SELECTION AND ADJUSTMENT OF PROVISIONAL INHALATION HEALTH GUIDANCE VALUES FOR SCREENING-LEVEL RISK ASSESSMENT

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Background

Human health risk assessment is used to characterize the potential for adverse health effects after exposure to chemical contaminants. When assessing chemical exposures, it is typical to use health guidance values (HGVs) for each chemical, as appropriate, to assess the potential health impacts from a specific short- or long-term exposure. HGVs are the amount of a chemical, such as concentrations in air or water, which is likely to pose little or no appreciable risk to human health. An HGV is derived from a point of departure (POD), such as an exposure level in an animal experiment or an epidemiological study at which no adverse effects (or at least minimal adverse effects) are observed, or a benchmark dose (a statistical estimate of a low response rate, typically 5%, in the dose response curve for the chemical of concern). Extrapolation from this point of departure to a HGV for the target human population is generally performed by means of uncertainty factors (UFs). HGVs and estimates of exposure are used to express the health risk as a hazard quotient for non-cancer effects and lifetime cancer risk for each individual chemical. Hazard quotients relating to the same target organ, endpoint, or mode of action can be summed to give a hazard index for non-cancer effects and individual chemical cancer risk values can be summed to give a cumulative lifetime cancer risk.

HGVs are a critical part of a risk assessment; however, derivation of a HGV per OEHHA methodology is not possible for all chemicals of concern due to lack of data and/or limited time and resources. Further, for some chemicals with potentially low toxicity (based on structure-activity relationship or other entities' HGVs) and/or limited exposure, the use of provisional HGVs would be a more efficient use of time and resources than more time-intensive derivations of traditional *de novo* HGVs, and would be unlikely to alter the conclusions of the risk assessment.

The methodology described here provides an approach for selecting and adjusting existing HGVs beyond those adopted by the state for inhalation health risk assessment to establish provisional HGVs and perform screening-level evaluations of potential risks. This methodology would be applied when there is limited time or resources to develop HGVs using traditional methodology. Risk levels of concern derived using these provisional HGVs may guide more refined development of HGVs for specific chemicals. More refined HGVs may be produced through other approaches not discussed in this document, including additional *in silico* or category approaches, expedited derivation of HGVs, and full traditional derivation of HGVs (such as the Reference Exposure Levels and Unit Risk Factors produced by OEHHA's Air Toxics Hot Spots Program). It is important that the decision context the provisional HGV is used in is appropriate for the level of confidence in that value.

The purpose of this document is to:

(1) identify and discuss common existing acute and chronic HGVs and cancer potency values used in risk assessment,
(2) discuss possible methodologies for the selection and adjustment of existing HGVs to establish provisional HGVs, and
(3) discuss an example methodology for the use of structural analogs to select provisional HGVs.

Types of HGVs

Non-Cancer HGVs

In general, non-cancer HGVs are based on the most sensitive, relevant, adverse health effect reported in toxicological or epidemiological studies. These values are designed to protect the most sensitive individuals in the population by the inclusion of factors that account for uncertainties as well as individual differences in human susceptibility to chemical exposures. Non-cancer HGVs typically used in risk assessments, with a focus on the inhalation route of exposure and US regulatory bodies, are presented in Table 1. The HGVs highlighted are from a variety of sources including the Office of Environmental Health Hazard Assessment (OEHHA), US Environmental Protection Agency (US EPA), Agency for Toxic Substances and Disease Registry (ATSDR), and Texas Commission on Environmental Quality (TCEQ), all government bodies tasked with protecting public health. The types of values vary by the intended media (e.g., air, water), the intended population (e.g., general population, children), and the considered critical effects (e.g., developmental/reproductive, all effects), but all serve to provide guidance in order to limit the deleterious health effects of chemical exposures.

Cancer Potency Values

Human health risk assessment is also used to assess lifetime cancer risk (i.e., the probability that an individual will develop cancer over a lifetime) resulting from exposure to a contaminant. When assessing the lifetime cancer risk by inhalation, it is typical to use cancer potency values, such as slope factors (SF) or inhalation unit risks (IUR). Cancer potency factors typically used in risk assessment, with a focus on the inhalation route of exposure and US regulatory bodies, are presented in Table 2. The cancer potency factors highlighted are from OEHHA and US EPA.

Table 1. Examples of Non-Cancer Health Guidance Values.

Source	Value	Definition	Duration(s)	Route	Reference
California OEHHA	Reference Exposure Level (REL)	An exposure at or below which adverse non-cancer health effects are not expected to occur in a human population, including sensitive subgroups (e.g., infants and children), exposed to that concentration for a specified duration.	Chronic, 8-hour, acute	Inhalation	OEHHA 2008
	Public Health Goal (PHG)	An estimate of level of a chemical contaminant in drinking water that does not pose a significant risk to health including sensitive subgroups that comprise a meaningful portion of the general population (e.g., infants, children, pregnant women, elderly).	Chronic	Oral	California Safe Drinking Water Act 1996
	Child-Specific Reference Dose (chRD)	Numerical HGVs developed to address the specific sensitivity of children.	Chronic	All routes	OEHHA 2010
	Maximum Allowable Dose Level (MADL)	A level of exposure to a known reproductive toxicant (Proposition 65) that has no observable effect assuming exposure at one thousand times that level.	Daily	All routes	California Code of Regulations

Source	Value	Definition	Duration(s)	Route	Reference
US EPA	Integrated Risk Information System (IRIS) Reference Concentration (RfC)	An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.	Chronic	Inhalation	US EPA 1994
	Provisional Peer-Reviewed Toxicity Value (PPRTV) Provisional Reference Concentration (p-RfC)	An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime (chronic) or portion of a lifetime (subchronic).	Chronic, subchronic	Inhalation	US EPA 2020b
	Health Effects Assessment Summary Tables (HEAST) Reference Concentration (RfC)	A provisional estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during lifetime (chronic) or portion of a lifetime (subchronic).	Chronic, subchronic	Inhalation	US EPA 1997

Source	Value	Definition	Duration(s)	Route	Reference
ATSDR	Minimum Risk Level (MRL)	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 duration of exposure.	Chronic, intermediate, acute	Inhalation	ATSDR 2018
TCEQ	Reference Values (ReV)	An estimate of an inhalation exposure concentration for a given duration to the human population (including susceptible groups) that is likely to be without an appreciable risk of adverse effects.	Chronic, acute	Inhalation	TCEQ 2015
American Conference of Governmental Industrial Hygienists (ACGIH)	Threshold Limit Value (TLV)	The airborne concentrations of chemical substances under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects.	Chronic (occupational)	Inhalation	ACGIH

Table 2. Examples of Cancer Potency Values.

Agency	Value	Definition	Route	Reference
OEHHA	Cancer slope factor (CSF) and unit risk (UR)	Characterize the relationship between an applied dose of a carcinogen and the risk of tumor appearance in a human. Usually expressed as a cancer slope factor ["potency" – in units of reciprocal dose – usually $(mg/kg\text{-}body\ weight/day)^{-1}$ or "unit risk" – reciprocal air concentration – usually $(\mu g/m^3)^{-1}$] for the lifetime tumor risk associated with lifetime continuous exposure to the carcinogen at low doses.	Inhalation/Oral	OEHHA 2009
US EPA IRIS	IUR	The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2×10^{-6} per $\mu g/m^3$, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical per m^3 of air.	Inhalation	US EPA 2011
US EPA PPRTV	p-IUR	An estimate of the increased cancer risk from inhalation exposure to a concentration of 1 $\mu g/m^3$ for a lifetime.	Inhalation	US EPA 2020b
US EPA HEAST	IUR	An estimate of the carcinogenic risk associated with a unit concentration of air.	Inhalation	US EPA 1997

Health Guidance Value Evaluation Criteria

In human health risk assessment, it is typical to use one HGV for each chemical and exposure duration to assess the potential health impacts from a specific chemical exposure. When several HGVs are available for a specific chemical or substance, a hierarchy can be used to consistently select HGVs that are of the highest quality or are the most relevant to the risk assessment. To create a hierarchy, each HGV source can be ranked based on parameters such as the extent of the external review process or the level of documentation provided. In addition, more specific quality parameters could be used to assess the relevancy of values for a particular risk assessment, such as the route of exposure or the population that the value is intended to protect (e.g., general population, occupational population). Here, values that are proposed for selection based on the hierarchy (outside of those already formally adopted by the state) are considered provisional.

Example of Non-cancer Chronic HGV Evaluation Criteria for General Population Inhalation Risk Assessment

There are several ways HGVs can be assessed and then ranked in a hierarchy. In this example, non-cancer HGVs were evaluated for their applicability to general population inhalation risk assessment by the following criteria:

- The level of peer review employed in HGV development (e.g., OEHHA and US EPA IRIS values undergo an external peer review process).
- The program that produced the HGV is still active, permitting updates of HGVs (e.g., US EPA's HEAST program is no longer active).
- The HGV is based on a study conducted by the inhalation route (e.g., PHGs based on inhalation studies receive greater consideration than PHGs based on studies by other routes).
- The HGV is intended to protect the general population, including sensitive subgroups.
- The HGV was developed following established guidance so that its derivation is based on a consistent, documented methodology that can be reviewed.
- The HGV reflects the legislative mandates and science policy choices that guide risk determinations in California. Only OEHHA HGVs are derived to meet this criterion.

Table 3 shows the results of this analysis for key risk assessment values with a focus on inhalation and values from U.S. regulatory agencies.

Table 3. Example of HGV Evaluation Criteria.

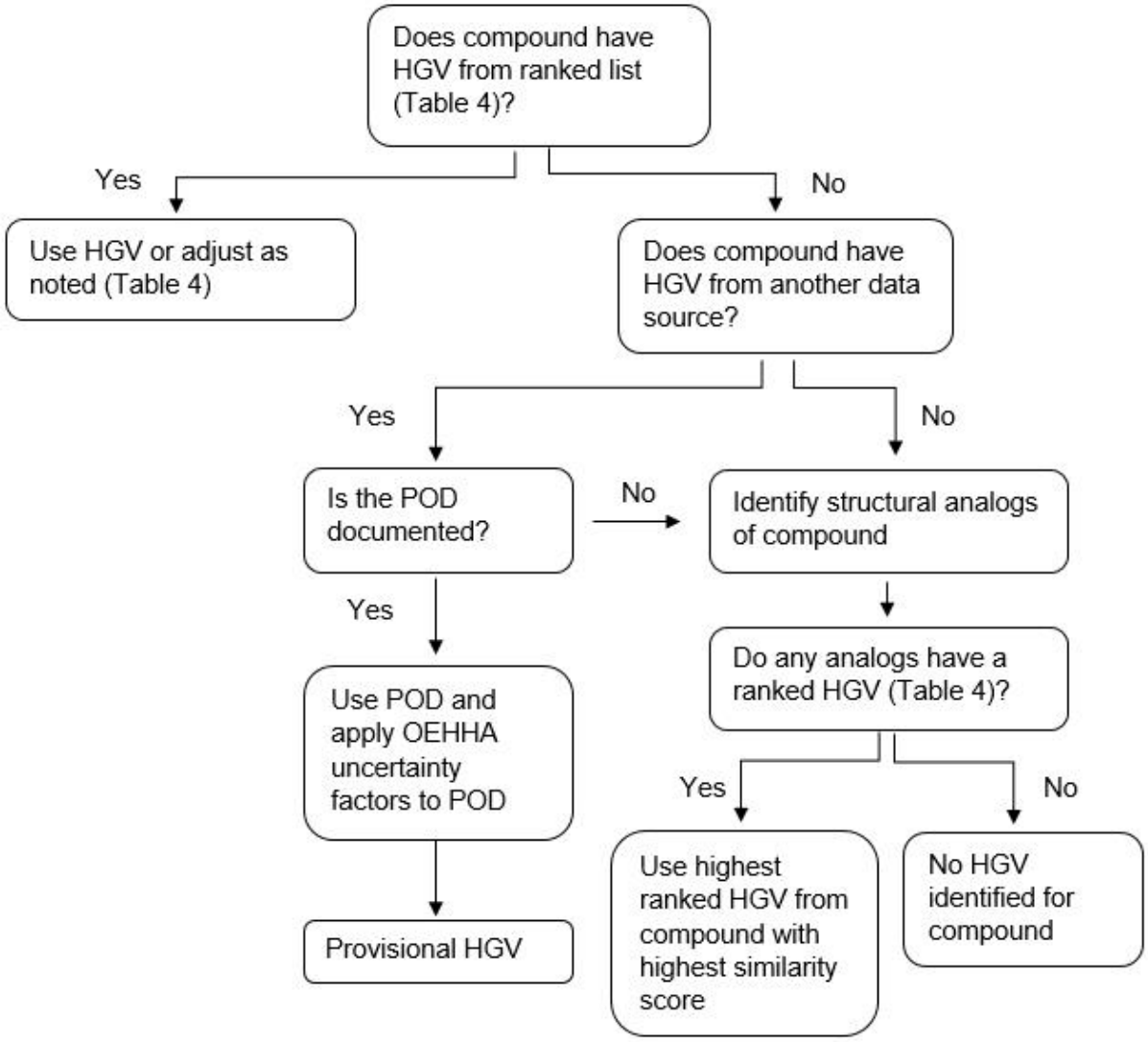
Source	Description	Review of HGV		Source program active	Intended for inhalation and/or derived from inhalation study	Intended to protect general population, including sensitive subgroups	Established guidelines for HGV development	Developed by OEHHA to meet California risk standards	References
		External review	Public comment						
OEHHA	RELs - chronic, 8-hr, acute	✓	✓	✓	✓	✓	✓	✓	California Health and Safety Code Division 26 ; OEHHA 2008, 2020a, b
OEHHA	PHGs (non-cancer endpoint)	✓	✓	✓	✓/—	✓	—	✓	California Safe Drinking Water Act 1996; OEHHA 2020c
US EPA IRIS	RfC -chronic	✓	✓	✓	✓	✓	✓	—	US EPA 1994, 2011, 2020c, e
ATSDR	MRLs – chronic, intermediate, acute	✓	✓	✓	✓	✓	✓	—	ATSDR 2018, 2020; Chou et al. 1998
US EPA PPRTV	p-RfCs - chronic and subchronic	✓	—	✓	✓	✓	✓	—	US EPA 1994, 2002, 2020a, b
OEHHA	chRD	✓	✓	✓	✓/—	✓/—	—	✓	California Health and Safety Code §901 ; California Health and Safety Code Division 37 ; OEHHA 2010, 2020a

Source	Description	Review of HGV		Source program active	Intended for inhalation and/or derived from inhalation study	Intended to protect general population, including sensitive subgroups	Established guidelines for HGV development	Developed by OEHHA to meet California risk standards	References
		External review	Public comment						
US EPA HEAST	RfC - chronic, subchronic	—	—	—	✓	✓	✓	—	ECOS-DoD Suitability Work Group 2007; US EPA 1990, 1997
OEHHA	MADL	✓	✓	✓	✓/—	✓/—	✓	✓	California Code of Regulations ; OEHHA 2001, 2020a, d
TCEQ	ReV - chronic, acute	✓/—	✓	✓	✓	✓	✓	—	TCEQ 2015, 2020
ACGIH	TLV-occupational	✓/—	✓	✓	✓	—	✓	—	ACGIH 2015, 2020, n.d

Methodology for Selection and Adjustment of Screening-Level Non-Cancer HGVs

Figure 1 gives an overview of a process to select, adjust, or develop a provisional HGV for use in screening-level risk assessment. The decision tree includes three main processes: (1) selection of an existing HGV with potential adjustment, (2) development of a provisional HGV based on the POD used for an existing HGV, (3) selection of a surrogate HGV using structural analogs. Other processes for establishing HGVs, such as expedited derivation of HGVs or full derivation of HGVs (e.g., by OEHHA's Air Toxics Hot Spots Program), may be more suitable depending on the chemical or the goals/resources of the risk assessment.

Figure 1. Decision Tree for HGV Identification, Selection, and Possible Adjustment.



Process 1: Selecting and Adjusting Existing HGVs

A hierarchy of HGVs can be developed based on a quality assessment of the sources and types of values (as illustrated above). Based on the evaluation criteria in Table 3, the hierarchy below (Table 4) represents a possible ranking of chronic non-cancer HGVs for use in a screening-level inhalation risk assessment for the general population. Chronic or 8-hour RELs developed by OEHHA for inhalation exposures were ranked first, followed by OEHHA Public Health Goals (PHGs) based on a non-cancer endpoint from an inhalation study. Subsequently ranked values are from OEHHA, US EPA, ATSDR, TCEQ, and ACGIH. Similar hierarchies for non-cancer acute HGVs and cancer potency values are shown in Appendix 1.

Example of Adoption of Existing HGV

Trimethylbenzenes do not currently have an OEHHA chronic REL or PHG based on an inhalation study, but have a US EPA IRIS RfC of 0.06 mg/m^3. Thus, the US EPA IRIS RfC would be the highest ranked value and could be adopted as a provisional HGV.

Table 4. Example Hierarchy for Chronic Non-Cancer Inhalation HGV Selection.

Rank	Source	Description	Evaluation/adjustment	Website
1	OEHHA	Chronic RELs/ 8-hr RELs	N/A	https://oehha.ca.gov/air/general-info/oehha-acute-8-hour-and-chronic-reference-exposure-level-rel-summary
2	OEHHA	PHGs (non-cancer endpoint derived from inhalation study)	Remove adjustment for drinking water consumption	https://oehha.ca.gov/water/public-health-goals-phgs
3	US EPA	IRIS RfC	N/A	https://www.epa.gov/iris
4	ATSDR	Chronic inhalation MRLs	N/A	https://www.atsdr.cdc.gov/mrls/mrllist.asp
5	US EPA	Chronic PPRTV p-RfCs and screening level PPRTV p-RfCs	N/A	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
6	ATSDR	Intermediate inhalation MRLs	Subchronic to chronic extrapolation (where appropriate)	https://www.atsdr.cdc.gov/mrls/mrllist.asp
7	US EPA	Subchronic PPRTV p-RfCs and screening level PPRTV p-RfCs	Subchronic to chronic extrapolation (where appropriate)	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
8	OEHHA	PHG (non-cancer endpoint derived from non-inhalation study)	Route-to-route extrapolation	https://oehha.ca.gov/water/public-health-goals-phgs

Rank	Source	Description	Evaluation/adjustment	Website
9	OEHHA	chRD	Route-to-route extrapolation (where appropriate)	https://oehha.ca.gov/risk-assessment/chrd/table-all-chrds
10	US EPA	HEAST RfC Chronic	N/A	https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=2877
11	US EPA	HEAST RfC subchronic	Subchronic to chronic extrapolation (where appropriate)	https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=2877
12	TCEQ	Chronic ReV	N/A	https://www.tceq.texas.gov/toxicology/esl/guidelines/about; https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome
13	US EPA	IRIS RfD	Route-to-route extrapolation	https://www.epa.gov/iris
14	OEHHA	MADL (based on reproductive toxicity)	Route-to-route extrapolation (where appropriate)	https://oehha.ca.gov/proposition-65/proposition-65-list
15	ACGIH	TLV 8-hour TWA	Adjustment for 24 hour exposure; adjustment factor of 300 if based on human study, 3000 if based on animal study	https://www.acgih.org/forms/store/ProductFormPublic/2018-tlvs-and-beis (not freely available)

Adjustment of HGVs

Table 4 describes the potential adjustments for each HGV type to align with an inhalation risk assessment for the general population. HGVs may be adjusted for the intended duration (subchronic to chronic), the route of exposure, and in the case of occupational values, to account for sensitive subgroups (e.g., children, elderly) or other uncertainties. As an alternative to adopting some HGVs- like US EPA IRIS RfCs - without adjustment, provisional HGVs may be developed through application of OEHHA UFs to the underlying POD (as discussed in process 2 of Figure 1.

Adjustment for Route-to-Route Extrapolation

When the highest ranked HGV is for an exposure route other than inhalation, route-to-route extrapolation can be performed. For example, if a chemical has an US EPA RfD for systemic effects (not portal of entry effects) it may be possible to use route-to-route extrapolation to estimate a provisional inhalation HGV.

To extrapolate oral exposures to inhalation exposures, toxicokinetic adjustments should be made which account for respiratory tract disposition, uptake, clearance, and metabolism. However, when a thorough analysis is beyond the scope of the assessment, a screening level route-to-route adjustment can be performed. The absorption for the oral and inhalation routes can be gleaned from the literature or assumed to be 100% (when appropriate). In the most simple route-to-route extrapolations, the dose delivered to the target organ is assumed to be the same for oral and inhalation exposures. Using this assumption, a simple route-to-route extrapolation can be performed by the equation below:

$$POD_{inhalation} = POD_{oral} \; x \; \frac{BW}{Air\ intake}$$

Where:

POD_{oral} – the POD that was the basis of the oral RfD (mg/kg/day)
BW – an adult body weight (70 kg)
Air intake – standard adult air intake (20 m^3/day)

<u>Adjustment for Occupational Values</u>

When the selected HGV is an occupational value, like the ACGIH TLVs, an adjustment for exposure duration and UFs can be applied to align with the risk assessment. Occupational HGVs are intended to be protective during the workday rather than under continuous exposure conditions. The occupational HGV can be adjusted for exposure duration and breathing rates using the equation below. These adjustments assume an occupational air intake of 10 m^3/day, a general population air intake of 20 m^3/day, and a workweek of five days (OEHHA 2008):

$$HGV\ \left(\frac{mg}{m^3}\right) = \frac{Occupational\ Value\ \left(\frac{mg}{m^3}\right)\ x\ 10\ \left(\frac{m^3}{day}\right)\ x\ 5\ \left(\frac{days}{week}\right)}{20\ \left(\frac{m^3}{day}\right) x\ 7\ \left(\frac{days}{week}\right)}$$

Occupational HGVs are intended to protect the working population, which is considered a healthier population compared with the general population, and are derived using minimal (if any) uncertainty factors. Thus, in the event that an ACGIH TLV 8-hour TWA is selected, it can be adjusted by 300 if the underlying POD was based on a human study and 3000 if based on an animal study. This factor is comprised of OEHHA's default intraspecies UF of 30 to protect sensitive populations, an interspecies UF of 10 if based on an animal study, and a remaining 10 to account for other potential uncertainties such as study duration, database deficiency, and the potential for additional susceptibility of children.

Adjustment for Subchronic to Chronic Exposure

HGVs that are intended for a subchronic exposure duration will be adjusted by a subchronic uncertainty factor (UF_s) to account for the potentially greater effects from a continuous lifetime exposure compared to a subchronic exposure. OEHHA guidelines recommend an adjustment based on the duration of the critical study (UF_S = 1 for study durations >12% of estimated lifetime; $UF_S = \sqrt{10}$ for study durations 8-12% of estimated lifetime; UF_S = 10 for study durations <8% of estimated lifetime) (OEHHA 2008).

Process 2: Development of a Provisional HGV based on the POD of an Existing HGV

If the only available HGV requires further refinement, it may appropriate to use the point of departure (POD) from that value and adjust it with UFs per OEHHA REL guidance (OEHHA 2008). The types of UFs that may be used are listed below (more detail is available in Appendix 2 and the REL guidance):

1) UF_L - LOAEL UF (adjusts for lack of a NOAEL in a study)
2) UF_S - subchronic UF (adjusts for exposure duration in derivation of a chronic REL; not applicable to acute RELs)
3) $UF_{A\text{-}k}$ - toxicokinetic component of interspecies UF
4) $UF_{A\text{-}d}$ - toxicodynamic component of interspecies UF
5) $UF_{H\text{-}k}$ - toxicokinetic component of intraspecies UF
6) $UF_{H\text{-}d}$ - toxicodynamic component of intraspecies UF
7) UF_D – database deficiency factor

Process 3: Selection of Surrogate HGV Using Structural Analogs

The basic assumption when using structural surrogates is that a chemical's structure imparts properties that relate to the chemical's activity. Structure-activity relationships have long been used in risk assessment and are based on the observation that structurally similar chemicals frequently share structurally similar metabolites, act at the same target sites and through the same mode(s) of action, and thus exhibit similar toxicity. In this methodology, when no appropriate HGV is available, a chemical's structural analogs can be identified and the corresponding HGVs can be considered.

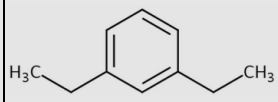
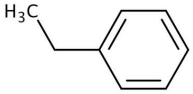
Structural analogs of chemicals can be identified using similarity scores/statistics such as the Tanimoto score. The target chemical's Tanimoto similarity scores can be obtained from publicly available software (e.g., US EPA CompTox Chemistry Dashboard, US EPA 2020c), which can also identify sets of structurally similar compounds based on the scores.

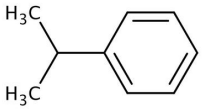
The analog with the highest similarity score and one or more HGVs from the ranked sources (Table 4) could be selected as the surrogate. The highest-ranked HGV for this surrogate may be selected and adjusted per Table 4.

Example of Structural Surrogate Approach

m-Diethylbenzene does not have an suitable existing HGV; thus, a structural surrogate approach can be used to identify a surrogate HGV. The US EPA Analog Identification Methodology (AIM) and the US EPA Chemistry Dashboard identified 51 and 306 structural analogs of *m*-diethylbenzene, respectively (US EPA 2012, 2020d). Structural analogs with an HGV from Table 4 (excluding ACGIH) are shown below. Ethylbenzene was selected as the structural surrogate because it had the highest similarity score and an existing ranked chronic HGV from Table 4. In this example, the OEHHA chronic REL of 2 mg/m^3 would be selected as the most appropriate provisional HGV for *m*-diethylbenzene.

Table 5. Selected Structural Analogs of m-Diethylbenzene and Corresponding Existing Ranked Chronic HGVs.

Chemical	CAS	Structure	Similarity Score*	Analog Identification Software	Chronic HGV (mg/m^3)	Source
m-Diethylbenzene	141-93-5		-	-	-	-
Ethylbenzene	100-41-4		1.00	US EPA AIM, US EPA CompTox Chemistry Dashboard	2	OEHHA chronic REL
					0.3 mg/L drinking water	OEHHA PHG
					1	US EPA IRIS RfC
					0.26	ATSDR chronic MRLs
					9	US EPA PPRTV subchronic p-RfC
					1.9	TCEQ chronic ReV
					0.1 mg/kg/day	US EPA IRIS RfD

Chemical	CAS	Structure	Similarity Score*	Analog Identification Software	Chronic HGV (mg/m^3)	Source
Isopropylbenzene (cumene)	98-82-8		0.88	US EPA CompTox Chemistry Dashboard	0.4	US EPA IRIS RfC
					0.1 mg/kg/day	US EPA IRIS RfD

** The similarity score from the US EPA CompTox Chemistry Dashboard as compared to m-diethylbenzene.*

(ATSDR 2020; TCEQ 2019; US EPA 2009, 2012, 2020d, e)

Conclusions

HGVs may be developed via a number of approaches that vary in their time and resource requirements and thus their level of refinement. The level of refinement and confidence in the HGV must match the context in which the HGV will be used. Adoption or adjustment of existing HGVs to produce provisional HGVs is appropriate for screening-level risk assessments, whereas more refined processes, such as OEHHA's REL development process, are appropriate for decision-making and risk management contexts. HGVs that may be adopted or adjusted are available from many sources, which may evaluated and ranked using criteria such as those presented herein. In the absence of an HGV, it is possible to use a surrogate approach in which an HGV for a structural analog is employed. These approaches seek to maximize the chemical universe that may be evaluated in a risk assessment. Future HGV development may incorporate additional approaches, such as use of new approach methodologies (NAMs; e.g., cell culture systems, organ-on-a-chip,) or the toxic equivalency approach (TEQ).

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Appendix 1

Table 6. Example Hierarchy for Acute Non-Cancer Inhalation HGV Selection.

Rank	Source	Description	Evaluation/adjustment	Website
1	OEHHA	Acute RELs	N/A	https://oehha.ca.gov/air/general-info/oehha-acute-8-hour-and-chronic-reference-exposure-level-rel-summary
2	ATSDR	Acute inhalation MRLs	Time extrapolation to 1 hour (where appropriate)	https://www.atsdr.cdc.gov/mrls/mrllist.asp
3	TCEQ	Acute ReV	N/A	https://www.tceq.texas.gov/toxicology/esl/guidelines/about; https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome
4	OEHHA	MADL (based on developmental toxicity)	Route-to-route extrapolation (where appropriate)	https://oehha.ca.gov/proposition-65/proposition-65-list
5	ACGIH	STEL	Adjustment for 1 hour exposure; adjustment factor of 300 if based on human study, 3000 if based on animal study	https://www.acgih.org/forms/store/ProductFormPublic/2018-tlvs-and-beis (not freely available)

Table 7. Hierarchy for Inhalation Cancer Potency Values.

Rank	Source	Description	Website
1	OEHHA	IUR or CSF (from Hot Spots program, Prop. 65 NSRL, or PHG for cancer endpoint based on inhalation study)	https://oehha.ca.gov/air/general-info/oehha-acute-8-hour-and-chronic-reference-exposure-level-rel-summary
2	US EPA	IRIS IUR	https://www.epa.gov/iris
3	US EPA	PPRTV IUR	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
4	OEHHA	PHG (cancer endpoint derived from non-inhalation study)	https://oehha.ca.gov/water/public-health-goals-phgs
5	US EPA	HEAST IUR or Inhalation Slope Factor	https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=2877

Appendix 2

Development of a Provisional HGV based on the POD of an Existing HGV

If a ranked HGV (Table 4) is not identified, additional data sources may be used as a starting point for development of a screening-level provisional HGV. The HGV will need to be assessed for quality and the underlying POD must be documented. The types of UFs that may be used are listed and described below; detail may be found in the REL guidance (OEHHA 2008).

- UF_L - LOAEL UF (adjusts for lack of a NOAEL in a study)
- UF_S - subchronic UF (adjusts for exposure duration in derivation of a chronic REL; not applicable to acute RELs)
- $UF_{A\text{-}k}$ - toxicokinetic component of interspecies UF
- $UF_{A\text{-}d}$ - toxicodynamic component of interspecies UF
- $UF_{H\text{-}k}$ - toxicokinetic component of intraspecies UF
- $UF_{H\text{-}d}$ - toxicodynamic component of intraspecies UF
- UF_D – database deficiency factor

Selection of the LOAEL Uncertainty Factor (UF_L)

OEHHA's REL guidance (OEHHA 2008) provides the following default values for the LOAEL uncertainty factor (UF_L):

- UF_L = 1 if NOAEL or benchmark is used (applies to acute, 8-hour, and chronic RELs)
- UF_L = 6 if LOAEL for a mild effect is used (applies to acute RELs)
- UF_L = 10 if LOAEL for a severe effect is used (applies to acute RELs)
- UF_L = 10 if LOAEL is used for any effect (applies to 8-hour and chronic RELs)

For example, if the POD for an acute HGV is a LOAEL for eye irritation, an UF_L of 6 may be used if the irritation is mild and observed in a fraction of the subjects, whereas a UF_L of 10 may be used if the irritation is severe and/or irritation is observed in all subjects.

Selection of the Toxicokinetic Component of the Intraspecies UF ($UF_{H\text{-}k}$)

OEHHA applies an $UF_{H\text{-}k}$ value of 10 as a default for gases acting systemically, and for particles that involve systemic exposure via dissolution and absorption in the lung or via the gastro-intestinal tract (OEHHA 2008). Gases that act solely at the portal of entry (i.e., lung or upper respiratory tract for inhaled toxicants) without involvement of metabolic activation or other complex kinetic processes use an $UF_{H\text{-}k}$ of √10 (OEHHA 2008).

Selection of the Toxicodynamic Component of the Intraspecies UF (UFH-d)

The UF_{H-d} is the toxicodynamic component of the intraspecies UF and is meant to account for human variability in the toxicodynamic action of a compound. Age is one factor that contributes to pharmacodynamic variability, as receptor levels (and functions) change during the course of development (OEHHA 2008). OEHHA uses a default value of √10 for UF_{H-d}; however, for certain endpoints, there is evidence that the differences between infants or children and adults may be greater. These endpoints include neurotoxicity and causation or exacerbation of asthma. A value of 10 for UF_{H-d} can be used if one or more of the following conditions was met:

1) Neurotoxicity was the critical endpoint
2) Neurotoxicity and the critical endpoint occur at similar exposure concentrations
3) The compound induces or exacerbates asthma
4) Effects observed around the POD (critical or non-critical endpoints) may be anticipated to affect children differentially (e.g., altered bone development).

Table 8. Example of UF Selection per OEHHA REL Methodology.

UFs	Value	Explanation
UF_L	1	NOAEL used
UF_S	1	Study duration ≥12% of estimated lifetime
UF_{A-k}	2	Residual TK differences in study of non-primate species using the HEC approach
UF_{A-d}	√10	Non-primate study with no TD interspecies difference adjustment
UF_{H-k}	10	Account for diversity, including infants and children, with no adjustment for human kinetic variability
UF_{H-d}	10	Suspect additional susceptibility of children (critical endpoint is neurotoxicity)
UF_D	√10	Account for substantial data gaps, specifically lack of a developmental toxicity study
Cumulative UF	2000	