Toxicity Testing in the 21st Century: A Vision and A Strategy

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In 2007, the US National Academy of Sciences released a report, Toxicity Testing in the 21st Century: A Vision and a Strategy. This report envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted in human cells or cell lines in vitro by evaluating cellular responses in a suite of toxicity pathway assays using high throughput tests, implemented with robotic assistance. Toxicity pathways are simply normal signaling pathways in cells that may be perturbed by test compounds. Risk assessment would shift towards the avoidance of significant perturbations of these pathways in exposed human populations. Dose response modeling of perturbations of pathway function would be organized around computational systems biology models of the circuitry underlying each toxicity pathway. In vitro to in vivo extrapolations would rely on pharmacokinetic models that would predict human blood and tissue concentrations under specific exposure conditions.

This re-direction of toxicity testing will lead to use of vastly smaller numbers of animals, improve knowledge of modes of action and molecular targets for environmental agents, enhance human relevance of test results, and provide much higher throughput, thereby permitting coverage of much larger numbers of test agents than is possible with current toxicological testing strategies. All the tools for making these changes in toxicity testing practices are either currently available or in an advanced state of development. The major prerequisites for achieving this paradigm shift are a commitment to change, and the necessary resources to enumerate the pathways by which chemicals can induce toxic responses in humans, to develop the suite of toxicity pathway assays needed to identify and prevent critical pathway perturbations, and to implement computational systems biology approaches to describe pathway function. A broad scientific discussion of this new vision for the future of toxicity testing is needed to motivate a departure from the current reliance on traditional animal-based toxicological tests towards a new approach more firmly grounded in human biology. This paper provides and overview of the original NRC report, and an update on subsequent events that have served to move the NRC vision forward.