DAMIER – A research project for the development and application of high accuracy in-silico models for REACH

Paul THOMAS[a], Pascal BICHEREL[a], Pascal ROUSSEAUX[b], Hector OSUNA[b], Jean-Baptiste DELAFOSSE[b], Steve KENT[c], David LEJON[c], Sylvie BETAT[d], Nicolas DELPIT[d], Emmanuelle VUILLET[e]

[a] KREATiS*, 23 Rue du Creuzat, 38080 L'Isle d'abeau, France
[b] Processium, 62 Boulevard Niels Bohr, 69100 Villeurbanne, France
[c] Rovaltain Research Company, Bâtiment B, 1 Avenue de la Gare, 26300 Alixan, France
[d] Laboratoires des Pyrénées et des Landes, Rue des Écoles – 64150 Lagor, France
[e] Institut des Sciences Analytiques, 5, rue de la Doua, 69100 Villeurbanne, France

KREATiS, Knowledge & Research in Environment And Toxicology in Silico
KREATiS SAS, 23 rue du Creuzat, ZAC St Hubert, 38080 L'ISLE D'ABEAU, FRANCE
www.kreatis.eu

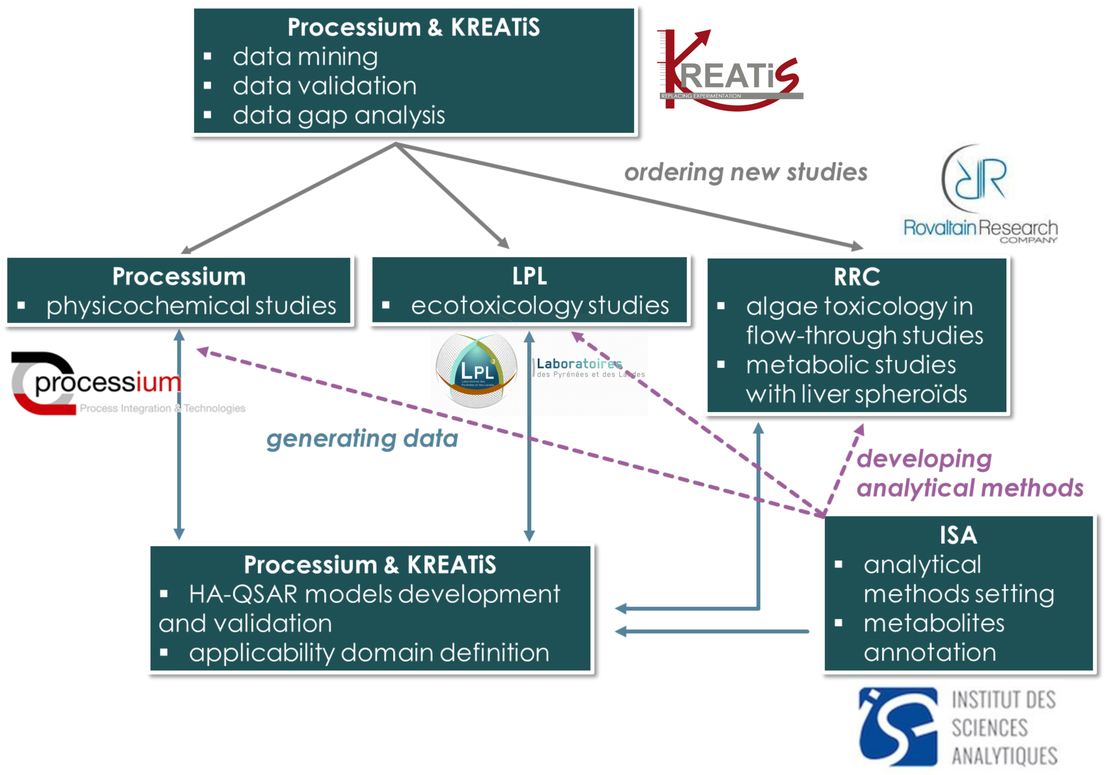
Replacing Experimentation

Introduction

About 80% of REACH dossier time and costs are associated with laboratory testing. Moreover, despite recommendations by the European Chemicals Agency (ECHA) to use *in silico* approaches as an alternative to replace animal testing, the majority of existing QSAR models have been designed for screening purposes and are therefore considered unacceptable to replace experimental studies due to lack of accuracy and strict validation. This was the basis for proposing DAMIER (stands for Développement et applications de modèles informatiques pour REACH) research project which was funded in 2014 under the 17th French FUI (Fond Unique Interministeriel) call for projects. Supported with funding by the State together with regional (Rhône-Alpes) and local (CAPI, Isère) authorities, DAMIER aims to, amongst other objectives, provide a set of High Accuracy QSARs (HA-QSARs) which will cover a large portion of the Annex VII and VIII studies required for tonnage bands between 1 and 100 TPA. The HA-QSARs are relatively cheap and much quicker than laboratory studies and have been designed to fulfil the regulatory obligations for use in REACH dossiers[1]. This poster provides some information on the role of each partner and the techniques used to create HA-QSARs.

The partners and their roles

Five partners (Two SMEs, KREATiS (co-ordinator) and Processium; the Institut des Sciences Analytiques (ISA); the Laboratoires des Pyrénées et des Landes (LPL) and Rovaltain Research Company) are collaborating:



KREATiS: Project co-ordinator and HA-QSAR modeller for the environmental aspects of the project. KREATiS has already designed several successful HA-QSARs (within the iSafeRat® Toolbox[2]) which are currently in use for log K_{OW}, water solubility, vapour pressure, acute fish, daphnid and algae studies. The aim of this project is to realise a fully validated acute QSARs for fish, daphnid and algae for MOA 2 substances, design QSARs for the ASRIT test and adsorption and chronic models for MOA 1 compounds;

Processium: will develop models to predict physico-chemical properties. Processium also has the capacity to perform new physico-chemical studies on substances when data for those structures is weak in order to reinforce modelling;

Laboratoires des Pyrénées et des Landes (LPL): is an analytical laboratory and an ecotoxicolgy CRO. LPL will provide a carefully chosen validation set of data for the fish, daphnid and algae studies which will be used to ensure the validity of the training set used in the HA-QSARs.

Rovaltain Research Company (RRCo): will be setting up and validating two new studies: A flow-through algae study and an *in vitro* metabolism assay using fish liver spheroids;

Institut des Sciences Analytiques (ISA): will be performing the development of the analytical protocols used in the studies and also performing the metabolite part of the liver spheroid protocol.

The methods

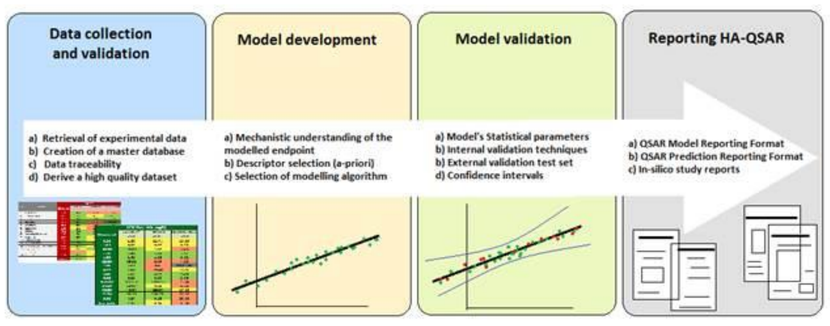
iSafeRat® Holistic approach to predict physicochemical and ecotoxicological endpoints (Delivrable early 2017)

The iSafeRat® Toolbox uses a holistic approach where a series of models interrelated by the laws of phase-equilibrium thermodynamics can be predicted in a cascade calculation (see Poster SETAC 2015 WE016 for further explanations).

The results are highly accurate as a feedback mechanism is included such that just one single accurate laboratory study can validate the full array of predictions in the "cascade".

The other models prepared in the project will be included in the holistic approach (where possible) following the scheme outlined in figure 1.

Figure 1: A scheme of the DAMIER approach



Algae flow-through study (Delivrable 2016)

The Algae study will be performed in a similar way to a chemostat and has therefore been named an "algaestat", where a flow-through method maintains the algae at approximately the same cell concentration throughout the study while test substance is pumped through the system at a known rate. Growth inhibition is determined as a reduction in cell concentration compare to the control. The study can be used for the determination of EC50s/EC10s for substances that are not stable in algae growth tests over a 72 hour period and therefore cannot be determined with accuracy using the current (static) OECD 201 method.

Fish liver spheroid in vitro metabolism assay (Delivrable mid-2017)

Liver spheroids represent a more robust system than single cells (hepatocytes) or S9 fractions but are still a relatively novel methodology. The aim of this part of the project is to use fish liver spheroids as a screening assay to determine the major metabolic breakdown products of test substances. Once identified, these metabolites can be determined using the KREATiS iSafeRat® models to assess whether they may be more toxic than the parent substance. If not, further consideration in the profile of the breakdown product is unnecessary.

Poster No. WE027

References

[1]ECHA – Practical guide 5: How to report (Q)SARs. April 2015
Link:http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf
[2]iSafeRat® – in Silico Algorithms For Environmental Risk And Toxicity version 1.3

This poster is presented at SETAC Europe 25th annual meeting 2015, Barcelona, Spain.