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# Towards the Replacement of in vivo Repeated Dose Systemic Toxicity Testing

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Coordination Action COACH: Grant Agreement N° : 26 7044

# 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


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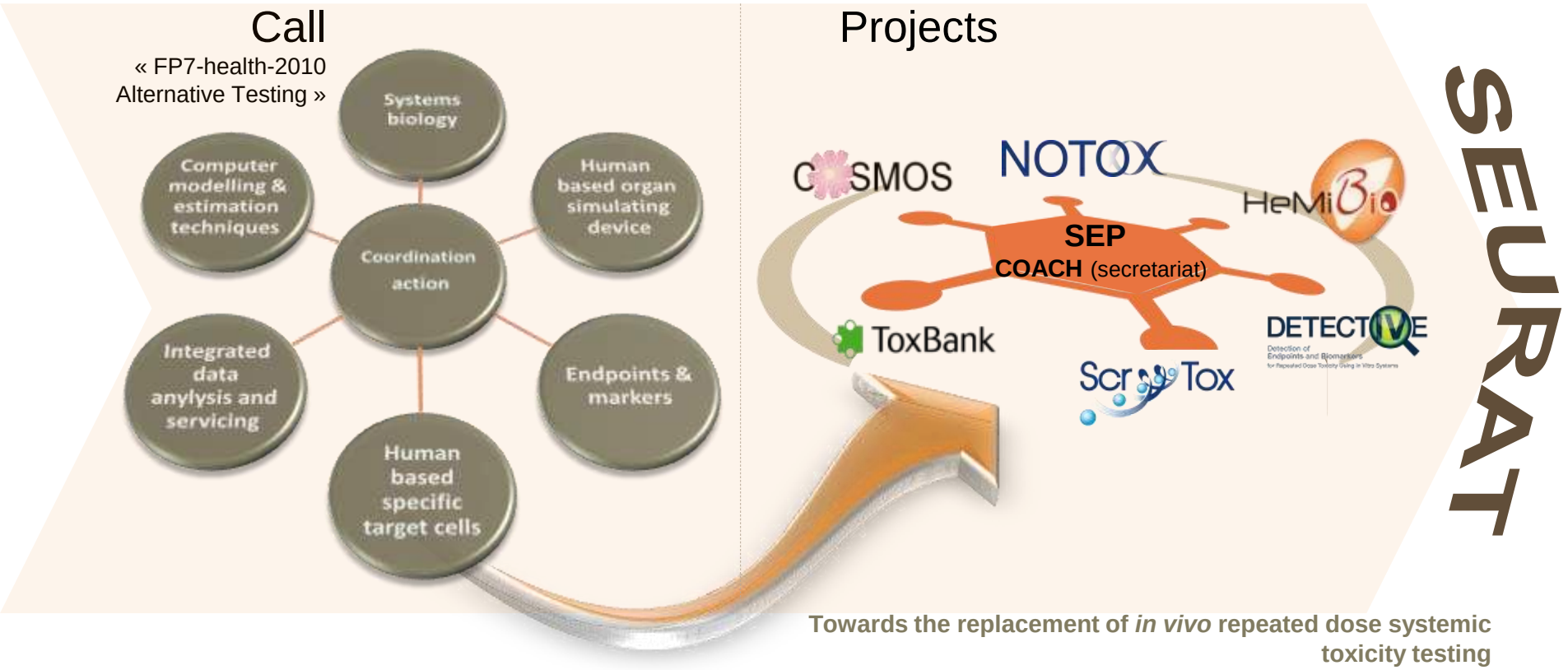
# The Building Blocks of SEURAT-1




**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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# 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.


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# Strategy Implementation

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.

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.

Development of in vitro assays suitable for HTS implementation.
Use of bioreactors to engineer tissue comprising multiple cell types to model complex toxicological processes.


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# Strategy Implementation

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.

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.

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.


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# 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



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# 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


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# 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


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# 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 |


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# 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


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# 1st Volume of SEURAT-1 Annual Report

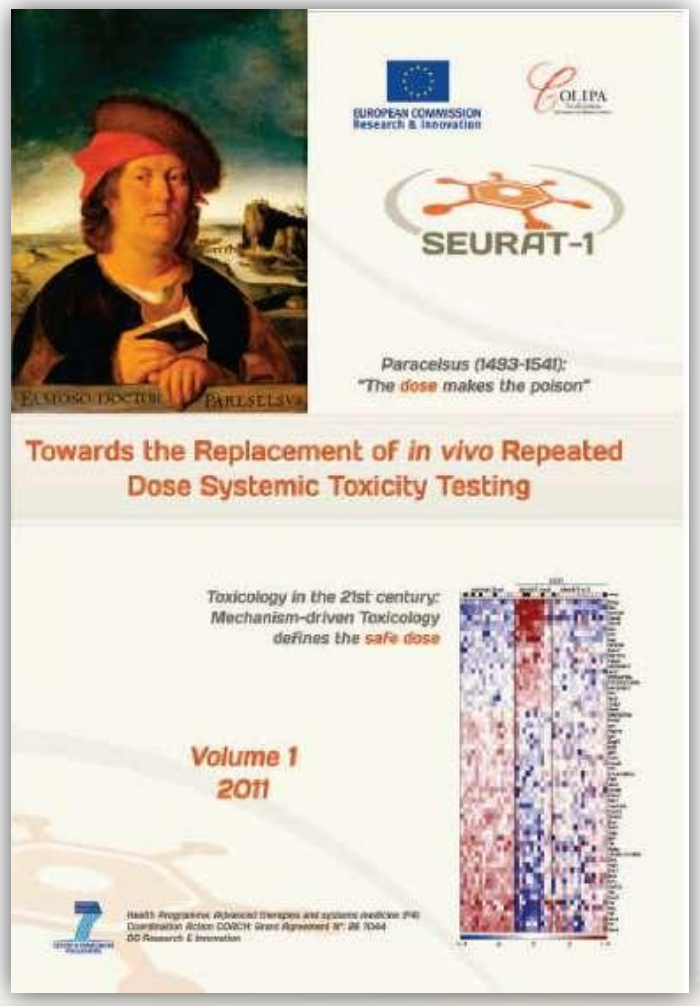
*Issue: 2011*

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**



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SEURAT-1

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## Thank you for your attention

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