3.3 Data requirements for new or updated risk assessments

3.3.1 General requirements

When considering the types of data required for new or updated risk assessments, articulation of the problem formulation may inform the approach to be utilized for the risk assessment (US EPA, 2014b).

For each substance requiring a new or updated risk assessment, toxicity data to be considered shall include, but not be limited to, assays of genetic toxicity, acute toxicity (1- to 14-day exposure), short-term toxicity (14- to 28-day exposure), subchronic toxicity (90-day exposure), reproductive toxicity, developmental toxicity, immunotoxicity, neurotoxicity, chronic toxicity (including carcinogenicity), and human data (clinical, epidemiological, or occupational) when available. To more fully understand the toxic potential of the substance, supplemental studies shall be reviewed, including, but not limited to, mode or mechanism of action, pharmacokinetics, pharmacodynamics, sensitization, endocrine disruption, and other endpoints, as well as studies using routes of exposure other than ingestion. Structure activity relationships, physical and chemical properties, and any other chemical-specific information relevant to the risk assessment shall also be reviewed.

Toxicity testing shall be performed in accordance with the most recent adopted toxicity testing protocols such as those described by the Organization For Economic Cooperation and Development (OECD), the US EPA, and the US FDA. All studies shall be reviewed for compliance with Good Laboratory Practice (21 CFR, Part 58 / 40 CFR Part 792).

> NOTE — Review of the study according to the approach suggested in Klimisch, et al., 1997, may also be used to determine the quality of reported data.

A key aspect of the problem formulation is to describe the intention of the risk assessment as well as the approach to be utilized (US EPA, 2014b). For this Standard, intentions of the risk assessment may include, but are not limited to, the following:

— preparation of a new drinking water risk assessment where no other toxicity reviews or prior risk assessments have been identified in the available scientific literature;

— preparation of a new drinking water risk assessment with existing toxicity review(s) available; or

— preparation of an updated drinking water assessment to incorporate new data or methodology since completion of the prior risk assessment.

Primary literature references shall be obtained and reviewed for critical studies whenever possible; however, toxicology data obtained from secondary sources may be relied upon in either new or updated risk assessments if the primary literature reference is unavailable. For supporting toxicity data outside of identified critical studies, the utilization of toxicity data derived from existing secondary sources may be considered appropriate.

For the purpose of this Standard, a secondary source may be defined as a document or database which contains a summary of factual toxicity data from a published or nonpublished primary study. Examples of secondary sources may include, but are not limited to, organizational publications (e.g., US EPA, Health Canada, ATSDR, etc.), toxicity review articles in which relevant toxicity data are summarized, or toxicity data obtained from online toxicity databases (e.g., European Chemicals Agency).

Toxicology data obtained from the secondary source shall be reviewed to assess both the quality of the secondary source as well as quality of the primary study summarized within the secondary source. In both cases, professional judgement is required to determine if there is sufficient information available to assess the adequacy of the method and quality of the study, and if the data are sufficiently robust to allow an independent characterization of hazard and risk for a given endpoint. Factors in the assessment of the secondary source may include, but are not limited to, whether that secondary source has been

peer-reviewed (preference should be given to authoritative or regulatory bodies such as defined in Section 3.2.4), knowledge expert qualifications of the investigator or reviewer, and general completeness of the primary study summary. The quality of the primary study itself as cited within the secondary source shall be reviewed by assessing the available study procedural details as compared to the most recently adopted toxicity testing protocols (as described above) or by using the approach as suggested by Klimisch et al. (1997). If the secondary source has assigned a reliability rating (e.g., a Klimisch score) to the primary study, such reliabilty rating may also be considered in assessing the quality of the primary study data.

The potential limitations of toxicology data obtained from secondary sources shall be described within the risk assessment.

NOTE — Citation of secondary sources should be in the following form: (primary source, year; as cited by secondary source, year).

A weight-of-evidence approach shall be employed in evaluating the results of the available toxicity data. This approach shall include considering the likelihood of hazard to human health and the conditions under which such hazard may be expressed. A characterization of the expression of such effects shall also be included, as well as the consideration of the substance's apparent mode of action. The quality and quantity of toxicity data available for the substance shall determine whether the evaluation is performed using a qualitative risk assessment approach (see Section 3.2.2) or a quantitative risk assessment approach (see Section 3.2.3).

3.3.2 Data requirements for qualitative risk assessment

Toxicity testing requirements for the qualitative risk assessment procedure are defined in Table 3.1. A minimum data set consisting of a gene mutation assay and a chromosomal aberration assay shall be required for the performance of a qualitative risk assessment. Modifications in the specified toxicity testing requirements (inclusions or exclusions) shall be permitted when well supported by peer reviewed scientific judgment and rationale.

NOTE — Modifications may include, but are not limited to, the following types of considerations: alternate assays of genetic toxicity and supplemental toxicity studies other than those specified.

Required studies and available supplemental studies shall be reviewed in order to perform a qualitative risk estimation in accordance with Section 3.6.2.

3.3.3 Data requirements for quantitative risk assessment

Toxicity testing requirements for the quantitative risk assessment procedure are defined in Table 3.2. A minimum data set consisting of a gene mutation assay, a chromosomal aberration assay, and a subchronic toxicity study shall be required for the performance of a quantitative risk assessment. The required studies and preferred criteria are defined in Table 3.2. Modifications to the minimum data set shall be permitted when well-supported by peer reviewed scientific judgment and rationale.

NOTE — Modifications may include, but are not limited, to acceptance of studies using alternate routes of exposure, alternate assays of genetic toxicity, and supplemental toxicity studies other than those specified.

Required studies, additional studies, and available supplemental studies shall be reviewed in order to perform a quantitative risk estimation in accordance with Section 3.6.3.

Additional studies for the evaluation of reproductive and developmental toxicity (as specified in Table 3.2) shall be required to be reviewed when:

— results of the required minimum data set studies and any supplemental studies indicate toxicity to the reproductive or endocrine tissues of one or both sexes of experimental animals; or

— the compound under evaluation is closely related to a known reproductive or developmental toxicant.

3.4 Data requirements for evaluating short-term exposures

Extractants from products used in contact with drinking water may be elevated initially, but rapidly decline with continued product contact with water. Examples include, but are not limited to, solvent-containing coatings and solvent cements. Short-term exposure paradigms, appropriate for potentially high initial substance concentrations, shall be used to evaluate potential acute risk to human health of short-term exposures. The short-term exposure period shall be defined as the first 14 days of in-service life of the product.

Sound scientific judgment shall be used to determine whether calculation of a STEL is appropriate for a given contaminant. The NOAEL or LOAEL for the critical short-term hazard of the substance shall be identified. The following types of studies shall be considered for identification of short-term hazard:

— short-term (less than 90-day duration) toxicity study in rodents or other appropriate species with a minimum 14-day post-treatment observation period, clinical observations, hematology and clinical chemistry, and gross pathology (preferably an oral study in rodents);

— reproduction or developmental assays (for substances having these endpoints as the critical effects); or

— subchronic 90-day study in rodents or other species (preferably an oral study in rats).

The critical study shall be used to calculate a STEL in accordance with Section 3.7.

Selection of UFs for calculation of a STEL shall consider the quality and completeness of the database for assessing potential short-term effects. Selection of UFs shall also consider data that quantify interspecies and intraspecies variations. Other parameters that shall be considered in the determination of a STEL include identification of any sensitive subpopulations, the potential for adverse taste and odor, and solubility limitations at the calculated STEL. The STEL shall be calculated using assumptions to protect for a child's exposure to the contaminant in the absence of data that demonstrate, or a different life stage, such as infants or pregnancy, adults are more sensitive than children. In the absence of appropriate data to calculate a STEL, see Section 3.6.1.2. If multiple short-term critical effects (i.e., points-of-departure) exist relative to different life-stages, multiple STEL derivations reflecting the relevant point(s)-of-departure and their associated life-stage specific exposure assumptions should be included, with the lowest STEL, or that most supported by available evidence, selected. Note that selection of UFs is specific for each point-of-departure.

STEL shall not exceed the TAC for nonmetallic contaminants regulated by the US EPA and established by Health Canada.

3.5 Risk estimation for published assessments

Calculation of the SPAC is intended to account for the potential contribution of a single substance by multiple products or materials in the drinking water treatment and distribution system. In any given drinking water treatment and distribution system, a variety of products and materials may be added to or contact the treated water prior to ingestion. The SPAC calculation is intended to ensure that the total contribution of a single substance from all potential sources in the drinking water treatment and distribution system does not exceed its acceptable concentration.

3.5.1 SPAC calculation for regulated substances

To calculate the SPAC, an estimate of the number of potential sources of the substance from all products in the drinking water treatment and distribution system shall be determined. The SPAC shall be calculated as follows:

$$\text{SPAC (mg/L)} = \frac{\text{[promulgated regulatory value (mg/L)]}}{\text{[estimated number of drinking water sources]}}$$

If available, the unrounded estimated risk estimation that the promulgated regulatory value is based on shall be used in the calculation of the SPAC. In the absence of specific data regarding the number of potential sources of the substance in the drinking water treatment and distribution system, the SPAC shall be calculated as 10% of the promulgated regulatory value. The calculated SPAC shall be rounded to one significant figure, unless it is based on a regulatory value with more than one significant figure. In that case the SPAC shall be rounded to the same number of significant figures as the regulatory value.

3.5.2 SPAC calculation for other published risk assessments

Review of the risk assessment shall include evaluation of the risk estimation, if one is provided. If the existing risk estimation has been performed in a manner consistent with the procedures in Section 3.6.3 for noncarcinogenic or carcinogenic endpoints, the SPAC shall be calculated as follows:

$$\text{SPAC (mg/L)} = \frac{\text{[existing risk estimation (mg/L)]}}{\text{[estimated number of drinking water sources]}}$$

The unrounded value of the estimated risk estimation shall be used in the calculation of the SPAC. In the absence of specific data regarding the number of potential sources of the substance in the drinking water treatment and distribution system, the SPAC shall be calculated as 10% of the existing risk estimation. The calculated SPAC shall be rounded to one significant figure.

If the existing risk estimation is not consistent with Section 3.6.3, or a risk estimation is not provided, a TAC and SPAC shall be calculated for the substance according to the procedures in Section 3.6.3.

3.6 Risk estimation using new and updated risk assessments

The method of risk estimation used for new and updated risk assessments shall be determined by the quantity and quality of toxicity data identified for the contaminant of concern (see Section 3.3). When available toxicity data are insufficient to perform the qualitative or quantitative risk assessments, or when toxicity data are available, but the normalized contaminant concentration does not exceed the applicable threshold of evaluation (TOE) value, a TOE shall be determined for the substance according to Section 3.6.1, if applicable. For all other data sets, the risk estimation shall be performed according to Section 3.6.2 or 3.6.3.

3.6.1 Threshold of evaluation (TOE)

The following thresholds of evaluation shall be considered when available toxicity data do not meet the minimum requirements to perform a risk estimation using either the qualitative or quantitative approaches. Application of the TOE shall also be considered for the evaluation of normalized contaminant concentrations which do not have existing risk assessments, and which do not exceed the defined TOE concentrations. In this case, a qualitative review of the available data shall be performed to determine whether adverse health effects can result at the TOE exposure concentrations defined in Section 3.6.1.1.

3.6.1.1 TOE for chronic exposure

Performance of a risk assessment shall not be required for an individual substance having a normalized concentration less than or equal to the following TOE values:

- static normalization conditions:

  — toxicity testing shall not be required for an individual substance having a normalized concentration less than or equal to the TOE value of 3 µg/L.

— flowing normalization conditions:

— toxicity testing shall not be required for an individual substance having a normalized concentration less than or equal to the TOE value of 0.3 µg/L.

These TOE values shall not apply to any substance for which available toxicity data and sound scientific judgment such as structure activity relationships indicate that an adverse health effect may result at these exposure concentrations.

3.6.1.2 TOE for short-term exposure

If an appropriate short-term toxic effect is not identified by the available data, the initial (Day 1) laboratory concentration shall not exceed 10 µg/L. This TOE value shall not apply to any chemical for which available toxicity data and sound scientific judgment, such as structure activity relationships, indicate that an adverse health effect can result at the 10 µg/L concentration upon short-term exposure to the chemical.

3.6.2 TAC determination for qualitative risk assessment

TACs for qualitative risk assessments shall be determined as indicated in Table 3.3.

3.6.3 TAC calculation for quantitative risk assessment

The procedure used to calculate the TAC for a new risk assessment (including qualitative assessments that are updated upon generation of new data) shall be determined by the toxicologic endpoint identified as the critical effect (see Section 2.11). For a substance having a noncarcinogenic endpoint, a TAC shall be calculated according to Section 3.6.3.1. For a substance having carcinogenic potential, a TAC shall be calculated according to Section 3.6.3.2.

The minimum data set for the quantitative risk assessment (as defined in Section 3.3.3 and Table 3.2) shall first be evaluated for genotoxic potential according to the requirements of Table 3.3. Based on the review of genotoxic potential, the need for supplemental studies or chronic toxicity and carcinogenesis data shall be determined.

3.6.3.1 Assessment of noncarcinogenic endpoints

For noncarcinogenic endpoints, the TAC shall be calculated using either the NOAEL/LOAEL procedure outlined in Section 3.6.3.1.2, or the benchmark dose (BMDL) procedure outlined in Section 3.6.3.1.3, as appropriate. The rationale for the selection of the procedure shall be provided in the assessment.

NOTE — Selection of the appropriate TAC calculation procedure will depend on the characteristics of the data set identified for the substance. Simple data sets consisting of a small number of studies may be best evaluated using the procedure in Section 3.6.3.1.2. Complex data sets consisting of several studies, or which involve reproduction or developmental endpoints may be best evaluated using the BMDL procedure in Section 3.6.3.1.3. The appropriateness of the fit of the data to the BMDL shall also be considered.

3.6.3.1.1 Calculation of HEDs

Selected NOAEL/LOAEL/BMDL values from animal studies shall be converted to HEDs using a cross-species body weight scaling approach to account for interspecies differences in toxicokinetics (based on US EPA, 2011c). This is the current default method to convert data between animal and human species for both cancer and noncancer endpoints, and should be used when physiologically-based toxicokinetics (PBPK) modeling is not feasible and no chemical-specific interspecies adjustment factors (e.g., CSAFs, DDEFs) data on interspecies weight conversion are available (US EPA, 2014a). When benchmark dose modeling is to be used, the HEDs shall be calculated, using study-specific body weight data when available, prior to modeling to determine the BMDL.

The HED conversion is conducted by use of body weight $(BW)^{3/4}$ scaling and the reduction of the overall interspecies UF default value from 10 to 3 to account for remaining uncertainty in toxicodynamics (see Section 3.6.3.1.3.2):

$$HED = Critical\ Dose_a \times (BW_a / BW_h)^{1/4}$$

Where:

HED = Human equivalent dose of the critical effect dose level (i.e., $NOAEL_h$, $LOAEL_h$ or $BMDL_h$)

$Critical\ Dose_a$ = Effect dose level established in animal studies (i.e., $NOAEL_a$, $LOAEL_a$ or $BMDL_a$)

BW_h = Average human body weight, which is 80 kg by default (US EPA, 2011a, 2015a)

BW_a = Mean animal body weight, which is either reported in the animal studies or the default value specified by the US EPA (1988)

NOTE — There are limitations to the HED conversion approach. Under the following circumstances, the default $BW^{3/4}$ scaling approach is not applicable (US EPA, 2011c), and use of the NOAEL/LOAEL/BMDL in combination with an UF of 10 for interspecies extrapolation (in addition to other requisite UFs) should be used:

— when metabolic pathways are saturated;

— when toxicity is a consequence of exposure to a very reactive parent compound or metabolite that is not removed from the site of formation by biological processes, but chemically reacts with cellular constituents;

— when toxicity is a caused by direct action of the chemical or metabolites on tissues of the gastrointestinal tract;

— when scaling to the body weights of young infants and children (< 6 months old) to derive an acute RfD or short-term guidance value intended to apply to a population that includes young infants and children, due to the comparatively slower clearance of xenobiotics during this period and limited available toxicokinetics data;[4] and

— under conditions of an acute exposure with the focus of the occurrence of immediate and severe or lethal effects, unless the operative physiological processes are comparable between acute and chronic exposure scenarios.

3.6.3.1.2 NOAEL or LOAEL approach

The substance data set shall be reviewed in its entirety, and the highest $NOAEL_{HED}$ for the most appropriate test species, relevant route of exposure, study duration, mechanism, tissue response, and toxicological endpoint shall be identified. If a $NOAEL_{HED}$ cannot be clearly defined from the data, the lowest $LOAEL_{HED}$ for the most appropriate test species, relevant route of exposure, and toxicological endpoint shall be utilized.

The general procedure for calculating the TAC using this approach is as follows:

a) Determine the critical study and effect from which the $NOAEL_{HED}$ or $LOAEL_{HED}$ will be identified according to the following hierarchy (US EPA, 1993 and Dourson et al., 1994):

[4] In instances when extrapolation from a young laboratory animal to a young human are desirable; key developmental processes must be matched in a species-dependent manner (US EPA, 2011c).

— adequate studies in humans;

— adequate studies in animal models most biologically relevant to humans (e.g., primates), or that demonstrate similar pharmacokinetics to humans;

— adequate studies in the most sensitive animal species (the species showing an adverse effect at the lowest administered dose using an appropriate vehicle, an adequate study duration, and a relevant route of exposure); and

— effects that are biologically relevant to humans.

b) Calculate the RfD according to the following equation (based on US EPA, 1993):

$$\text{RfD (mg/kg/d)} = \frac{[NOAEL_{HED} \text{ or } LOAEL_{HED}\text{(mg/kg/d)}]}{UF} \times \frac{[\text{number of days dosed per week}]}{7\text{ d}}$$

NOTE — When other than daily dosing was used in the critical study, the RfD calculation shall be adjusted to reflect a daily dosing schedule.

c) Calculate the TAC based on the RfD with adjustment for significant contribution(s) of the substance from sources other than drinking water according to the following equation:

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-d)} \times \text{RSC}}{IR_{ADULT}\text{(L/kg-d)}}$$

The calculated TAC shall be rounded to one significant figure.

Where:

$NOAEL_{HED}$ = Highest NOAEL for the critical effect in the most appropriate species identified after review of data set; if a $NOAEL_{HED}$ is not defined, the $LOAEL_{HED}$ shall be used with a corresponding adjustment in the UF (see Table 3.4)

UF = Total uncertainty factor (see Table 3.4)

RSC = Relative source contribution: Apply the US EPA (2000) Exposure Decision Tree to determine the RSC. If the data are available to quantify the relative drinking water contribution of a substance, a chemical-specific RSC shall be calculated. In the absence of data to determine significant contribution(s) of the substance from other sources, a default drinking water contribution of 20% shall be applied (US EPA, 1991). The calculation to determine the RSC considering all sources can be figured as follows:

$$\text{RSC} = \frac{\text{Exposure}_{\text{water}}}{\text{Exposure}_{\text{sum of all pathways}}} \times 100\%$$

IR_{ADULT} = Adult ingestion rate of 0.034 L/kg-d as indicated in the US EPA Exposure Factors Handbook (US EPA, 2019).[5]

3.6.3.1.3 Benchmark dose approach

The BMDL for the substance shall be calculated by modeling the substance's dose response curve for the critical effect in the region of observed responses. The benchmark response (BMR) concentration shall be

[5] Based on 90th percentile intake, consumers only, direct and indirect community water; NHANES 2005-2010; Table 3-21; rounded (US EPA, 2019).

determined by whether the critical response is a continuous endpoint measurement or a quantal endpoint measurement. The BMR shall be calculated at the 10% response level, as appropriate.

The general procedure for calculating the TAC using the BMDL is as follows:

a) Calculate the RfD according to the following equation:

$$\text{RfD (mg/kg/d)} = \frac{BMDL_{HED}(\text{mg/kg/d})}{UF} \times \frac{[\text{number of days dosed per week}]}{7\ \text{d}}$$

NOTE — When other than daily dosing was used in the critical study, the RfD calculation shall be adjusted to reflect a daily dosing schedule.

b) Calculate the TAC based on the RfD with adjustment for significant contribution(s) of the substance from sources other than water according to the following equation:

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-d)} \times \text{RSC}}{IR_{ADULT}(\text{L/kg-d})}$$

The calculated TAC shall be rounded to one significant figure.

Where:

$BMDL_{HED}$ = The lower confidence limit on the dose that produces a specified magnitude of change (e.g., 10%) in a specified adverse response ($BMDL_{10}$).

UF = Total uncertainty factor (see Table 3.4)

RSC = Relative source contribution: Apply the US EPA (2000) Exposure Decision Tree to determine the RSC. If the data are available to quantify the relative drinking water contribution of a substance, a chemical-specific RSC shall be calculated. In the absence of data to determine significant contribution(s) of the substance from other sources, a default drinking water contribution of 20% shall be applied (US EPA, 1991). The calculation to determine the RSC considering all sources can be figured as follows:

$$\text{RSC} = \frac{\text{Exposure}_{\text{water}}}{\text{Exposure}_{\text{sum of all pathways}}} \times 100\%$$

IR_{ADULT} = Adult ingestion rate of 0.034 L/kg-d as indicated in the US EPA Exposure Factors Handbook (US EPA, 2019).[6]

3.6.3.1.4 Selection of uncertainty factors (UFs)

UFs used for the risk estimation shall include consideration of the areas of uncertainty listed in Table 3.4. A default value of 10 shall be used for individual areas of uncertainty when adequate data are not available to support a data-derived UF. Selection of the values of each UF shall consider the following criteria (adapted from Dourson et al., 1996).[7]

[6] Based on 90th percentile intake, consumers only, direct and indirect community water; NHANES 2005-2010; Table 3-21; rounded (US EPA, 2019).

[7] The Food Quality Protection Act (FQPA) of 1996 reemphasized the review and evaluation of toxicity data for the protection of children's health. The US EPA has been very responsive to this initiative and published a document outlining the use of an UF for children's protection and other database deficiencies (US EPA, 2002b). Currently, this factor is applied to pesticide evaluations only. In addition, publications by Renwick (1993) and the International Programme on Chemical Safety (IPCS) (2005) suggest the use of specific data in lieu of default values for UFs. The use of data-derived UFs, or judgment, as replacements to default values of 10-fold for each area of uncertainty is

3.6.3.1.4.1 Human variability

Selection of the human variability factor shall be based on the availability of data that identify sensitive subpopulations of humans. If sufficient data are available to quantitate the toxicokinetic and toxicodynamic variability of humans (see Sections 2.52 and 2.51), factor values of 3, 1, or a value determined from the data shall be considered. In the absence of these data, the default value of 10 shall be used.

3.6.3.1.4.2 Interspecies variability

Selection of the interspecies variability factor shall be based on the availability of data that allow for a quantitative extrapolation of animal dose to the equivalent human dose for effects of similar magnitude or for a NOAEL. This includes scientifically documented differences or similarities in physiology, metabolism and toxic response(s) between experimental animals and humans. If sufficient data are available to quantitate the toxicokinetic and toxicodynamic variabilities between experimental animals and humans (see Sections 2.52 and 2.51), factor values of 3, 1, or CSAF(s) for toxicokinetics or toxicodynamics determined from the data shall be considered. In the absence of these data, the default value of 10 shall be used.

3.6.3.1.4.3 Subchronic to chronic extrapolation

Selection of the factor for subchronic to chronic extrapolation shall be based on the availability of data that allow for quantitative extrapolation of the critical effect after subchronic exposure to that after chronic exposure. Selection shall also consider whether NOAELs differ quantitatively when different critical effects are observed after subchronic and chronic exposure to the compound. When the critical effect is identified from a study of chronic exposure, the factor value shall be 1. When sufficient data are available to quantitate the difference in the critical effect after subchronic and chronic exposure, or when the principal studies do not suggest that duration of exposure is a determinant of the critical effects, a factor value of 3 or a value determined from the data shall be considered. In the absence of these data, the default value of 10 shall be used.

3.6.3.1.4.4 Database sufficiency

Selection of the factor for database sufficiency shall be based on the ability of the existing data to support a scientific judgment of the likely critical effect of exposure to the compound. When data exist from a minimum of five core studies (two chronic bioassays in different species, one two-generation reproductive study, and two developmental toxicity studies in different species), a factor value of 1 shall be considered. When several, but not all, of the core studies are available, a factor value of 3 shall be considered. When several of the core studies are unavailable, the default value of 10 shall be used.

3.6.3.1.4.5 LOAEL to NOAEL extrapolation

Selection of the factor for LOAEL to NOAEL extrapolation shall be based on the ability of the existing data to allow the use of a LOAEL rather than a NOAEL for noncancer risk estimation. If a well-defined NOAEL is identified, the factor value shall be 1. When the identified LOAEL is for a minimally adverse or reversible toxic effect, a factor value of 3 shall be considered. When the identified LOAEL is for a severe or irreversible toxic effect, a factor value of 10 shall be used.

3.6.3.2 Assessment of carcinogenic endpoints

Risk assessment for carcinogenic endpoints shall be performed using the linear approach, the nonlinear approach, or both, consistent with the proposed US EPA Cancer Risk Assessment Guidelines (US EPA, 2005a). For substances that have been identified as known or likely human carcinogens (as defined by these guidelines), a dose response assessment shall be performed. This dose response

encouraged by several federal and international agencies and organizations (Meek, 1994; Dourson, 1994; US EPA, 2014a).

assessment shall include analysis of dose both in the range of observation (animal and human studies) and in the range of extrapolation to lower doses.

3.6.3.2.1 Analysis in the range of observation

Curve-fitting models shall be selected based on the characteristics of the response data in the observed range. The model shall be selected, to the extent possible, based on the biological mode of action of the substance taken together in a weight of evidence evaluation of the available toxicological and biological data. The selected model shall be used to determine the LED_{10}, which will either be the POD (see Section 2.30) for linear low dose extrapolation or the basis of the margin of MOE analysis (see Section 2.23) for a nonlinear assessment.

NOTE — See Figure 1 for a graphical representation of this analysis.

The following types of models shall be considered, as appropriate to the mode of action of the substance under evaluation, the availability of adequate data, and the current state of risk assessment approaches:

- statistical or distribution models:
  - log-probit;
  - logit; or
  - Weibull.
- mechanistic models:
  - one-hit;
  - multi-hit;
  - multi-stage; or
  - cell kinetic multi-stage.
- model enhancement and dose scaling:
  - time to tumor response;
  - physiologically based toxicokinetic models;
  - biologically based dose-response models; or
  - surface area conversion.

If none of the available models provide a reasonable fit to the dataset, the following shall be considered to see if lack of fit can be resolved (US EPA, 1995):

- interference at higher dose concentrations from competing mechanisms of toxicity that are a progressive form of the response of interest;
- saturation of metabolic or delivery systems for the ultimate toxicant at higher dose concentrations; and
- interference at higher dose concentrations due to toxic effects unrelated to the response of interest.

NOTE — When adjusting for these possibilities does not provide a reasonable fit, one suggested approach is to delete the high dose data and refit the models based on the lower dose concentrations since these doses are the most informative of the exposure concentrations anticipated to be encountered by humans.

3.6.3.2.2 Analysis in the range of extrapolation

The choice of procedure for low dose extrapolation shall be based on the biological mode of action of the substance. Depending upon the quantity and quality of the data, and upon the conclusion of the weight of evidence evaluation, the following procedures shall be used: linear, nonlinear, or linear and nonlinear.

3.6.3.2.2.1 Linear analysis

The linear default assumption shall be used when the toxicological data support a mode of action due to DNA reactivity or another mode of action which is anticipated to be linear in nature. It shall also be used when no data are available to justify an alternate approach. For linear extrapolation, a straight line is constructed from the POD on the dose response curve to the zero dose / zero response point.

3.6.3.2.2.2 Nonlinear analysis

The nonlinear default assumption shall be used when the toxicological data are sufficient to support the assumption of a nonlinear mechanism of action, and no evidence for linearity is available. An MOE analysis shall be used for nonlinear assessment. The MOE shall be calculated by dividing the POD by the human exposure concentration of interest.

3.6.3.2.2.3 Linear and nonlinear analysis

Linear and nonlinear assessments shall be provided when the weight of evidence or the mode of action analysis indicates differing modes of action for different target tissues, or to evaluate the implications of complex dose response relationships. Where the results of linear and nonlinear evaluations differ, the range of estimates shall be discussed, along with a justification for the estimate used in evaluation of the substance.

3.6.3.3 Determination of the TAC for carcinogenic endpoints

The selected model shall be used to determine the dose equivalent to the LED_{10}. For linear analyses, the TAC shall be determined by linear extrapolation of the LED_{10} to the origin of the dose response curve for the selected level of risk (e.g., 10^{-5}). For nonlinear analyses, the TAC shall be equal to the human exposure concentration of interest that represents the selected MOE (LED_{10} / exposure of interest). For both types of analyses, the level of risk or MOE shall be selected in accordance with the US EPA Guidelines for Carcinogen Risk Assessment (US EPA, 2005a).

3.6.3.3.1 Determination of the TAC for carcinogens with a mutagenic mode of action

For carcinogens acting through a mutagenic mode of action, potency adjustment factors shall be applied as appropriate to determine unit risk by postnatal life stage according to US EPA (2005b) guidance, and the TAC shall be calculated using the total lifetime risk. These procedures shall not be applied for nonmutagenic carcinogens or when the mode of action is unknown (US EPA, 2005a), when there are sufficient data to calculate a chemical-specific early life cancer slope factor, if the cancer slope factors are derived from studies that incorporate exposures during early life, or when early life adjustment is not otherwise appropriate biologically, such as if a metabolite of the chemical is the ultimate carcinogen (US EPA, 2005a; MDH, 2010). When appropriate, the individual age group-adjusted unit risks ($Unit\ Risk_{age}$) associated with relevant time periods shall be calculated according to the equation below:

$$Unit\ Risk_{age} = \frac{CSF\ (\text{kg-d})}{\text{mg}} \times IR\ (\text{L/kg-d}) \times \frac{1\ \text{mg}}{1000\ \mu\text{g}} \times \frac{exposure\ (\text{y})}{70\text{y}} \times \frac{p.a.}{1}$$