DEVELOPMENT OF A SHOWER EXPOSURE MODEL FOR BENZENE

BACKGROUND WORK FOR POTENTIAL RECOMMENDED UPDATE TO THE RECENTLY DERIVED DRINKING WATER GUIDELINES

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Presentation Overview

• **History**

• **Relevance for Oil and Gas Sites**
  – influence on the drinking water guideline

• **Health Canada’s Model (Khrisnan)**
  – issues and limitations

• **Alternate Model Development**
  – advantages
History

• Late 1980’s chloroform exposure in the shower
  • (Pellizari et al., 1987; Wallace 1987)
    – ~50% of mass in water volatilizes
    – 40 to 80 µg/day via inhalation
    – 17 to 40 µg/day via ingestion
    – inhalation exposure is important
    – contribution will vary by chemical

• Experimental shower for testing

• Model development
  – McKone, 1987; three compartments:
    – shower, rest of bathroom, rest of house
      • some reasonable model fits to measured data for chloroform

• People now looking at the influence of dishwashers...
History

• Shower exposures examined for other volatile substances

• Radon
  – areas naturally high in radon, water well sources

• Trichloroethylene
  – dry cleaner groundwater impacts, water well sources

• Methyl tertiary butyl ether (MTBE)
  – gasoline additive, water well sources (municipal in the case of Santa Monica)

• Benzene
  – gasoline impacts from gas stations, water well sources
History

• In addition to inhalation...

• Attempts made to determine whether dermal exposure was important
  – volunteers exposed to chloroform in shower water
  – chloroform exhaled in breath was measured
  – with and without wetsuits
  – dermal exposure was found to be equivalent to inhalation

• Results indicate integrated exposure need to be considered for,
  – ingestion
  – inhalation
  – dermal
History

• Effects on guidelines

• In 2002, New Jersey Department of Environmental Protection developed a shower model
  – tested it for chloroform, trichloroethylene, cyclohexane (in F1 fraction), ethylbenzene, toluene, ethyl acetate, and acetone
  – reasonable model fit with measured data from different experimental shower setups,
    • underestimated by 40% to over-estimated by 10-fold
    • ethylbenzene and toluene were 1.2 to 3.4-fold overestimates
  – NJDEP revised some of their groundwater health criteria downward to account for inhalation and dermal exposure from showering

• Incorporation of shower exposures by other agencies including California EPA and Health Canada
Regulatory Approach

Calculate L-equivalent (L-eq) of drinking water from inhalation and dermal shower exposures
- example based on trichloroethylene (TCE)

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>Ingestion (L)</th>
<th>Inhalation (L-eqvt)</th>
<th>Dermal (L-eq)</th>
<th>Inhalation+ Dermal (L-eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Shower</td>
<td>1.5</td>
<td>0.56</td>
<td>0.24</td>
<td>0.8</td>
</tr>
<tr>
<td>Adult Bath</td>
<td>1.5</td>
<td>1.67</td>
<td>0.72</td>
<td>2.39</td>
</tr>
<tr>
<td>Child 14 yr Shower</td>
<td>1.2</td>
<td>0.54</td>
<td>0.21</td>
<td>0.75</td>
</tr>
<tr>
<td>Child 14 yr Bath</td>
<td>1.2</td>
<td>1.63</td>
<td>0.62</td>
<td>2.25</td>
</tr>
</tbody>
</table>
Approach Considered by HC

Two Tier Screening - determine whether shower exposure should be considered (> 10% of ingestion exposure)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Unitless Henry’s Constant</th>
<th>Air to Water Concentration Ratio</th>
<th>Tier 1 Result</th>
<th>L- eq Drinking Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>0.000174</td>
<td>0.000105</td>
<td>No; stop</td>
<td></td>
</tr>
<tr>
<td>Methylethyl ketone</td>
<td>0.00269</td>
<td>0.00135</td>
<td>Yes – T2</td>
<td>0.32</td>
</tr>
<tr>
<td>Toluene</td>
<td>0.243</td>
<td>0.00723</td>
<td>Yes – T2</td>
<td>1.71</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>1.04</td>
<td>0.00751</td>
<td>Yes – T2</td>
<td>1.77</td>
</tr>
<tr>
<td>n-Hexane</td>
<td>6.98</td>
<td>0.00759</td>
<td>Yes – T2</td>
<td>1.79</td>
</tr>
</tbody>
</table>

Models Structure

• How do we model exposures and risk from showering with impacted water?

• Two general types of models
  – simple used to estimate exposures
  – Integrated Physiologically Based Pharmacokinetic Model
How are Shower Exposures Estimated?

- hot water containing volatile compounds
- estimate air concentration
  - shower stall, bath, rest of house
- estimate inhaled dose
- skin contact – estimate dermal dose
### ‘Highly’ Parameterized Models

- **lots** - duration of shower, time spent in bathroom, house
  - number of people, successive showers, body size, inhalation rate

#### Chemical Parameters

<table>
<thead>
<tr>
<th>Exposure Factor</th>
<th>Parameter Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shower duration</td>
<td>10.4 min</td>
<td>U.S. EPA, 1996a</td>
</tr>
<tr>
<td>Shower rate</td>
<td>5.5 L/min</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>Shower volume</td>
<td>2.30 m³</td>
<td>U.S. EPA, 1996a</td>
</tr>
<tr>
<td>Water use</td>
<td>15 gal/d per person (median)</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>Bathroom volume</td>
<td>13.6 m³</td>
<td>U.S. EPA, 1996a</td>
</tr>
<tr>
<td>House volume</td>
<td>310 m³</td>
<td>U.S. EPA, 1996a</td>
</tr>
<tr>
<td>Shower vent rate</td>
<td>100 L/min</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>Bathroom vent rate</td>
<td>300 L/min</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>House vent. rate</td>
<td>0.45 air changes/h (2.325 L/min)</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>Bathroom water use</td>
<td>33 gal/d (125 L/d)</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>Fem, bathroom</td>
<td>0.50</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>Time toilet emits</td>
<td>1 h/d</td>
<td>McKone, 1987</td>
</tr>
<tr>
<td>House water use (tot)</td>
<td>53 gal/d (201 L/d)</td>
<td>McKone, 1987</td>
</tr>
</tbody>
</table>
Relevance to the Petroleum Industry

• Recent revision to the drinking water guideline for benzene
  – guideline changed from 0.005 mg/L to 0.001 mg/L
  – expected that other guidelines for toluene, ethylbenzene, xylenes, \( n \)-hexane, F1 fraction may follow

• Rationale?
  – includes inhalation and dermal exposures from showering and bathing
  – based on a simple model
Support for Guideline Revision

- Private residence (Lindstrom et al., 1994)
  - gasoline impacted groundwater, ~ 0.3 mg/L benzene (100x g.l.)
  - assess exposure in shower, bathroom, and house rooms
  - due to single 20-min shower
  - rest of house peak ½ to 1 hour afterwards
  - Estimated:
    - shower dose ~281 µg
    - 40% inhalation/ 60% dermal
    - 2 to 3.5 times > than mean
    - inhalation dose during a concurrent 6 h occupation
    - of the house

- Lopez et al. (2008) found contrasting results—ingestion most important
Issues

• Equilibrium asked to peer review methodology

• Large variability in exposure parameters
  – not evident that the parameter selection process was highly rigorous and specific to Canada
  – initially intended as a screening tool

• Bioavailability estimates may be too high

• Variety of dermal permeability coefficients
  – unclear whether these have been extensive evaluated

• Potential issue with methods for summing pathways to estimate risk via water exposure

• Different methods for developing drinking water guidelines
Default Exposure Parameters

- Lindstrom *et al.* (1994) data used as supporting evidence for magnitude of exposure adjustment - inhalation and dermal
  - the residence studied by Lindstrom *et al.* (1994) did not have a bathroom fan
  - may not provide a reasonable estimate of benzene indoor air concentrations in typical residences in Canada
  - house air exchange rate was 0.35 air changes per hour
    - lower than CCME value for petroleum hydrocarbon guidelines - residential land use
    - 1 air change per hour
Default Exposure Parameters

- Default exposure parameters sourced from Lindstrom et al. (1994); Krishnan (2004); and a few other
- Exposed body surface area
  - Krishnan (2004) assumed 100% (same as HC)
  - Lindstrom et al. (1994) assumed 75%
- Showering duration
  - 30 minutes assumed by Krishnan (2004) (and HC)
  - Lindstrom et al. (1994) used 20 minutes
  - longer duration may be more representative for multiple daily shower uses
  - may be high for dermal exposure risks
Default Exposure Parameters

- **Dermal permeability coefficient**
  - Health Canada
    - 0.14 cm/hr
  - Krishnan (2004)
    - 0.11 cm/hr
  - other values available

- **Stripping (or volatilization) efficiency** – key parameter
  - data has been generated for (Moya et al. 1999),
    - acetone, ethyl acetate, toluene, ethylbenzene, and cyclohexane
    - values ranged from 6.3% (acetone) to 80% (cyclohexane) for household showers used under normal conditions.
  - Ethylbenzene or toluene may be a reasonable surrogate for benzene
Some difference for inhalation

Considerable differences for dermal route
- occluded skin
  - 100% may be reasonable
- non-occluded skin
  - ~0.05%; Frank (1984)
  - Skowronski et al. (1988)
- other data 1%
Summation of Pathways

• kinetics and pathway-dependent metabolism may be very important

• liver has a high capacity for metabolism
  – benzene is rapidly metabolized, a portion to toxic metabolites, and a portion to non-toxic metabolites that are excreted
  – delivery of toxic metabolites to the hematopoietic system may differ significantly between inhalation, dermal, and oral routes

• implies that a PB/PK based approach may be the way to go
  – PB/PK models have been developed for benzene
  – it may be possible to integrate one with a shower model for developing a water quality guideline
Guideline Differences

• Different drinking water guidelines are available
  – Health Canada – based on animal study
    • 2 year NTP (1986) study
    • surface area correction from rodents to humans
    • leukemia and lymphomas in female mice
    • oral cavity squamous cell carcinomas in male rats
  – US EPA – based on human occupational exposure (Rinsky cohort)
    • inhalation data extrapolated to oral exposure

– Which limit is best?
– Both give generally similar limits, although a PB/PK approach should have been employed by the US EPA in the route to route extrapolation
Response from Guideline Developers

- How will these issues be addressed?
2009 PTAC Sponsored Work

• Literature search on available exposure models

• Compilation of relevant exposure parameters

• Evaluate application of PB/PK integrated model
  – model testing

• Preliminary risk estimates from water use

• Identify key data gaps and sources of uncertainty

• Re-evaluate potential implications for a drinking water and soil quality guideline

• Complete a state of the science report containing the information described above
PBPK Integrated Shower Model

- Complex
- Can evaluate mixture of acute and chronic exposure
- Simulates the kinetics of chemical loading into the bloodstream from various exposures
- Considers
  - Blood flow
  - Volume of organs
  - Metabolism in the liver
  - Metabolism in the skin (can be considerable)
  - Partition coefficients between alveolar air and blood
  - Excretion rates (urine, re-expired air)
- Models have been built for MTBE and TBA
- Could be used for a more accurate extrapolation of cancer risk from animals to humans?
  - metabolic rates do differ, types of cancer differ
PBPK Model Structure

- body compartments:
  - lungs
  - skin
  - fat
  - kidney
  - stomach
  - intestine
  - liver
  - rapidly perfused
  - slowly perfused

Kim et al., 2007. Refined PBPK model of aggregate exposure to methyl tertiary-butyl ether
Scientific evidence suggests metabolism plays an important role in benzene toxicity

- first metabolites - phenol, catechol, and hydroquinone, second pathway involves open ring forms of benzene
- toluene can inhibit the toxicity of benzene at higher doses (Snyder and Hedli, 1996)
- transgenic mice lacking CYP2E1 expression had lower benzene metabolism, cytotoxicity, genotoxicity (Valentine et al. 1996)
- liver first pass effect – benzene primarily metabolized in liver
- route of exposure can affect the metabolites formed and potentially amount of toxic metabolite
Conclusions

• Future water quality guidelines will likely incorporate shower exposures
  – necessary – significant exposure can occur

• Because of the potential magnitude in guideline change, a rigorous evaluation should be conducted for defining relevant exposure parameters

• Some primary research may be required such as for transfer efficiencies

• for certain substances, it may be possible to develop a PB/PK model for two purposes
  – route-to-route extrapolation to derive ingestion limits
  – integrated summation of exposure from multiple routes of exposure