, weeks or months, such as 24 hours/day, 7 days/week for inhalation, and daily exposure for ingestion.

Dose averaging: Defined as the mathematical averaging of a short exposure period over a much longer time, which may include periods of non-exposure.

Elimination half-life: The time it takes for half of the initial amount of a chemical in the body to be eliminated from the body through metabolism and excretion functions (i.e., the body's cleansing function that involves conversion of the chemical to become more water-soluble and subsequent elimination).

Exposure of interest: The exposure of interest is the exposure a person receives from a contaminated site that is to be evaluated for potential health effect.

Intermediate exposure duration: Defined in this document as repeated exposures lasting for more than 30 days, and up to less than 1 year (>30 days to <1 year).

Intermittent exposure: Exposures that are non-continuous, i.e., continuous exposures interrupted by one or more intervals of non-exposure, each lasting continuously for more than 2 days. For example, repeated exposure for 1 week per month over several years.

Mode of action: A series of measurable key biological events or critical steps following exposure to a chemical that result in an observable toxic effect in an organism.

Near-continuous exposure: Near-continuous exposure scenarios have periods of non-exposure that are a small proportion of the entire exposure duration. In this guidance, near-continuous exposure refers to exposures occurring regularly, such as for 5 to 6 days per week (i.e., with continuous non-exposure period up to two days per week), and for part of each consecutive day of exposure when inhaled (e.g., 10 hours/day) within a longer overall exposure scenario (e.g., 5 days per week for years).

Physiologically-based pharmacokinetic (PBPK) model: A type of model used to estimate the uptake and disposition (including such factors as absorption, distribution, metabolism and excretion) of a chemical in the body, using parameters based on physiological data. The compartments of PBPK models represent actual organs or tissue groups with experimentally measured rates.

Point of departure (POD): The point of departure represents a dose that is derived from observed data, is associated with an extra risk for a specific endpoint, and marks the beginning of a low-dose extrapolation. This point can be a No Observed Adverse Effect Level (NOAEL), a Lowest Observed Adverse Effect Level (LOAEL), a benchmark dose/concentration (BMD/BMC), or a BMDL/BMCL (a statistical lower confidence limit on the BMD/BMC) for a change in level of response.

Receptor: Receptors are people who may be exposed to contaminants from the site, including people who are on the site regularly or intermittently, as well as people who are off-site but may be affected by the contamination from the site.

Short-term exposure: Defined in this document as repeated exposures lasting for more than 24 hours, and less than or equal to 30 days (>24 hours to ≤30 days).

Subadverse biological effect: A biological change or perturbation resulting from chemical exposures, which in and of itself, may not be considered adverse (i.e., adversely affecting the function of the organism as a whole), but that may precede or contribute to an effect that is considered adverse.

Time-integrated exposure: Exposure or dose summed over a set time period, also referred to as total exposure in this guidance.

Toxicological reference value (TRV): The value used to quantify the toxicity of a chemical for exposure of a specified duration. For substances with no threshold of effects, TRV refers to the exposure level associated with negligible health risk for the effect(s). Typically, for substances with a threshold of effects, TRVs are expressed as (i) a tolerable daily intake (TDI) or (ii) a tolerable concentration (TC) in air.

EXECUTIVE SUMMARY

This document provides supplemental guidance for risk assessment of less-than-chronic and intermittent exposures to substances at contaminated sites funded under the Federal Contaminated Sites Action Plan (FCSAP). Health Canada (HC) provides guidance for evaluating health risks associated with chronic exposure to substances (HC, 2010a; 2024); however, at some sites, exposures may be of a shorter duration (whether single, repeated or intermittent), and a different approach may be more appropriate as described in this document. HC (2013) also provides guidance on substances with non-threshold effects.

For substances with threshold effects, this document defines a less-than-chronic exposure scenario as any exposure to environmental media impacted by contaminants that spans less than a year from the first day to the final day of exposure. Exposure of people at contaminated sites is site-specific and variable. For the purpose of this guidance document, exposures that are not considered to be continuous or near-continuous are referred to as 'intermittent exposures'. Intermittent exposures are defined in this guidance as exposures at federal contaminated sites that may be repeated, and are interrupted by one or more non-exposure intervals, with each of the non-exposure intervals lasting more than 2 days.

Table ES.1 summarizes the updated definitions of exposure duration categories to be used when conducting human health risk assessments (HHRAs) at FCSAP sites. If acute, short-term or intermediate exposures are repeated, some chemicals may persist in the body during non-exposure intervals, resulting in a chronic exposure even though the exposure from the site is not continuous (see **Section 3.3.2**).

Table ES.1 Updated Exposure Duration Categories for Threshold Effects in HHRAs at FCSAP Sites

Exposure Duration Category	Definition
Acute exposure[1]	exposure for 24 hours or less (≤24 hours)
Short-term exposure[1]	repeated exposure for more than 24 hours, up to 30 days (>24 hours to ≤30 days)
Intermediate exposure[1]	repeated exposure for more than 30 days, up to less than 1 year (>30 days to <1 year)
Chronic exposure	repeated exposure for 1 year or more, and up to a lifetime (≥1 year)

[1] These categories are considered less-than-chronic; however, if exposures are repeated annually, they may be considered chronic even if they are not continuous.

Each contaminated site may have a different exposure scenario that is identified in a site-specific risk assessment. HC (2021 or most recent version) provides chronic toxicological reference values (TRVs) for contaminants of potential concern (COPCs) that are common at federal contaminated sites, but TRVs for less-than-chronic duration are not provided due to the numerous potential exposure scenarios.

This supplemental guidance provides a tiered assessment framework, which outlines several key principles for addressing less-than-chronic and intermittent exposures:

- A tiered approach to risk assessment that requires increasing levels of toxicological understanding and expertise, as well as increasing levels of detailed analysis for each COPC in each exposure scenario. The required expertise and analyses include consideration of both toxicokinetic (elimination half-life) and toxicodynamic (persistence of effect) implications of intermittent exposures.
- The use of TRVs applicable to the site-specific exposure period under consideration.
- The use of dose averaging (also called "amortization") is discouraged as it may underestimate potential health risk. Dose averaging may be applicable only under limited, specified conditions, and should be accompanied by rigorous chemical-specific analysis. Guidance on when dose averaging may be appropriate is provided, including consideration of appropriate TRVs for specific scenarios.

The framework outlined in this supplemental guidance comprises four tiers. Assessments typically begin with Tier 0, which is consistent with a detailed quantitative risk assessment, as discussed in HC (2010a). Tier 0 assessment assumes chronic exposure with no dose averaging and use of an applicable chronic published TRV, thus not requiring extensive knowledge of toxicology. However, the higher tiers of the framework, as described in this guidance, require appropriate training and expertise in toxicological assessments. Not all tiers are required to adequately assess risk. A risk assessment professional should determine whether additional tiers would be expected to reduce uncertainty in the risk assessment or whether remediation/risk management measures would be recommended without completion of a higher tiered risk assessment. The reader is advised to consult with HC if additional information is needed regarding the methods described in this document and/or to determine whether additional toxicological expertise is required before proceeding.

1 INTRODUCTION

Human health risk assessments (HHRAs) are used by health agencies and risk assessment professionals to estimate the potential human health effects associated with chemical exposure. The majority of risk assessment guidance is for chronic exposure to chemicals. This guidance was developed to provide a standardized methodology to quantitatively assess less-than-chronic exposures at contaminated sites using a consistent, scientifically defensible framework on a chemical-specific basis. The approach is specifically designed for the assessment of sites that are to remain the responsibility of federal agencies and that require greater consistency in risk assessment methods and interpretation of results.

This supplemental guidance is intended for HHRAs at federal contaminated sites where there is less-than-chronic or intermittent exposure, and provides detail to supplement the guidance provided by Health Canada ([HC] 2010a; 2024). This document is focused on the exposure and toxicity assessment phases of a detailed quantitative risk assessment (DQRA)-level assessment (HC, 2010a). Guidance is provided on key issues and methods for use when completing HHRAs of less-than-chronic (also referred to as short-duration in this guidance) exposure to contaminants of potential concern (COPCs) at federal contaminated sites in Canada. Federal custodians are encouraged to engage HC staff to ensure the most current methods and procedures are applied at their sites. In addition, HHRAs addressing less-than-chronic exposures should be completed only by knowledgeable risk assessment professionals with specialization in toxicological evaluation.

HC (2010a) DQRA guidance focuses on the assessment of chronic exposure without application of dose averaging, and may be used to provide an estimate of potential risks associated with the exposure received on days when people are at a site. For substances with threshold effects, a less-than-chronic exposure scenario is any exposure to contaminated environmental media that spans less than a year from the first day to the final day of exposure. Intermittent exposures may be repeated for years, and are daily exposures interrupted by one or more non-exposure intervals, each lasting at minimum more than 2 days. Determining exposure patterns of people who may access a contaminated site is an integral part of this guidance as exposure patterns may impact the overall assessment.

A tiered approach is recommended. Prior to assessing risk from a less-than-chronic exposure scenario, an initial assessment determines if there are any health risks assuming no dose averaging (e.g., with chronic daily exposure). If there are no health risks above a target risk level, further assessment is not required. However, if the risk assessment identifies potential risks associated with chronic exposure using a chronic toxicological reference value, an assessment of short-duration or intermittent exposure can allow for more realistic risk estimates based on chemical-specific data and site-specific exposure. This guidance would also be applicable for the derivation of site-specific target levels (SSTLs). This guidance may not be applicable for use in all risk assessments, and many HHRAs will present unique situations not specifically addressed herein. Risk assessment reports should include all relevant potential exposures to substances at a contaminated site. Since a short-duration assessment is scenario-specific, reassessment would be needed if there were a change in exposure patterns at the site.

For issues requiring decisions by a private party or by provincial/territorial governments, risk assessments may need to comply with provincial/territorial regulations. These regulations may require the use of methods that differ from those described in this guidance document. When provincial/territorial regulations diverge significantly from those recommended herein, risk assessments should identify the differing assumptions, methods and interpretations and discuss their implications for risk characterization at federal contaminated sites.

Although detailed guidance is offered here, it is neither designed nor intended as a substitute for the sound professional judgement of a qualified and experienced risk assessment practitioner. The methods described should not be viewed as a prescriptive set of equations and assumptions. If alternative or unique approaches are deemed appropriate, these approaches should be sufficiently documented and described within the HHRA to enable technical review. Alternate approaches will be evaluated for their impact on risk estimates relative to the application of the standard methods prescribed.

This interim guidance recognizes that some of the underlying information and references provided may need to be updated in the future. The goal is to provide a general framework to promote use of the best available science in assessing federal contaminated sites in Canada. Specific technical methods considered current at the time of writing this guidance are further summarized in the appendices. The risk assessment should identify which technical methods are most appropriate and/or recommended by the applicable regulatory or government agencies.

1.1 Background

The assessment of potential health risks associated with short-duration and intermittent exposures may require a different approach from that used to assess potential health risk associated with chronic exposures. For instance, a chronic residential scenario may result in exposure to environmental media 7 days per week and 52 weeks per year. On the other hand, a typical chronic commercial/industrial land use scenario may result in exposure 5 days per week and 48 weeks a year (Canadian Council of Ministers of the Environment [CCME], 2006). Many federal contaminated sites are located in isolated remote locations, and it may be overly conservative to assume that people may be present at these sites on a chronic basis. On the other hand, should the risk assessment make use of mathematical dose averaging to dilute the impact of elevated short-duration exposures, health risks may be underestimated as the risk assessment may not account for the potential health effects associated with elevated short-duration exposures.

Short-duration exposures at contaminated sites may be associated with activities including, but not limited to, seasonal activities (e.g., camping) and site visits to remote locations. Some short-duration exposures may also be intermittent, as people may return to the same site annually or numerous times in a year. This guidance does not reiterate all aspects of published HC risk assessment guidance, but rather provides a tiered approach to the evaluation of potential non-cancer human health effects resulting from less-than-chronic exposures.

Dose averaging (also referred to as “amortization”) may result in an underestimation of risk, and can be defined as the mathematical averaging of a short exposure period over a longer time (e.g., exposure in one day averaged over a week or a six-month exposure averaged over a year). This practice

mathematically adjusts the daily exposure a person would receive by changing the number of days per week or weeks per year based on factors such as time spent at a site, or period of snow cover. As this practice involves averaging the total dose received during a shorter exposure period over a longer time, including period(s) of non-exposure, this mathematical calculation will result in an 'estimated daily exposure' that is lower than the actual exposure that a person may receive while at the site. While very limited dose averaging may be acceptable for some exposure scenarios and some substances, it may underestimate the potential risk associated with exposures to other substances. Therefore, HC does not recommend dose averaging in a HHRA at a federal contaminated site, unless it can be supported by a rigorous chemical-specific analysis. The analysis presented should include issues such as persistence (e,g., accumulation over time), toxicokinetics, toxicodynamics and TRVs that take into consideration health effects in the general public, including susceptible individuals.

The scope of this guidance document includes the following key elements:

- Four assessment tiers, in which higher tiers require greater levels of scientific judgement and information to assess potential risk. Higher tiers are correspondingly more labour- and data-intensive than lower tiers.
- The use of toxicity assessments based on exposure periods as similar as possible to the "actual" exposure periods, taking into consideration potential windows of susceptibility.
- Priority given to toxicological reference values (TRVs) published by regulatory agencies.
- Analysis of exposure duration and intermittency to consider both toxicokinetics and toxicodynamics.
- Use of dose averaging only under limited, specified conditions, with rigorous chemical-specific rationale.

The main difference in the HHRA of less-than-chronic exposures as compared to chronic exposures is in the exposure assessment and toxicity assessment stages. This guidance includes multiple sources of existing TRVs for less-than-chronic durations (and specifies limited modification that can be made to chronic TRVs), which can be used within this framework. In addition to supplementing the general risk assessment guidance provided by HC (2010a, 2024), this document also provides guidance to support other existing published HC guidance for federal contaminated sites (notably HC, 2010b, 2010c, 2013a, 2017a, 2017b, 2017c, 2018a, 2023). For example, the *Interim Guidance on Human Health Risk Assessment for Short-Term Exposure to Carcinogens at Contaminated Sites* (HC, 2013a) presents an updated risk assessment approach for evaluating cancer risks from lifetime or less-than-lifetime exposures to chemical carcinogens. Where there is inconsistency with regard to addressing short-duration exposures, the information contained in HC (2013a) and this supplemental guidance document supersedes the guidance related to short-duration exposure in the HC (2010a) DQRA guidance.

1.2 Information for Federal Custodians

This document was prepared to assist risk assessors in completing a HHRA for federal contaminated sites funded under the Federal Contaminated Sites Action Plan (FCSAP) with exposure scenarios that span less than one year as well as for sites with repeated short-duration exposures.

Dose averaging (also called "amortization") is generally discouraged as it may underestimate potential health risk. Dose averaging may be applicable only under limited, specified conditions, and should be accompanied by rigorous chemical-specific analysis and justification. Dose averaging is not recommended in an HHRA or in derivation of site-specific target levels (SSTLs), or for class risk assessments where several similar sites are assessed together. Further, it is important that application of SSTLs for class risk assessments identifies if there may be differences in site use patterns for different sites. For instance, some sites may have very similar contamination profiles, but sites that are closer to communities may have increased site use. Other sites may have traditional land use and may include camping, hunting or food collection that need to be considered in a risk assessment.

While this document is highly technical, it is not a requirement that all custodians review the document in its entirety. However, it is recommended that this supplemental guidance be referenced when writing a SOW to request an HHRA and that consultants use the guidance in preparation of risk assessments of sites with short-duration or intermittent exposures.

1.3 The Framework at a Glance

The framework is comprised of four tiers, which are discussed in detail in **Section 3**. In general, assessments should begin at Tier 0, which relies on default approaches used for the assessment of chronic exposure in a DQRA (HC, 2010a). Risk assessors may also choose to go directly to a higher-tiered assessment for some COPCs, depending on data availability (e.g., applicable published short-duration TRV) and the assessment objective. Tier 0 assessment does not require extensive knowledge of toxicology. However, higher tiers of the framework are correspondingly more labour- and data-intensive and require a greater understanding of how specific chemicals cause health effects including how the body processes and reacts to chemicals. The higher tiers should therefore only be completed by risk assessment professionals with the appropriate toxicology training and experience.

Framework Outline

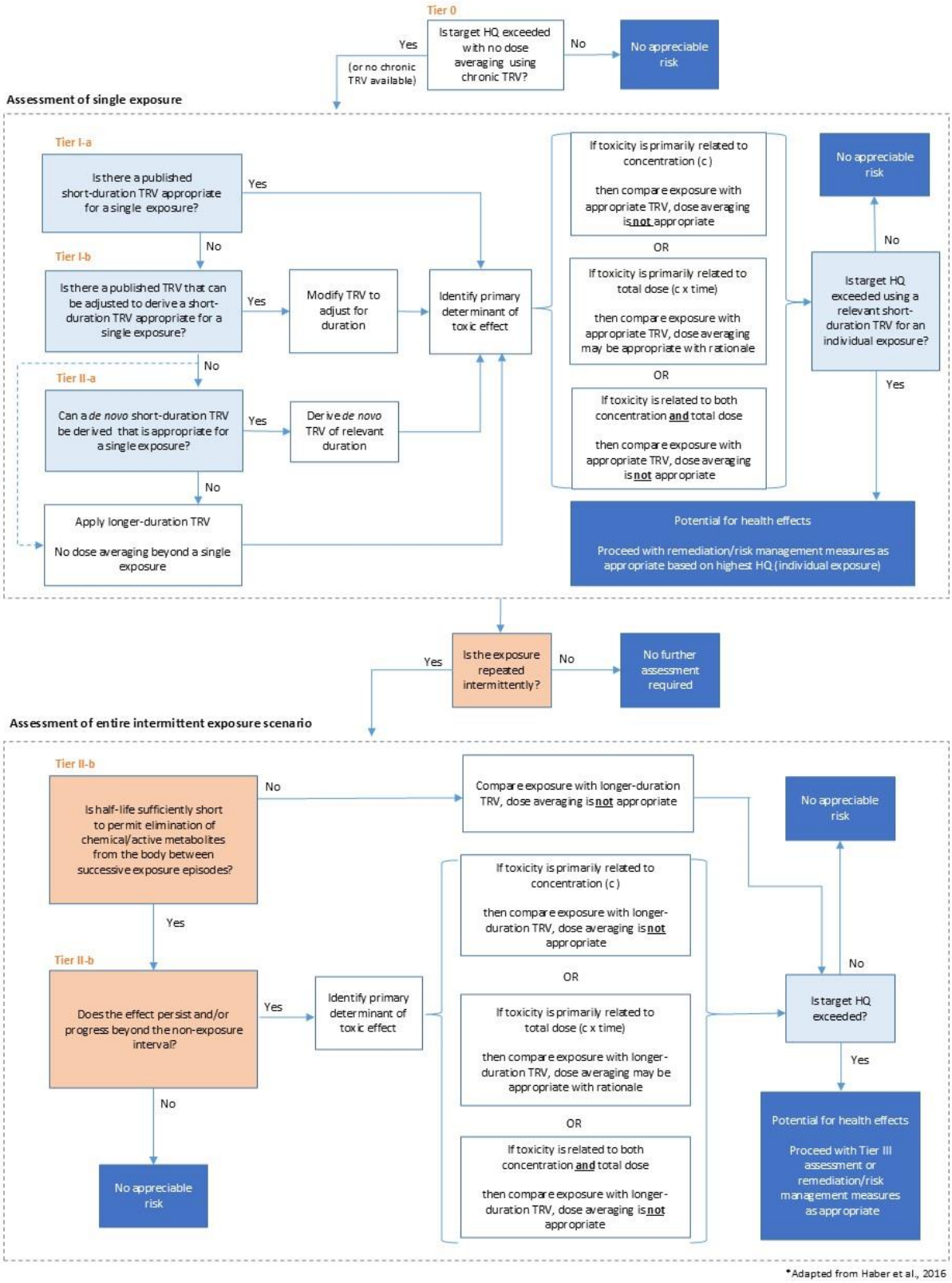
- ***Tier 0*** provides the unadjusted daily exposure that an individual would receive while present at a site compared to the chronic TRV with no dose averaging applied. This approach is similar to that specified in the HC (2010a) guidance for chronic exposure. Where negligible risks to human health are identified for the COPCs at Tier 0, these substances require no further consideration.
- ***Tier I*** assumes continuous exposure to a substance at a site; however, instead of using a chronic TRV, Tier I compares a published short-duration TRV of similar duration to the actual exposure period, without dose averaging beyond the actual exposure period.
- ***Tier II-a*** applies for situations where a published relevant short-duration TRV for the chemical of interest is not available and cannot be easily identified from existing published TRVs.

- ***Tier II-b*** describes additional analysis required to account for repeated intermittent exposures.
- ***Tier III*** involves complex exposure and dose-response modelling that may reduce uncertainty in a risk assessment where potential risk has been identified at lower tiers.

This document focuses primarily on Tiers 0, I and II. The more complex modelling involved in a Tier III evaluation is not discussed in detail within this document, although general principles are identified. Not all tiers are required for assessment of risk at each site and professional judgement is required to use the framework beyond Tier 0 to determine whether additional tiers may reduce uncertainty for specific substances or whether remediation/risk management measures may be required without further assessment. The level of uncertainty in the risk characterization phase of the HHRA may decrease with higher tiers. However, when a target hazard quotient (HQ) is exceeded in a lower tier, it may not be possible to proceed to a higher tier if there are insufficient data available for the COPCs of interest.

Figure 1.1 presents the tiered assessment framework as a step-wise decision tree to be used to evaluate the level of detail that may be required to adequately evaluate the risk associated with less-than-chronic exposure scenarios.

Figure 1.1 Framework for evaluating short-duration and intermittent exposures



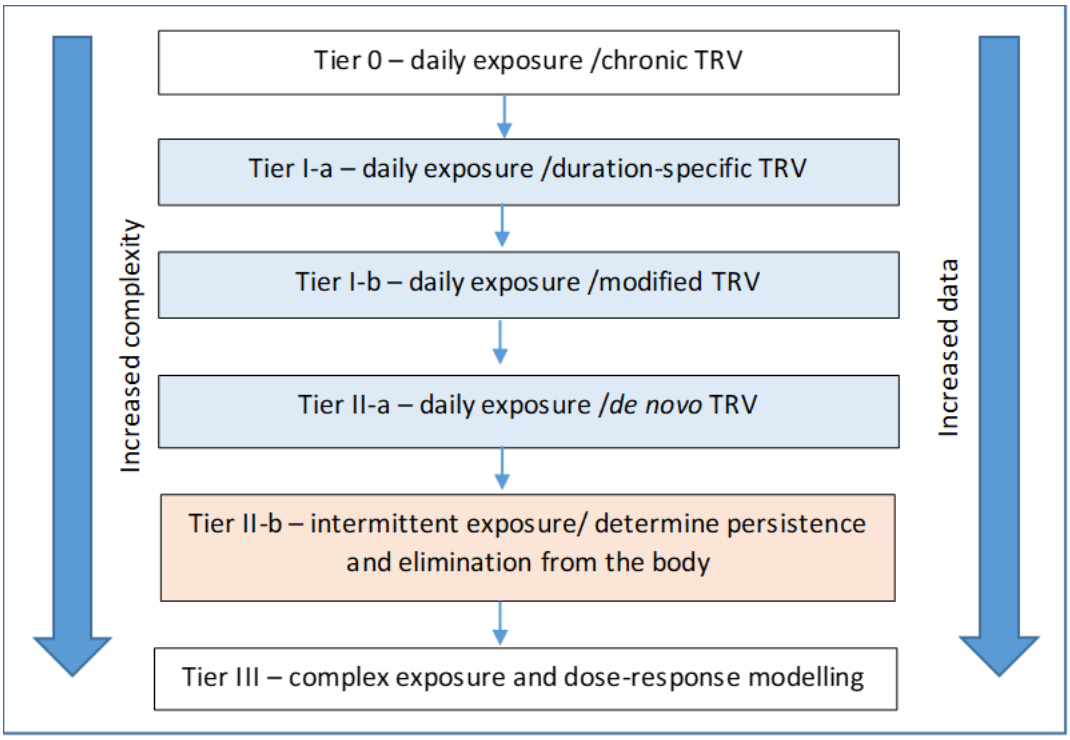
*Adapted from Haber et al., 2016

2 KEY CONCEPTS/CONSIDERATIONS

2.1 Tiered Framework

This document presents a tiered framework approach, which is a method of layering or arranging an assessment by progressive tiers or levels. The required level of effort in a site-specific risk assessment depends on the scope and goal of the assessment as well as data availability and data needs. **Figure 2.1** depicts the concept of assessing short-duration and intermittent exposures and illustrates the key determinants of each tier, which includes those aspects for which there are increasing data requirements. Throughout this guidance, figure elements addressing duration are colour-coded blue; those addressing aspects of intermittency are colour-coded orange. The initial tiers of the framework (Tier 0 and Tier I) rely to the extent possible on existing published TRVs, such as those from HC (2021 or most recent version). Modification of existing TRVs or derivation of TRVs from published literature, may be used where appropriate (Tier II-a). The higher tiers (Tier II-b and Tier III) use increasing complexity and data to inform the analysis.

Figure 2.1 Tiered framework summary



A conservative Tier 0 assessment may be adequate for decision-makers and risk managers to rule out the likelihood of non-carcinogenic health risks due to short-duration or intermittent exposures to contaminants. As part of an iterative process in assessing risks, a Tier 0 assessment may be followed by a more detailed evaluation in upper tiers using additional data if warranted. Many contaminated site risk assessments with short-duration or intermittent exposures may only require application of Tier 0 or Tier I assessments, which rely on published TRVs and toxicological reviews from regulatory agencies.

Advancing to tiers that involve greater toxicological complexity (Tier II-b and Tier III) requires increasingly more detailed information on the mode of action (MOA) related to toxicity, and a corresponding greater level of toxicological expertise to conduct the assessment. For example, Tier III assessment involves the use of complex exposure and dose-response modelling (i.e., physiologically-based pharmacokinetic [PBPK] modelling and biologically-based dose-response [BBDR] modelling), which should only be performed by risk assessors with specialized toxicological expertise.

2.2 Toxicological Reference Values (TRVs)

The TRV is a key component of a risk assessment and includes consideration of both exposure duration and patterns of exposure. Estimates of daily chronic exposure are typically compared with a TRV derived from a chronic study or from a shorter-duration study with uncertainty factors (UFs) applied to account for any differences in exposure duration (HC, 2010a, 2024). A TRV is expected to be protective of the general population, including young children, people who are pregnant or who may become pregnant, and the elderly. Other disproportionately impacted populations, which may include people with specific health conditions, are not generally addressed in TRV development. Unless chemical-specific toxicological/epidemiologic data are available for these populations, regulatory agencies typically apply an UF to account for variability among individuals when deriving TRVs.

The significance of exposure to a substance is typically characterized by comparison with a published TRV derived from epidemiological or toxicological studies. A TRV refers to a tolerable daily intake (TDI, expressed as mg/kg body weight per day) or tolerable concentration (TC, expressed as mg/m^3 of air) (HC 2021), reference doses (RfDs) and reference concentrations (RfCs) such as by the United States Environmental Protection Agency (US EPA), as well as minimal risk levels (MRLs) such as by the Agency for Toxic Substances and Disease Registry (ATSDR). This document applies the term TRV also to short-duration TRVs that could be applied to less-than-chronic exposures for non-cancer health effects. The reader should also be aware that agencies define these terminologies differently. For example, RfDs and MRLs differ in their meaning, utility and application. Refer to US EPA (2002) for a review of RfDs and MRLs. In a risk assessment report, it is important that the TRV is defined, used and referenced appropriately.

A risk assessment for a short-duration or intermittent exposure may involve application of a TRV originally developed for an exposure duration or pattern that differs from the exposure of interest, which can introduce uncertainty in characterizing potential health risks at contaminated sites. TRVs for short or intermittent exposures can be the same as those for chronic exposure; however, they can be different. Most substances with non-cancer effects have a threshold below which no effects are expected to occur; however, this level can differ depending on the exposure duration. Some substances are referred to as non-threshold substances, such as lead, and there may not be a clear identifiable threshold for non-cancer health effects (World Health Organization/Joint Expert Committee on Food Additives [WHO/JECFA], 2011; European Food Safety Authority Panel on the Contaminants in the Food Chain [EFSA CONTAM], 2013). For substances with non-threshold effects, the TRV is the exposure level associated with a negligible health risk.

Although toxicity assessment and exposure assessment are distinct components of risk assessments, they are not conducted in isolation. The toxicity of each substance and site-specific exposure patterns are considered in an integrated and iterative fashion. This basic principle is particularly important in the assessment of short-duration and intermittent exposures, which requires a clear understanding of the exposure and toxicity of substances (refer to discussion on exposure in **Section 2.5)**.

The exposure assessment at Tier 0 in a contaminated sites risk assessment for a short-duration exposure is similar to that of a chronic exposure assessment and the chronic TRV should be applied. However, the toxicity assessment can be more complex at higher tiers. The toxicity of a substance may vary depending on the level and duration of exposure. For instance, exposure to a low level of a chemical may not result in adverse effects; however, the low-level exposure may elicit some biological change or perturbation, which in or of itself may not adversely affect the function of the individual as a whole, and which is referred to as a 'subadverse effect' (See **Section 2.4.1** for a more detailed discussion). A subadverse effect may precede or contribute to an effect that is considered adverse.

2.3 Understanding TRV Derivation

This section briefly reviews the TRV derivation process, specifically issues related to dose adjustment and application of UFs. The term TRV refers to the derived value that is protective of human health, not the primary toxicity data that serve as the point of departure (POD) in the derivation of the TRV. The POD represents a dose that is derived from observed data, is associated with an extra risk for a specific endpoint, and marks the beginning of a low dose-extrapolation. The POD can be a No Observed Adverse Effect Level (NOAEL) or a Lowest Observed Adverse Effect Level (LOAEL) for an observed effect. A POD can be a benchmark dose/concentration (BMD/BMC), which refers to the dose or concentration that produces a predetermined change in response rate of an adverse effect as compared to the background (US EPA, 2023a). Alternately, the statistical lower confidence limit on the BMD or BMC (BMDL/BMCL) can be used as the POD (US EPA, 2023a). Most TRVs are derived by applying UFs to a POD, which is expressed either as mg/kg body weight/day or as a concentration in air or water. This approach is described in further detail below. Alternatively, some TRVs are derived using methods that incorporate advanced modelling techniques which may also be used to model complex exposure scenarios, as introduced in **Section 3.4**. A TRV is derived on the assumption that exposure is essentially constant and continuous during the period of exposure. An overview of the process used to derive a TRV is provided in HC (2010a) DQRA guidance, with TRVs provided in HC (2021).

Generally, a TRV is based on studies involving daily exposure; however, the POD may be obtained from a key study in which the exposure or dosing protocol was not continuous. To derive the TRV for continuous exposure, a POD may be adjusted mathematically to an equivalent dose under conditions of continuous exposure (also termed the adjusted point of departure; POD_{adj}, see equation below). Dose adjustment done in this manner results in a lower, more conservative TRV. For example, epidemiological studies may reflect a typical work schedule (i.e., 8 hours/day, 5 days/week, 48 weeks/year), or inhalation toxicity studies may reflect exposures of 6 hours/day, 5 days/week, but the resulting TRV may be intended to protect people under conditions of continuous daily exposure. Assuming that toxicity is related to total dose (estimated as the product of the concentration of the chemical in the inhaled air and duration of exposure) in the TRV study, the near-continuous laboratory exposure scenario (i.e., 5

days per week) may be adjusted to yield an equivalent continuous inhalation exposure concentration (the $POD_{adj\ inh}$) using the following equation.

$$POD_{adj\ inh} = POD_{inh} * H/24\ hours * D/7\ days$$

Where:

$POD_{adj\ inh}$	=	adjusted POD_{inh} (mg/m^3) after conversion of near-continuous exposure to equivalent continuous exposure concentration
POD_{inh}	=	exposure concentration in air from key inhalation study (mg/m^3)
H	=	hours per day of exposure
D	=	days per week of exposure

Similarly, for oral exposure, a POD obtained from a 5 day/week toxicological exposure protocol might be converted to an equivalent daily dose as follows.

$$POD_{adj\ oral} = POD_{oral} * D/7\ days$$

Where:

$POD_{adj\ oral}$	=	adjusted POD_{oral} (mg/kg bw/day) after conversion of near-continuous exposure to equivalent daily dose of continuous exposure
POD_{oral}	=	daily dose from key oral study (mg/kg bw/day)
D	=	days per week of exposure

The following UFs may be applied to the POD (or POD_{adj}) in deriving chronic TRVs.

$$TRV = POD/(UF_{interspecies} * UF_{intraspecies} * UF_{LOAEL} * UF_{subchronic} * UF_{database\ def})$$

Where:

TRV	=	toxicological reference value (same units as the POD)
POD	=	point of departure (e.g., units of mg/kg bw/day or mg/m^3)
$UF_{interspecies}$	=	typically a 3- to 10-fold factor to account for interspecies differences
$UF_{intraspecies}$	=	typically a 3- to 10-fold factor to account for intraspecies variability
UF_{LOAEL}	=	typically a 3- to 10-fold factor to account for the lack of a NOAEL and for the uncertainty involved in extrapolating from a LOAEL
$UF_{subchronic}$	=	typically a 3- to 10-fold factor to account for uncertainty in extrapolating from subchronic to chronic exposure
$UF_{database\ def}$	=	typically a 3- to 10-fold factor to account for deficiencies in the toxicological database (e.g., lack of reproductive or developmental studies, lack of chronic studies)

When chemical-specific data are available, chemical-specific adjustment factors can be used in place of the default UFs for interspecies or interindividual variability (WHO, 2005). Note that chemical-specific adjustment factors typically account only for the toxicokinetic portion of the interspecies UF. Additional considerations for the choice of UFs are provided in HC (2010a), Meek et al. (1994), Ritter et al. (2007) and in the supporting documentation for published TRVs of individual chemicals. Other agencies may use different UFs; the risk assessment should clearly identify the basis of TRVs from sources other than HC (2021).

2.3.1 Sources of TRVs

Chronic TRVs recommended for use at federal contaminated sites within the FCSAP program are published in HC (2021); however, additional HC TRVs produced by other HC program areas may be used in an HHRA where appropriate. Where relevant HC TRVs are not available, values published by other recognized regulatory agencies may be used in HHRAs. Additional information related to sources of TRVs is found in **Appendix A** and in HC (2010a, 2022a, 2024).

2.3.2 Selection of TRVs

Overall, a weight of evidence approach should be applied in selecting the most relevant TRV for the less-than-chronic exposure duration associated with site-specific land use. In general, the most recent TRV based on the latest toxicological information should be considered unless the derivation of the most recently published TRV does not reflect HC's recommended methodology for the development of TRVs (HC, 2024).

The selection of an appropriate TRV for use at a site should be documented and supported with rigorous scientific evidence. A summary of the strengths and limitations of the different TRV assessments for the chemical under review should be provided, along with a clear rationale in support of the TRV selected for use in the assessment. When selecting a less-than-chronic TRV, it is important to also consider the final toxic endpoint and how the chemical may affect the key events that may eventually lead to irreversible toxic endpoints. HC also recommends that the risk assessment evaluate whether the selected TRV is sufficiently protective of early lifestages or if an additional UF is required to address potential increased vulnerability. TRVs selected for use in an HHRA should be based on the most recent published information available for the chemical being evaluated.

Use of a short-duration TRV for an intermittent, repeated, exposure scenario should include chemical-specific toxicological rationale, to identify whether additional effects may occur as a result of repeated exposures. This is due to the fact that a short-duration TRV is typically based on a toxicological study involving a one-time short exposure which does not involve continuous intermittent exposure. Hence, an HHRA with intermittent exposures can be complex if a short-duration TRV is applied to a repeated exposure. If a short-duration TRV is used for repeated exposures, the report should include a description of evidence related to elimination kinetics and integration of the persistence of effects in order to determine whether toxicological effects would be expected to persist in the period following exposure and prior to the next exposure in an intermittent exposure scenario. Persistent effects could result because either the chemical (or its metabolite) is not effectively eliminated, or the effects of an exposure are not reversible.

Text Box 2.1 provides a non-exhaustive list of criteria to consider when selecting suitable TRVs (adapted from HC 2013c).

Text Box 2.1 Considerations for selecting TRVs (adapted from HC, 2013c)

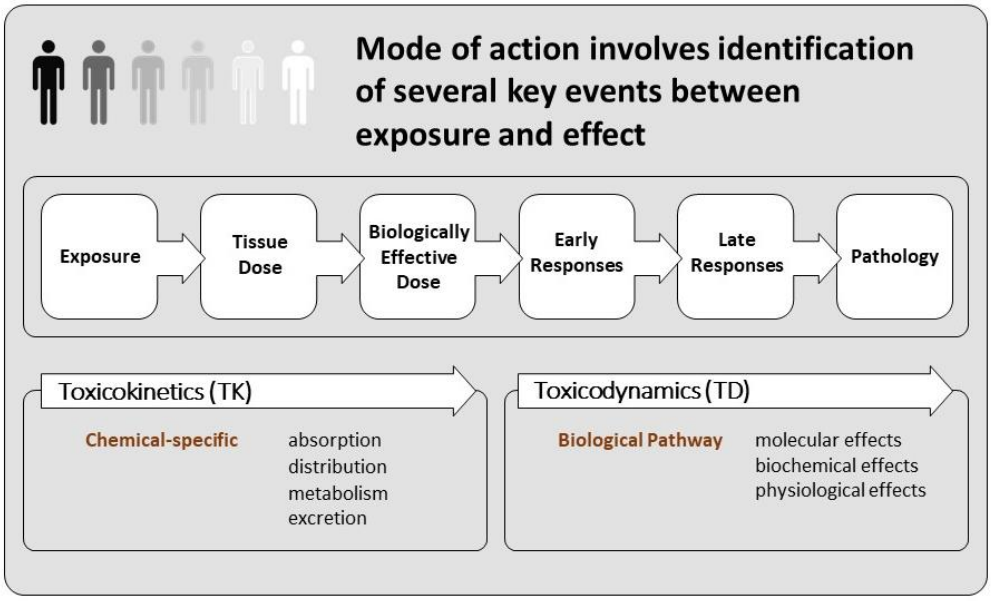
a) Strength of the underlying toxicological/epidemiological data used to derive the TRV.
b) Completeness of the toxicological/epidemiological database.
c) Use of epidemiological studies vs. animal bioassays for TRV derivation, when adequate epidemiological data are available.
d) TRV developed for the general population and not for occupational exposure.
e) Consideration of sensitive subpopulations.
f) Relevance of the TRV (e.g., route of exposure and exposure duration of interest), noting exposure duration categories.
g) Date of assessment and inclusion of new data.
h) Extent of independent peer review.
i) Rigour/scientific validity of data analysis, evidence synthesis and integration; appropriate adjustment made to exposure.
j) Consideration of MOA.
k) Adequate documentation on the derivation of the TRV, including relevance of the TRV to a single continuous exposure in a lifetime versus repeat exposure(s).
l) Composite UF (not exceeding 10,000) based on the available data.

2.4 Mode of Action (MOA)

The MOA is the process through which a chemical produces an effect in the body. In the context of risk assessments, the term MOA describes a series of measurable key biological events or critical steps following exposure to a chemical that may result in an observable toxic effect in an organism (see **Figure 2.2**). Characterizing the MOA for a chemical is an important aspect of the toxicological assessment, and can be a particularly complex element to consider when conducting a risk assessment using this framework.

When identifying the MOA for a chemical, a weight of evidence approach may be used to determine the key target organ for toxicity. The target organ or tissue is usually the one that is adversely affected at the LOAEL. However, in determining the key target organ or tissue, consideration should be given to key factors such as dose route, dosing vehicle, duration of exposure, and species differences in anatomy, absorption, metabolism, distribution, excretion or sensitivity where data allow.

Figure 2.2 Mode of action (MOA)

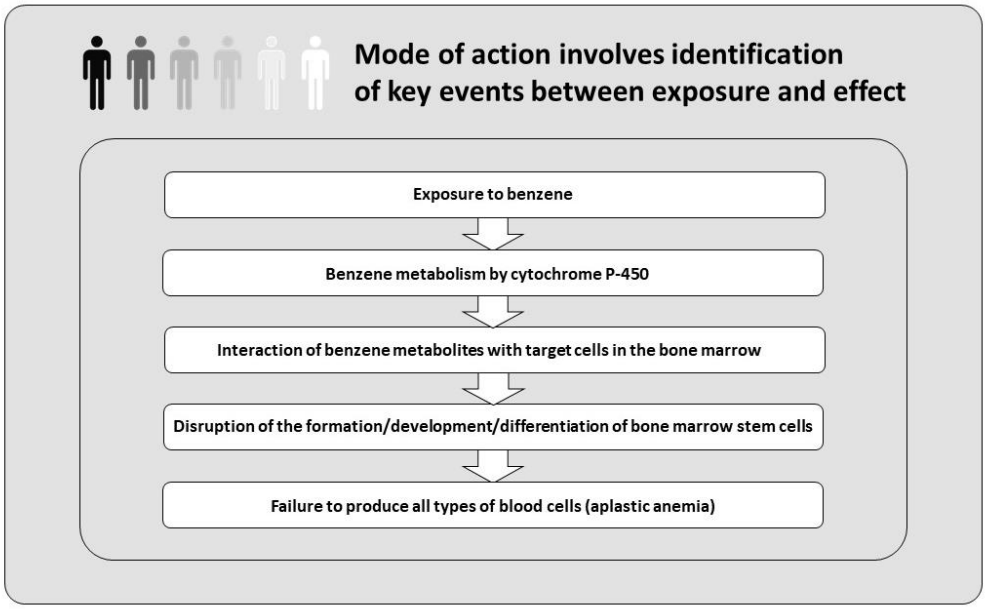


When conducting a less-than-chronic risk assessment, if the critical toxic effect(s) identified in the MOA is determined to be primarily related to the peak exposure (i.e., concentration of the chemical/active metabolite in a target tissue/blood), dose averaging would not be appropriate as the nature and severity of the effect would be the same regardless of the number of periods or length of exposure. If the critical toxic effect(s) identified by the MOA is determined to be primarily related to the total dose of the chemical/active metabolite (i.e., dose summed over a set period of time), dose averaging may be possible with supporting rationale. See **Sections 3.2.3** and **3.3.2.3** for detailed information on the considerations and impacts of MOA on dose averaging when conducting a less-than-chronic risk assessment.

The MOA and key events are important when identifying TRVs and may be different for a short-duration TRV as compared with a TRV derived from a chronic or reproductive study.

Figure 2.3 provides the key events likely involved in benzene-induced hematotoxicity (ATSDR, 2007; Bird et al., 2010; Meek and Klaunig, 2010). While benzene is a carcinogen, exposure to benzene for acute, intermediate and chronic periods may result in non-cancer effects, such as hematological effects (e.g., decrease in the relative numbers of circulating blood cells of all types). A progressive deterioration in hematopoietic function may follow exposure, including bone marrow damage, changes in circulating blood cells and altered immune response (ATSDR, 2007). The affected bone marrow may eventually fail to function resulting in hematopoietic stem cells in the bone marrow never reaching maturity (ATSDR, 2007). In this benzene example, the final non-cancer effect is aplastic anemia (failure to produce all types of blood cells). A TRV that protects against early key events – such as a small decrease in production of a single blood cell type – would, by extension, be expected to protect against an effect such as aplastic anemia. The final endpoint for exposure to benzene could also include carcinogenic effects that are preceded by, and dependent upon, threshold non-cancer effects.

Figure 2.3 Probable key events in benzene-induced hematotoxicity MOA



The MOA information is important for PBPK models, which mathematically describe the uptake and disposition of a chemical, using physiological parameters. The MOA information is also important for BBDR predictive models, which describe biological processes at the cellular and molecular level that link the target organ dose to the adverse toxicological effect. These types of models can be used to improve the understanding of parameters influencing the dose-response relationship of a given chemical, and require chemical-specific information.

2.4.1 Subadverse Biological Effects

As discussed in the above sections, a TRV is derived to be protective of adverse effects following exposure to a chemical. Subadverse effects associated with less-than-chronic exposures are important to consider and document when conducting a HHRA. A subadverse effect is a biological change or perturbation resulting from chemical exposures, generally within cells but that may also comprise changes in the biochemical characteristics of plasma, serum, urine or other body fluids (e.g., oxidative stress, glutathione depletion). The biological change, in and of itself, may not be considered adverse (i.e., adversely affecting the function of the organism as a whole). However, it may precede or contribute to an effect that is considered adverse. Such subadverse effects may, like adverse effects, be short-lived or may persist after elimination of the chemical from the body. Although still not considered "adverse", persistent subadverse effects are of concern. Even though a single exposure may produce no adverse effects, the subadverse effects may progress to adverse effects upon repeated exposures. In addition, the significance of such effects may be a question of magnitude. For instance, mild oxidative conditions may have no adverse effect in cells at levels below those easily managed by cellular defenses; more severe oxidative stress may lead to reversible biochemical changes in the cell; still more severe oxidative stress may lead to irreversible cell changes, including mutation and cell death. A similar progression of effects may be seen at the tissue and organism level.

The toxicological profile for each substance as well as the exposure pattern would require consideration and justification in an HHRA where chronic TRVs are not applied. These considerations are important in identifying the most appropriate TRV to be used for short-duration or intermittent exposures and should be presented as part of the supporting rationale for the use of a particular TRV.

2.4.2 Adverse Outcome Pathway (AOP)

The Adverse Outcome Pathway (AOP) Framework is a tool that can be used to assess effectively the safety of chemicals based on available information, though the toxicity database may not be complete. More specifically, the AOP framework is able to help address knowledge gaps by proposing a sequence of molecular and cellular events that may be involved in producing a toxic effect when a target tissue or organ is exposed to a substance. It should be noted that AOPs are not intended to be chemical-specific, but pathway-specific. Specifically, they allow for relevant linkages to be made between a particular biological activity that occurs at an exposure site and a biologically plausible pathway and/or outcome, which may have the potential to lead to downstream adverse health effects. Additionally, AOPs containing detailed quantitative information that can be mathematically modelled may provide valuable mechanistic information that can be used to further support quantification of potential human health risk as part of a DQRA.

When conducting a risk assessment, there may be some chemicals and exposure scenarios for which published TRVs are not available. Further, available toxicity studies may not be adequate for deriving a *de novo* TRV. In these instances, other sources of relevant information such as a well-described AOP may be useful to inform the risk assessment. Although AOPs in general are not chemical-specific, they can still include valuable information on the MOA, key events and key event relationships. AOPs can also describe relevant biological and toxicological responses that could potentially be related to several key events that may originate from a single molecular initiating event (Organisation for Economic Co-operation and Development [OECD], 2017). Since AOPs are not chemical-specific, the information used to develop each proposed pathway is generally based on available data from other, more well-studied chemicals. The intended use of AOPs to study data-poor chemicals as part of a risk assessment is to aggregate pathway-specific knowledge on more data-rich chemicals, which is currently available through multiple different sources, into a systematic and accessible format that facilitates use of this information.

In an intermittent exposure analysis, the dynamic relationship between chemical elimination kinetics and persistence of health effects (**Section 3.3.2**) would play an important role in determining whether such exposure scenarios may lead to an adverse health effect. An HHRA with intermittent exposures can be complex if dose averaging is included in the calculations or if a short-duration TRV is applied to a short-duration exposure episode that is repeated more than once. If the HHRA includes either of these approaches, the report should describe how evidence related to elimination kinetics and the persistence of effects can be integrated in order to determine whether chemical effects would persist in the period following exposure and prior to the next exposure in an intermittent exposure scenario. Persistent effects could result because either the chemical (or its metabolite) is not eliminated efficiently, or the effects of an exposure are not reversible. Use of information from AOP and toxicokinetic/toxicodynamic analyses can facilitate this type of assessment. The complexities of AOP are not discussed in detail in this

document. However, if the AOP framework is used in a risk assessment, detailed scientific rationale should be included as part of the HHRA.

2.5 Exposure Assessment

The exposure assessment component of a short-duration risk assessment is similar in concept to that in a chronic risk assessment as described in HC (2010a) and is informed by the problem formulation of the risk assessment. However, the assessment for a short-duration exposure scenario can be more complex, particularly when intermittent exposures are involved. The exposure assessment provides an estimate of the daily exposure that a person receives while at a contaminated site. In general, the exposure assessment does not include the interval when the person is not at the site, with the exception of foods that are harvested from the site and consumed after leaving.

Some sites may have variable chemical distribution patterns (i.e., microenvironments) or receptor site use patterns. People exposed to the conditions in these microenvironments may be disproportionately exposed to elevated levels of contaminants relative to receptors using other areas of the site. In these instances, it may be appropriate to use the conditions present in a microenvironment to represent the exposure point concentration that may be used to calculate the exposure that a person may receive while at a site (HC, 2010a). An analysis of receptor exposure in each microenvironment should be consistent with exposure pathways identified at the problem formulation stage of the risk assessment.

All receptors who may frequent a site or be exposed to COPCs from a site (e.g., people who consume foods harvested from a contaminated site) need to be considered. The assessment of exposure can be conducted for all age groups or can be based on consideration of the most sensitive lifestage of those present at the site. For example, if a family were at a contaminated site for 2 weeks every 2 months, then the exposure would be estimated for the 2-week period at the site for the most exposed and most sensitive family member (e.g., toddler, pregnant person). Exposure for this family member over the entire exposure scenario may also need to be estimated. It is not acceptable to simply average out the exposure while at the site over the total exposure scenario (including the non-exposure periods spent off-site) as this calculation has the potential to underestimate health risk. Similar to chronic TRVs, use of TRVs for less-than-chronic exposure also requires consideration of sensitive members of the population.

Soil ingestion is often the most sensitive exposure pathway at federal contaminated sites and is generally expressed as a daily rate, which can be calculated using the equations provided in this document. The equations in this document may also be modified to accommodate hourly exposures using hourly exposure rates, such as for inhalation of volatile chemicals and/or dusts (HC, 2017c), soil and dust ingestion (HC, 2018a) or sediment ingestion (HC, 2017a). However, this approach may require consideration of additional toxicokinetic and toxicodynamic factors.

At federal contaminated sites that people do not frequent daily, including remote and difficult to access sites, the evaluation of site-specific exposure scenarios should include a detailed chemical-specific rationale for any assumptions made in the HHRA report related to short-duration exposures. The information provided on the exposure scenario of interest in the HHRA should be site-specific and include a description of the pathways and routes of exposure, population (e.g., children, adults) who

may be exposed, activities, and a full account of the exposure duration and interval(s) of exposure for each receptor for all COPCs present on site.

The framework identifies key factors that should be provided in the analysis to account for short-duration and repeated intermittent exposures. These factors include, but are not limited to, consideration of a chemical's elimination half-life (i.e., how long a chemical is retained in the body), as well as the duration and persistence of any effects.

2.5.1 Exposure Duration Definitions and TRV Application

The exposure scenario is determined based on site-specific land use patterns, and would generally fall into the acute, subchronic and chronic categories; however the durations of these categories can differ among regulatory agencies. The HC DQRA guidance (2010a) uses the following definitions of exposure durations for humans: acute (less than 14 days, but often involving a single exposure), subchronic (greater than 14 days and up to 90 days) and chronic (greater than 90 days). However, these categories have been redefined in **Table 2.1** below.

The definitions of exposure duration categories are generally based on the durations of standardised mammalian toxicity testing protocols; however, other agencies may use alternate criteria to categorize exposure durations. HC (2010a) definitions for subchronic and chronic exposures for humans are comparable in duration to subchronic and chronic experimental animal studies, respectively, maintaining a 1:1 ratio in exposure duration between human and animal species. The definition of acute exposure presented in HC's DQRA guidance (2010a) does not differentiate between acute exposure (lasting for 1 day or less but often involving a single exposure) and moderate repeated exposures over a short term (2 weeks or less). Most regulatory agencies make a distinction between acute exposure (1 day or less) and short-term exposure, which is often defined as up to 1 month (US EPA, 2012a, 2023a). The definitions found in the DQRA (HC, 2010a) are for general reference purposes. **Appendix B** of this document presents a review of these definitions for exposure duration and the updated definitions are summarized in **Table 2.1**.

The acute exposure category has been redefined in this guidance to represent an exposure that lasts for 24 hours or less. Additionally, two new categories have been created in this document that supersede those presented in HC's DQRA guidance (2010a). The short-term exposure duration category involves repeated exposure of more than 24 hours and up to 30 days. An exposure period of 30 days is comparable in duration to repeated dose 28-day toxicity study test guidelines in rodents (OECD, 1981, 2008, 2018a; US EPA, 1998a, 2000); these studies can serve as the data source for a TRV applicable to short-term exposures of more than 24 days and up to 30 days. The intermediate exposure category (i.e., >30 days to <1 year) describes the exposure duration that is longer than short-term exposure but shorter than chronic exposure. The use of 1 year as the separation line between intermediate and chronic exposure duration is consistent with ATSDR and most animal test guidelines for chronic (at least 1 year) durations (OECD, 2018b; US EPA, 1998b; United States Food and Drug Administration [US FDA], 2007). The ATSDR library of intermediate MRLs, US EPA library of subchronic RfCs/RfDs and other agencies (listed in **Appendix A**) are potential sources of intermediate TRVs applicable to exposure duration of more than 30 days and up to less than 1 year for contaminated site HHRAs. Other sources

may also be relevant. Note that for some chemicals, if short-duration exposures are repeated annually, the chemical may persist and can create a chronic exposure situation, even if the exposure is not continuous (see **Section 3.3.2**). The most relevant TRV for the exposure duration of interest needs to be identified after careful consideration of all potential candidate TRVs, and this rationale should be clearly documented, with references, in the HHRA.

Table 2.1 Updated exposure duration categories for contaminated sites risk assessment

Exposure Duration Category	Definition
Acute exposure[1]	exposure for 24 hours or less (≤24 hours)
Short-term exposure[1]	repeated exposure for more than 24 hours, up to 30 days (>24 hours to ≤30 days)
Intermediate exposure[1]	repeated exposure for more than 30 days, up to less than 1 year (>30 days to <1 year)
Chronic exposure	repeated exposure for 1 year or more, and up to a lifetime (≥1 year)

[1] Note that if exposures are repeated, they may be considered chronic, even if they are not continuous.

2.5.2 Dose Averaging

In a contaminated site risk assessment, dose averaging can be defined as the mathematical averaging of a short-duration exposure over a longer time period (e.g., a six-month exposure averaged over a year). This approach is not recommended for estimating exposure to characterize risk in an HHRA unless it can be supported by a rigorous chemical-specific scientific analysis that considers the potential toxicological effects associated with people's actual exposure at the site. Dose averaging by mathematical manipulation would result in an underestimation of the actual exposure of a person while at a site, as the total dose received during a shorter exposure period is prorated over a longer time period, including period(s) of non-exposure. Dose averaging may also be characterized as amortization or calculation of the time-weighted average exposure. For example, dose averaging of a continuous exposure period of 2 weeks over the course of a year involves dividing the actual exposure received over 2 weeks by 52 weeks, which would underestimate the actual daily exposure over the 2-week period. This underestimation would result in a lower risk estimate than would have been calculated based on the actual on-site exposure because the dose-averaged exposure (which is 26-fold lower than the actual exposure) is inappropriately compared to the chronic TRV in this example.

Dose averaging is based on the assumption that toxicity is related to the total exposure, regardless of the timeframe during which the exposure is received. However, this assumption is not valid in all cases. The exposure calculated by dose averaging may not represent the relevant measure of exposure at the site and may underestimate potential risk associated with actual levels of exposure received over a short time period. Therefore, if dose averaging is considered in a site-specific risk assessment, the assessment would require a rationale on a chemical-specific basis to identify how dose averaging conducted would be adequately protective of human health.

Though the mathematical result may suggest equivalent exposure, dose averaging differs from ***dose adjustment*** applied in TRV derivation (e.g., **Section 2.3**) to convert a non-continuous exposure protocol in the key study to an equivalent continuous exposure used as the POD. Dose adjustment applied in TRV development is a conservative step, because it often results in a lower (more conservative) TRV. In contrast, dose averaging applied in scenario-specific exposure assessment reduces the quantitative value of the exposure estimate for comparison against the TRV to characterize health risk, and as such may not be health protective. Criteria for conducting dose averaging as part of exposure assessments are discussed in **Sections 3.2.3, 3.2.4** and **3.3.3**. In principle, for the purposes of the evaluation framework discussed in this guidance document, dose averaging is relevant only when it is supported by toxicological evaluation on a chemical-specific basis, is fully documented and referenced in the HHRA.

2.5.2.1 Commercial/Industrial Land Use

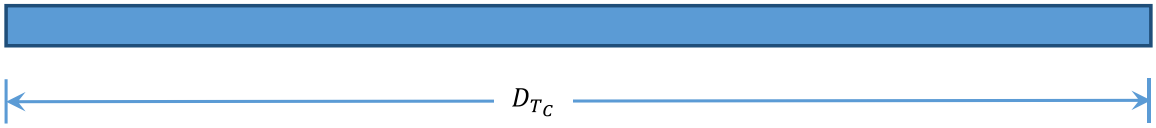
HHRAs conducted at federal contaminated sites traditionally assume chronic exposure scenarios for all land uses. In an HHRA and in the derivation of soil quality guidelines (CCME, 2006), commercial and industrial land use guidelines assume people are typically present at work 5 days per week. Given the chronic nature of the exposure scenarios, dose averaging of 5 days/7 days, 48 weeks per year and use of a chronic TRV may be considered acceptable in a Tier 0 assessment for commercial and industrial land use for some chemicals. Whether dose averaging is appropriate should still be evaluated on a chemical-specific basis. In addition, work schedules deviating from the above pattern should be assessed on a scenario- and chemical-specific basis in Tiers I and II to ensure any dose averaging is protective of human health.

2.5.3 Exposure Terms

Exposure terms that are used in this document are defined below. For the figures presented in the text boxes, the blue-coloured bars represent exposure, and the white-coloured bars represent non-exposure.

Continuous daily exposure (**Text Box 2.2**): Continuous daily exposure refers to uninterrupted exposure over several consecutive days, such as 24 hours/day, 7 days/week for inhalation, daily for oral and dermal exposures.

Text Box 2.2 Continuous daily exposure



Where:

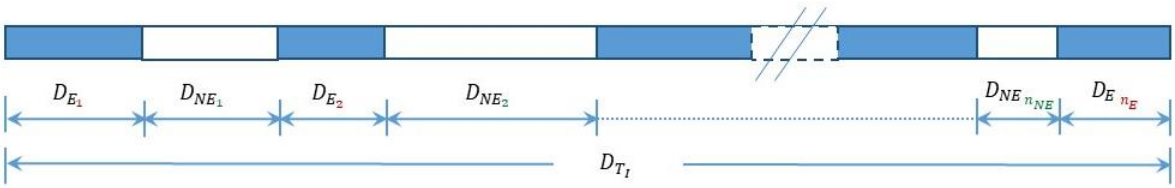
= Exposure

D_{T_C} = Duration of a continuous exposure scenario in days, spanning from first day to final day of exposure

Continuous daily exposure refers to uninterrupted exposure that could last for days, weeks or months (e.g., 24 hours/day, 7 days/week).

Intermittent exposure (**Text Box 2.3**): Intermittent exposures are exposure scenarios that are not continuous. For instance, an example of an intermittent exposure would be a continuous exposure interrupted by one or more intervals of non-exposure, with each non-exposure interval lasting continuously for more than 2 days.

Text Box 2.3 Intermittent exposure



Where:

= Exposure episode, denoted E

= Non-exposure interval, lasting > 2 days and denoted NE

D_{E_i} = Duration of exposure episode i in days, where i varies between 1 and n_E (the total number of exposure episodes)

D_{NE_j} = Duration of non-exposure interval j in days, where j varies between 1 and n_{NE} (the total number of non-exposure intervals)

D_{T_I} = Duration of the entire intermittent exposure scenario in days

$$= \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{NE}} D_{NE_j}$$

AET_i = Aggregate exposure time in days for intermittent exposure scenario

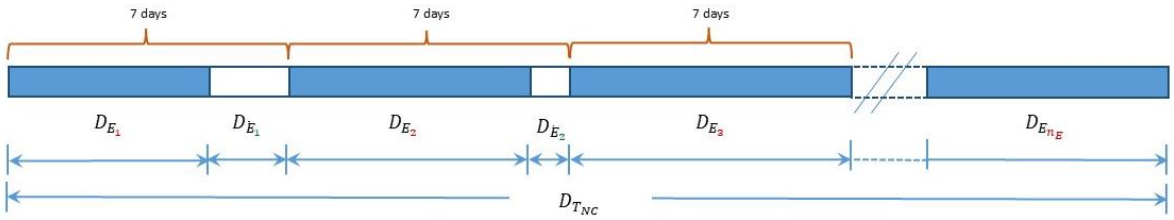
= Total number of days exposed for intermittent exposure scenario

$$= \sum_{i=1}^{n_E} D_{E_i}$$

Intermittent exposures are those that are not continuous, i.e., continuous exposures interrupted by one or more intervals of non-exposure (each lasting continuously for more than 2 days) where the non-exposure periods are of sufficient duration that steady-state is not maintained (Felter et al., 2011). For example, repeated exposures of one week/month over years are considered intermittent.

Near-continuous exposure (**Text Box 2.4**): Near-continuous exposure scenarios have periods of non-exposure that are a small proportion of the entire exposure duration. In this guidance, near-continuous exposure refers to those exposures occurring regularly such as for 5 to 6 days per week (i.e., with continuous non-exposure interval of up to 2 days per week) within a longer overall exposure scenario (e.g., 5 days per week for years). A valid supporting scientific rationale is required for any other exposure pattern to be treated as near-continuous exposure in a site-specific risk assessment.

Text Box 2.4 Near-continuous exposure



Where:

= Exposure episode, lasting 5, 6 or 7 days, and denoted E

= Non-exposure period, lasting 2, 1 or 0 days, and denoted $\bar{E}$

D_{E_i} = Duration of exposure episode i in days (must be 5, 6 or 7), where i varies between 1 and n_E (the total number of exposure episodes)

$D_{\bar{E}_j}$ = Duration of non-exposure period j in days (must be 2, 1 or 0), where j varies between 1 and $n_{\bar{E}}$ (the total number of non-exposure periods)

$D_{T_{NC}}$ = Duration of the entire near-continuous exposure scenario in days

$$= \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

AET_{NC} = Aggregate exposure time in days for a near-continuous exposure scenario

= Total number of days exposed for a near-continuous exposure scenario

$$= \sum_{i=1}^{n_E} D_{E_i}$$

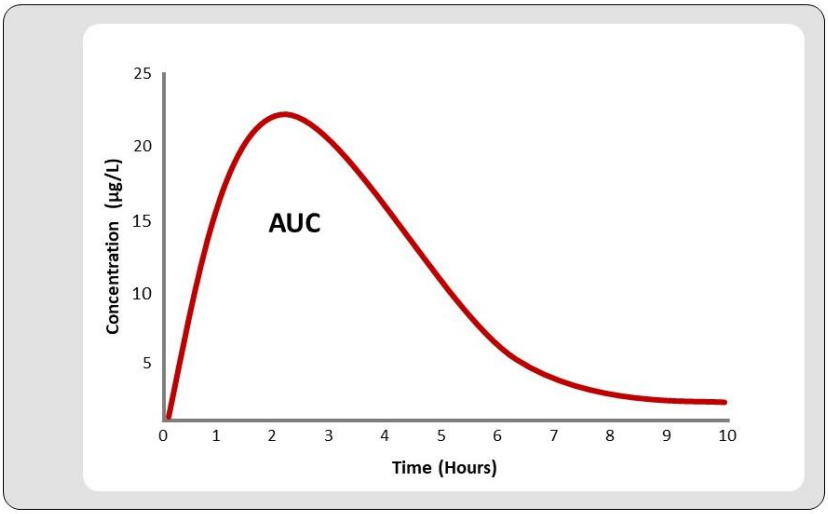
Special note: D_{E_i} of 7 consecutive days (D_{E_3} on the above graph) can apply when there is exposure by inhalation for a portion of each consecutive day

Near-continuous exposures refer to exposures occurring regularly, such as for 5 to 6 days per week (i.e., continuous non-exposure period up to 2 days per week) within a longer overall exposure scenario (e.g., 5 days per week for years). For inhalation exposures, near-continuous exposures also refer to exposures occurring for part of each consecutive day (e.g., 10 hours/day) within a longer overall exposure scenario. Many near-continuous exposure scenarios may be considered effectively continuous. For example, near-continuous inhalation exposure to a chemical with a 24-hour elimination half-life for 6 days per week over 6 months may be considered effectively continuous. This exposure pattern mirrors the exposure regimen in some toxicity studies, which may be converted to an equivalent continuous exposure to identify an appropriate TRV for use in assessment of human health risks.

Continuous non-exposure periods of up to 2 days within a 7-day period (e.g., exposure for 5 days per week) repeated over a long term is, strictly speaking, an intermittent exposure scenario that requires analysis of intermittency. However, consideration of these exposure patterns as near-continuous in this guidance is a practical approach with some level of uncertainty. For any other exposure pattern to be treated as near-continuous in a site-specific risk assessment, the risk assessment report should include a valid chemical-specific scientific rationale.

Total exposure (**Text Box 2.5**): Total exposure refers to exposure summed over a period of time and can be expressed as total external (or administered) dose, or total internal (or absorbed) dose.

Text Box 2.5 Total exposure



Total exposure is defined as time-integrated exposure and can be expressed as total external (or administered) dose or total absorbed dose.

- Total external or administered dose: This document uses the term "total exposure" to refer to the total external or administered dose (i.e., summed over a period of time).
- Total absorbed dose (or internal dose): The internal exposure of the body to the chemical after the chemical has been administered is reflected by the Area Under the Curve (AUC). The AUC is determined by the area under the plot of chemical concentration (usually in serum or plasma) against time. This document uses the AUC as a surrogate for the total absorbed dose or internal dose.

2.5.4 Intermittent Exposure

The term intermittent exposure, as used in this guidance, generally refers to scenarios that are non-continuous (See **Text Box 2.3**). These non-continuous scenarios can be defined as either continuous or near-continuous exposures interrupted by one or more periods of non-exposure, with each non-exposure period lasting continuously for more than two days. For instance, a typical recurring 5-day workweek would not be regarded as a non-continuous exposure as the period of non-exposure does not exceed two days.

The concept of intermittent exposure can be illustrated using an example where the total dose is the same but the exposure scenarios differ. An exposure period of 2 days per week for 36 weeks should not be considered identical to an exposure of 72 continuous days. The first scenario consists of 5 continuous non-exposure days between 2-day periods of continuous exposure. During the 5-day non-exposure

interval, a percentage of the chemical may have been eliminated from the body (varying from a very small amount up to 100%, depending on the chemical), which has the potential to reduce the amount of chemical in the body prior to the next exposure period. In contrast, the second scenario does not have a non-exposure period throughout the 72 days of continuous exposure, which may result in the build up of the chemical in the body. Prolonged exposure to the chemical may impede the ability of the body to repair adverse or subadverse biological effects given the body may not have had a chance to process and/or clear the chemical from the system. However, substances with long half-lives may not be fully eliminated during the non-exposure intervals in the first scenario, thus the total exposure duration would become 36 weeks. Since 36 weeks in the first scenario is a much longer exposure period than the 72 days of continuous exposure in the second scenario, application of a different TRV may be required. This variance in exposure pattern may result in different health effects even when the chemical concentration in the environmental medium is the same. Therefore, it is important to understand that while a mathematical calculation may suggest equivalent exposure, the risk assessment needs to consider both the *exposure assessment* and the *toxicity assessment*. Further, analysis of an intermittent exposure scenario may add an element of complexity to the overall HHRA.

It is important to note that consideration of the time between exposures should also include the potential for exposures to the same chemical in background environmental media (e.g., food, water, soil) or exposure to the same chemicals at other contaminated sites. This may involve consideration of the overall temporal pattern of the exposure.

Section 2.5.1 and **Appendix B** provide definitions that are important for assessment of exposure duration. **Appendices C** and **D** provide equations for use in the Exposure Assessment.

3 DETAILS OF THE TIERED ASSESSMENT FRAMEWORK

The tiered assessment framework presented earlier in **Figure 1.1** is a stepwise decision tree for evaluating whether an estimated exposure level for a less-than-chronic exposure scenario is associated with potential health risks. This section examines each element of the framework in detail.

Tiered assessments involve a decreasing use of default approaches, an increasing use of chemical-specific and site-specific data, and more advanced levels of toxicological expertise as the assessment moves to higher tiers. In general, the scope of a project and/or site-specific requirements to use complex modelling and analyses are some of the key determinants that inform the need to advance to a higher-tiered assessment. The exposure assessment portion of Tier 0, Tier I and Tier II-a in the tiered assessment framework is similar to that of DQRA, calculating the exposure that may be received on a given day with dose averaging not conducted beyond the exposure period. In higher tiers, the exposure assessment is more complex, as it depends on the exposure pattern and the MOA in Tier II-b and Tier III assessments. Tier III involves calculation of the internal dose at the target organ, requiring more input parameters. Risk characterization is conducted at each framework tier. Professional judgement is required to determine whether the risk assessment should proceed beyond Tier 0, to subsequent tiers of the framework or whether remediation/risk management measures may be a preferred option if potential risks are identified. Higher-tiered assessments typically involve a more time-intensive and costly risk assessment. Time and cost considerations may be important in making remediation/risk management decisions. Note that sufficient toxicological expertise will be required for any risk assessment incorporating less-than-chronic exposure, with increasing expertise required at higher tiers.

- Tier 0 is an assessment for determining the absence of appreciable non-cancer health risks using the most conservative TRV, usually the chronic TRV (as discussed in **Section 3.1**). In some cases, Tier 0 is the only assessment needed to provide sufficient information for making risk-management decisions. If the outcome of the risk characterization at Tier 0, using the chronic TRVs, concludes that there is no cause for concern, no further action is needed for those substances. However, if the outcome indicates a potential for risk that exceeds the target HQ, the assessment may advance to the next tier(s) using more relevant TRVs, exposure- and toxicology-specific data analyses, and models, all of which require more advanced toxicological expertise.
- Tier I (**Section 3.2.1**) applies an existing duration-specific TRV relevant to the exposure (Tier I-a) or an existing TRV adjusted to make it more relevant to the exposure duration under consideration (Tier I-b). For a single (continuous or near-continuous) exposure scenario, there is no need to proceed to additional tiers if risk estimates are acceptable using a Tier I-a or Tier I-b approach (e.g., risk estimates are at or below target HQ).
- Tier II-a (**Section 3.2.2**) applies a *de novo* 'duration-specific TRV' relevant to the route of exposure. The *de novo* TRV can be derived from a critical analysis of toxicity studies when a TRV of relevant duration does not exist and no existing TRV can be adjusted to make it more relevant (refer to HC, 2010a for guidance on derivation of *de novo* TRVs).
- Tier II-b (**Section 3.3**) describes additional analyses required to address intermittent exposure scenarios (i.e., episodes of continuous or near-continuous exposure interrupted by periods of

more than 2 days of continuous non-exposure). The analyses include determination of whether exposure episodes overlap to become effectively continuous, influenced by the potential of the chemical/active metabolites or subadverse/adverse effects to persist or progress following repeated exposures (see **Section 3.3.2**). Tier II-b requires integration of chemical-specific toxicokinetic and toxicodynamic data in the analysis (**Appendix F**).

- Tier III evaluation (**Section 3.4)** involves complex exposure and dose-response models (i.e., PBPK, physiologically-based toxicokinetic [PBTK] or BBDR models). PBPK/TK or BBDR models have been validated for only a very limited number of chemicals. Their application at Tier III requires significant and specialized toxicological expertise in this field, in addition to working with data that are not typically considered in contaminated sites risk assessments. Tier III approaches are not discussed in detail in the main body of this guidance as it is not common to require this level of assessment in the context of a FCSAP contaminated site HHRA. A brief overview of Tier III assessment is provided in **Section 3.4.**

Tiers 0, I-a, I-b and II-a apply to both single continuous (or near-continuous) and intermittent exposure scenarios. However, as discussed in the following sections, for the steps beyond Tier 0 (i.e., Tiers I-a, I-b and II-a), analyses differ for single continuous (or near-continuous) and intermittent exposures. Further, dose averaging consideration refers to exposure assessment only and does not apply to modification of the TRV except where specified in **Section 3.2.1.2**. Depending on the scope and resources, a risk assessment may proceed directly to higher-tiered levels when the required chemical-specific data, methods for analysis, exposure and toxicological expertise are available.

To simplify the framework, the text mainly provides guidance related to assessing exposure to a single chemical. Additionally, it assumes background concentrations in the environment to be zero for simplicity, although in a risk assessment a target HQ of 0.2 is applied for site-related exposures where background exposures (i.e., exposures to the same COPC from other sources such as food, water, consumer products, soil, air) are not considered. HC DQRA guidance (2010a) provides information on how to address background exposures. In specific sections, guidance is provided on the assessment of multiple exposure pathways and routes (**Section 4.2**) and the assessment of combined exposure to multiple chemicals is discussed in the risk characterization section (**Section 4.3**) and in HC (2010a).

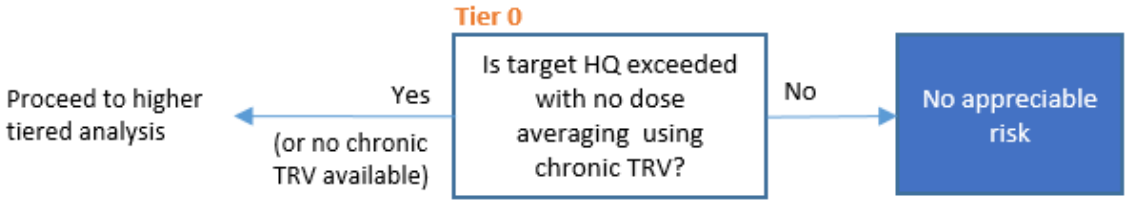
3.1 Tier 0: Assessment Using a Published Chronic TRV

Tier 0 (**Figure 3.1**) is the first step in the quantitative assessment for short-duration and intermittent exposure scenarios. The exposure during the most sensitive and exposed lifestage is calculated and compared to a published chronic TRV, as described in HC (2010a, 2021, 2024) (see sources of published TRVs in **Appendix A**). This calculation estimates the expected highest daily exposure[1] that a person would receive if the person remained on site each day for the whole time period, which is identical to the calculation for a chronic exposure period. No dose averaging is applied in a Tier 0 assessment beyond what is typical in the case of a commercial/industrial exposure as described in **Section 2.5.2.1.** The highest daily exposure is calculated for each COPC for the most sensitive population under the

[1] "Highest exposure" in Tier 0 refers to the estimated exposure for an individual during the most sensitive (and exposed) lifestage.

exposure scenario of interest and is similar to that which is calculated in a DQRA with no dose averaging (e.g., the daily exposure that is expected to be received while on-site is calculated). **Text Box 3.1** presents general exposure equations for a Tier 0 assessment. The highest daily exposure is expressed in a time unit that is compatible with the chronic TRV. The chronic TRV (HC, 2021), which is relevant to the route of exposure and based on the most sensitive endpoint and lifestage, is applied to the exposure estimate. Since the goal of a Tier 0 assessment is to provide a conservative estimate of potential risk associated with exposure, no dose averaging is conducted at this level, unless it can be supported with a chemical-specific rationale. For exceptions to the above, see **Section 2.5.2.1** for commercial/industrial land use considerations. If the estimated HQ for a COPC or the sum of the HQs for multiple COPCs that have the same effects on the same target organ do not exceed the target HQ in a Tier 0 assessment, there is no need to proceed to higher-tiered assessment for this COPC. See **Section 4.3** for guidance on risk assessment of combined exposure to multiple chemicals.

Figure 3.1 Tier 0 assessment



Exposure calculations for a Tier 0 assessment are similar to that conducted in a DQRA (HC 2010a), where sufficient data are available to characterize exposure (e.g., the contamination is delineated, and adequate data are available for statistical derivation of an exposure point concentration for each area of potential concern). If microenvironments are present at the site because of either the chemical distribution patterns or patterns of use by receptors, the chemical concentration data of the microenvironments require consideration. A more detailed discussion of microenvironment analysis can be found in HC (2010a, 2024). The exposure point concentration of the chemical in each environmental medium of interest (air, water, soil, food, etc.) is a statistical representation of the available concentration data that can be used to estimate potential exposure that people may receive while at the site. The statistical value used for each exposure medium will depend on the available data, and if there are inadequate data to evaluate potential exposure statistically, maximum concentrations may be used to calculate exposure. For instance, exposure to COPCs in air in a building or exposure to COPCs in water from a groundwater well may require application of the maximum concentration. Contamination should be well delineated for each area of potential concern at a site before the exposure point concentration is estimated. Depending on the quality of the available data, a measure of central tendency may be applicable in an area of potential environmental concern where contaminated soils may be accessed equally. This may include the mean value if the quality of the exposure data is high or the 95% upper confidence limit of the mean (95% UCLM). A 90th percentile concentration may be used for databases of lesser quality. Refer to HC (2024) for additional information on adequate delineation of site contamination, selection of exposure point concentrations and statistics. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA.

Text Box 3.1 General exposure equations for tier 0 assessment

The Tier 0 exposure equation for soil ingestion and inhalation are presented here for illustration purposes. Refer to HC (2010a, 2024) for general exposure equations for other exposure routes.

Inadvertent ingestion of contaminated soil:

$$Dose\ (mg/kg\ bw/day) = \frac{C_S * IR_S * RAF_{oral} * ET}{BW}$$

Where C_S = concentration of contaminant in soil (mg/kg)
IR_S = receptor soil ingestion rate (kg/day)
RAF_{oral} = relative absorption factor from the gastrointestinal tract (unitless)
ET = exposure term (unitless)
BW = body weight (kg)

For Tier 0 assessment of ingestion exposure, ET is defined as:

$$ET = D_2 * D_3$$

Where D_2 = 7 days per week exposed/7 days
D_3 = 52 weeks per year exposed/52 weeks

With the exception of inhalation exposure, ET in the general equations for dermal contact, ingestion of water, and ingestion of foods may assume the same ET presented for soil ingestion.

For Tier 0 assessment of inhalation exposure, the equation for estimating exposure is presented in HC (2024), and the ET is defined as:

$$ET = D_1 * D_2 * D_3$$

Where D_1 = 24 hours per day exposed/24 hours
D_2 = 7 days per week exposed/7 days
D_3 = 52 weeks per year exposed/52 weeks

Hence, ET assumes a value of 1 for all routes of exposure. Additional changes to ET are not recommended unless they are accompanied by scientific rationale on a chemical-specific basis.

For many chemicals, chronic effects may occur at levels of exposure that are lower than those that cause effects following a short-duration exposure. Thus, if a target HQ (i.e., exposure/TRV) using a chronic TRV is not exceeded in an HHRA where chronic exposure to a substance is assumed, no further quantitative analysis is required. However, if the highest estimated daily exposure exceeds the target HQ (i.e., site-specific HQ > target), more detailed analysis may be required in a higher tier to characterize potential non-cancer health risk.

Text Box 3.2 presents an example of a Tier 0 assessment.

Text Box 3.2 Tier 0 example

The exposures estimated in Tier 0 assessment for chemical A and chemical B from all sources (including background) at a hypothetical contaminated site are 0.01 and 0.02 µg/kg bw/day, respectively, based on conservative assumptions for the highest exposure period while at the site. A target HQ of 1 is applied in this example as exposure from all sources related to the site plus background are included in the exposure estimate.

- The published chronic TRV for chemical A is 0.08 µg/kg bw/day. This TRV is higher than the exposure of 0.01 µg/kg bw/day (i.e., HQ <1), therefore no significant health risk is anticipated. As such, no further assessment of risk beyond Tier 0 from short-duration exposure to chemical A is required.
- The published chronic TRV for chemical B is 0.01 µg/kg bw/day; comparison with the exposure of 0.02 µg/kg bw/day identifies a potential risk (i.e., HQ >1). For chemical B, the assessment of potential risk from short-duration exposure may proceed to Tier I if that option is identified as a feasible approach based on the toxicological information for this substance. Alternatively, a risk management approach may be considered to mitigate exposure to chemical B following the Tier 0 assessment.

Summary and Additional Considerations

If Tier 0 assessment identifies a potential risk, the results should be presented in the report and the risk assessment can proceed to a higher tier, such as Tier I, or Tier II-a. A Tier 0 assessment is not necessarily overly conservative for a short-duration exposure. For some COPCs, a higher tiered assessment may provide a similar risk estimate as Tier 0. For instance, if the applicable acute or intermediate TRV is the same as the chronic TRV (such as in the case of tetrachloroethylene with identical acute, intermediate and chronic MRLs [ATSDR, 2019]), the risk estimated using the acute or intermediate TRV in a higher tiered assessment for the time period while people are at the site would be identical to the Tier 0 risk estimate. Hence, there would be no benefit in proceeding to a Tier I assessment. Please refer to **Appendix E** for some worked examples that provide additional considerations and rationale.

This document discusses exposure for people while they are on-site; however, for some assessments it is possible that people may also receive exposure off-site as a result of off-site migration of COPCs or consumption of foods that are collected from a site and consumed at a later date. These considerations need to be identified in the problem formulation stage and addressed in the exposure assessment. It is important to note that people who go on an annual hunting trip and obtain food that is affected by a contaminated site may continue to consume foods obtained from the site over an extended period of time and may share those foods with other people. Under such circumstances, the exposure may be chronic rather than intermediate, and a chronic TRV would be applicable.

Considerations prior to initiating a higher tiered assessment include whether the exposure at the site is of an intermittent nature that may be repeated annually. It is therefore important to consider whether the exposure is chronic or if the exposure is truly of a short duration. The actual exposure pattern at the site is important for selection of applicable TRVs. These considerations are discussed further in the following sections on higher tiered assessments and should be documented in the risk assessment.

3.2 Single Continuous or Near-Continuous Exposures (Tiers I and II-a)

Tiers I and II-a compare a single continuous short-duration exposure event against a short-duration TRV relevant to the exposure scenario. No dose averaging beyond a particular single continuous exposure event is supported where there is no repeated exposure.

Conversely, near-continuous exposure scenarios can have periods of non-exposure that are a small proportion of the entire exposure duration. In this guidance, the term near-continuous exposure refers to exposures occurring regularly for a portion of each consecutive day of exposure (when inhaled) or 5 to 6 days per week (i.e., with a continuous non-exposure interval of 2 days or less per week) within a longer overall exposure scenario (e.g., 5/7 days per week for over a year). Many near-continuous exposure scenarios may be considered effectively continuous using these specific parameters. For example, near-continuous inhalation exposure to a chemical (with an elimination half-life of 24 hours) for 6 days per week over 6 months may be considered effectively continuous over the 6-month period, but not beyond 6 months (such as over a full year).

For the purpose of this framework, near-continuous exposures are grouped with continuous daily exposures. Near-continuous exposures (where periods of non-exposure are a small proportion of the entire exposure scenario) are considered to have the same duration as if they were continuous. The implication of the non-exposure periods in the near-continuous exposure scenario is addressed when identifying the primary determinant of toxic effect as described in **Figures 1.1** and **3.2**.

3.2.1 Tier I: Comparison with Published TRVs and Underlying Toxicity Data of Relevant Exposure Duration

A Tier I analysis is based on existing published TRVs and the underlying toxicity data, as compiled and evaluated within an authoritative review (see **Table A.1** in **Appendix A** for relevant sources of TRVs). To perform a Tier I analysis, the HHRA report should provide a summary of the health effects, a clear description of the exposure pattern, the scientific basis of each TRV developed by the regulatory authorities, and indicate how each of these TRVs is applicable to the exposure scenario of interest.

Tier I-a involves comparison of exposure (without dose averaging beyond the exposure period) with a published TRV for a comparable (or longer) exposure duration and requires experience in assessing toxicological data.

Tier I-b involves comparison of exposure (without dose averaging beyond the exposure period) against a modified TRV (usually involving modified UFs) relevant to or longer than the exposure duration of interest and requires expertise in dose-response assessment. Chemical-specific toxicity data are required for any modification of a TRV. No default factors are recommended to convert chronic TRVs to

shorter-duration TRVs (HC, 2010a). This conclusion is informed by a review of the ratios of shorter-duration TRVs to chronic TRVs for a number of chemicals. In some cases, chronic TRVs may be identical to shorter-duration TRVs. For instance, ATSDR (2024a) provides chronic and intermediate MRLs that are identical for barium, tetrachloroethylene and other substances. As such, applying a default value to create a short-duration TRV from a chronic TRV would be inappropriate. The rationale for any modified TRV should be presented in the HHRA for each of the substances assessed, with references.

Tier I addresses two questions (**Figure 3.2**).

a) Determine if a published TRV is available for the scenario of interest or for a sufficiently similar scenario (see **Section 3.2.1.1**). If yes, the scenario of interest is compared with the existing TRV (Tier I-a).

b) If a published TRV is not available for a sufficiently similar scenario, the next question is whether the study that forms the basis for a published TRV (i.e., the underlying toxicity study) is similar to or longer than the exposure scenario of interest (see **Text Box 3.3** below). If so, the published TRV can be adjusted (e.g., by modifying the UFs) to match more similarly the exposure scenario (Tier I-b).

3.2.1.1 Tier I-a: Direct Application of Published Short-Duration TRVs

The first step in Tier I-a is to determine whether a published short-duration TRV is available for the exposure scenario of interest or whether this exposure scenario is sufficiently similar to the one that is used to derive the TRV for a single exposure event. Exposure duration is the primary factor to consider when identifying an appropriate TRV. The short-duration TRV applied to a single event should match as closely as possible the duration of the exposure event that people receive at the site. For instance, it would not be appropriate to apply an acute TRV to a daily exposure that is repeated once a week as the acute TRV was derived for a single exposure of 24 hours or less and not for repeated weekly exposures.

3.2.1.2 Tier I-b: Comparison with Modified Existing TRVs by Adjusting for Duration

Tier I-b assessments require the input of a qualified toxicologist/risk assessor who is thoroughly familiar with the process and complexity of TRV derivation.

Many existing chronic TRVs are derived from subchronic studies[2] by applying an UF to extrapolate from subchronic to chronic exposures. In such cases, an intermediate TRV can be derived from the chronic TRV by removing the UF that extrapolates from subchronic to chronic exposure. In essence, the intermediate TRV is obtained by multiplying the chronic TRV by the same UF that was applied to the POD in the derivation of the chronic TRV. This factor would usually be identified as the $UF_{data\ def}$ in HC guidance documents (HC, 2010a) or the UF_S (subchronic to chronic UF) in US EPA documents (US EPA, 2002). In 2022, of the approximately 571 chemicals in the US EPA Integrated Risk Information System (IRIS) database, 127 have chronic RfDs and 41 have RfCs that were derived from data from a subchronic

[2] A study period of at least 90 days as per animal test guidelines (OECD, 2018c, 2018d; US EPA, 1998c, 1998d, 1998e; US FDA, 2007)

study; 113 of these TRVs used an UF of 10, 32 applied an UF of 3 and 21 applied an UF of 1 for extrapolation from the subchronic study.

On a chemical-specific basis, a valid scientific rationale can be provided to adjust a TRV (modification of TRV [Tier I-b], **Figure 1.1** and **Figure 3.2**). If the study that forms the basis of the TRV is similar in duration to the scenario of interest, the published TRV can be adjusted for duration. However, this adjustment can be considered only after the basis for its derivation has been carefully evaluated with respect to factors such as dosing duration, dosing interval and exposure route.

Where a TRV is so adjusted, the risk assessment must nonetheless evaluate the toxicity database to ensure that the critical toxic effect that forms the basis of the unadjusted TRV is the most sensitive toxic endpoint for the exposure duration of interest. In addition, the POD initially selected for the TRV must be the most sensitive LOAEL/NOAEL or appropriate BMD/BMDL for the exposure duration of interest. Otherwise, a Tier II-a assessment (derivation of *de novo* TRV) may be more appropriate than modification of the TRV in Tier I-b. Data arrays of endpoints by duration and effect level, such as those prepared by ATSDR (see **Figure 3.3**), provide valuable information that can be used to evaluate whether other toxic endpoints might be critical to the exposure duration of interest.

Information to support these analyses should be obtained from the original supporting documentation published by the regulatory agency that developed the TRV. The International Toxicity Estimates for Risk (ITER) database (**Appendix A**) includes many TRVs published by agencies and documents relevant adjustments, thus facilitating identification of TRVs that can be adjusted to the duration of interest.

See **Text Box 3.3** for examples of adjustment of TRVs for duration.

Where existing TRVs have been modified as described, supporting documentation to be submitted for review may include, but is not limited to the following.

- An analysis of the toxicity database to evaluate if the critical toxic effects for the duration of interest are similar to the critical effects in the study that forms the basis of the existing TRV.
- Determination of whether the POD initially selected for the TRV is also the most sensitive LOAEL/NOAEL or appropriate BMD/BMDL for the exposure duration of interest.
- Adjustment for duration made to the existing TRV, supporting scientific rationale and references.

Figure 3.2 Tier I and Tier II-a assessments for a single continuous (and near-continuous) exposure

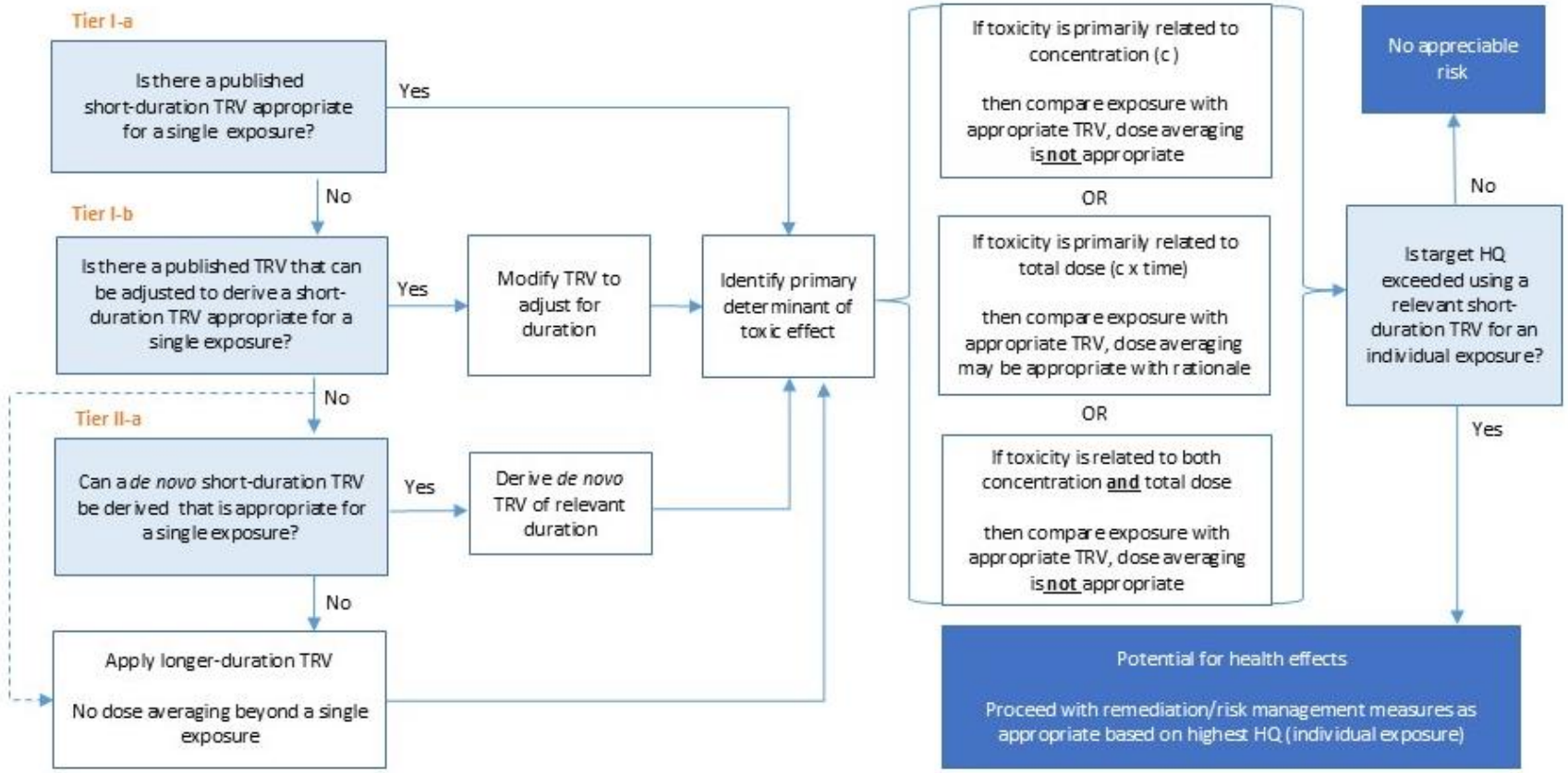
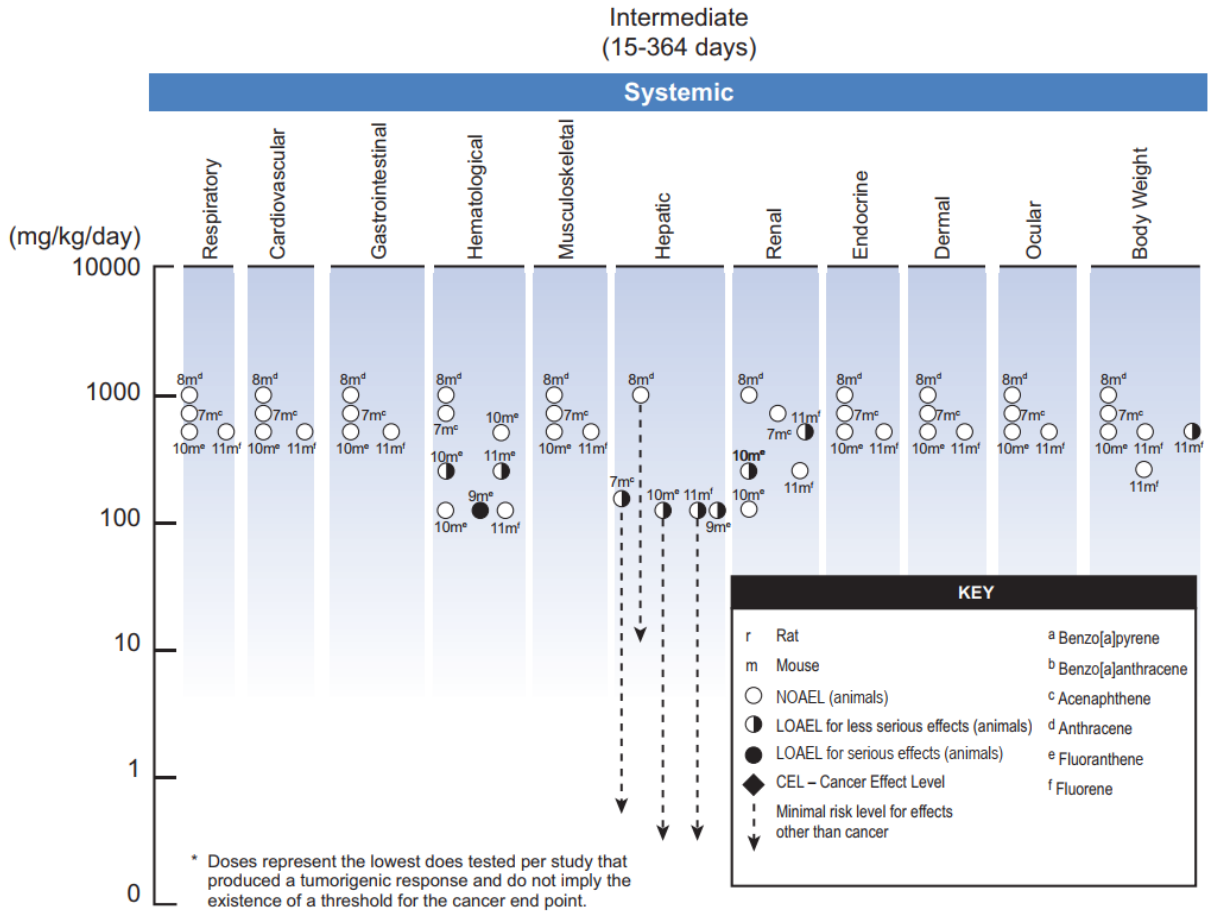


Figure 3.3 Example of figure presenting data arrays of endpoints by duration and effect level from ATSDR toxicological profile for polycyclic aromatic hydrocarbons (ATSDR, 1995)



The figure illustrates effect levels for different endpoints for each duration category.
The number adjacent to each symbol refers to a specific study, as listed in the accompanying table on Levels of Significant Oral Exposure from ATSDR (1995).

Text Box 3.3 Adjusting Toxicological Reference Values for duration

An evaluation of the toxicological data would be required to determine whether any adjustments to the published TRV would be possible. Two examples are provided below.

Adjust Uncertainty Factor (UF) in TRV derivation

The published chronic TRV for chemical C is 0.01 mg/kg bw/day, which was derived from a subchronic study in animals and incorporated a composite UF of 1000. The composite UF was made up of a factor of 10 for interspecies variation, 10 for intraspecies variation and 10 for extrapolation from a subchronic study to a chronic TRV. Based on the toxicological data available for this substance, it was possible to derive an intermediate TRV from the chronic TRV by removing the UF used to extrapolate from the subchronic study to the chronic TRV. Thus, for chemical C, the chronic TRV (0.01 mg/kg bw/day) can be multiplied by 10 to obtain an intermediate TRV of 0.1 mg/kg bw/day. This intermediate TRV can be used to calculate a HQ in the risk characterization stage of the HHRA involving an intermediate exposure scenario.

Adjust for Duration in TRV Derivation

It is possible to adjust the TRV for exposure duration where the published TRV involves exposure adjustment in its derivation. For instance, where exposure occurred in a toxicological study 5 days/week and the TRV was adjusted for 7 days/week, it is possible to re-calculate the TRV by removing the adjustment if the exposures at the site are 5 days/week. In some cases, the original study that forms the basis of the TRV may be more similar to the exposure scenario of interest than the scenario related to the TRV.

3.2.2 Tier II-a: Comparison with *de novo* TRV of Relevant Exposure Duration and Route

Tier II assessments require the input of a qualified toxicologist/risk assessor who is thoroughly familiar with the process and complexity of TRV derivation.

Tier II-a assessment involves comparison of the exposure received at the site (without dose averaging beyond the actual exposure period) with a TRV based on a toxicological study of relevant duration when no published TRV for that exposure duration is available (derivation of *de novo* TRV, **Figure 1.1** and **3.2**). A *de novo* TRV can be derived and applied to the exposure of interest following the procedures outlined in HC (2010a) using the following steps.

a) Review of the relevant toxicological data for the duration of interest, including a summary of the chemical's effects, the overall toxicokinetic and toxicodynamic profile.

b) Identification of a suitable toxicity study of relevant duration.

c) Application of appropriate UFs to the POD to derive a TRV.

d) Comparison of exposure to the *de novo* TRV for the relevant route and duration.

When the chemical of interest is a member of a larger group of related chemicals, a TRV for a similar surrogate chemical may sometimes be applied or modified for use.

HC's methods are consistent with those of other regulatory agencies worldwide, such as the US EPA, WHO, the Netherlands National Institute of Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM), ATSDR and other state agencies (e.g., California Environmental Protection Agency [CalEPA], Minnesota Department of Health [MDH], Texas Commission on Environmental Quality [TCEQ]). A summary of agency-specific methods can be found in the ITER database (available at https://tera.org/iter/riskmethods.html). The derivation starts with a critical review of the toxicity database, identification of appropriate critical study (studies) of relevant duration and exposure route for dose-response assessment, selection of appropriate POD(s) and calculation of TRV(s). More details on data requirements, key considerations in data analyses, weight of evidence assessment, POD selection, TRV derivation and reporting requirements can be found in HC (2010a).

Even when a TRV for the duration of interest is not available, the documentation produced in support of published TRVs for other durations of exposure may be a useful resource. The ATSDR toxicological profiles (ATSDR, 2024b) provide valuable summary figures of the key data on dose-response relationships for a range of endpoints, summarizing the NOAEL and LOAEL by target organ or system and by exposure duration (e.g., **Figure 3.3**). These review documents along with evaluations of primary literature can be particularly important for the consideration of short-duration exposures, where one endpoint (driven by concentration) may be the critical effect for a 1-day exposure, whereas a different endpoint (driven by total dose) may be the critical effect for a 14-day exposure. This information can be used to evaluate the potential risk associated with the exposure scenario of interest. HC health assessments for priority substances (HC, 2004) and toxicological summaries in support of other HC programs (e.g., Canadian drinking water guidelines [HC, 2022a], Canadian residential indoor air quality guidelines [HC, 2022b]) provide additional resources, as does the US EPA IRIS database.

Systematic review methods and protocols are increasingly being used to evaluate scientific literature, and to identify, evaluate and integrate evidence into the TRV development process. While the US EPA has identified ongoing work on its handbook for IRIS development (US EPA, 2013), additional protocols (including those for systematic review) are published for each chemical-specific assessment, such as chloroform (US EPA, 2018a). Refer to US EPA presentations (Taylor and Walker, 2017) and publications (National Academies of Sciences, Engineering, and Medicine, 2018) for the latest development and guidance on developing *de novo* TRVs.

A few methods are available to address chemicals lacking appropriate toxicological data to estimate chemical-specific potency, and these methods are reviewed in HC (2010a). For some substances, there may be toxicological data available for structurally related analogs. While quantitative structure-activity relationship [(Q)SAR] models in themselves may not represent a good source for identifying TRVs without further analysis, such models may be useful in identifying potential analogs with toxicological data, as well as potential effects based on substances with similar physical chemistry and structures (OECD, 2007a; European Commission, 2010). Various regulatory agencies are developing (Q)SAR guidance and tools for chemical assessments. Publications such as OECD (2007b, 2009), European

Chemicals Agency (ECHA, 2008, 2016) and the North American Free Trade Agreement Technical Working Group on Pesticides (2012) are some examples of available resources.

3.2.3 MOA Consideration and Impact on Dose Averaging for Non-Intermittent Exposures

MOA information (e.g., parameters that affect key events), including chemical reactivity, key targets and kinetic parameters that determine toxicity, needs to be considered in higher tiered assessments, which include dose averaging considerations. To determine whether dose averaging is appropriate, it is necessary to evaluate the critical toxic effect(s) for the exposure duration of interest. If the critical toxic effect(s) is primarily related to the peak exposure (i.e., concentration of the chemical/active metabolite in a target tissue/blood), dose averaging is not appropriate as the nature and severity of the effect would be the same regardless of the number of periods or length of exposure. If the critical toxic effect(s) is primarily related to the total dose of the chemical/active metabolite (i.e., dose summed over a set period of time), dose averaging may be possible with supporting rationale. *If both total dose and concentration contribute to the determination of toxicity, dose averaging is not appropriate*.

In the evaluation framework discussed in this guidance document, dose averaging is relevant only in the context of exposure assessment. Dose averaging assumes uniform distribution of the exposure over both non-exposure ("off") and exposure ("on") periods. For example, exposure to 10 mg/m^3, 8 hours/day, 5 days/week for a 4-week period is mathematically equivalent to a 4-week continuous exposure of 2.4 mg/m^3 (i.e., 10 mg/m^3 * 8 hours/24 hours * 5 days/7 days *4 weeks/4 weeks) if dose averaging were applied. However, this mathematical dose averaging provides an underestimate of what a person would actually be exposed to while at the site (i.e., 10 mg/m^3 vs. 2.4 mg/m^3) and the potential health effects associated with the actual peak exposure would have been missed with the mathematically calculated averaged dose. For a substance such as formaldehyde, where irritant effects are observed at elevated short-duration exposures (HC 2006), this approach would not be appropriate.

Dose averaging is generally not supported beyond the actual overall duration of an exposure (i.e., from the first day of exposure to the final day of exposure, irrespective of intermittency) in a continuous or near-continuous exposure scenario. Dose averaging may be considered for non-intermittent exposure scenarios (such as 5 days/7 days) with a long overall duration where toxicity is primarily related to total dose (**Figure 1.1** and **3.2**). For example, the exposure to 10 mg/kg bw/day, 5 days a week for a 4-week period may be dose averaged over the 4-week period but not beyond (i.e., applying a 4 weeks/4 weeks but *not* a 4 weeks/>4 weeks multiplication factor), resulting in a 4-week continuous exposure of 7.1 mg/kg bw/day (but *not* lower than 7.1 mg/kg bw/day). If this 4-week period was averaged over a year, the daily exposure would be underestimated, which may minimize the potential risk.

In general, dose averaging for short-duration exposures is not appropriate for chemicals for which concentration (or peak exposure) is the primary determinant of toxicity. A peak exposure has to be maintained for some minimal period (e.g., a few minutes) for an effect to occur. Therefore, it may be difficult to determine whether peak vs. total exposure is driving the toxicity. For this reason, the evaluation needs to identify which dose metric serves as the primary driver of toxicity. This evaluation is possible for typical non-intermittent exposure scenarios over the course of a week (i.e., 5-6 days/week) at contaminated sites. This framework may not be applicable to other more complex exposure scenarios

that require more in-depth analyses. On the other hand, dose averaging may be appropriate when all the following conditions are met (Haber et al., 2016).

a) The severity of the toxic effects is not primarily a function of concentration or peak exposure.

b) The toxic effects are primarily a function of the total dose (also represented by the average daily exposure over the duration of the exposure period), regardless of the exposure pattern.

c) Dose averaging can only be applied over a short time frame, such as over the non-exposure period in a near-continuous exposure scenario.

Furthermore, dose averaging may be considered, with chemical-specific rationale, where toxicity is related to the dose received during a critical lifestage or period of development (e.g., fetal development during pregnancy, early childhood) rather than to the total dose over a longer period. Analyses need to factor in issues such as the relative duration of the window of susceptibility vs. the proposed averaging time, chemical kinetics, dynamics, and variability within these critical periods. As such, the potential for effects occurring between the actual exposure level that may be received at the site (without dose averaging) and the averaged exposure over a longer period should be evaluated and summarized in the HHRA report to allow for technical review.

Dose averaging is generally not recommended for a substance when the TRV is based on developmental (teratogenic, e.g., malformations due to abnormal fetal development)[3] or reproductive effects. For example, the human heart begins to develop at conception and is fully formed by eight weeks into the pregnancy (Stanford Medicine Children's Health, 2023; University of Rochester Medical Center, 2023). If a pregnant person is exposed during this critical window of development to a chemical such as trichloroethylene, which can affect prenatal cardiac development (Johnson et al., 2003; Makris et al., 2016), congenital heart defects in the fetus may potentially occur. Thus, consideration should be given to determine whether elevated exposures over short time periods would exceed the TRV, and whether exposures may be sufficient to elicit an adverse developmental or reproductive effect. In general, evaluation on a chemical-specific basis is required when considering dose averaging, such as identifying whether the toxicity is related to peak exposure, or to the dose received during a critical lifestage or period of development (e.g., fetal development during pregnancy, early childhood), or to the total dose over a longer period.

For reactive chemicals and irritants, local toxicity is principally dependent on the peak concentration in the exposure medium (e.g., air, water, soil, dust, food) (Haber et. al., 2016). For reactive chemicals that target the portal of entry (e.g., respiratory tract for inhalation, gastrointestinal tract for oral, skin for dermal and eyes for ocular exposure, respectively), concentration is likely the driver of health effects (Costa and Gordon, 2019; Lehman-McKeeman, 2019). Further, ocular exposure may be a key risk driver for some irritants and gases (e.g., hydrogen sulphide, ammonia, formaldehyde [HC, 2006]). Dose averaging would not be appropriate for this class of chemicals given that concentration is likely the principal driver of toxicity.

[3] When the most sensitive endpoint for the TRV is based on a teratogenicity study where pregnant animals were dosed for a short time period (e.g., 3 days) that coincides with the window of structural development for a specific organ in the embryo or fetus, dose averaging is not appropriate.

Peak exposure concentration is also the primary determinant of toxicity for many chemicals causing asphyxia as a result of displacement of oxygen by inhaled gases, such as carbon dioxide (Hilal-Dandan and Brunton, 2016). After systemic absorption, toxicity can likewise be related to the peak internal dose (e.g., peak blood/target tissue concentration of the chemical/active metabolite) for some inhaled gases or ingested chemicals that have been found to cause central nervous system depression, including narcosis (Bruckner et al., 2019). Rapid effects on critical physiological systems that occur prior to adaptive responses (such as changes in blood pressure or blood glucose) have the potential to be driven by concentration. For this class of chemicals, dose averaging for short-duration exposures would not be considered appropriate (Haber et. al., 2016).

In the application of this framework, it can be a challenge to determine the appropriate dose metric (i.e., whether toxicity is due primarily to concentration/peak exposure or total dose). Authoritative reviews (toxicological profile of chemicals from ATSDR and/or the US EPA, systematic reviews and peer-reviewed publications) can help to provide information on the importance of short-duration peak exposures. If the appropriate dose metric cannot be identified from the above TRV documentation, other sources of information may also need to be consulted.

The following questions may assist in determining whether toxicity is primarily related to concentration/peak exposure rather than to total dose.

- Is toxicity for the duration of interest driven by concentration/peak exposure?
- Is the chemical reactive (e.g., irritants)?
- Do critical effects take place at the portal of entry?
- Is the critical effect narcosis, asphyxia, irritation or allergenicity?
- Does toxicity vary with a change in the dosing pattern? For example, is there evidence that a bolus dose may result in a greater effect when compared with the same total dose delivered in multiple smaller increments over a longer period[4]?

If the answer to all these questions is no and there is no reason to believe that toxicity is primarily driven by concentration, then dose averaging may be supported. However, the above list is not exhaustive and all relevant information for decisions made should be summarized in the report. In the absence of adequate available data to identify the primary determinant of toxicity (i.e., concentration or total dose/body burden), the default is to assume concentration to be the primary determinant of toxicity, with dose averaging not supported.

For practical purposes, dose averaging may be assumed appropriate for near-continuous exposures except when the effect is primarily driven by concentration for the duration of exposure. The estimated time-averaged daily exposure would then be compared with a TRV of relevant duration expressed as mg/kg bw/day. If the toxic effect is primarily driven by concentration for the duration of exposure, dose

[4] The observation of a greater effect after intravenous dosing than after diet or drinking water may also indicate that toxicity is not related to the total dose of parent compound but may reflect the impact of first-pass metabolism.

averaging cannot be supported. Whether dose averaging is appropriate for intermittent exposure scenarios should be evaluated in accordance with a Tier II-b assessment (see **Section 3.3.2.3**).

Text Box 3.4 Rationale for default dose averaging for near-continuous exposure (5 days per week for a long period) when toxicity is not primarily driven by concentration

Many TRVs are developed on the basis of experimental animal data. For many subchronic and chronic studies that require specified exposure regimens or repeated intermittent dosing (e.g., oral gavage studies), the dosing regimen may not be continuous (e.g., 5 days per week). For the purpose of this guidance document, this pattern fits the definition of near-continuous exposure scenarios (i.e., with a continuous non-exposure interval up to 2 days within a 7-day period that is repeated through a long overall duration).

Generally, short-term, intermediate and chronic TRVs are designed to address continuous exposures (i.e., 7 days per week). The near-continuous exposure pattern in the animal study is often adjusted to a continuous exposure pattern during TRV derivation, where the effect is not primarily driven by concentration. As such, a near-continuous exposure scenario can be given the same treatment in a site-specific risk assessment as in the TRV derivation process. Thus, for chemicals whose effects are not primarily driven by concentration and where there are no acute studies that identify effects at the estimated exposure levels, dose averaging (i.e., 5 days/7 days) of the near-continuous exposure can be made prior to comparison with the appropriate TRV of relevant duration. The HHRA must demonstrate that these two aforementioned conditions have been met for those chemicals. Such default dose averaging is acceptable because the comparison made during risk characterization is based on the same temporal pattern of exposure and the same dose averaging treatment (i.e., 5 days/7 days in the exposure scenario of interest vs. 5 days/7 days in the experimental study that forms the basis of the TRV).

Supporting scientific rationale is required for assessment of other exposure patterns as near-continuous on a chemical-specific basis.

3.2.4 Exposure Estimation for Continuous and Near-Continuous Scenarios (Tiers I and II-a)

Exposure estimation for substances in environmental media is similar for continuous, near-continuous and chronic exposure scenarios. However, some of the equations detailed for chronic exposures (HC, 2010a, 2024) may be modified for continuous and near-continuous short-duration exposures to chemicals present in contaminated soils eliciting threshold effects (refer to **Appendix C**). Similarly, equations for estimating exposure to contaminated sediments in HC (2017a) *Supplemental Guidance on Human Health Risk Assessment of Contaminated Sediments: Direct Contact Pathway* may be similarly adjusted to address short-duration continuous and near-continuous exposures. Where relevant, relative bioavailability adjustments can also be incorporated into the exposure calculations (HC, 2010a, 2017b, 2024). An analysis of receptor exposure in each relevant microenvironment may be considered.

The exposure point concentration of each COPC in each environmental medium (air, water, soil, vegetation, etc.) is identified based on the available data (refer to HC, 2010a and 2024) and are the

same as those used in Tier 0 assessment. The appropriate statistics for exposure factor parameters (e.g., intake rate) depend on the conditions present at the site, the onsite behaviour of the receptors and what primarily drives toxicity (i.e., concentration/peak exposure or total dose/body burden). The appropriate statistics for each input parameter should be determined from a careful analysis of the above factors. Rationale and supporting evidence for exposure point concentrations and receptor characteristics should be provided in the HHRA report. For example, for a site designated to be a soccer field, receptors are expected to be at a high activity level during the relatively brief periods players and spectators are occupying the field; a high (and not the mean) inhalation rate may be appropriate for exposure estimation.

In general, typical exposure (daily rate of exposure) is estimated for the entire duration of the exposure scenario. Unless stated otherwise (e.g., **Section 3.2.3**), no dose averaging beyond the exposure scenario is permitted (i.e., the averaging period cannot be longer than the total duration of the exposure scenario). Doing so may underestimate the actual exposure while present on site and thus the potential exposure-related health risks (see **Section 2.5.2** and **Appendix G** for more in-depth discussion).

When toxicity is primarily driven by concentration/peak exposure (e.g., irritation at high levels), dose averaging is not appropriate for either continuous or near-continuous exposure scenarios. For example, HC (2006) has established a short-duration (1-hour) formaldehyde indoor air quality guideline of 123 $\mu g/m^3$ to prevent eye irritation in the general population. This concentration should not be exceeded at any 1-hour interval during a day. As such, the maximum air concentration that occurs for any 1-hour interval would be applicable. It would therefore be inappropriate to compare exposure based on an average concentration over time or from multiple buildings, or concentrations that may vary over a longer time period to the 1-hour indoor air guideline, as this comparison may underestimate potential health effects (e.g., eye irritation). If toxicity is primarily driven by total exposure (i.e., time-integrated exposure; dose summed over a set period) or body burden, some dose averaging may be possible where rationale is provided on a chemical-specific basis.

3.3 Intermittent Exposures (Tier II-b)

Most TRVs intended for short-duration exposures are based on toxicological studies involving a one-time exposure period (e.g., one day or 14 days) but are not generally based on studies with repeated intermittent exposure events. However, intermittent exposures can occur at contaminated sites when people access a site multiple times for short visits, with a period of non-exposure between successive visits.

In practical terms, intermittent exposures in this guidance refer to scenarios that are non-continuous, which can be defined as continuous or near-continuous exposures interrupted by one or more intervals of non-exposure, with each non-exposure period lasting continuously for more than two days. For instance, a typical recurring 5-day workweek would not be regarded as non-continuous.

Intermittent exposures at contaminated sites pose a challenge with regard to HHRA as assuming chronic exposure may overestimate potential risk. However, treating each repeated visit as an independent exposure may underestimate potential risk as repeated exposures can result in different health effects as compared to a single exposure. This may be the case if the substance has the ability to build up in the

body over time or if subadverse biological effects (e.g., metabolism of chemical compounds by Cytochrome P450) associated with each exposure episode persists and/or progresses into the subsequent exposure episode. In some instances, an intermittent exposure, repeated over a period of years (potentially up to a lifetime), could be more consistent with a chronic, rather than a shorter-duration exposure. For example, an exposure occurring for 4 months of the year, every year over multiple years, would likely require application of a chronic TRV in an HHRA in order to not underestimate potential risk.

Repeated intermittent exposures can be addressed following the process illustrated in **Figure 1.1.** The process involves assessing each single exposure episode of a particular duration (Tier I and II-a) followed by assessment of the entire intermittent exposure scenario (Tier II-b), where applicable. Note that the assessment begins with a Tier 0 level assessment (discussed in **Section 3.1**, **Figure 3.1**). If the estimated HQ in Tier 0 assessment (by comparing the highest single day exposure [unadjusted] to the relevant published chronic TRV) does not exceed the target HQ, the risk assessment can conclude that there is no appreciable risk associated with the exposure and no further evaluation is required for that substance. For an intermittent exposure scenario (e.g., 5 days/month for 4 months every year), the Tier 0 estimated HQ is a conservative worst-case estimate, which is equivalent to an exposure that is continuous rather than intermittent. If the estimated HQ is higher than the target HQ, then further analysis would be necessary to reduce uncertainty in the HHRA or remediation/risk management measures can be implemented to mitigate exposure to the contaminant.

Figure 3.4 illustrates the following two separate analyses that need to be completed in an HHRA of intermittent exposures.

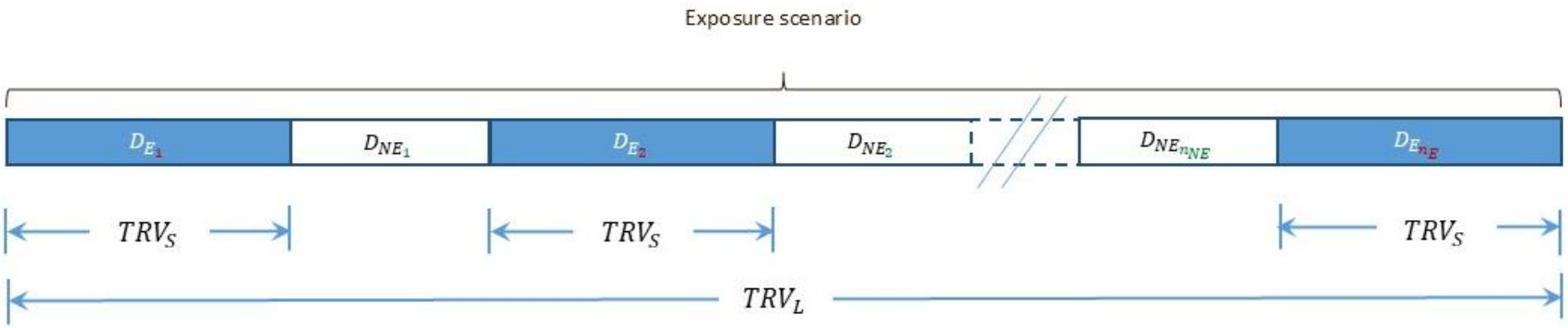
a) Evaluate whether a single exposure episode of a given duration might result in adverse health effects by comparing exposure with a shorter-duration TRV (TRV_S) relevant to the discrete continuous (or near-continuous) exposure episode (i.e., TRV for a similar or longer duration) for each individual exposure episode of a particular duration.

b) Evaluate whether the entire intermittent exposure scenario (combination of all single exposure episodes with intervening non-exposure intervals) might elicit health effects by comparing exposure against the longer-duration TRV (TRV_L) relevant to the entire duration of the exposure scenario.

It is important to compare the short-duration exposure episode against the relevant TRV (i.e., TRV_S) for each chemical and each individual exposure episode. It is also necessary to compare the entire intermittent exposure scenario to a relevant TRV_L where applicable, thus ensuring that the TRVs used are relevant to the entire intermittent exposure scenario. For instance, a short-duration TRV may apply to a single exposure; however a chronic TRV may apply in a situation where an exposure occurs one day per week, every week for several years. The dose metric (e.g., peak concentration, total dose) associated with a TRV may differ depending on the effects on which the TRV was based. Therefore, the dose metrics for evaluating an individual exposure episode may differ from that used to evaluate an entire exposure scenario.

Note that Tier II-b analysis is presented assuming contaminant concentrations in the environment during non-exposure intervals to be zero in order to simplify the discussion. However, many substances are present in background air, soil, water, sediment, food and consumer products. Depending on the contaminant, people may be exposed to background concentrations of the contaminant (i.e., exposure to the contaminant is not zero) during non-exposure intervals. If the background concentrations are not zero, the assessment needs to account for the off-site exposure by incorporating the estimated daily intake that people may receive while not at the site. HC (2010a) DQRA provides guidance related to how to address background exposures. Refer also to **Section 4.1** for guidance on how to account for exposure not related to the site (which is required if a target of 1 is applied).

Figure 3.4 Example of an intermittent exposure scenario illustrating analyses needed that involve application of relevant short-duration and longer-duration TRVs for assessing non-cancer effects associated with intermittent exposures



Where:

= Exposure episode denoted E

= Non-exposure interval denoted NE

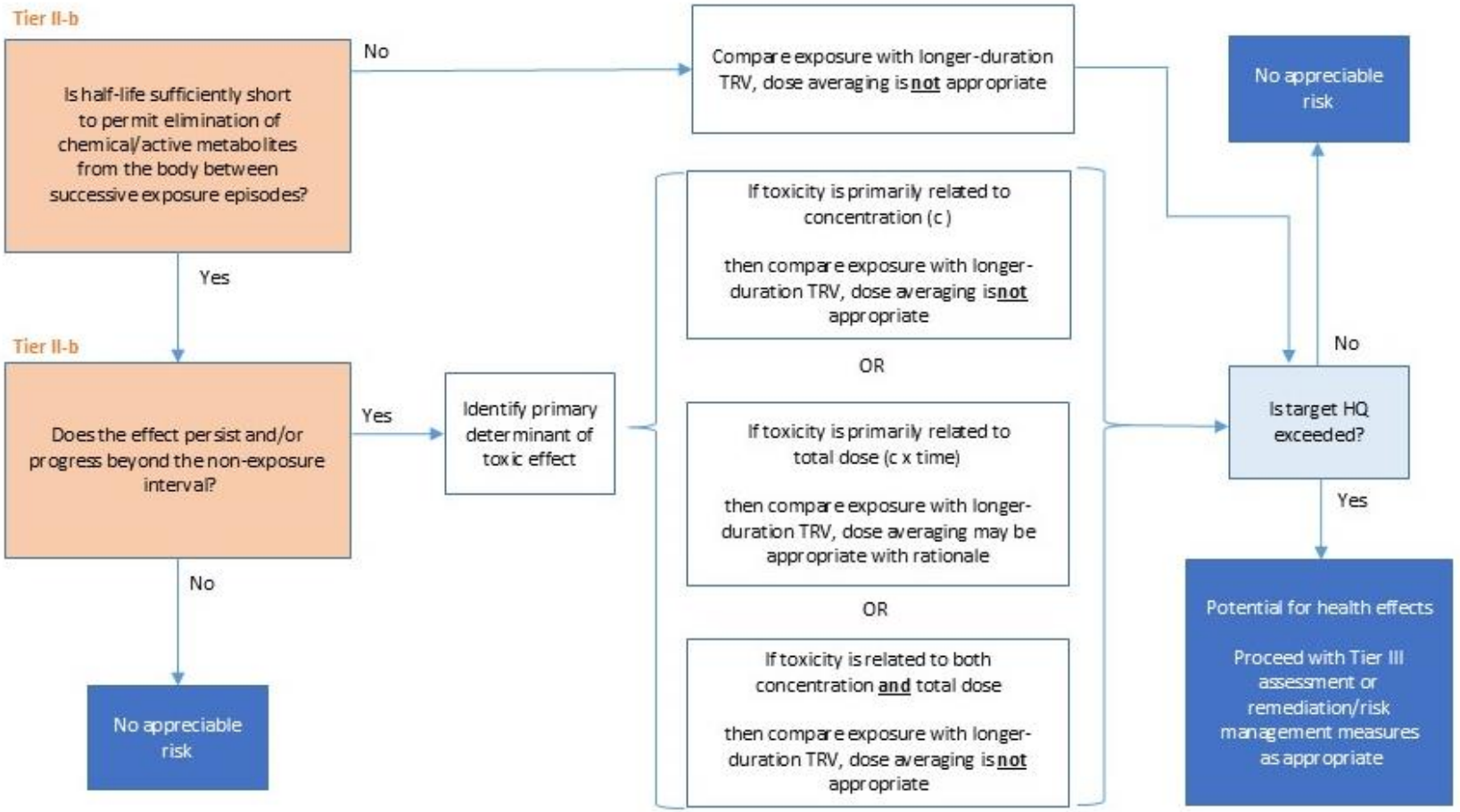
TRV_S = Shorter-duration TRV relevant to each single exposure episode of duration less or equal to the duration accounted for in TRV_S

TRV_L = Longer-duration TRV relevant to the entire exposure scenario

D_{E_i} = Duration of the exposure episode i in days, where i varies between 1 and n_E (the total number of exposure episodes)

D_{NE_j} = Duration of the non-exposure interval j in days, where j varies between 1 and n_{NE} (the total number of non-exposure intervals)

Figure 3.5 Tier II-b assessment for entire intermittent exposure scenario



3.3.1 Evaluation of Non-Cancer Health Risk as a Result of an Individual Exposure Episode (Tier I and Tier II-a)

Tier I and Tier II-a assessments as described in **Section 3.2** apply when evaluating whether a single discrete continuous or near-continuous exposure episode in an intermittent exposure scenario may result in potential non-cancer health effects. The steps to evaluate single discrete exposure episodes within an intermittent exposure scenario are described in **Figure 3.2**. Assessment of each individual exposure episode of a particular duration should be evaluated (i.e., if there are 7-day and 30-day continuous or near-continuous episodes, each episode would have to be assessed separately). If exposure is repeated intermittently and the highest individual exposure episode exceeds the relevant short-duration TRV (TRV_S) for the episode using Tier I and Tier II-a (**Figure 3.2**), then potential adverse health effects may occur. The custodian can choose to proceed directly to remediation or risk management to mitigate exposure where applicable.

On the other hand, if the individual exposure episode does not exceed the target HQ using an appropriate TRV, the risk assessment should proceed to additional Tier II-b assessment (as presented in **Figure 3.5** above) to evaluate whether there may be health effects associated with repeated exposure episodes.

The SSTLs derived in a risk assessment need to consider potential health effects resulting from (i) an individual exposure episode within an intermittent exposure scenario as well as (ii) the entire intermittent exposure scenario, which requires a Tier II-b analysis.

3.3.2 Evaluation of Non-Cancer Health Risk as a Result of Repeated Exposure Episodes in an Intermittent Exposure Scenario (Tier II-b)

Tier II-b assessments for repeated exposures (**Figure 3.5**) are conducted to assess whether recurring exposure episodes in an intermittent exposure scenario have the potential to result in adverse health effects. Comparison with a longer-duration TRV (TRV_L) relevant for the entire exposure scenario is required if exposure episodes are not independent of each other (refer to **Section 3.3.2.1** for assessment of how to identify whether exposure episodes are independent of one another).

Tier II-b assessments require the input of a qualified toxicologist/risk assessor familiar with analyses of toxicokinetics (i.e., absorption, distribution, metabolism and excretion of chemicals) and toxicodynamics (i.e., how chemicals affect the target tissues, their modes of action, persistence of biological changes and effects). The HHRA should provide a clear analysis of toxicokinetics and toxicodynamics for each exposure scenario and each substance, with references, to allow for peer review.

3.3.2.1 Evaluation of Whether Exposure Episodes Overlap to become Effectively Continuous

The toxicokinetics and toxicodynamics of the chemical are considered in HHRAs of intermittent exposures when determining whether a) individual exposure episodes can be treated as independent of each other or whether b) the overall internal exposures are effectively continuous. This determination is critical in deciding whether a relevant longer-duration TRV (TRV_L) should be applied to the entire

exposure scenario where the overall internal exposure is considered to be effectively continuous. Refer to **Figure 1.1** and **Figure 3.5** for details on assessment of an entire intermittent scenario (Tier II-b).

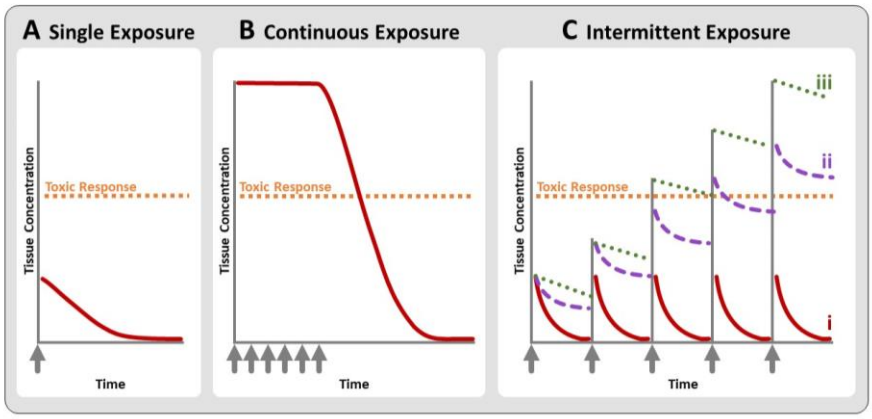
One goal of an intermittent exposure assessment is to determine whether the chemical (or its metabolites) is/are likely to persist in the body beyond the non-exposure interval between exposure episodes and/or whether the biological change resulting from one exposure episode is sufficiently persistent to progress between exposure episodes**. If either determination yields a positive result, comparison of exposure with a longer-duration TRV (TRV_L), such as a chronic TRV, may be required**.

a) Is the Chemical or Active Metabolite(s) Eliminated from the Body between Successive Exposure Episodes?

Assessment of an entire intermittent exposure scenario (Tier II-b, **Figure 1.1** and **Figure 3.5**) begins with a determination of whether the chemical would accumulate in the body between exposure episodes based on the elimination half-life(ves) of the chemical or its active metabolite(s) from the whole body. A chemical is considered to have been cleared from the body if there are at least five half-lives (of the chemical or active metabolite) between successive exposure episodes (i.e., from the time an exposure episode ceases to the beginning of the next exposure episode). Provided that elimination mechanisms are monophasic and have not been saturated (i.e., first-order elimination), a non-exposure interval of five half-lives removes approximately 97% of the chemical/active metabolite from the body, which is considered to be near complete removal (Ito, 2011). An illustration of the relationship between exposure and chemical accumulation at the target site in the body under different intermittent exposure scenarios and elimination rates (or half-lives) is provided in **Text Box 3.5**.

Text Box 3.5 Tissue concentration-time plots

The tissue concentration-time plots illustrate the relationship between dosing and tissue concentration at a target site in the body over time under different scenarios. Examples include potential tissue concentrations following: A) a single dose, B) repeated doses (continuous exposure), C) repeated doses (intermittent exposure). The plots focus on the elimination phase only. Arrows at the bottom of each chart represent a single dose. The lowest tissue concentration required to elicit a toxic response is identified as a horizontal dotted line.



Plot A shows the relationship between tissue concentration at the target site and time following a single exposure to a chemical. The internal tissue concentration in this example is below the tissue concentration of the chemical necessary to elicit a toxic response.

Plot B illustrates the target organ tissue concentration that has reached steady state following continuous repeated exposures. The steady state tissue concentration is above the tissue concentration of the chemical necessary to elicit a toxic response.

Plot C is a plot of target organ tissue concentration versus time for 3 different chemicals following repeat intermittent exposures. These 3 chemicals have different elimination rates; however, the lowest tissue concentrations required to elicit a toxic response are the same.

- Scenario (i) – the solid curve shows tissue concentrations for a chemical with an elimination rate faster than the exposure frequency (i.e., elimination half-life is short relative to the exposure interval): the chemical is cleared from the body before the next exposure and will not reach an internal target organ tissue concentration necessary to elicit a toxic response.
- Scenario (ii) – the dashed curve shows the tissue concentration for a chemical with an elimination rate equal to the exposure frequency (i.e., one half-life is equal to one exposure interval): the chemical is only partly eliminated from the body before the next exposure. The internal target organ tissue concentration increases on repeated exposure to above the tissue concentration necessary to elicit a toxic response over time. The increase occurs at a lower rate than scenario (iii).
- Scenario (iii) – the dotted curve shows the tissue concentration of a chemical with a very slow elimination rate (i.e., long elimination half-life relative to exposure interval): very little chemical is eliminated from the body between exposures. The internal tissue concentration at the target site increases rapidly on repeated exposure to above the target organ tissue concentration necessary to elicit a toxic response.

Dose averaging is incompatible with the build-up of internal tissue concentration seen in scenarios (ii) and (iii) and therefore is not appropriate for these scenarios. Instead, for the purposes of risk characterization, receptors are assumed to be exposed throughout an entire intermittent exposure scenario at the same rate as during individual exposure episodes. Alternatively, advanced models can be used to assess intermittent exposure scenarios (i.e., go to Tier III analysis, **Section 3.4**).

The HHRA analysis should provide the following information (including rationale), if applicable, to aid with decision-making.

a) Elimination half-life data from humans are preferred, but data from a suitable animal model relevant to humans are acceptable.

b) If the human relevance of the animal model has not been evaluated, the longest elimination half-life recorded in animals may be applied.

c) If the whole-body elimination half-life is not available, the longest available half-life from body tissues should be used.

d) Provided that elimination mechanisms are monophasic and have not been saturated (i.e., first-order elimination), a non-exposure interval of five half-lives removes approximately 97% of the chemical/active metabolite from the body, which is considered to be near complete removal (Ito, 2011).

e) The elimination of some chemicals or their associated metabolites are known to be bi- or multiphasic (i.e., the elimination profile includes an early rapid phase[s] of elimination with shorter half-life[ves] and a terminal elimination phase with a longer half-life). For these chemicals, the longer terminal elimination half-life should be used in order to be health protective, unless an appropriate justification can be provided for use of the shorter half-life.

f) If validated toxicokinetic models are available for the chemical of interest, toxicokinetic modelling may be used to predict the elimination of the chemical in Tier III analysis. The HHRA should include information on the model including absorption, distribution, metabolism and elimination kinetics, and validation with experimental or published data. Refer to **Section 3.4** for further details.

Some sources of chemical-specific elimination half-life data include, but are not limited to, ATSDR toxicological profiles, HC priority substances screening assessments, other HC chemical risk assessments and TRV supporting documentation, US EPA IRIS toxicological reviews, and WHO International Programme on Chemical Safety (WHO/IPCS) documents.

Refer to **Appendix F** for further discussion on identifying chemical-specific half-life. This appendix also provides an example of chemical characterization (based on elimination half-lives) for use in exposure scenarios that have a minimum of 2 weeks of non-exposure between exposure episodes. If no applicable information on the half-life of the chemical of interest is available, the chemical should be assumed to have a long half-life. The HHRA report should include a chemical-specific summary of the biological half-life analysis based on available information on absorption, distribution, metabolism and elimination kinetics (with references to peer-reviewed published scientific articles or textbooks).

If clearance (near complete removal, i.e., >97% removal of the chemical and metabolites) between successive exposure episodes is identified, the next consideration in the assessment is whether chemical-related biological effect(s) is persistent (persistence of effects [Tier II-b], **Figure 1.1** and **Figure 3.5;** as discussed below in **Subsection b** of **Section 3.3.2.1**).

b) Do Effects Persist Beyond Non-Exposure Intervals?

The next step in the assessment of an intermittent exposure scenario (Tier II-b, **Figure 1.1** and **Figure 3.5**) relates to whether biological effects may persist between consecutive exposure episodes (i.e., whether effects are reversible in the non-exposure interval or whether they remain/progress throughout the non-exposure period). The key question is whether non-adverse biological changes resulting from a single exposure episode may progress to adverse effects with repeated exposure.

In this regard, it is important to identify whether a TRV_L relevant to the entire exposure scenario needs to be applied when the exposure episodes are repeated intermittently even when a chemical and/or metabolite is completely eliminated from the body between exposure episodes. Assuming that the exposure from the contaminated site results in an acceptable target HQ using the TRV_S, a single exposure episode would be less than the level that may cause adverse effects. However, the TRV_S is not relevant to the entire intermittent exposure scenario with repeated exposures because there may be potential for a subadverse biological change (see **Section 2.4.1**) to persist in the target tissues following each exposure. A TRV_S is typically based on a single exposure period and is not based on studies with multiple repeated exposures. Thus, if there are repeated exposure episodes, it is possible that exposure at levels below the TRV_S may ultimately lead to an adverse effect. The persistence of subadverse biological changes between exposure episodes depends on the duration of the non-exposure interval and the severity of the exposure/biological change as well as the persistence of the chemical in the body (as discussed above). This guidance recommends the risk assessment report provide a site-specific and chemical-specific rationale for use of a TRV, with references, to allow for technical review.

Persistence of biological effects can be determined based on the reversibility of early and intermediate key events (i.e., biological perturbation). Since information on the status of key events is generally unknown at a specific exposure level, evaluation of persistence of biological effects can also be based on assessment of the reversibility of the downstream adverse health effects. This approach is conservative since downstream adverse effects are generally less reversible than upstream biological perturbations.

Theoretically, persistence of subadverse effects might be determined from estimates of the magnitude of the effects and experimentally verified “half-lives for biological repair” (Saltzman, 1996; Rhomberg, 2009). Such determination requires consideration of the potential for exposure episodes to occur during a sensitive lifestage, for which the extent and nature of adverse or subadverse effects and the rates of repair may be different from those for other lifestages. At present, biological half-lives for repair processes for a variety of early endpoints and the effects of various severities in a range of tissues are not available for either humans or laboratory animals. However, the reversibility can often be assessed, in part, through inference with respect to the reparability of certain types of damage.

For example, for some chemicals that cause liver necrosis (e.g., trichloroethylene, tetrachloroethylene, carbon tetrachloride, chloroform [Malaguarera et. al., 2012]), lower exposures may cause small changes in serum levels of enzymes indicative of liver damage (e.g., alanine aminotransferase). Although these lower exposures have been defined as subadverse, the changes in the serum would be considered to have long persistence (slow repair). In contrast, different early (subadverse) changes related to oxidative stress are rapidly reversible. An early biomarker of oxidative stress, namely reduced glutathione, is

rapidly regenerated, although continued or more severe oxidative stress can lead to changes that are more slowly reversible or irreversible (e.g., secondary oxidative damage to DNA). Thus, the HHRA needs to identify the types of effects that may occur and whether the changes may be reversible, or may be of concern, following repeated exposures.

Another example of an early key event is generation of reactive oxygen species (ROS) resulting in inflammation leading to atherosclerosis (build-up of plaques and hardening of arteries). Both ROS generation and inflammation are reversible. Atherosclerosis is reversible in the early stage but irreversible in advanced stages and can lead to ischemic heart disease (which is irreversible). ROS formation, chronic inflammation and atherosclerosis have been shown to be important elements contributing to arsenic-related ischemic heart disease (National Research Council, 2013). It is possible that a short-duration TRV based on an early key event may be protective of long-term health. Key events of long or short persistence (the latter often involving mild changes) can occur at environmental levels of exposure, which are often relatively low compared with other types of exposure. The determination of persistence of key events is based on numerous considerations, which should be documented in the HHRA on a chemical-specific basis.

Some key events are not easily characterized since persistence depends on many variables. Except for mutation, early key events in the path between exposure and health effects may be reversible upon cessation of exposure. However, the HHRA should clearly identify whether chemical-specific effects may be reversible and provide all supporting references. The HHRA should also identify whether the key events and/or biological effects may persist if the exposure continues.

The basic principle used to classify effect persistence is summarized as follows:

- All of the changes considered as having “short” persistence of effects are early key events that may lead to later (more adverse) effects upon continued exposure (e.g., mild sensory irritation, oxidative stress or other reversible health effects).
- The effects included in “long” persistence of effect category generally occur either at a later stage (e.g., cytotoxicity) or as a result of an impact during a sensitive period (e.g., developmental toxicity).

This proposed approach for HHRA at contaminated FCSAP sites reflects information currently available related to MOA and AOP analysis. It is based on the understanding and assumption that early key events are more likely to be readily reversible, while later key events and adverse outcomes are less likely to be reversible. The HHRA report should include chemical-specific rationale for any assumptions made related to this issue, noting uncertainties in data with intermittent exposures.

In addition, it is important to consider whether only early key events may have occurred, or whether there may be later key events that could persist and/or progress with repeated exposures. If the key events for the chemical of interest are not known, the default approach is to assume that the effects may have long persistence.

In summary, the report should include a qualitative or semi-quantitative analysis through inference regarding the reparability (if applicable) of certain types of damage (often based on analysis of

reversibility of downstream adverse effects). **Text Box 3.6** lists some considerations for evaluating the persistence of effects, which should be documented for each COPC, with references.

Text Box 3.6 Considerations for evaluating persistence of effects

- Evaluate the degree of chemical-specific damage.
- Evaluate whether the key events are early or later key events.
- Information can be drawn from the existing MOA framework and AOP analysis.
- Some analysis can be completed on how much greater or less the exposure is as compared to the applicable TRV.
- If exposure is much less than the no-effect level, or if only early key events have occurred.
- If exposure may result in later key events that can persist and/or progress with repeated exposures.
- If the key events for the chemical of interest are not known or there is no information on the persistence of key events, the default approach is to assume that they have long persistence.
- A scientific basis to support the analysis is required in the report.

3.3.2.2 Comparison with Longer-Duration TRV (TRV_L) Relevant to Entire Intermittent Exposure Scenario

- ***When Exposure Episodes Are Independent of Each Other***

Exposure episodes are considered independent of each other if the chemical (and active metabolites) is cleared from the body between exposure episodes and the biological perturbation from the individual exposure episode is not sufficiently persistent to lead to cumulative effects. In this situation, since the exposure is less than the relevant target HQ using a TRV_s for a single exposure episode (**Figure 1.1** and **Figure 3.2**) as determined in **Section 3.3.1**, the risk may not be considered significant. Chemical-specific rationale is important for each scenario, particularly as a TRV_s is typically derived for a single exposure episode and justification is required for use of a TRV_s for repeated exposures.

- ***When Exposure Episodes Overlap to Become Effectively Continuous***

As discussed in **Section 3.3.2.1**, an intermittent exposure scenario is deemed effectively continuous under either of the following two conditions:

a) When the chemical (or active metabolites) persist(s) in the body throughout the course of non-exposure intervals.

   - This occurs when there is not sufficient time for clearance of the chemical (and its active metabolites) from the body before the next exposure episode. In this scenario, the highest estimated exposure should be compared with the longer-duration TRV (TRV_L) relevant to the entire exposure scenario (e.g., equivalent to a single long-duration exposure). This comparison is illustrated in **Figures 3.4** and **3.5**.

- Relevant TRV refers to a TRV for similar or longer exposure duration than the entire intermittent exposure scenario based on the same principle described for single continuous exposures or near-continuous exposures in **Section 3.2.1**.

b) When the chemical (and active metabolites) is/are cleared from the body during non-exposure intervals, biological effects may persist.

- If the chemical (and active metabolites) is/are cleared from the body during the non-exposure interval but the biological perturbation from an individual exposure episode may persist and/or progress, the exposure needs to be compared with a longer-duration TRV relevant to the entire exposure scenario (TRV_L) (**Figure 3.4** and **Figure 3.5**).
- Relevant TRV refers to a TRV for similar or longer exposure duration than the entire exposure scenario based on the same principle described for single continuous exposures or near-continuous exposures in **Section 3.2.1**.

In summary, when exposure episodes have been determined to overlap to become effectively continuous, whether dose averaging can be supported across the non-exposure intervals in intermittent exposures depends on the MOA of each chemical. **Section 3.3.2.3** discusses how the MOA affects dose averaging for "continuous" intermittent exposures in a contaminated site HHRA. An exception to this are the special considerations described below.

- ***Special Considerations When Assessing Intermittent Exposure***

A special case in the application of the intermittent exposure assessment is when the chronic TRV is based on developmental toxicity, such as teratogenicity. The typical approach is to adopt the developmental toxicity TRV as a short-duration TRV, especially when the TRV is based on fetal toxicity from in-utero exposure. The exposure in these studies is usually of short duration. The shorter- and longer-duration TRVs are often the same value in this type of situation, an approach that is intended to be protective of any scenario that may involve people who are pregnant or may become pregnant, and children. Special consideration of other sensitive subpopulations (e.g., elderly, immunocompromised, asthmatics, chronic obstructive pulmonary disease patients) may also be required, depending on the chemical and exposure scenario.

3.3.2.3 MOA Consideration and Impact on Dose Averaging for Intermittent Exposures

The MOA for each chemical is important when considering the approach to intermittent exposure in an HHRA, including decisions related to dose averaging. As discussed in **Section 3.3.2.2**, a TRV_L relevant to the entire exposure scenario is applied when exposure episodes overlap with each other to become effectively continuous. Whether dose averaging can be supported depends both on the specific factors (i.e., half-life, persistence, primary determinant of toxic effect) that make the intermittent exposure scenario effectively continuous and on the MOA involved (see **Figure 1.1** and **Figure 3.5**). It is important to note that if dose averaging is applied across intermittent exposures, the dose averaging would involve averaging periods of both exposure and non-exposure. This approach can be supported only in limited situations as it results in a dilution of the overall exposure, thereby minimizing the anticipated effects from peak exposures, which may be inappropriate for some chemicals.

- ***When a Chemical (or Active Metabolites) Persists in the Body During Non-Exposure Intervals***

When a chemical (or active metabolites) persists in the body during non-exposure intervals, the internal exposure becomes continuous, and the tissue level may continue to increase over the entire exposure scenario (illustrated in **Text Box 3.5**). A TRV relevant to the entire exposure scenario (TRV_L) would have to be applied, and dose averaging is generally not appropriate for these chemicals.

However, the approach may be different for chemicals with long elimination half-lives if both of the following conditions are met:

- Each non-exposure interval is shorter than one-quarter of the biological (or elimination) half-life of the chemical (or its active metabolites).
- Kinetic modelling on a chemical- and scenario-specific basis demonstrates that dose averaging over a specified brief period would not result in significant changes in internal concentration/body burden during this period.

In this case, the HHRA can identify that dose averaging over this specified brief period may be supported when toxicity is primarily driven by total dose/body burden. Refer to **Appendix G** for a full discussion.

- ***When a Chemical (and Active Metabolites) is Cleared from the Body During Non-Exposure Intervals but Biological Effects Persist***

Even if the chemical is cleared from the body during non-exposure intervals, a biological effect may persist. In this instance, a longer-duration TRV relevant to the entire exposure scenario (TRV_L) would be required. The HHRA would need to provide supporting information regarding whether dose averaging in these intermittent exposures can be supported, based on the MOA and/or primary determinant of toxic effect (**Figure 1.1** and **Figure 3.5**).

For instance, dose averaging may underestimate potential risk if the concentration/peak exposure is the primary determinant of toxicity relevant to TRV_L. If total dose is the primary determinant of toxicity, dose averaging may be appropriate. However, if both total dose and concentration contribute to the determination of toxicity, dose averaging may underestimate potential risk and would not be appropriate. As a health-protective measure, the default in intermittent exposure assessments is not to apply dose averaging. Refer to **Section 3.2.3** for general guidance on determining whether concentration/peak exposure or total dose/body burden is the primary determinant of toxicity.

In all cases, if dose averaging is applied, an appropriate toxicological rationale with references needs to be presented on a chemical-specific basis. This rationale should discuss why dose averaging can be considered based on relevant factors such as the half-life of the chemical of interest and the persistence of effects. The rationale should include data supporting the conclusion that dose averaging across unexposed periods is adequately health protective, clearly presenting exposure and risk estimates with and without dose averaging.

3.3.3 Exposure Estimation for Intermittent Exposure Scenarios (Tier II-b)

Similar to what is presented in a typical DQRA, exposure is estimated for each chemical, each human receptor/age group (particularly sensitive receptors) and for each exposure pathway identified as being of concern. As discussed in **Section 3.3.2.2**, exposure assessment for intermittent exposure scenarios may involve estimating two types of exposure:

- Exposure that a person may receive for each discrete short-duration continuous (or near-continuous) exposure episode.
- Exposure for the entire duration of the exposure scenario (i.e., time between the start of the initial exposure episode and the end of the final exposure episode), when deemed appropriate based on the properties of each chemical.

The need for microenvironment analysis and for incorporating relative bioavailability in exposure assessments, as well as the necessary adjustment to address sediment contamination are discussed in **Section 3.2.4**. The discussion in **Section 3.2.4** also applies to analysis of intermittent exposure scenarios. Similar to HHRA of a chronic exposure, the exposures from multiple pathways and/or chemicals with similar MOA may be summed to derive total exposure for comparison with TRVs (e.g., oral and dermal exposure for all exposure pathways at the site are typically summed and compared with the oral TRV). Refer to **Sections 4.2** and **4.3**, respectively for detailed guidance.

3.3.3.1 Exposure Estimation for Each Individual Exposure Episode

The same recommended equations presented in **Appendix C** can be used to calculate the exposure for each individual short-duration exposure episode. No dose averaging beyond the duration of the exposure episode is recommended, which means that the averaging period cannot be longer than the full duration of the exposure episode.

When estimating exposure for an individual exposure episode in an intermittent exposure scenario, the same consideration for input data (such as exposure point concentrations, statistics) for a continuous or near-continuous short-duration exposure scenario can be applied. Refer to **Section 3.2.4**.

3.3.3.2 Exposure Estimation for the Duration of the Entire Exposure Scenario

As discussed in **Section 3.3.2**, when an intermittent exposure scenario has been determined to be effectively continuous, exposure levels for the entire exposure duration are compared with the relevant TRV_L. As stated above in **Section 3.3.2.1**, intermittent exposures are deemed an effectively continuous exposure scenario either:

- When the chemical or its active metabolite(s) is likely to persist in the body beyond the non-exposure ("off") interval between consecutive exposure episodes ("on" periods).
- When the biological change resulting from an exposure episode persists during the non-exposure interval, even if the chemical or its active metabolite(s) is cleared from the body during the "off" interval.

Appendix D provides general equations recommended for estimating exposure for the entire duration of intermittent exposure scenarios.

When an intermittent exposure scenario is deemed to be effectively continuous, the default approach for estimating exposure in a health-protective manner is to not allow dose averaging (i.e., averaging the dose over both exposure and non-exposure periods, thereby lowering the overall exposure level). Dose averaging may be appropriate only in very limited situations, such as when the chemical (or active metabolite) is cleared from the body during the "off" periods and the biological change resulting from the chemical exposure persists primarily as a function of total dose (as opposed to concentration or peak exposure) during these periods (see **Section 3.3.2.3** for specifics as to when dose averaging can be supported).

- ***When a Chemical (or Active Metabolite) Persists in the Body During Non-Exposure Interval***

For an intermittent exposure scenario where the non-exposure interval does not provide sufficient time for the chemical (or its active metabolites) to clear from the body before the next exposure (continuous or near-continuous), the intermittent exposures are considered to be effectively continuous. The internal concentration of the chemical in this circumstance may continue to increase over the entire exposure scenario. No dose averaging would be applicable in this case, as dose averaging would result in a lower estimate of the overall exposure rate, resulting in an underestimation of potential risk. For this reason, except for the situation discussed in **Section 3.3.2.3**, an appropriate daily exposure rate representative of the exposure episodes (continuous or near-continuous) should be calculated and compared against the TRV_L. Refer to **Section 3.3.3.1** for a discussion of exposure estimation for individual exposure episodes. This approach assumes that the daily exposure rate experienced during the exposure episodes applies not only to the periods of exposure while at the site but also throughout the entire intermittent exposure scenario.

- ***When a Chemical (and Active Metabolites) Is Cleared from the Body During Non-Exposure Intervals but the Biological Effects Persist***

In an intermittent exposure scenario, when chemicals (and active metabolites) of interest are entirely cleared from the body during the non-exposure interval, the exposure scenario can still be deemed effectively continuous. This conclusion is valid if the biological change elicited during the exposure episode persists and/or progresses during the periods when a person is not at the contaminated site. Dose averaging is not supported if (i) the concentration/peak exposure is the primary determinant of toxicity relevant to TRV; or (ii) the relevant TRV is based on a teratogenicity study.

For some substances, dose averaging can be supported when the total dose (i.e., time-integrated exposure) or body burden is the primary determinant of toxicity relevant to TRV_L. If both total dose and concentration contribute to the determination of toxicity, dose averaging is not appropriate. Refer to **Section 3.2.3** for general guidance on determining whether concentration/peak exposure or total dose/body burden is the primary determinant of toxicity.

Where dose averaging can be supported, the average exposure can be calculated for the entire exposure scenario. However, for volatile organic compounds that may attenuate over time, lower future

concentrations cannot be averaged with current concentrations, as this practice would underestimate peak exposures. Similarly, if groundwater is affected, then average concentrations from multiple wells cannot be used to provide mean exposure estimates if people may be exposed only to concentrations from one area and not another. For example, each residence would use water from a single groundwater well, which is not the average of all wells in the area. Use of a mean groundwater concentration could underestimate exposure for the most highly exposed individuals.

If the lower-tiered assessments indicate potential health risk, the risk assessment may proceed to a Tier III assessment, which may reduce uncertainty. Alternately, the need for remediation or risk management measures to mitigate exposure may be identified at any stage of the HHRA, as appropriate. **Section 3.4** provides general guidance on Tier III assessment; however, a full discussion of this level of HHRA is not provided in this guidance document as most contaminated site HHRAs do not proceed to a Tier III level.

3.4 Use of Advanced Models (Tier III)

Risk assessments completed using the lower tiers of the framework (Tiers 0 and I) mainly rely on existing chemical-specific TRVs, such as those from HC (2021) or other regulatory agencies. Risk assessments, which progress to the upper tiers (Tiers II and III) of this framework, involve greater complexity in toxicity assessment. These assessments require increasing use of information on the MOA (**Section 2.4**), as well as knowledge of chemical-specific toxicokinetics and toxicodynamics. As a result, a greater level of toxicological expertise is required to conduct these upper-tiered assessments. It should be noted that this document does not provide detailed guidance on risk assessments which may progress to Tier III of the framework due to the level of detail required to provide comprehensive guidance on this topic. Tier III of this framework includes the use of complex exposure and dose-response modelling (i.e., PBPK modelling and BBDR modelling). Use of modelling in Tier III assessment may be appropriate in cases where there is high uncertainty in a TRV or where there is a need to address complex intermittent exposure patterns.

Given the complexities of these modelling exercises, it is recommended that Tier III assessments, when deemed appropriate for a site, should only be conducted by a toxicologist or a risk assessor with expertise in the type of modelling being undertaken. When the use of Tier III assessment is deemed not to be appropriate at a contaminated site due to factors such as availability of data, model limitations or cost, custodians may consider mitigation or remediation/risk management strategies in lieu of Tier III assessment. When advanced modelling is conducted, sufficient information with references to validated models and modelled estimates is required in the HHRA report to allow for technical review.

3.4.1 Physiologically-Based Pharmacokinetic (PBPK) Modelling

PBPK modelling can be used to derive TRVs such as in the development of Canadian drinking water guidelines for trichloroethylene (HC, 2005) and vinyl chloride (HC, 2013d). TRV values developed with PBPK modelling can be used in contaminated site risk assessments as well as to evaluate the potential differences associated with bioavailability of a substance in site-specific soils on internal dose. PBPK models can also be used to address complex intermittent exposure patterns where appropriate. However, development of a PBPK model requires significant and specialized toxicological expertise as

well as availability of key data on a chemical to develop an appropriate PBPK model. Consequently, validated models may not be available for all chemicals typically found at federal contaminated sites.

PBPK models mathematically describe the uptake and disposition (including such factors as absorption, distribution, metabolism and excretion) of a chemical in the body, using parameters based on physiological data (Reddy et al., 2005; Meek et al., 2013; US EPA, 2018b). These models differ from classical compartmental toxicokinetic models in that the compartments of PBPK models represent actual organs or tissue groups with experimentally measured rates.

Several guidance documents on key aspects of PBPK modelling exist; however, they will not be summarized as part of this guidance. WHO/IPCS (2010) describes best practices for characterizing and applying PBPK models in risk assessment, and US EPA (2006) describes how model adequacy can be evaluated and provides specific examples of PBPK model application in risk assessment. A checklist for selecting PBPK models for use in risk assessments is available from WHO/IPCS (2010).

A key strength of PBPK modelling is that a PBPK model can improve the quantitative characterization of risk by reducing uncertainties in TRV development and overall exposure assessment, and by basing the risk value on an internal measure of dose (Lipscomb et al., 2004; US EPA, 2006). The use of an internal dose measure often provides a more meaningful basis for estimating risk than the use of an applied dose or inhalation exposure concentration (US EPA, 2006). This is because it can be important to quantify the amount of chemical that actually reaches an internal target organ in order to estimate any resulting adverse health effects. Issues such as different routes of exposure or bioavailability of a chemical in soils have the potential to affect the amount of a chemical that enters the body and reaches critical target organs. Ultimately, this information can help inform the potential for health effects based on the external dose to which people are exposed. PBPK models are useful for testing hypotheses about MOA (US EPA, 2006). The incorporation of toxicokinetic and mode-of-action information may improve the accuracy of the dose, route and species extrapolations required in the risk assessment process (Lipscomb et al., 2004; US EPA, 2006). PBPK models can also be useful in exposure assessments, particularly in evaluating less-than-chronic, intermittent and variable exposure scenarios, and for sites with multiple exposure pathways (Bailer and Dankovic, 1997). PBPK models can be used to improve the estimates of effects resulting from unusual exposure scenarios (e.g., fluctuating exposures) (US EPA, 2006; WHO/IPCS, 2010).

The use of a PBPK model for HHRA at a federal contaminated site should be limited to those models that have been validated for exposure scenarios that are reasonably similar to the exposure scenario of interest. Use of a validated PBPK model also allows for reduced uncertainty in development of TRVs, or in using toxicological studies that may have variable routes of exposure (US EPA, 2006). In addition, the use of human lifestage PBPK models can facilitate addressing age-related changes in physiology such as those associated with pregnancy (McLanahan et al., 2014), or the growth and development of infants/children (e.g., El-Masri et al., 2016).

The primary limitation of PBPK models is the skill and time investment required to develop and validate the models (WHO/IPCS, 2010). Additionally, properly designed toxicokinetic studies are needed for model parameterization and verification (Paini et al., 2017; Tan et al., 2018). Although development of a

model may be time-intensive, the development of standardized approaches to model validation and verification can enhance the use of PBPK models in risk assessments. While a PBPK model may refine the TRV value used in the risk assessment by reducing the associated uncertainty, use of PBPK modelling may not necessarily result in a difference in the estimated risk associated with exposure to a particular chemical at a site, and risk management measures may still be required to mitigate exposure. Further, PBPK models generally should not be used for large extrapolations in exposure duration (e.g., from acute to intermediate exposure), because the models are usually designed and evaluated in the context of a specific risk assessment application.

Table 3.1 provides a non-exhaustive list of chemicals for which validated models are currently available and have been used in risk assessments. Although only a limited number of validated models are currently available, the use of PBPK models may increase over time and references should be provided for any models used in support of a Tier III assessment. It should be noted that even where validated models are available, they may not necessarily be applicable to all sites and/or exposure scenarios.

An additional model of interest is the Integrated Exposure Uptake and Biokinetic (IEUBK) Model for lead, which was developed by the US EPA. This model can use default or site-specific data of soil and dust lead concentrations to predict blood lead levels and the percentage of the population with blood lead levels exceeding a specified value. Additional description of the model is available from US EPA (2023b).

Table 3.1 Sample chemicals for which PBPK models have been used in risk assessments

Substance	Reference
Benzene	HC (2009)
2-Butoxyethanol	EC[1] and HC (2002)
Chloroform	EC and HC (2001)
Dichloromethane	EC and HC (1993)
Naphthalene	HC (2013b)
Perfluorooctanoic acid (PFOA)	HC (2018b)
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	US EPA (2012b)
Tetrachloroethylene	US EPA (2012c)
1,1,1-Trichloroethane	US EPA (2007a)
Trichloroethylene	HC (2005)
Vinyl chloride	HC (2013d)

[1] Environment Canada

3.4.2 Biologically-Based Dose-Response (BBDR) Modelling

BBDR models are predictive models that describe biological processes at the cellular and molecular level linking target organ dose to an adverse effect. BBDR models can be used to improve the understanding of parameters influencing the dose-response relationship of a given chemical. Development of a BBDR

model requires significant and specialized toxicological expertise, and should only be conducted and used in an HHRA by qualified individuals who are experienced with this specific type of modelling.

A BBDR model includes a PBPK model component (linking the external dose to the internal target tissue concentration) and other mechanistic (or toxicodynamic) models that link internal target tissue concentration to the toxicological adverse outcome. BBDR modelling maximizes the use of relevant, mechanistic data to describe the exposure-dose-response linkage. BBDR modelling is explicitly designed to model the biological details from initial exposure to a substance to the ultimate pathological outcome (Lau et al., 2000; WHO/IPCS, 2009; Crump et al., 2010). WHO/IPCS (2009) provides a brief description of the use of BBDR modelling.

BBDR-based TRV values can be used to refine an HHRA for a contaminated site. Where a BBDR model is available for a chemical, it can be applied in an HHRA to estimate the magnitude of a predicted effect (e.g., percent-expected response) for different exposure scenarios, and to calculate site-specific target levels that are not expected to have adverse human health effects. The risk assessment may also use the BBDR model to investigate the relative importance of uncertainties in different aspects of the assessment.

BBDR models offer the advantage of combining the best available mechanistic data to define mathematical functions used to fit dose-response data, thereby allowing analysis of data sets with complex patterns of exposure to multiple toxicants (Hernandez, 2021). However, application of BBDR modelling is limited by the need for a large amount of relevant biological and MOA data, the difficulty in data interpretation and analysis, as well as the required quantitative skills to develop the model from the data. These needed resources may not be readily available. In addition, confidence in the models depends on current understanding of basic biology, which can be improved only by new discoveries.

Currently, there are no published guidelines for BBDR modelling available and few BBDR models have been developed for non-cancer endpoints. However, for further information on BBDR modelling principles, chemical-specific publications from various government agencies such as the BBDR model for perchlorate developed by the US EPA (2017a, 2017b, 2019, 2020) can be referenced.

3.4.3 Summary of Advanced Models (Tier III)

Tier III models may be used to reduce uncertainty in a risk assessment; however, the use of modelling may not be appropriate for all HHRAs. Reduction in uncertainty may not necessarily result in a change in risk estimates, therefore Tier III modelling should be used only when it is recommended by a risk assessor trained in advanced modelling techniques. At sites where Tier III modelling is not expected to alter the risk estimates or site-specific target levels for chemicals present on the site, remediation or other risk management considerations may be the preferred option to reduce exposure to chemicals.

3.5 Summary of Considerations for Use in the Tiered Assessment Framework

While many HHRAs for FCSAP sites may proceed beyond Tier 0, most are not expected to proceed to a Tier III assessment. Most of the technical information for the scenarios presented in **Section 3** is provided in the appendices of this guidance.

3.5.1 Selecting a TRV Relevant to the Exposure Duration

The TRV selected must be applicable to a timeframe relevant to (or longer than) the exposure period of interest. How this is accomplished depends on the following considerations.

- If toxicity is primarily driven by concentration/peak exposure in an exposure scenario, the applicable TRV would likely be the shortest duration TRV that would apply to the length of that exposure scenario. The exposure input into the HQ equation is the highest exposure estimated for an exposure period that matches (or is shorter than) the time period for which the available TRV has been derived.
- For continuous and near-continuous short-duration exposures, the applicable TRV is a TRV relevant to the entire exposure scenario when toxicity is primarily driven by total dose/body burden. The exposure input into the HQ equation is the estimated average daily dose or average daily air concentration; the averaging time spans the entire exposure period and not beyond the final exposure.
- There are two types of exposure periods of interest for intermittent exposures, corresponding to a) each exposure episode and b) the entire exposure scenario. TRVs relevant to these exposure periods would be used to estimate the respective HQs, as appropriate. The average daily exposure is used to calculate the HQs when toxicity is primarily driven by total dose/body burden. For exposure episodes, the averaging time spans the duration of the exposure episode and not beyond. The entire exposure scenario should be treated as continuous exposure where the averaging time spans the period from the first exposure to the moment when the receptor is last exposed, and not beyond.

3.5.2 Absence of Relevant Data

The following summarizes some default operational procedures and considerations when essentials related to identification of a TRV for a specific exposure scenario are not available.

- Tier 0 assessment compares a published chronic TRV of the relevant route of exposure with the highest estimated exposure for the most sensitive population for each chemical under the scenario of interest. In the absence of a chronic TRV, risk assessment should follow guidance outlined in HC (2010a) regarding derivation of a suitable *de novo* TRV of relevant duration. Refer to **Section 3.2.2** for a discussion on how to address chemicals lacking appropriate toxicological data.
- In the absence of a less-than-chronic TRV relevant to the exposure duration of interest, a *de novo* short-duration TRV relevant to the exposure scenario may be developed or the TRV relevant to the next longer exposure duration category may be chosen. Alternatively, a chronic TRV can be used as a default as it is considered to be health protective, whereas a TRV for a shorter exposure duration may not be protective.
- If the data necessary to proceed to upper-tiered assessments are unavailable, the default is to conduct a Tier 0 assessment (i.e., to apply a chronic TRV to a daily exposure with no dose averaging).

- In the absence of adequate available data to identify the primary determinant of toxicity (i.e., concentration/peak exposure or total dose/body burden), the default is to assume concentration to be the primary determinant of toxicity (with dose averaging not supported).
- Upper-tiered assessments require significant toxicological expertise and should be performed only by toxicologists with the appropriate knowledge and training.
- For analysis of intermittent exposures (Tier II-b), selection of a TRV depends on several factors as follows.
  - In the absence of data on elimination half-lives, the COPC and its active metabolite(s) can be assumed to have "long" half-lives relative to the non-exposure intervals. The exposure would need to be compared with a long-duration TRV (TRV_L) relevant to the entire exposure scenario. No dose averaging would be applied.
  - If the key events on the path to toxicity for the COPC are not known or there is no information on their persistence (when key events are known), the default approach is to assume that the key events have “long” persistence. The exposure would need to be compared with a long-duration TRV (TRV_L) relevant to the entire exposure scenario. The MOA (i.e., primary determinant of toxicity) needs to be considered to identify whether dose averaging over the entire exposure scenario is appropriate.

4 RISK CHARACTERIZATION

Risk characterization is the quantification and explanation of the potential risk associated with exposures to chemicals at a contaminated site. It is explained more fully in HC's Preliminary Quantitative Risk Assessment (PQRA; 2024) and DQRA guidance (2010a).

Potential health risks are characterized for the different receptor groups (e.g., different age or exposure pattern) by comparing the estimated or measured exposures to chemicals from the site with the appropriate duration TRVs. In general, for a threshold health effect, an HQ is estimated for each critical receptor as the ratio of the estimated or measured exposure to the TRV. It is important that exposures be expressed in the same units as the applicable TRV, as illustrated in the following equations.

In the case of oral, dermal or total exposures, the estimated daily exposure is compared with a TRV (usually expressed in either units of mg/kg bw/day or µg/kg bw/day).

$$Hazard\ Quotient = \frac{[Estimated\ Exposure\ from\ Site\ (mg/kg\ bw/day)]}{[Toxicological\ Reference\ Value\ (mg/kg\ bw/day)]}$$

For less-than-chronic exposure to chemicals with TRVs expressed as tolerable weekly intake (TWI) or tolerable monthly intake (TMI) (e.g., methylmercury [MeHg], TCDD, respectively), the estimated total exposure from the most exposed week or month would be compared to the appropriate TWI or TMI, respectively, as per the equations below. For example, in a 3-week exposure scenario involving MeHg in fish and shellfish, the highest total weekly exposure for any continuous one-week period would be compared to the published TWI so as not to underestimate potential risk from the site.

$$Hazard\ Quotient = \frac{[Estimated\ Exposure\ from\ Site\ (mg/kg\ bw/week)]}{[Toxicological\ Reference\ Value\ (mg/kg\ bw/week)]}$$

$$Hazard\ Quotient = \frac{[Estimated\ Exposure\ from\ Site\ (mg/kg\ bw/month)]}{[Toxicological\ Reference\ Value\ (mg/kg\ bw/month)]}$$

In the case of inhalation exposure with the TRV expressed in mg/m^3, the exposure (expressed in mg/m^3) is compared with the TRV.

$$Hazard\ Quotient = \frac{[Estimated\ Onsite\ Air\ Concentration\ (mg/m^3)]}{[Toxicological\ Reference\ Value\ (mg/m^3)]}$$

Note that these equations do not include background exposures (i.e., exposures to the same COPC from other sources such as food, water, consumer products, soil, air), which would be included if a target HQ of 1 is applied. Please refer to HC (2010a) for additional information related to inclusion of background exposure. This simplified approach is consistent with the description in **Section 3** that the framework addresses how health risks can be evaluated for exposures to a single chemical contaminant by a single

pathway/route. However, in a contaminated site HHRA, exposure from all potential sources and pathways would be calculated and included in calculations with the applicable target HQ.

To characterize non-cancer health risks from short-duration continuous, near-continuous and intermittent exposures to chemicals at contaminated sites, HQs should be estimated at various decision points as described in **Section 3**. HQs are estimated for individual exposure routes (i.e., oral, dermal and inhalation) where there are route-specific TRVs. The HQs are then summed across exposure pathways and routes (ingestion, dermal and inhalation) if there is evidence for same effects/same target organs/same modes of action (HC, 2010a).

The HQ indicates whether the estimated exposure exceeds target risk values when compared against the appropriate TRV. If background exposure (i.e., exposures to the same COPC from other sources such as food, water, consumer products, soil, air) is included in exposure estimates, a HQ less than or equal to 1 indicates that the exposure from the site plus background is less than or equal to the applicable TRV, representing a negligible health risk. An HQ greater than 1 indicates that the exposure exceeds the applicable TRV, representing a potential health risk. A higher tier assessment may be used to reduce uncertainty, alternatively remediation and/or risk management measures may be implemented. The magnitude of the HQ does not necessarily correspond to the magnitude of the expected health effects. Consult **Section 4.1** for more details when background exposure is not insignificant or is not known.

4.1 Background Multimedia Exposure Unrelated to Contaminated Site of Interest

If a comprehensive multimedia exposure assessment has been completed, an HQ of ≤1 can indicate that the total exposure (i.e., on-site + background) is associated with negligible risk (HC, 2010a). If a comprehensive multimedia exposure assessment has not been completed, exposure arising from the site (excluding background exposures) associated with a target HQ of ≤0.2 will be deemed to confer negligible health risk (HC, 2024). For some substances, such as petroleum hydrocarbons (PHCs), a target HQ value other than 0.2 may be used (CCME, 2008). Use of 0.2 (and values appropriate for PHCs) as the target HQ value is the default (in the absence of a comprehensive exposure assessment) unless scientific rationale, with references, is provided to identify that applying a HQ of >0.2 and <1 is protective on a chemical-specific basis (e.g., showing background exposure from all sources is insignificant). A sound analysis and supporting chemical-specific rationale is required for use of a target HQ greater than 0.2.

4.2 Multiple Exposure Pathways/Routes

At many contaminated sites, there may be multiple exposure pathways and routes of exposure. If exposures from different pathways occur simultaneously, exposures are normally summed for all pathways (e.g., soil ingestion, water ingestion, and food ingestion) relating to each operable exposure route; and risks are estimated for the summed exposures.

HQs for individual exposure routes should be calculated where there are route-specific TRVs. The HQs are then summed across exposure routes (e.g., ingestion, dermal and inhalation) if there is evidence that the COPC has the same effects/same target organs/same modes of action for all relevant routes of exposure. For some substances, published TRVs may not be available for one or more applicable exposure routes. Instead, so long as it is reasonable to assume that the effect is systemic and that the

toxic MOA and target organ(s) would be similar for the different exposure routes, exposures from multiple routes during the same time period should be combined for comparison with the oral TRV where appropriate. Refer to the PQRA guidance (HC, 2024) and the DQRA guidance (HC, 2010a) for more specific information on this topic, and to **Appendix E.1** for a worked example that evaluates multiple exposure routes.

4.3 Combined Exposure to Multiple Chemicals

At most contaminated sites, it is common for people to be exposed to several COPCs simultaneously. To assess the overall potential for non-cancer effects from combined exposure to multiple chemicals, dose/concentration additivity is assumed for chemicals that induce similar effects on a common target organ with similar modes of action[5]. Additivity can also be assumed for chemicals that affect a common target organ where no additional mechanistic data are available. This approach assumes that interactions either do not occur or are minor under general environmental conditions (Meek et al., 2011; WHO, 2017). For these substances, the HQs for individual chemicals should be summed for overlapping exposure periods in continuous, near-continuous and intermittent exposure scenarios. For intermittent exposure scenarios, it is important that HQs for all COPCs be summed for each exposure period of interest, which includes each individual exposure episode, and, if deemed appropriate, the period corresponding to the entire exposure scenario. For example, if a receptor is exposed simultaneously to COPC A and COPC B for 2 months every 3 months for a year, HQs for both chemicals should always be summed for the 2-month exposure episode. Further determination of whether the HQ needs to be calculated for the full year period will depend on whether the exposure episodes are independent of each other (see **Section 3.3.2.1**), and the relationship between exposure episodes may differ for each individual COPC.

In a situation where both COPC A and COPC B (or their active metabolites) are:

- Not cleared from the body between exposure episodes, HQs for the full year period would be calculated for both COPCs and then summed (i.e., $HQ_A + HQ_B$).
- Completely cleared from the body between exposure episodes but the effects of both persist, HQs for the full year period would have to be calculated for both COPCs individually and then summed (i.e., $HQ_A + HQ_B$).
- Completely cleared from the body between exposure episodes but the effects of COPC B (but not COPC A) are persistent, the HQ for the full year period would have to be calculated for COPC B only (i.e., HQ_B) with the combined HQs being equal to HQ_B.

[5] This approach is in agreement with HC (2010a) DQRA guidance and is based on the WHO/IPCS (Meek et. al., 2011; WHO, 2017) tiered framework for conducting HHRA of combined exposure to multiple chemicals. PQRA is a lower-tiered HHRA that can conservatively assume additivity for multiple chemicals that induce similar toxic effects on a common target organ. In contrast, the MOA of the chemicals is taken into consideration in chemical groupings at the DQRA level.

- Completely cleared from the body between exposure episodes and the effects of both COPCs do not persist, HQs for the full year period do not need to be calculated for either of the COPCs and the summed HQs for the total exposure scenario can be assumed to be below the target value.

It is possible to add HQs derived from different tiered assessments (e.g., a different tier for each co-existing COPC) and if the sum is below or equal to the target HQ, then there would be no requirement to advance all COPCs through higher tiers. The guidance recognizes that there may be more uncertainty associated with assessment at a lower tier, which may overestimate the HQ. If the summed HQs exceed the target value using this approach, advancing the other COPCs to higher tiers would need to be considered on a site-specific and chemical-specific basis.

Refer to the HC (2024) PQRA guidance for assessment methods using toxic equivalence factors for mixtures composed of a single class of structurally similar chemicals, such as polychlorinated dibenzo-p-dioxins. Risks estimated for chemicals with unique effects on different target organs or with different modes of action should be presented individually. Risk estimates for each exposure period associated with a total HQ ≤1 (with comprehensive multimedia exposure assessment completed for each chemical) where background exposure from all sources has also been incorporated, or ≤0.2 (without consideration of background exposure) will be deemed negligible.

A tiered approach to assessing potential health risks associated with combined exposure to multiple chemicals is described in recent WHO (2017) and HC Pest Management Regulatory Agency (PMRA, 2018) publications. In addition to HQ summation, US EPA (2007b) and WHO (2017) have provided other risk assessment methodologies, including those that can be used to evaluate mixtures of chemicals with dissimilar modes of action and mixtures that are interactive (i.e., effects that are either greater or less than what is observed as additive). The risk assessment may use these additional methods where appropriate. An adequate scientific rationale needs to be provided in support of using any of the above alternative methods.

The OECD (2018e) publication entitled *Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals* may be a useful reference document. This document provides tier-based approaches and addresses data needs, toxicokinetics, and technical aspects of risk assessment as well as specific considerations for grouping of chemicals, potency and co-exposures.

5 ADDITIONAL REQUIREMENTS FOR HHRA

5.1 Variability and Uncertainty Analysis

Variability and uncertainty analysis is an integral part of the risk assessment process. Variabilities and uncertainties in risk estimates should be reviewed and conclusions derived from the risk assessment findings should be put into context. These considerations will ultimately be integrated into the development of health-protective risk management decisions. Refer to HC's PQRA (2024) and DQRA (2010a) guidance documents for general guidance.

5.2 Recommendations

The report should list all recommendations that may stem from the results of the risk assessment. Recommendations may include the scope and details required for additional tiered assessment (for an assessment that stops at an earlier tier) to reduce uncertainty and to support decisions on remediation or risk management measures. For more detailed information, refer to HC's PQRA (2024) guidance document.

5.3 Conclusions and Discussion

The overall conclusions with respect to the potential human health risks posed by the contaminated site should be summarized in this section of the HHRA report. Any other issues that require discussion or that may affect risk management of the site should be included here and also presented in the executive summary. Key assumptions made in the risk assessment (e.g., assumptions about site conditions and human activities, or time spent at the site) should be noted. The conclusions and discussion should also identify whether additional sampling or modelling and/or a higher tiered analysis should be completed in order to characterize potential health risks more adequately.

5.4 References and Citations

The report should be thoroughly referenced to enable technical reviewers to identify and obtain all documents and authoritative sources cited. A complete list of those references is required.

6 SUMMARY

This document provides supplemental guidance for conducting HHRA where less-than-chronic exposure is identified at contaminated sites under federal jurisdiction in Canada. The information in this document will help standardize risk assessments and ensure that all relevant data are presented in HHRA reports to allow for technical review. Given that HHRA is a dynamic science, it is important to stress that its practices will change over time in accordance with new scientific developments. Certain elements of HHRA may be more likely than others to evolve; therefore, the most up-to-date guidance/information should be used to inform the HHRA. These elements include:

a) Information defining receptor characteristics.

b) Methods and data used to estimate exposures from chemicals, including modelling.

c) TRVs, and methods and data used to derive TRVs.

d) Methods used to estimate risks.

HC may periodically revise and update the current document to reflect changes in guidance and data. Notwithstanding such updates, a scientifically defensible risk assessment report should be prepared. The report should be accurate, thorough and transparent, and should be completed by knowledgeable risk assessment professionals. When there is doubt about the approaches and/or guidance to be used, discussion with HC staff is encouraged in order to ensure compliance with current methods and procedures for HHRA of FCSAP sites.

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APPENDIX A SOURCES OF TRVs

In general, HC published TRVs are preferred for use when conducting a risk assessment at a federal contaminated site funded under the FCSAP. HC (2021a or most recent version) provides TRVs for chronic exposure that may be used in the assessment of less-than-chronic exposures, although an HHRA may incorporate shorter-duration TRVs for less-than-chronic exposures to reduce uncertainty. In the absence of available HC TRVs, values from other jurisdictions may be considered for use where appropriate. In these cases, the relevance of the value and the consistency of its derivation with HC's chemical risk assessment methodology should be clearly identified in the report (e.g., protection of the general population).

Different agencies may derive TRVs for a given substance based on different key toxicological studies. The key studies selected for deriving TRVs may change over time as the findings of new research become available. Additionally, regulatory agencies may define exposure durations differently and have varying perspectives on the appropriateness of using short-duration studies to derive longer-duration TRVs or apply different UFs to a POD. Thus, various regulatory agencies may derive numerically different TRVs from the same key study.

TRVs for less-than-chronic exposures may include values developed by ATSDR and/or provisional peer-reviewed toxicity values (PPRTVs; US EPA, 2023a) from the US EPA's Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and Resource Conservation and Recovery Act (RCRA) hazardous waste programs. ATSDR's toxicological profiles and associated MRLs are developed for chemicals on the National Priorities List of contaminated sites (ATSDR, 1996). PPRTVs include provisional subchronic and chronic risk values for chemicals that are not included in IRIS (US EPA, 2024).

There are few sources for acute TRVs that may be relevant to contaminated sites. The ATSDR acute MRLs address exposures of up to 14 days, and the US EPA's acute reference exposures are intended to apply to occasional continuous exposures for a duration of 24 hours or less (US EPA, 1998; Strickland and Foureman, 2002). Many of the available acute TRVs (e.g., Acute Exposure Guideline Levels – https://www.epa.gov/aegl) are developed for emergency exposure scenarios involving once-in-a-lifetime inhalation exposures and are not further addressed here.

Table A.1 lists several recognized sources of TRVs relevant to contaminated sites: HC, the US EPA's IRIS and PPRTVs for CERCLA, WHO including the IPCS, RIVM, ATSDR and CalEPA. TRVs developed by other organizations or in the published literature may be used with appropriate supporting documentation.

The International Toxicity Estimates for Risk (ITER) database (available at Toxicology Excellence for Risk Assessment [TERA] website, https://tera.org/iter/riskmethods.html; www.projectiter.org) includes TRVs from HC, US EPA, ATSDR, IPCS, RIVM and TCEQ. ITER also includes independently developed and peer-reviewed values, along with information on the key elements in the TRV derivation. The TRVs on ITER are continuously updated as the respective organizations develop new values. Additionally, the US Department of Energy's Risk Assessment Information System (RAIS; available at https://rais.ornl.gov/cgi-bin/tools/TOX_search?select=chem) provides acute, short-term and subchronic TRVs from US federal government sources, such as ATSDR, IRIS and PPRTV.

Table A.1 lists sources for both chronic and less-than-chronic TRVs; however this list is not a comprehensive listing of all possible sources of TRVs.

Table A.1 Sources of TRVs[1]

Organization	URL	Duration and Route	Comments/Type of Value
Health Canada (HC)	https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/substances-list/toxic/schedule-1.html and https://www.canada.ca/en/health-canada/services/environmental-workplace-health/water-quality/drinking-water/canadian-drinking-water-guidelines.html and https://www.canada.ca/en/health-canada/services/air-quality/residential-indoor-air-quality-guidelines.html	Short-duration and chronic; oral and inhalation	Existing Substances Division (TDI or TC); Canadian drinking water guidelines (maximal acceptable concentrations); residential indoor air quality guidelines (maximum exposure limits)
United States Environmental Protection Agency Integrated Risk Information System (US EPA IRIS)	https://www.epa.gov/iris	Primarily chronic (>7 years), a few acute (24 hours or less), short-term (24 hours to 30 days), subchronic (>30 days to 7 years), oral and inhalation	RfD, RfC Less-than-chronic TRVs are available for very few chemicals; most TRVs are for chronic duration
World Health Organization/ International Programme on Chemical Safety (WHO/IPCS)	http://www.inchem.org/pages/ehc.html	Generally chronic; oral and inhalation	Documented in the Environmental Health Criteria series; TRV may be expressed in terms of ADI, TC, or other measures

Organization	URL	Duration and Route	Comments/Type of Value
World Health Organization/Joint Expert Committee on Food Additives (WHO/JECFA)	http://www.inchem.org/pages/jecfa.html	Chronic; oral only	ADI Toxicological evaluations of food additives and contaminants
Netherlands National Institute of Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu) (RIVM)	https://www.rivm.nl/bibliotheek/rapporten/711701004.pdf, https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf and https://www.rivm.nl/bibliotheek/rapporten/711701092.pdf	Chronic (lifetime); oral and inhalation	Maximum permissible risk levels Developed for generic soil quality standards
Institute of Medicine (IOM)	http://www.nap.edu/catalog/11537/dietary-reference-intakes-the-essential-guide-to-nutrient-requirements	Chronic; age-specific; oral only	Tolerable upper intake level Developed for essential elements
Agency for Toxic Substances and Disease Registry (ATSDR)	http://www.atsdr.cdc.gov/toxprofiles/index.asp	Acute (≤14 days), intermediate (15-364 days), chronic (≥1 year); oral and inhalation	MRL Developed for chemicals at National Priorities List sites
United States Environmental Protection Agency Provisional Peer-Reviewed Toxicity Values (US EPA PPRTV Program)	https://www.epa.gov/pprtv	Subchronic ("generally less than seven years") and chronic; oral and inhalation	PPRTV Often a less complete database than IRIS values
United States Department of Energy Risk Assessment Information System (RAIS)	https://rais.ornl.gov/cgi-bin/tools/TOX_search?select=chem	Acute, short-term, subchronic and chronic; oral and inhalation	Includes values from IRIS, ATSDR and Health Effects Assessment Summary Tables (HEAST[2]). Durations based on other agencies' definitions – does not define duration separately

Organization	URL	Duration and Route	Comments/Type of Value
United States Environmental Protection Agency Office of Water	https://www.epa.gov/sdwa/drinking-water-health-advisories-has	1-day, 10-day, lifetime drinking water health advisories; oral only	Health Advisory 1- and 10-day values are for a 10 kg child
Minnesota Department of Health (MDH)	http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html and https://www.health.state.mn.us/communities/environment/risk/guidance/air/table.html	Drinking water: acute (1-day), short-term (>1 to 30 days), subchronic (>30 days through 10% of lifetime), chronic. Air (exposure durations updated in 2020): acute (1-day or less), Short-term (>1 to 30 days), subchronic (>30 days through 10% of lifetime), chronic.	HBV, HRL Drinking water values are based on an intake rate for infants (1–3 months) for acute and short-term exposure, intake rate for birth through 8 years time-weighted average for subchronic exposure; the RfD/RfC used to calculate HBV is provided in the toxicology summary for individual chemicals
California Environmental Protection Agency (CalEPA)	http://www.oehha.ca.gov/air/allrels.html	1-hour, 8-hour, chronic (up to a lifetime); inhalation only	REL
Texas Commission on Environmental Quality (TCEQ)	https://www.tceq.texas.gov/downloads/toxicology/publications/rg-442.pdf and https://www.tceq.texas.gov/toxicology/database/tox	Acute (usually 1 hour but may be 24 hours), chronic (>10% of lifetime); inhalation only	ReVs
United States Environmental Protection Agency Homeland Security Research Program	https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NHSRC&count=10000&dirEntryId=200366&searchall=&showcriteria=2&simplesearch=0&timstype=	Acute (24 hour), short-term (>1 to 30 days) and long-term (>30 days to 2 years); inhalation and drinking water	PALs Developed for highly hazardous chemicals

Organization	URL	Duration and Route	Comments/Type of Value
European Chemicals Agency (ECHA)	https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment	Long-term (repeated exposure) and acute (single exposure of a few minutes up to 24 hours); Oral, inhalation and dermal	DNEL[3] Derived for local and systemic effects

ADI – acceptable daily intake; DNEL – derived no-effect level; HBV – health-based value; HRL – health risk limit; MRL – minimal risk level; PAL – provisional advisory level; PPRTV – provisional peer reviewed toxicity values; REL – reference exposure level; ReV – reference value; RfC – reference concentration; RfD – reference dose; TC – tolerable concentration; TDI – tolerable daily intake

[1] Note that TRVs are route- and duration-specific, as described by the organization that publishes them. Some TRVs may be provided in a medium-specific format, but the documentation provides either the underlying TRV or the information needed to calculate the TRV.

[2] HEAST is not updated and may only be relevant as a supplemental source of information as the data may be outdated.

[3] Only DNELs that have been reviewed, derived or approved by relevant authorities should be considered.

A.1 Additional Information on Sources of TRVs

Additional less-than-chronic TRVs are also available. Health advisories for chemicals in drinking water have been developed by the US EPA's Office of Water (OW; US EPA, 2018, 2023b) but values from this source require conversion to standard units for TRVs (mg/kg bw/day) when used in a risk assessment. The OW expresses 1-day and 10-day health advisories in the form of concentrations in drinking water for a 10 kg child who drinks 1 L of water per day (i.e., as per Child Health Advisories). The resulting value is a TRV relevant to a child for the duration of interest. A review of the corresponding TRV documentation would be required on a chemical-specific basis to identify whether the TRV is protective of sensitive subpopulations such as people who are pregnant, and developing fetuses. The TRV documentation also notes whether effects may occur in adults at doses below the TRV relevant to a child. Additional information on the basis of the health advisories is available from the OW web site.

Further, since 2008, the MDH has developed HRLs/HBVs for groundwater and air for acute (1 day or less), short-term (more than 1 day and up to 30 days), subchronic (more than 30 days to 10% of lifespan) and chronic (more than 10% lifespan) exposure durations. The TRVs used to derive the HRLs/HBVs are provided in the toxicological summaries of individual chemicals.

Other potentially relevant values include those developed by CalEPA, TCEQ and PALs developed by the US EPA. However, these TRVs may be less relevant to contaminated sites because of the short-duration of exposure for which they were developed (e.g., CalEPA, TCEQ, US EPA-PAL values) and/or because the chemicals are less likely to be found at contaminated sites. The CalEPA has developed 1-hour, 8-hour and chronic limits for hazardous air pollutants, and TCEQ has developed acute and chronic limits. These values may be considered for use at contaminated sites where appropriate for the exposure scenario.

PALs are developed for three levels of severity: PAL 1 (mild, transient, reversible effect), PAL 2 (serious, possibly irreversible effect) and PAL 3 (severe effect or lethality). Note that PALs are defined somewhat differently from other TRVs considered in this document. For example, PAL 1, the lowest severity level, is a threshold above which adverse effects may occur, although mild transient and reversible effects may occur at this level. Note also that oral PALs are expressed in terms of drinking water concentrations; the underlying TRV is available in the full documentation or can be determined on the basis of the underlying conversion parameters. In a contaminated sites risk assessment, TRVs are expected to be levels that do not result in adverse health effects for the general population, including sensitive subpopulations, and additional UFs may be required.

ECHA (2023) is another potential source of short-duration TRVs for some substances. DNELs for the general population have been developed for some chemicals under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Under this regulation, ECHA maintains a database of chemical-specific information it receives from industry, evaluation reports and DNELs. However, only DNELs that have been derived or approved by relevant authorities under REACH should be considered.

A.2 Use of Workplace Threshold Limit Values

Occupational exposure limits are not recommended for evaluating human health in a contaminated sites risk assessment that includes assessment of the general public. These values include different assumptions with regard to protection of workers and are not necessarily protective of the general population (e.g., children).

It is generally unacceptable to use threshold limit values (TLVs) developed for workplace exposures as TRVs for the assessment of risks to the public. Although often based on toxicological principles, the procedures used to develop TLVs for the protection of adult workers are distinct from the approach used to establish TRVs for the protection of the public. For example, TLVs generally assume that healthy adult workers are the persons requiring protection, whereas TRVs need to consider the protection of all members of the public, including people who are young, pregnant and elderly. Also, TLVs generally do not consider that exposures may occur continuously (24 hours/day). Instead, they are typically developed for a 40-hour work week and consider a typical career duration.

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APPENDIX B DEFINING EXPOSURE DURATION

B.1 Health Canada Historical Exposure Duration Definitions for Contaminated Sites

The definitions of the terms acute, subchronic and chronic exposure differ among the various regulatory agencies that publish TRVs and apply to different exposure durations in different animal species. The HC (2010) DQRA guidance document provided the following definitions of exposure durations for humans. Acute: less than 14 days, but often involving a single high-intensity exposure; Subchronic: greater than 14 days and up to 90 days; and Chronic: greater than 90 days. These definitions were based on their similarity to guidelines for mammalian toxicity testing studies understood at the time of publication. However, these definitions have been updated in **Section B.3** of this appendix.

The above definition of acute exposure (HC, 2010) did not differentiate between an acute exposure (lasting for 1 day or less but often involving a single intensive exposure) and moderate repeated exposures over a short period of time (2 weeks or less). More recently, US EPA (2012, 2023) provided a distinction between acute exposure (1 day or less) and short-term exposure, which is often defined as up to 1 month. The HC (2010) definitions of subchronic and chronic exposures for humans assume comparable duration with experimental animal studies, maintaining a 1:1 ratio in exposure duration between human and animal species. However, refinement of the HC (2010) definitions is provided in this guidance document to reflect more recent science and review of the exposure duration categories used by other regulatory agencies. A comprehensive review is not presented in this document; however, **Section B.2** of this appendix provides a short summary of exposure categories used by other agencies.

B.2 Summary of Exposure Duration Categories by Other Agencies

This section provides a brief overview of the exposure duration categories of several regulatory agencies including PMRA, the ATSDR and the US EPA (specifically the IRIS program). These agencies have developed both oral and inhalation TRVs for each of their exposure duration categories for characterizing potential health hazards of chemicals in the environment.

B.2.1 HC Pest Management Regulatory Agency

The PMRA's (2021) categorization of duration for exposure to pesticides is consistent with the terminology used by the US EPA Office of Pesticide Programs (US EPA, 2012). It is based on standard pesticide use patterns and typically available toxicity information, as follows:

- Acute exposure: exposure for 1 day or less
- Short-term exposure: exposure for 1 day to 30 days
- Intermediate-term exposure: exposure for 1 to 6 months
- Long-term exposure: exposure for greater than 6 months
- Lifetime exposure: exposure over a lifetime

B.2.2 US EPA Integrated Risk Information System

The US EPA IRIS program has defined four categories of duration for human exposure to environmental chemicals (US EPA, 2023), as follows:

- Acute exposure: exposure for 24 hours or less
- Short-term exposure: repeated exposure for more than 24 hours, up to 30 days
- Subchronic (or longer-term) exposure: repeated exposure for more than 30 days, up to approximately 10% of the lifespan in humans
- Chronic exposure: repeated exposure for more than 10% of the lifespan in humans

The definition of acute exposure makes a distinction between exposure (usually single exposure) of 24 hours (or less) and moderate repeated exposures over a short term (30 days as defined by the US EPA). In addition, the definition of short-term exposure of up to 30 days corresponds with the exposure duration of the 28-day rodent toxicity study (OECD, 1981, 2008, 2018a; US EPA, 1998a, 2000), which is a potential data source for hazard assessment for 30-day exposures.

B.2.3 US Agency for Toxic Substances and Disease Registry

The ATSDR publishes MRLs which are referred to as TRVs in this document. An MRL is an estimate of the daily human exposure to hazardous substances that is unlikely to pose an appreciable risk of non-cancer health effects over a specified route and exposure duration. MRLs are intended to be screening levels for identifying contaminants and adverse health effects that may be of concern at hazardous sites and releases; however, ATSDR emphasizes that MRLs are not intended to define clean-up or action levels (Risher and DeRosa, 1997; ATSDR, 1996, 2024).

MRLs are developed for three different duration categories, as follows:

- Acute exposure: exposure for up to 14 days
- Intermediate exposure: exposure for 15 to 364 days
- Chronic: exposure for 365 days or more

The ATSDR approach to MRL derivation was published in a *Federal Register* notice (ATSDR, 1996).

The ATSDR definition of acute exposure does not differentiate between an acute exposure (lasting for 1 day or less but often involving a single intensive exposure) and moderate repeated exposures over a short term (2 weeks or less). The current guidance document does not adopt the ATSDR's approach to defining acute exposure, as it differs from that of other regulatory agencies such as US EPA (2012, 2023).

B.3 Revised Exposure Duration Definitions for HC Contaminated Sites HHRAs

The updated HC definitions in this guidance document for use at federal contaminated sites distinguish between an intensive 1-day (or less) exposure and moderate repeated exposures over a short period of time. The updated definitions include addition of an exposure category that involves repeated exposure of more than 24 hours and up to 30 days. An exposure period of 30 days is comparable in duration to the test guidelines for repeated dose 28-day toxicity studies in rodents (OECD, 1981, 2008, 2018a; US

EPA, 1998a, 2000), which can serve as the data source for derivation of a TRV applicable to repeated exposure for more than 24 hours and up to 30 days. This exposure duration category is referred to as "short-term exposure".

The definition of chronic exposure is changed to repeated exposure for at least 1 year.

A new category was created to describe the exposure duration that is shorter than chronic exposure but longer than short-term exposure. This new category is referred to as "intermediate exposure". The use of 1 year as the separation line between intermediate and chronic duration in the revised definitions for FCSAP sites HHRAs is consistent with chronic toxicity studies (OECD, 2018b; US EPA, 1998b; US FDA, 2007).

Since longer-duration TRVs are generally more stringent than (or equally as stringent as) shorter-duration TRVs, it is health protective to apply a longer-duration TRV to a shorter exposure period. Hence, the US EPA library of subchronic RfDs/RfCs can also be used as intermediate-duration TRVs, applicable to exposure duration of more than 30 days and up to less than 1 year. It is important to recognize that the most relevant TRV has to be selected for the exposure duration of interest after careful consideration of all potential candidate TRVs following the guidance provided in **Section 2.3.2** of the main document. Rationale should be provided in the risk assessment report.

In summary, the revised exposure duration categories for use in HHRA at FCSAP sites are as follows:

- Acute exposure: exposure for 24 hours or less (≤24 hours)
- Short-term exposure: repeated exposure for more than 24 hours, up to 30 days (>24 hrs to ≤30 days)
- Intermediate exposure: repeated exposure for more than 30 days, up to less than 1 year (>30 days to <1 year)
- Chronic exposure: repeated exposure for 1 year or more and up to a lifetime (≥1 year)

For some chemicals, if acute exposures, short-term exposures or intermediate exposures are repeated annually, the exposures may be considered chronic even if the exposure is not continuous (see **Section 3.3.2** of the main document).

It is stressed that the use of the terms intermediate and chronic as defined in this guidance document is limited to risk assessments conducted for federal contaminated sites and that the toxicological reference values applied in the risk assessment are appropriate in duration according to the exposure scenarios presented.

B.4 References

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APPENDIX C RECOMMENDED GENERAL EQUATIONS FOR CONTINUOUS AND NEAR-CONTINUOUS EXPOSURES

This appendix presents general equations that can be used for estimating exposures associated with commonly evaluated exposure pathways for continuous and near-continuous less-than-chronic exposures to chemicals eliciting threshold effects. Depending on the COPC and how the primary determinant of toxicity for the critical health effect is related to the exposure duration of interest, a different set of equations may apply (see discussion in **Section 3.2.4** of the main document). These equations address assessment of environmental media at FCSAP sites associated with contaminated soils. Similarly, equations for estimating exposure to contaminated sediments in HC (2017a) may be adjusted to address short-duration continuous and near-continuous exposures.

Input parameters for the equations should be clearly stated and referenced in each HHRA report. Some receptor characteristics that can be used for chronic exposure in HHRAs, such as default body weights and drinking water intakes, are presented in the PQRA guidance document (HC, 2024). The exposure point concentration of each COPC in each environmental medium (air, water, soil, vegetation, etc.) is determined based on the available data from each site (refer to HC, 2010). The appropriate statistics for exposure factor parameters (e.g., intake rate) depend on the conditions present at the site, the onsite behaviour of the receptors and what primarily drives the toxicity of a substance (i.e., concentration/peak exposure or total dose/body burden). The risk assessment should include a rationale for the appropriate statistics for each input parameter after a careful analysis of the above factors. Rationale and supporting evidence for exposure point concentrations and receptor characteristics should be provided in the HHRA report. For example, for a site used as a soccer field, soccer players are expected to be at a high activity level during the relatively brief periods they are playing on the field. For this exposure scenario, a high (and not the mean) inhalation rate may be appropriate for exposure estimation during these brief periods.

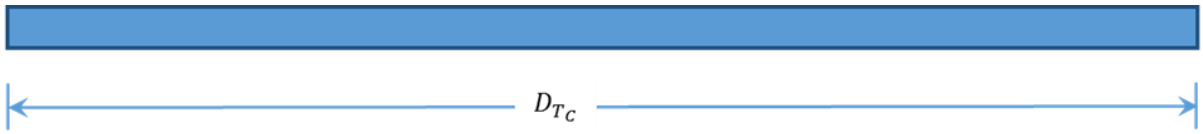
Bioavailability is another input parameter that may be incorporated into the exposure calculation. The relative bioavailability factor (RAF or RBA) in the equations refers to the ratio of the absolute bioavailability of a substance in the environmental matrix of interest (site-specific samples) to the absolute bioavailability of the same substance in the dosing medium under the conditions used to derive the TRV (discussed in HC, 2010, 2017b). For detailed guidance on in vitro bioaccessibility tests that can be used to derive oral RBA estimates for use in HHRAs, refer to HC's *Supplemental Guidance on Human Health Risk Assessment for Oral Bioavailability of Substances in Soil and Soil-like Media* (HC, 2017b).

C.1 Continuous Daily Exposures

Figure C.1 depicts a continuous daily exposure scenario of D_{T_C} days to chemical contaminants at a contaminated site. As stated in **Section 2.5.3**, continuous daily exposure refers to uninterrupted exposure over a number of consecutive days, such as 24 hours/day and 7 days/week for inhalation, or daily for oral and dermal exposures. Although oral and dermal exposures may be sporadic over the course of the day, "continuous daily exposure" can still be applied, and the oral and dermal exposure is measured based on daily dose.

Key considerations that relate to the equations provided in **Section C.1** are detailed in **Section C.1.7**. These considerations include, but are not limited to, the statistics used for input exposure point concentrations in the equations.

Figure C.1 Continuous daily exposure scenario



Where:

= Exposure

D_{T_C} = Duration of a continuous exposure scenario in days, spanning from first day to final day of exposure

C.1.1 Inadvertent Ingestion of Contaminated Soil

The predicted intake of a COPC via ingestion of contaminated soil in a continuous daily exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario is used for risk characterization.

$$Dose = \frac{C_S * IR_S * RAF_{oral}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
IR_S = soil ingestion rate (kg/day)
RAF_{oral} = relative absorption factor from the gastrointestinal (GI) tract (unitless)
BW = body weight (kg)

Notes: C.1-a (See **Section C.1.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario (see **Section 3.2.3** of the main document for explanation) may be used for risk characterization.

$$ADD = \frac{C_S * IR_S * RAF_{oral} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

Where ADD = average daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
IR_S = soil ingestion rate (kg/day)
RAF_{oral} = relative absorption factor from the GI tract (unitless)
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure (Note that the D_{T_C} terms in the numerator and denominator should always have the same value, hence the ratio D_{T_C}/D_{T_C} will always be equal to 1).
BW = body weight (kg)

Notes: C.1-b, C.1-c (See **Section C.1.7**).

C.1.2 Inhalation of Volatile Substances or Suspended Particulate Matter – with TRVs Expressed as Tolerable Concentration (TC)

HC (2017c) provides guidance on ris k assessment of contaminants in air. The exposure estimates should be expressed in the same units as the TRVs. Since the TRVs for inhalation exposures are often expressed as air concentrations, the equations used to estimate exposures by inhalation of volatile substances or suspended particulate matter vary accordingly. TRVs expressed as TCs in µg/m^3 or mg/m^3, when available, are preferred for characterizing risk from these exposures. The exposure for a continuous exposure scenario can be estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest air concentration experienced during the exposure scenario is used for risk characterization.

$$DC_A = C_A * RAF_{inh}$$

Where DC_A = highest estimated daily air concentration of contaminant (µg/m^3)
C_A = maximum concentration of contaminant in air (µg/m^3)
RAF_{inh} = relative absorption factor for inhalation, default value of 1 (unitless)

Notes: C.1-d (See **Section C.1.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average air concentration of the exposure scenario may be used for risk characterization.

$$TDC_A = C_A * RAF_{inh} * \frac{H}{H_D} * \frac{D_{T_C}}{D_{T_C}}$$

Where TDC_A = time-weighted average daily air concentration of contaminant (µg/m^3)
C_A = concentration of contaminant in air (µg/m^3)
RAF_{inh} = relative absorption factor for inhalation, default value of 1 (unitless)
H = hours per day exposed is always 24 hours in a continuous exposure scenario
H_D = 24 hours
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure (Note that the D_{T_C} terms in the numerator and denominator should always have the same value, hence the ratio D_{T_C}/D_{T_C} will always be equal to 1).

Notes: C.1-c, C.1-e (See **Section C.1.7**).

C.1.3 Inhalation of Suspended Particulate Matter from Contaminated Soils – with TRVs Expressed as Oral Tolerable Daily Intake (TDI)

When a TRV based on inhalation toxicity studies and expressed in mg/m^3 (or µg/m^3) is not available and the oral TRV (expressed in mg/kg bw/day) is appropriate for use (i.e., toxicological effects are expected to be similar for oral and inhalation exposure routes), the intake of COPCs via inhalation of particulate matter in air in a continuous daily exposure scenario can be estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization.

$$Dose = \frac{C_S * P_{air} * IR_A * RAF_{inh}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
P_{air} = particulate concentration in air (kg/m^3)
IR_A = air intake (inhalation) rate (m^3/day)
RAF_{inh} = relative absorption factor by inhalation (unitless)
BW = body weight (kg)

Notes: C.1-a, C.1-f (See **Section C.1.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \frac{C_S * P_{air} * IR_A * RAF_{inh} * \frac{H}{H_D} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

Where ADD = average daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)

P_{air} = particulate concentration in air (kg/m^3)
IR_A = air intake (inhalation) rate (m^3/day)
RAF_{inh} = relative absorption factor by inhalation (unitless)
H = hours per day exposed is always 24 hours in a continuous exposure scenario
H_D = 24 hours
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure (Note that the D_{T_C} terms in the numerator and denominator should always have the same value, hence the ratio D_{T_C}/D_{T_C} will always be equal to 1).
BW = body weight (kg)

Notes: C.1-b, C.1-c, C.1-f (See **Section C.1.7**).

C.1.4 Ingestion of Contaminated Drinking Water

For all contaminated sites, it is recommended that the water used for ingestion meet Canadian Drinking Water Guidelines. Where calculations are conducted to evaluate exposure from all media, the following equations can be used. These equations are not appropriate for derivation of a SSTL for potable water. The predicted intake of a COPC via ingestion of contaminated water in a continuous daily exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario is used for risk characterization.

$$Dose = \frac{C_W * IR_W * RAF_{oral}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
C_W = maximum concentration of contaminant in drinking water (mg/L)
IR_W = water intake rate (L/day)
RAF_{oral} = relative absorption factor from the GI tract (unitless)
BW = body weight (kg)

Notes: C.1-g, C.1-h (See **Section C.1.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario will be used for risk characterization.

$$ADD = \frac{C_W * IR_W * RAF_{oral} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

Where ADD = average daily dose (mg/kg bw/day)
C_W = concentration of contaminant in drinking water (mg/L)

IR_W = water intake rate (L/day)
RAF_{oral} = relative absorption factor from the GI tract (unitless)
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure (Note that the D_{T_C} terms in the numerator and denominator should always have the same value, hence the ratio D_{T_C}/D_{T_C} will always be equal to 1).
BW = body weight (kg)

Notes: C.1-c, C.1-g, C.1-h, C.1-i (See **Section C.1.7**).

C.1.5 Dermal Absorption from Contaminated Soil

The predicted intake of COPCs via dermal contact with contaminated soil in a continuous daily exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization.

$$Dose = \frac{\{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_V * RAF_{dermal}\}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
SA_H = surface area of hands exposed for soil loading (cm^2)
SL_H = soil loading rate to exposed skin of hands (kg/cm^2-event)
SA_O = surface area exposed other than hands (cm^2)
SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)
nE_V = number of dermal exposure events/day (default assumption is 1 event/day)
RAF_{dermal} = relative dermal absorption factor (unitless)
BW = body weight (kg)

Notes: C.1-a (See **Section C.1.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \frac{\left\{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_V * RAF_{dermal} * \frac{D_{T_C}}{D_{T_C}}\right\}}{BW}$$

Where ADD = average daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
SA_H = surface area of hands exposed for soil loading (cm^2)
SL_H = soil loading rate to exposed skin of hands (kg/cm^2-event)

SA_O = surface area exposed other than hands (cm^2)
SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)
nE_V = number of exposure events/day (default assumption is 1 event/day)
RAF_{dermal} = relative dermal absorption factor (unitless)
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure (Note that the D_{T_C} terms in the numerator and denominator should always have the same value, hence the ratio D_{T_C}/D_{T_C} will always be equal to 1).
BW = body weight (kg)

Notes: C.1-b, C.1-c (See **Section C.1.7**).

C.1.6 Ingestion of Contaminated Foods (Produce, Fish, Game, etc.)

The predicted intake of COPCs via ingestion of contaminated food in a continuous daily exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario is used for risk characterization.

$$Dose = \sum_{f=1}^{n_{food}} \frac{C_f * IR_f * RAF_f}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
n_{food} = number of foods included in the analysis
C_f = concentration of contaminant in food f (mg/kg)
IR_f = ingestion rate for food f (kg/day)
RAF_f = relative absorption factor from the GI tract for contaminant in food f (unitless)
BW = body weight (kg)

Notes: C.1-a (See **Section C.1.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \sum_{f=1}^{n_{food}} \frac{C_f * IR_f * RAF_f * D_{T_C}}{BW * D_{T_C}}$$

Where ADD = average daily dose (mg/kg bw/day)
n_{food} = number of foods included in the analysis
C_f = concentration of contaminant in food f (mg/kg)
IR_f = ingestion rate for food f (kg/day)

RAF_f = relative absorption factor from the GI tract for contaminant in food f (unitless)

D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure (Note that the D_{T_C} terms in the numerator and denominator should always have the same value, hence the ratio D_{T_C}/D_{T_C} will always be equal to 1).

BW = body weight (kg)

Notes: C.1-b, C.1-c, C.1-j (See **Section C.1.7**).

C.1.7 Notes for Equations in Section C.1

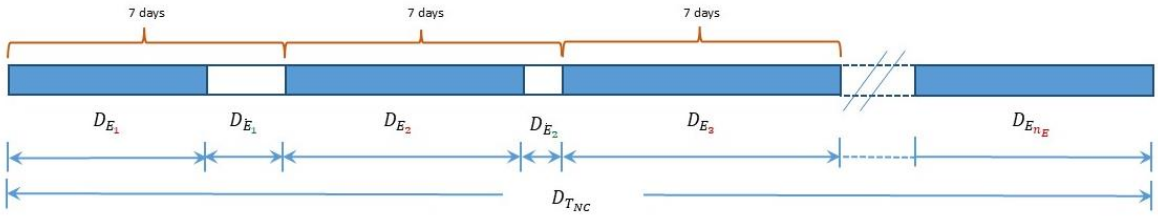
Note	Description
C.1-a	Depending on the available data, a statistic that represents reasonable maximum exposure (HC, 2024) may be used as the input concentration. Please consult HC's (2024) PQRA guidance document for examples of appropriate statistics that are representative of reasonable maximum exposures at a federal contaminated site. However, if the available data are not adequate to support statistical derivation of an exposure point concentration, the maximum concentration is used when assessing peak exposures.
C.1-b	If data from the environmental site investigation are adequate to support statistical derivation of an exposure point concentration (HC, 2024), a measure of central tendency of the available concentration data may be used as the input concentration when evaluating exposures based on total dose. Please consult HC's 2024 PQRA guidance document for examples of appropriate statistics that are representative of a measure of central tendency at a federal contaminated site. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. However, if the available data are inadequate, the maximum concentration is used. Refer to the equation in (i) when dose averaging cannot be supported.
C.1-c	For continuous exposure, when toxicity is driven by total dose, dose averaging may be possible. However, dose averaging must not extend beyond the end of the exposure scenario. Hence, the duration of exposure should match the duration of the exposure scenario (i.e., the ratio D_{T_C}/D_{T_C} will always be equal to 1).
C.1-d	For most chemicals, air concentrations are reported as 24-hour average concentrations, and TRVs are expressed as daily air concentrations. However, for some chemicals, the averaging time of reported air concentration may not match the averaging time of the available TRV. DC_A would be the highest air concentration based on the available data for an exposure period that matches (or is shorter than) the averaging time for which the available TRV has been derived. For example, HC (2006) has established a short-duration (1-hour) formaldehyde indoor air quality guideline of 123 µg/m^3 to prevent eye irritation in the general population, indicating that this concentration should not be exceeded for any 1-hour interval during a day. As such, the maximum air concentration that occurs for any 1-hour interval would be applicable and it would not be appropriate to compare exposure to an average concentration from multiple buildings or concentrations that may vary over a longer time period.
C.1-e	If data from the environmental site investigation are adequate to support statistical derivation of an exposure point concentration, a measure of central tendency of the available air concentration data for the site may be used as the input air concentration. TDC_A would be calculated based on the available data for the time period measurements were made and compared to a TRV derived for the same or longer exposure duration. Please consult HC's (2024) PQRA guidance document for examples of appropriate statistics that are representative of a measure of central tendency at a federal contaminated site. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. For example, if 8-hr air samples have been collected at the site, TDC_A would be calculated based on a measure of central tendency of the available 8-hr measurements and compared to an 8-hour TRV or a 24-hour TRV. However, if the available data are inadequate, and in case of an acute exposure, the maximum concentration is used.

Note	Description
C.1-f	P_{air} (particulate concentration in air [kg/m^3]) may be directly measured or may be estimated using the methods described in the HC (2024) PQRA guidance. Alternatively, C_A (i.e., airborne concentration of contaminant [mg/m^3]) may be directly measured and the measured value would replace the terms C_s and P_{air} in the equation.
C.1-g	The calculation of a site-specific drinking water guideline is not conducted for substances with existing Canadian Drinking Water Guidelines or HC interim drinking water screening values. The predicted intake of COPCs via contaminated drinking water should be included in the total exposure estimate that includes all exposure pathways.
C.1-h	Select drinking water screening values are available on request in cases where no Canadian Drinking Water Guidelines exist for a specific substance. Please contact HC for additional information.
C.1-i	When groundwater is affected, a measure of central tendency based on concentrations from multiple wells cannot be used to provide exposure estimates if people may be exposed only to concentrations from one area and not another. For example, each residence would use water from its groundwater well, not an average of all wells in the area. Use of a measure of central tendency from multiple wells in the neighbourhood could underestimate exposure for the most exposed individuals.
C.1-j	Food f is assumed to be consumed during the entire exposure scenario. Note that the exposure scenario relates to the duration when foods collected from the site are consumed and this duration may exceed the actual time spent on a contaminated site.

C.2 Near-Continuous Exposure

Figure C.2 depicts a near-continuous exposure scenario at a contaminated site. Near-continuous exposures in this guidance refer to exposures occurring regularly for a portion (e.g., 8 hrs/day) of each consecutive day of exposure (when inhaled), or 5 to 6 days per week (for inhalation, oral and dermal exposures with a continuous non-exposure interval of 2 days or less per week) within a longer overall exposure scenario. In a site-specific risk assessment, alternate assumptions are possible, with rationale, for use of a different exposure pattern in a near-continuous exposure; however, chemical-specific rationale would be required for the toxicity assessment. The equations presented below would then require adjustment accordingly.

Figure C.2 Near-continuous exposure scenario



Where:

= Exposure episode, lasting 5, 6 or 7 days, and denoted E

= Non-exposure period, lasting 2, 1 or 0 days, and denoted $\bar{E}$

D_{E_i} = Duration of exposure episode i in days (must be 5, 6 or 7), where i varies between 1 and n_E (the total number of exposure episodes)

$D_{\bar{E}_j}$ = Duration of non-exposure period j in days (must be 2, 1 or 0), where j varies between 1 and $n_{\bar{E}}$ (the total number of non-exposure periods)

$D_{T_{NC}}$ = Duration of the entire near-continuous exposure scenario in days

$$= \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

AET_{NC} = Aggregate exposure time in days for a near-continuous exposure scenario

= Total number of days exposed for a near-continuous exposure scenario

$$= \sum_{i=1}^{n_E} D_{E_i}$$

Special note: D_{E_i} of 7 consecutive days (D_{E_3} on the above graph) can apply when there is exposure by inhalation for a portion of each consecutive day

C.2.1 Inadvertent Ingestion of Contaminated Soil

The predicted intake via ingestion of contaminated soil in a near-continuous exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario is used for risk characterization. The highest daily dose can be calculated using the same equation as for continuous exposure (See **Section C.1.1, [i]**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario (see **Section 3.2.3** for explanation) may be used for risk characterization.

$$ADD = \frac{C_S * IR_s * RAF_{oral} * AET_{NC}}{BW * D_{T_{NC}}}$$

$$D_{T_{NC}} = \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

$$AET_{NC} = \sum_{i=1}^{n_E} D_{E_i}$$

Where
- ADD = average daily dose (mg/kg bw/day)
- C_S = concentration of contaminant in soil (mg/kg)
- IR_s = soil ingestion rate (kg/day)
- RAF_{oral} = relative absorption factor from the GI tract (unitless)
- AET_{NC} = aggregate exposure time in days for a near-continuous exposure scenario
- $D_{T_{NC}}$ = duration of the entire near-continuous exposure scenario in days, spanning from first day to final day of exposure
- n_E = total number of exposure episodes in a near-continuous exposure scenario
- D_{E_i} = duration of exposure episode i in days (must be 5 or 6), where i varies between 1 and n_E
- $n_{\bar{E}}$ = total number of non-exposure periods in a near-continuous exposure scenario
- $D_{\bar{E}_j}$ = duration of non-exposure period j in days (must be 2 or 1), where j varies between 1 and $n_{\bar{E}}$
- BW = body weight (kg)

Notes: C.2-a, C.2-b (See **Section C.2.7**).

C.2.2 Inhalation of Volatile Substances or Suspended Particulate Matter – with TRVs Expressed as Tolerable Concentration (TC)

TRVs expressed as TCs in µg/m^3 or mg/m^3, when available, should be used for characterizing risk from inhalation of volatile substances or suspended particulate matter. The exposure for a near-continuous exposure scenario can be estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily air concentration experienced during the exposure scenario will be used for risk characterization. The highest daily air concentration can be calculated using the same equation as for continuous exposure (See **Section C.1.2, [i]**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily air concentration of the exposure scenario may be used for risk characterization. It is imperative that the air concentration during any part of the exposure does not exceed the acute TRV.

$$TDC_A = C_A * RAF_{inh} * \frac{H}{H_D} * \frac{AET_{NC}}{D_{T_{NC}}}$$

$$D_{T_{NC}} = \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

$$AET_{NC} = \sum_{i=1}^{n_E} D_{E_i}$$

Where TDC_A = time-weighted average daily air concentration of contaminant (µg/m^3)

C_A = concentration of contaminant in air (µg/m^3)

RAF_{inh} = relative absorption factor for inhalation, default value of 1 (unitless)

H = hours per day exposed

H_D = 24 hours

AET_{NC} = aggregate exposure time in days for a near-continuous exposure scenario

$D_{T_{NC}}$ = duration of the entire near-continuous exposure scenario in days, spanning from first day to final day of exposure

n_E = total number of exposure episodes in a near-continuous exposure scenario

D_{E_i} = duration of exposure episode i in days (must be 5, 6 or 7), where i varies between 1 and n_E

$n_{\bar{E}}$ = total number of non-exposure periods in a near-continuous exposure scenario

$D_{\bar{E}_j}$ = duration of non-exposure period j in days (must be 2, 1 or 0), where j varies between 1 and $n_{\bar{E}}$

Notes: C.2-c, C.2-d, C.2-e, C.2-f (See **Section C.2.7**).

C.2.3 Inhalation of Suspended Particulate Matter from Contaminated Soils – with TRVs Expressed as Oral Tolerable Daily Intake (TDI)

When an inhalation TRV expressed in mg/m^3 (or µg/m^3) is not available and the oral TRV (expressed in mg/kg bw/day) is appropriate for use (i.e., toxicological effects are expected to be similar for oral and inhalation exposure routes), the intake of COPCs via inhalation of particulate matter in air in a near-continuous exposure scenario can be estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization. The highest daily dose can be calculated using the same equation as for continuous exposure (See **Section C.1.3, [i]**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization. It is imperative that the acute TRV is not exceeded during any part of the exposure.

$$ADD = \frac{C_S * P_{air} * IR_A * RAF_{inh} * \frac{H}{H_D} * AET_{NC}}{BW * D_{T_{NC}}}$$

$$D_{T_{NC}} = \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

$$AET_{NC} = \sum_{i=1}^{n_E} D_{E_i}$$

Where
ADD = average daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
P_{air} = particulate concentration in air (kg/m^3)
IR_A = air intake (inhalation) rate (m^3/day)
RAF_{inh} = relative absorption factor by inhalation, default value of 1 (unitless)
H = hours per day exposed
H_D = 24 hours
AET_{NC} = aggregate exposure time in days for a near-continuous exposure scenario
$D_{T_{NC}}$ = duration of the entire near-continuous exposure scenario in days, spanning from first day to final day of exposure

n_E = total number of exposure episodes in a near-continuous exposure scenario

D_{E_i} = duration of exposure episode i in days (must be 5, 6 or 7), where i varies between 1 and n_E

$n_{\bar{E}}$ = total number of non-exposure periods in a near-continuous exposure scenario

$D_{\bar{E}_j}$ = duration of non-exposure period j in days (must be 2, 1 or 0), where j varies between 1 and $n_{\bar{E}}$

BW = body weight (kg)

Notes: C.2-b, C.2-c, C.2-d, C.2-f, C.2-g (See **Section C.2.7**).

C.2.4 Ingestion of Contaminated Drinking Water

For all contaminated sites, it is recommended that the water used for ingestion meet Canadian Drinking Water Guidelines. Where calculations are conducted to evaluate exposure from all media, the following equations can be used. These equations are not appropriate for derivation of a SSTL for potable water. The predicted intake of the COPC via ingestion of contaminated water in a near-continuous exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization. The highest daily dose can be calculated using the same equation as for continuous exposure (See **Section C.1.4, [i]**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \frac{C_W * IR_W * RAF_{oral} * AET_{NC}}{BW * D_{T_{NC}}}$$

$$D_{T_{NC}} = \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

$$AET_{NC} = \sum_{i=1}^{n_E} D_{E_i}$$

Where ADD = average daily dose (mg/kg bw/day)

C_W = concentration of contaminant in drinking water (mg/L)

IR_W = water intake rate (L/day)

RAF_{oral} = relative absorption factor from the GI tract (unitless)

AET_{NC} = aggregate exposure time in days for a near-continuous exposure scenario

$D_{T_{NC}}$ = duration of the entire near-continuous exposure scenario in days, spanning from first day to final day of exposure

n_E = total number of exposure episodes in a near-continuous exposure scenario

D_{E_i} = duration of exposure episode i in days (must be 5 or 6), where i varies between 1 and n_E

$n_{\bar{E}}$ = total number of non-exposure periods in a near-continuous exposure scenario

$D_{\bar{E}_j}$ = duration of non-exposure period j in days (must be 2 or 1), where j varies between 1 and $n_{\bar{E}}$

BW = body weight (kg)

Notes: C.2-a, C.2-b, C.2-h, C.2-i, C.2-j (See **Section C.2.7**).

C.2.5 Dermal Absorption from Contaminated Soil

The predicted intake of COPCs via dermal contact with contaminated soil in a near-continuous exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization. The highest daily dose can be calculated using the same equation as for continuous exposure (See **Section C.1.5, [i]**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \frac{\{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_V * RAF_{dermal} * AET_{NC}\}}{BW * D_{T_{NC}}}$$

$$D_{T_{NC}} = \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

$$AET_{NC} = \sum_{i=1}^{n_E} D_{E_i}$$

Where ADD = average daily dose (mg/kg bw/day)

C_S = concentration of contaminant in soil (mg/kg)

SA_H = surface area of hands exposed for soil loading (cm^2)

SL_H = soil loading rate to exposed skin of hands (kg/cm^2-event)

SA_O = surface area exposed other than hands (cm^2)

SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)

nE_V = number of dermal exposure events/day (default assumption is 1 event/day)

RAF_{dermal} = relative dermal absorption factor (unitless)

AET_{NC} = aggregate exposure time in days for a near-continuous exposure scenario

$D_{T_{NC}}$ = duration of the entire near-continuous exposure scenario in days, spanning from first day to final day of exposure

n_E = total number of exposure episodes in a near-continuous exposure scenario

D_{E_i} = duration of exposure episode i in days (must be 5 or 6), where i varies between 1 and n_E

$n_{\bar{E}}$ = total number of non-exposure periods in a near-continuous exposure scenario

$D_{\bar{E}_j}$ = duration of non-exposure period j in days (must be 2 or 1), where j varies between 1 and $n_{\bar{E}}$

BW = body weight (kg)

Notes: C.2-a, C.2-b (See **Section C.2.7**).

C.2.6 Ingestion of Contaminated Foods (Produce, Fish, Game, etc.)

The predicted intake of COPCs via ingestion of contaminated food in a near-continuous exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization. The highest daily dose can be calculated using the same equation as for continuous exposure (See **Section C.1.6, [i]**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \sum_{f=1}^{n_{food}} \frac{C_f * IR_f * RAF_f * AET_{NC_f}}{BW * D_{T_{NC}}}$$

$$D_{T_{NC}} = \sum_{i=1}^{n_E} D_{E_i} + \sum_{j=1}^{n_{\bar{E}}} D_{\bar{E}_j}$$

$$AET_{NC_f} = \left[\sum_{i=1}^{n_E} D_{E_i}\right]_f$$

Where ADD = average daily dose (mg/kg bw/day)

n_{food} = total number of foods included in the analysis

C_f = concentration of contaminant in food f (mg/kg)

IR_f = ingestion rate for food f (kg/day)

RAF_f = relative absorption factor from the GI tract for contaminant in food f (unitless)

AET_{NC_f} = aggregate number of days in a near-continuous exposure scenario when consumption of food f occurs

$D_{T_{NC}}$ = duration of the entire near-continuous exposure scenario in days, spanning from first day to final day of exposure

n_E = total number of exposure episodes in a near-continuous exposure scenario

D_{E_i} = duration of exposure episode i in days (must be 5 or 6), where i varies between 1 and n_E

$n_{\bar{E}}$ = total number of non-exposure periods in a near-continuous exposure scenario

$D_{\bar{E}_j}$ = duration of non-exposure period j in days (must be 2 or 1), where j varies between 1 and $n_{\bar{E}}$

BW = body weight (kg)

Notes: C.2-a, C.2-b, C.2-k (See **Section C.2.7**).

C.2.7 Notes for Equations in Section C.2

Note	Description
C.2-a	$AET_{NC}/D_{T_{NC}}$ should be based on the site-specific exposure pattern. Dose averaging should be evaluated on a chemical-specific basis and may not be applicable for substances with a teratogenic or reproductive endpoint in the study used to derive the TRV.
C.2-b	If data from the environmental site investigation are adequate to support statistical derivation of an exposure point concentration (HC, 2024), a measure of central tendency of the available concentration data may be used as the input concentration when evaluating exposures based on total dose. Please consult HC's (2024) PQRA guidance document for examples of appropriate statistics that are representative of a measure of central tendency at a federal contaminated site. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. However, if data are inadequate, the maximum concentration is used. Refer to the equation in (i) when dose averaging cannot be supported.
C.2-c	D_{E_i} of 7 days can apply when there is inhalation exposure for a portion of each consecutive day.
C.2-d	H/H_D and $AET_{NC}/D_{T_{NC}}$ should be based on site-specific exposure patterns. Dose averaging should be evaluated on a chemical-specific basis and may not be applicable for substances with teratogenic or reproductive endpoint in the study used to derive the TRV.

Note	Description
C.2-e	When dose averaging can be supported, a measure of central tendency of the available air concentration data may be used as the input air concentration if data from the environmental site investigation are adequate to derive a statistical estimation of the exposure point concentration. TDC_A would be calculated based on the available data for the time period measurements were made and compared to a TRV derived for the same or longer exposure duration. Please consult HC's (2024) PQRA guidance document for examples of appropriate statistics that are representative of a measure of central tendency at a federal contaminated site. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. For example, if 8-hr air samples have been collected at the site, TDC_A would be calculated based on a measure of central tendency of the available 8-hr measurements and compared to an 8-hour TRV or a 24-hour TRV. However, if data are inadequate, the maximum air concentration is used. Refer to the equation in (i) when dose averaging cannot be supported. This guidance is applicable to both indoor and outdoor air.
C.2-f	In the case of airborne particulate matter associated with contaminated soils, readers are referred to HC (2017c) supplemental guidance on air quality and the DQRA (HC, 2010) documents for guidance.
C.2-g	P_{air} (particulate concentration in air [kg/m^3]) may be directly measured or may be estimated using the methods described in the HC (2024) PQRA guidance. Alternatively, C_A (i.e., airborne concentration of contaminant [mg/m^3]) may be directly measured and the measured value would replace the terms C_s and P_{air} in the equation.
C.2-h	The calculation of a site-specific drinking water guideline is not conducted for substances with existing Canadian Drinking Water Guidelines or HC interim drinking water screening values. The predicted intake of COPCs via contaminated drinking water should be included in the total exposure estimate that includes all exposure pathways.
C.2-i	Select drinking water screening values are available on request in cases where no Canadian Drinking Water Guidelines exist for a specific substance. Please contact HC for additional information.
C.2.j	When groundwater is affected, a measure of central tendency based on concentrations from multiple wells cannot be used to provide exposure estimates if people may be exposed only to concentrations from one area and not another. For example, each residence would use water from its groundwater well, not an average of all wells in the area. Use of a measure of central tendency from multiple wells in the neighbourhood could underestimate exposure for the most exposed individuals.
C.2.k	Food f is assumed to be consumed during the entire exposure scenario. Note that the exposure scenario relates to the duration when foods collected from the site are consumed and this duration may exceed the actual time spent on a contaminated site.

C.3 References

Health Canada (HC), 2006. Residential Indoor Air Quality Guideline: Formaldehyde. Water and Air Quality Bureau, Safe Environments Directorate, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. https://www.canada.ca/en/health-canada/services/publications/healthy-living/residential-indoor-air-quality-guideline-formaldehyde.html

HC, 2010. Federal Contaminated Site Risk Assessment in Canada, Part V: Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals ($DQRA_{CHEM}$). Contaminated Sites Division, Safe Environments Directorate, Ottawa.

HC, 2017a. Federal Contaminated Site Risk Assessment in Canada: Supplemental Guidance on Human Health Risk Assessment of Contaminated Sediments: Direct Contact Pathway. Contaminated Sites Division, Safe Environments Directorate, Ottawa.

HC, 2017b. Federal Contaminated Site Risk Assessment in Canada: Supplemental Guidance on Human Health Risk Assessment for Oral Bioavailability of Substances in Soil and Soil-like Media. Contaminated Sites Division, Safe Environments Directorate, Ottawa.

HC, 2017c. Federal Contaminated Site Risk Assessment in Canada: Supplemental Guidance on Human Health Risk Assessment of Air Quality, Version 2.0. Contaminated Sites Division, Safe Environments Directorate, Health Canada, Ottawa.

HC, 2024. Federal Contaminated Site Risk Assessment in Canada: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 4.0. Contaminated Sites Division, Safe Environments Directorate, Ottawa.

APPENDIX D RECOMMENDED GENERAL EXPOSURE EQUATIONS FOR ENTIRE DURATION OF INTERMITTENT EXPOSURE SCENARIOS

Equations are provided in this appendix for scenarios where there is no exposure during non-exposure intervals (e.g., when people are not at a contaminated site and not consuming foods from a site). It should be noted that many substances are also present in background exposures, which are not associated with a contaminated site, and this issue needs to be addressed in each HHRA on a chemical-specific basis.

D.1 When Chemicals Persist in the Body during Non-Exposure Intervals

When chemicals (or active metabolites) persist in the body during non-exposure intervals ("off" periods), the exposure episodes overlap with each other, and the intermittent exposures become effectively continuous. In addition, the internal exposure level will continue to increase over the entire exposure scenario. For these types of substances, dose averaging is not appropriate. Instead, receptors are assumed to be exposed throughout the entire duration of the intermittent exposure scenario at the same rate as individual exposure episodes. The same equations presented in **Appendix C** can be used for estimating exposures experienced for these chemicals during these exposure episodes ("on" periods).

D.2 When Chemicals are Cleared during Non-Exposure Intervals but Effects Persist

This appendix presents general exposure equations that can be used for commonly evaluated exposure pathways associated with the entire duration of an intermittent exposure scenario when effects persist even though the chemical(s) (and active metabolite[s]) are cleared during the "off" periods. A different set of equations apply depending on the primary determinant of toxicity for the critical health effect of the chemical related to the duration of exposure (see **Section 3.3.3** of the main document for discussion). These equations address assessment of chemicals that originate from soils at FCSAP sites, and equations for estimating exposure to contaminated sediments in HC (2017a) may be adjusted to address intermittent exposures in a similar fashion.

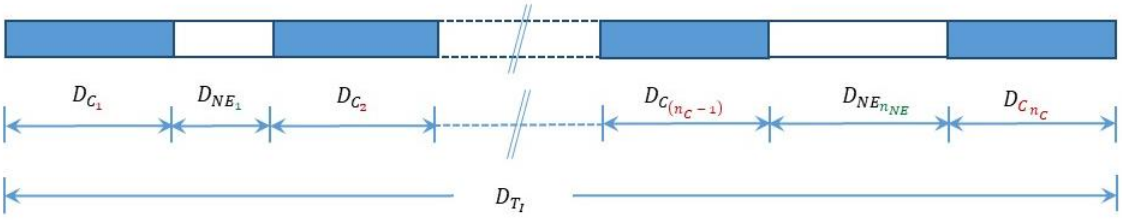
Some receptor characteristics that can be used for chronic exposure in HHRAs, such as body weights, drinking water intake rates, soil ingestion rates, are presented in HC (2024). The exposure point concentration of each chemical in each environmental medium (air, water, soil, vegetation, etc.) is determined on a site-specific basis, and the statistics used are based on the available data (refer to HC, 2010; 2024). The appropriate statistics for exposure factor parameters (e.g., intake rate) may depend on the conditions present at the site, the on-site behaviour of the receptors and what primarily drives toxicity of each substance (i.e., concentration/peak exposure or total dose/body burden). The risk assessment should determine the appropriate statistics for each input parameter after a careful analysis of the above factors. Rationale and supporting evidence for exposure point concentrations and receptor characteristics should be provided in the HHRA report.

Readers can refer to Appendix C for a brief discussion on bioavailability. For detailed guidance on in vitro bioaccessibility tests that can be used to derive oral relative bioavailability factor (RAF or RBA) estimates for use in HHRAs, refer to HC (2017b).

At FCSAP sites, intermittent exposure scenarios vary depending on site use and should be clearly defined in the report with rationale. Some scenarios consist only of continuous exposure episodes, some only of near-continuous exposure episodes, and some have both types of exposure. Some intermittent exposure scenarios consist of exposure episodes of equal duration, separated by non-exposure intervals of equal duration. Other scenarios may include exposure episodes and non-exposure intervals of varying duration.

Figure D.1 depicts an intermittent exposure scenario with exposure episodes consisting of consecutive daily exposure (described as continuous exposure episodes). **Figure D.2** presents an intermittent exposure scenario with near-continuous exposure episodes. **Figure D.3** represents a generic intermittent exposure scenario that can consist of both continuous and near-continuous exposure episodes of any duration.

Figure D.1 Intermittent exposure scenario with continuous exposure episodes



Where:

= Continuous exposure episode, denoted C

= Non-exposure interval, denoted NE

D_{C_i} = Duration of continuous exposure episode i in days, where i varies between 1 and n_C (the total number of continuous exposure episodes)

D_{NE_j} = Duration of non-exposure interval j in days, where j varies between 1 and n_{NE} (the total number of non-exposure intervals)

D_{T_I} = Duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when final exposure episode ends

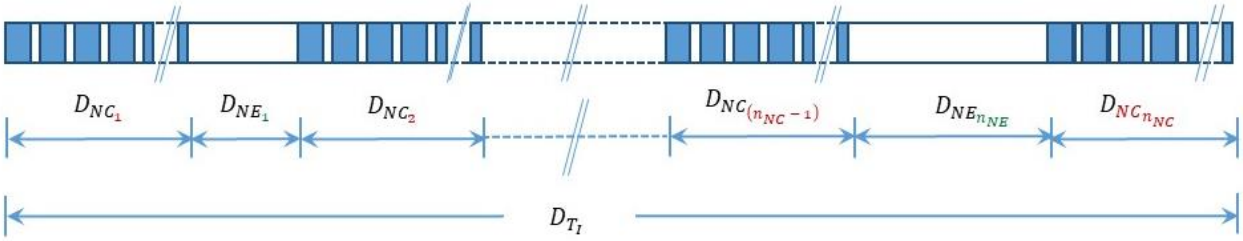
$$= \sum_{i=1}^{n_C} D_{C_i} + \sum_{j=1}^{n_{NE}} D_{NE_j}$$

AET_{iC} = Aggregate exposure time in days for an intermittent exposure scenario with several continuous exposure episodes

= Total number of days exposed for an intermittent exposure scenario with several continuous exposure episodes

$$= \sum_{i=1}^{n_C} D_{C_i}$$

Figure D.2 Intermittent exposure scenario with near-continuous exposure episodes



Where:

= Near-continuous exposure episode, denoted NC

= Non-exposure interval, denoted NE

D_{NC_i} = Duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC} (the total number of near-continuous exposure episodes)

D_{NE_j} = Duration of non-exposure interval j in days, where j varies between 1 and n_{NE} (the total number of non-exposure intervals)

D_{T_I} = Duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when final exposure episode ends

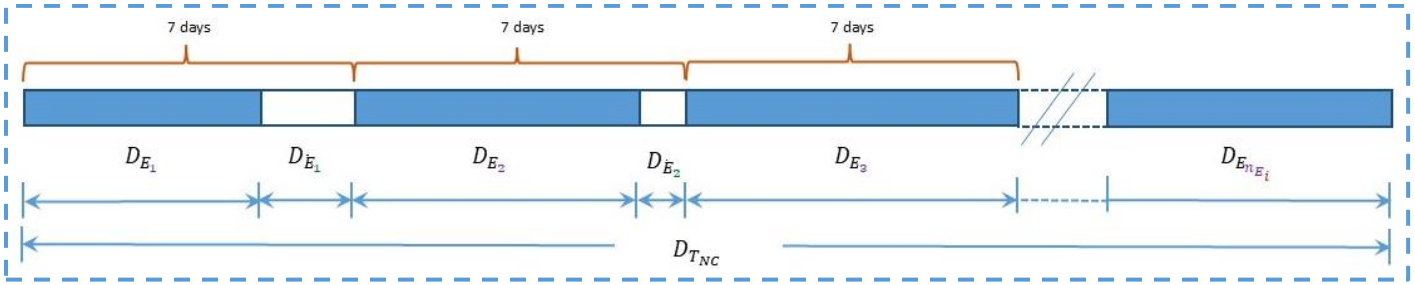
$$= \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j}$$

AET_{iNC} = Aggregate exposure time in days for an intermittent exposure scenario with several near-continuous exposure episodes

= Total number of days exposed for an intermittent exposure scenario with several near-continuous exposure episodes

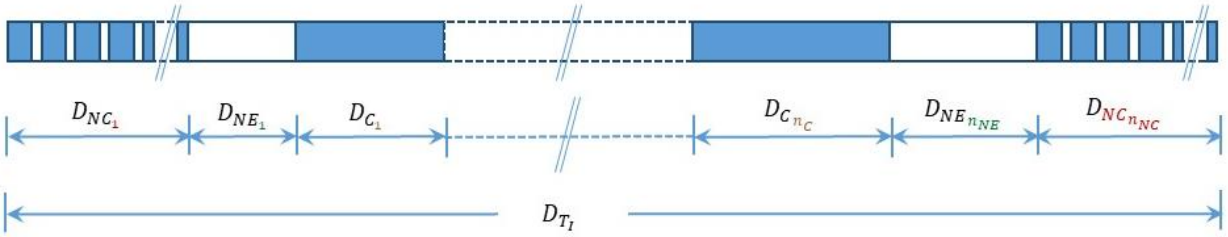
$$= \sum_{i=1}^{n_{NC}} D_{NC_i}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} D_{E_{i,u}} \right)$$



= refer to **Text Box 2.4** (**Section 2.5.3**) for more details on near-continuous exposure episode

Figure D.3 Intermittent exposure scenario with both continuous and near-continuous exposure episodes



Where:

= Near-continuous exposure episode, denoted NC

= Continuous exposure episode, denoted C

= Non-exposure interval, denoted NE

D_{NC_i} = Duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC} (the total number of near-continuous exposure episodes)

D_{NE_j} = Duration of non-exposure interval j in days, where j varies between 1 and n_{NE} (the total number of non-exposure intervals)

D_{C_k} = Duration of continuous exposure episode k in days, where k varies between 1 and n_C (the total number of continuous exposure episodes)

D_{T_I} = Duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when final exposure episode ends

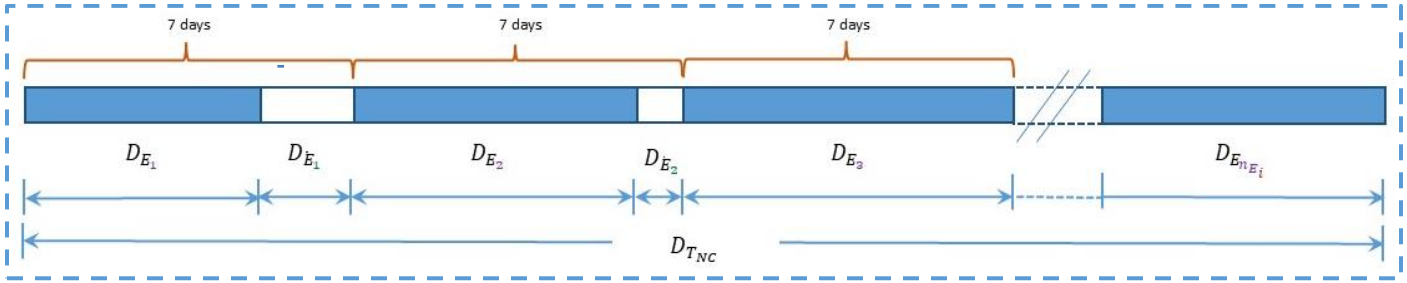
$$= \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

AET_{iMixed} = Aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous episodes

= Total number of days exposed for an intermittent exposure scenario with several near-continuous and continuous episodes

$$= \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} D_{E_{i,u}} \right) + \sum_{k=1}^{n_C} D_{C_k}$$



= refer to **Text box 2.4 (Section 2.5.3)** for more details on near-continuous exposure episode

The general equations provided below apply to the generic intermittent exposure scenario (represented by **Figure D.3**) and can be adjusted accordingly to the specific intermittent exposure scenario of interest, as needed. They are intended for estimation of exposure for the entire exposure scenario when effects persist even though the chemical(s) (and active metabolite[s]) are cleared entirely from the body during the non-exposure (i.e., "off") periods.

D.2.1 Inadvertent Ingestion of Contaminated Soil

The predicted intake of the COPC via ingestion of contaminated soil in an intermittent exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose experienced during the exposure scenario will be used for risk characterization.

$$Dose = \frac{C_S * IR_S * RAF_{oral}}{BW}$$

Where $Dose$ = highest daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
IR_S = soil ingestion rate (kg/day)
RAF_{oral} = relative absorption factor from the GI tract (unitless)
BW = body weight (kg)

Notes: D.2-a (See **Section D.2.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario (see **Section 3.3.3.2** for explanation) may be used for risk characterization.

$$ADD = \frac{C_S * IR_S * RAF_{oral} * AET_{iMixed}}{BW * D_{T_I}}$$

$$D_{T_I} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

$$AET_{iMixed} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} D_{E_{i,u}} \right) + \sum_{k=1}^{n_C} D_{C_k}$$

Where ADD = average daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
IR_S = soil ingestion rate (kg/day)

RAF_{oral} = relative absorption factor from the GI tract (unitless)
AET_{iMixed} = aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous episodes
BW = body weight (kg)
D_{T_I} = duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when the final exposure episode ends
n_{NC} = total number of near-continuous exposure episodes
D_{NC_i} = duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC}
n_{NE} = total number of non-exposure intervals
D_{NE_j} = duration of non-exposure interval j in days, where j varies between 1 and n_{NE}
n_C = total number of continuous exposure episodes
D_{C_k} = duration of continuous exposure episode k, where k varies between 1 and n_C
n_{E_i} = total number of exposure periods within the near-continuous exposure episode i
$D_{E_{i,u}}$ = duration of exposure period u within the near-continuous exposure episode i in days (must be 5 or 6, as discussed in **Section C.2.1**, **[ii]**), where u varies between 1 and n_{E_i}

Notes: D.2-b, D.2-c (See **Section D.2.7**).

D.2.2 Inhalation of Volatile Substances or Suspended Particulate Matter – with TRVs Expressed as Tolerable Concentration (TC)

TRVs expressed as TCs in µg/m^3 or mg/m^3, when available, should be used for characterizing risk from inhalation of volatile substances or suspended particulate matter. The exposure for an intermittent exposure scenario can be estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest air concentration during the exposure scenario will be used for risk characterization.

$$DC_A = C_A * RAF_{inh}$$

Where DC_A = highest estimated daily air concentration at the site (µg/m^3)
C_A = maximum concentration of contaminant in air (µg/m^3)
RAF_{inh} = relative absorption factor for inhalation, default value of 1 (unitless)

Notes: D.2-d, D.2-f (See **Section D.2.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily air concentration of the exposure scenario may be used for risk

characterization. It is imperative that the air concentration during any part of the exposure does not exceed the acute TRV.

$$TDC_A = \frac{C_A * RAF_{inh} * AET_{iMixed}}{D_{T_I}}$$

$$D_{T_I} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

$$AET_{iMixed} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} \frac{H_{i,u}}{H_D} * D_{E_{i,u}} \right) + \sum_{k=1}^{n_C} D_{C_k}$$

Where TDC_A = time-weighted average daily air concentration of contaminant (µg/m^3)

C_A = concentration of contaminant in air (µg/m^3)

RAF_{inh} = relative absorption factor for inhalation, default value of 1 (unitless)

AET_{iMixed} = aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous exposure episodes

D_{T_I} = duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when final exposure episode ends

n_{NC} = total number of near-continuous exposure episodes

D_{NC_i} = duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC}

n_{NE} = total number of non-exposure intervals

D_{NE_j} = duration of non-exposure interval j in days, where j varies between 1 and n_{NE}

n_C = total number of continuous exposure episodes

D_{C_k} = duration of continuous exposure episode k, where k varies between 1 and n_C

$H_{i,u}$ = hours exposed in a day during the exposure period u within the near-continuous exposure episode i, where u varies between 1 and n_{E_i}

H_D = 24 hours

n_{E_i} = total number of exposure periods within the near-continuous exposure episode i

$D_{E_{i,u}}$ = duration of exposure period u within the near-continuous exposure episode i in days (must be 5, 6 or 7, as discussed in **Section C.2.2, [ii]**), where u varies between 1 and n_{E_i}

Notes: D.2-b, D.2-e, D.2-f (See **Section D.2.7**).

D.2.3 Inhalation of Suspended Particulate Matter from Contaminated Soils – with TRVs Expressed as Oral Tolerable Daily Intake (TDI)

When an inhalation TRV expressed in mg/m^3 (or µg/m^3) is not available and the oral TRV (expressed in mg/kg bw/day) is appropriate for use (i.e., toxicological effects are expected to be similar for oral and inhalation exposure routes), the intake of COPCs via inhalation of particulate matter in air in an intermittent exposure scenario can be estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose during the exposure scenario will be used for risk characterization.

$$Dose = \frac{C_S * P_{air} * IR_A * RAF_{inh}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
P_{air} = particulate concentration in air (kg/m^3)
IR_A = air intake (inhalation) rate (m^3/day)
RAF_{inh} = relative absorption factor by inhalation, default value of 1 (unitless)
BW = body weight (kg)

Notes: D.2-a, D.2-f, D.2-g (See **Section D.2.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization. It is imperative that the acute TRV is not exceeded during any part of the exposure.

$$ADD = \frac{C_S * P_{air} * IR_A * RAF_{inh} * AET_{iMixed}}{BW * D_{T_I}}$$

$$D_{T_I} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

$$AET_{iMixed} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} \frac{H_{i,u}}{H_D} * D_{E_{i,u}} \right) + \sum_{k=1}^{n_C} D_{C_k}$$

Where ADD = average daily dose (mg/kg bw/day)

C_S = concentration of contaminant in soil (mg/kg)

P_{air} = particulate concentration in air (kg/m^3)

IR_A = air intake (inhalation) rate (m^3/day)

RAF_{inh} = relative absorption factor by inhalation (unitless)

AET_{iMixed} = aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous exposure episodes

BW = body weight (kg)

D_{T_I} = duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when final exposure episode ends

n_{NC} = total number of near-continuous exposure episodes

D_{NC_i} = duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC}

n_{NE} = total number of non-exposure intervals

D_{NE_j} = duration of non-exposure interval j in days, where j varies between 1 and n_{NE}

n_C = total number of continuous exposure episodes

D_{C_k} = duration of continuous exposure episode k, where k varies between 1 and n_C

$H_{i,u}$ = hours exposed in a day during the exposure period u within the near-continuous exposure episode i, where u varies between 1 and n_{E_i}

H_D = 24 hours

n_{E_i} = total number of exposure periods within the near-continuous exposure episode i

$D_{E_{i,u}}$ = duration of exposure period u within the near-continuous exposure episode i in days (must be 5, 6 or 7, as discussed in **Section C.2.3**, **[ii]**), where u varies between 1 and n_{E_i}

Notes: D.2-b, D.2-c, D.2-f, D.2-g (See **Section D.2.7**).

D.2.4 Ingestion of Contaminated Drinking Water

For all contaminated sites, it is recommended that the water used for ingestion meet Canadian Drinking Water Guidelines. Where calculations are conducted to evaluate exposure from all media, the following equations can be used. These equations are not appropriate for derivation of a SSTL for potable water.

The predicted intake of the COPC via ingestion of contaminated water in an intermittent exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose during the exposure scenario will be used for risk characterization.

$$Dose = \frac{C_W * IR_W * RAF_{oral}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
C_W = maximum concentration of contaminant in drinking water (mg/L)
IR_W = water intake rate (L/day)
RAF_{oral} = relative absorption factor from the GI tract (unitless)
BW = body weight (kg)

Notes: D.2-h, D.2-i (See **Section D.2.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario may be used for risk characterization.

$$ADD = \frac{C_W * IR_W * RAF_{oral} * AET_{iMixed}}{BW * D_{T_I}}$$

$$D_{T_I} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

$$AET_{iMixed} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} D_{E_{i,u}} \right) + \sum_{k=1}^{n_C} D_{C_k}$$

Where ADD = average daily dose (mg/kg bw/day)
C_W = concentration of contaminant in drinking water (mg/L)
IR_W = water intake rate (L/day)
RAF_{oral} = relative absorption factor from the GI tract (unitless)
AET_{iMixed} = aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous exposure episodes
BW = body weight (kg)
D_{T_I} = duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when the final exposure episode ends

n_{NC} = total number of near-continuous exposure episodes

D_{NC_i} = duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC}

n_{NE} = total number of non-exposure intervals

D_{NE_j} = duration of non-exposure interval j in days, where j varies between 1 and n_{NE}

n_C = total number of continuous exposure episodes

D_{C_k} = duration of continuous exposure episode k, where k varies between 1 and n_C

n_{E_i} = total number of exposure periods within the near-continuous exposure episode i

$D_{E_{i,u}}$ = duration of exposure period u within the near-continuous exposure episode i in days (must be 5 or 6, as discussed in **Section C.2.4**, **[ii]**), where u varies between 1 and n_{E_i}

Notes: D.2-b, D.2-c, D.2-h, D.2-i, D.2-j (See **Section D.2.7**).

D.2.5 Dermal Absorption from Contaminated Soil

The predicted intake of COPCs via dermal contact with contaminated soil in an intermittent exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose during the exposure scenario is used for risk characterization.

$$Dose = \frac{\{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_V * RAF_{dermal}\}}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)

C_S = concentration of contaminant in soil (mg/kg)

SA_H = surface area of hands exposed for soil loading (cm^2)

SL_H = soil loading rate to exposed skin of hands (kg/cm^2-event)

SA_O = surface area exposed other than hands (cm^2)

SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)

nE_V = number of dermal exposure events/day (default assumption is 1 event/day)

RAF_{dermal} = relative dermal absorption factor (unitless)

BW = body weight (kg)

Notes: D.2-a (See **Section D.2.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose (or average daily dose) of the exposure scenario will be used for risk characterization.

$$ADD = \frac{\{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_V * RAF_{dermal} * AET_{iMixed}\}}{BW * D_{T_I}}$$

$$D_{T_I} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

$$AET_{iMixed} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}$$

$$= \sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} D_{E_{i,u}} \right) + \sum_{k=1}^{n_C} D_{C_k}$$

Where ADD = average daily dose (mg/kg bw/day)

C_S = concentration of contaminant in soil (mg/kg)

SA_H = surface area of hands exposed for soil loading (cm^2)

SL_H = soil loading rate to exposed skin of hands (kg/cm^2-event)

SA_O = surface area exposed other than hands (cm^2)

SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)

nE_V = number of dermal exposure events/day (assumed to be 1 event/day)

RAF_{dermal} = relative dermal absorption factor (unitless)

AET_{iMixed} = aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous exposure episodes

BW = body weight (kg)

D_{T_I} = duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when the final exposure episode ends

n_{NC} = total number of near-continuous exposure episodes

D_{NC_i} = duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC}

n_{NE} = total number of non-exposure intervals

D_{NE_j} = duration of non-exposure interval j in days, where j varies between 1 and n_{NE}

n_C = total number of continuous exposure episodes

D_{C_k} = duration of continuous exposure episode k, where k varies between 1 and n_C

n_{E_i} = total number of exposure periods within the near-continuous exposure episode i

$D_{E_{i,u}}$ = duration of exposure period u within the near-continuous exposure episode i in days (must be 5 or 6, as discussed in **Section C.2.5**, **[ii]**), where u varies between 1 and n_{E_i}

Notes: D.2-b, D.2-c (See **Section D.2.7**).

D.2.6 Ingestion of Contaminated Foods (Produce, Fish, Game, etc.)

The predicted intake of COPCs via ingestion of contaminated food in an intermittent exposure scenario is estimated as follows.

i) If toxicity is driven by concentration (or peak exposure), the highest daily dose during the exposure scenario will be used for risk characterization.

$$Dose = \sum_{f=1}^{n_{food}} \frac{C_f * IR_f * RAF_f}{BW}$$

Where *Dose* = highest daily dose (mg/kg bw/day)
n_{food} = number of foods included in the analysis
C_f = concentration of contaminant in food f (mg/kg)
IR_f = ingestion rate for food f (kg/day)
RAF_f = relative absorption factor from the GI tract for contaminant in food f (unitless)
BW = body weight (kg)

Notes: D.2-a (See **Section D.2.7**).

ii) If toxicity is driven by total time-integrated dose (or body burden), the time-weighted average daily dose of the exposure scenario may be used for risk characterization.

$$ADD = \sum_{f=1}^{n_{food}} \frac{C_f * IR_f * RAF_f * AET_{iMixed_f}}{BW * D_{T_I}}$$

$$D_{T_I} = \sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{j=1}^{n_{NE}} D_{NE_j} + \sum_{k=1}^{n_C} D_{C_k}$$

$$AET_{iMixed_f} = \left[\sum_{i=1}^{n_{NC}} D_{NC_i} + \sum_{k=1}^{n_C} D_{C_k}\right]_f$$

$$= \left[\sum_{i=1}^{n_{NC}} \left(\sum_{u=1}^{n_{E_i}} D_{E_{i,u}}\right) + \sum_{k=1}^{n_C} D_{C_k}\right]_f$$

Where ADD = average daily dose (mg/kg bw/day)

n_{food} = total number of foods included in the analysis

C_f = concentration of contaminant in food f (mg/kg)

IR_f = ingestion rate for food f (kg/day)

RAF_f = relative absorption factor from the GI tract for contaminant in food f (unitless)

AET_{iMixed_f} = aggregate exposure time in days for an intermittent exposure scenario with several near-continuous and continuous exposure episodes for food f

BW = body weight (kg)

D_{T_I} = duration of the entire intermittent exposure scenario in days, spanning from initial exposure to the moment when the final exposure episode ends

n_{NC} = total number of near-continuous exposure episodes

D_{NC_i} = duration of near-continuous exposure episode i in days, where i varies between 1 and n_{NC}

n_{NE} = total number of non-exposure intervals

D_{NE_j} = duration of non-exposure interval j in days, where j varies between 1 and n_{NE}

n_C = total number of continuous exposure episodes

D_{C_k} = duration of continuous exposure episode k, where k varies between 1 and n_C

n_{E_i} = total number of exposure periods within a near-continuous exposure episode

$D_{E_{i,u}}$ = duration of exposure period u within the near-continuous exposure episode i in days (must be 5 or 6, as discussed in **Section C.2.6**, **[ii]**), where u varies between 1 and n_{E_i}

Notes: D.2-b, D.2-k. D.2-l (See **Section D.2.7**).

D.2.7 Notes for Equations in Section D.2

Note	Description
D.2-a	Depending on the available data, a statistic that represents reasonable maximum exposure (HC, 2024) may be used as the input concentration. Please consult HC's (2024) PQRA guidance document for examples of appropriate statistics that are representative of reasonable maximum exposures at a federal contaminated site. However, if the available data are not adequate to support statistical derivation of an exposure point concentration, the maximum concentration is used when assessing peak exposures.
D.2-b	Dose averaging should be based on the site-specific exposure pattern and evaluated on a chemical-specific basis and may not be applicable for substances with teratogenic or reproductive endpoint in the study used to derive the TRV.
D.2-c	When dose averaging can be supported, a measure of central tendency of the available concentration data may be used as the input concentration if data from the environmental site investigation are adequate to support the statistical derivation of an exposure point concentration. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. However, if data are inadequate, the maximum concentration is used. Refer to the equation in (i) when dose averaging cannot be supported.

Note	Description
D.2-d	For most chemicals, air concentrations are reported as 24-hour average concentrations, and TRVs are expressed as daily air concentrations. However, for some chemicals, the averaging time of reported air concentration may not match the available TRV. DC_A would be the highest air concentration based on the available data for an exposure period that matches (or is shorter than) the averaging time for which the available TRV has been derived.
D.2-e	When dose averaging can be supported, a measure of central tendency of the available air concentration data may be used as the input air concentration if data from the environmental site investigation are adequate to support statistical derivation of an exposure point concentration. TDC_A would be calculated based on the available data for the time period measurements were made and compared to a TRV derived for the same or longer exposure duration. Please consult HC's (2024) PQRA guidance document for examples of appropriate statistics that are representative of a measure of central tendency at a federal contaminated site. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. For example, if 8-hr air samples have been collected at the site, TDC_A would be calculated based on a measure of central tendency of the available 8-hr measurements and compared to an 8-hour TRV or a 24-hour TRV. However, if data are inadequate, the maximum air concentration is used. Refer to the equation in (i) when dose averaging cannot be supported. This guidance is applicable to both indoor and outdoor air. Any dose averaging needs to be supported by chemical-specific toxicological data.
D.2-f	In the case of airborne particulate matter associated with contaminated soils, refer to HC (2017c) supplemental guidance on air quality and the DQRA (HC, 2010) documents for guidance.
D.2-g	P_{air} (particulate concentration in air [kg/m^3]) may be directly measured or may be estimated using the methods described in the HC (2024) PQRA guidance. Alternatively, C_A (i.e., airborne concentration of contaminant [mg/m^3]) may be directly measured and the measured value would replace the terms C_s and P_{air} in the equation.
D.2-h	The calculation of a site-specific drinking water guideline is not conducted for substances with existing Canadian Drinking Water Guidelines or HC interim drinking water screening values. The predicted intake of COPCs via contaminated drinking water should be included in the total exposure estimate that includes all exposure pathways.
D.2-i	Select drinking water screening values are available on request in cases where no Canadian Drinking Water Guidelines exist for a specific substance. Please contact HC for additional information.
D.2-j	When groundwater is affected, a measure of central tendency based on concentrations from multiple wells cannot be used to provide exposure estimates if people may be exposed only to concentrations from one area and not another. For example, each residence would use water from its groundwater well, not an average of all wells in the area. Use of a measure of central tendency from multiple wells in the neighbourhood could underestimate exposure for the most exposed individuals.
D.2.k	Food f is assumed to be consumed during the entire exposure scenario. Note that the exposure scenario relates to the duration when foods collected from the site are consumed and this duration may exceed the actual time spent at a contaminated site.
D.2.l	When dose averaging can be supported, a measure of central tendency of the available food concentration data may be used as the input concentration if data from the environmental site investigation are adequate to support the statistical derivation of an exposure point concentration. The central tendency estimate used should be justified based on data distribution, which needs to be presented and discussed in the HHRA report. However, if data are inadequate, the maximum chemical concentration of each food is used. Refer to the equation in (i) when dose averaging cannot be supported.

D.3 References

Health Canada (HC), 2010. Federal Contaminated Site Risk Assessment in Canada, Part V: Guidance on Human Health Detailed Quantitative Risk Assessment for Chemicals ($DQRA_{CHEM}$). Contaminated Sites Division, Safe Environments Directorate, Ottawa.

HC, 2017a. Federal Contaminated Site Risk Assessment in Canada: Supplemental Guidance on Human Health Risk Assessment of Contaminated Sediments: Direct Contact Pathway. Contaminated Sites Division, Safe Environments Directorate, Ottawa.

HC, 2017b. Federal Contaminated Site Risk Assessment in Canada: Supplemental Guidance on Human Health Risk Assessment for Oral Bioavailability of Substances in Soil and Soil-like Media. Contaminated Sites Division, Safe Environments Directorate, Ottawa.

HC, 2017c. Federal Contaminated Site Risk Assessment in Canada: Supplemental Guidance on Human Health Risk Assessment of Air Quality, Version 2.0. Contaminated Sites Division, Safe Environments Directorate, Health Canada, Ottawa.

HC, 2024. Federal Contaminated Site Risk Assessment in Canada: Guidance on Human Health Preliminary Quantitative Risk Assessment (PQRA), Version 4.0. Contaminated Sites Division, Safe Environments Directorate, Ottawa.

APPENDIX E CASE EXAMPLES OF SHORT-DURATION AND INTERMITTENT EXPOSURE ANALYSIS

E.1 Worked Example #1: Dioxins and Furans, Short-Duration Continuous Exposure

This section provides a worked example of a Tier I-a assessment of a one-time short-duration continuous exposure to polychlorinated dibenzo-p-dioxins (dioxins) and polychlorinated dibenzofurans (furans), collectively referred to as "PCDD/Fs". This is a simplified example in a hypothetical risk assessment. The analysis presented is specific to the exposure scenario described below, including land use, site conditions, exposure duration, receptors, site-specific behaviour and activity patterns.

This worked example may not apply to a particular site-specific risk assessment, as site-specific differences in the hypothetical scenario and changes in any one of the exposure parameters would warrant a separate analysis using appropriate TRVs relevant to the exposure durations of interest. Exposure scenarios analysed should be relevant to each site and justified based on site-specific information. The risk assessment report should include scientific rationale, with references, to support TRVs selected for both chronic and less-than-chronic exposure scenarios.

Note that on occasion, HC becomes aware of new critical toxicological or other data that dictate a need to revise HC (2021 or most recent version) TRV for a given substance to ensure the protection of the health of Canadians. In such a case, the revision of the TRV could subsequently require a change in the approach to the risk assessment of short-duration and intermittent exposures to be consistent with the TRV.

E.1.1 PCDD/F Problem Formulation Summary

The worked example provided below involves a continuous exposure scenario at a hypothetical camping site in a remote park with elevated concentrations of PCDD/Fs in soil (95% UCLM of 0.0006 mg/kg).

The scenario is subject to the following parameters:

- The site may be used by visitors, including people who are pregnant or may become pregnant, and toddlers. Given the remote nature of this hypothetical site, the visit is for recreational use up to a maximum duration of 3 days within a month. Exposure may be continuous over the time they are at the site (i.e., daily for 3 consecutive days).
- Contact with PCDD/Fs may occur via incidental ingestion of soil, dermal contact with soil and inhalation of fugitive dust. The HHRA should consider all these potential routes for calculation of the total dose. Since PCDD/Fs are not volatile substances, inhalation of vapours is not considered in the calculation. If foods or drinking water from the site are consumed, then these exposure pathways could also be operable. However, for this worked example, both drinking water and local food consumption pathways were deemed inoperable.

E.1.2 PCDD/F Assessment Considering Soil Ingestion Exposure Pathway Only

The quantitative exposure assessment in an HHRA takes into account all operable exposure pathways for each receptor. However, for the sake of simplicity, this hypothetical example calculates only *ingestion* of soil exposure for a toddler. Please refer to **Appendix C** and HC (2024) guidance for equations to assess exposure pathways. Note that PCDD/Fs are known to be present at background levels in market foods and other environmental media, which should be included in a risk assessment if a target HQ of 1 is used.

E.1.2.1 Tier 0 Assessment

Even though the exposure is of short duration, a Tier 0 assessment should be conducted, as discussed in the main document. The exposure during the most sensitive and exposed lifestage is calculated and compared to the chronic TRV. This calculation estimates the expected highest daily exposure that a person would receive for each day of exposure while on site, which is identical to the daily exposure in a calculation for a chronic exposure period. No dose averaging is applied in a Tier 0 assessment. If the assessment identifies a HQ below or equal to 0.2 for all operable exposure pathways, then no further action is required. Only COPCs with an HQ > 0.2 for an operable pathway (for the most sensitive and exposed lifestage) in a Tier 0 assessment would be assessed in a higher tier.

E.1.2.1.1 Exposure Assessment for Tier 0 Assessment

The equation below calculates the estimated daily exposure from incidental soil ingestion that people may receive from the site. A toddler is typically the most sensitive receptor based on the soil ingestion rate, as compared with an adult receptor. In a chronic risk assessment, the chronic TRV for PCDD/Fs is expressed as a TDI, based on developmental toxicity, to which a pregnant person can be exposed without appreciable health risk to the developing fetus (HC, 2021). This TRV is also protective of other lifestages.

For a toddler receptor exposure to PCDD/Fs, the Tier 0 assessment would assume chronic daily exposure as per the following (see **Section 3.1** of the main document for general equation):

$$Dose = \frac{C_S * IR_S * RAF_{oral} * D_2 * D_3}{BW}$$

$$= \frac{0.0006\,mg/kg * 0.00008\,kg/day * 1.0 * \left(\frac{7\ days}{7\ days}\right) * \left(\frac{52\ weeks}{52\ weeks}\right)}{16.5\,kg}$$

$$= 2.9 * 10^{-9} mg/kg\ bw/day$$

$$= 2.9\ pg/kg\ bw/day$$

Where $Dose$ = daily dose (mg/kg bw/day); C_S = concentration of contaminant in soil (mg/kg); IR_S = receptor soil ingestion rate (kg/day); RAF_{oral} = relative absorption factor from the GI tract, assumed to be 100% or 1 (unitless); D_2 = days per week exposed/7 days; D_3 = weeks per year exposed/52 weeks; BW = body weight (kg)

E.1.2.1.2 Applicable TRV for Tier 0 Assessment

The Tier 0 assessment applies the chronic provisional tolerable daily intake (pTDI) of 2.3 pg/kg bw/day (HC, 2021) to assess potential risks from chronic PCDD/Fs exposure. This pTDI is based on reproductive effects observed in the male offspring of exposed pregnant female rats. This long-lasting effect results from short-duration exposure during a specific window of susceptibility. The pTDI was derived from the provisional tolerable monthly intake (PTMI) of 70 pg/kg bw/month developed by WHO/JECFA (2002). The PTMI is the midpoint of PTMIs estimated from two developmental studies (Faqi et al., 1998 and Ohsako et al., 2001) in which female rats were exposed to TCDD. Faqi et al. (1998) exposed female rats subcutaneously on a weekly basis, beginning 2 weeks prior to mating and throughout mating, gestation and lactation. Ohsako et al. (2001) dosed pregnant female rats by gavage on gestation day 15. These two studies indicate maternal body burden (incremental to background) lowest observed effect levels (LOELs) and no observable effect levels (NOELs) for reproductive effects in the male offspring of 25 ng/kg bw and 13 ng/kg bw, respectively. These values were adjusted upwards to account for the estimated background body burden of 3 ng/kg bw in the animals, resulting in estimated total toxic equivalent body burden of 28 ng/kg bw for the LOEL and 16 ng/kg bw for the NOEL. The equivalent human monthly intakes (EHMIs) corresponding to these animal body burdens were estimated. To derive the PTMIs, UFs were applied: 9.6 (3.2 for intraspecies variability; 3 for use of LOEL) to the EHMIs based on the study of Faqi et al. (1998); and 3.2 (intraspecies variability) to the EHMIs based on the Ohsako, et al. (2001) study (See **Section E.1.4.1**).

The TRV is protective of the general public and can be applied to all age groups (including children, people who are pregnant and who may become pregnant). The additional epidemiological evidence of a causal relationship between infancy/prepuberty and semen quality reported by EFSA CONTAM (2018) further supports the application of the pTDI to toddlers. PCDD/Fs potencies are expressed as TCDD toxic equivalents (refer to HC, 2021, 2024).

E.1.2.1.3 Risk Characterization for Tier 0 Assessment

The HQ is calculated during the risk characterization step by dividing the exposure received from the site, referred to as the dose, by the TRV.

$$HQ = \frac{Dose}{TRV} = \frac{2.9\ pg/kg\ bw/day}{2.3\ pg/kg\ bw/day} = 1.3$$

As previously noted, this calculation is a simplified example illustrating the process of a Tier 0 assessment but is limited to a single exposure pathway. An HHRA should consider all operable exposure pathways, including but not limited to, soil ingestion, dermal contact with soil and inhalation of fugitive dust, as well as any other operable exposure pathways as relevant, with the total exposure from all operable exposure pathways compared to a target HQ of 0.2. Alternately, a target HQ of 1 may be used if background exposures (i.e., exposures to the same COPC from other sources such as food, water, consumer products, soil, air) from all sources plus exposure from all site-related pathways are included.

Since the Tier 0 assessment above resulted in an HQ > 0.2 for PCDD/Fs via soil ingestion alone under a chronic exposure scenario, this worked example will proceed to assess the short-duration exposure to PCDD/Fs in soil using a Tier I-a assessment.

E.1.2.2 Tier I-a: Assessment Based on Direct Application of TRV of Relevant Duration

Tier I-a assessment is conducted by using a published TRV that is applicable for the entire duration of a single exposure episode. For this hypothetical scenario, a published TRV is relevant for a 3-day exposure period, which is consistent with the exposure period at this site.

E.1.2.2.1 Applicable TRV for Short-Term Exposure in a Tier I-a Assessment

For PCDD/Fs, insignificant changes are often reflected on the estimated steady-state body burden with brief exposures above background due to the relatively long half-lives and long-term storage of PCDD/Fs in humans. For this reason, the WHO/JECFA (2002) PTMI for assessing potential risks to PCDD/Fs is considered appropriate for a monthly exposure. It is noted that the HC (2021) pTDI was generated by dividing the WHO/JECFA PTMI by 30 days (or one month) for use in equations for chronic exposure that include TDIs. However, a risk assessment may include use of the PTMI for exposures up to 30 days as long as the PTMI is not exceeded.

Since high exposures to PCDD/Fs may result in acute or chronic health effects, the PTMI can be used as the TRV to assess potential risk associated with the total intake received in 3 days over a month in a Tier I-a assessment. See **Section E.1.2.1.2** for the basis of the PTMI.

E.1.2.2.2 Primary Determinants of Toxic Effects

To determine whether dose averaging may be appropriate for a specific substance, the risk assessment should include a summary of the primary determinant of toxic effects for each chemical using information from key studies cited in the development of a TRV for a particular duration. The critical effects that form the basis for deriving the oral TRV for PCDD/Fs were developmental reproductive effects in male offspring resulting from *in-utero* exposure during a specific short window of susceptibility (See **Section E.1.4** for more details on health effects). Body burden is considered the most appropriate measure of dose for oral exposure to PCDD/Fs (WHO, 2000). The applicable short-term TRV for this exposure scenario is the WHO PTMI (WHO/JECFA, 2002). To evaluate the non-cancer health risk, the total monthly exposure from all operable exposure pathways at a site would be calculated and compared to the PTMI (WHO/JECFA, 2002) for exposures up to and including one month.

E.1.2.2.3 Tier I-a Exposure Assessment for PCDD/Fs

The Tier I-a assessment calculates the exposure that visitors may receive while at the site. For the purpose of this example, where people may be at a site for 3 consecutive days, the exposure assessment provides a calculation of the exposure that may be received during that 3-day period. The total exposure over a month is calculated for a short-term exposure in order to compare the exposure with the PTMI.

Table E.1.1 Duration of Exposure for a Seasonal Camper for a 3-day Continuous Exposure in a Month

Day	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30
Time on site	-	-	-	✓	-	-	-	-	-	-
Total Duration				3 days						

✓ = 3 days of exposure on site

For the purposes of this example, the estimated daily dose (D) for the days on site as a result of incidental soil ingestion is calculated for a toddler using the equation presented in **Section C.1.1** for a continuous exposure scenario. All operable exposure pathways would be assessed in a risk assessment. The exposure point concentration for PCDD/Fs in soil was identified from the Tier 0 assessment as 0.0006 mg/kg.

$$Dose = \frac{C_S * IR_S * RAF_{oral} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

$$= \frac{0.0006\, mg/kg * 0.00008\, kg/day * 1 * \frac{3\ days}{3\ days}}{16.5\ kg}$$

$$= 2.9 * 10^{-9}\, mg/kg\ bw/day$$

$$= 2.9\ pg/kg\ bw/day$$

Where $Dose$ = daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
IR_S = receptor soil ingestion rate (kg/day)
RAF_{oral} = relative absorption factor from the GI tract, assumed to be 100% or 1 (unitless)
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure
= 3 days
BW = body weight (kg)

In summary, the exposure (e.g., daily dose) to PCDD/Fs from soil ingestion for each day while at the site is 2.9 pg/kg bw/day. Since the problem formulation identified that visitors may access the site for a maximum of 3 consecutive days, the total monthly exposure at this site is calculated as 3 days multiplied by 2.9 pg/kg bw/day, for a total exposure of 8.7 pg/kg bw per month for direct exposure via soil ingestion alone. In an HHRA, the assessor would calculate exposure for all operable exposure pathways and add these together prior to the risk characterization phase. For the purposes of this worked example, an exposure of 8.7 pg/kg bw per month from soil ingestion would be used as the exposure to be compared with the PTMI.

E.1.2.2.4 Risk Characterization for Tier I-a for 3-Day Continuous Exposure

The HQ calculated in the risk characterization stage is the total exposure from all operable exposure pathways divided by the appropriate TRV. As previously noted, this worked example is limited to assessment of potential risks for a toddler exposed to PCDD/Fs via incidental soil ingestion while at the site for 3 consecutive days. The HQ for the soil ingestion pathway for a toddler, calculated as shown below (dose divided by the TRV), is lower than a target HQ of 0.2.

$$HQ = \frac{Dose\ (pg/kg\ bw/month)}{TRV\ (pg/kg\ bw/month)} = \frac{8.7\ pg/kg\ bw/month}{70\ pg/kg\ bw/month} = 0.12$$

In an HHRA for a contaminated site, the assessment would need to consider the HQ from all operable exposure pathways. For instance, in addition to exposure via soil ingestion, dermal contact with soil and inhalation of fugitive dust would also be relevant for direct contact with soils. Further, if there are other operable exposure pathways, such as consumption of foods from the site, these pathways would need to be included in the exposure calculation prior to comparison with the TRV and a target HQ of 0.2. In an HHRA where background exposures (i.e., exposures to the same COPC from other sources such as food, water, consumer products, soil, air) are included in the calculations, a target HQ of 1 may be used. If the HQ from all applicable exposure pathways does not exceed the target HQ, no higher tiered assessment would be required.

Figure E.1.1 Estimated exposure to PCDD/Fs from soil ingestion by a toddler for 3-day recreational use in a Tier I-a assessment

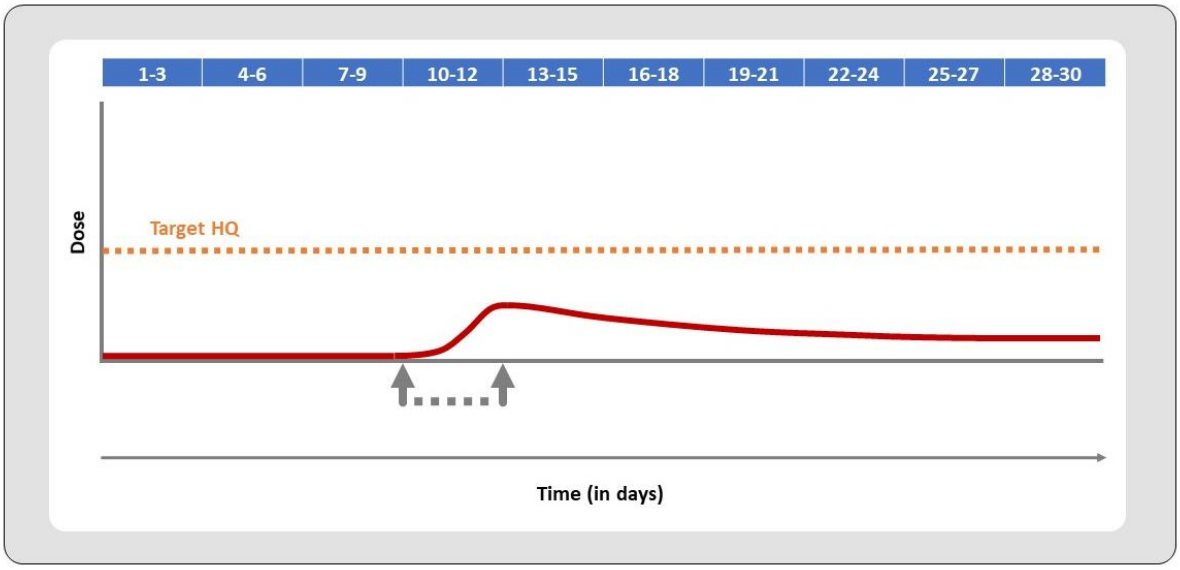
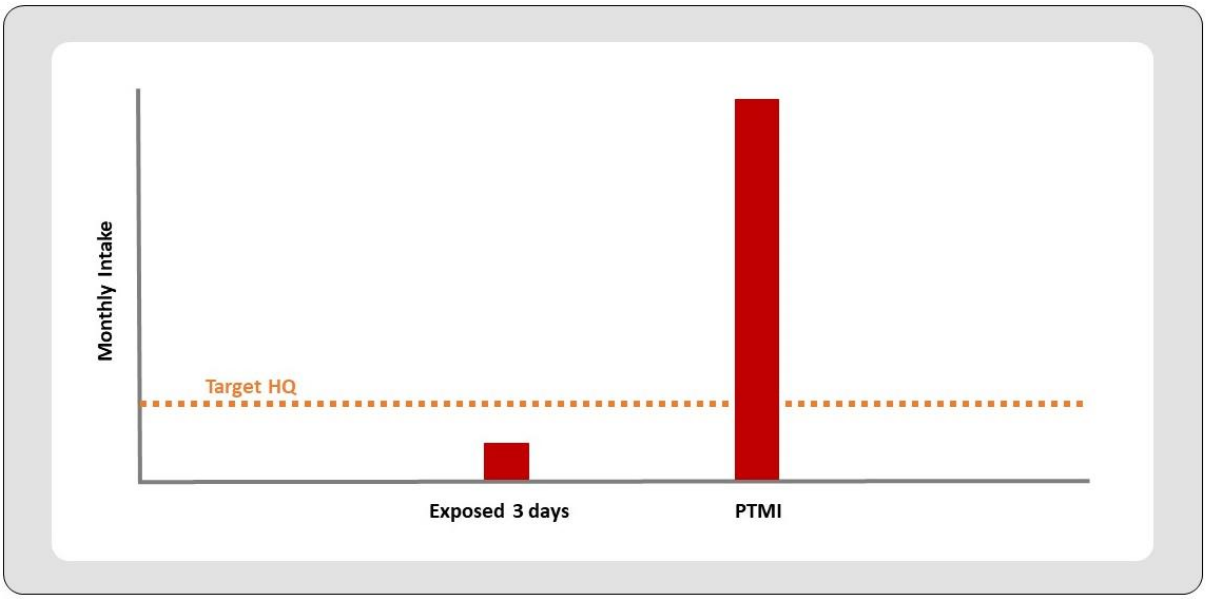


Figure E.1.2 Estimated monthly intake of PCDD/Fs from soil ingestion by a toddler for 3-day recreational use in a Tier I-a assessment as compared to PTMI



A complete HHRA needs to consider all operable exposure pathways, including dermal contact with soil, inhalation of fugitive dust, consumption of foods and other pathways if relevant. This worked example for soil ingestion alone was prepared for simplicity.

E.1.2.3 Mathematical Dose Averaging May Underestimate Potential Health Risks

The following example explains why applying dose averaging to the potential 3-day site exposure over a year could underestimate potential health risks. The chronic pTDI of 2.3 pg/kg bw/day was used as the TRV in calculating the HQ. The following use of the equation for soil ingestion is incorrect and should not be used.

$$Dose = \frac{C_s * IR_s * RAF_{oral} * D_2 * D_3}{BW}$$

$$= \frac{0.0006\,mg/kg * \ 0.00008\,kg/day * 1.0 * \frac{3\ days}{7\ days} * \frac{1\ week}{52\ weeks}}{16.5\,kg}$$

$$= 2.4 * 10^{-11}\,mg/kg\ bw/day$$

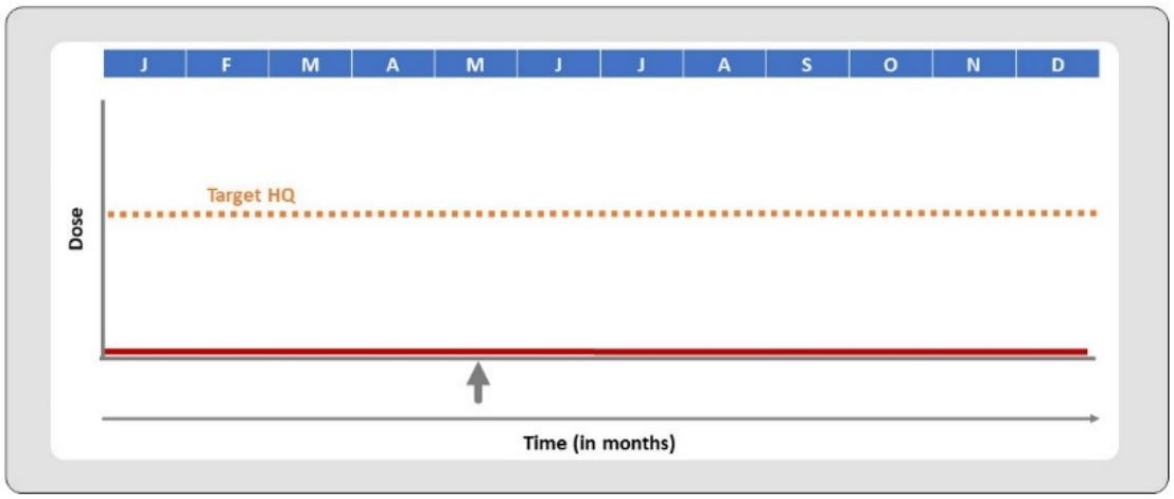
$$= 0.024\ pg/kg\ bw/day \text{ assuming 3 days averaged over 12 months}$$

Where	$Dose$	=	daily dose (mg/kg bw/day)	D_2	=	days per week exposed/7 days
	C_S	=	concentration of contaminant in soil (mg/kg)	D_3	=	weeks per year exposed/52 weeks
	IR_S	=	receptor soil ingestion rate (kg/day)	BW	=	body weight (kg)
	RAF_{oral}	=	relative absorption factor from the GI tract, assumed to be 100% or 1 (unitless)			

$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.024\ pg/kg\ bw/day}{2.3\ pg/kg\ bw/day} = 0.010$$

Although the above calculation appears to be mathematically correct, the equation would suggest that a visitor would receive a smaller level of exposure daily as compared with the actual daily exposure. This error could result in an inaccurate conclusion of "no risk".

Figure E.1.3 Estimated yearly exposure to PCDD/Fs from soil ingestion by a toddler for 3-day recreational use incorrectly applying dose averaging



E.1.2.4 Conclusion

Based on this worked example that is limited to exposure to elevated levels of PCDD/Fs in soil via soil ingestion, the target HQ was not exceeded in a Tier I-a assessment and no higher tiered assessment would be required in the HHRA. Note that in an actual HHRA, all operable exposure pathways need to be assessed. In conclusion, all exposure pathways, including but not limited to dermal contact with soil, inhalation of fugitive dust, and ingestion of foods impacted from the site, must also be considered and applied in the assessment, as applicable, in order to fully characterize potential health risks. Refer to **Section E.1.3** for an example of an assessment involving multiple exposure pathways.

The HHRA should provide chemical-specific toxicological rationale for each COPC, the toxicological summary should include information on both the chronic and less-than-chronic TRVs relevant to the exposure periods.

E.1.3 PCDD/F Assessment Considering All Exposure Pathways

As discussed in **Section E.1.1**, visitors at the site (including toddlers) can be exposed to PCDD/Fs in soils through incidental ingestion of soil, dermal contact with soil and inhalation of suspended soil

particulates. This section illustrates assessment of these exposure pathways and how health risk can be evaluated when background exposure from all pathways unrelated to the site is not considered. If foods or drinking water from the site were affected, then these exposure pathways could also be operable for PCDD/Fs. However, for the purposes of this worked example, only exposure to soil was shown in the dose calculations.

E.1.3.1 Tier 0 Assessment for All Exposure Pathways

The exposure during the most sensitive and exposed lifestage is calculated and compared to the chronic TRV in a Tier 0 assessment. This calculation provides an estimate of the highest daily exposure that a person would receive if the person remained on site each day for the whole time period, and is mathematically identical to the calculation for a chronic exposure period. This exposure is also the estimated daily exposure that a person would receive while on the site for a day. No dose averaging is applied in a Tier 0 assessment.

If a Tier 0 assessment identifies a HQ below or equal to 0.2 for all operable exposure pathways for the site, then no further action is required. Alternately, an overall HQ of 1 or less than 1 may be used if background exposure from all pathways is included in addition to exposures from the site, indicating that adverse health effects would be unlikely (since the exposure from all sources would not exceed the TRV).

The risk assessment can be considered complete at Tier 0 for all COPCs that do not exceed the target HQ. Only those COPCs found to have an HQ > 0.2 (for an individual during the most sensitive and exposed lifestage) or an HQ > 1 for all operable exposure pathways including background exposure from all pathways in a Tier 0 assessment would carry forward to the next tier.

E.1.3.1.1 Dermal Exposure to Soils for Tier 0 Assessment

For a toddler's dermal exposure to PCDD/Fs in soils, the Tier 0 assessment would assume chronic daily exposure as per the following (see HC [2010, 2024] for general equation):

$$Dose = \frac{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_v * RAF_{derm} * D_2 * D_3}{BW}$$

$$= \frac{C_S * (SA_H * SL_H + SA_O * SL_O) * nE_v * RAF_{derm} * D_2 * D_3}{BW}$$

$$= \frac{0.0006\,mg/kg * (430\ cm^2 * 1 * 10^{-7}\ kg/cm^2 - event + 3010\ cm^2 * 1 * 10^{-8}\ kg/cm^2 - event) * 1 * 0.03 * 1.0 * 1.0}{16.5\ kg}$$

$$= 8.0 * 10^{-11}\ mg/kg\ bw/day$$

$$= 0.080\ pg/kg\ bw/day$$

Where $Dose$ = daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
SA_H = surface area of hands exposed to soil loading (cm^2)
SL_H = soil loading rate to exposed skin of hands (kg/cm^2-event)
SA_O = surface area exposed other than hands (i.e., surface area of exposed arms, legs and feet [cm^2])

SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)
nE_v = number of dermal exposure events/day (default assumption is 1 event/day)
RAF_{derm} = relative dermal absorption factor (unitless) = 0.03 for PCDD/Fs (HC, 2021)
D_2 = days per week exposed/7 days = 7days/7days = 1.0
D_3 = weeks per year exposed/52 weeks = 52 weeks/52 weeks = 1.0
BW = body weight (kg)

E.1.3.1.2 Inhalation Exposure to Suspended Soil Particulates for Tier 0 Assessment

For a toddler's inhalation exposure to PCDD/Fs in suspended particulate matter from soils, the Tier 0 assessment would assume chronic daily exposure as per the following (see HC [2010, 2024] for general equation):

$$Dose = \frac{C_S * P_{air} * IR_A * RAF_{inh} * D_1 * D_2 * D_3}{BW}$$

$$= \frac{0.0006\, mg/kg * 0.76 * 10^{-9}\, kg/m^3 * 8.3\, m^3/day * 1.0 * \left(\frac{24\ hours}{24\ hours}\right) * \left(\frac{7\ days}{7\ days}\right) * \left(\frac{52\ weeks}{52\ weeks}\right)}{16.5\ kg}$$

$$= 2.3 * 10^{-13}\ mg/kg\ bw/day$$

$$= 2.3 * 10^{-4}\, pg/kg\ bw/day$$

Where $Dose$ = daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
P_{air} = particulate concentration in air (kg/m^3)
IR_A = receptor inhalation rate (m^3/day)
RAF_{inh} = relative absorption factor by inhalation, assumed to be 100% or 1 (unitless)
D_1 = hours per day exposed/24 hours
D_2 = days per week exposed/7 days
D_3 = weeks per year exposed/52 weeks
BW = body weight (kg)

E.1.3.1.3 Total Exposure for Tier 0 Assessment

For the purposes of this worked example, both drinking water and edible foods were deemed inoperable exposure pathways for this site. Contact with PCDD/Fs may occur at this site via incidental ingestion of soil, dermal contact with soil and inhalation of suspended soil particulates. In a Tier 0 assessment, exposure of a toddler at the site is the sum of exposures from incidental ingestion of soil (2.9 pg/kg bw/day; **Section E.1.2.1.1**), dermal contact with soil (0.080 pg/kg bw/day; **Section E.1.3.1.1**) and inhalation of fugitive dust (i.e., suspended particulate matter) from soil (2.3 *10^{-4} pg/kg bw/day; **Section E.1.3.1.2**). Hence, the site-related exposure of the toddler to PCDD/Fs in a Tier 0 assessment was estimated at 3.0 pg/kg bw/day.

E.1.3.1.4 Risk Characterization for Tier 0 Assessment

As discussed in **Section E.1.2.1.2,** Tier 0 assessment applies the chronic pTDI of 2.3 pg/kg bw/day (HC, 2021) to assess potential risks from chronic PCDD/Fs exposure. The HQ for the toddler is calculated

during the risk characterization step by dividing the total exposure received while on site (with no background exposure included) by the TRV.

$$HQ = \frac{Dose}{TRV} = \frac{3.0\ pg/kg\ bw/day}{2.3\ pg/kg\ bw/day} = 1.3$$

As previously noted, this worked example serves to illustrate the process of a Tier 0 assessment. When all operable exposure pathways excluding background exposure from all sources are considered, an overall HQ of 0.2 may be used as the target to identify the potential for adverse health effects.

Since the Tier 0 assessment above resulted in an HQ > 0.2 for PCDD/Fs via all operable exposure pathways under a chronic exposure scenario, this worked example proceeds to assess the short-duration exposure to PCDD/Fs in soil using a Tier I-a assessment.

E.1.3.2 Tier I-a: Assessment Based on Direct Application of TRV of Relevant Duration

The Tier I-a assessment provides a calculation of exposure that visitors may receive while at the site. For this example, where people may be at a site for 3 consecutive days, the exposure assessment provides a calculation of the exposure that may be received during that 3-day period. As discussed **in Section E.1.2.2.2**, the total exposure within one month is calculated for a short-term exposure (i.e., >24 hrs to ≤30 days) in order to compare the exposure with the PTMI.

E.1.3.2.1 Tier I-a Dermal Exposure Assessment to PCDD/Fs

For the purposes of this example, the estimated daily dose of PCDD/Fs from exposure to soil through dermal contact while at the site is calculated for a toddler using the equation presented in **Section C.1.5** for a continuous exposure scenario as follows. The exposure point concentration for PCDD/Fs in soil was identified from the Tier 0 assessment as 0.0006 mg/kg.

$$Dose = \frac{[(C_S * SA_H * SL_H) + (C_S * SA_O * SL_O)] * nE_v * RAF_{derm} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

$$= \frac{C_S * (SA_H * SL_H + SA_O * SL_O) * nE_v * RAF_{derm} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

$$= \frac{0.0006\,mg/kg * (430\ cm^2 * 1 * 10^{-7}\ kg/cm^2 - event + 3010\ cm^2 * 1 * 10^{-8}\ kg/cm^2 - event) * 1 * 0.03 * \frac{3\ days}{3\ days}}{16.5\ kg}$$

$$= 8.0 * 10^{-11}\ mg/kg\ bw/day$$

$$= 0.080\ pg/kg\ bw/day$$

Where $Dose$ = daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
SA_H = surface area of hands exposed to soil loading (cm²)
SL_H = soil loading rate to exposed skin of hands (kg/cm²-event)
SA_O = surface area exposed other than hands (i.e., surface area of exposed arms, legs and feet [cm²])

SL_O = soil loading rate to exposed skin other than hands (kg/cm^2-event)
nE_v = number of dermal exposure events/day (default assumption is 1 event/day)
RAF_{derm} = relative dermal absorption factor (unitless) = 0.03 for PCDD/Fs (HC, 2021)
D_{T_C} = duration of the continuous exposure scenario in days, spanning from first day to final day of exposure
= 3 days
BW = body weight (kg)

In summary, the exposure to PCDD/Fs from dermal contact with soil for each day while at the site is 0.080 pg/kg bw/day. Because of the relatively long half-lives and long-term storage of PCDD/Fs in humans, a PTMI is available for use and the exposure is expressed over a month. Since the problem formulation identified that visitors may access the site for a maximum of 3 consecutive days, the total monthly exposure at this site is calculated as 3 days multiplied by 0.080 pg/kg bw/day, which is a total of 0.24 pg/kg bw per month for dermal exposure.

E.1.3.2.2 Tier I-a Inhalation Exposure Assessment to PCDD/Fs in Suspended Soil Particulates

The estimated daily exposure to PCDD/Fs via inhalation of suspended soil particulates while at the site is calculated for a toddler using the equation presented in **Section C.1.3** for a continuous exposure scenario as follows. The exposure point concentration for PCDD/Fs in soil was identified from the Tier 0 assessment as 0.0006 mg/kg.

$$Dose = \frac{C_S * P_{air} * IR_A * RAF_{inh} * \frac{H}{H_D} * \frac{D_{T_C}}{D_{T_C}}}{BW}$$

$$= \frac{0.0006\, mg/kg * 0.76 * 10^{-9}\, kg/m^3 * 8.3\, m^3/day * 1 * \frac{24\ hr}{24\ hr} * \frac{3\ days}{3\ days}}{16.5\ kg}$$

$$= 2.3 * 10^{-13}\ mg/kg\ bw/day$$

$$= 2.3 * 10^{-4}\, pg/kg\ bw/day$$

Where $Dose$ = daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
P_{air} = particulate concentration in air (kg/m^3)
IR_A = receptor inhalation rate (m^3/day)
RAF_{inh} = relative absorption factor by inhalation, assumed to be 100% or 1 (unitless)
H = hours per day exposed = 24 hours in a continuous exposure scenario
H_D = 24 hours
D_{T_C} = duration of the continuous exposure scenario in days, from first day to final day of exposure = 3 days
BW = body weight (kg)

In summary, the exposure to PCDD/Fs from inhalation of suspended soil particulates for each day while at the site is 2.3*10^{-4} pg/kg bw/day. Because of the relatively long half-lives and long-term storage of PCDD/Fs in humans, a PTMI is available, and the exposure to PCDD/Fs is expressed over one month. Since the problem formulation identified that visitors may access the site for a maximum of 3 consecutive days, the total monthly exposure at this site is calculated as 3 days multiplied by 2.3*10^{-4} pg/kg bw/day, which is a total 6.9 *10^{-4} pg/kg bw per month for inhalation of suspended soil particulates.

E.1.3.2.3 Total Exposure for Tier I-a Assessment

As indicated in **Section E.1.1**, for the purposes of this worked example, both drinking water and edible foods were deemed inoperable exposure pathways for this site. Contacts with PCDD/Fs via incidental ingestion of soil, dermal contact with soil and inhalation of suspended soil particulates are considered operable exposure pathways. In a Tier I-a assessment, the exposure the toddler experienced at the site for a month is calculated as the sum of exposures from these three operable exposure pathways without consideration of background exposure (unrelated to the site) for 3 consecutive days within a month at the site as follows.

- Exposure from incidental ingestion of soils = 8.7 pg/kg bw/month (See **Section E.1.2.2.3**)
- Exposure from dermal exposure with soils = 0.24 pg/kg bw/month (See **Section E.1.3.2.1**)
- Exposure from inhalation of suspended soil particulates = 6.9 $*10^{-4}$ pg/kg bw/month (See **Section E.1.3.2.2**)

Total exposure to PCDD/Fs the toddler received while present at the site for 3 days in a month, including all operable exposure pathways and without consideration of background exposure

= 8.7 pg/kg bw/month + 0.24 pg/kg bw/month + 6.9 $*10^{-4}$ pg/kg bw/month

= 8.9 pg/kg bw/month

E.1.3.2.4 Risk Characterization for Tier I-a for 3-Day Continuous Exposure

The PTMI for PCDD/Fs of 70 pg/kg bw per month (WHO/JECFA, 2002) is suitable to assess potential risks associated with the total exposure to PCDD/Fs that may be received over a period of one month. This PTMI is based on fetal toxicity from in-utero exposure, an exposure of short duration during a specific window of susceptibility. Since the PTMI is based on the most sensitive toxic effects among the most affected subpopulation, this approach is protective of the general public and can be applied to all age groups (including children, people who are pregnant and who may become pregnant) who may be present at the site. The additional epidemiological evidence of a causal relationship between infancy/prepuberty and semen quality reported by EFSA CONTAM (2018) further supports the application of the PTMI to toddlers. See **Section E.1.2.1.2** for a description of the basis of the PTMI.

The HQ for all operable exposure pathways for this site is calculated for a toddler during the risk characterization step by dividing the total exposure (dose) received while on site (with no background exposure included) by the TRV.

$$HQ = \frac{Dose\ (pg/kg\ bw/month)}{TRV\ (pg/kg\ bw/month)} = \frac{8.9\ pg/kg\ bw/month}{70\ pg/kg\ bw/month} = 0.13$$

Since all operable exposure pathways (not including background exposure) have been taken into consideration, an overall HQ of 0.2 may be used as the benchmark to indicate that adverse health effects would be unlikely. The HQ for all operable exposure pathways for this toddler while at the site for 3 consecutive days is lower than a target HQ of 0.2. Note that in an HHRA where background exposures from all sources are included in the calculations, a target HQ of 1 may be used.

Figure E.1.4 Estimated exposure to PCDD/Fs from all operable exposure pathways at the site by a toddler for 3-day recreational use in a Tier I-a assessment

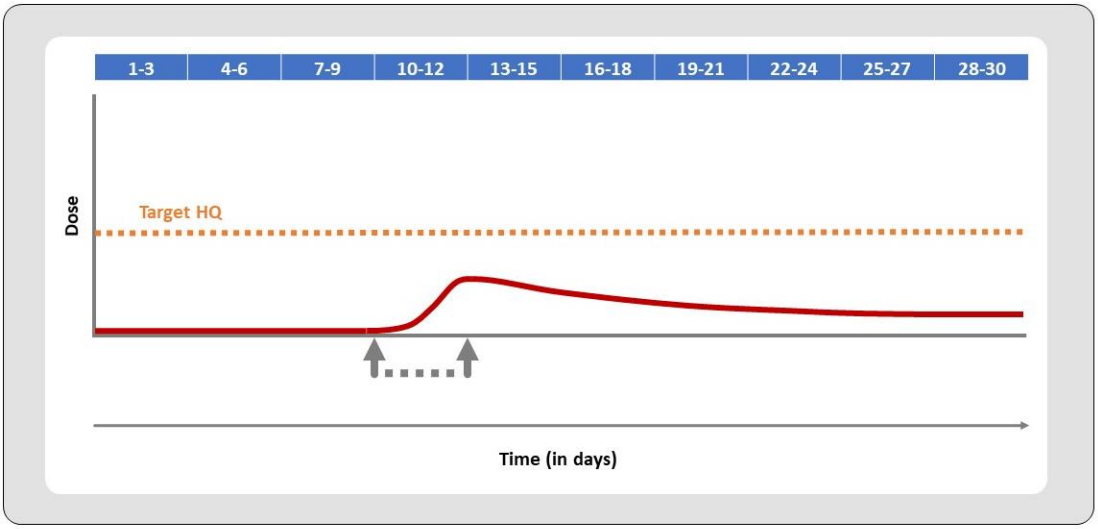
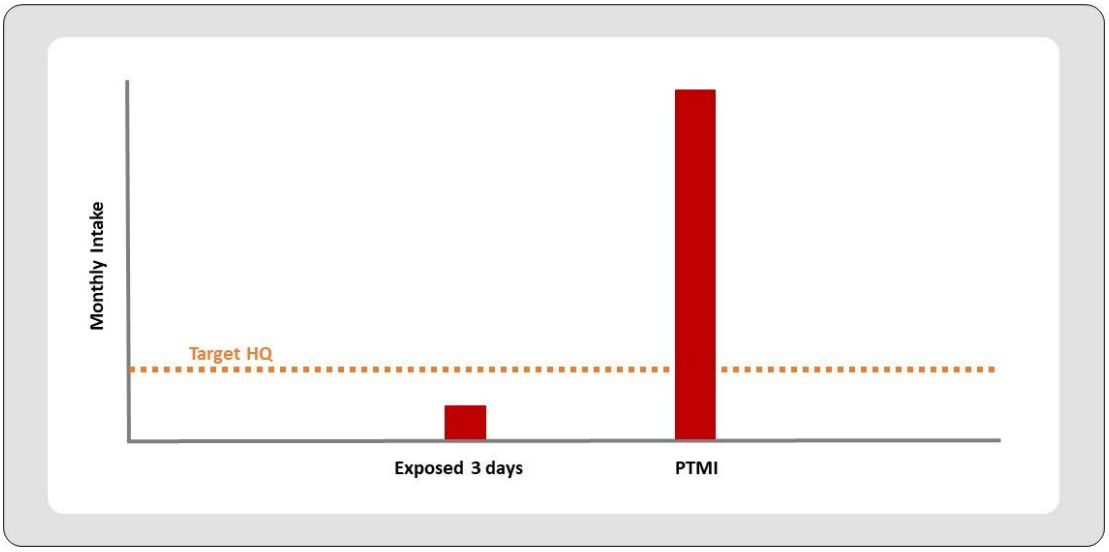


Figure E.1.5 Estimated monthly intake of PCDD/Fs from all operable exposure pathways at the site by a toddler for 3-day recreational use in a Tier I-a assessment as compared to PTMI



E.1.3.3 Conclusion

Based on this worked example that addresses exposure to elevated levels of PCDD/Fs in soil via incidental soil ingestion, dermal contact, inhalation of suspended soil particulates (with no consideration for background exposure from sources unrelated to the site), the target HQ of 0.2 has not been exceeded in a Tier I-a assessment. Therefore, no further assessment of PCDD/Fs would be required in the HHRA. HC emphasizes that all other operable exposure pathways for each site, including but not

limited to ingestion of drinking water and ingestion of foods impacted from the site, would also be considered and applied in a risk assessment to fully characterize the potential health risks.

The HHRA should provide chemical-specific scientific rationale for each COPC, ensuring that the toxicological summary includes information on both the chronic and less-than-chronic (e.g., short-term) TRVs relevant to the exposure periods. The HHRA should include intermittent exposures (e.g., repeated monthly exposures) as relevant to each site, and inclusion of all operable exposure pathways. See **Section E.3** for an example illustrating the process of assessing intermittent exposures.

E.1.4 Background Information: Short-Duration TRV Selection, Toxicokinetics and Toxicodynamics Considerations Used to Determine Whether Dose Averaging is Appropriate for PCDD/Fs

E.1.4.1 Oral Chronic TRV

PCDD/Fs are ubiquitous and persistent in the environment (soil, sediments and air). Excluding occupational or accidental exposure, most humans are exposed to PCDD/Fs through ingestion of high-fat foods (e.g., milk, eggs, meat, fish and related products) that tend to accumulate these substances (International Agency for Research on Cancer [IARC], 2012).

Body burden is considered the most appropriate measure of dose for exposure to PCDD/Fs for interspecies comparison (WHO, 2000). Due to the relatively long half-lives and long-term storage of PCDD/Fs in humans, estimating steady-state body burden often reflects an insignificant increase upon a brief intake above background (WHO, 2000). Intake on any particular day would have only a minor impact on the overall burden, with the bulk of body burden consisting of PCDD/Fs input over several previous years (WHO, 2000). WHO/JECFA (2002) determined that the appropriate period for evaluating the mean intake of these compounds is one month and expressed the tolerable intake (TI) as a PTMI for assessing long- or short-term risks to PCDD/Fs. While total intake over a month is the best determinant of toxicity, HC (2021) has derived a pTDI from the WHO PTMI applicable to chronic continuous exposure.

At its 57th meeting (June 2001), JECFA performed a comprehensive safety assessment of PCDDs/Fs and coplanar polychlorinated biphenyls (PCBs), and established a PTMI of 70 pg TEQ/kg bw/month (WHO/JECFA, 2002). WHO/JECFA (2002) concluded that a TI could be established for TCDD based on the assumption that a threshold exists for all effects, including cancer.

The most sensitive adverse effects reported for PCDD/Fs were on the reproductive system of male rat offspring, and immunological deficits in rats after prenatal exposure to TCDD. WHO/JECFA (2002) identified two critical studies, Faqi et al. (1998) and Ohsako et al. (2001), for deriving the TI. Faqi et al. (1998) exposed female rats subcutaneously, on a weekly basis beginning 2 weeks prior to mating and throughout mating, gestation and lactation, while Ohsako et al. (2001) dosed pregnant female rats by gavage on gestation day 15. Since the Ohsako study involved a single bolus dose, the maternal body burden in the study had to be converted to a maternal body burden corresponding to an exposure regimen of repeated doses that resulted in the same fetal body burden. WHO/JECFA (2002) used two approaches for the extrapolation, assuming a linear and a nonlinear relationship between fetal and maternal body burden, respectively. Using the linear approach, WHO/JECFA (2002) estimated the maternal body burden NOEL to be 13 ng/kg bw (Ohsako et al., 2001) and the maternal body burden

LOEL to be 25 ng/kg bw (Faqi et al., 1998). These values were incremental to the background body burden from laboratory feed.

WHO/JECFA (2002) identified two studies (Vanden Heuvel et al., 1994; Viluksela et al., 1998) that could be used to estimate the body burden of rats resulting from the presence of PCDD/Fs and co-planar PCBs in laboratory feed. These studies were mutually consistent and predicted that "unexposed" laboratory rats had toxic equivalents of 3-12 ng/kg bw, depending on age. The addition of background body burden of 3 ng/kg bw to the body burdens calculated using the linear model resulted in estimated total toxic equivalent maternal body burdens of 16 ng/kg bw for the NOEL (Ohsako et al., 2001) and 28 ng/kg bw for the LOEL (Faqi et al., 1998). These maternal body burdens in rodents corresponded to equivalent human monthly intakes (EHMIs) of 240 and 420 pg/kg bw, respectively. Similarly, fitting the NOEL and LOEL into the power equation resulted in EHMIs of 330 pg/kg and 630 pg/kg, respectively.

To derive the PTMIs, WHO/JECFA (2002) applied an UF of 3.2 to the results calculated from the NOEL in Ohsako et al. (2001) to account for interindividual differences in toxicokinetics among humans. An additional UF of 3 was used for the study by Faqi et al. (1998) to account for the use of a LOEL instead of a NOEL (Total UF = 3.2 x 3 = 9.6). The range of PTMIs derived from the two studies was 40-100 pg/kg bw/month. The mid-point of this range, 70 pg/kg bw/month, was chosen as the PTMI (WHO/JECFA, 2002). This TI is applied to the intake of PCDD/Fs and coplanar PCBs expressed in WHO toxic equivalency factors (TEFs) (van den Berg et al., 2006).

The established PTMI of 70 pg/kg bw/month also took into account the previous WHO (1998) evaluation, supplemented with additional toxicokinetics data. These data were based on a comparison of the fetal transfer of TCDD after bolus and repeated dosing (Gray et al., 1997a, b); studies of developmental toxicity (Gehrs et al., 1997; Gehrs and Smialowicz, 1999); and information from a study in rhesus monkeys (Rier et al., 2001a, b).

The HC (2021) pTDI was derived as follows:

$$pTDI = \frac{70\ pg/kg\ bw/month}{30\ days/month} = 2.3\ pg/kg\ bw/day$$

E.1.4.2 Supporting Rationale for Absorption, Distribution, Metabolism and Elimination

The toxicokinetics of PCDD/Fs have been extensively studied in animals while more limited studies have been completed with people. PCDD/Fs are reasonably absorbed across the gastrointestinal tract while much less absorption occurs dermally, and little is known about inhalation absorption. Upon entering the body, PCDD/Fs are primarily distributed to fatty tissues with the greatest concentrations tending to occur in the liver, adipose and skin tissues. They can also be found in breast milk. Many studies indicate a body elimination half-life greater than 7.2 years (IARC, 2012). The cytochrome P-450 mixed function oxidase enzyme system is most important in the biotransformation of PCDD/Fs and their eventual excretion as glutathione and glucuronoside conjugates. However, as the long half-life suggests, metabolism of PCDD/Fs only occurs at a very slow rate. While excretion of PCDD/Fs is primarily in feces and urine, its presence in breast milk can be important as a pathway of dietary exposure for breastfeeding infants.

E.1.4.3 Selection of Short-Duration TRV

Two TRVs were identified in the literature that can be potentially used for the assessment of a 3-day continuous exposure scenario: the acute MRL (applicable up to 14 days of exposure) by ATSDR (1998) and the WHO PTMI (WHO/JECFA, 2002). The ATSDR acute MRL of 200 pg/kg bw/day was based on a study in mice (Burleson et al., 1996), which were administered a single gavage dose of TCDD intranasally. The study identified a NOAEL of 0.005 µg/kg bw based on impaired resistance to influenza A virus infection. A total UF of 30 was applied (3 for interspecies extrapolation, 10 for human variability) in deriving the MRL. The PTMI developed by WHO/JECFA (2002) was based on reproductive effects observed in male offspring of the exposed pregnant female rats. This long-lasting effect results from short-duration exposure within a specific critical window of susceptibility.

The ATSDR MRL was derived in 1998, prior to the publication of the key pivotal studies (Faqi et al., 1998 and Ohsako et al., 2001) that formed the basis of the WHO/JECFA (2002) PTMI. The ATSDR value was not selected for use as it was not protective of developmental toxicity.

The worked example in this document applied the WHO PTMI to the 3-day exposure for the protection of the general public who may be present at the site, including people who are pregnant, who may become pregnant and children.

E.1.4.4 Susceptibility to PCDD/Fs Toxicity and Mechanistic Relevance to Humans

TCDD is the most studied and the most toxic compound among PCDD/Fs. Other PCDD/Fs can be evaluated as TCDD toxic equivalents (HC, 2021, 2024). Exposures to PCDD/Fs are calculated as a simple weighted sum of the individual amounts multiplied by their individual TEFs to yield the equivalent dose in units of TCDD exposure (HC, 2021. 2024).

Although IARC (2012) has classified TCDD as a human carcinogen, carcinogenicity is not the most sensitive toxic endpoint. Carcinogenicity due to TCDD is not linked to mutagenicity or DNA binding, and there is ample evidence to support a receptor-mediated (binding to AhR) mechanism of action for TCDD-associated carcinogenesis in humans (IARC, 2012). AhR binding is also the initial step for essentially all other toxic endpoints (ATSDR, 2012). As carcinogenicity occurred at higher body burdens in animals than other toxic effects, WHO (2000) concluded that establishing a TI based on effects other than cancer would also address any carcinogenic risk.

The most sensitive adverse effects reported for TCDD were on the reproductive system of the male offspring and immunological deficits in rats after prenatal exposure to TCDD (WHO, 2000). Since the AhR is well conserved across species and is present essentially in all tissues, similar health effects are expected to occur in humans, though susceptibility to the effects may vary.

Although the PTMI was established based on animal studies with TCDD, WHO (2000) concluded that this TI should be applied to intake of PCDDs and PCDFs expressed as TEFs.

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E.2 Worked Example #2: Tetrachloroethylene (Perchloroethylene), Short-Duration Continuous Exposure

This section provides a worked example of Tier 0 and Tier I-a assessments for a one-time short-duration continuous exposure to tetrachloroethylene at a hypothetical contaminated site. The analysis presented is specific to the exposure scenario described below, including land use, site conditions, exposure duration, receptors, onsite behaviour and activity patterns.

Site-specific differences to this hypothetical scenario and variation in any one of the exposure parameters would warrant a separate analysis using appropriate TRVs relevant to the exposure durations of interest. Exposure scenarios analysed should be relevant to each site and justified based on site-specific information. The assessor should provide scientific rationale, with references, for TRVs selected for both chronic and relevant less-than-chronic exposure durations.

Note that on occasion, HC becomes aware of new critical toxicological or other data that dictate a need to revise HC (2021) TRV for a given substance to ensure the protection of the health of Canadians. In such a case, the revision of the TRV could subsequently require a change in the approach to the risk assessment of short-duration and intermittent exposures to be consistent with the TRV.

E.2.1 Problem Formulation Summary

The worked example provided below entails a continuous exposure scenario at a hypothetical camping site in a remote national park. The site has elevated concentrations of tetrachloroethylene in the soil, air and surface water. The scenario is subject to the following parameters:

- It is expected that visitors, including toddlers, may access the site for a short duration (e.g., 2 weeks) or a seasonal recreational use for a maximum duration of 12 weeks. Exposure may be continuous over those periods (i.e., 2 weeks and 12 weeks, respectively).
- Contact with tetrachloroethylene may occur via incidental ingestion of soil, dermal contact with soil, inhalation of fugitive dust, inhalation of vapour, ingestion of surface water and dermal contact with surface water. The assessor should consider all these routes in a HHRA and in the calculation of total exposure.
- Recreational use of the site may include all age groups, and the HHRA should therefore consider the most sensitive receptors.

While all the above exposure routes remain operative, for the sake of simplicity, this particular worked example calculates only *inhalation* of vapour exposure for a toddler receptor, as this exposure represents the most likely risk driver for volatile substances such as tetrachloroethylene. Note that the additional exposure routes cited above may also be important, and that the inhalation of vapour values calculated for this hypothetical example are for illustration purposes only. Please refer to **Appendix C** and HC (2024) guidance for equations to assess other exposure routes.

Maximum 24-hour average air concentration of tetrachloroethylene at this site was measured at 20 $\mu g/m^3$.

E.2.2 Tier 0 Assessment

The Tier 0 assessment estimates the highest daily exposure that an individual may receive while on site (i.e., exposure during the most sensitive and exposed lifestage) and compares this exposure to the chronic TRV. This calculation shows the expected exposure that a person would receive if the person remained on site for the whole time, which is identical to the calculation for a chronic exposure period (e.g., 365 days/365 days). If this Tier 0 assessment is completed for a non-carcinogenic effect and the HQ is equal to or below 0.2, then no further action would be required. Only those COPCs found to have an HQ > 0.2 in the assessment would carry forward to the next tier.

E.2.2.1 Exposure Assessment for Tier 0 Assessment

The estimated daily exposure for inhalation of vapour that a person would receive while present on this site is calculated using the equation below, assuming chronic daily exposure in a Tier 0 assessment (see **Section 3.1** of the main document for general equation). The sample calculation shown is for a toddler.

$$TDC_A = C_A * RAF_{inh} * D_1 * D_2 * D_3$$

$$= 20\ \mu g/m^3\ * 1.0 * (24\ hours)/(24\ hours) * (7\ days)/(7\ days) * (52\ weeks)/(52\ weeks)$$

$$= 20\ \mu g/m^3$$

Where TDC_A = time-adjusted average daily air concentration (µg/m³)
C_A = concentration of contaminant in air (µg/m³)
RAF_{inh} = relative absorption factor for inhalation (unitless), default value is 100% or 1
D_1 = hours per day exposed/24 hours
D_2 = Days per week exposed/7 days
D_3 = Weeks per year exposed/52 weeks

E.2.2.2 Applicable TRV for Tier 0 Assessment

The Tier 0 assessment applies the chronic TC of 40 µg/m³ to assess potential risks from chronic exposure to tetrachloroethylene in air (HC, 2021; HC, 2017; US EPA, 2012; ATSDR, 2019). This TRV is based on two epidemiological studies of dry cleaning workers exposed for an average of 8.8 and 15 years in Cavalleri et al. (1994) and Echeverria et al. (1995), respectively. The studies identified a LOAEL of 42 mg/m³ (Cavalleri et al., 1994; adjusted to a $LOAEL_{HEC}$ [human equivalent continuous exposure] of 15 mg/m³) and of 156 mg/m³ (Echeverria et al., 1995; adjusted to $LOAEL_{HEC}$ of 56 mg/m³), respectively, based on such neurotoxic effects as impaired colour vision, alteration in cognitive function and reaction times. A total UF of 1000 was applied (10 for interindividual human variability, 10 for uncertainties in extrapolating from a LOAEL to a NOAEL, and 10 for database uncertainties) in deriving the chronic RfC (US EPA, 2012). The chronic RfC of 40 µg/m³ is the midpoint of candidate RfCs derived from these two epidemiological studies (US EPA, 2012).

E.2.2.3 Risk Characterization for Tier 0 Assessment

The HQ is calculated during the risk characterization step by dividing the exposure received while on site by the TRV.

$$HQ = \frac{TDC_A\ (\mu g/m^3)}{TRV\ (\mu g/m^3)} = \frac{20\ \mu g/m^3}{40\ \mu g/m^3} = 0.50$$

The HHRA should consider all operable exposure pathways and compare the total exposure from all operable exposure pathways with a target HQ of 0.2. An overall HQ of 1 or less than 1 (including background exposure which include exposures to the same COPC from other sources such as food, water, consumer products, soil, air) indicates that adverse health effects would be unlikely.

In this example, the Tier 0 assessment found an HQ > 0.2 for tetrachloroethylene via inhalation of vapour alone under a chronic exposure scenario. For the purpose of this example, the 2-week exposure and 12-week exposures to tetrachloroethylene in air will be assessed using Tier I-a assessment to evaluate whether a more detailed assessment can reduce uncertainty in a Tier 0 assessment.

E.2.3 Tier I-a: Assessment Based on Direct Application of TRVs of Relevant Duration

The Tier I-a assessment applies a short-duration TRV that is relevant for the entire duration of a single exposure episode. **Table E.2.1** below outlines the exposure categories used in assessing short-duration and intermittent exposures. Consistent with the two exposure periods at this site, the table indicates a published short-term TRV relevant for a 14-day exposure period and an intermediate duration TRV relevant for a 90-day exposure period.

Table E.2.1 Updated exposure duration categories for contaminated sites risk assessment

Exposure Duration Category	Definition
Acute exposure[1]	exposure for 24 hours or less (≤24 hours)
Short-term exposure[1]	repeated exposure for more than 24 hours, up to 30 days (>24 hours to ≤30 days)
Intermediate exposure[1]	repeated exposure for more than 30 days, up to less than 1 year (>30 days to <1 year)
Chronic exposure	repeated exposure for 1 year or more, and up to a lifetime (≥1 year)

[1] Note that if exposures are repeated, they may be considered chronic even if they are not continuous.

E.2.3.1 Primary Determinant of Toxic Effects

To determine whether dose averaging may be appropriate for a specific substance, the HHRA must confirm the primary determinant of toxic effects for each individual chemical using information from key studies cited in the development of a TRV for a particular duration. The critical effects of the inhalation TRVs for tetrachloroethylene were:

- Impaired colour vision (US EPA, 2012).
- Alteration in reaction times, impaired cognitive function (US EPA, 2012).

While it is not certain that the neurological effects of tetrachloroethylene result from the parent compound or one or more of its metabolites, US EPA (2012) concluded that the AUC of the tetrachloroethylene blood concentration-time curve derived from PBPK modelling represents the best surrogate for internal dose. The PBPK modelling conducted by ATSDR (2019) using the same PBPK model (Chiu and Ginsberg, 2011) as the USEPA showed that at the same continuous exposure of 1.7 ppm in air,

the 24-hour AUC concentration-time values (expressed as mg-hr/L-day) were very similar after 14 days, 90 days, 1 and 2 years of exposure. These simulations predicted the 24-hour AUC value to be nearly constant after 2 weeks of exposure. The blood concentration of tetrachloroethylene reached 90% of steady state at about 2 weeks of continuous exposure and 99% of steady state at 90 days of continuous exposure (ATSDR, 2019). ATSDR (2019) has identified an air concentration of 1.7 ppm (or 11.5 mg/m^3) as the $LOAEL_{HEC}$ after chronic exposure in humans based on the Cavalleri et al. (1994) study.

The basic assumption underlying the use of PBPK modelling in HHRA is that the same internal dose (or target tissue concentration) elicits the same effect to the same intensity. Given the 24-hour AUC value is predicted to be the same after 14 days, 90 days, and 2 years of exposure to an inhaled air concentration of 1.7 ppm (or 11.5 mg/ m^3) tetrachloroethylene, ATSDR (2019) assumed the $LOAEL_{HEC}$ for continuous exposure of any duration over 14 days to be 1.7 ppm (or 11.5 mg/ m^3). ATSDR's assumption is supported by the controlled human exposure study by Altmann et al. (1990, 1992), which identified a $NOAEL_{HEC}$ of 2 ppm for neurobehavioural changes in which exposures were only for 4 hours/day for 4 days. While the 24-hour AUC value remains the same irrespective of exposure duration, the total dose, expressed as the AUC for the whole exposure duration (i.e., 24-hour AUC multiplied by duration) would not remain constant but would increase as the exposure duration increases. Since the LOAEL remains the same irrespective of exposure duration, neurotoxicity of tetrachloroethylene is likely related to peak concentration and not to total dose. As such, dose averaging is not recommended, which applies also to exposures that occur at commercial/industrial sites (i.e., use of an ET of 1).

When conducting an HHRA, chemical-specific rationale on the toxicokinetics and toxicodynamics (such as the information provided above for tetrachloroethylene) should be included within the report to identify whether dose averaging may be appropriate or not.

E.2.3.2 Exposure Assessment for Tier I-a for 2-Week and 12-Week Continuous Exposures

The Tier I-a assessment calculates the exposure a visitor may receive for the time period the individual is at the site (i.e., 2 weeks or 12 weeks in this example). Since neurotoxicity of tetrachloroethylene is likely related to peak concentration, the estimated daily exposure is calculated for a toddler using input air concentrations that represent reasonable maximum exposures (see **Appendix C**). In this example, the highest daily air concentration of tetrachloroethylene was calculated based on the maximum 24-hour average air concentration of 20 µg/m^3. The calculation does not involve dose averaging.

$$DC_A = C_A * RAF_{inh}$$

$$= 20\,\mu g/m^3 * 1.0$$

$$= 20\,\mu g/m^3$$

Where DC_A = highest estimated daily air concentration (µg/m^3)
C_A = maximum concentration of contaminant in air (µg/m^3)
RAF_{inh} = relative absorption factor for inhalation (unitless), default value is 100% or 1

The highest daily air concentration of tetrachloroethylene would be the same (i.e., 20 µg/m^3) whether the individual stays at the site continuously for one day, 2 weeks or 12 weeks.

Table E.2.2 Duration of exposure for a site visitor for a 2-week or 12-week continuous exposure

a) 2-week continuous exposure (in weeks)

Week	1	2	3	4
Time on site	-	✓	✓	-
Total Duration		2 weeks		

✓ = 1 week of exposure on site

b) 12-week continuous exposure (in months)

Month	J	F	M	A	M	J	J	A	S	O	N	D
Time on site	-	-	-	-	-	✓	✓	✓	-	-	-	-
Total Duration						12 weeks						

✓ = 1 month of exposure (approximately 4 weeks) on site

E.2.3.3 Applicable TRVs for Short-Term and Intermediate Exposures

ATSDR (2019) provides an acute MRL of 40 µg/m^3 applicable to an exposure period of up to 14 days. Based on the definition in this guidance, this MRL meets its definition of a short-term TRV (i.e., > 24 hours and up to 30 days) and may be applied to the 2-week exposure period in the example.

ATSDR (2019) provides an intermediate MRL of 40 µg/m^3, applicable to an exposure period of up to 364 days. This MRL meets the definition in this guidance of an intermediate TRV (i.e., > 30 days to <1 year) and may be applied to the 12-week exposure period in the example.

In this example, both TRVs for tetrachloroethylene are numerically the same and are based on ATSDR's (2019) adoption of its chronic MRL as its acute- and intermediate-duration MRLs. Note that the tetrachloroethylene 24-hour AUC after a 14-day, 90-day, 1-year or 2-years of exposure is very similar to that after chronic exposure to the same inhaled concentration (See **Section E.2.3.1**). The ATSDR (2019) chronic MRL of 40 µg/m^3 is based on the Cavalleri et al. (1994) study by applying a total UF of 300 (10 for use of a LOAEL, 10 for human variability, 10 for database deficiency). The ATSDR chronic MRL is numerically the same as the US EPA (2012) chronic RfC, therefore, no dose averaging would be appropriate for tetrachloroethylene.

E.2.3.4 Risk Characterization for Tier I-a for Short-Term and Intermediate Exposures

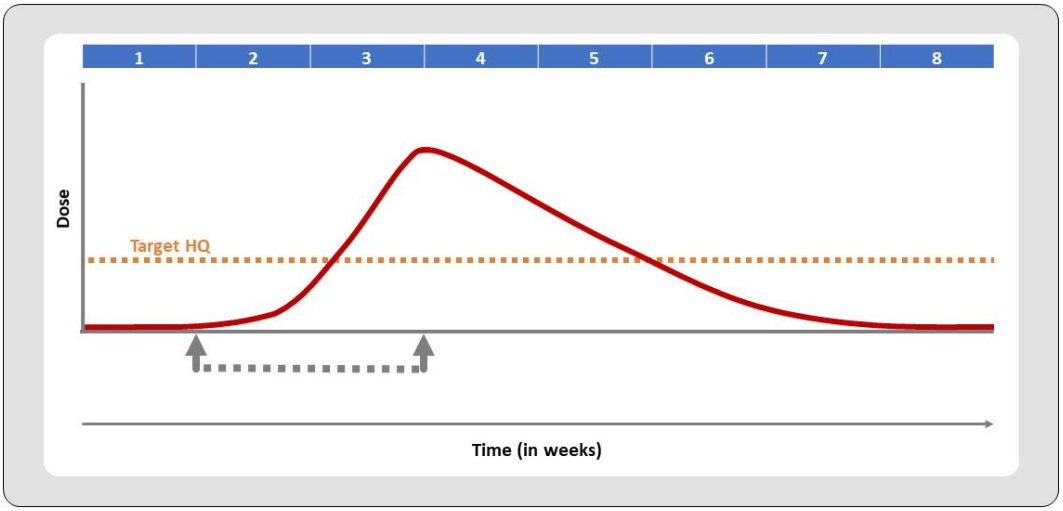
Since tetrachloroethylene toxicity from inhalation exposure is primarily driven by concentration/peak exposure, the HQ calculated in the risk characterization stage is the highest exposure estimated for the exposure period divided by the TRV applicable to the time period. As the estimated highest exposure

and applicable TRVs are numerically the same for the 2-week and 12-week exposures, the HQs would be the same for both exposure scenarios, as presented below.

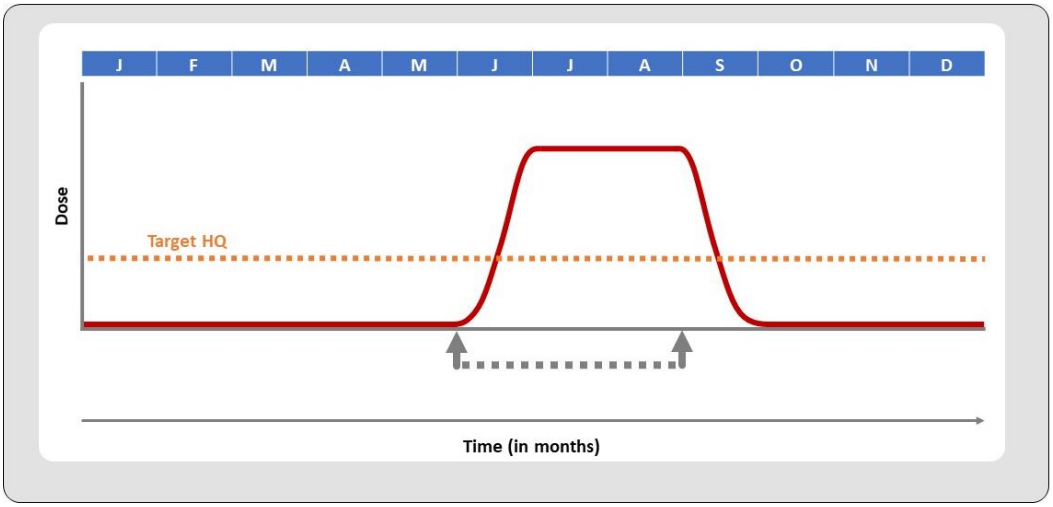
$$HQ = \frac{Estimated\ onsite\ air\ concentration\ (\mu g/m^3)}{TRV\ (\mu g/m^3)} = \frac{20\ \mu g/m^3}{40\ \mu g/m^3} = 0.50$$

Figure E.2.1 Estimated exposure to tetrachloroethylene from vapour inhalation by a toddler for 2-week and 12-week seasonal recreational use in a Tier I-a assessment

a) 2-Week continuous exposure



b) 12-Week continuous exposure



In this hypothetical example, the calculated HQ exceeds a target of 0.2 for inhalation of vapour for an individual who remains on site for the entire 2-week or 12-week exposure periods. It would also be important to evaluate if exposure for less than 24 hours (acute exposure) would pose a risk. US EPA (2020) has developed PODs of 68 mg/m^3 and 11 mg/m^3 (UF =10 for human variability) for exposure durations of 4 hours/day and 24 hours/day, respectively. The corresponding TRVs would be 6.8 mg/m^3

(4 hours/day) and 1.1 mg/m^3 (24 hours/day). The HQ for an one-day exposure would be 0.018 as shown below, and does not exceed a target of 0.2 for inhalation of vapour only.

$$HQ = \frac{Estimated\ onsite\ air\ concentration\ (\mu g/m^3)}{TRV\ (\mu g/m^3)} = \frac{20\ \mu g/m^3}{1100\ \mu g/m^3} = 0.018$$

The HHRA would also need to consider all other operable exposure pathways, such as soil ingestion and dermal contact with soil, and compare the total exposure to the TRV with a target HQ of 0.2. In an HHRA where background exposures from all sources are included in the calculations, a target HQ of 1 may be used. It should be noted that repeated use of an acute TRV is not appropriate for the evaluation of recurring exposures.

> A complete HHRA needs to consider all operable exposure pathways, including inhalation of vapour, soil ingestion, dermal contact with soil, and other pathways if relevant. This worked example for inhalation of vapour alone was prepared for simplicity.

E.2.4 Mathematical Dose Averaging May Underestimate Potential Health Risks

The following example explains why averaging the potential 12-week site exposure over a year could underestimate potential human health risks. The following equation for vapour inhalation would be incorrect and should not be used.

$$TDC_A = C_A * RAF_{inh} * D_1 * D_2 * D_3$$

$$= 20\ \ \mu g/m^3 * 1.0 * (24\ hr/24\ hr) * (7\ d/7\ d) * (12\ weeks/52\ weeks)$$

$$= 4.6\ \ \mu g/m^3\ assuming\ 12\ weeks\ averaged\ over\ 1\ year$$

Where TDC_A = time-adjusted average daily air concentration (µg/m^3)

C_A = air concentration µg/m^3 D_2 = days per week exposed/7 days

D_1 = hours per day exposed/24 hours D_3 = weeks per year exposed/52 weeks

RAF_{inh} = relative absorption factor for inhalation (unitless), default value is 100% or 1

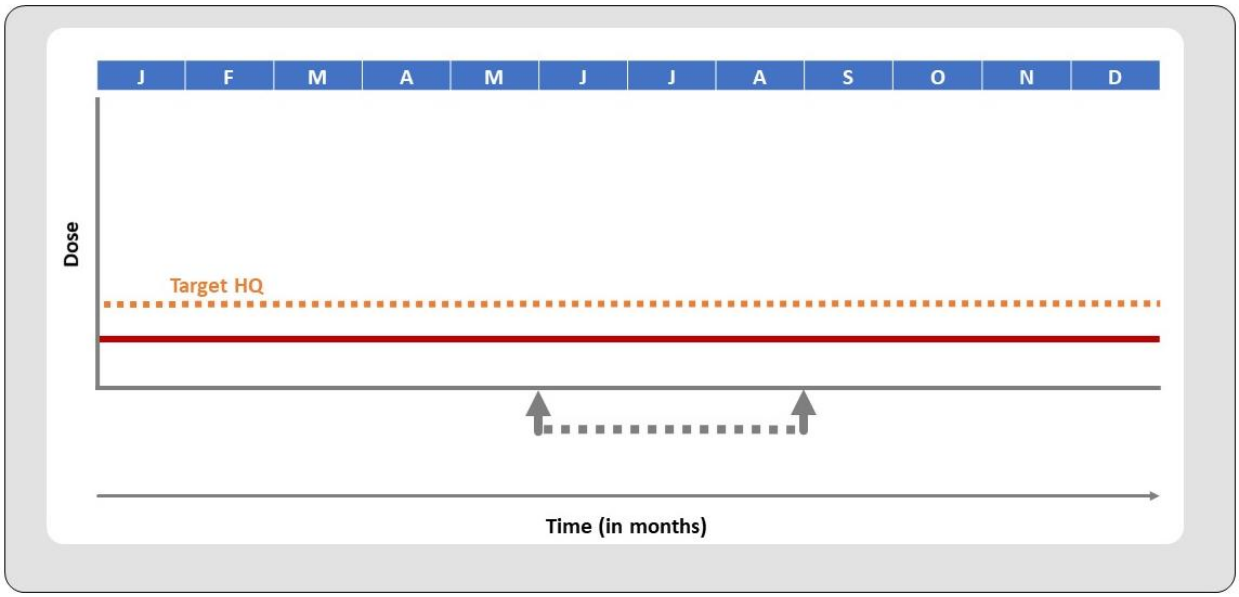
$$HQ = \frac{Estimated\ onsite\ air\ concentration\ (\mu g/m^3)}{TRV\ (\mu g/m^3)} = \frac{4.6\ \mu g/m^3}{40\ \mu g/m^3} = 0.12$$

A similar calculation could be conducted for averaging a potential 2-week exposure on the site (detailed calculation is not shown here), which would yield an even lower average exposure (0.77 µg/m^3) and a lower HQ (0.02) than averaging a 12-week exposure.

Although the calculation appears to be mathematically correct, it assumes that a visitor would receive an average daily exposure over the course of a year. The calculated exposure would be lower than the expected peak concentration and would not consider toxicity associated with the potential elevated exposure received while on site. In other words, peak levels of exposure received over each day of the 2 weeks (or 12 weeks) at the site would not be consistent with the mathematically calculated amortized exposures. The resulting assessment underestimates health risks because the total daily exposure of a

person is assumed to be spread over 12 months instead of the actual exposure received during peak exposure (with related toxic effect) during the 2 weeks (or 12 weeks) when the visitor is at the site.

Figure E.2.2 Estimated yearly exposure to tetrachloroethylene from vapour inhalation by a toddler for seasonal recreational use incorrectly applying dose averaging



E.2.5 Conclusion

Based on this worked example, the HHRA may conclude that the level of tetrachloroethylene in the air found on site (i.e., 20 µg/m^3) poses a potential health risk to visitors from inhalation of vapour for 2 weeks (or for 12 weeks). The example evaluates exposure through the inhalation of vapour pathway only, to illustrate the risk characterization process in a simplified manner. To fully delineate potential health risks from exposure to the site, the HHRA needs to consider all other potential exposure pathways.

The HHRA should provide chemical-specific scientific rationale for each COPC, ensuring that the toxicological summary includes information on both the chronic and less-than-chronic (e.g., intermediate) TRVs relevant to the exposure periods. The report should also ensure that intermittent exposures (e.g., repeated monthly exposures) as well as all exposure pathways are addressed, as relevant to each site. See **Section E.3** for an example illustrating the process of assessing intermittent exposures.

E.2.6 Background Information: Toxicokinetic Consideration

Tetrachloroethylene is readily absorbed by humans through inhalation, dermal (in both vapour and liquid forms) and oral exposures (US EPA, 2012; ATSDR, 2019). Absorption via the lungs following inhalation is dependent on the ventilation rate and the duration of exposure. At low levels, absorption can also be impacted by the concentration present in inspired air (ATSDR, 2019).

Regardless of exposure route, once absorbed, tetrachloroethylene distributes to every tissue in the body in both humans and animals (US EPA, 2012; ATSDR, 2019). Due to its high lipophilicity, tetrachloroethylene partitions readily into fatty tissue and breast milk. It has also been shown to cross the blood:brain barrier and the placenta. Animal and human data show that the highest tissue concentrations were found in the adipose tissue, brain and liver, with skeletal muscles having the lowest concentrations.

Tetrachloroethylene is metabolized through two irreversible pathways in humans, rats and mice: oxidation by cytochrome P-450 and glutathione conjugation via glutathione-S-transferase (ATSDR, 2019). The metabolism is qualitatively similar among species; however, the extent of metabolism and the predominant pathways vary between species and exposure routes. Based on limited volunteer studies, the amount of tetrachloroethylene metabolized was also found to vary among different ethnic human populations (ATSDR, 2019).

Oxidative metabolism is hypothesised to occur as a multi-step process in the liver, lung and kidney (Chiu and Ginsberg, 2011), with trichloroacetic acid (TCA) as the primary metabolite. TCA can be further metabolized to dichloroacetic acid. Glutathione conjugation is proposed to occur primarily in the liver and kidney (Chiu and Ginsberg, 2011) with N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine (NAcTCVC) as the primary metabolite. In exposed humans, while TCA, NAcTCVC and other metabolites have been detected in the urine, TCA is the major urinary metabolite (ATSDR, 2019) and is suspected to be the key contributor to the hepatotoxic effect of tetrachloroethylene.

In humans, regardless of the route of exposure, the majority of the absorbed dose of tetrachloroethylene is eliminated by exhalation of the parent compound in breath (80%; ATSDR, 2019) and urinary excretion of metabolism products (about 20% over a long period; ATSDR, 2019) although uncertainty and variability are high (US EPA, 2012). Pulmonary excretion in exhaled breath occurs from desaturation of blood vessel-rich tissues, muscles and adipose tissues. For humans, the half-times for elimination from these three tissue groups are estimated to be 12-16 hours, 30-40 hours and 55-65 hours, respectively (Monster et al., 1979). In a study of 13 individuals occupationally exposed to tetrachloroethylene, the mean biological half-time of urinary excretion of trichloro-metabolites was determined to be 144 hours, or 6 days (Ikeda and Imamura, 1973). Hence, the biological half-life of tetrachloroethylene from inhalation exposure is determined to be 144 hours, based on the half-time of excretion of urinary metabolic products. For intermittent exposures, assessment of half-life and body burden is an important component of the report and should be provided for each chemical of interest as part of a short-duration assessment.

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E.3 Worked Example #3: Antimony, Single Short-Duration Continuous Exposures and Intermittent Exposures

Two worked examples are presented for antimony, a single short-duration continuous exposure scenario and an intermittent exposure scenario. The analysis presented in each case is specific to the exposure scenario as described, including land use, site conditions, exposure duration, receptors, their onsite behaviour and activity patterns.

Any change to the scenario and to any one of the associated exposure parameters would warrant a separate analysis using appropriate TRVs relevant to the exposure durations of interest. The exposure scenarios chosen for analysis must be relevant and justified based on site-specific information, with rationale provided in the HHRA for any TRVs selected for the relevant less-than-chronic exposure durations.

Note that on occasion, HC becomes aware of new critical toxicological or other data that dictate a need to revise HC (2021) TRV for a given substance to ensure the protection of the health of Canadians. In such a case, the revision of the TRV could subsequently require a change in the approach to the risk assessment of short-duration and intermittent exposures to be consistent with the TRV.

E.3.1 Problem Formulation Summary

The worked examples provided below entail exposure scenarios using a hypothetical, remote lighthouse site on an island with elevated concentrations of antimony in soil (95% UCLM of 34 mg/kg). The site includes a dwelling, a few uninhabited buildings and a lighthouse. The scenarios are subject to the following parameters:

- The main dwelling is used as a seasonal residence by the lighthouse keeper and other residents that may include children and adults of all ages for approximately 12 weeks each season from April to October. The actual exposure pattern is unknown.
- The island is accessible by boat, canoe and kayak. People could visit the lighthouse and camp around the area from April to October.
- Contact with antimony in soil may occur via incidental ingestion, dermal contact and inhalation of fugitive dust (all these routes should be considered in calculating the total dose within an HHRA).

While the above exposure pathways remain operative, for the sake of simplicity, these worked examples calculate only *ingestion* of soil exposure for a *toddler* receptor. Please refer to **Appendix C** and HC (2024a) guidance for equations to assess other exposure routes. Note that the soil ingestion values calculated for these hypothetical examples are for illustrative purposes only.

E.3.2 Single Short-Duration Continuous Exposure Scenario

Since the actual exposure pattern of the lighthouse keeper and other residents (that may include people of all ages) is unknown, this example assumes an uninterrupted exposure for a continuous 12 weeks at the site sometime between April 1 and October 31 as a worst-case scenario.

E.3.2.1 Tier 0 Assessment

Tier 0 assessment estimates the highest daily exposure that an individual may receive while on site (i.e., exposure during the most sensitive and exposed life stage) and compares this exposure to the chronic TRV. This calculation shows the expected exposure that a person would receive if the person remained on site over the 12-week period. If this assessment is completed for a non-carcinogenic effect and the HQ is 0.2 or below 0.2, then no further action would be required. Only those COPCs found to have an HQ > 0.2 (for an individual during the most sensitive and exposed life stage) in Tier 0 assessment would carry forward to the next tier.

E.3.2.1.1 Exposure Assessment for Tier 0 Assessment

The estimated daily exposure for soil ingestion that a person would receive while present on this site is calculated using the equation below, assuming continuous chronic daily exposure at a Tier 0 assessment (see **Section 3.1** for general equation). The sample calculation for soil ingestion shown below is for a toddler – a receptor typically known for higher soil ingestion rates due to frequent hand-to-mouth activity.

$$Dose = \frac{C_S * IR_S * RAF_{oral} * D_2 * D_3}{BW}$$

$$= \frac{34\ mg/kg * 0.00008\ kg/day * 1.0 * \frac{7\ days}{7\ days} * \frac{52\ weeks}{52\ weeks}}{16.5\ kg}$$

$$= 0.00016\ mg/kg\ bw/day \text{ each day while on site}$$

Where $Dose$ = daily dose (mg/kg bw/day)
C_S = concentration of contaminant in soil (mg/kg)
IR_S = receptor soil ingestion rate (kg/day)
RAF_{oral} = relative absorption factor from the GI tract, assumed to be 100% or 1 (unitless)
D_2 = days per week exposed/7 days
D_3 = weeks per year exposed/52 weeks
BW = body weight (kg)

E.3.2.1.2 Applicable TRVs for Tier 0 Assessment

The Tier 0 assessment applies the chronic TRV of 0.00014 mg/kg/day (CalEPA, 2016) to assess potential risks from chronic antimony exposure. The CalEPA chronic RfD is based on a rat study (Poon et al., 1998) in which the experimental animals were exposed daily to antimony in drinking water for 90 days. The study identified a NOAEL of 0.06 mg Sb/kg bw/day based on liver effects (liver anisokaryosis) in the male rats. CalEPA (2016) derived a POD of 0.14 mg Sb/kg bw/day (BMDL) based on a benchmark response of 10% (instead of 5%) over background because the observed effects were considered mild and of minimal biological significance. A total UF of 1000 (10 for interspecies extrapolation, 30 for variation in the human population, $\sqrt{10}$ for extrapolation from subchronic to lifetime exposure) was applied to the POD to derive the RfD. Readers can refer to **Section E.3.4.3** for the rationale why the CalEPA chronic TRV of 0.00014 mg/kg/day has been selected for this worked example.

E.3.2.1.3 Risk Characterization for Tier 0 Assessment

The HQ is calculated by dividing the daily exposure (dose) received while on site by the TRV.

$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.00016\ mg/kg\ bw/day}{0.00014\ mg/kg\ bw/day} = 1.1$$

As previously noted, this simplified worked example serves to illustrate the process of a Tier 0 assessment. An HHRA should consider all operable exposure pathways, including but not limited to dermal contact with soil and inhalation of fugitive dust, with the total exposure from all operable exposure pathways then compared to the TRV with a target HQ of 0.2. Alternately, if background exposures from all pathways (i.e., exposures to the same COPC from other sources such as food, water, consumer products, soil, air) are also included, an overall HQ of 1 or less than 1 indicates that no adverse health effects would be expected.

The Tier 0 assessment above found an HQ > 0.2 for antimony via soil ingestion alone under a chronic exposure scenario, therefore a short-duration exposure to antimony in soil will be assessed using Tier I-a level assessment.

E.3.2.2 Tier I-a: Assessment Based on Direct Application of TRVs of Relevant Duration

Tier I-a assessment is conducted by using a short-duration TRV that is applicable for the entire duration of a single exposure episode. As indicated above, this assessment assumes an uninterrupted exposure for 12 continuous weeks as the worst-case scenario. **Table E.3.1**, below, outlines the exposure categories used in assessing less-than-chronic exposures. As per this table, a published intermediate duration TRV relevant for a 12-week exposure period would be applicable, which is consistent with the exposure period at this site.

Table E.3.1 Updated exposure duration categories for contaminated sites risk assessment

Exposure Duration Category	Definition
Acute exposure[1]	exposure for 24 hours or less (≤24 hours)
Short-term exposure[1]	repeated exposure for more than 24 hours, up to 30 days (>24 hours to ≤30 days)
Intermediate exposure[1]	repeated exposure for more than 30 days, up to less than 1 year (>30 days to <1 year)
Chronic exposure	repeated exposure for 1 year or more, and up to a lifetime (≥1 year)

[1] Note that if exposures are repeated, they may be considered chronic even if they are not continuous.

E.3.2.2.1 Primary Determinant of Toxic Effects

To determine whether dose averaging may be appropriate for a specific substance, the HHRA must confirm the primary determinant of toxic effects for each individual chemical using information from key

studies cited in the development of a TRV for a particular duration. The critical effects that form the basis for deriving the oral TRVs for antimony were:

- Focal ulceration of forestomach in mice (TRV applied to 14-day exposure) (ATSDR, 2019).
- Decreased blood glucose levels (intermediate TRV) (ATSDR, 2019).

Experimental mice exhibited focal ulceration in their forestomachs from oral exposure to antimony for 16 days (National Toxicology Program [NTP], 1992; Dieter et. al., 1991). This effect is indicative of GI tract irritation, which has also been reported in exposed humans (Dunn, 1928) and other animals (Tylenda et al., 2021) resulting in vomiting and diarrhea. Haber et. al. (2016) suggested that these GI effects are likely due to elevated concentration of antimony in the GI tract rather than the total dose. Likewise, decrease in blood glucose levels, a rapid physiological effect on life-critical systems that occurs before adaptive responses, is typically driven by tissue concentration (Haber et. al., 2016).

As the literature indicates that peak concentration may play a role in the toxicity of antimony following oral short-term and intermediate exposures, dose averaging is not recommended for these exposure durations.

E.3.2.2.2 Exposure Assessment for Tier I-a for 12-Week Continuous Exposure

The Tier I-a assessment calculates the exposure of the seasonal resident for a continuous 12-week period from April to October. Since peak tissue concentration has been shown to play a role in antimony toxicity, the estimated daily dose is calculated for a toddler using input soil concentrations that represent reasonable maximum exposures (see **Appendix C**). In this example, the statistics used to estimate the daily exposure (dose) were based on the 95% UCLM of antimony in soil of 34 mg/kg. This calculation yields a daily exposure (dose) of 0.00016 mg/kg bw/day, which is similar to the Tier 0 assessment, and does not involve dose averaging.

$$Dose = \frac{34\ mg/kg * 0.00008\ kg/day * 1.0}{16.5\ kg} = 0.00016\ mg/kg\ bw/day$$

Table E.3.2 Duration of exposure for a seasonal resident (months) for 12-week continuous exposure

Month	A	M	J	J	A	S	O
Time on site	✓	✓	✓	-	-	-	-
Total Duration	12 weeks						

✓ = 1 month of exposure (approximately 4 weeks) on site

E.3.2.2.3 Applicable TRV for Intermediate Exposure

ATSDR (2019) provides an intermediate MRL of 0.0006 mg Sb/kg bw/day for antimony based on a 13-week study, which is appropriate for use in a Tier I-a assessment for a 12-week exposure. This TRV is based on a 13-week study in female rats (Poon et al., 1998) exposed to antimony in drinking water. The study identified a NOAEL of 0.06 mg Sb/kg bw/day based on a decrease in serum glucose levels. A total

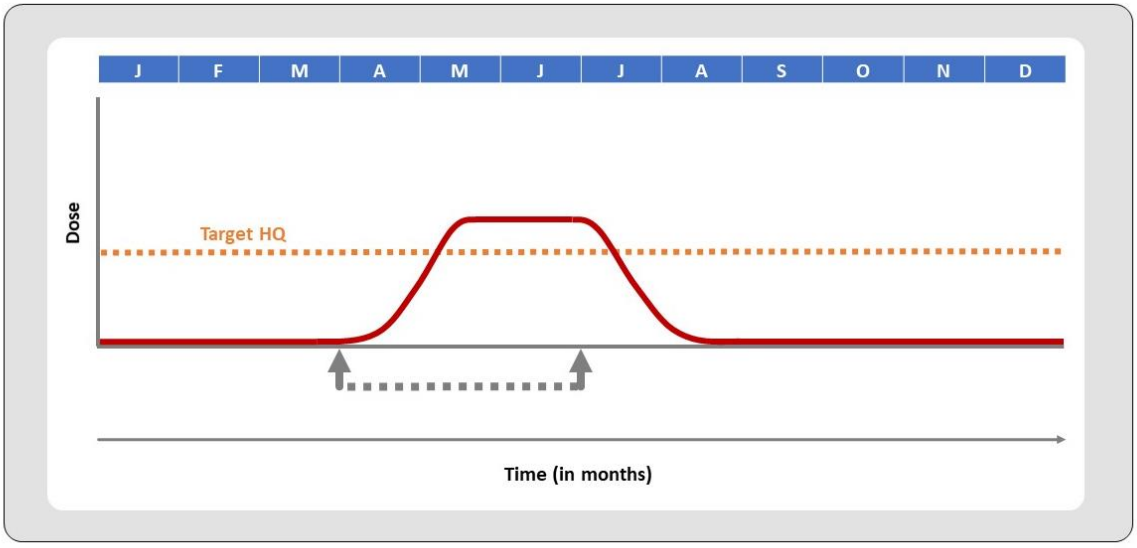
UF of 100 was applied (10 for extrapolation from rats to humans; 10 for human variability) in deriving the intermediate TRV. Readers can refer to **Section E.3.4.2** for why the ATSDR intermediate MRL of 0.0006 mg Sb/kg bw/day has been selected for this worked example.

E.3.2.2.4 Risk Characterization for Tier I-a for 12-Week Continuous Exposure

The HQ calculated in the risk characterization stage is the dose divided by the intermediate TRV, which exceeds a target HQ of 0.2 when calculating potential risks due to ingestion of antimony in soil for a toddler who remains on site for the entire 12 weeks in this hypothetical example. As previously indicated, the HHRA would also need to consider all other operable exposure pathways, such as dermal contact with soil and inhalation of fugitive dust, and compare the total exposure to the TRV with a target HQ of 0.2. In an HHRA where background exposures from all sources are included in the calculations, a target HQ of 1 may be used.

$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.00016\ mg/kg\ bw/day}{0.0006\ mg/kg\ bw/day} = 0.3$$

Figure E.3.1 Estimated exposure to antimony from soil ingestion for a 12-week seasonal toddler resident in a Tier I-a assessment



> A complete HHRA needs to consider all operable exposure pathways, including dermal contact with soil, inhalation of fugitive dust, and other pathways if relevant. This worked example for soil ingestion alone was prepared for simplicity.

E.3.2.3 Mathematical Dose Averaging May Underestimate Potential Health Risks

The following example explains why averaging the potential 12-week site exposure over a year could underestimate potential human health risks. For antimony, the following equation for soil ingestion would be incorrect and should not be used.

$$Dose = \frac{C_S * IR_S * RAF_{oral} * D_2 * D_3}{BW}$$

$$= \frac{34\ mg/kg * 0.00008\ kg/day * 1.0 * \frac{7\ days}{7 days} * \frac{12\ weeks}{52\ weeks}}{16.5\ kg}$$

$$= 0.000038\ mg/kg\ bw/day$$ assuming 12 weeks averaged over 12 months

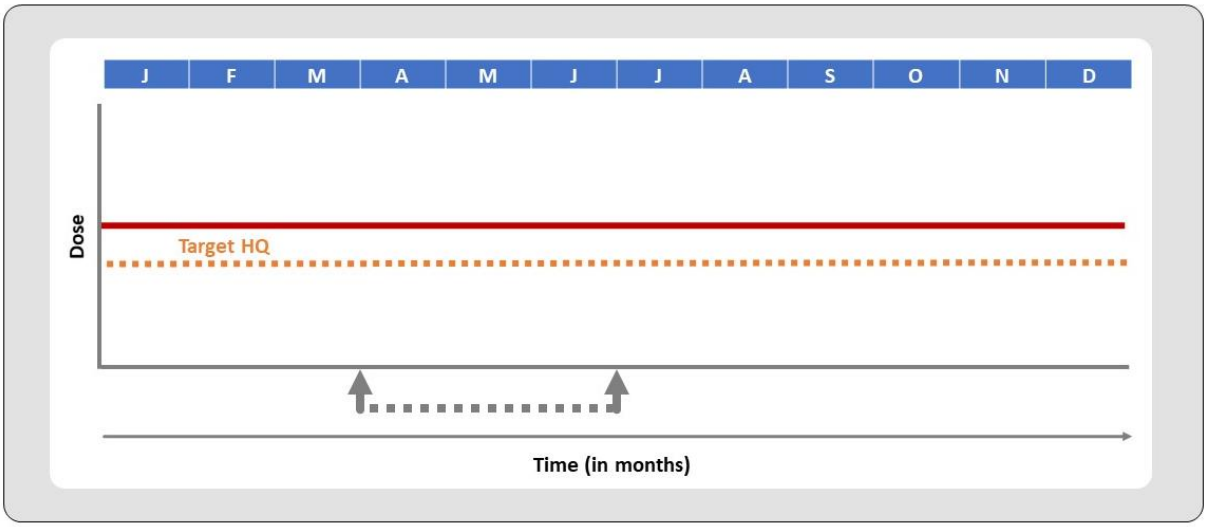
Where

$Dose$	=	daily dose (mg/kg bw/day)	D_2	=	days per week exposed/7 days
C_S	=	concentration of contaminant in soil (mg/kg)	D_3	=	weeks per year exposed/52 weeks
IR_S	=	receptor soil ingestion rate (kg/day)	BW	=	body weight (kg)
RAF_{oral}	=	relative absorption factor from the GI tract, assumed to be 100% or 1 (unitless)			

$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.000038\ mg/kg\ bw/day}{0.00014\ mg/kg\ bw/day} = 0.27$$

Although the calculation appears to be mathematically correct, it assumes that the seasonal resident would receive an average daily exposure over the course of a year, which is incorrect. Because of the exposure characteristics in this worked example, the chronic and intermediate TRV values (as well as other factors), which are specific to antimony, averaging a 12-week exposure over a year yields an HQ with a similar numerical value as the Tier I-a assessment (**Section E.3.2.2**). Nevertheless, peak levels of exposure received over each day of the duration at the site would not be consistent with the mathematically calculated amortized exposure. The resulting assessment may underestimate potential health risks because the total daily intake of a person is assumed to be spread over 12 months instead of capturing peak exposure and related toxic effects during the short exposure duration (e.g., 12 weeks). Hence, the site-specific risk assessment report should demonstrate that dose averaging would not underestimate risk.

Figure E.3.2 Estimated yearly exposure to antimony from soil ingestion for a seasonal toddler resident incorrectly applying dose averaging



E.3.2.4 Conclusion

Based on this worked example, the HHRA may conclude that the levels of antimony found on site (i.e., 34 mg/kg) may pose a potential health risk due to soil ingestion to a seasonal toddler resident who remains on site for 12 continuous weeks. The example evaluates exposure through the soil ingestion pathway only, in order to illustrate the risk characterization process in a simplified manner. To delineate fully the potential health risks from exposure to the site, each HHRA report needs to include all relevant exposure pathways.

The HHRA should provide chemical-specific scientific rationale for each COPC, ensuring that the toxicological summary includes information on both the chronic and less-than-chronic TRVs (e.g., intermediate TRV for this scenario) relevant to the exposure periods. The HHRA should also ensure that intermittent exposures (e.g., repeated monthly exposures) as well as all exposure pathways are addressed, as relevant to each site. See **Section E.3.3** below for a worked example illustrating the process of assessing intermittent exposures to antimony.

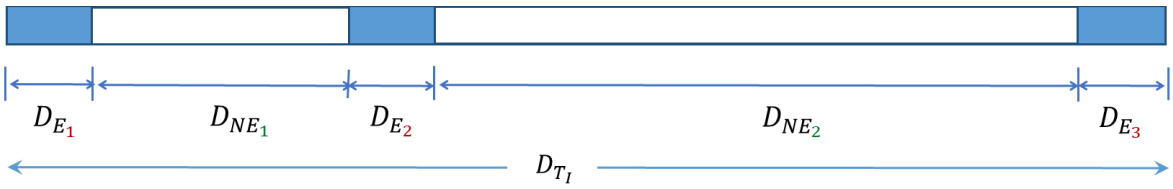
E.3.3 Intermittent Exposure Scenario

In this hypothetical scenario, campers are visiting this remote site intermittently during the season from June to August and each visit is expected to last for one week. While any intermittent exposure pattern is possible, for illustrative purposes, the exposure scenario of interest for the visiting camper at this site is defined by the following parameter, as depicted in **Figure E.3.3** below.

- The visiting campers spend one week every time they visit the site.
- They stay off the site for 20 days between the first and second visit; the gap between the second and third visit lasts 51 days.
- From June to August, the campers spend a total of 3 weeks (or 21 days) at the site.

- The total duration (time between when initial exposure begins and when the final exposure episode ends) of the intermittent exposure scenario for the visitor is 92 days.

Figure E.3.3 Intermittent exposure scenario of a visiting camper



Where:

= Exposure episode, denoted E

= Non-exposure interval, lasting > 2 days and denoted NE

D_{E_i} = Duration of exposure episode i of 7 days, where i varies between 1 and 3 in this exposure scenario

D_{NE_1} = Duration of the non-exposure interval NE_1 of 20 days

D_{NE_2} = Duration of non-exposure interval NE_2 of 51 days

D_{T_I} = Duration of the entire intermittent exposure scenario of 92 days

E.3.3.1 Tier 0 Assessment

The Tier 0 assessment for this intermittent exposure scenario would be identical to the one performed in **Section E.3.2** for a single continuous exposure. As Tier 0 calculates the highest daily exposure for each day spent on site (i.e., exposure during the most sensitive and exposed life stage), which provides a daily exposure identical to the calculation for chronic exposures, the result is a daily exposure estimate of 0.00016 mg/kg bw/day from soil ingestion for a toddler camper. Since this daily exposure yields an HQ > 0.2 via soil ingestion alone under a chronic exposure scenario, more detailed evaluation is required to estimate potential risk associated with intermittent exposure to antimony in soils on the site.

E.3.3.2 Evaluation of Non-Cancer Health Risk due to an Individual Exposure Episode (Tier I-a Assessment)

Tier I-a assessment of the health impact from a single exposure episode uses a less-than-chronic TRV that is applicable to the duration of each individual episode. In this instance, for an individual 1-week exposure episode, the HHRA would choose a published short-duration TRV for a minimum one week in duration to avoid underestimating potential health risks for the toddler camper. As discussed above in **Section E.3.2.2.1**, since peak concentration may play a role in health effects, dose averaging would not apply.

E.3.3.2.1 Tier I-a Exposure Assessment for 1-Week Exposure Episode

For the purposes of this worked example, Tier I-a assessment of a single exposure episode calculates exposure for a 1-week period. The assessment does not consider periods of non-exposure that separate multiple exposure periods at this stage (see **Figure E.3.3** above for clarification on occurrence of exposure episodes).

Since it has been determined that peak concentration may play a role in antimony toxicity (See **Section E.3.2.2.1**), the Tier I-a exposure calculation for a toddler for a single 1-week exposure would be similar to the Tier I-a calculation for a 12-week continuous exposure shown above in **Section E.3.2.2.2**. Hence the estimated daily exposure (dose) would be 0.00016 mg/kg bw/day for a toddler camper on a site with antimony in soil at levels of 34 mg/kg.

E.3.3.2.2 Applicable TRV for 1-Week Exposure

ATSDR (2019) provides an MRL of 1 mg Sb/kg bw/day, which they identify as applicable to an exposure period of up to 14 days. For this reason, this MRL may be applied to an individual exposure episode of one week in this assessment. The ATSDR TRV is based on a study (NTP, 1992; Dieter et al., 1991), in which mice were exposed to antimony potassium tartrate (APT) in drinking water for 14 days. A NOAEL of 99 mg Sb/kg bw/day was identified based on an increased incidence of focal ulceration in the forestomach. A total UF of 100 was applied (10 for interspecies extrapolation; 10 for human variability) to derive this TRV.

Application of this short-term TRV would be appropriate for a single individual 1-week exposure episode, but would not provide insight on the potential health effects at a site where an exposure episode is repeated intermittently over an extended period. The latter scenario requires consideration of toxicokinetics and toxicodynamics, on a chemical-specific basis (see **Section E.3.3.3**, below).

E.3.3.2.3 Risk Characterization for Tier I-a for 1-Week Exposure Episode

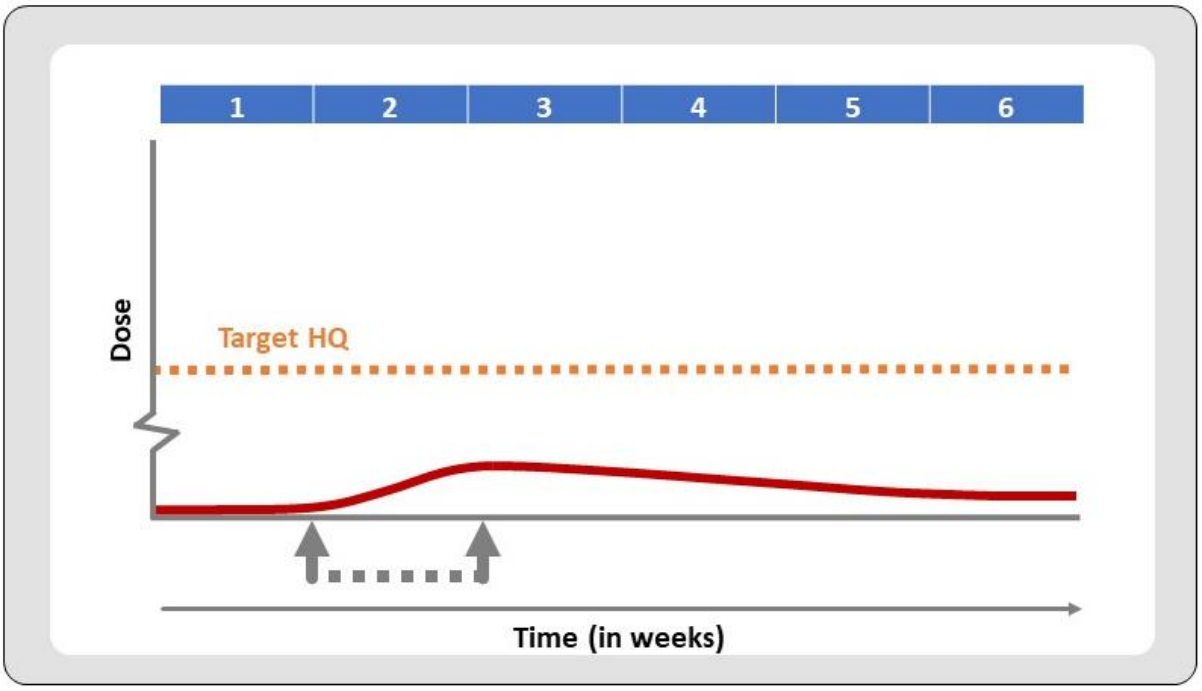
The HQ calculated in the risk characterization stage for a 1-week exposure period is below a target HQ of 0.2, indicating that no appreciable health effects are expected from an individual exposure episode of one week via the soil ingestion pathway.

$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.00016\ mg/kg\ bw/day}{1\ mg/kg\ bw/day} = 0.0002$$

As previously indicated, the risk assessment would also need to consider all operable exposure pathways, including but not limited to dermal contact with soils and inhalation of fugitive dust, and compare the total exposure to the TRV with a target HQ of 0.2. In an HHRA where background exposures from all sources are included in the calculations, a target HQ of 1 may be used. Should repeat visits to the site be involved, the HHRA would also need to assess potential health effects associated with intermittent weekly exposures (see **Section E.3.3.3**, below).

Note: In this scenario, because TRVs of relevant duration are available for antimony, Tier I-b (Modify Existing TRVs by Adjusting Uncertainty Factors) and Tier II-a (Derivation of *de novo* TRVs for Single Continuous Exposures) would not be required as part of the assessment for an individual exposure episode before proceeding to Tier II-b to assess potential impacts of repeated episodes. In cases where relevant TRVs for single continuous exposures are not available for a given scenario and chemical combination, Tier I-b and II-a assessment may be considered on an as-needed basis.

Figure E.3.4 Estimated exposure to antimony from soil ingestion by a toddler for a 1-week stay in a Tier I-a assessment



E.3.3.3 Evaluation of Non-Cancer Health Risk due to Weekly Exposure Episode Repeated Intermittently from June to August (Tier II-b Assessment)

As noted above, if visiting campers are expected to access the site recurrently, then the HHRA needs to consider potential impacts associated with repeated exposures. The HHRA must also consider all other operable exposure routes.

The need to compare the exposure to a longer-duration TRV relevant to the entire seasonal exposure scenario is contingent upon whether the exposure episodes are discrete or overlapping in a manner that become effectively continuous. Two analyses have been conducted, as illustrated below.

E.3.3.3.1 Is the Chemical or Active Metabolite(s) Entirely Eliminated Between Exposure Episodes?

As discussed in **Section 3.3.2.1** of the main document, a chemical is considered to not accumulate in the body if there are at least five elimination half-lives (of the chemical or active metabolite) between consecutive exposure episodes. Hence, the ability for antimony to accumulate between exposure periods was evaluated. Gerber et al. (1982) reported that antimony was cleared from the body in two phases, with an average half-life ($t_{1/2}$) of 10 days in newborn mice exposed to radioactive antimony in utero. Based on these findings, the non-exposure interval should be at least 50 days (i.e., 5 $t_{1/2}$) for antimony to be 97% cleared from the body, which is near complete removal.

For a visiting camper with three 1-week exposure episodes (21 days total) throughout the season (92 days), the first non-exposure interval is 20 days (shorter than 50 days), resulting in continual accumulation of antimony during the first 34 days of the season. **Therefore, dose averaging over this**

34-day period would not be appropriate in this scenario. Since the second non-exposure interval lasts 51 days, the additional antimony body burden from the first and second on-site exposure episodes would be cleared from the body before the third visit. Whether the first 34-day and the last 7-day exposure episodes can be treated as two separate exposure events depends on whether any significant biological changes occurring in the first 34 days will accumulate and progress through the next 51 days even though antimony is not expected to physically persist in the body during this period.

Figure E.3.5 below provides a synopsis of the exposure timeline to antimony the body experiences internally from June to August.

Figure E.3.5 Temporal exposure pattern to antimony experienced internally by a visiting camper resulting from intermittent exposure scenario shown in Figure E.3.3

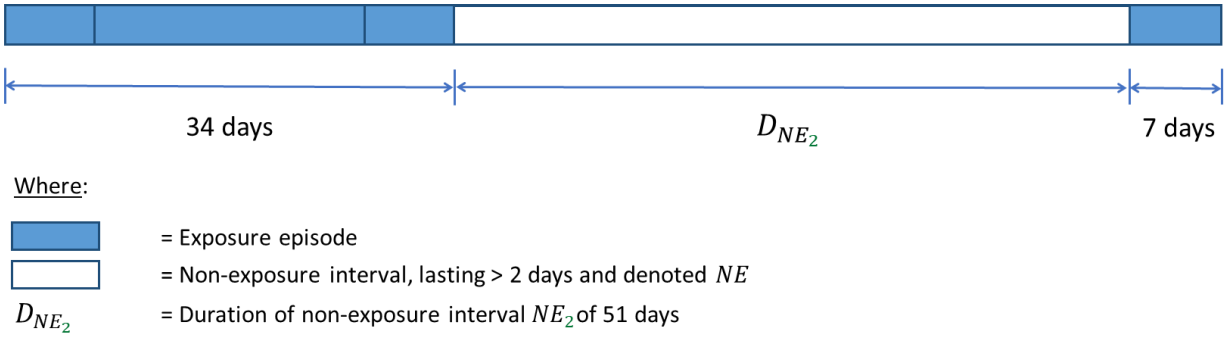
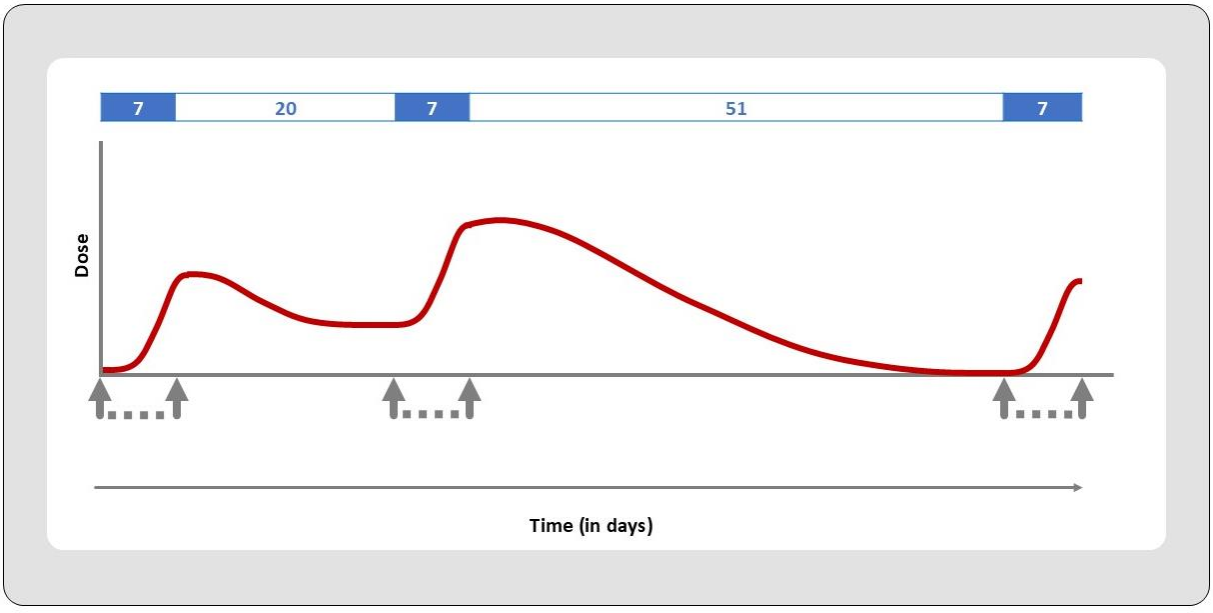


Figure E.3.6 Internal exposure to antimony from soil ingestion by a toddler for a 1-week visit repeated intermittently from June to August based on visiting schedule as shown in Figure E.3.3



E.3.3.3.2 Do Effects Persist Beyond Non-Exposure Interval?

While antimony from on-site exposure may not physically persist in the body during the D_{NE_2} non-exposure interval, whether any significant biological changes will accumulate and progress with repeated exposure requires further assessment.

Since antimony persists in the body in the first 34 days of the season, an intermediate TRV (applicable to an exposure of more than 30 days and less than a year) would be relevant. As discussed in **Section E.3.2.2.3**, the basis of the available intermediate TRV is a decrease in serum glucose levels in rats (Poon et al., 1998). In addition, antimony has been shown to elicit developmental effects in rats from in utero exposure, such as delay in fetal skeletal development (ECHA, 2014). Combined pre- and postnatal exposure to antimony has been shown to result in developmental effects such as reduced postnatal growth and impaired vasomotor response in rat pups (Rossi et al., 1987). Postnatal exposure alone also induced impaired vasomotor response in pups (Angrisani et al., 1988). Both developmental toxicity and decrease in serum glucose levels were considered suspected effects in humans (ATSDR, 2019). Since key events related to developmental effects are likely persistent (discussed in **Section 3.3.2.1** in the main document**)**, the biological changes resulting from the first 34 days of antimony exposure is expected to accumulate through the 51-day non-exposure interval. Therefore, the exposure episodes overlap each other to become effectively continuous from June through August. This information is a key factor in identifying the applicable TRV for the intermittent scenario under consideration, as discussed in **Section E.3.3.3.3**.

E.3.3.3.3 Comparison with Longer-Duration TRV Relevant to Entire Intermittent Exposure Scenario

As discussed in **Sections E.3.3.3.1 and E.3.3.3.2**, the exposure episodes in the intermittent exposure scenario (shown in **Figure E.3.3** above) to antimony are deemed to overlap to become effectively continuous throughout the 92 days from June to August. As such, daily exposure for the entire exposure duration (from June to August) would need to be compared with a TRV relevant to 92 days. A published intermediate duration TRV (applicable to repeated exposures of >30 days and <1 year as per **Table E.3.1** above) of 0.0006 mg Sb/kg bw/day is relevant in this case. Refer to **Section E.3.2.2.3** for the basis of this intermediate duration TRV.

Two factors contribute to making the internal exposure of this intermittent exposure scenario effectively continuous:

- Continual accumulation of antimony in the body in the first 34 days (discussed in **Section E.3.3.3.1**).
- Persistence of effects through the 51 days in-between the first 34-day and the last 7-day periods even though the visiting camper is not on-site and elimination of antimony from the body is expected to be near complete in 50 days (discussed in **Section E.3.3.3.2**).

The first factor results in a continual increase in the tissue levels of antimony throughout the first 34 days of exposure; dose averaging during this time period is therefore not appropriate. Whether the second factor can support dose averaging through the 51 days of non-exposure depends on the MOA involved and the primary determinant of toxic effect. As discussed in **Section E.3.2.2.3**, the available

intermediate TRV relevant to the first 34 days was based on a decrease in serum glucose levels in rats (Poon et al., 1998). Since decrease in blood glucose levels is typically driven by tissue concentration (Haber et. al., 2016), dose averaging is not recommended. The potential for developmental toxicity further supports the recommendation not to dose average (See **Section 3.2.3** of the main document).

Since peak concentration is determined to drive antimony toxicity, the exposure calculation for a toddler for a single 92-day "continuous" exposure scenario would be similar to the Tier I-a calculation for a 12-week continuous exposure shown above in **Section E.3.2.2.2**. Hence the estimated daily exposure (dose) would be 0.00016 mg/kg bw/day for a toddler camper on the site intermittently from June to August with antimony in soil at levels of 34 mg/kg.

E.3.3.3.4 Risk Characterization

The HQ calculated in the risk characterization stage (dose divided by the intermediate TRV) exceeds a target HQ of 0.2 when estimating potential risks due to ingestion of antimony in soil for a toddler who visits the site intermittently from June to August as described in this section (see **Section E.3.3**).

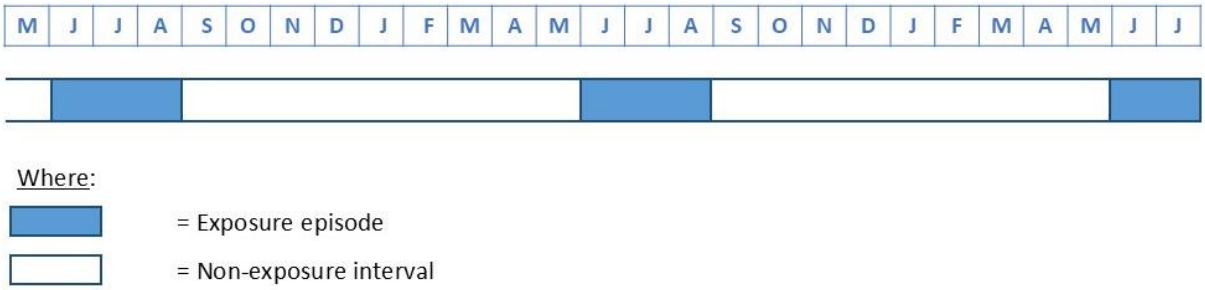
$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.00016\ mg/kg\ bw/day}{0.0006\ mg/kg\ bw/day} = 0.3$$

This HQ exceeds the target HQ of 0.2. As previously indicated, the HHRA would also need to consider all operable exposure pathways, such as dermal contact with soil and inhalation of fugitive dust, and compare the total exposure to the TRV with a target HQ of 0.2. In an HHRA where background exposures from all sources are included in the calculations, a target HQ of 1 may be used. Should repeat annual visits to the site be involved, the HHRA would also need to assess potential health risks associated with seasonal intermittent exposures that are repeated annually (See **Section E.3.3.4**).

E.3.3.4 Evaluation of Non-Cancer Health Risk for Campers from Making Intermittent Weekly Visits to the Site from June to August Every Year

As discussed in **Sections E.3.3.3.1** and **E.3.3.3.2**, the exposure episodes in the intermittent exposure scenario (shown in **Figure E.3.3** above) to antimony are deemed to overlap to become effectively continuous throughout the 92 days from June to August. Should the camper maintain the same exposure pattern annually between June to August at the site, the June-to-August periods would in effect become continuous "exposure episodes". These June-to-August "exposure episodes" and the September-to May non-exposure intervals would become a multi-year intermittent exposure scenario. **Figure E.3.7** presents the temporal exposure pattern to antimony the visiting camper would experience internally under such conditions.

Figure E.3.7 Temporal exposure pattern to antimony experienced internally by a visiting camper resulting from a 1-week visit repeated intermittently from June to August every year



The Tier I-a assessment of this multi-year intermittent exposure scenario evaluates the health risk from a single June-to-August "exposure episode", which has been completed (described in **Section E.3.3.3**) and will not be repeated. The next step in the intermittency analysis (Tier II-b) evaluates whether the chemical or its effect would persist through the September-to-May non-exposure interval. This non-exposure interval lasts 9 months, which exceeds 50 days (i.e., 5 $t_{1/2}$), the minimum antimony requires to be cleared from the body. Though antimony does not physically persist in the body during the September-to-May non-exposure interval (i.e., the chemical is mostly cleared from the body by the end of May), for the same reason provided in **Section E.3.3.3.2**, the biological changes due to antimony exposure are expected to accumulate/progress during this period. Therefore, the June-to-August "exposure episode" would overlap with the June-to-August "exposure episodes" of subsequent years, which is equivalent to a single chronic "continuous" exposure scenario. As such, a chronic TRV is relevant to the entire multi-year exposure scenario and daily exposure would need to be compared with a chronic TRV.

Since peak concentration has been determined to drive antimony toxicity (See **Sections E.3.2.2.1, E.3.3.3.3**), the exposure calculation for a toddler for a multi-year "continuous" exposure scenario would be similar to the Tier I-a calculation for a 12-week continuous exposure shown above in **Section E.3.2.2.2**. Hence, the estimated daily exposure (dose) would be 0.00016 mg/kg bw/day for a toddler camper on the site intermittently from June to August for multiple years with antimony in soil at levels of 34 mg/kg.

The HQ is calculated in the risk characterization stage by dividing the dose by the chronic TRV of 0.00014 mg/kg bw/day (CalEPA, 2016).

$$HQ = \frac{Dose\ (mg/kg\ bw/day)}{TRV\ (mg/kg\ bw/day)} = \frac{0.00016\ mg/kg\ bw/day}{0.00014\ mg/kg\ bw/day} = 1.1$$

The HQ due to ingestion of antimony in soil for a toddler who visits the site intermittently from June to August on a yearly basis exceeds a target HQ of 0.2. As previously indicated, the HHRA would need to consider all operable exposure pathways, such as dermal contact with soil and inhalation of fugitive dust, and compare the total exposure to the TRV with a target HQ of 0.2. In an HHRA where background exposures from all sources are included in the calculations, a target HQ of 1 may be used.

E.3.3.5 Conclusion

Based on this worked example, the HHRA may conclude that the level of antimony estimated for the site, with an exposure point concentration of 34 mg/kg, has the potential to pose a health risk to visitors exposed for one week every 20 days with a gap of 51 days between the second and third visits (i.e., spanning a total of 92 days from the first day to the last day of visits) from ingestion of soil. The potential for health risk applies to visitors who repeat the same exposure pattern on a yearly basis. As stated above, this worked example evaluates exposure through the soil ingestion pathway only, in order to illustrate the risk characterization process in a simplified manner. To fully delineate potential health risks from exposure at a site, the HHRA needs to consider all operable exposure pathways.

The HHRA should provide chemical-specific scientific rationale for each COPC, ensuring that the toxicological summary includes information on both the chronic and less-than-chronic (e.g., short-term) TRVs relevant to the exposure periods. The HHRA should also ensure that intermittent exposures (e.g., repeated monthly or yearly exposures) as well as all exposure pathways have been addressed in the risk characterization phase, as relevant to each site.

E.3.4 Background Information: TRV Selection for Antimony

E.3.4.1 Short-Term TRV Applicable to 1-Week Exposure Episode

ATSDR (2019) provides an acute MRL of 1 mg Sb/kg bw/day, which they define as applicable to an exposure period of up to 14 days. This MRL is consistent with the definition of a short-term TRV in this guidance (i.e., > 24 hours and up to 30 days) and may therefore apply to an exposure period of less than 2 weeks. This MRL was based on a study (NTP, 1992; Dieter et al., 1991), in which mice were exposed to APT in drinking water for 14 days. A NOAEL of 99 mg Sb/kg bw/day was identified, based on an increased incidence of focal ulceration in the forestomach. A total UF of 100 was applied (10 for interspecies extrapolation; 10 for human variability) to derive this TRV.

Another study was reviewed for the purpose of this worked example, with a developmental endpoint. In 2020, Environment and Climate Change Canada (ECCC) and HC identified a 14-day developmental study conducted with sodium hexahydroxoantimonate, which reported a slight delay in fetal skeletal development (ECHA, 2014), and adopted the NOAEL of 49 mg Sb/kg bw/day as the POD. In this study, pregnant female rats were treated orally by gavage (intubation) with dose levels of 0, 100, 300 and 1000 mg/kg bw/day in Methocel once daily from day 6 to 19 of gestation. This POD can potentially be adopted for deriving a TRV applicable to an exposure period of 14 days. However, in its current posting, ECHA (2024) concludes that the effects on skeletal retardation observed in the pre-natal developmental toxicity study with sodium hexahydroxoantimonate to be of low or minimal toxicological significance. The observed delayed ossification effects are considered common findings, spontaneous in nature, can be readily repaired during remodelling postnatally and are not mechanistically linked to malformation (Carney and Kimmel, 2007). These effects were observed only in a small number, with most incidences only slightly above historical control levels (ECHA, 2024). In addition, there is evidence that the effects might be secondary related to disruption of calcium homoeostasis in mothers and not a direct effect of the test substance related to bone development in fetuses, although no maternal toxicity was evident in the study (ECHA, 2024). The high prevalence of this observation also among the controls and the

absence of other critical adverse effects in the fetuses lend further support to the position that the observed effects are not demonstrative of an adverse effect on fetal development (ECHA, 2024). As such, the ATSDR acute MRL of 1 mg Sb/kg bw/day was used in this worked example.

E.3.4.2 Intermediate-Duration TRV for Antimony

Two candidate TRVs may be applicable to an intermediate exposure period of more than 30 days and up to 364 days: the ATSDR (2019) intermediate MRL of 0.0006 mg Sb/kg bw/day and the US EPA (2008) provisional subchronic RfD of 0.0004 mg Sb/kg bw/day. The US EPA (2008) adopted the chronic oral RfD developed in 1987 as the provisional subchronic RfD. The US EPA chronic oral RfD (1987) was based on the Schroeder et al. (1970) study, which was considered less ideal for TRV development (see discussion in **Section E.3.4.3**) than the ATSDR (2019) intermediate MRL of 0.0006 mg Sb/kg bw/day, which was adopted as the intermediate TRV for this worked example. The ATSDR (2019) based the intermediate MRL on a decrease in serum glucose level in female rats (Poon et al., 1998) exposed to APT in drinking water for 13 weeks and applied a total UF of 100 (10 for extrapolation from animals to humans; 10 for human variability).

E.3.4.3 Chronic TRV for Antimony

E.3.4.3.1 Published Antimony TRVs for Consideration

a) Chronic RfD by USEPA (1987)

The chronic US EPA (1987) RfD of 0.0004 mg Sb/kg bw/day was based on a LOAEL of 0.35 mg Sb/kg bw/day for reduced life span, altered blood glucose and serum cholesterol levels reported in a rat study by Schroeder et al. (1970). Schroeder et al. (1970) exposed male and female rats to 0 or 5 mg/L of APT in drinking water from weaning until death (about 1000 days). A total UF of 1000 (10 for interspecies conversion, 10 to protect sensitive individuals and 10 to account for use of a LOAEL in the absence of a NOEL) to derive this TRV. The Schroeder et al. (1970) study remains the only chronic oral toxicity study conducted on antimony compounds.

b) TDI by HC (2024b)

HC (2024b) developed a drinking water guideline based on a TDI derived from the NOAEL of 0.06 mg Sb/kg bw/day reported in a subchronic exposure study in rats by Poon et al. (1998) due to histological changes observed in the liver. A total UF of 300 was applied (10 for intraspecies variation, 10 for interspecies variation, and 3 for the use of a subchronic study), resulting in a TDI of 0.0002 mg Sb/kg bw/day.

Poon et al. (1998) exposed rats (15 per sex per dose) to 0, 0.5, 5.0, 50 and 500 mg/L of APT in drinking water (corresponding to 0.06, 0.56, 5.58, 42.17 mg Sb/kg bw/day for males; 0.06, 0.64, 6.13, 45.69 mg Sb/kg bw/day for females) for 90 days. Ten animals per sex were added to each of the control and highest dose groups and were given tap water for a further 4 weeks of recovery for observation. Although the authors did not observe any clinical sign of toxicity in any animal, they reported histological changes in some internal organs such as the liver, thyroid, spleen, thymus and pituitary gland. Some of these changes (such as changes in the thyroid) were considered adaptive in nature and

some showed an apparent dose trend (such as increases in liver anisokaryosis [i.e., variation in size and shape of the nuclei] reaching moderate severity in the high dose groups). The authors reported dose-related decrease in serum glucose in female rats starting at 0.6 mg/kg bw/day and reaching statistical significance in the highest dose group. They observed marked dose-related accumulation of antimony in red blood cells and the spleen starting at 0.6 mg/kg bw/day in both males and females; the accumulation in the spleen persisted among high dose animals through the recovery period. Other reported effects include: decreased red blood cell and platelet counts with increased mean corpuscular volume in the high dose males; reduced body weight gain, as well as reduced food and water intake at the highest dose groups. Based on the histological changes, the marked accumulation of antimony in the spleen and red blood cells and biochemical changes (i.e., decrease in serum glucose level in female rats), 0.06 mg Sb/kg bw/day was identified as the NOAEL for this study.

c) TDI by WHO (2003)

WHO (2003) used the Poon et al. (1998) study; however, WHO derived a TDI from a NOAEL of 6.0 mg Sb/kg bw/day suggested by Lynch et al. (1999) based on reduced body weight gain and reduced water and food intake. Application of a total UF of 1000 (100 for inter- and intraspecies variations and 10 for use of a subchronic study) to the NOAEL yielded the TDI.

d) RfD by CalEPA (2016)

The chronic RfD by CalEPA (2016) and the intermediate MRL by ATSDR (2019) were also based on the Poon et al. (1998) study. CalEPA (2016) identified liver anisokaryosis in male rats as the key health endpoint, as supported by evidence of liver damage and impaired liver metabolism in humans due to antimony exposure from leishmaniasis treatment and in animals in repeated dose studies with antimony. In addition, liver anisokaryosis has been documented as a treatment-related lesion in animals followed by exposure to other xenobiotics such as hydroquinone (NTP, 1989) and toxaphene (ATSDR, 2014). CalEPA (2016) derived a POD of 0.14 mg Sb/kg bw/day (BMDL) based on a benchmark response of 10% (instead of 5%) over background because the observed effects were considered mild and of minimally biological significance. A total UF of 1000 (10 for interspecies extrapolation, 30 for variation in the human population, √10 for extrapolation from subchronic to lifetime exposure) was applied to the POD to derive a chronic RfD of 0.00014 mg Sb/kg bw/day.

e) ECCC and HC (2020) Screening Assessment

Under the Chemicals Management Plan, ECCC and HC (2020) evaluated the risks of 11 antimony-containing substances to human health and the environment using a screening assessment approach. ECCC and HC (2020) adopted a NOAEL of 49 mg Sb/kg bw/day based on a slight delay in fetal skeletal development reported in a developmental rat study conducted with sodium hexahydroxoantimonate (ECHA, 2014) as the POD. This POD was used to characterize health risk in the Canadian general population associated with oral exposure to antimony-containing substances from environmental media, drinking water, food and consumer products. The risk characterization used a margin of exposure approach and no TDI was derived.

E.3.4.3.2 Chronic TRV Selected for Antimony

As there is uncertainty as to which form of antimony people are exposed to from consumer products, the ECCC and HC (2020) assessment assumed that consumers are exposed to trivalent or pentavalent antimony compounds except APT and antimony trichloride. As such, APT and antimony trichloride toxicity data were not considered relevant for risk characterisation. It is worth noting that assessment under the Chemicals Management Plan focuses on exposure of the Canadian population and is generally not specific to a location. On the other hand, risk assessments conducted for contaminated sites are site-specific, generally with environmental levels much higher than typical levels in the Canadian environment. These sites could be contaminated due to industrial and other anthropogenic activities. Since APT has been used in textile and leather processing, as an insecticide and a medicinal ingredient, and is detected in many products, APT can be a potential source of antimony contamination at the sites. Hence, APT may be relevant in the context of contaminated sites risk assessments. Trivalent antimony (such as APT and antimony trichloride) may be more toxic than pentavalent antimony (WHO, 2003). The POD identified in animal studies with APT (Schroeder et al., 1970; Poon et al. 1998; Lynch et al. 1999) is much lower than that based on sodium hexahydroxoantimonate (ECCC and HC, 2020), which is pentavalent, and therefore is protective of all forms of antimony. Hence, for the purpose of this worked example, a POD based on APT exposure was selected. This approach is consistent with the methods used for deriving shorter-duration TRVs (i.e., short-term and intermediate TRVs) that are currently available.

Schroeder et al. (1970) and Poon et al. (1998) exposed animals to APT in drinking water. These studies serve as the data sources for the published TRVs to date. Lynch et al. (1999) and CalEPA (2016) have identified a number of limitations in the Schroeder et al. (1970) study, which makes the study less ideal for TRV development. Some of the limitations are: 1) single dose level that did not provide a clear dose-response relationship; 2) loss of animals due to infection, but the differential impact of infection on animal life span was not considered; 3) flaws and inconsistency in the use of control data to compare to impact due to APT treatment; and 4) limited toxicity evaluation and no evidence of toxicity to substantiate decreased life span. On the other hand, the Poon et al. study (1998) used multiple doses of APT, monitored several more parameters and reported effects at much lower levels than the Schroeder et al. (1970) study. As such, the US EPA (1987) RfD was not selected as the chronic TRV for this worked example.

HC (2024b), WHO (2003) and CalEPA (2016) all derived their TRVs based on the Poon et al. (1998) study. As discussed in **Section E.3.4.3.1,** the WHO derived its TDI from a NOAEL based on reduced body weight gain, reduced food intake and water intake. On the other hand, both HC (2024b) and CalEPA (2016) determined that there are other adverse effects (such as liver effects) at lower doses and derived their TRVs accordingly. The NOAEL used by WHO (2003) is two orders of magnitude higher than the NOAEL identified for liver effects (Poon et al., 1998). Given the increasing supporting evidence of liver damage in humans and in repeated dose animal studies, as well as the documentation of liver anisokaryosis as a toxic response to other chemicals (CalEPA, 2016), the WHO (2003) TDI is not considered further for use in this worked example.

The HC (2024b) TDI of 0.0002 mg Sb/kg bw/day and CalEPA (2016) RfD of 0.00014 mg Sb/kg bw/day are similar in value. Because the CalEPA (2016) RfD was developed using benchmark dose modelling based on the original raw data, it was used as the chronic TRV in the antimony worked example for illustrative purposes.

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E.4 Worked Example #4: Trichloroethylene (TCE)

This section presents a short rationale related to dose averaging of TCE exposure. Whether dose averaging is appropriate is influenced by the primary determinant of toxic effects for individual chemical using information from key studies cited in the development of a TRV for a particular duration.

Note that on occasion, HC becomes aware of new critical toxicological or other data that dictate a need to revise HC (2021) TRV for a given substance to ensure the protection of the health of Canadians. In such a case, the revision of the TRV could subsequently require a change in the approach to the risk assessment of short-duration and intermittent exposures to be consistent with the TRV.

E.4.1 Dose Averaging Recommendation

Key health effects of TCE from ingestion, inhalation and dermal exposures include developmental, reproductive, liver, kidney, immuno- and neuro- toxicity, as well as cancer. Developmental effects, effects on the thymus and immune systems are currently considered to be the non-cancer health effects that occur at the lowest levels and are the basis of the HC (2021) non-cancer TRV for TCE.

Dose averaging of a short-duration exposure over a longer time frame is not recommended for a substance when the TRV is based on teratogenic effects during a critical period of development (e.g., cardiac malformations due to abnormal fetal development). For instance, female pregnant rats exposed to TCE via drinking water reported increased incidences of heart abnormalities in fetal rats (Johnson et al., 2003; Dawson et al., 1993). There is also epidemiological evidence in humans reporting associations between in utero TCE exposure and an increased risk of congenital heart defects (Bove et al., 1995; Bove 1996; Forand et al., 2012; Goldberg, 1990; Yauck et al., 2004). The US EPA has published a weight of evidence analysis on gestational TCE exposures and the congenital heart defects endpoint (Makris et al., 2016). This peer-reviewed published article provides a summary and a systematic evaluation of the available literature including epidemiology studies, animal toxicity studies, and mechanistic studies. This systematic evaluation formed the basis of US EPA's recent determination of positive overall evidence that TCE exposure may result in congenital heart defects in humans (US EPA, 2020). Based on the available information, if a pregnant person is exposed to elevated levels of TCE within the crucial eight weeks during which the fetal heart develops (Stanford Medicine Children's Health, 2023; University of Rochester Medical Center, 2023), there is a potential for an increased incidence of congenital heart defects in the fetus.

In addition to developmental effects, short-duration exposure to elevated concentrations of TCE can lead to CNS effects. Neurobehavioural function effects and CNS depression (light-headedness, dizziness, or lethargy) have been reported in humans exposed to high concentrations over short durations (US EPA National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances, 2009). In addition to anesthetic effects at high concentrations, TCE exposure in humans has also been associated with neurodegenerative disorders (US EPA, 2011). These neurological effects have been confirmed in animal studies. Kishi et al. (1993) reported concentration-dependent effects in male Wistar rats exposed to TCE in air, with higher doses being associated with marked CNS-depression and anesthesia. A number of other animal neurotoxicity studies reported effects on the central vestibular system and trigeminal nerve, ototoxicity, incapacitation of postural maintenance and seizures (Niklasson et al., 1993; Crofton

and Zhao, 1997; Arito et al., 1993; US EPA, 2011). According to WHO (2010), the acute neurological effects of TCE may be more related to maximum blood concentrations than the total dose. This finding provides additional support for the recommendation of no dose averaging of short-duration and intermittent exposures to TCE.

The recommendation of no dose averaging for TCE applies to exposures associated with all land uses, including commercial/industrial land use (i.e., ET is 1 for all land uses and all exposure durations).

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APPENDIX F CATEGORIZATION OF CHEMICALS BY HALF-LIFE

This appendix addresses approaches for identifying the elimination half-life of a substance. The elimination half-life, also known as the biological half-life, is the time it takes for the substance in the body to decrease by 50% (i.e., by half). This metric is useful in determining the rate of elimination for a substance. After five elimination half-lives, approximately 97% of the substance is estimated to have been eliminated from the body, which is considered near complete removal (Ito, 2011).

Substances have varying elimination half-lives. For environmental chemicals, substances having elimination half-lives ranging from months to years would generally be considered as having long half-lives.

Identifying half-lives is a necessary aspect of intermittent exposure analyses because it is important to determine the presence and level of residual chemical in the body during the non-exposure interval before the next exposure. This information is used in conjunction with evaluation of the persistence of effects from the toxicity assessment to determine if a longer-duration TRV is applicable to the entire intermittent exposure scenario for each chemical considered. Note that the shortest non-exposure interval of the intermittent scenario at the site would apply in the assessment. For instance, people may be at a contaminated site for 2 weeks on and 2 weeks off during July and August, then revisit the site the following year. In this example, the assessment would consider re-exposure following the 2-week non-exposure intervals in the summer, as well as re-exposure the following year. Refer to **Section 3.3.2.1** of the main document for guidance on determining whether exposure episodes overlap to become effectively continuous and if a longer-duration TRV is applicable to the entire intermittent exposure scenario.

This appendix provides guidance on approaches to identify elimination half-life data and to categorize a chemical as having “long” or “short” half-life relative to a non-exposure interval at a federal contaminated site. Note that for intermittent exposure analyses, the terminology “short” and “long” is relative to the non-exposure interval in the exposure scenario at each site. Hence, if the interval between exposure episodes is 9 months, then the definition of “short” and “long” half-lives may vary from the definition used when the non-exposure interval is 2 weeks.

F.1 Approaches to Identifying Half-Life Data and Categorizing Chemicals by Half-Life

An HHRA of a contaminated site that includes an assessment of intermittent exposure requires consideration of chemical-specific elimination half-life data, if available. The calculation of half-life is often subjective and highly dependent on the experimental study design and analytical capability, hence chemical-specific data on half-life should include references to the scientific literature used, to allow for technical review. The HHRA should provide information regarding the behaviour of the chemical, using the principles described in the following paragraphs.

If half-life data for a COPC are not available from published literature, a categorical evaluation of its half-life (e.g., “long” or “short” relative to the non-exposure interval) may be based on the chemical structure and the chemical’s basic toxicological information, including mechanistic data. Where distribution data indicate that the chemical accumulates or is stored in an organ or tissue, the organ or

tissue in which the chemical accumulates may be a target for toxicity (e.g., cadmium in kidney [WHO, 2011]). Consideration regarding release of the substance from storage in the future may also be relevant to the HHRA. For example, when lead is stored in bones, it may be released later in life due to bone resorption or lead mobilization, such as during pregnancy, postpartum period and lactation (Gulson et al., 2016; Gulson, Taylor and Eisman, 2016; HC, 2019; ATSDR, 2020). The release from bone can lead to increase in blood lead concentrations from historical exposures and add to the internal dose associated with exposure from the site.

If information is not available on the half-life or distribution of the chemical, the chemical's K_{OW} (octanol:water partition coefficient) can be used to provide information on the propensity of an organic molecule to have a long half-life. K_{OW} is a measure of a chemical's lipophilicity or its propensity to distribute to fat, rather than to the cell's cytosol (OECD, 2002). The more lipophilic the chemical, the higher the K_{OW} value would be. A log K_{OW} equal to or greater than 5 can be interpreted as indicating a likelihood of accumulation in fat (Persistence and Bioaccumulation Regulations, 2000) and thus a tendency to have a long half-life in the body (Sarver et al., 1997). However, this approach can be overly conservative, since it does not account for removal via chemical biotransformation (e.g., metabolism), and care should be used in relying on K_{OW} as the sole basis for estimating half-life categories (OECD, 2002). Since biotransformation may affect the half-life of a chemical, any available data on a chemical's biotransformation should be considered in the assessment. The report should include chemical-specific rationale for any half-lives estimated. If insufficient data were available to estimate the half-life of the COPC, it would be conservative to classify the chemical as having a "long" half-life and to assume that it would remain in the body during non-exposure intervals. Thus, a longer-duration TRV would be applicable to the entire exposure scenario for this chemical.

F.2 Example: Chemical Half-lives in Intermittent Exposure Analysis

This section provides a short discussion of how a chemical's half-life informs the assessment of risk if people are exposed to chemicals at a site intermittently. The discussion is illustrated by an example with each non-exposure interval lasting for 2 weeks or more. The analysis below would be applicable if the non-exposure interval is 6 months. However, if the non-exposure interval is less than 2 weeks, the analysis will be different.

The categorization of half-life for each chemical depends on the intermittent exposure scenario that is considered in an HHRA. Categorization would allow the risk assessor to identify whether the chemical will be expelled from the body during the non-exposure interval or whether the chemical would persist in the body before the next exposure. This issue is important for assessing the exposure that people receive as well as identifying the appropriate TRV to use as it would not be appropriate to use a shorter-duration TRV if the exposure is in fact chronic (e.g., continues to be present in the body between external exposure episodes).

People have background exposure to many COPCs due to their presence in the environment, such as food, water, consumer products, soil and air. The amount or concentration of these substances in the human body at any given time reflects the body burden as a result of consistent background exposure. When people visit contaminated sites and are exposed to a COPC, the amount or concentration of the

COPC in the body would increase. It takes about 5 biological (or elimination) half-lives for the COPC concentration in the body to reach a new steady state (Ito, 2011). If people leave the site and exposure to the COPC ceases, the COPC concentration in the body would gradually decrease. It would take about 5 biological half-lives for the COPC concentration in the body to come down to the original baseline level due to near complete removal of the added dose from exposure at the site (Ito, 2011). If people revisit the site intermittently, whether the additional COPC exposure from the site is cleared from the body during the non-exposure interval depends on whether the non-exposure interval is longer than 5 elimination half-lives. The amount of body burden has no impact on whether the additional COPC exposure from the site visit would completely clear from the body during the non-exposure interval prior to return to the site. Should the time between visits be less than 5 biological half-lives, the internal exposure would be determined by the new steady state COPC concentration in the body (i.e., sum of original baseline level and added level due to new exposure).

The approach used in an HHRA should be health protective and should include all relevant data. **Table F.1** provides a list of some common COPCs at contaminated sites, their estimated elimination half-lives, and half-life classifications (i.e., "short" or "long" relative to the non-exposure interval). For each of the chemicals listed in this table, the relevant document(s) was reviewed for information on the elimination half-lives for the chemical and its metabolites following oral or inhalation exposure[6]. For most of the listed chemicals, information on half-life in humans was available. Where no data on the whole-body half-life in humans were identified, the half-life data in the most relevant experimental animal species (or the species with the longest half-life) were adopted. If information on the half-life of the chemical of interest is not available, the chemical should be assumed to have a "long" half-life relative to the non-exposure interval in order to not underestimate potential risk in an HHRA. Note that for some substances, such as styrene and vinyl chloride in **Table F.1**, the half-lives are either "short" or "long" depending on the length of the non-exposure intervals.

The risk assessment needs to identify the half-life and calculate when the chemical would be effectively eliminated from the body. Provided that elimination mechanisms are monophasic and have not been saturated (i.e., first-order elimination), a non-exposure interval of five half-lives removes approximately 97% of the chemical/active metabolite from the body, which is considered to be near-complete removal (Ito, 2011). For example, for chemicals with half-lives of 60 hours (2.5 days) or less, five half-lives correspond to 12.5 days or less. A 2-week (14 days) non-exposure interval would be sufficient time for these chemicals/metabolites to be removed from the body. In an intermittent exposure scenario with at least 2 weeks between exposures, these chemicals (i.e., with half-lives of 60 hours or less) would be considered to have "short" half-lives relative to the non-exposure interval. Hence, clearance of these chemical/metabolites (near-complete removal, i.e., >97% removal of the chemical and metabolites) from the body between exposures can be assumed. The consideration of time between exposures should also include the potential for exposure to the same chemical in background environmental media (e.g., food, water soil) or at other contaminated sites.

[6] For dermal exposure, the time required for dermal absorption would need to be considered as well as the time shown for removal of the chemical and its metabolites from the body. A similar issue applies to inhaled chemicals that are slowly absorbed from the lung.

It is important that the HHRA considers sensitive populations who may have a longer elimination period, as relevant. For instance, elderly people may have slower renal clearance than younger populations (Weinstein and Anderson, 2010; Zhang et al., 2013; Glassock and Rule, 2016; Aaseth et al., 2021).

Table F.1 Oral or inhalation biological half-lives of some chemicals and their classification relative to non-exposure interval between consecutive exposure episodes

Chemical	Biological Half-Life	Reference	Half-Life classification		
			Non-Exposure Interval of 2 Weeks	Non-Exposure Interval of 2 Months	Non-Exposure Interval of 6 Months
Inorganic arsenic	300 hours	Lai et al. (2005); US EPA (2011)	"long"	"long"	"short"
Benzene	13-31 hours	WHO/IPCS (1993)	"short"	"short"	"short"
Benzo[a]pyrene	22-30 hours	ATSDR (1995)	"short"	"short"	"short"
Boron	~24 hours	ATSDR (2010a)	"short"	"short"	"short"
Cadmium	10-33 years	WHO (2011)	"long"	"long"	"long"
Ethylbenzene	25 hours	ATSDR (2010b)	"short"	"short"	"short"
Lead	10-30 years	HC (2013, 2021)	"long"	"long"	"long"
PCBs	4.6-41 years	Seegal et al. (2011)	"long"	"long"	"long"
PCDDs/PCDFs	2-15 years	ATSDR (1998)	"long"	"long"	"long"
Perfluorooctanoate (PFOA)	2.1-8.5 years	ATSDR (2021)	"long"	"long"	"long"
Perfluorooctane sulfonate (PFOS)	3.1-7.4 years	ATSDR (2021)	"long"	"long"	"long"
Styrene	2-5 days	ATSDR (2010c)	"long"	"short"	"short"
Tetrachloroethylene	6 days	ATSDR (2019); US EPA (2012)	"long"	"short"	"short"
Vinyl chloride	30 days	IARC (2012)	"long"	"long"	"short"
Xylene	20 hours	ATSDR (2007)	"short"	"short"	"short"
Zinc	376 days	Watson et al. (1999)	"long"	"long"	"long"

For intermittent exposure to chemicals, it is also important to consider the persistence of the subadverse biological effect(s) that occur and may be present after the non-exposure period is complete (**Figure 1.1** and **Figure 3.5**). This analysis would involve a full review of the toxicological literature. The analysis would evaluate the potential for these biological effects to continue to be present at the end of the non-exposure interval before the individual is exposed again, and the potential for these effects to progress further if this exposure pattern repeats intermittently.

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APPENDIX G DOSE AVERAGING

G.1 Background

In a contaminated sites risk assessment, dose averaging (also referred to as “amortization”) can be defined as the mathematical averaging of a short exposure period over a longer time (e.g., one day over a week or a six-month exposure averaged over a year). As this practice involves averaging the total dose received during a shorter exposure period over a longer time, including period(s) of non-exposure, this mathematical calculation may underestimate the actual daily exposure a person may receive from environmental media. While this practice may be acceptable for some exposure scenarios and some substances, it may underestimate the potential risk associated with elevated exposures to other substances. Therefore, HC does not recommend dose averaging in a HHRA at a FCSAP site, unless it can be supported by a rigorous chemical-specific analysis. The analysis presented should include issues such as persistence (e.g., accumulation over time), toxicokinetics, toxicodynamics and toxicological reference values that take into consideration health effects in susceptible individuals. For example, no dose averaging should be considered where developmental (fetal) or reproductive effects are concerned, as these effects may result from exposures during a particular “window of susceptibility”. For instance, if 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 requires consideration that this exposure would not exceed a TRV for this endpoint.

While dose averaging is discussed in relevant sections of this guidance document, this appendix provides a summary of the type of information to be provided in an HHRA to support the appropriate use of dose averaging on a site-specific and chemical-specific basis. It is the responsibility of the risk assessor and/or toxicologist to provide a scientific rationale for any dose averaging, identifying whether there is a potential that risk may be underestimated using this approach.

G.2 Determining Factors for Dose Averaging

As discussed in the main document, for non-carcinogenic health effects, no dose averaging beyond the actual exposure period (and the entire intermittent exposure scenario, as applicable) is appropriate as dose averaging may underestimate potential risk. For example, dose averaging of a continuous 2-week exposure period over a year (i.e., 2 weeks/52 weeks) would provide a mathematical underestimate of the actual daily exposure during that 2-week period. This underestimation would result in a lower risk estimate within the HHRA than would have been calculated based on the actual on-site exposure.

Dose averaging may be scientifically defensible in some scenarios for certain substances when exposure episodes are separated by non-exposure periods. Dose averaging is based on the assumption that toxicity is related to the total exposure, regardless of the timeframe during which the exposure is received. However, this assumption is not valid in all cases. The dose-averaged exposure may not represent the relevant measure of exposure at the site and may underestimate potential risk associated with actual exposure received over a short time period. Therefore, if dose averaging is considered in a site-specific risk assessment, the assessment would require a rationale on a chemical-specific basis to identify how dose averaging conducted would be adequately protective of human health.

Two key factors that determine whether dose averaging is appropriate or not are:

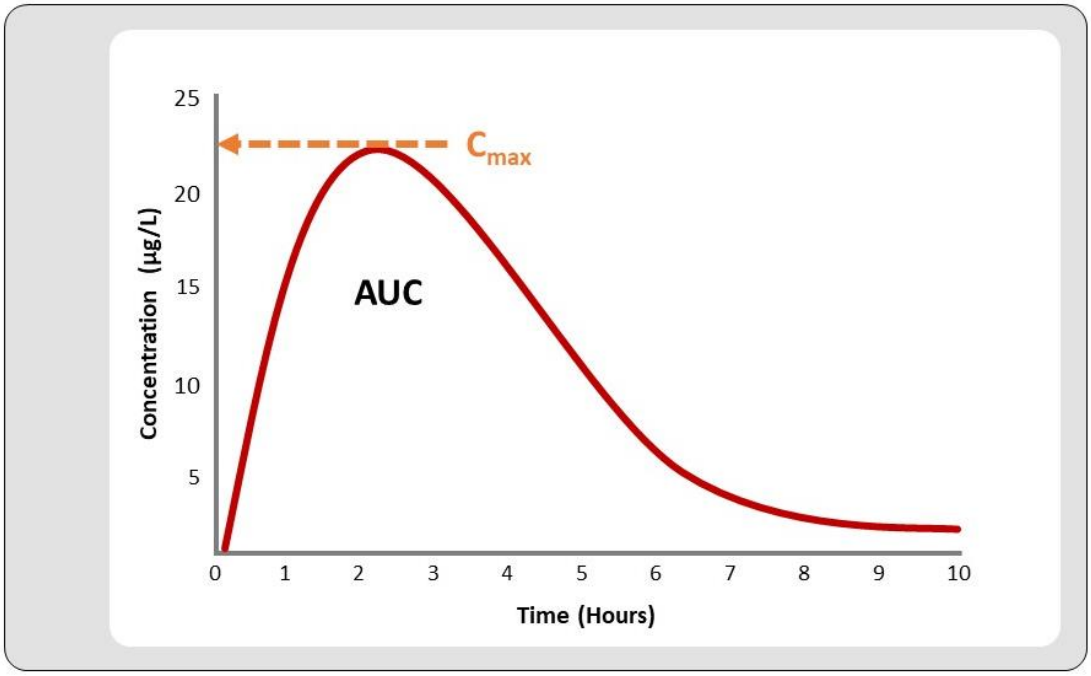
1. Whether the critical toxic effect(s) of the chemical is(are) primarily related to concentration in the environmental medium of exposure rather than to the total dose.
2. Whether toxicity is primarily related to the concentration (or peak exposure) rather than to the total dose of the chemical at the target tissue.

With regard to factor 1, "concentration in the environmental medium of exposure" refers to the concentration in either: (i) air for inhalation exposure (e.g., $\mu g/m^3$), (ii) soil, sediment, water or food for oral exposure (e.g., µg/g), or (iii) the direct contact medium for dermal exposure (e.g., µg/g soil). Toxicity may be dependent primarily on exposure concentration, and independent of duration or intermittency under some scenarios. Under these scenarios, use of dose averaging may underestimate potential risk. For instance, toxicity is dependent principally on the exposure concentration in the case of reactive chemicals and dermal irritants. Reactive chemicals target the portal of entry (e.g., respiratory tract for inhalation, gastrointestinal tract for oral, skin for dermal and eyes for ocular exposure, respectively), and include chemicals such as strong acids and bases (Costa and Gordon, 2019; Lehman-McKeeman, 2019). Formaldehyde is an example of a substance which may elicit health effects over a very short time at peak concentration (HC 2006). In addition, Zhang et al. (2018) demonstrated that mice exposed to formaldehyde intermittently experienced more severe adverse effects (e.g., inflammatory response) than mice exposed at constant concentration (total exposure [i.e., concentration x time] being the same for the two exposure groups) over the same time period. Hence, peak concentration, rather than total exposure, determines the toxicity following exposure to formaldehyde. Exposure concentration can also be the primary determinant of toxicity for some chemicals causing asphyxia as a result of displacement of oxygen by inhaled gases, such as carbon dioxide (Hilal-Dandan and Brunton, 2016). *Dose averaging is not appropriate for chemicals for which concentration is the primary determinant of toxicity.*

The second factor addresses whether toxicity is related to peak internal levels (e.g., peak serum or tissue concentrations of either the parent compound or active metabolites, referred to as C_{max}), or to total internal dose. The total internal dose or AUC, reflects the total dose that occurs in the target tissue. **Figure G.1** illustrates the concepts of AUC and C_{max}. A key concept underlying this factor is whether toxicity varies with the pattern of dosing. For instance, the observation of a greater effect after a bolus dose (e.g., intravenous administration or gavage) compared with the same total dose delivered in multiple smaller dose increments (e.g., via diet or drinking water) could be one of the lines of evidence that toxicity is likely not related to AUC. For some inhaled gases or ingested chemicals that have been found to cause central nervous system depression, including narcosis, toxicity can be related to the peak internal dose (e.g., peak blood/target tissue concentration of the chemical/active metabolite) after systemic absorption (Bruckner et al. 2019). **Section 3.2.3** of the main document provides a list of questions that may be helpful in identifying situations where toxicity is not related to AUC.

Regardless of the above two factors, dose averaging should not be applied for chemicals with developmental or reproductive health outcomes.

Figure G.1 Concentration-time plot of the internal exposure to a chemical (AUC = area under the curve; C_{max} = highest tissue concentration)



For those chemicals for which concentration is not the principal determinant of effect, dose averaging may be acceptable under certain continuous/near continuous and intermittent exposure scenarios. For instance:

- Dose averaging may be appropriate for some short-duration and intermittent exposures, such as 5 days per week, repeated weekly over a year (which is in effect a near-continuous exposure). However, exposure over a shorter time period (e.g., < 5 days per week) requires a supporting chemical-specific rationale as the shorter exposure time results in more significant underestimation of the exposure, hence health risk, on days while the person is at the site.
- Dose averaging of a short exposure duration is not appropriate over a long time period. For example, it is recommended that a single 1-week exposure not be averaged over a longer exposure period (such as a year), as this would require further analysis and possibly comparison to a short-duration TRV. Any dose averaging of less than 48 week/year requires a supporting chemical-specific rationale and higher-tiered assessments.

If both total dose and concentration contribute to the determination of toxicity, dose averaging is not appropriate. An additional factor applies to intermittent exposure scenarios, as follows.

If exposure is deemed effectively continuous due to the chemical (or active metabolites) not being cleared from the body during non-exposure intervals, the internal exposure will continue and may increase over the entire exposure scenario. Under these circumstances, dose averaging is generally not appropriate, with one exception. For a chemical with long elimination half-life and its toxicity driven by total dose/body burden, dose averaging may be supported if each non-exposure interval is shorter than

one-quarter of the elimination half-life and chemical/scenario-specific kinetic modelling can demonstrate that dose averaging would not result in significant changes in internal concentration/body burden (see **Section G.3** below for more detailed discussion).

In summary, dose averaging may be appropriate for some chemicals under specific exposure scenarios based on the primary determinants of toxic effects. **Table G.1** lists some key decision criteria that can assist in determining if dose averaging is appropriate; however, the decision is not always a simple yes/no answer as there can be much variability in site-specific exposure scenarios which create complexity in the analysis. Where the table reads "no" to the question "Is dose averaging appropriate?", dose averaging is **not** an option since doing so would likely underestimate potential health risk. However, the table does not provide a definitive 'yes' answer as a rationale will be required on a chemical-specific basis for each exposure scenario. An HHRA should include the rationale used on a chemical-specific basis for the specific exposure scenario under consideration. Dose averaging may be appropriate for some substances but not for other substances considered at a site.

Table G.1 Is Dose Averaging[1] Appropriate?

Key Decision Criteria	Is Dose Averaging Appropriate?
Toxicity primarily related to concentration (c)	Not appropriate
Toxicity primarily related to total dose $(c*t)^2$	May be appropriate with rationale
Toxicity related to concentration and total dose	Not appropriate
Chemical or active metabolites persist in the body through the shortest non-exposure interval in an intermittent exposure	Not appropriate[3]
Chemical or active metabolites elicit adverse developmental or reproductive health effects	Not appropriate

[1] No dose averaging beyond the actual exposure period (and the entire intermittent exposure scenario, as applicable) is appropriate as it may underestimate potential risk.

[2] Dose averaging may be appropriate only over short time periods (e.g., 5 days per week; 48 weeks over a year)

[3] Dose averaging is not appropriate if the chemical persists in the body through the non-exposure interval, with one exception. For a chemical with a long elimination half-life (e.g., generally months to years) and its toxicity driven by total dose/body burden, dose averaging may be supported if each non-exposure interval is shorter than one-quarter of the elimination half-life and chemical/scenario-specific kinetic modelling can demonstrate that dose averaging over a specified brief period would not result in significant changes in internal concentration/body burden during this period. Elimination half-life is the time it takes for half of the initial amount of a chemical to be eliminated from the body through metabolism and excretion functions. See **Section G.3** for additional information.

G.3 Dose Averaging During Brief Periods of Concentration Fluctuations

When a chemical (or active metabolite) persists in the body during non-exposure intervals, the internal exposure becomes continuous even though the external exposure from the contaminated site has ceased. Since the tissue level continues to persist in the body and may increase with ongoing exposure over the entire intermittent exposure scenario, dose averaging is generally not appropriate. There are exceptions, and chemical-specific rationale can be provided in an HHRA for specific exposure scenarios. Exceptions may include chemicals with long half-lives in exposure scenarios that have only brief periods

of concentration fluctuations. This guidance document does not provide rationale for individual scenarios for all substances as there are many different exposure scenarios at contaminated sites. Some literature is available regarding analyses that may provide rationale for limited dose averaging for specific chemicals.

One example related to dose averaging over a brief exposure period that considers the half-life of a substance is based on the analysis of carbon monoxide (CO) exposure by Saltzman (1996). Saltzman (1996) provided modelled evidence that as long as toxicity is not driven primarily by concentration (or peak exposure), dose averaging over a short time period may be feasible when pollutant concentration fluctuates over a time scale of shorter than about ¼ of a half-life. This analysis showed that brief air concentration fluctuations over such a time scale essentially "averaged out" the internal concentration in the body (by the process of combining new uptake with the accumulated burden from earlier exposure). As a result, such fluctuations do not appreciably affect the time course of blood levels: the fluctuating exposure results in a blood concentration curve over time that is comparable with the blood concentration curve associated with constant exposure to the averaged air concentration. Additional detail is provided in **Section G.3.1** below.

G.3.1 Example: Inhalation Exposure to Brief Periods of Air Concentration Fluctuations

Dose averaging of brief exposures may be acceptable for some substances when toxicity is not related to peak concentration. Saltzman (1996) modelled the "biological effective" concentrations for an 8-hr exposure to CO in a stepwise fashion for four different scenarios. Using an equation derived by Saltzman and Fox (1986), Saltzman (1996) converted time-averaged external CO concentrations to "biological effective" concentrations representative of percentages of blood carboxyhemoglobin (COHb) resulting from CO exposure. This equation relied only on the biological half-life value of COHb. Saltzman and Fox (1986) validated this equation using experimental data of COHb concentration in the blood from rabbits exposed to fluctuating concentrations of CO. Saltzman (1996) used the same 8-hr average concentration in modelling all four scenarios below, but the detailed concentration patterns within the 8-hour periods were different. The specific scenarios modelled for "biological effective" concentrations associated with CO air fluctuations over an 8-hour period included the following.

- Scenario 1: Air concentration was the same for each of the 8 hours and was equal to the 8-hour average.
- Scenario 2: Air concentration was different for each of the 8 hours; air concentrations were in an ascending order.
- Scenario 3: The air concentrations were the same as in scenario 2 but in random order.
- Scenario 4: Each hourly concentration from Scenario 3 was expanded into 4 different 15-minute concentrations, with the hourly average staying the same.

The modelling (Saltzman, 1996) assumed linear kinetics (i.e., 1st order kinetics) using a one-compartment model. The linear kinetics correspond to a situation in which none of the internal processes has reached steady state, which is likely when the exposure does not exceed the TRV by much. The modelling also assumed that the "biological effective" concentrations are proportional to the internal concentrations.

Scenarios 2 and 3 were compared with Scenario 1; Scenario 4 was compared to Scenario 3. Although all the patterns had the same 8-hour mean external concentrations, internal concentration patterns differed in each scenario. The internal concentration pattern significance depended on the relationship between the time-averaged sampling windows and the biological half-life for CO. Each averaging time period represented a pulsation within a longer exposure duration. For CO, if the sampling averaging period was less than ¼ of the biological half-life, the modelled internal concentration patterns from exposure to fluctuating CO air concentrations and from continuous exposure to the time-averaged CO air concentration were not significantly different. This phenomenon was best demonstrated by Scenario 4, when compared to Scenario 3.

Using kinetic modelling, Rhomberg (2009) examined the relationship between the intensity of exposure (i.e., air concentrations) and exposure durations that lead to equally toxic responses in inhalation exposures. This study also investigated how an increase/decrease in intensity can be balanced by a decrease/increase in duration to yield equally toxic responses. An exposure duration of up to 48 hours was modelled and analysed for an inhaled chemical for which the systemic dose is important for toxicity. Rhomberg (2009) concluded that the intensity/duration relationship was not a property of the chemical itself but was affected by exposure duration and the chemical's half-life. The impact of half-life is important even in complex exposure patterns with fluctuations in air concentration over the course of the exposure. Rhomberg (2009) attributed the finding by Saltzman (1996) to "averaging out" of air concentration fluctuations over a time scale of less than ¼ of a biological (or elimination) half-life due to the process of combining new uptake with the accumulated burden from earlier exposure such that fluctuations do not appreciably affect the time course of the blood level. In this example, the fluctuating exposure results in a blood concentration curve over time that is comparable with the blood concentration-time curve produced by a constant exposure to the averaged air concentration.

While Saltzman's analyses (1996) of CO exposure are for very short-duration inhalation exposures (8 hours), Rhomberg's analyses (2009) suggest that it is possible to apply these analyses to exposure fluctuations over an exposure duration of several days. For example, for a chemical with a half-life measured in days, the fluctuations due to non-continuous periods of daily exposure (e.g., 6 hours a day) would be on too short a time scale to have significantly dissimilar effect compared to a continuous exposure over several days to an air concentration equal to the daily average.

G.3.2 Example: Brief Periods of Oral Exposure Fluctuations

MeHg has a biological whole-body half-life of approximately 80 days (ATSDR, 2022), averaging approximately 50 days in fish-eating humans and is eliminated rather slowly (WHO/IPCS, 1990). Sakamoto et al. (2017) evaluated the difference in outcome between daily oral exposure versus less frequent exposure by conducting an in vivo study with rats and modelling the mercury body burden in humans. With the total cumulative dose kept constant, Sakamoto et al. (2017) administered MeHg to adult male rats for 5 weeks and to pregnant females on gestation day 1 to 20 either daily (stable) or once every few days (bolus dose, weekly for males and every 5 days for females). The animal data indicate that when the total MeHg exposure remained the same, the two MeHg exposure patterns (stable and bolus) did not result in a difference in mercury levels in the blood and in the brain, or in neurological alterations in the brain (adult male and fetal brains; results with maternal brains were not

reported). Sakamoto et al. (2017) used a one-compartment model to simulate mercury body burden in humans when the same total dose of MeHg was administered daily at 7 µg/70 kg bw (i.e. 0.1 µg/kg bw/day, which is the current US EPA RfD), 48 µg/70 kg bw (i.e. 0.7 µg/kg bw) once per week or 96 µg/70 kg bw (i.e. 1.4 µg/kg bw) once every two weeks. Sakamoto et al. (2017) concluded that the overall mercury body burden would plateau within a narrow range (i.e., the relative amplitudes of the dose-dependent waves became small). Based on this study, as long as the total dose is the same, the dosing regimens would not result in differences in mercury accumulation in the brain whether MeHg is administered in smaller daily doses or in bolus doses once every week or every two weeks. Hence, there is reasonable amount of information to support that short exposure to MeHg within a two-week period can be dose averaged over the two weeks.

G.3.3 Implication

For the purpose of this discussion, **brief** is defined as shorter than ¼ of a chemical's biological (or elimination) half-life and applies to both exposure period or non-exposure gap (or interval)[7]. Dose averaging of **brief** concentration fluctuations is scientifically defensible when a new absorbed uptake dose is combined with the accumulated body burden from earlier exposure. When a new exposure period occurs after a non-exposure gap (or interval), the new uptake attenuates the decrease in body burden associated with the end of the previous exposure period. The same phenomenon would occur when either the exposure window or non-exposure gap (or interval) is **brief**, which would fit the definition of **brief** fluctuations. However, this phenomenon occurs only if there is a new uptake from an ensuing exposure (as in "intermittent exposure"); it does not apply if there is no further exposure (such as at the end of the entire exposure scenario). The analyses identified in this section (Saltzman, 1996; Rhomberg, 2009) do **not** support dose averaging beyond the actual total exposure scenario by an additional duration equal to ¼ of a half-life. On the other hand, these analyses support dose averaging for near-continuous exposure (e.g., 8 hr/24 hr and 5d/7d) for chemicals with long half-lives, provided that toxicity is not driven primarily by concentration.

In an intermittent exposure situation, if the chemical (or active metabolites) is not eliminated from the body between exposure episodes, the tissue concentration would continue to increase over the entire exposure scenario. Application of a longer-duration TRV to the entire exposure scenario would be required and dose averaging is generally not appropriate. However, there could be exceptions. Based on the analyses summarised in this section, provided that toxicity is not driven primarily by concentration, dose averaging may be possible for a brief period of intermittent exposure if the exposure episode (or non-exposure interval) is shorter than ¼ biological half-life, even though the chemical has not been completely eliminated between exposures.

Chemical-specific rationale to support such exceptions can be provided in a site-specific HHRA for specific exposure scenarios. The HHRA must demonstrate that toxicity is not driven primarily by concentration, the exposure episode or non-exposure interval is shorter than ¼ of a biological half-life, and dose averaging over a specified brief period would not result in significant changes in internal

[7] Since the uptake curve mirrors the elimination curve, it also takes a similar amount of time to get to a steady state as it takes to near complete elimination (i.e., 5 half-lives).

concentration/body burden during this period on a chemical- and scenario-specific basis by kinetic modelling or published references. Any kinetic model used must take into consideration absorption, distribution, metabolism and elimination kinetics and needs to be validated with experimental or published data.

G.4 Addressing Chemicals with Long Half-lives Using TWI or TMI

For chemicals with long biological half-lives, body burden is often considered the most appropriate measure of exposure for toxicity assessments. TIs for some of these chemicals can be expressed as either TMI (WHO, 2000, 2011) or TWI (EFSA CONTAM, 2011, 2018). In the case of cadmium, the kidney contains about 50% of the body burden in humans (WHO, 2011). The half-life of cadmium in human kidneys is approximately 15 years; WHO (2011) estimated that it would take 45-60 years of exposure to achieve steady state. WHO (2011) used the cadmium concentration in urine as a marker of exposure, which reflects the concentration in the kidneys, in its dose-response analysis. Data relating the urinary cadmium concentrations and β_2-microglobulin excretion in urine (biomarker of renal tubular dysfunction) for individuals aged 50 years and older were used to establish a critical urinary concentration of cadmium. Below this level, the cadmium concentration in the urine was not found to be associated with an increase in β_2-microglobulin excretion. A toxicokinetic model was then used to determine the dietary exposure that would lead to this critical urinary cadmium concentration.

Since cadmium has a very long biological half-life, intake on any particular day would only have a minor or negligible impact on the overall exposure. WHO (2011) determined that evaluating long- or short-term health risk from cadmium exposure should be based on the total or average intake over months. Hence, WHO (2011) expressed the TI as a PTMI of 25 µg/kg bw per month, which may be used for comparison with each total monthly exposure to cadmium at a contaminated site even if the exposure is not continuous within that month.

In the case of PCDD/Fs, WHO (2000) considered body burden the most appropriate measure of exposure for interspecies comparison. Due to the relatively long half-lives of greater than 7.2 years (IARC, 2012) and long-term storage of PCDD/Fs in humans, estimating steady-state body burden often reflects insignificant increase upon a brief intake above background (WHO, 2000). Intake on any particular day would only have a minor impact on the overall burden, with the bulk of body burden consisting of PCDD/Fs input over several previous years (WHO, 2000). Based on this finding, WHO/JECFA (2002) determined that the appropriate period for evaluating the mean intake of these compounds is one month and expressed the TI as a PTMI for assessing long- or short-term risks to PCDD/Fs.

G.5 Summary

As discussed above, the mathematical averaging of a short exposure over a longer timeframe (often referred to as dose averaging or exposure amortization) has the potential to underestimate potential health risks related to ingestion, dermal contact or inhalation of COPCs. The risk assessment should ensure that the potential for short periodic exceedances of a chronic TRV has been reasonably addressed and that there is no mathematical dose averaging that would inappropriately suggest that people would receive lower COPC exposures and lower associated health risk from the site.

For instance, exposure to elevated concentrations for a short period may be associated with health concerns, even though mathematically calculated 24-hour average values or an annual average may suggest the exposure to be much less than the chronic exposure level, which is associated with chronic health impacts. These health effects may be acute or chronic and can range from slight and reversible (e.g., mild irritation) to severe and irreversible (including reproductive and developmental effects). Therefore, the full range of health effects needs to be considered. Acute, short-term and/or intermediate exposure may be of concern if short-duration exposures at the site exceed chronic or short-duration TRVs. Consequently, the risk assessment should clearly identify any health effects associated with elevated short-duration exposures on a chemical-specific basis and how the HHRA addresses these effects in a defensible manner.

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