Application of New Approach Methods, Surrogates, and Read Across in Rapid Development of Physiologically Based Pharmacokinetic (PBPK) Models for Human Health Risk Assessment

Presented May 27, 2021
Public Meeting of the Interagency Coordinating Committee on Validation of Alternative Methods

by Lisa M. Sweeney, Ph.D., DABT, CHMM
UES, Inc., assigned to US Air Force Research Laboratory 711th Human Performance Wing, Wright-Patterson, Air Force Base, Ohio USA
LSweeney@ues.com

Disclaimers

- I am a contractor working with the 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 (DOD), 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
- 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

USAF photo by SrA Ryan Callaghan

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

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

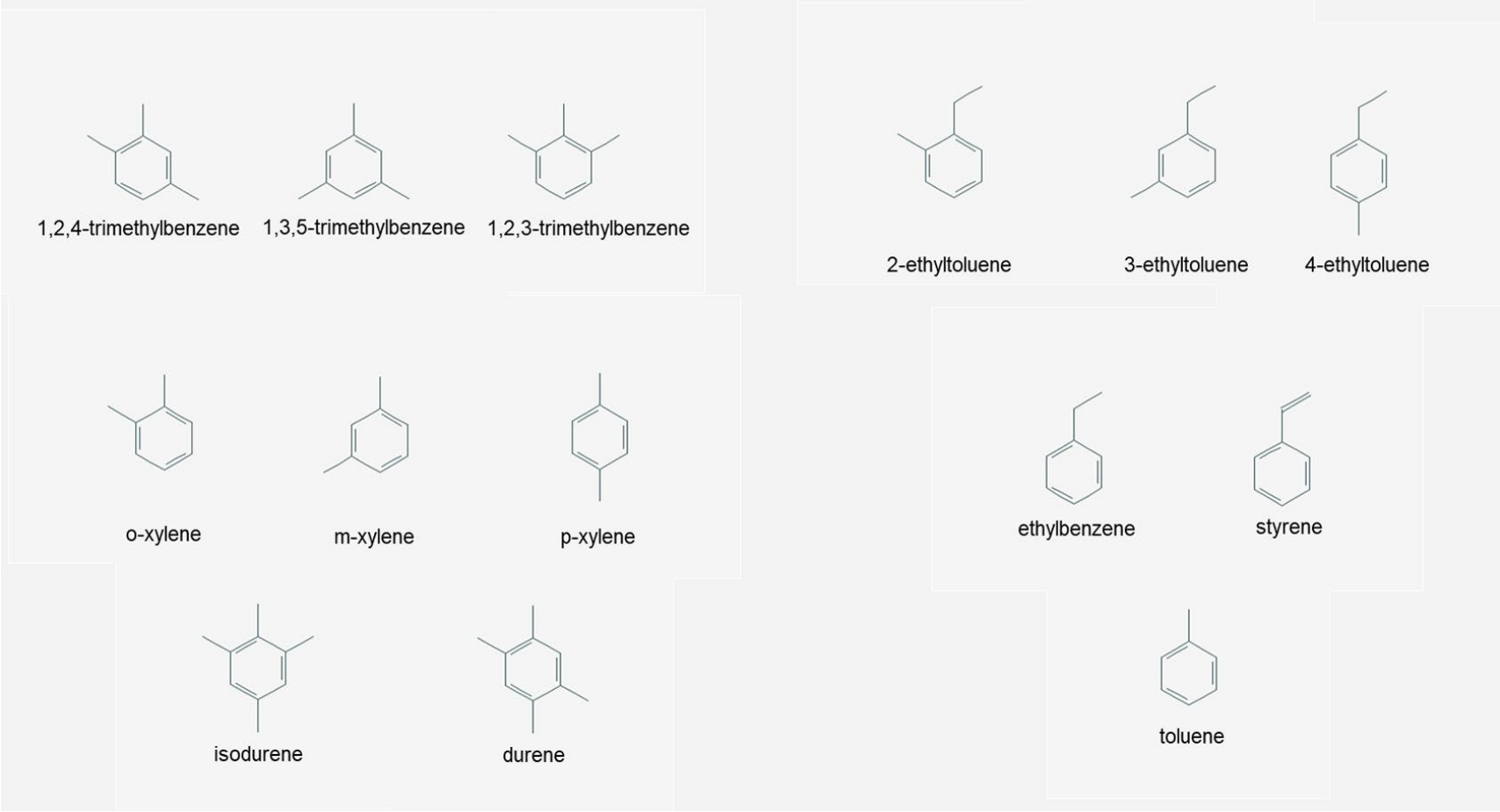
- Parameterization
  - Develop Vmax and Km estimates from in vivo, in vitro, and in silico data for the subject chemical
    - Literature searches
    - Identify online in silico tools
    - Evaluate QSARs per Patel et al. (2018)
    - Interspecies extrapolation
    - In vitro (or in silico) to in vivo 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)

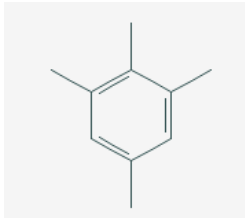
Progress: Case study, possible case series, and surrogates

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

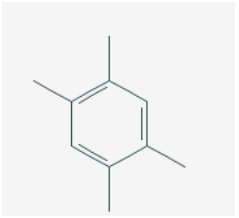


Progress: Surrogates

- 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



isodurene



durene

- 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

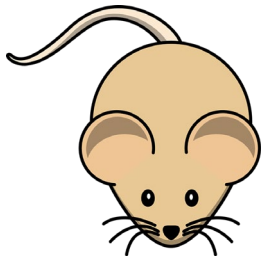
Progress: Summary of human 1,2,4-TMB Vmax and KM estimates

- 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

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

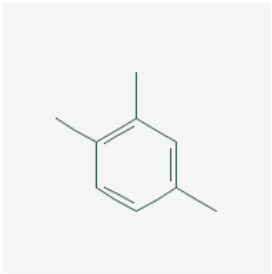


IN VITRO DATA (3):
One rat liver slice study:
Generic scaling
Categorical scaling
One human liver microsome study

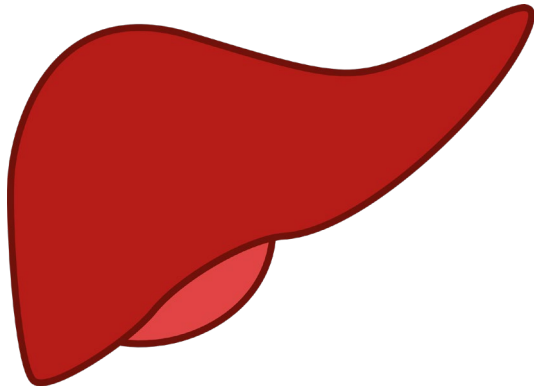
USER-IMPLEMENTED QSAR without 1,2,4-TMB SOURCE DATA (1):
Rat and rabbit in vitro data

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 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

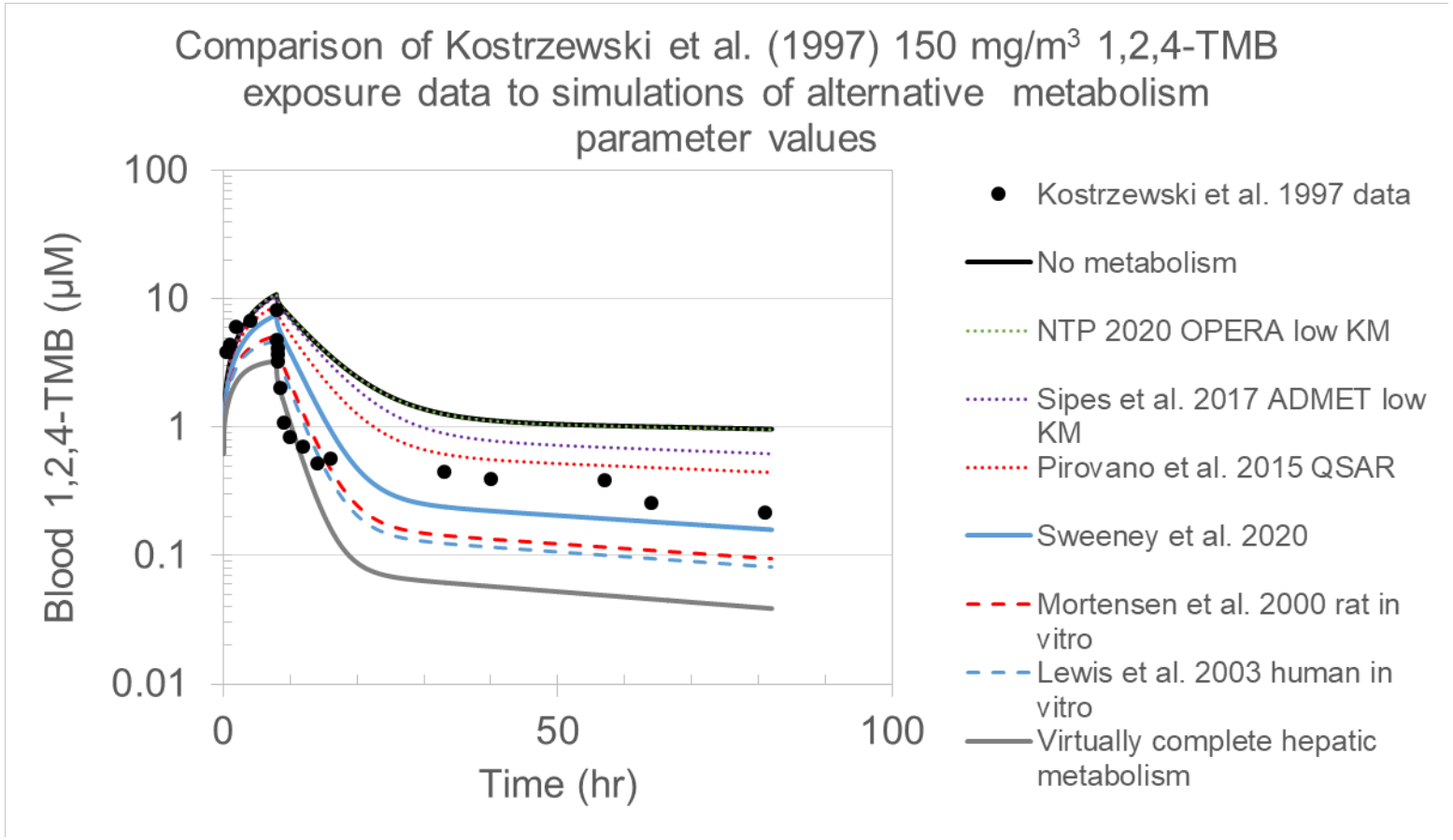


Findings: Summary of QSARs evaluated

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

- 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

Progress: Performance of Vmax and Km estimates

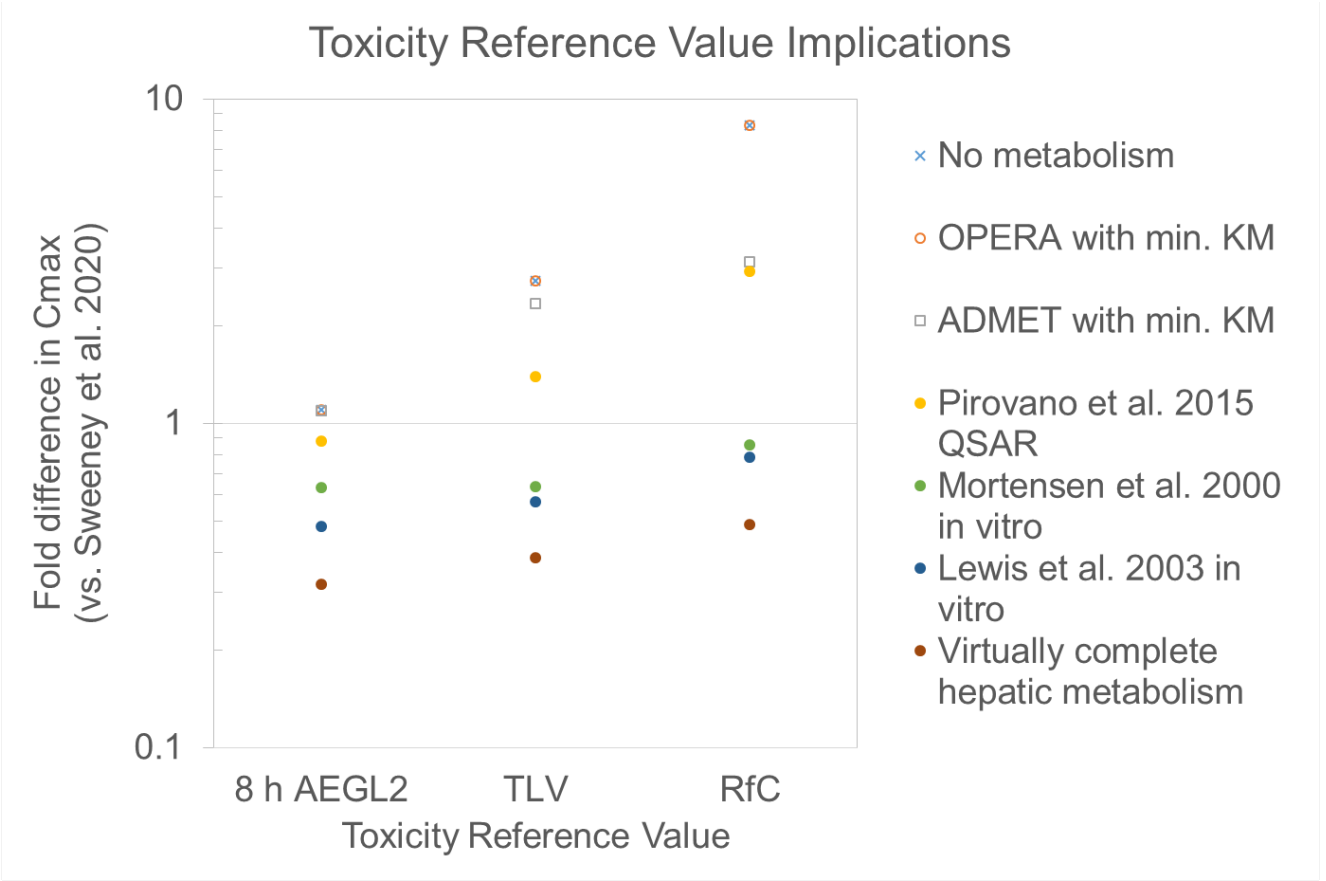


- Subset of parameter estimates for clarity
- The chemical specific in vitro estimates tended to over predict metabolic clearance and QSARs based on broader data sets under estimated metabolism

Progress: Toxicity Reference Value implications of Vmax and KM estimates

Acute Exposure Guideline Level (AEGL) 2	Threshold Limit Value	Reference Concentration
Single 8 h exposure	8 h/d, 5 days/week	Continuous exposure
738 mg/m^3	123 mg/m^3	0.06 mg/m^3
National Research Council (2012)	American Conference of Governmental Industrial Hygienists (ACGIH, 2018)	U.S. EPA (2016)

- 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



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
- Future plans
  - Finalize QSARs and conduct PBPK model sensitivity analyses
  - **Articulate a rationale for anticipated PBPK model reliability/predictivity based on calibration/validation approaches and findings**
  - Expand case study approach
    - 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 a different chemical category

Acknowledgements

- This effort was financially supported under the Virtual Airman SimulaTion (VAST) task
- AFRL contributors
  - Jeff Gearhart
  - Matt Linakis
  - Teri Sterner
  - Tammie Covington
  - Slava Chushak

References

- American Conference of Governmental Industrial Hygienists (ACGIH): 2018. TLVs and BEIs. Cincinnati, OH, American Conference of Governmental Industrial Hygienists, 2018.
- Barter ZE, Bayliss MK, Beaune PH, Boobis AR, Carlile DJ, Edwards RJ, Houston JB, Lake BG, Lipscomb JC, Pelkonen OR, Tucker GT, Rostami-Hodjegan A. Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver. Curr Drug Metab. 2007 Jan;8(1):33-45. doi: 10.2174/138920007779315053.
- Béliveau M, Lipscomb J, Tardif R, Krishnan K. Quantitative structure-property relationships for interspecies extrapolation of the inhalation pharmacokinetics of organic chemicals. Chem Res Toxicol. 2005 Mar;18(3):475-85. doi: 10.1021/tx049722k.
- Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP. Physiological parameter values for physiologically based pharmacokinetic models. Toxicol Ind Health. 1997 Jul-Aug;13(4):407-84. doi: 10.1177/074823379701300401
- Covington TR., Pangburn HA, Gearhart JM, Ott, DK. Incorporation of Operational Features of Flight into a Physiologically-Based Pharmacokinetic (PBPK) Model. 711 HPW/RHMO Wright-Patterson AFB United States. 2019-09-20. AFRL-RH-WP-TR-2020-0015 (AFRLRHWPTR20200015). AD1096307.
- Jałowiecki P, Janasik B. Physiologically-based toxicokinetic modeling of durene (1,2,3,5-tetramethylbenzene) and isodurene (1,2,4,5-tetramethylbenzene) in humans. Int J Occup Med Environ Health. 2007;20(2):155-65. doi:10.2478/v10001-007-0012-6.
- Kostrzewski P, Wiaderna-Brycht A, Czerski B. Biological monitoring of experimental human exposure to trimethylbenzene. Sci Total Environ. 1997 Jun 20;199(1-2):73-81. doi: 10.1016/s0048-9697(97)05504-6.
- Lewis DF, Sams C, Loizou GD. A quantitative structure-activity relationship analysis on a series of alkyl benzenes metabolized by human cytochrome p450 2E1. J Biochem Mol Toxicol. 2003;17(1):47-52. doi: 10.1002/jbt.10055.
- Lipscomb JC, Poet TS. In vitro measurements of metabolism for application in pharmacokinetic modeling. Pharmacol Ther. 2008 Apr;118(1):82-103. doi: 10.1016/j.pharmthera.2008.01.006
- Lu J, Goldsmith MR, Grulke CM, Chang DT, Brooks RD, Leonard JA, Phillips MB, Hypes ED, Fair MJ, Tornero-Velez R, Johnson J, Dary CC, Tan YM. Developing a physiologically-based pharmacokinetic model knowledgebase in support of provisional model construction. PLoS Comput Biol. 2016 Feb 12;12(2):e1004495. doi: 10.1371/journal.pcbi.1004495.

References

- Mortensen B, Løkken T, Zahlsen K, Nilsen OG. Comparison and in vivo relevance of two different in vitro head space metabolic systems: liver S9 and liver slices. Pharmacol Toxicol. 1997 Jul;81(1):35-41. doi:10.1111/j.1600-0773.1997.tb00028.x.
- Mortensen B, Eide I, Zahlsen K, Nilsen OG. Prediction of in vivo metabolic clearance of 25 different petroleum hydrocarbons by a rat liver head-space technique. Arch Toxicol. 2000 Aug;74(6):308-12. doi: 10.1007/s002040000135.
- National Research Council 2012. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 13. Washington, DC: The National Academies Press. https://doi.org/10.17226/15852.
- National Toxicology Program 2020. OPERA. http://ntp.niehs.niih.gov/whatwestudy/niceatm/comptox/ct-opera.html.
- Paini A, Leonard JA, Joossens E, Bessems JGM, Desalegn A, Dorne JL, Gosling JP, Heringa MB, Klaric M, Kliment T, Kramer NI, Loizou G, Louisse J, Lumen A, Madden JC, Patterson EA, Proença S, Punt A, Setzer RW, Suciu N, Troutman J, Yoon M, Worth A, Tan YM. Next generation physiologically based kinetic (NG-PBK) models in support of regulatory decision making. Comput Toxicol. 2019 Feb;9:61-72. doi: 10.1016/j.comtox.2018.11.002.
- Patel M, Chilton ML, Sartini A, Gibson L, Barber C, Covey-Crump L, Przybylak KR, Cronin MTD, Madden JC. Assessment and reproducibility of quantitative structure-activity relationship models by the nonexpert. J Chem Inf Model. 2018 Mar 26;58(3):673-682. doi: 10.1021/acs.jcim.7b00523
- Pirovano A, Brandmaier S, Huijbregts MA, Ragas AM, Veltman K, Hendriks AJ. The utilization of structural descriptors to predict metabolic constants of xenobiotics in mammals. Environ Toxicol Pharmacol. 2015 Jan;39(1):247-58. doi:10.1016/j.etap.2014.11.025.
- Price K, Krishnan K. An integrated QSAR-PBPK modelling approach for predicting the inhalation toxicokinetics of mixtures of volatile organic chemicals in the rat. SAR QSAR Environ Res. 2011 Mar;22(1-2):107-28. doi:10.1080/1062936X.2010.548350.
- Sarigiannis DA, Papadaki K, Kontoroupis P, Karakitsios SP. Development of QSARs for parameterizing physiology based toxicokinetic models. Food Chem Toxicol. 2017 Aug;106(Pt A):114-124. doi: 10.1016/j.fct.2017.05.029.
- Sipes NS, Wambaugh JF, Pearce R, Auerbach SS, Wetmore BA, Hsieh JH, Shapiro AJ, Svoboda D, DeVito MJ, Ferguson SS. An intuitive approach for predicting potential human health risk with the Tox21 10k library. Environ Sci Technol. 2017 Sep 19;51(18):10786-10796. doi: 10.1021/acs.est.7b00650

References

- Sweeney LM, Gearhart JM, Ott DK, Pangburn HA. Considerations for development of exposure limits for chemicals encountered during aircraft operation. Mil Med. 2020 Jan 7;185(Suppl 1):390-395. doi: 10.1093/milmed/usz318.
- Sweeney LM. Impact of stressors in the aviation environment on xenobiotic dosimetry in humans: physiologically based prediction of the effect of barometric pressure or altitude. J Toxicol Environ Health A. 2020 Apr 17;83(8):302-312. doi: 10.1080/15287394.2020.1755403
- Sweeney LM. Impact of stressors in the aviation environment on xenobiotic dosimetry in humans: physiologically based prediction of the effect of +Gz forces. J Toxicol Environ Health A. 2020 May 18;83(10):395-403. doi: 10.1080/15287394.2020.1767249.
- Sweeney LM Effect of Exertion on Adult Breathing Parameters: Literature Review and Meta-analysis. 711 HPW/RHM Wright-Patterson AFB United States. 2020-03-05. AFRL-RH-WP-TR-2020-0013 (AFRLRHWPTR20200013). AD1096857.
- Williams AJ, Grulke CM, Edwards J, McEachran AD, Mansouri K, Baker NC, Patlewicz G, Shah I, Wambaugh JF, Judson RS, Richard AM. The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. J Cheminform. 2017 Nov 28;9(1):61. doi: 10.1186/s13321-017-0247-6.

Questions?