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# Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: The first steps

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**Abstract**

The increasing use of tissue dosimetry estimated using pharmacokinetic models in chemical risk assessments in various jurisdictions necessitates the development of internationally recognized good modelling practice (GMP). These practices would facilitate sharing of models and model evaluations and consistent applications in risk assessments. Clear descriptions of good practices for (1) model development i.e., research and analysis activities, (2) model characterization i.e., methods to describe how consistent the model is with biology and the strengths and limitations of available models and data, such as sensitivity analyses, (3) model documentation, and (4) model evaluation i.e., independent review that will assist risk assessors in their decisions of whether and how to use the models, and also model developers to understand expectations for various purposes e.g., research versus application in risk assessment. Next steps in the development of guidance for GMP and research to improve the scientific basis of the models are described based on a review of the current status of the application of physiologically based pharmacokinetic (PBPK) models in risk assessments in Europe, Canada, and the United States at the International Workshop on the Development of GMP for PBPK Models in Greece on April 27–29, 2007.


*Keywords:* Good modelling practice; PBPK; Risk assessment

## 1. Introduction

The increasing use of tissue dosimetry estimated using pharmacokinetic models in chemical risk assessments in a number of countries necessitates the need to develop internationally recognized good modelling practices. These practices would facilitate sharing of models and model evaluations and consistent applications in risk assessments. Clear descriptions of good practices for:

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1. Model development i.e., research and analysis activities,
2. Model characterization i.e., methods to describe how consistent the model is in capturing the relevant biological events with respect to mode of action and the strengths and limitations of available model and data, e.g., sensitivity analyses,
3. Model documentation, and
4. Model evaluation i.e., independent review,will assist risk assessors in their decisions of whether and how to use the models, and assist model developers to meet various expectations (e.g., research versus application in risk assessment) (Cobelli et al., 1984; Portier and Lyles, 1996; Rescigno and Beck, 1987).

For risk assessors, good modelling practice would provide guidance as a basis to evaluate the potential for a pharmacokinetic model, particularly a physiologically based pharmacokinetic (PBPK) model, to contribute to a risk assessment. PBPK models represent part of a continuum of increasingly data-informed approaches to dose–response characterization that increasingly incorporate more information and as such, contribute to better understanding and precision in estimating risks. These approaches range from default (''presumed protective'') to more ''biologically-based predictive'' (Meek et al., 2001). Default approaches are based on empirical observations from broad databases of information that are not group, species or chemical specific; pharmacokinetics and dynamics are not explicitly addressed. ''Categorical'' and ''species-specific'' approaches incorporate category or group specific information and increasingly along the continuum, chemical-specific data are incorporated. This includes development of chemical specific adjustment factors (CSAF) incorporating compound-related or chemical-specific pharmacokinetic (including PBPK models) or pharmacodynamic data (Gundert-Remy and Sonich-Mullin, 2002; IPCS, 2005) When appropriate, fully data-derived, chemical-specific, biologically-based dose–response risk assessment methods can be employed for chemicals of high concern or with high economic impacts thus entailing fuller quantitative characterization of toxicokinetic and toxicodynamic aspects.

Increasingly, data-derived approaches to dose–response assessment are based on weight of evidence descriptions of known or hypothesized modes of action, the latter being a description of the key events leading to toxicity rather than a full mechanistic understanding. A framework for organizing and evaluating the weight of evidence supporting modes of action in animals and their relevance to humans has been developed which is applicable to all toxicity endpoints. This framework has evolved from consideration of the weight of evidence of an animal mode of action (Sonich-Mullin et al., 2001) to extension to human relevance (Boobis et al., 2006; Meek et al., 2003b) and from cancer (Boobis et al., 2006; Meek et al., 2003b) to non cancer endpoints (Boobis et al., 2008; Seed et al., 2005). This framework which is now widely used in assessments nationally and internationally continues to evolve, currently being extended to integrate dose–response analysis. As such, it provides a transparent basis for defining the sufficiency of data on mode of action that is needed to inform the use of physiologically based pharmacokinetic models in risk assessment.

For modellers, GMP is important to delineate the nature of model characterization and documentation that is optimal for application in risk assessment. The initial creation of models, along with needed laboratory experimentation, can be a creative and unpredictable process that will be minimally altered by GMP. However, even at this very early stage, awareness of GMP can be valuable, including recommendations regarding transparency for publication of the models in the peer reviewed literature (Andersen et al., 1995). For example, modellers often try several alternative structures as they attempt to reconcile the available data and the description of the biology in the model. While documentation to the same degree as a model proposed for use in risk assessment is unnecessary, understanding of the alternatives considered is important in supporting the model structure eventually selected (Barton et al., 2007).

The International Workshop on the Development of GMP for PBPK models[1] was convened with two principal themes:

1. The selection and evaluation of an appropriate *deterministic*[2] model structure.
2. Increasing the understanding of regulators and risk assessors through increased transparency and accessibility to user-friendly modelling techniques.

This was the first forum dedicated to promotion of best practice in deterministic PBPK model development and parameterisation, including consideration of transparency in documentation with clear audit trails for model components. Increase in consistency and transparency of supporting documentation is expected to facilitate dialogue and understanding between PBPK practitioners, risk assessors and regulators. By bringing together PBPK modellers, mathematicians, statisticians, risk assessors, regulators and laboratory scientists, the sponsors of this workshop seek increased implementation of PBPK modelling in risk assessment internationally, which GMP for PBPK should

[1] April 26–April 28, 2007, at the Mediterranean Agronomic Institute of Chania, Crete, Greece. Presentations, and discussion papers are at http://www.hsl.gov.uk/news/news_pbpk.htm. Additional information is available at www.pbpk.org.

[2] A ''deterministic'' model is the mathematical representation of the biological/chemical system (e.g., PBPK model and metabolic scheme) as opposed to a ''non-deterministic'' model, which is the mathematical/statistical representation of the uncertainty, variability, and covariance of the data and parameters of the deterministic model (e.g., statistical model for measurement errors and population variability). Non-deterministic modelling was a focus of the International Workshop on Uncertainty and Variability in PBPK Models, 2006, North Carolina, US http://www.epa.gov/ncct/uvpkm/ (Barton et al., 2007).

facilitate. This paper presents the results and conclusions of the GMP workshop.

## 2. Current practice—where do we stand?

The structure of PBPK models may differ to reflect the requirements of the application, e.g., research (hypothesis testing) and risk assessment. Appropriate practice for these different uses and various stages of model development are desirable. Past efforts to develop GMP for other types of models applied in environmental regulation are informative in terms of their form, content, and application.

## 3. Value of PBPK models in risk assessments

The need for increasing incorporation of kinetic data in the current risk assessment paradigm is due to an increasing demand from risk assessors and regulators for higher precision of risk estimates, a greater understanding of uncertainty and variability (Allen et al., 1996; Barton et al., 1996; Clewell et al., 1999, 2002b; Cox, 1996; Delic et al., 2000), more informed means of extrapolating across species, routes, doses and time (Clewell and Andersen, 1987), the need for a more meaningful interpretation of biological monitoring data (Georgopoulos et al., 1994; Hays et al., 2007) and reduction in the reliance on animal testing (Barratt et al., 1995; Blaauboer et al., 1996, 1999; DeJongh et al., 1999). Incorporating PBPK modelling into the risk assessment process can advance all of these objectives. Further, the increasing trend to cost-benefit analysis should also increase the utility of biologically based approaches in the support of risk management decisions by regulatory agencies (US EPA, 2006).

In addition, increasingly, testing and risk assessment is being driven by considerations of mode of action and resulting in more data-informed approaches to characterization of dose response, which should facilitate the incorporation of PBPK modelling. These approaches are increasingly being adopted by risk assessment and regulatory communities, based on, for example, international initiatives such as the IPCS harmonization initiative for the risk assessment of chemicals (Sonich-Mullin et al., 2001). The latter initiative seeks to improve methods and to increase understanding and acceptance through the pursuit of common principles and approaches by drawing on global expertise, leading ultimately to greater consistency and convergence which will permit the sharing of assessments and avoid duplication. Potential areas of convergence for which analytical frameworks, guidance and associated training materials have been developed through this initiative include weight of evidence for mode of action, CSAFs and more recently PBPK modelling (Boobis et al., 2006, 2008; IPCS, 2005; Meek et al., 2001, 2002, 2003a,b; Meek and Renwick, 2006; Sonich-Mullin et al., 2001).

## 4. Current status of implementation of PBPK models in risk assessments

One of the first PBPK models to be adopted in regulatory risk assessment was that for methylene chloride, whose evolution involved an iterative hypothesis testing process for the pharmacokinetics and glutathione transferase-mediated mode of action leading to cancers in rodents. The mathematical model gave a quantitative form to the researcher's conception of the biological system, permitting the development of a testable, quantitative hypothesis, the design of informative experiments and the ability to recognize inconsistencies between theory (model) and data. The explicit description of model parameters also led to the ability to study and quantify uncertainty. The model has been widely applied in risk assessments by the US Consumer Products Safety Commission (Babich, 1998), by the US Occupational Safety and Health Administration for establishing the permissible exposure level including use of Bayesian statistical parameter estimation and characterization of uncertainty and variability (OSHA, 1997), by the US Environmental Protection Agency in the Integrated Risk Information System (IRIS) assessment for inhalation cancer risk (Dewoskin, 2007; US EPA, 1987) and Health Canada in their assessment for the general population under the Canadian Environmental Protection Act (Government of Canada, 1993).

An overview of the use of PBPK modelling by various risk assessment/regulatory authorities is presented in Table 1.

The results of this limited analysis presented in Table 1 indicate that PBPK models are increasingly being adopted in risk assessment by regulatory agencies in Europe and North America, most often to date, as a basis for quantitatively considering interspecies differences as a basis to replace the default approach. The extent of documentation of the rationale for accepting or rejecting the use of particular models varies considerably and is likely to be dependent upon access to relevant expertise. In most cases, lack of adoption of particular models within risk assessment has been a function of insufficient weight of evidence of the underlying hypothesized mode of action and/or the lack of a standardized procedure for the evaluation of PBPK models and their output.

## 5. What can we learn from other similar modelling experiences?

While the use of quantitative modelling in human health risk assessment has been more limited, particularly biologically-based dose–response analyses, modelling for environmental fate and transport has gained increased acceptance since the 1990s and is now widely accepted in European, Canadian, and US regulatory contexts. Today in Europe modelling endpoints for groundwater are decisive in the registration of pesticides. In North America and Europe, risk assessments for specific con-

Table 1
The use of PBPK modelling by various risk assessment/regulatory authorities

| Assessments | Use of PBPK Models | Impact/Rationale |
|---|---|---|
| Random selection of 80/141 EU Existing Substances Reports (1996–2007) (European Chemicals Bureau) | *Mentioned in 8/80* | |
| | *Adopted in 4/8* (vinyl acetate, 2-butoxyethanol, propylene methyl glycol,styrene) | Reduction of uncertainty factor for interspecies differences or reduction of classification category |
| | *Not used in 4/8* (benzene, | Mode of action judged to vary between humans and animals |
| | acrylic acid, | *In vitro* activity of enzymes in one tissue as surrogates of *in vivo* activity in another tissue judged to be implausible |
| | cyclohexane, methyl methacrylate,) | No reason provided |
| UK Health and Safety Executive | Formaldehyde | Lack of biological plausibility of association with leukaemia (Franks, 2005) |
| | 2-butoxyethanol | Consideration of validity of a biomarker and robustness of past regulatory decisions (Delic et al., 2000, Franks et al., 2006) |
| French Agency for Environmental and Occupational Health | Consideration in setting reference values for reproductive health | (INERIS, 2007) |
| Health Canada Priority Substances under the Canadian Environmental Protection Act (n = 44 on the first Priority Substances List (PSL 1) and 25 on PSL 2 (1989–1994) (Health Canada Priority Substances Assessment Program) | *Considered inadequate* for quantifying interspecies differences for tetrachloroethylene, styrene and diethylhexylphthalate (PSL 1) | |
| | *Adopted* for | |
| | Cadmium (PSL 1) | Quantification of human variability |
| | Formaldehyde | Quantification of interspecies differences in biologically motivated case specific model |
| | Chloroform | Quantification of interspecies differences |
| | 2-butoxyethanol | Quantification of interspecies differences |
| US FDA | Trans retinoic acid | Consideration of potential risk of dermal application (Clewell et al., 1997, Rowland et al., 2004) |
| US EPA (IRIS) | *Not applied* for | |
| | Acetone | Lack of necessary exposure route in model. |
| | Chloroform | Lack of model parameterization in species with critical effect. |
| | Methyl ethyl ketone | Lack of sufficient supporting data for model and demonstration of predictive capability. |
| | *Adopted for* | |
| | Dichloromethane | Quantification of interspecies differences. |
| | Ethylene glycol monobutyl ether | Quantification of interspecies differences. |
| | Vinyl chloride | Quantification of interspecies differences in PK and demonstration of interspecies similarities in cancer PD. Route-to-route extrapolations to derive point of departure. |
| | Xylene | Comparison to default RfC[a] |

[a] The concentration of a chemical in air that is very unlikely to have adverse effects if inhaled continuously over a lifetime (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55365).

taminated sites or permitting of industrial facilities also rely heavily on often complex models for exposure pathways including food chains (US EPA, 1989). More recently, in view of the introduction of demanding mandates to consider much larger numbers of existing chemical substances (e.g., categorization and screening of the Domestic Substances List (DSL) (Health Canada Domestic Substances List) in Canada and the Registration, Evaluation and Authorization of Chemical Substances (REACH) (European Community Regulation REACH) in Europe, there is increasing development of quantitative structure activity relationship (QSAR) models particularly for application in human health risk assessment and associated GMP. These experiences provide perspectives that are potentially useful for the development of GMP for PBPK modelling.

## 6. Environmental modelling-achieving acceptance in the regulatory world

The development of good practice in environmental fate modelling may provide a relevant perspective for the development of GMP for PBPK modelling. GMP for environmental fate modelling evolved in Europe as a result of two issues; firstly EU legislation in the late 1980s set a maximum pesticide residue concentration of 0.1 μg $L^{-1}$ in both drinking and ground water and secondly lysimeter[3] studies which took between three to four years leading to long delays on decisions on the use of critical products in agriculture while avoiding contamination of groundwater resources. Environmental fate modelling was recognized as a promising approach to address these issues but questions were raised concerning whether model predictions were sufficiently reliable and how to ensure the integrity of model calculations.

Clear divisions in attitudes among environmental fate modellers, regulators, and registrants emerged following initial discussions. Researchers used the models for the investigation of processes and systems, requiring flexibility and adaptability while maintaining full control of processes and algorithms in the models. Regulators and registrants wanted to predict exceedence or adherence to a regulatory limit. They required scientific and legal certainty and preferred models for which the code could not be altered, and had complete documentation with clear audit trails for calculations. Further conflicts arose because version control and documentation of research models was rudimentary at best, no guidance on the selection of appropriate input parameters was available, and it was rarely properly established whether a model design was suitable for regulatory purposes. These issues reflected the variations in objectives of models developed for research versus regulatory application with the former being intended for use by a specialist with specific and intensive training, which at the time was almost totally lacking in regulatory agencies and companies assessing the environmental behaviour of plant protection products. As a consequence, results for different modellers using the same models in similar applications varied.

Initially, software packages comprising models with a user-friendly graphical interface and pre-configured scenarios were developed. However, non-expert users still produced poor results for two main reasons (i) model processes, algorithms and standard parameters did not appropriately reflect substance properties, and (ii) substance data from standard environmental fate studies were conceptually different from these required for model implementation. This led to proposals from regulatory agencies to apply good laboratory practice (GLP) for modelling to ensure that all data could be 'verified'. Also, GLP had just been successfully transferred from toxicology to metabolism, environmental fate and residue analysis laboratories. On the other hand, measurements are never perfectly reproducible (especially not for living systems) whereas simulations are and GLP is difficult to apply to electronic data systems and calculations.

This led to the development of a short document by the Federal Biological Research Centre for Agriculture and Forestry (BBA), the Federal Environmental Agency (UBA), the Fraunhofer Institute for Environmental Chemistry and Ecotoxicology (FhG IUCT) and the German Agrochemical Industry (IVA) entitled, "Rules for the correct performance and evaluation of model calculations for simulation of the environmental behaviour of pesticides" (Görlitz, 1993). Later referenced as the 'Codex' this document outlined general principles of GMP, rather than prescriptive guidance. It focused on leaching models but was generally applicable to other simulation models and addressed the following topics: selection of models, documentation of models, validation, support, official recognition and version control, selection and treatment of input data, consistency of input data and models, documentation of simulations, reporting and interpretation. The Codex led to regulatory acceptance of simulation models on a national scale in Germany, as well as providing a basis to address the requirements of the European directive 91/414 (European Community Regulation Council Directive 91/414).

After several informal meetings between modellers, regulators and registrants, the *FO*rum for the *C*oordination of pesticide fate models and their *US*e (FOCUS) was created in 1993 through an initiative of the European Commission (European Commission FOCUS). The steering committee of FOCUS met under the auspices of the EU Directorate General for Health and Consumer Affairs (DG SANCO) for the first time in 1993 and approved two research area themes on models for groundwater and surface water. FOCUS has an equal representation of regulators, researchers and industry that operate by consensus and offer technical support to the EU registration process 91/414. It has no administrative infrastructure but DG SANCO provides funds for attendance at meetings for regulatory experts and researchers. The FOCUS committee meets approximately four times per year and has two permanent institutions. The FOCUS website (European Commission FOCUS) provides all the reports of past FOCUS projects, the actual recommended versions of models as well as essential scenario data. Members of the supporting technical Version Control Group are model developers/supporters. This group approves new model versions, and the content of the website, by correspondence.

Currently, FOCUS reports figure prominently in exposure assessments for the registration of plant protection products in the EU. This is best illustrated by the fact that the present draft of the revision of the EU directive 91/414 on the authorization of plant protection products references directly FOCUS reports as guidance on important decision points. FOCUS outputs are also widely adopted as guidance by member states in their exposure and risk assessments.

[3] The measurement of the water percolating through soils and the determination of the materials dissolved in the water.

## 7. Evolving acceptance of QSAR modelling

Evolving advancements internationally in the documentation and implementation of quantitative structure activity relationship (QSAR) models to meet demanding mandates to consider much larger numbers of existing substances may also contribute in the development of GMP for PBPK models. These include principles for verification of QSAR model output (OECD, 2007) and proposed templates for QSAR development, prediction and reporting (http://ecb.jrc.it/qsar/) (European Chemicals Bureau RIP 3.3). Whilst the documentation is still evolving internationally, information on the training domain, internal validation, cross validation and external validation requirements has been proposed to be included in a 'development template' whereas substance-specific information is proposed to be included in a 'prediction template'.

## 8. Future directions—where do we need to go?

The following sections briefly summarize some of the major issues considered and recommendations from the workshop designed to facilitate the development of GMP for PBPK modelling as well as to identify research priorities.

### 8.1. Risk assessors needs and their role in the process

Two possible paradigms were proposed for the involvement of the risk assessor throughout the modelling process: (1) issues raised by the risk assessor are included during model development, and (2) at appropriate times, the model would be evaluated for fitness for regulatory use. To the extent that it is possible, the former process is clearly preferred and necessitates involvement of an interdisciplinary team in model development and characterization (Barton et al., 2007), whereas the latter process is more typical for models that have already been published.

Risk assessors have important roles to play in mode of action and dosimetry-based risk assessments utilizing PBPK models. These include transparently assessing the weight of evidence of hypothesized modes of action as a basis for clearly delineating the goals for using the model in the risk assessment (Clewell et al., 2002a; US EPA, 2006) and participating in a transparent process that brings together appropriate interdisciplinary expertise to evaluate the model and its proposed risk assessment applications (Chiu et al., 2007; Clark et al., 2004). Furthermore, risk assessors play pivotal roles in organizing the information on mode of action and dose–response e.g., critical studies and endpoints that form the context for applying a dosimetry model. Transparent frameworks developed for this purpose (Boobis et al., 2008; IPCS, 2005) may assist the risk assessor in assimilation of this information. Determining whether a PBPK model is parameterised for the chemical(s), including metabolites, species and life stages, exposure routes and matrices in the toxicity studies used in dose–response analysis or the human exposures relevant for the risk assessment, can be accomplished by non-modellers. Identifying the dose metrics relevant to the modes of action under consideration and evaluation of the biology captured by the model often requires communication among risk assessors, toxicologists, and modellers. Evaluation of the mathematical and computer implementation as well as characterization of its consistency with available data and the model's strengths and weaknesses for the proposed risk assessment applications will generally require involving those with appropriate mathematical, statistical and computational expertise. However, to ensure a transparent process, communications describing the review process and its conclusions need to be clear and comprehensible to all parties.

### 8.2. Model development practices

Model standardization can facilitate intra- and inter-disciplinary communication but creates challenges of adapting to a variety of software used to produce a range of model structures necessary to describe different kinetic behaviours and address varying model purposes. There are significant benefits to the use of generic model structures, including the establishment of standard abbreviations or parameter nomenclature and glossary, which would facilitate efficient communication of models and avoid confusion in semantics that can hinder understanding. In addition, the need to justify selected aspects of the model could be eliminated as is currently done by citing existing literature. To be truly generic, however, a model would have to encompass a wide range of physiological compartments and all useful dose metrics.

Standard methodology for model building might be a more viable alternative than a fixed model form (Cobelli et al., 1984). Moreover, the use of a hybrid approach whereby a simple standard model is used as a starting point and refinements during the modelling workflow are conducted utilising a standardized model building methodology may be a viable compromise. In discussing the issues associated with model code that is specific to a particular solver package, it was agreed by the workshop delegates that the use of a standard representation similar to Systems Biology Mark-up Language (SBML) or Cell Mark-up Language (cellML)[4] would improve communication between modellers and risk assessors. Mark-up Language (ML) is a type of representation that gives a structured description of the conceptual model, free of mathematical equations and confusing syntax. The provision of an intuitive graphical interface such as MEGen[5] could make such standard formats more accessible to non-modellers by allowing rapid generation of this 'PBPKML' representation.

[4] http://sbml.org; www.cellml.org
[5] www.opentox.com/megen

### 8.3. Model verification

Models can be analysed to demonstrate that they are mathematically and computationally free of errors and that the behaviour of the model in the region of parameter space that is biologically plausible, reasonably approximates the available data (Barton et al., 2007; Oreskes, 1998). Demonstration that a model is mathematically and computationally correctly implemented can involve checks incorporated in the model, e.g., mass balance checks, rigorous manual checking of the equations and computer code, and independent recoding of the model using another software environment. The ease of implementing these options varies with the particular software used. A PBPK model code generator tool such as MEGen[5] could facilitate these checks by permitting rapid recoding of models.

#### 8.3.1. Roles and methods of sensitivity analysis

Sensitivity analysis is a tool for model characterization that can address a number of issues frequently raised concerning PBPK models.

Sensitivity analyses can be implemented in model development, characterization and evaluation to address several aspects including the following:

1. Characterizing parameters that are well determined by available data.
2. Iterating with experiments and evaluating the sensitivity of parameters to new data that will be collected (Cho et al., 2003; Gueorguieva et al., 2006; Nestorov et al., 1998).
3. For dose–response analysis predictions, evaluating the sensitivity of dose metrics predicted under the conditions relevant to the toxicity studies (or epidemiological studies) to the parameters in the model.
4. For risk assessment, evaluating the predicted dose metrics in humans under relevant environmental exposure conditions to characterize their sensitivity with respect to the model parameters.

The many existing sensitivity analysis methods can be grouped into two categories: (1) local methods that consider sensitivities close to a specific set of input parameter values, and (2) global methods that calculate the contribution of a parameter over the set of all possible input parameters. Currently, gaining insight into a model often involves the adjustment of individual model parameters and observation of the predicted changes in model output, either at a single time or throughout a time course. This useful practice can be supplemented by examining the time-dependent global sensitivities of the chosen dose-metric for dominant parameters. When trying to establish the contribution of a parameter to model predictions, local sensitivity analysis techniques are fairly rapid and simple to implement but can give somewhat misleading results if there are substantial interactions among multiple parameters.

Global sensitivity analysis using the Extended Fourier Amplitude Sensitivity Test (FAST) is a variance-based method that is independent of any assumptions about the model structure and is effective for monotonic, exclusively increasing or decreasing predictions, and non-monotonic models (Campolongo and Saltelli, 1997). The FAST is preferable over other global methods due to its computational efficiency and capability to consider parameter interactions as well as main effects. Since PBPK models are likely to become increasingly complex as more pertinent data become more readily available more robust sensitivity analysis techniques will be required and FAST appears to satisfy these criteria.

### 8.4. Model documentation

Suggestions for documenting models in publications have been presented previously (Andersen et al., 1995). As noted therein, model documentation must address a diverse readership. Recommendations from this workshop were to develop a standard, brief model description summary for the broad risk assessment audience and more detailed documentation for specialists. The summary would contain at least seven elements including:

1. Introduction including problem formulation (applicability of model).
2. A text description of the model (species, routes, etc) with schematic diagram, and an overview of the information and data supporting the model structure.
3. Metabolic pathways for the chemical and an overview of the supporting information and data.
4. Relationship to mode of action including dose metric predictions and supporting information.
5. Distributional predictions of model outputs and their implications (e.g., Monte Carlo simulation of human variability).
6. Overview of uncertainty and sensitivity analyses.
7. Source of complete information (e.g., citation).

Further recommendations for more complete model documentation could include the possibility of utilising hyperlinked documents that facilitate easy access to supporting materials, including calculations done to convert published scientific information into the form used in the model. This extended model documentation would be utilized by subject experts in the model evaluation process and would ideally be publicly accessible via the Internet. The documentation would strive for transparency through the integration of diagrams of model structure and metabolic pathways, tables of model state variables and parameters and mathematical equations and model code.

### 8.5. Model evaluation

Best practices allow efficient evaluation of models through standardization, documentation, and transparency. The six-step process of assessment of model purpose, assessment of model structure and biological characterizations, assessment of mathematical descriptions, assessment of computer implementation, parameter analysis and assessment of model fit and assessment of any specialized analyses described by Clark et al. (2004) and extended by providing more detail by Chiu et al. (2007) provides a useful framework for model evaluation. Further, specification of criteria that would assist reviewers in determining the strengths and limitation of a specific model and a process for implementation of model evaluation, which must be transparent and involve independent review, would be valuable.

Development of a robust model evaluation process must take into account the need for external review since while involvement of risk assessors and modellers throughout the steps leading from model development to application in risk assessment is valuable, it can impact on the perception of the model evaluation as an independent process. An independent review is essential to identify and correct mistakes and to make judgments on the adequacy of the model and its supporting scientific database. Such reviews present a challenge internationally, not least because of the limited PBPK modelling expertise globally. For this reason, it would be valuable to be able to share model evaluations among countries, by agreeing upon a common framework and process even if the final decisions concerning model use might be different, for example due to risk assessment needs.

A major challenge of model evaluation is to provide perspective on the scientific uncertainties identified by a model and its supporting scientific database. Models allow characterization of uncertainty in a way that default analyses cannot: for example, a default value of 10 is commonly applied for interspecies extrapolation, but the uncertainty for any specific chemical with regard to the toxicity it causes in animals ranges from close to zero (the effect only occurs in the animals) to a much larger value (the effect only occurs in humans). While the factor of 10 represents a judgment concerning the general tendency across many chemicals, it cannot describe the uncertainties for a specific chemical whereas this is possible using biologically based-modelling. However, this creates a challenge for considering whether the model adequately captures the science and thus, should be implemented in the risk assessment.

### 8.6. Improving the scientific basis supporting models

Efforts to use PBPK models more broadly have also resulted in a range of scientific issues that require additional research. These include improving methods for using *in vitro* data in order to limit controlled animal and human studies, for model development by extrapolating from widely studied chemicals to those with limited information and for better characterizing uncertainty and variability in PBPK models.

#### 8.6.1. In vitro to in vivo extrapolations

Ideally, *in vitro* data should be used in PBPK models because they can limit the need for *in vivo* studies in animals or humans. However, limitations of models to predict *in vivo* rat data using metabolic parameters estimated from *in vitro* studies have been noted (Csanady and Filser, 2007; Faller et al., 2001; Lee et al., 2005; Osterman-Golkar et al., 2003).

*In vitro* to *in vivo* extrapolation, particularly with regards to metabolism, requires further detailed study (Blaauboer et al., 1999, 1996; DeJongh et al., 1999; Gulden and Seibert, 2003; Houston, 1994; Kedderis, 1997; Lipscomb et al., 1998; Miners et al., 1994; Rostami-Hodjegan and Tucker, 2004; Verwei et al., 2006; Wilson et al., 2003). The importance of protein and non-specific binding and partitioning of substrates are fundamental to improving the utility of *in vitro* systems and the use of such data in PBPK models. While there are initiatives underway to assist in addressing many of these issues[6] and encouraging results have recently been reported (Acutetox Newsletter July, 2007), the limitations of *in vitro* metabolism data must be borne in mind until and unless they can be demonstrated to be reliable surrogates.

#### 8.6.2. Cross chemical extrapolation

Risk assessors are increasingly having to address prioritisation and assessment for the large numbers of chemicals in commerce, notably the REACH legislation in Europe or the Categorization and Screening of the Domestic Substances List under the Canadian Environmental Protection Act (1999)[7]. Methods to develop initial PBPK models for chemicals using cross-chemical prediction methods would be valuable and efforts to date have primarily been directed at predicting tissue:blood or tissue:air partition coefficients (Beliveau et al., 2005), though *in vitro* to *in vivo* extrapolation for metabolism and other aspects of pharmacokinetics are also receiving attention.

#### 8.6.3. Uncertainty and variability in PBPK models

Much of the focus in the development of PBPK models has been to identify and capture the average behaviour of the key biological processes controlling the pharmacokinetics of a chemical. These models have successfully assisted in evaluating biological hypotheses for mode of action e.g., methylene chloride carcinogenesis described previously, as well as identifying previously unrecognised pharmacokinetic behaviours. The increasing application of PBPK models in risk assessment has led to a range of efforts to better characterize the relationship between

[6] (http://www.acutetox.org/)

[7] (http://www.ec.gc.ca/substances)

the model and supporting data and quantify uncertainty and variability.

Improved computing power is essential to more widespread use of distributional analyses to characterize human variability with Monte Carlo sampling techniques and methods of parameter estimation ranging from optimisation of selected chemical specific parameters (e.g., metabolic rates) to global parameter estimation using Bayesian statistical characterization of uncertainty and variability. Priorities for research and implementation of concepts of uncertainty and variability in risk assessments using PBPK models have been previously described (Barton et al., 2007).

### *8.7. Good modelling practices for PBPK models: developing a description, case studies and training materials*

The International Programme on Chemical Safety (IPCS) steering group of the World Health Organization (WHO) identified PBPK modelling as an important component of chemical risk assessment that merits international harmonization[8]. The ability to review a PBPK model according to accepted criteria would greatly facilitate widespread acceptance, in particular amongst regulators. While agreement amongst PBPK model developers is paramount for the development of GMP, the guidelines must also be acceptable to regulators and risk assessors. Development of guidelines for GMP is best achieved through a cross-disciplinary exchange of experience and ideas among laboratory scientists, PBPK modellers, regulators and risk assessors.

The adequacy of the GMP description can be evaluated using case studies that in turn could form the basis for training materials on GMP. Some recommendations were proposed for case studies:

- Comparing a dose metric for which data were directly available versus one where they were not.
- Examples where PBPK models were accepted and used by regulatory Agencies and ones where they were rejected to ensure appropriate documentation.
- Comparisons of data-rich chemicals with data-limited chemicals including not just comparison of pharmacokinetic or metabolic data, but also mode of action data such as toxicogenomic or metabolomic data.
- Illustrations of different risk assessment applications.

Potential chemicals to use as case studies would include those for which PBPK models had been considered or applied in risk assessments in Europe, Canada, and the United States. Other chemicals could include isopropanol (with acetone metabolite sub model) for non-cancer endpoints, styrene as an example of an inaccessible dose metric, acrylamide as an example of great current regulatory interest with multiple proposed modes of action and target sites and 1,3-butadiene due to the substantial animal modelling and uncertainty in human metabolism resulting in assessment based upon epidemiology.

Finally, development of training materials and hiring of personnel with the required expertise will be essential to facilitate implementation of mode of action and dosimetry-based risk assessment by regulatory Agencies. Training materials are needed so that risk assessors and managers with diverse expertise can successfully interact with modellers to implement PBPK models in risk assessment. Training will also be important for modellers to learn about newer methodologies for characterizing uncertainty and variability in PBPK models or implementing local and global sensitivity analyses at appropriate stages of model maturation. A longer-term strategy would be to include a more quantitative, computationally based study of toxicology in university courses. The adaptation of a PBPK model generator tool such as MEGen as a teaching tool would be very useful in demonstrating to students how biological knowledge can be applied to solve real-world problems.

## 9. Conclusions and recommendations

The use of PBPK modelling in risk assessment is increasing in various jurisdictions but would benefit from development of principles and guidance for GMP to assist modellers during design and verification and risk assessors in evaluation for application. Experience in development of similar guidance in other areas such as environmental fate modelling and more recently evolving principles and documentation prototypes for QSAR response modelling can inform this process. Recommendations for aspects to be addressed in GMP for model development, characterization, documentation and evaluation were based on an international workshop and include:

1. Transparency of model documentation and the weight of evidence for the underlying hypothesized mode of action is needed to aid transition of models from developers to evaluators and users.
2. Independent review of models is essential to evaluate documentation and implementation quality for applications in risk assessment.
3. Consistent model evaluation approaches would facilitate international sharing of the analyses that would then form the basis for decisions appropriate to different regulatory applications. An international committee would be valuable to further this goal.
4. Successful development, evaluation and application of a PBPK model requires multidisciplinary skills throughout the process. Regulatory agencies need to develop access to those who can provide those skills through training, hiring or other approaches.

[8] http://www.who.int/ipcs/methods/harmonization/areas/pbpk/en/index.html

5. Training in toxicology at the university and professional levels needs to recognize that quantitative risk assessment applications are major drivers for interest in toxicological data by providing more quantitative, computationally-based studies.

These recommendations will be considered further in the development of relevant guidance in an ongoing initiative of the IPCS harmonization project.

## Disclaimer

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