What **further research** do we need in order to **prevent/manage** the **health impact** of EDCs?

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JUST TO REMIND PIVOTAL ISSUES

(Solecki et al., Arch Toxicol, 2017;

italian EDC website http:old/iss.it/inte)

EDC: multiple and diverse substances, uses, environmental fates, toxicological effects

***shared feature*: EDC elicit adverse effects by targeting the endocrine system**

EDC affect the most complex (highly different tissues and hormones) signalling system of the organism = One action (e.g., thyroid hormone inhibition) leads to different adverse effects (lifestage, gender)

of

Developing lifestages (in utero, but also infancy through to puberty) are considered more susceptible (programming role endocrine signals)

The current EU regulations (REACH, PPP, biocides)..

Require that EDCs are
IDENTIFIED primarily on the basis of toxicological (hazard) considerations (comparison with other toxic effects to conclude whether ED is a primary or secondary effect)
Identification then leads to a process for *restriction/replacement*
But two main gaps still emerge

a) how to use the many -available and under development- non-animal approaches?

b) how to include more, and public health relevant, endocrine targets in testing?

Non-animal approaches

Numerous, increasing, potentially fast and cost-effective, and mode-of-action driven

but how to use the information for decision-making?

1) **do they predict adversity?**
2) **how to support decision making = whether to proceed or not with the sequence of in vivo assays (waiving criteria).**

eg., by inserting *quantitative* considerations?

let's leave the toxicology silos and *exploit* the impressive progress of basic and medical research:

Non-animal approaches

Adverse Outcome Pathways (*Leist et al., Arch Toxicol, 2017; Eu-ToxRisk, H2020 project on AOP implementation, www.eu-toxrisk.eu*)

AOP = chain of events from molecular interaction through to in vivo adverse effects (e,g., from inhibition of an enzyme of thyroid hormone synthesis through to impaired brain development)
Academic ? Not really =
understand results of existing tests, identify new predictive assays/endpoints
- how and where the mechanism of chemical X does fit into AOP Y

Next step: quantitative AOP (*how much enzyme inhibition is needed to trigger the downstream event*)

The developnent of quantitative AOP shall support *decision making:*

We gather non-animal data, we need to interpret and use

Quantitative AOP can be a way forward

A more comprehensive view on Endocrine Disruption

Current approaches cover a critical but limited spectrum of pathways:
E(strogen), A(ndrogen), T(hyroid)
What about other pathways?

Need to tackle main endocrine-related public health issues:
diabetes and related metabolic syndrome events
(*lot of scattered* evidence, potential AOP involving hypothalamus, thyroid, fat, liver, pancreas: *Heindel et al., Reprod Toxicol, 2017*)

Out of sheer public health relevance:
A robust, efficient, predictive screen of existing/new chemicals for their ability to impinge on metabolic syndrome manifestations

Again, fit-for-purpose science:
avoid *endless debate*
estimate the problem size (how many problem chemicals besides the *usual suspects, e.g.,* BPA...)
support *decision making*

Research on EDC and risk assessment

EDC that are *unavoidably* present in the environment
e.g., legacy bioaccumulating contaminants that are present in food chains and are passed to the next generation even though banned (e.g., PBDE)

Scenarios call for Risk Assessment *(hazard x exposure)* (there are many throughout EU, e.g., PFAS in north-estern Italy)

Unfeasible to *ban water or foods due to the presence of* identified EDC

The mode-of-action driven approaches should be directed to

Research on EDC and risk assessment

- Predictive early biomarkers of effect to catch early signals of a possible impact om population health (e.g., using sperm as a "sensor", *Bergamo et al., Repr Toxicol, 2016*)
- humans and animal populations as well (*one health*)
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- Toxicologically-driven numbers
Tolerable levels in order to protect susceptible population group and taking into account *cumulative exposures* to different EDC with shared effects (EFSA, 2013

***Protection goals* in order to adress**
adaptations of the polluted environment (farming systems, etc.)
Reduction of body burden in humans and food-prosucing organisms

Let's avoid drowning into complexity

- *integrate, read-across, exploit, use,* the available information (not just toxicology! Cellular and molecular endocrinology and pathology..AOP!)
After then, knowledge gaps *might look smaller*

- we do not need *just "more research"* on EDC;
rather, we need "fit-for-purpose" research to support regulators risk managers and policy makers in EU and outside (this is a global world).

- The current H2020 call on EDC is an example of a research call driven by the needs of regulatorrs and policy makers

- Let's identify *further and relevant knowledge gaps* (EFSA and ECHA activities...) and proceed on this path