

Group 3: Prediction

Final Report-out

Thanks to...

- Frederic Bois
- Weihsueh Chiu
- Bas Blaauboer

- and all the participants in the Model Prediction group!

**What changes to PBPK and
statistical models and
parameters are needed for
risk assessment prediction?**

Methods available (including alternatives to probabilistic methods)?

- Point estimates
- Fuzzy numbers or other interval methods
- Monte Carlo (alone, or after Bayesian calibration)
- Sensitivity analysis – local and global
 - Global analyses, in particular, could be better utilized.

Issues in Methods selection/implementation

- Need for standardization/defaults
 - Scenarios for point estimates
 - Distributions or databases from which to sample (e.g., P3M, CHAD)
- Dealing with correlations
 - Can be addressed deterministically
 - More difficult to do statistically (nxn covariance matrix)

Issues/suggestions for other groups

- Specification
 - Appropriate sampling of parameter values (e.g., to maintain summation constraint on tissue volues/flows).
- Calibration
 - Better use of (global) sensitivity analysis to reduce dimensionality.
 - Doing traditional MC prior to MCMC (related to sensitivity analysis).

How to incorporate specific physiological/
pharmacokinetic data (not in vivo kinetic
data – that's for calibration groups) on
populations of interest?

- New point estimates on specific populations of concern.
- Tailor prior distributions to populations of concern.

Issues

- Conceptualization of “susceptible” population.
 - Goal is to identify a specific subgroup through its particular characteristics, rather than to only describe them as the tail of the distribution (loose definition, not very operational).
 - This could be identified a priori (should be included in model).
 - Or, after generating a distribution, use sensitivity analysis to identify what are the determinants of susceptibility (inversion problem)? Feedback to data collection needs: try to validate whether (i) they really exist; (ii) are they really at higher risk [harder].

Issues/suggestions for other groups

- Calibration
 - After population analysis (in calibration), can examine unused covariates from the data (e.g., sex, age) to see if they correlate with predictions of interest. These could be candidates for inclusion into the model.

Yesterday up to here

What sources of uncertainty/variability should be carried over (or not) to prediction from specification and calibration steps?

- For prediction of internal doses, should try to exclude any variability caused by measurement error.
- Intra-individual variability (different observations of the same individual) – depends on application and on the pharmaco/toxico-dynamics of the compound.

Structural changes based on differences between available data and risk assessment needs?

- Risk assessment need should drive the model structure from the start
- Should have as “complete” (PBPK and statistical) a model [e.g., in terms of target organs] as is needed for risk assessment from the start.
- If the model is modified then should recalibrate

Structural changes based on differences between available data and risk assessment needs?

- If you don't have data directly (or highly) informative for the desired dose metric, then
 - evaluate the uncertainty in the model
 - compare with a surrogate dose metric (e.g., compartment in the model with similar characteristics) that is more directly calibrated.

How to characterize uncertainty from alternative PBPK and statistical models [i.e., structure differences]?

- If you only have one model, can only quantify parameter uncertainty, not quantify structural uncertainty (but can state uncertainty qualitatively).
- You have eliminated a number of “bad” models in developing your “best” model.

How to characterize uncertainty from alternative PBPK and statistical models [i.e., structure differences]?

- Do we need to generate multiple models as a matter of principle?
 - Do need to think about reasonable alternatives (e.g., metabolic pathways) – part of model building process.
 - 2007 meeting in Crete on good modeling practice

How to characterize uncertainty from alternative PBPK and statistical models [i.e., structure differences]?

- Not starting from a “random” set of models
 - need to carefully consider what constitutes different models
 - carefully characterize prior beliefs about the validity of each of them.
 - Or, analyze and try to combine/harmonize/include into a larger model to the extent possible [convert to parameter uncertainty].

How to characterize uncertainty from alternative PBPK and statistical models [i.e., structure differences]?

- Possible procedure:
 - Eliminate some models based on fits to data, and check the rest in terms of their domains of applicability
 - (Calibration group question).
 - With remaining model, check if different alternatives make a difference in predictions (also, relative to parameter uncertainty, i.e., from MC).
 - If you need your answer now – use each of your remaining set of models to make predictions
 - If you have chance to iterate, then collect more data that can reduce the number of models under consideration, and thereby reduce uncertainty.

How to characterize uncertainty from alternative PBPK and statistical models [i.e., structure differences]?

- Suggestion for future workshop
 - Potential value in comparison with non-PBPK (e.g., classical PK, empirical, or non-parametric approaches) models
 - looking at uncertainty in relative terms and (hopefully) demonstrating progress in reducing uncertainty.

How to provide feedback to data needs and experimental design?

- Current practices have been more intuitive, less formal methods of feedback to data needs and experimental designs
- Sensitivity analysis identifies the parameters of interest, and can be used for preliminary/informal feedback to data needs.

How to provide feedback to data needs and experimental design?

- Optimal design
 - Incorporates identification of data and experimental design that will most efficiently inform those parameters.
 - Also, can design optimal experiments to distinguish between models.

How to provide feedback to data needs and experimental design?

- Repositories of data and models could help make this more efficient.
 - Being considered in EPA/NCCT.
 - Journals, journal editors need to assist
 - places to deposit data
 - recommendations (requirements?) as to what should be archived.

Comments contributed through
e-mail after the meeting

- If we need to take into account variability in the (physiological) model parameters, we need to know more about the way in which these parameters are co-variable.
- Further consideration should be given to the proposed audience for the report; is it intended to be of interest only to the risk assessment community, or of relevance to a wider audience, i.e. the pharmaceutical industry also? If the latter, then perhaps some slight changes in emphasis would be appropriate.

- Regarding comparison of PBPK with non-PBPK approaches (e.g., classical PK, empirical, or non-parametric) as a benchmark. How can one compare an empirical model output to a PBPK model output? What criteria will be used to determine how good a PBPK model is relative to some other 'benchmark'? Empirical models nearly always fit the data perfectly because they are data based. With PBPK models we are first of all interested in the qualitative behaviour of model output. The question is within how many standard deviations of the mean data is a good prediction?

- There should be a little more emphasis on tailoring the approach according to the question that the modelling is seeking to address.

- A cautionary note about using a model to predict far beyond the limits of the data used to estimate the parameters. In particular with respect to slide 13, you don't always know that the data you have is not directly informative on the estimation of a particular parameter. We are working right now with some simulated data sets and have run across a parameter that seemed to be estimable for each of 1,000 simulated data sets with reasonable looking estimates. Although these estimates were quite wrong most of the time, prediction using the model with the incorrect parameter estimates was not affected as long as our predictions were made (in this case) over the same time intervals as our observations. That is, the 'wrongness' of the parameter estimates was neither noticeable nor important within those time intervals. Trying to predict far beyond those time intervals (where observations would have been more directly informative), produced wrong answers.

- When we are using PBPK models to predict we are by definition moving into an area where we have no data and may never be able to get data so all our suggestions to gather more data to improve the model (slides 17 & 19) are meaningless. I found many colleagues had the concept that if only they could get the "correct" model then most problems would disappear. Clearly without data in the area of interest we cannot be sure what the correct model there is and there may not be a single model to suit all individuals and or occasions.
- I think we need more radical thoughts about dealing with model uncertainty. How can we with our limited computing capacity deal with the whole population of models or even a random selection of models to assess goodness of fit to the data we have and uncertainty in prediction? One approach would be to convert as much as possible into parameter uncertainty but this may simply produce a model with so many parameters that it is not tractable. We should try to work out whether variability in our area of parameter knowledge in any way
- predicts uncertainty in our realm of ignorance e.g. does variability amongst animals predict variability in man.
- Specific suggestions (to slide topics)
- slide 8 I think we need to be clearer here about what we are suggesting. How would we identify real individuals from the tail of a distribution to check their characteristics and risk?
- slide 12 we should acknowledge that we don't always know what a complete model is as we may not know the target organ in our area of uncertainty
- slide 15 I think a positive area was the suggestion about considering multiple models but should this be part of model building. A model that doesn't fit data from the rat might be the ideal one for man. Maybe we should keep data from all models considered and weight their predictions according to goodness of fit (in some way)
- slide 16 we discussed a lot the problems about not having a random selection of models. This will only preclude certain statistical assumptions about their predictions. However if we have 2 models with equally good fits to oral data but radically different predictions for inhaled data it must say something about the uncertainty of the prediction. Perhaps we need to work out what.
- slide 17 see above I am not sure we should suggest eliminating model

- I agree very much that as much a possible biological and physiological information should be included in predictions. This holds particularly for the prediction of variability in humans, where known values for the variability of influencing physiological properties and the correlations between them should be used instead of trying to determine them statistically from PK-data. Using the statistical approach we more or less waste the strength of PBPK modeling - the P in its name. All the statistical methods discussed during the workshop are in principle crutches which are needed in the case of conventional PK-modeling because there the parameters have only an indirect physiological background and can therefore not be determined independently. Moreover, particularly for the interesting case of prediction of human toxicokinetics the statistical methods are not really applicable in many cases, because they need human data, which are usually not available. The best statistical model to describe variability in rats does not help to predict human variability!