How to Develop Generic Effects Screening Levels for Chemicals with Limited Toxicity Information

Excerpts from the TCEQ Guidelines to Develop Toxicity Factors (Revised RG-442)

Table of Contents

Chapter 3 Common Procedures Used to Derive Acute and Chronic Toxicity Factors

3.15 Chemicals with Limited Toxicity Data

The TCEQ frequently evaluates chemicals with limited toxicity data (LTD). Every effort is made to obtain as much information on the chemical of interest as possible. However, when the minimum database requirements for development of an acute ReV (Section 4.3) or chronic ReV (Section 5.4) are not met, then acute or chronic generic ESLs may be derived on an as needed basis using route-to-route extrapolation or use of relative toxicity/relative potency. If route-to-route extrapolation or relative toxicity/relative potency is used to derive inhalation values, then the value is referred to as a generic ESL, not a ReV. Other methods to derive generic ESLs are discussed in Section 4.5 for acute inhalation exposure.

When the minimum database requirements for development of a chronic RfD (Section 5.4) are not met, a chronic RfD may be derived on an as needed basis, based on route-to-route extrapolation or use of relative toxicity/relative potency approach. URF and SFo values may be developed based on route-to-route extrapolation, if scientifically defensible. Generally, URF and SFo values are not routinely developed based on a relative toxicity/relative potency approach except in certain cases (e.g., relative potency factors for polycylic aromatic hydrocarbons (Chapter 6)). Other methods to derive RfDs are discussed in Section 5.6.

3.15.1 Route-to-Route Extrapolation

In the absence of human and animal dose-response data for either the oral or inhalation route of a given agent, the TCEQ may derive toxicity factors or generic ESLs based on data from inhalation or non-inhalation (e.g., most likely oral) exposure routes, respectively, only if strict criteria are met. However, for TCEQ's purposes it is anticipated that the most likely route-to-route extrapolation will be derivation of a generic ESL from oral data. Route-to-route extrapolation for purposes of deriving a Generic ESL or RfD will be performed on the $POD_{HED/HEC}$ of the critical study, not on the final toxicity factor so that appropriate UFs can be applied. Most specifically, a UF_D considers and accounts for the uncertainty of deriving a toxicity factor based on route-to-route extrapolation. Route-to-route extrapolation for purposes of deriving a SFo or URF will be performed on the toxicity factor for the exposure route with carcinogenicity data as UFs are not used in the derivation of carcinogenic toxicity factors.

Extrapolation of dose-response data from one exposure route to another is accompanied by uncertainty, which is important to minimize as much as the available data and methods allow. The major factors contributing to the uncertainties associated with route-to-route extrapolation include: (1) the presence of POE effects in the lung or gastrointestinal tract and the potential for such effects for the exposure route being extrapolated to; (2) liver first-pass effects following oral dosing which would result in an expectation of adverse effects different than those due to inhalation exposure; and (3) accurate dosimetry to normalize the internal dose and biologically effective dose achieved by the compared exposure routes (i.e., pharmacokinetic differences) is unknown. USEPA states that if either a first-pass effect or POE effect is present, route-to-route extrapolation is not recommended for derivation of chronic health reference values such as the RfC (USEPA 1994a).

Oral ingestion is the most common exposure route from which toxicity is estimated for other routes, including inhalation. Data from parenteral exposure may also be considered although accurate dosimetry is still required to normalize internal and effective doses to those expected from inhalation. Honma and Suda (1998) performed a correlation of lethal doses of industrial chemicals between oral administration and inhalation exposure (i.e., oral LD_{50} and LC_{50} data) and between intraperitoneal administration and inhalation exposure (i.e., intraperitoneal LD_{50} and LC_{50} data). They demonstrated that the correlations between LC_{50} and LD_{50} data with intraperitoneal administration were higher than those between LC_{50} and LD_{50} with oral administration in both rats and mice.

Given the uncertainties associated with route-to-route extrapolation, the TCEQ does not perform route-to-route extrapolation if any of the following circumstances would be expected based on available data or information (refer to Figure 4-3 in Section 4.1.2 of USEPA 1994a):

- Different critical adverse effects are expected to result from the compared exposure routes, which can be the case for metals, irritants, and sensitizers;
- POE effects occur (e.g., irritants, sensitizers);
- Respiratory or hepatic first-pass effects are expected;
- A respiratory or oral effect is known to occur, but accurate dosimetry between the two routes is not established;
- Referenced oral/inhalation studies do not include adequate assessment of respiratory tract or gastrointestinal effects, respectively; or
- Studies are not of adequate quality to establish a toxicity factor for the exposure route from which to extrapolate.

If the above mentioned route-to-route concerns are addressed, toxicity information from other exposure routes may be used to add to the WOE, determine the MOA, or address other issues when deriving a toxicity factor for another route of exposure. For example, if a 2-generation study is available via the oral route showing no reproductive/developmental effects, and oral absorption is known to occur, then this information may be used to support the

likelihood that the chemical is not a reproductive/developmental toxicant via the inhalation route (assuming no POE effects, etc. are expected).

The preferred method for route-to-route extrapolation is the use of PBPK modeling, which provides the best estimate of a toxicant's internal and biologically effective dose as a function of exposure. PBPK modeling accomplishes this by application of algorithms for physiologic factors such as ventilation/perfusion ratios, renal clearance and metabolism, as well as properties of the given toxicant (e.g., partition coefficients, reactivity). The combination of PBPK modeling and supporting toxicity data allows route-to-route extrapolation with fewer uncertainties than other methods, and the TCEQ utilizes this method whenever possible to derive toxicity factors for a constituent. When the available data are inadequate for PBPK modeling, other available mathematical dosimetry models can be used based on MOA of the chemical and whether necessary physiologic factors are available. For extrapolation of oral to inhalation, the following papers provide several case studies for different chemicals illustrating the use of mathematical models and approaches for route-to-route extrapolation that are particularly informative (e.g. chloroform, cadmium, carbon tetrachloride, and trichloroethylene) (Overton and Jarabek 1989a, 1989b; Gerrity and Henry 1990; Overton 1990; USEPA 1994a).

For deriving a generic ESL, if a more appropriate chemical-specific model is not available, the POD_{HEC} can be calculated from the corresponding POD_{HED} as follows (Equation 3-8):

Equation 3-1 POD_{HEC} Derived from POD_{HED}

$$POD_{HEC} = \left(POD_{HED} \times BW_H \times \frac{day}{20\ m^3}\right) \times \left(\frac{A_{oral}}{A_{inh}}\right)$$

Where:

POD_{HEC} = human equivalent concentration POD (mg/m^3)
POD_{HED} = human equivalent dose POD (mg/kg-day)
BW_H = human body weight (70 kg)
A_{oral} = absorption via oral exposure (unitless)
A_{inh} = absorption via inhalation exposure (unitless)

For deriving a RfD, the POD_{HED} can be calculated from the corresponding POD_{HEC} as follows (Equation 3-9):

Equation 3-2 POD_{HED} Derived from POD_{HEC}

$$POD_{HED} = \frac{\left(POD_{HEC} \times \frac{20\ m^3}{day}\right)}{BW_H} \times \left(\frac{A_{inh}}{A_{oral}}\right)$$

As for noncarcinogenic effects, the appropriateness of route-to-route extrapolation of dose data for carcinogenic effects relies on a case-by-case analysis of available data (USEPA 2005a). For deriving a URF, assuming route-to-route extrapolation is considered scientifically defensible, the following equation may be used to convert the SFo (Equation 3-10):

Equation 3-3 URF Derived from the SFo

$$\text{URF (risk per } \mu g/m^3) = \left(\frac{\text{SFo}}{BW_H}\right) \times \frac{20\ m^3}{\text{day}} \times \left(\frac{1\ \text{mg}}{1{,}000\ \mu g}\right) \times \left(\frac{A_{inh}}{A_{oral}}\right)$$

Where:

SFo = oral slope factor (risk per mg/kg-day)
BW_H = human body weight (70 kg)
A_{oral} = absorption via oral exposure (unitless)
A_{inh} = absorption via inhalation exposure (unitless)

Rearranging the equation to derive a SFo from a URF yields (Equation 3-11):

Equation 3-4 SFo Derived from the URF

$$\text{SFo (risk per mg/kg-day)} = \left(\frac{\text{URF}}{\frac{20\ m^3}{\text{day}}}\right) \times BW_H \times \left(\frac{1{,}000\ \mu g}{1\ \text{mg}}\right) \times \left(\frac{A_{oral}}{A_{inh}}\right)$$

Chemical-specific values for A_{inh} and A_{oral} should preferentially be used but A_{inh} and A_{oral} data from a structurally-related chemical or chemical-class may be used if data indicates it is relevant and scientifically defensible. Otherwise, a default absorption ratio (A_{inh} / A_{oral} or A_{oral} / A_{inh}) of 1 may be used. The TCEQ utilizes best scientific judgment on a case-by-case basis in determining whether to perform route-to-route extrapolation for derivation of a particular toxicity factor (generic ESL, RfD, SFo, URF). It is noted that the oral-to-inhalation extrapolations could result in POD_{HEC} and/or toxicity factor air concentration values that are unlikely given the physical/chemical properties (e.g., low vapor pressure) of the particular chemical.

3.15.2 Relative Toxicity/Relative Potency Approach

3.15.2.1 Background

Relative potency can be defined as a procedure to estimate the "toxicity" of a LTD chemical in relation to a reference or an index chemical(s) for which toxicity has been well defined. The concept of relative potency has been used for polycyclic aromatic hydrocarbons (PAHs) (Collins et al. 1998) and organophosphate pesticides (USEPA 2002b). PAHs are considered a class of structurally and toxicologically similar chemicals. Therefore, the concept of relative toxicity has been used to derive toxicity values for PAHs with limited toxicity information based on the toxicity information of benzo[a]pyrene, for which there is a wealth of information (Collins et al. 1998).

Various government and regulatory agencies have adopted the relative potency approach or have adopted comparable methodologies for the purpose of estimating toxicity values for chemicals with limited information. The relative potency approach was used to determine Acute Exposure Guideline Level (AEGL) values for some nerve agents based on the toxicity data of nerve gas sarin. The

rationale for the relative potency approach was that other nerve gases such as tabun, soman, cyclosarin, and VX were similar in structure and toxicity to sarin gas (NRC 2003). The emergency planning and safety analysis divisions within the US Department of Energy (USDOE) complex often need to derive Temporary Emergency Exposure Levels (TEELs) for chemicals with limited toxicological information until ERPGs are available (USDOE 2008). The methodology for deriving TEELS for LTD chemicals involves comparing 50% lethality data of a structurally-similar chemical with adequate inhalation reference values to the lethality data of the LTD chemical in order to estimate values for the LTD chemical if that is the only available data (USDOE 2008).

3.15.2.2 Quantitative Structure Activity Relationships versus Structural Activity Relationships

Quantitative structure activity relationships (QSARs) use a mathematical model to quantitatively predict pharmacological or toxicological activity for a series of compounds from chemical structure (USEPA 1999a). While QSARs have proven to be very useful for predicting mutagenicity, their use in risk assessment is limited as they require highly trained toxicologists who are proficient in the use of the appropriate software to correlate complex molecular structures to varied health effects (e.g., acute vs. chronic, *in vitro* vs. *in vivo*, mutagenicity vs. general toxicity vs developmental toxicity). Therefore, QSARs can become time consuming, data-intensive, and expensive tools in risk assessment. In addition, there may not be a highly predictive model available for the toxicological endpoint of interest. For example, there are very few QSARs available to evaluate and predict acute inhalation toxicity. Ones that are available have not proven to be useful in the diverse setting of regulatory toxicology. Due to these reasons, the TCEQ does not directly perform QSAR to predict acute or chronic inhalation toxicity endpoints but does use information from QSAR studies published in the scientific literature when available. Below is a list of QSAR software that may be of use to individuals wishing to apply these tools in a risk assessment:

- 3-Dimensional QSAR: www.3d-qsar.com/
- E-Dragon Software: www.vcclab.org/lab/edragon/
- OECD QSARs: www.oecd.org/env/chemicalsafetyandbiosafety/oecdquantitativestructure-activityrelationshipsprojectqsars.htm
- QSAR World: www.qsarworld.com/free-programs.php
- Toxicity Estimation Software (TEST): www.epa.gov/nrmrl/std/qsar/qsar.html
- VEGA QSAR: www.insilico.eu/use-qsar.html

Structural activity relationships (SARs) can be described as the relationship of the molecular structure of a chemical with a physical/chemical property, environmental fate, and/or specific effect on human health or on environmental species (USEPA 1999a). Both the USEPA and European Chemical Bureau have recognized the benefits of using SARs as a way to reduce the amount of testing

required for chemicals with limited information. USEPA and the European Chemical Bureau define a category as a group of chemicals whose physical/chemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. The underlying premise of SARs is that members of a chemical group or class share similar physical and chemical properties and MOA, and therefore, they will tend to behave in a similar toxicological manner (USEPA 1999a, USEPA 1999b). For example, the similarities among the chemicals in the category can be based on a common functional group (e.g., aldehyde, epoxide, ester, etc.) or an incremental and constant change across the category (e.g. the dimethylene group difference between adjacent members of the alpha-olefins or the presence of homologous series as in glycol ethers) (USEPA 1999b).

The TCEQ uses the principles of SAR to choose an appropriate analog chemical or to categorize chemicals into groups or classes. An analog is defined as a chemical compound that is structurally similar to another compound but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group). In order to use the analog approach, there should be unambiguous structural and metabolic relationships between the LTD chemical and the chemical with toxicity information. A potential category can be formed by grouping a series of chemicals or using chemical categories that have been defined by USEPA such as the high production volume chemical classes (USEPA1999b).

3.15.2.3 Steps to Perform Relative Toxicity/Potency

The TCEQ uses the principles of SAR coupled with the knowledge of the MOA of an index chemical or a class of chemicals in conjunction with expert judgment of trained staff to develop generic toxicity factors for LTD chemicals. Procedures used previously by others are used by TCEQ staff to estimate toxicity factors based on relative potency (USDOE 2008, Glass et al. 1991). The TCEQ maintains the generic toxicity factors on an interim basis until additional toxicological information becomes available. The estimation process is especially valuable for estimating toxicity factors for categories of chemicals that are known to be relatively less toxic (Globally Harmonized System (GHS) Categories 3, 4 and 5; UN 2005) and for which traditional testing may not occur. Use of scientifically-valid estimation tools for the relatively less toxic chemicals allows more resources (time and resources) to be directed toward toxicity factor development for the more toxic chemicals (GHS Categories 1 and 2) which warrant a higher level of review. The following steps briefly describe the qualitative expert judgment approach that the TCEQ uses to apply the concept of SAR and relative potency for estimating generic ESLs or other toxicity factors for LTD chemicals. These steps can be employed when similar chemical categories or an analog chemical approach is used:

Step 1: Identify potential index chemical(s) for which toxicity factors have been developed.

Step 2: Gather data on physical/chemical properties, toxicity, etc. for the potential index chemical(s) and the LTD chemical.

Step 3: Construct a matrix of data for all chemicals. Table 3-7 is an example of how to organize endpoint information for a series of potential index chemicals and the LTD chemical.

Step 4: Evaluate the data to determine if there is a correlation among chemicals and the endpoints by conducting a simple trend analysis to determine whether a predictable pattern exists amongst the chemicals.

Step 5: Perform an MOA analysis and determine the relevant endpoints that can be used for a relative potency approach. Relevant endpoints should be determined using similar testing techniques, exposure durations, and species.

Step 6: Calculate the relative potency of the pertinent endpoint based on an MOA analysis of the index chemical to the pertinent endpoint of the LTD chemical (Equation 3-12):

Equation 3-5 Relative Potency

$$\text{Relative Potency} = \frac{\text{Relevant Endpoint}_{\text{LTD Chemical}}}{\text{Relevant Endpoint}_{\text{Index Chemical}}}$$

Step 7: Estimate the generic toxicity factor of the LTD chemical by adjusting the index chemical's value by the relative potency factor. The following equation shows this adjustment for a generic ESL, but it could also be used for a chronic generic ESL or RfD (Equation 3-13):

Equation 3-6 Generic ESL for LTD Chemicals

$$\text{Generic ESL}_{\text{LTD Chemical}} = \text{ESL}_{\text{Index Chemical}} \times \text{Relative Potency}$$

Relevant endpoint data used to ratio toxicity may be as straightforward as mortality measurements (e.g., LC_{50} and LD_{50} data). In addition, MOA can be used to identity other relevant endpoints whose ratio is expected to describe the difference in toxicity between the two chemicals. For example, if one needs to estimate a generic RfD for a limited-data organophosphate pesticide based on the RfD of another organophosphate pesticide, measurements of brain cholinesterase inhibition could be the relevant endpoint. The RfD of the index organophosphate pesticide would be multiplied by the ratio of cholinesterase inhibition of the limited-data chemical to the cholinesterase inhibition of the index chemical.

If multiple values of relative potency based on the same or different relevant endpoint are available, a geometric mean of the calculated relative potency ratios (R_{GM}) is obtained. The generic value for the LTD chemical can then be calculated by multiplying the R_{GM} by the value of the structurally-similar index chemical. This process may be repeated if more than one chemical similar to the chemical of interest is identified.

Alternately, depending on data availability and time and resource constraints, the lowest, most conservative toxicity factor for a series of structurally-similar compounds can be used as a generic value for other structurally-similar

compounds with limited toxicity information. For example, OEHHA developed a reference exposure level (REL) for metallic mercury vapor, but there was less information on mercury salts. However, OEHHA stated “Since mercury salts have no significant vapor pressure under normal atmospheric conditions, they would only be of concern as hazards if aerosolized in aqueous solution or burned. This REL is developed for metallic mercury vapor and would be an overestimate of the REL for mercury salts.” (OEHHA 1999)

Table 3-1 Example of How to Organize Endpoint Information for a Series of Chemicals

Endpoint	**Potential Index Chemical #1**	**Potential Index Chemical #2**	**LTD Chemical**	**Potential Index Chemical #3**
Category				
Molecular weight				
Chemical Formula				
Chemical Structure				
Physical Form				
Boiling Point				
Melting Point				
Vapor Pressure at 25^{o} C				
Partition Coefficient				
Log K_{ow}				
Solubility				
Odor				
Health effects				
Short-term ESL				
LC_{50}				
LD_{50}				
RD_{50}				
NOAEL				
LOAEL				
Reproductive/ Developmental				

Chapter 4 Derivation of Acute Toxicity Factors

4.5 Chemicals with Limited Toxicity Data

On an interim basis during the air permit review process, the TCEQ frequently evaluates chemicals with limited toxicity data (LTD chemicals). Every effort is made to obtain as much information on the chemical of interest as possible, including requesting supporting information/ documentation from the facility whose permit application is under review. However, when the minimum database requirement (Section 4.3) is not met, an acute ReV is not developed. Instead, a tiered approach is used to either set a default ESL or derive a generic health-based ESL depending on the availability of toxicity information and time and resource constraints (Figure 4-2).

- Tier I – Threshold of Regulation (default ESL = 2 µg/m^3)
- Tier II – Use of LC_{50} Data (generic ESL)
- Tier III – Relative Toxicity/Potency Approach (generic ESL)

When a facility requests an ESL for a LTD chemical, then a Tier I, II, or III approach is used based on time and resource constraints and judgment of TCEQ staff. The following sections discuss the procedures the TCEQ uses to set health-protective concentrations for LTD chemicals based on a tiered approach.

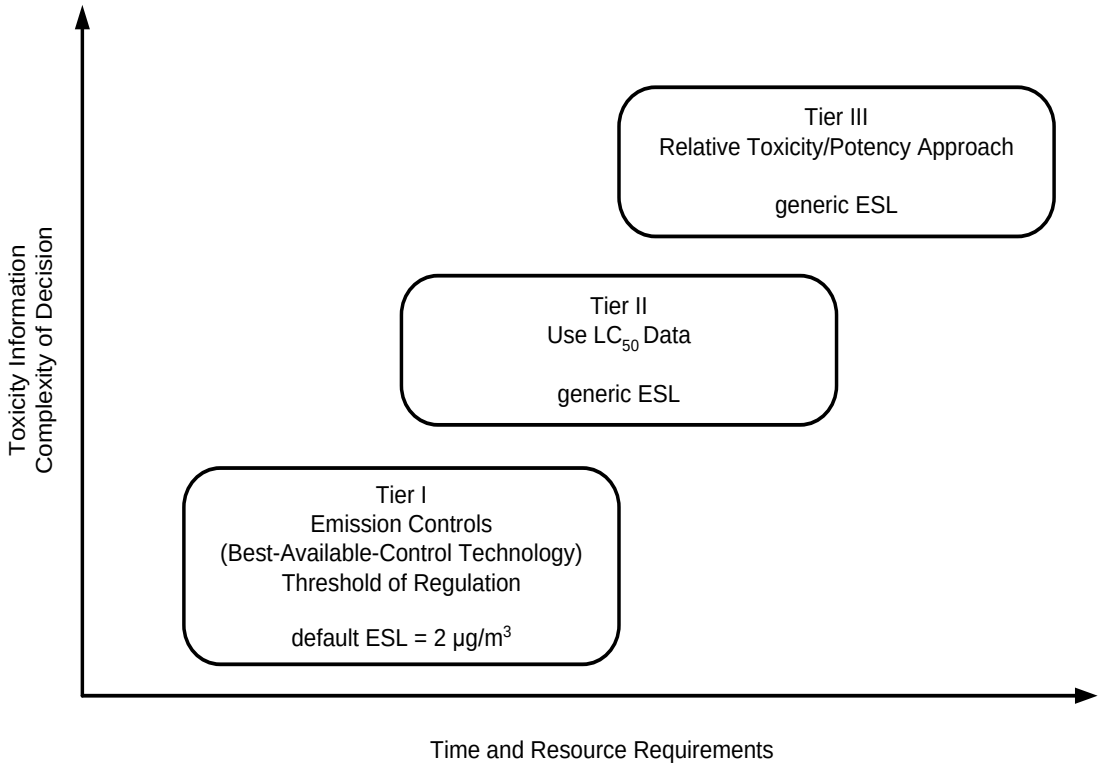

Figure 4-1 A three-tiered approach to setting a default or a generic health-based ESL

4.5.1 Tier I Default ESL: Threshold of Regulation Approach

According to the Modeling and Effects Review Applicability (MERA) guidelines (TCEQ 2009a), the applicant and/or the air permit engineer reviews the non-criteria pollutants to be emitted by the facility and assesses whether best-available-control technology has been proposed to control emissions. If the emissions from a non-criteria pollutant meet the MERA guidelines, then no ESL review is required (i.e., the emissions are deemed to be insignificant). If the emissions are deemed to be significant, worst-case emission rates are modeled to predict resulting short-term substance-specific maximum ground-level concentrations (GLC_{max}), which are compared to substance-specific, short-term ESLs. If an ESL is not published for a chemical, a default short-term ESL of 2 $\mu g/m^3$ can be used (TCEQ 2009a). If the GLC_{max} is below the default short-term ESL, then the potential for that chemical to cause health effects is deemed to be low, and an ESL does not need to be developed for that chemical. This approach is similar to the threshold of regulation approach used by the Food and Drug Administration (FDA) for food contact articles with limited toxicity information (FDA 1995).

If the default short-term ESL of 2 $\mu g/m^3$ is not attainable for an applicant for a LTD chemical, a Tier II or Tier III approach is used to estimate a generic short-term ESL.

4.5.2 Tier II Generic ESL: NOAEL-to-LC_{50} Ratio Approach

The evaluation of toxicity following short-term exposure to a chemical is an integral step in the assessment of its toxic potential by regulatory agencies. The TCEQ uses the information from standard acute LC_{50} toxicity tests and a NOAEL-to-LC_{50} (N-L) ratio approach to estimate a Tier II generic ESL (Grant et al. 2007). In the past, a Threshold of Concern (TOC) Approach was also used to estimate a Tier II generic ESL (Grant et al. 2007). However, a study by Phillips et al. (2011) demonstrated that the N-L ratio approach was more predictive of toxicity when using acute lethality data, whereas the TOC approach was overly conservative. If inhalation or oral lethality data are available, the N-L ratio approach is used preferentially. The N-L ratio approach is discussed in detail in the following sections. However, if inhalation or oral lethality data are not available and data indicate that a chemical is corrosive or an eye or skin irritant, the TOC approach may be used. For a discussion of the TOC approach, refer to Grant et al. (2007).

4.5.2.1 Criteria for Selection of Acute Lethality Data

For the N-L ratio approach, acute inhalation lethality data are multiplied by a tenth percentile composite factor N-L ratio to estimate health-protective air concentrations. The first step is selection of scientifically-defensible acute lethality data using the following criteria.

For many substances, more than one LC_{50} may be identified from the literature, resulting from the fact that many substances are tested in more than one species and sex and/or at different exposure durations. This may lead, in some cases, to multiple LC_{50} values for individual substances. Figure 4-3 illustrates the steps that are followed for selection of LC_{50} data used for the N-L ratio approach. First, LC_{50} data for all species $\leq$ 4 h are obtained (Step 1). Values are adjusted to correspond to a 4-h exposure duration because a 4-h exposure duration for LC_{50} data is more commonly available than other exposure durations. Duration adjustments for LC_{50} data are made using Haber's Law (Rinehart and Hatch 1964) as modified by ten Berge et al. (1986) as discussed previously in Sections 3.8 and 4.2. If all extrapolated values produce the same LC_{50} data, no further action is required. If the extrapolated values produce different LC_{50} data, then the lowest value is chosen although the quality of the experimental study, physical/chemical characteristics of the chemical, and other data such as eye/skin irritation, etc., can be used in the decision process. If LC_{50} data $\leq$ 4 h are not available, then LC_{50} data > 4 h but $\leq$ 12 h are obtained (Step 2). Duration adjustments are not performed on LC_{50} data > 4 h because of the uncertainties involved with extrapolating exposure durations from longer exposure to shorter exposure durations (Jarabek 1995a). If all values produce the same LC_{50} data, no further action is required. If the extrapolated values produce different LC_{50} data, then the lowest LC_{50} data is chosen. The quality of the experimental study, physical/chemical characteristics of the chemical, and other data such as eye/skin irritation, etc., are also used to decide the chemical's LC_{50}. If LC_{50} data $\leq$ 12 h are not available, then all other pertinent inhalation lethality data (i.e., LC_{low}, LC_{33}, etc.) are used (Step 3). This is generally a conservative approach because these values are lower than LC_{50} data.

Acute toxicity testing is generally performed by the most relevant route of exposure in order to provide information on health hazards likely to arise from short-term exposure

by that route. Therefore, the inhalation route may not have been evaluated for a product or chemical if the most relevant route of exposure is oral or dermal. Oral data may be used to extrapolate to LC_{50} values, but only if the chemical meets the strict criteria discussed in Section 3.15.1 and is determined not to be corrosive and/or reactive (Step 4).

If inhalation or oral lethality data are not available, then information on whether a chemical is corrosive or an eye or skin irritant can be used to categorize a chemical using the TOC Approach (Grant et al. 2007) (Step 5). In order to determine whether a chemical is corrosive, available empirical data are used. If a chemical is an oxidizer, an inorganic or organic acid or base, reacts with water to form corrosive or reactive products, or is readily hydrolyzed by nasal carboxylesterases, it is more likely to be corrosive or reactive or result in POE effects. The European Union has devised a tiered testing strategy to determine whether or not compounds cause skin irritation and corrosion based on the integrated use of physicochemical properties, QSAR, and *in vitro* data (Cronin et al. 2003). If information on a chemical is derived using this tiered testing strategy, then the TCEQ uses this information to evaluate whether or not a chemical is corrosive. Information based on MOA for specific chemical classes, physical/chemical parameters, reactivity and all other available information from acute toxicity tests is used to categorize a chemical into the appropriate toxicity category if the TOC Approach is used. In addition, the facility can be contacted and additional information can be obtained.

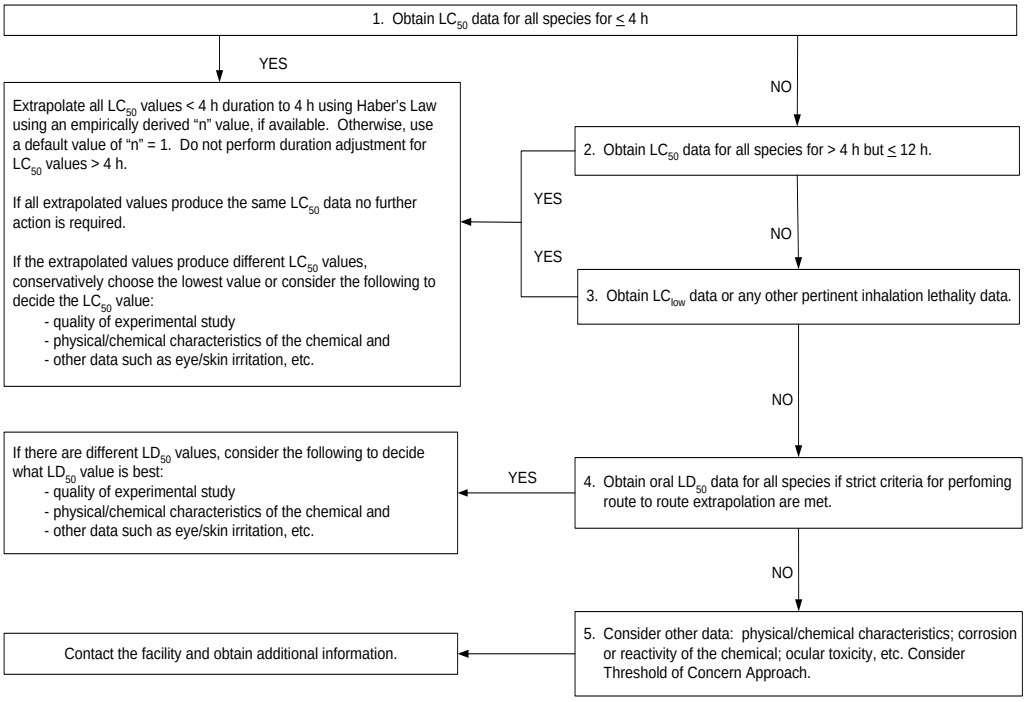

Figure 4-2 Criteria to select LC_{50} data

4.5.2.2 N-L Ratio Approach

After choosing an LC_{50} value for a LTD chemical as described in the previous section, an N-L ratio-based Tier II generic ESL can be determined by multiplying the LC_{50} by 8.3×10^{-5}. The background of the N-L ratio approach is discussed in detail in Grant et al. (2007) and is briefly discussed below.

Several investigators have suggested using readily-available acute toxicity data to estimate chronic endpoints for LTD chemicals. This procedure was proposed by Layton et al. (1987) for estimating acceptable daily intakes (ADI) for the evaluation of exposures to contaminants at hazardous waste sites. Venman and Flaga (1985) used this procedure to establish provisional ADIs for the evaluation of waste water contaminants. Both investigators calculated NOAEL-to-oral LD_{50} ratios from chronic animal studies for different chemicals and determined the fifth percentile of the cumulative distributions of the ratios. The LD_{50} value for contaminants with limited toxicity data was multiplied by the fifth percentile ratio to derive a surrogate NOAEL. The surrogate NOAEL was divided by an uncertainty factor of 100 in order to establish a conservative threshold dose below which no appreciable risk to human health would occur.

Grant et al. (2007) used the basic approach of Layton et al. (1987) and Venman and Flaga (1985) to establish a procedure to estimate Tier II generic ESLs for LTD chemicals using available LC_{50} data. Grant et al. (2007) provides a detailed discussion of how an acute inhalation N-L ratio was calculated for the evaluation of acute inhalation toxicity, so only a brief discussion is provided here. A large reference database consisting of LC_{50} data and acute inhalation NOAELs for 55 chemicals was compiled. The database consisted of acute toxicity data tested for a variety of acute inhalation endpoints where the exposure durations of the NOAEL studies were less than 24 h. The N-L ratio was calculated for each chemical and the tenth percentile of the cumulative distribution of the ratios was calculated and divided by an uncertainty factor of 100. The tenth percentile composite factor N-L ratio was 8.3×10^{-5}. For a LTD chemical, this factor is multiplied by LC_{50} values which have been adjusted to 4 h or other appropriate inhalation lethality data based on criteria in Figure 4-3 to estimate a conservative generic ESL below which no appreciable risk to human health would occur (Grant et al. 2007).

TCEQ has implemented the N-L ratio approach and the TOC approach to determine Tier II generic ESLs for pentene isomers (TCEQ 2007a) and n-hexane (TCEQ 2007b). For both pentene and n-hexane, the N-L ratio approach was deemed to be more applicable than the TOC approach. Phillips et al. (2011) conducted a validation exercise where health-based ^{acute}ESLs derived using the guidelines were compared to Tier II generic ESLs using the N-L ratio approach and the TOC approach. For 3 of 19 chemicals, the generic ESLs derived using the N-L ratio approach were slightly higher but were within a factor of two of the health-based ^{acute}ESLs. For 16 of the 19 chemicals, the generic ESLs using the N-L ratio approach were lower than the health-based ^{acute}ESLs. Generally, the TOC method was more conservative than the N-L ratio approach, especially for relatively nontoxic chemicals.

4.5.2.3 TOC Approach

As mentioned previously in Section 4.5.2, if inhalation or oral lethality data are available, the N-L ratio approach is preferentially used. However, if inhalation or oral lethality data are not available and data indicate that a chemical is corrosive or an eye or skin irritant, the TOC approach may be used (Step 5). For a discussion of the TOC approach, refer to Grant et al. (2007).

4.5.3 Tier III Generic ESL: Relative Toxicity/Relative Potency Approach

Conservative Tier I default ESLs and Tier II generic ESLs are developed on an interim basis upon request. The TCEQ will consider development of a Tier III generic ESL based on a relative toxicity/relative potency approach as discussed in Section 3.15.2. Development of a Tier III generic ESL is more time- and labor-intensive (Figure 4-2).

References

Collins, J. F., Brown, J. P., Alexeeff, G. V., & Salmon, A. G. (1998). Potency equivalency factors for some polycyclic aromatic hydrocarbons and polycyclic aromatic hydrocarbon derivatives. Regul Toxicol Pharmacol, 28(1), 45-54. doi: 10.1006/rtph.1998.1235

Cronin, M. T., Dearden, J. C., Walker, J. D., & Worth, A. P. (2003). Quantitative structure-activity relationships for human health effects: commonalities with other endpoints. [Review]. Environ Toxicol Chem, 22(8), 1829-1843.

Food and Drug Administration (FDA). (1995). Food Additives; Threshold of Regulation for Substances Used In Food-Contact Articles. Federal Register 60 (136): 36582-96.

Gerrity, T. R., & Henry, C. J. (1990). Summary Report of The Workshops on Principles of Route-To-Route Extrapolation for Risk Assessment Principles of Route-to-Route Extrapolation for Risk Assessment, Proceedings Of The Workshops; March and July; Hilton Head, S.C. and Durham, N.C. (pp. 1-12). New York, N.Y.: Elsevier Science Publishing Co., Inc.

Glass, L. R., Easterly, C. E., Jones, T. D., & Walsh, P. J. (1991). Ranking of carcinogenic potency using a relative potency approach. Arch Environ Contam Toxicol, 21(2), 169-176.

Grant, R. L., Kadlubar, B. J., Erraguntla, N. K., & Honeycutt, M. (2007). Evaluation of acute inhalation toxicity for chemicals with limited toxicity information. Regul Toxicol Pharmacol, 47(3), 261-273. doi: 10.1016/j.yrtph.2006.11.003

Jarabek, A. M. (1995a). Consideration of Temporal Toxicity Challenges Current Default Assumptions. Inhal Toxicol, 7(6), 927-946. doi: 10.3109/08958379509012801

National Research Council (NRC). (2003). Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 3. Washington, D.C.: National Academy Press.

Office of Environmental Health Hazard Assessment (OEHHA). (1999). Acute Toxicity Summary, Mercury (Inorganic). California Environmental Protection Agency.

Overton, J. H. (1990). Respiratory Tract Physiological Processes and the Uptake of Gases. In: Principles of Route-to-route Extrapolation for Risk Assessment. New York, NY: Elsevier Science Publishing Co., Inc.

Overton, J., & Jarabek, A. (1989a). Estimating Human Equivalent No Observed Effect Levels for VOCs Based on Minimal Knowledge of Physiological Parameters. (USEPA, EPA/600/D-89/097 (NTIS PB89224588)). Washington, D.C.

Overton, J. H., & Jarabek, A. M. (1989b). Estimating equivalent human concentrations of no observed adverse effect levels: a comparison of several methods. Exp Pathol, 37(1-4), 89-94.

Phillips, T. D., Ethridge, S. E., & Grant, R. L. (2011). Practical implementation of the threshold of concern and NOAEL-to-LC50 ratio factor approach to determine acute effects screening levels. The Toxicologist, Suppl 2 to Tox Sci 120, Abstract No. #1523.

Rinehart, W. E., & Hatch, T. (1964). Concentration-Time Product (CT) as an Expression of Dose in Sublethal Exposures to Phosgene. Am Ind Hyg Assoc J, 25, 545-553. doi: 10.1080/00028896409342641

ten Berge, W. F., Zwart, A., & Appelman, L. M. (1986). Concentration—time mortality response relationship of irritant and systemically acting vapours and gases. Journal of Hazardous Materials, 13(3), 301-309.

Texas Commission on Environmental Quality (TCEQ). (2007a). Development Support Document for Pentenes, CAS Registry Numbers: 1-pentene: 109-67-1, c-2-pentene: 627-20-3, t-2 pentene: 646-04-8. Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2007b). Development Support Document for n-Hexane, CAS Registry Numbers: 100-54-3. Retrieved from www.tceq.texas.gov/toxicology/dsd/final.html.

Texas Commission on Environmental Quality (TCEQ). (2009a). Modeling and Effects Review Applicability: How to Determine the Scope of Modeling and Effects Review for Air Permits. (APDG-5874). Austin, TX.

Texas Commission on Environmental Quality (TCEQ). 2012. TCEQ guidelines to develop toxicity factors (Revised RG-442). Texas Commission on Environmental Quality. Office of the Executive Director. Available from: http://www.tceq.texas.gov/publications/rg/rg-442.html

Texas Risk Reduction Program (TRRP). (2006). Rule 30 TAC §350 and Sub chapters A and S of 30 TAC §335. Retrieved from www.tceq.texas.gov/rules/indxpdf.html#350.

United States Department of Energy (USDOE). (2008). DOE Handbook Temporary Emergency Exposure Limits for Chemicals: Methods and Practice. (DOE-HDBK-1046-2008). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1994a). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. (EPA/600/8-90/066F). Washington, D.C.

United States Environmental Protection Agency (USEPA). (1999a). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. Washington, D.C.

United States Environmental Protection Agency (USEPA). (1999b). Development of Chemical Categories in the High Production Volume Chemicals Challenge Program. Washington, D. C.