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

Tri-Service Environmental Risk Assessment Work Group
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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).

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."

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, because managers are interested in making decisions that protect public health.

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})
- 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.

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.

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 how "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

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

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

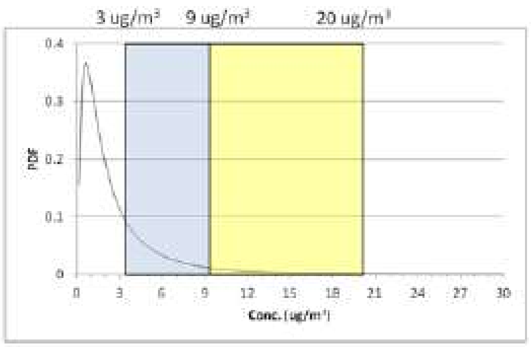
a. Size of the uncertainty factor as on IRIS

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.

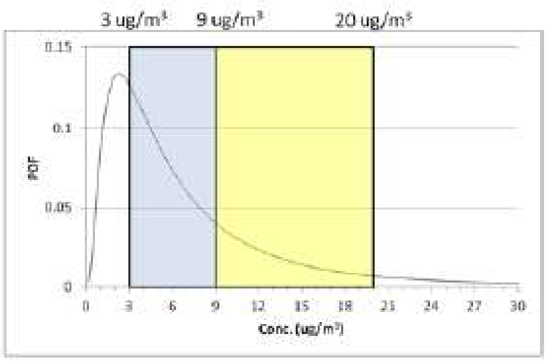
c. Confidence in the choices of critical effect, as per Section 4.

d. Confidence in the POD, as per Section 4.

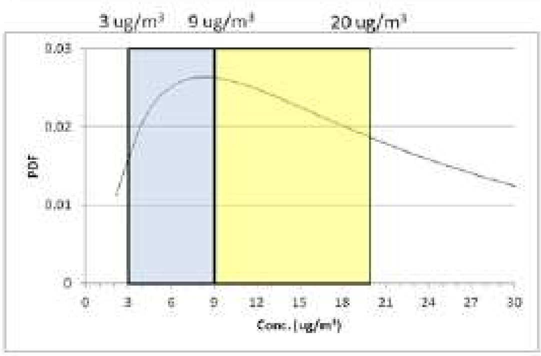
Practical Application of the Hazard Range for Noncancer Effect (e.g., TCE)



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.

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.

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

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
Chromium (VI)	3E-3	2.5	300 x 3	Low	Low	Low	3E-3	3E-2	3E-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*")

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*")

Panel and Audience Comments

- Midpoint" may not be an appropriate term, but rather a best estimate of the sensitive human LOAEL. The authors noted the intent for the "midpoint" was to identify a value that will protect sensitive populations, based upon greater understanding of uncertainty.
- When greater uncertainty exists, one might want the "midpoint" to be closer to the RfD, rather than farther. The authors noted that larger uncertainty suggests a larger range between the floor and the ceiling.
- Regardless, all agreed that it is important to clearly communicate that the value is a judgment.

More comments at:
http://www.allianceforrisk.org/Workshop/WS8/DR8_Meeting_Report_and_Appendices.pdf

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)

Summary

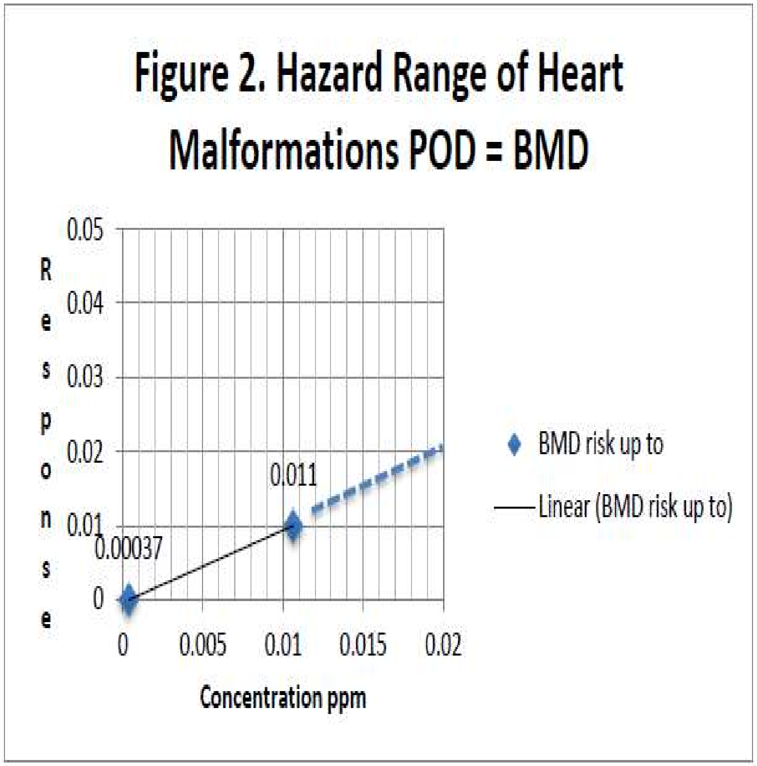
- The suggested method allows the development of a range in a non-cancer health risk value based on readily available information.
- The development of floor, midpoint and ceiling of the suggested range is consistent with the problem formulations of risk managers at waste sites. This range may be helpful with other contaminated media.
- Science Panel comments suggested several improvements including the possible integration with the work offered by Dr. Nancy Beck in the presentation on "Understanding Uncertainties and Confidence in Hazard Databases: An Example Using IRIS."

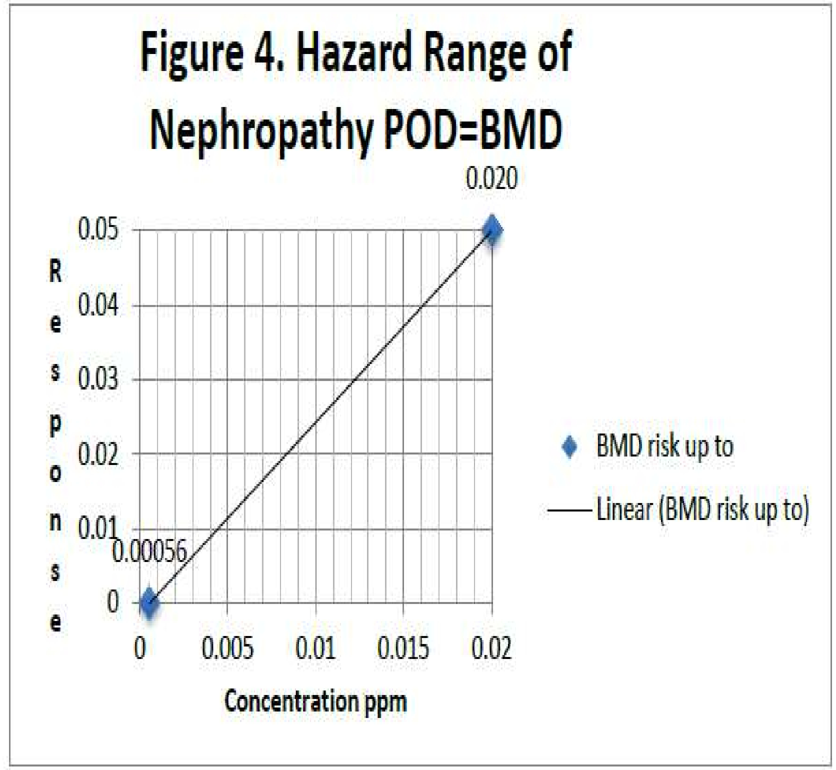
Extra Slides

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% ($BMDL_{01}$)

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





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/m³

- Decreased thymus weight endpoint
  - Midpoint of 20 μg/m³ 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

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

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

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*")

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.