Using the Non-cancer Safety Range to Develop Risk Management Options and Action Levels for TCE

Edward J. Pfau, Hull & Associates, Inc.

Michael L. Dourson, Risk Science Center at the University of Cincinnati

Rod B. Thompson, Indiana University Purdue University Indianapolis

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The Problem: Assessment and Management of Indoor Air Risks Associated with TCE

- Widely used solvent
- Common environmental contaminant
- Fate and transport in the environment
- Vapor intrusion chemical of concern
- Current Toxicity Criteria: US EPA IRIS (October 2011)
  - RfC = 0.002 mg/m^3 = 2 $\mu g/m^3$
  - Inhalation Unit Risk = 4.1×10^{-6} $(\mu g/m^3)^{-1}$

TCE Indoor Air Acceptable Exposure Levels Based on IRIS Toxicity Values (October 2011)

- Based on Residential Land Use
  - HQ = 0.1: 0.21 $\mu g/m^3$
  - HQ = 1: 2.1 $\mu g/m^3$
  - ELCR = 1×10^{-6}: 0.48 $\mu g/m^3$
  - ELCR = 1×10^{-5}: 4.8 $\mu g/m^3$
  - ELCR = 1×10^{-4}: 48 $\mu g/m^3$
- Based on Industrial Land Use
  - HQ = 0.1: 0.88 $\mu g/m^3$
  - HQ = 1: 8.8 $\mu g/m^3$
  - ELCR = 1×10^{-6}: 3.0 $\mu g/m^3$
  - ELCR = 1×10^{-5}: 30 $\mu g/m^3$
  - ELCR = 1×10^{-4}: 300 $\mu g/m^3$

Consequences of the Current 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 short-term (developmental) endpoints
- Prompt/short term exposure action levels
  - Application of lifetime RfC to subchronic and acute exposures
- Confounding effects of assessing ambient background concentrations of TCE in air

State and Regional Action Levels

State	Urgent/Immediate Action Residential	Urgent/Immediate Action Commercial	Imminent Action Residential	Imminent Action Commercial
Alaska	2	8.4		
California	6	(24)		
Connecticut	5	8		
Indiana	20			
Massachusetts	6	24	20	60
New Hampshire	2	8.8		
New Jersey	4	18		
New York	20			
Ohio	6.3	26	20	60
Region 09	6	24		
Region 10	2	8		
Region 7	2	8		

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Ohio	6.3	26	20	60
Region 09	6	24		
Region 10	2	8		
Region 7	2	8		

State and Regional Guidance on Short-term Risk Management of the RfC for TCE

- EPA Region 7: strict RfC
- New Hampshire DES: strict RfC
- EPA Region 9: HQ = 3
- California DTSC: HQ = 3
- Massachusetts DEP: UF adjustment on FCM RfC
- Ohio EPA: HQ = 3 / UF adjustment on FCM RfC
- New York DOH: implicit order of magnitude
- Indiana DEM: implicit order of magnitude

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

- **Safety Range: providing a tool for risk management with respect to the non-cancer endpoint**

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.

NAS (2009) & Hazard Assessment

- NAS (2009):
  - Suggested that methods for assessing non-cancer toxicity have the capability of determining hazard ranges.
- Alliance for Risk Assessment (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 non-cancer *risk* (at different doses)
    - Each was vetted by a Science Panel

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." [emphasis added]

Problem Response: Alliance for Risk Assessment (ARA)

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

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.

- *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.

Problem Response: Alliance for Risk Assessment (ARA)

- Refinement of the Methodology:
  - *Managing risks of non-cancer health effects at hazardous waste sites; a case study using the Reference Concentration (RfC) of trichloroethylene (TCE).*

    Dourson, M.L., Gadagbui, B.R., Thompson, R.B., Pfau, E.J., and Lowe, J.

    Regulatory Toxicology and Pharmacology **80**(2016): 125-133.

Hazard Range Development

- Hazard Range
  - Floor
  - Intermediate value
  - 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.
- **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}) based on critical dose (POD) from the toxicological study
- POD_{adj} includes 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).

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.
  - Intraspecies variability (for sensitive human subpopulations) and toxicodynamic interspecies variability are still a part of this range.
- **Value above which risk managers are likely to take regulatory action**
  - specific toxic effects can sometimes be associated with values above it, based on continuous inhalation lifetime exposures or chronic daily intakes

Hazard Range Intermediate Value

- It is a plausible estimate of the concentration or dose that is likely to be protective of the general population, including sensitive subpopulations
- 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

Hazard Range Intermediate Value

- Intermediates values 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

- Intermediate values 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

Developing the Safety Range for TCE

- In the IRIS Summary for TCE, U.S. EPA identified three candidate RfC values from principal and supporting studies for the noncancer inhalation toxicity of TCE. These are:
  - Candidate RfC of 2 $\mu g/m^3$ based on decreased thymus weight in female mice (Keil *et al.*, 2009);
  - Candidate RfC of 2 $\mu g/m^3$ based on fetal heart malformations in rats (Johnson *et al.*, 2003); and
  - Candidate RfC of 3 $\mu g/m^3$, based on toxic nephropathy in female rats (NTP, 1988).
- Each of these candidate RfCs may be evaluated with respect to the imprecision and the uncertainty inherent in its derivation.

TCE Safety Range, 2013. All values µg/m^3.

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.

Limitations of the Johnson *et al.* study and the FCM endpoint as basis for quantitative assessment of the RfC

- High rate of observations in control group
- Lack of robust dose-response relationship
- Lack of repeatability of results
- Study based on oral exposure (five other inhalation studies with negative response)
- 1% benchmark response level, HEC_{99} for point of departure in RfC derivation

Revised Safety TCE Range, 2016: All values are in µg/m^3.

Study	IRIS UF [a]	Steep [b] Slope	Confidence		Uncertainty Ranges		
			Critical [c] Effect	Point of [d] Departure	Floor	Intermediate	Ceiling
Johnson et al (2003)	10	Lower	Low	Low	2	10	20
NTP (1988)	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	100	NA	Medium	Medium to Low	2	20	190

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

Safety Range for TCE Short-Term Action Levels. All values are in $\mu g/m^3$

Study	IRIS UF [a]	Steep [b] Slope	Confidence		Uncertainty Ranges		
			Critical [c] Effect	Point of [d] Departure	Floor	Intermediate	Ceiling
Johnson et al (2003)	10	Lower	Low	Low	2	10	**20**
NTP (1988)	10	Higher	Medium	Medium to Low	3	9	30
Keil et al. 2009	100	NA	Medium	Medium to Low	2	20	190

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

TCE Short-term Action Levels

Exposure Scenario	Normal Response Action	Accelerated Response Action	Prompt Response Action
Residential			
Observed Concentrations	> 3.2 and ≤ 9.4 µg/m^3	> 9.4 and ≤ 21 µg/m^3	> 21 µg/m^3
Response Timeframe	< 1 year	< 6 months	< 10 days
Remedial Objective*	3.2 - 4.8 µg/m^3	3.2 - 4.8 µg/m^3	3.2 - 4.8 µg/m^3
Commercial/Industrial			
Observed Concentrations	> 13 and ≤ 39 µg/m^3	> 39 and ≤ 88 µg/m^3	> 88 µg/m^3
Response Timeframe	< 1 year	< 6 months	< 10 days
Remedial Objective*	13 - 30 µg/m^3	13 - 30 µg/m^3	13 - 30 µg/m^3
* upper end of remedial objective range based on cancer endpoint			

Risk Communication

- Essential component in accelerated and prompt response actions
- Engagement of public health and environmental agencies with public and stakeholders
- Safety range considerations in risk communication
  - Comparison to cancer risk range
  - Contrast with bright line of RfC
  - Association of the bright line with the threshold concentration (experimental NOEC)

Safety Range as a Risk Management Tool

- Chemical-specific evaluation
- Assessment of the uncertainty of the following factors associated with each critical study:
  - Point of departure
  - Critical effect
  - Nature of dose-response relationship
  - Magnitude of the composite uncertainty factor
- Provides a tool for quantifying the uncertainty and confidence associated with each RfD or RfC

Next Steps

- Continue dialogue regarding vapor intrusion risk assessment issues, including agencies and responsible parties.
- Study the proposed method for the noncancer safety range.
- Resolve discrepancies in TCE fetal heart findings from one lab compared with negative findings in all other labs.
- Determine appropriate averaging time for TCE concentrations.

Alliance for Risk Assessment

For more information go to:

http://www.allianceforrisk.org/Projects/TCE.html

Thank You

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