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in lungs, kidneys and brain, was used as a reference compound to test this approach.

Cytotoxicity after PQ exposure (24/48h) was determined by MTT or ATP assay for each system. Then the models were exposed to 2–4 concentrations (at least one below IC10 value for cytotoxicity) for 24 or 48h. Samples were collected for TempOSeq™ analysis with a set of 3565 probes. Raw data were subjected to probe and sample filtering and were carefully quality controlled. Differentially expressed genes (DEG) were detected using DESeq2 R package. Pathway analysis using the full list of DEG per model and the database CONSENSUSPathDB® showed the disruption of “Oxidative stress induced gene expression via nrf2 markers”, as expected since it is the well-known PQ mechanism of action. Furthermore, two other pathways previously involved in PQ toxicity, “ESR-mediated signaling” and “Photodynamic therapy-induced unfolded protein response”, were also deregulated. Genes belonging to these pathways, such as MAFF (MAF BZIP Transcription Factor F), PPP1R15 (Protein Phosphatase 1 Regulatory Subunit 15A), ATF4 (Activating Transcription Factor 4) and GDF15 (Growth Differentiation Factor 15), showed various levels of expression in the distinct models, suggesting cell type- or organ-specific ability to respond to PQ exposure.

This strategy allowed to determine known mechanisms of PQ toxicity, although we used a restricted cost-effective, number of probes in TempOSeq analysis. The main advantages of this strategy are to assess chemical toxicity on multiple organs in parallel, exclusively in human cells, and on cell-type- or organ-specific models derived from the same donors, eliminating the interspecies and genetic background biases, and allowing a better evaluation of the differential sensibility of the diverse organs. Furthermore, although we focused on the common mechanisms of action of PQ, this strategy would allow at the same time for organ-specific toxicity testing, by using an increased number of probes for TempOSeq analyses. In conclusion, we believe this strategy will participate in the further improvement of chemical risk assessment for human health.

**SOC04-06**

**Brain Organoids to Study SARS-CoV-2 Infection of Developing CNS**

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Early reports from Wuhan suggested that 36% of COVID-19 patients show neurological symptoms, later European studies showed as much as 60%; cases of viral encephalitis have been reported. This suggests that the virus might be neurotropic under unknown circumstances. This is well established for other coronaviruses. Many questions remain with regard to the current pandemic, including the influence of SARS-CoV-2 on the developing brain. In order to understand why some patients develop such symptoms and others do not and whether developing brain might be more susceptible than adult counterpart, we addressed the infectability of the central nervous system (CNS). Reports that the ACE2 receptor – critical for virus entry into lung cells – is found in different neurons support this expectation. We employed a human induced pluripotent stem cell (iPSC)-derived BrainSphere model. A short-term infection of the BrainSpheres with SARS-CoV-2 led to infection of a fraction of neural cells with replication of the virus evident at 72 hpi. Virus particles were found in the neuronal cell bodies extending into apparent neurite structures. PCR measurements corroborated the replication of the virus, suggesting at least a tenfold increase in virus copies per total RNA. Immature and more mature cultures have been compared. 12-week BrainSpheres were more sensitive to infection than 5-week ones, suggesting that maturation processes (such as synaptogenesis and network formation) might render more sensitive to the infection. These findings were supported by others in similar brain organoid models. These recent findings will be summarized to understand the advantages and limitations of brain organoids in infectious diseases in particular for the developing nervous system, as brain organoids mimic embryonic stages of development.

**SOC04-07**

**Evaluating new approach methodologies for consumer-based risk assessments: challenges and future perspectives**

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Using the risk assessment of 0.1% coumarin in a face cream and body lotion as an exemplar case study, we recently demonstrated how new approach methodologies (NAMs) can be applied in Next Generation Risk Assessment (NGRA) to assess the safety of consumer product ingredients [Baltazar et al, 2020]. While this study helps build confidence in the use of NAMs for consumer-based risk assessments, there is an on-going need to demonstrate that these approaches can be used to define low-risk consumer exposures for a wider range of chemicals and scenarios. To that end, we are evaluating a potential toolbox for systemic toxicity, which comprises several NAMs for characterising bioactivity (high throughput transcriptomics, in vitro cellular stress [Hatherell et al., 2020] and the Eurofins Safety44® Screen), together with and computational models for estimating relevant human exposures (physiologically-based kinetics (PBK) modelling [Moxon et al, 2020], skin penetration and free concentration models). These tools can be combined to estimate a margin of safety (MoS) for a given chemical exposure. In this presentation we will discuss the overall strategy for evaluating the toolbox, namely to generate data for at least forty chemical-exposure scenarios that are either known to be either associated with adverse systemic toxicity effects, or are known to present a low risk to humans. These data will be used to develop a Bayesian statistical model for characterising uncertainties in the MoS distribution, which in turn could be used to identify appropriate low risk exposures as part of an overall safety assessment for novel consumer ingredients. Preliminary toolbox results for twelve chemical-exposure scenarios (generated as part of a pilot study) will be used to illustrate the overall concepts and future perspectives of the work.

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