



# **Predictive Toxicology: Bringing Chemical Risk Assessment into the 21st Century**

Maria Saluta

# Predictive Toxicology: Bringing Chemical Risk Assessment into the 21st Century

Traditional toxicology methods, using *in vivo* animal testing, is an unrealistic approach to test the 80,000 chemicals currently used commercially, and hundreds more that are being introduced every year.

Technological advances in molecular biology and computational sciences during the last two decades are increasingly being used to inform chemical risk assessment. In particular, mechanistic modeling and simulation (M&S) approaches, eg, quantitative systems toxicology (QST), physiologically-based pharmacokinetic (PBPK) modeling, and *in vitro* to *in vivo* extrapolation (IVIVE), combined with high throughput *in vitro* screening (HTS) and high content screening (HCS), are providing faster and more predictive approaches to toxicity testing and show great promise to refine and replace traditional methods.

Classic toxicity testing on anthropogenic and naturally-occurring chemicals involves administering high doses of chemicals to animals and using *in vitro* assays to define developmental, reproductive, neurotoxic, and hepatotoxic endpoints, or mechanisms of action. Approximately 80,000 chemicals are currently used commercially, and hundreds more are introduced every year. The majority of these chemicals have not been evaluated for their toxicological potential and pose a risk. Furthermore, the enormous amount of chemicals makes testing all these chemicals in animals unrealistic. Additionally, the doses given to animals are often orders of magnitudes higher than the environmental levels, and the process is slow, expensive, and ethically questionable. Predictive modeling and simulation approaches can provide a more effective alternative to traditional methods and reduce the use of animals to assess risk.

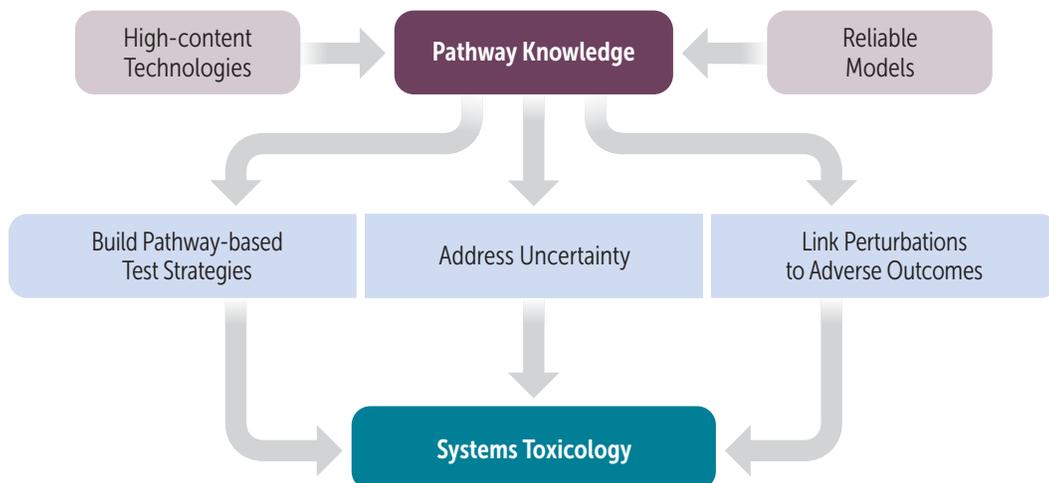
## The ToxCast program for chemical risk assessment

In 2007, the US Environmental Protection Agency (EPA) recognized the need for a comprehensive review of toxicity-testing methods and requested that the National Research Council (NRC) conduct this review and propose a long-range vision and strategy. The outcome of this review resulted in the ToxCast™ program, a high throughput chemical screening and prioritization systems biology-based research program, led by the National Center for Computational Toxicology (NCCT) within the EPA. The goals of ToxCast are to develop tools to aid prioritizing more than 10,000 environmental chemicals for further study.

The EPA contributes the results of ToxCast to the Toxicity Testing in the 21st Century (Tox21) collaboration: a joint project of the US EPA, National Institutes of Health (NIH), National Center for Advancing Translational Sciences (NCATS), National Institute of Environmental Health Sciences (NIEHS), and the Food and Drug Administration (FDA).

During the past decade, ToxCast has compiled HTS data on nearly 10,000 chemicals, including industrial and consumer products, food additives, and potentially “green” chemicals that may be safer alternatives to existing chemicals.

## Systems Toxicology: The Integration of *In Vitro*, *In Vivo*, and *Ex Vivo* Data with Computational Modeling



### A systems-based approach to toxicological screening

QST is another emerging approach to better predict and characterize adverse drug reactions (ADRs) and predict toxicity in the drug discovery process. QST integrates classical toxicology using *in vitro*, *in vivo*, and *ex vivo* toxicity data with quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organization.

Certara's Simcyp Division, leaders in PBPK modeling and simulation, has established a new QST initiative that will focus on understanding the mechanistic determinants of drug toxicity and the development of predictive QST software tools. Leveraging Simcyp's quantitative system pharmacology (QSP) expertise, the combined efforts will provide a holistic, quantitative approach to simultaneously predict a drug's efficacy, safety, and therapeutic index. Certara is also working with EU ToxRisk/Tox21 to reduce the use of animals and achieve more efficient chemical safety assessments.





The advantages of PBPK-IVIVE, QST, and other mechanistic M&S methods over traditional toxicological methods for chemical risk assessment include:

- Understanding dose-response relationships at the molecular level
- Correlating *in vitro* results with *in vivo* toxicology outcomes
- Quantifying population variability

## The use of PBPK modeling for predictive toxicology

PBPK modeling is a quantitative and mechanistic framework to predict the absorption, distribution, metabolism, and elimination (ADME) of synthetic or naturally-occurring chemical substances in humans. PBPK can also explore the effects of various physiologic parameters such as life-stage, ethnicity, or disease status on human pharmacokinetics (PK), guide dose and dose regimen, and predict drug-drug interactions. In chemical health risk assessment, physiologically-based toxicokinetic (PBTK) modeling is used to determine toxicokinetic (TK) properties and human exposure characteristics of compounds.

Xenobiotic exposure can vary by age, gender, ethnicity, and renal/hepatic function. The TK of xenobiotics varies by age due to changes in protein binding, tissue blood flows, and the expression of xenobiotic-metabolizing enzymes, primarily cytochrome P450-dependent monooxygenases (CYPs) and uridine 5'-diphospho-glucuronosyltransferases (UGTs). Genetic polymorphisms in CYPs and UGTs, which can vary between ethnic populations, also impact their xenobiotic metabolizing capability. Traditional toxicology approaches do not account for variability across different life stage, ethnic, or disease-based populations. This omission could result in significant underestimation of risk to a particular life stage or subpopulation group.

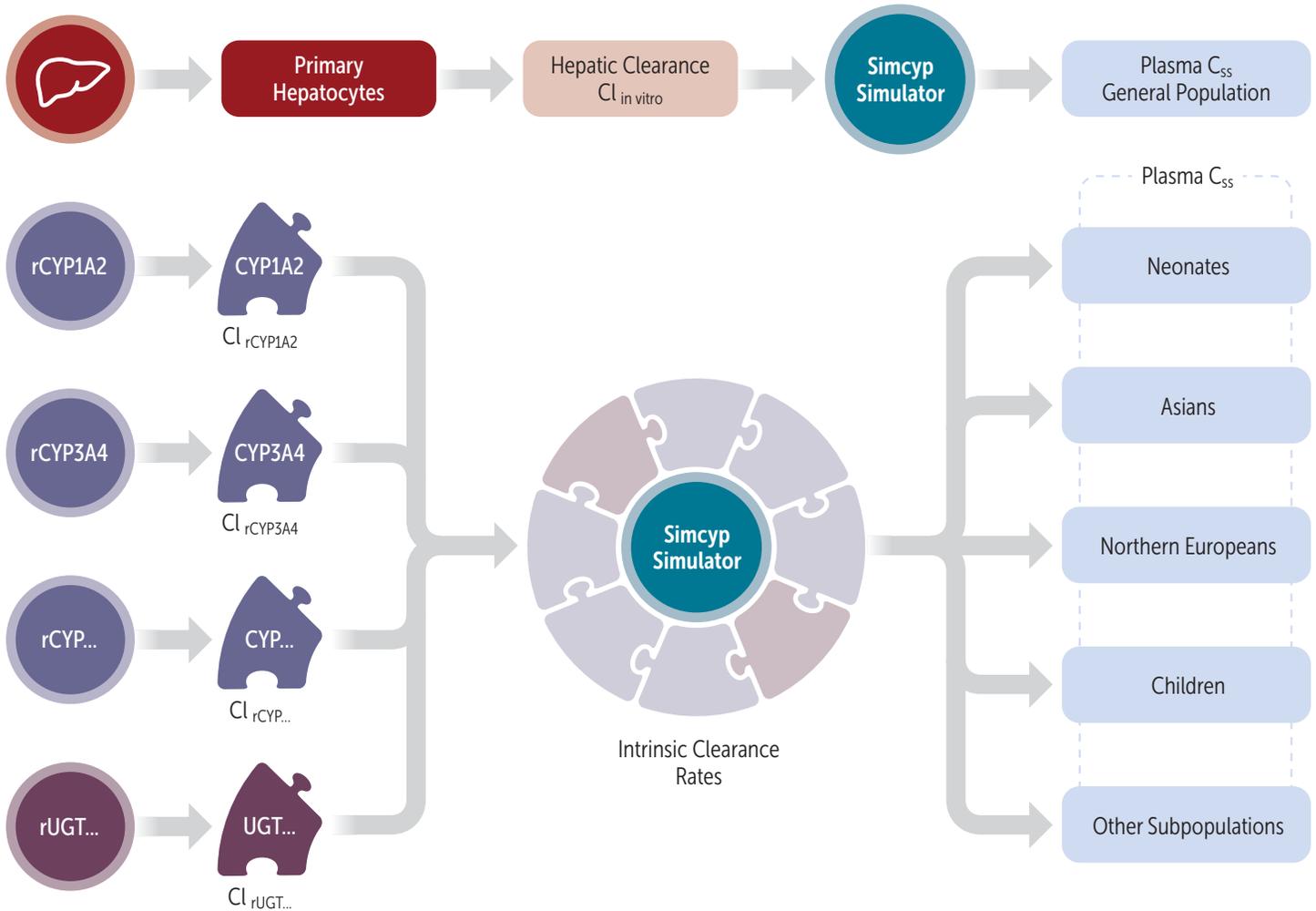
Another key challenge of *in vitro* assay screening is accurately relating xenobiotic concentrations that induce *in vitro* toxicity to *in vivo* exposure concentrations. Applying PBPK with animal to human IVIVE models simplifies the quantitation of these concentrations. The PBPK-IVIVE paradigm provides an alternative to animal testing and can estimate chemical-specific TK variability across multiple subpopulations

## Quantitating population variability for chemical risk assessment

By combining physiologic and pharmacologic differences, variability between different life-stage, ethnic, and disease-based populations can be quantified. Comprehensive preliminary studies incorporate dosimetry—a method that uses PK/TK models to relate exposure concentrations to a blood or tissue concentration—with HTS screening data. This approach focuses on hepatic clearance using donor pools of adult human hepatocytes incorporated with plasma protein binding data, key determinants of chemical steady state behavior. Certara's PBPK platform, the Simcyp Simulator, can be used to simulate population variability across the adult donor pool. However, a general adult population may differ in exposure compared to particular life-stage groups, potentially susceptible populations such as pediatrics, geriatrics, and renally/hepatically impaired patients, or certain ethnicities.

To determine the range of PK variability across these subpopulations, further testing incorporated population-based IVIVE studies using reverse dosimetry (when PK models are reversed to relate blood or tissue concentrations to an exposure concentration) and recombinant-expressed CYP and UGT isozymes. The isozymes are expressed in differing amounts by these populations. Incorporation of isozyme-specific metabolic clearance data into IVIVE modeling with reverse dosimetry provided an assessment of PK variability across populations. It also enabled determination of subpopulation-based oral equivalent doses that can be directly compared to subpopulation-based exposure rates.

### Population-based *In Vitro* and *In Vivo* Extrapolation



This assessment led to several conclusions, including (1) the determination of the newborn group, from zero to six months of age, as the most sensitive group for the chemicals examined, (2) how this approach might be utilized as a new paradigm for toxicity testing, and that (3) pharmacodynamic (PD)-based differences should be examined to determine how PD contributes to variability across different life-stages and how an individual responds to a particular chemical exposure.

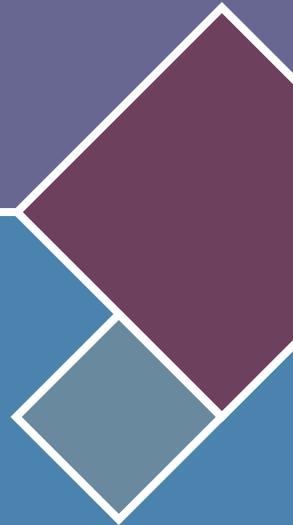
## Predictive modeling and simulation—the future of toxicology testing

M&S approaches such as PBPK-IVIVE and QST can expedite toxicological screening, support the prioritization for testing compounds that merit greater study, and reduce unnecessary animal testing. Recently, the US FDA announced the implementation of a Predictive Toxicology Roadmap for evaluating new methodologies and technologies, including predictive modeling, for their potential to offer greater predictive ability to toxicity testing. The integration of predictive *in silico* systems biology-based approaches with more advanced *in vitro* and *ex vivo* testing, and high throughput screening methods promises to provide a more effective approach to accurately predict toxicities and chemical risks.

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## About Certara

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