TCE Non-Cancer and Developmental Risks: Issues and Interim Resolution

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Background

- Practical Application of EPA RfC
- Risk Managers perspective
  - Need more clarity on risks and exposures, cannot communicate what numbers mean
  - Balancing is impossible
- Consequences of RfC
  - Fetal Heart Malformations is such a serious consequence of exposure
  - What short term exposure level should be used for prompt action
  - Low exposure levels 2 ug/m^3 at upper percentiles of indoor air background.
  - Commercial/residential exposures and liability

Issues

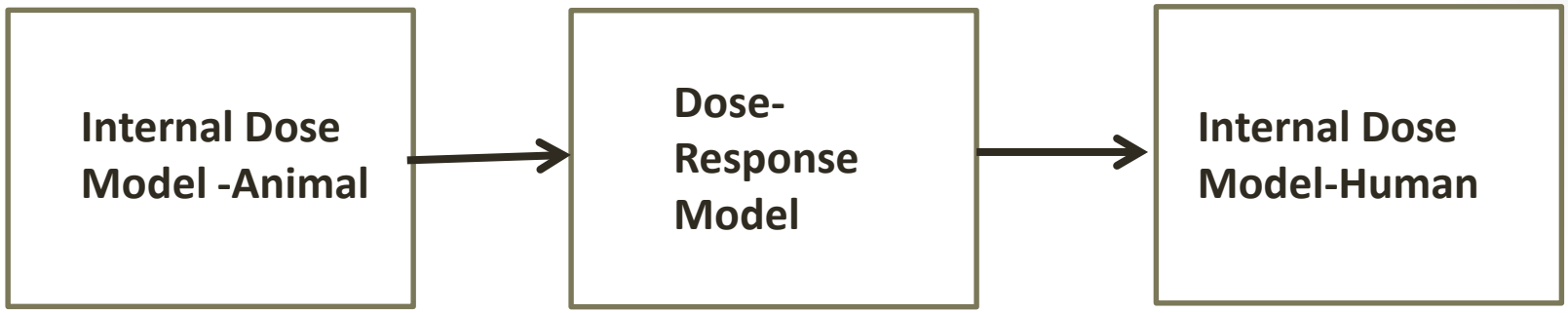
- Non-Cancer actionable risk
  - Not really a strict threshold-risk has range
  - Range concept for closure decisions is similar in concept to cancer risk range (ARA)
- Developmental risk
  - Short-term (24 hr) exposure risk levels
  - Short-term sampling methods
- Conflicting National Health Agencies Perspectives
  - Need harmonization for adequate risk communication information

Non-Cancer Risk

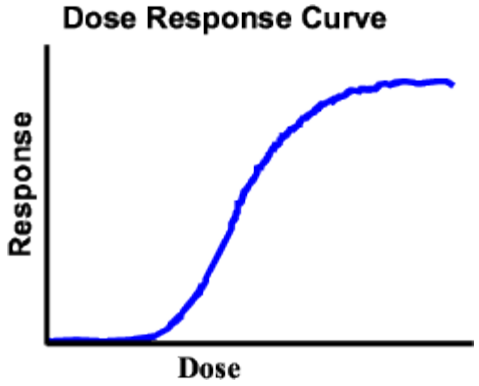
- Historically viewed Non-Cancer RfC as a strict threshold
- This is consistent with how we “used” to calculate the RfC, commonly using NOAEL from animal studies and uncertainty factors to establish “human” exposure dose

$$\textbf{\textit{Human Non} - \textit{Cancer Exposure Level}} = \frac{\textbf{\textit{NOAEL}}}{\textbf{\textit{Uncertainty Factors}}}$$

Now, RfC generally modeled value



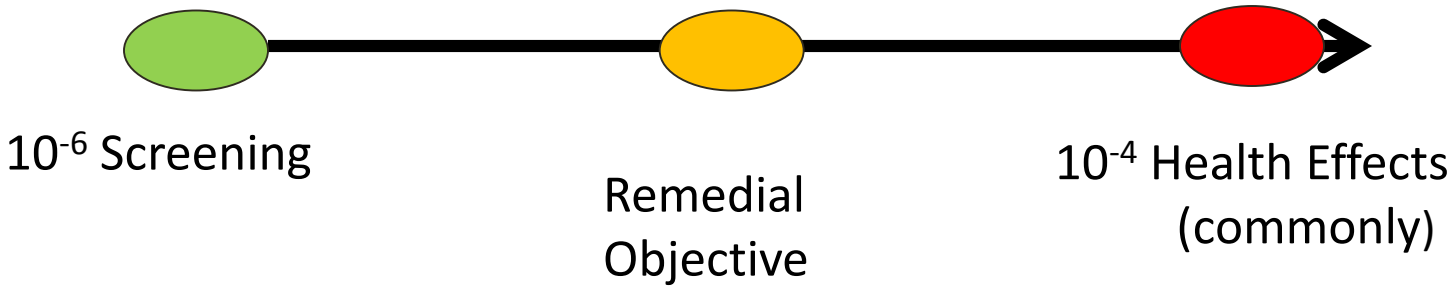
Use model to predict internal concentration as a function of applied or exposed dose



Exposure dose for humans that insures internal dose is below the selected "protective level"

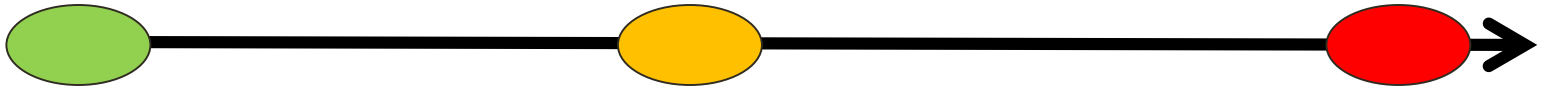
Cancer Risk Range

- **Cancer Screening, Remedial Objectives and Health Effects Level are all established using a risk range of 10^{-6} to 10^{-4}**



TCE Non-Cancer Risk Range

- **RfC defined as: an estimate with uncertainty "spanning perhaps up to an order of magnitude" of a continuous…**



2.1 ug/m^3

Non Cancer Screening

9 ug/m^3

Remedial Objectives Level

21 ug/m^3

Health Effects Level

Risk Managers perspective: What is the risk above the RfC where does the true exposure risk lie

Complete Range and Risk Management Analysis

- **Alliance for Risk Assessment: Guidance for Contaminated Sites: Trichloroethylene (TCE) Risk Assessment at:**

http://www.allianceforrisk.org/index.htm

Developmental Risk

- Acceptable short term exposure levels
  - Considerable disagreement between ATSDR, EPA-Superfund, EPA-TSCA
- Once we understand acceptable exposure levels then:
  - How to sample in a manner that characterizes the true “exposure risk”

Regulatory Comparison of Acceptable TCE Exposure Levels				
	All units in ug/m3			
Regulatory Body	Residential Short-term Action Levels	Commercial Short-term Action Levels	Residential Health Effects Level (HEC_{99})	Commercial Exposure Health Effects Level
USEPA Region 09[1] (2012)	**6**	**15**		
USEPA Region 10 (2012)	**2**	**8.4**		
New Hampshire (2013)	**2**	**8.8**		
ATSDR (resident al , 2013) Short-term action levels	**21**		**21**	
TSCA[2] (commercial, inhalation studies only 2013)				
Short-term-Developmental (R,FW)		**1,110**		**33, 320**
Short-term –Neurotoxicity		**859**		**25.796**
Chronic -Kidney				**70**
USEPA AEGLs (8 hr) (2013)	**413,816**			
ACGIH TWA (8 hr) (2010)		**53,742**		
ACGIH STEL[3] ,NIOSH 10 hr TWA (2013)		**134,356**		

ATSDR Millsboro, DE TCE Health Consultation August 2013

- "EPA's reference dose and reference concentration are both intend[ed] for comparison to chronic or longer duration exposure scenarios"
- "Of note, a suitable comparison value does not yet exist for the intermediate duration (one year or less) of exposure that was experienced in Millsboro. Therefore, ATSDR compared the estimated exposure doses with effect levels from available studies."
- ATSDR used effects levels: human equivalent dose (HED_{99}) for ingestion and the human equivalent concentration (HEC_{99}) for inhalation during showering."

ATSDR Millsboro, DE Health Consultation August 2013

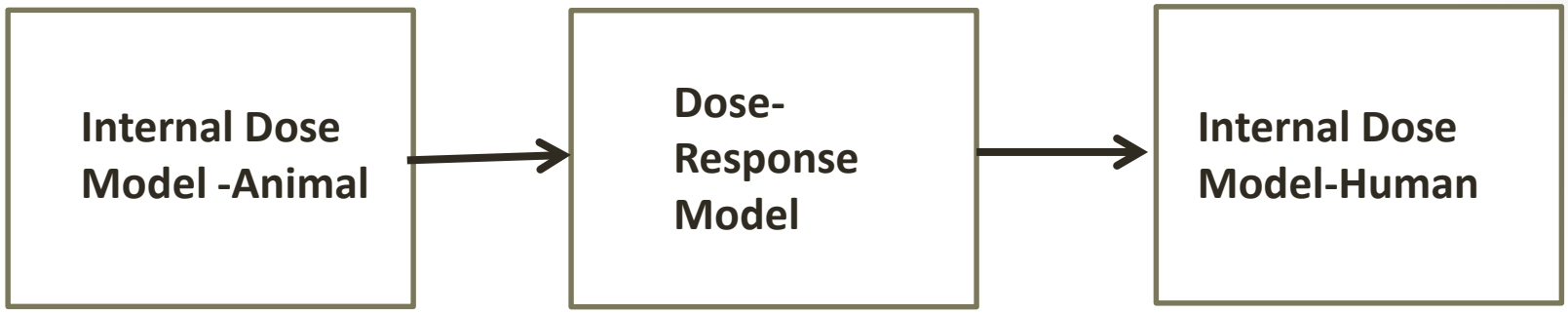
- ATSDR used one time daily shower event assumed no exposure the rest of the day and averaged a 24 hour level concluding:

"The HEC_{99} of 0.021 mg/m^3 was exceeded by all age groups ……. This suggests that there may be an increased likelihood of adverse fetal cardiac effects."

ATSDR Pohatocong Valley NJ

- " "TCE concentrations in indoor air exceeded….21 u*glm*^{3} …..
- ….pregnant workers, as well as any women of child-bearing age who become pregnant while employed at this facility, are at risk for fetal heart malformations to occur to their children."

What is HEC_{99}



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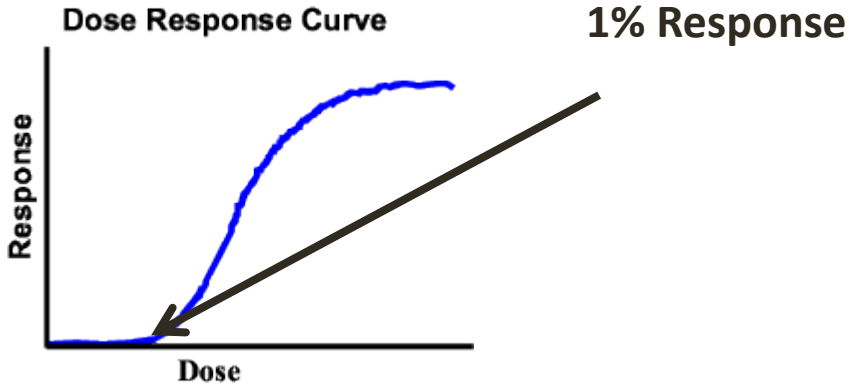


What is the human exposure concentration that will keep 99% of the human population below the 1% response rate in the animal model ($BMDL_{01}$)

What is HEC_{99}

- The HEC_{99} is the human exposure concentration for which there is a 99% likelihood that a randomly selected individual will have an internal dose less than or equal to, in this case, the $BMDL_{01}$.
- What does this mean in practical application
  - How would the 1% response rate in the animal study compare to a NOAEL
- Commonly, no less than a 5% response rate ($BMDL_{05}$) is generally equal to the NOAEL in these types of studies
- According to EPA BMD guidance the BMD selected should be near the low end of observable range of data-here BMD is a factor of 60 below the observable range.

Risk Managers Should Evaluate Margin of Safety, WOE

- TSCA in their draft light commercial risk assessment state they will only use inhalation studies
  - The study used to define 21 ug/m^3 was an oral study and the inhalation toxicity was route extrapolated
  - If one does not use the route extrapolated study inhalation studies do no show FHM as a critical effect
  - Resulting in short term exposure concentrations about 50 times greater than 21 ug/m^3 and neurotoxicity is the critical effect.
- ARA has conducted a complete analysis of the Margin of Safety and Weight of Evidence

WOE Highlights

- There are no data evidencing FHM as a critical effect by inhalation, despite several well conducted studies
- The only animal studies evidencing FHM results were conducted by a single laboratory
  - Direct attempts to duplicate the FHM study (Johnson et al 2003) results using both a subsequent oral and inhalation study were negative
- The dose response, controls and assessment relationships from Johnson et al. (2003) were particularly confounded.
- A number of well conducted epidemiology studies that do not evidence fetal heart malformations

Highlights Margin of Safety

- Using the dose response modeled 1% response rate significantly lower than NOAEL
- Using $BMDL_{01}$ as opposed to BMD_{01} is half an order of magnitude
- Using upper HEC percentile as opposed to median is half an order of magnitude
- Conservative models used successively, where the conservative output of one is the starting input to the next model, significantly increases the margin of safety

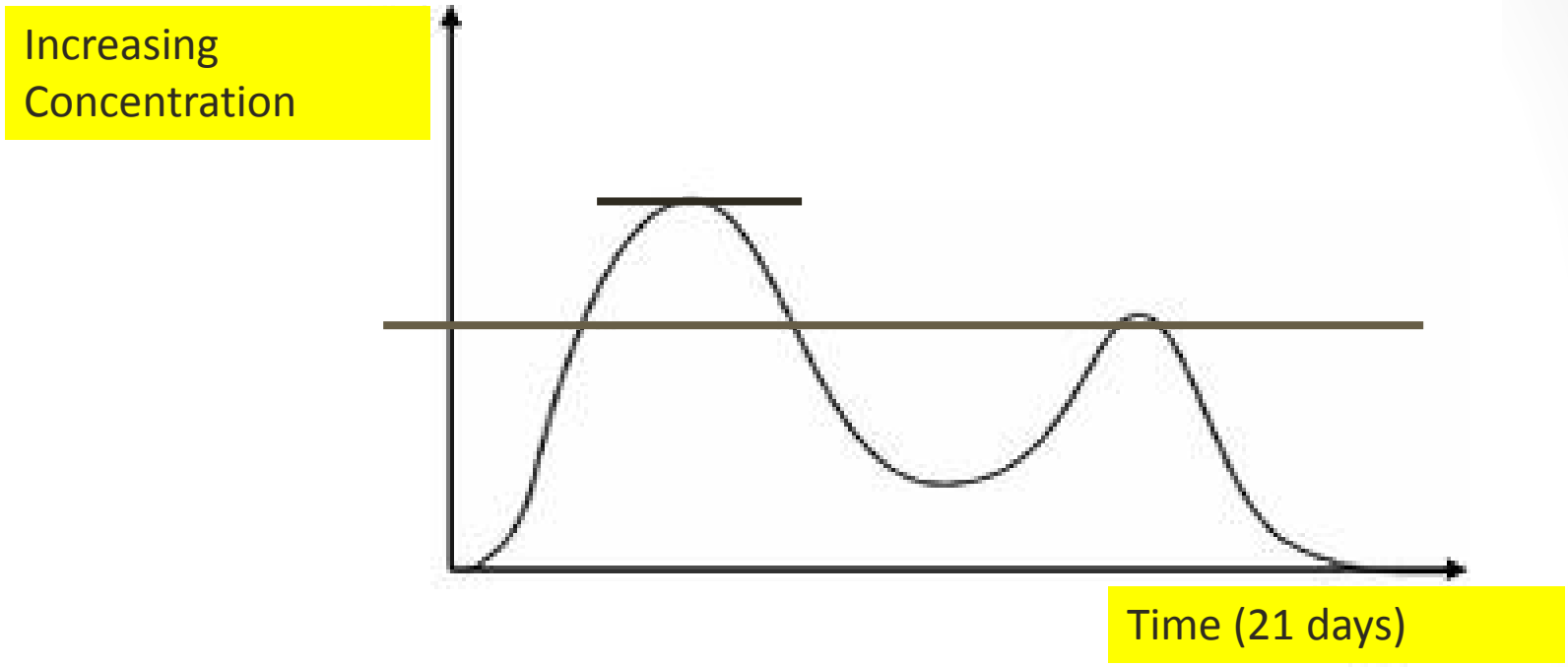
VI Sampling

- Whenever the RfC or 2 ug/m^3 is exceeded (assessed as a 24 hr average), undertake developmental risk sampling
  - EPA developmental guidance states that even a single exposure may be sufficient to cause a developmental effect
  - ATSDR makes the point that they are averaging across a 24 hour exposure period and treat the 24 hour unit as the complete exposure period (do not adjust for time away from structure, etc.)
  - The critical effect study also used 24 hour averages

VI Sampling Concerns: Duration

- Animals exposed 0-22 days (entire pregnancy) fetal heart malformations in humans occur across a 24 day window
- Thus, sampling across 2-3 week period of time should be sufficient to assess average 24 hour exposure level and peak 24 hour concentrations given indoor air variability
- Sample across more than the winter season (winter and summer)

Sampling Concerns



Continuous measurement inside structure

VI Sampling, Three (3) choices

- Deploy passive samplers for 24 or more days assume average is representative of episodes
- Take 8-10 summa canister samples
  - Compare peak 24 hr levels to 21 ug/m^3
  - Also compute UCL and compare to 21 ug/m^3
- Use a continuous recording instrument for 14-28 days.
  - Compare peak 24 hour average levels
  - Compute average and UCL of 24 hour exposures

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This and the following three slides contain references for Regulatory Comparison of Acceptable TCE Exposure Levels Table on slide 10

USEPA Region 09[1]: Information taken from Inside EPA Superfund Report Volume XXVI, No. 12-June 11, 2012 and TCE Interim Short-Term Removal Action Level White Paper prepared by Exponent and Geosyntec, April 17, 2012.

USEPA Region 09 used the RfC at 2.0 ug/m^3 and multiplied it by a 24/10 factor to simulate 10 hour commercial work day, rounded 4.8 to 5 ug/m^3 and then multiplied 5 ug/m^3 by the recommended factor of 3 from the USEPA 2008 Remedial Action Level (RAL) Memo. In the USEPA RAL Memo an HI of 3 for removal actions is used. A residential immediate action level of 6 ug/m^3 could be derived similarly for comparison by using the RAL memo recommendation for an HI of 3 x 2 ug/m^3.

USEPA Region 10 values taken from Dec 12, 2012 Memorandum: OEA Recommendations Regarding Trichloroethylene Toxicity in Human Health Risk Assessments

TSCA: Data taken from TSCA Workplan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses CASRN: 79-01-6 Ethene, 1,1,2-trichloro. This is considered a "light commercial exposure."

Here TSCA used a margin of safety approach to make risk management recommendations. Similar to ATSDR, TSCA used the HEC_{99} as the effects level.

However, TSCA used only data from the inhalation studies. TSCA did not use the USEPA 2011 TCE oral to inhalation modeling extrapolations in their risk assessment.

Health effects levels were divided by the Exposure levels and then compared to a Margin of Exposure (MOE) of 30 to determine acceptable risk. MOE based on a factor of 10 for intraspecies variability times an uncertainty and a factor of 3 for the pharmacodynamic portion of the interspecies extrapolation factor; the latter being reduced based on the kinetic modeling performed to arrive at an HEC (at page 61 of TSCA Risk Assessment)

The use of the MOE is conceptually similar to standard USEPA practice of using uncertainty factors in the derivation of the RfC. Using the following equation:

$$\textbf{MOE}_{\text{acute or chronic}} = \textbf{Hazard value (POD)/Exposure value}$$ (pg 60)

The acceptable exposure screening level is determined by dividing the POD by the MOE (POD/MOE = Acceptable Exposure Level).

Acute levels taken from the lowest HEC_{99} from acute studies listed in TSCA conceptually consistent with the ATSDR Millsboro approach (see slide 10).

AEGL-1 information from http://www.epa.gov/oppt/aegl/pubs/define.htm is the airborne concentration, expressed as parts per million or milligrams per cubic meter (ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. TCE has Interim AEGLs 77 ppm is most sensitive or all the AEGL categories. Note that "AEGLs are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals"

ACGIH STEL is short term exposure limit from 2010 ACGIH published values; ACGIH TWA is from same reference.
Agrees with or less than NIOSH 10 hr. TWA see:
http://www.cdc.gov/niosh/npg/nengapdxc.html

New Hampshire values taken from February 7, 2013 Waste Management Division Update RE: Revised Vapor Intrusion Screening Levels and TCE Update

ATSDR Health Consultation Millsboro TCE Millsboro Delaware. February 13, 2013 U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry Division of Community Health Investigations Atlanta, Georgia 30333

At page 20: “Of note, a suitable comparison value does not yet exist for the intermediate duration of exposure that was experienced in Millsboro. Therefore, ATSDR must compare its estimated 24-hour concentrations with effect levels from available studies.

Also at page 20: …..“to obtain a 99th percentile HEC99 of 0.021 mg/m3” and at page 21: “ATSDR compared the preceding HEC99 with the estimated 24-hour average concentrations for men, women, and children at the Millsboro site to evaluate the potential for adverse health effects resulting from past [intermediate duration] exposure while showering “