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Title of talk:
"Applying Adverse Outcome Pathways (AOP) to the protection of human health"

Abstract:
Regulatory toxicology is undergoing an exciting transformation. Whereas in the past the emphasis has primarily been on observation of toxicological effects of substances using animal models, nowadays the aim is to combine a variety of different models to determine the mechanistic basis of those effects. Moreover, this push towards more systematic use of mechanistic knowledge and reasoning in regulatory toxicological opens the door for predicting potential toxicological effects of a substance rather than having to measure them directly. So how do we go about establishing a knowledge-based framework for safety assessment decision making in relation to human health, and what practical steps can we take to harvest the knowledge we need and make it available in a form that can be exploited for regulatory purposes?

Although there is already a phenomenal amount of mechanistic toxicological information available in the literature, researchers continue to dig deeper and deeper. But with a gain in knowledge resolution, the trade-off is usually a loss in coverage, and eventually a loss of coherence. Thus an uncomfortable paradox is emerging where the more toxicological knowledge we generate as a scientific community, the more difficult it is to exploit for regulatory purposes. But if we assume that in fact most of the knowledge on mechanisms and modes of toxicological action that we need to make informed safety assessment decisions actually exists, then efforts should be directed towards the collection, curation and dissemination of relevant knowledge to ensure that it is fully exploited in regulatory toxicology processes. In doing so it is likely that on occasion knowledge gaps will be identified which should trigger knowledge-discovery related research activities. However such considerations are of secondary concern in the short-term. Important now is the establishment of methodology and tools for the gathering and management of knowledge on mechanistic toxicology on an international scale, similar in a way to global initiatives undertaken in the last decade in relation to warehousing and sharing of data on substance properties and test results.

Rising to the challenge of how to work with mechanistic knowledge, to embrace the opportunity of establishing a knowledge-based framework for regulatory toxicology, the Organisation for Economic Cooperation and Development (OECD) launched in January 2013 the Adverse Outcome Pathway (AOP) Development programme, managed within the OECD

Extended Advisory Group on Molecular Screening and Toxicogenomics (EAG-MSTG). An AOP is reductionist at the (toxicological) process level, describing a sequential chain of causally linked 'key events' occurring at different levels of biological organisation that lead to an adverse health or ecotoxicological effect. Thus an AOP is a unique instrument to capture and organise mechanistic knowledge in an explicit and structured manner, rendering it more amenable to evaluation, elaboration, communication, and exploitation. AOPs can vary in resolution and expanse and can include both qualitative and quantitative descriptions of key events and the causal relationships that link them. Initial development and elucidation of an AOP can start at the apical Adverse Outcome (i.e. the regulatory health effect of concern) and work upstream towards the initial cause, or at the Molecular Initiating Event, or at any key event in between. Ultimately however the aim is to postulate the continuous chain of key events that comprise the full AOP and importantly, to provide the evidence that substantiates the AOP to ensure that it can stand up to scrutiny before gaining acceptance. AOPs can serve multiple uses and provide the blueprint for a computational prediction model, design of an integrated assessment and testing strategy, or the basis for structuring information for a weight-of-evidence analysis.

The AOP Development programme at OECD is well underway and has a dynamic work plan comprising different categories of projects including AOP development projects, AOP case studies, AOP guidance, and AOP knowledge management tools. In April 2013 the OECD published its "Guidance document and a template for developing and assessing adverse outcome pathways" which AOP developers should follow to ensure consistency in their approach and compliance with AOP standards related to content, structure and presentation. A wiki-based AOP Knowledge Base (AOP-KB) has also been developed recently which is currently undergoing a beta-testing phase before being publically released in early 2014. This AOP-KB provides a web-accessible collaboration-space for AOP development teams to work together in an efficient and convenient manner. It will also serve to crowd-source knowledge on a global scale to refine existing AOPs and trigger the development of new ones where gaps in the AOP landscape are identified. Of course the AOP-KB will also be the primary hub for the regulatory science community to rapidly and efficiently access AOP knowledge to serve their needs.