A Walk Through the National Academies Review of EPA's IRIS Process: Implications for Hazard Assessment

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NCAC-SOT Fall Webinar
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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.
  - Uncertainty analysis should become integral to IRIS evaluation.

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 [of a range] for a cancer slope factor but remains a lower bound [of a range] for a reference value.

What Does [a Range] Look Like to a State: TCE Residential Exposure

Based on CalEPA values (2000)

- Noncancer hazard Quotient = 1: 630 $\mu g/m^3$
- Upper bound cancer risk 1 in 10^6: 1.2 $\mu g/m^3$
- Upper bound cancer risk 1 in 10^5: 12 $\mu g/m^3$
- Upper bound cancer risk 1 in 10^4: 120 $\mu g/m^3$

Based on US EPA IRIS (October 2011)

- Noncancer hazard Quotient = 1: 2.1 $\mu g/m^3$
- Upper bound cancer risk 1 in 10^6: 0.48 $\mu g/m^3$
- Upper bound cancer risk 1 in 10^5: 4.8 $\mu g/m^3$
- Upper bound cancer risk 1 in 10^4: 48 $\mu g/m^3$

Hazard Range and a State: Problem Formulation

Does the development of a hazard range help to address the following problems:

- Hazardous waste site remedial objectives for chronic exposure levels
- Prompt/short term exposure action levels
- Application of lifetime RfC/RfD to acute and subchronic exposures
- Communicating risk/hazard of exposure above RfC/RfD
- Confounding effects of assessing ambient background concentrations in air

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

Hazard Range Development

- Floor
- Intermediate value (Midpoint)
- Ceiling

- *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.

U.S. EPA (IRIS, 2014)

- The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day.
- In general, the RfD is 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…

- That is, the RfC/RfD is expected to be a sensitive human subgroup No Observed Adverse Effect Level (NOAEL). It is below the expected threshold for adverse effect in a sensitive human subgroup.

Imprecision vs. Uncertainty

- Imprecision of a RfD/C is on both sides. A 2nd expert group might estimate a RfD/C higher or lower than 1st group, if given the same information.

- Uncertainty in a RfD/C, in contrast, lies mainly above. This is because RfD/Cs are based on lower bounds and UFs are known to be protective.

- For state risk management decisions, uncertainty in the RfD/C is generally more informative, since managers are interested in making decisions that protect public health.

Floor of the Hazard Range

- Identified as the RfC/RfD based on a single candidate value, consistent with NAS suggestion to use a reference value as a lower bound of a range.

- In the case of an RfC/RfD based on two or more candidate values, identify the RfC/RfD with the higher confidence.

- The floor of the hazard range may be denoted as a point *at or below which* risk managers are unlikely to recommend remedial action or exposure control.

Ceiling of the Hazard Range

- Is defined as the adjusted point of departure (POD)
- The adjusted POD is based on the critical concentration/dose from a value directly obtained from the toxicity or epidemiology study.
- Managers are likely to take regulatory action above this ceiling due to the fact that specific toxic effects can sometimes be associated with values above it.

Hazard Range Intermediate Value

- It is a plausible estimate of the concentration of dose that is likely to be protective of the general population, including sensitive subgroups…
  - given a greater understanding of the range of uncertainty associated with RfC/RfD development and
  - consistent with the definition of how "uncertainty of up to an order of magnitude" impacts the RfC/RfD
- Managers are likely to monitor exposures above this midpoint closely, due to the fact that specific toxic effects can sometimes be associated with sensitive subgroups.

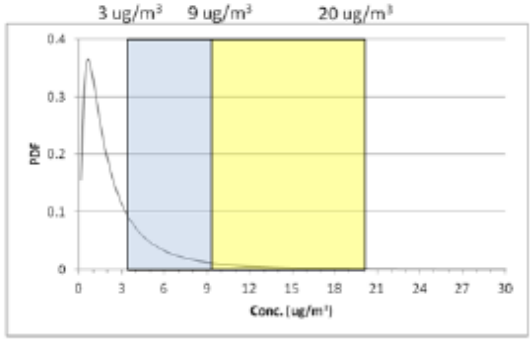
TCE as an Example

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.

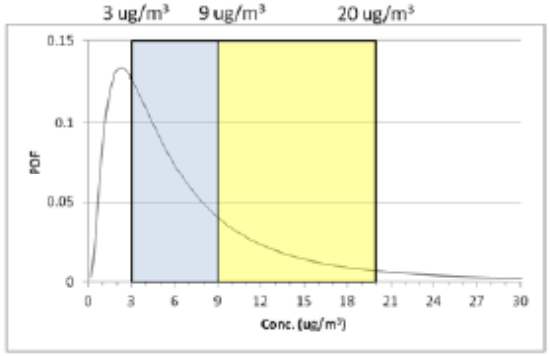
Study	Endpoint	IRIS UF [a]	Steep Slope [b]	Confidence		Uncertainty Ranges		
				Critical Effect [c]	Point of Departure [d]	Floor	Intermediate	Ceiling
Johnson et al (2003)	Fetal malformation	10	Lower	Low	Low	2	10	20
NTP (1988)	Toxic nephropathy	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	Decreased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

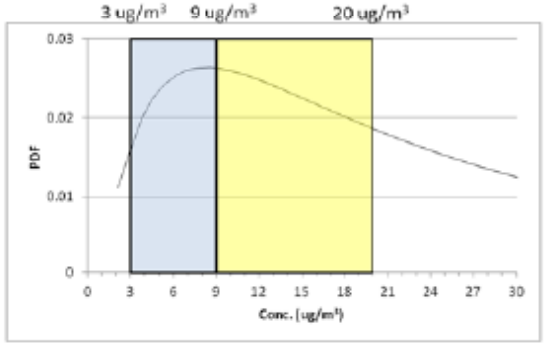
Practical Application of the Hazard Range for TCE



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.

Uncertainty ranges for different RfDs on IRIS (2014). All values for these ranges are in mg/kg-day.

Chemical	IRIS UF [a]	Steep [b] Slope	Confidence		Uncertainty Ranges		
			Critical [c] Effect	Point of [d] Departure	Floor	Intermediate	Ceiling
Arsenic [range as on IRIS]	3	Low	High	Medium	1E-4	3E-4	8E-4
Tetrachloroethylene	1000	Low	High	Low	6E-3	6E-2	6E-1
Chromium 6	300 x 3	Low	Low	Low	3E-3	3E-2	3E-1

- Size of the uncertainty factor, as per IRIS
- Steepness of the hazard slope (*i.e.*, the slope of a hypothetical line describing population responses at concentrations above the RfD), as per Section 3.
- Confidence in the choices of critical effect, as per Section 4.
- Confidence in the point of departure, as per Section 4.

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Independent Panel's Thoughts on CDC Results for 4-Methyl-cyclo-hexane-methanol (MCHM)

- CDC used traditional methods and reasonable assumptions to develop their screening levels.
- The panel chose to consider additional routes of exposure (inhalation and skin).
- The panel was not constrained to use any particular methods.
- The panel included international and US state experts.

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Independent Panel's Approach

- The Panel agreed with CDC on the choice of key toxicity data for MCHM.
- The Panel agreed with CDC on the choice of uncertainty (safety) factors for MCHM.
- The Panel chose to consider additional routes of exposure (inhalation and skin).
- The Panel chose to calculate values based on the most highly exposed population (that is, formula-fed infants).

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Preliminary Conclusions

- The panel developed a safe level of exposure for MCHM, 120 ppb, that is protective for all populations.
- This level is an average for exposures up to 28 days.
- The difference between the original CDC number and the panel value was explained in part due to the availability of additional information in the panel's hands.

However, a post meeting realization was that development of a range would have been helpful to the state and its public.

Summary

- States have practical problems that necessitate the development of ranges for risk assessment values.
- EPA's methods allow the development of ranges for both cancer and noncancer toxicity.
- The NAS is encouraging EPA and others to
  - develop IRIS-specific guidelines to frame uncertainty analysis,
  - make this integral to IRIS evaluations, and to
  - estimate a central estimate and a lower-bound estimate for risk assessment values.