Application of a coordinated OMICS research program and data into regulatory frameworks: case-studies and perspectives

Chairs: Bruno Campos, Adam Biales, Philipp Antczak, Geoffrey Hodges

During the past decade, governments from around the world are reassessing the effectiveness of current regulations at protecting human and environmental health against the potential harmful effects of chemical and nano compounds. These are critical and complex rules that are either based on the observed adverse effects of compounds, or based on precautionary principles. Most recently, the Adverse Outcome Pathway (AOP) framework is proposed to consolidate mechanistic information on how compounds disrupt biological processes that result in adverse outcomes. This latest approach to understand toxicity thresholds (useful for regulation) can potentially also bridge the artificial divide between toxicology applied to human and the environment. However, persistently huge scientific constraints remain at determining the environmental and human health risks for an ever increasing number and diversity of consumer products introduced to the market, primarily because toxicity testing fails to keep pace with modern biology. This has created an enormous backlog of chemicals that have yet to be experimentally assessed for potential health hazards (especially as mixtures), combined with inadequate methods at monitoring for the presence of contaminants in the environment and determining the level of risk so policy makers and regulators can make informed decisions, balancing economic priorities with the need to protect vital ecosystems and public health.

Recognizing that the main challenge of implementing proposed methods to improve environment and health protection stems from the lack of useful experimental data, an innovative and coordinated scientific approach is underway. This approach pursues toxicology as foundational science, having the same effect that genetics and genomics have at revealing fundamental principles useful for understanding and treating human disease. This proposed session and discussion among investigators and stakeholders begins by forecasting that a big data scientific enterprise - using high-throughput toxicity testing with data-rich OMICS (e.g. genomics, transcriptomics, proteomics, metabolomics) in non-mammalian model organisms and in vitro cell models - will deliver fundamental principles of how genes and their products functionally associate into corresponsive networks. In parallel, systems biology approaches are in development that utilize this vast amount of information and are able to extract key components central to the AOP framework.

Closing the gap between these approaches and the regulatory application is therefore a key component of this session. We invite presentations of case studies and perspectives using OMICS that result in (or lead towards) better understanding of regulatory decisions. These may include examples of OMICS-based predictions of apical endpoints, approaches for AOP identification, cross-validation studies, supporting categorisation, selection/de-selection of alternative substances, supporting toxicity assessment contributions for faster screening and prioritization and weight-of-evidence contributions. We also seek contributions from industry and regulators, presenting visions, objectives or hurdles on the way towards a Knowledgebase of new toxicological understanding and principles. We propose to bring together science, industry and policy makers to discuss present usages of these technologies, increasing the value and robustness of this data-driven knowledge and its applications to meet the requirements of industry and regulators, in order to make a step forward in environmental protection, while supporting the needs of cost-effective industrial innovation.

Preliminary session type: Platform and Poster

Development and application of oxidative stress biomarkers and models in ecotoxicology and environmental monitoring

Chairs: Agneta Oskarsson, Johan Lundqvist

Oxidative stress is involved in a wide range of toxicological end-points (e.g. tissue toxicity, genotoxicity, mutagenicity, carcinogenicity and teratogenicity). The nuclear factor erythroid 2-related factor 2 (Nrf2) is a regulator in the cellular defense against oxidants and a key event in the oxidative stress pathway is the release of Nrf2. In an investigation of the effects of more than 300 pesticides on nuclear receptors and transcription factors, the Nrf2 pathway was one of the most commonly affected target and activated by the largest number of chemicals (Martin et al., 2010). Further, the Nrf2 activity was highly correlated with classical toxicological endpoints.

A key mission in the strategy of using in vitro bioassay in ecotoxicology and environmental monitoring is the establishment and selection of suitable bioassays. The bioassay development has been focused on finding molecular events that are important for a wide range of toxicological end-points and that is triggered by a large number of the known hazardous substances. Based on the findings described above, oxidative stress in general and Nrf2 activity in particular has been highlighted as very promising molecular events for bioassay establishments.

Environmental samples are often highly complex mixtures of known and unknown chemical compounds. Effect-driven fractionation and chemical analysis is a promising strategy where in vitro toxicity assays leads the way in the identification of toxic compounds. Furthermore, in vitro toxicity testing can be a valuable tool to asses the total toxicity exerted by mixtures of chemical compounds.

During the last years, a wide range of methods to study oxidative stress response and Nrf2 activity has been presented; e.g. gene expression studies of Nrf2, gene expression studies of downstream genes in the oxidative stress pathway (HO-1, NQO1, SOD etcetera), Nrf2 responsive luciferase reporter assay systems and Nrf2 responsive green fluorescent protein transgenic zebra fishes. Some, but not all, of these assays has also been used in ecotoxicology or environmental monitoring settings.

The aim of this session is to present and discuss biomarkers for oxidative stress, their correlation to toxicity endpoints in various organisms and their application in effect-driven identification of novel hazardous compounds in the environment.

Reference:

Martin M.T., Dix D.J., Judson R.S., Kavlock R.J., Reif D.M., Richard A.M., Rotroff D.M., Romanov S., Medvedev A., Poltoratskaya N., Gambarian M., Moeser M., Makarov S.S., Houck K.A., 2010. Impact of environmental chemicals on key transcription regulators and correlation to toxicity end points within EPA's ToxCast program. Chem Res Toxicol. 23, 578-90.

Preliminary session type: Platform and Poster

Epigenetic effects of environmental stressors: new scientific challenges for environmental risk assessment

Chairs: Jana Asselman, Benjamin Pina, Jean Lou Dorne

There is a growing body of scientific evidence indicating that environmental stressors, including chemicals, biocides and plant protection products, may contribute to the de-regulation of epigenetic mechanisms. Yet, their disruptive potential in environmental toxicology is largely unknown due to a limited knowledge of epigenetic effects in ecotoxicological model organisms. Epigenetic disruptors may act by directly impacting on components of epigenetic regulation pathways, like DNA methylases or histone modification enzymes, or may even irreversibly alter the "epigenetic code". Epigenetic effects present a new challenge for risk assessment as their adverse outcomes may still be detected long after the actual exposure occurred. An increase in scientific research reporting of multigenerational effects that could be detected generations after the actual exposure occurred. Evidence for these trans-generational effects of pollutants is accumulating across a diversity of systems, and this reality cannot be ignored in future assessment procedures.

In addition, epigenetic studies may provide substantial insight in how chemicals can alter regulatory processes at levels that do not necessarily result in overt toxicity but may significantly affect subsequent unexposed generations. (see SETAC Meeting sessions from 2008, see Ecotoxicology Special Issues; see key note by Juliette Leger at SETAC Basel 2014; see top research questions selected by the SETAC-Horizon Scanning Workshop, held in Barcelona, 6-7 May 2015).

However, scientific findings, even if they are obtained from the most sophisticated approaches (e.g., epigenomics), still need to be tested for their relevance to risk assessment, which would ideally require a dialog from the early stages between scientists and stakeholders (see EVOGENERATE Work Group of the SETAC ERA AG). Therefore, this session, proposed by the EVOGENERATE Work Group, will address the development of new methods and model systems for the characterization of the epigenetic effects, hazard identification of epigenetic effects, both at short- and long-terms, and the integration of epigenetic data in ecological and human health risk assessment. These methodologies and model systems should provide scientific guidance to support optimized decision making, through a sustainable trade-off between human demand on, and conservation of natural resources.

Sponsored by: Ecological Risk Assessment Advisory Group (Global)

Preliminary session type: Platform and Poster

Genetic and evolutionary effects of pollutants: how to implement scientific knowledge to long-term ERA

Chairs: Marie-Agnes Coutellec, Carlos Barata, Arnaud Chaumot

Many organisms, populations and species are currently facing severe degradation of their environment due to global change. Human activities, among which the continuous release of potentially toxic substances into the environment, contribute significantly to this pervasive change. There is growing evidence that environmental change may affect organisms beyond exposed generations and trigger rapid micro-evolutionary processes. Furthermore, biological responses may also depend on population standing genetic variation and evolutionary history, and on phylogenetic constraints. Assessing pollutant driven selection in the field is extremely difficult, due to confounding factors that also shape the distribution of genetic diversity. This explains why it is still so challenging to integrate evolutionary indicators into ecological risk assessment (ERA). Nevertheless, evidence for evolutionary (genetic) and trans-generational (non genetically inherited) impact of pollutants is accumulating across a diversity of systems, and this reality cannot be ignored in future assessment procedures (see SETAC Meeting sessions from 2008, see Ecotoxicology Special Issues; see top research questions selected by the SETAC-Horizon Scanning Workshop, held in Barcelona, 6-7 May 2015). However, scientific findings, be they obtained from the most sophisticated approaches (e.g., population genomics, genome- and environment-wide association studies, quantitative genetics in the wild using so-called animal models, etc.), still need to be tested for their relevance to ERA, which would ideally require a dialog from the early stages between scientists and stakeholders (see EVOGENERATE Work Group of the SETAC ERA AG). Therefore, it becomes urgent to acquire tools and methods to measure, anticipate, and even predict genetic and evolutionary ecotoxicological effects, the genetic and non-genetic basis of adaptation/maladaptation to environmental stress and the adaptive potential of natural populations, as well as to understand their consequences for ecosystems, including species distribution and persistence. These tools should provide scientific guidance to support optimized decision making, through a sustainable trade-off between human demand on, and conservation of natural resources.

This session is proposed by the EVOGENERATE workgroup (SETAC, ERA-AG) together with a companion session which specifically focuses on epigenetic effects of pollutants.

We are inviting scientists from Academia, Industry and State Environmental Agencies to present studies addressing trans-generational and micro-evolutionary responses to pollutants: applicability of evolutionary concepts to ERA ; population genomics and system biology: understanding adaptive responses through a mechanistic angle, from molecular processes to higher levels of organization; phylogenetic signal: improving assessment of species sensitivity, identifying phylogenetic components of, -and constraints on lineage response, comparative toxicology.

Sponsored by: Ecological Risk Assessment Advisory Group (Global)

Preliminary session type: Platform and Poster

MetaOMICs in ecotoxicology: evaluation of alterations in the structure and functions of ecosystems

Chairs: Susana Cristobal, Martin Eriksson, Mechthild Schmitt-Jansen

MetaOMICs in ecotoxicology play a new role in the evaluation of alterations in the structure and functions of ecosystems. Metagenomics, metaproteomics and metametabolomics analyses respectively the DNA sequences of a community, the translated proteins and the metabolites resulting from cellular processes. Therefore "meta-omics" data could capture the functional interactions occurring in a given ecosystem and provide community analysis tools that could link ecology, physiology and functional analysis.

By discovering a huge novel prokaryote and eukaryote biodiversity in terrestrial and aquatic ecosystem, metaOMICs is having a profound impact on our understanding of how the biosphere is organised and how it functions, and will be leading to a true paradigm shift in ecotoxicology. Metagenomics has been used in community ecotoxicology and field studies describing effects of contaminants and selection pressures in the environment. Metaproteomics has been applied to define the role that microbial species have in an ecosystem, or understanding the microbial community response and adaptation to environmental stressors. The metametabolomics studies provide complementary data for the functional characterization of a community and generate indirect measurement of the molecular phenotype.

This session welcomes research focus on meta-omics data analysis and its application to aquatic and terrestrial ecotoxicology. The metadata analysis from environmental samples could cover several levels of biological complexity from metagenetics (amplicon sequencing of specific genes), metagenomics and functional proteins in communities, or genetics, genomics or proteomics of populations and metametabolomics, expression the community at the metabolic level. The session will present studies that assess how toxicants or other anthropogenic stressors change the diversity and/or function of communities or populations, studies presenting metagenome mining, metaproteome characterization of relevant environmental samples, methodological implementation for data analysis and functional characterization, and novel environmental assessment methodologies. The robustness and capability from meta-omics data is highlighting importance of understanding the microbial population dynamics and community ecology to safeguard our environmental for future generations.

Keywords: metagenomics, metaproteomics, metametabolomics, next generation sequencing, networks, bioinformatics, mass spectrometry

Preliminary session type: Platform and Poster