Report by Rachel Bowsher

Introduction

The British Toxicology Society held its 2023 Congress in Birmingham providing an invaluable insight into the current toxicology research. It was a great opportunity to discuss research and network with other toxicologists from industry, academia and the government. I thoroughly enjoyed the variety of symposium topics ranging from nano-particle toxicology through to regulatory toxicology. I also attended the Continuing Education Programme and the Network for Early-Stage Toxicologists networking session. Both enabled me to meet other early-stage toxicologists and learn more about toxicology across a broad range of sectors. Dose-response and threshold values were recurring discussions throughout Congress as these are essential for risk assessments and to help to determine the doses utilised in exposure studies. Symposium 1 contained various talks detailing important factors to consider.

Symposium 1: Dose-response relationships in chemical risk assessment – is there a new paradigm shift

The first seminar "New application of dose-response analysis: deriving relative potencies for mixture risk assessment" was by Dr Bas Bokkers from RIVM, the Dutch National Institute for Public Health and the Environment. This talk focussed on benchmark dose analysis and associating this to probabilistic human exposure assessments, risk assessments and hazard characterisation. It was highlighted that risk assessments for mixtures are complex and may require different approaches due to the potential effects that can accumulate and therefore alter the mode of action, toxicity effect(s) or the target(s). Factors to consider for individual components within a mixture or in a mixture of a known composition, include the hazard index, targets and relative potency factor (RPF). The RPF refers to the ability of a test sample of unknown potency to produce a response to a reference sample under the same conditions. Therefore, the RPF can be influenced by other factors so data with the same or similar protocols are preferred to limit this as much as possible. Parallel dose-response curves are essential for deriving RPFs as the curve, shape and scale of a dose response model can determine the different parameters. It is also important to note that external RPFs are not the same as internal RPFs.

The next seminar "Non-monotonic dose-responses – state of the art" was by Dr Alan Boobis OBE from the National Heart and Lung Institute at Imperial College London. Non-monotonic dose-response refers to when a dose-response curve changes sign during the range of doses examined. This can happen for many reasons including a different response occurred with an opposing effect, there may be more than one adverse outcome pathway (AOP), the response could be adaptive, there may be an atypical concurrent control, or biological variation within/between studies. Whilst non-monotonic dose-relationships can be common in high doses, in low doses it is much less common and usually indicative of immediate or upstream effects. This can cause a lack of empirical interpretation for dose-responses and demonstrates the need to understand the biological mechanisms responsible with more than one AOP usually involved with differing dose-response relationships. It is essential that the correct dose range of concern is determined for human exposures.

The third seminar "Thresholds for genotoxicity" was presented by Prof Gareth Jenkins from the Medical School at Swansea University. A lack of data in the field has previously led to a poor understanding and controversies but new *in vitro* data supports threshold responses with the same expected *in vivo* for DNA reactive genotoxins. Currently regulation prefers the linear no-threshold model which assumes there is no safe exposure level so is precautionary and a 'one hit target'. However, regulators are moving towards a genotoxic threshold if the data is available. Currently

accumulating data is accepted on a case-by-case basis and understanding the mechanisms involved is vital for plausibility and regulatory acceptance.

The final seminar in this symposium “Endocrine disruptors: Is a threshold approach justified?” was by Dr Christopher Borgert from the Applied Pharmacology & Toxicology Inc. An endocrine disruptor is defined as a chemical that produces adverse effects as a consequence of an endocrine mode of action (MOA) and a threshold is the limit below which a stimulus causes no reaction. Therefore it is important to consider both the threshold for adverse effects and the threshold for endocrine mode of action. It was highlighted that the fraction of endocrine effector macromolecules occupied by endogenous metabolic milieu and the relative potencies of all competing ligands should be considered when identifying endocrine disrupting chemicals. A potency threshold approach for this is justified and required to scientifically defend the identification of endocrine disrupting chemicals.

Conclusion

This symposium highlights the importance of threshold values and understanding mechanistic toxicity to ensure that dose-responses are being interpreted correctly for both regulatory toxicology and exposure studies. In summary, the entire BTS Congress program has enabled me to gain a wealth of knowledge and I am very grateful to have attended. I look forward to attending and presenting more research at future BTS Congress’.