Summing Up the Second Day: OSIRIS Third Workshop, 2 March 2010

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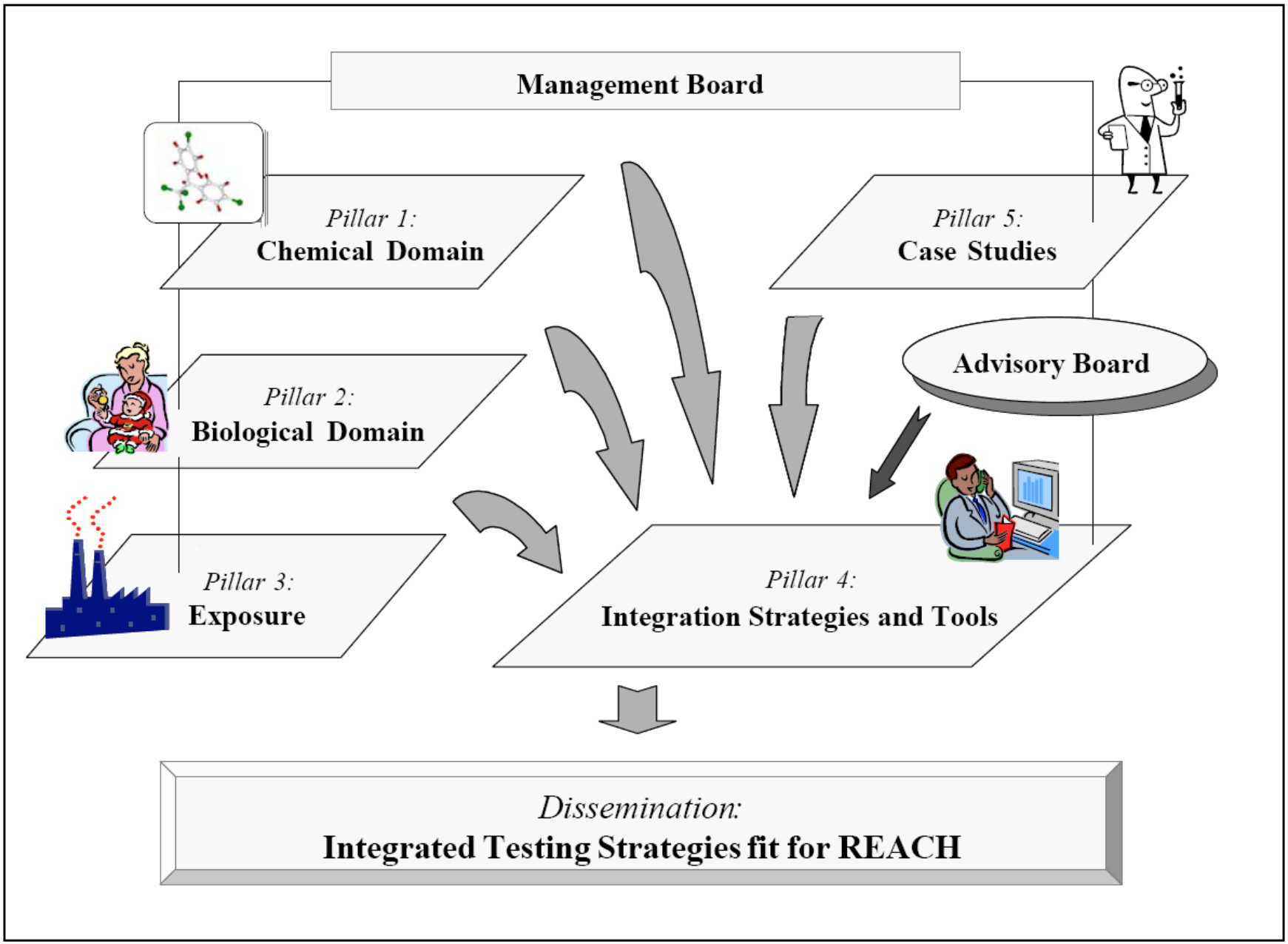
Management Board
Pillar 1:
Chemical Domain
Pillar 5:
Case Studies
Advisory Board
Pillar 2:
Biological Domain
Pillar 3:
Exposure
Pillar 4:
Integration Strategies and Tools
Dissemination:
Integrated Testing Strategies fit for REACH

BfR Decision Support System

- A tool for predicting local effects i.e. skin irritation and corrosion
- Based on confidential business information
- Strong mechanistic basis, assists in regulatory acceptance
- Predicts non-irritants as well as irritants
- Includes cut-offs and structural alerts for toxicity
- Implemented in Toxtree / OECD (Q)SAR Application Toolbox

Skin Sensitisation: *In Vitro*

- No validated *in vitro* tests are available
- *In vitro* assays for skin sensitisation should be mechanistically based
  - Immune cell migration
  - Allergen presentation in lymph node
  - Proinflammatory cytokine / chemokine release
  - T cell differentiation
  - Tissue damage
- Colipa and Sens-it-iv projects – cover the whole range of mechanisms
  - *In silico*, peptide reactivity, metabolic capacity, microarray analysis of dendritic cells, signal transduction in DC maturation etc
- DC-TC interaction (BfR CAATC assay) – dendritic cell-induced expression of lineage specific T-cell transcription factors
- Timeframe for (accelerated) acceptance – 6 years ?
- ECVAM: peptide reactivity; hCLAT; MUSST

Skin Sensitisation: *In Silico*

- Various *in silico* approaches exist
- Five approaches are used in the web-tool
- The approaches overlap but differ in terms of
  - Number and type of data
  - Mechanistic vs non-mechanistic approaches
  - Modelling philosophy
- Other approaches are available to predict skin sensitisation
- A method to integrate the predictions is required and is provided by the web-tool

Skin Sensitisation: Integrating Results with Bayesian Approaches

- Need to move to a simulation intense, data intense, explicit representation of mechanisms
- Bayesian Networks allow for causal effects etc to be retained.
- Hypotheses are developed and tested
  - Identify key parameters (i.e. Mechanistic tests)
  - Develop non-animal test methods
  - Integrate data from different test methods

Skin Sensitisation: Integrating Results with Bayesian Approaches

- Aim to Predict LLNA: non, weak, moderate, strong
- *In silico*: TIMES
- Battery of bioavailability indicators: log P, Potts and Gut, Kasting skin permeability
- *In chemico*: peptide reactivity: Lys, Cys, Luc
- *In vitro*: DC cells: IL-8, CD86
- 142 LLNA data – many missing values for "alternatives" especially, Dendritic Cells
- Bayesian network illustrates which variables are important for activity (reactivity NS, M, S; bioavailability for W)

Bayesian WoE for REACH ITS Generation

- WoE needs: defined endpoints vs alternatives
- Defined endpoint is a REACH endpoint and acts as the gold standard; determine threshold probability using a gold standard / intra-test variability / expert judgement
- Need quality factors (e.g. Klimisch-like codes) for alternatives – method performance compared to REACH endpoint / gold standard
- Posterior Probability is compared to threshold.
- Optimisation function for the test proposal
- Various implementations: Excel, Hugin, Web-tool

World Cafe: Proof of Concept

- Sensitisation may be a categorical endpoint, but also partly continuous
- Proof of Concept: if endpoint is both categorical / continuous – use both
- There is no perfect system, take note of limitations e.g. Impurities and formulations.
- Build a system for pure substances (deal with impurities / formulations separately)
- This approach is not possible for reproductive toxicity (development and fertility) as it is too complex – note relevance of ReProTect and ChemScreen EU FP projects

World Cafe: Proof of Concept

- Whilst alternatives for Repro Tox exist, for C&L – OECD test is required. However for REACH, other tests are required.
- Regulatory acceptance is required to indicate whether proof of concept is valid – what is probability / certainty threshold required by regulators.

World Cafe: Can Reduced *in Vivo* Tests be Applied?

- More reduced versions are desirable:
  - Necessary to define an applicability domain for reduced test
  - Analyse existing *in vivo* data for sensitivity
- Ideas: reduced method for dermal toxicity and tests for multiple endpoints
- Move towards “realistic” test concentrations based on exposure concentrations
- Intelligent use of OECD guidelines to implement alternatives – ITS
- Use models to help getting to reduced tests

World Cafe: Can Reduced *in Vivo* Tests be Applied?

- Could perform mechanistic studies to direct reduced *in vivo* tests
- Flexibility is required in being able to choose a suitable test – LLNA may still be required
- Data requirements will also dictate whether a reduced test can be used
- Reducing can also enhance testing via mechanistic hypothesis

World Cafe: Regulatory Approach to Uncertainty

- To require same level of probability is over-restricted
- +ve or –ve may have different levels of probability
- For continuous vs categorical – probability should not be different (although QSAR treats them differently)
- Costs / animal welfare should be taken into account
- Gold standard should be choosen using Bayesian approach not only to include LLNA but also human and GPMT.

World Cafe: Regulatory Approach to Uncertainty

- What is acceptable becomes a political issue

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