CHARACTERIZING THE IMPACTS OF UNCERTAINTY AND SCIENTIFIC JUDGMENT IN EXPOSURE LIMIT DEVELOPMENT

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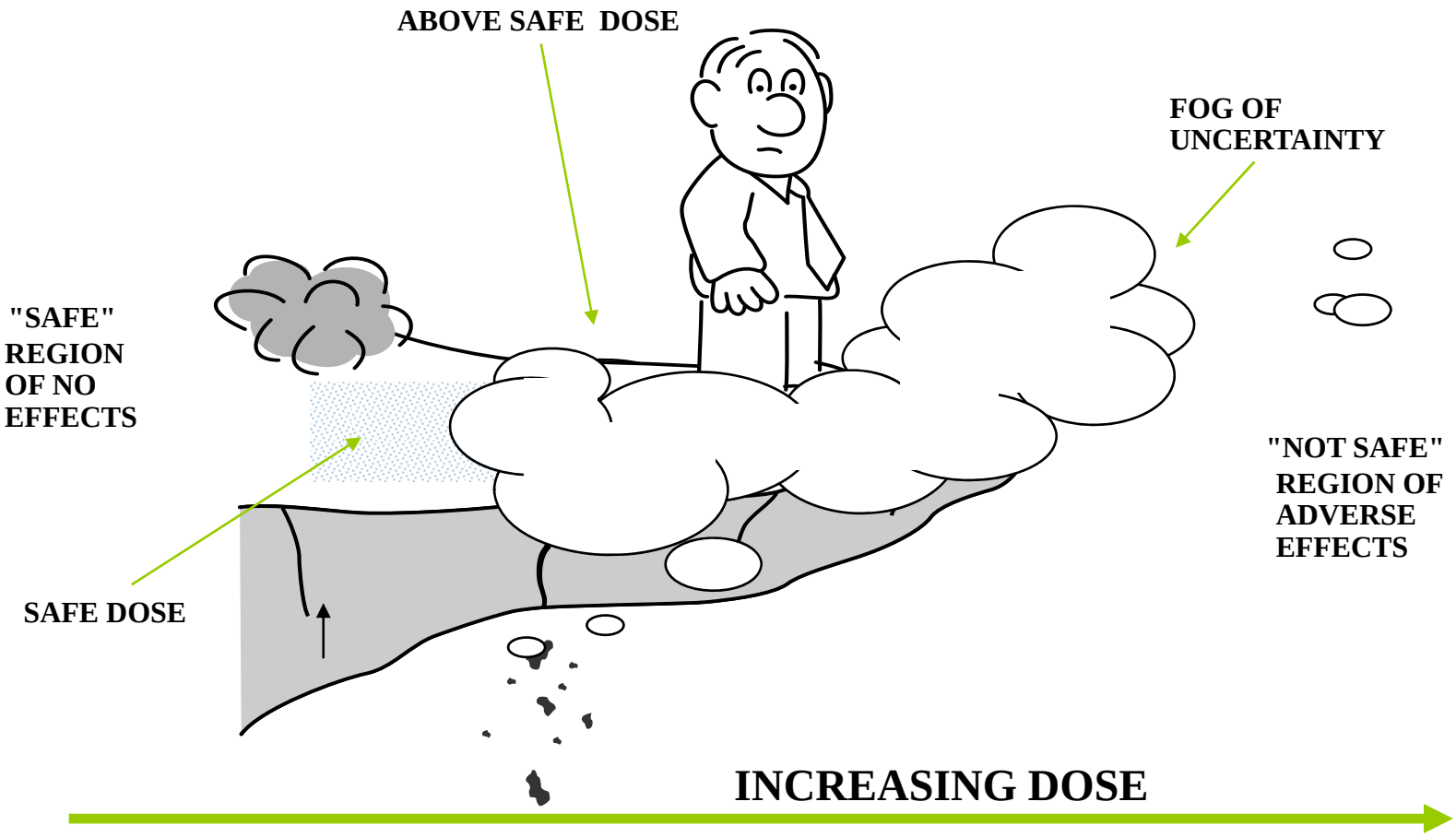
ABSTRACT

Situation/problem: There is a misperception by some that exposure limits are precise estimates. In the eyes of risk managers, one discrete value is often considered to be "correct" and all others considered "incorrect". Resolution: Exposure limits should be evaluated based on whether the value is derived in a manner "consistent with current principles" or "not consistent". An analysis of current risk assessment methods was conducted to identify the bases for variability in exposure limits for individual chemicals. The role of scientific judgments, risk policy perspectives, and evolving science methods were evaluated in the context of exposure limit setting methods. Results: A systematic methods analysis shows that important drivers to be considered in evaluating acceptability of an exposure limit include: thoroughness of the review of available data, interpretation of results according to current scientific principles under the regulatory framework being used, and consideration of sufficient sources of variability and uncertainty. Sources of variability that may be encountered in risk assessments performed by different IH or toxicology professionals using identical data sets include: selection of the point of departure, uncertainty factors used for data extrapolation, use of adjustments for toxicokinetics, among others. These and related considerations form the basis of a "quality evaluation" process proposed for assessing the robustness of an exposure limit. Lessons learned: Transparency in methods to assure robustness is a core principle embedded in risk assessment methods harmonization. Application of a systematic quality evaluation process provides for more informed use of exposure limits for risk management. A clear understanding of the basis for disparate values can provide useful information regarding the current level of uncertainty in the science and the level of confidence appropriate in using different exposure limits to characterize risk.

Deriving the OEL Requires Science Judgment

The OEL Development Process



Dose-Response Assessment – The OEL

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

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

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)

Areas of Science Judgment in OEL

- Point of Departure - The dose that best estimates the boundary between no adverse effect and adverse effect from the available epidemiology and toxicology
  - What are the relevant adverse effects that are likely to occur at the lowest level of exposure – i.e. the critical effect?
  - 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?

Areas of Science Judgment in OEL

- Uncertainty Factors are used to account for uncertainties in extrapolation from the POD to safe concentration for all or nearly all workers.
  - UFA – used for variability among species in extrapolating from findings in laboratory animals to humans
  - UFH – used for human variability in sensitivity
  - UFL – used when the POD is a dose that causes and adverse effect (LOAEL) rather than a dose with no adverse effects observed (NOAEL)
  - UFS – used for the possibility of the same effect occurring at a lower dose when using short-term exposure or dosing data as the POD
  - UFD – used to account for the possibility that new data would identify a different effect with a lower POD

Do the Values Really Differ? If so, Why?

Exposure Guideline Disharmony?

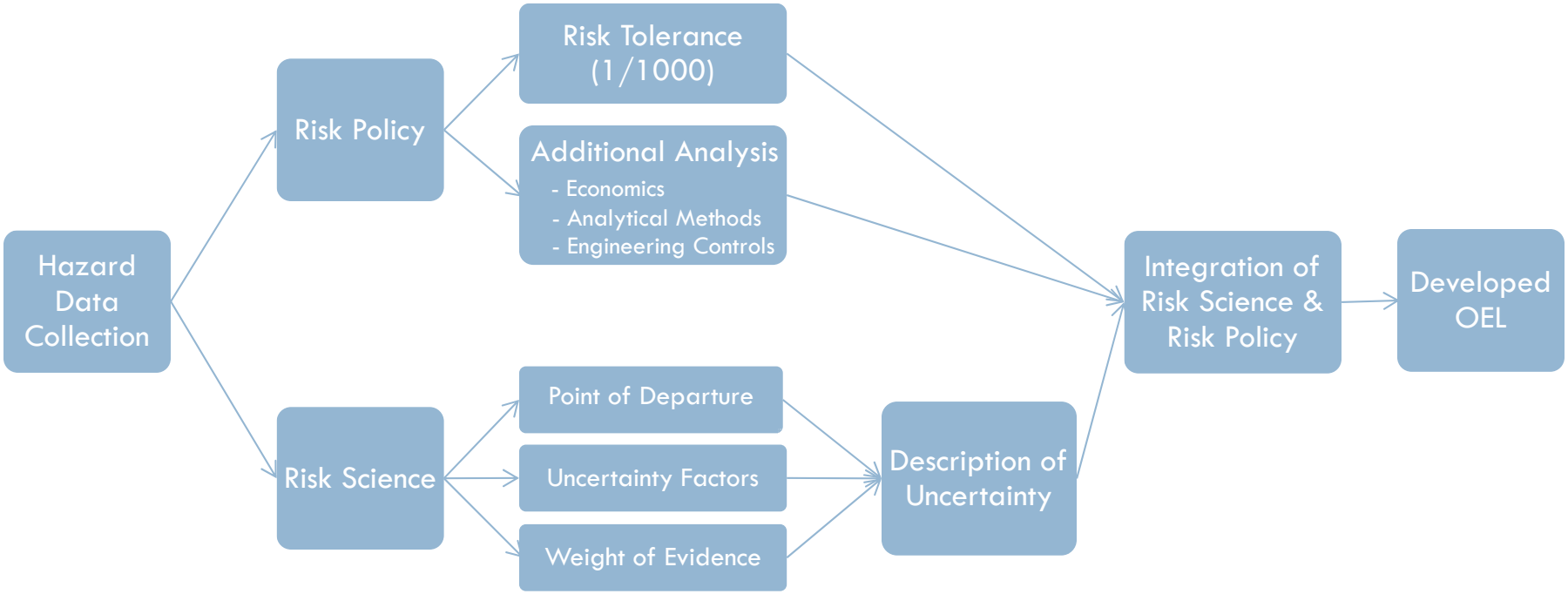
n-Hexane Exposure Guidelines

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

Types of Exposure Guidance

- There are many sources and types of exposure limit information that can be applied to different scenarios:
  - Purpose of assessment
    - Priority setting, Registration, Worker exposure assessment?
  - Exposure duration
    - Acute versus chronic?
  - Exposure population
    - Responders, workers, general population?
  - Exposure frequency
    - Routine or infrequent?
- How do you find these and select one for your scenario?

OEL	Definition	Health Basis	Analytical Feasibility	Economic Feasibility	Engineering Feasibility
ACGIH TLV	Threshold Limit Values (TLVs®) refer to airborne concentrations of chemical substances and represent conditions under which it is believed that *nearly all* workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects. TLVs® are developed to protect workers who are normal, healthy adults. They are not fine lines between safe and dangerous exposures, nor are they a relative index of toxicology.	Yes	No	No	No
NIOSH REL	RELs are occupational exposure limits recommended by NIOSH as being protective of worker health and safety over a working lifetime. The REL is used in combination in engineering and work practice controls, exposure and medical monitoring, labeling, posting, worker training and personal protective equipment. This limit is frequently expressed as a time-weighted average (TWA) for up to a 10-hour workday during a 40-hour workweek. Exposures to the skin are designated separately through the NIOSH Skin Notations.	Yes	Yes	No	Yes
OSHA PEL	OSHA sets enforceable permissible exposure limits (PELs) to protect workers against the health effects of exposure to hazardous substances. PELs are regulatory limits on the amount or concentration of a substance in the air. They may also contain a skin designation. OSHA PELs are based on an 8-hour time weighted average (TWA) exposure.	Yes	Yes	Yes	Yes
DFG MAK	The MAK-values are daily 8-hour time-weighted average values and apply to healthy adults. MAKs give the maximum concentration of a chemical substance in the workplace. Substance-specific acceptable peak concentrations, including the highest possible duration of such peaks, are defined. If the substance can be taken up through the skin, this is indicated.	Yes	No	No	No
EC SCOEL	The SCOEL include both 8-hr time weighted average exposures and short term exposure limits. The 8-hr TWAs represent levels to which an employee may be exposed via the airborne route for 8 hours per day, 5 days per week over a working lifetime which will not result in adverse effects on health of the worker or their progeny. Skin notations to the OEL are assigned if significant possibility of uptake through the skin exists.	Yes	No	No	No
TERA WEEL		Yes	No	No	No


Hazard Data Collection
Risk Policy
Risk Tolerance (1/1000)
Additional Analysis
- Economics
- Analytical Methods
- Engineering Controls
Risk Science
Point of Departure
Uncertainty Factors
Weight of Evidence
Description of Uncertainty
Integration of Risk Science & Risk Policy
Developed OEL

Why OEL Values May Differ

- Difference in the underlying data set
  - New data has 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

Why OELs May Differ

- Risk Policy Choices
  - Assumptions about low-dose behavior
  - Tolerance for residual risk (protect all versus nearly all workers)
- Risk Method Preferences
  - POD selection
  - Uncertainty Factors
  - Other Adjustments
- Science Judgments
  - Weight of Evidence and Value of Information

The Nature of Science Judgment

- Key quantitative decision points that are ultimately reflected in the OEL are typically made based on the weight of evidence.
- 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. The Value of Information of a source reflects can be characterized by its relevance to the risk assessment issue and reliability
- There are frameworks to describe these concept, but their application takes judgment of experts.

Guidance for the Occupational Risk Manager

The Risk Management Role

- 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 policy

Key Points on 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
- 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

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IPCS Harmonization Project

Harmonization of approaches to the assessment of risk from exposure to chemicals

The International Programme on Chemical Safety (IPCS) (WHO/ILO/UNEP) is leading a project to harmonize approaches to the assessment of risk from exposure to chemicals. The goal of this project is to globally harmonize approaches to risk assessment by increasing understanding and developing basic principles and guidance on specific chemical risk assessment issues. Harmonization enables efficient use of resources and consistency among assessments.

About the Project

- Harmonization Project information brochure: A4 format [pdf 104kb]
- Harmonization Project information brochure: Trifold format [pdf 115kb]
- Strategic Plan
- Stocktake of the Project, including how the products are used
- How the work is organized
- Contact us

Project focus areas

- Aggregate/cumulative risk assessment
- Cancer risk assessment
- Non-cancer risk assessment
- Exposure assessment
- Exposure assessment and risk assessment terminology
- Mutagenicity
- PBPK Modelling
- Skin sensitization risk assessment
- Reproductive/developmental toxicity
- Chemical-Specific Adjustment Factors

RELATED PUBLICATIONS

Harmonization Project publications
Full text

Descriptions of key generic terms
Full text

Risk assessment model for insecticide treatment and subsequent use of mosquito nets
Full text

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Switzerland

http://www.who.int/ipcs/methods/harmonization/en/

OEL Interpretation - Precision

- OELs are not intended as bright lines between safe and dangerous – they are to be used and evaluated in the context of the uncertainties in their derivation.
- Precision – "varying minimally from a defined standard". OELs are not precise!
- OEL precision
  - 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 in the data.

OELs Precision

A Typical Example Data Set:

- Rats were exposed for 6 hours/day 5 days a week to 0, 10, 25, and 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 or developmental effects are available.
- The chemical has moderate acute toxicity and is not genotoxic.

OEL Interpretation - Precision

An OEL might derived as:

- 10 ppm (NOAEL) / 10 (UFA) x 3 (UFH) x 1 (UFL) x 1(UFS) x 10 (UFD) = 0.0333 ppm

Questions:

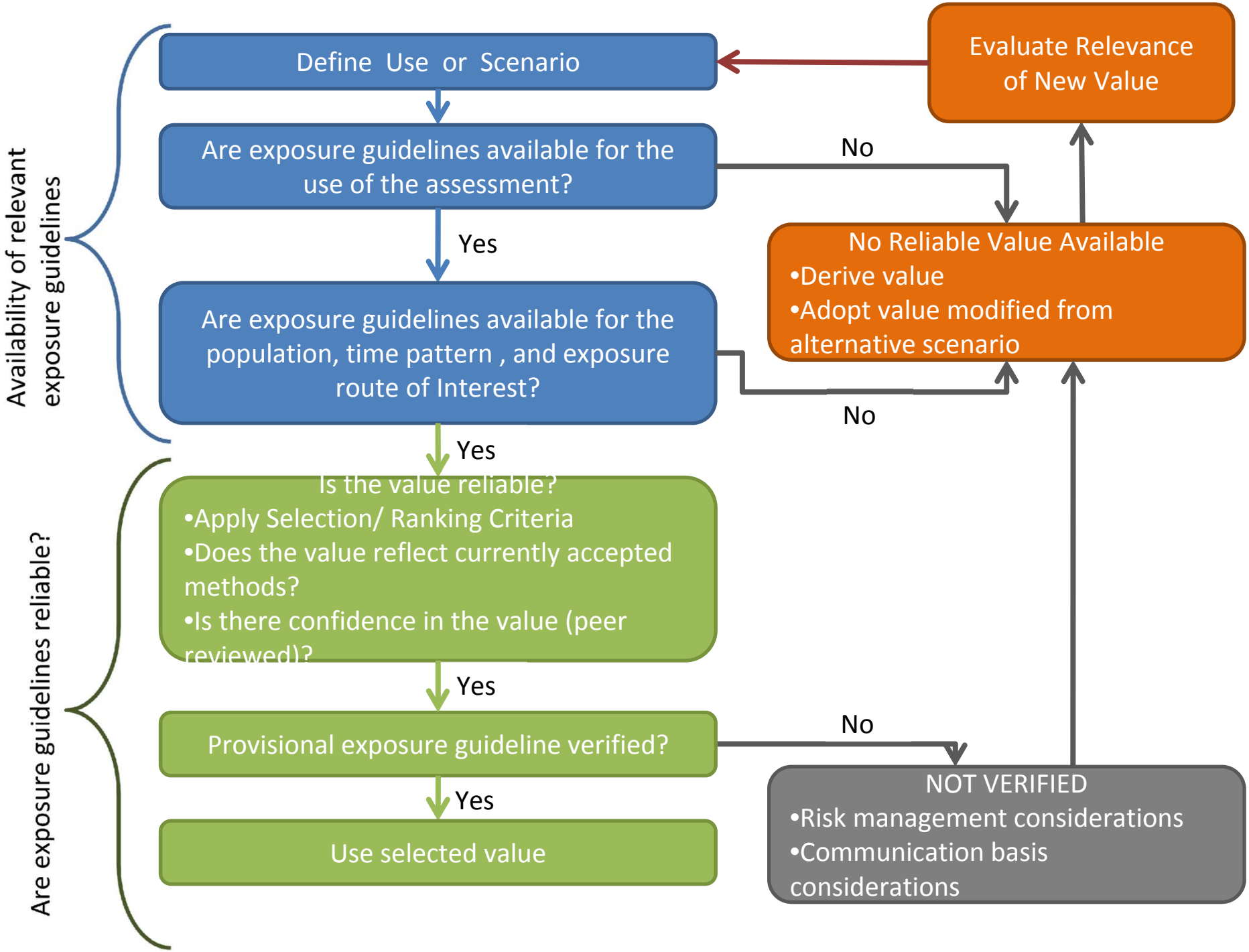
- Is the OEL 0.033 ppm, 0.03 ppm, or 0.01 ppm? Typically use 1 significant digit (i.e., 0.03 ppm).
- If another group derived an OEL of 0.02 by using a factor of 5 for UFH would these value be inconsistent? No, evaluate the impact of differences.
- If average exposures are 0.04 ppm can you assume significant potential for health risks? No, evaluate the nature of the effect and variability in exposure.

OEL Interpretation - Accuracy

- Accuracy – "in exact conformity to fact". Are OELs accurate?
  - OELs are often accurate estimates of a dose that is safe, but may be poor estimates of the actual boundary between effect and no effect.
- OELs are accuracy:
  - Interplay between risk tolerance and distance from the effect versus no effect boundary. In general the level of residual risk that may be viewed as acceptable is less 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.

Selecting Among Resources

- How to decide which value among many?
- 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)


Availability of relevant exposure guidelines
Are exposure guidelines reliable?
Define Use or Scenario
Are exposure guidelines available for the use of the assessment?
Yes
No
Are exposure guidelines available for the population, time pattern , and exposure route of Interest?
Yes
No
Is the value reliable?
•Apply Selection/ Ranking Criteria
•Does the value reflect currently accepted methods?
•Is there confidence in the value (peer reviewed)?
Yes
Provisional exposure guideline verified?
No
Yes
Use selected value
Evaluate Relevance of New Value
No Reliable Value Available
•Derive value
•Adopt value modified from alternative scenario
NOT VERIFIED
•Risk management considerations
•Communication basis considerations