

# SEURAT-1 HIGHLIGHTS

Painting the future animal-free safety assessment of chemicals



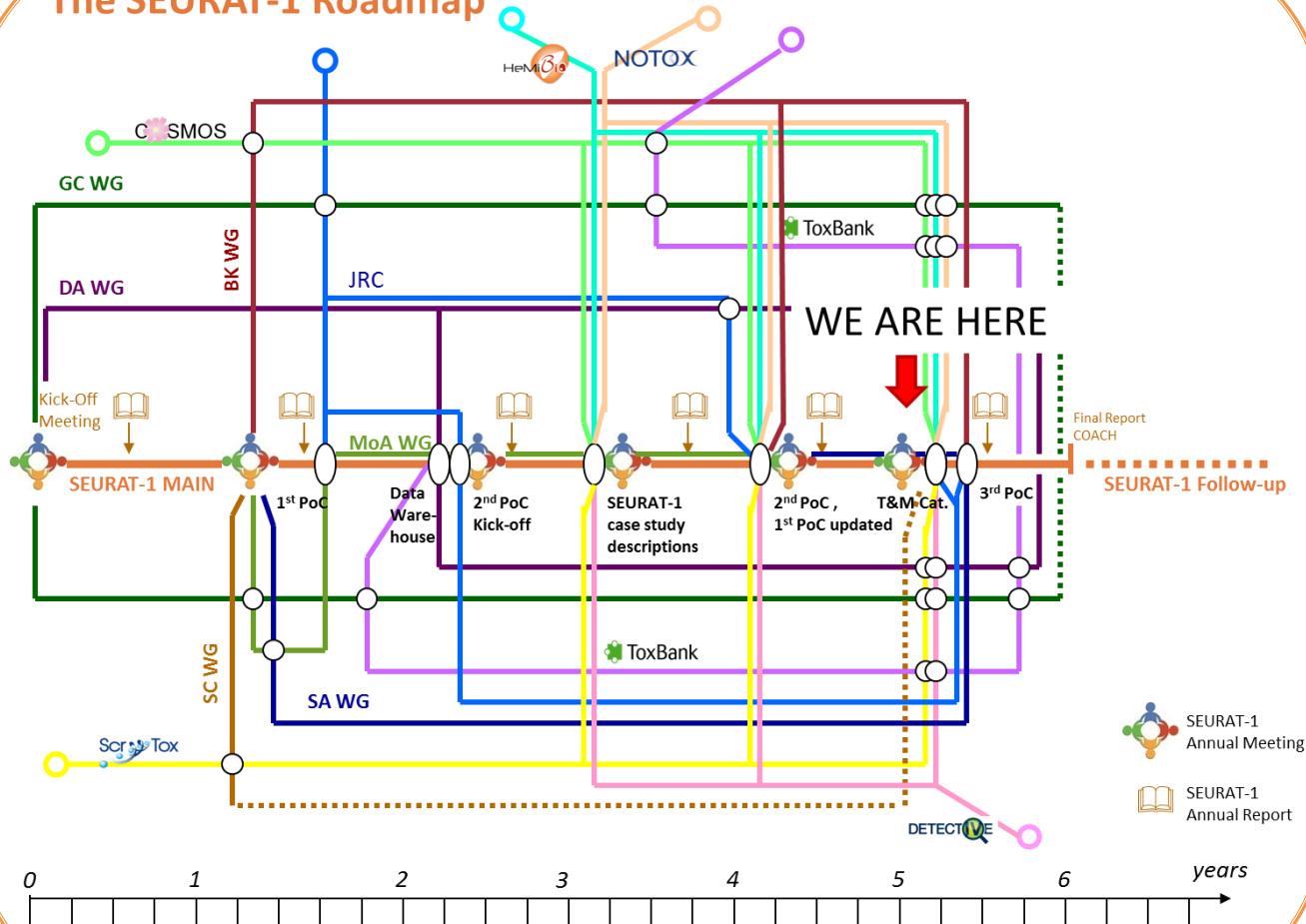
<http://www.seurat-1.eu>

*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.*



- ✓ Cluster of 7 collaborative projects
- ✓ 50 million Euro investment
- ✓ Co-financed by EC and Cosmetics Europe
- ✓ Over 70 research partners
- ✓ 16 countries plus EC
- ✓ 2011-2015 research activities

## The SEURAT-1 Roadmap



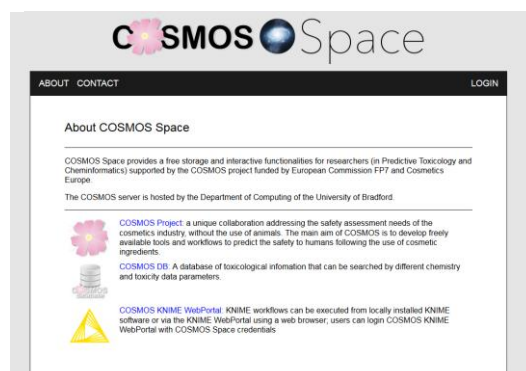
## COSMOS - *in silico toxicology*

**COSMOS DB** (<http://cosmosdb.cosmostox.eu>) is an **open-source database with high quality data** including 12,538 toxicity studies for 1,660 compounds across 27 endpoints.

**COSMOS Cosmetics Inventory** (accessible through COSMOS DB) is the biggest single inventory of cosmetics-related substances, over 19,000 substances in total, with a very large dataset suitable for TTC (Threshold of Toxicological Concern) analysis.

### COSMOS KNIME Webportal

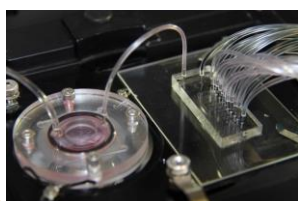
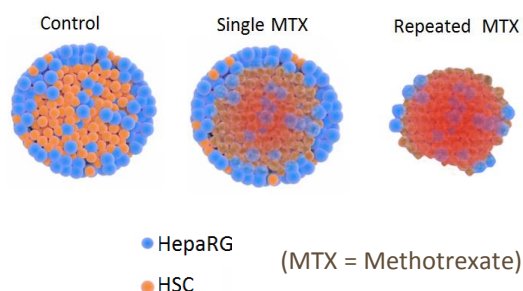
(<http://knimewebportal.cosmostox.eu>) provides freely available computational models developed within COSMOS, predicting **oral and dermal absorption, toxicity and the IVIVE models**.



## HeMiBio - *the in vitro liver*

HeMiBio developed an *in vitro* **drug-induced liver fibrosis model**. Spheroids with co-cultured HepaRG and Hepatic Stellate Cells <<(HSC) show accumulation of collagen, after repeated exposure. The model can be used for **screening of pro-fibrotic drugs** with relevance to human and can contribute to the **development of anti-fibrotic therapies**.

Van Grunsven, Leite, Roosens and Taghdouini (unpubl.)



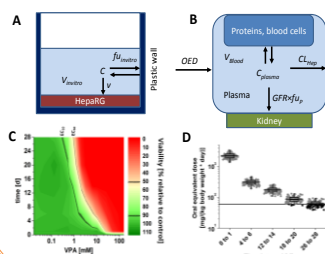
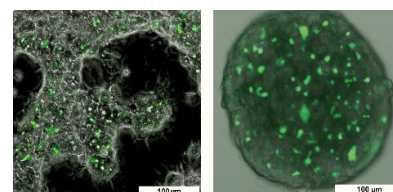
The project also developed a **real-time monitoring of metabolic function in liver-on-chip** microdevices using tissue-embedded biosensors useful to predict long term effects in liver for example in drug discovery.

The model is capable of maintaining metabolically active liver organoids for over a month. Prill et al. Archives of Toxicology, May 2015 ; Ezra et al. Biomedical Microdevices, July 2015; Bavli et al. In review

## NOTOX - *thinking in systems*

NOTOX developed a **3D-hepatic model** using HepaRG cells cultures amenable to high throughput screening of compounds, are a promising preclinical tool in the study of **human relevant long-term repeated-effects** and in the **assessment of chronic drug-induced hepatotoxicity**.

Mueller, Gunness, Krämer, Schevchenko, Heinzle, Ingelman-Sundberg and Noor



**NOTOX combined *in silico* modeling** for the prediction of dose and pathway related the adverse effects in humans **from *in vitro* repeated-dose studies**. The combination of modeling based on long-term *in vitro* data from HepaRG cultures retaining viability for 28 days, and feeding in data to the *in vitro* *in vivo* prediction model allows **the prediction of human *in vivo* hepatotoxicity**.

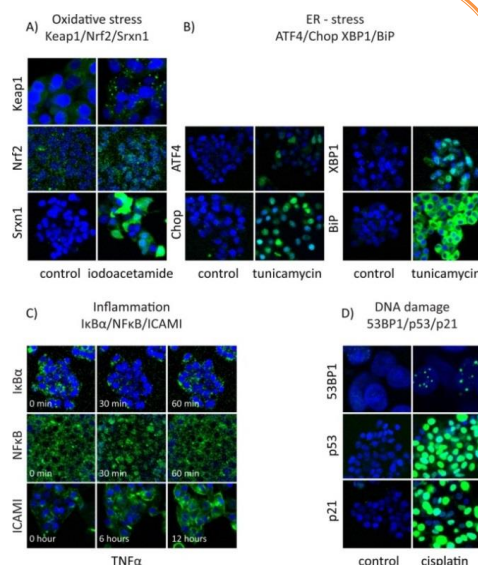
Klein, Maggioni, Bucher, Mueller, Niklas, Shvchenko, Mauch, Heinzle and Noor

## DETECTIVE - biomarkers and functional assays

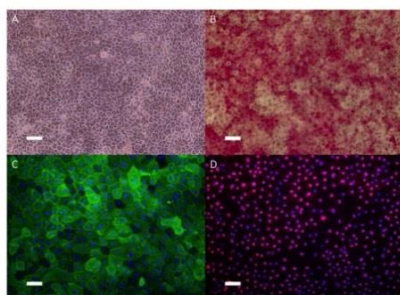
The project created a **toxicogenomics directory of chemically exposed human hepatocytes**. Identification of biomarkers and prediction of hepatotoxicity *in vitro* was established for **148 substances** on a basis of transcriptomics data and is publicly available (<http://wiki.toxbank.net/toxicogenomics-map/>)

**DETECTIVE** identified **liver cell toxicity reporters** to identify hepatotoxicant-induced cellular stress responses and generated a toxicity reporter platform based on BAC (Bacterial Artificial Chromosome) engineering of the human HepG2 cells.

Wink et al. *Chem. Res. Toxicol.*, 27: 338-355, 2014.



## Scr&Tox - the cell factory

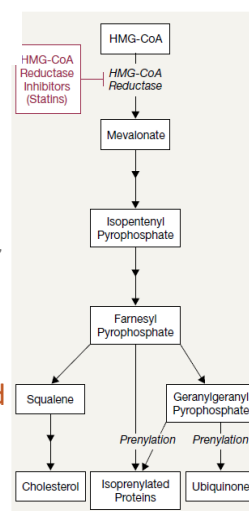


For the first time ever **human induced pluripotent stem cell (hiPS)** derived from hepatocytes was **used for repeated dose toxicity studies**.

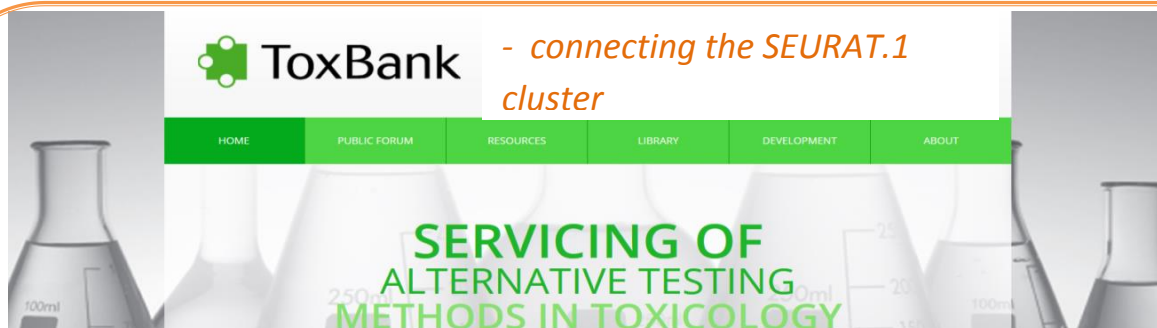
Holmgren et al. *Drug Metab. Disp.*, 42(9): 1401-1406, 2014.

Within Scr&Tox **myotoxicity** was predicted from upstream events in the adverse outcome pathway in an *in vitro* model based on **mesodermal progenitors derived from hiPS**.

Peric et al., *Stem Cells*, 33, 2936, 2015.



## ToxBank - connecting the SEURAT.1 cluster



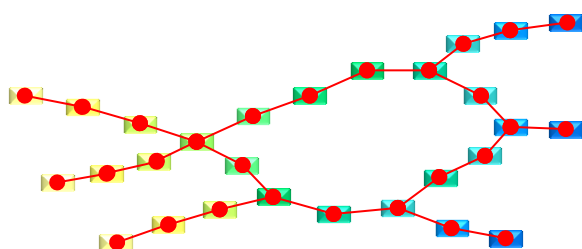
The **ToxBank Data Warehouse** (<http://www.toxbank.net/data-warehouse>) is establishing a **centralised compilation of data for systemic toxicity** generated under SEURAT-1. Additional public data was uploaded and integrated whenever possible into computerised models capable of predicting repeated-dose toxicity.

The **integrated data analysis** by combining public data from sources, such as Open TG-GATES, ToxCast and PubChem, with **SEURAT-1** data supported AOP development and case study risk assessments.



The **SEURAT-1 Gold Compounds** were selected based on their **Mode-of-Action** by the SEURAT-1 Gold Compound Working Group, and were used to **estimate the predictive power** of the methods developed within all projects in the cluster.

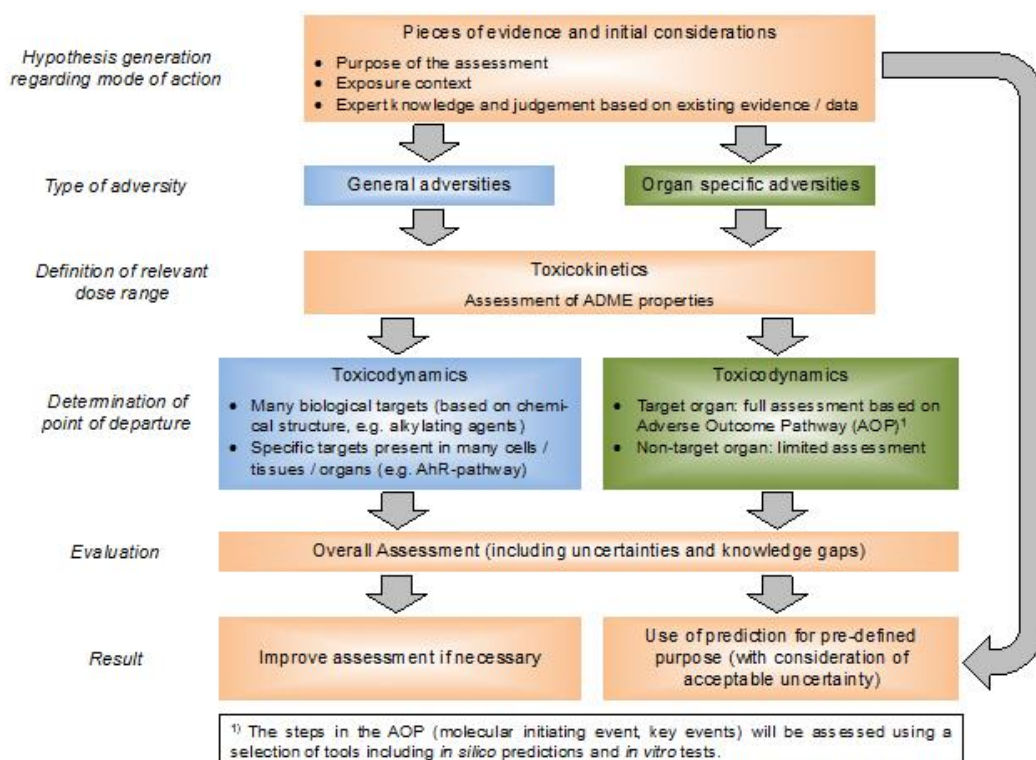
All information on the Gold Compounds is available at:  
<http://www.toxbank.net/compound-wiki>



Theoretical **Adverse Outcome Pathways** for three specific liver toxicity mechanisms - **fibrosis, steatosis and cholestasis** – were identified and reported in the AOP Wiki (<https://aopkb.org>).

Landesmann B, Vinken M. SEURAT-1 Annual Report, Vol

A conceptual framework was developed for regulatory safety assessment based on *in vitro* and *in silico* evidence. Daston et al, Arch. Toxicol. DOI 10.1007/s00204-014-1421-5, 2014.



The framework was applied in three case studies: (1) Threshold of Toxicological Concern (TTC), (2) Read-across strengthened with alternative data and (3) The ab initio case study based on only alternative data.

The **SEURAT-1 Tools&Methods Catalogue** is currently completed by the SEURAT-1 partners in DB-ALM: <http://ecvam-dbalm.jrc.ec.europa.eu/>