Practical Guidance on the Development of a Non-cancer Hazard Range for Effective Risk Assessment and Risk Management of Contaminated Sites: A Case Study with Trichloroethylene and Other Chemicals

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Observers: over 300 scientists from multiple international organizations, including government, industry, academia and NGOs, on 6 conference calls and one webinar.

Problem Formulation

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

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.

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]

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.

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.

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).

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]

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."

Hazard Range Development

- Hazard Range
  - Floor
  - Midpoint
  - Ceiling

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.

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.

Ceiling of the Hazard Range

- Is defined as the adjusted point of departure (POD_{adj})
- The POD is based on the critical concentration/dose
  - A value directly obtained from the toxicological study

Ceiling of the Hazard Range

- POD_{adj} is the POD with appropriate adjustments:
  - For the dosing regime in the critical study;
  - Toxicokinetic differences between the test organism and the human population in order to determine the human equivalent concentration or dose (HEC or HED);
  - And…

Ceiling of the Hazard Range

- The POD is also reduced to account for other uncertainties (if needed):
  - 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.

- *Note: Intraspecies variability (for sensitive human subpopulations) is still a part of this range.*

Ceiling of the Hazard Range

- 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.
  - Based on continuous inhalation lifetime exposures or chronic daily intakes

Midpoint of the Hazard Range

- Even though it is higher than the RfC/RfD, the midpoint is a value within the hazard range that is unlikely to be associated with adverse effects in a human population, 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
- It is a plausible estimate of the concentration of dose that is likely to be protective of the general population, including sensitive subpopulations

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

Midpoint of the Hazard Range

- Midpoints are closer to the floor, the RfC, if:
  - The UF is small
  - The hazard slope is steep
  - The confidence is high in the critical effect, and
  - The confidence is high in the POD

- Midpoints are further from the RfC if:
  - The uncertainty factor is large,
  - Hazard slope is shallow, and
  - Confidence is low in the critical effect and in the POD

Midpoint of the Hazard Range

- Collective magnitude of the UFs on IRIS.
- Steepness of the hazard slope describing exposures above the RfC/RfD
  - Slope of the line from the BMD to the RfC/RfD
  - Compare slopes with multiple RfC/RfDs
  - If only one candidate RfC/RfD value compare steepness to average dose response slope:
    - 2 probits per 10-fold dose = average
    - If > 2 probits, steep slope
    - If ≤2 probits, shallow slope

Midpoint of the Hazard Range

- If data not amenable to dose-response modeling (i.e., no BMD estimated):
  - If only NOAEL available:
    - Assume shallower slope

- If only LOAEL available:
  - Evaluate severity of the critical effect
    - If severe, assume steeper slope
    - If mild, assume shallower slope

Midpoint of the Hazard Range

- If both NOAEL and LOAEL available:
  - If ratio between LOAEL and NOAEL ≤ 3
    - Assume steeper slope
  - If ratio is > 3
    - Assume shallower slope

Confidence in the Selection of the Critical Effect

- If critical effect matches the expected human situation or there is consensus among toxicologists on the critical effect
  - Confidence is higher

- If not, or when highest level of exposure is associated with lack of a critical effect
  - Confidence is lower

Confidence in the POD

- If the derived POD, such as a BMDL, is judged to match, or is close to, the data
  - Confidence is higher

- If the derived POD, such as a BMDL, does not match, or is distant from, the data
  - Confidence is lower

- LOAELs have lower confidence when used as PODs

Arsenic as an Example

Oral RfD Summary (after IRIS)

Critical Effect	Experimental Doses	UF	MF	RfD
Hyperpigmentation, keratosis and possible vascular complications Human Chronic oral exposure Tseng, 1977; Tseng *et al*., 1968	NOAEL: 0.009 mg/L, converted to 0.0008 mg/kg-day LOAEL: 0.17 mg/L, converted to 0.014 mg/kg-day	3	1	3E-4 mg/kg-day

Summary of data for the Development of the Hazard Range for the Arsenic

Chemical	IRIS RfD	IRIS POD	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
	(mg/kg-day)				Critical Effect[c]	POD[d]	Floor	Midpoint (Inter-mediate)	Ceiling
Arsenic*	3E-4	8E-4	3	Low	High	Medium	1E-4*	3E-4	8E-4*

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.

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.

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

Figure 2. Hazard Range of Heart Malformations POD = BMD

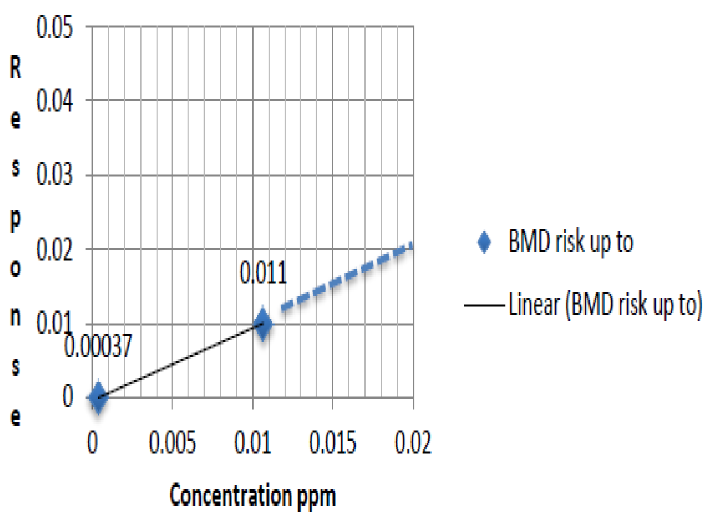
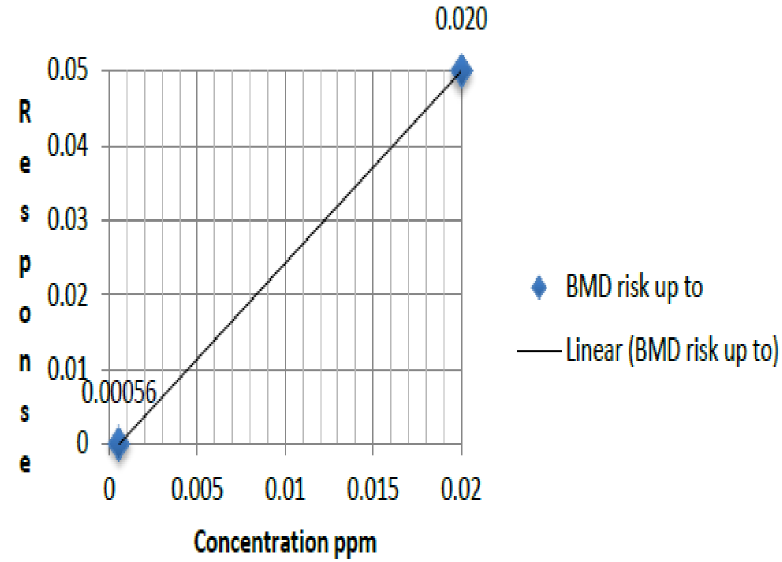


Figure 4. Hazard Range of Nephropathy POD=BMD



Johnson et al., 2003
RfC = 2 μg/m^3

- Fetal malformation endpoint
  - Midpoint of 10 μg/m^3 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% ($BMDL_{01}$)

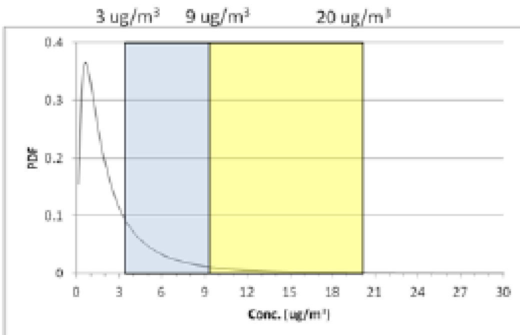
NTP, 1988
RfC = 3 μg/m^3

- Toxic nephropathy endpoint
  - Midpoint of 9 μg/m^3 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% ($BMDL_{05}$)

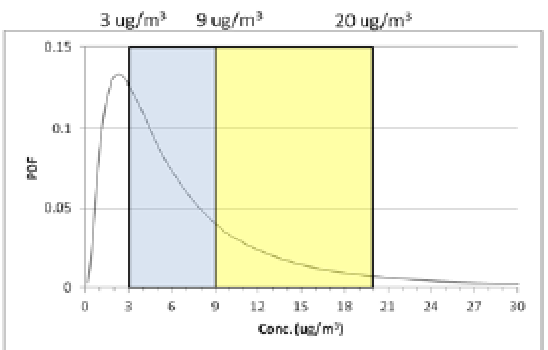
Keil et al., 2009
RfC = 2 µg/m^3

- Decreased thymus weight endpoint
  - Midpoint of 20 µg/m^3 is judged to be 10-fold above the candidate RfC due to:
    - Its larger UF of 100, medium confidence in the critical effect, and medium to low confidence in its choice of a LOAEL as the POD
    - The effect shown by Keil et al. (2009) does not lend itself to dose-response modeling, so steepness of the slope was not assessed

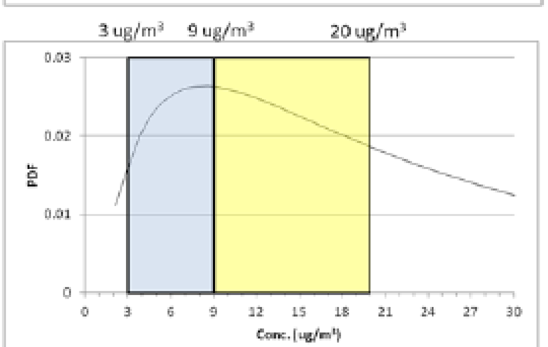
Practical Application of the Hazard Range for TCE



ES Figure 1a. Exposure distribution of indoor air concentrations primarily below the 3 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Relatively small proportion of exposures is higher than 3 $\mu g/m^3$. 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 $\mu g/m^3$ to 20 $\mu g/m^3$ hazard range. Relatively small proportion of exposures is higher than 9 $\mu g/m^3$. Limited action may be warranted for risk management



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

Hazard Range and the Problem Formulation

- Does the development of a hazard range help to address the following problems:
  - Hazardous waste site remedial objectives for chronic exposure levels
  - Communicating risk/hazard of exposure above RfC/RfD
  - Prompt/short term exposure action levels
    - Prompt action exposure concentrations
    - Application of lifetime RfC/RfD to acute and subchronic exposures
  - Confounding effects of assessing ambient background concentrations in air (TCE, Petroleum)

Thank You

Tetrachloroethylene

Oral RfD Summary (after IRIS)

Principal Study/Critical Effect	POD (mg/kg-day)*	UF	Candidate RfDs (mg/kg-day)	RfD (mg/kg-day)**
Echeverria *et al.* (1995): neurotoxicity (reaction time, cognitive effects) in occupationally-exposed adults	LOAEL = 9.7	1,000[a]	0.0097	0.006
Cavalleri *et al.* (1994): neurotoxicity (color vision) in occupationally-exposed adults	LOAEL = 2.6	1,000[a]	0.0026	

*Derived by route-to-route extrapolation from inhalation exposure using PBPK model of Chiu and Ginsberg (2011).

**The RfD is supported by the two principal studies, as a midpoint of the range of available values (then rounded to one significant figure).

[a]Judged to be 100 (see text under "*Evaluation*")

Summary of data for the Development of the Hazard Range for the Tetrachloroethylene

Chemical	IRIS RfD	IRIS POD	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
	(mg/kg-day)				Critical Effect[c]	POD[d]	Floor	Midpoint (Inter-mediate)	Ceiling
Tetrachlor oethylene	6E-3	6E-0	1000	Low	High	Low	6E-3	6E-2	6E-1**

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.

**Range judged to be 100 (see text under "*Evaluation*")

Chromium (VI)

Oral RfD Summary (after IRIS)

Critical Effect	Experimental Doses	UF	MF	RfD
None Reported Rat, 1-year drinking water study MacKenzie et al., 1958	NOAEL: 25 mg/L of chromium as K_2CrO_4 2.5 mg/kg-day (adj.)	300	3	3E-3 mg/kg-day

Summary of data for the Development of the Hazard Range for the Chromium (VI)

<table>
<tr><th rowspan="2">Chemical</th><th>IRIS RfD</th><th>IRIS POD</th><th rowspan="2">IRIS UF[a]</th><th rowspan="2">Steep Slope[b]</th><th colspan="2">Confidence</th><th colspan="3">Hazard Ranges (mg/kg-day)</th></tr>
<tr><th colspan="2">(mg/kg-day)</th><th>Critical Effect[c]</th><th>POD[d]</th><th>Floor</th><th>Midpoint (Inter-mediate)</th><th>Ceiling</th></tr>
<tr><td>Chromium (VI)</td><td>3E-3</td><td>2.5</td><td>300 x 3</td><td>Low</td><td>Low</td><td>Low</td><td>3E-3</td><td>3E-2</td><td>3E-1***</td></tr>
</table>

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.

***Range judged to be 100 (see text under "*Evaluation*")

Table 1. Summary of data for the Development of the Hazard Range for the Arsenic, Tetrachloroethylene and Chromium (VI) RfDs on IRIS (2014).

(All values for these ranges are in mg/kg-day).

Chemical	IRIS RfD	IRIS POD	IRIS UF[a]	Steep Slope[b]	Confidence		Hazard Ranges (mg/kg-day)		
	(mg/kg-day)				Critical Effect[c]	Point of Departure[d]	Floor	Midpoint (Intermediate)	Ceiling
Arsenic*	3E-4	8E-4	3	Low	High	Medium	1E-4*	3E-4	8E-4*
Tetrachloroethyl-ene	6E-3	6E-0	1000	Low	High	Low	6E-3	6E-2	6E-1**
Chromium (VI)	3E-3	2.5	300 x 3	Low	Low	Low	3E-3	3E-2	3E-1***

*The floor to ceiling range as found on IRIS

**Range judged to be 100 (see text under *"Evaluation"*)

***Range judged to be 100 (see text under *"Evaluation"*)

a. Size of the uncertainty factor, as per IRIS

b. 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 of eth case Study Report.

c. Confidence in the choices of critical effect, as per Section 4 of the Case Study Report.

d. Confidence in the point of departure, as per Section 4 of eth Case Study Report.