# In Vitro Models of Human Toxicity Pathways

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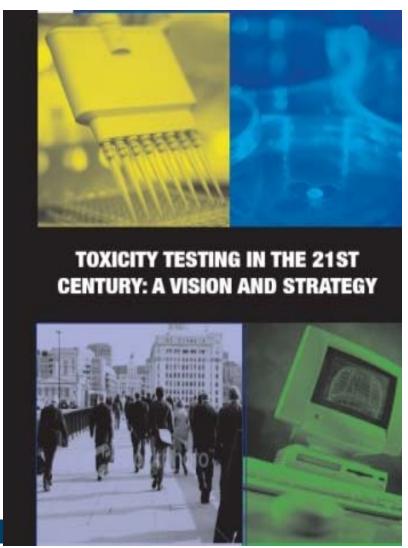
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### A New Focus in Toxicology: Human Toxicity Pathways



#### **POLICY**FORUM

### **Transforming Environmental Health Protection**

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National Toxicology Program (NTP), funded a project at the National Research Council (NRC) to develop a long-range vision for toxicity testing and a strategic plan for implementing that vision. Both agencies wanted future toxicity testing and assessment paradigms to meet evolving regulatory needs. Challenges include the large numbers of substances that need to be tested and how to incorporate recent advances in molecular toxicology, computational sciences, and information technology; to rely increasingly on human as opposed to animal data; and to offer increased efficiency in design and costs (1-5). In response, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents produced two reports that reviewed current toxicity testing, identified key issues, and developed a vision and implementation strategy to create a major shift in the assessment of chemical hazard and risk (6, 7) Although the NRC reports have laid out a solid theoretical rationale, comprehensive and rigorously gathered data (and comparisons with historical animal data) will determine whether the hypothesized improvements will be realized in practice. For this purpose, NTP, EPA, and the National Institutes of Health Chemical Genomics Center (NCGC) (organizations with expertise in experimental toxicology, computational toxicology, and high-throughput technologies, respectively) have established a collaborative research program.

#### EPA, NCGC, and NTP Joint Activities

In 2004, the NTP released its vision and roadmap for the 21st century (1), which established initiatives to integrate high-

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\*The views expressed here are those of the individual authors and do not necessarily reflect the views and policies of their respective agencies

n 2005, the U.S. Environmental Protection throughput screening (HTS) and other auto-Agency (EPA), with support from the U.S. mated screening assays into its testing program. In 2005, the EPA established the

> anism-based, biological observations in vitro (1, 4) (see figure, below). Toxicity pathways. In vitro and in vivo tools are being used to identify cellular responses after chemical exposure expected to result in adverse health effects (7). HTS methods are a primary means of discovery for drug development, and screening of >100,000 compounds per day is routine (8). However, drug-discovery HTS methods tra-

ditionally test compounds at one concentra-

National Center for Computational Toxi-

cology (NCCT). Through these initiatives,

NTP and EPA, with the NCGC, are promot-

ing the evolution of toxicology from a pre-

dominantly observational science at the

level of disease-specific models in vivo to a

on broad inclusion of target-specific, mech-

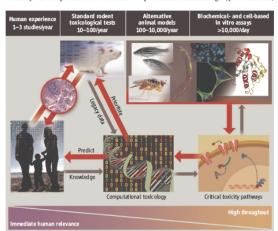
tion, usually between 2 and 10 µM, and tolerate high false-negative rates. In contrast, in the EPA, NCGC, and NTP combined effort, all compounds are tested at as many as 15 concentrations, generally ranging from ~5 nM to ~100 µM, to generate a concentrationresponse curve (9). This approach is highly reproducible, produces significantly lower false-positive and false-negative rates than the traditional HTS methods (9), and facilipredominantly predictive science focused tates multiassay comparisons. Finally, an informatics platform has been built to compare results among HTS screens; this is being expanded to allow comparisons with historical toxicologic NTP and EPA data (http://ncgc.nih.gov/pub/openhts). HTS data collected by EPA and NTP, as well as by the NCGC and other Molecular Libraries Initiative centers (http://mli.nih.gov/), are being made publicly available through Web-

based databases [e.g., PubChem (http://

pubchem.ncbi.nlm.nih.gov)]. In addition,

We propose a shift from primarily in vivo animal

studies to in vitro assays, in vivo assays with lower organisms, and computational modeling

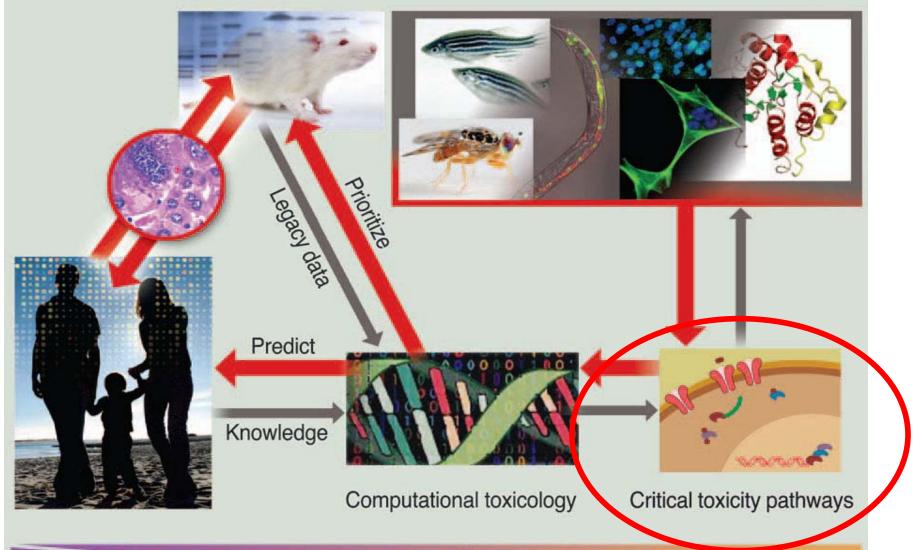


Transforming toxicology. The studies we propose will test whether high-throughput and computational toxicology approaches can yield data predictive of results from animal toxicity studies, will allow prioritization of chemicals for further testing, and can assist in prediction of risk to humans.

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Human experience 1–3 studies/year Standard rodent toxicological tests 10–100/year Alternative animal models 100-10,000/year Biochemical- and cellbased *in vitro* assays ≥10,000/day



High-throughput molecular mechanisms

Immediate human relevance



# ToxCast Data Analysis Summit EPA RTP campus, May 14-15, 2009

- Hosted by EPA's National Center for Computational Toxicology
- Modeling of ToxCast data to generate predictive signatures
- Derivation of significant toxicity pathways
- Committed to stakeholder involvement and public release of data and results
- ToxCast summit websitehttp://www.epa.gov/ncct/toxcast/summit.html



## In Vitro Models of Human Toxicity Pathways

**Evaluation of the ToxCast Suite of Cellular and Molecular Assays for Prediction of** *In Vivo* **Toxicity** 

Keith Houck, U.S. EPA, Research Triangle Park, NC

Use of Nuclear Reporter Assays to Investigate Species Differences in Toxicity

Richard Peffer, Syngenta Crop Protection Inc., Greensboro, NC

Towards New *In Vitro* Toxicology Strategies for Decision Making: Acute Toxicity as a Case Study

Gladys Ouedraogo, L'Oreal, Aulnay sous bois, France

Three-Dimensional Human Cellular and Metabolizing Enzyme Microarrays for High-Throughput Toxicity Screening

Jonathan Dordick, Rensselaer Polytechnic Institute, Troy, NY

Microscale Liver Models for Drug Development and Toxicity Screening Sangeeta Bhatia, MIT, Cambridge, MA