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

COT STATEMENT ON PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING

Introduction

1. In February 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 workshop comprised several presentations; these considered the use of PBPK models in risk assessment, requirements for PBPK models and parameters for incorporation of PBPK methods into risk assessment. The presentations were followed by a general discussion which focussed on the strengths and weaknesses of PBPK modelling, whether PBPK models could be integrated into COT risk assessments and how this could be achieved.

Background.

2. Pharmacokinetics describes the relationship between exposure and the concentration-time profile of a chemical within the body. This relationship is usually expressed as an equation based on a representation of the body as one or more compartments. These approaches are limited, since the equation or model used is essentially empirical, and may bear little relation to the physiological processes involved. A more meaningful approach based on physiological principles rather than observed data would provide greater understanding of what actually occurs following exposure to a chemical. This is the concept of PBPK modelling as first described by Thorsten Teorell in 1937. However, at that time the lack of computing power to solve the resulting mathematical equations meant that the approach was impracticable.

3. Because PBPK modelling accounts for the underlying physiological processes and the physico-chemical properties of the chemical administered it facilitates prediction of events in humans from animal data and explains differences across chemicals. PBPK modelling permits prediction of chemical concentrations at specific target sites and can incorporate different exposure scenarios, disease states or changes with age and co-administration of other chemicals.

4. PBPK models are based on three main elements; physiological parameters, chemical specific parameters and design of the model. The physiological parameters are independent of the chemical and define each tissue or organ by its structure, size, blood flow, and functionality. Overlaid

onto physiological parameters in the model are the chemical specific parameters: binding within blood (e.g. to proteins, red cells), tissue affinity (binding, partitioning), membrane permeability, and sensitivity to enzymic modification. The complexity of the model can be varied according to the information required. In a simplified model, tissues with similar physiological properties are considered as a single tissue. Variation of the biological parameters of a model (e.g. body weight) allows some PBPK models to simulate population response to exposure to a chemical by producing a distribution of outputs.

5. PBPK models, although complex and initially demanding of data and resources;

- are highly informative
- allow ready integration and scaling of *in vitro* and structural information
- allow ready exploration of a wide variety of conditions and
- improve successful modelling and prediction of pharmacokinetic events.

6. The use of PBPK modelling has become increasingly common in the development and selection of pharmaceutical candidates. The majority of work on development and validation of PBPK models has occurred in this context, although there have been some detailed studies of specific environmental chemicals.

7. Interest in PBPK modelling as a tool in risk assessment is increasing in North America and the EU. Regulators will need to be in a position to respond intelligently to use of PBPK by industry. The information generated will be useful in risk assessment and might provide insights when developing positions on generic risk assessment issues.

Validation of PBPK Models

8. A PBPK model requires validation to establish that the model accurately predicts what happens following exposure to a chemical. Validation contrasts the predictions generated by a model to data observed experimentally. However, little consensus exists on the nature and extent of experimental data required for validation of a model.

9. Where there are considerable data on the concentration of a chemical in human and animal systems, validation is relatively straightforward. When a model appears to predict the empirical fate of a chemical in the body with accuracy over a range of inputs there can be a high level of confidence in the model. This is relatively easy for a pharmaceutical compound where there are generally human data available to compare with the model output. There might occasionally be sufficient data available to validate a model in occupational settings.

10. In the case of contaminants and other non-pharmaceutical chemicals of toxicological concern human data is often scarce. The validation process may be limited to contrasting model predictions with observed data in animals. However, in contrast to the situation in humans, in animal studies it is also possible to undertake mechanistic validation, e.g. by manipulating the activity of a specific process. Nevertheless, generally there will be greater uncertainty about the accuracy of models generated for non-pharmaceutical chemicals and their ability to predict the behaviour of the chemical in humans.

Utility of PBPK modelling in the risk assessment/management process.

11. Validated models can be very useful for informing the risk assessment and risk management of chemicals. An example is the use of PBPK to determine tissue levels following different exposure scenarios based on occupational exposure limits for carbon monoxide in order to examine options for setting new limits. However, generation and validation of a PBPK model is resource and time intensive, and it would be neither possible nor practicable to generate PBPK models for all chemicals. The emphasis should be that where models are available they have the potential to decrease the reliance on default assumptions about interspecies extrapolation and animal experiments.

The applicability of PBPK to risk assessments as carried out by the Committee

12. The majority of the risk assessments undertaken by the Committee are reactive. The effort and time required to produce and validate a model mean that it would not be feasible to generate a model in the usual time-scale for preparing papers for the Committee. However, where PBPK models already exist for a chemical these should be included in the information considered by the Committee in undertaking the risk assessment. The Committee noted that for many chemicals there were limited toxicological databases and little or no pharmacokinetic data. In addition, for most contaminants it was unlikely to be ethically possible to generate human pharmacokinetic data to fully validate the model. The adequacy and predictability of the model would then be a greater source of uncertainty.

13. There may, however, be the possibility to generate models that inform the risk assessment process for a chemical in more proactive risk assessments. This would require identifying and defining specific questions that the model would need to answer but could be valuable in an integrated risk assessment examining the relative contributions of different routes when exposure occurs via several routes. Considerable resource investment would be necessary in order to generate the model and, if necessary, data for validation.

14. The development of a small range of generic models with consensus biological parameters might be of value in comparing chemicals with different but limited data.

Conclusions

15. We *conclude* that PBPK modelling is an established technique, capable of predicting the behaviour of chemicals in the body, which is widely used in the development and assessment of pharmaceuticals. We *consider* that PBPK models can be used as part of the risk assessment process. We *note* that PBPK modelling may also be helpful in evaluating risk management options. PBPK models can also be valuable in identifying those parameters exerting most influence on the behaviour of the compound (sensitivity analysis) and as a means of exploring inter-individual variability.

16. We *conclude* that the generation and development of PBPK models is an iterative process and that each model requires validation. We *note* that the concept of validation is often based on empirical verification but currently there appears to be little consensus amongst practitioners on criteria for the adequacy of validation.

17. We *recognise* that full validation usually requires verification of the model predictions with human data. We *recognise* that for many chemicals it may not be possible to generate human data. We *note* that animal data can go a long way towards validation if it can be assumed, or there is evidence, that the chemical behaves similarly in animals and humans. We *conclude* that there would be limited confidence in the predictions of such models; this would need to be expressed as a source of greater uncertainty in the risk assessment.

18. Whilst validation requires data on the pharmacokinetics of a chemical in human and/or animal systems, we *note* that for many chemicals evaluated by this Committee there are very limited data on pharmacokinetics. We *conclude* that for many of these chemicals full validation of a specific PBPK model would not yet be possible. Validation could be enhanced by mechanistic studies in experimental animals

19. We *note* that the generation and validation of a PBPK model is resource and time intensive. We *conclude* that it would not be feasible to undertake PBPK modelling routinely for our risk assessments but that we should incorporate existing published PBPK models into our assessment when available.

Selected References

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