Government/Research Councils Initiative on Risk Assessment and Toxicology

Physiologically-based pharmacokinetic modelling:

A potential tool for use in risk assessment

Report of a workshop organised by the Risk Assessment and Toxicology Steering Committee

Based on contributions from L Aarons, HJ Clewell, RB Conolly, JI Delic, JB Houston, AM Jarabek, G Loizou, HJ Mason,I Nestorov, M Rowland, C-L Tran, GT Tucker

The Risk Assessment and Toxicology Steering Committee aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Committee takes forward the work of the Government/Research Councils Initiative on Risk Assessment and Toxicology. The Initiative was established in response to a statement in the 1995 UK Government *'Forward Look of Government Funded Science, Engineering and Technology'*, which recognised the inherent limitations of current procedures and committed the Government to pursuing opportunities presented by scientific advances.

The Steering Committee comprises participants from the Department of the Environment, Transport and the Regions, the Department of Health, the Department of Trade and Industry, the Home Office, the Ministry of Agriculture, Fisheries and Food, the Environment Agency, the Health and Safety Executive, the Medicines Control Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the Natural Environment Research Council and the Institute for Environment and Health.

The secretariat is based at the Medical Research Council's Institute for Environment and Health.

The Risk Assessment and Toxicology Steering Committee operates as a subgroup of the Interdepartmental Liaison Group on Risk Assessment.

The Interdepartmental Liaison Group on Risk Assessment is an informal committee of officials responsible for policy development and practical application of risk assessment in UK Government departments. The group reports periodically to Ministers on a co-ordinated programme to promote consistency and coherence in risk assessment practices across Government.

This document is a report of a workshop held in Leicester on 24–25 April 1997. Opinions and recommendations expressed are those of the participants. The Government/Research Councils Initiative on Risk Assessment and Toxicology's Steering Committee will consider the recommendations further before making its own proposals for future work.
The report is based on original drafts by L Aarons, HJ Clewell, RB Conolly, JI Delic, JB Houston, AM Jarabek, G Loizou, HJ Mason, I Nestorov, M Rowland, C-L Tran, GT Tucker

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Contents

Executive summary

A workshop was convened by the Risk Assessment and Toxicology Steering Committee to evaluate the use of physiologically-based pharmacokinetic (PBPK) modelling in chemical risk assessment in relation to human health, particularly within the regulatory context. The participants included scientists experienced in the practice and application of PBPK modelling and representatives from UK Government departments and agencies. The aim of the workshop was to assess the potential of this type of modelling for improving risk assessment in the UK and to make recommendations on areas for future research activity.

PBPK modelling has already undergone significant development, particularly in the USA where it has made a valuable contribution to the risk assessment process, but its application to regulatory activity has been relatively limited.

The workshop participants concluded that the application of PBPK modelling could improve the risk assessment process, bringing potential benefits for government and industry. However, if the UK Government is to make use of this technique, even on an occasional basis, there is a need to develop groups within the UK with experience of using it. These groups could provide a future resource on which to call; they could also apply PBPK modelling to the investigation of wider issues in risk assessment.

Recommendations

As a result of the above conclusions a number of recommendations were made, as follows.

- Research and development on PBPK modelling should be undertaken in the UK, to increase knowledge and expertise and as an investment for improving the predictive value of chemical risk assessment.

Several areas of potential future research activity were identified in which research groups could develop their experience and knowledge of PBPK modelling, as well as providing specific outputs; these are summarised below. There are clearly links between these different areas and they should not been seen as necessarily independent. A number of specific recommendations were also made concerning research related to the regulatory application of PBPK modelling.

- Research to develop expanded databases for basic morphological and physiological parameters, particularly for human populations, to be used for PBPK modelling, is to be encouraged; this could be carried out as part of other PBPK modelling research activities.

- New ‘template’ models for defined structurally and/or functionally related chemicals, not already the subject of existing models, should be developed.

- Specific research projects designed to bring together the experience and skills of researchers working on PBPK modelling of industrial chemicals and pesticides and related areas of pharmaceutical research should be undertaken, in order to explore issues of relevance to chemical risk assessment, such as human variability.

- The application of PBPK modelling to biological monitoring in occupational (and other) settings, particularly within the context of establishing guidance values and standards, should be continued.

- Research is needed into the application of PBPK modelling to dosimetry assessment for naturally occurring substances (e.g. in foods).

- The application of PBPK modelling to risk assessment in non-human species should be investigated, to facilitate extrapolation between these species; this has direct application to human safety in relation to drug residues in animal tissues and would benefit wider environmental considerations outside the remit of the Risk Assessment and Toxicology Steering Committee.

- A cross-government interdepartmental group should be established to coordinate the application of PBPK methods and any government-sponsored research.

1 General introduction

UK Government/Research Councils Initiative on Risk Assessment and Toxicology

A number of UK Government departments have a responsibility for assessing risk to human health from potentially toxic substances that may be found in food, household products, human medicines, the environment or the workplace. Since reliable data from human populations exposed to known levels of a substance are rarely available, except in the case of human medicines, the assessment is often based on animal data. Such an approach has to accommodate the uncertainties inherent in extrapolating from animals to humans, from high to low dose and from one population to another. The uncertainties in the risk assessment process necessitate the adoption of appropriate uncertainty factors to ensure protection. It is clearly desirable to reduce the uncertainties as far as possible and to secure optimal use of resources.

The uncertainties inherent in current methodologies are widely recognised, as is the absence of scientific knowledge to define them more precisely. Recent advances in scientific techniques, such as use of novel biomarkers, *in vitro* toxicology, molecular modelling and computer simulations, may offer new possibilities. Furthermore, the use of such techniques should contribute to the reduction of animal use and the refinement and replacement of animal tests, a principle to which Government departments and agencies are committed. Government departments, together with the relevant research councils, have decided to make a co-ordinated drive to pursue these important opportunities. Their commitment was set out in the 1995 UK Government report '*Forward Look of Government Funded Science, Engineering and Technology*' (HMSO, 1995) and resulted in the establishment of the Government/Research Councils Initiative on Risk Assessment and Toxicology in 1996.

The work of the Initiative is being taken forward by the Risk Assessment and Toxicology Steering Committee, which comprises participants from relevant Government departments and research councils and is co-ordinated from the Medical Research Council's Institute for Environment and Health. The Initiative aims to stimulate research so that new, improved approaches to chemicals risk assessment can be developed. It does not have its own research funds, but provides a focus, co-ordination and positive encouragement for research financed by individual Government departments or research councils (or consortia of these bodies).

The Steering Committee has organised a series of workshops on different aspects of risk assessment, with the aim of bringing together regulatory toxicologists, policy-makers from government and experts from academic institutions and industry to develop research specifications.

The problems of extrapolation from high to low dose have already been articulated many times. Consequently the Steering Committee decided that it would be useful to hold a workshop on a technique that has the potential to provide a solution. Accordingly a workshop was convened to consider the use of physiologically-based pharmacokinetic (PBPK) modelling in chemical risk assessment. The workshop, which forms the basis of this report, was held in June 1997 in Woodford, Cheshire, UK. The workshop participants included scientists experienced in the practice and application of PBPK modelling and representatives from UK Government departments and agencies.

Aims of the workshop

In the UK little emphasis has so far been placed on PBPK modelling and virtually no use has been made of it in formal regulatory risk assessment processes. The main aim of the workshop was, therefore, to explore the possibilities for using this technique within the UK regulatory framework.

Two aspects were considered at the workshop: first, the general information needed by those responsible for the development of policy on risk assessment within Government departments and/or actively involved in the use of or interested in the application of PBPK modelling to risk assessment (this part of the workshop was sponsored by the Government/Research Councils Initiative on Risk Assessment and Toxicology); and second, technical issues, including practical use of the outputs of PBPK modelling for risk assessment (sponsored by the Health and Safety Laboratory, Sheffield).

Presentations by acknowledged experts from the USA and the UK in the development, practice and application of PBPK modelling, particularly within the regulatory context, provided the workshop with an overview of how PBPK modelling works, how it can be applied in human health chemical risk assessment and how it has been used by risk assessors in the regulatory context, particularly in the USA. Against this background, the workshop considered the following questions.

- What are the current strengths and limitations of PBPK modelling?
- What lessons can be learned from the US experience of the use of PBPK modelling in risk assessment?
- How widely can PBPK modelling be applied (e.g. what about substances with very limited databases)?
- Apart from contributing directly to the risk assessment process, how can PBPK modelling be used as an investigative tool, either alone or in combination with experimental studies, to address wider issues within risk assessment such as human population variability, variations in exposure profiles and complex combinations of mixtures?
- Should UK regulatory bodies and Government departments consider, when feasible, the adoption of PBPK modelling as part of their risk assessment approach?
- If so, what does the UK need to do in order to enable the risk assessor to employ these techniques in particular, on a routine basis?
- What research areas can be identified to develop PBPK modelling within the context of chemical risk assessment?

Workshop report

Sections 2,3, and 4 of this report are based on background papers presented by invited experts at the workshop. Section 2 describes the historical development of PBPK modelling, and outlines the main features of the technique. Section 3 describes models developed for assessing the risk to humans of certain specific chemicals. Various additional aspects of PBPK modelling in risk assessment are dealt with in Section 4 and the conclusions and recommendations arising from the workshop are set out in Section 5. The report concludes with a list of articles cited herein, together with several other selected references relevant to PBPK modelling. The participants in the workshop are listed at the end of the report.

The recommendations, which concern potential areas in which PBPK modelling could be developed as a contribution to risk assessment and the use of such modelling within the UK regulatory framework, will be considered by the Risk Assessment and Toxicology Steering Committee.

2 An overview of PBPK modelling

2.1 Introduction

The process of assessing the risk associated with human exposure to environmental chemicals inevitably relies on a number of assumptions, estimates and rationalisations. Some of the greatest challenges result from the need to extrapolate outside the range of conditions found in experimental studies. For risk assessments based on animal data, the most obvious extrapolation that has to be performed is from the tested animal species to humans (i.e. the conversion of the animal dose–response relationship to a predicted human dose–response relationship). Furthermore, there is a need to extrapolate beyond the bounds of the animal data, outside of the known dose–response region, to areas of likely human exposure both in terms of level of exposure as well as other factors such as route (e.g. oral versus inhalation) and duration of exposure.

A key consideration for such extrapolation is how and at what rate a substance is absorbed, distributed, metabolised and eliminated (i.e. the pharmaco- or toxicokinetics of the substance) in different species. Various approaches have been developed and employed depending upon the situation in question and the amount of data available. For example, a very simple approach when few data are available may be to assume that the exposure–dose–response* relationship in animals for a particular effect is directly equivalent to that in humans; in the case of most end-points, an arbitrary factor may then be applied to allow for uncertainty in that assumption. This uncertainty may be applied as part of the risk assessment process (e.g. in the derivation of an acceptable daily intake) or as part of a risk management process (e.g. in the setting of occupational exposure limits). Alternatively, 'allometric' relationships may be used which assume that the rates of absorption, distribution, metabolism and elimination of a substance are a function of body size; as the body size varies between species, adjustments to allow for this can be made. Such relatively simple approaches result in default positions which are rather crude in nature and generally employ fairly conservative factors to allow for the uncertainties in the process. It should be noted that in the case of some end-points, such as cancer thought to arise as a direct result of genetic damage induced by a substance (or a metabolite), such approaches would not normally be used in the UK to predict quantitative levels of risk.

A more relevant but also more complex approach is to model the dose or degree of exposure at the level of the target tissue, cell and/or even within the cell both within the experimental species and the human population of interest. This is the philosophy underlying PBPK modelling. PBPK models are therefore intended to evaluate the relationship between external exposure, target tissue dose and biological outcome. A concise overview of the principles of PBPK modelling and highlights of some of the uses to which it has been put in the field of toxicology are given in an article by Andersen (1995).

2.2 Historical background

PBPK modelling has been used for more than 70 years to investigate the disposition (absorption, distribution, metabolism and elimination) of drugs and other foreign substances (xenobiotics). It began in 1924 with studies of volatile anaesthetics, using a fairly simple model that specified the role of

* Because the tissue dose of the putative toxic moiety is not always proportional to the applied dose (or exposure) of a compound, emphasis has been placed on the need to distinguish clearly between exposure concentration and dose to critical target tissues. The description 'exposure–dose–response' is therefore recommended as more accurate and comprehensive than 'dose–response'. The expression 'exposure–dose–response assessment' thus refers not only to the determination of the quantitative relationship between exposure concentrations and target tissue dose, but also to the relationship between tissue dose and the observed response in laboratory animals and humans.

ventilation, blood flow and blood:air solubilities in chemical uptake into the body (Haggard, 1924). This work continued in subsequent decades (Kety, 1951; Mapleson, 1962; Riggs, 1963) and, in the 1970s, was extended to metabolised gases of occupational interest (Fiserora-Bergerova, 1975). PBPK models for pharmaceuticals date from the 1930s (Teorall, 1937). Early work was hampered by computational limitations but by the 1970s it became possible to apply these models for forecasting the disposition of various chemotherapeutic agents (Himmerstein & Lutz, 1979; Gerlowski & Jain, 1983). In toxicology, PBPK models were used to study the pharmacokinetics initially of lipophilic chemicals (Lutz *et al.*, 1977; Bungay *et al.*, 1981; King *et al.*, 1983) and then volatile organic compounds which had been demonstrated to cause cancer in animals and were therefore of interest in chemical risk assessment. The first quantitative model was developed for dichloromethane (DCM) in 1987 (Andersen *et al.*, 1987) and models for a variety of other compounds have since been proposed (Leung, 1991; Krewski *et al.*, 1994; see also Section 3).

2.3 Developing a PBPK model

The structure of a PBPK model is based to as large an extent as practicable on the actual physiological and biochemical structure of the animal being described. Absorption, distribution, metabolism and excretion of the chemical are simulated with equations describing actual physiological processes, such as transport in the blood, partitioning into tissues and enzymatic conversion. Thus saturable metabolism and other non-linear biological processes can be incorporated into the model and the dose-dependent behaviour of the chemical in the biological system can be predicted over a wide range of conditions. Of particular importance for risk assessment, the physiological and biochemical parameters in the model can be changed from those for the test species to those which are appropriate for humans in order to perform the animal-to-human extrapolation. The ultimate aim of using PBPK modelling in risk assessment is to provide a measurement of dose which better represents the 'biologically effective dose' — the dose which causally relates to the toxic outcome. The improved figure can then be used in place of traditional dose measurements (such as total amount absorbed) to provide a more accurate extrapolation to human exposure conditions.

The steps involved in developing a PBPK model for risk assessment are:

- specification of the model based on the anatomical/physiological structure of the species of interest and the determinants of disposition and biotransformation of the substance concerned;
- development of a mathematical description of the biological processes involved, including physiological, physicochemical and biochemical constants;
- design of new experiments to test the robustness of the model description;
- collection of the necessary experimental data to confirm or refute the model structure; and
- adjustments to refine the model.

Correct specification of the model is a critical factor in the likely success of the PBPK approach. At a minimum there is a requirement for accurate anatomical and physiological information in the test animals and humans, including data on blood flows, pulmonary ventilation, organ volumes and growth characteristics. Also, in most PBPK models each tissue in the body is depicted as a simple well-stirred box, when in reality organs and tissues are far more complex and it may be important to recognise and incorporate specific features when considering, for example, hepatic elimination or renal excretion.

A sound mechanistic and quantitative understanding of the various factors controlling the rate and extent of absorption, distribution, metabolism and excretion of compounds, such as membrane permeability, plasma and tissue binding, and transport and enzymatic processes is also required. With small lipophilic molecules most membranes of the body offer little resistance to permeation and tissue distribution is limited by blood flow; when elimination is also so limited, extrapolation from animals to humans is fairly reliable. However, the situation becomes more complex and extrapolation more difficult with larger and more polar compounds.

Experimental parameters associated with routes and duration of exposure and timing of sampling for tissues and excreta must also be incorporated.

Another important aspect of model specification is the degree of complexity of the whole body structure. The model needs to be sufficiently complex to facilitate accurate extrapolation, but not overly complex. Currently, the choice of the

complexity of the model is somewhat arbitrary and a more formal approach is needed.

In extrapolation to humans, it is generally assumed that drug-specific parameters, such as tissue binding, are the same in all species, so that size alone is the only relevant factor. While this may hold for tissue binding, although not necessarily, it is certainly unlikely to be true for active processes, such as metabolism, and allometric scaling of metabolism as a function of body surface may be used. Furthermore, the increasing abundance of *in vitro* human systems, for example, hepatic preparations, expression systems and epithelial cell lines, offers the real possibility of confidently predicting the major aspects of *in vivo* pharmacokinetic behaviour in both animals and humans from *in vitro* data. This is only likely to occur, however, through careful studies of the important determinants, with a critical eye to the underlying mathematical structures coupled with attention to validation and standardisation.

2.4 Data on hepatic biotransformation

A PBPK model constructed using the physicochemical/partitioning properties of the chemical together with known physiological constants can predict distribution into tissues where no metabolism occurs. However, in the case of the liver, particular problems exist since this organ is not only a distribution site for chemicals but invariably the major site of metabolism. The impact of hepatic biotransformation in modelling is substantial, and it is crucial to the success of the model that *in vitro* data on biotransformation are incorporated in a judicious manner.

There has been recent notable success in relating the rate of *in vitro* metabolism with the corresponding events *in vivo* for certain chemicals. In many cases, prediction of *in vivo* metabolic clearance can be achieved using *in vitro* techniques (e.g. Houston, 1994; Houston & Carlile, 1997). Michaelis–Menten parameters can be estimated in hepatic microsomes of freshly isolated hepatocytes and scaled from the *in vitro* situation to provide the corresponding *in vivo* estimates. PBPK modelling then provides the hepatic clearance estimates. However there is need for caution as the current database on *in vitro* to *in vivo* scale-up contains examples of both successes and failures, with no clear indications, to date, of the theoretical requirements for the successful cases. There is clear evidence that it is preferable to use intact cellular systems rather than the subcellular microsomal preparation, presumably as the former minimises the disruption of the environment in which the enzymes(s) normally operate.

The basis of the scaling procedure is the use of the parameter 'intrinsic clearance', which is a pure measure of enzyme activity towards a drug *in vivo* and is not influenced by other physiological determinants of clearance, such as hepatic blood flow or blood binding. Experimentally, intrinsic clearance can often be determined from the ratio of the Michaelis–Menten parameters V_{max} (maximal velocity of the reaction) and K_m (Michaelis constant).

While these developments are extremely encouraging, since hitherto the value of *in vitro* metabolising systems was considered to be purely qualitative in nature, the level of success in prediction varies from chemical to chemical. It is important to address the reasons for failure and it is noteworthy that the current approach simplifies several key issues.

2.5 *In vivo* data

Probe substrates for various isoforms of cytochrome P450 and other drug-metabolising enzymes are now widely used to assess genetic, environmental and ethnic differences in the *in vivo* metabolism of drugs and other xenobiotics. The key issues in determining variations in drug-metabolising activity *in vivo* include separation of genetically determined differences (with the aid of genotyping) from differences due to exposure, choice of the best experimental index to use, the selection and number of subjects for study, and the use of objective criteria for assessing multimodality in frequency distributions of *in vivo* data. In order to avoid misinterpretation and overinterpretation of data, it is essential to have a good understanding of the pharmacokinetic basis of indirect measures of *in vivo* drug-metabolising activity, and of appropriate statistical procedures for the analysis of frequency distributions. For example, at least six urinary 'metabolic ratios' of caffeine have been proposed as empirical probes for *in vivo* CYP1A2 activity, and their use has led to claims for the frequency distribution of the activity of this enzyme ranging from 'log normal' to 'trimodal'. Computer simulations based on pharmacokinetic–pharmacogenetic models help to visualise the impact of complicating factors (e.g. renal excretion, urine flow rate, parallel and sequential routes of metabolism, time of sampling) on the interpretation of data. Non-specific graphical methods, such as probit plots, continue to be used to define polymorphic drug metabolism.

The latter should be established by hypothesis-testing approaches, with appropriate recognition of assumptions. (See also, Jackson & Tucker, 1986; Jackson *et al.*, 1989a,b; Jackson & Tucker 1990; Rostami-Hodjean *et al.*, 1996; Tucker *et al.*, 1998)

2.6 Summary

PBPK modelling could prove an important tool for improving the accuracy of human health risk assessments for hazardous substances in the environment. Proper use of this technique can reduce uncertainties that currently exist in risk assessment procedures by providing more scientifically credible extrapolations across species and routes of exposure, and from high experimental doses to potential environmental exposures. Current applications of PBPK models range from relatively straightforward uses for the extrapolation of chemical kinetics across species, route and duration of exposure to much more demanding chemical risk assessment applications requiring a description of complex pharmacodynamic phenomena, such as mitogenicity and hyperplasia secondary to cytotoxicity. PBPK modelling helps to identify the factors that are most important in determining the health risks associated with exposure to a chemical, and provides a means for estimating the impact of those factors on the average risk to a population and on the specific risk to an individual. The chief challenge in the application of PBPK modelling in human health risk assessment lies in the need to generate chemical-specific data to support the development and validation of the models. Extensive use of rapidly developing *in vitro* and structure–activity relationship techniques is needed to provide the data required for the large number of hazardous chemicals currently contaminating the environment. Many advances in PBPK modelling have been made over the last two decades. There is every reason to expect greater successes in the future.

3 Applications of PBPK modelling in risk assessment for specific chemicals

3.1 Chloroform

A weight-of-evidence evaluation of the available data indicates that chloroform is not directly genotoxic in mammalian systems and that its hepatic and renal carcinogenicity in rodents is always secondary to cytolethality and regenerative proliferation. Thus the prediction of the exposure–response curve for cytolethality in humans and use of an appropriate uncertainty factor should be sufficient to identify exposure levels without carcinogenic risk.

A PBPK model for chloroform has been developed and extended to include a link between liver dose of chloroform, cytolethality and regenerative cellular proliferation. Versions of the model have been developed for male and female mice and rats, and for humans. Although still in a preliminary form, the model is capable of predicting the relationship between exposure and hepatic and renal cytolethality for any chloroform exposure scenario of interest. Applications have included simulations of chloroform-induced regenerative cellular proliferation in rodents and investigation of a case of human chloroform poisoning, and it is hoped to use the model to predict the risk of cancer in humans from exposure to this chemical. (See also, e.g., Reitz *et al.*, 1990)

3.2 Dichloromethane

The first use of a PBPK model by a government agency in determining the risk from a chemical carcinogen was the reassessment of the inhalation cancer risk from dichloromethane (DCM) by the US Environmental Protection Agency (EPA) in 1987. Inhalation studies in mice showed that DCM, an important solvent used in many industries, increased the incidence of liver and lung cancer. There is strong evidence that the production of a reactive, carcinogenic metabolite by a glutathione-dependent process is responsible for the tumours observed.

In the traditional DCM risk assessment previously proposed by EPA, the relationship between administered dose and tumour response had been assumed to be linear. In contrast, the PBPK tissue dose extrapolation is distinctly non-linear. This occurs because a protective oxidative pathway is favoured at low environmental concentrations, but is readily saturated at the concentrations used in the animal bioassay exposures. In addition, owing to their relatively lower rate of glutathione-dependent metabolism, the tissue dose of the carcinogenic metabolite in humans is significantly lower than that in mice for the same DCM exposure concentration. EPA had previously assumed that humans are more sensitive to carcinogens than mice, not less sensitive as predicted by the PBPK analysis in this case. As a result of the incorporation of DCM pharmacokinetics in the risk assessment, EPA reduced its estimate of the human inhalation risk from this solvent by a factor of approximately ten. (See also, e.g., Andersen *et al.*, 1987; Clewell, 1995a,b).

3.3 Formaldehyde

In a new model for formaldehyde, which has pharmacokinetic and pharmacodynamic components, computational fluid dynamics software is used to simulate airflow and regional deposition of inhaled formaldehyde in anatomically realistic, digital representations of the nasal air passages of rats and humans. For rats, data are available on formaldehyde-stimulated regenerative cellular proliferation and on DNA–protein cross-links. Both these end-points were measured at sites in the rat nasal respiratory epithelium where tumours arose. Predictions obtained with this software of the relationship between concentration of formaldehyde in inhaled air and the

corresponding regional flux of formaldehyde allow the flux-cell proliferation and flux-DNA–protein crosslink relationships to be defined. The computational fluid dynamics model for the human nose is then used to define the relationship between formaldehyde concentration in inhaled air and regional flux. The flux-cell proliferation and flux-DNA–protein crosslink relationships as defined for the rat are used in the human model, since no adequate species-specific data sets are available. Using this approach, the relationships between inhaled concentration of formaldehyde, formation of DNA–protein crosslinks, and stimulation of regenerative cellular proliferation for humans can be predicted using an extrapolation method that accounts for anatomical differences in the nasal airways of rodents and humans. Use of these relationships in formaldehyde cancer risk assessment with a benchmark dose approach or a two-stage clonal growth model is currently being investigated. (See also, e.g., Conolly *et al.*, 1992).

3.4 Lead

A recent European Community (EC) directive applying to women workers who are pregnant or breast-feeding, and a Health and Safety Executive (HSE) review of regulations and exposure limits for lead has stimulated renewed interest in occupational lead exposure in women. Concerns have centred on the possible effects to the fetus and breast-fed infant from concurrent maternal exposure and from lead mobilised from body stores as a result of the physiological changes that occur during pregnancy and lactation. The build-up of lead in maternal bone due to previous occupational exposure has been suggested as a potential risk to the fetus or breast-fed infant. The need for extra calcium in pregnancy and lactation may involve increased resorption of calcium from bone, also releasing lead which had been co-deposited with calcium in the mineral structures. For the infant, the expression of lead in maternal breast-milk constitutes a potential variable source of lead uptake in comparison with other dietary sources, such as formula-feed, or exposure routes such as air and dust. The level of lead in breast-milk may reflect both current and historical maternal lead exposure. In monitoring subjects exposed to lead, the widely measured whole-blood lead concentration remains a central parameter for making decisions concerning health risk for both mother and infant.

A number of biokinetic models for lead have been published. They range from empirical solutions to specific data sets and those with much greater physiological realism. Unfortunately calcium metabolism and bone physiology are not similar in humans and small animals, therefore the type of data that can be used for development and validation of any model is limited. A published biokinetic lead model (Leggett, 1993) has been used to describe the build up of lead in bone and to validate two key aspects of the model against recent findings in human *in vivo* studies. Estimates of the changes in bone resorption and formation rates in pregnancy and lactation, derived from specific biomarkers of these processes, have also been used to modify the original model to take into account these physiological changes. The relationship between lead levels in maternal blood and breast milk over a wide range of maternal exposure remains unclear, although analytical techniques are now adequate to investigate it. A precautionary ratio of breast milk lead to blood lead can be used to estimate the additional lead burden for a breast-fed infant depending on differing maternal exposure scenarios. These investigations may help in the development of risk management strategies for occupationally exposed women in order to ensure protection of the developing fetus and infant.

3.5 Trichloroethylene

For trichloroethylene, there is evidence of increased cell proliferation due to receptor interaction or cytotoxicity in every instance in which tumours are observed in experimental animals, and the tumours typically represent an increase in the incidence of a commonly observed, species-specific lesion. Virtually safe exposure estimates for human exposure to trichloroethylene, predicted with a PBPK model and a margin-of-exposure approach, were higher than those obtained by the conventional low-dose linear approach by a factor of 100 or more. The margin-of-exposure approach is recommended as an alternative to the low-dose linear approach for chemicals with a carcinogenic mode of action which entails increased cell proliferation, leading to the expectation of a highly non-linear cancer dose–response. (See also, e.g., Clewell *et al.*, 1995).

3.6 Vinyl chloride

Recently, at the request of EPA, PBPK modelling was used to produce an integrated oral and inhalation, chronic, non-cancer risk assessment for vinyl chloride. Vinyl chloride is a well-characterised liver toxicant, the effects of which are attributed to production of reactive metabolites, chloroethylene oxide and chloroacetaldehyde. Evidence regarding mode of action includes direct reaction of a

metabolite with DNA, resulting in DNA adducts and mistranscription, and cross-species target-tissue correspondence of a rare tumour type. The no-observed-adverse-effect level calculated using the PBPK dose measurement (amount of vinyl chloride metabolised per gram of liver) was used to derive the proposed oral and inhalation exposure guidelines. Application of the PBPK model made it possible to use a chronic oral study as the critical study for the derivation of both the inhalation and oral exposure guidelines. The oral study was preferred to available subchronic inhalation studies for deriving the chronic inhalation guideline because it had more complete reporting of results and was a lifetime study. Risk estimates for human exposure to vinyl chloride predicted with a PBPK model and the linearised multistage model were lower than those currently used in environmental decision-making by a factor of 30 to 50, and were more consistent with human epidemiological data. (See also, e.g., Clewell *et al.*, 1995; Reitz *et al.*, 1996).

3.7 *m*-Xylene

A lumped-parameter, one skin-compartment, PBPK model has been developed and used to simulate dermal absorption of *m*-xylene in humans. In this type of model, the skin is assumed to be a single homogeneous compartment with mass transfer resistance occurring at an infinitesimally thin layer at the air:skin interface.*

Volunteers were exposed for 4 hours to air containing *m*-xylene at a concentration of 50 mg/m^3 under controlled conditions in a dynamic exposure chamber in two separate experiments. In the first, total uptake (by inhalation and dermal penetration) was investigated and in the second, volunteers breathed clean air through a mask while being exposed to vapour via the dermal route only. The kinetics of *m*-xylene were studied by post-exposure measurement of exhaled alveolar air.

The model successfully simulated both total and dermal-only exposure. A skin surface area of 1.236 m^2 was assumed and a permeability constant of 0.005 m/hour was estimated using the model. The shape of the exhaled alveolar air curve following dermal-only exposure was dependent on the value of the skin:air partition coefficient.

Estimates made using the model indicate that for *m*-xylene vapour (under the conditions of the experiment) the dermal route contributes 1.8% of the total systemic dose.

In a third experiment, volunteers were exposed to *m*-xylene at a concentration of 50 mg/m^3 for two 12-hour periods with a 12-hour break. Simulation of the urinary excretion of the major metabolite, methylhippuric acid, was good. The model was used to estimate the dermal exposure concentration required to deliver the same systemic dose as that achieved by inhalation. This provides an indication of the protection afforded by efficient respiratory protective equipment. The model predicted that a dermal exposure concentration of 3000 mg/m^3 would be required in order to deliver the same systemic dose as 50 mg/m^3 via inhalation.

* This study was funded by HSE, Sheffield, UK and undertaken by the Health and Safety Laboratory, with PBPK analysis of the data performed by the Institute of Occupational Medicine in Edinburgh, UK.

4 Other aspects of PBPK modelling for risk assessment

4.1 The situation in the USA

In 1983, the US National Academy of Sciences (1983) stated that

> The dominant analytic difficulty (in risk assessment) is pervasive uncertainty... there is often great uncertainty in the estimates of the types, probability, and magnitude of health effects associated with a chemical agent, (and) of the economic effects of a proposed regulatory action...

At that time and continuing to the present, most risk assessments in the USA, while quantitative, have not been based directly on a scientific understanding of the determinants of the shape of the exposure–response curve for the chemical in question. In the absence of such an understanding, the exposure–response relationship has been characterised using default assumptions that are intended to be conservative and thereby to ensure protection of the public health, although perhaps at the expense of regulating chemicals more stringently than is actually necessary. PBPK modelling has the potential to reduce uncertainty in exposure–response assessments while maintaining the protection of public health and minimising the chance that regulation is unnecessarily stringent.

Partitioning of the overall exposure–toxic response relationship into its pharmacokinetic (exposure–tissue dose) and pharmacodynamic (tissue dose–toxic response) components is useful for the purpose of considering progress toward the goal of reducing uncertainty in risk assessment. The rapid development in recent years of PBPK modelling has dramatically improved understanding of the relationship between exposure to a chemical in the air, drinking-water, or food and the dose that arrives at critical target tissues, such as the liver and kidney in the case of chloroform, or the nasal epithelium in the case of formaldehyde. Moreover, PBPK models have been developed for the mouse and rat strains in which most toxicological data are collected and for the humans of primary concern for risk assessment. Progress in the development of pharmacodynamic models has been much slower, probably because the biochemical mechanisms that comprise pharmacodynamics are typically not well understood.

In most cases, the default assumptions used in the USA for interspecies extrapolation have not distinguished between pharmacokinetic and pharmacodynamic parameters. For carcinogens, dose is scaled between species as a fractional power of body weight ($BW^{0.75}$); for non-carcinogens, an uncertainty factor of ten is used to adjust a rodent dose for use in human risk assessment. Both of these approaches predict that, for a given toxic effect, the required human dose is smaller than the rodent dose, that is humans are more sensitive than rodents. The availability of PBPK models means that interspecies scaling strategies can be partitioned into their pharmacokinetic and pharmacodynamic components. EPA guidance for inhaled non-carcinogens uses this approach, stating that a factor of three may be used to account for interspecies extrapolation of pharmacodynamic uncertainty when pharmacokinetic uncertainty is addressed with a mechanism-based approach.

Many US laboratories are adding new test protocols to their programmes directed at ascertaining the mechanisms of action of toxic chemicals. In response to the evolving science of toxicology, new guidance from EPA provides an analytical framework for incorporating all relevant mechanistic information. The framework includes evaluation of dosimetry models based on the degree of incorporation of mechanistic determinants of the exposure–dose–response continuum.
In characterising the potential cancer risk,

consideration is also given to incorporating all relevant biological information about toxicant–target interactions and response processes, for example distinguishing between agents that directly interact with and damage DNA versus those that operate through epigenetic or nonmutagenic mechanisms (e.g. receptor-mediated pathways, hormonal or physiological disturbances).

An understanding of the mechanistic determinants of an agent's toxicokinetics and tissue interactions will begin to break down the dichotomy between quantitative approaches to cancer and non-cancer risk assessment because the underlying bases of dosimetry and of certain toxicities may have several common features. This will be especially true as the prognostic significance of intermediate lesions in pathogenesis becomes known. For example, chemicals can induce cytotoxicity. Surviving cells may then compensate for that injury by increasing cell proliferation (hyperplasia). If this proliferative activity continues unchecked, it may result in tumours. Thus, the same basic toxic mechanisms may be related to the cancer outcome and to other types of toxic effects. Elucidation of the mechanistic processes underlying the pharmacokinetic and pharmacodynamic components along the exposure–dose–response continuum can be used to reduce uncertainty and define the variability inherent in the extrapolations from laboratory animal data required for dose-response assessment.

4.2 Application of dosimetry models to aid data interpretation

Approaches to dose–response assessment for chemicals have in past years attempted to account adequately for a variety of factors that contribute to interspecies differences in chemical-induced toxicity. The state of the science of contemporary bioassays is now such that mechanistic data are becoming increasingly available for toxicological assessment. Concurrently, mathematical models have become useful for characterising interspecies dosimetry* as well as dose–response functions. Mathematical models should improve the accuracy of the various extrapolations required in dose–response assessment because they include explicit descriptions of the major mechanistic determinants of the exposure–dose–response continuum.

Although it is ultimately desirable to have a comprehensive biologically-based dose–response model that incorporates the mechanistic determinants of chemical disposition (deposition, absorption, distribution, metabolism and elimination), toxicant–target interactions, and tissue responses, integrated into an overall model of pathogenesis (i.e. characterisation of the entire exposure–dose–response continuum), data to construct such comprehensive models do not exist for the majority of chemicals that require assessment. The availability of key anatomical and physiological parameters for different mammalian species (including humans) and of physicochemical parameters for individual chemicals is an important consideration in the formulation of model structures and in the application of simplifying assumptions to develop default approaches.

Construction of a framework for evaluation of dosimetry models based on the degree of incorporation of mechanistic determinants of the exposure–dose–response continuum provides for iterative development of dosimetry models commensurate with available data. The framework permits integration of diverse data from independent experiments (e.g. general physiological parameters for the animal species, metabolic data for the individual chemical) to predict complex kinetic behaviour. Development of the description of mechanistic processes in an iterative fashion also provides for the capability to 'lump' or 'split' model structures in an attempt to explore the sensitivity of the exposure–dose–response relationship to different model structures. Such an approach provides for the use of template model structures for use across species and for the reduction of data-testing requirements.

The principles of model formulation also can be used to generate hypotheses, identify areas where research is needed and frame efficient experimental designs. Effective application of these principles requires new approaches to toxicology that are outside routine testing paradigms aimed at elucidating mechanisms of action through hypothesis-driven research. Risk assessment can be improved by reducing uncertainties associated with interspecies extrapolation on this basis.

Assessing the toxicology of inhaled particles and gases is especially challenging, owing to the many

* 'Dosimetry modelling' can be used as a more comprehensive term than 'PBPK modelling'; it covers models used to investigate irritant gases and particles as well as volatile organic chemicals. Mathematical modelling is defined as the use of the physical laws of mass, heat and momentum conservation to quantify the dynamics of a system of interest. Dosimetry modelling is defined as the application of mathematical modelling to characterise the determinants of exposure–dose–response.

anatomical, physiological and biochemical differences between test species and humans. The various species used in inhalation toxicology studies that typically serve as the basis for dose–response evaluation do not receive identical doses in comparable respiratory tract regions (extrathoracic, tracheobronchial, pulmonary) when exposed to the same aerosol or gas. These differences are important because the toxic effect is more likely to be related to the quantitative pattern of deposition and subsequent distribution, clearance and re-distribution than to the exposure concentration. The major processes of particle deposition (interception, impaction, sedimentation, diffusion and electrostatic precipitation) and gas transport (convection, diffusion, absorption, dissolution and chemical reactions) must be integrated with the physicochemical properties of these agents (e.g. particle diameter and hygroscopicity for particles, chemical reactivity and water solubility for gases) in order to describe dosimetry. Consideration of interspecies differences in anatomical factors (gross and microscopic structures, including cell types and location), and physiological (e.g. ventilation rate) and biochemical (e.g. metabolic capabilities and capacities) differences must also be superimposed. Default algorithms need to be developed to account for these factors.

Perhaps the most frequent application of modelling principles is the evaluation of the database for a given chemical. By definition, a database for derivation of an exposure–dose–response estimate for non-cancer toxicity of inhaled exposures should ensure that an adequate number of appropriate potential end-points have been evaluated. If the objective is to derive an estimate for a 'lifetime' of exposure, then end-points representative of critical life stages (e.g. developmental and reproductive toxicity) must be included for the database to be considered comprehensive. However, consideration of the physicochemical and toxicokinetic properties of the chemical (e.g. data indicating that significant remote distribution of toxic entities is unlikely) may mitigate the requirements for reproductive and developmental data. Determination of the likelihood of portal-of-entry versus remote effects also underlies guidance on route-to-route extrapolation.

Insight into the key determinants of disposition and toxicity for specific chemicals can thus be used, for example, to evaluate existing databases with a view to determining testing requirements for various hazardous air pollutants, and interpreting available data on chemicals in the same class.

The identification of key processes and mechanistic determinants can aid the development of models and provide for evaluation of chemicals not yet in major production. A parallelogram approach using a PBPK model template has been used to predict the toxicokinetics in humans of HCFC-123, a chemical not yet in production but targeted as a chloroflurocarbon substitute. The approach was based on analogy of the structure and toxicokinetics of the new chemical to those of halothane, an anaesthetic for which laboratory animal and human data already exist.

Simulation modelling exercises have also been used to help evaluate control strategies and to generate hypotheses used in targeting mechanistic research to improve future scheduled revision of the standard-setting process for particulate matter.

(See also, e.g., Jarabek *et al.*, 1994; Bogdanffy, 1995; Jarabek, 1995a,b,c; Jarabek *et al.*, 1997).

4.3 Population analysis

There has been much recent interest in the area of population pharmacokinetics, which can be loosely defined as the study of the factors that contribute to interindividual variability in pharmacokinetics. Although the field is referred to as population pharmacokinetics there is a compelling case to extend the scope of the studies to include pharmacodynamics. Traditionally, pharmacokinetics studies have involved intensive experimentation in small groups of subjects, often healthy volunteers, in which a relatively large number of blood samples are withdrawn after administration of a medicine. The design and analysis of such experiments is well established. However, there are many situations where only fragmentary data, in some cases only one sample per individual, are available for analysis. With such data, often termed 'sparse data', it is not possible to characterise the disposition of a drug in an individual with a pharmacokinetic model that may contain four or more parameters. To make progress, it is better to concentrate, initially at least, on the central trend of the data, that is to determine the population pharmacokinetics, rather than on individual analysis.

Sparse data arise from many experimental settings, including those listed below.

- **Toxicokinetics** Many preclinical animal experiments are terminal, particularly where tissue sampling is involved. Relatively few analyses of sparse data arising from such studies have been reported so far.

- **Neonates** In certain clinical populations, particularly neonates, intensive sampling is not possible, and sparse data are the norm.

- **Tissue samples** Just as with animals, human data obtained from physiological fluids other than plasma, such as synovial fluid, are usually limited, as only one or two samples are drawn per individual.

- **Developing countries** For logistical reasons, large-scale field trials of medicines, such as antimalarials, in developing countries are likely to generate patchy, incomplete data.

- **Phase III and IV drug development** Large-scale clinical trials undertaken during Phase III of a drug's development and during early marketing, Phase IV, are mainly efficacy and safety studies. Consequently, few blood samples are drawn, although recently there has been a heightened awareness of the potential pharmacokinetic information in data from such samples.

The analysis of sparse data, combining information across individuals, requires specialised data analysis techniques and sophisticated software. Several approaches to the analysis of data arising from nonlinear mixed-effect models have been suggested.

PBPK modelling of preclinical animal data has been used to study the relationship between the chemical structure of a homologous series of barbiturates and their pharmacokinetic behaviour. The drugs studied were administered by intravenous bolus to rats. The data set contains tissue profiles for 16 body tissues/organs. The general structural model developed consists of the 18-compartment whole-body PBPK model of the series and the relationship between the drug-dependent parameters (partition coefficients and total clearance) and the lipophilicity of the compounds. In this way, the lipophilicity of the drug can be looked upon as a covariate for the tissue kinetics and NONMEM has been applied for the parametric identification of the general model.

(See also, e.g., Aarons, 1996; Blakey *et al.*, 1997; Nestorov *et al.*, 1998)

4.4 Lung particulates

Mathematical models have been used to produce a quantitative description of the retention and clearance mechanisms of inhaled particles in the alveolar region of the lung. Earlier models described these mechanisms during chronic exposure in terms of few compartments, namely, clearance to the tracheobronchial region, transfer to lymph nodes, sequestration of particles and overloading of clearance mechanisms. More recent modelling at the Institute of Occupational Medicine has focused on the cellular mechanisms involved in the clearance of particulate dusts from the lung.

The model describes: (1) phagocytosis of particles by resident alveolar macrophages; (2) necrosis of macrophages and the subsequent release of clusters of particles onto the alveolar surface; (3) the inflammatory recruitment of alveolar macrophages and neutrophils in response to cell necrosis caused by phagocytosis of particles; and (4) the interstitialisation of free particles on the alveolar surface — once in the interstitium, particles may be phagocytosed by interstitial macrophages, and eventually transferred to the hilar lymph nodes.

The model was originally developed and tested with data from inhalation studies with rats exposed to a low-toxicity dust, titanium dioxide, or a cytotoxic dust, quartz. Currently, the model is being extended to describe the retention and clearance of short fibres (length <20 mm) and the disappearance of long fibres (length >20 mm). The general structure of the model can be modified to describe the retention/clearance of environmental pollutants such as ultrafine particles. The model has been used to design short-term inhalation studies with two low-toxicity dusts (titanium dioxide and barium sulphate) and predict the no-observed-adverse-effect level for each dust.

Finally, since the model is physiologically based, it is possible to extrapolate data from animal studies to humans by changing the appropriate model parameters. Current research will examine the feasibility of such extrapolation by using the model to predict the lung burden of coalminers at autopsy in relation to their estimated lifetime exposures.

5 Conclusions and recommendations

PBPK modelling, sometimes referred to as 'dosimetry modelling', essentially addresses the refinement and reduction of uncertainty in estimating, in humans or any other species, the target tissue dose for toxic chemicals or their metabolites, where these are responsible for the toxic effect. In the case of extrapolation from experimental species to humans, PBPK modelling helps to reduce the uncertainty resulting from different exposure conditions by calculating equivalent tissue dose(s) producing the same level(s) of effect. Similarly, within the same species (e.g. humans) the uncertainty in extrapolating from high to low dose and across differing exposure profiles can be reduced. The technique also provides a methodology for organising information in a formal manner and providing greater transparency in the dosimetry component of the risk assessment process. This approach therefore offers the opportunity to identify and clarify areas of uncertainty, permitting more focused research and understanding, with a view to improving chemical risk assessment in relation to human health. Further research and development is needed to improve knowledge and expertise in this field in the UK.

PBPK modelling: Research and development needs

Although there have been significant advances and models now exist for a substantial number of substances, PBPK modelling still has limitations in respect of the procedures employed and its application to risk assessment. The models depend on a knowledge of the basic morphology and physiology of the species to which they are applied. However, current models have been developed on the basis of relatively limited data, in particular for humans. For example, data relating to different age groups are rarely available, yet they are important in ensuring that the models are appropriate for the population of concern; a model used to estimate tissue doses in the average adult human may not be suitable for application to the young or old in the population. The accumulation of such basic information, in order to expand the available databases for a number of key species, would be relatively straightforward and could employ new non-invasive technologies, particularly for humans. In some instances, all that may be required to produce a usable resource is for existing data sources to be combined. Such basic information would also be of value in helping with mechanistic understanding and interpretation in toxicology, irrespective of its value in the application of PBPK modelling (e.g. comparative nasal air-flows in rats and humans in relation to formaldehyde; intra- and interspecies variations in the expression of xenobiotic biotransforming enzymes).

Research to develop expanded databases for basic morphological and physiological parameters, particularly for human populations, to be used for PBPK modelling, is to be encouraged; this could be carried out as part of other PBPK modelling research activities.

Current PBPK modelling is largely substance-specific and requires relatively detailed data sets on each substance. In most cases, the data required to perform the modelling would not normally be submitted as part of a standard regulatory package. However, once a model has been developed for a specific substance it has the potential for use as a 'template' model for other substances with similar modes of action and structural and physicochemical properties. The template approach has already been used but there is scope for significant expansion in this area. Information on structure–activity relationships could be particularly useful in developing template models. There has been relatively little activity in exploring the remaining uncertainties in relation to the data used and the application of the models. The development and testing (i.e. validation) of

templates within groups of chemicals would therefore also provide a useful means of exploring these uncertainties and of identifying those general and specific factors in both the overall strategy of PBPK modelling and in specific models (and also the data) that are critical to the development and use of PBPK modelling.

New 'template' models for defined structurally and/or functionally related chemicals, not already the subject of existing models, should be developed.

Much of the PBPK modelling work undertaken in relation to pharmaceuticals has focused on the way variability within populations may affect response to pharmaceuticals and the approaches needed to account for this in terms of practical measurements (e.g. *in vitro* testing) and mathematical modelling. Workers in this field have gained significant experience which could usefully be applied to the use of PBPK modelling in chemical risk assessment. For example, human pharmacokinetic data are available on many substances and could be used to validate many aspects of the use of animal and *in vitro* data, as well as any particular model, not only in predicting the mean performance in humans but also in testing the confidence of the prediction. However, in the UK there is relatively little interaction or even awareness between the two fields of activity. Significant advances in the application of PBPK modelling to risk assessment (and risk assessment itself) could be made by supporting practical interaction (i.e. joint projects) between groups involved in the two areas. Human variability is one topic of shared interest. Various mathematical techniques (e.g. Monte Carlo simulations) have been applied to take human individual variability into account in PBPK modelling for specific defined situations, for example with industrial chemicals. In pharmaceutical research, techniques such as population pharmacokinetics have been developed to investigate population variability using sparse data sets. There may be significant benefits in applying this experience to PBPK modelling for chemical risk assessment.

Specific research projects designed to bring together the experience and skills of researchers working on PBPK modelling of industrial chemicals and pesticides and related areas of pharmaceutical research should be undertaken, in order to explore issues of relevance to chemical risk assessment, such as human variability.

Regulatory application

Although PBPK modelling for chemical risk assessment has undergone significant development in the USA, its application to regulatory activity appears to have been relatively limited. Where it has been used in the USA, it has proved successful, making a useful contribution to the risk assessment process.

In the UK, a great deal of weight is placed on mechanistic considerations in chemical risk assessment. In some respects these considerations contain elements akin to an informal PBPK assessment. PBPK modelling provides information linking exposure and tissue dose and should only be used in the light of available toxicity information. However, where effects seen in animals are considered to be of relevance to human health then the use of mechanistic data to improve human target tissue dosimetry would be of significant value in improving the overall risk assessment process. There is concern that PBPK modelling only deals with dosimetry and is still a developing methodology. There are also concerns about the effort and cost involved in generating the essentially compound specific data needed for PBPK modelling, which would probably only be justified for commercially important substances, where the existing data package suggests a low margin of safety and thus raised concerns. Nevertheless, PBPK modelling does allow for the integration of diverse data and provides a structured framework permitting the organisation of data so that key parameters and processes are more clearly defined and appreciated. This in itself helps to highlight and direct areas for research, which in turn helps not only to improve the modelling process but also to provide information about the suitability of default assumptions and procedures. Thus this is an iterative process helping to refine and improve knowledge.

For the UK regulatory framework, PBPK modelling is a new field of interest with considerable potential benefits to government and industry. Nevertheless, it is felt that the UK should adopt a cautious approach with respect to changing current practice in chemical risk assessment until more experience and confidence have been gained with this technique. Certainly PBPK modelling should not be seen as an immediate alternative to current practice but as an iterative process that may be used by the risk assessor, particularly within the regulatory framework and most probably on a substance-by-substance basis, to help improve the risk assessment process. Eventually PBPK

modelling may provide an alternative to some of the default assumptions used in the current risk assessment process but this is likely to be a long-term goal, at least in the UK. However, in order to be able to use (even if only on an occasional basis) such a tool in any meaningful manner, some independent experience and expertise in the field needs to be established. Moreover, viewed from an academic perspective, a commitment to continuing funding would be needed in order to create relatively stable groups of workers of critical mass producing appropriately-trained personnel. Despite the need for caution in applying such PBPK models to risk assessment in a formal manner in the UK, the potential improvements such an approach could bring are acknowledged. PBPK modelling may benefit risk assessment by providing improved information on tissue dosimetry and variations between species and individuals.

Research and development on PBPK modelling in human health chemical risk assessment should be undertaken to increase knowledge and expertise in this area in the UK and as an investment for improving the predictive value of such assessments.

In the occupational setting in the USA, PBPK modelling has seen significant use in the development of Biological Exposure Indices™ by the ACGIH (BEIs™ are measures of a substance or metabolite in biological media and are used to assess adequacy of control of exposure.) Such approaches are starting to be used in the UK by HSE. Furthermore, the application of PBPK modelling to data gathered from studies in humans for the development of biological monitoring standards is seen to provide the opportunity to investigate issues of human variability, particularly when other forms of analysis used for pharmaceutical research are also applied. Continuation of this activity in the UK will increase knowledge and experience in the field.

The application of PBPK modelling to biological monitoring in occupational (and other) settings, particularly within the context of establishing guidance values and standards, should be continued.

Another area in which PBPK modelling may be of potential benefit to regulatory activity is in the assessment of endogenous substances in food, for example, consideration of the balance between a substance (e.g. vitamin A) which is a nutritional requirement and its potential to cause adverse health effects at higher body burdens. However, no single industry currently has a specific responsibility that would lead to significant research being conducted to consider the fate of naturally-occurring chemicals in the human population.

Research is needed into the application of PBPK modelling to dosimetry assessment for naturally occurring substances (e.g. in foods).

In addition to their use in human health risk assessment, PBPK modelling techniques can also be applied to other species, for example, in the prediction of residue levels in the edible tissues of minor food-producing species — a concern with respect to the consumer. Although residue studies (and thus data) are available for the major species, generation of residues data for minor species can be financially uneconomical, potentially restricting the availability of veterinary medicines for these species. PBPK modelling may provide an alternative way of estimating residue levels. PBPK modelling can also be applied to environmental risk assessment for non-human species, perhaps using the technique to identify potential 'receptor organisms' and/or to simulate the fate of specific substances in environmentally relevant species. However, species-specific biological and physiological parameters are needed for the species of interest.

The application of PBPK modelling to risk assessment in non-human species should be investigated, to facilitate extrapolation between these species; this has direct application to human safety in relation to drug residues in animal tissues and would also have benefits to wider environmental considerations outside the remit of the Risk Assessment and Toxicology Steering Committee.

PBPK modelling may prove useful in informing the need for data-gathering and the targeting of toxicity testing within the regulatory context. The general regulatory approach to toxicity testing is to require a basic set of information and then, depending on issues such as levels of supply, potential for exposure and/or identified concerns or gaps in knowledge, to call for further testing as necessary. Clearly there are a number of ethical (e.g. animal usage) and resource considerations in the development of such testing requirements. Often there may be uncertainty about the value of carrying out particular tests. For example, if a gaseous substance expresses its activity essentially locally in the respiratory tract then is it necessary to carry out testing to investigate its potential chronic oral or reproductive toxicity? Similarly, if a substance acts systemically and the effect is expressed independently of exposure route, then why test by expensive inhalation exposure if a comprehensive oral database already exists? In the USA, much use has been made of PBPK modelling for route-to-route extrapolation, demonstrating that it can provide a valuable tool in helping to inform the decisions on the need to carry out testing. In the UK, any practical activity in this area is likely

to be handled on a case-by-case basis within individual Government departments. However, there is a need to ensure consistency of approach between departments and the availability of independent expertise within the UK on which they can call.

The validation and quality assurance of models and the associated implementation with respect to regulatory activity will be critical. There is the obvious need to ensure that the outputs of any methods are representative of the real situation they are intended to simulate. This is the case for current default approaches in risk assessment which are not necessarily biologically motivated but default to be protective rather than predictive. A move towards predictive approaches, such as PBPK modelling, could increase the accuracy of risk assessment. However, there is a need for clarity and transparency in the way assumptions are made in a particular model and in determining what the consequences of deviating from these assumptions might be. It is also important that those using a model should understand its principles and limitations, and apply it correctly; some form of 'peer-review' process may be useful in this regard. In the UK regulatory setting, formal rules for the application of PBPK modelling in chemical risk assessment are probably not required. However, it is essential to ensure consistency and provide confidence in the application of the technique, and appropriate guidance will be needed. Input from industry could be useful in this connection.

UK Government departments currently have differing levels of knowledge, views and interests in PBPK modelling and its application to risk assessment. Some departments have already undertaken limited initiatives in this field but there is little coordination of such activity.

For the UK regulatory framework, PBPK modelling is a new field of interest, with considerable potential benefits to government and industry. If adopted by Government departments, there is a need for a consistent approach.

A cross-government interdepartmental group should be established to co-ordinate the application of PBPK methods and any government-sponsored research.

Such a group would comprise an informal network of regulatory toxicologists. The remit of the group should be to develop guidance on the use of PBPK modelling in chemical risk assessment in the regulatory framework in order to ensure consistency of approach between departments. It could also act as a central focus for research funded by Government (co-sponsored or departmental) in the area, providing a forum for exchange of information and ensuring an integrated approach to such research.

References and selected bibliography

Aarons L (1996) Population approaches/sparse data analysis for human variability in kinetics and dynamics. *Environ Toxicol Pharmacol, 2,* 197–199

Aarons L, Balant LP, Gex-Fabry M, Gundert-Remy UA, Karlsson MO, Mentre F, Morselli PL, Rombout F, Rowland M, Steimer J-L & Vozeh S (1997) *The Population Approach: Measuring and Managing Variability in Response, Concentration and Dose,* Luxembourg, Commission of the European Community

Andersen ME, Clewell HJ, Gargas ML, Smith FA & Reitz RH (1987) Physiologically-based pharmacokinetics and the risk assessment for methylene chloride. *Toxicol Appl Pharmacol, 87,* 185–205

Andersen ME, Mills JJ, Gargas ML, Kedderis LB, Birnbaum LS, Neubert D & Greelee WF (1993) Modelling receptor-mediated processes with dioxin: Implications for pharmacokinetics and risk assessment. *Risk Anal, 13,* 25–36

Andersen (1995) Physiologically based pharmacokinetic (PB-PK) models in the study of the deposition and biological effects of xenobiotics and drugs. *Toxicol Letts, 82/83,* 341–348

Andersen ME, Clewell HJ & Frederick CB (1995) Applying simulation modelling to problems in toxicology and risk assessment — a short perspective. *Toxicol Appl Pharmacol, 133,* 181–187

Andersen ME, Clewell HJ & Krishnan K (1995) Tissue dosimetry, pharmacokinetic modelling, and interspecies scaling factors. *Risk Anal, 15,* 533–537

Beck BD, Conolly RB, Dourson ML, Guth D, Hattis D, Kimmel C & Lewis SC (1993) Improvements in quantitative noncancer risk assessment. *Fundam Appl Toxicol, 20,* 1–14

Blakey GM, Nestorov IA, Arundel PA, Aarons LJ & Rowland M (1997) Quantitative structure-pharmacokinetics relationships: I. Development of a whole-body physiologically based model to characterize changes in the pharmacokinetics across a homologous series of barbiturates in the rat. *J Pharmacokinet Biopharm, 25,* 227–312

Bogdanffy MS & AM Jarabek (1995) Understanding mechanisms of inhaled toxicants: Implications for replacing default factors with chemical-specific data. *Toxicol Letts, 82/83,* 919–932

Bungay PM, Dedrick RL & Matthews HB (1981) Enteric transport of parent chlordecane ('kepone') in the rat. *J Pharmacokinet Biopharm, 9,* 30

Carlile DJ, Zomorodi & K Houston JB (1997) Scaling factors to relate drug metabolic clearance in hepatic microsomes, isolated hepatocytes and the intact liver. Studies with induced livers involving diazepam. *Drug Metab Dispos, 25,* 903-911

Carlile DJ, Stevens AJ, Ashforth EIL, Waghela D & Houston, JB (1998) *In vivo* clearance of ethoxycoumarin and its prediction from *in vitro* systems. *Drug Metab Dispos, 26,* 216–221

Carrier G, Brunet RC & Brodeur J (1995) Modelling of the toxicokinetics of polychorinated dibenzo-*p*-dioxins and dibenzofurans in mammalians, including humans. I. Non-linear distribution of PCDD/PCDF body burden between liver and adipose tissues. *Toxicol Appl Pharmacol, 131,* 253–266

Clewell HJ & Andersen ME (1985) Risk assessment extrapolations and physiological modeling. *Toxicol Ind Health, 1,* 111–131

Clewell HJ (1993) Coupling of computer modeling with *in vitro* methodologies to reduce animal usage in toxicity testing. *Toxicol Letts, 68,* 101–117

Clewell HJ & Jarnot BM (1994) Incorporation of pharmacokinetics in non-carcinogenic risk assessment: Example with chloropentafluorobenzene. *Risk Anal, 14,* 265–276

Clewell HJ (1995a) Incorporating biological information in quantitative risk assessment: An example with methylene chloride. *Toxicology, 102,* 83–94

Clewell (1995b) The use of physiologically based pharmacokinetics modelling in risk assessment: A case study with methylene chloride. In: Farland S, Park W, Rhomberg C, Scheuplein L, Starr T & Wilson J, eds, *Low-Dose Extrapolation of Cancer Risks: Issues and Perspectives.* Washington DC, USA, ILSI Press, pp 199–221

Clewell HJ (1995c) The application of physiologically based pharmacokinetic modelling in human health risk assessment of hazardous substances. *Toxicol Letts, 79,* 207–217

Clewell HJ, Gentry PR, Gearhart JM, Allen BC & Andersen ME (1995) Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: Examples with vinyl chloride and trichloroethylene. *Chemosphere, 31,* 2561–2578

Clewell HJ & Andersen ME (1996) Use of physiologically-based pharmacokinetic modeling to investigate individual *versus* population risk. *Toxicology, 111,* 315–329

Clewell HJ (1997) Investigation of the potential impact of benchmark dose and pharmacokinetic modelling in noncancer risk assessment. *J Toxicol Environ Health, 52,* 475–515

Conolly RB, Morgan KT, Andersen ME, Monticello TM & Clewell HJ (1992) A biologically-based risk assessment strategy for inhaled formaldehyde. *Comm Toxicol, 4,* 269–293

Crapo JD, Smolko ED, Miller FJ, Graham JA & Gayes AW, eds (1989) *Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases,* New York NY, USA, Academic Press Inc

EPA (1994) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA/600/8-90/066F), Research Triangle Park NC, USA, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office

EPA (1996) Proposed guidelines for carcinogen risk assessment. *Federal Register, 61,* 17960–18011

Fiserova-Bergerova V (1975) Mathematical modeling of inhalation exposure in man. *J Combust Toxicol, 32,* 201

Frederick CB (1993) Limiting the uncertainty in risk assessment by the development of physiologically based pharmacokinetic and pharmacodynamic models. *Toxicol Letts, 68,* 159–175

Gargas ML, Clewell HJ III & Andersen ME (1986) Metabolism of inhaled dichloromethanes *in vivo*: Differentiation of kinetic constants for two independent pathways. *Toxicol Appl Pharmacol, 82,* 211–223

Gerlowski LE & Jain RJ (1983) Physiologically based pharmacokinetic modeling: Principles and applications. *J Pharm Sci, 72,* 1103–1127

Gerrity TR & Henry CJ (1990) *Principles of Route-to-Route Extrapolation for Risk Assessment,* New York NY, USA, Elsevier

HMSO (1995) *Forward Look of Government-funded Science, Engineering and Technology (Volume 1),* London, UK, HMSO

Haggard HW (1924) The absorption, distribution, and elimination of ethyl ether. II. Analysis of the mechanism of absorption of such a gas or vapor as ethyl ether. *J Biol Chem, 59,* 753

Himmelstein KJ & Lutz (1979) A review of the applications of physiologically based pharmacokinetic modeling. *J Pharmacokinet Biopharm, 72,* 1103

Houston JB (1994) Utility of *in vitro* drug metabolism data in predicting *in vivo* metabolic clearance. *Biochem Pharmacol, 47,* 1469–1479

Houston JB & Carlile DJ (1997) Incorporation of *in vitro* drug metabolism data into physiologically-based pharmacokinetic models. *Toxicol In Vitro, 11,* 473–478

Houston JB & Carlile DJ (1997) Prediction of hepatic clearance from microsomes, hepatocytes and liver slices. *Drug Metab Rev, 29,* 891–922

Jackson PR & Tucker GT (1990) Pharmacokinetic-pharmacogenetic modelling in the detection of polymorphisms in xenobiotic metabolism. *Ann Occup Hyg, 34,* 653–662

Jackson PR, Tucker GT & Woods HF (1989a) Testing for bimodality in frequency distributions of data suggesting polymorphism of drug metabolism — histograms and probit plots. *Brit J Clin Pharmacol, 28,* 647–653

Jackson PR, Tucker GT & Woods HF (1989b) Testing for bimodality in frequency distributions of data suggesting polymorphism of drug metabolism — hypothesis testing. *Brit J Clin Pharmacol, 28,* 655–662

Jackson PR, Tucker GT, Lennard MS & Woods HF (1986) Polymorphic drug oxidation: Pharmacokinetic basis and comparison of experimental indices. *Brit J Clin Pharmacol, 22,* 541–550

Jarabek AM, Fisher JW, Rubenstein R, Lipscomb JC, Williams RJ, Vinegar A & McDougal JN (1994) Mechanistic insights aid the search for CFC substitutes: Risk assessment of HCFC-123 as an example. *Risk Anal, 14,* 231–250

Jarabek AM (1995a) Consideration of temporal toxicity challenges current default approaches. *Inhal Toxicol, 7,* 927–946

Jarabek AM (1995b) Interspecies extrapolation based on mechanistic determinants of chemical disposition. *Human Ecolog Risk Assess, 1,* 641–662

Jarabek AM (1995c) The application of dosimetry models to identify key processes and parameters for default dose–response assessment approaches. *Toxicol Letts, 79,* 171–184

Kedderis LB, Mills JJ, Andersen ME & Birnbaum LS (1993) A physiologically-based pharmacokinetic model of 2,3,7,8-tetrabromodibenzo-*p*-(TBDD) in the rat: Distribution and CYP1A induction. *Toxicol Appl Pharmacol, 121,* 87–98

Kety SS (1951) The theory and applications of the exchange of inert gas at the lungs. *Pharmacol Rev, 3,* 1

King FG, Dedrick RL, Collins JM, Matthews HB & Birnbaum LS (1983) Physiological model for the pharmacokinetics of 2,3,7,8-tetrachorodibenzofuran in several species. *Toxicol Appl Pharmacol, 67,* 390–400

Kissel J & Rombarge G (1988) Assessing the elimination of 2,3,7,8-TCDD from humans with a physiologically based pharmacokinetic model. *Chemosphere, 17,* 2017–2021

Kohn MC, Lucier GW, Clark GC, Sewall C, Tritscher AM & Portier CJ (1993) A mechanistic model of the effects of dioxin on gene expression in the rat liver. *Toxicol Appl Pharmacol, 120,* 138–154

Krewski D, Withey JR, Ku LF & Andersen ME (1994) Applications of physiologic pharmacokinetic modeling in carcinogenic risk assessment. *Environ Health Perspect, 102(suppl 11),* 37–50

Leggett RW (1993) Research advances: An age-specific kinetic model of lead metabolism in humans. *Environ Health Perspect, 101,* 598–616

Leung H-W (1991) Development and utilization of physiologically based pharmacokinetic models for toxicological applications. *J Toxicol Environ Health, 32,* 247–267

Lunn DJ & Aarons L (1997) Markov chain Monte Carlo techniques for studying interoccasion and intersubject variability: Application to pharmacokinetic data. *Appl Stat, 46,* 73–91

Lutz RJ, Dedrick RL, Matthews HB, Eling TE & Andersen MW (1977) A preliminary pharmacokinetic model for several chlorinated biphenyls in the rat. *Drug Metab Dispos, 5,* 386–396

Mapleson WW (1962) An electric analogy for the uptake and exchange of inert gases and other agents. *J Appl Physiol, 18,* 197

Miller FJ & Mensel DB (1984) *Fundamental of Extrapolation Modeling of Inhaled Toxicants*, New York NY, USA, Hemisphere Publishing Corporation

National Research Council (1987) *Pharmacokinetics in Risk Assessment. Drinking Water and Health* (Volume 8), Washington DC, USA, National Academy Press

Nestorov I, Aarons LJ, Arundel PA & Rowland M (1998) Lumping of whole body physiologically based pharmacokinetic models. *J Pharmacokinet Biopharm, 26,* 21–46

Nestorov IA, Aarons, LJ & Rowland M (1997) Physiologically based pharmacokinetic modelling of a homologue series of barbiturates in the rat. II. Sensitivity of the model. *J Pharmacokinet Biopharm, 25,* 413–449

Oliver RE, Heatherington AC, Jones AF & Rowland M (1997) A physiologically-based pharmacokinetic model based on dispersion principles to describe solute distribution in the perfused rat hindlimb preparation. *J Pharmacokinet Biopharm, 25,* 389–413

Reitz RH, Gargas ML, Andersen ME, Provan WF & Green T (1996) Predicting cancer risk from vinyl chloride exposure with a physiologically based pharmacokinetic model. *Toxicol Appl Pharmacol, 136,* 1–16

Reitz RH, Mendrala AL, Corley RA, Quast JF, Gargas ML, Andersen ME, Staats DA & Conolly RB (1990) Estimating the risk of liver cancer associated with human exposures to chloroform using physiologically based pharmacokinetic modeling. *Toxicol Appl Pharmacol, 105,* 443–459

Reitz RH, Mendrala AL, Park CN, Andersen ME & Guengerich FP (1988) Incorporation of *in vitro* enzyme data into the physiologically-based pharmacokinetic (PB-PK) model for methylene chloride: Implications for risk assessment. *Toxicol Letts, 43,* 97–116

Riggs DS (1963) *The Mathematical Approach to Physiological Problems: A Critical Primer,* Cambridge MA, USA, MIT Press

Rostami-Hodjegan A, Nurminen S, Jackson PR & Tucker GT (1996) Caffeine urinary metabolite ratios as markers of enzyme activity: A theoretical assessment. *Pharmacogenetics, 6,* 121–149

Snipes MB, James AC & Jarabek AM (1997) The 1994 ICRP66 human respiratory tract dosimetry model as a tool for predicting lung burdens from exposures to environmental aerosols. *Appl Occup Environ Hyg, 12,* 547–554

Teorell T (1937) Kinetics of distribution of substances administered to the body. 1. The extravascular mode of administration. *Arch Int Pharmacol, 57,* 205

Tucker GT, Rostami-Hodjegan A & Jackson PR, (1998) Determination of drug metabolising enzyme activity *in vivo:* Pharmacokinetic and statistical issues. *Xenobiotica, 28,* 1255–1273

US National Academy of Sciences (1983) *Risk Assessment in the Federal Government: Managing the Process*, Washington DC, National Academy Press

Welsch F, Blumenthal GM & Conolly RB (1995) Physiologically based pharmacokinetic models applicable to organogenesis: Extrapolation between species and potential use in prenatal toxicity risk assessments. *Toxicol Letts, 82/83,* 539–547

Wiltse J & Dellarco VL (1996) US Environmental Protection Agency's guidelines for carcinogen risk assessment: Past and future. *Mutat Res, 365*, 3–15

Yang RS, el-Masri HA, Thomas RS, Constan AA & Tessari JD (1995) The application of physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling for exploring risk assessment approaches of chemical mixtures. *Toxicol Letts, 79*,193–200

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