Title: Physiological maps and chemical-induced disease ontologies: tools to support NAMs development for next-generation risk assessment

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Physiological maps (PM) can be defined as a graphical representation of cellular and molecular processes associated to specific organ functions (Vinken et al. 2021). Within the ONTOX project, we designed a total of 6 PMs describing physiological processes in the liver, the kidney and the brain. These PMs are then used as a tool to assess relevant mechanistic coverage and linkage between a specific organ function and a toxicological endpoint.

Based on the Disease Maps project (Mazein et al. 2018) pipeline, we developed the first version of 6 PMs describing the following physiological processes: bile secretion & lipid metabolism (liver), vitamin D metabolism & urine composition (kidney), neural tube closure (update of the work of Heusinkveld et al. 2021) & brain development (brain). Our workflow included: (i) data collection from expert curated literature (ii) identification of the relevant biological mechanisms, (iii) screening of online databases (e.g. Wikipathways, Reactome, and KEGG) for previously described pathways, (iv) manual curation and integration of the data into a PM using CellDesigner, and (v) visualization on the MINERVA platform (Hoksza et al. 2019).

These qualitative PMs represent an important tool for exploring curated literature, analyzing networks and benchmarking the development of new adverse outcome pathways (AOPs). These PMs provide the basis for developing quantitative disease ontologies, integrating different layers of pathological and toxicological information, chemical information (drug-induced pathways) and kinetic data. The resulting chemical-induced disease ontologies will provide a multi-layered platform for integration and visualization of such information. The ontologies will contribute to improving understanding of organ/disease related pathways in response to chemicals, visualize omics datasets, develop quantitative methods for computational disease modeling and for predicting toxicity, set up an *in vitro* & *in silico* test battery to detect a specific type of toxicity, and develop new animal-free approaches for next generation risk assessment.

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