HESI

ILSI Health and Environmental Sciences Institute

Thought starter for Integrated Testing Strategies related to Bioaccumulation (B)
Based on ILSI-HESI and SETAC-NA / -Europe presentations (2004-2006)

These are the basic HESI-SETAC 'B' network messages:

1. We experts can help most by identifying a) what tools (e.g., cut-off values, models, tests) and qualifiers are helpful for assessors to use today to produce accurate B assessments and b) areas where flexibility in implementation is advisable to account for current concepts and new tools that should become available in 1-5 years as this field grows (e.g., in alternative testing methods).
2. Assessment processes need to be practical: conducting hundreds of OECD 305 BCF tests in 10 years is very unlikely due to the small number of contract labs doing these tests, the high cost of these tests, and pressure from animal welfare groups to reduce *in vivo* testing. Multiple computer models and test alternatives (e.g., *in vitro*) need to be allowed in some way so regulatory timings and valid information demands can be met. This is the case globally.
3. Bioaccumulation is not a simple hydrophobicity driven process; it results from ADME processes which should be considered in assessments of diverse chemical classes.

Below is a running list of models and assays that could be considered in tiered approach schemes for B assessment that the HESI-SETAC participants have used or are developing. References are generally available, but not included in the thought starter for simplicity:

Lowest Tier: We know nothing about the chemical

a) Cut-off values for chemicals with very high or very low Kow, large mol size, highly charged, highly metabolized by mammals & fish (Mekenyan et. al., De Wolf et. al.)

b) BCF, BAF, BSAF data for analogs within the chemical class (HESI B data sources manuscript, Weisbrod et. al.)

c) phys-chem analyses for Kow; use measured not predicted Kow in B models

d) BCF, BAF, BSAF models predictions for chemical

- use weight of evidence from several models to estimate B - not just one model - and models are appropriately used within chemical applicability domain (e.g., SRC BCFWIN, Mekenyan POPs, Gobas BCF, 2 TGD equations, Bonnell food web, Tarazona BAF, Nichols PBPK B model)

e) ADME information to evaluate the reliability of B model predictions, especially if they must be used for chemicals outside domain of applicability

- literature searches for existing fish & mammal data on membrane permeability and biotransformation within the chemical class
- predictions by ADME models developed for mammals and used for high through-put screening of these properties by pharmaceutical industry (e.g., ADMET for permeability potential, METEOR for metabolism potential)

Mid tier: Low tier indicates chemical could be absorbed and stored

Integrate HESI in vitro research tools, gaps & decision tree manuscript (Erhardt, Nichols, Plotzke, et. al.)

a) in vitro methods to evaluate absorption/bioavailability

- Caco2, PLHC-1, and other cell line assays to indicate permeability in specific tissues (e.g., ME Dowty et. al., M Moore & L Vasiluk)
- Semi-permeable membrane devices (SPMD) to indicate uptake potential (e.g., JH Kwon et. al., R Heltsley et. al.)
- bioaccumulation tests with aquatic invertebrates to indicate uptake potential for vertebrates (L Schuler et. al., Gunnarsson et. al.)

b) in vitro methods to evaluate metabolism

- fish or mammal liver S9, microsome, homogenate subcellular fractions to assess low or high metabolic capability (S Erhardt et. al., L Burkhard et. al.)
- fish perfused liver & GI (K Kleinow & M James)

c) in vitro methods to evaluate cell accumulation

- fish hepatocyte or other cellular cultures to examine accumulation and result in cells (S Dyer & JP Cravedi)

d) techniques to translate in vitro results into in vivo B predictions (J Nichols et. al., Cowan-Ellsberry et. al.)

High tier: Low and mid tier indicate chemical might be 'B'

a) Modified in vivo methods - Less slow, less resource intensive (<$70,000)

- cannulated fish to measure ADME rates (D Huggett et. al.)
- modified OECD 305 test, single concentration for exposure (not 2) (Woodburn et. al.)
- modified OECD 305 test, uptake OR depuration measurements only to calculate BCF (Woodburn & Springer),

- modified OECD 305 test, with shorter duration of uptake & depuration for biotransformable organics - kinetic measurements to calculate BCF (W Bishop & A Maki)
- BAF via exposure through food, and ability to test mixtures (Parkerton et. al.)
- Uptake & depuration rates for invertebrates (Schuler et. al.)
- Critical body burden limit test (Clairant paper?)

b) Standard in vivo methods - Slow, resource intensive (~$125,000)

- OECD 305 Bioconcentration in Fish (1995)
  - HESI BCF study quality criteria manuscript (Parkerton et. al.)
- METI Bioconcentration Study with Medaka (1974, amended 1998)
- ASTM E1688-00 Bioaccumulation by Benthic Invertebrates (2000) - produces BSAF
- There are no standard tests for BAF to account for exposure through food (Parkerton et. al. could fill that gap)

Highest Tier: Field monitoring (little HESI-SETAC work in this area, so far)
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