Summing Up the First Day: OSIRIS Third Workshop, 1 March 2010

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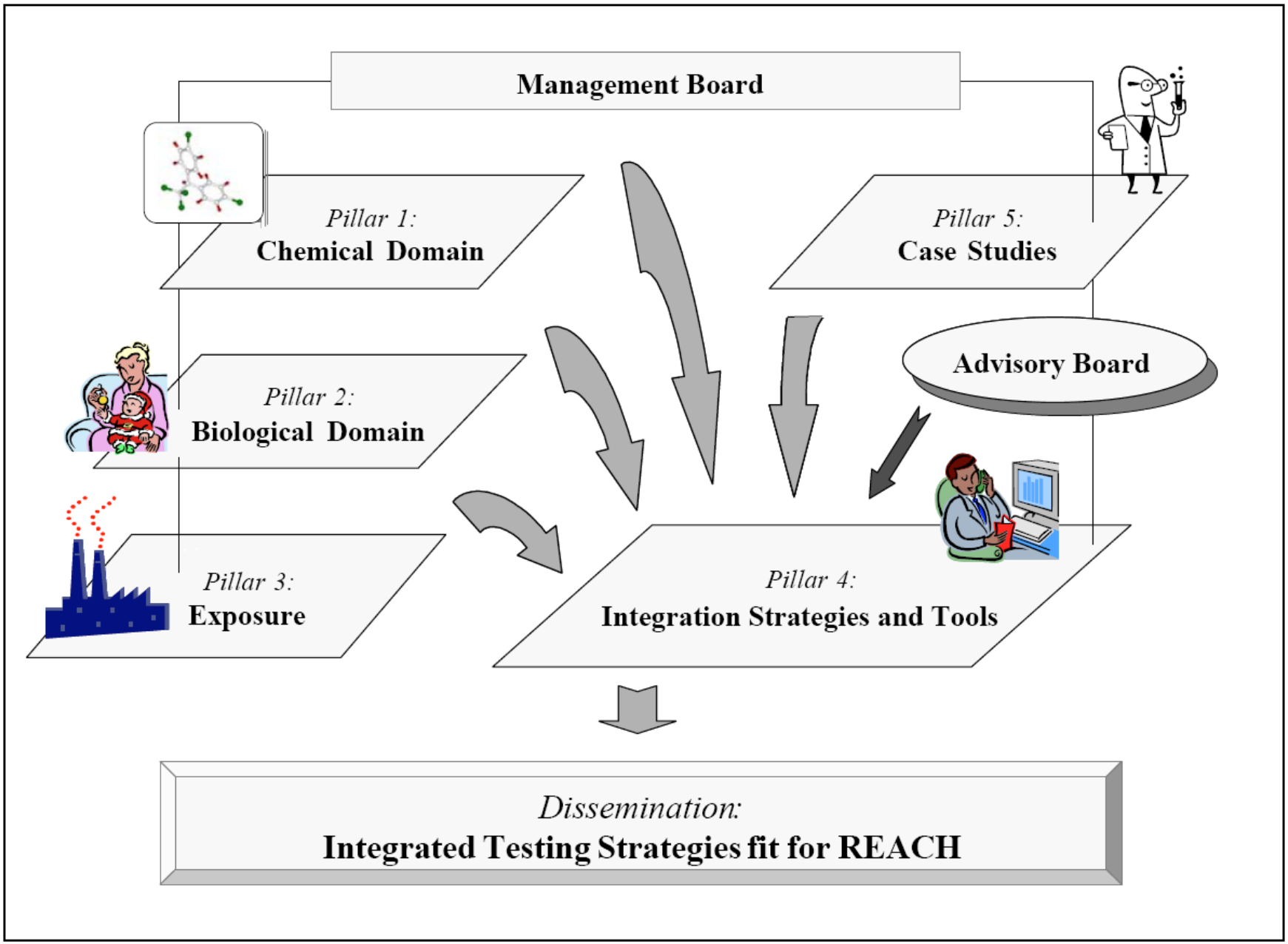
Management Board
Pillar 1:
Chemical Domain
Pillar 5:
Case Studies
Advisory Board
Pillar 2:
Biological Domain
Pillar 3:
Exposure
Pillar 4:
Integration Strategies and Tools
Dissemination:
Integrated Testing Strategies fit for REACH

In Silico Predictive Methods

- Many tools being developed:
  - Data and databases (including data quality)
  - Domain definition
  - Category formation tools
  - (Q)SARs
  - Metabolism simulator
  - Exposure
- Form “building blocks” of an ITS
- Regulatory acceptance is not yet established

Point of Concept for Web-Tool

- Clear focus and template(s) exists for ITS
- Web-tool exists for skin sensitisation, mutagenicity, BCF and aquatic toxicity
  - Continuous human health endpoint required
- TTC / EBW need to be incorporated
- Continuous endpoints vs categorical endpoints are being considered for ITS
  - Use separate Bayesian approaches "*what is the probability of X if Y….*"
  - Weight of Evidence will be used
- Process
  - Gather data – non-testing options
  - Exposure-based waiving – is TTC relevant?
  - *In vivo* testing – can tests be adapted e.g. rLLNA
- Selection of Golden Standard data is subjective

Validation of Testing Strategies

- Various (integrated) testing strategies exist
  - Top down (irritation / corrosion)
  - Bottom up (irritation / corrosion)
  - Decision tree (acute toxicity)
  - Combination of tests (*in vitro* skin sensitisation)
- Validation is required, but difficult due to the expert judgement implicit in strategies
- Validation of strategies is only starting to be considered now – although may be complex and expensive
- Given (differing) applicability domain of individual tests in an ITS, we need larger test data sets

Web-Based Tool for BCF

- Terms and definitions are required before development of an ITS
- ITS need high quality data taking account of experimental tests
  - Intra-database variability is obvious
  - What is an acceptable degree of uncertainty?
  - Validation requires further data
- Predictions include a variety of models and cut-offs
  - Cut-offs will stimulate debate
- Strategy is optimised to be over-protective – could be optimised in another direction

Web-Based Tool for BCF

- Illustrates the need to consider many factors within a strategy
- Illustrate role of assessing uncertainty of data (reliability scores → weights) and how to combine results to reduce uncertainty
- Much debate over problems and how to deal with them
  - Surface active agents
  - Calculation of log P
  - Careful definition of domain and warnings to user…

Key Features of Web Tool

- Substance management
- Study record management
- ITS management
- Endpoints
- IUCLID5 import
- WoE approach
- ORISIS database integration
- Access to Chemical Space Navigation tool
- User manual

World Cafe: Is BCF a Proper Endpoint?

- Yes, for aquatic species
- Experimental limitations e.g. solubility
- Need to consider BAF and BMF
- Need to ensure log P value etc are valid. Volatility may be an issue
- Consider test conditions and metabolites

World Cafe: Is BCF a Proper Endpoint?

- For chemical safety assessment, BCF is relevant to assess / predict “secondary poisoning” i.e. effects to top predators.
- Future developments:
  - Artificial membranes
  - Liver microsomes
  - Fish models including ADME

World Cafe: Which BCF Cut-Offs are Most Relevant

- All values are relevant as REACH have various endpoints
- 100, 500 are relevant but can be substituted by log Kow; 1000, 5000 important for PBT assessment
- Values from science, but mostly from applicability of values

World Cafe: How to Define Limits of Applicability Domain for BCF

- Domain for whole ITS... not a model domain, domains are needed for the ITS components
- Definition of applicability domain is not “concrete” yet
- Many different approaches:
  - Physico-chemical properties – ranges and cut-offs
  - Chemical classes (problems e.g. Surfactants, organometallics)
  - ADME – metabolism
  - Environmental fate (cut-offs)
- Combination of approaches may be way forward

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World Cafe: How Much Uncertainty in BCF Predictions is Acceptable

- Margins of safety may be built into cut-offs
- Cannot predict with more certainty than available for the test
- Uncertainty for experimental measurements and predictions will be substance-dependent
- … Substance that is B – not is a problem if not P !
- No consensus on levels of uncertainty i.e. 2x, 5x

World Cafe: How Much Uncertainty in BCF Predictions is Acceptable

- Uncertainty – variability or accuracy
- What is acceptable – industry or regulatory viewpoint; public perception of what is acceptable – will drive level of uncertainty
- Cost – how much does it cost if bioconcentrating
- Uncertainty relates to prediction and also what the consequence of reaching the cutoff means

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