

Physiologically-Based Pharmacokinetic (PBPK) Modeling and Reporting for Chemical Risk Assessment and Analysis of Environmental Compounds

Pharsight© Reporting and Analysis Services (RAS) is a highly skilled team of modelers, toxicologists and pharmaceutical scientists committed to providing high-quality, regulatory-compliant PBPK modeling for chemical risk assessment and analysis of environmental compounds. All RAS work is executed to the highest professional standards, in minimum time, at competitive rates.

BACKGROUND

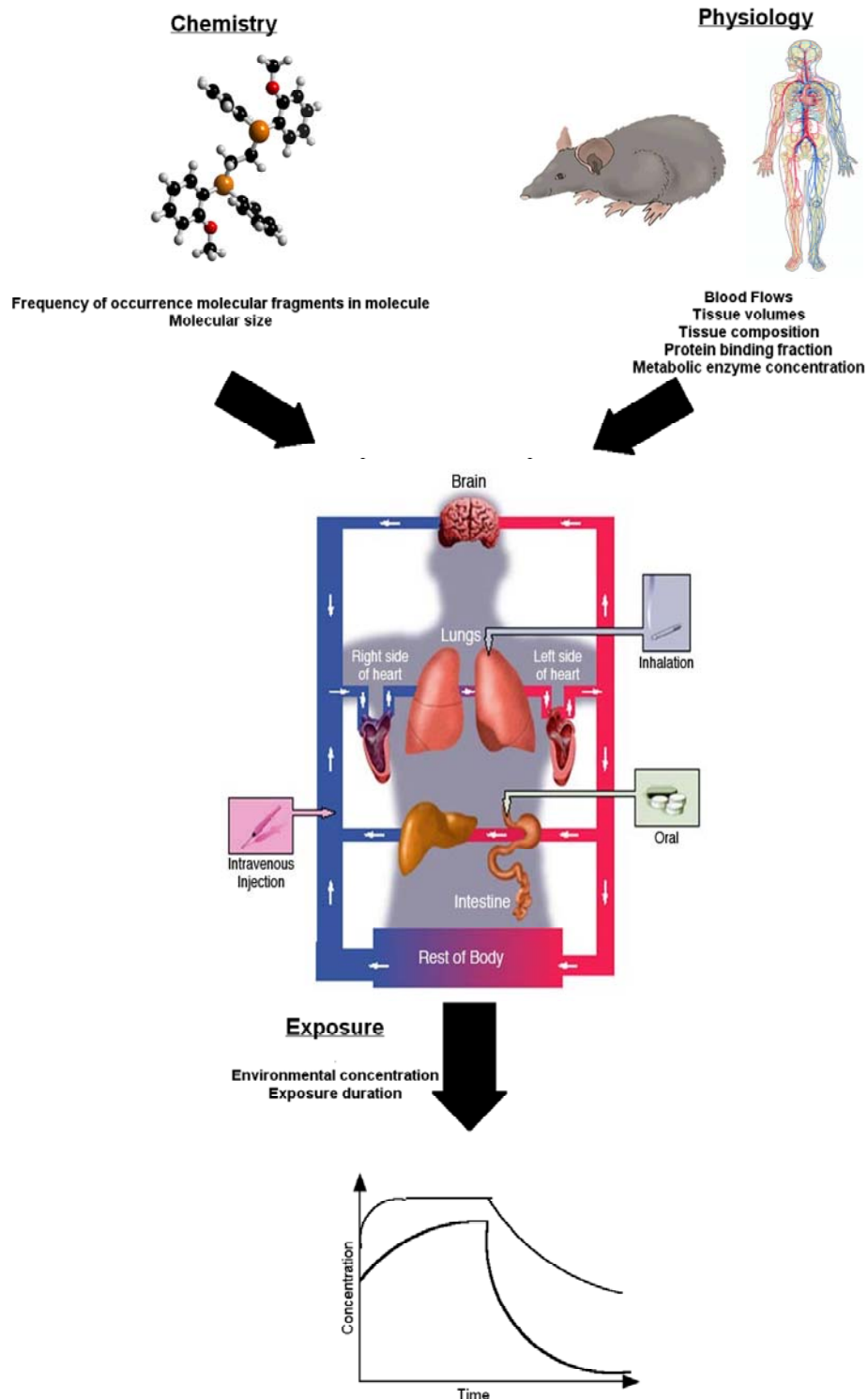
- **Pharsight Software:** RAS scientists use Pharsight's industry-leading software tools to provide timely, high-quality modeling for risk/safety assessments to support chemical deployment programs and occupational safety assessments.
- **Expert Staff, Global Reach:** Pharsight RAS is comprised of a core group of scientists with expertise in toxicology, risk assessment, pharmacokinetics (PK), pharmacodynamics (PD), statistical analysis, regulatory strategy and report writing. Our scientists have successfully conducted more than 400 client engagements in the past several years.
- **Delivery Approach:** RAS conducts its business according to four key principles: (1) uncompromising scientific integrity; (2) teamwork; (3) technical innovation; and (4) commitment to customer service in all aspects of project execution.

CAPABILITIES

- **PBPK Model Development:** RAS scientists use Pharsight's [Trial Simulator®](http://www.pharsight.com/products/prod_pts_home.php) software for efficient PBPK modeling (http://www.pharsight.com/products/prod_pts_home.php):
 - **PBPK Conceptual Model Development and Parameter Estimation:**
 - *"In the absence of chemical-specific data, physiologically based toxicokinetic modeling is potentially the most comprehensive way to account for biological processes that determine internal dose."* Guidelines for Carcinogen Risk Assessment. US EPA 2005
 - Literature review of available information in species of interest
 - Physiological Parameters: blood flows, tissue volumes, ventilation rates
 - Physicochemical Parameters: partition coefficients
 - Biochemical Parameters: Affinity constants, capacity limited metabolic rates, intrinsic clearances, rate constants
 - Variability Estimates
 - Mode of action; internal dose surrogate
 - *In silico* modeling for de novo chemicals
 - QSAR-type approaches

○ **PBPK Model Build-Up and Validation:**

- A schematic representation of a PBPK model is presented below:



CAPABILITIES -- Continued

- **PBPK Model Application:** RAS scientists leverage the use of Trial Simulator® for:
 - Route-to-route extrapolation: PO to inhalation, concomitant multiple route exposures.
 - Temporal Scenario extrapolation: Single, repeated intermittent and continuous exposures.
 - High dose to low dose extrapolation: leveraging toxicity data to environmental/occupational levels.
 - Interspecies extrapolations: Rat-to-human extrapolation, ecosystem biodistribution to identify sentinel species.
 - Intraspecies extrapolations: Adult-to-juvenile, Caucasian-to-Asian
 - Single to multiple chemical extrapolations: Modeling of complex chemical interactions within a single system.
 - Health Risk Assessment: Establish links between safety levels and biomarkers of exposure or of effects for different exposure scenarios.
- **Monte Carlo Simulation:** By integrating what we know with regards to variability in the parameters into the modeling approach, RAS scientist can provide simulations for specific scenarios:
 - Parameter sensitivity analyses
 - Susceptible population identification
 - Chemical substitution (using QSAR tools)
 - Uncertainty analyses
- **Health Risk Assessment :** RAS scientists integrate their expertise in toxicology and modeling to perform health risk assessment of chemicals based on relevant guidelines (e.g., from US EPA, Cal-EPA):
 - Hazard Identification
 - Exposure Assessment
 - Dose-Response Assessment
 - Risk Characterization
- **Regulatory and Scientific Writing:** RAS has scientific writing capabilities to support writing of integrated reports for regulatory review by EPA and FDA.

CONTACT PHARSIGHT

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Selected Publications on PBPK and Risk Assessment by Pharsight Scientists

1. Gosselin, N.H., Valcke, M., Belleville, D., Samuel, O. (2008) Human exposure to malathion during a possible vector-control intervention against West Nile Virus I: Methodological framework for exposure assessment. *Human and Ecotoxicological Risk Assessment*, 14, 1118-1137.
2. Valcke, M., Gosselin, N.H., Belleville, D. (2008) Human exposure to malathion during a possible vector-control intervention against West Nile Virus II: Evaluation of the toxicological risk using a probabilistic approach. *Human and Ecotoxicological Risk Assessment*, 14, 1138-1158.
3. Gosselin, N.H., Brunet, R.C., Carrier, G., Bouchard, M., Feeley, M. (2006). Reconstruction of methylmercury intakes in indigenous population from biomarker data. *Journal of Exposure Science and Environmental Epidemiology*, 16, 19-29.
4. Béliveau, M., Lipscomb, J. C., Tardif, R., Krishnan, K. (2005). Quantitative structure property relationships for interspecies extrapolation of the inhalation pharmacokinetics of organic chemicals. *Chem. Res. Toxicol.* 18, 475-485.
5. Gosselin, N.H., Brunet, R.C., Carrier, G., Dosso, A. (2005). Worker exposures to tricloropyr : risk assessment through measurements in urine samples. *The Annals of Occupational Hygiene* 49, 415-422.
6. Béliveau, M., Tardif, R., Krishnan, K. (2005). Molecular structure-based prediction of the steady-state blood concentrations of inhaled organics in rats. *Toxicol. Mech. Meth.* 15, 361-366.
7. Béliveau, M., Tardif, R., Krishnan, K. (2005). A Spreadsheet Program For Modeling Quantitative Structure-Pharmacokinetic Relationships For Inhaled Volatile Organics In Humans. *SAR QSAR Environ. Res.* 16, 63-77.
8. Gosselin, N.H., Bouchard, M., Brunet, R.C., Dumoulin, M.-J., Carrier, G. (2005). Toxicokinetic modeling of parathion and its metabolites in humans for the determination of biological reference values. *Toxicology Mechanisms and Methods*, 15, 33-52.
9. Béliveau, M., Tardif, R., Krishnan, K. (2003). Quantitative structure-property relationships for physiologically-based pharmacokinetic modeling of volatile organic chemicals in rats. *Toxicol. Appl. Pharmacol.* 189, 221-232.
10. Bouchard, M., Carrier, G., Brunet, R.C., Bonvalot, Y., Gosselin, N.H. (2005). Determination of biological reference values for chlorpyrifos metabolites in human urine using a toxicokinetic approach. *Journal of Occupational and Environmental Hygiene* 2, 155-168.
11. Béliveau, M., Krishnan, K. (2003). In silico approaches for physiologically-based pharmacokinetic modeling. In: *Alternative Toxicological Methods*, Ed. by Salem and Katz. CRC Press, Boca Raton FL.
12. Gosselin, N.H., Brunet, R.C., Carrier, G. (2003). Comparative occupational exposures to formaldehyde released from inhaled wood product dusts versus that in vapor form. *Journal of Applied Occupational and Environmental Hygiene* 18, 384-392.
13. Bouchard, M., Gosselin, N.H., Brunet, R.C., Samuel, O., Dumoulin, M.-J., Carrier, G. (2003). Development of a toxicokinetic model for predicting the fate of malathion and its metabolites in humans and its application for the risk assessment of exposure through measurements in urine samples. *Toxicological Sciences* 73, 182-194.
14. Krishnan, K., Haddad, S., Béliveau, M., Tardif, R. (2002). Physiological modeling and extrapolation of pharmacokinetic interactions from binary to more complex chemical mixtures. *Environ. Health Perspec.* 110 (Suppl. 6), 989-994.
15. Haddad, S., Béliveau, M., Tardif, R., Krishnan, K. (2001). A PBPK modeling-based approach to account for interactions in the health risk assessment of chemical mixtures. *Toxicol. Sci.* 63: 125-131.
16. Fouchécourt, M.-O., Béliveau, M., Krishnan, K. (2001) Quantitative Structure-Pharmacokinetic Relationship Modeling. *Sci. Tot. Env.* 274: 125-135.
17. Béliveau, M., Krishnan, K. (2001) Blood:air partition coefficients of individual and mixtures of trihalomethanes. *Chemosphere* 44, 377-381.
18. Béliveau, M., Krishnan, K. (2000) Estimation of rat blood:air partition coefficients of volatile organic chemicals using reconstituted mixtures of blood components. *Toxicol. Lett.* 116, 183-188.
19. Béliveau, M., Krishnan, K. (2000) Concentration dependency of rat blood:air partition coefficients of some volatile organic chemicals. *J. Toxicol. Env. Health, Part A*, 60: 101-113.
20. Poulin, P., Béliveau, M., Krishnan, K. (1999) Mechanistic animal-replacement approaches for predicting pharmacokinetics of organic chemicals, In *Toxicity Assessment Alternatives: Methods, Issues, Opportunities*, Ed. by Salem and Katz, Chap 11, p 115-139 Humana Press Inc, New Jersey.