

Can alteration in metabolism lead to disease?

There are several health conditions that are directly related to an alteration in metabolism.

Metabolic syndrome:

is a combination of at least 3 of the following symptoms, that occur together: hypertension, increased triglyceride lipids, decreased HDL cholesterol (the good cholesterol), high blood glucose and abdominal obesity, which may increase risks of stroke, heart disease...

Diabetes:

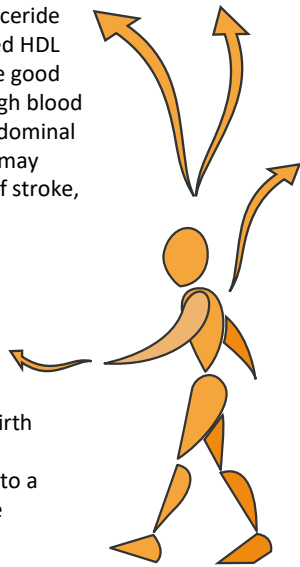
corresponds to sustained increased blood levels of glucose, and if not controlled can lead to severe outcomes including kidney diseases, neurological diseases, infections, etc.

Obesity

is also related to metabolic dysfunction. Obesity has been on the rise since several decades and is a risk factor for a variety of diseases including cancer and cardiovascular diseases.

Inherited metabolic diseases

are severe conditions at birth or later in life corresponding to a genetic disease targeting a metabolic pathway.



- **Metabolism** plays a critical role in **cancer** (*oncometabolites*), in **cardiovascular diseases**. Immune, neurological, kidney, liver, growth and reproductive diseases also involve metabolic dysregulation.
- **Metabolism** influences critical biological processes
 - Energy homeostasis in cells and organisms.
 - Oxygen-related pathways (and lack of oxygen thereof, hypoxia).
 - Epigenetic regulation which may account for long-term effects.

OBERON partners around Europe



OBERON is not alone

OBERON is part of the **EURION cluster** (<http://eurion-cluster.eu/>) which includes eight projects aiming at developing EDC tests. Three of these projects are involved in metabolism (OBERON, GOLIATH, EDCMET) and a close coordination of efforts among these projects is foreseen.



Why should we assess metabolic effects of endocrine disruptors?

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.

What is metabolism?

The Greek word "metabole" means change or transformation. Metabolism is the ensemble of chemical reactions that occur in our body to synthesize molecular components of cells and tissues and communication and signaling substances, to degrade other components, to produce the energy required for life and to support the detoxication and elimination of hazardous compounds. It is now considered as part of the criteria to identify a living organism. The small chemical substances involved in metabolic reactions are called metabolites which are functionally grouped in metabolic pathways.

Can EDCs dysregulate metabolic pathways?

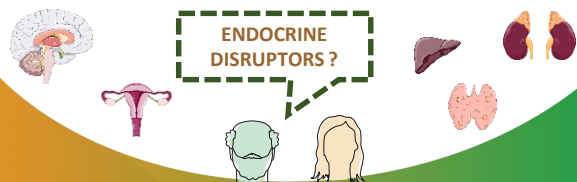
There are good reasons to believe that hormones influence metabolic pathways. In some cases, this is the major mechanism of action of hormones such as insulin, glucagon and, to a certain extent, thyroid hormones and glucocorticoids. But it is also the case of sexual hormones such as estrogens and androgens. As a consequence, women metabolism is distinct from that of men (true for female vs males in other species often used experimentally).

Since EDCs can alter hormone amounts or effects, they are likely to dysregulate metabolic pathways. This will depend on which type of hormones are altered. Implications are:

- **Increased risks** for certain diseases and health conditions
- **Gender differences** in EDC effects implying caution in interpreting single gender data
- Short, medium and **long term effects** are expected (epigenetic effects)

Why is it important to detect EDCs with metabolic effects?

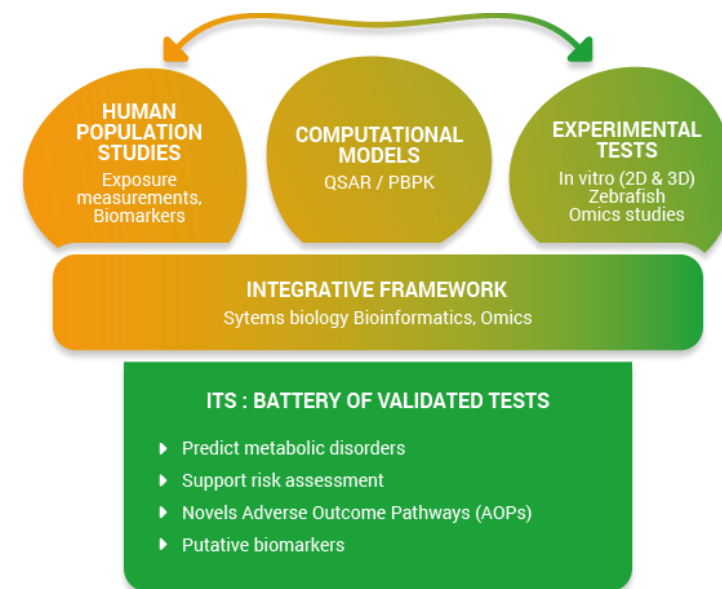
There are several regulations and directives at EU level targeting EDCs. Regulations are important but if the right tests are not available, they can be useless. Since metabolism is so critical for health and disease, exogenous substances that alter this biological process should be detected and ultimately regulated. Current tests are not satisfactory: they may detect other effects of EDCs but are not sufficient to identify metabolic effects. Thus, identifying a **test strategy** with this aim is a critical step towards a better identification of hazardous EDCs and their regulation.



The OBERON concept and methods

OBERON aims at developing a battery of tests that would reveal metabolic outcomes of EDCs. The guiding principles of the project are:

- Tests are developed based on **relevance to human studies**
- The test strategy follows the 3R principles tending to reduce animal use
- An **integrated testing strategy** is developed to optimize the test usefulness
- Applicability and validation of the tests for **risk assessment** is our ultimate goal



“Oberomics” the methods and tools of OBERON.

OBERON uses several human cell lines in 2D or 3D as well as zebrafish larvae. A variety of large scale “omics” are used to characterize the effects of EDCs. Large scale omics data are integrated and analyzed using a systems biology approach to identify the most relevant biological pathways. Biological processes are organized into “Adverse Outcome Pathways” and EDCs are linked to components of these pathways. Ultimately an integrated test strategy is developed and validated.

Contribution to chemical risk assessment

Improved chemical risk assessment is at the top of the agenda to protect citizens and prevent hazardous contamination. EDCs are chemicals of high concern, therefore filling gaps in EDC tests is critical. In addition to EDCs, the testing strategy developed by Oberon can be used for other chemicals of concern (putative carcinogens, immune-disruptors, neuro-disruptors, etc.) since metabolism is so critical in many disease processes.



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