AXLR8

Accelerating the transition to a toxicity pathway-based paradigm for chemical safety assessment through internationally co-ordinated research and technology development

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Background

Current reliance on high-dose animal toxicity studies and the application of default extrapolation procedures is a source of considerable uncertainty in human-health risk assessments. Additionally, conventional animal tests are in general quite time consuming, low throughput, costly in both economic and animal welfare terms, and offer little mechanistic understanding of how chemicals act in the body. However, dramatic advancements in molecular and cellular biology in recent years have made available a wide range of new tools – including functional genomics, proteomics, metabolomics, high data content screening, and systems biology – for studying the effects of chemical stressors on cells, tissues and organisms in a rapid and cost-efficient manner. This convergence of factors, coupled with the need to evaluate the safety of an increasingly large number of chemicals and their mixtures, has prompted some of the world's leading scientific authorities to call for a fundamental paradigm shift in toxicology.

Instead of focusing on signs of gross toxicity at high doses in living animals, an alternative approach advocated by the US National Research Council and others is to work towards a mechanistic understanding of how chemicals interact with cellular response pathways in the human body at environmentally relevant exposure levels. As critical pathways are identified, human cell-based assays can be developed to study chemical interactions at key cellular and molecular targets within a pathway, and through robotic automation, cell-based *in vitro* methods can enable the high throughput testing of thousands of substances in a single day. Data from toxicity pathway assays could then be integrated and interpreted with the aid of systems biology tools of the cellular 'circuitry' controlling pathway function, together with pharmacokinetic modelling to relate *in vitro* conditions to expected real-world human exposure levels.

The technology required to move toward a '21st century' paradigm in toxicology is already available or in a state of advanced development. What is needed is the elucidation of unmapped toxicity pathways, linking them closely with relevant human health outcomes, the development of appropriate high throughput cellular assays, improved bioinformatics to analyse large databases, and to combine this information through systems biology. In addition, pharmacokinetic models must be established to describe the concentrations of chemicals over time. Taken together, this should enable the prediction of dose-response *in vitro*, and the effective integration of these approaches for risk assessment purposes. This new paradigm will change the traditional toxicity testing and risk assessment approaches and needs reflection and acceptance not only by the scientific community but also by the all stakeholders who are involved in health and safety issues.

Objectives

AXLR8 is a multi-year coordination action designed to fulfil the growing need for a focal point for discussion and coordination among key European and international research, development and translational activities related to the implementation of a 21st century paradigm in toxicology. This project will provide a wide range of tools and opportunities for increased networking, information exchange, problem solving, strategic planning and collaboration among relevant scientific disciplines and stakeholder groups, both within the EU and globally. AXLR8 also aims to accelerate the acceptance and use of suitable animal replacement, reduction and refinement methods into regulatory decision-making, and to pave the way for a transition to 21st century technologies designed to detect biologically significant perturbations of toxicity pathways.

Approach

A cornerstone of the AXLR8 project will be the establishment of a pan-European scientific dialogue and advisory committee comprising leading experts from the academic, industry, government and regulatory sectors, and relevant EU- and Member State-funded initiatives as well as key international experts, to promote enhanced interdisciplinary and global communication, coordination, collaboration and exchange of best practices.

AXLR8 will organise three expert workshops to map existing research results germane to a pathway-based paradigm in toxicology and identify needs and priorities for future R&D and targeted funding. These workshops will invite participation from key sectoral experts from relevant disciplines, and thereby promote focused dialogue and the creation of new synergies among these communities. A public report will be prepared following each workshop, as well as one or more manuscripts for submission to a peer reviewed journal.

Promotion of greater scientific, stakeholder and public awareness and communication regarding 21st century approaches to toxicology and risk assessment will be fostered through the creation of a specific online 'community of practice' discussion forum on http://alttox.org/. Additionally, proactive outreach will be undertaken via presentations at several key EU toxicological conferences each year.

AXLR8 will convene an additional expert meeting to identify bottlenecks and barriers to the acceptance and use of 3R methods and testing strategies to their full potential for regulatory purposes. On the basis of these findings and expert advice regarding strategies for overcoming barriers, AXLR8 will work with regulatory authorities to implement new procedures, as needed, to facilitate a more expeditious and efficient uptake of both existing and second-generation alternative approaches to reduce reliance on *in vivo* testing.

Finally, AXLR8 will produce an authoritative report of the state of the science, including a practical road map detailing priority research and funding targets, in order to ensure a prominent role for EU scientists in this rapidly developing global research area.

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