New approach methodologies (NAMs) for hazard assessment of chemicals and materials at human biological barriers

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1. Introduction

The rapidly increasing development of novel chemicals and materials requires fast, predictive and ethical tools for the assessment of their potential human health hazards. Therefore, we aim to develop, refine and validate new approach methodologies (NAMs) centering on human-based bio-barrier models covering important exposure routes and regulatory relevant endpoints. Specifically, this will include experimental NAMs for next-generation *in vitro* hazard assessment of oral exposure at the intestinal barrier, dermal exposure at the skin barrier and developmental toxicity at the placenta barrier. These tools should contribute to a safe and sustainable design and use of emerging technologies, chemicals and materials.

2. Methods

The intestinal model is based on a combination of epithelial (Caco-2), mucus secreting (HT29-MTX) and immune (Raji-B; induces transdifferentiation of enterocytes into M-cells) cells cultured in inserts. Dermal exposure is studied in a skin model using keratinocytes, the major cell type of human skin. For the placental barrier, a co-culture model of human trophoblasts (BeWo b30) and placental microvascular endothelial cells (HPVEC) is established in microporous inserts.

3. Strategy

We are currently developing and refining three NAMs for skin, intestine and placenta barrier to provide robust and validated models and methods that can address regulatory relevant endpoints such as uptake, translocation, direct toxicity (e.g. cytotoxicity, barrier integrity, inflammation, endocrine function, lipid uptake) and long-term health effects (e.g. sensitization). The performance of the NAMs will be assessed using reference substances with known toxicity. Additionally, an in-project validation and interlaboratory comparison of each NAM will be performed to ensure transferability of the models. In a second phase, other materials, including (nano-pesticides, 2D materials and PFAS will be tested. Furthermore, for the placenta model, the *in vitro* predictions (e.g., for

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translocation and toxicity) will be compared to the results obtained with *ex vivo* perfusion models of intact human placenta.

4. Conclusions

The use of advanced human-based *in vitro* methodologies will facilitate the hazard analysis of novel chemicals and materials, reducing reliance on cost-intensive and ethically problematic animal models. Further integration of experimental NAMs with *in silico*/computational NAMs into a next generation SSbD framework for hazard assessment is expected to address industrial and regulatory needs and to fill important knowledge gaps in understanding the interaction of materials with human tissues.

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