Toxicity Testing Moves Ahead

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The Tox21 Partnership aims for far faster and less expensive screening.

Who would have thought that an automated laboratory working around the clock could screen chemical substances for interactions with biological targets at speeds mere mortals could hardly consider — let alone match? Well, this is exactly what is occurring today thanks to a collaborative effort known as "Tox21" among the U.S. Environmental Protection Agency (EPA), the National Toxicology Program (NTP), and the National Institute of Health Chemical Genomics Center (NCGC). Recently, the U.S. Department of Health and Human Services, Food and Drug Administration (FDA) joined the initiative. This column describes this ground-breaking partnership.

Background

Technology is revolutionizing chemical screening, which historically has been known for its time- and resource-intensive nature. To elicit the biological effects of chemical substances, whole animal (in vivo) testing has been the mainstay for many years. Test results would then be further refined, safety and uncertainty factors applied, and the results used in risk assessments that would then be relied upon by governmental bodies and others for purposes of setting standards. The process takes years, many animals are sacrificed, and the costs are notoriously high.

Enter technology. New high-throughput screening tools such as those housed at the NCGC, other in vitro (cellular) assays, and computational methods are enabling the assessment of an astonishing number of chemicals efficiently and quickly. These tools are contributing to assessments of human toxicity at rates thought impossible just a few years ago.

These new techniques are more the product of a research imperative than merely the logical evolution of toxicological testing. In 2004, for example, the NTP released its "Vision and Roadmap for the 21st Century" (http://ntp.niehs.nih.gov/go/vision). The linchpin of the vision is to develop in vitro biochemical and cell-based assays in lieu of rodent screening assays and integrate them into its testing program. Similarly, EPA for its part established in 2005 the National Center for Computational Toxicology (NCCT) within EPA's Office of Research and Development. NCCT develops computational tools and other research aids to facilitate chemical evaluation.

Also in 2005, EPA funded a project at the National Research Council (NRC) to develop a long-range vision and roadmap for toxicity testing. A report, "Toxicity Testing in the 21st Century: A Vision and a Strategy," that was issued two years later, lays out a coherent vision for the future of toxicity testing using new tools, at reduced cost, involving more substances, and fewer animals.

The collective commitment of the noted government agencies to respond to the challenge made in the 2007 NRC report was formalized in a 2008 Memorandum of Understanding (MOU) between NIEHS/NTP and NCGC and EPA, dubbed "Tox21." The partnership is intended to develop models to better predict how chemicals will affect humans. The Tox21 collaboration merges federal agency resources — research, funding and testing tools — to develop ways to predict more effectively how chemicals will affect human health and the environment. FDA will collaborate with other Tox21 members to prioritize chemicals that need more extensive toxicological evaluation and to develop models that can predict human response to chemicals.

The Premise of Tox21

Tox21 is predicated upon the belief that scientists can reasonably infer human harm from chemicals on the basis of how chemicals activate pathways in cells. A "toxicity pathway" refers to a chemically induced sequence of events that leads to an adverse response. The theory is that left to their own devices, these pathways ably coordinate normal processes. If, however, they are altered by chemical intervention or other "stressors," harm may occur.

The challenge for scientists is to identify and map toxicity pathways and zero in on the ways chemicals interact with the biochemical process involved in cell function and communication in ways that lead to pathway perturbation, an alteration of the pathway's typical functioning. The tricky part is being able credibly to extrapolate a blood or tissue dose from a cell-based response. Such extrapolation relies upon physiologically based pharmacokinetics, or PBPK, modeling and other state-of-the-art risk assessment tools. These cell-based assays facilitate rapid testing of many doses, including very low doses, quickly and efficiently. Not everyone buys into the concept that pathway perturbations and various modeling tools can accurately predict human health effects, and whether they can is at the heart of a scientific debate.

To date, over 2,000 chemicals have already been screened against dozens of biological targets. The goal is to increase the number of chemicals to 10,000 by the end of the year. The Tox21 partnership is a big step in meeting this goal.

More information on the Tox21 collaboration is available at http://epa.gov/ncct/Tox21/.

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