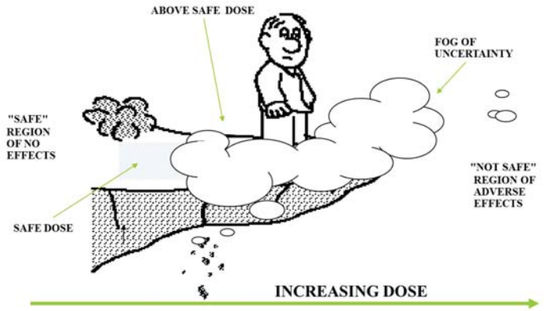
Characterizing the Impacts of Uncertainty and Scientific Judgment in Exposure Limit Development

Andrew Maier[1], Robert Sussman[2], Bruce Naumann[3], Robert Roy[4]

[1]Toxicology Excellence for Risk Assessment, [2]SafeBridge Consultants, Inc., [3]Merck and Co., [4]3M

Setting OELs Takes Science Judgment



$$\text{Risk Value} = \frac{\text{Point of Departure}}{\text{Factors to Address Uncertainty in Extrapolation}}$$

$$\text{OEL} = \frac{\text{NOAEL or LOAEL or BMDL}}{\text{Composite UF}}$$

Point of Departure (POD) - The dose that best estimates the boundary between no adverse effect and adverse effect from the available epidemiology and toxicology data.

- What are the relevant adverse effects that are likely to occur at the lowest dose: distinguishing between adverse effects and non-adverse effects (e.g., adaptive changes)
- What is the best estimate of the POD from the array of NOAELs, LOAELs, BMDLs?
- What methods are used to convert the study dose to a human equivalent dose?

Uncertainty Factors (UF) are used to account for uncertainties in extrapolation from the POD to safe concentration for all or nearly all workers. Common UF:

- UF_A – used for variability among species in extrapolating from findings in laboratory animals to humans
- UF_H – used for human variability in sensitivity
- UF_L – used when the POD is a dose that causes an adverse effect (LOAEL) rather than a dose with no adverse effects observed (NOAEL)
- UF_S – used for the possibility of the same effect occurring with prolonged exposure at a lower dose when using short-term exposure data as the POD
- UF_D – used to account for the possibility that new data would identify a different effect with a lower POD

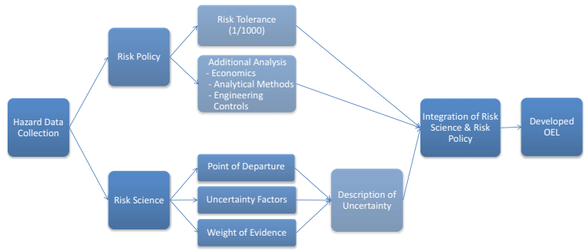
Using Uncertainty Factors

UFs	Health Canada	WHO	ATSDR	EPA
Inter-individual (H)	10 (3.16 x 3.16)	10 (3.16 x 3.16)	10	10 (3.16 x 3.16)
Interspecies (A)	10 (2.5 x 4.0)	10 (2.5 x 4.0)	10	≤10 (3.16 x 3.16)
Subchronic to chronic (S)	1-100	1-100	NA	≤ 10
LOAEL to NOAEL (L)			10	≤ 10
Incomplete Database (D)			NA	≤ 10
Modifying Factor (MF)	1-10	1-10	NA	0 to ≤ 10 (discontinued)

Do These Exposure Guidelines Differ?

Type of Limit	Value (ppm)	Agency
DNEL – Derived No Effect Level	4.7	REACH – European Union
IOELV - Indicative Occupational Exposure Limit Values	20	SCOEL – European Union
TLV® – Threshold Limit Value	50	ACGIH – American Conference of Governmental Industrial Hygienists
AEGL2 – Acute Exposure Guideline Level (2)	4800 (10-min) 3300 (30-min to 8-hr)	NRC – National Research Council
IDLH – Immediately Dangerous to Life and Health	1,100	NIOSH – National Institute for Occupational Health and Safety
RFC – Inhalation Reference Concentration	0.2	U.S. EPA – Environmental Protection Agency

Reasons Exposure Guidelines Differ



Types of Exposure Guidance

- Purpose of assessment (priority setting, registration, worker exposure)
- Exposure duration (acute, chronic, task-based)
- Exposure population (responders, workers, general population)

Difference in the Underlying Data Set

- New data have become available since the latest update (most groups update their OELs only over a cycle of years)
- Differences in policies regarding use of different sources (some groups use unpublished if vetted, while others do not)
- Literature search methods vary and key results may not have been identified (there is no uniform guidance of all relevant resource databases)

Risk Policy Choices

- Consideration of economic impact and technical feasibility to meet OEL
- Assumptions about low-dose behavior
- Tolerance for residual risk (protect all versus nearly all workers)

Risk Method Preferences

- Endpoint selection (assessing adversity NOEL versus NOAEL)
- POD adjustment (use of Benchmark dose modeling versus NOAEL
- Uncertainty factors (default factors versus use of chemical-specific data)
- Other adjustments (bioavailability assumptions and use of dosimetry models)

Science Judgment Process

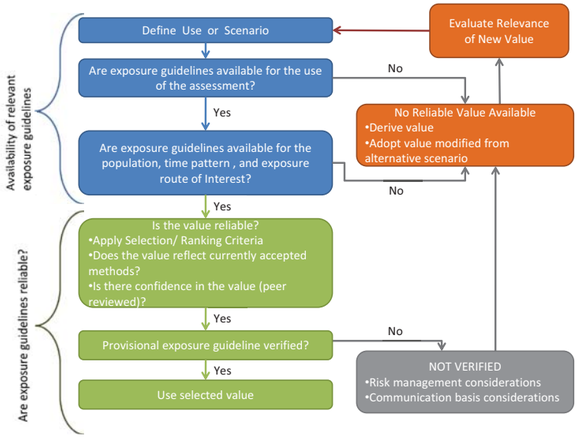
- Weight of Evidence (WOE) refers to a process of integrating the totality of all the evidence from diverse sources based on the value of information provided by each source. Key quantitative decision points that are ultimately reflected in the OEL are typically made based on the weight of evidence.
- The Value of Information of a source can be characterized by its relevance to the risk assessment issue and reliability, Not all OEL groups use the same hierarchy of data. There are frameworks to describe these concept, but their application takes judgment of experts.

Role of OEL Method Harmonization

- OELs play a critical role in occupational health
- Methods and resulting OELs and other occupational exposure guidelines differ among agencies
- There is growing emphasis on harmonization of methods – seeking to understand basis of differences and move toward common approaches (e.g., IPCS)
- Shared information facilitates harmonization
- Numerous sources of information are available, but no unified source has been compiled
- Decision guides assist to sort through the confusing landscape of guidance

How to Decide Which Value to Use?

- Mandated regulatory hierarchy in-place?
- Other considerations to weigh in decision:
  - Relevance of the guide value to the scenario or use of interest
  - The degree to which the exposure guidance includes current literature and methods
  - Confidence in the value (screening vs. full assessment; robustness of limit setting process (e.g., authoritative agency, peer review, etc.)
- A systematic approach is recommended.



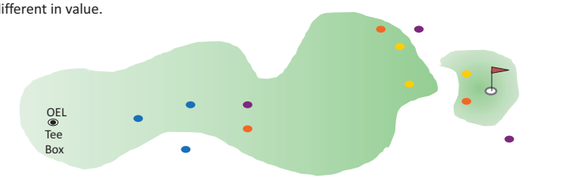
Evaluate OEL Precision and Accuracy

OELs are not bright lines between safe and dangerous.

- OELs are to be used and evaluated in the context of the uncertainties in their derivation.
- Precision is defined as "varying minimally from a defined standard".
- OELs are not precise!
- OEL precision – Key considerations
  - Derived using semi-quantitative UF factors that often reflect order of magnitude differences in judgment.
  - The variability in OELs reflects many parameters – data differences, method differences, risk tolerance differences.
  - After adjusting for risk tolerance and methods differences – residual variability can inform us about the strength of the data and identify data gaps.

Different OEL values for the same chemical can all be accurate.

- Accuracy is defined as "in exact conformity to fact".
- Are OELs accurate? OELs are often accurate in that they are estimates of a concentration that is safe, but may be poor estimates of the actual boundary between effect and no effect.
- OEL Margin of Safety
  - There is an Interplay between risk tolerance and acceptable distance from the effect versus no effect boundary. This concept refers to the "margin of safety". In general the level of residual risk that may be viewed as acceptable is lower and the margin of safety desired is higher the more severe the effect.
- OEL may be viewed as best estimate, upper bound estimate, or lower bound estimate of the "safe concentration" depending on the organization or OEL user. Thus very different OEL values may all be protective – below the actual human dose-response threshold, but highly different in value.



Round	P	A1	A2	Typical Scenario
1	Low	High	Low	Full but inconsistent dataset; similar risk methods and polices
2	High	High	Low	Limited dataset; similar risk methods and policies
3	Low	Low	Low	Full but inconsistent dataset; varying risk methods and policies
4	High	High	High	Full and consistent dataset; similar risk methods and policies

Precision (P) – Are the OELs repeatable by different groups with same data set?
Accuracy (A1) – Are the OELs safe concentrations - below the threshold between effect and no effect?
Accuracy (A2) – Are the OELs good predictors of the threshold between effect and no effect?

A Typical Example Data Set:

- Rats were exposed for 6 hours/day 5 days a week to 0, 10, 25, or 50 ppm solvent for 2 years. No effects were observed at 10 ppm, but signs of liver toxicity occurred at 25 ppm and above.
- No significant effects data are available in humans.
- No studies of reproductive effects are available.
- The chemical has moderate acute toxicity and is not genotoxic. An OEL might derived as:

  10 ppm (NOAEL) / 3 (UF_A) x 3 (UF_H) x 1 (UF_L) x 1(UF_S) x 3 (UF_D) = 0.37 ppm

Questions:

- Is the OEL 0.37 ppm, 0.4 ppm, or 0.1 ppm? Typically use 1 significant digit (i.e., 0.4 ppm).
- If another group derived an OEL of 0.2 by using a factor of 5 for UF_H would these value be inconsistent? No, evaluate the impact of differences.
- If average exposures are 0.5 ppm can you assume significant potential for health risks? No, evaluate the nature of the effect and variability in exposure and the margin of safety relative to the LOAEL.

Take Home Message

- Understand the basis for apparent differences and how to evaluate them
- Understand that an OEL value *is not* arbitrary, but *it is* imprecise
- Develop a systematic approach for OEL use and selection as part of your occupational risk management program