In Vitro Data and In Silico Models for Predictive Toxicology
The SEURAT project

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Seurat-1: towards replacement of \textit{in vivo} repeated dose systemic toxicity testing

- Cluster of seven collaborative projects
- 50 million Euro investment
- Co-financed by EC and Cosmetics Europe
- Over 70 research partners
- 16 countries plus EC
- 6 year programme

http://www.seurat-1.eu/
The SEURAT-1 Roadmap

0 1 2 3 4 5 6
years

SEURAT-1 MAIN

GC WG
DA WG
BK WG

SEURAT-1 case study descriptions

2nd PoC Kick-off

1st PoC

2nd PoC, 1st PoC updated

3rd PoC

SEURAT-2

SC WG
SA WG

COSMOS

GC WG

JRC

MoA WG

Data Warehouse

ToxBank

HEMT 3rd

NOTOX

WE ARE HERE

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

Final Report
COACH

SEURAT-1 Annual Meeting

SEURAT-1 Annual Report

Towards the Replacement of in vivo Repeated Dose Systems Toxicity Testing

Volume 5
2015

WE ARE HERE
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.
Scientific Tools

Cells exchange development underpinned by mode-of-action rationale

AOPs

... development underpinned by mode-of-action rationale
Structure the information in order to be able to PREDICT adverse health effects

Adverse Outcome Pathway:

Molecular Effects | Organelle Effects | Cellular Effects | Tissue Effects | Organ Response | Individual Response | Population Response

Toxicity Pathway

Mode of Action

Adverse Outcome Pathway

Key Events

Molecular Initiating Events

Adverse Outcomes
SEURAT-1 Proof of Concept on three levels:

Level 3, APPLICATION:
Predictive systems to support regulatory safety assessment

Level 2, PREDICTION: Integrated systems including in vitro and computational methods to predict toxicity

Level 1, KNOWLEDGE:
Adverse Outcome Pathway (AOP) constructs
Structure the AOP information in collaboration with the rest of the world

Visit AOP Wiki (https://aopkb.org) to explore currently mapped AOPs, improve them or add new ones.
Arch Toxicol (2014) 88:2099–2133
DOI 10.1007/s00204-014-1410-8

REVIEW ARTICLE

SEURAT-1 liver gold reference compounds: a mechanism-based review

Paul Jennings · Michael Schwarz · Brigitte Landesmann · Silvia Maggioni · Marina Goumenou · David Bower · Martin O. Leonard · Jeffrey S. Wiseman
A flavor of highlights from the SEURAT-1 projects

Development of an in vitro drug-induced liver fibrosis model

Differentiation of stem cell-derived hepatocytes

For the first time ever hiPS-derived hepatocytes was used for repeated dose toxicity studies (Holmgren et al. (2014) in Drug Metab. Disp., 42(9): 1401-1406
A flavor of highlights from the SEURAT-1 projects

Liver cell toxicity reporters to identify hepatotoxicant-induced cellular stress responses


Prediction of steatosis through repeated dose exposure to 3D HepaRG system combined with Biokinetic modelling
COSMOS database

- Open-access
- High-quality toxicity data (quality controlled, curated structures)
- User-friendly query builder (chemical name, structure, toxicity data)
- 44,765 unique chemical structures
- 12,538 toxicity studies for 1,660 compounds across 27 endpoints

Webinar and tutorial:
http://cosmosdb.cosmostox.eu/
http://www.cosmostox.eu/what/COSMOSdb/
Models are Freely Available Through COSMOS KNIME WebPortal and Space
"SEURAT-1 meets Tox21": international cooperation in safety assessment of chemicals using animal-free methods

Workshop brings forward concrete proposals for working together towards common research aims
Scientific Tools

how to translate them into solutions for safety assessment?
Safety Assessment Working Group

One conceptual framework - three case studies:

- Purpose of the assessment
- Exposure context
- Expert knowledge...
- Type of adversity
- Definition of relevant dose range
- Determination of point of departure
- Evaluation
- Result

[Diagram with TTC and other elements]

Pieces of evidence and initial considerations

READ ACROSS

AB INITIO
Four different scenarios

I. Chemical similarity of compounds that do not require metabolic transformation to exert a potential adverse human health effect

II. Chemical similarity involving metabolic transformation resulting in exposure to the same/similar proximal toxicant

III. Chemicals with general low or no toxicity

IV. Distinguishing chemicals in a structurally similar category with variable toxicities based on Mode of Action hypothesis
Chemical Safety Assessment Using Read-Across: Assessing the Use of Novel Testing Methods to Strengthen the Evidence Base for Decision Making

Elisabet Berggren,1 Patric Amcoff,2 Romualdo Benigni,3 Karen Blackburn,4 Edward Carney,5 Mark Cronin,6 Hubert Deluyker,7 Francois Gautier,8 Richard S. Judson,9 Georges E. N. Kass,7 Detlef Keller,10 Derek Knight,11 Werner Lilienblum,12 Catherine Mahony,13 Ivan Rusyn,14 Terry Schultz,15 Michael Schwarz,16 Gerrit Schüürmann,17 Andrew White,18 Julien Burton,1 Alfonso M. Lostia,1 Sharon Munn,1 and Andrew Worth1

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

A strategy for structuring and reporting a read-across prediction of toxicity

T.W. Schultz3, P. Amcoffb, E. Berggren c, F. Gautier d, M. Klarc b, D.J. Knight e, C. Mahony f, M. Schwarz g, A. White h, M.T.D. Cronin l, *
Topical Scientific Workshop - New Approach Methodologies in Regulatory Science

19-20 April 2016 | Helsinki, Finland

Topical scientific workshops of the European Chemicals Agency (ECHA) aim to foster discussion among academia, regulators, industry and other stakeholders on the possible regulatory impacts of the latest scientific developments. An anticipated outcome of these workshops is the emergence of new or improved approaches which may be applied to the implementation of the REACH, CLP and biocides regulations.

Aim of the workshop

The Topical Scientific Workshop on New Approach Methodologies in Regulatory Science will explore the potential regulatory benefits arising from fundamental change in scientific thinking. Complex toxicological apical endpoints cannot be predicted by a single non-standard test. Instead, it is necessary to combine multiple lines of evidence (including 'omics' and high-throughput screening methods) to predict the hazardous property with tools to facilitate this integration of evidence.

Two motivating drivers for the workshop are:

- A better understanding of the underlying biology behind how chemicals cause adverse effects to human health; and
- New tools and techniques that provide a huge amount of data to be used in solving regulatory issues.

The workshop draws inspiration from the EU research programme SEURAT-1 and the US Tox21 initiative, but also takes into account general progress from the scientific field.
Final Reporting

You are all welcome

Register at: http://www.seurat-1.eu/

Horizon 2020 project: EUToxRisk21
Starting this autumn will continue what SEURAT-1 started.
Thanks for the attention!