In Silico Screening of Primary Clearance Mechanisms

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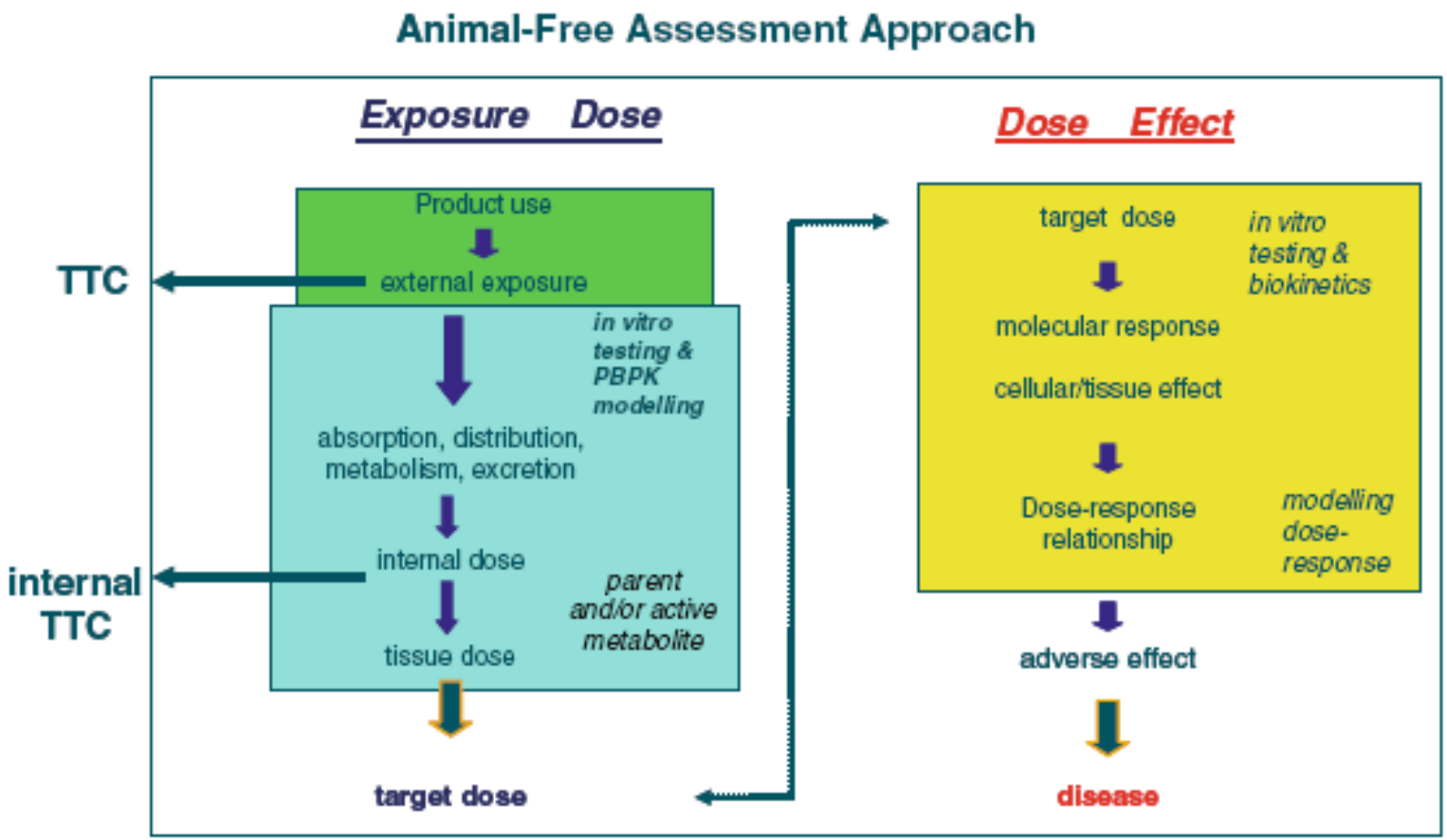
17Feb2016

P&G

Acknowledgements

- Karen Blackburn (P&G)
- George Daston (P&G)
- Corie Ellison (P&G)
- Joanna Jaworska (P&G)
- Cathy Lester (P&G)
- John Manwaring (P&G)
- Sheppard Martin (P&G)
- Yuri Dancik (A*STAR)

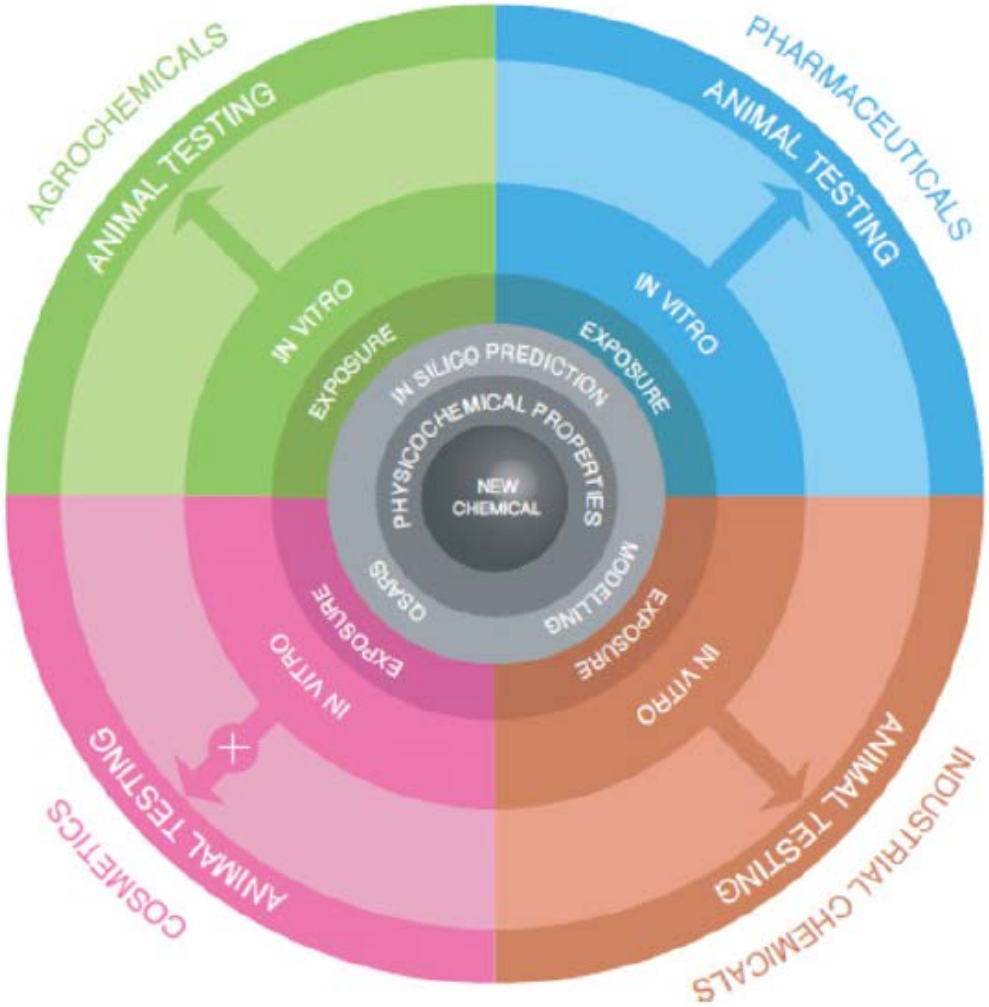
Vision: From Exposure to Effect



Toxicokinetic understanding is a critical information need to help facilitate the extrapolation of silico and in vitro hazard data into a quantitative risk assessment

Arch Toxicol (2011) 85:367–485

Alternative Approaches in Safety Testing

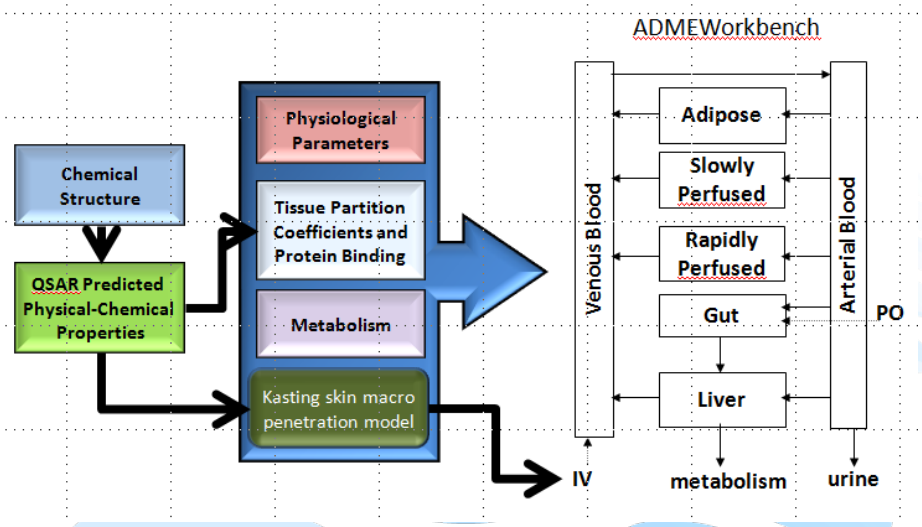


K. Schroeder et al. / Toxicology in Vitro 25 (2011) 589–604

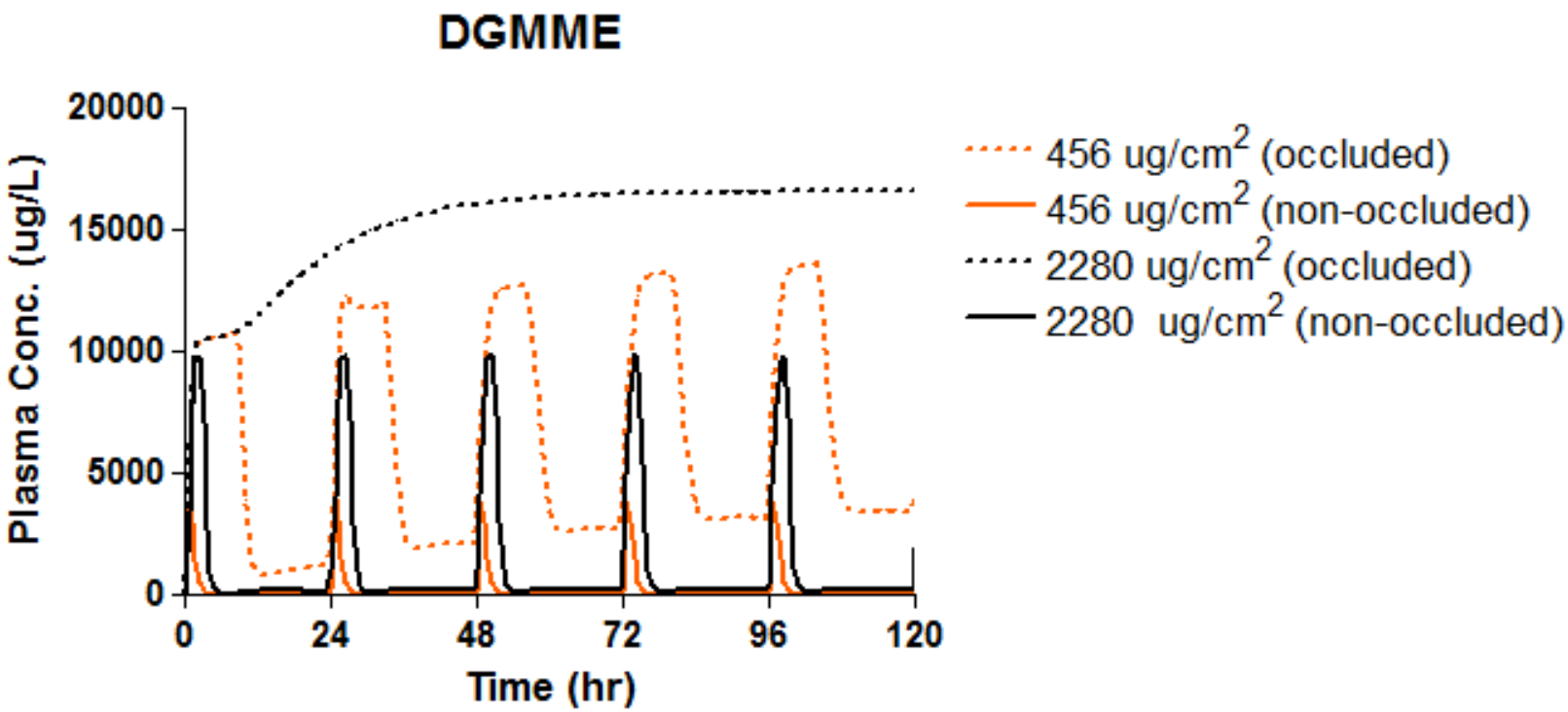
21st Century Toxicity Testing exposure toolbox

- Deliver more precision and quantification of uncertainty
- Allow to better use historical data for read-across
- Provide capability to base safety assessment on internal concentration and in vitro toxicity data

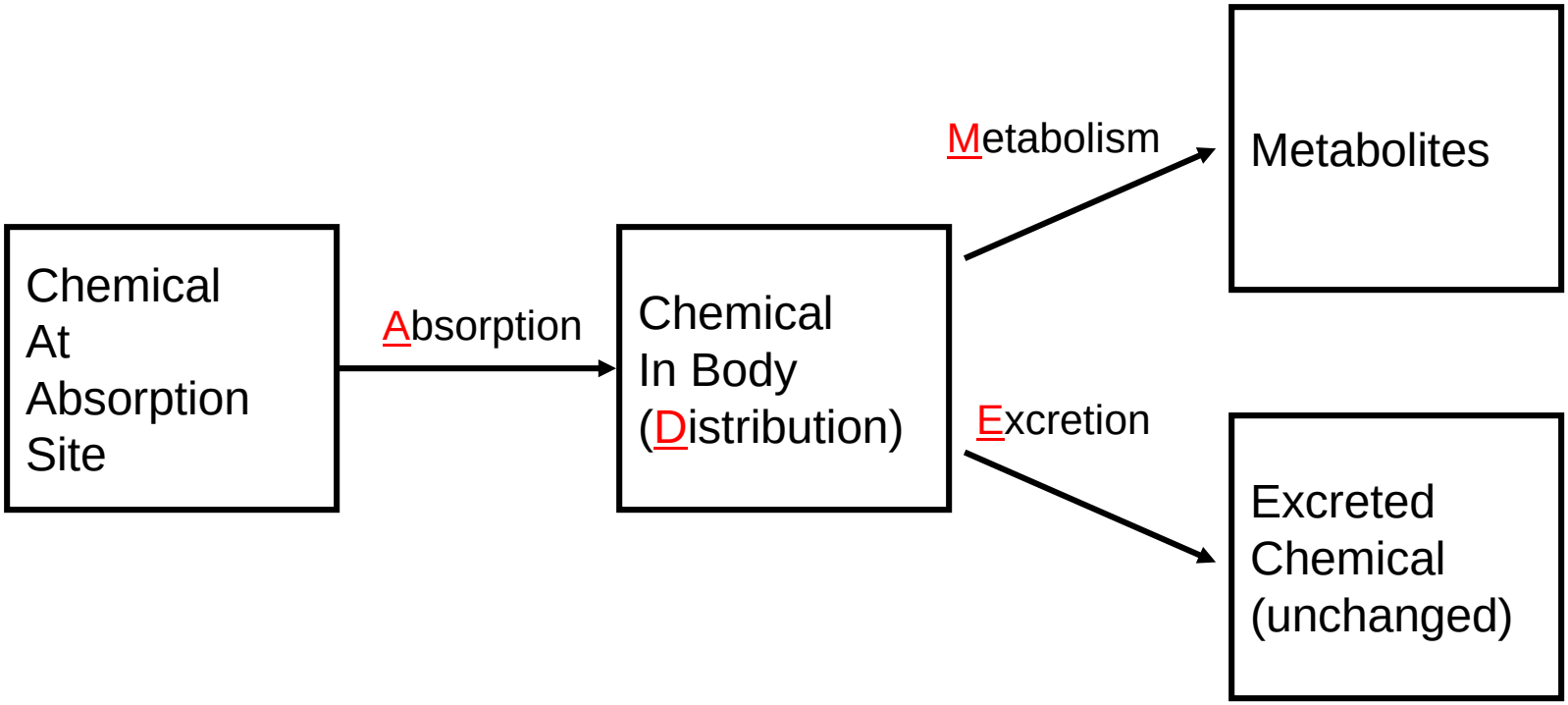
And the above translates to:
Reliable internal exposure estimation following realistic exposure scenerios:
Forward dosimetry prediction to obtain relevant dose metrics for quantitative risk assessment and regulatory acceptance



Model-predicted human plasma conc-time data (occluded vs non-occluded)



Absorption and Disposition Basics

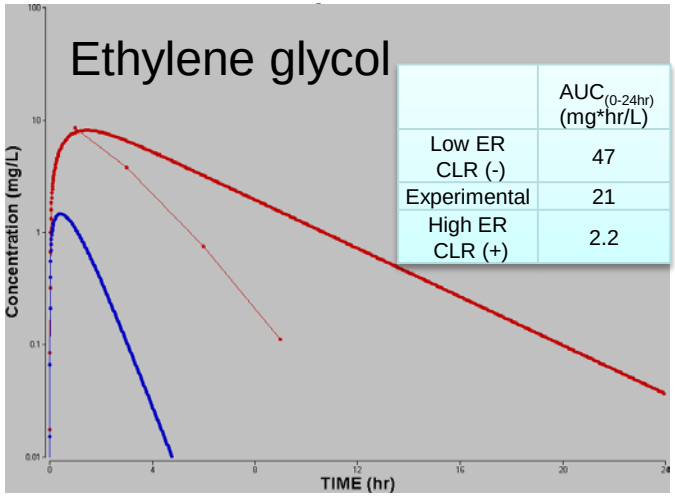


A priori identification of primary elimination pathways will provide an initial guide for the selection of methods/approaches for characterizing elimination pathways to drive efficiency in building PK dosimetry models

Research in Applying PBPK Models to Risk Assessment…

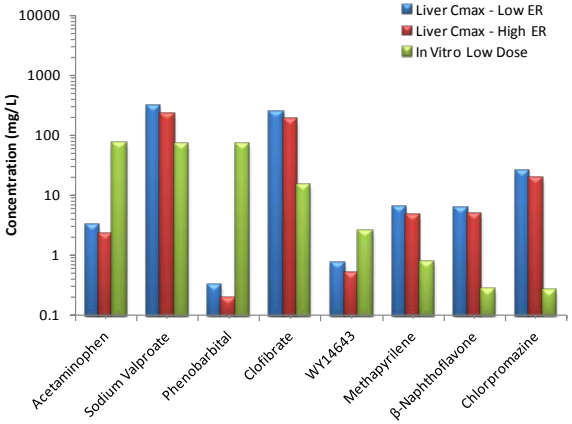
In the absence ADME data, a generic PBPK modeling approach has been developed using a mechanistic tissue distribution model and bracketing conservative assumptions of chemical elimination

In vivo predictions – oral



	$AUC_{(0-24hr)}$ (mg*hr/L)
Low ER CLR (-)	47
Experimental	21
High ER CLR (+)	2.2

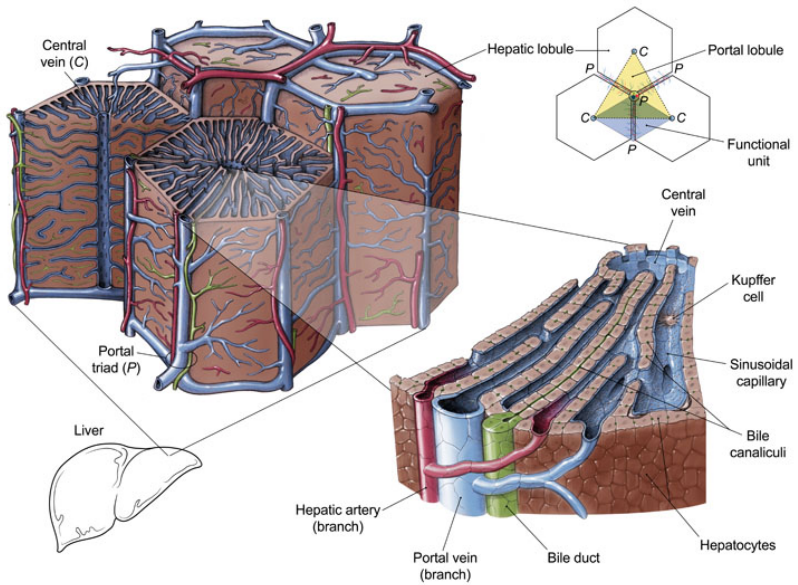
***in vitro to in vivo* dose extrapolation**



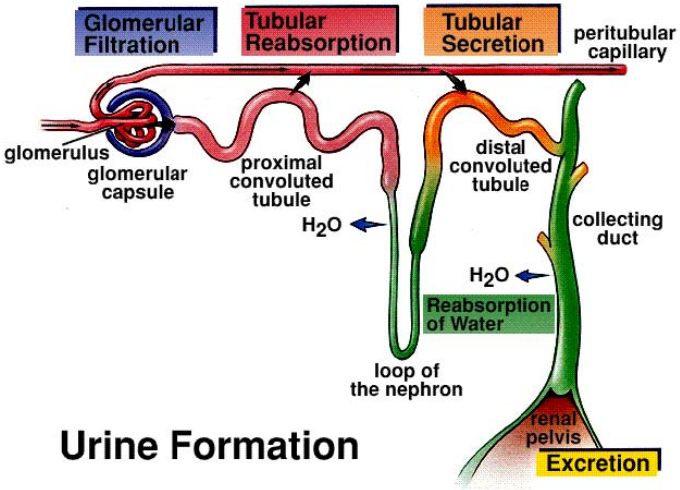
Goal is to enable routine extrapolation (IVIVE, oral rat to dermal human), support read-across assessments, improve risk decision-making

A highly versatile PBPK simulation tool has been developed for routine use

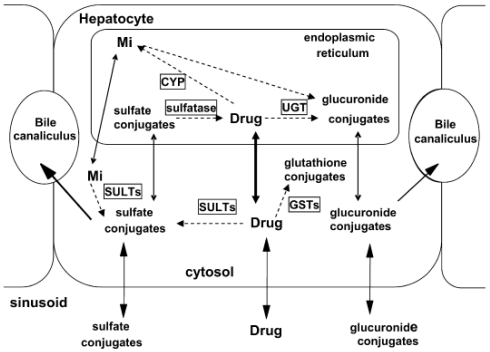
Liver Lobule



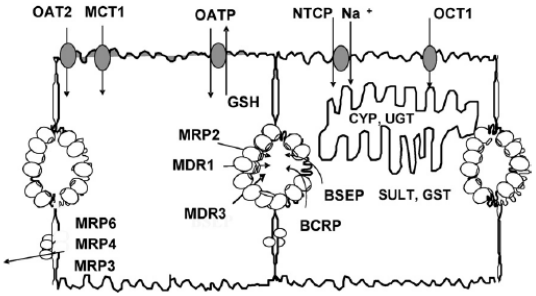
Nephron



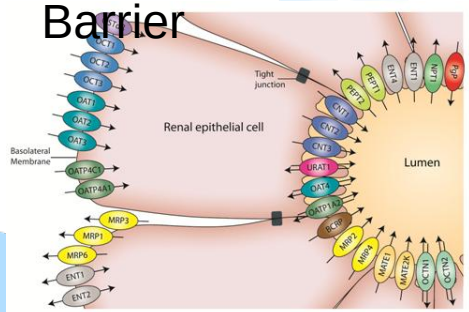
Hepatic Metabolism



Hepatic Uptake/Efflux



Transporters in the Human Renal Barrier



Publications

Pharm Res
DOI 10.1007/s11095-015-1749-4

PERSPECTIVE

Predicting Clearance Mechanism in Drug Discovery: Extended Clearance Classification System (ECCS)

Manthena V. Varma[1] • Stefanus J. Steyn[2] • Charlotte Allerton[1] • Ayman F. El-Kattan[2]

Journal of Medicinal Chemistry
Article
pubs.acs.org/jmc

Clearance Mechanism Assignment and Total Clearance Prediction in Human Based upon in Silico Models

Franco Lombardo,*,† R. Scott Obach,§ Manthena V. Varma,§ Rowan Stringer,‡ and Giuliano Berellini*,†

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, 2016
http://dx.doi.org/10.1517/17425255.2016.1132308

REVIEW

Hepatic drug transporters: the journey so far

R. J. Riley[a], S. A. Foley[a], P. Barton[b], M. G. Soars[c] and B. Williamson[a]

[a]Evotec, Abingdon, UK; [b]School of Life Sciences, University of Nottingham, Nottingham, UK; [c]Drug Metabolism and Pharmacokinetics, Bristol-Myers Squibb, Wallingford, CT, USA

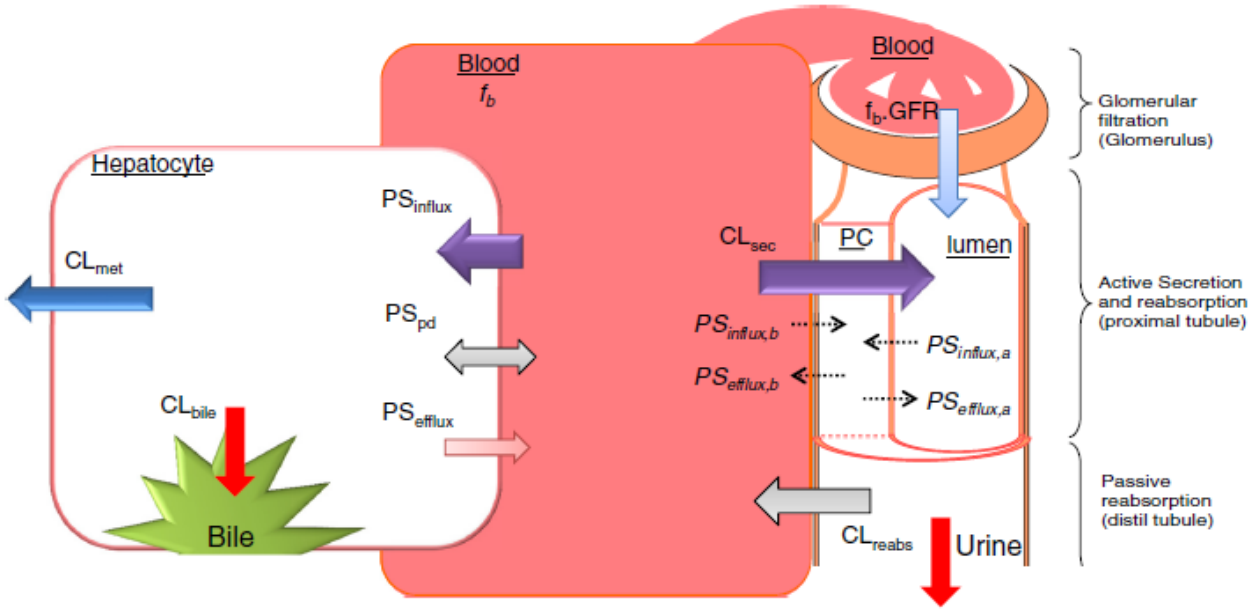
A Hierarchical QSAR Model for Urinary Excretion of Drugs in Humans as a Predictive Tool for Biotransformation

Na'ngono Manga, Judith C. Duffy, Philip H. Rowe, Mark T. D. Cronin*

School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, England

Predicting Clearance Mechanism in Drug Discovery: Extended Clearance Classification System (ECCS)

Manthena V. Varma [1] • Stefanus J. Steyn [2] • Charlotte Allerton [1] • Ayman F. El-Kattan [2]



Hepatic clearance

$$CL_{int,h} = \frac{(PS_{influx} + PS_{pd}).\,CL_{met+bile}}{(PS_{efflux} + PS_{pd} + CL_{met+bile})}$$

Rapid-equilibrium

if, $CL_{met+bile} << PS_{pd}$ & PS_{influx} and $PS_{efflux} << PS_{pd}$

$$CL_{int,h} = CL_{met+bile}$$

Metabolism+biliary CL are rate-determining steps

Uptake-determined

if, $CL_{met+bile} >> PS_{pd} + PS_{efflux}$

$$CL_{int,h} = (PS_{active} + PS_{passive})$$

Hepatic uptake is the rate-determining step

Renal clearance

$$CL_{renal} = (f_b.GFR + CL_{sec}).(1 - F_{reabs})$$

Low passive permeable

if, $F_{reabs} = 0$

$$CL_{renal} = (f_b.GFR + CL_{sec})$$

Renal CL is likely predominant mechanism

High passive permeable

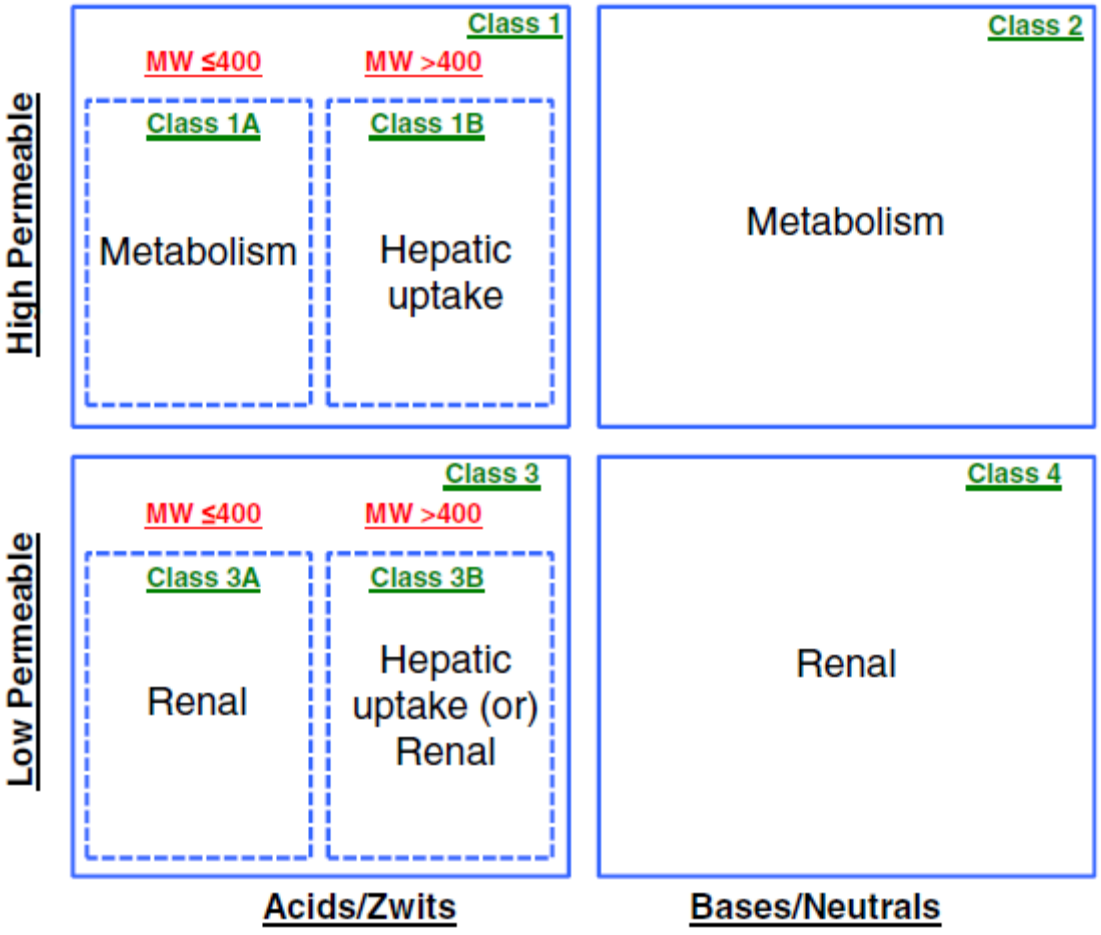
if, $F_{reabs} = 1$

$$CL_{renal} = 0$$

No renal CL expected

Pharm Res
DOI 10.1007/s11095-015-1749-4

Extended Clearance Classification System Framework



Pharm Res
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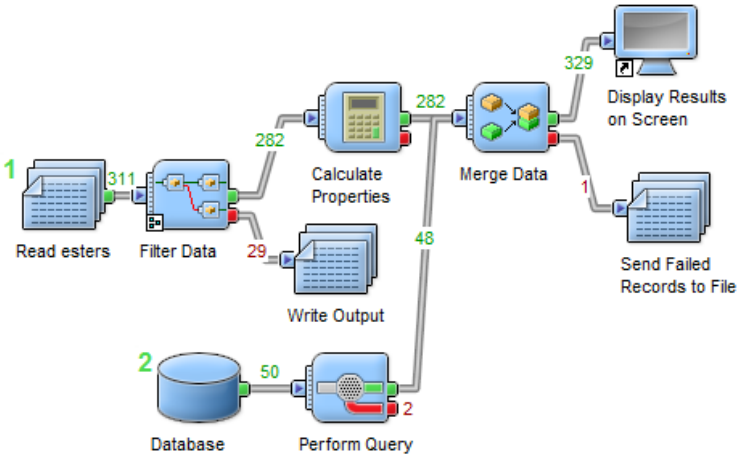
Pipeline Pilot

Scientific workflow software for automating data processing, analysis and reporting by Biovia Inc.

Uses data pipelining - data flow through pipes and are processed through a branched network of steps (components).

Protocol = a program consisting of components connected by pipes where each component performs a specific function



Permeability Protocol

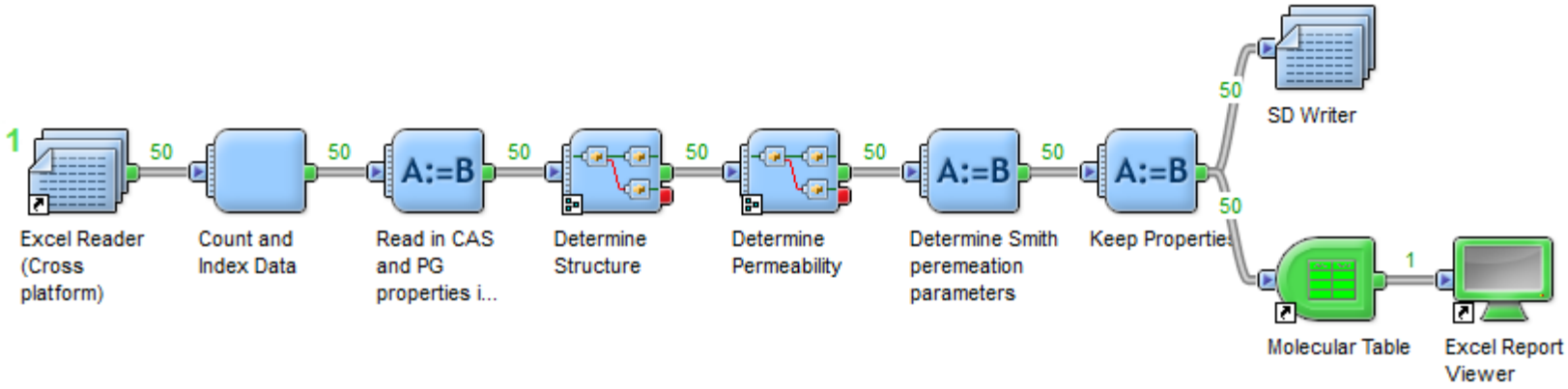
Determine structures from CAS (read structure from internal DB) or from SMILES

Calculate passive permeability using two models from ACD

Across Caco-2 cell monolayers

Across jejunum epithelium

Use LogD and Polarizability to determine role of transporter mediated versus passive diffusion across cellular membranes



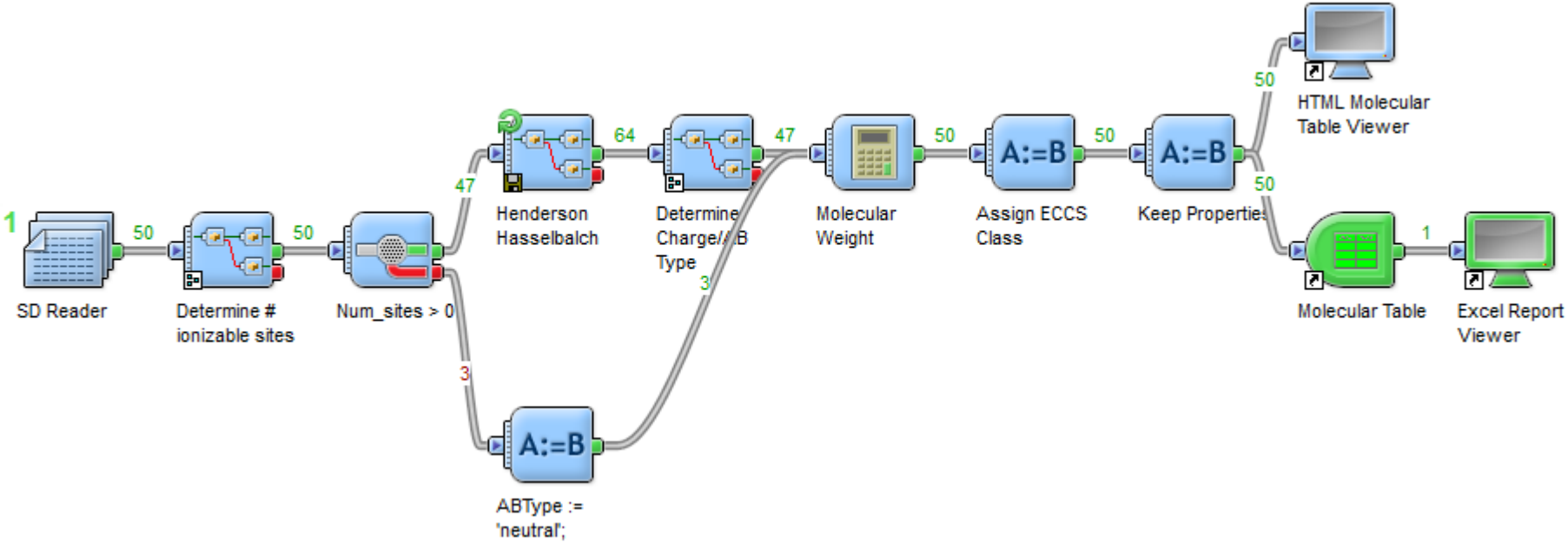
ECCS Protocol

Identify ionizable groups in molecules – identify as acids/bases

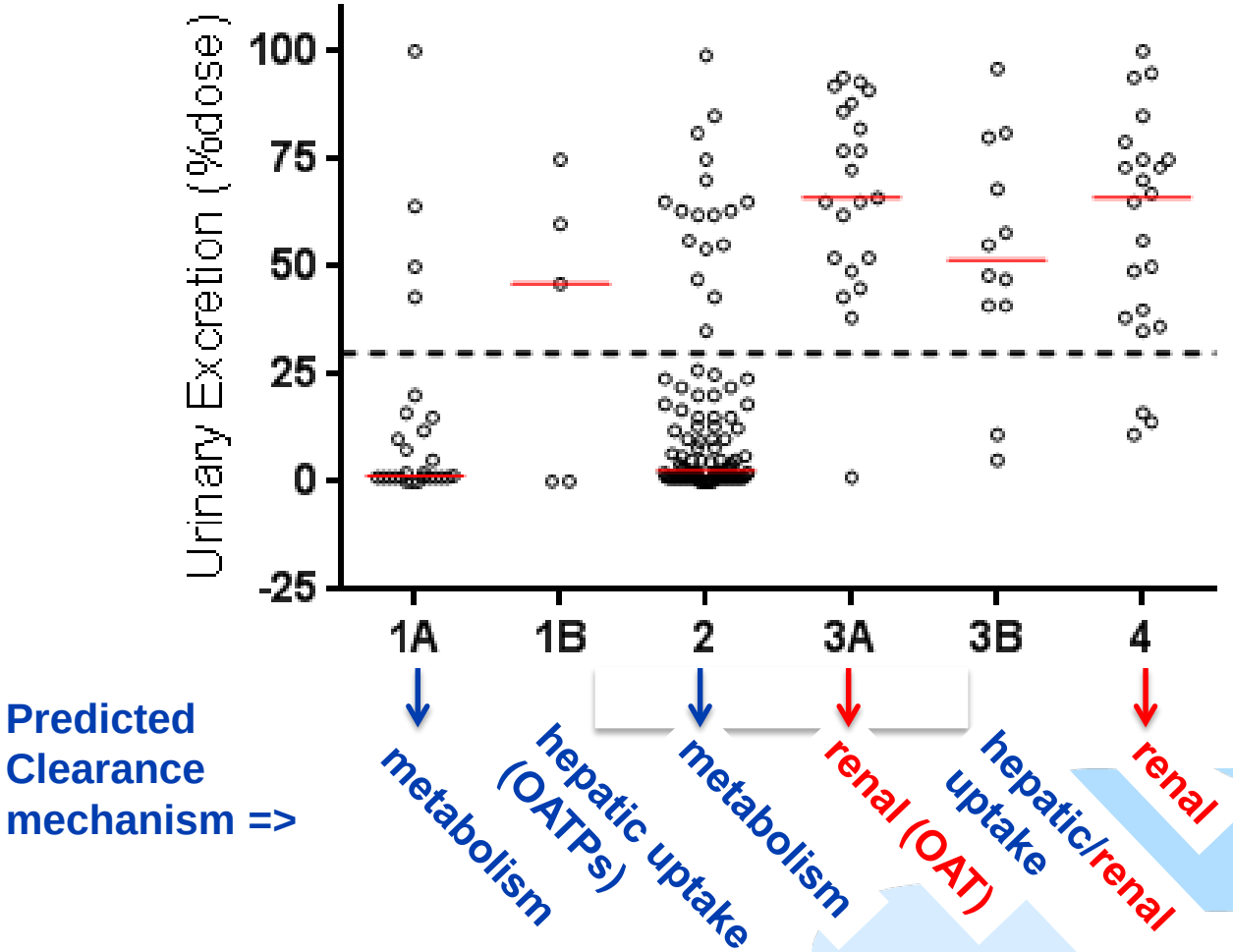
Calculate populations of ionized species in solution as a function of pH (Henderson-Hasselbalch equation)

Calculate MW

Assign ECCS class based on permeability (input), ionization states (acid/zwitterion; base/neutral)



Comparison of Measured Urinary Excretion and Predicted Clearance Mechanism for 200 drugs (Magna et al, 2003, QSAR Comb. Chem.)



Implementation of QSAR-derived PBPK model at P&G

Model Inputs

Chemical Structure

↓

QSAR-derived chemical-specific data

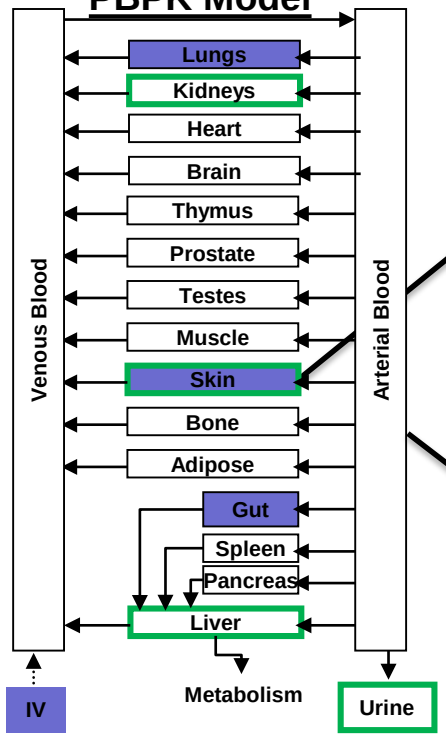
Exposure:
- Applied dose, duration
- Exposure scenario
- Application conditions

Elimination:
Conservative Assumptions

Clearance Mechanism Prediction

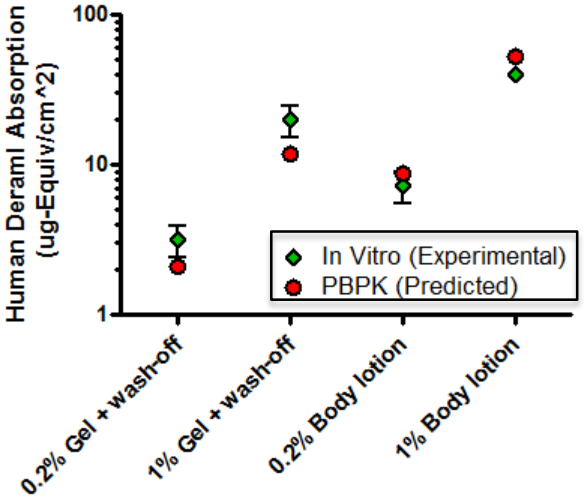
Rapid Lab Methods

Multi-route, species-gender- and age-specific PBPK Model

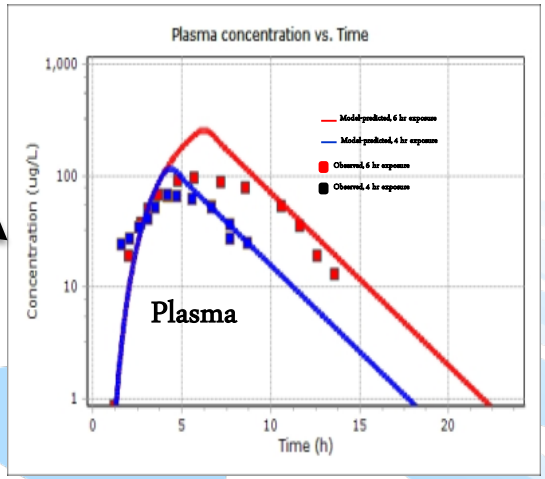


In vitro human skin pen

Model Simulations



In vivo human dermal study



Portals of chemical entry

Elimination pathways

Summary and Conclusions

- Understanding ADME processes lead to a more complete use of biological and toxicological data to support in vitro to in vivo extrapolation of dose-response information in human health risk assessments.

- We have outlined a framework for rapid parameterization of a screening level dermal PBPK model based solely on in silico QSAR-derived chemical inputs that include a provisional model for a priori prediction of primary clearance mechanisms.

- It is anticipated that this screening level information can be used to assess the need for additional data generation when greater accuracy is required (based on projected worst case margins of safety) and to inform decisions on which types of measured data would be most useful (e.g. whether to further pursue in vitro metabolism studies or renal excretion mechanisms).

Thank you for your attention!