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The challenge of the application of 'omics technologies in chemicals risk assessment: Background and outlook

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ABSTRACT

This survey by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) highlights that 'omics technologies are generally not yet applied to meet standard information requirements during regulatory hazard assessment. While they are used within weight-of-evidence approaches to investigate substances' modes-of-action, consistent approaches for the generation, processing and interpretation of 'omics data are not applied. To date, no 'omics technology has been standardised or validated. Best practices for performing 'omics studies for regulatory purposes (e.g., microarrays for transcriptome profiling) remain to be established. Therefore, three frameworks for (i) establishing a Good-Laboratory Practice-like context for collecting, storing and curating 'omics data; (ii) 'omics data processing; and (iii) quantitative WoE approaches to interpret 'omics data have been developed, that are presented in this journal supplement. Application of the frameworks will enable between-study comparison of results, which will facilitate the regulatory applicability of 'omics data. The frameworks do not constitute prescriptive protocols precluding any other data analysis method, but provide a baseline for analysis that can be applied to all data allowing ready cross-comparison. Data analysis that does not follow the frameworks can be justified and the resulting data can be compared with the Framework-based common analysis output.

Abbreviations: AOP, Adverse outcome pathway; C&L, Classification and Labelling; CATTPTRA, Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment; CEBS, Chemical Effects in Biological Systems database; CEFIC, European Chemical Industry Council; CLP, Classification, labelling, packaging of substances; DEG, Differentially expressed gene; DETECTIVE (project), Detection of endpoints and biomarkers of repeated dose toxicity using *in vitro* systems; DMEL, Derived minimum effect level; DNEL, Derived no effect level; EAGMST, Extended Advisory Group on Molecular Screening and Toxicogenomics; ECETOC, European Centre for the Ecotoxicology and Toxicology of Chemicals; ECHA, European Chemicals Agency; EURL ECVAM, European Union Reference Laboratory for Alternatives to Animal Testing; GHS, Globally harmonised system of classification and labelling of substances; GLP, Good laboratory practice; IATA, integrated approach for testing and assessment; IPCS, International Programme on Chemical Safety; ISATAB, Investigation/Study/Assay tab-delimited format; ITS, Integrated testing strategy; LOAEL / LOAEC, Lowest-observed adverse effect level / concentration; LRI, Long-range Research Initiative; MAD, Mutual acceptance of data; MAQC Consortium, MicroArray Quality Control Consortium; MGED Society, Microarray Gene Expression Society; MIAME, Minimum Information About Microarray Experiments; MIE, Molecular initiating event; MoA, Mode-of-action; NOAEL/C, No-observed adverse effect level / concentration; NRC, National Research Council; OECD, Organisation for the Economic Cooperation and Development; PHE, Public Health England; PoD, Point-of-departure; qRT-PCR, Quantitative real-time polymerase chain reactions; REACH, Registration, Evaluation, Authorisation, Restriction of Chemicals; TG, Test guideline; TG-GATES, Toxicogenomics Project-Genomics Assisted Toxicity Evaluation System; TRF, Transcriptomics reporting framework; WHO, World Health Organisation; WoE, Weight-of-evidence.

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1. Introduction

This survey summarizes legal, regulatory, scientific and technical challenges that have to be met to facilitate the regulatory use of 'omics technologies. Thereby, it serves as background information to the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) workshop report *Applying 'omics technologies in chemicals risk assessment* (Buesen et al., 2017); *the Framework for the quality assurance of 'omics technologies considering GLP requirements* (Kauffmann et al., 2017); *the generic Transcriptomics Reporting Framework (TRF) for 'Omics Data Processing and Analysis* (Gant et al., 2017); *and the Framework for the quantitative weight-of-evidence analysis of 'omics data for regulatory purposes* (Bridges et al., 2017) that are all combined in this journal Supplement.

The following parts of the introduction provide definitions for different 'omics technologies, generally describe how 'omics could be used for regulatory purposes, and discuss how the regulatory use of 'omics differs from their use within research projects that are unrelated to regulatory purposes. The introduction is followed by 4 Sections:

Section 2 presents the outcome of a written inquiry that was undertaken with chemical companies producing for the global market. These key players were invited to share their views on the regulatory use of 'omics technologies, to identify reasons why 'omics are not commonly used, or to share their experience in using them, as applicable.

Section 3 supplements the responses received during the written inquiry. Taking the example of *Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation, and Restriction of Chemicals* (REACH; EP and Council of the EU, 2006), it discusses the legal and regulatory framework that is relevant for the regulatory use of 'omics technologies.

Section 4 explores specific scientific and technical aspects that may stand in the way to the use of 'omics data for human health hazard assessment of substances. This appraisal is focused on microarray technologies used for transcriptome profiling. Other 'omics technologies (e.g. quantitative real-time polymerase chain reactions (qRT-PCR), RNA-sequencing), proteomics and metabolomics are not considered. Also, the use of 'omics technologies for ecotoxicological assessments is excluded.

Section 5 discusses the outcome of the survey and aims at designing a roadmap to facilitate the regulatory acceptance and use of 'omics technologies.

1.1. What are 'omics?

The term 'omics as used in this survey refers to the study of systemic genome responses to substances in cellular systems or whole organisms. For convenience, the major different 'omics technologies currently available can be viewed as follows (OECD, 2005, 2009; CATTPTRA–NRC, 2007):

- **Genomics**: The study of the structure and function of the genome (toxicogenomics in the context of toxicology);
- **Transcriptomics**: The study of genomic-scale changes in RNA expression (e.g. messenger RNA and noncoding RNA (Aigner et al., 2016));
- **Proteomics**: The study of cell- and tissue-wide protein expression;
- **Metabolomics**: The study of cell- and tissue-wide metabolite profiling;
- **Epigenomics**: The study of reversible heritable changes in gene function that occur without a change in the sequence of nuclear DNA (e.g. DNA methylation and histone modifications).

'Omics data first started appearing in the late 1980s with the development of spectroscopy techniques, such as nuclear magnetic resonance. However, the term 'omics really came into use in the late 1990s with the invention of microarrays for transcriptome profiling. It was then applied to the further development of mass spectrometry and nuclear magnetic resonance that made possible proteomics and metabolomics in addition to transcriptomics. High throughput transcriptome sequencing has also been used in 'omics studies (Gant et al., 2009; Rouquié et al., 2015; Xu et al., 2016).

'Omics (and epigenomics) technologies all encompass the collection of large data sets. Analysis of these high volume data requires bioinformatic methods (whereas interpretation of data from 'omics studies often requires input from conventional biology, pathophysiology, and toxicology). Therefore, 'omics technologies have advanced conjointly with the science of bioinformatics that incorporates the established principles of statistical data interpretation specifically for application to 'omics data sets. The advances in bioinformatics that developed in parallel to 'omics technologies allowed more measurements to be stored and processed.

In the last decades, 'omics technologies have been applied extensively in research (Raja et al., 2017). 'Omics technologies have the capability of providing a profound insight into the biochemistry and physiology of the cell and any perturbing effects of xenobiotics. This has led to an enthusiastic adoption by research toxicologists. Hopes were expressed that 'omics technologies would provide the tools to identify an array of biomarkers of adverse effects and modes-of-action (MoAs) of toxicity to improve the prediction of human effects during substance hazard assessment and that they would contribute to the development of alternative methods to animal testing (Storck et al., 2002; OECD, 2005, 2009; CTTAEA-NRC, 2007; Gant, 2007; Gant et al., 2009; Phillips et al., 2009; Goodsaid et al., 2010; Buick et al., 2015; Li et al., 2015; Williams et al., 2015). Despite this, the translation of 'omics into the regulatory domain remains at best cautious (Tralau et al., 2015).

1.2. What are 'omics applications?

In toxicological research, 'omics methodologies have been applied as a means to evaluate if substances induce whole genome alterations that could ultimately lead to or be assessed with the development of adverse effects and to identify the MoAs of potentially toxic substances by reference to established adverse outcome pathways (AOPs; see below).

When testing for substance-induced effects (hazard), 'omics data can be used for class comparisons, predictions or discovery. Taking the example of microarray experiments for transcriptome profiling, class comparisons address the question, which genes best distinguish data classes (e.g. the control group and the test group). Class predictions use the pattern of gene expression induced by the test substance to predict the MoA and its effects (Box 1). In a similar manner, the gene expression pattern can be used for comparison with other data and using unsupervised clustering methods to make new predictions about the MoA of the chemical.

1.3. What are MoAs and AOPs and how do 'omics contribute to their understanding?

MoAs describe the biologically plausible sequence of chemical-

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