Title:

TT21C/AOPs: Putting mechanism and toxicity pathways at the heart of new safety assessments - Prof Paul Carmichael Ph.D.

Abstract:

Development of novel ingredients that can provide new functional benefits is the life blood of several industries, including the pharmaceutical and consumer product sectors. It is essential however that robust scientific approaches are used to assure the safety of these new ingredients for the patients and consumers who will use them, the workers who manufacture them, and the environment into which they may ultimately be disposed. Traditionally, toxicology data generated in mammals, fish and invertebrates, together with information on levels of human and environmental species exposure, have been used to enable informed safety decisions to be taken. The current reliance on animal data in these safety assessments is reflected in the majority of global regulations concerned with drug, consumer product and environmental safety. In 2007 the United States National Academies of Science report “Toxicity Testing in the 21st Century (TT21C): a Vision and a Strategy” (www.nap.edu/catalog.php?record_id=11970) challenged Toxicologists to think differently. Since then, the OECD Adverse Outcome Pathway (AOP) program (http://www.oecd.org/env/ehs/testing/) has strengthened the growing trend to frame new safety assessments in terms of human- (or environmental species-) relevant mechanism(s) of action. In Europe the SEURAT research program (http://www.seurat-1.eu/), along with the US multi-agency ToxCast and Tox21 programs (http://www.epa.gov/ncct/toxcast and http://www.epa.gov/ncct/Tox21) reflect the growing body of work aiming to modernize and improve this field; seeking to provide greater human health and/or environmental relevance and more efficient tools for safety assessments. Case study examples that utilize high content, high throughput in vitro systems, complemented by computational modeling linking exposure biokinetics with cellular biodynamics, are being put in place to illustrate the value of these novel safety assessments. Mechanisms of mitochondrial toxicity can be considered a key molecular target in such pathways-based safety assessments. The opportunities presented to Industry by these new approaches and their place in a framework for exposure- and pathways-based safety assessments will be discussed. Such in vitro tools combined with mechanistic chemistry information on ingredients allow the identification of potential biological targets, toxicological liabilities and mechanistic information for elucidation of adverse outcome pathways.