TCE CHRONIC RFC = 2 MCG/M$^3$

Two co-critical endpoints (each can support RfC independently)
- Autoimmune disease following chronic exposure in adults (1.8 µg/m$^3$)
- Heart defects following exposure during early pregnancy (2.0 µg/m$^3$)

One supporting endpoint (less confidence than critical endpoints)
- Nephrotoxicity (kidney effects) following chronic exposure in adults (3.0 µg/m$^3$)
“CONTROVERSIES”

The moon landing is a hoax.

911 was an inside job.

TCE is a cardiac teratogen.

Wait...what?
Controversy – Should we use the 2011 IRIS TCE toxicity values?
  - History of the TCE IRIS Assessment
  - OSWER Directive 9285.7-53

Conundrum – How should we apply the IRIS TCE RfC?
  - …to assess risks?
  - …to derive screening/action levels?
  - …to inform sampling?
  - …to justify actions?

Conflict – How are other regions & states applying the 2011 IRIS TCE RfC?
  - Region 9
  - Region 10
  - Massachusetts
SHOULD WE USE THE 2011 IRIS TCE TOXICITY VALUES?
HISTORY OF THE IRIS TCE ASSESSMENT

Draft #1  2001 – IRIS External Review Draft

SAB 2002 – Science Advisory Board Peer Review Report

2004 – Symposium on New Scientific Research (hosted by EPA)

2005 – EPA submitted four TCE issue papers to NAS

NAS 2006 – National Academy of Sciences report

Draft #2  2009 – IRIS Interagency Science Consultation Draft

Draft #3  2009 – IRIS External Review Draft

2010 – Five Public SAB meetings

SAB Jan 2011 – Science Advisory Board Peer Review Report

Draft #4 June 2011 – IRIS Final Agency/Interagency Review Draft

Final!! Sept 2011 – Final IRIS Toxicological Review

Follow-up 2014 – IRIS TCE Developmental Cardiac Toxicity Assessment Update
A 2- to 3-fold increase in risk of congenital heart defects was found in multiple studies, and the most frequently found defects were the same in animal and human studies (defects of the interventricular septae and the valves).

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.

The two endpoints for immune effects from Keil et al. (2009) and the cardiac malformations from Johnson et al. (2003) should be considered the principal studies supporting the RfC.

The report explains logically why the Johnson et al. (2003) study was used to derive some reference points.

TCE effects on the cardiac system were specific for a narrow window of development … consistent with the definition of a teratogen.
OSWER DIRECTIVE 9285.7-53

“IRIS normally represents the official Agency scientific position regarding the toxicity of the chemicals based on the data available at the time of the review.”

- Current
- Transparent / Publicly available
- Peer-reviewed
- Final

Region 7 will use the IRIS TCE values until they are revised or rescinded.
HOW SHOULD WE APPLY THE 2011 IRIS TCE RFC?

• Critical window of susceptibility
• Critical exposure period of concern used to develop cRfC
• Appropriate exposure parameters
• Action levels/sampling/responses
CALCULATING RISKS & SCREENING/ACTION LEVELS TYPICAL CHRONIC SCENARIO

\[ HQ = CA(\mu/m^3) \cdot ET(hr/day) \cdot (1 \text{ day}/24 \text{ hrs}) \cdot EF(\text{days/year}) \cdot ED(\text{years})/AT\downarrow nc(\text{days}) \cdot RfC(\mu/m^3) \]

Action Level(\mu/m^3) = THQ \cdot AT\downarrow nc(\text{days}) \cdot RfC(\mu/m^3)/ET(hr/day) \cdot (1 \text{ day}/24 \text{ hrs}) \cdot EF(\text{days/year}) \cdot ED(\text{years})

\[ TCE \text{ Ind Air RSL}(\mu/m^3) = 1.9,125(\text{days}) \cdot 2(\mu/m^3)/8(hr/day) \cdot (1 \text{ day}/24 \text{ hrs}) \cdot 250(\text{days/year}) \cdot 25(\text{years}) = 8.8(\mu/m^3) \]
EXPOSURE PARAMETERS MUST REFLECT CRITICAL ENDPOINT

Risk = f(Hazard x Exposure)

Hazard

- A critical endpoint is the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases, regardless of the exposure duration.
- TCE critical endpoints = cardiac malformations & adult autoimmune disease

Exposure

- NRC (1991) – Exposure assessments must taken into account the time scale related to the specific biological response.
- Time-weighted average exposures over a lifetime are not relevant if the adverse effects only occur during a particular stage of development.
Atrial septal defect (ASD). Oxygenated blood from the left atrium shunts via this hole into the right atrium. This volume load causes enlargement of both atria, the right ventricle and the pulmonary artery.

Ventricular septal defect (VSD). Oxygenated blood from the left ventricle shunts via the hole into the right ventricle. This volume load causes enlargement of both ventricles and the pulmonary artery, and exposes the right ventricle and pulmonary arteries to abnormally high pressures.
TYPES OF CARDIAC MALFORMATIONS: PULMONARY STENOSIS

Normal heart. The pulmonary valve opens completely to allow low-oxygen blood to flow out of the heart, into the pulmonary artery and then to the lung.

Pulmonary stenosis. Thickened and fused valve leaflets prevent full opening.
TYPES OF CARDIAC MALFORMATIONS: AORTIC STENOSIS

Normal heart. The aortic valve opens completely to allow oxygen-rich blood to flow out of the heart, into the aorta, and out to the body.

Aortic stenosis. Thickened and fused valve leaflets prevent full opening.
MAGNITUDE OF CARDIAC MALFORMATIONS

http://www.noozhawk.com/noozhawk/print/081712_letter_to_editor_pulse_o_x_newborn_screening

http://www.mendmaddiesheart.com

Lexi Behrnot
Writer: Scrabbles and Crumbs

10 Things You Need to Know About Congenital Heart Disease From a Mom Who Lost Her Son To It

http://www.huffingtonpost.com

06/29/2015
Thank you everyone that made Maddie’s 5th birthday a memorable one!

To the doctor that said we might not see her turn 5..... What do you think now?

http://www.mendmaddiesheart.com
CRITICAL WINDOW OF SUSCEPTIBILITY

<table>
<thead>
<tr>
<th>Estimated Gestational Age (Weeks)</th>
<th>6 4/7</th>
<th>6 6/7</th>
<th>7 3/7</th>
<th>7 3/7</th>
<th>7 5/7</th>
<th>8 2/7</th>
<th>8 4/7</th>
<th>8 6/7</th>
<th>9 1/7</th>
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<tbody>
<tr>
<td>Carnegie Stage</td>
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<td>1. Cardiac Loop</td>
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<tr>
<td>2. Atrial Septation</td>
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<td>A. Septum Primum</td>
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<td>B. Septum Secundum</td>
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<td>3. Interventricular Foramen</td>
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<td>4. Ventricular Septation</td>
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<td>A. Muscular Interventricular Septum</td>
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<tr>
<td>B. Inlet Interventricular Septum</td>
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<td>C. Outlet Interventricular Septum</td>
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<td>5. Atrioventricular Junction/Valve Formation</td>
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<tr>
<td>A. Mitral Valve</td>
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<td>B. Tricuspid Valve</td>
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<td>6. Outflow Septation</td>
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<td>7. Semilunar Valve Formation</td>
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<td>A. Aortic Valve</td>
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<td>B. Pulmonary Valve</td>
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</table>

Note: “Gestational age” dates from the last menstrual period, not from fertilization. “Fertilization age” is approximately 2 weeks less.

Dhanantwari, P; Lee, E; Krishnan, A; Samtani, R; et al. Human cardiac development in the first trimester: a high resolution magnetic resonance imaging and episcopic fluorescence image capture atlas. Circulation 2009;120:343–51.
CRITICAL EXPOSURE PERIOD OF CONCERN FOR THE RFC

One day? *Not with the available data.*

- EPA’s Developmental Toxicity Risk Assessment Guidelines states that “a single exposure at a critical time in development may produce an adverse developmental effect.”
- A single exposure to *some* level of TCE at any time during the three week critical window of valvuloseptal morphogenesis could result in one or more types of heart defects.

Three weeks? *Yes.*

- IRIS combined the incidence of all the types of heart defects observed in the critical study to calculate the BMDL associated with a 1% excess risk of an “abnormal heart.”
- Since the heart defects occurred throughout valvuloseptal morphogenesis, the critical exposure period used to derive the RfC = 3 weeks.
Residential HQ = CA(\(\mu/m^3\)) \cdot 24(\text{hrs/day}) \cdot 7(\text{days/week}) \cdot 3(\text{weeks/exposure period}) / 504(\text{hrs/exposure period}) \cdot 2(\mu/m^3)

Worker HQ = CA(\(\mu/m^3\)) \cdot 8(\text{hrs/day}) \cdot 5(\text{days/week}) \cdot 3(\text{weeks/exposure period}) / 504(\text{hrs/exposure period}) \cdot 2(\mu/m^3)

Must = 3 weeks!

Must = 504 hrs!
CALCULATING ACTION LEVELS

Residential Action Level ($\mu/m^3$) = $1.504 (hrs/exposure period) \times 2 (\mu/m^3) / 24 (hrs/day) \times 7 (days/week) \times 3 (weeks/exposure period) = 2 (\mu/m^3)

Worker Action Level ($\mu/m^3$) = $1.504 (hrs/exposure period) \times 2 (\mu/m^3) / 8 (hrs/day) \times 5 (days/week) \times 3 (weeks/exposure period) = 8 (\mu/m^3)$

ET & EF can be modified to reflect the actual work day
CONSIDERATIONS FOR SAMPLING/ACTIONS

HOW ARE OTHER REGIONS & STATES APPLYING THE 2011 IRIS TCE RFC?

- Region 9
- Region 10
- Massachusetts
An HQ of 3 has been used as a science policy choice to prioritize removal actions at the “worst” sites.

Assuming chronic health effects, all sites are eventually remediated to an HQ of 1, before exposures occur long enough to pose risks.

TCE poses unacceptable risks in days to weeks.

How long has exposure already occurred?

---

### EPA Region 9 Interim TCE Indoor Air Response Action Levels - Residential and Commercial TCE Inhalation Exposure from Vapor Intrusion

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Accelerated Response Action Level (HQ=1)</th>
<th>Urgent Response Action Level (HQ=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residential *</td>
<td>2 µg/m³</td>
<td>6 µg/m³</td>
</tr>
<tr>
<td>Commercial/Industrial ** (8-hour workday)</td>
<td>8 µg/m³</td>
<td>24 µg/m³</td>
</tr>
<tr>
<td>Commercial/Industrial ** (10-hour workday)</td>
<td>7 µg/m³</td>
<td>21 µg/m³</td>
</tr>
</tbody>
</table>

* The residential HQ=1 accelerated response action level is equivalent to the inhalation reference concentration (RfC) since exposure is assumed to occur continuously.

** Commercial/industrial accelerated response action levels are calculated as a time-weighted average from the RfC, based on the length of a workday and rounding to one significant digit (e.g., for an 8-hour workday: Accelerated Response Action Level = (168 hours per week/40 hours per week) x 2 µg/m³ = 8 µg/m³). Time-weighted adjustments can be made as needed for workplaces with longer work schedules.

Note: Indoor air TCE exposures corresponding to these accelerated response action levels would pose cancer risks near the lower end of the Superfund target cancer risk range, considering the IRIS toxicity assessment; thus, the health protective risk range for both accelerated response actions and long-term exposures becomes truncated to: 0.5 – 2 µg/m³ for residential exposures and 3 – 8 µg/m³ for 8-hour/day commercial/industrial exposures.
"...to protect against potential noncancer fetal malformation outcomes, it is appropriate to recommend that average exposures over any 21-day period of time not exceed the concentrations in air or other media that are calculated to be protective..."

Not to be exceeded, average 21-day exposure to women of reproductive age to prevent fetal cardiac malformations, HQ=1.0

- Residential settings = 2.0 µg/m³
- Industrial/commercial settings = 8.4 µg/m³
  - Based on 260 days/year (i.e., 5 days/week for 52 weeks/year)
As with the residential value, this value is equivalent to workplace RfC adjusted upwards by a factor of three, reflecting the use of a reduced pharmacodynamic uncertainty factor.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Indoor Air Concentration</th>
<th>Concern Level</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal developmental effects</td>
<td><strong>&gt; 6 µg/m³</strong></td>
<td>Imminent Hazard 2-hr Notification</td>
<td>Immediate Response Action Goal to reduce levels to <em>at least</em> less than 6 µg/m³ ASAP (within several days if possible)</td>
</tr>
<tr>
<td>(Subchronic Exposure Noncancer Risk, HQ=1)</td>
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<tr>
<td><strong>Typical Workplace Exposure Scenario</strong></td>
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</tr>
<tr>
<td>Fetal developmental effects</td>
<td><strong>&gt; 24 µg/m³</strong></td>
<td>Imminent Hazard 2-hr Notification</td>
<td>Immediate Response Action Goal to reduce levels to <em>at least</em> less than 24 µg/m³ ASAP (within several days to a week if possible)</td>
</tr>
<tr>
<td>(Subchronic Exposure Noncancer Risk, HQ=1)</td>
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</tbody>
</table>

This value was derived by reducing the uncertainty factor (UF) for pharmacodynamics applied by US EPA to the HEC99 in the RfC derivation by the square root of 10.
TCE INHALATION UNIT RISK = 4.1E-06 (MCG/M$^3$)$^{-1}$

Classified as “Carcinogenic to Humans” by all routes of exposure
- Based on convincing evidence of a causal association between TCE exposure & kidney cancer

Kidney Cancer (Renal Cell Carcinoma) – *mutagenic mode of action*

Non-Hodgkin’s Lymphoma

Liver & Biliary Tract Cancer
DISCUSSION

Questions?