CSAP Technical Guidance for

Use of Uncertainty Factors in Deriving

Ecological Toxicity Reference Values (TRVs)

(MOE Policy Decision Summary Issue 8)

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Issue Definition

This guidance is proposed to replace the technical basis for Issue 8 in the Tier 1 Policy Decision Summary[1]. It is anticipated that MOE could use this review as the basis for revisions to that policy.

Toxicity reference values (TRVs) are a commonly used and important tool in effects assessment for ecological risk assessment (ERA). In combination with exposure data, TRVs are used during the risk characterization phase of an ERA. One way to use TRVs is to derive hazard quotients (HQs). A TRV can be defined as "an exposure concentration or dose of a contaminant of potential concern (COPC) that is not expected to cause an unacceptable level of effect in a receptor of concern (ROC)" (Environment Canada 2012). This definition includes TRVs that are:

- Dose-based (units of mg chemical/kg body weight/day - evaluates risks due to dietary ingestion of contaminants),
- Concentration-based for external exposure media (units of mg chemical/kg media or mg/L; risks measured in terms of exposure to contaminated media) and
- Concentration-based for internal (tissue) exposure media (units of mg chemical/kg tissue).

While TRVs are widely used, there are gaps in the data upon which they are based for many COPC / ROC combinations, which contributes to uncertainty in risk estimates.

To address the uncertainty involved in using literature-based data for TRVs, uncertainty factors have typically been applied. Uncertainty factors (UFs; also known as safety factors) are a conservative approach for dealing with uncertainty that involves adjusting a toxicity endpoint estimate by an arbitrary factor (often 10x) to estimate a safe level for a substance in the environment (Chapman et al. 1998, Fairbrother 2010). Historically, the use of uncertainty factors in the application of TRVs has been common place. Protocol 1: Recommended Guidance and Checklist for Tier 1 Ecological Risk Assessment of Contaminated Sites in British Columbia (1998), recommends the use of uncertainty factors when extrapolating toxicity data between species, from acute laboratory exposure to chronic field exposure, and in other cases.

Over recent years there has been increasing dissatisfaction with the use of uncertainty factors in ecological risk assessment. Recently, funded in part by MOE through Pacific Northwest Society of Environmental Chemistry and Toxicology (SETAC), a group of experts in the field of ecological risk assessment met to review and recommend the best course of action for the development and use of wildlife TRVs. This group effort led to a paper published to describe their consensus (Allard et al. 2010). These recommendations have since been added to through federal environmental risk assessment guidance (FCSAP Guidance for Ecological Risk Assessment, Technical Module on Toxicity Reference Values (Environment Canada 2012)).

The importance of the use of TRVs is obvious; many risk assessments rely on hazard quotients as one line of evidence in evaluating potential risks. Indiscriminate application of uncertainty factors to TRVs can result in biased characterization of potential risks. This CSAP guidance targets the use of TRVs in ERA that is consistent with best practice, specifically related to the application of uncertainty factors.

[1] http://www.env.gov.bc.ca/epd/remediation/standards_criteria/standards/tier1policy.htm

Disclaimer/Limitation Statement

This document does not constitute regulatory guidance or policy. It is the intent that this document will be used by members of the Society of Contaminated Sites Approved Professionals (CSAP) of British Columbia conducting reviews of sites/reports for which they may be making recommendations in accordance with BC Ministry of Environment (BCMOE) Protocol 6: Eligibility of Applications for Review by Approved Professionals.

The guidance provided in this document reflects what is considered good practice for conditions found at most sites. The guidance is based on the current regulatory regime and scientific methods, and hence may be updated as new information becomes available. Please note that the guidance may not be applicable to all sites, and therefore that sound professional judgment must be applied to ensure that the guidance is applicable to the particular site/report under consideration.

Issue Analysis

The use of uncertainty factors in deriving TRVs stems from a need to extrapolate data when gaps are present. Common data gaps where uncertainty factors have been used for extrapolation in TRV derivation include (Chapman et al. 1998; McDonald and Wilcockson 2003; EPT (Ecological Planning and Toxicology Inc) 1996; Fairbrother 2010):

- Data do not exist for ROC, but are available for another taxa;
- Data do not exist for targeted exposure duration (e.g., acute exposure data available, but chronic exposure is appropriate);
- Data do not exist for targeted effects (e.g., only survival data are available, but sub-lethal responses are relevant); and
- Data do not exist for targeted effects level (e.g., Lowest Observed Adverse Effects Level (LOAEL) to No Observed Adverse Effects Level (NOAEL).

Historically, a 10-fold increase to the point estimate of toxicity was typically applied for each extrapolation required. While the intent was to conservatively address data gaps, the indiscriminate use of nominal or arbitrary uncertainty factors masks the underlying dose and response relationship, making meaningful risk predictions virtually impossible (particularly when predicted exposure doses for an ROC exceed a TRV).

Allard et al. (2010) developed principles for dealing with uncertainty and uncertainty factors in wildlife TRV derivation. These guiding principles have been adapted here to apply to TRV derivation for all ecological receptors, including plants, invertebrates, fish and wildlife. The commonality among these principles is the goal of developing a better understanding of the underlying dose-response relationship used to derive a TRV. Compared to the practice of using a single NOAEL or LOAEL-based TRV (often derived with arbitrary uncertainty factors), the dose-response relationship approach provides a more complete understanding of the toxicity profile of a COPC. In general, rather than blindly applying arbitrary uncertainty factors, risk assessors should clearly document data gaps or limitations and their implications to risk predictions in the uncertainty assessment. However, it is recognized that there might be situations where empirical data will support use of uncertainty factors in TRV development. Key principles of using uncertainty factors in wildlife TRV derivation are as follows:

Consider relative species sensitivity when conducting interspecies extrapolation.

Uncertainty in the TRV applied can be minimized through selection of test species that are physiologically and taxonomically similar to the species of interest (Allard et al. 2010). When constructing the toxicity profile for a COPC, the sensitivity of the ROC should be considered, relative to the species upon which the TRV is

based. Extrapolating between closely related taxa (e.g., species or genera) is generally acceptable if they are physiologically similar. However, as relatedness decreases, the uncertainty in the TRV derived increases (Raimondo et al. 2007; Fletcher et al. 1990); extrapolating between taxonomic classes is not acceptable (Allard et al. 2010). Generic uncertainty factors should not be used; specific uncertainty factors, if warranted, should have a scientific basis (Chapman et al. 1998) that is documented in the ERA.

Do not use allometric dose-scaling with body mass when extrapolating between species.

Allometric scaling is based on the premise that key processes, such as ingestion or contaminant metabolism, are a function of animal size (i.e., due to metabolic rate). While allometric scaling is commonly used and accepted to estimate ingestion rates for food and water in wildlife risk assessments (e.g., Nagy equations), it should generally not be used to extrapolate TRVs from test species to target species (Science Advisory Board for Contaminated Sites in British Columbia (SAB) 2008). Early allometric scaling models were developed from acute exposures to anticancer drugs, which may or may not be applicable for chronic exposures to environmental contaminants. Physiological differences and respective toxicity sensitivities are not captured in this extrapolation method; hence its use is discouraged.

Unless data justify the extrapolation, do not extrapolate chronic TRVs from acute exposure data.

Acute and chronic exposures result in significantly different physiological effects and toxicological endpoints, primarily due to variations in absorption, distribution, metabolism and elimination (ADME) rates. The mechanism of action of any particular chemical can vary greatly between acute and chronic exposures, due in large part to differences in ADME kinetics. Toxic effects that stem from carrying a chronic body burden of a compound may differ greatly from acute exposure to a large dose (e.g., chronic exposure to DDT resulting in reproductive toxicity versus acute poisoning resulting in neurotoxicity).

A decision about extrapolation from acute data to a chronic TRV should be evaluated on a species and COPC basis. There are no appropriate generic acute-to-chronic ratios that can be applied to wildlife TRV derivation. Published literature (Kenaga 1982; Länge et al. 1998; Di Toro and McGrath 2000; Di Toro et al. 2000) and water quality guidelines (particularly CCME guidelines) provide values for acute-to-chronic extrapolations for a contingent of contaminants and a selection of aquatic species (both fish and aquatic invertebrates). Limited information is available for acute to chronic extrapolation in plants and in soil invertebrates.

Without explicit documented data supporting an extrapolation from acute to chronic exposure, developing chronic TRVs based on extrapolation from acute data sets should not be conducted. Applying a safety factor to the developed TRV will not compensate for the potential errors in the calculation. If proper data for development of a chronic TRV are lacking, this should be identified as a data gap and incorporated into the discussion of uncertainty analysis.

Endeavour to use TRVs derived from dose–response distributions (e.g., EC_x or ED_x) instead of NOAELs and LOAELs.

In British Columbia, preference for dose-response based TRVs as stated in Technical Guidance 7 (British Columbia Ministry of Environment 2012). The use of specified effects levels (EDx or ECx values) for estimating risks to ecological receptors at the population/species level is generally preferred. The Ministry does not recommend the use of NOELs, NOECs, LOELs, or LOECs; unless no other alternative benchmark can be found for a site. However, Technical Guidance 7 also states “the following sources should be used for ecological benchmarks”:

- US Environmental Protection Agency, various sources including:
  http://www.epa.gov/ecotox/ecossl/
  http://cfpub.epa.gov/ecotox/
  http://www.epa.gov/iriswebp/iris/index.html

- Oak Ridge National Laboratory (ORNL), the Risk Assessment Information System, Ecological Benchmarks:
  http://rais.ornl.gov/cgi-bin/eco/ECO_select

Of these, the EcoSSLs and ORNL TRVs are the most widely used; however, both are based on NOELs and LOELs which is contradictory to MOE's stated preference in Technical Guidance 7. Our review of the derivation procedures for these TRVs concluded that it is more likely that the EcoSSLs will function as conservative screening values than the ORNL values.

The use of LOAELs and NOAELs is prevalent in the scientific literature and this unfortunate practice continues due to policy decisions in some jurisdictions that allow for their use as TRVs. However, it is widely agreed that the extrapolation from LOAEL to NOAEL has no technical basis (Kooijman 1996; Fox 2008; Laskowski 1995; Hoekstra and van Ewijk 1993; Chapman et al. 1996). Both levels (no-effect and low-effect) are primarily a function of the dose concentration spacing in the original experiment (McDonald and Wilcockson 2003). Understanding the dose (exposure)-response relationship for the contaminant in question and the target species is paramount in toxicology; LOAELs and NOAELs do not adequately reflect the dose-response relationship (Allard et al. 2010; Landis and Chapman 2011).

Statistical models or graphical analysis methods can be applied to dose-response data to derive an effective concentration (EC_x [for media-based TRVs]) or dose (ED_x [for dose-based TRVs]) for the TRV, where the "x" corresponds to a percentage reduction in an endpoint considered as the threshold for "acceptability" of the response (e.g., defined in the problem formulation as per BC Ministry of Environment policy). The advantage of this method is that it makes better use of the underlying dose-response data and allows better interpretation of predicted effects when predicted exposure exceeds the TRV. It also provides a clearer understanding of uncertainties related to the effects assessment.

Explicitly and transparently present the basis for TRV selection, including level of uncertainty.

Transparency in TRV derivation includes tracking all areas of uncertainty, whether quantitative or qualitative. Uncertainty related to extrapolating from laboratory studies to field exposure can include, but is not limited to: changes in COPC bioavailability; presence of other stressors (physical, chemical and biological); exposure duration (short term toxicity tests, long term field exposure); and extrapolation from homogeneous laboratory test species to variable, free-living populations. Other potential uncertainties include extrapolating between exposure durations (e.g., acute to chronic), taxa or endpoint types (e.g., lethal to sublethal). Where possible and appropriate, uncertainty should be described quantitatively; otherwise, it should be qualitatively assessed and expressed in well-defined categorical terms (e.g., low, moderate or high) (Science Advisory Board for Contaminated Sites in British Columbia (SAB) 2008).

In most cases, it is preferable to develop the TRV from a data set without incorporating uncertainty factors that cloud the underlying dose-response relationship. If scientific rationale exists to derive quantitative uncertainty factors, then that information should be well-documented in the uncertainty assessment for a given ERA.

Recommendations

The guidance and policy for the use of TRVs in BC should be reconciled with the more recent direction taken in the scientific literature and in federal guidance and policy (Environment Canada, 2012). Options for addressing uncertainty (and use of uncertainty factors) in TRV derivation include:

1. Use or derivation of EC_x (or ED_x)-based TRVs (rather than LOAELs and NOAELs):
    - Comprehensively search and rigorously evaluate the literature for available data and TRVs
    - Plot dose and response to visually display results of literature searches

- Make TRV derivation transparent (clearly identify the selection criteria for studies used in derivation, and methods used to derive the TRV based on the data)

- If possible and appropriate, fit quantitative models to dose-response data to aid in characterizing the data and selecting an EC_x- or ED_x-based TRV.

2. If choosing to use a previously published TRV that is based on a NOAEL/LOAEL, evaluate the published study that the TRV is based upon. Plot the treatment doses and effect sizes to understand the dose-response relationship, within the context of site exposure concentrations. Confirm that the endpoints and study design are appropriate for the site. Evaluate whether the TRV is adequately conservative, particularly if ORNL values are used.

3. If a scientifically rigorous TRV is not available or cannot be developed, other lines of evidence should be used to evaluate risks in addition to or instead of the use of NOAEL/LOEL-based TRVs. Some examples include:

    - Direct field studies to assess impacts on resident organisms and local populations

    - Laboratory toxicity testing

4. Uncertainty factors should only be used when supported by a strong scientific rationale (Allard et al. 2010; Chapman et al. 1998) that is documented in the ERA.

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