

An Industry Approach to Prioritise Endocrine Disruption Evaluation of UVCB Substances

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Conflict of Interest: The authors declare that there is no real or perceived conflict of interest. The authors are employed by entities that manufacture or distribute the material that is subject to this presentation or have received service fees from those entities.

Introduction

The Lower Olefins and Aromatics (LOA) REACH Consortium register approximately 143 substances¹, including complex substances of Unknown or Variable composition, Complex reaction products, or Biological materials (UVCBs), produced by steam-cracking of petroleum-based feedstocks (e.g. naphtha, LPG), see [Figure 1](#). These legacy chemicals are important as they are used in the production of, for example (and not limited to): food packaging, detergents, pharmaceuticals, agrochemicals, paints and coatings, adhesives, disposable nappies (diapers), engine parts, computers, textiles, electric and electronic appliances, construction, and cosmetics.

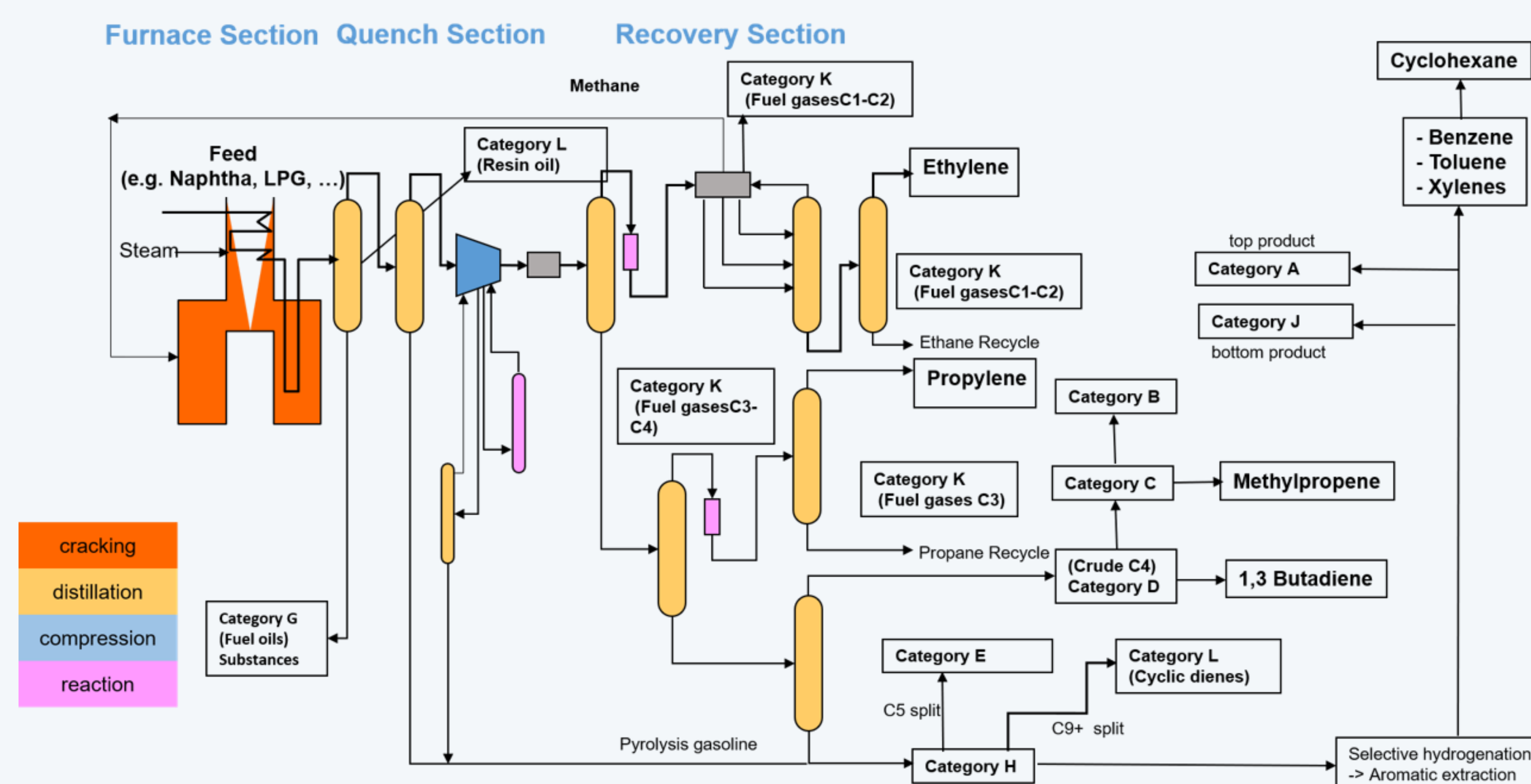
LOA UVCBs can contain complex combinations of different constituents. In REACH, chemicals manufactured from similar starting materials (feedstocks) with comparable compositions are grouped into categories to facilitate hazard and risk assessment.

Under recent EU requirements², Endocrine Disruption (ED) assessment is required. ED evaluation for UVCBs is challenging due to their complex composition, limited publicly available data for many constituents, and the lack of validated frameworks specifically tailored for UVCBs; making the task of linking endocrine activity to adversity highly complex.

In an aim to tackle this complexity, and prioritise LOA UVCB substances for ED assessment, LOA UVCB constituents were screened for potential endocrine activity using available QSAR models, focusing on estrogenic (E), androgenic (A), thyroid (T) and steroidogenic (S) (EATS) modalities.

Objective: This work aims to develop modernised techniques, utilising tools for chemical hazard evaluation at a category level by conducting a screening level assessment of potential ED properties of LOA UVCBs.

Figure 1: Manufacturing process schematic of LOA substances



Methods

Virtual Screening Workflow

- Structure Curation & Standardization: Raw chemical structures were curated and standardized to satisfy model applicability domains and ensure predictive reproducibility
- Predictive QSAR Modeling: Endocrine-related bioactivity and nuclear receptor binding were predicted across targets using validated QSAR models (OPERA^{3,4}, VEGA⁵, PERCEPTA⁶ and OECD QSAR ToolBox⁷, [Figure 2](#))
- Ontological Normalization: Model predictions were mapped to a unified ontology framework to harmonize disparate results
- Rule-Based Consensus Integration: Predictions were integrated using predefined expert decision trees to establish consensus bioactivity flags and reduce single-model bias

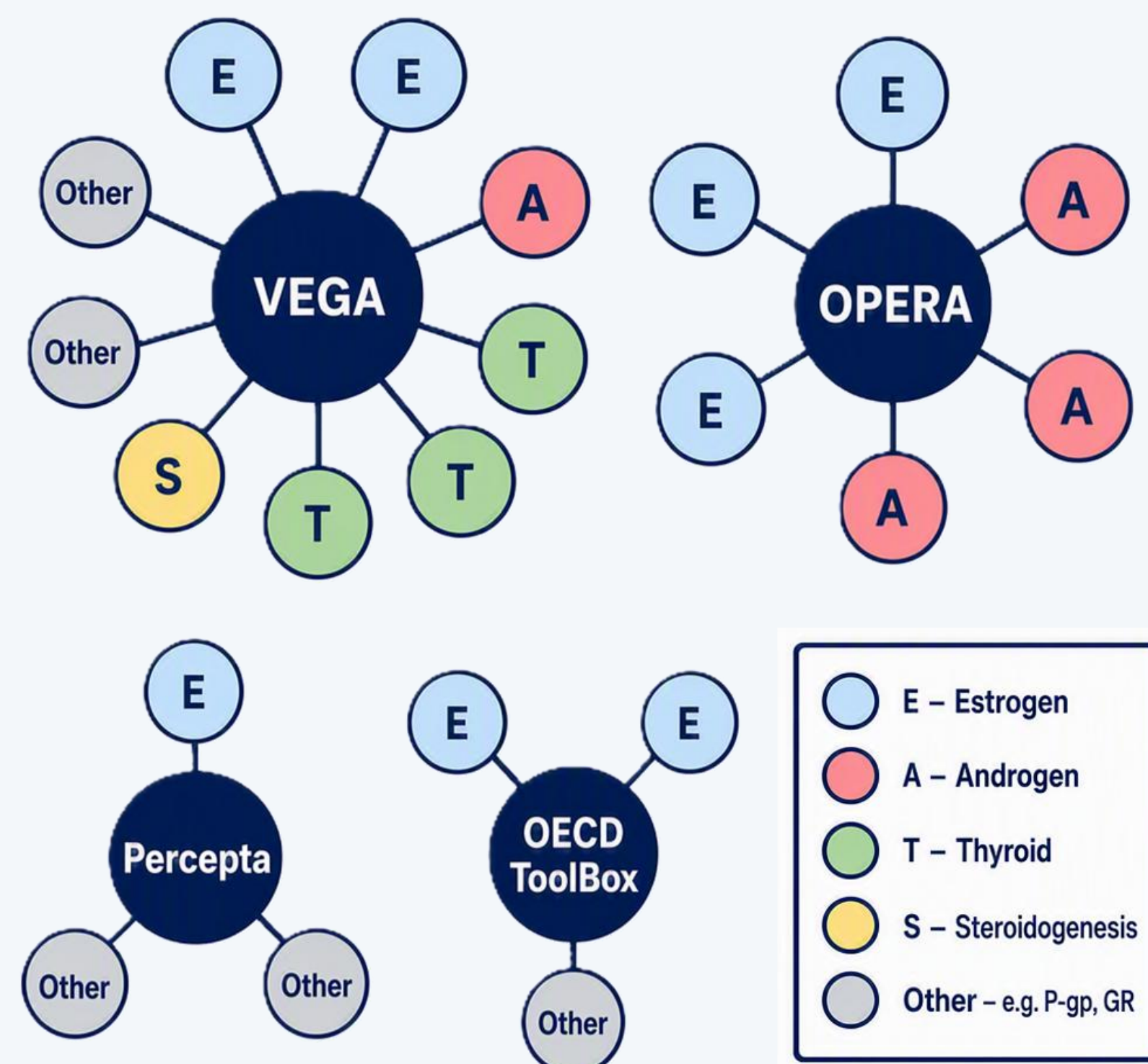
Scoring Architecture & Target Modalities

The decision tree outputs two normalized metrics for each chemical: a Receptor Score (R) indicating predicted activity, and a Confidence Score (C) evaluating prediction reliability based on model domain concordance and data availability

- R Score (evaluates receptor interaction):
 - R = 1.0
 - Active; R = 0.5: Inconclusive / Data gap
 - R = 0.0: Inactive
- C Score: Continuous metric from 0.0 (low confidence/high uncertainty) to 1.0 (high confidence/high concordance)

Figure 2: ED modalities measured using different models associated with employed QSAR tools

Each ED modality (EATS or "Other") indicates a specific model used.



Evaluated Pathway Modalities

- Core EATS Pathways: Captures canonical endocrine disruption targets aligned with regulatory frameworks
- Ancillary Endocrine & Disposition Modality (OTHER Score): Consolidates QSAR predictions and available empirical bioassay data for non-EATS targets to account for broader hormonal toxicity and toxicokinetics:
 - GR: Glucocorticoid Receptor
 - RAR: Retinoic Acid Receptor
 - P-gp: P-glycoprotein efflux transporter

Results Processing

Results were normalised (positive, negative) based on R- and C-scores, where positive and negative results were further split into experimental or predicted results when the QSAR models returned either experimental data or a predicted outcome.

Results were then mapped onto LOA UVCB categories by listing each category's constituent results on the category boundary composition to enable a visual snapshot of overall results to assess where effort needs to be focused to evaluating categories for ED potential.

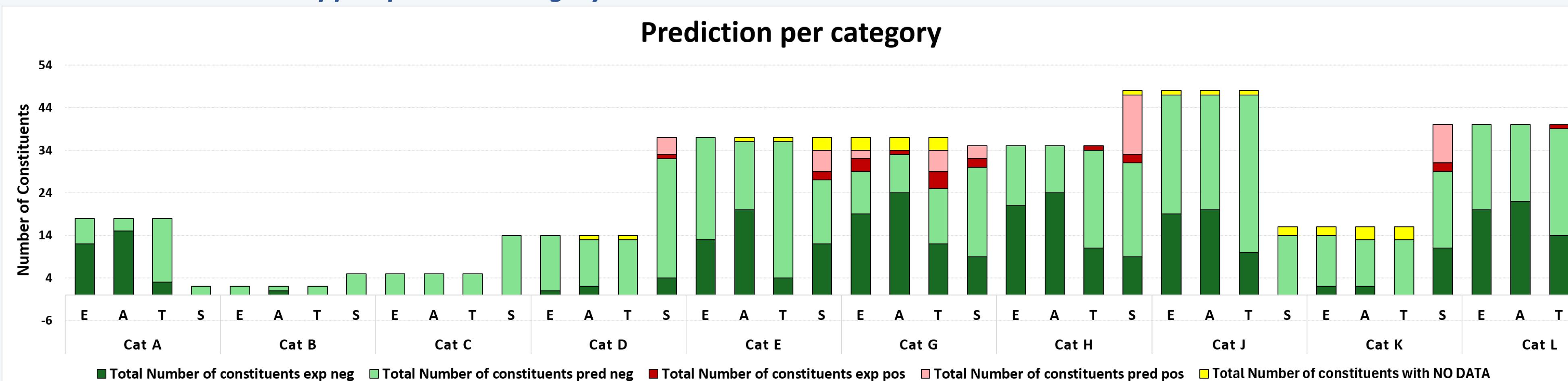
Results

A total of 149 constituents were used in this exercise; however, not all constituents were able to have SMILES assigned (11 constituents).

- 104 constituents were identified as low priority, having high confidence for inactivity or robust negative predictions across all modalities evaluated
- 12 constituents were identified as high-priority, suggesting some of the constituents may interact with more than one endocrine pathway (multiple modality hits) or have high confidence for activity
- 19 constituents were identified to have weak biological activity, and 3 constituents fell outside the applicability domain

Mapping the activity profiles for LOA categories against their constituents (see [Table 1](#)) allowed for the identification of specific UVCB groups (Categories) requiring further ED evaluation.

Table 1: QSAR results mapped per LOA Category



Discussion & Conclusion

Category-level integration of QSAR outputs were effective for identifying UVCB groups (categories) requiring further ED assessment. This approach provided a transparent, reproducible, and resource-efficient method to support prioritisation decisions that will allow resources to be focused on further weight of evidence assessment of UVCB substances that have the highest potential for ED activity.