Quantitative systems modeling of qAOP and its data integration – ONTOX perspective

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Funded by the Horizon 2020 Framework Programme of the European Union

ONTOX

esqLABS
WE EMPOWER HEALTH CARE

ecetoc

Workshop on Quantitative Response-Response Relationships (qAOPs)

Brussels & online, 2022-10-18

ASPIS

Scope of ONTOX

ONTOX:

Ontology-driven and artificial intelligence-based repeated dose toxicity testing of chemicals for next generation risk assessment

Goal

Development of an animal-free and human-relevant strategy for the prediction of chemical-induced toxicity

Focus

- Systemic repeated dose toxicity
- 6 case studies
  - Liver: steatosis and cholestasis
  - Kidney: tubular necrosis and crystallopathy
  - Brain: neural tube closure and cognitive function defects
- Drugs, cosmetics, biocides and food ingredients

Driving principles

- 3Rs
- 21st century toxicity testing
- Next generation risk assessment

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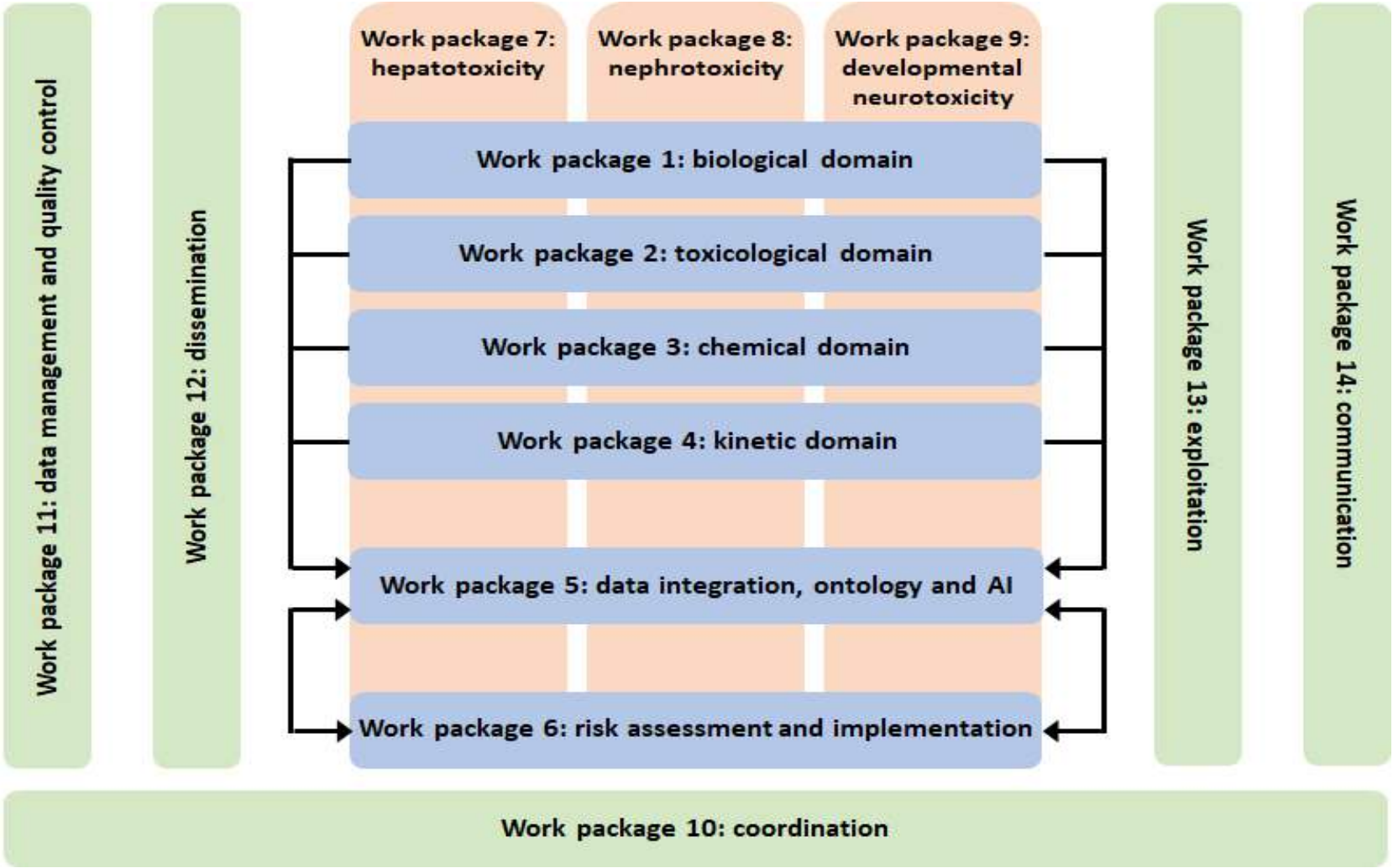
Organisation



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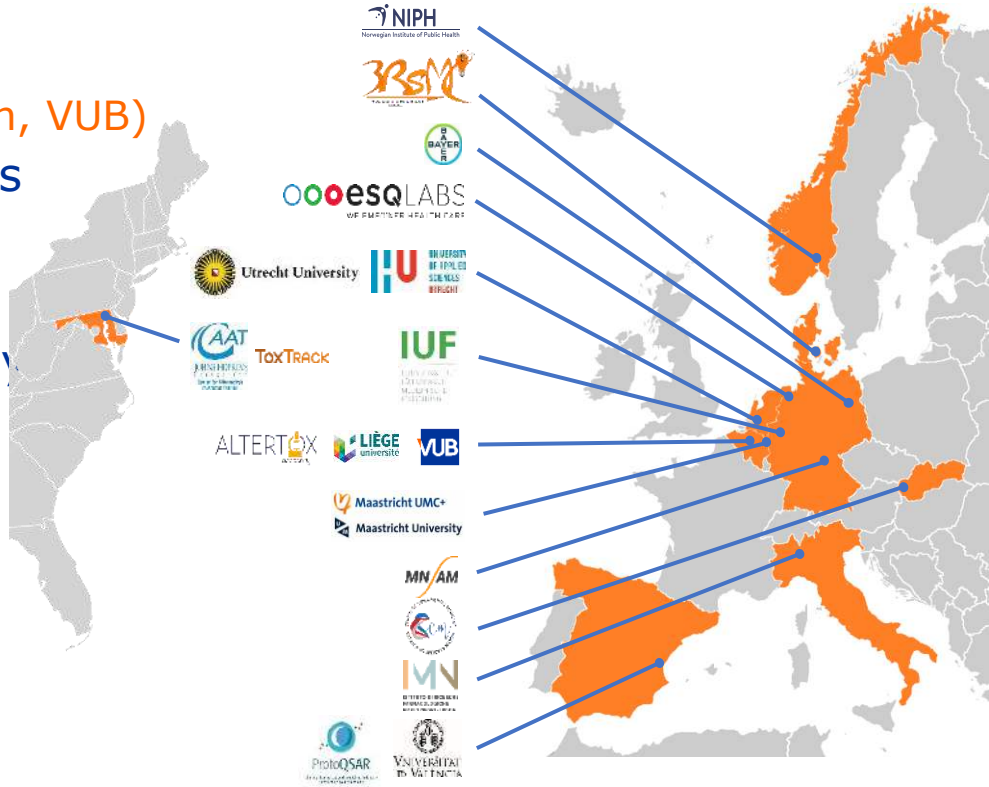
Consortium, budget en advisory board

Consortium

(coordinated by prof.dr. Mathieu Vinken, VUB)

- 18 partners from 9 countries
- 100 researchers
- 10 academic institutions
- 6 SMEs and 1 large company
- 1 public health institution



Budget

- €17 M

Advisory board

- 7 academic / industrial / regulatory advisors
- 1 ethical advisor

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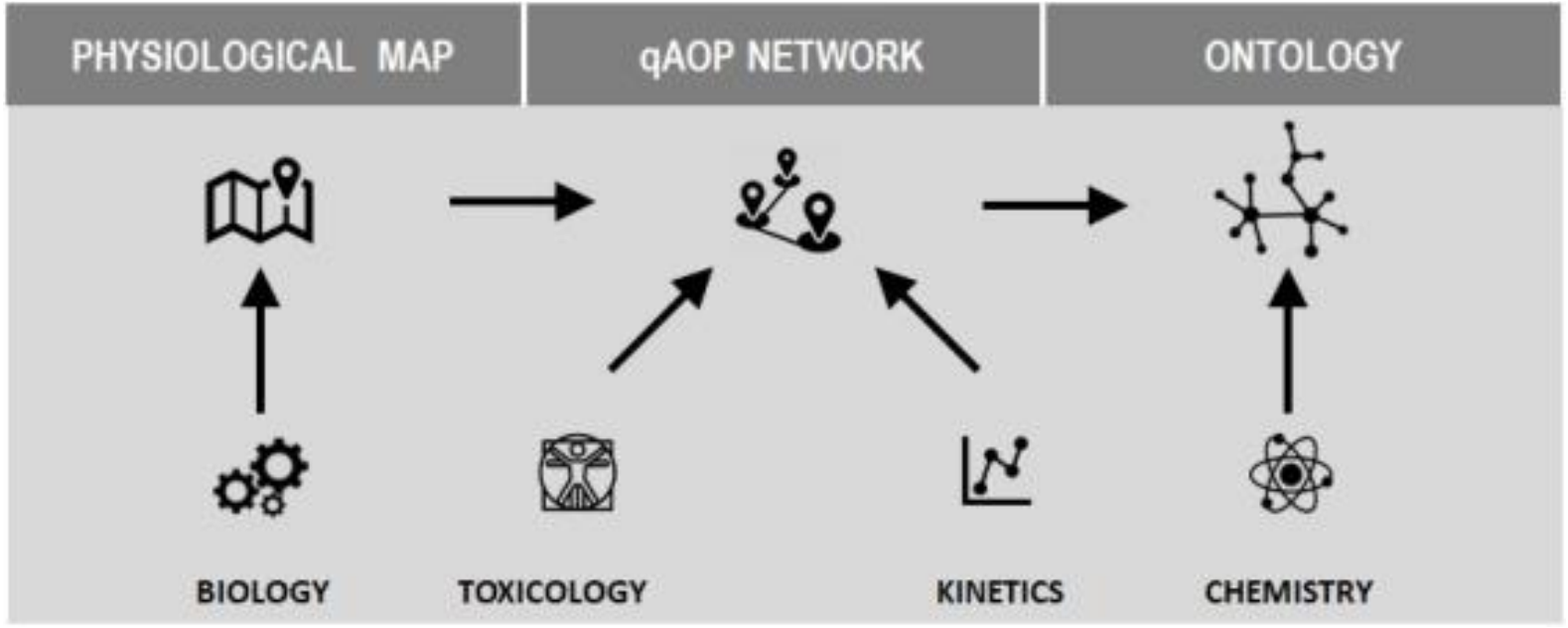
Tools to integrate data in ONTOX



Vinken *et al.* (2021) *Toxicology.*

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Progresses in qAOP efforts

- Modeling of common cellular KEs in AOPs
- Case study of qAOP of steatosis (ONTOX/ASPIS)
- Uncertainty quantification of quantitative systems AOP modeling
- Perspectives towards Quantitative Systems Toxicology (QST)

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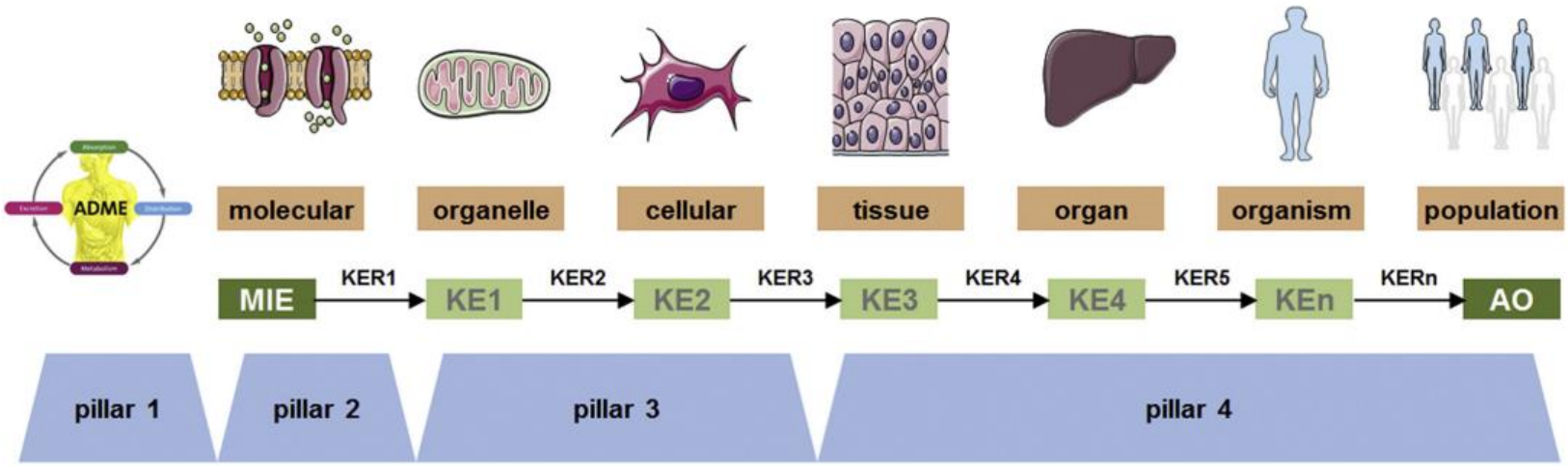
Background information

Adverse outcome pathway (AOP)



Desprez *et al.* (2019) *Toxicology in Vitro*

Motivation to model common cellular KEs

High relevance of cellular stress pathways as key event (KE)in AOPs

- KE of oxidative stress exists in 29 AOPs in the AOPwiki.
- Over 50 AOPs contain KEs related to activation of cellular stress pathways.

Quantitative AOP aim to gain quantitative understanding about

- Response-response relationship
- Time-scale
- Modulating factors
- Feedback loops

Impact:
facilitate to classify "*Extent of quantitative understanding*" requested in Annex 2 of OECD-ENV/JM/MONO(2016)12

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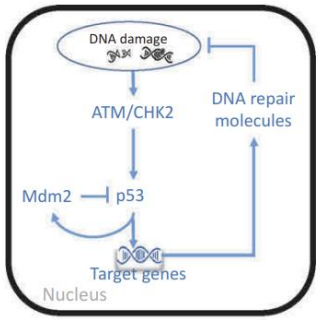
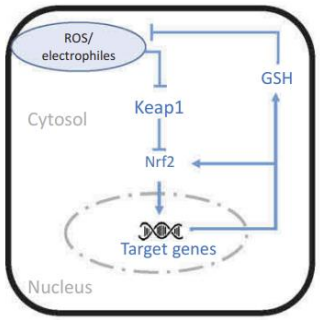
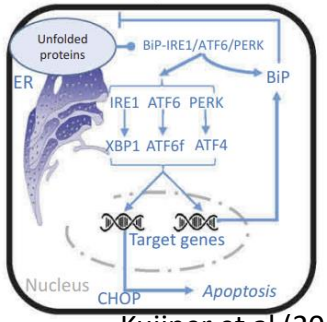
Cellular KEs and its quantification

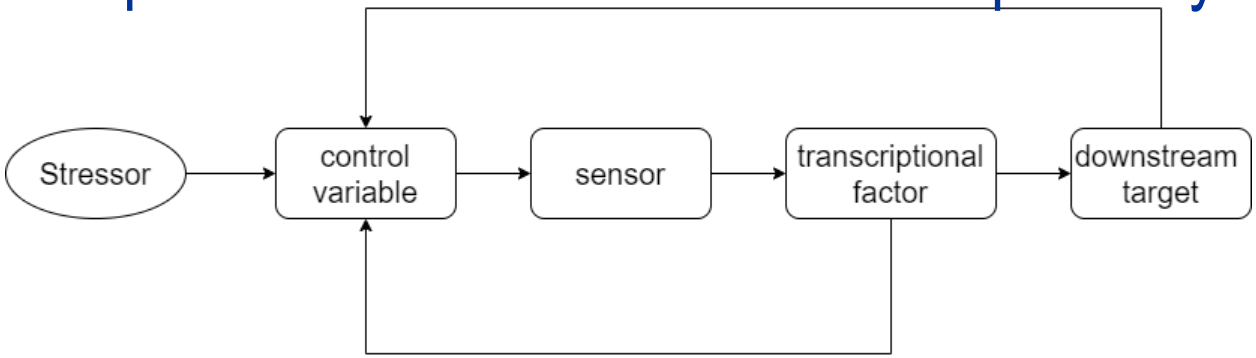






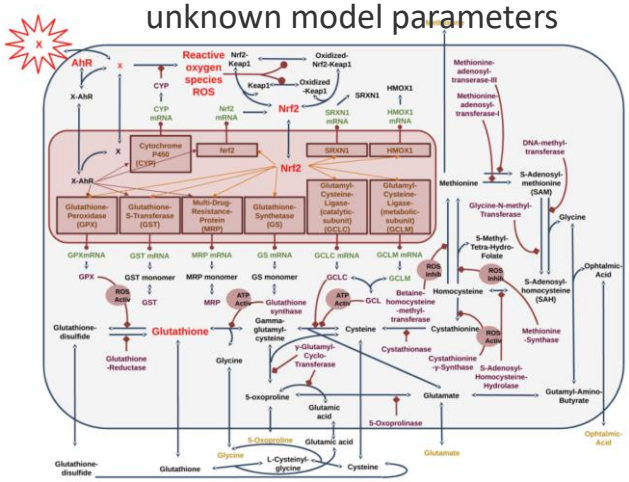
Kuijper et al (2017)
Expert Opin. Drug Metab. Toxicol.

Simplified network of cellular stress pathways



Similar to Zhang and Andersen. *PLoS Comput. Biol. 2007*

Detailed model with a lot of unknown model parameters



Zgheib et al. *(2019) Comput. Toxicol.*

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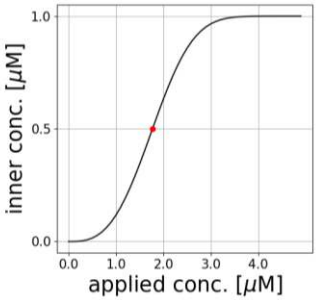
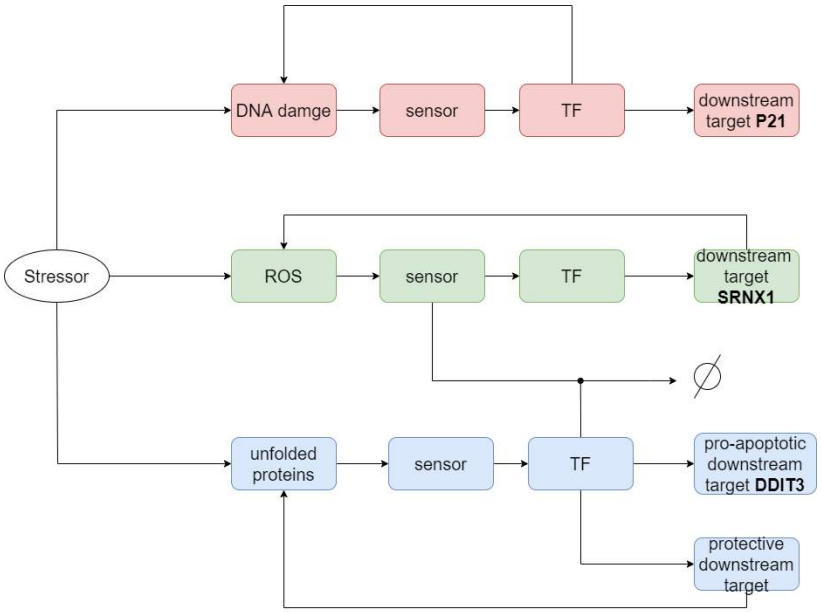
Quantitative systems modeling
using ordinary differential equation (ODE)

- Causality
- Mechanistic representation of biological processes
  - Homeostatic regulation
  - Cross-talk between multiple pathways
  - Quantitative representation based on law of mass action, Michaelis–Menten kinetics etc.
- *in-vitro* pharmacokinetics
  - Link the applied concentration to inner one (EC50)





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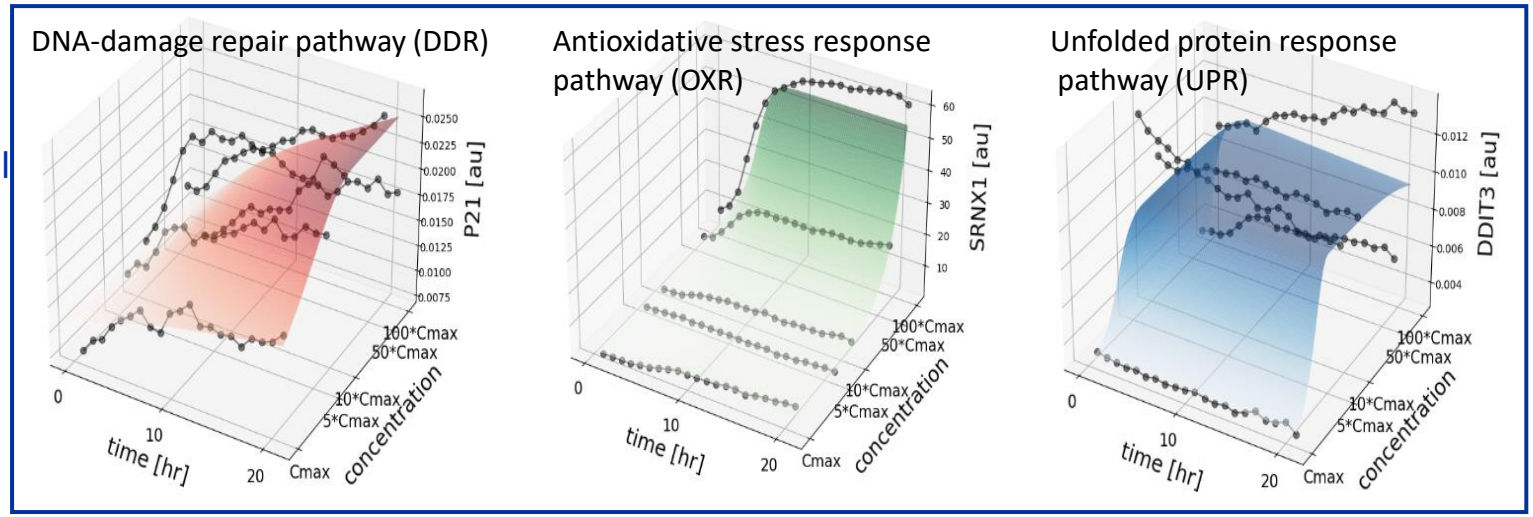
Model calibration using *in-vitro* data

Data source:
BioStudies S-BSST117 for 118 FDA-DILI labeled drugs

Representative model fitting to data of oxytetracycline



adapted from talk in SOT 2022 (Yang & Schaller)

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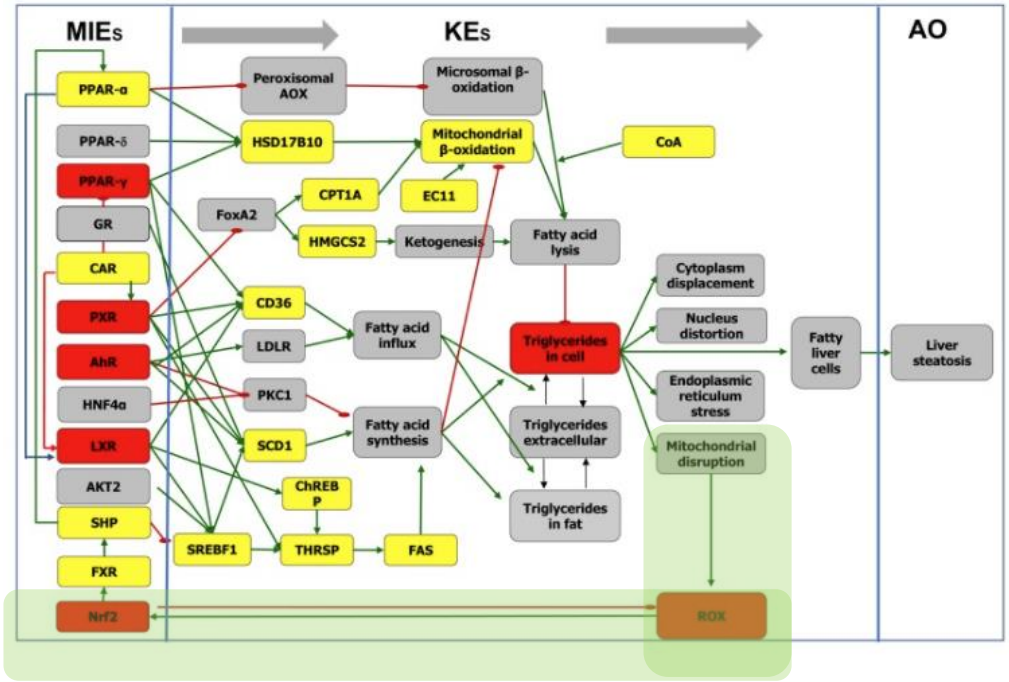
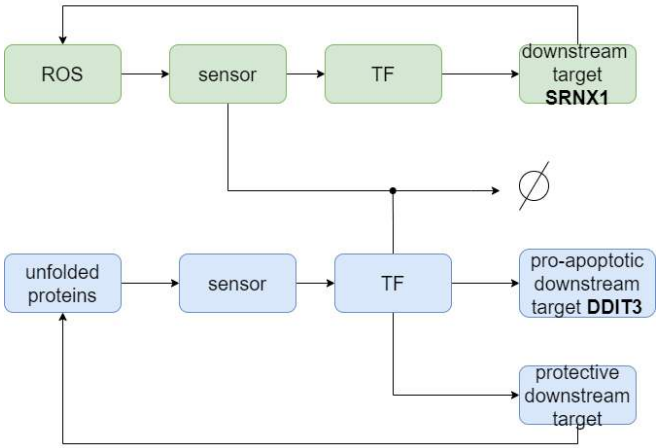
Integration of quantitative cellular KEs into qAOP networks (e.g. liver steatosis)





Escher *et al.* (2022) *Toxicology in Vitro*

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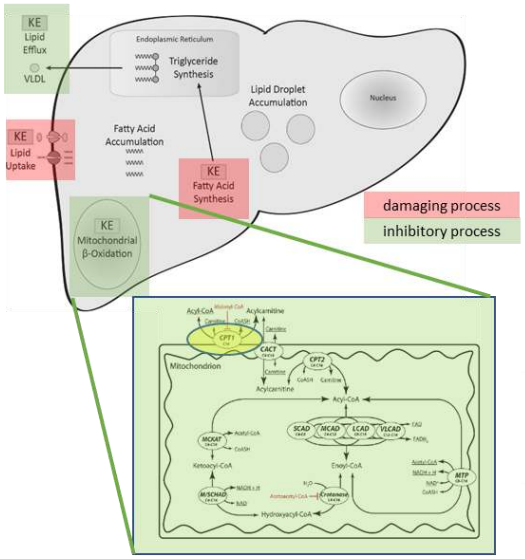
Case study: qAOP of steatosis

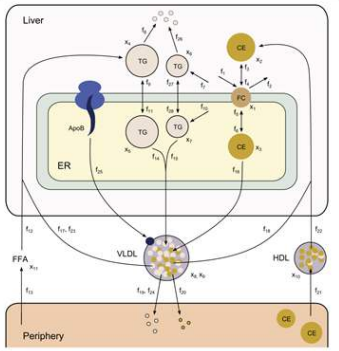
- Essentials for qAOPs of steatosis

"An important precondition for qAOP is knowledge on **basic homeostatic processes**, which are supposed to be perturbed by toxicant exposure. In a **dynamic process** such as liver steatosis, for example, there is no hope of developing a correct qAOP if we do not have **a detailed understanding and description of fatty acid balance** in hepatocytes. This is where toxicology meets general **systems biology** and cooperation with other disciplines is particularly helpful. An approach of only exposing cells to toxicants is not sufficient to feed the information requirements of qAOPs. In addition, information on **gene and metabolic regulatory networks and signaling pathways** will be required."

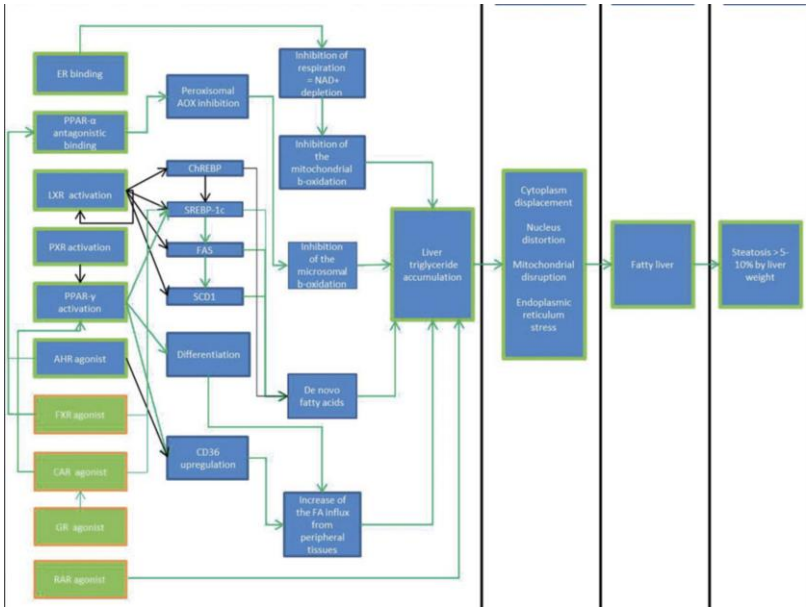
Leist et al. (*2017*) *Arch. Toxicol.*

- quantification of apical KEs





f_8	Hepatic catabolism of triglyceride (cytosol)
f_9	Hepatic transport of triglyceride from the ER to the cytosol
f_{10}	Hepatic *de novo* synthesis of triglyceride (ER)
f_{11}	Hepatic transport of triglyceride from the cytosol to the ER
f_{12}	Hepatic uptake of free fatty acid
f_{13}	Net efflux of free fatty acid from peripheral tissues to plasma
f_{14}	Hepatic secretion rate of VLDL-triglyceride
f_{15}	Hepatic secretion rate of VLDL-cholesterol



Angrish *et al.* (2016) *Toxicol. Sci.;* van Eunen *et al. (2013) PLoS Comput. Biol.;* Mellor *et al.* (2016) *Crit Rev Toxicol.;*Tiemann *et al.* (2013) *PLoS Comput. Biol.*

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Uncertainty quantification of qAOP models

ONTOX are applying two possible approaches

Frequentist offers maximum likelihood estimate + confidence interval

- **Pros**: parameterization invariant, fully data-determined, probabilistic for the bounds of the intervals
- **Cons**: robust computational technique needed to construct the intervals

Bayesian offers maximum a posteriori (MAP) + posterior distribution or credible interval

- **Pros**: probabilistic for parameter and bounds of intervals
- **Cons**: variant (parameterization does matter), prior needed

Raue et al. (2013) *Phil. Trans. R. Soc. A.*
Fröhlich et al. (2014) *Lecture Notes in Computer Science*
Spinu et al. (2020) *Arch. Toxicol*

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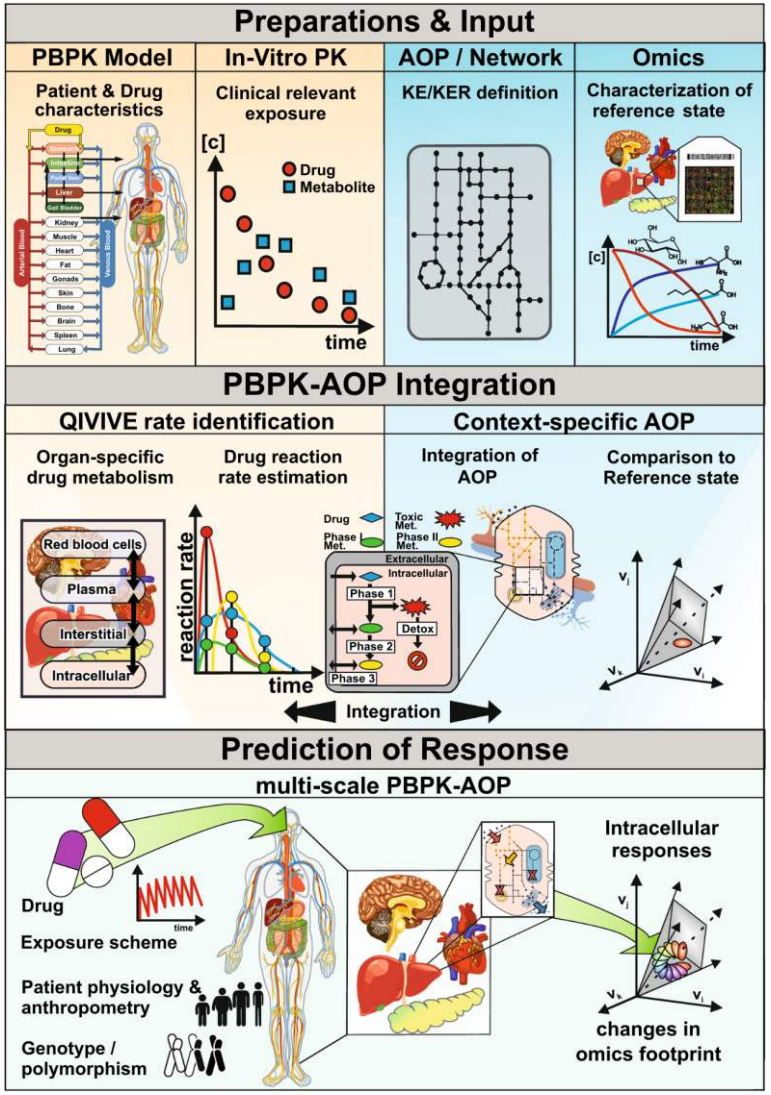
Development & Integration towards QST

- Leveraging a professional open-source framework

OPEN SYSTEMS PHARMACOLOGY

https://www.open-systems-pharmacology.org/



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- **Collaboration within ONTOX**
- **Collaboration across ASPIS cluster & qAOP WG**

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Thanks!
Questions?

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