

Towards the Replacement of in vivo Repeated Dose Systemic Toxicity Testing

Maurice Whelan.

European Commission Joint Research Centre, Ispra, EU



SEURAT - The Vision

The SEURAT vision is to fundamentally change the way we assess the safety of chemicals, by superseding traditional animal experiments with a predictive toxicology that is based on a comprehensive understanding of how chemicals can cause adverse effects in humans.

SEURAT - The Strategy

The SEURAT strategy is to adopt a toxicological mode-of-action framework to describe how any substance may adversely affect human health, and to use this knowledge to develop complementary theoretical, computational and experimental (in vitro) models that predict quantitative points of departure needed for safety assessment.

Safety Evaluation Ultimately Replacing Animal Testing (SEURAT)

Step 1 ...

**Towards the replacement of *in vivo* repeated dose
systemic toxicity testing (SEURAT-1)**

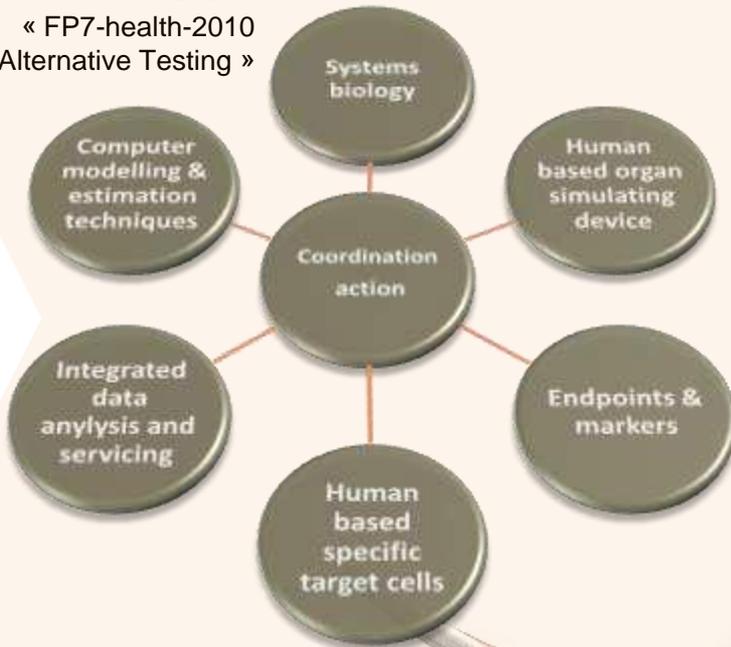
Joint funding by the European Commission and a
specific industrial sector (cosmetics industry / Colipa)

€ 25 million EC / € 25 million Colipa

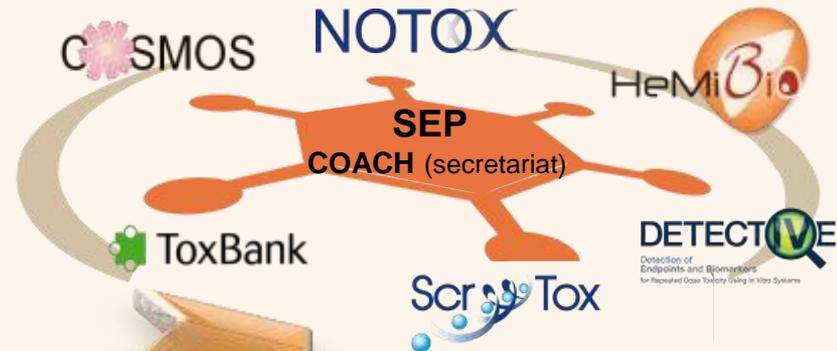
The Building Blocks of SEURAT-1

Call

« FP7-health-2010
Alternative Testing »



Projects



SEURAT

Towards the replacement of *in vivo* repeated dose systemic toxicity testing

~ 70 research groups from European Universities,
Public Research Institutes and Companies
(more than 30% SMEs)

What makes SEURAT-1 unique

- Largest ever single research initiative in the area of safety assessment science using alternative methods.
- First time the Commission (DG RTD) has employed such a model to fund a cluster of related projects.
- Novel public-private partnership (Commission and Colipa) where direct financing is equally shared.
- Cluster is supported by a servicing project and a dedicated coordination-action project.
- Broad array of scientific disciplines and tools being developed and integrated with one purpose.
- Realistic goals which build towards the next step

SEURAT-1 objectives

- Development of innovative and predictive toxicological assessment and testing methods that are relevant for regulatory decision making.
- Formulation and translation of a mode-of-action based research strategy for repeated dose toxicity.
- Demonstration of proof-of-concept at multiple levels (conceptual, methodological, application)
- Provide the blueprint for expanding the applicability domains - chemical, toxicological and regulatory.

Strategy Implementation

A brown, 3D-style arrow pointing to the right, indicating the start of the first strategy point.

Selection of well-studied chemicals with evidence of chronic systemic toxicity.

Hypothesis-driven approach to elucidating modes-of-action and identifying associated key events and biomarkers.

A brown, 3D-style arrow pointing to the right, indicating the start of the second strategy point.

Emphasis on in vitro models that capture modes-of-action directly relevant to human physiology.

Exploit stem cell technology to develop in vitro systems with cellular diversity to model higher level functions.

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Development of in vitro assays suitable for HTS implementation.

Use of bioreactors to engineer tissue comprising multiple cell types to model complex toxicological processes.

Strategy Implementation

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Biokinetic modelling to extrapolate between in vitro test concentrations and repeated dose organ exposure in vivo.
Computational toxicology to associate chemicals with molecular initiating events and describe metabolism.

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Use of high content analysis tools including `omics to describe modes-of-action at the molecular level.
Systems biology approaches to model modes-of-action dynamics at the molecular scale for quantitative analysis.

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Proof-of-concept exercise to demonstrate a mode-of-action based integrated test system to predict sub-chronic liver toxicity.
Feasibility study to show how test data can be used in a safety assessment context.



The building blocks

- : **SCR&Tox**: Stem cell differentiation for providing human-based organ specific target cells
- : **HeMiBio**: Development of a hepatic microfluidic bioreactor with *in situ* biosensing
- : **DETECTIVE**: Identification of *in vitro* biomarkers and read-outs to predict toxicity in humans
- : **COSMOS**: Deliver a suite of freely available integrated computational models and tools for toxicity profiling
- : **NOTOX**: Development of multi-scale systems biology models and prediction tools based around 3D tissue cultures
- : **ToxBank**: Supporting integrated data analysis and knowledge management to serve common project needs



Cluster level Coordinating and Support Action

COACH Objectives

- Analysis of the projects' work plans and progress towards the cluster objectives
- Identification of opportunities and needs for close collaboration
- Organisation of cluster annual meetings
- Editing of Annual Books presenting the strategy of the research initiative and the progress made
- Promoting the strategy and results of the initiative to major stakeholders
- Dissemination of results to the broader scientific community and the general public
- Facilitate the operation of the Scientific Expert Panel (SEP) to enable cluster level strategic coordination

Fostering cross-cluster interaction

- Unified set of thoroughly described reference chemicals that are specific to identified modes-of-action
- Establishment of harmonised approach and rationale to the design of in vitro exposure protocols
- Harmonisation and standardisation of protocols for differentiation and characterisation of stem cell models
- Agreed format for reporting data and describing methods
- Material Transfer Agreements spanning the cluster
- Establishment of Working Groups on specific topics
- Multiple workshops per year on relevant topics
- Collective organisation of joint summer schools

SEURAT-1 Scientific Expert Panel (SEP)

• SEP composed of project coordinators and seven external experts:

Project Coordinators		
Marc Peschanski	INSERM/UEVE 861, I-STEM/AFM, Evry /France	SCR&TOX
Mark Cronin	School of Pharmacy and Chemistry, Liverpool John Moores University / UK	COSMOS
Catherine Verfaillie	Interdepartmental Stem Cell Institute, Katholieke Universiteit Leuven / Belgium	HEMIBIO
Jürgen Hescheler	Institute for Neurophysiology, University Hospital Cologne / Germany	DETECTIVE
Elmar Heinzle	Biochemical Engineering, Saarland University, Saarbrücken / Germany	NOTOX
Barry Hardy	Douglas Connect, Zeiningen / Switzerland	TOXBANK

External Experts	
Hans Juergen Ahr	Bayer Health Care AG, Wuppertal / Germany
Ian Cotgreave	AstraZeneca Safety Assessment, Södertälje / Sweden
Gabrielle Hawksworth	Division of Applied Medicine, University of Aberdeen / UK
Catherine Mahony	Colipa (Procter & Gamble), London Innovation Centre / UK
Derek Knight	European Chemicals Agency, Helsinki / Finland
Roger Arnold Pedersen	Laboratory for Regenerative Medicine and Cambridge Stem Cell Initiative, University of Cambridge / UK
Emanuela Testai	National Institute for Health, Dept. of Environment & Primary Prevention - Mechanism of Toxicity Unit, Rome / Italy

SEURAT-1 Scientific Expert Panel (SEP)

Role:

- Provide scientific expert advice to the entire cluster
- Define long term strategy and conduct strategic reviews
- Oversee strategy implementation and the achievement of the cluster objectives
- Identify opportunities and propose measures to foster collaboration between projects
- Identify knowledge gaps and research priorities and propose solutions



The screenshot shows the SEURAT-1 website homepage. At the top left is the SEURAT-1 logo with the tagline "Towards the Replacement of or the Aligned Over-Systemic Toxicity Testing". To the right are logos for OLIPA, the European Commission, and the European Union flag. A search bar and a "Workspace scores" button are also visible.

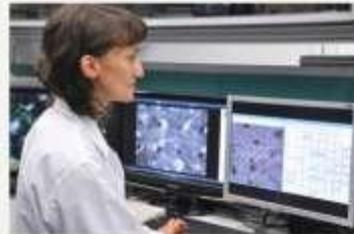
The main navigation menu includes: Homepage, Background, About us, The Cluster Projects, Partners and People, Library, and Contact.

The central content area features a "Welcome to the SEURAT-1 website" section. It contains a paragraph about the initiative's creation in June 2009, a photograph of a scientist at a computer workstation, and a detailed description of the research initiative's goals and structure. Below this is a list of six complementary research projects and a coordination action.

On the left side, there is a "News" section with several entries, each with a date and a "More" link. At the bottom left, there is an "Events Calendar" for the year 2011.

Welcome to the SEURAT-1 website

This FP7 Research Initiative was created through a call for proposals by the European Commission that was published in June 2009. The European cosmetics industry offered to match the European Commission's funds to make a total of EUR 50 million available to try to fill current gaps in scientific knowledge and accelerate the development of non-animal test methods. The Research initiative focuses on the complex area of repeated dose toxicity.



The Research Initiative is a first step to addressing the long term strategic target of "Safety Evaluation Ultimately Replacing Animal Testing (SEURATY)". It is called "SEURAT-1", indicating that more steps have to be taken before the final goal will be reached. SEURAT-1 will develop knowledge and technology building blocks required for the development of solutions for the replacement of current repeated dose systemic toxicity testing in vivo used for the assessment of human safety.

The SEURAT-1 Research Initiative is composed of six research projects, which started on 1 January 2011 and will run for five years. These projects will closely cooperate with a common goal and combine the research efforts of over 70 European universities, public research institutes and companies.

The collaboration between these six research projects, the dissemination of results, the cooperation with other international research teams, and the continuous updating on research priorities will be facilitated by the coordination and support action project "COACH".

SEURAT-1 has been launched on 1 January 2011 as a cluster, composed of six complementary research projects ...:

- **SCRATCH**, "Stem Cells for Relevant Efficient Extended and Normalized Toxicology"
- **HeMBO**, "Hepatic Microfluidic Biomatrix"
- **DETECTIVE**, "Detection of endpoints and biomarkers of repeated dose toxicity using in vitro systems"
- **COSMOS**, "Integrated in Silico Models for the Prediction of Human Repeated Dose Toxicity of Cosmetics to Optimise Safety"
- **NOI/OX**, "Predicting long-term toxic effects using computer models based on systems characterization of organotypic cultures"
- **ToxBatch**, "Supporting Integrated Data Analysis and Servicing of Alternative Testing Methods in Toxicology"

... and a coordination and support action.

1st Volume of SEURAT-1 Annual Report

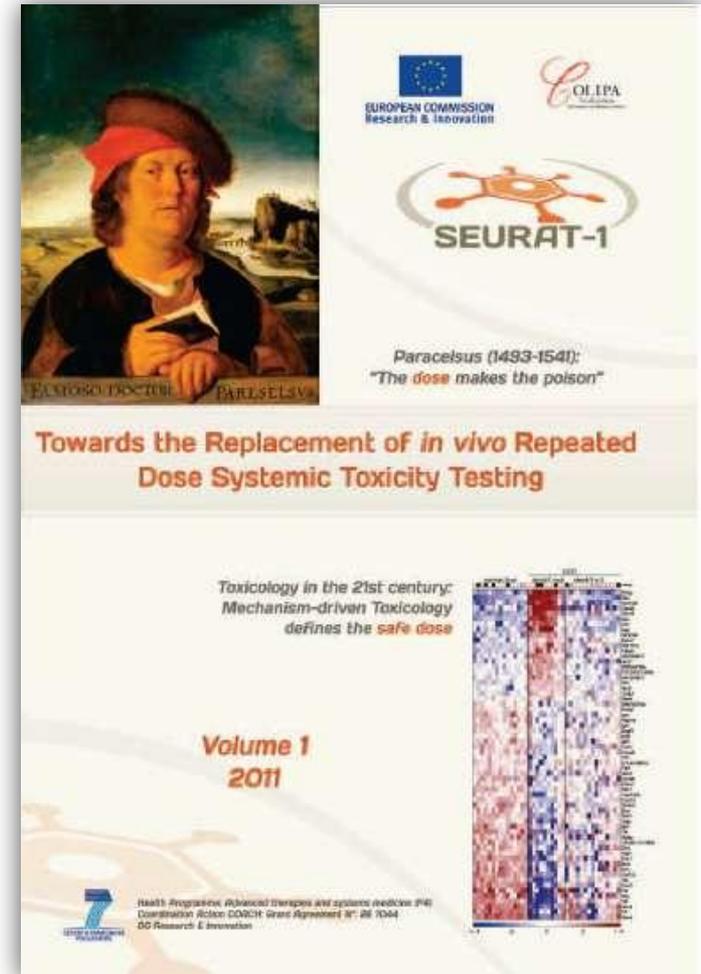
Issue: 2011

The SEURAT-1 research initiative will publish a series of six Annual Reports. As the first volume, this book describes:

- scientific progress,
- strategic development,
- evolution of the legislative and regulatory context,

in the field of repeated dose systemic toxicity testing.

Download PDF of the Annual Report from www.seurat-1.eu or request a paper copy to be sent to you





Towards the Replacement of in vivo Repeated Dose Systemic Toxicity Testing

Thank you for your attention

**Contact : coach-arttic@eurtd.com
Coordinating Action COACH - Grant Agreement N°: 26 7044**