The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.

FDA U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

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Subject: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products

1 Purpose

Different national and international agencies develop inhalation toxicity reference values to protect the health of the general population and occupational exposure levels or limits (OELs) to protect workers in occupational settings from harmful exposures. Substantial equivalence (SE) reports often cite these toxicity reference values and they are likely to be included in other regulatory applications [e.g., premarket tobacco product applications (PMTA) and modified risk tobacco product applications (MRTPA)]. This memorandum represents current thinking of the Division of Nonclinical Science (DNCS) on the use of toxicity reference values in evaluating inhalation exposure to constituents in tobacco smoke or aerosols.

2 Executive Summary

This memorandum provides an overview of the current thinking of DNCS in evaluating the use of toxicity reference values, including OELs, in tobacco product applications. All toxicity reference values for inhaled constituents should be evaluated on a case-by-case basis using the framework and approaches outlined in this memorandum. DNCS concludes that for tobacco product applications, the selection and use of toxicity reference values for the general population should be consistent with the EPA tiering hierarchy (detailed in Section 4.1), which does not include OELs. With respect to OELs, DNCS will evaluate OELs that applicants use to support the levels of non-carcinogenic inhaled tobacco constituents

in tobacco product applications, if the appropriate supporting information (detailed below) is provided. OELs may only inform the toxicity evaluation for non-cancer effects. DNCS does not consider OELs appropriate to use for the evaluation of carcinogenic tobacco product constituents. For carcinogenic tobacco constituents in tobacco product applications, DNCS considers any increase in exposure to be associated with an increase in risk, in the absence of data to the contrary, which is consistent with a recent policy change by NIOSH. Nonetheless, DNCS will evaluate the use of cancer toxicity references values for the general population if the applicant has provided sufficient information demonstrating that the reference value is appropriate for the evaluation of a specific tobacco constituent-related endpoint and comparison, as discussed below. Merely noting that a reference value exists for a chemical, and what that level is, without providing appropriate supporting information, would not be sufficient to demonstrate the applicability of that value to the evaluation of tobacco constituents in product applications.

3 Background

Toxicity reference values are established for a route-specific critical health effect to a given chemical exposure over time (e.g., acute, sub-chronic or chronic) and can set the upper margin of exposure to a given chemical for the general population; this represents a level below which adverse health effects are unlikely to occur. OELs are a specific subtype of reference values designed for the protection of occupational populations, designated based on documented toxicological, epidemiological, and clinical information related to inhalation exposure, and typically consider factors that are not directly related to health, such as the economic, analytical and engineering feasibility of meeting any exposure concentrations recommended as guidance or promulgated as a regulatory control [1]. In SE Reports related to inhaled tobacco products (e.g., cigarettes, roll-your-own tobacco, or electronic nicotine delivery systems), applicants often compare exposure levels of specific tobacco constituents (e.g., constituents identified by FDA as “harmful and potentially harmful constituents” (HPHCs)) with toxicity reference values, including OELs, while evaluating potential inhalation toxicity and risk from the use of tobacco products. Applicants also select and use reference values as a component of relative comparisons between products (e.g. new and predicate products in SE reviews). It should be noted however, that the use of cancer and non-cancer toxicity reference values for comparative risk or hazard evaluations is a different analysis than the direct comparison of tobacco product constituent exposure estimate with a toxicity reference value.

Generally, to be useful in evaluation of tobacco product applications, the weight of evidence from the principal and supporting studies used to derive the reference values should identify the most sensitive toxicity endpoint for the relevant route of exposure. To determine whether available toxicity reference values used for individual tobacco constituents reflect the best available information and are consistent with tobacco product inhalation, other factors such as the confidence in the key studies, dosimetry adjustments, extrapolation to human exposure conditions, and likelihood of variable response in human subpopulations also require consideration. For example, the biological effects (non-cancer or cancer) related to each constituent should be evaluated individually and as a component of the overall tobacco smoke or aerosol mixture on a case-by-case basis. Further, to compare measured values of specific chemicals (e.g., mass per cigarette) in combusted and other inhaled tobacco products with toxicity reference values, the constituent value should include the necessary adjustments for tobacco-product specific exposure characteristics, such as inhalation volumes during smoking, exposure timeframe, intensity, frequency, and duration.

4 Inhalation Reference Values for the General Population

Toxicity reference values that are established for a given critical effect via the inhalation route for a specific chemical exposure can be used in the risk assessment of airborne or inhaled chemicals to support regulatory decision-making. A two-part approach separating cancer and non-cancer effects is the current paradigm as there are significant differences in the risk assessment methods for these effects. These differences include the shape of the dose-response curve, the time-course for measurable endpoints, and the presumptive models (stochastic vs deterministic, for cancer and non-cancer effects, respectively). As outlined in Table 1 (Appendix), existing toxicity reference values often vary among national and international agencies for non-cancer (e.g., RfC, MRL, TC, TCA) and cancer (e.g., CSF, URF, TC_{05} and $CR_{inhalation}$) effects. In general, the basis for differences in toxicity reference values for the same chemical reflects a mix of differences in policy and scientific methodology. Text Box 1 summarizes the definitions of toxicity reference values from some national and international agencies with respect to cancer risk and non-cancer hazard.

Text Box 1: Definitions of toxicity reference values for the general population

Non-Cancer Evaluations

National:

RfC (Reference Concentration) (EPA): An estimate (with uncertainty that can span an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious non-cancer health effects during a lifetime.

MRL (Minimal Risk Level) (ATSDR): An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified exposure duration (1-14 days (acute); 15-364 days (intermediate); >365 days (chronic).

International:

TC (Tolerable Concentration) (Health Canada): An airborne concentration to which a person can be exposed continuously over a lifetime without deleterious effect (often expressed in mg/m^3).

TCA (Tolerable Concentration in Air) (RIVM, Netherlands National Institute for Public Health and the Environment): The highest concentration in air that does not adversely affect the general public's health over a lifelong exposure (70 years, 365 days/year, 24 hours/day).

Cancer Evaluations

National:

CSF (Cancer Slope Factor) (EPA): An upper-bound estimate (approximating a 95% confidence limit) of the increased human cancer risk from a lifetime exposure to an agent. Expressed as $(mg/kg\text{-}d)^{-1}$.

URF (Unit Risk Factor) (EPA): The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 g/m^3 in air. URF is calculated from the slope factor.

URE (Unit Risk Estimate) (for linear carcinogens) (EPA): The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent over a lifetime at a concentration of 1 $\mu g/m^3$.

International:

TC_{05} (Tumorigenic Concentration at 5%) (Health Canada): The concentration in air (expressed, for example, in mg/m^3) associated with a 5% increase in incidence or mortality due to tumors.

$CR_{inhalation}$ (Cancer Risk from Inhalation Exposure) (RIVM, Netherlands National Institute for Public Health and the Environment): The inhalation exposure that is associated with a 1 in 10,000 (E-4) excess lifetime cancer risk. $CR_{inhalation}$ is comparable to the TCA but it is derived for genotoxic carcinogenic substances.

In developing cancer and non-cancer toxicity reference values, agencies obtain information from a wide array of sources, ideally using the most current toxicological information available to accurately and precisely determine benchmark values from which the lower 95% confidence limit is used to develop individual reference values [2]. Key factors in evaluating the quality and usability of toxicity studies include but are not limited to:

- the route of administration;
- relevance of animal species tested;
- dose-response profile;
- duration of exposure;
- how adverse and critical effects are defined [e.g. No Observable Adverse Effect Level (NOAEL), Lowest Observable Adverse Effect Level (LOAEL), point of departure (PoD)];
- choice of critical effect;
- relevance of uncertainty factors used (Text Box 2);
- adjustment of the critical effect level to the dose metric of interest;
- gender and strain-specific effects;
- interpretation of results; and
- availability of supporting scientific evidence that is relevant to humans.

Ultimately, the combination and robustness of these criteria inform and funnel into mathematical models of a dose-response relationship for a particular chemical. For example, the benchmark dose (BMD) approach developed by US Environmental Protection Agency (EPA), which is a widely accepted approach, involves dose-response modeling to obtain doses corresponding to specific responses near the low end of the observable range of the data. This predetermined response corresponds to a specified increase (%) in the probability or incidence of an adverse health effect, compared to zero or control background exposure [3-5]. The lower 95% confidence of the benchmark dose is by definition, not likely to be associated with a response larger than the specified predetermined response and is therefore often used as the default point of departure (PoD), or the starting reference point for the human health risk assessment [5]. Compared to NOAEL or LOAEL derivations, the benchmark approach incorporates all available dose-response data and allows uncertainty quantification with validated statistical methods [2-4]. Additional methodologies may also be used on a case-by-case basis in the derivation process and may incorporate specialized modeling techniques, such as multivariate analysis, categorical regression, time-to-response analysis, distributional analysis and Bayesian approaches, depending on the case-specific best available scientific methods [3]. Therefore, when a cancer or non-cancer toxicity reference value for the general population is used by an applicant to provide information on either carcinogens or non-carcinogenic toxicants , DNCS reviewers should consider the methodology and factors listed above, as well as the data used to obtain toxicity reference values, in general, but also in instances where multiple values for one chemical are available from different sources. For carcinogenic tobacco constituents, the current view of DNCS is that there is no level of carcinogen

exposure that is assumed to be without an increase in cancer risk, in the absence of specific data to the contrary (see Memorandum: Evaluating carcinogenic HPHC increases, November 17, 2017).

Text Box 2: Possible uncertainties in toxicity reference value-derived data and the basis for their consideration*

Area of Uncertainty	Description of Underlying Principle
Database Insufficiency (UF_D)	Adjusts for the possibility of identifying a lower PoD or more sensitive toxic effect, if additional studies were available.
Laboratory Animal to Human Inter-Species Differences (UF_A)	Adjusts for interspecies differences in sensitivity between animals and the average human, when the PoD is based on animal exposure data.
Extrapolating from less than chronic studies (UF_S)	Adjusts for the possibility of identifying a lower PoD for chronic toxicity when extrapolating from a study of shorter duration.
Extrapolating from LOAEL-to-NOAEL (UF_L)	Adjusts for uncertainty in the value of the PoD as an estimate of the threshold for the onset of the critical effects, if based on a LOAEL rather than a NOAEL (or benchmark dose).
Intra-Species Variation: Average Human to Sensitive Human (UF_H)	Adjusts the PoD for pharmacokinetic and pharmacodynamic differences between the average human and the most sensitive applicable sub-population.

*Modified from Dankovic et al. (2015)[6] and EPA (1994)[7]

4.1 Three-tier System for the Use of Toxicity Reference Values for the General Population

For either carcinogens or non-carcinogenic toxicants, different toxicity reference values may be available from different sources, and agencies can differ in the tiering approaches adopted when considering available data. For example, the EPA established a three-tier hierarchy to determine which cancer and non-cancer toxicity reference values to use when more than one is available. In establishing this tiered hierarchy, EPA considers Tier 1 values preferential to other values, as these values have undergone extensive review and validation both within and outside EPA. Text Box 3 summarizes the three-tier hierarchy of resources for toxicity reference values for the general population.

Text Box 3: **Three-tier system developed by EPA for toxicity reference values**

Tier 1 – IRIS (Integrated Risk Information System): If a toxicity reference value is available in IRIS [8], that value should be used in preference to any other value as these values have undergone extensive review and validation both within and outside EPA.

Tier 2 – PPRTVs (Provisional Peer Reviewed Toxicity Values): These values are developed by the Office of Research and Development/National Center for Environmental Assessment/Superfund Health Risk Technical Support Center (STSC) on a chemical-specific basis. If toxicity values for a substance of potential concern are not available in IRIS, the next source to consult is EPA's PPRTVs [9].

Tier 3 - Other Toxicity Values: This tier includes additional EPA and non-EPA sources for toxicological information. Priority should be given to those sources that are the most current, peer-reviewed, transparent, and publicly available.

The California EPA (Cal/EPA)'s Toxicity Criteria Database [10]. In general, Cal/EPA values are consistent with those shown in IRIS.

The Agency for Toxic Substances and Disease Registry (ATSDR)'s Minimal Risk Levels (MRLs) for Hazardous Substances [11] are peer-reviewed estimates of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.

The EPA's Health Effects Assessment Summary Tables (HEAST) were last updated in 1997 (EPA-540-R-97-036, July 1997), but may be consulted for toxicity reference values if these values are not available from more current sources, including IRIS. [12]

Although EPA's three-tier system has been widely followed by state agencies, some states have modified this hierarchy due to the limited availability or age of certain reference values. For example, Cal/EPA and US EPA exposure values may differ for a small fraction of chemicals. The EPA Risk Assessment Advisory Committee lists potential reasons for these differences as follows:

- Reference values might be derived at different time periods; the availability of more appropriate data; or greater consistency with standard risk assessment approaches
- Selection of different studies as the basis of toxicity value development
- The results of the same study might be interpreted differently by the two agencies.

As another example, the state of Maine recommends additional tiers to select the most appropriate available toxicity reference values for a specific substance. Table 2 (Appendix) displays this modified hierarchy and added tiers. In general, when multiple toxicity reference values are available for a single chemical, these tiering approaches provide a framework for evaluating the suitability and appropriateness of reference values used by applicants. In this respect, the EPA hierarchy could be used in assessing whether toxicity reference values selected by applicants are appropriately designated and used. Occupational reference values are typically not included in these tiering systems.

4.2 Occupational Reference Values

OELs are also used by applicants in SE reports for a comparative toxicological evaluation of tobacco constituents. OELs are generally time-weighted average (TWA) concentrations of airborne substances to which a healthy worker may be exposed during defined work periods and under specific work conditions throughout a working lifetime, without any health impairment. Text Box 4 (below) summarizes definitions of common OEL terms. OELs are designated based on documented toxicological, epidemiological, and clinical information related to inhalation exposure. However, the establishment of OEL values is often constrained by considerations that are not directly health related, such as the cost of control measures or design engineering, technical feasibility, and limitations in analytical detection [2]. In addition, depending on an agency's priorities, legal mandates, and assumptions, agencies may use different criteria to evaluate scientific evidence in deriving OEL values. Lastly, OEL values in general are biased towards the healthy worker and may not be applicable to the general population. Table 3 (Appendix) lists OELs developed by different agencies.

Text Box 4: Definitions of Occupational Exposure Levels

PEL (Permissible Exposure Limit) (OSHA): PEL is the maximum concentration of a chemical that a worker may be exposed to under OSHA regulations. It is usually given as a time-weighted average (TWA).

RELs (Recommended Exposure Level) (NIOSH): The REL is a level that would be protective of worker safety and health over a working lifetime. **This term and usage thereof are no longer recommended for chemical carcinogens as of December 27, 2016 [13].**

RML-CA (Risk Management Limit for Carcinogens) (NIOSH): The RML-CA is a recommended initial starting point for control (*NIOSH no longer uses REL for chemical carcinogens*). For each chemical identified as a carcinogen, this level corresponds to the 95% lower confidence limit of the risk estimate of one excess cancer case in 10,000 workers in a 45-year working lifetime. Keeping exposures within the risk level of 1 in 10,000 is the minimum level of protection.

TLV (Threshold Limit Value) (ACGIH): TLV is a level to which it is believed a worker can be repeatedly exposed day after day for a working lifetime without adverse health effects.

TLV-C (Ceiling exposure concentration) (ACGIH): A ceiling exposure concentration that should not be exceeded during any part of the working lifetime.

TLV-TWA (Threshold Limit Value–Time-Weighted Average) (ACGIH): The TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect.

TLV- STEL (Short Term Exposure Limit) (ACGIH): A 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV–TWA.

TWA (Time Weighted Average): TWA is the worker's average airborne exposure in any 8-hour work shift of a 40-hour work week which shall not be exceeded.

WEELs (Workplace Environmental Exposure Levels) (AIHA): WEELs are expressed as either TWA concentrations or ceiling values.

OELs are distinct from toxicity reference values for the general population due to their derivation methods, assumptions, and intended application. Adjustments need to be made in order to use OELs for the risk assessment of the general population. First, OELs pertain to exposures that occur only during a work-week, whereas reference values for the general population are established to protect against continuous exposure over a defined period (e.g. acute, intermediate, or chronic). Therefore, OELs may differ from values for the general population in severity of effect. . The evaluation of toxicological data by agencies deriving OELs may differ from that of EPA (and other agencies) with respect to weight-of-evidence classification, application of uncertainty factors (UFs), and exposure paradigm. In addition, OELs do not take into account exposure of unprotected individuals or susceptible subpopulations. The use of OELs is established to protect average healthy workers (ages 18 to 65 years) who are exposed to inhaled agents only during a portion of a day (e.g., 8-hour work shift). A worker can meet the recommended level using a variety of protective methods according to the hierarchy of controls [15]. Thus, OELs may not be health-protective for the general population when used to evaluate inhalation exposures due to the use of tobacco products. Conversely, toxicity reference values for the general population are relevant to those of any age or health status, and have an aim of protecting the most sensitive individuals in the population, assuming chronic exposures.

The current view of DNCS has evolved since the beginning of the SE program regarding the use of OELs for tobacco product constituent evaluation. Presently, DNCS is more knowledgeable of the differences in

toxicant exposure assumptions between OELs and the exposures that occur from tobacco use and consequently, has gained an understanding that OELs may not fully account for exposures specific to tobacco user populations. OELs are typically time-weighted averages representing repeated sampling of workplace chemical concentrations that can remain relatively constant for a defined period during a work shift, whereas tobacco product inhalation exposures are the summation of several intense short duration exposures that are repeated throughout the day and over a chronic time period. Consequently, inhalation exposure to smoke constituents that occur during the use of a tobacco product is likely to be substantially different from exposure in an occupational setting. As stated above, for carcinogenic constituents specifically, the current view of DNCS is that there is no level of carcinogen exposure that is assumed to be without an increase in cancer risk, in the absence of specific data to the contrary (see Memorandum: Evaluating carcinogenic HPHC increases, November 17, 2017).

Consistent with this latter point, NIOSH has also changed its policy with respect to occupational exposure to carcinogenic substances. In the past, NIOSH usually recommended occupational exposures to carcinogens be limited to the lowest feasible concentration. NIOSH now no longer uses the term "Recommended Exposure Level (REL)" for carcinogens. Instead NIOSH will only recommend an initial starting point for control, called the "Risk Management Level for Carcinogens (RML-CA)" (Text box 4). NIOSH states:

> *Underlying this policy is the recognition that there is no safe level of exposure for most carcinogens, and therefore, reduction of worker exposure to chemical carcinogens as much as possible through elimination or substitution and engineering controls is the primary way to prevent occupational cancer. Accordingly, this policy no longer uses the term recommended exposure limit (REL) for chemical carcinogens; rather NIOSH will only recommend an initial starting point for control, called the Risk Management Limit for Carcinogens (RML-CA)" [13].*

Therefore, OELs would not be appropriate to use for the evaluation of carcinogenic tobacco product constituents. In evaluating an applicant's comparison of exposure estimates of non-carcinogenic tobacco product constituents with OELs, the data used to derive the OEL should be taken into consideration, specifically the biological endpoints, populations of concern, quality and nature of the underlying data sets, and the relevance of exposure scenarios. The OEL database, containing the principal and supporting studies, helps to identify the most sensitive endpoint in chronic occupationally-exposed humans, and the appropriate PoD [7]. In addition, the uncertainty and modifying factors listed in Text Box 2 should be considered when adjusting occupational exposure scenarios to continuous exposure conditions [6, 7].

5 Summary

The aim of this memorandum is to provide an overview of current thinking of DNCS for reviewers in evaluating the use of toxicity reference values, including OELs, in tobacco product applications. Although toxicity reference values developed for the general and occupational populations are not intended to be used for tobacco product exposure evaluation, they can inform the overall toxicity of tobacco products. In this respect, EPA's tiering system and related toxicity reference values for the general population provide a framework for the evaluation of individual tobacco constituent levels. It is recommended that the evaluation process consider several factors, including but not limited to, properties of the specific chemical of interest, related biological effects (non-cancer or cancer), and the inhalation paradigm (e.g., intensity, frequency, and duration of exposure), all consistent with exposure to the inhaled tobacco

product. Then, relevant toxicity reference values should be gathered and the scientific basis for their derivation, adjustments, and target populations should be evaluated. In situations where there are numerous toxicity reference values derived by different agencies, the EPA tiering hierarchy can be a primary resource, and consideration can also be given to any toxicity reference value that has been established with current approaches and key studies. Toxicity reference values for the general population are considered to be the most health protective and therefore preferable for estimating any potential hazards and risks. In contrast, the use of OELs may only inform the toxicity evaluation for non-cancer effects. Since OELs differ from toxicity reference values for the general population, as discussed above, they should only be considered if the data used to derive the OEL are also provided, specifically the biological endpoints, populations of concern, the quality and nature of the underlying data sets, and the relevance of exposure scenarios. If the applicant develops their own toxicity reference value based on their (or published) data, the derivation process should follow commonly accepted practices used in deriving such values and be provided by the applicant for evaluation.

6 Conclusion

Going forward, all toxicity reference values for inhaled constituents should be evaluated using the framework and approaches outlined in this memorandum. For OELs specifically, DNCS reviewers will evaluate OELs that applicants use to support the levels of non-carcinogenic inhaled tobacco constituents in tobacco product applications, if appropriate supporting information is provided. Additional supporting data needs to address the relevance of occupational reference values to a general population that may contain susceptible individuals, along with other important factors as described above. Regarding the use of OELs for evaluation of carcinogenic toxicants (e.g., inhaled tobacco constituents), toxicology reviews will be consistent with the recent policy change made by NIOSH in withdrawing use of RELs for chemical carcinogens in recognition that there is no level of exposure to most carcinogens that does not increase health risk. Therefore, DNCS will not consider the use of OELs for the evaluation of carcinogenic tobacco constituents in tobacco product applications. In cases where multiple toxicity reference values are available, DNCS will apply the EPA tiering hierarchy, which does not include occupational reference values. In addition, DNCS will consider alternative values that are established using current approaches and key studies, if there is evidence that they would be more appropriate for a specific evaluation. DNCS will continue to update thinking regarding the use of toxicity reference values and OELs discussed within this memorandum as additional scientific evidence becomes available.

7 Appendix

Table 1: Toxicity Reference Values

Federal	Agency	Non-cancer	Cancer	Source
The Integrated Risk Information System (IRIS)	U.S.EPA	RfC	CSF, URF, URE	http://www.epa.gov/iris
Provisional Peer Reviewed Toxicity Values (PPRTVs)	U.S.EPA (Superfund)	RfC		https://hhpprtv.ornl.gov/
Agency for Toxic Substances and Disease Registry (ATSDR)	US Department of Health and Human Services	MRL		http://www.atsdr.cdc.gov/mrls/index.asp
Health Effects Assessment Summary Tables (HEAST)	U.S.EPA (Superfund and RCRA)	RfC		http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=2877&CFID=46295777&CFTOKEN=84338358
State				
Toxicity Criteria Database (2009)	Cal EPA	REL		http://oehha.ca.gov/risk/ChemicalDB/index.asp
TCEQ Guidelines, 2015	Texas Commission on Environmental Quality (TCEQ)	RfC	URF	http://www.tceq.state.tx.us/toxicology/esl/guidelines/about.html
International				
The International Toxicity Estimates for Risk (ITER) database	Compiled by TERA and contains data from ATSDR, Health Canada, RIVM, U.S. EPA, IARC, NSF International	RfC		www.tera.org/iter http://toxnet.nlm.nih.gov/newtoxnet/iter.htm
Re-evaluation of human-toxicological maximum permissible risk levels, 2001	National Institute of Public Health and the Environment (RIVM)	TCA	$CR_{inhalation}$	http://rivm.openrepository.com/rivm/handle/10029/9662

RfC: Reference concentration; MRL (Minimal Risk Level); REL (Reference Exposure Level); TC (Tolerable Concentration); CSF (Cancer Slope Factor); URF (Unit Risk Factor); URE (Unit Risk Estimate); TC05 (Tolerable Concentration at 5%); $CR_{inhalation}$ (Cancer Risk inhalation)

Table 2: Five-Tier System Used by the State of Maine for Reference Exposure Values

Tier 1	IRIS (Integrated Risk Information System)	IRIS should be the first consulted. However, if the date of the last IRIS revision is greater than 5 years old, Tier II through Tier V sources should be consulted for more current and technically-defensible values.	http://www.epa.gov/iris
Tier II	California's Office of Environmental Health Hazard Assessment (CA-OEHHA) Toxicity Criteria Database	If IRIS does not provide a toxicity value for a given chemical or the IRIS value is outdated.	http://www.oehha.ca.gov/risk/ChemicalDB/
Tier III	ATSDR chronic Minimal Risk Levels	In the absence of IRIS and CA-OEHHA values or if the IRIS/CA-OEHHA value is outdated	http://www.atsdr.cdc.gov/mrls/index.html
Tier IV	USEPA Provisional Peer-Reviewed Toxicity Values (PPRTVs)	In the absence of a chronic toxicity value from above sources or in cases where the IRIS/CA-OEHHA/ATSDR record is outdated	http://rais.ornl.gov/
Tier V	The Health Effects Assessment Summary Table (HEAST)	May be consulted for toxicity values that are not available from more current sources, including IRIS	http://nepis.epa.gov/

Table 3: Occupational Exposure Levels or Limits (OELs)

National	OEL	Source
ACGIH (American Conference of Governmental Industrial Hygienists)	TLV	http://www.acgih.org/
AIHA (American Industrial Hygiene Association)	WEELs (TWA)	https://www.aiha.org/Pages/default.aspx
NIOSH (National Institute for Occupational Safety and Health)	RELs (TWA, STEL, C)	http://www.cdc.gov/niosh/
OSHA (Occupational Safety and Health Administration)	TWA, C	https://www.osha.gov/
International		
EU-Scientific Committee on Occupational Exposure Limits (SCOEL)	TWA, STEL, UF	http://ec.europa.eu/

OEL: Occupational Exposure Level; TLV: Threshold Limit Value; TWA: Time Weighted Average; STEL: Short Term Exposure Level; C: Ceiling; UF: Uncertainty factor; WEEL: Workplace Environmental Exposure Levels

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