Toward Regulatory Confidence in NAMs for Endocrine Disruption: Scientific Promise and Practical Gaps Across EU Sectors

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I. Introduction

- Nearly three decades ago, the European Union began taking steps to regulate endocrine disruptors (EDs) due to their potential impacts on both human health and the environment. EDs are of particular concern, as exposure, especially early in life, has been associated with developmental, reproductive, immune and neurological disorders, as well as an increased cancer risk.
- Among EDs, thyroid-mediated disruption represents a particularly complex scientific and regulatory challenge across sectors such as plant protection products (PPP), biocides, industrial chemicals, and pharmaceuticals. Conventional animal studies provide limited mechanical insights and extrapolation to humans is not always straightforward. To address these gaps, New Approach Methodologies (NAMs), defined as *in vitro, in silico*, and *ex vivo methods*, are being developed, though regulatory acceptance remains in its early stage.

II. Regulatory context

- **Crop Protection & Biocides:** In 2018, EFSA and ECHA published their Guidance for identifying ED properties with clear criteria; ED evaluation became operational under PPPR and BPR. Focus on EATS modalities (Oestrogen, Androgen, Thyroid and Steroidogenesis)
- **Industrial chemicals:** Delegated Regulation 2023/707 amending the CLP regulation introduced new hazard classes (ED Human Health (HH) and ED Environment (ENV)) which trigger REACH registration dossier updates. New hazard classes also applies to PPP and biocides
- **Pharmaceuticals**: EMA Environmental Risk Assessment Guidance (2024) introduced requirements for tailored ED assessments

Figure 1. The three criteria of ED identification

III. ED Assessment steps

Data gathering
Standard tox studies | Published literature | Databases (e.g. ToxCast)

Initial analysis of the evidence
EATS adversity/activity sufficiently investigated? | EATS adversity/activity observed?

Mode of Action Analysis (MoA), if required
Postulate MoA | Adverse Outcome Pathways (AOP) | Generate evidence (e.g. NAMs)

Overall conclusion
Based on Weight of evidence (WoE) | Separate conclusion for HH and ENV

IV. Thyroid modality: AOP network

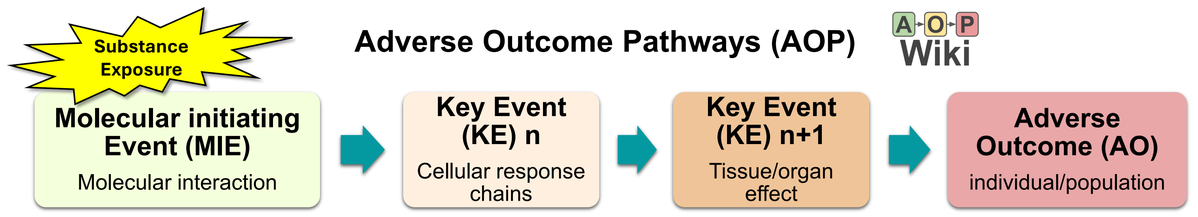


Figure 2. Structure of the AOP network

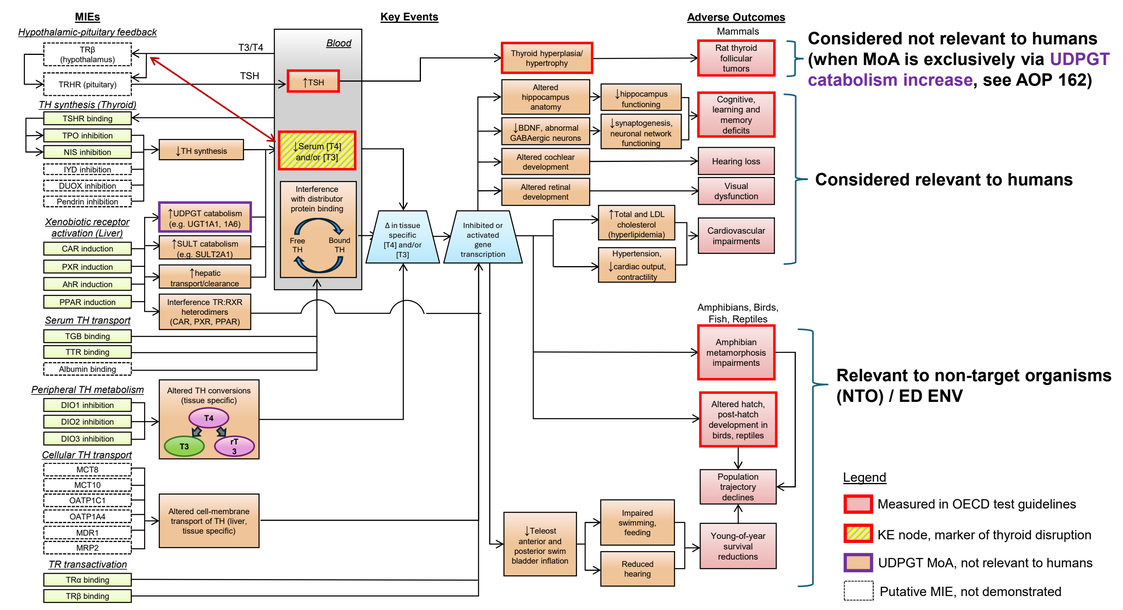


Figure 3. Thyroid AOP, adapted from Noyes *et al.* (2019)

- **Currently:** Endocrine adversity exclusively assessed with *in vivo* data, NAMs can be used to provide information on endocrine activity and substantiate WoE
- **Challenges**: Thyroid modality is highly complex, no validated methods to investigate these pathways, potential co-occurring MoA should be dismissed when assessing human relevance, limited regulatory acceptance of recent NAMs
- **Opportunities**: NAMs can provide mechanistic insights, AOP network supports integration and evaluation of human relevance. Further development of NAMs is needed and dialogue between CROs, industry and regulatory authorities to enhance regulatory confidence and acceptance

V. NAMs for ED assessment : examples

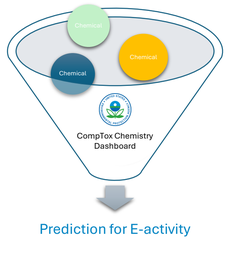
Comparative Liver Enzyme Induction Study (T-modality)

- Comparison of liver enzyme induction (UDPGT) in rat and human hepatocytes and species differences following chemical exposure
- Can provide evidence of the non-human relevance of the UDGPT MoA, if T4-UGT is increased in rat cells but not in human cells
- Validation issues (positive controls), regulatory acceptance still uncertain

ToxCast ER Bioactivity Model (E-modality)

- Developed by the U.S. EPA (Browne *et al*., 2015 and 2017)
- Computational model based on 18 high-throughput *in vitro* assays (HTS)
- Recognized in updated CLP Guidance (Nov 2024) as equivalent to the Uterotrophic assay (OECD TG 440) for low-metabolism compounds

→ supports reduction of *in vivo* assays



VI. Discussion

- Regulatory trust in NAMs relies on their reliability, reproducibility, and ability to be scaled
- Scientific strengths of NAMs: mechanistic insights, potential for human-relevant predictions, higher throughput for screening/prioritization, and reduction of animal use (3Rs principle)
- Thyroid endocrine disruption involves complex interacting mechanisms, is highly linked to development and is difficult to assess. Most recent NAMs related to thyroid disruption lack formal validation
- EU initiatives such as PARC, EURION, and ASPIS are driving the development of robust fit-for-purpose NAMs while the Joint Research Centre (JRC) and EU-NETVAL network of laboratories is advancing the validation of methods addressing thyroid hormone disruption
- Suggestions for the future: harmonize sectoral expectations (EFSA, ECHA, REACH, EU Member State regulators), embed NAM acceptance criteria into guidance, and promote early multi-stakeholder dialogue (industry, CROs, regulators, academia, and EU projects)

Figure 4. Ongoing EU projects / research centers fostering NAM development, validation and integration

VII. Conclusion

- NAMs offer clear scientific promise to enhance ED assessments and reduce reliance on *in vivo* testing
- Realizing regulatory confidence requires coordinated action: further development of AOPs, representative case studies, validation and interlaboratory work, clear guidance outlining NAMs acceptability, active cross-sector regulatory dialogue and experience sharing
- With these steps, NAMs can transition from promising science to practical tools that support protective, efficient and humane regulatory decisions across EU sectors

VIII. References

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