Exposure- and Risk-Based Prioritization of Chemical Life Cycle Emissions and Chemicals in Consumer Products

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1191 The OECD QSAR Toolbox as an Integrated Platform for Chemical Screening and Regulatory Risk Assessment

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The OECD QSAR Toolbox is a free software application developed by ECHA and OECD with over 25,000 users. In recent years, the Toolbox functionalities have been extended beyond QSARs to all aspects of chemical hazard assessment, from advanced chemical searches to handling of data and reporting. After developing a satisfactory set of functionalities, the focus is now on simplifying the use of Toolbox with a new interface and on the connection with other software to create an integrated platform that reads relevant data, operates on them, and then links back to the data source or produce new results. With this vision in mind, a cornerstone is the development of a comprehensive plug-in to link Toolbox with IUCLID databases, which represent the standard among regulatory agencies and industry for data on chemical substances in the format of the OECD Harmonised Template. A Toolbox repository has also been launched. Here, third parties can upload and share with other users their own extensions and connect their tools to Toolbox, as has already happened for the QSAR platforms VEGA and KATE. A workflow editor has been introduced to allow users to program their own automated workflows in Toolbox for batch execution of tasks. At the same time, the work on functionalities for hazard assessment has not stopped: the newly developed automated workflow for skin sensitization defined approaches in the QSAR Toolbox has become the first *in silico* tool part of an OECD Guideline. The Toolbox is the result of over a decade of commitment from ECHA and OECD to promote the correct use of alternative methods. With these new connection possibilities, now third parties can more easily contribute to Toolbox developments, e.g. towards their specific hazard assessment needs.

1192 Integration of New Approach Methodologies for Prospective Selection of Chemicals for Additional Study

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Use of new approach methodologies (NAMs), including high-throughput, *in vitro* bioactivity data, in setting a point-of-departure (POD), has the potential to accelerate the pace of human health risk assessments. Combining hazard and exposure predictions as a bioactivity:exposure ratio (BER) for use in risk-based prioritization of substances that may not have a complete data profile represents a prospective approach to employing new approach methodologies (NAMs). Further, NAMs may provide some support for derivation of bioactivity flags, i.e. potential hazards that are of concern for further mechanism-based screening and/or hazard prediction. In this work, we describe the first phase of an effort conducted via the Accelerating the Pace of Chemical Risk Assessment initiative, a consortium of international toxicologists and regulatory scientists. This prospective case study involves generation of NAM data for 200 chemicals, with the primary objective of developing reusable and adaptable approach for prioritization of chemicals for additional short-term studies in rats using a combination of the BER and bioactivity-based flags for indication of putative endocrine, developmental, neurological, and immune suppressive effects. Multiple hazard data streams, including targeted biochemical and cell-based assays, high-throughput transcriptomics, and high-throughput phenotypic profiling data, will be used to inform hazard and risk indications, along with generic high-throughput toxicokinetic models parameterized with chemical-specific data. The goal of this case study is to enable regulatory scientists from different international contexts to develop efficient approaches for chemical management, while possibly reducing the need for animal studies by identifying key areas for hazard characterization. This work demonstrates the feasibility, and continuing challenges, of using toxicodynamic and toxicokinetic NAMs in screening level safety assessment. *This abstract does not necessarily reflect US EPA, Health Canada, EFSA, ECHA, A*STAR, or JRC policy.*

1193 Chemical Hazard Assessment Based on *In Vitro* Phenotypic Profiling and Mechanistic Reasoning

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Current chemical safety assessments are mostly based on phenotypic endpoints derived from animal models. New approach methods based on predictive *in vitro* molecular and phenotypic endpoints have the potential to enable assessments based on mechanistic reasoning that are more efficient and relevant to human health. This presentation will provide an update on the development of "High-Throughput *in Vitro* Phenotypic Profiling for Toxicity Prediction" (HIPPTox), which uses high-throughput cellular imaging and machine learning to automatically identify cell models and phenotypic endpoints predictive of chemical-induced toxicity. We have used HIPPTox to develop highly predictive *in vitro* toxicity models based on human proximal tubular cells, bronchial epithelial cells, and hepatocytes. In collaboration with the Accelerating the Pace of Chemical Risk Assessment (APCRA) initiative, we have also developed a HIPPTox-based analysis method to rapidly and efficiently estimate the Points of Departure (POD) in cellular responses. These models and methods can be used to accelerate the prioritization of chemicals with little or no human safety data.

1194 Exposure- and Risk-Based Prioritization of Chemical Life Cycle Emissions and Chemicals in Consumer Products

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The presence of thousands of marketed chemicals in a wide range of daily consumer goods requires approaches that go beyond traditional methods that focus mostly on well-studied chemicals. We propose an approach for quantitatively screening human and ecological exposure to indicate potential risk from chemicals emitted along product life cycles and chemicals used in consumer products. In this high-throughput approach, we combine stochastic chemical-product use information, mass-balanced near-field/far-field exposure models, and probabilistic dose-response methods, coupled with decision trees for deriving reliable dose- or concentration-response factors for human toxicity and ecotoxicity effect modeling. Applying our approach, we estimate multi-pathway near- and far-field exposures for several thousand chemical-product combinations by calculating chemical intake fractions per mass unit emitted or in products ranging from 0.001 to ~1, and related exposure doses that vary over more than nine orders of magnitude. Based on curated experimental animal data available from the US EPA's ToxValDB, Points of Departure (PODs) were derived for >9000 chemicals based on the 5th percentile of a fitted log-normal distribution, showing good correlation with 746 chemicals that have available regulatory PODs. Combining predicted exposures with chemical-specific dose-responses and reference doses demonstrates that risks can be substantial for multiple home maintenance products, such as paints or paint strippers, for some home-applied pesticides, leave-on personal care products, and cleaning products. Ecotoxicological impacts were found the highest for specific chemicals in floor cleaning liquids, laundry detergents, bath oils, surface cleaners, and outdoor spray insecticides. Our results reveal large variations of up to 10 orders of magnitude in impacts across both chemicals and product combinations, demonstrating that prioritization based on hazard only is not acceptable, since it would neglect orders of magnitude variations in both product usage and exposure that need to be quantified. Our framework is applicable for evaluating chemical emissions and product-related exposure in life cycle assessment, chemical alternatives assessment and chemical substitution, consumer exposure and risk screening, and high-throughput chemical prioritization.

1195 Assay Gaps in the Developmental Neurotoxicity (DNT) New Approach Methodologies (NAMs) Battery for Human Health Risk Assessment

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The developing brain is more vulnerable to environmental perturbations than the mature brain, partly due to the complex events of neurodevelopment (such as proliferation, migration, and differentiation). Interference with these key processes by chemical exposure can contribute to neurodevelopmental disorders in children. The current *in vivo* developmental neurotoxicity (DNT) guidelines have several challenges and limitations, and consequently regulatory bodies have focused on new approach methodologies (NAMs). Over the years, alternative tests and their readiness for regulatory purposes to understand the mechanisms and key processes of DNT have been identified. With support from the European Food Safety Authority (EFSA) and US Environmental Protection Agency (US EPA), a testing battery of *in vitro* and nonmammalian assays was selected and challenged with ~100 chemicals. At the same time, an Organisation for Economic Co-operation and Development (OECD) guidance document is in preparation to inform on the testing battery, its usage, and its interpretation. It was recently discussed in a public virtual peer-review meeting organized by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), US EPA. Although the overall impression by the scientific advisory panel of applying NAMs to DNT was positive, one concern was the limited or missed coverage of some critical processes of brain development. These processes include glial cells differentiation, maturation, and function; endocrine disruption; and more mechanistic assays such as ontogeny of neurotransmitter function (e.g., receptors and neurotransmitter ratio). This session will go beyond the assays in use that have been presented previously and focus on key processes currently missing in the NAMs battery for DNT assessment. The introduction will give a short overview of the current EFSA/OECD/US EPA *in vitro* testing battery and the identified gaps. The presenters have been selected to present novel assays using, for example, more complex 3D cell cultures, chip platforms, and computational approaches that potentially can be incorporated into the battery to enhance the coverage of DNT. The final presentation also will discuss integration of other data streams and consideration of critical stages of development when using toxicokinetics to evaluate *in vitro* positive results. All presenters have been encouraged to describe the rationale for the new assays, the benefits, and the limitations. Presentations will be followed by an interactive panel discussion about these new assays' readiness for inclusion in the testing battery, with perspectives from academia, government, and industry. Moreover, the presenters will review how the battery described in the OECD guidance document can be further improved, additional gaps to consider, and how the approach translates to DNT *in vivo*, preferably in humans. Furthermore, the panel will discuss the challenges and best ways to combine and apply the battery of *in vitro* tests to risk assessment.