# ONTOX

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

## safer chemicals using less animals

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#### 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
- 21<sup>st</sup> century toxicity testing
- Next generation risk assessment











### Rationale

- Rely as much as possible on available data, models and methods
- Fill data gaps by means of targeted *in vitro* and *in silico* testing

### Toolbox

- Human data and biological material
- In vitro methods and stem cell technology
- In silico methods and artificial intelligence











### New approach/non-animal methodology (NAM)

- ONTOX will deliver 6 NAMs:
  - Liver: steatosis and cholestasis
  - Kidney: tubular necrosis and crystallopathy
  - Brain: neural tube closure and cognitive function defects
- An artificial intelligence-based strategy linked with a battery of in vitro assays and in silico tools for hazard prediction to be combined with customized exposure assessment for the purpose of human risk assessment





















# Artificial intelligence





Definition

Simulation of human intelligence by means of computers

Application 1: (big) data collection

- Type: biology, toxicology, chemistry and kinetics (ontology)
- Sources: safety dossiers, databases, papers, text books, other projects, ... (FAIR principles)

## Application 2: hazard identification / prediction

- Goal: create a blueprint of toxicological effects
- Technique: machine learning (advanced read-across structureactivity relationship)









## Data collection tools









# Physiological map



































Physicochemical properties of chemicals triggering the MIE/KE







Ontology











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# In vitro / in silico tests 💣 🗖

## Definition

- In vitro: cell culture methods
- In silico: computer-based methods

### Set-up

- Mapping of mechanisms underlying physiological functions
- Mapping of mechanisms underlying adverse effects and identification of key events
- Selection / optimisation of 1 or more in vitro and / or in silico tests per key event
- Battery of *in vitro* and *in silico* tests for each adverse effect































### Phase I

- Data-rich chemicals with well-known toxicological profiles
- Optimisation of the artificial intelligence system and the *in vitro* and *in silico* tests

## Phase II (ab initio case studies)

- Data-poor chemicals with less clear-cut toxicological profiles
- Step 1: apply the artificial intelligence system
- Step 2: fill data gaps with *in vitro* and *in silico* testing
- Step 3: exposure assessment / modelling
- Step 4: probabilistic risk assessment







# Organisation -





Work package 10: coordination







# Consortium, budget and advisory board

#### Consortium

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

#### Budget: €17.211.050

#### Scientific advisory board

- Patience Browne (OECD-France)
- Paul Carmichael (Unilever-United Kingdom)
- Sandra Coecke (JRC-Italy)
- Stéphane Dhalluin (L'Oréal-France)
- Mariana Novič (National Institute of Chemistry-Slovenia)
- Freddy Van Goethem (Janssen Pharmaceutica-Belgium)
- Paul Whaley (Lancaster University, United Kingdom)

#### Ethical advisor: Signe Mezinska (University of Latvia-Latvia)







**NIPH** BAYER **OOOESQ**LABS OF RPPLIER Schences Utrecht University IUF TOXTRACK ALTERT **ILIÈGE** 🕐 Maastricht UMC+ Maastricht University MN/AM VNIVERSITAT D VALENCIA otoOSAR

Animal-free safety assessment of chemicals: project cluster for implementation of novel strategies

- 3 projects
- 70 partners in 17 countries
- €60 million

### RISK-HUNT3R

- Coordinator: Bob van de Water
- Goal: human-centric chemical safety assessment utilizing systems toxicology

### PrecisionTox

- Coordinator: John Colbourne
- Goal: leveraging evolutionary diversity to reveal the molecular basis of toxicity

Danish 3R-Center





























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The vision of the ONTOX consortium is to provide a functional and sustainable solution for advancing human risk assessment of chemicals without the use of animals in line with the principles of 21st century toxicity testing and next generation risk assessment.					
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