Defining the range of the reference dose: imprecision versus uncertainty.

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Hazard Range and Problem Formulation

- The development of a hazard range should help to address the following problems:
  - Hazardous waste site remedial objectives for chronic exposures
  - Communicating risk/hazard of exposure above RfC
  - Prompt/short term exposure action levels
  - Inform the confounding effects of assessing ambient background concentrations in air

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TCE Residential Indoor Air Acceptable Exposure Levels

- Based on CalEPA values (2000)
  - HQ = 1: 630 μg/m^3
  - ELCR = 1 x 10^{-6}: 1.2 μg/m^3
  - ELCR = 1 x 10^{-5}: 12 μg/m^3
  - ELCR = 1 x 10^{-4}: 120 μg/m^3
- Based on US EPA IRIS (October 2011)
  - HQ = 1: 2.1 μg/m^3
  - ELCR = 1 x 10^{-6}: 0.48 μg/m^3
  - ELCR = 1 x 10^{-5}: 4.8 μg/m^3
  - ELCR = 1 x 10^{-4}: 48 μg/m^3

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Risk Assessment and Risk Management

- Excess Lifetime Cancer Risk (ELCR) Range: 10^{-6} to 10^{-4}
  - Provides risk managers flexibility to balance acceptable exposure levels with closure needs:
    - Technical feasibility
    - Implementability
    - Timeliness
    - Economic considerations
    - Cultural or other concerns
- **How may a similar evaluation be performed with respect to the non-cancer endpoint?**

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Problem Response: Alliance for Risk Assessment (*ARA*)

- *ARA* TCE Workgroup formed in the Fall of 2012
  - Open invitation, broad interest and participation
  - Trichloroethylene (TCE) Risk Assessment Guidance for Contaminated Sites (April 2013)
  - Webcast: Practical Guidance for Contaminated Sites: TCE Risk Assessment Case Study (November 4, 2013)
  - Observers: over 300 scientists from multiple international organizations, including government, industry, academia and NGOs, on 6 conference calls and one webinar.

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NAS (2014) & IRIS Process

- "**Finding:** EPA could improve documentation and presentation of dose-response information.
- **Recommendation:** EPA should clearly present two dose-response estimates: **a central estimate (such as a maximum likelihood estimate or a posterior mean) and a lower-bound estimate for a POD from which a toxicity value is derived.** The lower bound becomes an upper bound for a cancer slope factor but remains a lower bound for a reference value." [emphasis added]

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NAS (2014) & IRIS Process

- "**Finding**: IRIS-specific guidelines for consistent, coherent, and transparent assessment and communication of uncertainty remain incompletely developed. The inconsistent treatment of uncertainties remains a source of confusion and causes difficulty in characterizing and communicating uncertainty.
- **Recommendation**: Uncertainty analysis should be conducted systematically and coherently in IRIS assessments. To that end, EPA should develop IRIS-specific guidelines to frame uncertainty analysis and uncertainty communication. Moreover, uncertainty analysis should become an integral component of the IRIS process."

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Reference Dose (IRIS)

- "The RfD (expressed in units of mg of substance/kg body weight-day) is defined as an estimate (**with uncertainty spanning perhaps an order of magnitude**) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." [emphasis added]
- That is, the RfC/RfD is expected to be below the actual threshold for adverse effect in a sensitive subgroup.

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Uncertainty vs. Imprecision

- Alternative interpretations:
  - Imprecision of a RfC is on both sides of the RfC. This is because a 2nd expert group might estimate a RfC higher or lower than the 1st group, if given the same information.
  - Uncertainty in a RfC, in contrast, lies mainly above the RfC. This is because RfCs are based on lower bounds on PODs and UFs are known to be protective.
  - For risk management decisions, uncertainty in the RfC is generally more important than imprecision.
  - Managers are interested in making decisions that protect public health and uncertainties in a RfC are generally more informative.

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Hazard Range Development

- Hazard Range
  - Floor
  - Intermediate value (Midpoint)
  - Ceiling

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Floor of the Hazard Range

- Identified as the RfC/RfD based on a single candidate value
- In the case of an RfC/RfD based on two or more candidate values
  - identified as the candidate RfC/RfD with the higher(est) confidence.
    - The reference value is not likely to change with further testing, except for mechanistic studies that might affect the interpretation of prior test results.
    - RfC could be modified if refined data are obtained to modify uncertainty factors – e.g., kinetic data for chemical-specific adjustment factors.

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Floor of the Hazard Range

- The RfC/RfD is developed:
  - using UFs that are protective based on the observed behaviors of a typical toxicant
    - so that the RfC/RfD is an underestimate of the expected threshold value.
  - The floor of the hazard range may be denoted as a point below which risk managers are unlikely to recommend remedial action or exposure control.

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Ceiling of the Hazard Range

- Is defined as the adjusted point of departure (POD_{adj})
- POD based on the critical concentration/dose of chosen study.
- Managers likely to take regulatory action above this ceiling since specific toxic effects can sometimes be seen.

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Ceiling: Adjusted POD

- Adjustments for the dosing regime in the critical study, such as…
- Toxicokinetic differences between the test organism and humans
- Database quality, lack of NOAEL, and study duration; reductions are based on available data, or a factor of 3 used as a default for each area.
- The intent of these adjustments and reductions is to estimate the likely ceiling of the RfD/C by using the median value of the Ufs.

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Midpoint of the Hazard Range

- Unlikely to be associated with adverse effects in a human population, based on…
  - Greater understanding of the range of uncertainty associated with RfC/RfD development and
  - Consistent with the definition of "uncertainty of up to an order of magnitude" impacts the RfC/RfD
- It is a plausible estimate of the upper concentration or dose that is likely to be protective of the general population, including sensitive subpopulations

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Midpoint of the Hazard Range

- Is a judgment that meshes four considerations:
  - Collective magnitude of the UFs
  - Steepness of the hazard slope describing exposures above the RfC/RfD
  - The confidence in the selection of the critical effect
  - The confidence in the POD

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Johnson et al., 2003
RfC = 2 μg/m³

- Fetal malformation endpoint
  - Intermediate value of 10 μg/m³ is judged to be 5-fold above the candidate RfC due to:
    - Its small UF of 10,
    - Shallower hazard slope,
    - Low confidence in the critical effect, and
    - Low confidence in the choice of a benchmark response of 1% ($BMDL_{01}$)

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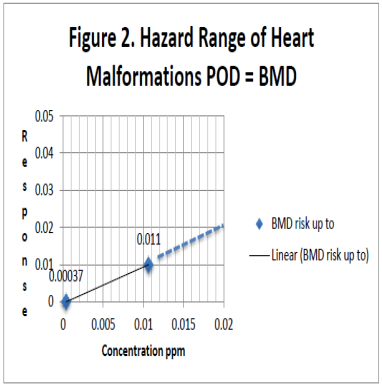
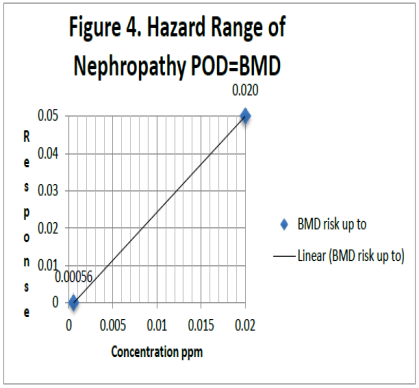
Hazard Ranges of Two Candidate RfCs for TCE (as per Gentry et al.)





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NTP, 1988
RfC = 3 µg/m³

- Toxic nephropathy endpoint
  - Intermediate value of 9 µg/m³ is judged to be 3-fold above the candidate RfC due to:
    - Its small UF of 10,
    - Steeper hazard slope,
    - Medium confidence in the critical effect, and
    - Medium to low confidence in the choice of a benchmark response of 5% ($BMDL_{05}$)

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Keil et al., 2009
RfC = 2 µg/m³

- Decreased thymus weight endpoint
  - Intermediate value of 20 µg/m³ is judged to be 10-fold above the candidate RfC due to:
    - Its larger UF of 100,
    - The effect shown by Keil et al. (2009) does not lend itself to dose-response modeling, so steepness of the slope was not assessed
    - Medium confidence in the critical effect, and
    - Medium to low confidence in its choice of a LOAEL as the POD

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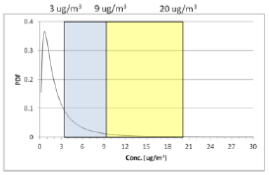
TCE as an Example

Table 7. Different uncertainty ranges for different TCE RfCs. All values are in µg/m^3. Shaded areas indicate best **overall uncertainty range** for risk management purposes.

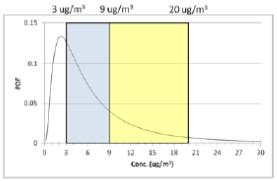
Study	Endpoint	IRIS UF [a]	Steep [b] Slope	Confidence		Uncertainty Ranges		
				Critical [c] Effect	Point of [d] Departure	Floor	Intermediate	Ceiling
Johnson et al (2003)	Fetal malformation	10	Lower	Low	Low	2	10	20
NTP (1988)	Toxic nephropathy	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	Decreased thymus weight	100	NA	Medium	Medium to Low	2	20	60

a. Size of the uncertainty factor as on IRIS
b. Steepness of the hazard slope (*i.e.*, the slope of the line describing hypothetical population responses at concentrations above the RfC), as per Section 3.
c. Confidence in the choices of critical effect, as per Section 4.
d. Confidence in the POD, as per Section 4.

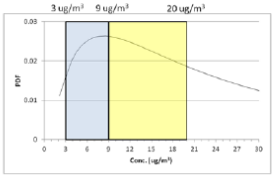
Practical Application of the Hazard Range for TCE



ES Figure 1a. Exposure distribution of indoor air concentrations primarily below the 3 µg/m^3 to 20 µg/m^3 hazard range. Relatively small proportion of exposures is higher than 3 µg/m^3. Nominal actions or no further action may be warranted for risk management.



ES Figure 1b. Exposure distribution of indoor air concentrations falling within the 3 µg/m^3 to 20 µg/m^3 hazard range. Relatively small proportion of exposures is higher than 9 µg/m^3. Limited action may be warranted for risk management



ES Figure 1c. Exposure distribution of indoor air concentrations primarily above the 3 µg/m^3 to 20 µg/m^3 hazard range. Actions to reduce exposures may be warranted for risk management.

For more information http://www.allianceforrisk.org/Projects/TCE.html

Guidance for Contaminated Sites: Trichloroethylene Case Study. Gadagbui, et al., SOT, 53rd Annual Meeting & ToxExpo, 23-27 March 2014, Phoenix, AZ.

Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with TCE and Other Chemicals, Beyond Science & Decisions: Problem Formulation to Dose-Response Assessment, Workshop VIII, 21-22 May 2014, Austin, TX.

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Thank You!

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TCE Criteria: *Through the Years*

- Withdrawn US EPA IRIS (1989)
  - Inhalation Unit Risk = 1.7×10^{-6} $(\mu g/m^3)^{-1}$
- CalEPA values (2000)
  - Chronic inhalation REL = 600 $\mu g/m^3$
  - Inhalation Unit Risk = 2×10^{-6} $(\mu g/m^3)^{-1}$
- Draft US EPA TCE Assessment (2001)
  - Prov. RfC = 0.04 mg/m^3 = 40 $\mu g/m^3$
  - Prov. Inhalation Unit Risk = 5.7×10^{-6} $(\mu g/m^3)^{-1}$ to 1.1×10^{-4} $(\mu g/m^3)^{-1}$
- US EPA IRIS (October 2011)
  - RfC = 0.002 mg/m^3 = 2 $\mu g/m^3$
  - Inhalation Unit Risk = 4.1×10^{-6} $(\mu g/m^3)^{-1}$

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Consequences of the New TCE Toxicity Values (Problem Formulation)

- Risk-based indoor air levels now based upon non-cancer endpoint (RfC)
- The RfC is based on both chronic and developmental endpoints
- Prompt/short term exposure action levels based on the RfC
  - Prompt action exposure concentrations
  - Application of lifetime RfC to acute and subchronic exposures
- Confounding effects of assessing ambient background concentrations of TCE in air

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NAS *Science and Decisions: Advancing Risk Assessment* (2009)

- "For noncancer end points, it is assumed that homeostatic and defense mechanisms lead to **a dose threshold** (that is, there is low-dose nonlinearity), below which effects do not occur or are extremely unlikely. For these agents, risk assessments have focused on defining the reference dose (RfD) or reference concentration (RfC), a putative quantity that is 'likely to be without an appreciable risk of deleterious effects' (EPA 2002a, p. 4-4)." [emphasis added]
- That is, the RfC/RfD is expected to be below this actual threshold for adverse effect.

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NAS *Science and Decisions: Advancing Risk Assessment* (2009)

"The "hazard quotient" (the ratio of the environmental exposure to the RfD or RfC) and the "hazard index" (HI)… An HI less than unity is generally understood as being indicative of lack of appreciable risk, and a value over unity indicates some increased risk.

The larger the HI, the greater the risk, but the index is not related to the likelihood of adverse effect except in qualitative terms: 'the HI cannot be translated to a probability that adverse effects will occur, and is not likely to be proportional to risk' (EPA 2006a)." [emphasis added]

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NAS (2009) & Hazard Assessment

- NAS (2009):
  - Suggested that methods for assessing non-cancer toxicity have the capability of determining hazard ranges.
- ARA project "Beyond Science and Decisions: From Problem Formulation to Dose Response"
  - Built on NAS (2009) report
  - Six of its cases studies are about evaluating noncancer *risk* (at different doses)
    - Each was vetted by a Science Panel
- We focus on:
  - modeling risk above the RfC/RfD using the benchmark dose method (Gentry *et al.,* 2011).

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Problem Response: Alliance for Risk Assessment (ARA)

- *Guidance for Contaminated Sites: Trichloroethylene Case Study*. Gadagbui, *et al*., SOT, 53rd Annual Meeting & ToxExpo, 23-27 March 2014, Phoenix, AZ.
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