

# Addressing Unassessed Chemicals: Selection and Adjustment of Inhalation Health Guidance Values

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# Today's presentation

## Outline

- ▶ Background on HGVs
- ▶ Nature of the Problem
- ▶ Potential methodology for developing provisional HGVs
  - ▶ Adopt HGVs
  - ▶ Adapt HGVs
  - ▶ Other approaches (e.g., structural analogs)
- ▶ Items for discussion



# Background: Health Guidance Values (HGVs)

- ▶ HGVs are the amount of a chemical, such as the concentration in air, which is likely to pose little or no appreciable risk to human health
  - ▶ Noncancer HGV: generally derived from a point of departure (POD) with uncertainty factors (UFs) applied
  - ▶ Cancer HGV: usually a potency reflecting increase in cancer risk with dose
  - ▶ HGVs are used in risk assessment to express a hazard quotient or lifetime cancer risk for a chemical
  - ▶ Hazard quotients (for similar endpoints) and lifetime cancer risks can be summed to give a cumulative risk for multiple chemicals



# Unassessed Chemicals

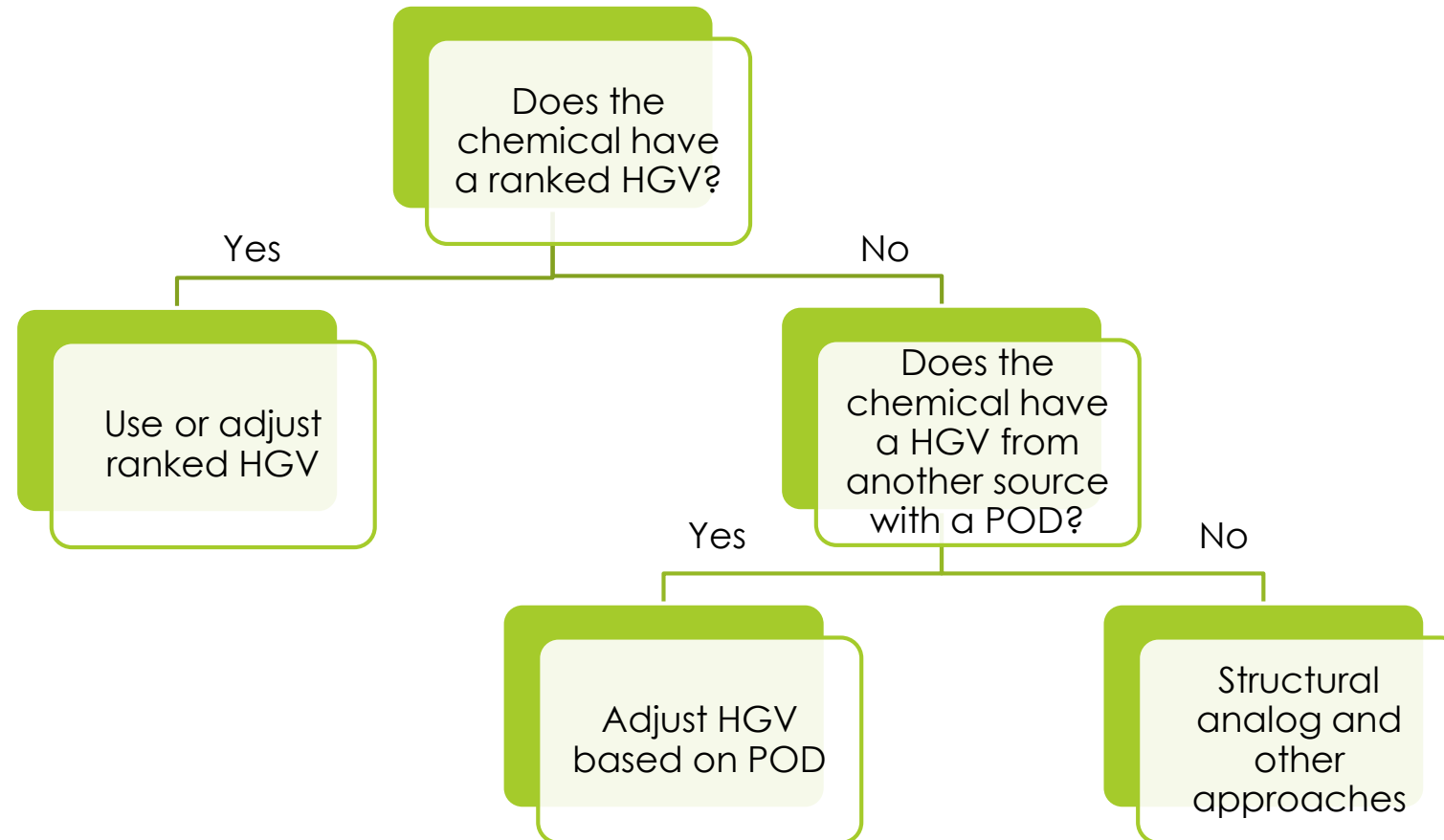
- ▶ Nature of the Problem:
  - ▶ OEHHA has established HGVs for a fraction of potential air contaminants
  - ▶ Establishing health guidance values (e.g., RELs, Unit Risk Factors) by traditional approaches can be time- and resource-intensive
- ▶ Possible Solution:
  - ▶ A mechanism to provide information in a more expedited manner on the potential for health risks from exposure to toxic chemicals
  - ▶ Likely to carry greater uncertainty than traditional procedures



# Potential Approaches for Developing Provisional HGVs

- ▶ Use work from other entities when it exists
  - ▶ *Adopt* others' existing HGVs, such as values from US EPA's IRIS program
  - ▶ *Adapt* others' existing HGVs, to make more consistent with established California methodologies (e.g., adjustment of occupational values)
- ▶ Use alternative approaches when there are no values from existing authorities
  - ▶ Structural analog approach
  - ▶ Other methods (e.g., expedited derivation of HGVs, additional *in silico* approaches)

# Decision Tree for Provisional HGVs



# Ranked HGVs from Other Entities

- ▶ Potential HGV Evaluation Criteria
  - ▶ Peer-review of HGV
  - ▶ HGV for inhalation route of exposure
  - ▶ Source program is active
  - ▶ Protection of general population including sensitive subgroups
  - ▶ Established guidance for derivation of HGV
  - ▶ Developed by OEHHA to meet California risk standards



# Example of HGV Evaluation

	External review	Public comment	Active source program	Intended for inhalation/ derived from inhalation study	Intended for gen. pop. and includes sensitive subgroups	Established guidelines for HGV development	Developed by OEHHA to meet California risk standards
OEHHA RELs	✓	✓	✓	✓	✓	✓	✓
OEHHA PHGs	✓	✓	✓	✓/-	✓	-	✓
US EPA IRIS RfCs	✓	✓	✓	✓	✓	✓	-
ATSDR MRLs	✓	✓	✓	✓	✓	✓	-
US EPA PPRTV p-RfCs	✓	-	✓	✓	✓	✓	-
OEHHA chRDs	✓	✓	✓	✓/-	✓/-	-	✓
US EPA HEAST RfCs	-	-	-	✓	✓	✓	-
OEHHA MADLs	✓	✓	✓	✓/-	✓/-	✓	✓
TCEQ ReVs	✓/-	✓	✓	✓	✓	✓	-
ACGIH TLVs/STELs	✓/-	✓	✓	✓	-	✓	-



# Ranked Hierarchy of Chronic Non-Cancer Inhalation HGVs

Rank	Source	Description	Adjustment	Rank	Source	Description	Adjustment
1	OEHHA	Chronic/8-hr RELs	N/A	9	OEHHA	chRDs	Route-to-route extrapolation
2	OEHHA	PHGs (based on inhalation study)	Remove drinking water adjustments	10	US EPA	HEAST Chronic RfCs	N/A
3	US EPA	IRIS RfCs	N/A	11	US EPA	HEAST Subchronic RfCs	Subchronic to chronic
4	ATSDR	Chronic MRLs	N/A	12	TCEQ	Chronic ReVs	N/A
5	US EPA	Chronic PPRTV p-RfCs	N/A	13	US EPA	IRIS RfDs	Route-to-route extrapolation
6	ATSDR	Intermediate MRLs	Subchronic to chronic	14	OEHHA	MADLs (reproductive endpoints)	Route-to-route extrapolation
7	US EPA	Subchronic PPRTV p-RfCs	Subchronic to chronic	15	ACGIH	TLVs (8-hr TWA)	Time extrapolation, UFs
8	OEHHA	PHGs (not based on inhalation study)	Route-to-route extrapolation				

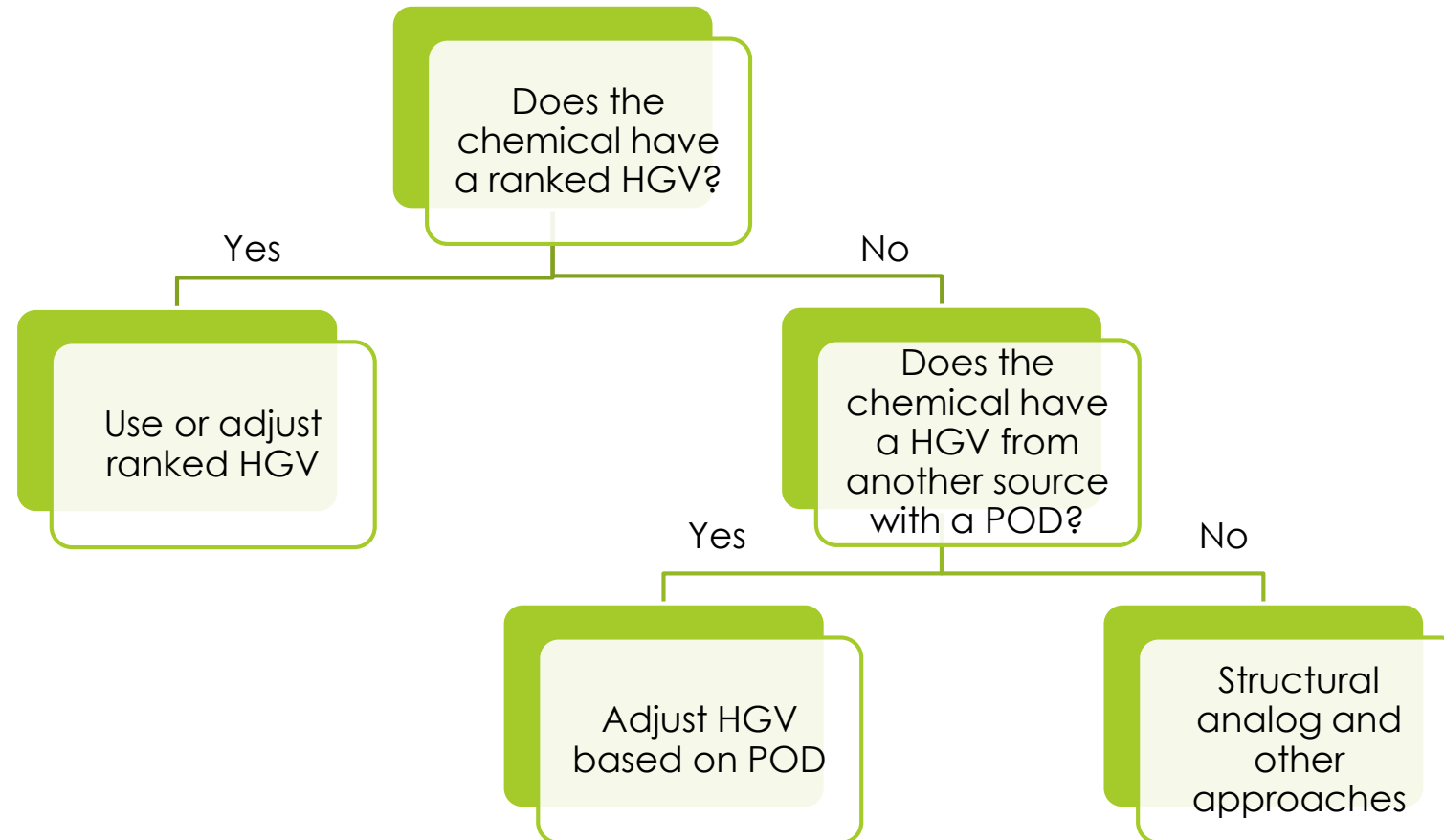
# Ranked Hierarchy of Acute Non-Cancer Inhalation HGVs

Rank	Source	Description	Adjustment
1	OEHHA	Acute RELs	N/A
2	ATSDR	Acute MRLs	Time extrapolation
3	TCEQ	Acute ReVs	N/A
4	OEHHA	MADLs (developmental endpoints)	Route-to-route extrapolation
5	ACGIH	STELs	Time extrapolation, UFs

# Occupational HGV Adjustments

- ▶ Adjustment of ACGIH HGVs
  - ▶ Adjust for exposure duration
  - ▶ Adjust with UFs
    - ▶ UF = 300 if the underlying POD was based on a human study
    - ▶ UF = 3,000 if the underlying POD was based on an animal study

# Decision Tree for Provisional HGVs

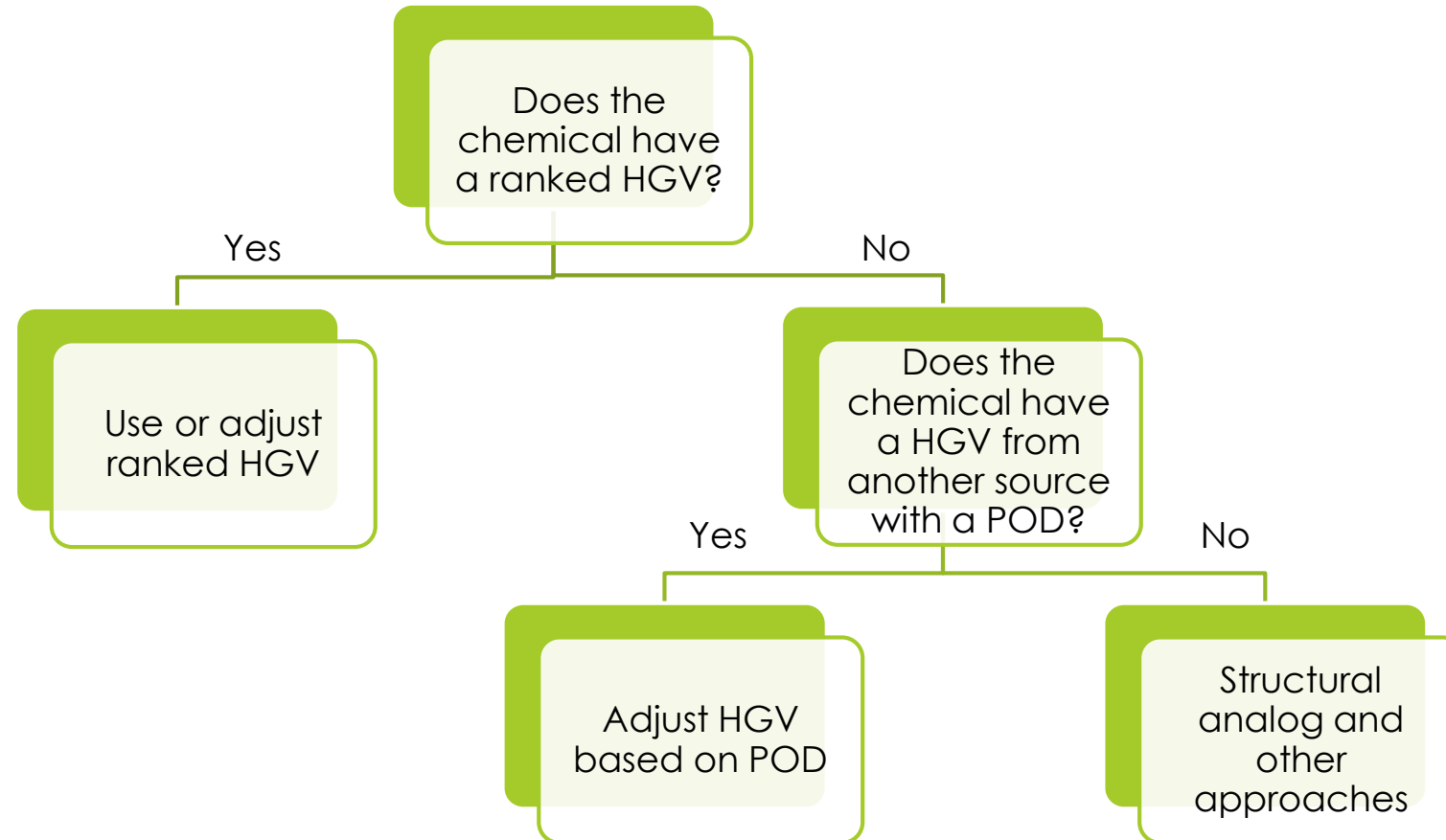


# Adjust HGVs based on POD

- ▶ If HGV requires further refinement, use POD and adjust with UFs per OEHHA REL guidance
  - ▶ *Provisional HGV* = 
$$\frac{\text{POD from existing HGV}}{\text{UFs}}$$
- ▶ Types of UFs
  - ▶ LOAEL ( $UF_L$  - adjusts for lack of NOAEL in a study)
  - ▶ Subchronic ( $UF_S$  - adjusts for exposure duration)
  - ▶ Animal to human ( $UF_{A-k}$ ,  $UF_{A-d}$  – toxicokinetic/toxicodynamic components of interspecies UF)
  - ▶ Human variability ( $UF_{H-k}$ ,  $UF_{H-d}$  – toxicokinetic/toxicodynamic components of intraspecies UF)
  - ▶ Database deficiency ( $UF_D$ )



# Decision Tree for Provisional HGVs



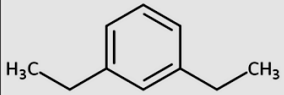
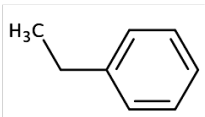
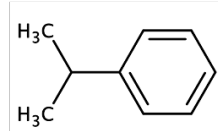
# Structural Analog Approach



- ▶ Identify structural analogs using US EPA software (AIM, Chemicals Dashboard)
- ▶ Determine if analogs have ranked HGV
- ▶ Select analog with highest similarity score that has a ranked HGV
  - ▶ If multiple HGVs, selection/adjustment based on ranked hierarchy

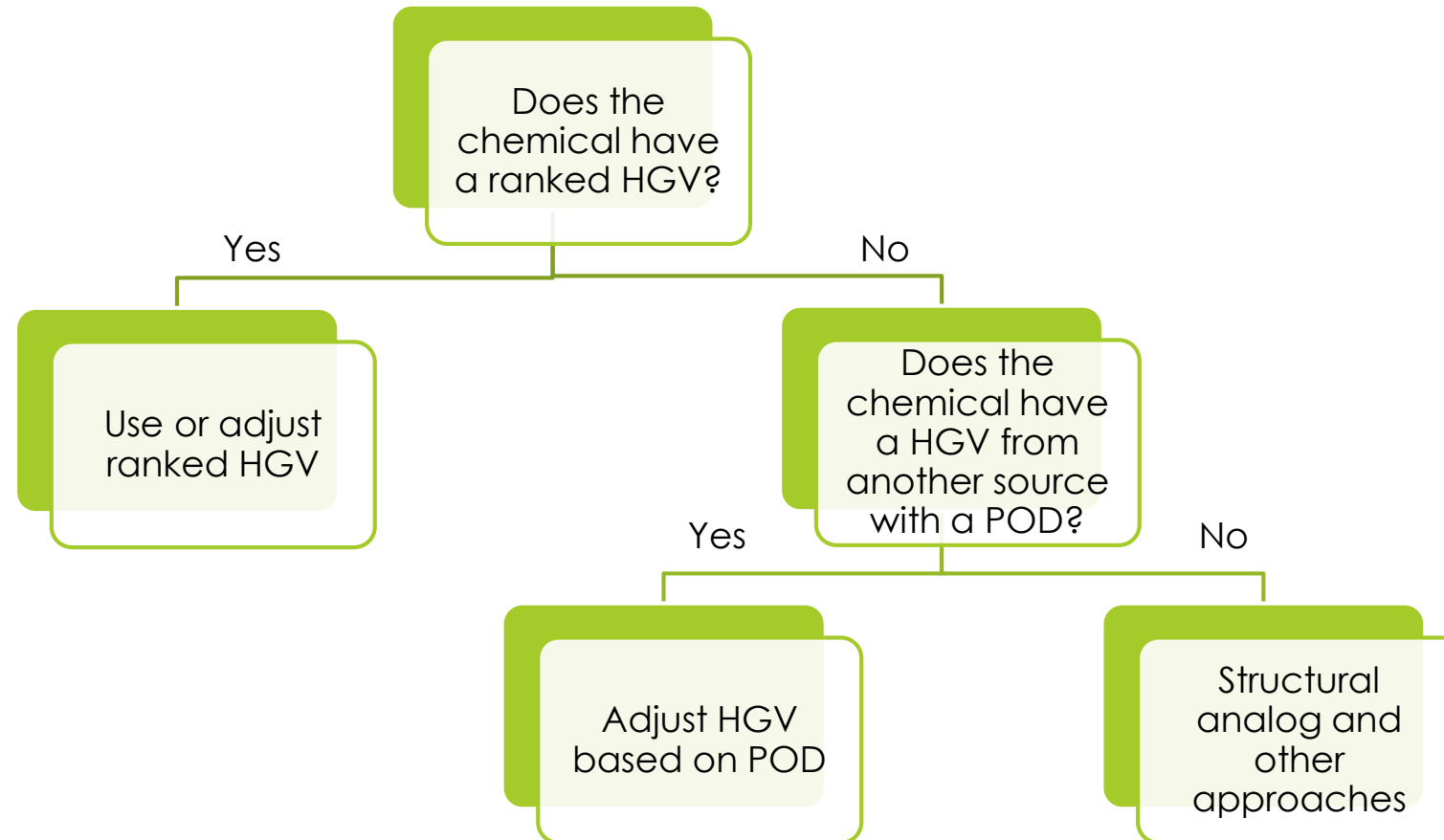
# Example of Structural Analog Approach

- Structural analogs of m-diethylbenzene and corresponding existing ranked chronic HGVs

Chemical	CAS	Structure	Similarity Score*	Analog Identification Software	Chronic HGV (mg/m <sup>3</sup> )	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
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



# Decision Tree for Provisional HGVs



## ► **Identification and Selection of Health Guidance Values:**

- Do the sources of potential HGVs for acute and chronic non-cancer endpoints appear complete?
- Are the criteria described appropriate for selection of useful HGVs?
- Is it reasonable to use these HGVs for risk screening purposes with the limited adjustments described?
- Are there alternative approaches to adjusting HGVs that we should consider?

## ► **Adjustment of Occupational HGVs:**

- We propose to adjust ACGIH HGVs with a factor of 300 when the underlying point-of-departure (POD) is from a human study and 3,000 when it is from an animal study. Is this reasonable?

## ► **Surrogate HGVs from Structural Analogs:**

- What factors should we consider in using a surrogate approach in the context of a screening-level, multi-pollutant risk assessment?
- Is it reasonable to identify analogs based on structural similarity?
- Are there other platforms for analog identification that we should consider (other than AIM and the Comptox Dashboard)?
- For this risk screening context, is it reasonable to select the highest ranked HGV for the analog with the highest similarity score?