In Silico Models: Risk Assessment With Non-Testing Methods in OSIRIS – Opportunities and Limitations

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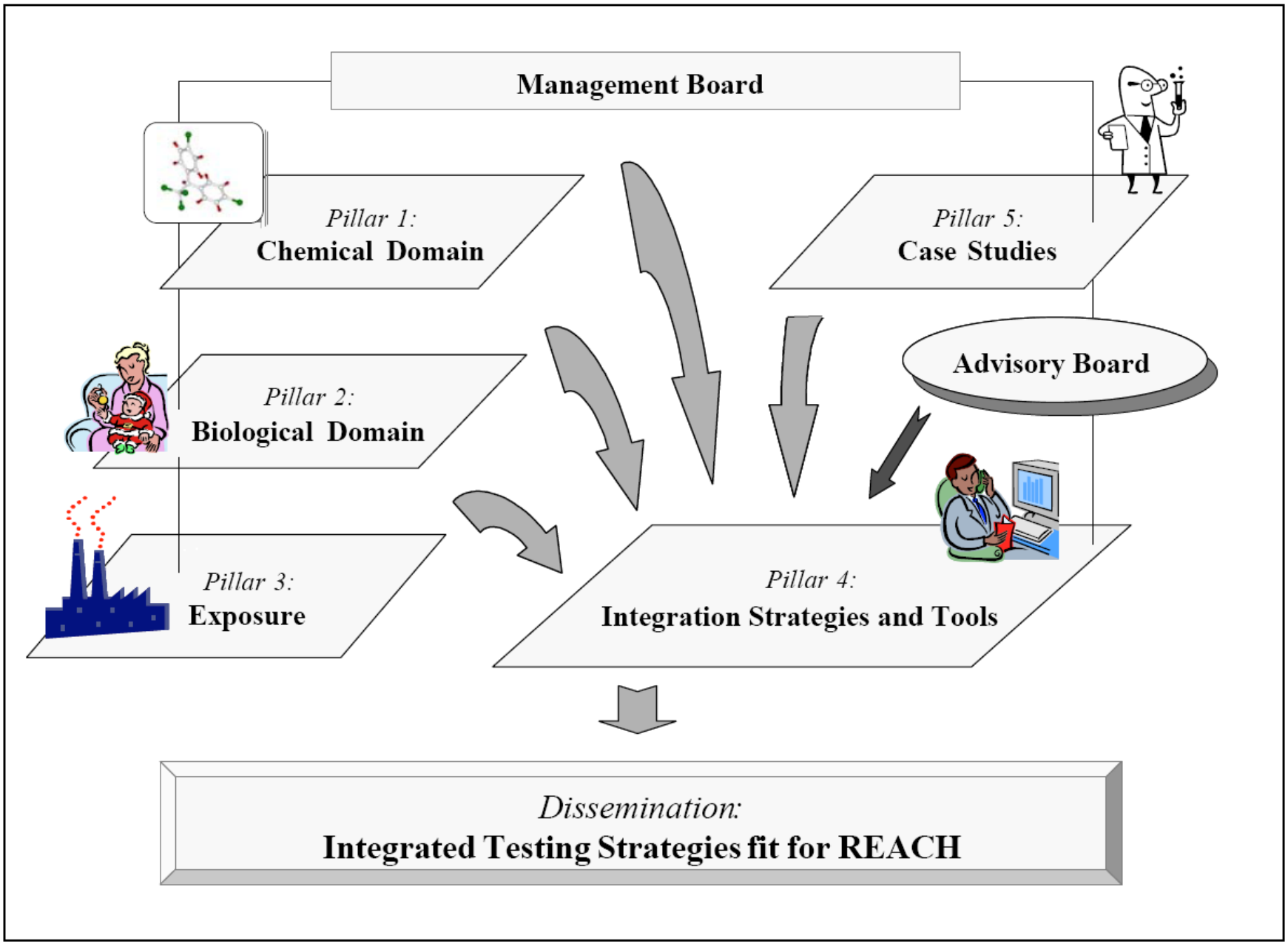

Management Board
Pillar 1:
Chemical Domain
Pillar 5:
Case Studies
Advisory Board
Pillar 2:
Biological Domain
Pillar 3:
Exposure
Pillar 4:
Integration Strategies and Tools
Dissemination:
Integrated Testing Strategies fit for REACH

In Silico Predictive Methods

- Data gathering
  - In-house
  - Public
- (Q)SAR
- Category formation
- Consensus, Weight of Evidence
- Integration

In Silico Tools are Being Developed in OSIRIS

- Pillar 1
  - Applicability domain
  - (Q)SARs
  - Data quality
- Pillar 2
  - Data compilation
  - Category formation
  - Mode and mechanism of action
- Pillar 3
  - Exposure models
- Pillar 4
  - Integration into web-tool

Criteria to Assess Data Quality

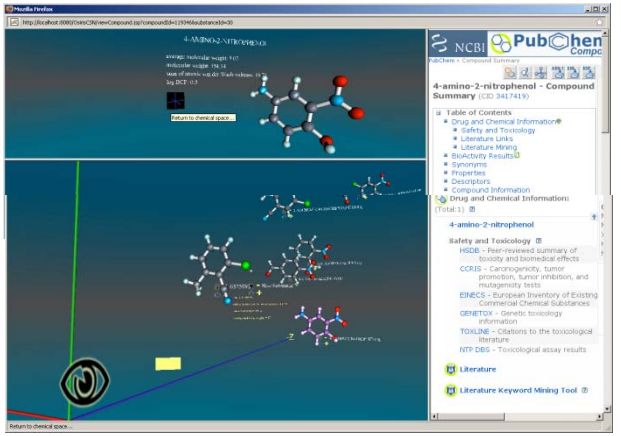
- Initial work considered how to assess quality of data from heterogenous sources
  - *In vitro*
  - *In vivo*
  - *In silico*
- Parameters including uncertainty, specificity and accuracy were investigated

Data Quality Assessment for *In Silico* Toxicology

- The assessment of data quality relates to:
  - (Eco)toxicological and physico-chemical data
  - Calculated descriptors in QSAR
  - Data integration and cost-effectiveness analysis
- Description of chemical and biological factors of data variability
- Formal data quality scoring schemes
- Checklist approaches to data quality assessment

OSIRIS Chemical and Biological Space Navigation Tool

- Designed to explore the relationship between environmental endpoints and chemical structure and physico-chemical properties



- Advanced virtual platform for visual screening of the chemical and biological space of REACH compounds
- Integration of new version into ITS web tool
- Available online

Applicability Domain Definition – Tool

- The tool will be available as the “OASIS Domain Manager”
- Applicability domain defined by methods including:
  - Atom pairs
  - Topological torsions
  - Atom centred fragments

Databases

- OSIRIS Mammalian Toxicity Database
  - Development ongoing
  - New data sources include:
    - Skin Deep Cosmetics Database
    - PAN Pesticides Database
    - Inclusion of EDETOX database possible
- E-Sovtox – toxicity data for 377 compounds
- Toxicity of substituted anilines to algae and luminescent bacteria

Development of Toxicity Database

- Contains publicly available data
  - Includes carcinogenicity, mutagenicity, skin sensitisation, endocrine disruption, reprotox, and repeat dose toxicity data
  - Updates to the ISSCAN database
  - Novel *in vivo* micronucleus database
  - Environmental toxicity
- Supplemented with data from other past/present EU projects (e.g. CAESAR)

Breath - A Database of Occupational Exposure Limits and Local Irritation

- Physicochemical features describing the intrinsic properties
- RD_{50} values for irritation
- OELs (human and animal)

- Breath will further be used to derive SAR concepts for locally irritation based on RD_{50} values, NOELs (animal and human) and OELs as surrogates for NOELs

RepDose: A Database of Repeat-Dose Toxicity Values

Study Type		Number of	
		Chemicals	Studies
All		577	1712

- http://www.fraunhofer-repdose.de/

Workshop on Modes and Mechanisms of Action (MOA)

- Agreement of definition of terms (mechanism and mode of action)
- Modes and mechanisms of action can assist in the formation of categories
- MoA classification requires criteria and data
- Use of MoA in an ITS is not a stand-alone approach but must form part of a WoE

The Use of Mechanisms and Modes of Toxic Action in Integrated Testing Strategies: The Report and Recommendations of a Workshop held as part of the European Union OSIRIS Integrated Project

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Summary This report on *The Potential of Mode of Action (MoA) Information Derived from Non-testing and Screening Methodologies to Support Informed Hazard Assessment*, resulted from a workshop organised within OSIRIS (Optimised Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-test and Test Information), a project partly funded by the EU Commission within the Sixth Framework

- Detailed findings published – Vonk JA et al (2009) *ATLA* 37:557-571

Screening Using Reactivity Parameters for MoA Classification

- Feasibility of screening investigated
- MoA data from LC_{50} values (Fathead Minnow)
- Phys-chem properties / atom-centred fragments and 3D quantum similarity classifiers assessed

- Phys-chem properties - poor classification (66%)
- Atom-centred fragments – best (81%)
- 3D information does not significantly improve classification

Read-Across to Predict Skin Sensitisation and Repeat Dose Toxicity

- Applying OECD (Q)SAR Application Toolbox for grouping of chemicals and filling data gap
- Categorising chemicals based on covalent skin protein binding properties
- Further subcategorising upon chemical similarity
- Not yet possible to perform read-across for the repeat dose toxicity because of lacking data

Read-Across to Predict Toxicity of Water Contaminants

- Read across is of regulatory importance
- Categorising chemicals based on structural similarities or mechanism of toxic action
  - OECD (Q)SAR Application Toolbox
  - Toxmatch
- Prediction the toxicity of untested chemicals
- Comparing the predicted toxicity for tested chemicals with classic test outcome

Implementation and Sensitivity Analysis of Bioaccumulation Model

- Sensitivity to partitioning coefficients (Kow and Koa) and biotransformation rates (fish and mammals) investigated.
- Predictions sensitive to partitioning only when very hydrophobic or volatile – low priority for exposure
- Fish biotransformation rate - less sensitive than mammalian – most sensitive
- Obtaining precise values of mammalian biotransformation rates crucial on determining human exposure to organic chemicals.

Implementation and Sensitivity Analysis of Models for Ionisable Compounds

- Verification of coherence and robustness of Multimedia Activity Model for Ionics (MAMI)
- Identification of the key parameters affecting the output and their ranking
- MAMI tested on 1 neutral, 4 acidic and 2 basic compounds
- Ionisation most important feature of MAMI
- Humidity increases air activity capacity of air for non-volatiles, whereas ionic strength was not significant
- Identifies most sensitive input parameters

QSARs for Hydrolysis, Photolysis and K_{oc}

- Hydrolysis:
  - New fragment model for carboxylic ester hydrolysis
  - Model outperforms available literature methods
- Photolysis:
  - MOOH approach to predict rate constants for indirect photolysis through reaction of OH radicals
  - AM1 vs. HF/6-31G** theory level
  - Increased level of theory yielded improved correlation
- K_{oc}
  - Model developed within OSIRIS
  - Additional pH-dependant experimental K_{oc} values for bases required to test sufficiently

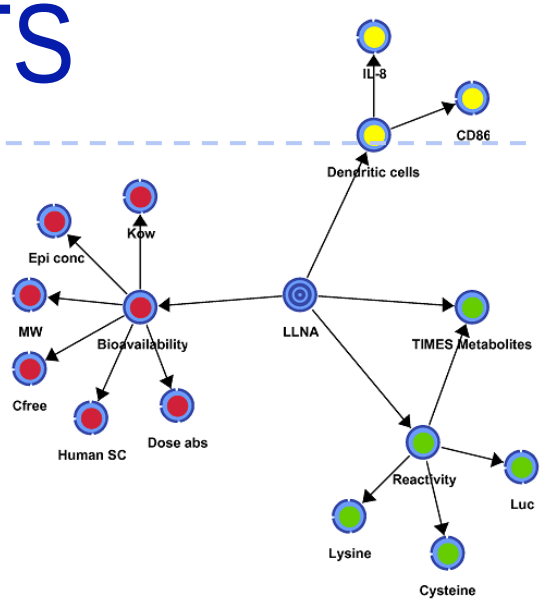
Development and Validation of Metabolic Simulator

- Simulator of metabolic fate in soil evaluated
- Data on 106 new documented metabolic pathways for 68 compounds were collected
- Sensitivity = 84%, Predictivity = 54% using the model domain approach.
- If domain is ignored, performance is significantly reduced.

Development of Exposure Models

- Exposure informed testing (exposure-based waiving)
  - Environmental (WP 3.1)
  - Human (WP 3.2)
    - Definition of probability density functions for exposure assessment
  - Internal (WP 3.3)
    - Toxicokinetic modelling
- Probabilistic exposure assessment
- Decision tree proposed for use of EBW in ITS
- New tools for EBW (D3.2.8)
  - Advanced REACH Tool (ART) for inhalation exposure assessment

Use of Bayesian Networks Within Expert-Defined ITS



- Bayesian networks can be:
  - Manually developed using expert knowledge
  - "learnt" from the data
  - Developed using a mixture of the two
- Mixed approach can optimise expert networks and deal with missing data
- Mechanistically relevant input = interpretability
- ITS for skin sensitisation developed
  - LLNA activity potential predicted from *in vitro/in chemico* and *in silico* data

ChemProp

- Integrated software platform for modelling and databases
- Calculation of QSAR descriptors and toxicities
- Data retrieval
- Assignment of mode and mechanism of action

Opportunities

- Multiple methods to predict toxicity
- Flexible approaches building on the state of the *in silico* art
- Integration with other EU projects

Limitations

- Current data availability
- Understanding of mechanisms / modes of action for complex toxicological endpoints
- Regulatory acceptance

Conclusions

- Many *in silico* approaches being developed in OSIRIS
- Weight-of-Evidence approaches will help to combine the outcomes
- The web-tool will be vital to use the *in silico* tools and the WoE

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