

**McLaughlin Centre for Population Health Risk Assessment,
University of Ottawa, University of Surrey, U.K. Health and Safety
Laboratory)**

**EVALUATING THE HUMAN RELEVANCE OF MODES OF ACTION IN ANIMALS (in
collaboration with the ILSI Research Foundation)
INTRODUCTION TO PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK)
MODELS
REPLACING DEFAULT UNCERTAINTY FACTORS WITH DATA DERIVED VALUES
(in collaboration with the International Programme on Chemical Safety)**

**January 17th – 19th, 2011
University of Surrey, U.K.**

Facilitators: Bette Meek, University of Ottawa, Jennifer Seed, US Environmental Protection Agency, Douglas Wolf, US Environmental Protection Agency, Kevin Crofton, U.S. Environmental Protection Agency, George Loizou, UK Health and Safety Laboratory

This course presents a systematic approach to characterizing the mode(s) of action (MOA) of toxicants and will give participants “hands-on” experience in the application of a framework for evaluating the relevance of modes of action/key events in assessing human risk, including integration of evolving genomic data. Opening tutorial presentations introduce workshop participants to basic concepts and walk them through a model case study. This leads into facilitated interactive case studies in which participants analyze examples involving “real world” chemicals.

This sets the scene for an introduction to fundamental concepts underlying physiologically based pharmacokinetic (PBPK) modeling. This includes introductory presentations and hands on sessions, with examples of data modeling using state of the science software.

Agenda

Day 1

- 9:00 Welcome/Introductions/Outline
- 9:15 Tutorial: Mode of Action in Animals and Humans
Basic concepts, framework for assessing mode of action (MOA) in animals, key events, weight of evidence, human relevance framework, kinetic and dynamic factors
- 10:00 Model Case Study: Thyroid Disruption
Step-wise application of each element of the human relevance framework, cancer and non-cancer effects, use of data, concordance analysis, assumptions
- 10:45 Discussion & Background for Break-out Groups
- 11:00 ***BREAK***
- 11:15 Interactive Case Studies (in break-out groups)
Facilitated exploration of a series of chemicals, based on summaries of published data, working in

small breakout groups

Framework Question 1 – Is the weight of evidence sufficient to establish the MOA in animals?

Case study for Chemical M illustrating the process and the range of data available to support the determination of MOA in animals

12:30 **LUNCH**

1:30 Report out and discussion in plenary

Reports from each Breakout Group, with discussion.

14.15 Breakout Group work on Chemical C (Coffee break around 15:15).

Framework Question 1 – Is the weight of evidence sufficient to establish the MOA in animals?

Framework Question 2 – Can human relevance of the MOA be reasonably excluded on the basis of fundamental qualitative differences in key events between animals and humans?

Framework Question 3 – Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between animals and humans?

Case study illustrating the evaluation of the weight of evidence for key events in animals and humans and comparative kinetics and dynamics.

17:00 End of Day

Day 2

9:00 Introduction to Day 2 (announcements, if necessary)

9:10 Breakout groups report out and discussion in plenary on Chemical C

10:00 Mode of Action and Dose-Response; Incorporating Data from Evolving Testing Technologies

10:30 **BREAK**

11:00 Introductory Toxicokinetics

12:00 Chemical Specific Adjustment Factors

Framework for subdividing default factors for interspecies differences and human variability to address chemical specific kinetic and dynamic data, guidance for adequacy of data to replace default, examples.

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1:00 **LUNCH**

2:00 Chemical Specific Adjustment Factors (cont'd)

Exercise

Extension to Dose-Response for Chemical C

2:30 Review of the Model Case Study and Additional Examples – Dose/Response

This involves a review of the mode of action/dose response analysis for Chemical C and associated, more complex variants of the case.

3:00 **BREAK**

4:00 Future Directions

An overview of a number of current and future risk assessment methodology projects pertinent to the incorporation of good assessment practice and evolving tools in regulatory risk assessments will be provided. Implications for toxicity testing will also be addressed.

4:45 Discussion and Feedback

5:00 Close

Day 3

9:00 Introduction to Day 3 (announcements, if necessary)

9:10 Introduction to PBPK Modelling

10:30 **BREAK**

11:00 Introduction to hands-on session

11:15 Hands-on session 1

Construction of a PBPK model from a peer reviewed paper using model equation generator

- Visualisation and analysis of PBPK model using Berkeley Madonna[®] software
- Model evaluation
- Use of PBPK modeling as a research tool
- Rudimentary sensitivity analysis

1:00 **LUNCH**

2:00 Hands-on session 2

Simulation of a repeated dose chronic bioassay

- Estimation of a dose metric

3:00 **BREAK**

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- 3:30 Interspecies extrapolation
- Estimation of human equivalent concentrations
- 4:45 Discussion and Feedback/Wrap Up
- 5:00 Close