Summary - COT FSA PBPK for Regulators Workshop Report 2021

In this guide

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1. The future of food safety assessment in the UK depends on the Food Standards Agency's (FSA) adaptability and flexibility in responding to and adopting the accelerating developments in science and technology. The Tox21 approach is an example of one recent advancement in the development of alternative toxicity testing approaches and computer modelling strategies for the evaluation of hazard and exposure (New Approach Methodologies (NAMs). A key aspect is the ability to link active concentrations *in vitro* to likely concentrations *in vivo*, for which physiologically based pharmacokinetic (PBPK) modelling is ideally suited.
2. The UK FSA and the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) held an "PBPK for Regulators" workshop with multidisciplinary participation, involving delegates from

regulatory agencies, government bodies, academics, and industry. The workshop provided a platform to enable expert discussions on the application of PBPK to health risk assessment in a regulatory context.

3. Presentations covered current application of PBPK modelling in the agrochemical industry for *in vitro* to *in vivo* extrapolation (IVIVE), pharmaceutical industry for drug absorption related issues (e.g., the effect of food on drug absorption) and drug-drug interaction studies, as well as dose extrapolations to special populations (e.g., those with a specific disease state, paediatric/geriatric age groups, and different ethnicities), environmental chemical risk assessment, an overview of the current regulatory guidance and a PBPK model run-through. This enabled attendees to consider the wide potential and fitness for purpose of the application of PBPK modelling in these fields. Attendees considered applicability in the context of future food safety assessment for refining exposure assessments of chemicals with narrow margins of exposure and/or to fill data gaps from more traditional approaches (i.e., data from animal testing).
4. The overall conclusions from the workshop were as follows:

- PBPK modelling tools were applicable in the areas of use covered, and that expertise was available (though it is in small numbers).
- PBPK modelling offers opportunities to address questions for compounds that are otherwise not possible (e.g., considerations of human variability in kinetics) and allows identification of “at risk” subpopulations.
- The use of PBPK modelling tends to be applied on a case-by-case basis and there appears to be a barrier to widespread acceptance amongst regulatory bodies due to the lack of available in-house expertise (apart from some medical and environmental agencies such as the European Medicines Agency, United States Food and Drug Administration, and the US Environmental Protection Agency, respectively).
- Familiarisation and further training opportunities on the application of PBPK modelling using real world case studies would help in generating interest and developing more experts in the field, as well as furthering acceptance.
- In a regulatory context, establishing fitness for purpose for the use of PBPK models requires transparent discussion between regulatory agencies, government bodies, academics, and industry and the development of a harmonised guidance such as by the Organisation for Economic Co-operation and Development (OECD) would provide a starting point.
- Finally, PBPK modelling is part of the wider “new approach methodologies” for risk assessment, and there should be particular emphasis in modelling both toxicodynamics and toxicokinetics.