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Toxicokinetics in Risk Evaluations

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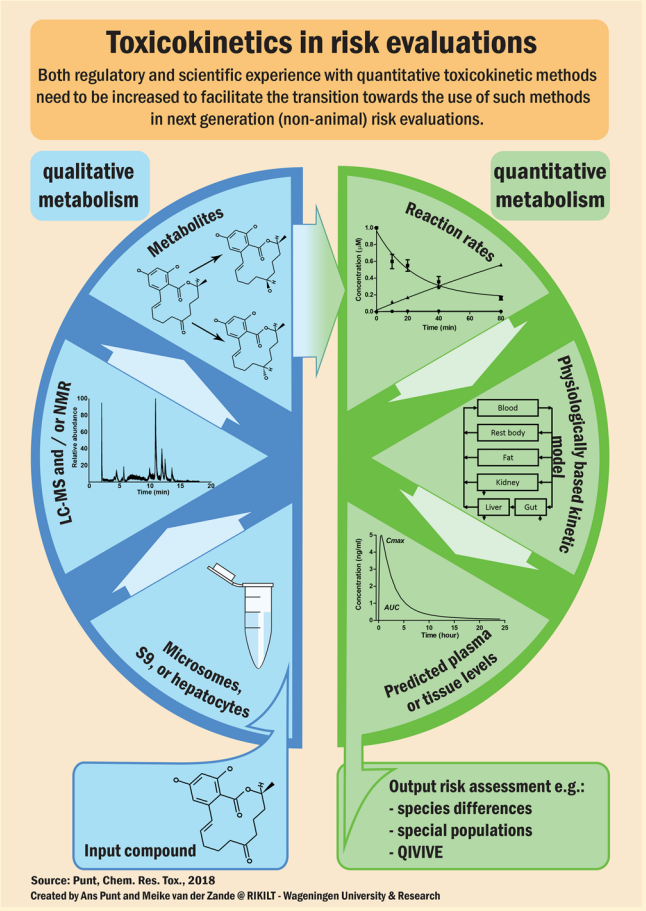
ABSTRACT: Quantitative predictions of *in vivo* chemical levels based on *in vitro* data will become a cornerstone of next generation nonanimal risk evaluations. Both regulatory and scientific experience with quantitative toxicokinetics must increase now for this transition to happen.



The importance of changing current toxicity testing strategies toward nonanimal methods that better reflect human exposure is increasingly acknowledged. Though science is progressing, risk assessment paradigms remain stringent and difficult to change. This indicates the importance of defining intermediate steps in the transition toward nonanimal toxicity testing. Particularly for data that describe the fate of chemicals in a body (i.e., toxicokinetics), drastic changes are needed in the utilization of such data in risk evaluations. Quantitative predictions about plasma and tissue levels of chemicals in humans will become a cornerstone within next generation (nonanimal) risk evaluations.[1] Such predictions allow one to convert *in vitro* data into human dose−response or potency information. However, current risk evaluations primarily focus on qualitative descriptions of the fate of chemicals in the body including the type of metabolites formed or whether absorption occurs. For metabolism studies, key steps for quantitative predictions include measuring metabolite formation at different substrate concentrations or at different time points as well as the scaling and integration of individual reaction rates into physiologically based kinetic (PBK) models to predict the ultimate fate in the body. Despite the potential of such *in vitro*-based PBK predictions, regulatory use is still limited.[2] Nonetheless, recent developments in risk evaluation procedures, particularly of drugs and pesticides in the EU, USA, and Japan, can be regarded as critical steps toward regulatory acceptance of *in vitro*-based PBK models and serve as examples for other regulatory domains.

The use of nonanimal kinetic data to simulate plasma and tissue concentrations of chemicals has progressed most in the case of drug evaluations. Various software packages, including SimCyp, PK-SIM, and GastroPlus, are increasingly used in regulatory dossiers to simulate the fate of drugs in populations

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based on *in vitro* input data. As a consequence, draft guidance documents have recently been issued by the US Food and Drug Administration (FDA) and the European Medicine Evaluations (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA):[3]

(1) Physiologically Based Pharmacokinetic Analyses — Format and Content, Guidance for Industry. FDA, December 2016.
(2) Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modeling and simulation. EMA, July 2016.
(3) Revision of Technical Conformance Guide on Electronic Study Data Submissions. PMDA, August 2016.

Although the FDA and PMDA guidance documents primarily focus on uniform submission, the EMA guideline also provides examples of the main purposes of PBPK models in regulatory submissions for pharmaceuticals: to qualitatively and quantitatively predict drug−drug interactions and support initial dose selection in pediatric and first in human trials. An important remark in the EMA guideline is that the extent of use of PBPK modeling is expected to expand as additional systems knowledge is gained and confidence increases.

A small but relevant step has also been taken within the new pesticide regulation within the EU (Regulation (EU) No 283/2013). This regulation lays down the requirements for pesticide active substance evaluations. According to annex 5.1.1., comparative *in vitro* metabolism studies need to be performed with relevant experimental animal and human materials (microsomes or intact cell systems) to determine the relevance of toxicological animal data. Though the focus still lays on a qualitative comparison of metabolites that are formed between experimental animals and humans, the implementation of this regulation resulted already in a significant change in actual inclusion of *in vitro* metabolism data, which were not considered before the implementation.[2]

These changes in regulation and guidance documents promote regulatory experience with *in vitro* methods for toxicokinetics and *in vitro*-based PBK modeling; however, the ultimate results are still included in risk evaluations to obtain additional (nice to know, but not need to know) insights. For example, for pesticide active substance in the EU, the focus lays on deriving human data that cannot be derived experimentally. In the case of drugs, data on drug−drug interactions and pediatric dose-selection are difficult to obtain otherwise. Stand-alone predictions on plasma and tissue concentrations without the support of *in vivo* data for validation of the predictions remains a challenge but ultimately will be needed in next generation (nonanimal) toxicity testing strategies. Standardization and the development of guidance documents on how to perform *in vitro* absorption, metabolism, distribution, and excretion studies and the integration of the data in PBPK models will play a crucial role herein. This importance is supported by the various activities that are organized to achieve this standardization.[1] In addition, there is a need for case studies within the regulatory domain as well as scientific research on quantitative predictions of the fate of chemicals in a body. Relevant scientific examples include Strikwold et al.[4] and Jones and Rowland.[5] The latter provides a generic human PBK model structure in which *in vitro* data can be integrated. Only by increasing both regulatory and scientific experience with quantitative kinetics now can an ultimate transition toward the use of such methods in next generation (nonanimal) risk evaluations be made in the future.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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