TOX/2019/34

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of physiologically-based pharmacokinetic (PBPK) modelling used for human health risk assessment.

What are PBPK models?

1. PBPK models are mathematical representations of the processes affecting a chemical's *in vivo* toxicology: absorption, distribution, metabolism and excretion (ADME). These processes are represented by a series of differential equations which describe the rate of change in the amount of a chemical in target organs and blood. To simulate a "dose metric" (defined in paragraph 33), the differential equations are solved through integration, which typically must be performed numerically using appropriate computer software.

2. The differential equations of a PBPK model are functions of model parameters. Each parameter describes a biochemical property of the xenobiotic or a physiological or physicochemical property of the biological system the model is intended to represent. This feature of PBPK models allows the values of many physicochemical and biochemical parameters to be determined from *in vitro* assays. These parameters include, for example, gut permeability (P_{eff}) and the octanol: water partition coefficient ($LogP_{o:w}$), respectively.

3. Figure 1 shows the structure of an exemplar PBPK model. The tissues can be modelled as "perfusion-limited", where the rate of chemical uptake into tissues is limited by the blood flow rate to that tissue. With respect to "model fitting" (described in paragraphs 22-24), the perfusion-limited tissue model is generally suitable for lipophilic compounds. Alternatively, tissues can be modelled as "permeability-limited", where the rate of uptake is limited by relatively slow permeability across the tissue's basolateral membrane. This tissue model is generally suitable for relatively non-lipophilic compounds.

4. PBPK models are based on some general assumptions regarding ADME (Rideout 1991), deviations from which should be justified and documented (WHO 2010):

- the mixing of the chemical in the effluent blood from the tissues is instantaneous and complete,
- blood flow is unidirectional, constant and non-pulsatile, and
- the presence of chemicals in the blood does not alter the blood flow rate.

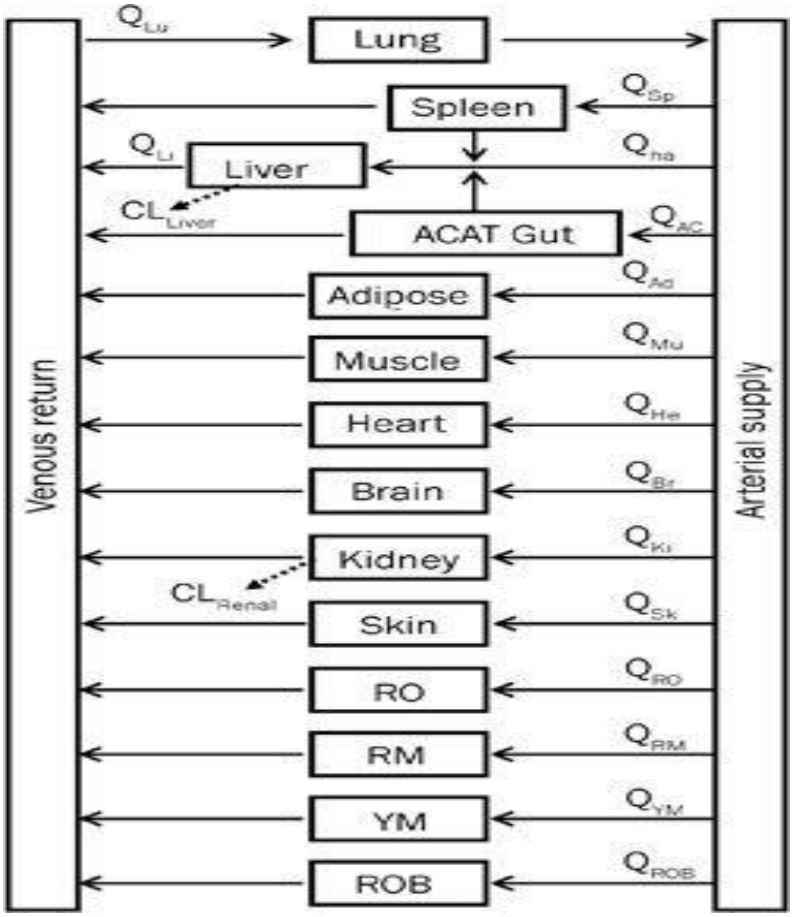

Figure 1: Schematic structure of a whole-body PBPK model used to predict in vivo behaviour of xenobiotics. The blood flow rates associated with the modelled compartments- lung (Lu), liver (Li), spleen (Sp), gut (AC), adipose (Ad), muscle (Mu), heart (He), brain (Br), kidney (Ki), skin (Sk), reproductive organ (RO), red marrow (RM), yellow marrow (YM), rest of body (ROB), - are represented by Q, subscripted with the corresponding compartment. Q_{ha} is the blood flow rate to the liver via hepatic artery (ha). Schematic taken from Li *et al.* 2012.

Applications of PBPK models in risk assessment

5. PBPK models are used in the pharmaceutical industry to guide the optimisation of certain drug physicochemical properties and dosing regimens to provide an optimised pharmacokinetic profile in humans before first-in-human clinical trials. In addition, PBPK models are used by various health protection agencies such as the U.S. EPA to assess environmental chemical exposure to xenobiotics such as methylene chloride (Andersen *et al.* 1987).

6. The ways in which PBPK models have been used for chemical risk assessment include extrapolations, exposure reconstruction and the derivation of biomonitoring equivalents and chemical-specific adjustment factors (CSAFs). These applications are described in further detail below.

Extrapolations

7. Intraspecies extrapolations can be performed by implementing equations into the model which describe the age- or gender-specific changes in a parameter (Clewell *et al.* 2004). In addition, interspecies extrapolations can be performed with PBPK models by substituting parameter values for one species into a model developed for another. For example, the dose metric that corresponds to a POD

dose in an animal model would, after extrapolation, provide an estimate of the dose metric in humans to which an uncertainty factor may be applied for the derivation of a health-based guidance value (Gentry *et al.* 2004). These procedures are only appropriate if the same mechanism of action occurs in both life stages, genders or species. For interspecies extrapolation to humans, generally the most sensitive relevant animal species is used.

8. In addition, PBPK models allow for route-route extrapolations where, the model is used to extrapolate a point of departure available for one exposure route to another on the basis of an equivalent dose metric (Chiu *et al.* 2007). Appropriate equations that represent each exposure pathway should be included in the PBPK model. Due to route-specific ADME processes, such as first-pass liver metabolism with respect to exposure via the oral route, the model can also be used to investigate the corresponding differences in systemic exposure. The confidence in the route-to-route extrapolation will be high when the pharmacokinetics and/or dose metric is evaluated for both routes in one or more species (WHO 2010).

9. PBPK models can also be used for high-to-low dose extrapolation. Here the simulated dose metric is related to the observed incidence of toxicity. The resulting calibration curve gives the expected incidence of toxicity at other doses. The confidence in a PBPK model would be undermined if it used different values for a given parameter (e.g. intrinsic clearance) in order to provide adequate simulations of kinetic profiles at each dose level (WHO 2010).

Exposure reconstruction

10. Human biomonitoring is the assessment of human chemical exposure, by measuring these chemicals, and/ or metabolites, reaction products thereof (i.e. ‘biomarkers’) in easily accessible human biospecimens such as blood and urine. Hence, human biomonitoring data provides aggregate measures of dose from all sources and exposure pathways as they occur in real-life scenarios.

11. In a process known as exposure reconstruction or reverse dosimetry, PBPK models are used with human biomonitoring data to identify and quantify corresponding exposure pathways. This can be done to assess domestic, environmental or occupational exposures, depending on the biomonitoring database used. Examples include the quantification of dermal and inhalation exposures from urinary pesticide concentrations (Cooper *et al.* 2019), and quantification of oral exposure to chloroform in tap water from chloroform measurements in blood (Lyons *et al.* 2008). However, it is not currently possible for the analysis of human biomonitoring data to provide information on the exposure scenario such as the duration or frequency of exposures (Sohn *et al.* 2004). Therefore assumptions on the exposure scenario can be made, or information can be ascertained through surveys or surveillance studies to facilitate the exposure analysis.

Biomonitoring equivalents

12. The original approach used for deriving a biomonitoring equivalent was developed by Hays *et al.* in 2007. It is the calculation of chemical concentration within a readily accessible human biofluid (such as urine or blood) for a known

external exposure for example the oral reference dose (RfD). The RfD is the maximum acceptable daily oral intake rate with minimal risk of developing an adverse health effect over one's lifetime. The corresponding biomonitoring equivalent can then be compared alongside human biomonitoring data to facilitate interpretation of this data for health risk assessment purposes, for example by calculating a margin of safety (MOS) (biomonitoring equivalent / biomonitoring data) (Phillips *et al.* 2014).

13. In order to calculate a biomonitoring equivalent, a model is required that deterministically links external dose with exposure at the physiological site of interest. Recent developments in the field include using PBPK models with parameters with fixed values (Hays *et al.* 2012) leading to parameters having distributions (Phillips *et al.* 2014). The latter is particularly important to calculate ranges of plausible values for the biomonitoring equivalent, taking population physiological heterogeneity into account. However, the parameter distributions are often treated as univariate without relationships existing between them.

Chemical-specific adjustment factors (CSAFs)

14. In order to extrapolate a NOAEL from an animal study to humans for the calculation of an external reference dose, an uncertainty factor is required. Its value of 100 was proposed over 60 years ago and is comprised of two ten-fold factors (Lehman & Fitzhugh 1954). The first ten-fold factor allows for interspecies differences in ADME (Renwick 1991, 1993), and the second is for intraspecies differences (variability) in humans (Renwick & Lazarus 1998). More recently, division of each of the ten-fold factors into subfactors has been suggested in order to account for variations in toxicokinetics and toxicodynamics (WHO 2005) (Figure 2). Quantitation of this subdivision is supported by PBPK and toxicodynamics modelling studies (Renwick 1993, Renwick & Lazarus 1998). The value of a subfactor can then be replaced with a CSAF.

15. Guidance has been published for the derivation of CSAFs using appropriate toxicokinetic and toxicodynamic data (WHO 2005). For example, it would be possible to use a PBPK model to adjust the value of:

- $10^{0.6}$ for AK_{UF} by dividing the mean of a relevant human toxicokinetic endpoint such as the maximum plasma concentration (plasma C_{max}) by the mean of the animal plasma C_{max}.
- $10^{0.5}$ for HK_{UF} by obtaining an estimate at a particular percentile (e.g. 95th, 97.5th, or 99th) of the population variability distribution of plasma C_{max} and then dividing by the mean.

16. Consequently, a composite uncertainty factor (CUF) could be calculated to replace the traditional 100 x uncertainty factor, where adjusted uncertainty factors (AFs) are used to substitute their UF counterparts as follows:

$$CUF = [AK_{AF} \text{ or } AK_{UF}] \times [AD_{AF} \text{ or } AD_{UF}] \times [HK_{AF} \text{ or } HK_{UF}] \times [HD_{AF} \text{ or } HD_{UF}] \quad [1]$$

17. If CUF < 100, this represents a reduction in uncertainty in the risk assessment (Meek *et al.* 2003) and recalculation of the external reference dose would provide a higher level of acceptable human exposure.

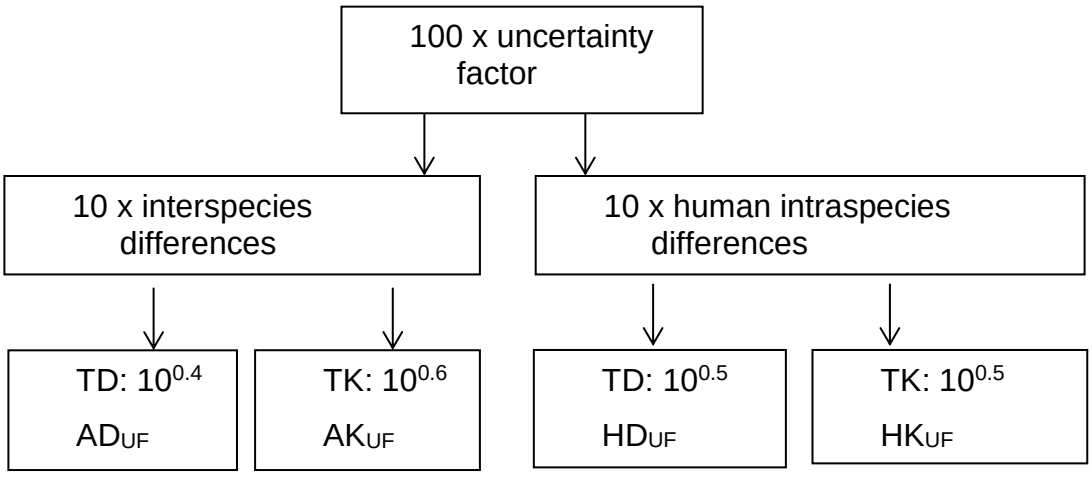

Figure 2: Subdivision of the traditional 100 x uncertainty factor used in setting guidance values for exposure of the general population. The product of values assigned to toxicodynamics (TD) and toxicokinetics (TK) subfactors gives the original default values of 10. AD_{UF}: uncertainty factor for animal to human differences in toxicodynamics, AK_{UF}: uncertainty factor for animal to human differences in toxicokinetics, HD_{UF}: uncertainty factor for human variability in toxicodynamics, HK_{UF}: uncertainty factor for human variability in toxicokinetics. Figure reproduced from WHO 2005.

Approaches to building PBPK models

18. The development of a PBPK model may adopt the “bottom-up” approach, where the parameterisation of the model is based on *in vitro* and/ or in silico data (no *in vivo* data are used). Interspecies extrapolations can then be performed in order to predict an *in vivo* pharmacokinetic profile in humans without performing human exposure studies. Two methods for extrapolation are used: allometric scaling and *in vitro* to *in vivo* extrapolation (IVIVE).

19. Allometric scaling is the use of a regression equation involving body weight to predict a parameter of interest in a different animal species (Lindstedt & Schaeffer 2002). The general allometric equation takes the form $y = a(\text{body weight})^b$, where y is the model parameter of interest. These parameters typically include absorption and metabolism rates. However the inherent uncertainty/ variability of body weight and the allometric coefficient (a) and exponent (b) is often not taken into account (Bois 1999, Bois 2000).

20. IVIVE, on the other hand, relies on an understanding of the experimental and biological factors that influence *in vivo* estimation, and requires the use of scaling factors. For example, a value of enzymatic Vmax derived from *in vitro* assays using isolated hepatocytes is sometimes expressed as metabolism rate per million cells

(mg/ sec/ 10^6 cells). Subsequently a scaling factor, hepatocellularity per gram of liver (HPGL), is required to estimate the rate for the whole liver (Kenyon 2012) as follows:

Whole liver Vmax (mg/ sec) =
Vmax (mg/ sec/ 10^6 cells) x HPGL (cells/ g-liver) x liver weight (g) [2]

21. Other approaches that can be taken to develop PBPK models are the "middle-out approach" (where parameter values of the mechanistic PBPK model can be further refined by fitting the model to pharmacokinetic data once available), and the "top-down" approach (where model development is initiated based on fitting model parameters to pharmacokinetic data) (Tsamandouras *et al.* 2015). The parameters to be refined are those associated with a degree of uncertainty due to technical difficulties in their measurement. Usually, the refined models are capable of interpolating data, but extrapolation to outside the data space used to fit the model is challenging.

Methods of model fitting

22. A common technique used to fit a PBPK model to pharmacokinetic data is to use an algorithm which results in the 'fit of least-squares'. This algorithm involves running the model with an initial value of a parameter being optimised, then squaring the difference between the model's predictions and observed data at each time point, and then summing these differences. This process is repeated with different parameter values until the summed differences are minimised and the 'fit of least-squares' is obtained, thereby generating a single optimised value (Campbell *et al.* 2012). This procedure can be applied to many parameters simultaneously which is appropriate for PBPK models that are highly parameterised.

23. Bayesian inference can also be used for model fitting and has two unique advantages: the fit of each parameter is 1) a posterior probability distribution of values, rather than a point estimate, which takes account of measurement uncertainty and variability of parameter values, and 2) informed by both experimental data and prior knowledge (Jonsson & Johanson 2003).

24. Methods taken to evaluate the model's fit to pharmacokinetic data includes visual inspection and the use of statistical tests and discrepancy indices. Visual inspection is a frequently used approach (Chiu *et al.* 2007). This is a visual assessment of the model's ability to reproduce the shape of the time course of chemical concentrations in biological matrices. The correspondence between predictions and experimental data should be not only at the level of individual values (e.g. blood concentration values), but also at the level of the profile (i.e. peaks and valleys in the pharmacokinetic curve).

Model validation

25. In 2010, the World Health Organisation (WHO) published key principles and best practices for characterising and applying PBPK models in risk assessment (WHO 2010). This was conducted within the International Programme on Chemical Safety (IPCS) project on the Harmonisation of Approaches to the Assessment of Risk from Exposure to Chemicals.

26. The WHO 2010 publication addressed model validation, which is required before a PBPK model can be used confidently as a tool in risk assessment. Validation is defined here as the "process by which the reliability and relevance of a particular model are established for a defined purpose" (IPCS 2005). Validation should be conducted by considering the 1) biological basis of the model structure and parameters, 2) closeness of the model simulations to chemical-specific pharmacokinetic data, and 3) reliability of simulated dose metrics, as they relate to a specific purpose or application in risk assessment. Supplementary analyses of 4) sensitivity, 5) uncertainty, and 6) variability might be important, depending upon the end use and extent of comparison with real-life data. (WHO 2010). These criteria are described in further detail below.

1) Biological basis of the model structure and parameters

27. The model structure should reflect a balance between the principle of parsimony (i.e. minimal but essential elements characterising a system) and biological plausibility (i.e. consistent with the available knowledge regarding the physiology of the modelled organism and the chemical's ADME) in order to simulate dose metrics of relevance to risk assessment (WHO 2010).

28. To conform with the principle of model parsimony, tissues exhibiting similar concentration versus time course behaviour are typically lumped together, for example as "richly perfused tissues" and "poorly perfused tissues". This is to avoid uncertain parameters that are nonessential contributing uncertainty to the simulated dose metric.

29. Values of physiological parameters such as tissue volumes and blood flow rates should be within the range that has been documented for the particular species and life stage (e.g. Brown *et al.* 1997). Values of fitted model parameters should be biologically plausible for the particular species and life stage. If biologically implausible parameters are required for the model to reproduce pharmacokinetic data, this would indicate either the pharmacokinetic data are erroneous or deficiencies exist in the model structure in terms of the biological system it is intended to represent.

2) Closeness of the model simulations to pharmacokinetic data

30. The model should reproduce the pharmacokinetic data used for model fitting, in addition to a set of independent experimental data that were not used to estimate parameters with. Confidence in a PBPK model will be greater if it reproduces a variety of pharmacokinetic data under a variety of experimental and exposure conditions (Gentry *et al.* 2004).

31. In comparing model simulations against experimental data, it is important to note that both are subject to uncertainty (IPCS 2008). Predictions that are within two-fold of the pharmacokinetic data have frequently been considered adequate (WHO 2010, Shebley *et al.* 2018). However, results from a controlled clinical study with a small sample size may not be representative of the entire range of values or the central tendency of the values found in a larger population. Thus, Abduljalil *et al.*

(2014) proposed to evaluate the success of model predictions by taking into account study sample size and the observed variance of the parameter of interest.

32. Tan *et al.* 2018 reviewed the scientific literature for studies in which human PBPK models had been extrapolated from experimental animals and, in addition, evaluated with human pharmacokinetic data. A total of 44 publications were found, where the human model adequately predicted the human pharmacokinetic data and thus did not require additional fitting. Tan *et al.* (2018) noted that many of these publications took the "bottom-up" approach for model development (described in paragraph 18) (e.g. Loccisano *et al.* 2011). On the other hand, 46 publications were identified where the human pharmacokinetic data were to used fit the human model post extrapolation. Tan *et al.* (2018) noted that most of these publications took the "top-down" approach for model development (described in paragraph 21) (e.g. Sterner *et al.* 2013).

3) Reliability of simulated dose metrics relevant to the risk assessment

33. The "dose metric" has been defined as the dose measure that is causally related to the toxic outcome (Andersen *et al.*1987, Clewell *et al.* 2002, Andersen, 2003). It is more closely associated with tissue response than external dose. When the direct measurement of a dose metric is unethical or not technically feasible, PBPK models can be used to simulate it.

34. The dose metric relates to the form of chemical (e.g. parent chemical or metabolite), its level (free or total concentration or amount), duration (instantaneous, daily, lifetime or a specific developmental period), intensity (maximum, average or integral), and the biological matrix (e.g. blood, target tissue) (US EPA 2006).

35. For application to risk assessment, the model should be able to simulate the dose metric of relevance to the chemical's mode of action (MOA). The dose metric that is estimated may correspond to an external reference dose such as the NOAEL or BMDL or another exposure scenario of interest to risk assessors. When there are several candidate dose metrics, the appropriate one for use in risk assessment should be chosen on the basis of plausibility. The plausibility of a particular dose metric is determined by its consistency with available information on the chemical's MOA as well as dose-response information for the toxicological endpoint of concern. (WHO 2010).

36. The reliability of the simulated dose metric can be assessed by comparing it with experimental data obtained under exposure conditions relevant to the risk assessment. However obtaining such data is not always possible and this is illustrated by the case of vinyl acetate.

37. The cytotoxicity of vinyl acetate is hypothesised to be associated with a reduction in intracellular pH caused by acetic acid, one of its metabolites (Bogdanffy *et al.* 2001). To assess the health risk of inhalation exposure to vinyl acetate, a PBPK model was developed for rats and extrapolated to humans (Bogdanffy *et al.* 1999). However, experimental data on the dose metric relevant to risk assessment (pH changes in nasal tissues) were not available in rats or humans due to technical difficulties in its measurement. The PBPK model reproduced the pharmacokinetics of

vinyl acetate and its metabolites in the upper respiratory tract of rats. However, the closeness of the model simulations to human pharmacokinetic data could not be assessed because human data were not available. Despite this deficiency, the level of confidence in this PBPK model for the intended purpose was characterised as "medium" on the basis of biological basis, performance and reliability of the simulated dose metric (the latter, in this case, being supported by a sensitivity analysis to identify key parameters determining the dose metric in rats and humans) (WHO 2010).

38. WHO 2010 recommends that "if no PK data are available in humans or if only parent chemical data are available in humans (and not the relevant dose metric, i.e. concentration of metabolite), then the reliability of the model predictions of dose metrics should be evaluated on the basis of appropriate sensitivity and uncertainty analyses". These kinds of analyses are described in further detail below.

4) Sensitivity analysis

39. Sensitivity analysis involves changing the value of each model parameter (within the range of its measurement variability) and quantitatively assessing the impact on the simulated dose metric. The results can be used to identify which model parameters have the greatest impact on the simulated dose metric. Such parameters are described as being "sensitive", and subsequently an "uncertainty analysis" (described in paragraphs 42-43) can be done with them.

40. If a change in a parameter value less than typical variability of its measurement results in changes in the predicted value of the dose metric that are less than the variation expected from experimental measurement of the dose metric, the model is said to be robust with respect to small uncertainties in the values of its parameters. Conversely, the model should be sensitive to large uncertainties in the values of its parameters. A change in a parameter value greater than typical experimental error should result in changes in the predicted value of the dose metric that exceed the variation expected from experimental measurement of the dose metric. (Kohn 1995).

41. A sensitivity ratio of 1 implies that a 1% change in parameter value leads to a 1% change in the simulated dose metric. Parameters with absolute ratio values of ≥ 0.1 to < 0.2, ≥ 0.2 to < 0.5, and ≥ 0.5 are said to have low, medium or high sensitivity, respectively. (WHO 2010).

5) Uncertainty analysis

42. A degree of uncertainty may be associated with the *in vitro* data used to populate model parameters, and therefore the values of the model parameters themselves. Accordingly, an uncertainty analysis evaluates the impact of the lack of precise knowledge of parameter values on dose metric simulations. This is beneficial for PBPK models that do not adequately simulate the pharmacokinetic data, or have been evaluated only with limited pharmacokinetic data sets (WHO 2010).

43. An uncertainty analysis can be performed by assigning uncertainty distributions to model parameters and using Monte Carlo sampling to iteratively

calculate a dose metric. The ratio of the 95th percentile value over the median value of the dose metric is a measure of the uncertainty in dose metric predictions. Parameters with uncertainty ratio values of ≤ 0.3, 0.3 to 2, and ≥ 2 could have low, medium or high uncertainty, respectively (WHO 2010). Following this evaluation, additional *in vitro* or *in silico* data may be collected in order to reduce the uncertainty of the corresponding parameter values.

6) Variability analysis

44. PBPK models can be used to simulate a dose metric for a population if appropriate distributions are assigned to its physiological, biochemical and physicochemical parameters (e.g. Haber *et al.* 2002). Distributions assigned to model parameters should reflect the uncertainty regarding the population mean value and the degree of interindividual variability in the population of interest. The uncertainty and variability should be appropriately quantified and separated through the use of a hierarchical model structure (Bois 2001).

45. A variability analysis that assesses the impact of parameter uncertainty and variability on plasma C_{max} is fundamental to the use of PBPK models in estimating HK_{UF} for the derivation of a CSAF (described in paragraph 15).

46. Despite the utilities of variability analysis, the parameterisation of PBPK models is sometimes done using fixed values. Although less computationally burdensome, risk assessments conducted for public health that use such models should compensate for an absent variability analysis. For example, Phillips *et al.* 2014 divided their biomonitoring equivalent derived from a PBPK model by an appropriate uncertainty factor to account for intraspecies variability in ADME.

Other considerations

Structural "identifiability"

47. In fitting a PBPK model to pharmacokinetic data, there may be combinations of parameter values that result in an equally good fit to the pharmacokinetic data in a way that individual parameters cannot be uniquely identified. This issue becomes more prominent when the number of unknown parameters is large relative to the information contained in the pharmacokinetic data that is being fitted.

48. Proposed approaches to address identifiability issues include, if possible, reducing the total number of unknown model parameters, and generating additional pharmacokinetic data to fit the model with (Slob *et al.* 1997).

49. Overall, structural identifiability is not an issue for PBPK models when the model structure and parameter values are justified mechanistically and the pharmacokinetic properties are verified against observed data (Shebley *et al.* 2018).

Documentation

50. The documentation of a PBPK model intended for use in risk assessment requires the inclusion of the original model code and supporting files (i.e.

exposure/dose calculations and comparison of model simulations with experimental data) that would allow regulatory scientists to accurately reproduce and evaluate its performance (WHO 2010). Overall, PBPK model documentation should address the following broad topics (WHO 2010):

- scope and purpose of the model,
- model structure and biological characterisation,
- mathematical description of ADME,
- computer implementation and verification,
- parameter estimation and analysis,
- model validation and evaluation,
- evaluation/ justification of dose metrics, and
- specialised analysis, if any.

Statements and other guidance

51. Due to advancements in molecular biology, toxicology, and computing the risk assessment paradigm has shifted away from use of traditional whole animal toxicity testing towards a focus on modes of toxicity. Interest in PBPK modelling across industry, particularly in North America and the EU, is increasing because these models can be used to assess 'internal dose' and how it relates to 'early biological effects' which is central to the concept of modes of toxicity. This has prompted regulatory bodies to release statements and guidance on the development and documentation of PBPK modelling to support regulatory submissions. However, there is generally a lack of scientific consensus in terms of how PBPK models are evaluated, due to their perceived complexity and diverse applications. For example, there appears to be a lack of clear distinction within the PBPK and computational science communities with regards to the terms model "validation" (defined in paragraph 26) and model "qualification" (defined in paragraph 58) (MISG 2014).

COT statement (2003)

52. In February 2003, COT hosted a workshop on PBPK modelling which comprised of several presentations concerning the incorporation of PBPK models into risk assessment paradigms. The presentations were followed by a general discussion which focussed on the strengths and weaknesses of PBPK modelling, and whether it can be integrated into COT risk assessments.

53. The Committee considered PBPK modelling to be an established technique capable of predicting the *in vivo* behaviour of chemicals. PBPK modelling is widely used in the development and risk assessment of pharmaceutical products, where there is often sufficient human data available with which to validate the models. However, for many chemicals evaluated by COT, it was noted 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.

54. 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.

55. The Committee agreed that it would not be feasible to undertake PBPK modelling routinely for COT risk assessments because the generation and validation of a PBPK model is resource and time intensive. However COT should incorporate existing published PBPK models into assessments when available, for example when submitted in support of a risk assessment by industry.

EMA guidance (2018) and FDA guidance (2018)

56. These guidelines describe the expected format and content of PBPK modelling and simulation reports that are included in regulatory submissions for medicinal products. The main purposes of PBPK models in regulatory submissions are to predict drug-drug interactions (DDIs), and support initial dose selection in first-in-human clinical trials and paediatric investigation plans.

57. Subsequent to guidance published by FDA and EMA, PBPK modelling scientists in the Simcyp Consortium (a collaborative research centre for PBPK modelling) collaborated to develop a perspective review on the qualification and verification of PBPK models intended for regulatory submission of new drug therapies (Shebley *et al.* 2018).

58. Model qualification is “the process of establishing confidence in a PBPK platform to simulate a certain scenario, in a specific context, on the basis of scientific principles and ability to predict a large dataset of independent data thereby showing the platforms ability to predict a certain purpose” (EMA 2018).

59. Model verification is “part of the qualification focused on the assessment of the correctness of the mathematical model structure including details of the differential equations used and the parameterisations of the model” (EMA 2018). According to WHO (2010), this includes ensuring the units of parameters are accurate, the chemical mass balance is respected at all times, and the cardiac output specified in the model is equal to the sum of blood flow rates to the tissue compartments. In addition, the computer implementation of a PBPK model must be correct. For example, the model codes should be devoid of syntax or mathematical errors, and there should be no numerical integration errors. This can be addressed by independently coding and running the model in a different computer language or program.

<u>Questions on which the views of the Committee are sought:</u>

60. The Committee are asked to consider the following questions:

i). Does the Committee consider that this summary is helpful and does it indicate the need for further guidance on the use and application of PBPK models?

ii). If Members consider that further guidance is necessary what aspects do members consider most important and how would they wish to take this forward?

iii). In the absence of human toxicokinetic data for the validation of a human PBPK model intended for risk assessment (as illustrated by the case of vinyl acetate), to what extent does the Committee consider sensitivity and uncertainty analyses sufficient for assessing the reliability of a simulated dose metric?

Secretariat
July 2019

References

Abduljalil K., Cain T., Humphries H., *et al.* (2014) Deciding on success criteria for predictability of pharmacokinetic parameters from *in vitro* studies: an analysis based on *in vivo* observations. *Drug Metab. Dispos.* **42:** 1478-1484

Andersen M.E., Clewell H.J., Gargas M.L., *et al.* (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicology and Applied Pharmacology* **87:** 185–205.

Andersen M.E. (2003) Toxicokinetic modeling and its applications in chemical risk assessment. *Toxicology Letters* **138:** 9-27

Bogdanffy M.S., Sarangapani R., Plowchalk D.R., *et al.* (1999) A biologically based risk assessment for vinyl acetate–induced cancer and noncancer inhalation toxicity. *Toxicological Sciences* **51:** 19-35

Bogdanffy M.S., Plowchalk D.R., Sarangapani R., *et al.* (2001) Mode-of action-based dosimeters for interspecies extrapolation of vinyl acetate inhalation risk. *Inhalation Toxicology* **13:** 377-396

Bois F.Y. (1999). Analysis of PBPK models for risk characterisation. *Ann. N Y Acad Sci*. **895:** 317- 337

Bois F.Y. (2000). Statistical Analysis of Clewell *et al.* PBPK Model of Trichloroethylene Kinetics. *Environ. Health Perspect.* **108:** 307-316

Bois F.Y. (2001) Applications of population approaches in toxicology. *Toxicology Letters* **120:** 385-394

Brown R.P., Delp M.D., Lindstedt S.L., *et al.* (1997) Physiological parameter values for physiologically based pharmacokinetic models. *Toxicology and Industrial Health* **13:** 407-484

Campbell J.L., Clewell R.A., Gentry P.R., *et al.* (2012). Ch. 18. Physiologically Based Pharmacokinetic/ Toxicokinetic Modeling. In: Reisfeld B., & Mayenoo A.N. (eds), Computation Toxicology. Humana Press, New York, p. 457, 473

Chiu W.A., Barton H.A., Dewoskin R.S., *et al.* (2007) Evaluation of physiologically based pharmacokinetic models for use in risk assessment. *Journal of Applied Toxicology* **27:** 218-237

Clewell H.J., Andersen M.E., & Barton H.A. (2002) A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. *Environmental Health Perspectives* **110:** 85-93

Clewell H.J., Gentry P.R., Covington T.R., *et al.* (2004) Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Toxicological Sciences* **79:** 381-393

Cooper A.B., Aggarwal M., Bartels M.J., *et al.* (2019) PBTK model for assessment of operator exposure to haloxyfop using human biomonitoring and toxicokinetic data. *Regul Toxicol Pharmacol.* **102**: 1-12

EMA (2018) Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

FDA (2018) Physiologically Based Pharmacokinetic Analyses — Format and Content. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

Gentry P.R., Clewell H.J., & Andersen M.E. (2004) Good modeling practices for pharmacokinetic models in chemical risk assessment. Unpublished contract report submitted to Health Canada, Ottawa, Ontario.

Haber L.T., Maier A., Gentry P.R., *et al.* (2002) Genetic polymorphisms in assessing interindividual variability in delivered dose. *Regulatory Toxicology and Pharmacology* **35:** 177-197

Hays S.M., Becker R., Leung H.W., *et al.* (2007). Biomonitoring Equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. *Regul. Toxicol. Pharm.* **47:** 96-109

IPCS (2005) Principles of characterizing and applying human exposure models. Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 3; p. 67 http://whqlibdoc.who.int/publications/2005/9241563117_eng.pdf).

IPCS (2008) Part 1. Guidance document on characterizing and communicating uncertainty in exposure assessment. In: Uncertainty and data quality in exposure assessment. Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 6; http://www.who.int/ipcs/publications/methods/harmonization/exposure_assessment.pdf).

Jonsson F. & Johanson G. (2003). Bayesian population approach to physiological toxicokinetic-toxicodynamic models - an example using the MCSim software. *Toxicol. Lett.* **138:** 143-150

Kenyon E.M. (2012). Ch. 19: Interspecies extrapolation. In: Computational Toxicology: Methods in Molecular Biology, Brad Reisfeld and Arthur N. Mayeno (eds.) **929:** 501-520

Kohn M.C. (1995) Achieving credibility in risk assessment models. *Toxicology Letters* **79:** 107-114

Lehman A.J. & Fitzhugh O.G. (1954). 100-fold margin of safety. *Assoc. Food Drug Off. U. S. Quant. Bull.* **18:** 33-35

Li G.F., Wang K., Chen R., *et al.* (2012) Simulation of the pharmacokinetics of bisoprolol in healthy adults and patients with impaired renal function using whole-body physiologically based pharmacokinetic modelling. *Acta Pharmacol Sin.* **33:** 1359-71

Lindstedt L. & Schaeffer P.J. (2002). Use of allometry in predicting anatomical and physiological parameters of mammals. Lab Anim. **36:** 1-19

Loccisano A.E., Campbell J.L., Andersen M.E., *et al.* (2011). Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. *Regul. Toxicol. Pharmacol.* **59:** 157-175

Lyons M.A., Yang R., Mayeno A.N., *et al.* (2008). Computational toxicology of chloroform: reverse dosimetry using Bayesian inference, Markov chain Monte Carlo simulation, and human biomonitoring data. *Environ. Health Perspect.* **116:** 1040-1046

Meek B., Renwick A., & Sonich-Mullin C. (2003). Practical application of kinetic data in risk assessment—an IPCS initiative. *Toxicol. Lett.* **138:** 151-160

Ministerial Industry Strategy Group (2014) MISG New technologies forum on physiologically based pharmacokinetic (PBPK) modelling and simulation. Association of the British Pharmaceutical Industry, London, p. 26 Available at: http://www.abpi.org.uk/publications/misg-new-technologies-forum-on-physiologically-based-pharmacokinetic-pbpk-modelling-and-simulation/

Phillips M.B., Sobus J.R., George B.J., *et al.* (2014). A new method for generating distributions of biomonitoring equivalents to support exposure assessment and prioritization. *Regul. Toxicol. Pharm.* **69:** 434-442

Renwick A.G. (1991). Safety factors and establishment of acceptable daily intake. *Food Addit. Contam.* **8:** 135-150

Renwick A.G. (1993). Data-derived safety factors for the evaluation of food additives and environmental contaminants. *Food Addit. Contam.* **10:** 275-305

Renwick A.G. & Lazarus N.R. (1998). Human variability and noncancer risk assessment - An analysis of the default uncertainty factor. *Regul. Toxicol. Pharm.* **27:** 3-20

Rideout V.C. (1991) Mathematical and computer modeling of physiological systems. New York, NY, Prentice-Hall, 272 pp.

Shebley M., Sandhu P., Riedmaier A.E., *et al.* (2018) Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective. *Clin Pharmacol Ther.* **104:** 88-110

Slob W., Janssen P.H., & van den Hof J.M. (1997) Structural identifiability of PBPK models: practical consequences for modeling strategies and study designs. *Crit. Rev. Toxicol.* **27:** 261-272

Sohn M.D., McKone T.E., & Blancato J.N. (2004). Reconstructing population exposures from dose biomarkers: inhalation of trichloroethylene (TCE) as a case study. *J. Expo. Anal. Env. Epid.* **14:** 204-213

Sterner T.R., Ruark C.D., Covington T.R., *et al.* (2013). A physiologically based pharmacokinetic model for the oxime TMB-4: Simulation of rodent and human data. *Arch. Toxicol.* **87:** 661-680

Tan Y.M., Worley R.R, Leonard J.A., *et al.* (2018) Challenges Associated With Applying Physiologically Based Pharmacokinetic Modeling for Public Health Decision-Making. *Toxicological Sciences* **162:** 341-348

Tsamandouras N., Rostami-Hodjegan A., & Aarons L. (2015) Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. *Br. J. Clin. Pharmacol.* **79:** 48-55

U.S. EPA. (2006) Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment (Final Report). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-05/043F

WHO (2005). Harmonization Project Document No. 2: Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use on data in dose/ concentration-response assessment.

WHO (2010) Characterization and application of physiologically based pharmacokinetic models in risk assessment. Harmonization Project Document No. 9 Available at: https://www.who.int/ipcs/methods/harmonization/areas/pbpk/en/