From Literature Search to Regulatory Assessment:

Addressing Endocrine Disruption with Non-Standardized Data

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Background

- In 2023, the EU Classification, Labelling and Packaging (CLP) Regulation was amended (2023/707) to include **new hazard classes for endocrine disruption (ED)**
- Classification as an endocrine disruptor requires evidence of endocrine activity, adverse effects, and a biologically plausible link between the two
- Under CLP, assessment relies mainly on existing information, including REACH data and published literature
- To address data gaps and regulatory constraints, this work explores how **non-standardised literature** (e.g. academic literature, non-guideline studies) can be systematically evaluated to support **ED classification for a series of rare earth elements (REEs)**

Approach

Literature search
- STNext + Pubmed
- 1994-2025
- 101 papers identified

Initial relevance screening
- Based on title/abstract
- 29 papers deemed relevant

Reliability check
- How to assess the reliability?

Development of a template for reliability and in-depth relevance assessment

Regulatory and guidance-based input for the template

Information on endpoints, study design, requirements for ED identification from existing guidance documents:

- OECD Guidance Document 150
- ECHA REACH Endpoint Specific Guidance Chapter R.7a - c
- ECHA Guidance on the Application of CLP Criteria Part 3-5
- OECD testing and assessment guidance documents on histopathology
- WHO State of the Science on Endocrine Disruptors

Evaluation criteria applied within the template

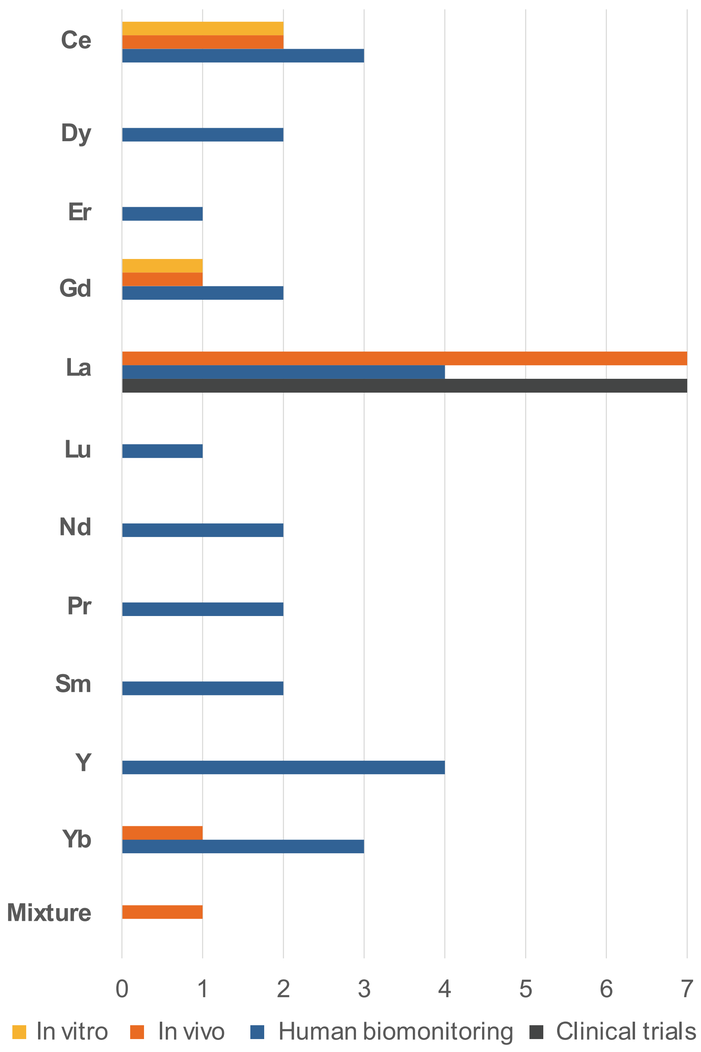
1. Study reliability
- Study design
- Test system
- Exposure duration, concentration and analytical verification

2. Endocrine relevance
- Modality studied (EATS/non-EATS)
- ED endpoints assessed

3. Weight-of-evidence considerations
- Key limitations (e.g. other non-ED MoA)

Results

Studies for which reliability was assessed per REE



Availability of evidence
- Marked variability in the number of studies identified across REEs
- For most REEs, the evidence base was very limited, with many REEs considered data-poor
- In some cases, ED-relevant information originated from a single human biomonitoring study, precluding ED classification under CLP

Study quality and interpretability
- The structured evaluation template enabled consistent and transparent evaluation of non-standardised studies
- Most studies showed (methodological) limitations, complicating regulatory interpretation
- Reported in vivo effects were mainly attributable to non-endocrine modes of action (oxidative stress)

Type of evidence
- **Human biomonitoring studies:** predominantly associations, without mechanistic confirmation
- **Clinical trials:** Available for La (hyperphosphatemia), but not designed to assess ED activity or adversity
- **In vivo studies:** mostly non-guideline and mainly addressing non-EATS modalities
- **In vitro studies:** limited, often not optimised for metals or focused on highly specific nanoforms unlikely to be representative for the REE in general

Conclusions and future perspectives

- For most REEs, ED classification criteria could not be fulfilled
- Structured evaluation improves transparency and consistency, but does not resolve data gaps
- Classification for data poor substances stays difficult
- Clearer guidance on use of non-standardized ED data is required
- Challenges remain for metals and inorganic substances especially regarding mechanistic information as in vitro studies are limited