COT FSA PBPK for Regulators Workshop Report 2021

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COT FSA PBPK for Regulators Workshop Report 2021 - Cover page

In this guide

In this guide

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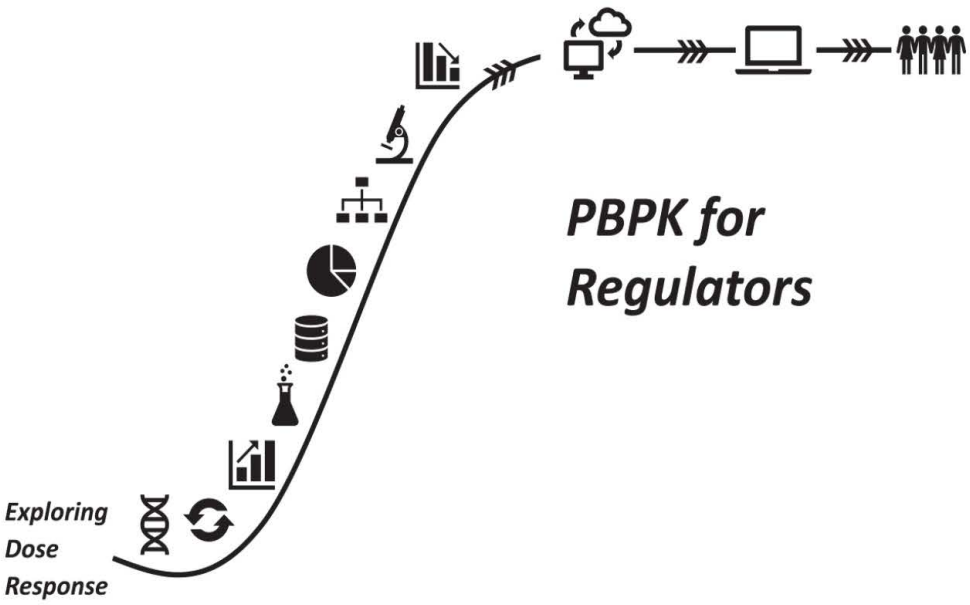
Workshop Report

December 2021



Committee on Toxicity

Food Standards Agency

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COT FSA PBPK for Regulators Workshop Report 2021

Summary - COT FSA PBPK for Regulators Workshop Report 2021

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1. The future of food safety assessment in the UK depends on the Food Standards Agency’s (FSA) adaptability and flexibility in responding to and adopting the accelerating developments in science and technology. The Tox21 approach is an example of one recent advancement in the development of alternative toxicity testing approaches and computer modelling strategies for the evaluation of hazard and exposure (New Approach Methodologies (NAMs). A key aspect is the ability to link active concentrations *in vitro* to likely concentrations *in vivo*, for which physiologically based pharmacokinetic (PBPK) modelling is ideally suited.

2. The UK FSA and the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) held an “PBPK for Regulators” workshop with multidisciplinary participation, involving delegates from regulatory agencies, government bodies, academics, and industry. The workshop provided a platform to enable expert discussions on the application of PBPK to health risk assessment in a regulatory context.
3. Presentations covered current application of PBPK modelling in the agrochemical industry for *in vitro* to *in vivo* extrapolation (IVIVE), pharmaceutical industry for drug absorption related issues (e.g., the effect of food on drug absorption) and drug-drug interaction studies, as well as dose extrapolations to special populations (e.g., those with a specific disease state, paediatric/geriatric age groups, and different ethnicities), environmental chemical risk assessment, an overview of the current regulatory guidance and a PBPK model run-through. This enabled attendees to consider the wide potential and fitness for purpose of the application of PBPK modelling in these fields. Attendees considered applicability in the context of future food safety assessment for refining exposure assessments of chemicals with narrow margins of exposure and/or to fill data gaps from more traditional approaches (i.e., data from animal testing).
4. The overall conclusions from the workshop were as follows:

- PBPK modelling tools were applicable in the areas of use covered, and that expertise was available (though it is in small numbers).
- PBPK modelling offers opportunities to address questions for compounds that are otherwise not possible (e.g., considerations of human variability in kinetics) and allows identification of “at risk” subpopulations.
- The use of PBPK modelling tends to be applied on a case-by-case basis and there appears to be a barrier to widespread acceptance amongst regulatory bodies due to the lack of available in-house expertise (apart from some medical and environmental agencies such as the European Medicines Agency, United States Food and Drug Administration, and the US Environmental Protection Agency, respectively).
- Familiarisation and further training opportunities on the application of PBPK modelling using real world case studies would help in generating interest and developing more experts in the field, as well as furthering acceptance.
- In a regulatory context, establishing fitness for purpose for the use of PBPK models requires transparent discussion between regulatory agencies, government bodies, academics, and industry and the development of a harmonised guidance such as by the Organisation for Economic Co-operation and Development (OECD) would provide a starting point.

- Finally, PBPK modelling is part of the wider “new approach methodologies” for risk assessment, and there should be particular emphasis in modelling both toxicodynamics and toxicokinetics.

Background - COT FSA PBPK for Regulators Workshop Report 2021

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5. In 2003, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) hosted a workshop on physiologically based pharmacokinetic (PBPK) modelling. The presentations considered the use of PBPK models in risk assessment, and the requirements to allow their incorporation in risk assessment. The presentations were followed by a general discussion which focused on the strengths and weaknesses of PBPK modelling, whether PBPK models could be integrated into risk assessments conducted by the COT, and how this might be achieved (COT TOX/2003/40).

6. A COT statement on PBPK modelling was published in 2003, where the COT considered PBPK modelling to be an established technique capable of predicting the *in vivo* behaviour of chemicals. PBPK modelling was widely used in the development and risk assessment of pharmaceutical products, where there were often sufficient human data available with which to validate the models. However, for many chemicals evaluated by COT, it was noted that there are limited or no human pharmacokinetic data available that can be used for model validation. Members expressed their reservations in assessing a PBPK model that had not been validated in this way.

7. Furthermore, the COT considered that animal data can provide partial validation if it can be assumed, or there is evidence, that the chemical behaves similarly in animals and humans. Additionally, validation could be enhanced by mechanistic studies in experimental animals that show human relevance. However, there would be less confidence in the predictions of such models, and this would need to be expressed as a source of greater uncertainty in the risk assessment.

8. The Committee concluded that it would not be feasible to undertake PBPK modelling routinely for COT risk assessments because the generation and validation of a PBPK model was resource and time intensive. However, the COT agreed that relevant published PBPK models should be incorporated into risk assessments, when possible, for example when submitted to support a risk assessment by industry.

9. In 2007, the COT held an open workshop on “Evolving Approaches to Chemical Risk Assessment”. A statement was published that summarises the presentations and Committee’s discussions. PBPK models were briefly discussed as part of the presentation on exploring uncertainty using sensitivity analysis.

10. The COT’s overall conclusions were as follows: the need to assess and describe the uncertainty in the available data, the use of more transparent and reproducible methods (e.g. framework approaches and systematic rather than narrative reviews) more explicitly.

11. Additionally, new technologies should be adopted with caution, and only implemented if they offer a clear benefit in terms of improving the risk assessments by the Committee. Although, where appropriate, NAMs should be initially performed in parallel with existing methods, allowing for further investigation of divergent outcomes.

12. In 2009, the COT held a workshop on 21st century toxicology. The workshop addressed the US National Academy of Sciences report entitled "Toxicity Testing in the 21st Century: A Vision and a Strategy". A statement was published where the COT welcomed the systematic approach of the strategy for the use of *in vitro* and *in silico* approaches to better understand toxicity.

13. Since it has now been almost 20 years since the COT workshop on PBPK modelling, Members thought it would be timely to revisit the topic once again in order to review advances in the approach for use in a regulatory context.

UK Food Standards Agency (FSA) requirement for PBPK modelling - 2021

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14. PBPK models are mathematical models that simulate the pharmacokinetic behaviour (absorption, distribution, metabolism and excretion)

of chemicals in the different tissues in the body, based on physiological, anatomical, biochemical and physicochemical parameters. They are an essential aspect in alternative toxicity testing and computer modelling strategies for the evaluation of chemical hazard and exposure, as they offer a means of linking active concentrations *in vitro* to likely concentrations *in vivo*. The use of *in silico* tools such as PBPK models also reduces the need to perform animal testing.

15. The UK FSA are exploring ways for more accurate internal exposure estimation to aid in refining risk assessments. The use of PBPK modelling offers an opportunity to address questions for environmental chemicals, novel foods, and food contaminants that are otherwise not possible (e.g., human variability in kinetics).

COT Discussions

16. In 2019, the COT reviewed PBPK modelling used for human health risk assessment (TOX/2019/34). The discussion of the Committee focused on ways to assess the reliability of human PBPK models in the absence of human pharmacokinetic data. Approaches that were considered to assess model reliability in this context included the use of the read-across approach and conducting interspecies extrapolations to animal species other than humans. The Committee agreed that it would be useful to have further information in the form of case studies, where *in vitro* data had been successfully extrapolated to *in vivo*, or cases where risk assessments considered in retrospect may have benefitted from PBPK modelling.

17. A follow-up paper (TOX/2019/73) was then presented in response to this request. The paper summarised a number of PBPK case studies that have been used in risk assessment (PFOS & PFOA, dioxins, bisphenol A, acrylamide & glycidamide, chloroform & carbon tetrachloride, vinyl acetate, methylene chloride, and vinyl chloride), in addition to cases where *in vitro* to *in vivo* extrapolation has been conducted (PFOS, triclosan, pyridaben & fluazinam, estragole, and trichloroethylene). Furthermore, examples involving 2-butoxyethanol, persistent organic pollutants, amphetamine analogues and electronic nicotine (and non-nicotine) delivery systems devices were described where the use of PBPK modelling may have facilitated their risk assessment.

18. The Committee noted that PBPK models have predominantly been developed and applied on a case-by-case basis, for example to assess exposures of chemicals with narrow margins of exposure or to fill in data gaps from more

conventional approaches.

19. The Committee recognised that PBPK modelling is of current interest to regulators in the field of chemical risk assessment; however, it is still largely used more in research capacities to refine estimates of health risk. PBPK models are not routinely applied or assessed by regulatory bodies because they are generally complex and both labour and data intensive, for example in terms of the data required for model parameterisation.

20. Whilst there are a multitude of case specific PBPK models, systems are now being developed to enable generic PBPK models to be generated. Software platforms such as these may be used in conjunction with the read-across approach to assess human health risks without the need for animal testing.

21. In March 2020, the FSA COT held a workshop entitled “Exploring Dose Response” which was attended by scientists from regulatory agencies, government bodies, academia, and industry. The workshop provided a platform from which to address and enable expert discussions on the latest *in silico* prediction models, new approach methodologies, PBPK modelling, future methodologies, integrated approaches to testing and assessment, as well as validation of methodology. Several case studies involving plastic particles, polymers, tropane alkaloids, and selective androgen receptor modulators were used to explore approaches fit for purpose in the context of future food safety assessment. Furthermore, possible future research initiatives were discussed, such as establishing points of departures using new approach methodologies models and improving use of exposure metrics in risk assessment.

22. The key issues identified in respect to PBPK models would be further developed through the current workshop.

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Objectives and outline of the workshop - 2021

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Objectives

23. The application of alternative strategies to health risk assessment in a regulatory context requires effective collaborations between scientists including chemists, toxicologists, informaticians, computational biologists, risk assessors, and policy makers. As such, this workshop drew upon speakers and delegates (~80) with varied backgrounds including academia, industry, and regulatory agencies whose collective experience is diverse and multi-disciplinary.

24. This workshop on PBPK modelling techniques thus provides a platform from which to address the following objectives:

- To gain a better understanding of what PBPK models are and their application to risk assessment in regulatory fields.
- Advantages and limitations of PBPK modelling.
- What must be achieved to overcome limitations for integration into current health risk assessment practices.
- An interactive session involving a model run-through.
- Any lessons learnt from authoritative bodies or industry.

Outline of the workshop

25. Overall, there were seven presentations that explored the current applications and regulatory guidance of PBPK modelling. The workshop was divided into three sessions (introduction and its applications, PBPK model run-through, and PBPK in a regulatory context), two panel discussions and an open

discussion regarding future research needs (See this web page: Handbook Cover Page - 2021 Workshop | Committee on Toxicity (food.gov.uk) for the Handbook).

Questions put forward for the discussion sessions- 2021

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22. The below were the questions put forward for the discussion sessions.

Limitations / Ensuring fitness for purpose

- What are (if there are any), the limitations of using PBPK modelling in an agrochemical/pharmacological setting?
- Can PBPK models fully replace animal testing, or are there some cases where animal studies may still be required?
- Are there any circumstances where we can use simpler *in silico* compartmental models versus PBPK?

Potential applications

- Can PBPK models be used to provide relevant substances to benchmark against known human biomonitoring data?
- Exploration into intracellular dosing.
- Could PBPK modelling be used to convert estimates of external exposure into an estimate of internal exposure at the site where toxicity occurs to refine estimates of risk?
- PBPK modelling provides a way to incorporate kinetics into consideration in animal-free, *in vitro* based safety/risk assessment and to relative *in vitro* toxicity assay findings to human safe exposure estimates.
- Can PBPK models lower the reliance on default uncertainty factors, and would it reduce this uncertainty?

Validation for regulatory application

- Are there any harmonised guidelines available for regulators?
- Have there been any cases where there has been a human PBPK model developed without human data? If so, how was the model validated (if at all)?
- What are some of the hurdles to PBPK modelling being used more widely by scientists, and accepted by regulators?

Duties as regulators

- What aspects of the model do regulators have to check before it can be used in risk assessment?
- Are regulators expected to use PBPK models (for example, to double-check calculations, to examine the source code) or can regulators just take simulation results at face value?
- How could PBPK modelling be used more extensively in food safety assessment?
- Is the integration of PBPK models into current human health assessment methodologies a risk worth embracing?

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Presentations and Panel discussions - 2021 Workshop report

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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.

Overarching conclusions - 2021 Workshop Report

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75. The overall conclusions from the workshop were as follows:

- PBPK modelling tools were applicable in the explored areas of use, and that expertise was available (though numbers are small).

- PBPK modelling offers opportunities from which to address questions for compounds that are otherwise not possible (e.g., considerations of human variability in kinetics) and allows identification of “at risk” subpopulations.
- The use of PBPK modelling tends to be applied on a case-by-case basis and there appears to be a barrier to widespread acceptance amongst regulatory bodies due to the lack of available in-house expertise (apart from some medical and environmental agencies such as the EMA, US FDA, and the US EPA, respectively).
- Familiarisation and further training opportunities on the application of PBPK modelling using real world case studies would help in generating interest and developing more experts in the field, as well as furthering acceptance.
- In a regulatory context, establishing fitness for purpose for the use of PBPK models requires transparent discussion between regulatory agencies, government bodies, academics, and industry and the development of harmonised guidance such as that from the OECD would provide a starting point.
- Finally, PBPK modelling is part of the wider “NAMs” for risk assessment, and there needs to be emphasis in modelling not just toxicokinetics but also toxicodynamics.

Appendix

Handbook Cover Page - 2021 Workshop | Committee on Toxicity (food.gov.uk)

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Technical Terms - 2021 Workshop Report

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Forward dosimetry	Forward dosimetry is an estimation of internal exposures from measurements of external exposure in studies characterising chemical toxicity.
Integrated External and Internal Exposure (INTEGRA)	Integrated External and Internal Exposure (INTEGRA) is a unified computational platform that integrates environmental fate, exposure and internal dose dynamically in time.
Magnolia	Magnolia is an environment for modelling systems whose behaviour can be described by systems of differential equations. Magnolia provides the tools for developing models using an equation-based modelling language, scripting the execution of simulations using either the Python programming language or a simple command-based language, and for interactively exploring model behaviour using an intuitive user interface.
Mixed-model approach	The mixed-model approach allows for modelling of both population level and individual differences in effects that have a non-linear effect on the observed outcome.
Monte Carlo Simulation (MCSim)	Monte Carlo Simulation (MCSim) is a general-purpose modelling programme which performs Monte Carlo simulations to generate a distribution of estimates.

Ontogeny	Ontogeny is the development or course of development, especially of an individual organism.
Population Life-course Exposure to Health Effects Model (PLETHEM)	Population Life-course Exposure to Health Effects Model (PLETHEM) suite, is a modular open-source modelling platform that provides users the ability to create, run, share, and audit PBPK models.
Point of departure	The point of departure (POD) is defined as the point on a toxicological dose-response curve established from experimental data or observational data; generally responding to an estimated low effect level or no effect level used as the starting point to establish a safe level or level of low concern.
Read across	Read-across is a technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s); the source substance(s).
Reverse dosimetry	Reverse dosimetry us an estimation of environmental exposures consistent with measured biological data.
Tox21	Toxicology in the 21st Century (Tox21) is a United States federal research collaboration, testing thousands of environmental chemicals using non-animal methods for potential health effects. Further information is available on the Tox21 website. See also the US Environmental Protection Agency's website for adopting new approach methodologies.

Abbreviations - 2021 Workshop Report

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ADME	Absorption, Distribution, Metabolism and Excretion
BfR	Bundesinstitut für Risikobewertung-The German Federal Institute for Risk Assessment
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EFSA	European Food Standards Authority
EMA	European Medicines Agency
FSA	Food Standards Agency
GSA	Global sensitivity analysis
INTEGRA	Integrated External and Internal Exposure

IPCS	International Programme on Chemical Safety
IVIVE	*In vitro* to *in vivo* extrapolation
JPMDA	Japanese Pharmaceuticals and Medical Devices Agency
MCSim	Monte Carlo Simulation
MoA	Mode of action
MoE	Margin of exposure
NAM	New approach methodology
NGRA	Next generation risk assessment
NLME	Non-linear mixed effects
NOAEL	No-observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBPK	Physiologically based pharmacokinetic modelling
PFOA	Perfluorooctanesulfonic acid
PFOS	Perfluorooctanoic acid
PK	Pharmacokinetics
PLETHEM	Population Life-course Exposure to Health Effects Model

POD	Point of departure
QIVIVE	Quantitative *in vitro* to *in vivo* extrapolation
SA	Sensitivity analysis
SCCS	Scientific Committee on Consumer Safety
SME	Small and medium-sized enterprises
TK	Toxicokinetics
UA	Uncertainty analysis
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
WHO	World Health Organisation

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6. Questions put forward for the discussion sessions - 2021
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9. Technical Terms - 2021 Workshop Report
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11. References - 2021 Workshop Report
12. Organizing Committee, Committee Members and COT Secretariat - 2021 Workshop Report

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COT statement on the COT workshop on 21st century toxicology:

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Organizing Committee and COT Secretariat - 2021 Workshop Report

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