BUILDING IMPROVED IN-VITRO EXPOSURE ASSESSMENT CAPABILITY: TOWARDS THE DEVELOPMENT AND IMPLEMENTATION OF ENHANCED QIVIVE TOOLS

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SUMMARY OF TOOLS AND CHALLENGES

**in vitro**
- Hazard based bioassays
- Modelling tools

**in vivo**
- Clinical studies
- PBPK modelling
- ADME / TK/TD models
LINKING EXPOSURE AND HAZARD
ADVERSE OUTCOME PATHWAYS

- An AOP is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment.
  - Relationships among levels of organization may be causal, mechanistic, inferential, or correlation-based, and information on which they are derived may be based on in vitro, in vivo or in silico.
OECD REPORT: “THE AOP FOR SKIN SENSITIZATION INITIATED BY COVALENT BINDING TO PROTEINS”

• Key events of the AOP:

  • Penetration of the sensitizing ingredient into the viable layers of the skin
  • Modification of skin protein by the sensitizing ingredient (either directly or via metabolic or abiotic transformation of a precursor)
  • Production of danger signals and inflammatory mediators by keratinocytes, fibroblasts, and skin-resident dendritic cells
  • Maturations and migration of dendritic cells to the local lymph node
  • Antigen presentation to specific naïve T-cells, and subsequent T-cell proliferation and differentiation
  • The generation of a sufficient population of antigen-specific memory T-cells required to mediate an elicitation response at the site of re-exposure
PENETRATION OF THE SENSITIZING INGREDIENT INTO THE Viable LAYERS OF THE SKIN
PENETRATION OF THE SENSITIZING INGREDIENT INTO THE VAILABLE LAYERS OF THE SKIN

Intensive properties

Extensive properties
Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework


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Purpose of protecting ecologic and public health. Historically, exposure assessment has played a complementary role with the fields of epidemiology and toxicology, helping identify and mitigate health impacts of environmental exposures, of which lead and radon serve as good examples.

Recognizing the historical value of exposure science and recent demands to meet the growing need to conduct more comprehensive exposure assessment (thousands of stressors), more quickly and more accurately, a committee of the National...
Whereas assessing hazard based on AOPs is meant to be non-chemical specific, assessing exposure based on AEPs needs to consider the properties of the chemical.
DIFFERENTIATING BETWEEN INTENSIVE AND EXTENSIVE PROPERTIES

**Intensive**

**Chemical ingredient**
- Dipolarity / polarizability
- Sub-cooled liquid vapour pressure
- Refractive index
- Hydrogen donor / acceptor
- Molecular weight
- Molar volume
- Charge surface area

**Diffusion**
- Lipids
- Water

**Partitioning behaviour**
- $K_{ow}$
- Reversible protein binding
- Henry’s Law constant

**Reactivity**
- Aibiotic
- Metabolic transformation
- Non-reversible binding

**Toxicity**

**Basic formulation**
- Dose / % inclusion
- Surfactants
- Polymers
- Silicones

**Stabilizer**

**Emulsifier**

**Oil**

**Water**

**Physiological parameters**
- Variability in volume and thickness of corneocyte layers
- Variability in lipid bilayer volume and orientation for chemical diffusion
- Availability of enzymes for metabolic transformation / Phase 1 activation
- Nature and number of protein modifications

**Extensive**

**Skin care**

**Hair care**

**Deodorant**

Illustrative example related to the use of a consumer product with a dermal exposure route
SCOPE OF THIS SESSION

• Provide some preliminary thoughts on addressing QIVIVE
• Demonstration of cross-domain expertise to address both human and environmental exposure scenarios
  • Role of expertise within the Exposure Modelling Advisory Group
• Focus aimed at improved characterization of $C_{free}$

Ideally across the source-to-receptor continuum
MODELLING IN VITRO SYSTEMS

Uncertainties and variance
- Variable uses of chemicals in society
- Differences in exposure scenario between dermal, oral, and inhalation
- Variance in individual behaviours
- Extrapolating to different levels of biological organization
Bioavailability of organic micropollutants in cell-based bioassays

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Figure 1: Processes taken into account in the current version of the mass balance model.
ADDRESSING UNCERTAINTY IN ASSUMPTIONS USED IN QIVIVE

Uncertainties
- Partitioning
- Metabolism

Uncertainties and variance
- Variable uses of chemicals in society
- Differences in exposure scenario between dermal, oral, and inhalation
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- Extrapolating to different levels of biological organization
Examining underlying assumptions when translating in vitro bioassay results to in vivo conditions

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Addressing the uncertainties in assuming nominal concentrations based from in vitro assays are equivalent to Cblood, and implications towards assessing dose-response relationships in vivo.
THE IMPORTANCE OF DEGRADATION

Uncertainties and variance

• Variable uses of chemicals in society
• Differences in exposure scenario between dermal, oral, and inhalation
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Uncertainties

• Partitioning
• Metabolism
Getting biotransformation kinetic parameters as a bonus out of bioaccumulation experiments

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Guidance towards better understanding of in vivo biotransformation to be used to more accurately model the toxicokinetics of chemicals.
PUTTING IT ALL TOGETHER FOR USE AS A RISK ASSESSMENT TOOL

Uncertainties and variance
- Variable uses of chemicals in society
- Differences in exposure scenario between dermal, oral, and inhalation
- Variance in individual behaviours
- Extrapolating to different levels of biological organization

Uncertainties
- Partitioning
- Metabolism
Putting it all together:

• Dose-response
• Mode of Action identification and classification
• Levels of biological organization
• Primary validity and relevance of toxicity data