Background - COT FSA PBPK for Regulators Workshop Report 2021

In this guide

5. In 2003, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) hosted a workshop on physiologically based pharmacokinetic (PBPK) modelling. The presentations considered the use of PBPK models in risk assessment, and the requirements to allow their incorporation in risk assessment. The presentations were followed by a general discussion which focused on the strengths and weaknesses of PBPK modelling, whether PBPK models could be integrated into risk assessments conducted by the COT, and how this might be achieved (COT TOX/2003/40).

6. A COT statement on PBPK modelling was published in 2003, where the COT considered PBPK modelling to be an established technique capable of predicting the *in vivo* behaviour of chemicals. PBPK modelling was widely used in the development and risk assessment of pharmaceutical products, where there were

often sufficient human data available with which to validate the models. However, for many chemicals evaluated by COT, it was noted that there are limited or no human pharmacokinetic data available that can be used for model validation. Members expressed their reservations in assessing a PBPK model that had not been validated in this way.

7. Furthermore, the COT considered that animal data can provide partial validation if it can be assumed, or there is evidence, that the chemical behaves similarly in animals and humans. Additionally, validation could be enhanced by mechanistic studies in experimental animals that show human relevance. However, there would be less confidence in the predictions of such models, and this would need to be expressed as a source of greater uncertainty in the risk assessment.

8. The Committee concluded that it would not be feasible to undertake PBPK modelling routinely for COT risk assessments because the generation and validation of a PBPK model was resource and time intensive. However, the COT agreed that relevant published PBPK models should be incorporated into risk assessments, when possible, for example when submitted to support a risk assessment by industry.

9. In 2007, the COT held an open workshop on "Evolving Approaches to Chemical Risk Assessment". A statement was published that summarises the presentations and Committee's discussions. PBPK models were briefly discussed as part of the presentation on exploring uncertainty using sensitivity analysis.

10. The COT's overall conclusions were as follows: the need to assess and describe the uncertainty in the available data, the use of more transparent and reproducible methods (e.g. framework approaches and systematic rather than narrative reviews) more explicitly.

11. Additionally, new technologies should be adopted with caution, and only implemented if they offer a clear benefit in terms of improving the risk assessments by the Committee. Although, where appropriate, NAMs should be initially performed in parallel with existing methods, allowing for further investigation of divergent outcomes.

12. In 2009, the COT held a workshop on 21st century toxicology. The workshop addressed the US National Academy of Sciences report entitled "Toxicity Testing in the 21st Century: A Vision and a Strategy". A statement was published where the COT welcomed the systematic approach of the strategy for the use of *in vitro*

and *in silico* approaches to better understand toxicity.

13. Since it has now been almost 20 years since the COT workshop on PBPK modelling, Members thought it would be timely to revisit the topic once again in order to review advances in the approach for use in a regulatory context.