dexamethasone therapy, we apply physiologically-based pharmacokinetic (PBPK) modelling to predict foetal exposure after maternal dosing.

Methods: To characterize the placental handling of dexamethasone *ex vivo*, we performed dual-side perfused isolated human cotyledon experiments (n = 3) with term placenta in closed-closed setting. The tissue was perfused for 3 hours with 70 ng/mL dexamethasone in Krebs-Henseleit buffer. Next, intrinsic unbound placental transfer values were derived from the perfusion data using a physiologically-based semi-mechanistic placenta (PBMP) model in Matlab. Values were used for parameterization of Simcyp's pregnancy-PBPK (p-PBPK) model to predict maternal and foetal exposure. In addition, to evaluate whether placental exposure to the drug may result in adverse effects on placental syncytiotrophoblasts, a toxicity screening exposing BeWo cells to dexamethasone concentrations in a range of 5–25.000 nM for 24 hours was executed.

Results: Perfusion experiments showed that dexamethasone extensively crosses the placenta. The PBMP model adequately described the perfusion data. The intrinsic unbound transfer values derived, were estimated to be 1033.5 mL/min and 15.2 mL/min for the maternal placental uptake and efflux, and 1311.1 mL/min and 10.7 mL/min for foetal placental uptake and efflux, respectively. For an intramuscular dose of 8 mg at 28 weeks of gestation, whole body p-PBPK modelling predicted a C_{max} and $AUC_{0-\infty}$ of 46.09 ng/mL and 230.46 ng/ml*h in maternal plasma and a C_{max} and $AUC_{0-\infty}$ of 18.60 ng/mL and 100.25 ng/ml*h in the umbilical vein, respectively. Umbilical vein plasma concentrations derived from literature (range 5.5–23.7 ng/mL) are in accordance with the estimated C_{max} concentration. None of the drug concentrations studied affected placental cell viability or progesterone production in BeWo cells.

Conclusion: *Ex vivo* placenta perfusion in combination with p-PBPK modelling is a relevant approach for foetal exposure predictions. Outcomes can be used in re-evaluation of current dosing regimens of dexamethasone during pregnancy. It is expected that this approach can be used to predict foetal exposure to other pharmaceutical drugs as well, even in absence of umbilical vein concentrations of a drug.

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P12-60
Dose-response analysis of nanomaterial toxicity

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As nanomaterials are increasingly used in many different products, it becomes important to know their potential toxicity. In the risk assessment of nanomaterials, *in vitro-in vivo* extrapolation (IVIVE) techniques are interesting to be explored since they have advantages of maximizing the use of *in vitro* studies, and reducing the financial and time costs, especially when high numbers of nanomaterials are to be analyzed.

The H2020 NanoInformaTIX project is a research project that partly focuses on the study of nanomaterial toxicity, with our goal being, implementing IVIVE methods for use in a strategy for risk assessment of nanomaterials. The initial step of our research includes building a software program (the R package NMTox) to explore the data gathered through the project and to perform preliminary analysis on the dose-response relationship of nanomaterial toxicity. Methods available in this package, such as the Likelihood ratio test, are used to test for the monotonic trend in dose-response relationships, and thus to screen for potential significant dose-response relationships of nanomaterials toxicity, that can be analyzed further. To identify the toxic concentrations, dose-response models are fitted on the subsets of data with a significant trend.

The risk assessment strategy will involve applying IVIVE methods described in the literature and will use the estimated *in vitro* toxic concentration as the basis for the risk calculation. The current stage of our research is focusing on PBPK models to estimate *in vivo* toxic doses of nanomaterials and to aid the risk assessment strategy. The feasibility of applying this strategy is currently being investigated. We will illustrate this approach using data available in the NanoInformaTIX database and in the literature.

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P13 | Inhalation and respiratory toxicology

P13-01
Distribution and uptake of gold nanoparticles under air-liquid interface and submerged conditions, investigated using the conventional inverted microscopy and CytoViva 3D technology

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Most studies assess the possible adverse effects of exposure to airborne nanomaterials (NMs) using submerged culture systems; however, air-liquid interface (ALI) exposure systems are far better suited for the assessment of *in vitro* pulmonary effects of NMs as they are more representative of the *in vivo* respiratory system. Although ALI exposure is preferred over submerged conditions, it is not known how toxicity, uptake and intracellular fate of NMs in cells may be influenced when ALI is compared with submerged exposure conditions.

The aim of this study was to compare the distribution, toxicity, and cellular uptake of 14 nm citrate stabilised gold nanoparticles (AuNPs) exposed to human alveolar basal epithelial (A549) cells at the ALI (0.13, 0.21 and 0.443 μg/cm^2), using the VITROCELL® Cloud 12 *in vitro* exposure system, to submerged conditions (10, 20, 40 μg/cm^2, a 10-fold increase to account for sedimentation and diffusion). The toxicity of A549 cells was monitored using the lactate dehydrogenase (LDH) assay as this assay has previously shown to not be affected by interference of AuNPs. The distribution and intracellular uptake were assessed using conventional inverted microscopy and the CytoViva 3D Enhanced Darkfield Imaging System.

The AuNPs were shown to be relatively non-toxic under both ALI and submerged conditions, however the cells showed increased sensitivity at the ALI. The distribution and intracellular uptake of the AuNPs were found to be more uniformly distributed, over the exposure area of the transwell insert, at the ALI whereas submerged conditions resulted in agglomerated NPs, outside cells as well as intracellularly. The use of the CytoViva 3D system has shown to be beneficial when assessing uptake of non-labelled NPs within a three-dimensional space.

Physiological exposure conditions are better represented when assessing the pulmonary effects of nanomaterials at the ALI. This is shown by the increased sensitivity of the cells and uniform distribution of the AuNPs exposure at the ALI as compared to cells exposed under submerged conditions.

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P13-03
Propylene glycol monobuthyl ether (PGBE) exerts higher toxicity than propylene glycol monomethyl ether (PGME) in human lung cells

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Glycol ethers are widely used in paints, glues, inks, and cleaning products for both professional and private use. Inhalation exposure to glycol ethers can occur while using these products. Our previous human exposure study suggested that inhalation exposure to glycol ethers, in particular, propylene glycol monomethyl ether (PGME, CAS # 107-98-2) and propylene glycol monobuthyl ether (PGBE, CAS # 5131-66-8) can probably impair oxygen diffusion and induce inflammation in the lungs. Therefore, the adverse effects of exposure to PGME and PGBE on the lung cells were investigated regarding cytotoxicity, epithelial layer integrity, and pro-inflammatory responses. We started with the submerged exposure of human alveolar epithelial type II (A549) cells to PGME at a range of 0–128 mg/mL and PGBE at a range of 0–32 mg/mL to gain a basic understanding of their toxicity. Following submerged exposures, the potential hazards of PGME and PGBE at non-cytotoxic concentrations were further evaluated under ALI exposure conditions with a more in *vivo*-like 3D lung model composed of A549 cells, human monocyte-derived macrophages (MDMs), and dendritic cells (MDDCs). Submerged exposures revealed that PGME and PGBE at tested dose-ranges can impair epithelial cell layer integrity and reduce cell viability. Dose-response relationships of PGME and PGBE for cell viability have been established in submerged A549 cells grown in cell culture wells and on permeable inserts. According to their median lethal concentration (LC50), PGBE (5.8 mg/mL) are more toxic than PGME (23 mg/mL). Moreover, the first experiments of ALI exposure showed that PGBE at the relatively low dose-range (0–170 µg/cm^2) can affect epithelial membrane permeability and induce pro-inflammatory responses in the 3D lung cell model. Our results corroborate the findings in the human exposure study that inhalation of PGME and PGBE may induce inflammation in the lungs and suggest that exposure to PGME and PGBE can cause lung toxicity, reflecting the potential hazards of propylene glycol ether.

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P13-04
Toxicity of airborne particulate matter in port, industrial and urban areas and effects on epithelial-to-mesenchymal transition in lung A549 cells

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The relationship between increase of environmental pollution, in particular by fine particulate matter ($PM_{2.5}$) and the incidence of respiratory diseases such as asthma or lung cancer are currently proven. In 2013, the International Agency for Research on Cancer (IARC) classified air pollution and fine particles as carcinogenic to humans[1]. Among the mechanisms proposed to explain these effects, oxidative stress, DNA damage or mutagenic process, and inflammatory response are often proposed[2,3]. Epithelial-to-mesenchymal transition