

Cosmetics: pioneering the way towards animal free testing

Necessity breeds invention, and the prospect of a complete ban on the use of animal testing in the EU cosmetics sector is a powerful driver for ambitious research and innovation across industry and academia. Methods to trick cells into reinventing themselves, a prototype bioreactor to engineer living tissue and a computer model to predict the fate of a chemical in your body - these are just some of the recent achievements of *SEURAT-1*, a major European private-public research consortium that's working towards animal free testing and the highest level of consumer protection. With the European Commission's Joint Research Centre as a key partner, this biggest ever initiative in animal free toxicology is committed to doing things differently. A research strategy formulated around harnessing knowledge rather than simply generating data and an organisational model that marries crowd-sourcing with individual excellence, the proof of the pudding will be in demonstrating the concepts on which SEURAT-1 is built. Results in this field will also be useful in a wide range of other industrial and medical sectors and will have a positive impact on the competitiveness and innovation of EU companies.

Some of the latest results of SEURAT-1 have been presented at the Euroscience Open Forum (ESOF) taking place in Dublin on 14 July. The new SEURAT-1 report on progress and related international efforts was launched on this occasion.

SEURAT-1 is the first phase of a longer term research initiative aiming at *Safety Evaluation Ultimately Replacing Animal Testing*. Although there is an initial focus on chemicals found in cosmetics and personal care products, the methodology and tools being developed by SEURAT-1 scientists are intended for application in a variety of fields. These include the assessment of vast array of industrial chemicals, pesticides, and biocidal agents used for example as household disinfectants. In addition, the knowledge being generated regarding the workings of fundamental biological processes at the molecular, cellular and tissue levels can be translated to the fields of personalised medicine and synthetic biology.

Moreover, a smart, toxicity-mechanistic approach to safety assessment leads to an intimate understanding of the complex relationship between the structure of a molecule and the biological activity it can induce. This structure-activity knowledge provides the premise for more rational and efficient molecular design, whether aimed at the formulation of 'greener' chemicals for a higher level of environmental and human health protection, or the development of more effective drugs with lesser side effects.

Scientific achievements

New human cell models for in vitro toxicity testing

Taking normal human cells such as those found in adult skin or blood and then reprogramming them to be able to 'differentiate' into various cell types is set to revolutionise in vitro toxicity testing. Creating these 'induced pluripotent stem cells' and then controlling their differentiation allows a test to capture the intricacies of human biology to a far greater extent when compared to the more common models derived from animal or cancer cells.

The challenge being met in SEURAT-1 is in getting the culturing and differentiation protocols of induced pluripotent stem cells right, to coax them to jump through the right biological 'hoops' and commit to transforming themselves into cells that form the heart, liver, brain, or muscle tissue. A recent breakthrough has shown how to produce stable human skin cells which will prove invaluable for studies related to topical toxicity for example.

Bioreactors for creating organ tissues in vitro

Bioreactors are sophisticated in vitro devices for simulating the complex micro-environment within an organ in order to grow tissue that has the composition and structure of its in vivo counterpart. Moreover, once grown, the bioreactor can maintain the tissue in a healthy and functional state for weeks, providing a holistic tissue model on which chemicals can be tested. Although more costly and resource intensive when compared to typical mono-layer cell cultures, bioreactors capture higher level physiological processes such as cell-to-cell interactions that are usually missed in simpler systems.

Thanks to the collaboration between material scientists, bioengineers and cell biologists, SEURAT-1 has already demonstrated the first prototype of a miniaturised bioreactor to produce a “liver on a chip” device to detect chemicals that are potentially hepatotoxic. A set of different sensors contained within the reactor allows on-line measurements of physiological and chemical parameters that indicate toxicological effects on the tissue that are only manifest after long term exposure.

Computational methods for toxicity prediction

SEURAT-1 scientists have recently compiled a database of properties on around 40 000 chemicals, which is a key resource to build and evaluate computational models for predicting safety thresholds for groups of chemicals and different exposure scenarios. Combining data related to molecular structure, physical and chemical properties and activity within in vitro assays allows the formation of robust chemical categories which can be used to infer the potential toxicity of one untested or 'unknown' chemical from a set of similar 'known' chemicals within the same category. This structure-and-activity based 'read-across' to predict the likely toxicity properties of a chemical is a highly efficient approach to animal free safety assessment which is being championed within SEURAT-1. The intention is to make the database and the computational tools freely available to the research and end-user communities later in the project.

Often the *Achilles' heel* of in vitro toxicity testing is identified as the difficulty in relating the concentration at which an effect is observed in a cell-based experiment with the equivalent internal dose of a chemical that would be needed to trigger the same effect in the body. Hence, there is a real need to be able to “translate” the results from in vitro experiments into the in vivo situation. This requires mathematical and computational models that capture the physiological processes underpinning the absorption, distribution, metabolism and excretion of a chemical – that is, models that predict what the body does to a chemical, to compliment methods that predict or measure what the chemical does to the body.

SEURAT-1 scientists have already devised models that allow prediction of the concentration of a chemical at a target organ following dermal application or oral ingestion, and can even predict what the internal concentration of a test chemical will be within a cell over time after being exposed in vitro.

SEURAT-1: Safety Evaluation Ultimately Replacing Animal Testing

This consortium is the first private-public research initiative of its kind, launched in January 2011 and which will run for a period of 5 years. It has an overall budget of €50 million,

equally financed by the European Commission (FP7) and Cosmetics Europe. It aims at paving the way to replace in vivo repeated-dose systemic toxicity testing.

SEURAT-1 is composed of five research projects supported by a data handling and servicing project, plus a coordination action, bringing together more than 70 partners that are united by a common strategy and high-level objectives.

SEURAT-1 aims to expedite a shift in the toxicological testing paradigm, with its partners committed to understanding molecular and cellular pathways that lead to toxicity, moving away from purely observational 'black-box' animal testing. SEURAT-1 is about using mechanistic knowledge in a novel way to generate and test hypotheses, establish theory, to ultimately make predictions. This is reflected in the fact that the SEURAT-1 research strategy is formulated with a view to understanding the toxicological modes-of-action associated with different categories of chemicals and to use this as the basis for a rational and purpose-driven design of integrated assessment and testing systems.

The European Commission's Joint Research Centre (JRC) is one of two scientific partners involved in the cluster's coordination action and also contributes heavily to three of the SEURAT-1 research projects. The JRC has a long established expertise in the development, validation and promotion of methods that can reduce, refine or replace the use of laboratory animals. It also hosts the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM).

Regulatory background

The Cosmetics Directive foresees a phasing-out of animal testing for cosmetic products. A ban of animal *testing* of finished cosmetic products has been in force since September 2004 and a testing ban on *ingredients* or *combinations of ingredients* since March 2009. As from March 2009, it is also prohibited in the EU to *market* cosmetic products and their ingredients which have been tested on animals, irrespective of the origin of these products. This marketing ban applies to all but the most complex human health effects to be tested to demonstrate the safety of cosmetic products (repeated-dose toxicity including skin sensitisation and carcinogenicity, reproductive toxicity and toxicokinetics), for which the legislator extended the deadline to March 2013.

The SEURAT-1 Annual Reports together with other information on the initiative and the research being conducted are available at: <http://www.seurat-1.eu/>