Providing risk assessments of complex real-life mixtures for the protection of Europe's citizens and the environment

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[1]Type of document – R: Report, Document (excluding the periodic and final reports); DEM: Demonstrator, pilot, prototype, plan designs; ORDP: Open Research Data Pilot; OTHER; ETHICS: Ethics requirement
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Purpose of the document

This document provides **policy recommendations to support the uptake of New Approach Methodologies (NAMs)** in the context of **chemical mixture risk assessment**, based on the scientific evidence, tools and experiences generated within the PANORAMIX project.

The recommendations are intended to inform **European and national policymakers, regulatory authorities and standard-setting bodies** on how NAMs, such as in vitro bioassays, high-throughput screening, effect-based approaches, computational modelling and integrative data frameworks, can be effectively integrated into existing risk assessment and risk management frameworks.

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Policy brief

NAMs for chemical mixture risk assessment

PANORAMIX evidence in support of the EU Roadmap towards phasing out animal testing

Executive summary

The European Commission is finalising its *Roadmap towards phasing out animal testing for chemical safety assessments* (adoption expected Q2/2026). Stakeholders surveyed in the Commission's 2024 Call for Evidence and 2025 group interviews agree that regulatory accepted New Approach Methodologies (NAMs) are still lacking for complex endpoints — endocrine disruption, carcinogenicity, reproductive and developmental toxicity, DNT — and, crucially, for real-world chemical mixtures. PANORAMIX (Horizon 2020, GA 101036631) has developed and applied a ready-to-use NAMs toolkit that directly addresses these scientific gaps and generates policy-relevant evidence. This brief summarises the evidence and recommends three concrete actions to support the progressive integration of PANORAMIX outputs into the Commission's Next-Generation Risk Assessment (NGRA) framework, the Regulatory Science Network, and the EU Test Method Development & Validation Strategy (ERA NAMs, 2025–2028).

The EU policy context

- Adoption in Q2/2026 of a Commission Communication + Staff Working Document covering 15 legislative areas, followed by an implementation phase (NGRA framework, Safe Spaces, Regulatory Exploration Spaces).
- Stakeholder consensus (Call for Evidence 2024, 90 responses; 85 % positive): accelerate validation and regulatory acceptance of NAMs for complex hazard endpoints and strengthen cross-sector collaboration.
- Effect-based monitoring already introduced in EU water regulation under the Water Framework Directive, where effect-based methods for estrogenic activity are adopted as complementary tools alongside chemical analysis.
- Proposed governance: Roadmap Steering Team, Regulatory Science Network on phasing out animal testing, Agency collaborative structures (ECHA/EFSA/EMA) and an Inter-Agency Working Group within EUAN — all requiring an evidence base on real-world exposures.
- Key Areas of Regulatory Challenge (KARC) reports and the EPAA partnership will shape priorities; peer-reviewed NAMs for chemical mixtures are an identified gap.

PANORAMIX evidence: a NAM-based toolkit for chemical mixtures

PANORAMIX has tested real-life samples from the environment–food–human continuum across multiple EU countries in human-relevant bioassays. Key outputs:

- A battery of 22 human/mammalian in vitro bioassays mapped to four Adverse Outcome Pathway networks: thyroid hormone disruption, developmental neurotoxicity, reproductive toxicity and genotoxicity/stress.
- Integrated chemical profiling (target, suspect and non-target screening): 24 chemicals quantified in ≥3 extracts; 547 HRMS features; 63 suspect-identified substances, including PFAS mixtures, plasticisers, pesticides and parabens.
- Concentration addition was confirmed as the default mixture behaviour across the endpoints tested, justifying a mixture-ready extension of NGRA.

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- A framework using bioanalytical equivalents (BEQ_{bio}) that - combined with chemical analysis - quantifies how much of the measured biological effect is explained by known chemicals (BEQ_{chem}) and how much remains invisible ($BEQ_{unknown}$) in the mixture, illustrating the underestimation of health risks in substance-by-substance regulation.
- High-throughput Effect-Directed Analysis (HT-EDA) identifying active drivers (e.g. propylparaben, methylparaben and imiprothrin in human blood) and candidate Effect-Based Trigger Values for water, food and blood matrices.
- Linkage to human-health outcomes via 750 cord-blood samples of the Odense Child Cohort (anogenital distance, language development, ADHD, IQ), demonstrating regulatory relevance.
- Peer-reviewed evidence: Motteau et al., Environ. Sci. Technol. 2025; Escher et al., Science 2020 and IJERPH 2022; Treschow et al. on PFAS mixtures 2026.

Three Policy recommendations

1. Embed effect-based mixture testing in the EU NGRA framework. Extend the Human Safety Assessment matrix (Endocrine Disruption, DNT, Repro/DART, Genotoxicity, Carcinogenicity, Systemic Toxicity) to explicitly cover chemical mixtures, using concentration addition as the default.
2. Adopt Bioanalytical Equivalent (BEQ) metrics and Effect-Based Trigger Values in EU regulatory workflows (Water Framework Directive, Food Contact Materials, HBM4EU/PARC follow-up, EFSA opinions) to capture the unknown fraction of mixture risk.
3. Leverage the CMC 2.0 stakeholder training (Feb–Apr 2026) as a regulator-facing uptake model, and channel PANORAMIX outputs into KARC reporting, the EPAA project teams and the Regulatory Science Network on phasing out animal testing.

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