Presentations and Panel discussions - 2021 Workshop report

In this guide

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Session One: Introduction to PBPK and its applications

Presentation 1: Introduction to, and research needs of PBPK modelling in chemical risk assessment.

27. **Professor Mark Cronin** (Liverpool John Moores University) introduced the concept of PBPK as an *in silico* tool to establish, following exposure via various routes (e.g., inhalation, oral or dermal), internal exposure levels in different parts to the body. They are also used to predict/simulate the absorption, distribution, metabolism, and excretion (ADME) or simply the toxicokinetic profile of chemical substances in humans (or other species).

28. PBPK models describe the structure of the body in terms of anatomy and physiology. Mathematically, they are multicompartmental models with interconnections corresponding to blood flow based on differential equations to try and describe the conditions within the compartment (i.e. tissue/organ) itself. There are several parameters that can further define these conditions.

29. It was described that in the past, PBPK modelling was used to calculate safe and effective dosing for drug administration by calculating the point of departure (POD), and it is now being used to establish animal free toxicology. If the POD is greater than the level of exposure, one can assume safety, otherwise further information or risk management measures will be needed.

30. A basic PBPK model is typically made up of 7 major compartments; however, it can be adapted for a specific purpose. The requirements in order to build a PBPK model are a statement of purpose, understanding of the chemical's physiochemical properties, the level of exposure/dose, the route of administration and the overall complexity of the model (i.e. how many compartments).

31. With all the parameters described above, one is able to adapt a PBPK model to suit a defined statement or purpose. For example, the use of multi-scale models in predicting concentrations within an organ, gaining mechanistic understanding of an organ (e.g., distribution of salicylic acid in the kidney; Pletz, 2021), and the use of PBPK models in "Next Generation Risk Assessments (NGRAs)" to better understand internal exposure.

32. As a closing remark for his presentation, Professor Cronin offered his thoughts on current and future needs of PBPK models. He is of the view that the theory of PBPK is well established, and it offers various functionalities; however, there are two factors that must always be considered. These are the purpose of model development and its intended use. He recommended that there is a need to curate a database that lists all current PBPK models available (both commercial and open source) of which there is estimated to be ~500, in order to review what is already available and develop what is further required. There is also a need to consider the practical, functional and application aspects of PBPK models in order to ensure that they are fit for purpose. Additionally, there is an urgent need for a standardised reporting template, a robust framework for the assessment of PBPK models in a regulatory context, and to ensure model transparency.

Presentation 2: PBPK: What is all the fuss about?

33. **Professor Amin Rostami-Hodgejan** (University of Manchester) reviewed the context of use of PBPK models. In this, it was expressed that PBPK modelling is well established and is not considered a novel approach for understanding the toxicokinetic profiles of chemicals in the pharmaceutical industry. It has impacted drug development and regulatory decision making.

34. It was observed that there has been an increase in the number of regulatory PBPK related publications between 2007-2018, where more than 70 pharmaceutical products have been approved for use where no clinical studies have been performed (El-Khateeb et al, 2020), showing that there is a general trend of acceptance for the utilisation of PBPK model outputs in regulatory pharmaceutical applications (e.g., for the US Food and Drug Administration and European Medicines Agency).

35. Within the literature, there are a large number of publications on PBPK model comparisons and outputs and whilst each have their own respective merits, such publications often offer little insight as to how these output differences actually occurred. For instance, was it due to the different model(s) used or the modeller's interpretation of the output? A 'glass box' approach for reviewing PBPK models was introduced, whereby applicants need to ensure transparency of their models to the regulators, where the importance of quality assurance and reproducibility have been considered.

36. It was emphasised that there needs to be an understanding of the different drivers between PBPK model use in research and regulatory applications. Although, the use of PBPK models in reducing reliance on animal studies is a common objective between the two fields.

Presentation 3: Including variability in pharmacokinetic modelling and simulation approaches to reduce uncertainty in risk assessments.

37. **Dr Alexander J. Stevens** (Syngenta) presented the use of PBPK modelling in the agrochemical sector. In this, it was explained that current safety assessments for agrochemicals use standardised uncertainty/assessment factors to the POD arbitrarily without necessarily having a true scientific basis. Modelling has the potential to provide a better basis for selection of the assessment factors.

38. Obtaining toxicokinetic data to describe the systemic exposure in toxicology studies is relatively new for agrochemicals, however, it is now becoming more routine. Obtaining human systemic data is more challenging as the generation of human data by experimentation is not allowed; data can only

be obtained from epidemiological studies. It is also necessary to be able to characterise subpopulations such as children.

39. One way to address this is to use *in vitro* to *in vivo* extrapolation (IVIVE) and PBPK modelling. If *in vivo* exposure in rats can be predicted using *in vitro* data, and if rat *in vitro* data can be extrapolated to human *in vitro* data, then human *in vivo* models can be built.

40. A case-study of consumer risk assessment for an agrochemical was presented for chemical ‘X’ (full name classed as confidential), where the process described above was used. In brief, translation of the animal POD (from the *in vivo* and *in vitro* studies) to an internal dose metric using an animal PBPK model; the human-equivalent dose (or concentration) was then calculated using a human PBPK model. The PBPK models were able to model rat toxicokinetic (TK) variability, offered insight in inter-individual human TK variability, was able to calculate margin of exposure (MoE) values between the rat and human no-observed effect levels (NOAELs), and the process reduced uncertainty associated in both species’ systemic exposure estimates.

41. Furthermore, the human model can also be adapted to simulate different exposure scenarios (e.g., acute versus chronic), ‘at risk’ populations (e.g., paediatrics, or those with several renal impairment issues/other disease states).

42. An ecotoxicological case-study was also presented as a ‘proof-of concept’, in which population pharmacokinetic (PK)/toxicokinetic (TK) modelling and simulation were applied to predict systemic exposures of chemicals ‘Y’ and ‘Z’ (full names classed as confidential) in voles.

43. Mixed effects PK modelling was used since the focus was to study the variability in concentrations between individuals rather than focusing on a typical individual. The individual concentration data for all individuals were assessed using a non-linear mixed effects (NLME) modelling approach. Conclusions from this study showed that a mixed-effects PK/TK modelling and simulation approach was fit for purpose and allowed the prediction of internal exposures to chemicals ‘Y’ and ‘Z’. The impact on risk assessment was that the concentrations predicted by simulations could be compared to concentrations observed or calculated from a study to define the no-effect level, and thus further refine the safety margin.

Presentation 4: PBPK applications in the pharmaceutical industry today

44. **Dr Sheila-Annie Peters** (Merck KGaA) presented on PBPK applications in the pharmaceutical industry today. In this, PBPK modelling was considered a component of model-informed drug discovery and drug development and can be applied in clinical pharmacology safety assessments.

45. The unique strengths of PBPK were described as:

- They are mechanism-based absorption, distribution, metabolism and excretion (ADME) models. This allows dose extrapolation across species, populations, doses, and routes of administration. They can also help with hypothesis generation.
- They provide a framework for data integration (e.g. combining drug data, physiology, demography, and PK mechanisms).
- Target tissue kinetics, especially with toxicokinetics (concentrations in target organs). The tissue partitioning coefficients need to be validated.

46. PBPK studies can also be used to support regulatory filing:

- Broaden eligibility criteria: they can simulate vulnerable population exposure and justify their inclusion into clinical trials.
- Supplement clinical data (e.g. organ concentrations of an impaired population because it is usually very difficult to recruit these subpopulations).
- Contribute to totality of evidence (e.g. can simulate untested scenarios to waive studies and inform drug label).

47. PBPK models can be used to support clinical studies in a number of ways: absorption-related applications; drug-drug interaction risk; and dose extrapolation to specific populations. As such, PBPK modelling can be integrated along the drug development chain (e.g. in lead optimisation and pre-clinical development).

48. Although, there are still some challenges including: the characterisation of drug disposition for compounds that do not utilise P450 enzymes or lesser-known transporters; IVIVE; parameter non-indefinability for oral drugs; and knowledge gaps in systems parameters (e.g. transporter expression/activity and ontogeny).

Panel discussion summary

49. **Professor Alan Boobis** (COT Chair and Emeritus Professor of Toxicology, Imperial College London) chaired the first panel discussion. The main

discussion points are summarised below:

- The use of PBPK modelling is more readily observed and accepted in the pharmaceutical industry since there was a drive from regulators to understand and request additional data on potential drug effect(s) that could not be answered by human clinical studies – as such this acted as the driver to develop alternative testing strategies to address these (e.g., PBPK for understanding variability in PK/TK).
- The effectiveness of using PBPK to predict active transport and metabolic processing was discussed and the panel confirmed that this functionality can be modelled; however, it is tricky and only currently being used on a case-by-case basis. Overall, it is still work in progress.
- It was highlighted that in order for PBPK modelling to be successfully integrated into other industries (i.e., non-pharma, cosmetic and agrochemical), problem formulation needs to be clearly defined. For example, in Government, a centralised common goal could be developed and then each government department will have to have its own specific problem formulation. This would then allow cross-industry learning.
- Barriers for acceptance include the lack of consistency for reporting PBPK modelling outputs for regulatory applications and perhaps public perceptions, where the risk-benefit of utilising PBPK compared to conventional testing approaches has not been properly explained.

Session Two: PBPK model run-through and discussion

Presentation 5: RVis: An open access PBPK modelling platform

50. **Dr George Loizou** (Health and Safety Executive) presented a software tool called RVis which is a prototype application for the analysis of structure and performance of physiologically-based PK and other models. It is provided as a free-to-use platform and can run models written in MCSim or R syntaxes (RVis: open access PBPK modelling platform- Cefic Website).

51. The input parameters comprise anatomical, physiological, metabolic, and physicochemical values and the calculated outputs are the rates of uptake, elimination and organ and tissue concentrations (i.e., the internal dose). The application allows the user to evaluate variability and uncertainty in either the input or output parameters. Global sensitivity analysis (GSA) may be performed to ascertain output uncertainty as influenced by the quantified sensitivity of input parameter(s). Inter-individual differences (e.g., in organ and/or tissue

distributions) are incorporated through the application of Monte-Carlo sampling. Retrospective exposure or dose reconstruction, commonly known as ‘reverse dosimetry’, can be performed using Bayesian inference and Markov Chain Monte Carlo sampling. An algorithm for quantitative *in vitro* concentration response to *in vivo* dose response extrapolation (QIVIVE) has been developed for future incorporation in to RVis.

52. The advantages of utilising RVis as a tool for probabilistic PBPK is that it accounts for human inter-individual variability, has the ability to determine a credible interval for BMD lower bound values, and also offers a fully quantified measure of uncertainty for quantitative *in vitro* to *in vivo* extrapolation.

Panel discussion summary

53. The subject of PBPK models in general was discussed and was chaired by Professor Boobis. The main discussion points are summarised below:

- It was noted that the development of PBPK models is both data and resource intensive; however, it is worth investing in as it is a more ethical and ultimately labour-saving tool than the use of animals.
- Many parameters can be adjusted to suit a hypothesised scenario (e.g., the size of liver, kidneys, lungs, flow rates, etc.,); however, it is important to remember and consider that the model must represent a human being (i.e., the model structure and parameters should have a reasonable biological basis).
- PBPK models can also be used for ‘forward dosimetry’ estimations which could prove useful in linking human biomonitoring values in blood and urine samples to internal exposure but there needs to be an understanding of the parameters that would have in-built uncertainties (e.g., bioanalytical issues) and variability among the samples.
- There are or may be few instances where the use of PBPK models for regulatory decisions is essential. It may be possible to utilise it to group chemicals together that show the same kinetics, however, in order to start this work, there needs to be a large investment in the technology.
- In general, from a regulatory perspective, rather than specifying a PBPK model that should be used, it may be better to specify the requirements that must be met by way of evidence and the criteria for evaluation of models. The advantages of this are that other jurisdictions/countries will have their own preferences, and with time some platforms may develop whilst others not. For example, with statistical analysis of efficacy data, it is possible to

specify the type of analysis. Some small and medium-sized enterprises (SMEs) will be able to access and use open source software, whilst large companies may have access to consortia-owned tools. Although, within the literature, variability in PBPK outputs is still observed even with modellers utilising the same data and platform and as such it is difficult to overcome discrepancies.

- It was highlighted that there are not many consultancies offering to undertake PBPK work (for companies who would wish to outsource such as SMEs), and that assessment of competency often depends on the individual's academic profile and experience in the field.
- The ease of use and transparency of the PBPK model and its assumptions were highlighted to be important features for mass uptake. As an example, RVis was developed to shift focus away from maths and programming to a level where biological processes are easy to understand for both the end-user (or modeller) and the regulator by using familiar open source syntaxes (i.e., MCSim and R).

Session Three: PBPK in a regulatory context

Presentation 6: Review of the guidance on application and reporting of PBPK models in regulatory settings.

54. **Dr Judith Madden** (Liverpool John Moores University) presented a review of the guidance on application and reporting of PBPK models in regulatory settings. In this, the World Health Organisation (WHO) and the International Programme on Chemical Safety (IPCS) guidance on "Characterisation and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment" (WHO & IPCS, 2010) was first introduced. It was explained that a matrix to characterise confidence in the model was included in this guidance - **Table 1**). This involved consideration of the following questions:

1) Biological basis – do the model structure and parameters have a reasonable biological basis?

2) Comparison of model simulations with data – how well does the PBPK model reproduce the chemical-specific PK data under various experimental or exposure conditions?

3) Reliability of dose metric predictions (model testing, uncertainty and sensitivity analyses) – how reliable is the PBPK model with regards to its predictions of dose metrics relevant to risk assessment?

Table 1. The level of confidence matrix against three key criteria: biological basis; model simulation comparison with experimental data; and reliability of model predictions (adapted from WHO & IPCS, 2010).

Criterion	Level of confidence: Low [(a)]	Level of confidence: Standard [(b)]	Level of confidence: High [(c)]
Biological basis of the model structure and parameters.	Inconsistent with known biology.	Questionable for some elements or assumption.	Parameters and structure consistent with known data.
Comparison of model simulations with experimental data.	Cannot reproduce shape of PK time course.	Reproduces part of time course.	Reproduces all PK data; including shape of time course.
Reliability of model predictions relevant to risk assessment*.	Not tested against known data UA / SA not performed.	Not tested against known data; UA / SA indicate high confidence.	Compares to known data and UA / SA indicate high confidence.

(a) Improve model – data revision required.

(b) Use data as supplementary information.

(c) Use to inform your risk assessment.

*To include model testing, uncertainty and sensitivity analyses.

Abbreviations: SA = sensitivity analysis; UA = uncertainty analysis.

55. Since 2010, other guidance has also been published: the European Food Safety Authority (EFSA) on good modelling practice in the context of mechanistic effect models for risk assessment of plant protection products (EFSA, 2014); the Scientific Committee on Consumer Safety (SCCS) produced guidance for the testing of cosmetic ingredients and their safety evaluation (SCCS, 2018); the US FDA 2018 publication on PBPK analyses, which provides format and

content guidance for industry (US FDA, 2018); and the EMA reporting of PBPK modelling and simulation (EMA, 2018).

56. There are two guidance documents which are in preparation: the Organisation for Economic Co-operation and Development (OECD) draft guidance document on the characterisation, validation and reporting of PBK modes for regulatory purposes (now published at Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes (oecd.org), 2021), and the Japanese Pharmaceuticals and Medical Devices Agency (JPMDA) guidelines on the use of PBPK model simulations for drug development.

57. Within the last 10 years, there has been an evolution of risk assessment to shift from traditional PK models (which rely on *in vivo* data for calibration and evaluation- representing a “familiar uncertainty”) to NAMs and NGRAs in which human-relevant *in vitro* and *in silico* data are generated where mechanistic knowledge is gained but due to its novelty represents “unfamiliar uncertainty” (Paini et al., 2017).

58. Comparisons between the OECD draft guidance (in preparation) and the WHO & IPCS (2010) guidance were discussed. It was noted that the six core steps of the guidance were based on the same principles; however, the case studies are applied in different contexts (**Table 2**). The OECD guidance focuses on alternatives, whereas the WHO & IPCS focuses on characterising the closeness of the model simulation(s) to chemical-specific PK data.

Table 2. The similarities of the OECD and WHO PBPK guidance.

Step	OECD Guidance (In preparation)	WHO (2010)
1	Scope and purpose of the model (Problem formulation).	Scope and purpose
2	Model conceptualisation (model structure, mathematical representation).	Model structure and biological characterisation mathematical description.

3	Model parameterisation (parameter estimation and analysis).	Parameter estimation and analysis.
4	Computer implementation (solving the equations).	Computer implementation and verification.
5	Model performance - Model validation - Sensitivity variability and uncertainty analyses - Predictive capacity.	Model validation and evaluation: Ability of PBPK models to address PK uncertainty relative to other approaches.
6	Model reporting and dissemination	Documentation
6	XIII Case studies. Examples focus on alternative approaches.	Case study: Application in Risk assessment. Examples focus on closeness of the model simulations to chemical specific PK data.

Abbreviations: PBPK = Physiologically based pharmacokinetic modelling; PK = Pharmacokinetics; OECD = Organisation for Economic Co-operation and Development; WHO = World Health Organisation.

59. A PBPK model reporting template by Tan et al., (2020) was presented. The template aims to facilitate efficient, consistent, and timely review of PBPK regulatory submissions, and can also be used as a training and communication tool.

60. Despite the guidance developments described above, the following topics are not covered: technical information on building models and best practice; software selection; assessment of quality of *in vitro* assays or *in silico*

models or software input parameters; and specific considerations for application to complex chemicals (e.g., nanoforms, biologicals, macromolecules, and metals). As such, a guidance must not be treated as a tutorial and considering fitness for purpose is a key element in choosing PBPK models for risk assessments.

61. Dr Madden noted the common ongoing needs indicated in the guidance documents described above and the opportunities to resolve them **(Table 3**). Other ongoing issues must also be acted on, these are: transparent communication and acceptance of “unfamiliar uncertainties” (especially parametrisation without animal data); harmonisation of acceptance criteria between agencies and countries; and increased collection, use and sharing of biomonitoring and historic animal data.

Table 3. The identified needs for further integration of the use of PBPK models in a regulatory setting, and the respective opportunities on how to meet these needs.

Need	**Opportunity**
Expertise training.	Community of peer-reviewers Tutorials / user friendly software.
Improved communication between model developers and users.	Assessment of “pseudo-unknowns” What is needed for confidence? Directed case studies.
More guidance?	Consistent application of guidance Role of regulators.

62. One way to fully integrate the use of PBPK models in risk assessment is to present case studies where the application has been successful. Although, the main current impediment of utilising the approach (and associated guidance) seems to be the lack of internal expertise and capacity.

Presentation 7: Applications of PBPK modelling by regulatory agencies: Examples and lessons learned.

63. **Dr Harvey J. Clewell III** (Ramboll US Consulting, Inc.) presented the applications of PBPK modelling by regulatory agencies. In this, he first discussed the role of biological modelling in risk assessment, how pharmacodynamics as well pharmacokinetics influence the observed biological effects.

64. The purpose of using a PBPK model in risk assessment is to define the relationship between an external measure of (administered) exposure/dose and an internal measure of (biologically effective) exposure/dose in both the experimental animal and the human.

65. A brief history of the consideration of PBPK modelling by regulators was presented.

66. In 1987, the US National Research Council held a workshop on pharmacokinetics in risk assessment, which recommended the use of PBPK modelling in regulatory risk assessments. The first properly publicised use of PBPK was by the US Environmental Protection Agency (EPA) in 1988 for the risk assessment of dichloromethane or methylene chloride (Blancato & Rhomberg, 1988).

67. By 1999, the Medical Research Council Institute for Environment and Health workshop on PBPK modelling concluded that application of PBPK could improve the risk assessment process in the United Kingdom. Soon thereafter in 2001, Simcyp® developed a generic PBPK platform incorporating *in vitro* to *in vivo* extrapolation of metabolism to predict potential drug-drug interactions.

68. A decade later, WHO/IPCS guidance was published (WHO & IPCS, 2010). A decade thereafter in 2020, the OECD developed a draft guidance document on the characterization, validation and reporting of PBK models for regulatory purposes (now published, 2021).

69. Six examples of the use of PBPK modelling in regulatory risk assessments were provided: methylene chloride (US EPA); 2-butoxy ethanol (Health Canada); vinyl chloride (US EPA); coumarin (Federal Institute for Risk

Assessment (BfR)); all-trans retinoic acid (US FDA) and siloxanes (SCCS).

70. Through the various case studies, it was demonstrated how different challenges and questions were overcome and what lessons were learnt:

1) Methylene chloride – where the mode of action (MoA) was unclear. Comparisons of the PBPK model output with animal studies helped determine which metabolic pathway was involved in the MoA. The lesson learned was that it takes confidence in the model to predict the risk (Blancato & Rhomberg, 1988).

2) 2-Butoxy ethanol – where the uncertainty of TK could be lowered through conceptual, model parameters and dose metrics (Meek et al., 2013).

3) Vinyl chloride used extrapolation across routes and species using cross metrics. Animal-based risk estimates for human inhalation exposure to vinyl chloride using total metabolism estimates from the PBPK model were consistent with risk estimates based on human epidemiological data and were lower than those currently used in environmental decision-making by a factor of 80 (Clewell et al., 2001).

4) Coumarin - the concern was kinetic differences between skin versus oral exposure and by using PBPK, BfR was able to show that the toxicity of coumarin was more relevant to peak concentration in the liver rather than average concentration (Mielke et al., 2011).

5) All-trans retinoic acid - key determinants were identified as species differences in predominant metabolism, exposure route differences in bioavailability and kinetic differences between isomers in humans.

6) Siloxanes - the SCCS evaluated the model, and it was found suitable for risk assessment application – by using the model it was shown that the internal doses were much lower than what was calculated using the traditional calculation (SCCS , 2016).

71. It was discussed how we should identify key determinants and establish a platform for risk assessment from various countries, then agree certain criteria creating a patchwork quilt.

72. Lessons learned from Tan et al., (2018) were presented and summarised below:

- Regulators have experienced difficulties in recruiting peer reviewers with appropriate modelling expertise and experience in PBPK modelling.

- Regulatory reliance on *in vivo* tissue/plasma concentration data for PBPK model evaluation/validation severely limits potential applications of PBPK models for environmental chemicals.
- Limitations of available modelling platforms.

73. Finally, some recommendations were put forth:

- Support further development of open-source PBPK modelling platforms that could provide user-friendly environments that support the needs of regulators such as: RVis, Population Life-course Exposure to Health Effects Model (PLETHEM) (Pendse et al., 2020), Monte Carlo Simulation MCSim (Bois & Maszle, 1997), Berkeley Madonna, Magnolia and Integrated External and Internal Exposure (INTEGRA).
- Work to develop a consensus for acceptance of PBPK models without *in vivo* human validation data.
- Define open sourcing and modelling transparency throughout.

Panel discussion summary: Future research needs

74. **Dr Melvin Ernest Andersen** (ScitoVation, LLC) chaired the final panel discussion on future research needs. The summary of the discussion is presented below:

- The role of biological modelling is to determine the dose to the tissue and where the toxic effect occurs. Intracellular doses will be key, in order to achieve this, observations from both top down and bottom-up approaches are required to refine, validate and predict PBPK outputs.
- PBPK models are also tools useful for characterisation and understanding of mechanisms such as the MoA, understanding kinetics and dynamics, comparisons of exposure, and thus allow an opportunity to learn from pharmacokinetics how the metabolites and/or parent compound interact with tissues for better predictability.
- There needs to be an understanding that in some cases simpler models (i.e., compartmental models) may be more appropriate to use rather than a full PBPK model; however, the associated assumptions for these must be communicated transparently.
- It was noted that peer reviewing of PBPK model outputs from the same applicant by different agencies might prove a challenge, as each could potentially have different criteria for acceptance. As such, there is a need to gain assurance from harmonised guidelines (e.g., setting standards like the OECD and having advisory process(es) to assist in early problem

formulation). Even so, guidelines are only advisory, they need to be put into legislation and/or their addition into the legislation must be supported by those in academia, industry, and regulatory agencies.

- The low number of experts in the field was again highlighted. To help improve this, cross-sector learning in a workshop type setting is invaluable in order to provide opportunities for discussions and learn about new PBPK models and their applicability in risk assessment and regulatory settings. Case studies can be worked on together, whilst involving different scientific disciplines can help generate ideas and understanding to combat the underlying confidence issue in PBPK model integration for risk assessment and regulatory purposes.
- There is still a data need for consistent benchmarking *in vivo* and *in vitro* to provide evidence to enhance confidence in the safety assessment.