

***Training Workshop on “Evaluating the Human Relevance of Modes of Action in Animals and Chemical Specific Adjustment Factors”***

The McLaughlin Centre for Population Health Risk Assessment of the University of Ottawa, in collaboration with the ILSI Research Foundation, and scientists from the U.S. Environmental Protection Agency, held a training workshop on February 18<sup>th</sup> to 19<sup>th</sup> entitled ***“Evaluating the Human Relevance of Modes of Action in Animals and Chemical Specific Adjustment Factors”***. Approximately 45 participants attended from government and academia.

This workshop illustrated application of a Human Relevance Framework that has been in development for a number of years under the auspices of the International Programme on Chemical Safety/WHO (IPCS) and the International Life Sciences Institute Risk Science Institute (ILSI) (Meek et al., 2008). The IPCS/ILSI Human Relevance framework starts with the concept that for a given adverse response (tumors, malformations, neurotoxicity, etc) produced by a compound in laboratory animals, it is sometimes possible to establish a series of key events that are along a causal path. Involvement of the key events in the mode of action (MOA) is established in a weight of evidence approach taking into account factors such as dose-response and temporal concordance, biological plausibility, coherence and consistency. Once an MOA is established, qualitative and quantitative comparison of each key event between the experimental animal and humans enables a conclusion as to likely relevance of the MOA for humans. Insight gained from this analysis can be invaluable in the risk assessment process informing selection of the most appropriate approaches to extrapolation of dose response between species and within humans. The Framework is an analytical tool that enables greater transparency, identification of key missing data and helps ensure consistency in evaluations.

The course featured opening remarks by Professor Daniel Krewski, Director of the McLaughlin Centre, on “Toxicity Testing in the 21<sup>st</sup> Century: A Vision and A Strategy” (National Research Council, 2007). Dr. Krewski highlighted the need for more efficient and relevant toxicity testing based on mode of action to better inform risk assessment. Following Dr. Krewski’s presentation, Dr. Jennifer Seed (US EPA, Office of Pollution Prevention and Toxics) provided an overview of the Human Relevance Framework, indicating its utility in increasing transparency in risk assessment and increasing the relevance of chemical specific research. Dr. Douglas Wolf (US EPA, Office of Research and Development) presented a case study on disruption of thyroid homeostasis to illustrate how to apply the framework approach to evaluate the human relevance of thyroid tumors and neurodevelopmental outcomes. The workshop continued with interactive case studies in which participants were divided into small groups facilitated by Bette Meek (McLaughlin Centre, University of Ottawa on interchange from Health Canada) and Dr. Kevin Crofton (US EPA, Office of Research and Development), in addition to Drs. Seed and Wolf.

Participants were given toxicological information and data on hypothetical chemicals and asked to work through the framework and come to conclusions concerning: whether there was enough information to establish a mode of action

in animals, whether there were qualitative or quantitative species differences between the animal mode of action and humans, and lastly whether there were any susceptible population issues that might impact the use of the mode of action in humans.

The course continued the next day with a plenary tutorial given by Bette Meek on chemical specific adjustment factors (CSAF) including examples of their development for kinetic and dynamic components for interspecies differences and human variability, followed by illustration through a case example of the relationship between mode of action and CSAF. The relationship between the mode of action/human relevance framework and evolving toxicity testing strategies to incorporate more mechanistic data and initiatives to improve methodology in dose-response assessment was also illustrated.

This workshop is the thirteenth in a series of training workshops on the IPCS/ILSI Human Relevance Framework and/or chemical specific adjustment factors with similar courses and/or workshops having been held in the U.S., Europe, Asia and Australia.

#### References

*Meek, M.E. (2008) Recent Developments in Frameworks to Consider Human Relevance of Hypothesized Modes of Action for Tumours in Animals. Environmental and Molecular Mutagenesis 49:(2) 110-116.*

*Meek, B. and Renwick, A. (2006) Guidance for the development of chemical specific adjustment factors - Integration with mode of action frameworks. Toxicokinetics and Risk Assessment, Ed. Lipscomb, J.C. and Ohanian, E.V., Informa Healthcare, New York, N.Y.*

*National Research Council. (2007). Toxicity Testing in the 21<sup>st</sup> Century: A Vision and A Strategy. Washington, D.C.: National Academy Press.*