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

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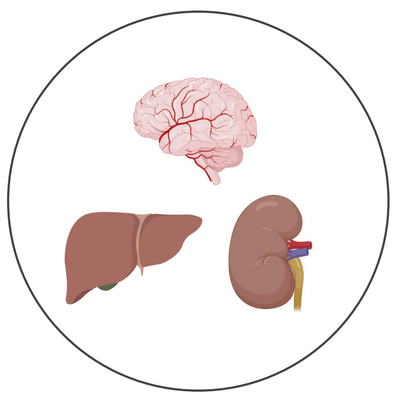
INTRODUCTION

Physiological maps (PM) can be defined as a graphical representation of cellular and molecular processes associated to specific organ functions [1].

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.



Focus
- Systemic repeated dose toxicity;
- Liver, kidneys and (developing) brain;
- Drugs, cosmetics, biocides, and food ingredients.

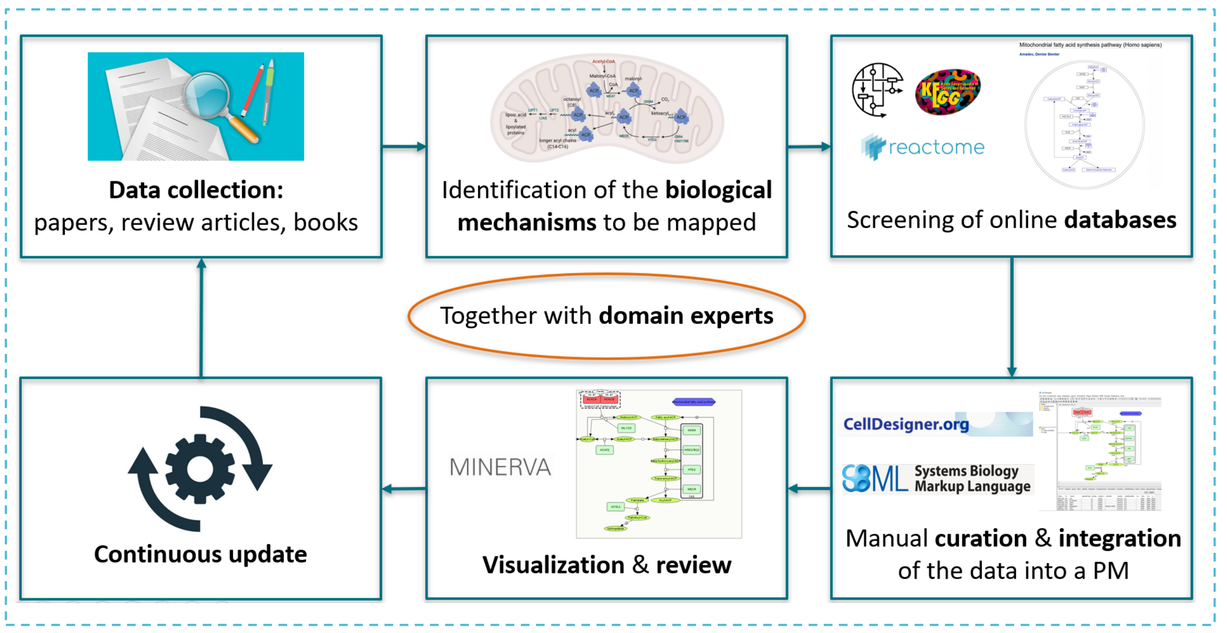
Case studies
Liver: steatosis and cholestasis.
Kidney: tubular necrosis and crystallopathy.
Developing brain: neural tube closure and cognitive function defects.

Scan to download the ONTOX inaugural paper [1].

METHODS

We adapted the workflow from the Disease Maps project [2] to construct our PMs.

- First, relevant physiological literature was curated with the help of domain experts.
- Next, we listed the fundamental mechanisms to be mapped and screened online databases (e.g. Wikipathways, Reactome, KEGG) for previously described pathways.
- Finally, we integrated pathways and data from the literature using the CellDesigner software and displayed them using the MINERVA platform [3].

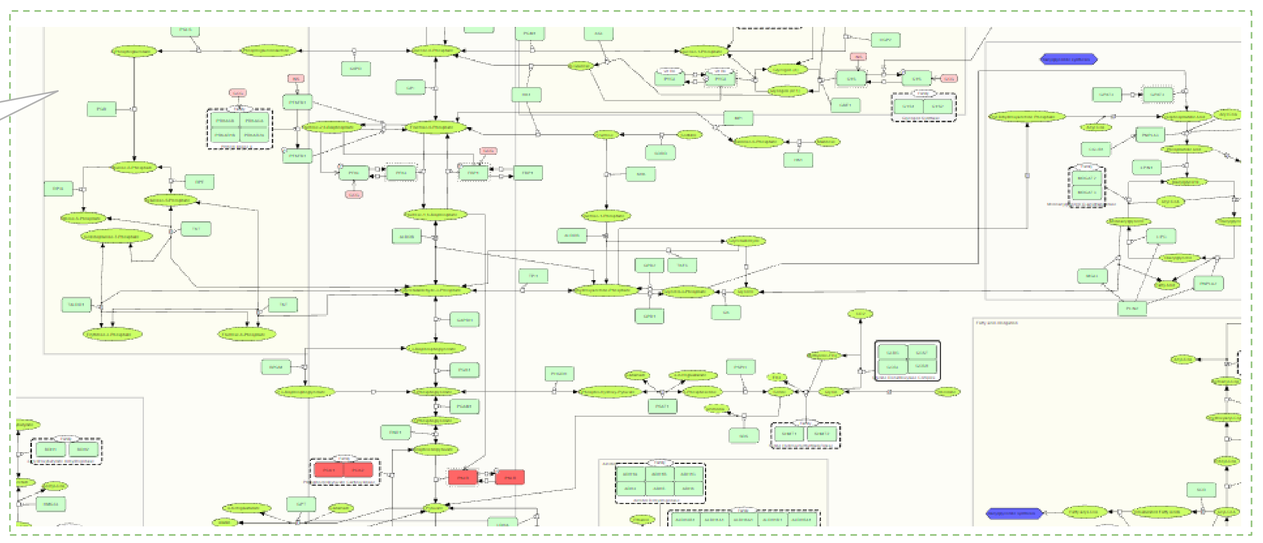


RESULTS

We developed the first version of 6 PMs describing the following physiological processes:

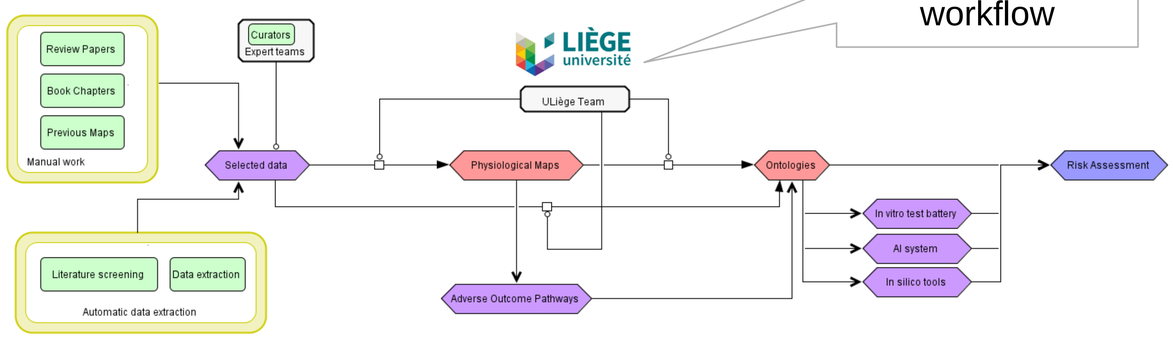
1. Bile secretion (liver),
2. Lipid metabolism (liver),
3. Vitamin D metabolism (kidney),
4. Urine composition (kidney),
5. Neural tube closure (update of the work of Heusinkveld et al. 2021 [4]),
6. Brain development (brain).

An example of part of the Physiological Map of the Liver Lipid Metabolism



Overview:
- Expert-curated maps;
- Human physiology-oriented networks;
- Qualitative and Quantitative layers;
- Continuously updated.

ULiège activities within the ONTOX workflow



sysrev → SBtab → Phymdos → SBML CellDesigner.org MINERVA

Semi-automated workflow for data extraction from a systematic review approach (Sysrev), translation text info into Systems Biology Graphical Notation (Phymdos, using SBtab), and integration and visualization of the pathways using CellDesigner and MINERVA.

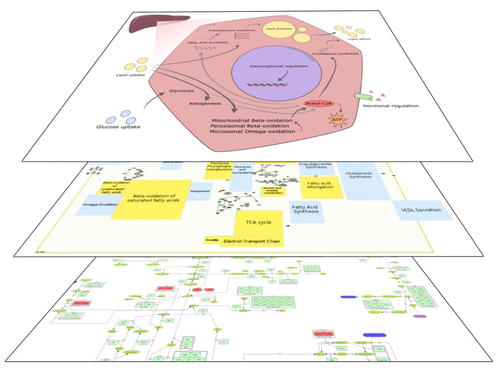
FUTURE STEPS

PMs are cornerstones to create **ontologies,** integrating different layers of pathological, toxicological, and chemical information, and quantitative kinetic data.

They will contribute to:

(1) better understand organ- and disease-specific pathways in response to chemicals;
(2) visualize omics datasets;
(3) develop quantitative methods for disease modelling and for predicting toxicity;
(4) set up an *in vitro* & *in silico* test battery to detect a specific type of toxicity;
(5) develop new **animal-free approaches** for **next generation risk assessment**.

These tools will be continuously updated, resulting from expert curation and revision in an open community effort.



Graphical concept of the ONTOX liver ontology

References: [1] Vinken, Mathieu, et al. 2021. https://doi.org/10.1016/j.tox.2021.152846, [2] Mazein, Alexander, et al. 2018. https://doi.org/10.1038/s41540-018-0059-y, [3] Hoksza, David, et al. 2019. https://doi.org/10.1093/bib/bbz067, [4] Heusinkveld, Harm J., et al.2021. https://doi.org/10.1016/j.reprotox.2020.09.002.

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