



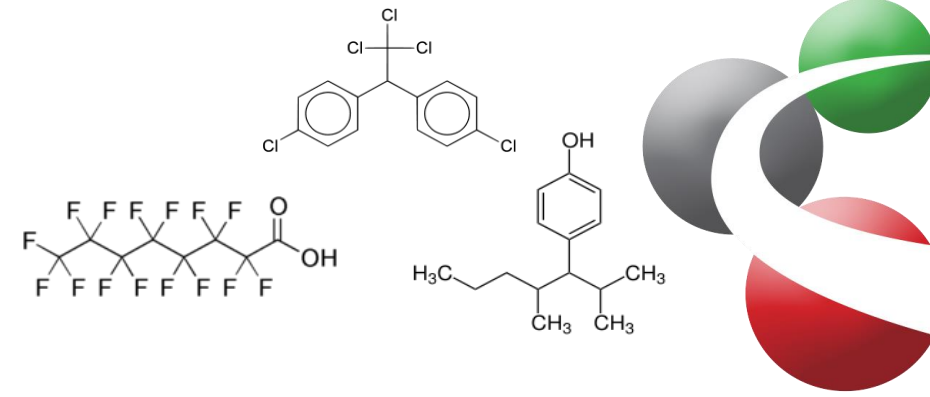
Metabolic effects of **Endocrine Disrupting Chemicals**: novel testing **METHODS** and adverse outcome pathways (EDCMET)

# Introduction and highlights

EDCMET Stakeholder workshop 24 April 2024  
Professor Anna-Liisa Levonen, EDCMET coordinator

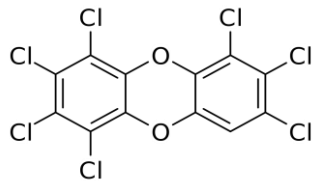
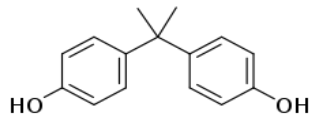
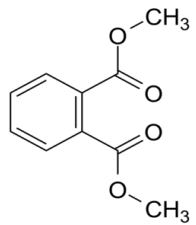


# Endocrine disruptors



Endocrine disruptors are chemicals which under certain conditions can affect the hormonal system of humans and animals and cause adverse health effects in the organism or its progeny. Endocrine disruption is one way of looking at the toxicity of chemicals.

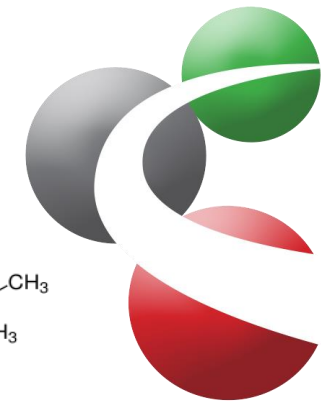
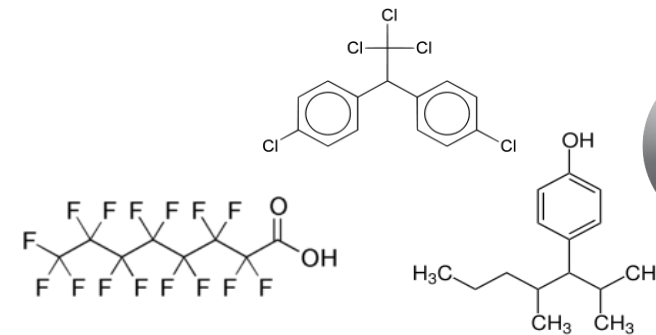
[https://ec.europa.eu/health/endocrine\\_disruptors/overview\\_en](https://ec.europa.eu/health/endocrine_disruptors/overview_en)



# Exposure



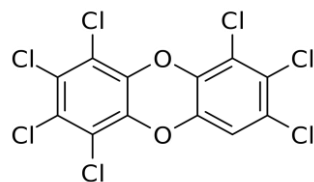
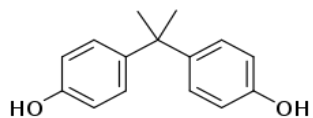
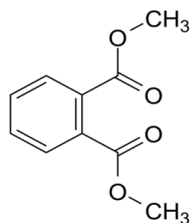
# Regulatory work



The new EU hazard criteria for ED identification adopted in late 2022 by an update to the Classification, Labelling and Packaging Regulation EC 1272/2008

<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R0707&from=EN>

➤ the ECHA Guidance is being developed on the application of the new EU hazard criteria for ED identification





## New hazard classes 2023

The European Commission has published a Delegated Regulation amending CLP Regulation, which sets out new hazard classes and criteria for the classification, labelling and packaging of substances and mixtures.

It applies to all chemical substances and mixtures placed on the EU market under REACH. It also applies to active substances in biocidal products and plant protection products, which are normally prioritised for harmonised classification in the EU.

This EU legislation is binding to manufacturers, importers, downstream users and distributors placing substances on the European Union market. Member States will also refer to the new hazard classes and criteria when making proposals for harmonised classification and labelling.

The new hazard classes are:

- ED HH in Category 1 and Category 2 (Endocrine disruption for human health)
- ED ENV in Category 1 and Category 2 (Endocrine disruption for the environment)
- PBT (persistent, bioaccumulative, toxic), vPvB (very persistent, very bioaccumulative)
- PMT (persistent, mobile, toxic), vPvM (very persistent, very mobile)

<https://echa.europa.eu/new-hazard-classes-2023>

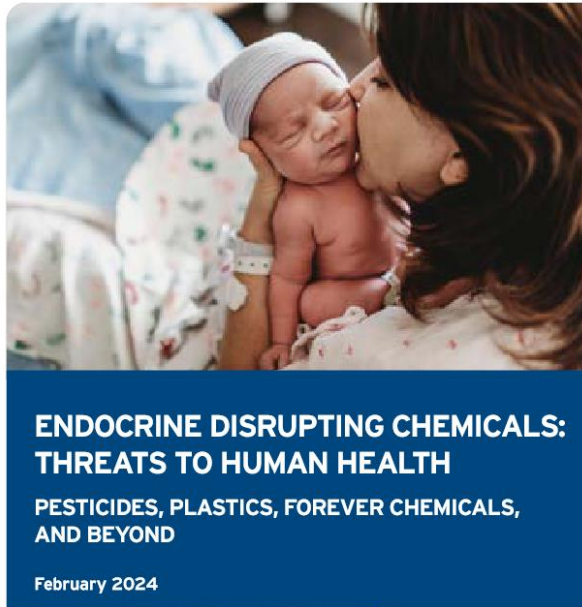
NEWS ARTICLE | 20 April 2023 | Directorate-General for Environment | 1 min read

Sustainable chemicals: New rules to identify endocrine disruptors and long-lasting chemicals enter into force



[https://environment.ec.europa.eu/news/sustainable-chemicals-new-rules-identify-endocrine-disruptors-and-long-lasting-chemicals-enter-force-2023-04-20\\_en](https://environment.ec.europa.eu/news/sustainable-chemicals-new-rules-identify-endocrine-disruptors-and-long-lasting-chemicals-enter-force-2023-04-20_en)

# A JOINT ENDOCRINE SOCIETY & IPEN INITIATIVE TO RAISE GLOBAL AWARENESS ABOUT ENDOCRINE DISRUPTING CHEMICALS



## REGULATORY GAPS

Although consensus is building on how exposures to EDCs pose risks to humans, there is still a gap between endocrine science and regulatory policy, particularly around the concept of low-dose exposures to EDCs. IPEN and the Endocrine Society call for chemical regulations based on the most modern scientific understanding of how hormones act and how EDCs can perturb these actions. We work to educate policy makers in global, regional, and national government assemblies and help ensure that regulations correlate with current scientific understanding.

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**...RECENT DATA INDICATE THAT AN EXPANDING NUMBER  
OF CHEMICALS HAVE THE CAPACITY TO DISRUPT  
METABOLIC FUNCTION AND ARE ASSOCIATED WITH  
METABOLIC DISORDERS IN HUMAN COHORTS.**

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<https://www.endocrine.org/-/media/endocrine/files/advocacy/edc-report2024finalcompressed.pdf>



# Bisphenol A



## SCIENTIFIC OPINION

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ADOPTED: 6 December 2022

doi: 10.2903/j.efsa.2023.6857

## **Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs**



# PFAS

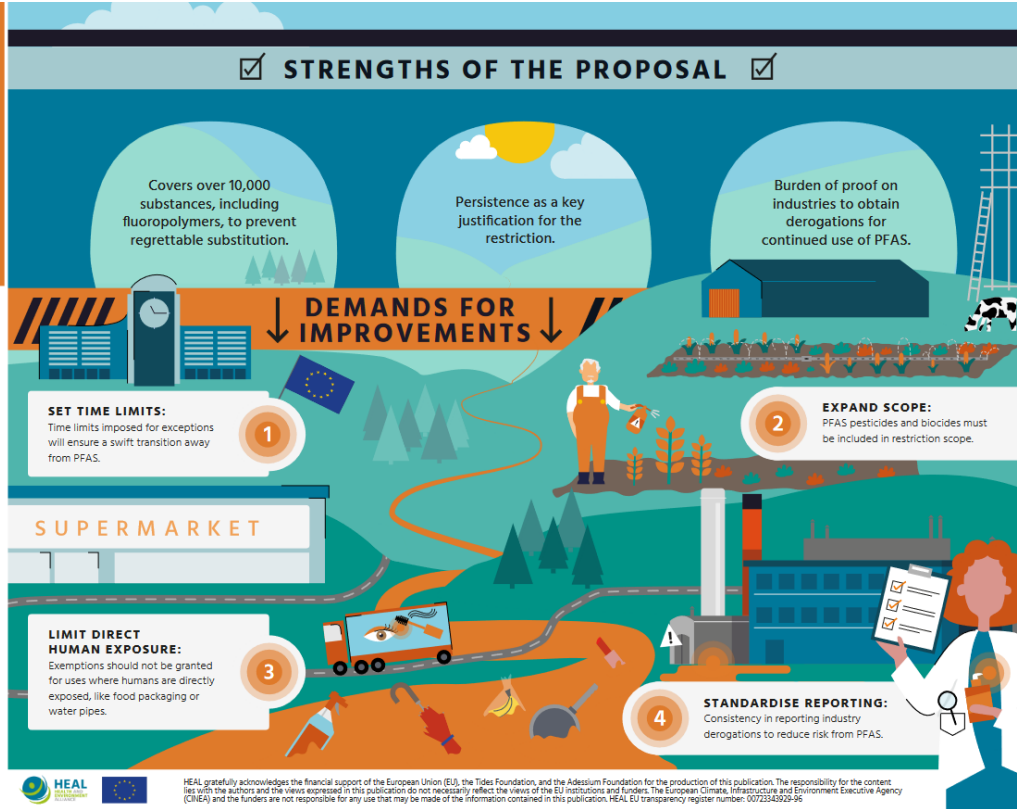


## AN EU-WIDE PFAS RESTRICTION THAT PROTECTS HEALTH



### PROBLEMS WITH PFAS

- They are everywhere and are accumulating in our bodies and the environment
- Linked to many health impacts: cancer, thyroid disease, immune dysfunction and hormone disruption
- Europe's annual health costs related to PFAS is estimated at €52-84 billion
- Used in everyday products such as food packaging, non-stick pans, waterproof clothing, cosmetics, paints and pesticides
- Class of over 10,000 chemicals
- 12,5 million Europeans are estimated to be exposed to drinking water polluted by PFAS
- 17,000 sites across Europe are estimated to be contaminated with PFAS



### Latest updates

Universal PFAS restriction proposal:

- Dossier Submitter's ongoing role in the PFAS restriction proposal - news from German BAuA, 15 April 2024
- Next steps for PFAS restriction proposal, 13 March 2024
- Highlights from November RAC and SEAC meetings, 7 Dec 2023
- Enforcement Forum's advice on enforceability of the proposed PFAS restriction, 8 Nov 2023
- All comments submitted to the PFAS restriction proposal now online, 2 Nov 2023
- ECHA receives more than 5 600 comments on PFAS restriction proposal, 26 Sept 2023

Restriction proposal on PFAS in firefighting foams:

- ECHA's committees: EU-wide PFAS ban in firefighting foams warranted, 22 June 2023

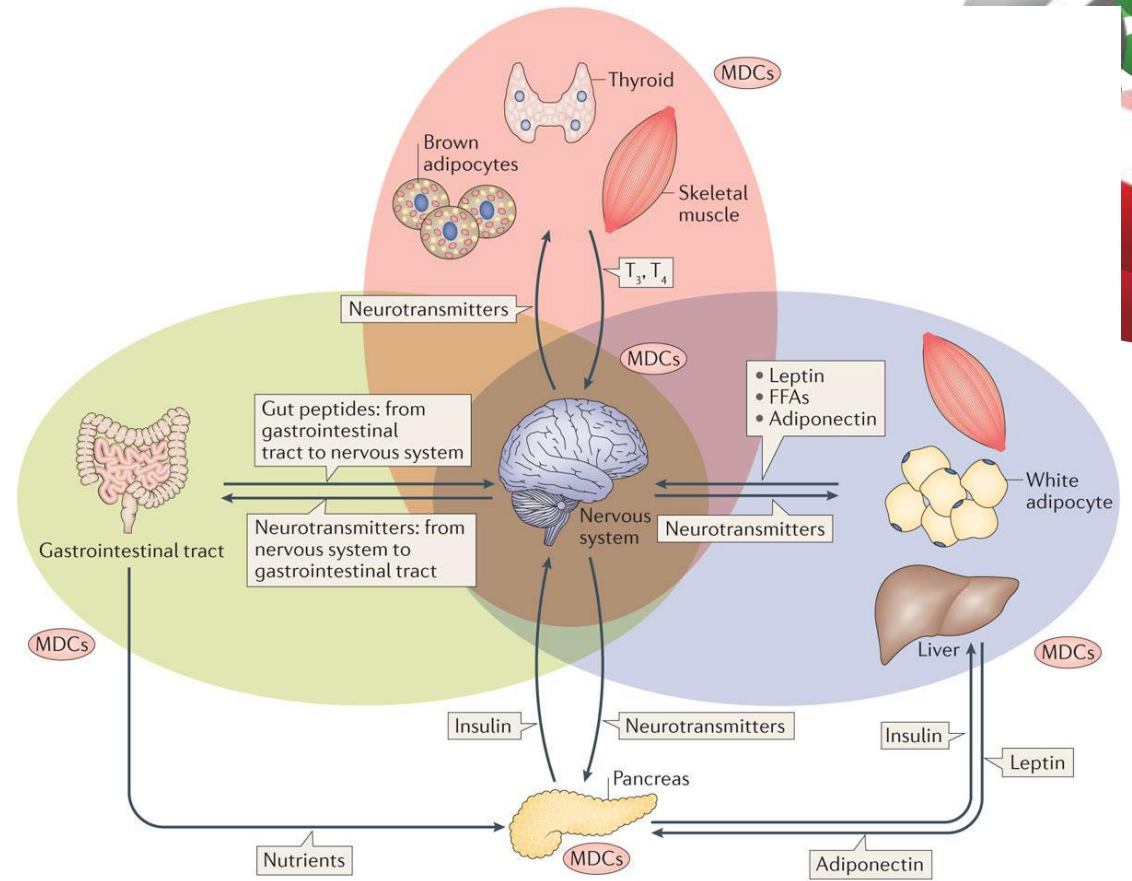
Other:

- Member States vote to restrict PFHxA in the EU, 29 February 2024
- Perfluoroheptanoic acid (PFHpA) and its salts added to Candidate List of substances of very high concern, 17 January 2023



# Metabolic disruptors

- Endocrine disrupting chemicals causing adverse effects on energy metabolism and promoting initiation or progression of metabolic diseases (obesity, MASLD, diabetes)
- Exact mechanisms unknown; multiple pathways



Nature Reviews | Endocrinology

Nadal, A. *et al.* (2017) Endocrine-disrupting chemicals and the regulation of energy balance  
*Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2017.51

# Background

- Endocrine disruptor research has focused mainly on reproductive endocrinology and related hormones, which is reflected in the available regulatory test methods.
- The current testing tools do not appropriately identify effects related to less-studied endocrine-mediated pathways and health outcomes, such as disruption of lipid and glucose metabolism, in humans.
- New and improved approaches are needed to increase the quality, efficiency, and effectiveness of the methods to evaluate the effects of these metabolic disruptors and to meet the demanding and evolving regulatory requirements worldwide.



# EDCMET

Metabolic effects of  
Endocrine Disrupting  
Chemicals:  
novel testing METHODS  
and adverse outcome  
pathways

## DURATION:

1 January 2019 - 30 June 2024

## BUDGET:

5 980 409 €

## PROGRAMME:

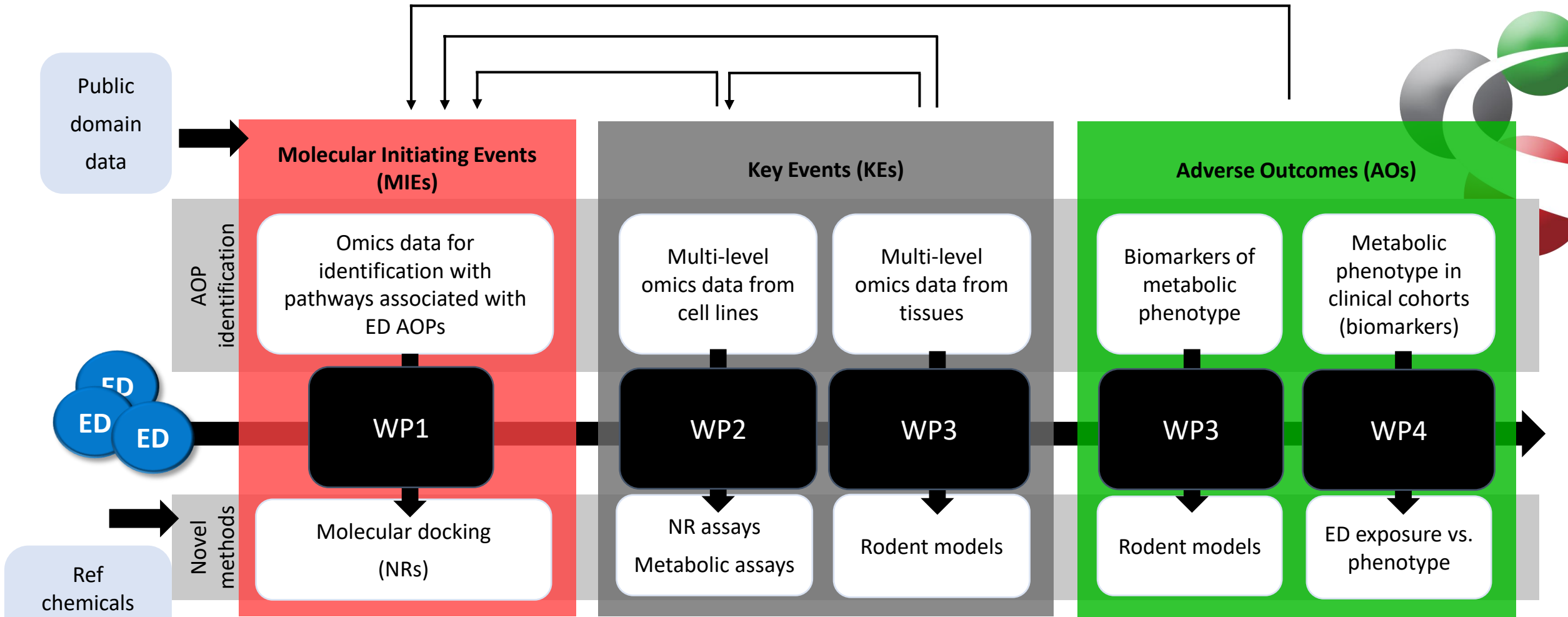
European Union Horizon 2020 Research  
and innovation programme

## GRANT AGREEMENT NUMBER:

825762



- 11 academic and non-academic partners from several European countries, over 40 experts from various research fields
- During its 5½-year journey, EDCMET aimed to identify novel ED mechanisms of action, to generate (pre)validated test methods to assess the metabolic effects of EDs, and to predict emergent adverse biological phenotypes by following the adverse outcome pathway (AOP) paradigm.



# Impact



EDCMET has laid the groundwork for future testing and ED toxicity assessment and contributed to a better understanding of human exposure to chemicals and the associated burden of metabolic diseases

- Array of new or improved testing tools for risk assessment of MDCs
- Increased human relevance of testing and risk prediction
- Identification of novel disrupted pathways in human liver
- Linking human exposure and EDC levels with metabolic endpoints and health outcomes
- Increased knowledge on metabolic diseases and novel biomarkers

All data on ED effects as well as test protocols will be made available to the scientific community, stakeholders and regulatory bodies.



# Publications



Cordis: <https://cordis.europa.eu/project/id/825762/results>

> [Bioinformatics](#). 2022 Mar 28;38(7):2066-2069. doi: 10.1093/bioinformatics/btac045.

## EDTox: an R Shiny application to predict the endocrine disruption potential of compounds

Amirhossein Sakhteman<sup>1</sup>, Arindam Ghosh<sup>1</sup>, Vittorio Fortino<sup>1</sup>

Affiliations + expand

PMID: 35134136 PMID: [PMC8963299](#) DOI: [10.1093/bioinformatics/btac045](#)

> [ChemMedChem](#). 2023 Feb 14;18(4):e202200556. doi: 10.1002/cmdc.202200556. Epub 2022 Nov 30.

## When Two Become One: Conformational Changes in FXR/RXR Heterodimers Bound to Steroidal Antagonists

Alejandro Díaz-Holguín<sup>1,2</sup>, Azam Rashidian<sup>3,4</sup>, Dirk Pijnenburg<sup>5</sup>, Glaucio Monteiro Ferreira<sup>6</sup>, Alzbeta Stefela<sup>7</sup>, Miroslav Kaspar<sup>8,9</sup>, Eva Kudova<sup>8</sup>, Antti Poso<sup>3,4,1</sup>, Rinie van Beuningen<sup>5</sup>, Petr Pavek<sup>7</sup>, Thales Kronenberger<sup>3,4,1</sup>

[Review](#) > [Int J Mol Sci](#). 2023 Jan 31;24(3):2686. doi: 10.3390/ijms24032686.

## Metabolism-Disrupting Chemicals Affecting the Liver: Screening, Testing, and Molecular Pathway Identification

Kristin Fritsche<sup>1</sup>, Andrea Ziková-Kloas<sup>2</sup>, Philip Marx-Stoelting<sup>2</sup>, Albert Braeuning<sup>1</sup>

Affiliations + expand

PMID: 36769005 PMID: [PMC9916672](#) DOI: [10.3390/ijms24032686](#)

> [Arch Toxicol](#). 2024 Mar;98(3):911-928. doi: 10.1007/s00204-023-03658-2. Epub 2024 Jan 5.

## Metabolic effects of nuclear receptor activation in vivo after 28-day oral exposure to three endocrine-disrupting chemicals

Brecht Attema<sup>#1</sup>, Outi Kummu<sup>#2</sup>, Sini Pitkänen<sup>#3</sup>, Jonna Weisell<sup>4</sup>, Taina Vuorio<sup>3</sup>, Erika Pennanen<sup>3</sup>, Maria Vorimo<sup>2</sup>, Jaana Rysä<sup>5</sup>, Sander Kersten<sup>1</sup>, Anna-Liisa Levonen<sup>3</sup>, Jukka Hakkola<sup>6</sup>

Affiliations + expand

PMID: 38182912 PMID: [PMC10861694](#) DOI: [10.1007/s00204-023-03658-2](#)

> [Environ Int](#). 2021 Nov;156:106766. doi: 10.1016/j.envint.2021.106766. Epub 2021 Jul 13.

## Non-occupational exposure to pesticides and health markers in general population in Northern Finland: Differences between sexes

Saranya Palaniswamy<sup>1</sup>, Khaled Abass<sup>2</sup>, Jaana Rysä<sup>3</sup>, Jon Øyvind Odland<sup>4</sup>, Joan O Grimalt<sup>5</sup>, Arja Rautio<sup>6</sup>, Marjo-Riitta Järvelin<sup>7</sup>

Affiliations + expand

PMID: 34271428 DOI: [10.1016/j.envint.2021.106766](#)

[Review](#) > [Arch Toxicol](#). 2023 Nov;97(11):2861-2877. doi: 10.1007/s00204-023-03575-4.

Epub 2023 Aug 29.

## Adverse outcome pathway for pregnane X receptor-induced hypercholesterolemia

Anna Itkonen<sup>1</sup>, Jukka Hakkola<sup>2</sup>, Jaana Rysä<sup>3</sup>

Affiliations + expand

PMID: 37642746 PMID: [PMC10504106](#) DOI: [10.1007/s00204-023-03575-4](#)





European Cluster to  
Improve Identification  
of Endocrine Disruptors



- European Cluster to Improve Identification of Endocrine Disruptors
- 8 projects
- Over 70 research groups
- 50 million euros
- Common working groups, events and advisory board

EURION Final event  
13-14 June 2024  
Brussels

<https://eurion-cluster.eu/>





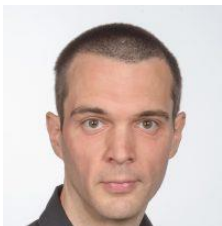
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# Thank you!



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825762.

