Innovations in the Risk Assessment of Low-Risk Active Substances of Botanical Origin for Crop Protection: AOPs, and NAMs

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Section 1: Background and rationale

- **Regulatory basis: Reg (EC) No. 1107/2009** allows **active substances (AS)** to qualify as **low-risk (LRs),** promoting their use as alternatives to synthetic **plant protection products (PPPs).**
- **Limited uptake:** Despite this provision, botany-based **LRs** remain **undefined** in the EU system; **LRs** accounting for **<10%** of approvals, with **botanicals** being a **minor share.**
- **Assessment challenge:** Although botanicals are biologically derived and expected to present lower risk profiles, their regulatory assessment **remains complex** and **data-intense.**
- **Data requirements:** Botanical **LRs** are subject to the same toxicological data package as synthetic **AS** under **Reg (EU) No. 283/2013** and **284/2013.**
- **Mismatch of testing frameworks:** The standard toxi- and ecotoxicological tests **(OECD/EFSA)** are often ill-suited to botanicals, which are chemically complex mixtures.
- **Burden on applicants-data gaps:** This approach results in **high costs** and **lengthy timelines,** disproportionately affecting **botanical** products and **limiting innovation** and **market access.**

Section 2: Core definitions

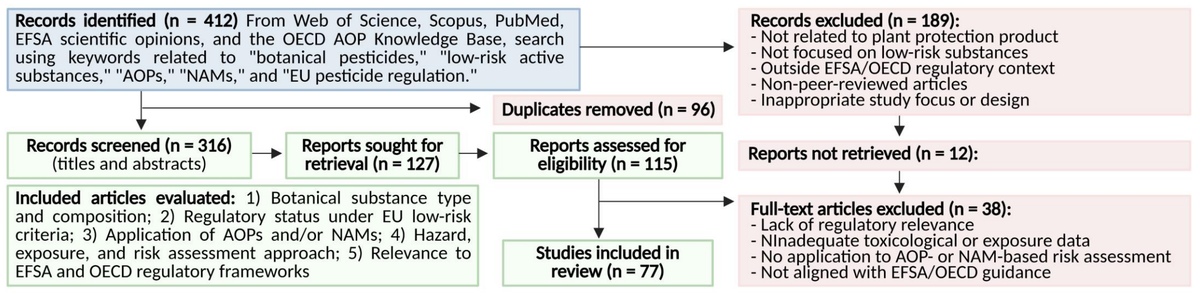
a) LRs of botanical origin: plant-derived **AS** used in **PPP** that meet **the low-approval criteria of Reg (EC) No. 1107/2009** (Article 22; Annex II). They must be adequately characterized (e.g., **plant source, extract process, compositional markers**) and not be classified as carcinogenic, mutagenic, or toxic for reproduction **(CMR Cat. 1A/1B)** under **Reg (EC) No 1272/2008 (CLP);**

- **not meet the criteria for endocrine disruption;**
- **not exhibit neurotoxic or immunotoxic properties;**
- **be non-persistent** (soil DT_{50} ≤ 60 days; water DT_{50} ≤ 40 days);
- **be non-bioaccumulative** (BCF ≤ 100);
- **not cause unacceptable effects on non-target organisms**

b) Adverse outcome pathways (AOPs): mechanistic frameworks recognized in **EU regulatory** science that describes a biologically plausible and causally linked sequence of key **events**, from a molecular initiating stage to an adverse outcome relevant for regulatory decision-making.

c) New Approach Methodologies (NAMs): sets of **non-animal and alternative testing** (*in vitro, in silico*, and mechanistic approaches) endorsed in **EU risk assessment (RA)** to generate data for hazard identification and characterization, support **mechanism-based decision-making,** and **enable the reduction of animal testing (Figure 1).**

Section 3: Methodology



Section 4: Results

The **multifaceted nature** of **botanical extracts** can lead to data gaps regulatory **bottlenecks**. Barriers to approval include perceived **toxicity**, **limited ecotoxicological data**, and the inability to apply **single-molecule hazard models**. Case studies comparing botanical and chemically derived **AS** reveal that adopting the full **synthetic-style dossier** for plant-based products hinders their approval and implementation. **AOP-informed** and **NAM-based strategies** effectively identify mechanistic hazards, refining **exposure** and risk characterization in line with **EFSA uncertainty** and **weight-of-evidence** principles to reduce reliance on vertebrate testing. **Figure 2** exemplifies the **decision-making process** for botanical **LRs** using **exposure-driven logic** to evaluate effective regulatory protection while eliminating unnecessary testing. These advances promote a **proportionate**, **predictive**, **ethics-aligned RA** process tailored to botanical **LRs.**

Section 5: Conclusions

Within the framework of **next-generation RA** for **PPP**, complementary approaches, such as the **Qualified Presumption of Safety (QPS), AOPs, Weight-of-Evidence (WoE) assessment, read-across,** and **NAMs**, can be integrated to develop **fit-for-purpose RA** schemes for specific **LRs pesticides**, including **botanicals**. In this context, **AOPs** and **NAMs** were occupied to design a **tiered strategy** for **prioritizing testing** methods, enabling **faster** and more **cost-efficient** authorization of **botanical pesticides** while maintaining a **high level of safety.**

Acknowledgements

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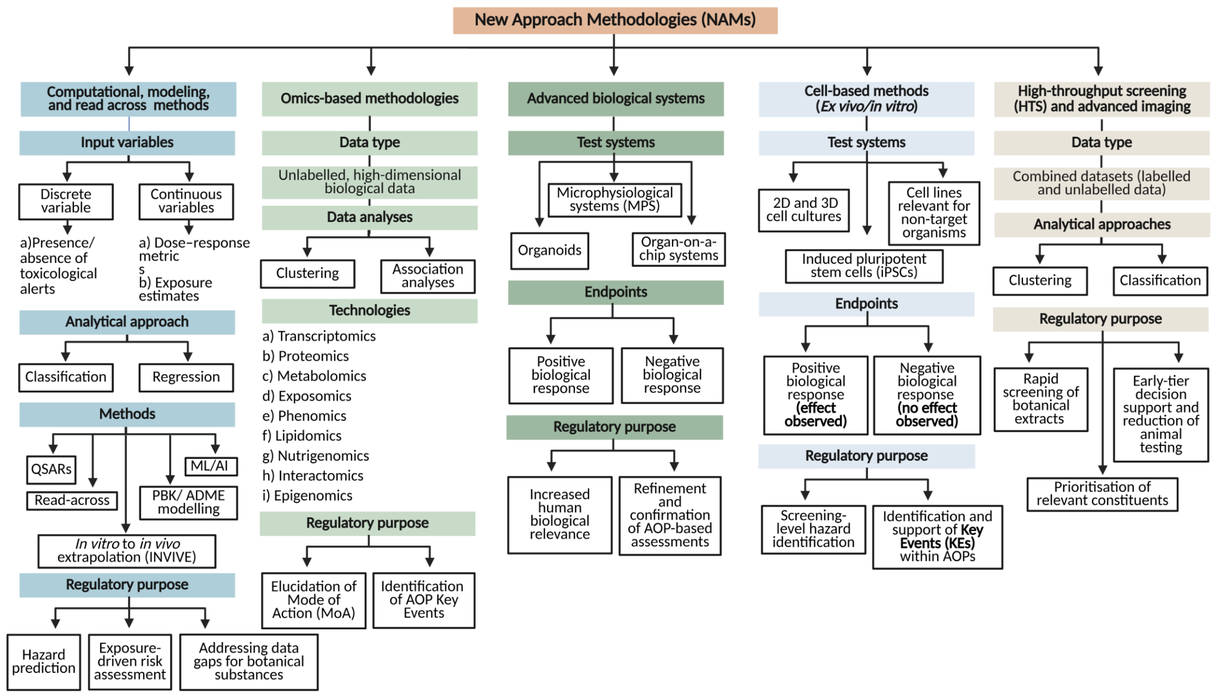

Figure 1. Methods, tools, applications, and systems commonly encompassed under the umbrella of NAMs. Created in https://BioRender.com

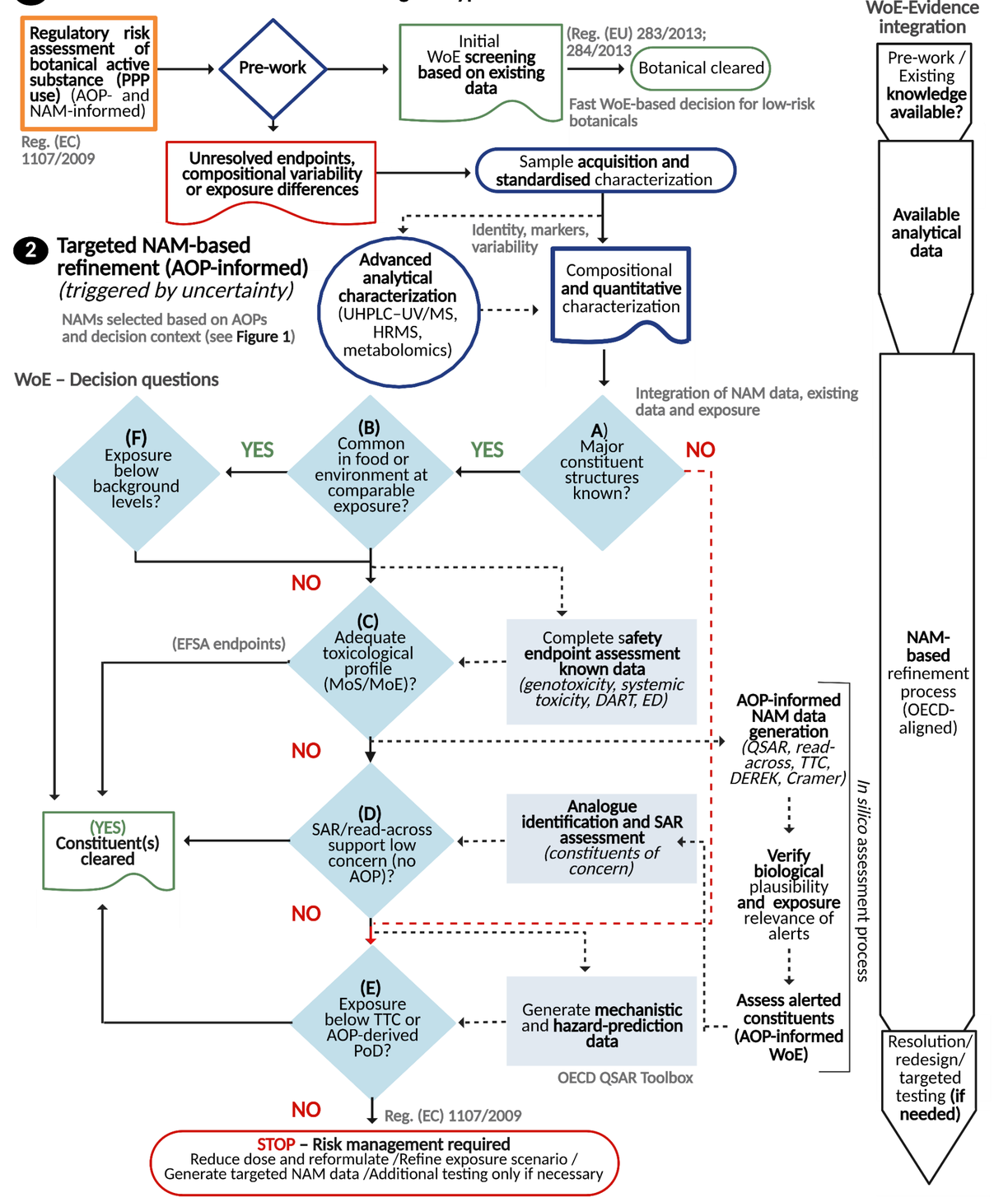

Figure 2. AOP- and NAM-informed decision tree based on EFSA and OECD guidelines for the regulatory RA of LRs botanical AS. Irregular hexagons = decision points; Rounded boxes = data/evidence; Dashed arrows = NAM-based refinement; Green = clearance; Red = risk management. Created in https://BioRender.com