Dear readers,

In light of comments from DG Environment's Katrin Schütte at the recent ONE 2022 conference reported by *Chemical Watch*[1], which indicate that the European Commission considers that current "*NAM [New approach methodology] methods today are not able to demonstrate adversity*" and that therefore animal testing will have to increase to fulfill the Commission's chemicals strategy for sustainability (CSS), it is apt that this issue's Food for Thought … contribution written by Paul Carmichael and colleagues from Unilever's Safety & Environmental Assurance Centre (SEAC) challenges the dogma that risk assessment must be built on predicting potential adversity (in rodents) and argues that protection of human health can already be achieved with NAM within next generation risk assessments (NGRA). This is complemented by the strategy paper of RISK-HUNT*3R* by Giorgia Pallocca et al., which outlines how this large Horizon 2020 project will assemble NAMs from computational toxicology, *in vitro* toxicology, and systems biology into NGRA strategies.

This theme is continued by the first four articles of our new *Special Issue* on Development of an Evidence-Based Risk Assessment[2], introduced by Thomas Hartung and Daniel Krewski. Robert Baan and Kurt Straif describe the evolution of the procedure by which the International Agency for Research on Cancer (IARC) Monographs Programme performs its evaluations, which now considers mechanistic evidence and exposure assessment methods, and integrates human data, experimental animal data, and mechanistic data from NAMs, thus potentially reducing or avoiding experimental animal use. Elisa Aiassa and colleagues present two building blocks of the European Food Safety Agency (EFSA)'s framework for evidence-based scientific assessments, i.e., how scientific assessments are conducted and how uncertainty analysis is performed, to enable integration of multiple evidence sources, including alternative methods and testing strategies, in the regulatory scientific assessment process. Nawal Farhat et al. explain how systematic reviews of existing human, animal and mechanistic data can reduce reliance on animals and help avoid duplication of animal experiments while helping to validate and implement alternative test methods. Salomon Sand presents an approach to combine data on multiple health or gene-level effects of chemicals or mixtures. This involves relating the dose or concentration used in an assay to standardized severity reference points such as benchmark doses. Working with such reference point profiles can support the combination of data from different data streams and the transition towards a NAM-based risk assessment paradigm.

Further main articles in this issue include the paper by Rebecca von Hellfeld et al., which assesses the effects of neonicotinoids on embryonic development and behavior using the zebrafish embryo. They find that the embryo behavior outcomes correlate with findings in mammalian studies and that this assay could be integrated into a tiered testing scheme for (developmental) neurotoxicity testing.

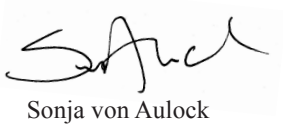
UVCB substances, i.e., substances of unknown or variable composition, complex reaction products, and biological materials, such as petroleum substance extracts, pose special challenges for hazard and risk assessment. John House and colleagues extend their previous work on using *in vitro* assays to group UVCBs by investigating the use of transcriptomic profiling to support such grouping and provide mechanistic information.

While commercially available full skin models are highly standardized and convenient, they may be too expensive for some users, cannot be tailored to specific applications, and shipment to some countries may be problematic. Patrícia Zoio et al. assess the use of their open-source full thickness skin model as well as an open-source reconstructed human epidermis model for skin irritation testing.

Knee joints of goats from food production that are exposed to interleukin-1β, a physiological inflammatory signal, display matrix degradation, expression of inflammatory and degradative markers, and chondrocyte hypertrophy that are comparable to human osteoarthritis patient samples and can be ameliorated with drugs commonly used to treat osteoarthritis. This *ex vivo* model, developed by Arijit Bhattacharjee and Dhirendra Katti, could be used to screen for more effective drugs to halt or reverse disease progression.

How systematic review can be integrated with the evaluation of mechanistic evidence, especially with regard to the development of adverse outcome pathways (AOP), is the subject of a t[4] Workshop Report by Sebastian Hoffmann and colleagues. Two further meeting reports and the Corners give insight into recent activities in the field. Finally, the BenchMarks contribution by Giorgia Pallocca and Marcel Leist continues to explore how to evaluate the usefulness of animal models by defining use domains.

Wishing you a good summer and a successful EUSAAT conference in September,



Sonja von Aulock
Editor-in-chief

[1] https://chemicalwatch.com/513543/european-commission-increase-in-animal-testing-unavoidable-with-chemicals-strategy

[2] doi:10.14573/altex.22S2