



HESI

ILSI Health and Environmental Sciences Institute

**DEVELOPMENT OF METHODS FOR A TIERED APPROACH TO ASSESS
BIOACCUMULATION OF CHEMICALS SUBCOMMITTEE
IN VITRO ADME WORKSHOP
MARCH 3-4, 2006**

Breakout Session III: Interspecies Extrapolation

Goals of the session:

Review current methodology for in vitro – in vivo scaling and interspecies extrapolation of biotransformation and other toxicokinetic data relevant to bioaccumulation. Identify the best approaches for fish that are currently available and important knowledge gaps.

Key questions for the session:

What is the primary goal of metabolic prediction with regard to bioaccumulation: restrict prediction to initial metabolism *or* prediction of all reasonable phase I and phase II metabolites?

What do we want to scale / extrapolate?

- Intrinsic metabolic clearance (V_{\max}/K_m ratio)
- Total hepatic clearance (CL_h)
- Whole body metabolic clearance (CL_m)
- BCF / BAF (after adjustment for biotransformation)

How best to utilize existing mammalian data?

- In-silico systems to predict metabolism in fish:
 - knowledge-based / expert systems
 - structure–metabolism relationships

Prediction of bioaccumulation

Can a simplified expert system be developed to interpret mammalian data towards fishes be effectively used to predict bioaccumulation?

Is it feasible and/or useful to develop a fish based conceptual framework for substrate selectivity to rank substrates according to their relative rate of biotransformation by a specific enzyme for a specific reaction, in a defined organ or tissue group?

Are more empirical approaches more realistic / better suited for fish extrapolation?

- Crop grouping:
 - Arbitrarily group species based on similarities in physiology and drug metabolism

Can a few surrogate fish species be used for in vitro studies and adequately characterize the extremes of metabolism in fish?

If so, which fishes are most appropriate as surrogates?

Key outcomes of the session:

Identify and prioritize specific research needs to improve the use of in vitro metabolism and bioavailability data for interspecies extrapolation of bioaccumulation in fish.