Food for thought …
Katya Tsaion, Bas J. Blaauwboer and Thomas Hartung

Evidence-based absorption, distribution, metabolism, excretion (ADME) and its interplay with alternative toxicity methods

Concept Article
Miriam N. Jacobs, Annamaria Colacci, Kimmo Louekari, Mirjam Luijten, Betty C. Hakkert, Martin Paparella and Paule Vasseur

International regulatory needs for development of an IATA for non-genotoxic carcinogenic chemical substances

Research Article
Florian Groeber, Lisa Engelhardt, Julia Lange, Szymon Kurdyn, Freia F. Schmid, Christoph Rücker, Stephan Mielke, Heike Walles and Jan Hansmann

A first vascularized skin equivalent as an alternative to animal experimentation

Research Article
Ilona J. Kosten, Sander W. Spiekstra, Tanja D. de Graaf and Susan Gibbs

MUTZ-3 Langerhans cell maturation and CXCL12 independent migration in reconstructed human gingiva

Workshop Report
Antonio Planchart, Carolyn J. Mattingly, David Allen et al.

Advancing toxicology research using in vivo high throughput toxicology with small fish model

Ex vivo assessment of testicular toxicity induced by carbendazim and iprodione, alone or in a mixture

Research Article
Cédric Pisani, Sébastien Voisin, Karim Arafah, Philippe Durand, Marie-Hélène Perrard, Marie-Roberte Guichaoua, Philippe Bulet and Odette Prat

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Dear readers,

Many in vitro experiments involve exposing cells to a fixed amount of a substance and measuring an outcome of interest after a chosen time. Pharmacology teaches us that to characterize a drug we need to know not only how it works but also how much of the applied dose reaches the bloodstream, how it is distributed to the various organs, how it is processed in the liver and how and over what time it is excreted. These parameters are also relevant for in vitro experiments and for translating information from in vitro tests to in vivo predictions for toxicological safety assessments. If a would-be toxin is not absorbed into the organism, it cannot have harmful effects. But if a seemingly harmless substance is metabolized in the liver to a toxin, it is a liability. The importance of ADME for alternative methods in toxicology is this issue’s Food for Thought … by Katya Tsaioun and colleagues.

Nongenotoxic carcinogens are cancer causing agents that do not directly interact with DNA but cause or promote cancer by other mechanisms. Currently there is no defined strategy to identify such substances. Miriam Jacobs et al. propose such a strategy that can provide the necessary information for regulators to make well-founded decisions. Designing the strategy has identified what kinds of tests reflecting mechanisms of cancer initiation or propagation still need to be developed to fill out the strategy at its different decision levels.

Pesticide residues in food have been linked to a decrease in human fertility. Cédric Pisani and colleagues investigated the possible mechanisms of action of two pesticides using the seminiferous tubules of pubescent rats grown in culture over three weeks. These were assessed for changes in mRNA and protein expression at different time points when exposed to either or both pesticides. The results show what effects the pesticides have on the cells, point towards useful biomarkers by which to test for these effects in a more efficient manner, and demonstrate that mixtures of pesticides, as they are often used in agriculture, can lead to stronger or different effects than either substance alone. This is a first step towards addressing the challenge of assessing the toxicological risk posed by mixtures of substances.

Artificial skin tissue can be grown using the relevant cell types, however it cannot be connected to and fed via the blood system as natural tissue would be because it lacks vasculature. Florian Groeber et al. overcame this drawback by clearing a piece of pig intestine of cells and reseeding it with endothelial cells via the blood vessels and with skin cells via the surface. This model can add a further dimension to in vitro skin testing and research as well as open new possibilities for grafting of wounds.

Ilona Kosten and collaborators present a new in vitro model of the inner surface of the human mouth and compare its response to allergens to that of a model of skin epithelium. The antigens activated the immune cells in both models but via different mechanisms and they also caused differential changes in surface markers. This is in line with observations that different tissues react differently to allergens and indicates that a single tissue will not suffice for the purpose of sensitization testing.

In a short communication, Amy Clippinger and colleagues investigate why to date only few antimicrobial cleaning products have been tested for their eye irritation potential using an in vitro and ex vivo EPA-endorsed approach instead of the in vivo test and suggest measures to promote the use of the alternative approach in the future. And in a second short communication, Joaquín Valdés et al. describe cultures of rat retinae that respond to sugar changes in the medium that emulate diabetes with cell death of retinal neurons as well as photoreceptors, especially cone receptors. The model may provide insight into the mechanisms of diabetic retinopathy without using live animals.

EU Directive 2010/63 calls for more detailed reporting of animal use for scientific purposes by member states, especially including the number of genetically modified animals bred but not used in experiments and the severity of animal experiments. Katy Taylor and Laura Rego have compiled this data for the year 2014 and uncover numerous shortcomings to report the required information by the member states.

As always, current news, corners and the calendar of events inform you of relevant developments in the 3Rs field.

We thank you for your continued support of and interest in ALTEX in 2016 and look forward to the innovations and breakthroughs that await us in 2017.

Sonja von Aulock
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