Ed Pfau

HULL & ASSOCIATES, INC.
DUBLIN, OHIO

Alliance for Risk Assessment

Building a Risk Assessment Community

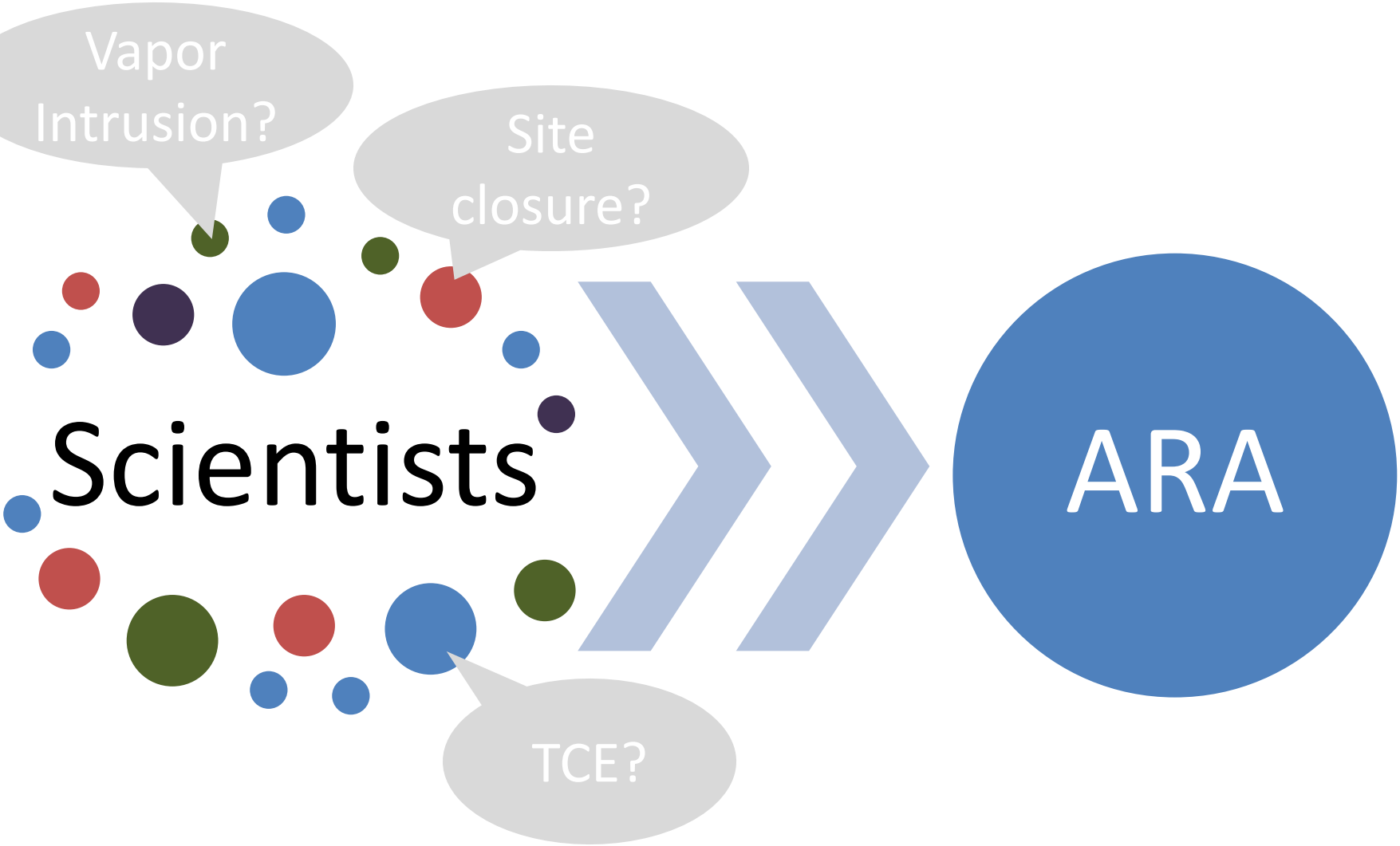
ARA Partners

Concurrent Technologies Corporation

Guiding Principles

- Promote science-based decision making.
- Enhance harmonization and consistency in risk assessments… *through an open, transparent, multi-stakeholder approach.*
- Maintain access to risk assessment experts not normally available within an organization.
- Increase the capacity and quality of risk values by…… *sharing costs, information, and human resources.*

Working together to solve complex issues



RiskIE

Risk Information Exchange

www.allianceforrisk.org/RiskIE.htm

- The **only** place to keep up with In-Progress Risk & Toxicity Assessments
- Includes over 5500 projects being conducted by more than 30 organizations representing 13 countries
- **Free** for anyone to contribute and use

How does ARA select projects?

Steering Committee Considerations:

- Is the project likely to benefit public health?
- Who else is working on this issue?
- Are there any clear conflicts of interest or ethical issues to be considered?

ARA Steering Committee

- **Anita Meyer**, United States Army Corps of Engineers
- **Annette Dietz**, Oregon Department of Environmental Quality
- **Edward Ohanian**, United States Federal Employee
- **Michael Dourson**, Toxicology Excellence for Risk Assessment
- **Michael Habeck**, Indiana Department of Environmental Management
- **Michael Honeycutt**, Texas Commission on Environmental Quality
- **Ralph Perona**, Neptune & Company, Inc.

Emeritus

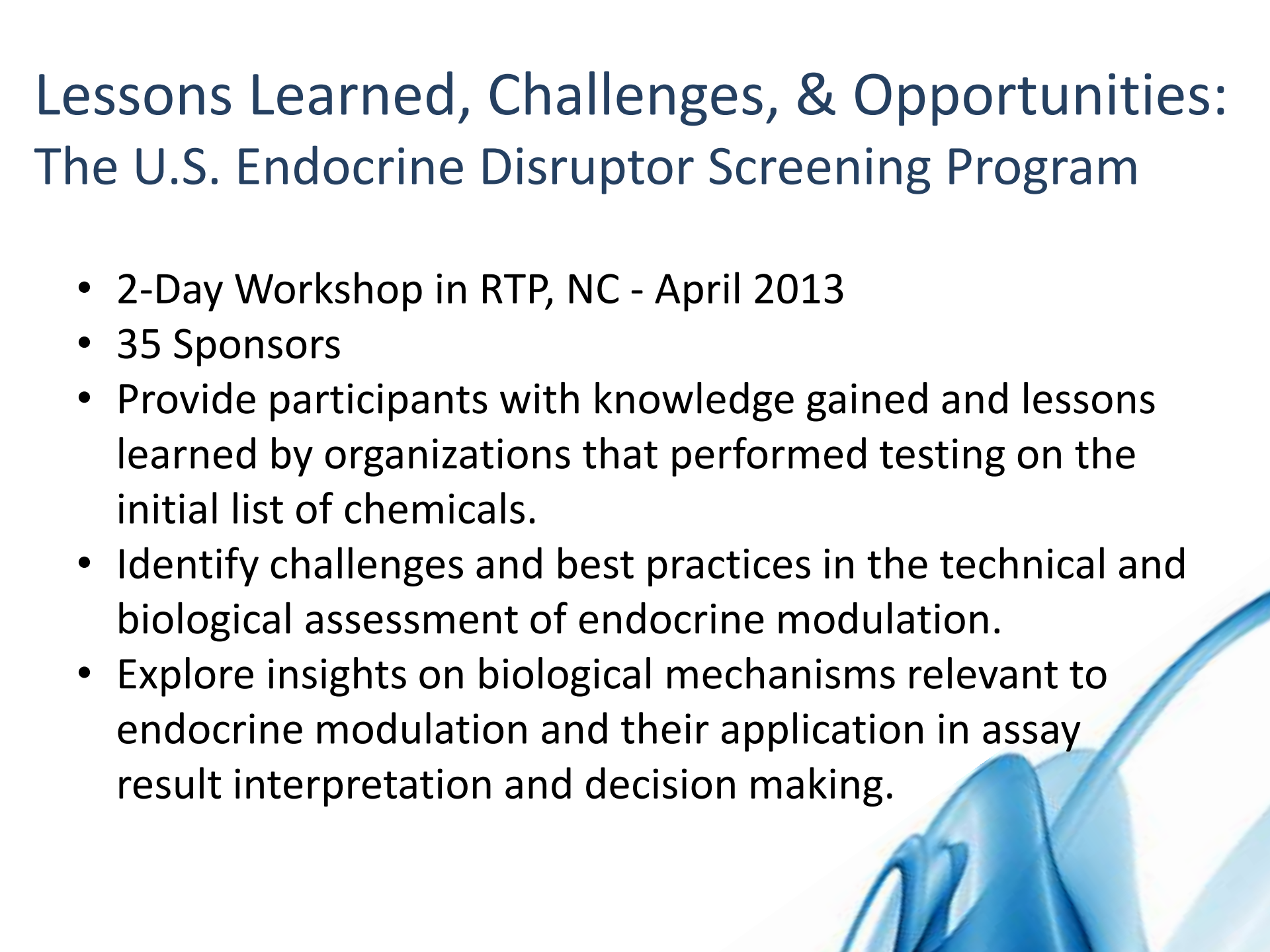
- **Barbara Harper**, Confederated Tribes of the Umatilla Indian Reservation
- **William Hayes**, State of Indiana
- **Bette Meek**, University of Ottawa/Health Canada
- **Ruthann Rudel**, Silent Spring Institute
- **Phil Wexler**, National Library of Medicine (NLM)

* Affiliations are for identification purposes only.

Examples of Projects

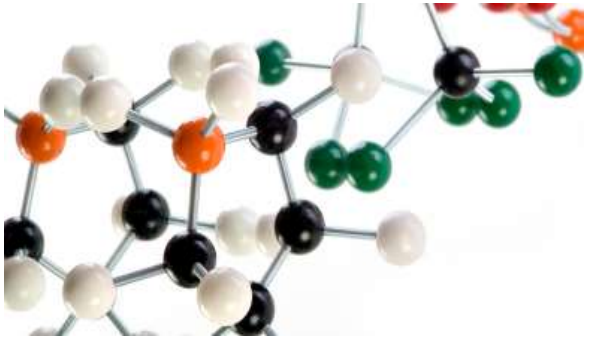
Lessons Learned, Challenges, & Opportunities:
The U.S. Endocrine Disruptor Screening Program

- 2-Day Workshop in RTP, NC - April 2013
- 35 Sponsors
- Provide participants with knowledge gained and lessons learned by organizations that performed testing on the initial list of chemicals.
- Identify challenges and best practices in the technical and biological assessment of endocrine modulation.
- Explore insights on biological mechanisms relevant to endocrine modulation and their application in assay result interpretation and decision making.



Beyond Science and Decisions:

Problem Formulation to Dose-Response



- Ongoing workshop series since 2010
- 55+ Sponsor Organizations
- Workshop discussions build on the recommendations of NAS (2009) Silverbook
- Science Panel reviews risk methods case studies, with focus on problem formulation, and “fit-for-purpose” risk assessment
- Developing a risk methods framework to help risk assessors navigate evolving methods – chemicalriskassessment.org/methods

56 sponsors and collaborators:

- 13 government agencies
- 19 industry groups
- 7 scientific societies
- 9 non-profit organizations/consortia
- 8 consulting groups

OUTREACH

KidsChemicalSafety.org

- Balanced, scientifically accurate chemical health information
- 8 partner organizations
- Fueled by reader submitted health questions

StateHELP

- State Hazard Evaluation Lending Program – 10 hours of pro bono risk issue assistance annually
- Currently assisting Wyoming Dept. of Environmental Quality with the use of a surrogate in a site clean up

Peer Review

- Interdisciplinary Panel review of risk science
- Example: Carcinogenic Potential of Hexavalent Chromium for Texas Commission on Environmental Quality

ITER

International Toxicity Estimates for Risk

www.tera.org/iter or
http://toxnet.nlm.nih.gov/

Database of chronic human health risk values and cancer classifications from organizations around the world for 700+ chemicals

- Risk value data in a side-by-side table format
- A synopsis that explains the underlying basis and rationale for each risk value and differences in risk values
- A link to each organization's website or source document
- A forum through which independent parties can share their peer reviewed risk values
- A resource to ensure that risk managers do not "miss" useful data

Collaboration brings:

Credibility

Publicity

Efficiency

allianceforrisk.org

Oliver Kroner

kroner@tera.org

513.542.7475 x.19

The Practical Risk-Based Implications of Trichloroethylene Regulation

Alliance for Risk Assessment Webcast
Practical Guidance for Contaminated Sites:
Trichloroethylene (TCE) Risk Assessment Case Study
November 4, 2013

Rod Thompson
Alliance for Site Closure

TCE Three Major Issues

- TCE Non-Cancer (RfC) exposure risk is often greater than cancer risk (10^{-5})
  - Results in major changes to the way exposure risk is assessed and regulated
- TCE non-cancer critical effects include fetal heart malformations
  - RfC is used to evaluate chronic exposures
  - Developmental critical effects may occur over a 21 day time period
    - Results in concerns with exposures that are less than chronic
- Risk Communication difficult
  - No practical guidance and widespread national disagreement

TCE RfC Non-Cancer Risk

- TCE has both a cancer toxicity and non-cancer toxicity
- Determine acceptable exposure levels such as screening levels using nationally accepted algorithms or equations (RSLTs)
- When developing acceptable regulatory exposure levels, both a cancer and a non-cancer value are calculated and the lesser of the two is used

Screening and Closure
Cancer and Noncancer Endpoints

- Exceeding any screening level triggers investigation….
  - Investigate nature and extent
  - Assess exposure population, levels and determine risk
  - Make Risk Management decision on acceptable exposure levels (remedial objectives)

Risk Management Cancer-Noncancer Closure decisions

- Commonly risk managers use a 100 fold cancer risk range with which to "bound" risk management closure decisions (10^{-6} to 10^{-4})
  - **TCE 0.43 ug/m^3 to 43 ug/m^3 (factor of 100)**

Now, TCE Risk Management range is bounded by the RfC non-cancer endpoint,

- **0.43 ug/m^3 to 2.1 ug/m^3 (factor of 5)**

- The RfC is used to derive the upper end of the risk management range at 2.1 ug/m^3
  - This value is often used as the absolute upper end of the risk management decision range.

Risk Management of Cancer-Noncancer Closure decisions

- Historically, non-cancer effects have been viewed as a threshold response , i.e., “an on-off switch”
- In the past RfC generally determined by first taking animal data and establishing a “No Observed Adverse Effects Level”
- Then, NOAEL extrapolated to humans using uncertainty factors which became the RfC
- Generally assumed exceeding this would cause adverse effects (potentially).

Risk Management of Cancer-Noncancer Closure decisions

- RfC never intended to be a “bright line” due to implicit uncertainty, even when based on a NOAEL threshold response
- Now we commonly use mathematical “probability based” models
  - To determine the internal dose in the animal
  - To determine a response rate in the animal
  - To extrapolate internal dose to humans

Cancer, Non-cancer Decisions

- Because bright line never intended and given new probabilistic approach to the RfC

- What does IRIS mean when it states:

"The RfC is an estimate (**with uncertainty spanning perhaps an order of magnitude**) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Non-cancer risk

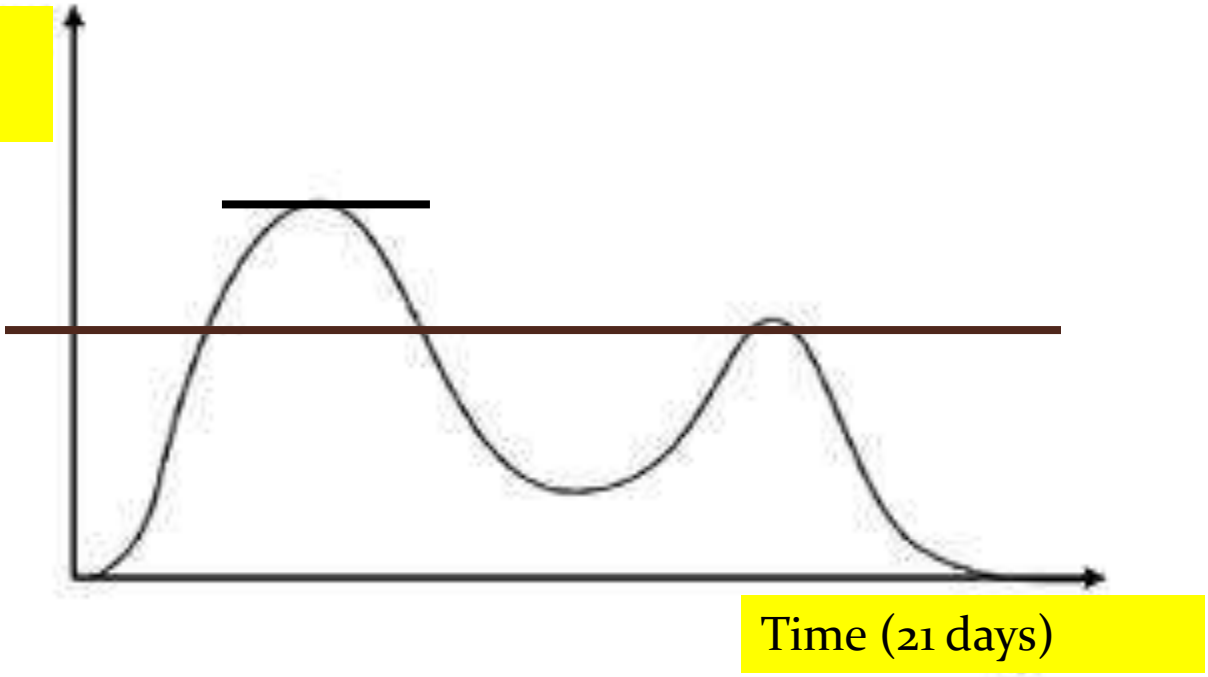
- Answering the order of magnitude question also addresses:
  - What does the RfC, or values slightly above the RfC really mean relative to the "risk" of a toxic effect?
  - What is the margin of safety?
    - Additional safety factors used in RfC derivation
  - What is the weight of evidence
    - Toxic effect is seen in the human population
    - Repeatable in the animal population?

Risk Communication

- Important to note screening levels are not generally considered the final acceptable remedial objectives or "Closure Exposure Levels"
- Challenge in communicating the risk of a non-cancer toxic effect and exposure levels
  - Screening versus closure
  - What is the risk if RfC is slightly exceeded?
- Vapor Intrusion
  - Indoor Air Background
  - Screening levels

Developmental Risk

- EPA two primary critical effects in RfC
- Study used to define developmental risk dosed animals for 21 days
- USEPA RfC derived a lifetime (chronic) value from the 21 day study
- What is shorter term risk-if exposure occurred over 21 days in rats then could a similar toxic effect occur over 21 days (or less) in humans?



Continuous measurement inside structure

Developmental Risk

- At what concentration and over which time frame should we be concerned about developmental toxic effects
  - Average chronic (≥ 7 years, *i.e.*, 10% human lifespan)
  - Average over short period of time (21 days)
  - Peak Value instantaneous or for some extended period of time (1 hour, 24 hours, 21 days)
- 21 day window for a pregnant female at home is same as pregnant female at work

Developmental-Residential versus Commercial

- Typically, residential default exposure is assumed to occur
  - 24 hrs/day,350 days/yr, 30-70 years
- By contrast commercial default exposure is assumed to occur
  - 8 hour day-250 days per year (5 days/wk x 50 wks), 25 years
- Example: Residential at 2.1 and Commercial at 8.8 ug/m^3
  - Is it a safe assumptions to increase residential exposure levels to commercial and still protect against developmental toxic effects

Developmental Endpoint

- A very controversial and pivotal study was used to define the dose-response for fetal heart malformations
  - Oral to inhalation extrapolation
  - USEPA RfC derivation process changes may be inconsistent with commonly accepted science for developmental toxicity assessments

New RfC Evaluation Criteria

- Animal inhalation studies do not list fetal heart malformations as critical effect
  - TSCA defines kidney toxicity as most sensitive chronic risk from inhalation and;
  - Neurotoxicity, resorptions and reduced fetal weight for acute risk from inhalation
- Widespread regulatory differences in how, or if, short term exposure developmental risk should be addressed

Conflicting State and Federal Guidance

- Regional/States
  - Regions 9 and 10 have each issued Short Term exposure guidance
  - Regions 9 and 10 each use different action levels
  - New Hampshire
- Other National Health Agencies
  - ATSDR has published at least two public health assessments where they have publically determined an intermediate exposure "effects level" at 21 ug/m^3
  - TSCA light commercial risk assessment completely avoided oral extrapolations used only inhalation studies and effects levels
- Industrial/NIOSH/AEGLs/ACGIH

Regulatory Comparison of Acceptable TCE Exposure Levels					
		All units in ug/m3			
Regulatory Body		Residential Immediate Action Levels	Commercial Immediate Action Levles	Health Effects Level (HEC_{99})	Residential Screening Levels
USEPA Region 09[1] (2012)		6	15		0.43
USEPA Region 10 (2012)		2	8.4		0.2
New Hampshire (2013)		2	8.8		0.4
ATSDR (resident , 2013)				21 (intermediate)	
					2.1 (MRL)
TSCA[2] (commercial, inhalation studies only 2013)					
Acute -Developmental (R,FW)			1,110	33,320	
Acute -Neurotoxicity			859	25,796	
Chronic -Kidney				70	2.3
USEPA AEGLs 1 (8 hr) (2013)		413,816			
ACGIH TWA (8 hr) (2010)			53,742		
ACGIH STEL[3] ,NIOSH 10 hr TWA (2013)			134,356		

Rod Thompson
Regulatory Toxicologist
317-691-9857
rodbthompson@comcast.net

This and the following three slides contain references for Regulatory Comparison of Acceptable TCE Exposure Levels Table on slide 18.

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. The residential immediate action level of 6 ug/m^3 was 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[2]: 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:

$$\mathbf{MOE}_{\text{acute or chronic}} = \mathbf{Hazard\ value\ (POD)/Exposure\ value}$$ (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 23).

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 “

TCE Vapor Intrusion: Risk Communication and Management

Lenny Siegel

Center for Public Environmental Oversight

Guidance for Contaminated Sites: TCE Risk Assessment

November 4, 2013

- For now EPA's IRIS values for TCE are the law of the land—including the Reference Concentration for developmental risk.
- Public has a weak understanding of risk.
- Spatial and temporal variability drive sampling strategies.
- Short-term risk requires new monitoring technologies and/or pre-emptive mitigation.

The public is diverse.

- Some are worried about property values.
- People are concerned about the health of children.
- Trust is central.
- Few pay attention to the numbers.

Key Messages of Risk Communication

- Failure to notify builds mistrust.
- Effort counts.
- No pathway, no risk.
- Exceeding protective standards doesn’t mean people will get sick.
- “Added risk” vs. causality

Sampling

- Once or twice a year in a fixed location is not enough.
- May be more costly than mitigation.
- Real/Near-Real-Time sampling is the wave of the future.
  - Believable if quality controlled/assured
  - Identify pathways and indoor sources.
  - Catch peaks that could cause short-term risk.

Risk Management

- Personal Risk Management is a right.
- Starting point should be reducing exposure to background.
- Depressurization better description than ventilation.
- Pre-emptive mitigation is a no-brainer for new construction.
- Pre-emptive mitigation may be cost-effective for existing buildings.
- Source remediation is the long-term solution.

Long-Term Monitoring

- Must not be ignored.
- Entropy: Buildings tend to get worse.
- Source term may vary.
- Cost-effective strategies necessary to promote voluntary pre-emptive mitigation.
- Real-time or indirect measurement valuable (TCE, radon, pressure).

E-mail me or give me your card if you want to join CPEO's free *Brownfields Internet Forum* and/or *Military Environmental Forum* newsgroup.

Lenny Siegel

Center for Public Environmental Oversight

c/o PSC, 278-A Hope St., Mountain View, CA 94041

Voice: 650/961-8918 — Fax: 650/961-8918

lsiegel@cpeo.org — http://www.cpeo.org

Perspective on Developing and Recommending Human Toxicity Benchmarks and Risk Management Support

Alliance for Risk Assessment Webcast

Practical Guidance for Contaminated Sites:

Trichloroethylene (TCE) Risk Assessment Case Study

4 November 2013

Tania Onica

Standards Development Branch

Ontario Ministry of the Environment

Ontario

Purpose and Overview

The purpose of the this presentation is to discuss:

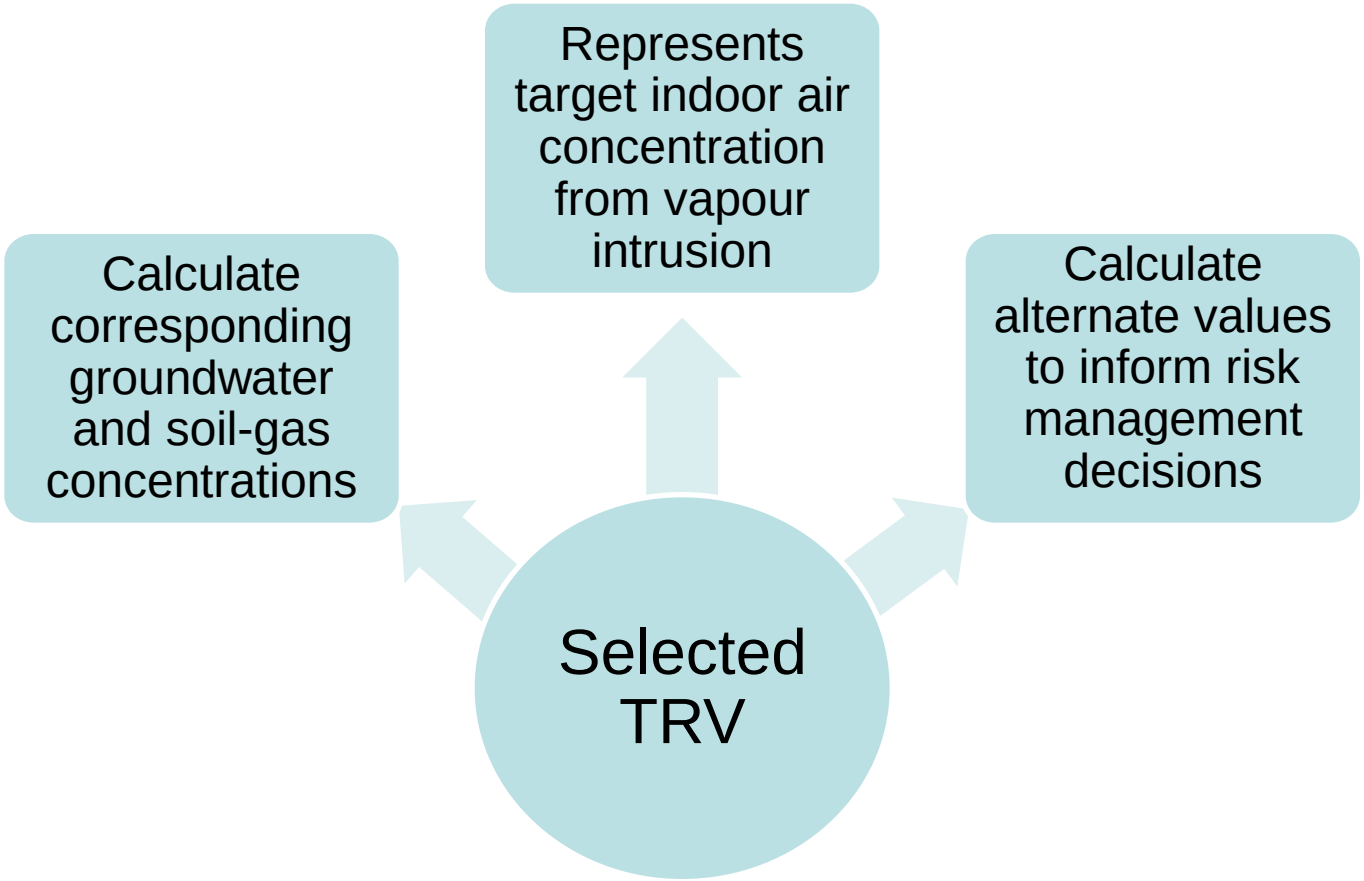
- The development and recommendation of human toxicity benchmarks for assessment and management of community contamination cases where vapour intrusion from subsurface contamination is considered a potential exposure pathway
- The review and selection of the cancer- and non-cancer based values developed by the US EPA for trichloroethylene
- Considerations for risk management response and stakeholder communication

Vapour Intrusion Assessment:
Human Toxicity Benchmarks

- SDB reviews scientific studies and approaches of other jurisdictions to set benchmarks (called Toxicity Reference Values, or TRVs) for contaminants at concentrations that reflect negligible risk
  - For cancer, the TRV is equivalent to one in one million (10^{-6}) incremental lifetime cancer risk
  - For non-cancer effects, the TRV is the concentration at which no adverse effects are expected over a lifetime

- The TRV serves as the basis for assessment of exposure information related to vapour intrusion

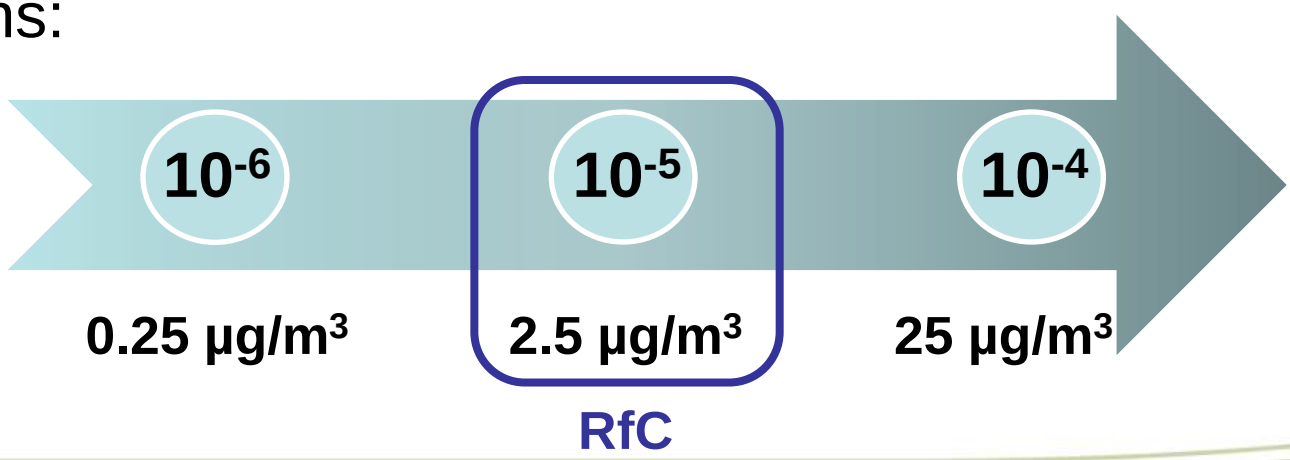
Vapour Intrusion Assessment:
Human Toxicity Benchmarks



Ontario

Residential Indoor Air Program:
Trichloroethylene (TCE)

- SDB recently reviewed the US EPA analysis of TCE and selected:
  - the 10^{-6} risk specific concentration of 0.25 µg/m^3 (cancer)
  - the RfC of 2 µg/m^3 (developmental- & immunotoxicity)
- Interpreting toxicity information to inform risk management decisions:



Ontario

Trichloroethylene (TCE)
Developmental Toxicity-Based RfC

- Cardiac malformations during early fetal development as a result of maternal TCE exposure appears to be well supported:
  - Observed across multiple species
  - Observed from both inhalation and drinking water exposures
  - Emerging mechanistic data
- The Canadian Drinking Water Quality Guideline (introduced in 2005) and later adopted as the Provincial Drinking Water Standard for TCE is based on cardiac malformations

Trichloroethylene (TCE)
Developmental Toxicity-Based RfC

- Discussion proposals:
  - Given the debate surrounding the fetal cardiac endpoint, what is the appropriate WOE required to support its use?
  - There is some concern that the concept of the "uncertainty surrounding a toxicity value" may be construed by some as being a default rationale for a less stringent risk management response. We propose touching on this point, given the default definition of an RfC being:

> *"An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of a chemical to the human population through inhalation (including sensitive subpopulations), that is likely to be without risk of deleterious noncancer effects during a lifetime."*

Developmental Toxicity-Based RfC
Implications for Risk Management

- Application of the RfC of 2 µg/m^3 may reduce flexibility in the risk management response relative to a critical effect observed after longer exposures (e.g. cancer)
  - However, application of the RfC is thought to be warranted due to:
    - Critical window of exposure during heart formation (~ 3 weeks)
    - Severity of effect
- Challenge of Limited Monitoring Data
  - RfC can be used to inform or prioritize risk management decisions even in data limited scenarios if measurements suggest that the RfC has been exceeded

Developmental Toxicity-Based RfC
Implications for Risk Communication

- Challenges to effective stakeholder communication
  - Audiences may lack toxicological expertise
  - Sensitivity surrounding fetal health
  - Limited exposure data
  - Sensitivity surrounding involuntary exposures
  - RfC often interpreted as a bright line between “safe” and “unsafe”

Work towards providing quantitative interpretations of risk

Developmental Toxicity-Based RfC
Implications for Risk Communication

- Quantitative interpretations of risk at concentrations above the RfC
  - \+ Better informs stakeholders
  - \+ Increases flexibility in risk management response
  - \+ Transparent, based on desired levels of protection
  - \- Some agencies lack capacity to carry out quantitative analysis

- For Discussion: using alternate points of departure (e.g. the 95% lower CI of the HEC_{50} or the HEC_{50} central tendency estimate)* to develop "provisional RfCs"

*W. Chiu, US EPA, personal communication, October 2012 and August 2013

Geosyntec consultants

Practical Guidance for Contaminated Sites: TCE Case Study

Practical Application Overview: Regulatory Background and Consultant Perspective

National Webinar: November 4, 2013

Helen Dawson, Ph.D.
Senior Consultant
Hdawson@Geosyntec.com

Geosyntec consultants

Timeline of EPA Activities Related to TCE Toxicity Assessment

- 1985 – EPA posts TCE health assessment in IRIS
- 1989 – Withdrawn from IRIS
- 2001 – Draft EPA TCE health assessment for review
- 2006 – NRC review report
- 2009 – Revised draft EPA TCE toxicity review
- 2011 – EPA SAB, 21-member external panel review report
  - "The Panel … recommended that the endpoints for immune effects from Keil et al. (2009) (decreased thymus weights) and Peden-Adams et al. (2009) (developmental immunotoxicity) and the cardiac malformations from Johnson et al. (2003) be considered as the principal studies supporting the RfD. (Page 4, SAB panel report).
  - The Panel also noted some "recent publications confirm and reinforce the results obtained in the Johnson et al. (2003) study and could be cited to make a stronger argument." (Page 16, SAB report)
- 2011 – EPA posts revised TCE health assessment in IRIS
  - Includes chronic RfD/RfC derived using SAB recommended studies

Geosyntec consultants

Implications of the IRIS TCE RfC on VI Assessment and Mitigation

- The application of EPA's IRIS TCE RfD/RfC values to less than lifetime exposures arises from concern that:
  - a single exposure at a critical time in development may produce an adverse developmental effect (EPA-RAF 1991), and
  - chronic exposure is not a prerequisite for developmental toxicity to be manifested" (EPA 1989, RAGS Part A).

Implications of the TCE RfC on VI Assessment and Mitigation

- Risk Assessment
  - Time frame for assessment:
    - Assessing potential risks (especially future upper bound concentrations) with standard VI assessment approach (e.g., 24-hr Summa canister samples) is difficult.
    - Need rapid assessment technologies capable of estimating maximum likely exposures.
  - Inherent variability of indoor air concentrations
    - We already we have to deal with that variability when assessing long-term exposures.
    - We now have to consider maximum values over a limited time frame, rather than average values over a longer time frame.

Implications of the TCE RfC on VI Assessment and Mitigation

- Risk Management
  - Non-cancer threshold levels:
    - Time frame of critical exposure has little impact on levels.
    - Residential setting: threshold level (HQ=1) is 2 $\mu g/m^3$ whether a day, weeks, or a year are used as the time frame of exposure.
    - Commercial settings: threshold level (HQ=1) ranges from about 6 to 9 $\mu g/m^3$ depending on work day.
  - Final cleanup levels:
    - Final site cleanup values typically are based on cancer risk
      - Residential settings – typically have been around 1 $\mu g/m^3$
        Commercial settings – typically have been between 5 and 10 $\mu g/m^3$ for commercial settings where TCE not used in workplace.
    - Future final cleanup values are likely to be similar.

Implications of the TCE RfC on VI Assessment and Mitigation

- Risk Mitigation
  - Options for mitigating risk
    - Depend on risk management decisions
    - Time frame for implementing response actions
  - Engineered controls
    - Building Ventilation
    - HVAC System Modifications (Building Pressurization)
    - Passive Vapor Barrier (membranes and seals)
    - “Radon System” (Sub-slab Depressurization)
    - Aerated Flooring
  - Institutional controls

BARNES & THORNBURG LLP

Practical Guidance for Contaminated Sites: TCE Case Study

Practical Application Overview: Business Perspective

National Webinar: November 4, 2013

David R. Gillay, Esq.

Partner, Environmental Department

Overview

- Dramatic Ripple Effect
  - After 20 years, PCE and TCE toxicity updates
  - Federal programs
- Brownfield & Economic Redevelopment
  - Due Diligence
  - Cleanup/Closure
- Liability Implications
  - Risk Communication
  - Toxic Torts
- Managing liability in future
  - Pre-emptive mitigation for VI exposure pathway
  - IC Plan or Stewardship Agreement

Overarching Changes

- Harmonizing Federal Environmental Programs
  - RCRA: Final rule on solvent-contaminated wipes, shop rags, and towels (Effective Jan. 2014). Note that disposable wipes contaminated with TCE are ineligible for the exclusion.
  - RCRA – "contained in" policy for hazardous wastes
  - TSCA Chemical Risk Assessment for TCE: Degreaser and Arts/Crafts Uses. http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPPT-2012-0723
  - ATSDR: Updated Toxicity Profile for TCE (Jan. 2013) *CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years"*

Overarching Changes

- Harmonizing Federal Environmental Programs

  - OSWER/Superfund Program
    - Draft Vapor Intrusion Guides (Apr. 2013)

      Where the aggregated carcinogenic risk to an individual based upon a reasonable maximum exposure condition for both current and future land use is less than one per ten thousand (i.e., 10-4 or one hundred per million) and the noncancer HI is less than 1, response action is generally not warranted for vapor intrusion. (Sec. 7.4)
    - TCE Short Term Indoor Air levels – Regional Screening Levels, NCEA work; EPA HQ
    - Five Year Reviews - remedy and risk assessment
  - OSHA : General Duty Clause; HazCom Programs

Brownfield Redevelopment

- Brownfield Amendments (2002) add important landowner liability protections; can buy with knowledge o of contamination and not be liable for cleanup

- Threshold Test – Conduct All Appropriate Inquiry
  - ASTM adopts new Phase I ESA Standard E1527-13
  - vapor migration/encroachment

- Post- Closure Continuing Obligations
  - *Prevent or limit any human, environmental or natural resource exposure to any previously released hazardous substances.*

Liability Implications

- Re-opening of closed Sites
- Risk Communication
  - Getting access to assess risk
  - how to explain the use of ranges for RfC
  - history of TCE over past 10 years; (1 - 11 ug/m3); now 2.1 ug/m3 over a matter of hours or days?
- Toxic Tort Suits
  - Bodily injury
  - Property damage

• TCE will drive groundwater screening levels below MCL; EPA policy on technical impracticability under review.

Managing Liability

- Pre-emptive mitigation for VI pathway (TCE driver).
- In most States, ICs are generally necessary unless the site meets unlimited use and unrestricted exposure.
- EPA's *NEW* National Policy on Use and Roles of ICs is to develop an IC Plan or long-term Stewardship Plan:
  - *Institutional Controls: A Guide to Planning, Implementing, Maintaining, and Enforcing Institutional Controls at Contaminated Sites*, EPA-540-R-09-001 (Dec. 2012) [referred to as the "IC Guidance"]
  - *Institutional Control: A Guide to Preparing Institutional Control Implementation and Assurance Plans at Contaminated Sites*, EPA-540-R-09-002 (Dec. 2012) [referred to as "ICIAP Guidance" or "IC Plan"]

Questions or Comments

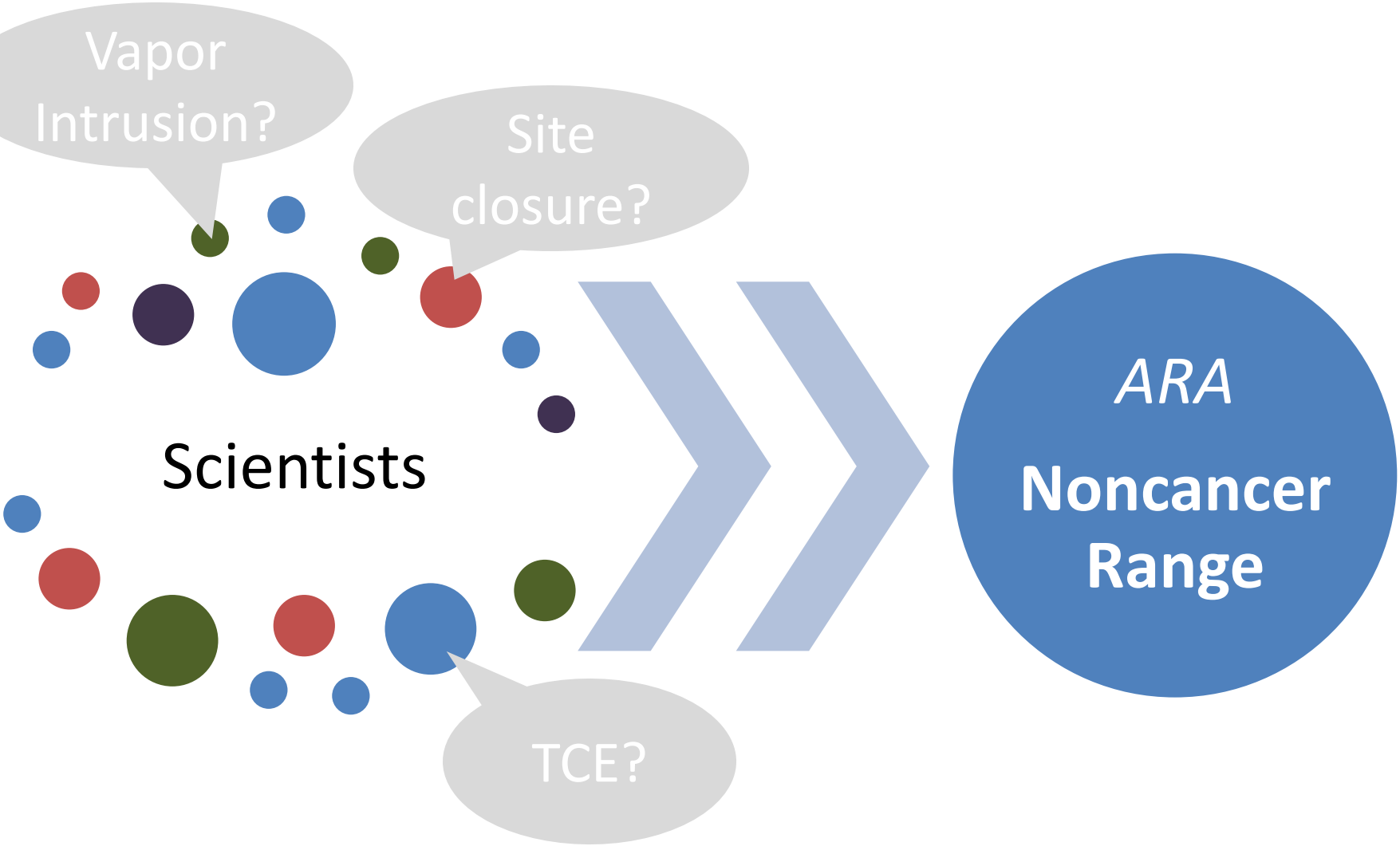
Please contact:

David R. Gillay, Esq.
Chair, Brownfields & Environmental Transactional Diligence
Co-Chair, Remediation, Corrective Action & Voluntary Cleanup

(317) 231-7474 or (317) 946-9267
david.gillay@btlaw.com

BARNES & THORNBURG LLP

Alliance for Risk Assessment (*ARA*)



Purpose: Guidance for Noncancer Range at Contaminated Sites

- Develop a range in noncancer risks, similar to the range used for cancer risks in management of waste sites, using readily available information from U.S. EPA and elsewhere.
- Create range to enable evaluation of uncertainty in the noncancer benchmark.
- Demonstrate confidence in this range so that the range can be considered in the determination of management choices.

Summary: Noncancer Range at Contaminated Sites

- A general range was developed for noncancer risk values, such as Reference Concentrations (RfCs). Ranges included floor, midpoint and ceiling.
- Range for EPA's TCE RfC was judged to be ***3 to 20 µg/m³***.
  - The results of the NTP study-based RfC were used to determine the floor and midpoint of this uncertainty range.
  - The highly controversial results from the Johnson et al. (2003) study-based RfC, while associated with low confidence, were nevertheless used to determine the ceiling level of this uncertainty range.
  - This 3 µg/m^3 to 20 µg/m^3 range was entirely within the wider individual uncertainty range from the Keil et al. (2009) study; therefore, this latter study was considered to be confirmatory.

Developing the Range

An RfC is an estimate (with uncertainty spanning perhaps an **order of magnitude**) of a **daily oral** (for RfD) **or continuous** inhalation (for RfC) exposure to the human population (including **sensitive** subgroups) that is **likely to be without** an appreciable risk of deleterious effects during a lifetime.

- Arsenic RfD on IRIS.
  - There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude.

Developing the Range (con't)

- NAS (2009) suggested development of methods for noncancer toxicity that can determining hazard ranges.

- *ARA* project entitled "Beyond Science and Decisions: From Problem Formulation to Dose Response" responded to this NAS suggestion with 6 methods.

- We focus on 2 methods for the purposes of this work, specifically:
  - Use of biomarkers in the benchmark dose method; and
  - Estimate Risk Above the RfD Using Uncertainty Factor Distributions

Developing the Range (con't)

- In the IRIS Summary for TCE, U.S. EPA identified three RfC values for the noncancer inhalation toxicity of TCE. These are:
  - RfC of 2 µg/m^3 based on decreased thymus weight in female mice (Keil *et al.*, 2009);
  - RfC of 2 µg/m^3 based on fetal heart malformations in rats (Johnson *et al.*, 2003); and
  - RfC of 3 µg/m^3, based on toxic nephropathy in female rats (NTP, 1988).

- Each of these RfCs may be evaluated with respect to the imprecision and the uncertainty inherent in its derivation.

Imprecision Versus Uncertainty

- 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 points of departure & uncertainty factors 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.

Different Uncertainty Ranges for TCE RfCs

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	IRIS UF [a]	Steep Slope [b]	Confidence		Uncertainty Ranges		
			Critical Effect [c]	Point of Departure [d]	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

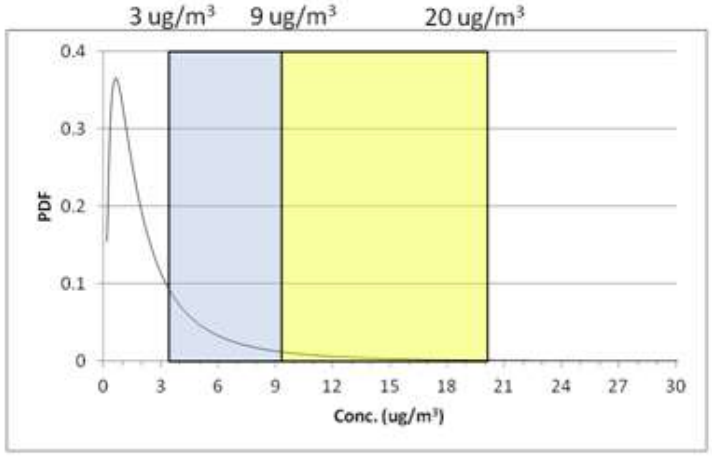


Figure 3a. Exposure distribution of indoor air concentrations primarily below the 3 µg/m3 to 20 µg/m3 hazard range. Relatively small proportion of exposures is higher than 3 µg/m3. Nominal actions or no further action may be warranted for risk management.

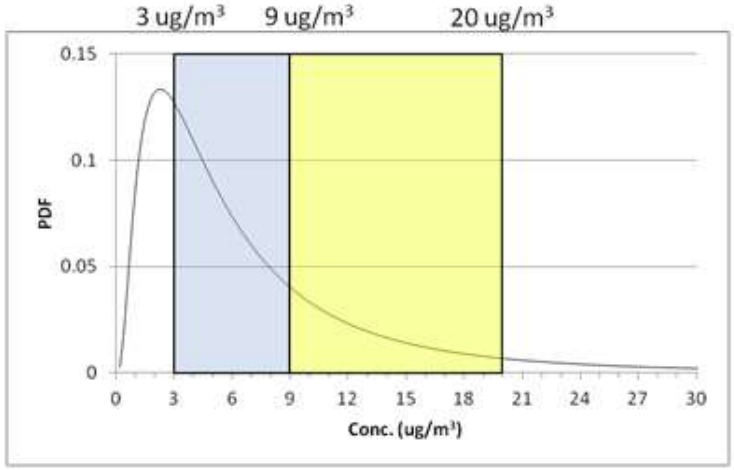


Figure 3b. Exposure distribution of indoor air concentrations falling within the 3 µg/m3 to 20 µg/m3 hazard range. Relatively small proportion of exposures is higher than 9 µg/m3. Limited action may be warranted for risk management.

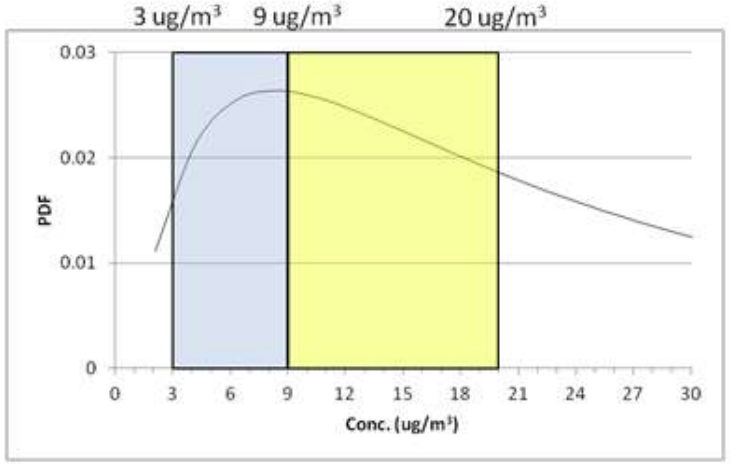


Figure 3c. Exposure distribution of indoor air concentrations primarily above the 3 µg/m3 to 20 µg/m3 hazard range. Actions to reduce exposures may be warranted for risk management.

Collaboration thru *ARA* brings:

Credibility

Publicity

Efficiency

Trust

ARA – Building a Risk Assessment Community

allianceforrisk.org

Michael L. Dourson, Ph.D., DABT, ATS

dourson@tera.org

513.542.7475 x.14

ARA Building a Risk Assessment Community

Need for Further Effort

- Continue this dialogue regarding vapor intrusion risk issues, including agencies, responsible parties & community stakeholders.
- Peer review proposed method for the noncancer risk range.
- Resolve discrepancies in TCE fetal heart findings from one lab compared with negative findings in all other labs.
- Determine appropriate TCE “safe” range, averaging time, & action levels.

The Alliance for Risk Assessment (ARA) is a collaboration of 501c3 organizations. All contributions are tax-deductible. (https://www.givedirect.org/give/givefrm.asp?CID=4930)

ARA  *Building a Risk Assessment Community*

TCE and Congenital Cardiac Defects in Sprague-Dawley Rats

CALVIN C. WILLHITE
NOVEMBER 4, 2013

US EPA Integrated Risk Information

- "In summary, the RfC is 2 ug/m3 based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations (rats)..."
- "For developmental cardiac effects, although the available study (Johnson et al., 2003) has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development."

US EPA Integrated Risk Information

- "Thus, due to the important limitations of the available study coupled with the high confidence in the dose-response analysis, the confidence in the candidate RfC derived from the study is medium."

Chiu et al. 2013. Environmental Health Perspectives 121: 308.

- "The outcomes of studies in rodents exposed to TCE during gestation show an inconsistent pattern. Some studies identified significant treatment-related increases in the overall incidence of cardiac anomalies at environmentally-relevant exposure levels (Johnson et al., 2003) whereas others reported no excess cardiac abnormalities at much higher dose levels…"

Chiu et al. 2013. Environmental Health Perspectives 121: 309

- "Development. Strong evidence based on weakly suggestive epidemiological studies, limited experimental animal studies and multiple mechanistic studies, that TCE causes fetal cardiac malformations…"
- "The approaches and conclusions of the US EPA's analyses (US EPA, 2011d) are consistent with the recommendations of the NRC (2006)…"

Cardiac Teratogenicity

Cardiac teratogenicity is the developmental end point in animal studies that has received the greatest attention. The committee is aware that considerable controversy has existed regarding cardiac teratogenesis, with some reviewers on both sides of the argument (Kaneko et al. 1997; Johnson et al. 1998b; Bove et al. 2002; Hardin et al. 2005). Multiple studies in several animal models, including mammalian (Smith et al. 1989, 1992; Epstein et al. 1992; Dawson et al. 1993; Drake et al. 2006) and avian (Bross et al. 1983; Loeber et al. 1988), suggest that trichloroethylene, or one or more of its metabolites (trichloroacetic acid and dichloroacetic acid), can cause cardiac teratogenesis. Of the studies performed, the avian studies are the most convincing, and mechanistic studies in birds have been performed. Although some rodent studies have shown effects (Smith et al. 1989, 1992; Dawson et al. 1993; Epstein et al. 1992), other studies have not (NTP 1985, 1986b; Fisher et al. 2001), suggesting either methodological or strain differences. The committee noted that the rodent studies showing trichloroethylene-induced cardiac teratogenesis at low doses were performed by investigators from a single institution. Also noted were the unusually flat dose-response curves in the low-dose studies from these investigators. For example, the incidences of heart malformations at trichloroethylene concentrations of 1.5 and 1,100 ppm (almost three orders of magnitude greater) were 8.2% to 9.2% (prepregnancy and during pregnancy) to 10.4% (during pregnancy only) (Dawson et al. 1993). The same pattern occurred with dichloroethylene. Thus, the animal data are inconsistent, and the apparent species differences have not been addressed.

FINDINGS AND RECOMMENDATIONS

The fundamental question for this chapter is whether there is necessary and sufficient evidence from the animal and epidemiologic studies that trichloroethylene, at environmentally relevant doses or concentrations, causes adverse effects on reproduction or birth outcomes. In synthesizing the large body of literature addressing developmental and reproductive toxicity, the committee identified those end points for which the animal and human evidence generates the greatest level of plausibility. These end points are discussed below and include impaired intrauterine growth, cardiac teratogenesis, and altered spermatogenesis. Although the evidence suggests that trichloroethylene can generate such effects, the lowest-observed-adverse-effect level for human risk assessment remains unclear. Some information suggests that certain human subpopulations might be at increased risk because age, genetic polymorphisms, or disease (see Chapter 9). Selection of these three end points indicates not that other reproductive or developmental end points do not have an association with trichloroethylene, but rather that the combined human and animal evidence generated to date does not reach levels of reasonable plausibility.

Trichloroethylene Inhalation Developmental Toxicity Study in Rats

Ed Carney, Ph.D.
Scientific Director –Toxicology Research
The Dow Chemical Company

Alliance for Risk Assessment webinar on TCE
November 4, 2013

Objectives

- Briefly review a TCE inhalation developmental toxicity in rats conducted by Dow at the request of ATSDR

- Compare fetal heart examination techniques across key studies

Study Rationale and Time Line

- *Why another TCE study?*
  - Requested by ATSDR
  - Needed GLP-compliant inhalation study according to newly revised EPA, OECD prenatal developmental toxicity guidelines (870.3700, OECD 414)
- *Time line*
  - Conducted by Dow, April-May, 2000
  - Detailed peer-review by 4 independent experts
  - Report finalized in 2001
  - Published 2006: Carney et al. *Birth Defects Research (Part B)* 77:405–412

Study Design

- Exposures:
  - 0, 50, 150, 600 ppm (≈ 3.2 mg/L; exceeded EPA limit concentration of 2 mg/L).
  - 6 h/day from gestation Day (GD) 6-20
- Test material:
  - Purity=99.0 ±0.05% by GC
  - ID confirmed by IR, MS and NMR
- Animals:
  - Time-mated Crl:CD (SD) rats (Charles River, Portage, MI)
  - N=27 mated females/group
- Maternal necropsy and fetal exams on GD 21

Study End Points

Maternal

- Daily clinical observations
- Feed consumption
- Body weights
- Body weight gains
- Kidney weights
- Liver weight
- Gross pathology

Developmental

- Implantations/litter
- Viable fetuses/litter
- Resorptions/litter
- Gravid uterine weight
- Fetal weight
- Fetal sex
- Fetal external anomalies
- Fetal visceral anomalies (including detailed heart exam)
- Fetal skeletal anomalies

Results

Maternal Body Weights (G)				
GD	**0 ppm**	**50 ppm**	**150 ppm**	**600 ppm**
0	**222 ± 13**	**218 ± 12**	**219 ± 12**	**218 ± 12**
6	**256 ± 14**	**250 ± 14**	**253 ± 13**	**257 ± 13**
15	**310 ± 17**	**301 ± 16**	**307 ± 14**	**309 ± 19**
21	**383 ± 23**	**371 ± 27**	**383 ± 20**	**379 ± 23**
Maternal Body Weight Gains (G)				
6-9	**16 ± 3**	**15 ± 3**	**14 ± 4**	**12* ± 5**
6-21	**127 ± 14**	**121 ± 18**	**130 ± 16**	**123 ± 14**

* Significantly different from control, α=0.05

Maternal Organ Weights

	0 ppm	50 ppm	150 ppm	600 ppm
Kidney (g/100 g body wt.)	**0.50 ± 0.04**	**0.52 ± 0.05***	**0.51 ± 0.03**	**0.53* ± 0.04**
Liver (g/100 g body wt.)	**3.69 ± 0.25**	**3.85 ± 0.29**	**3.75 ± 0.22**	**3.91* ± 0.27**

* Significantly different from control, α=0.05

Other maternal end points

No effects on clinical observations, feed consumption, or gross pathology

Developmental End Points

Exposure level (ppm)	0	50	150	600
No. bred	27	27	27	27
% pregnant	93	100	100	100
No. litters	25	27	27	27
Corpora lutea	14.0 ± 2.3	13.4 ± 2.2	13.9 1.5	14.4 ± 1.9
Implantations	13.2 ± 2.0	12.3 ± 3.2	13.6 ± 1.3	13.4 ± 1.8
Mean litter size	12.7 ± 1.9	11.7 ± 3.0	13.0 ± 1.4	12.8 ± 1.8
% intrauterine deaths	3.3	4.8	4.4	4.7
Fetal weight (g) - Males	5.72 ± 0.33	5.91 ± 0.27	5.93 ± 0.31*	5.81 ± 0.29
- Females	5.46 ± 0.29	5.59 ± 0.27	5.68 ± 0.29	5.54 ± 0.30
- Combined	5.60 ± 0.29	5.75 ± 0.24	5.80 ± 0.28	5.68 ± 0.28

No effects of TCE exposure

Fetal Malformations

Exposure level (ppm):	0	50	150	600
		Number examined Fetuses (Litters)		
External	318 (25)	315 (27)	351 (27)	345 (27)
Visceral	167 (25)	164 (27)	182 (27)	179 (27)
Skeletal	152 (25)	151 (27)	169 (27)	166 (27)
		Number affected Fetuses (Litters)		
Cutis laxa	0	0	0	1 (1)
Missing carotid artery	1 (1)	0	0	0
Missing subclavian artery	1 (1)	0	0	0
Right-sided aortic arch	1 (1)	0	0	0
Dilated cerebral ventricles	0	0	1 (1)	0
Anophthalmia	0	0	0	1 (1)

One fetus with multiple malformations

Conclusions

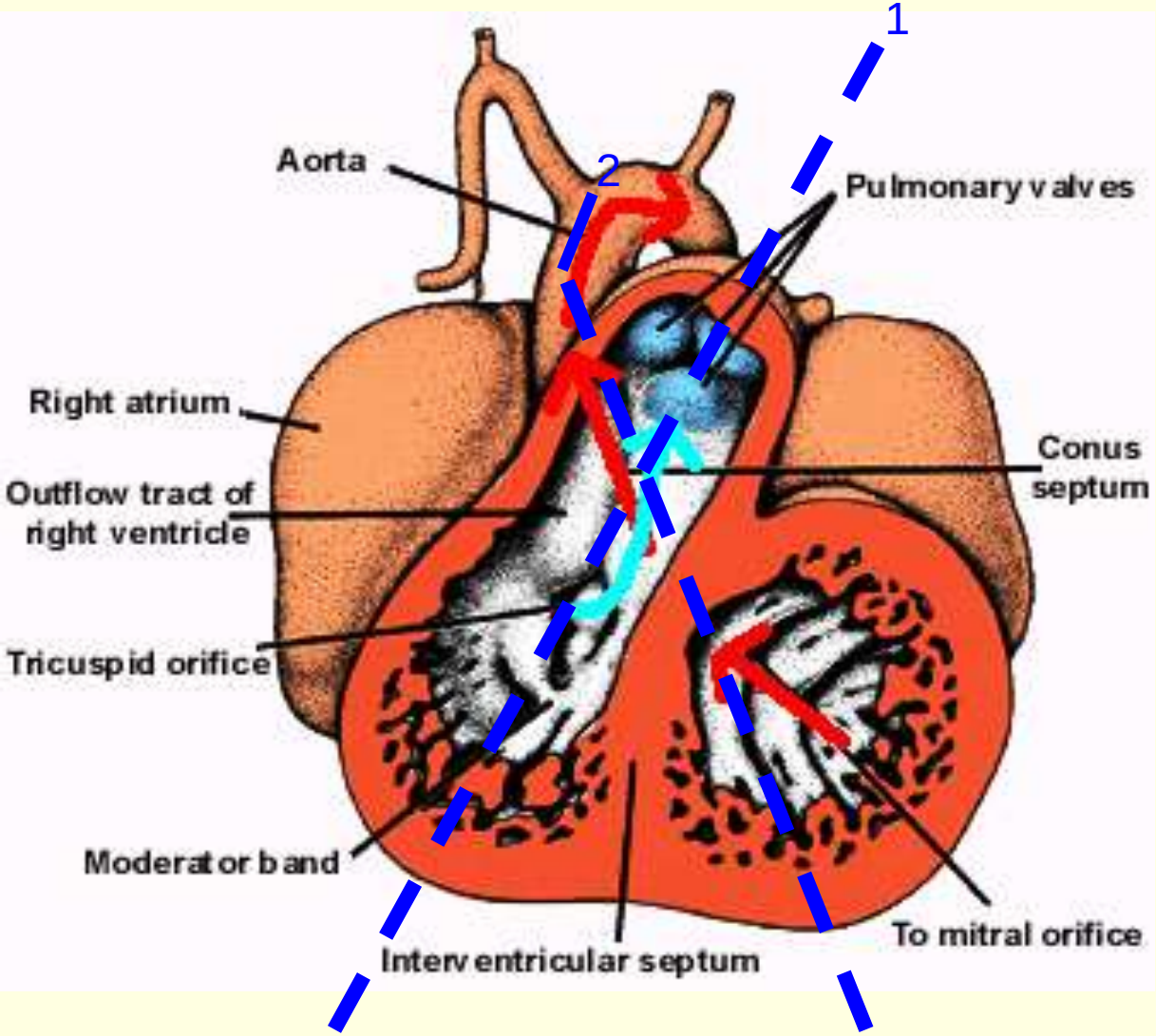
- **600 ppm caused slight maternal toxicity (transient, decreased body weight gain)**
- **No maternal toxicity at 50 or 150 ppm**
- **No developmental toxicity at any exposure level**
- **No heart defects found**
- **Maternal NOEC = 150 ppm; developmental NOEC = 600 ppm**

Comparison of heart exam techniques

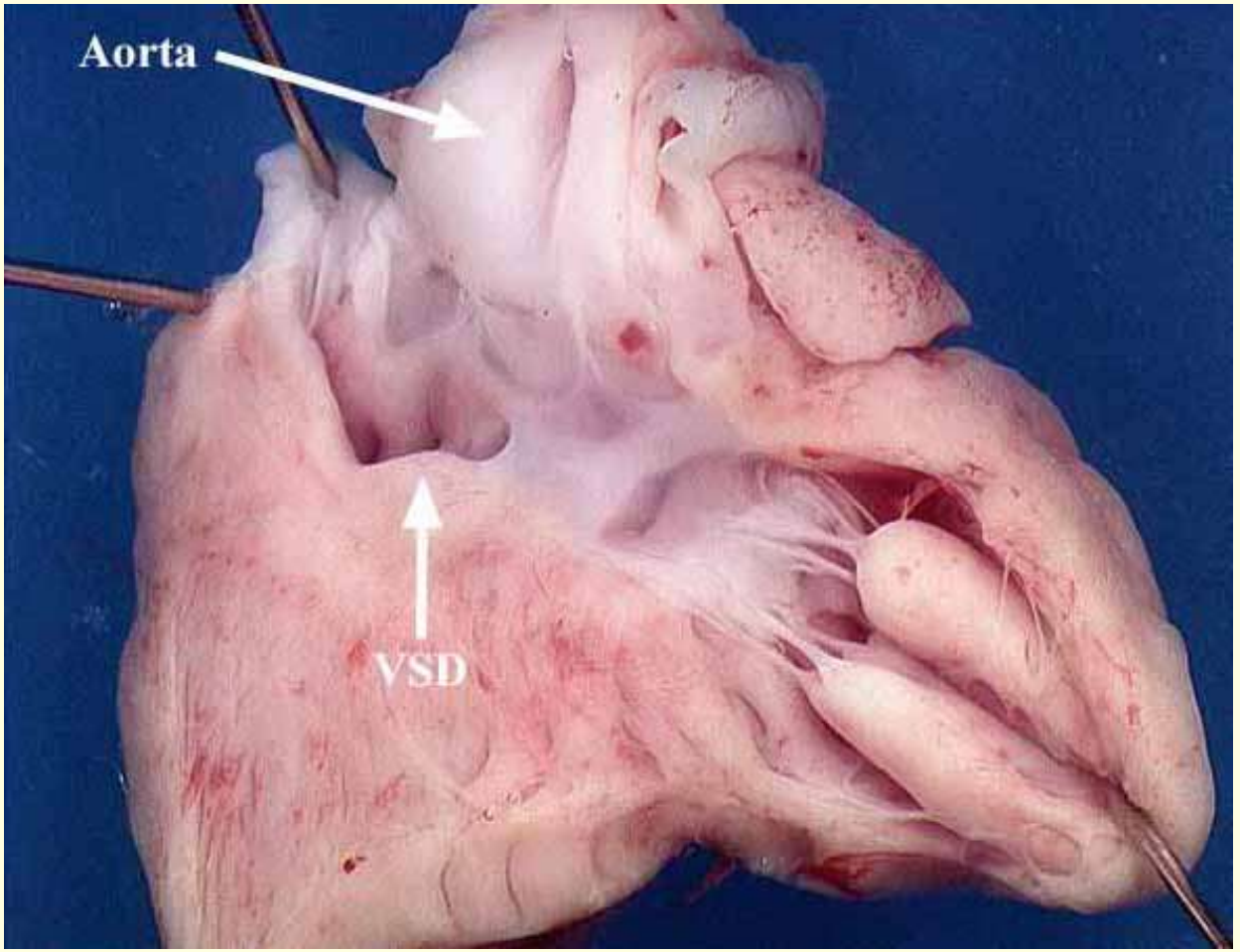
Staple's technique

- Staples (1974) *Teratology 9:*37-38; Stuckhardt and Poppe (1984) *Teratogen. Carcinogen. Mutagen.* 4: 181-188
- Method used in Dow TCE study
- Fetuses examined fresh, under stereoscope
  - includes major vessels and internal structures of heart
    - Valves, septa, papillary muscles, etc.
- Extensive use for regulatory studies worldwide
  - One of only two fetal visceral exam methods specified in test guidelines
- Extensive historical control data within and across labs

Staple's technique – internal structures of the heart



Staple’s technique – septal defect



Dow training program

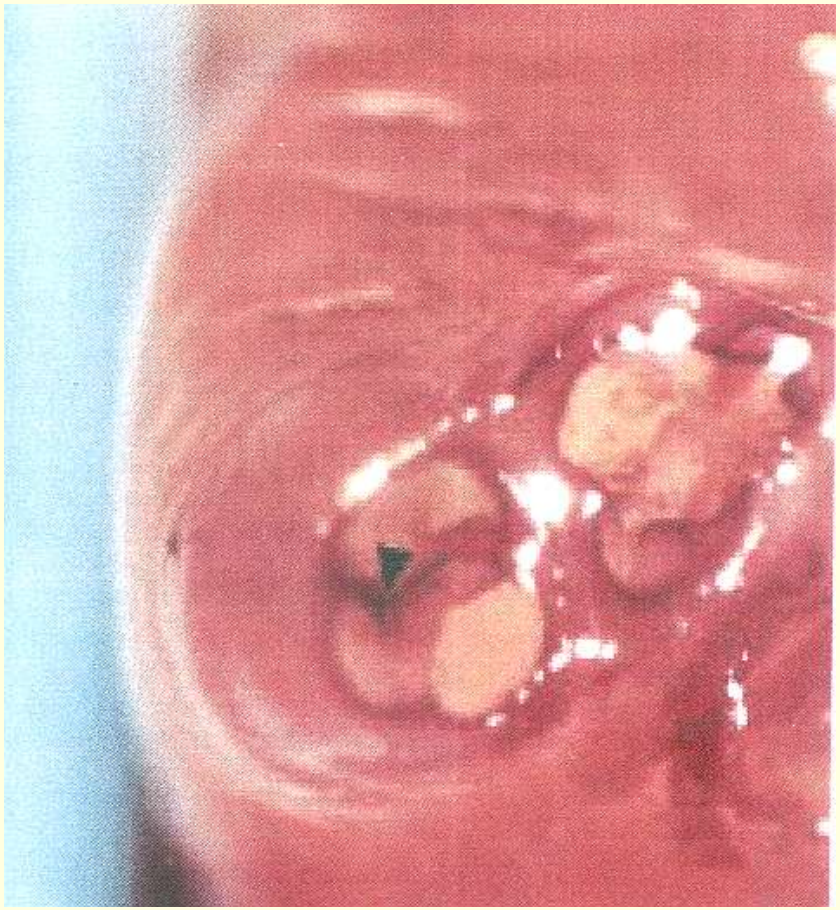
- Starts with background reading and observation
- Practice on control fetuses
- Positive control fetuses –
  - methoxyethanol, 6-aminonicotinamide and acetylsalicylic acid used in period preceding TCE study (wide range of heart defects)
- Practical examination
- Once certified: verification of calls, group discussion of calls (viewed on monitor), random spot checks
- Well trained, experienced fetal examiners are extremely attuned to subtle changes

Dawson technique

- Used in Univ. Arizona studies
- Not a standard regulatory method
- Involves fixation of hearts, removal from body, trimming away of atria to visualize valves *en face*
- Manually pump heart under saline to view movement of valves
- Labor intensive (15-20 min/fetal heart)
- Very limited historical control
- Fisher study – used same methods (trained by Johnson), blinded, hearts examined by veterinary pathologists

Dawson technique

Pulmonary and aortic valves



Examine for adhesions, clefts, fenestrations, patency, stenosis, movement of valves (submerged and “pumped”).

Eggers et al., Teratology 59:173-5 (1999)

Summary – heart exam methods

- Staple's method can detect the majority of cardiac malformations reported in the Arizona studies
- Challenges interpreting the Arizona studies
  - limited historical control
  - findings only seen in one lab
  - very high control incidence
  - not repeatable in Fisher study (same method)
- Possible explanations
  - effect of fixation
  - removal of hearts from thoracic cavity
  - variation associated with manual pumping

Dr. Linval Depass, DABT

Executive Director of Non-clinical Safety and Principal Scientist

Durect Corporation

TCE and Fetal Heart Development

Linval R. DePass, Ph.D., DABT, ATS

Does TCE Cause Heart Defects?

- Epidemiology data are suggestive but inconclusive
- Mechanistic studies are suggestive but relevance to mammals and humans is unclear

Mammalian Studies

- Five inhalation studies on mice, rats and rabbits were uniformly negative
- A high-dose (500 mg/kg) gavage study was negative
- A drinking water study was positive for heart defects, but there are study design and reporting issues

Mammalian Studies

- Fisher et al. (2001)
  - High gavage dose (500 mg/kg/day)
  - Adequate power to detect a treatment effect
  - Dawson method used to examine fetuses as was used in the positive drinking water study(ies)
  - No evidence of heart defects

Mammalian Studies

- Carney et al. (2006)
  - High inhalation exposure (≤600 ppm)
  - Exposure exceeded EPA test guideline by 50%
  - Adequate power to detect a treatment effect
  - Accepted regulatory method (Staples) used to examine fetuses
  - GLP-compliant
  - No evidence of heart defects

Conclusions and Recommendation

- Negative inhalation and oral studies cannot refute a positive drinking water study because the maternal plasma and fetal exposures may be significantly different
- Recommend a drinking water study in rats conducted by an expert teratology team under GLP regulations
- Conduct fetal examinations using an accepted regulatory method familiar to the team

Spontaneously Occurring Cardiovascular Malformations in Crl:CD(SD) Fetal Rats: WIL Research (U. S.)

Stephen B. Harris, PhD, FATS, FSB
Stephen B. Harris Group
San Diego, CA USA
November 4, 2013

Spontaneously Occurring Cardiovascular Malformations in Crl:CD(SD) Fetal Rats – GD 20*

Database (186 Studies)

- **Total No. Fetuses Examined Viscerally – 67,338**
- **Total No. of Litters Examined Viscerally – 4,453**

Cardiovascular Malformations (No. Fetus/No. Litter)

• Aortic Arch - Retroesophageal	5/5
• Great Vessel(s) - Malpositioned	3/3
• Aortic Arch - Interrupted	2/2
• Aorta - Narrowed	1/1
• Aortic Arch - Right-Sided	1/1
• Great Vessel(s) - Transposed	1/1
• Heart and/or Great Vessel Malf	1/1
• Interventricular Septal Defect	1/1

Total No. Fetuses w/ CV Malformations (%)	15 (0.02%)
Total No. Litters w/ CV Malformation (%)	15 (0.34%)

*Permission from Dr. E. Sloter WIL Research to Dr. S. B. Harris (10-24-13)

Spontaneously Occurring Cardiovascular Malformations in Crl:CD(SD) Fetal Rats – GD 21*

Database (25 Studies)

- Total No. Fetuses Examined Viscerally – 8,459
- Total No. of Litters Examined Viscerally – 562

Cardiovascular Malformations (No. Fetus/No. Litter)

• Aortic Arch - Retroesophageal	1/1
• Great Vessel(s) - Malpositioned	1/1
• Interventricular Septal Defect	1/1
Total No. Fetuses w/ CV Malformations (%)	3 (0.04%)
Total No. Litters w/ CV Malformations (%)	3 (0.53%)

*Permission from Dr. E. Sloter, WIL Research to Dr. S. Harris (10-24-13)

Spontaneously Occurring Fetal Rat Cardiovascular Malformations - WIL Research vs Johnson et al.*

WIL Fetal Rat Cardiovascular Malformations

Gestation Day 20

- Total No. Fetuses w/ CV Malformations — 15 (0.02%)
- Total No. Litters w/ CV Malformations — 15 (0.34%)

Gestation Day 21

- Total No. Fetuses w/ CV Malformations — 3 (0.04%)
- Total No. Litters w/ CV Malformations — 3 (0.53%)

Johnson et al. Fetal Rat Cardiovascular Malformations

- Total No. Fetuses w/ CV Malformations/Examined — 13/606 (2.1%)
- Total No. Litters w/ CV Malformations/Examined — 9/55 (16.4%)

* Johnson et al. EHP 111: 289-292, (2003)

Melissa C. Marr

Research Toxicologist and Study Coordinator

RTI Reproductive and Developmental Toxicology Laboratory

Control Cardiac Malformation Data

- Johnson et al. (2003) control incidence for Sprague-Dawley rat cardiac malformations is 16.4% (55 litters with 606 fetuses).
- Historical control incidence of Sprague-Dawley rat cardiac malformations is 0.19% (517 litters with 3617 fetuses) (Lang, 1988).
- Congenital cardiac defect incidence in the Johnson et al. (2003) controls is 86 times the historical control for Charles River Crl:CD rats.

Need for Further Effort

- Continue this dialogue regarding vapor intrusion risk issues, including agencies, responsible parties & community stakeholders.
- Peer review proposed method for the noncancer risk range.
- Resolve discrepancies in TCE fetal heart findings from one lab compared with negative findings in all other labs.
- Determine appropriate TCE “safe” range, averaging time, & action levels.

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