UK Food Standards Agency (FSA) requirement for PBPK modelling - 2021

In this guide

14. PBPK models are mathematical models that simulate the pharmacokinetic behaviour (absorption, distribution, metabolism and excretion) of chemicals in the different tissues in the body, based on physiological, anatomical, biochemical and physicochemical parameters. They are an essential aspect in alternative toxicity testing and computer modelling strategies for the evaluation of chemical hazard and exposure, as they offer a means of linking active concentrations *in vitro* to likely concentrations *in vivo*. The use of *in silico* tools such as PBPK models also reduces the need to perform animal testing.

15. The UK FSA are exploring ways for more accurate internal exposure estimation to aid in refining risk assessments. The use of PBPK modelling offers

an opportunity to address questions for environmental chemicals, novel foods, and food contaminants that are otherwise not possible (e.g., human variability in kinetics).

COT Discussions

16. In 2019, the COT reviewed PBPK modelling used for human health risk assessment (TOX/2019/34). The discussion of the Committee focused on ways to assess the reliability of human PBPK models in the absence of human pharmacokinetic data. Approaches that were considered to assess model reliability in this context included the use of the read-across approach and conducting interspecies extrapolations to animal species other than humans. The Committee agreed that it would be useful to have further information in the form of case studies, where *in vitro* data had been successfully extrapolated to *in vivo*, or cases where risk assessments considered in retrospect may have benefitted from PBPK modelling.

17. A follow-up paper (TOX/2019/73) was then presented in response to this request. The paper summarised a number of PBPK case studies that have been used in risk assessment (PFOS & PFOA, dioxins, bisphenol A, acrylamide & glycidamide, chloroform & carbon tetrachloride, vinyl acetate, methylene chloride, and vinyl chloride), in addition to cases where *in vitro* to *in vivo* extrapolation has been conducted (PFOS, triclosan, pyridaben & fluazinam, estragole, and trichloroethylene). Furthermore, examples involving 2-butoxyethanol, persistent organic pollutants, amphetamine analogues and electronic nicotine (and non-nicotine) delivery systems devices were described where the use of PBPK modelling may have facilitated their risk assessment.

18. The Committee noted that PBPK models have predominantly been developed and applied on a case-by-case basis, for example to assess exposures of chemicals with narrow margins of exposure or to fill in data gaps from more conventional approaches.

19. The Committee recognised that PBPK modelling is of current interest to regulators in the field of chemical risk assessment; however, it is still largely used more in research capacities to refine estimates of health risk. PBPK models are not routinely applied or assessed by regulatory bodies because they are generally complex and both labour and data intensive, for example in terms of the data required for model parameterisation.

20. Whilst there are a multitude of case specific PBPK models, systems are now being developed to enable generic PBPK models to be generated. Software platforms such as these may be used in conjunction with the read-across approach to assess human health risks without the need for animal testing.

21. In March 2020, the FSA COT held a workshop entitled “Exploring Dose Response” which was attended by scientists from regulatory agencies, government bodies, academia, and industry. The workshop provided a platform from which to address and enable expert discussions on the latest *in silico* prediction models, new approach methodologies, PBPK modelling, future methodologies, integrated approaches to testing and assessment, as well as validation of methodology. Several case studies involving plastic particles, polymers, tropane alkaloids, and selective androgen receptor modulators were used to explore approaches fit for purpose in the context of future food safety assessment. Furthermore, possible future research initiatives were discussed, such as establishing points of departures using new approach methodologies models and improving use of exposure metrics in risk assessment.

22. The key issues identified in respect to PBPK models would be further developed through the current workshop.