Rapid Development of Physiologically Based Pharmacokinetic (PBPK) Models for Human Health Risk Assessment: Application of Diverse Approaches to Estimating Metabolism

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• I am a contractor working with Air Force Research Laboratory/711 Human Performance Wing and the views expressed in this presentation are my own and do not necessarily reflect the views of the Air Force, Department of Defense, or my employer, UES, Inc.
Outline

• Context/Background/Inspiration
• Goals
  • Specific aims
  • Outline and methods of case study approach (work in progress)
• Progress/Interim Findings
  • Deeper dive on Quantitative Structure Activity Relationship (QSAR) resource evaluation
• Lessons Learned
• Plans
• Summary
• Acknowledgements
• References
Context/Background

• Strategic Objective: apply new and improved approaches to characterizing risk in DOD work settings, particularly the Air Force operational environment
  • Applications to PBPK modeling
    • Physiological parameters: reflect Air Force-relevant stressors (Covington et al. 2019; Sweeney 2020 a, b, c; Sweeney et al. 2020)
    • New Approach Methods (NAMs), surrogates, and/or read across for points of departure and physicochemical or biochemical parameters

• How are NAMs, surrogates, and read across (potential) improvements?
  • Speed
  • Cost
  • Human relevance
  • Ethical concerns of traditional in vivo approaches
Inspiration

- Paini et al. (2019) proposed both read across and in silico approaches for PBPK modeling
  - In the **read across or surrogate** approach (Lu et al. 2016), one would use an existing PBPK model for a structurally similar chemical
  - Alternatively, models can be developed from **in silico resources** (see Madden et al. 2019) or in vitro sources
  - Limited guidance and examples on using **NAMs** for **developing, assessing, and applying** PBPK models
    - Most of the databases and tools developed to date have limited applicability to environmental and occupational chemicals
- The Air Force has an ongoing need to understand potential human health risks from inhalation exposure to compounds in the work environment.
  - The increasingly popular **high-throughput in vitro techniques technically challenging for volatile organic compounds** due to nonspecific losses through volatilization and to test components (e.g., plastic plates)
    - QSARs are thus an especially important resource for properties of materials present in the vapor form
  - The airborne hazards of concern to the Air Force include jet fuels, combustion exhaust, and repair shops
    - Variable and often incompletely characterized composition
    - Not all components are well-studied both from toxicological and toxicokinetic standpoints
  - Rather than necessarily trying to develop a single “best” predictor, consideration of multiple approaches can yield a range of estimates that reflect the uncertainty of the process and the merits of different data sets and approaches.
Goals and Strategy

- **Goals**: Develop work flows for (1) rapid development of PBPK models for application to chemicals of new/emerging interest to DOD with respect to risk in the operational environment and (2) characterization of model confidence

- **Strategy to narrow the scope**:
  - Start with a case study or case series of a previously modeled chemical(s) with some human and/or rodent in vitro and in vivo data available
  - Rather than necessarily trying to develop a single “best” predictor, consideration of multiple approaches can yield a range of estimates that reflect the uncertainty of the process and the merits of different data sets and approaches
  - Vmax and Km were selected as chemical specific parameters of interest (partition coefficients were assumed to be more confidently assessed in vitro and using QSAR
Outline and Methods of Case Study Approach—Work in Progress

• Parameterization
  • Develop $V_{\text{max}}$ and $K_m$ estimates from in vivo, in vitro, and in silico data for the subject chemical
    • Literature searches
    • Identify online in silico tools
    • Evaluate QSARs per Patel et al. (2018)
    • Interspecies extrapolation
    • In vitro (or in silico) to in vivo extrapolation (scaling)
  • Limiting cases
  • Identify potential surrogate substances with existing PBPK models
    • US EPA CompTox Chemicals Dashboard (Williams et al. 2017)
Outline and Methods of Case Study Approach—Work in Progress

• Performance
  • Compare predictive performance of various Vmax and Km estimates with respect to fit to an example human in vivo chemical time course
    • Bias, average fold error

• Risk assessment implications
  • Internal dose metrics at toxicologically relevant exposure concentrations and durations for various Vmax and KM estimates
    • Chronic
    • Acute
  • Sensitivity analyses (not yet initiated)
Progress: Case study, possible case series, and surrogates

- Selected 1,2,4-trimethylbenzene, with other C9 aromatics as potential candidates for a case series
Progress: Surrogates

- Identification via a comprehensive PBPK model database linked with structural information would be most efficient
  - Personal knowledge and literature searches were needed to match candidates with mammalian PBPK models
- 1,2,3,5- and 1,2,4,5-tetramethylbenzene (durene and isodurene; Jalowiecki and Janasik, 2007)
  - Human liver volume of 3.9 L reported and possibly in Vmax scale up from microsomes

- Multiple model options for toluene
  - 30 publications examined
  - 12 did not explicitly report bodyweight scaling factors for Vmax
  - Multiple families of models
  - Authors sometimes reused VmaxC values, but altered the bodyweight scaling factor
- Multiple model options for o-, m-, p-, and mixed xylenes and styrene as well
Progress: Summary of human 1,2,4-TMB Vmax and KM estimates

- Total of two limiting cases and 17 VmaxC and KM pairs

**LIMITING CASES (2):**
- No metabolism
- Complete hepatic clearance

**IN VIVO DATA (4):**
- Calibration with rat data (2)
- Calibration with human data alone
- Calibration with mix of rat and human data

**IN VITRO DATA (3):**
- One rat liver slice study:
  - Generic scaling
  - Categorical scaling
- One human liver microsome study

**USER-IMPLEMENTED QSARs with 1,2,4-TMB SOURCE DATA (5):**
- Human in vitro data (1)
- Two investigations using overlapping rat data (4)
  - Generic Vmax scaling
  - Categorical Vmax scaling

**USER-IMPLEMENTED QSAR without 1,2,4-TMB SOURCE DATA (1):**
- Rat and rabbit in vitro data

**DERIVED FROM COMMERCIAL OR GOVERNMENT IMPLEMENTED CLEARANCE ESTIMATORS (4):**
- Two estimates of clearance
  - For each clearance estimate, two KM assumptions were used
Progress: Vmax and KM

- In vivo, in vitro, and in silico data presented in order of expected reliability (subjective/personal judgement)

- Subject chemical Vmax and KM data from in vivo
  - Optimized with human data
    - Sweeney et al. (2020); rat model KM value (US EPA, 2016) and human VmaxC optimized to one human in vivo data set near the TLV (Kostrezewski et al. 1997) (comparator)
    - Jarnberg and Johanson (1999); average of 10 individually optimized human Vmax and KM values; simulations they presented used one individual’s parameter values—not the average
  - Optimized with rat data; simulations of human in vivo data judged to be adequate
    - US EPA (2016) optimized rat VmaxC and KM values (modified from Hissink et al. 2007)
    - Hissink et al. (2007) optimized rat VmaxC and KM values
Progress: Vmax and KM from in vitro data

- Subject chemical Vmax and KM from human in vitro data
  - Lewis et al. 2003 (human liver microsomes)
  - In vitro to in vivo extrapolation (IVIVE)
    - 34 mg microsomal protein/g human liver (Barter et al. 2007, as cited by Lipscomb and Poet, 2008)
    - Liver mass 2.6% of human body weight (Brown et al. 1997)
    - 70 kg body weight for a standard human
- Subject chemical Vmax and KM from rat in vitro data
  - Mortensen et al. 2000 (rat liver slices)
  - IVIVE
    - Typical liver slice weight and liver weight reported (Mortensen et al. 1997)
    - Two approaches used for interspecies extrapolation
      - Categorical approach for likely CYP2E1 substrates (Beliveau et al. 2005)
      - Traditional BW$^{0.7}$ scaling
Progress: Vmax and KM from QSARs calibrated with subject chemical data

• QSAR evaluation per Patel et al. (2018) strategy will be discussed in more detail

• Human in vitro data: Lewis et al. (2003)
  • IVIVE same as Lewis et al. (2003) in vitro data

• Rat in vivo and in vitro data
  • Price and Krishnan (2011)
  • Sarigiannis et al. (2017) (subset of Price and Krishnan 2011 endpoint data)
  • Interspecies extrapolation same as Mortensen et al. (2000) rat in vitro data
Progress: Vmax and KM from other QSAR(s)

- Pirovano et al. (2015) (purified, nonrecombinant rat and rabbit liver CYP enzymes)
  - Benzyl alcohols, neutral organics, anilines, phenols, amides, phenol amines, esters, and aldehydes
    (training: 81, test: 40; not explicitly identified but could be guessed from figures)
  - Approximately 2000 descriptors from the Online Chemical Modeling Environment (OCHEM) were considered, but narrowed down to 6 or fewer
  - QSAR equations and statistics were reproduced with high precision after an earlier “obsolete” version of a descriptor estimation routine was substituted for the most recent version

Performance of putative QSAR training and test sets based on CYP endpoints and descriptors of Pirovano et al. (2015).

KM units: µM, Vmax units: µmol/min/mg microsomal protein
Progress: Clearance estimates from in silico software/applications

- KM estimates were taken from in vitro and in vivo estimates (minimum and maximum values)
- Vmax estimates were backed out from in silico metabolic clearance estimates (metabolic clearance = Vmax/KM)
- Other in silico estimators are available; these examples are not exhaustive, but were freely available
- Sipes et al. 2017
  - ADMET Predictor 7.2 clearance estimates (in original units of µL/min/mg liver microsomal protein) reported in supplementary material
    - Considers CYP 1A2, 2C9, 2C19, 2D6, and 3A4
  - IVIVE same as Lewis et al. 2003
- Open Structure-activity/property Relationship App (OPERA), National Toxicology Program (NTP), 2020
  - Estimated with units of µL/min/10^6 cells using a 5-nearest neighbors approach, with low confidence (personal communication from Kamel Mansouri)
  - IVIVE same as Lewis et al. 2003, with exception that scaling was based on hepatocellularity data of Barter et al. (2007) rather than microsomal protein yield.
Deeper Dive on QSAR Resource Evaluation

  • Select paper for analysis
  • Evaluate adherence to Organisation for Economic Cooperation and Development (OECD) Principles for the validation of QSARs (OECD 2004)
  • Follow proscribed workflow for QSAR model implementation
• Three QSAR papers that incorporated 1,2,4-TMB data will be discussed
• Spoiler: all three had flaws
Findings: Summary of QSARs evaluated

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoints</th>
<th>Nature of experimental system</th>
<th>Descriptors</th>
<th>Chemical Domain, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al. 2003</td>
<td>Vmax and Vmax/KM</td>
<td>Human liver microsomes</td>
<td>Computed molecular orbital energies and experimental logP (log of the octanol:water partition coefficient) values</td>
<td>Alkylbenzenes (7)</td>
</tr>
<tr>
<td>Price and Krishnan 2011</td>
<td>Vmax and KM</td>
<td>Rat, not explicitly reported (in vivo, microsomes, or liver slices)</td>
<td>Structural fragments</td>
<td>Volatile organic chemicals (53)</td>
</tr>
<tr>
<td>Sarigiannis et al. 2017</td>
<td>Vmax and KM</td>
<td>Rat, not explicitly reported (in vivo, microsomes or liver slices)</td>
<td>Abraham solvation descriptors</td>
<td>Subset of Price and Krishnan (2011) data set; halogenated hydrocarbons, alcohols, ketones, hydrocarbons, ethers, esters, and aromatic hydrocarbons (29)</td>
</tr>
</tbody>
</table>

- Due to errors, none of the QSARs were suitable for use “as is”
- The Price and Krishnan (2011) endpoint values were not well referenced
- Allometric scaling of the Price and Krishnan (2011) endpoint values was inconsistent
- Reporting was generally incomplete
Lewis et al. 2003 (alkylbenzenes)

- Problems with published documentation
  - One QSAR was provided that did not match the reported descriptors
  - One log Vmax value and one log (Vmax/KM) value did not match the tabulated Vmax and KM data
  - Electronic structural descriptor values were provided that were not used in any reported QSAR

<table>
<thead>
<tr>
<th>Corrected QSAR Expression (± standard error for coefficients and intercept)</th>
<th>n</th>
<th>r</th>
<th>Standard error</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Log Vmax = (13.333 ± 0.984) –(1.0620 ± 0.101) × ΔE</td>
<td>6</td>
<td>0.982</td>
<td>0.0375</td>
<td>109.7</td>
<td>0.00047</td>
</tr>
<tr>
<td>3. Log Vmax = (27.3278 ± 5.9711) × ΔE – (1.46183 ± 0.31567) × (ΔE)² – (124.568 ± 28.212)</td>
<td>7</td>
<td>0.944</td>
<td>0.0661</td>
<td>16.4</td>
<td>0.0119</td>
</tr>
<tr>
<td>4. Log (Vmax/KM) = (7.777 ± 1.160) × logP – (1.2426 ± 0.1812) × (logP)² – (10.2735 ± 1.8492)</td>
<td>7</td>
<td>0.964</td>
<td>0.0428</td>
<td>26.4</td>
<td>0.00495</td>
</tr>
</tbody>
</table>

All intercept and coefficient p values < 0.05
Price and Krishnan (2011)

- Errors in reporting of descriptors for 4 chemicals
  - 1 typo, 3 used in QSAR derivation
- Errors/uncertainties in VmaxC values
  - Unit conversion error (6-fold)
  - Inappropriate scaling (linear scaling with respect to body weight in original)
  - Sources not cited; identified from other papers from group, my personal knowledge, and lit searches
- Inconsistencies in scaling
  - Sources often used BW^{0.7} while Price and Krishnan used BW^{0.75} with no adjustment
  - Authors used 0.25 kg BW to normalize Vmaxs, not study-specific BW
- Mixture of sources, including unvalidated rat liver slice data
- Lack of statistical information on QSAR expression parameterization
Price and Krishnan (2011) corrections

- VmaxC consistently scaled to BW^{0.7}
- VmaxC consistently normalized to study specific BW
- Sources explicitly identified
- Statistical details reported

New expression for logVmaxC based on updated Price and Krishnan (2011) descriptors and endpoint values (VmaxC in µmol/h/kg^{0.7})

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Standard Error</th>
<th>t Statistic</th>
<th>P-value</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CH3</td>
<td>0.2574</td>
<td>0.122</td>
<td>2.11</td>
<td>0.0409</td>
<td>0.01121</td>
</tr>
<tr>
<td>CH2</td>
<td>0.07139</td>
<td>0.0430</td>
<td>1.66</td>
<td>0.105</td>
<td>-0.01546</td>
</tr>
<tr>
<td>CH</td>
<td>-0.01259</td>
<td>0.161</td>
<td>-0.0782</td>
<td>0.938</td>
<td>-0.3378</td>
</tr>
<tr>
<td>C</td>
<td>-0.9065</td>
<td>0.291</td>
<td>-3.12</td>
<td>0.00326</td>
<td>-1.493</td>
</tr>
<tr>
<td>C=C</td>
<td>-0.6961</td>
<td>0.541</td>
<td>-1.29</td>
<td>0.205</td>
<td>-1.788</td>
</tr>
<tr>
<td>H</td>
<td>0.4538</td>
<td>0.195</td>
<td>2.33</td>
<td>0.0249</td>
<td>0.06027</td>
</tr>
<tr>
<td>Br</td>
<td>0.6558</td>
<td>0.134</td>
<td>4.88</td>
<td>1.57×10^{-5}</td>
<td>0.3846</td>
</tr>
<tr>
<td>Cl</td>
<td>0.5419</td>
<td>0.0779</td>
<td>6.96</td>
<td>1.66×10^{-8}</td>
<td>0.3847</td>
</tr>
<tr>
<td>Fl</td>
<td>0.3503</td>
<td>0.130</td>
<td>2.70</td>
<td>0.00993</td>
<td>0.0885</td>
</tr>
<tr>
<td>AC</td>
<td>0.7190</td>
<td>1.34</td>
<td>0.536</td>
<td>0.595</td>
<td>-1.987</td>
</tr>
<tr>
<td>H_AC</td>
<td>0.1292</td>
<td>0.265</td>
<td>0.488</td>
<td>0.628</td>
<td>-0.4050</td>
</tr>
</tbody>
</table>
Price and Krishnan (2011) corrections

New expression for log KM based on updated Price and Krishnan (2011) descriptors and endpoint values (KM in µM)

<table>
<thead>
<tr>
<th></th>
<th>Coefficients</th>
<th>Standard Error</th>
<th>t Statistic</th>
<th>P-value</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0</td>
<td>#N/A</td>
<td>#N/A</td>
<td>#N/A</td>
<td>#N/A</td>
<td>#N/A</td>
</tr>
<tr>
<td>CH₃</td>
<td>0.149978</td>
<td>0.09518</td>
<td>1.57528</td>
<td>0.122592</td>
<td>-0.0421</td>
<td>0.34206</td>
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<tr>
<td>CH₂</td>
<td>0.14739</td>
<td>0.033579</td>
<td>4.389396</td>
<td>7.52 × 10⁻⁵</td>
<td>0.079625</td>
<td>0.215154</td>
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<tr>
<td>CH</td>
<td>0.105545</td>
<td>0.125717</td>
<td>0.839543</td>
<td>0.405918</td>
<td>-0.1486</td>
<td>0.359253</td>
</tr>
<tr>
<td>C</td>
<td>0.015109</td>
<td>0.226675</td>
<td>0.066655</td>
<td>0.947173</td>
<td>-0.44234</td>
<td>0.472557</td>
</tr>
<tr>
<td>C=C</td>
<td>0.566287</td>
<td>0.422025</td>
<td>1.341835</td>
<td>0.186859</td>
<td>-0.28539</td>
<td>1.417968</td>
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<tr>
<td>H</td>
<td>-0.14138</td>
<td>0.15215</td>
<td>-0.92924</td>
<td>0.358076</td>
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<td>0.165667</td>
</tr>
<tr>
<td>Br</td>
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<td>0.104851</td>
<td>0.529939</td>
<td>0.598945</td>
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<tr>
<td>Cl</td>
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<td>0.060753</td>
<td>1.706198</td>
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<tr>
<td>Fl</td>
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<td>0.101188</td>
<td>1.354852</td>
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<tr>
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<td>0.295377</td>
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<td>3.219524</td>
</tr>
<tr>
<td>H_AC</td>
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<td>0.206533</td>
<td>-0.70777</td>
<td>0.482997</td>
<td>-0.56298</td>
<td>0.270622</td>
</tr>
</tbody>
</table>

New expression for log KM based on updated Price and Krishnan (2011) descriptors and endpoint values (KM in µM)
Sarigiannis et al. (2017)

- Endpoint values are a subset of the (corrected) Price and Krishnan (2011) data
  - Reasons for exclusions are not articulated
  - In Sarigiannis et al. 2017, the $V_{\text{max}}C$ for chlorodibromomethane was used in place of the value for bromodichloromethane
- Descriptor “v” was in error for two compounds
  - Transposition of digits (once)
  - Duplication of value of neighboring entry

New expression for log $V_{\text{max}}C$ based on updated Sarigiannis et al. (2017) descriptors and endpoint values ($V_{\text{max}}C$ in $\mu$mol/h/kg$^{0.7}$)

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Standard Error</th>
<th>t Statistic</th>
<th>P-value</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.6150</td>
<td>0.215</td>
<td>7.524</td>
<td>$1.21 \times 10^{-7}$</td>
<td>1.1710 \ 2.0590</td>
</tr>
<tr>
<td>E</td>
<td>0.1972</td>
<td>0.442</td>
<td>0.447</td>
<td>0.659</td>
<td>-0.7165 \ 1.1109</td>
</tr>
<tr>
<td>S</td>
<td>-0.1307</td>
<td>0.560</td>
<td>-0.233</td>
<td>0.818</td>
<td>-0.233 \ 0.818</td>
</tr>
<tr>
<td>A</td>
<td>1.8689</td>
<td>1.187</td>
<td>1.575</td>
<td>0.129</td>
<td>-0.5861 \ 4.3239</td>
</tr>
<tr>
<td>B</td>
<td>4.0795</td>
<td>1.025</td>
<td>3.979</td>
<td>0.001</td>
<td>1.9584 \ 6.2006</td>
</tr>
<tr>
<td>V</td>
<td>-0.6453</td>
<td>0.194</td>
<td>-3.328</td>
<td>0.003</td>
<td>-1.0464 \ -0.2442</td>
</tr>
</tbody>
</table>
New expression for log KM based on updated Sarigiannis et al. (2017) descriptors and endpoint values (KM in µM)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercept</td>
<td>0.2373</td>
<td>0.361</td>
<td>0.6568</td>
<td>-0.5100</td>
<td>0.9845</td>
</tr>
<tr>
<td>E</td>
<td>-0.0363</td>
<td>0.743</td>
<td>-0.0489</td>
<td>0.9614</td>
<td>-1.5740</td>
<td>1.5013</td>
</tr>
<tr>
<td>S</td>
<td>0.4667</td>
<td>0.943</td>
<td>0.4949</td>
<td>0.6254</td>
<td>-1.4840</td>
<td>2.4174</td>
</tr>
<tr>
<td>A</td>
<td>-2.6389</td>
<td>1.997</td>
<td>-1.3213</td>
<td>0.1994</td>
<td>-6.7704</td>
<td>1.4926</td>
</tr>
<tr>
<td>B</td>
<td>-2.5017</td>
<td>1.726</td>
<td>-1.4498</td>
<td>0.1606</td>
<td>-6.0712</td>
<td>1.0679</td>
</tr>
<tr>
<td>V</td>
<td>0.6700</td>
<td>0.326</td>
<td>2.0533</td>
<td>0.0516</td>
<td>-0.0050</td>
<td>1.3450</td>
</tr>
</tbody>
</table>
Progress: Performance of $V_{\text{max}}$ and $K_{\text{m}}$ estimates

- Subset of parameter estimates for clarity
- OPERA was indistinguishable from “no metabolism”
- The chemical specific in vitro estimates tended to over predict metabolic clearance and QSARs based on broader data sets under estimated metabolism
Progress: Toxicity Reference Value implications of Vmax and KM estimates

<table>
<thead>
<tr>
<th>Acute Exposure Guideline Level (AEGL) 2</th>
<th>Threshold Limit Value</th>
<th>Reference Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single 8 h exposure</td>
<td>8 h/d, 5 days/week</td>
<td>Continuous exposure</td>
</tr>
<tr>
<td>738 mg/m³</td>
<td>123 mg/m³</td>
<td>0.06 mg/m³</td>
</tr>
</tbody>
</table>

- Duration required for periodicity/steady state for chronic exposure was determined with VmaxC = 0, with simulation until the AUC for the last week increased by less than 1% over the preceding week (10 weeks).
- While multiple metrics could be considered, only blood Cmax is presented for illustration purposes.
- Impact for this metric varies with exposure conditions, likely due to differential sensitivity to Vmax and/or KM.

![Toxicity Reference Value Implications](image-url)
Lessons learned/confirmed to date:

- Published PBPK models often have incomplete information on Vmax scaling
- Vmax and KM estimation is not a simple matter even for a limited data set
- QSARs generated to support PBPK modeling do not conform to current transparency standards
  - Clerical errors identified
  - Scaling and protocol inconsistencies identified
  - Referencing/sourcing of underlying data was challenging even for a practitioner with extensive experience and knowledge of the field
- Consideration of multiplicity of models for a single chemical was not addressed in previous surrogate example (Lu et al. 2016) and is a substantial issue for many chemicals
Future plans and possibilities

- Closure on QSAR usability efforts
- Complete and further evaluate metrics from TRV impact analysis
- Conduct sensitivity analysis
- **Articulate a rationale for anticipated PBPK model reliability/predictivity based on calibration/validation approaches and findings**
- Complete similar analysis for a C9-aromatic without an existing PBPK model, but with human in vivo data
- Complete similar analysis for C9-aromatics without human in vivo data or an existing PBPK model; develop an approach for making recommendations in the absence of validation data
- Apply similar approach to partition coefficient estimates
- Apply similar approach to a different chemical category
Summary

• In an effort to improve and expedite data-driven risk assessment for occupational settings, we are exploring the use of NAMs, surrogates, and read-across for PBPK model development

• An initial case study is underway with a subject chemical with existing, validated human PBPK models and limited in vivo and in vitro toxicokinetic data

• Existing QSARs were generally found to require correction and/or improved documentation to establish confidence

• The approach being implemented is expected to evolve with experience and multidisciplinary, multi-stakeholder feedback from the scientific community
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References


References


Questions?