Editorial

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The study of adverse effects of chemicals on living organisms is a field of knowledge rife with uncertainties about how best to identify causes and predict effects. Such uncertainties are inherent to the growing complexity of the object of toxicology studies, namely: dose-response relationships for countless chemicals acting either in isolation or in concert, in different organisms subject to diverse environmental conditions; mechanistic actions and the relevance of the effects identified; and implications for human beings of toxicology tests done on laboratory animals.

The term toxicogenomics and its conceptualisation – a subdiscipline dealing with the identification of human and environmental toxicants and their putative mechanisms of action through the use of genomics resources – arose at least 20 years ago in a seminal article by Nuwaysir et al. (1999). Since then, dozens of books and thousands of articles have discussed the potential for applying toxicogenomics in risk assessments of toxic chemicals. That vast bibliography has helped build up a new field whose forecasting potential has generated great expectations, both for the screening of new chemical

molecules and for risk assessments of those molecules by regulatory agencies. This new research and regulatory paradigm is emerging from a number of initiatives with scientific, technological, health, ethical, economic, policy-making and institutional implications.

The coming together of disciplines such as toxicology, genomics and information technology has helped generate technologies capable of profiling the transcription of genes (transcriptomics), the biology of protein expression (proteomics) and the resulting metabolites (metabolomics) in organisms exposed to chemical agents. By bringing together the development of imagery, robotics and bioinformatics technologies, promising steps have moved beyond traditional toxicology's analytical methods, such as early detection of pathological alterations, at the genome level; greater sensitivity of tests to detect chemical noxiousness; simulation of environmental conditions to assess reactions by live organisms; the ability to support extrapolations with more precise and sound statistical results; and the possibility of obtaining faster and more reliable tests for responses by live organisms during different life stages, based on their genetic variability (Aardema and MacGregor, 2002; Harrill and Rusyn, 2008; North and Vulpe, 2010).

The progress of statistical models to compile, treat and simulate vast masses of data generated by those technologies makes it feasible to develop compendiums that can catalogue the fingerprints of cellular responses to various classes of chemicals. This allows scientists to classify chemical molecules based on the biological reactions they cause, to systematise and compare the mechanisms of action of cellular disorders caused by different chemical exposure conditions (hazard and risk identification) and to identify specific biomarkers for different kinds of molecular damage (MacGregor, 2003; Smith and Robert, 2008). The use of toxicogenomics thus promises quicker, more effective, sounder and less expensive toxicological assessments for drugs and other chemicals, thus reducing the cost of developing new molecules.

Toxicogenomics may also replace, at least partially, *in vivo* testing in laboratory animals with in vitro tests on live cells and tissues. Beyond the ethical motivation for this replacement, this new technology is a chance to cut major expenditures on a large volume of experimental animals to meet increasingly rigid toxicological criteria for the introduction and maintenance of commercial chemicals (Hartung, 2009; Chen et al., 2012).

Even so, these technologies' current stage of development, in terms of knowledge and actual application, still leaves such promises subject many uncertainties. Interpreting a massive volume of data generated by toxicogenomics depends on gaining a better grasp on cellular mechanisms and on possible dose-response relationships. Understanding these causal links is a key condition for the data generated to be useful as evidence in risk analyses for health and the environment. The variety of detection methods and equipment currently used in toxicogenomics also tends to generate uneven results, thus compromising the technology's reproducibility and reliability. Data gathering and processing costs are still high, considering the tens of thousands of chemicals now on the market (Ulrich and Friend, 2002; Suter and Babiss, 2004; Oberemm et al., 2005; Khan et al., 2014).

The solution to gain economies of scale and scope in data collection and analysis has been the sharing of information and operational integration with public databases (Mattes et al., 2004; Hendrickx et al., 2014; Davis et al., 2014). This interaction, however, is hindered by the fact that much of the data is generated by private companies zealous of their intellectual property rights or even the privacy of their data (Freeman, 2004).

Meanwhile, emerging public-private partnerships and consortia are building microarray databases, such as the Consortium for Metabonomic Toxicology (COMET), made up of five major pharmaceutical laboratories and the Imperial College of London (Lindon et al., 2005); Innovative Medicines for Europe – Predictive Toxicology (InnoMed Predtox), with 15 pharmaceutical laboratories and three universities (Mulrane et al., 2008); and the Liver Toxicity Biomarker Study, involving the National Center for Toxicological Research, BG Medicine Inc. and ten pharmaceutical laboratories (McBurney et al., 2009).

Another major challenge to achieve new risk-analysis parameters is that tests must be validated before regulatory agencies recognise and adopt them. Scientific criteria must be established to ensure the reproducibility, sensitivity, and robustness of tests done in different research centres (Aardema and MacGregor, 2002). Initiatives to build a 'regulatory science' grounded in toxicogenomics have relied on collaborative research strategies, training programs and discussion and harmonisation fora, involving public regulatory and research agencies (Corvi et al., 2003; Slikker et al., 2012; Tong et al. 2015).

Furthermore, the pathways being blazed in the development of toxicogenomics can, or actually should, provoke epistemological shifts in the very notion of risk analysis. Reductionist, case-by-case procedures to analyse chemicals' toxicological effects tend to be rethought, in a global context of biological systems that expose a continuum of chemical-ecological-biological interactions (Nicholson and Wilson, 2003). As Smith and Robert (2008, p.228) stated, "After all, genes do not themselves interact with exogenous environments – bodies do. Bodies are material, dynamic, historical, organic, phenomenal, and are not easily reduced to dots on a slide".

Considering all these aspects, toxicogenomics can be viewed as a multiple construct, whose institutionalisation as a field of research and a regulatory tool involves a variety of players in a path creation process. Research, commercial and market-control opportunities visualised today, as well as their ensuing trajectories, do not, however, imply a break with traditional toxicology. Rather they are elements of continuity, which innovation agents disembed out of their day-to-day activities "... in ways that mobilize, rather than alienate, constituents of a technological field" [Garud and Karnøe, (2001), p.3].

The articles in this special issue are the fruit of a workshop held at the Federal University of Paraná (Curitiba, Brazil) in September 2014, with the same title we have given this publication, and present reflections on this potential paradigm shift in the field of toxicology. B. Alex Merrick, Richard S. Paules and Raymond R. Tice present the pioneering experience of the US National Institute of Environmental Health Safety (NIEHS), in the creation of a high-throughput toxicology-screening technological development program identified as Tox21. This ambitious program coordinates the major conceptual and instrumental aspects of prospective toxicology present at the outset of this new century: adverse outcome pathways, genomics technology, bioinformatics, computerised robotic analysis and less reliance on *in vivo* testing with laboratory animals. The authors offer a comprehensive view of the history of Tox21's accomplishments over the past decade, and stress that the program's success was only achieved through the collaboration of a pool of US Government research and regulatory agencies in the fields of human health and the environment.

Susan Hester, David A. Eastmond and Virunya S. Bhat assessed the performance of transcriptional benchmark dose-response (BMDT) compared to BMD calculated from

conventional toxicological (apical) endpoints at cellular and tissue levels (BMDA). Their studies with diuron and conazole pesticides, as well as with phenobarbital and phthalates, showed that key gene and pathway-level BMDT were concordant and phenotypically anchored to BMDA for target tissues responses identified by *in vivo* studies in rodents. Their results corroborate the possibility that transcriptomic simulation and analytical tools may help make today's toxicological tests more efficient. This type of approach, carried out by researchers at the US National Health and Environmental Research Lab, at the Environmental Protection Agency, is the result of that agency's policy to develop knowledge and apply genomics in risk-assessment regulatory processes. Since it was launched in 2002, the Interim Policy on Genomics has evolved to establish a working group for the area, as well as to build a centralised genomics facility to further enhance proficiencies in genomics and bioinformatics.

Bennard van Ravenzwaay et al. describe their ten years of experience at Metanomics GmbH, a subsidiary of BASF Co., in the development of a data base with the toxicological and metabolomics profiles of approximately 750 chemicals studied in conventional, 28-day tests with rats. Their paper presents the methodology developed to control for variability in biological tests, in terms of sampling, collection and statistical assessment of the data obtained. They provide recommendations for research centres interested in setting up similar data banks and help move discussions forward on the sources of variability in the results of applied 'omics technologies', with reference to a cross-comparison between different laboratories over time.

Ivy Moffat, Carole L. Yauk, Julie Bourdon-Lacombe and Andrew Atkinson present the results of a survey at the Health Canada regulatory agency, on opinions of genomics experts doing genomics and risk-assessment research. The purpose of the survey was to identify tendencies, challenges and strategies to be adopted in the development of genomics as a tool to support that agency's regulatory process. The outcome corroborates expectations for genomics as a tool to reduce uncertainties in toxicological risk assessments of chemicals. The authors underline the importance of Health Canada's cooperation strategies with other national and international regulatory and research agencies. They highlight the need for more personnel trained in bioinformatics and biostatistics, in order to meet demand for this kind of knowledge in Canada. Finally, they identify the main challenges to the application of genomics as the lag in the agency's own knowledge about the field and the absence of legal means to oblige regulated companies to file data obtained from toxicogenomics.

References

Aardema, M. and MacGregor, J. (2002) 'Toxicology and genetic toxicology in the new era of 'toxicogenomics': impact of '-omics' technologies', *Mutation Research*, Vol. 499, No. 1, pp.13–25.

Chen, M., Zhang, M., Borlak, J. and Tong, W. (2012) 'A decade of toxicogenomic research and its contribution to toxicological science', *Toxicological Sciences*, Vol. 130, No. 2, pp.217–228.

Corvi, R., Ahr, H., Albertini, S., Blakey, D., Clerici, L., Coeke, S., Douglas, G., Gribaldo, L., Groten, J., Haase, B., Hmarnik, K., Hartung, T., Inoue, T., Indans, I., Maurici, D., Orphanides, G., Rembges, D., Sansone, S., Snape, J., Toda, E., Tong, W., van Delft, J., Weis, B. and Shechtman, L. (2003) 'Meeting report: validation of toxicogenomics-based test systems: ECVAM-ICCVAM/NICEATM considerations for regulatory use', *Environmental Health Perspectives*, March, Vol. 114, No. 2, pp.420–429.

Davis, A., Grondin, C., Lennon-Hopkins, K., Saraceni-Richards, C., Sclaky, D., King, B., Wlegers, T. and Mattingly, C. (2014) 'The comparative toxicogenomics database's 10th year anniversary: update 2015', *Nucleic Acids Research*, Vol. 43, pp.D914–D920, doi: 10.1093/nar/gku935.

Freeman, K. (2004) 'Toxicogenomics data: the road of acceptance', *Environmental Health Perspective*, Vol. 112, No. 12, pp.A678–A685.

Garud, R. and Karnøe, P. (2001) 'Path creation as a process of minful deviation', in Garud, R. and Karnøe, P. (Eds.): *Path Dependence and Creation*, pp.1–38, Lawrence Erlbaum Associates, London.

Harrill, A. and Rusyn, I. (2008) 'Systems biology and functional genomics approaches for the identification of cellular responses to drug toxicity', *Expert Opinion on Drug Metabolism & Research*, Vol. 4, No. 11, pp.1379–1389.

Hartung, T. (2009) 'Toxicology for the twenty-first century', *Nature*, July, Vol. 460, No. 9, pp.208–212.

Hendrickx, D., Boyles, R., Kleinjans, J. and Dearry, A. (2014) 'Workshop report: identifying opportunities for global integration of toxicogenomics databases, 26–27 June 2013, Research Triangle Park, NC, USA', *Archives of Toxicology*, Vol. 88, No. 12, pp.2323–2332.

Khan, S., Baghdasarina, A., Fahlman, R., Michail, K. and Siraki, A. (2014) 'Current status and future prospects of toxicogenomics in drug discovery', *Drug Discovery Today*, Vol. 19, No. 5, pp.562–578.

Lindon, J., Keun, H., Ebbels, T., Pearce, J., Holmes, E. and Nicholson, J. (2005) 'The Consortium for Metabonomic Toxicology (COMET): aims, activities and achievements', *Pharmacogenomics*, Vol. 7, No. 7, pp.691–699.

MacGregor, J. (2003) 'The future of regulatory toxicology: impact of the biotechnology revolution', *Toxicological Sciences*, Vol. 75, No. 2, pp.236–248.

Mattes, W., Pettit, S., Sansone, S., Bushel, P. and Waters, M. (2004) 'Database development in toxicogenomics: issues and efforts', *Environmental Health Perspectives*, March, Vol. 112, No. 4, pp.495–505.

McBurney, R., Hines, W., Von Tungeln, L., Schnackenberg, L., Beger, R., Moland, C., Han, T. Fuscoe, J., Chang, C., Chen, J., Su, C., Fan, X., Tong, W., Booth, S., Balasubramanina, R., Courchesne, P., Campbell, J., Graber, A., Guo, Y., Juhasz, P., Li, T., Lynch, M., Morel, N., Plasterer, T., Takach, E., Zeng, C. and Beland, F. (2009) 'The liver toxicity biomarker study: phase I design and preliminary results', *Toxicology Pathology*, Vol. 37, No. 1, pp.52–64.

Mulrane, L., Rexhepaj, E., Smart, V., Callanan, J., Orhan, D., Eldem, T., Mally, A., Schroeder, S., Meyer, K., O'Shea, D. and Gallagher, W. (2008) 'Creation of a digital slide and tissue microarray resource from a multi-institutional predictive toxicology study in the rat: an initial report from the PredTox group', *Experimental and Toxicology Pathology*, Vol. 60, Nos. 4–5, pp.235–245.

Nicholson, J. and Wilson, I. (2003) 'Understanding 'global' systems biology: metabonomics and the continuum of metabolism', *Nature*, August, Vol. 2, No. 8, pp.668–676.

North, M. and Vulpe, D. (2010) 'Functional toxicogenomics: mechanism-centered toxicology', *International Journal of Molecular Sciences*, Vol. 11, No. 12, pp.4796–4813.

Nuwaysir, E., Bittner, M., Trent, J., Barrett, J. and Afshari, C. (1999) 'Microarrays and toxicology: the advent of toxicogenomics', *Molecular Carcinogenesis*, Vol. 24, No. 3, pp153–159.

Oberemm, A., Onyon, L. and Gundert-Remy, U. (2005) 'How can toxicogenomics inform risk assessment?', *Toxicology and Applied Pharmacology*, Vol. 207, No. 2, pp.S592–S598.

Slikker Jr., W., Miller, M., Valdez, M. and Hamburg, M. (2012) 'Advancing global health through regulatory science research: summary of the Global Summit on Regulatory Science Research and Innovation', *Regulatory Toxicology and Pharmacology*, Vol. 62, No. 3, pp.471–473.

Smith, A. and Robert, J. (2008) 'Conceptual and normative dimensions of toxicogenomics', in Sharp, R., Marchant, G. and Grodsky, J. (Eds.): *Genomics and Environmental Regulation*, pp.219–241, The Johns Hopkins U.P., Baltimore.

Suter, L. and Babiss, L. (2004) 'Toxicogenomics in predictive toxicology in drug development', *Chemistry & Biology*, Vol. 11, No. 2, pp.161–171.

Tong, W., Ostroff, S., Blais, B., Silva, P., Dubuc, M. and Healy, M. (2015) 'Genomics in the land of regulatory science', *Regulatory Toxicology and Pharmacology*, Vol. 72, No. 1, pp.102–106.

Ulrich, R. and Friend, S. (2002) 'Toxicogenomics and drug discovery: will new technologies help us produce better drugs?', *Nature*, January, Vol. 1, No. 1, pp.84–88.