OBERON - NEWS

Pilot Newsletter

Welcome to the first issue of the OBERON biannual newsletter !

This newsletter will keep you inform on this European Research project on endocrine disruptors which aims to build an integrated approach for testing and assessment (IATA), to detect EDs related to metabolic disorders by developing, improving and validating a battery of test systems.

In addition to giving insights into our work, this newsletter serves as a window on the **OBERON website** containing more detailed information and invites readers to join us on Twitter **@OBERON_4EU**, Instgram **@oberon4eu** and TikTok **@oberon4eu**.

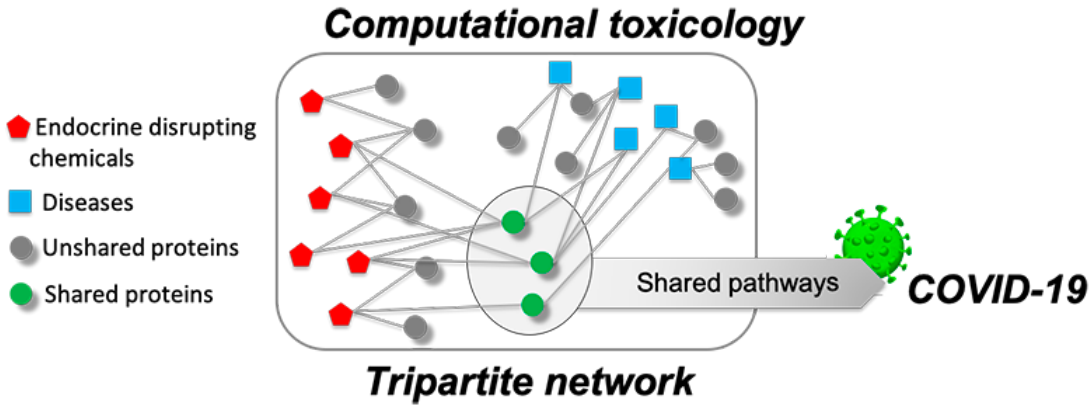
Learn more about the project

Why do we need OBERON ?

Exposure to chemical substances that can produce endocrine disrupting effects represents one of the most critical public health threats nowadays. In line with the regulatory framework implemented within the European Union to reduce the levels of endocrine disruptors (EDs) for consumers, new and effective methods for ED testing are needed.

Project coordinator: Ass. Prof. Karine AUDOUZE (Université de Paris/INSERM)

Endocrine Disruptors and COVID-19



The COVID-19 pandemic is still hitting hard and researchers around the world are still investigating its process in the human body. STEEP Co-Director Philippe Grandjean has collaborated with a research group from the University of Paris lead by Dr. Karine Audouze (coordinator of OBERON) to work on EDC interaction with COVID-19 contamination pathway.

Take a closer look

Events - Lectures

OBERON members will talk about AOP network in these two conferences

22nd of March, 2021

SOT 2021

Construction of a AOP Network

3 - 6 May, 2021

SETAC

Artificial intelligence and systems

Related to Metabolism Disorders Induced by an Endocrine-Disrupting Chemical Mixture Using Artificial Intelligence and Systems Toxicology.

Presented by Karine Audouze.

Elias Zgheib[1], Min Ji Kim[1], Florence Jornod[1], Etienne Blanc[1], Kevin Bernal[1], Xavier Coumoul[1], Nabil Benhajkassen[2], Christophe Rousselle[2], Robert Barouki[1], Karine Audouze[1]

[1]Université de Paris, Inserm U1124, 75006 Paris, France

[2]ANSES, Direction de l'Evaluation des Risques, 94700 Maison-Alfort

toxicology for the construction of a AOP network related to metabolic disorders induced by an endocrine-disrupting chemical mixture.

Presented by Karine Audouze.

Elias Zgheib[1], Min Ji Kim[2], Florence Jornod[1], Etienne Blanc[1], Kevin Bernal[1], Xavier Coumoul[1], Nabil Benhajkassen[3], Christophe Rousselle[3], Robert Barouki[1], Karine Audouze[1]

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[3]ANSES, Direction de l'Evaluation des Risques, 94700 Maisons-Alfort, France

Young OBERON Challenge

TikTok

Communication is key, so we are preparing content for TikTok videos involving our youngest researchers to reach the new generation !

OBERON
@OBERON_4EU

Find us on tiktok! Soon with content https://t.co/bD3lVTgp0h

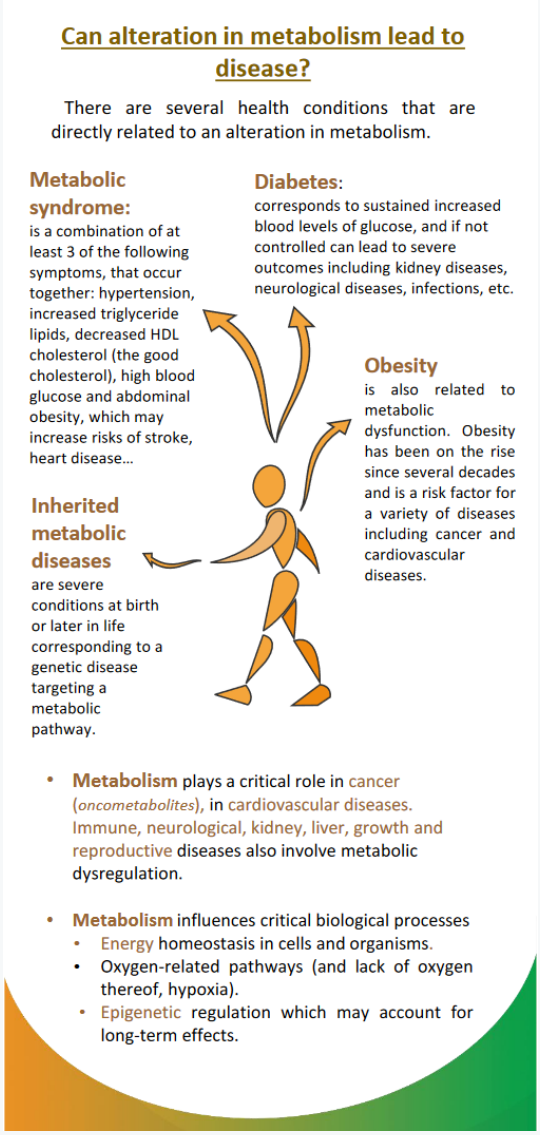
7:15 PM - Feb 9, 2021

5 See OBERON_4EU's other Tweets

Webinar on TOXsigN

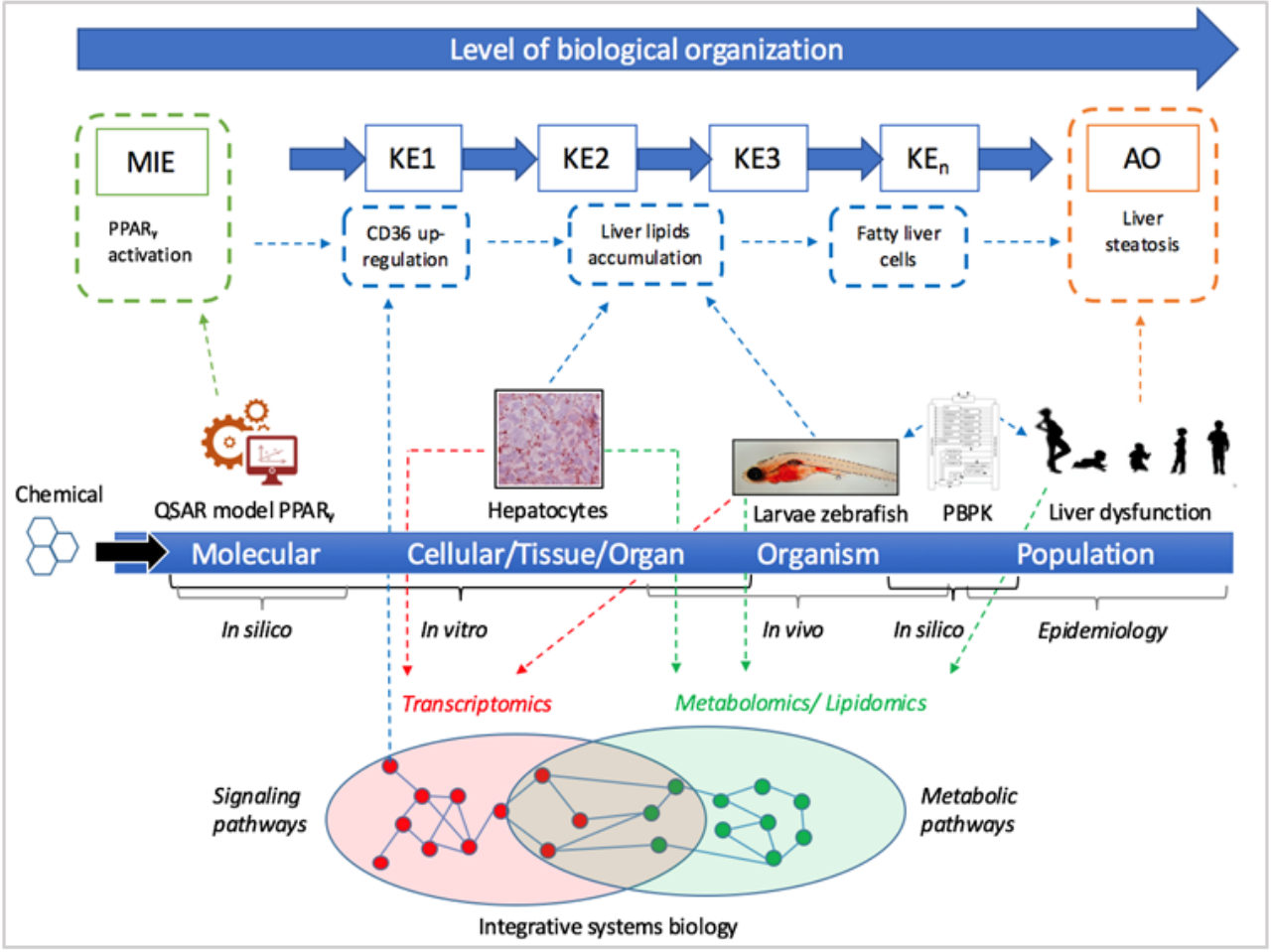
As part of the EURION cluster, OBERON is organizing this first training: *Share and compare toxicogenomics data using the TOXicogenomic sIgNatures database (TOXsIgN) in chemical risk assessment* on **June 15th, 2021 at 10 AM - 11:30 AM (CET).**

What are Endocrine Disrupting Compounds (EDCs)?



EDCs are exogenous compounds or mixtures of compounds that interfere with the endocrine / hormonal system and consequently elicit toxic outcomes. The endocrine system encompasses the synthesis, transport, degradation and effects of hormones which control a variety of physiological processes including development, growth, reproduction, metabolism, etc. Examples of hormones are sex steroids (estrogens, androgens, progestogens...), thyroid hormones, as well as peptide hormones such as insulin and growth hormone.

An introduction to the OBERON project



In April 2020, the OBERON WP leaderspublished an article in direct covering the project: Integrative Strategy of Testing Systems for Identification of Endocrine Disruptors Inducing Metabolic Disorders (Int J Mol Sci. 2020 Apr 23;21(8):2988.).

"The OBERON project has now started for a bit more than a year. Much of the effort was devoted to establishing the different experimental systems, taking into account ethical considerations. [...]. As an illustration, we performed a pilot study to assess the metabolomic profile of 20 human serum samples, and we are currently analyzing those initial results, and preparing the extension of the assays."

Read more

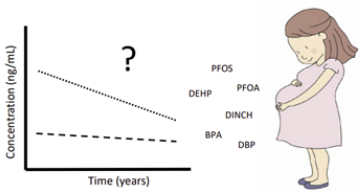
Epidemiology: Human exposure children/adolescents & adults cohorts (WP1)

1. To characterize EDs exposure levels in Europe

Already published data to:

- Obtain temporal-trends
- Predict current levels from the temporal-trends

➢ **Decline in levels of PFOS, PFOA, and MnBP metabolite in European pregnant women (*poster)**



2. To evaluate the metabolic effects of EDs exposure in children and adolescents

Longitudinal cohorts in Europe to assess the obesogenic, cardiometabolic, and metabolomics effects of prenatal exposure to EDs

➢ **Prenatal exposure to persistent EDs may increase the risk of metabolic disorders until adolescence (*poster)**

3. To evaluate the metabolic effects of EDs exposure in adults

- Longitudinal cohort in Czech Republic with data on EDs and metabolic health
- Intensive follow-up of pregnant women to assess the metabolomic effects of EDs during pregnancy

➢ **Work in progres**

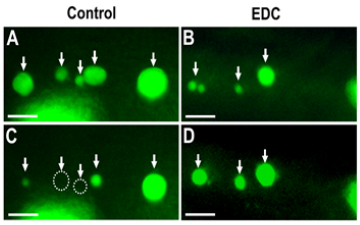
The main objective is to show potential metabolic effects of EDs in human population and recommendations on how epidemiological and biomonitoring data can help find information on ED exposure levels and metabolic effects. This work package starts with characterizing EDs exposure levels in Europe, then evaluates metabolic effects of EDs exposure in children and adolescents and finally evaluates metabolic effects of EDs exposure in adults.

Work package leader: Ass. Pr. Maribel Casas (ISGlobal)

Develop whole organism test systems to identify EDs implicated in metabolic disorders (WP2)

1. Zebrafish obesogenic test (ZOT) to screen EDs acting as obesogens*.

- Whole-organism mechanism-based assay for screening substances acting as potential obesogens **(*poster)**.

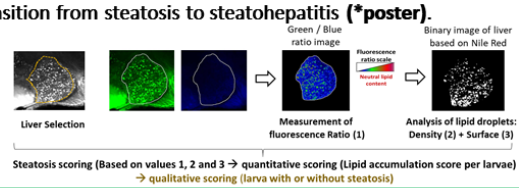


4. Increase toxicological knowledges

- Biological activity of selected chemicals with zebrafish PPARγ *in vitro*.
- Analytical chemistry analyses.
- Omics signatures of EDs effects.

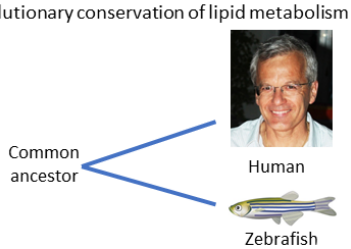
2. Zebrafish-based bioassays to screen EDs involved in NAFLD progression*.

- Optimization of test methods used to evaluate EDCs for their involvement in steatosis and in the transition from steatosis to steatohepatitis **(*poster)**.



3. The demonstration of intra- and inter-laboratory reproducibility of ZOT and NAFLD progression bioassays.

Evolutionary conservation of lipid metabolism



This work package develops whole organism test systems to identify endocrine disruptors (EDs) implicated in metabolic disorders. Zebrafish is used as a convenient *in vivo* test

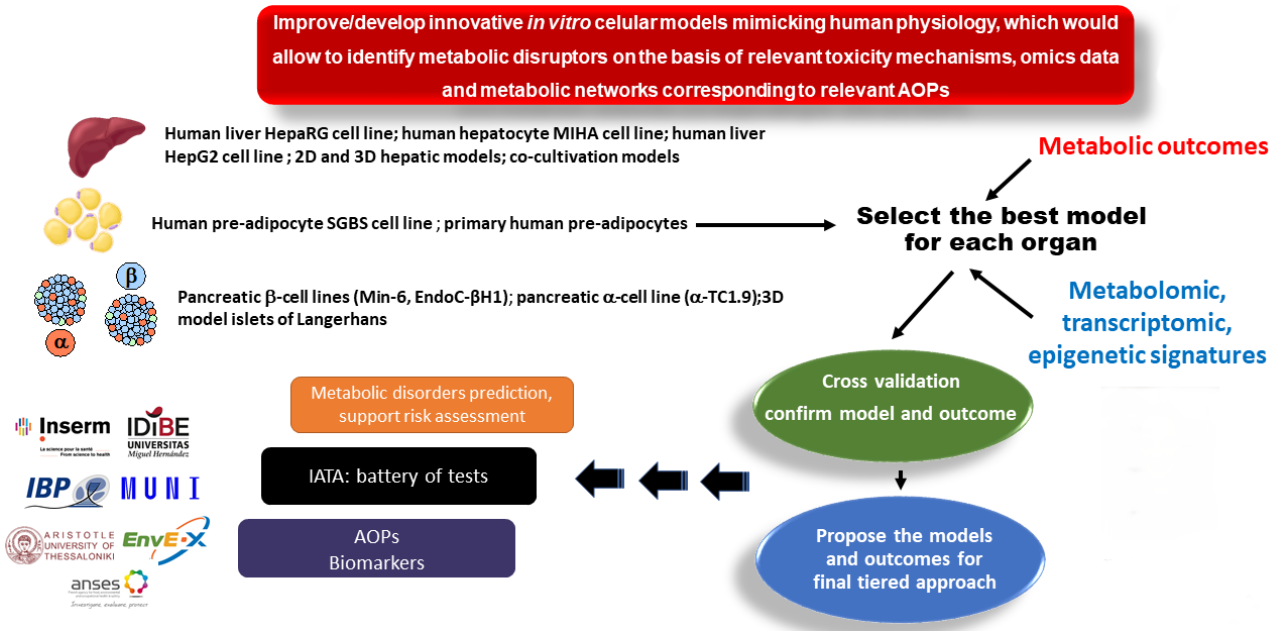
system with evolutionarily conserved lipid metabolism pathways linked to human obesity and liver diseases. The main objectives of this WP are:

- Perform the validation of the zebrafish obesogenic test (ZOT) to screen EDs and mixtures acting as obesogens
- Set up and validate zebrafish-based bioassays to screen EDs involved in NAFLD progression
- Increasing toxicological knowledges is also expected through biological activities characterization, analytical chemistry analyses and omics signatures of EDs effects

These new and convenient testing and screening methods for EDs will be candidates for regulatory use in providing relevant information for environmental and human risk assessments.

Work package leader: PR. PAtrick Babin (INSERM)

Improve and develop human in vitro cellular models to identify EDc (WP3)



This work package works to develop and improve innovative *in vitro* cellular models mimicking human physiology to identify metabolic disruptors. Different liver, adipose tissue and endocrine pancreas cell lines are being tested in order to select those that most faithfully represent human *in vivo* responses and to integrate them in testing strategies. The rationale for the selection will be based on the study of the capacity of selected EDCs to disrupt relevant metabolic endpoints which precede or exacerbate metabolic disorders. These include: altered fatty acid synthesis and -oxidation, enhanced adipogenesis or impaired insulin secretion etc. It will also be based on scale metabolomics and transcriptomics analysis.
This will also help us determine the most relevant outcomes to be selected in a final tiered test. *In vitro* data will be further linked with *in vivo* data obtained in zebrafish models (WP2) as well as epidemiology and human biomonitoring studies (WP1) and advanced

computational models (in silico and computational systems biology) (WP4) in order to confirm the relevance of the *in vitro* test systems developed.

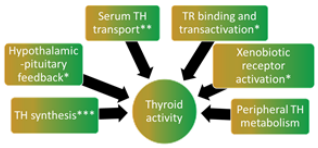
Work package leader : Paloma Alonso-Magdalena (UMH)

Predictive computational methods: QSAR and toxicokinetic models (WP4)

1. QSAR models to predict ED potential of compounds (*)

Metabolism and obesity endpoints:
- ✓ Thyroid interference
- ✓ Steroidogenesis alteration

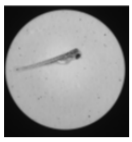
Toxicokinetic properties of EDs
- ✓ Partitioning of EDCs in the tissues
- ✓ Metabolism
- ✓ Placental transfers mother:fetus

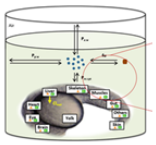


2. Toxicokinetic model for in vitro in vivo extrapolation (*)

The models will provide time-courses of cellular concentrations of substances in target organs during and following experimental exposures

Test compound: bisphenol S





3. PBPK modeling for predicting internal exposure

Develop lifetime and pregnancy PBPK models usable for **dose reconstruction and extrapolation** of in vitro data to human populations

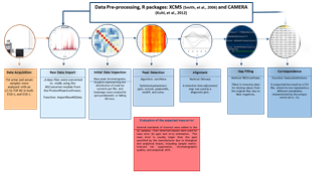
- ➢ **A human PBPK model for pregnancy**

- ➢ **Improving the modelling of the metabolism during windows of susceptibility (prenatal life, neonates, young children)**

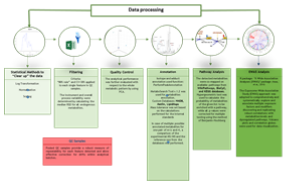
This work package provides computational methods (QSAR) to predict metabolism and obesity endpoints, and toxicokinetic properties of EDCs. Thyroid disorders and steroidogenesis are investigated. Another aim is to develop PK models for the tests systems developed in the project. The models will provide time-courses of cellular concentrations of substances in target organs during and following experimental exposures. A human PBPK model is also developed to predict lifetime and pregnancy internal exposure to EDCs.

Work package leader : Dr. Céline Brochot (INERIS)

Integrative framework (WP5)

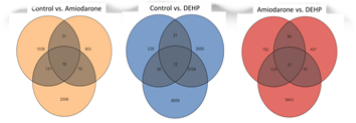


Data pre-processing workflow

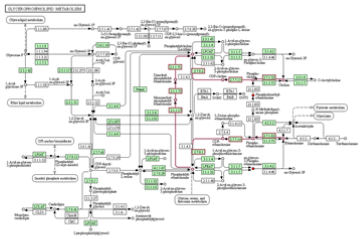


Data processing workflow

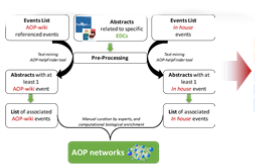
Integration of cross-omics data



Number of common entities for each treatment separately after pairwise comparison out of 2D and 3D cells experiments together



Perturbations of sphingolipid metabolism after exposure of cellular models with DEHP and amiodarone (insulin resistance and metabolic syndrome)



AOP-helpFinder tool workflow

AOP-helpFinder tool application in bisphenol F (BPF). In blue, biological events identified using the AOP-wiki list, in green using the in-house list, and in orange via both lists.

Perturbations of sphingolipid metabolism identified also in human sample metabolomics analysis

This work package aims at integrating information from WP2 (in vivo models), WP3 (in vitro models) and WP4 (in silico models) to interpret WP1 data. It also works on providing tools to elucidate the mechanistic links between exposure to EDs and metabolic disease, and on proposing an integrative testing strategy.

Work package leaders : Pr. Dimosthenis Sarigiannis (AUTH)

Ethics requirements (WP8)

This work package sets out the 'ethics requirements' that the project must comply with. Justification and information documents must be set out for the use of commercially available human cells or tissues and when sensitive personnal data is processed. Consent forms template must be created and an Ethics Board has been established.

In addition to Twitter, we are now on Instagram and TikTok. Follow us for more!

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