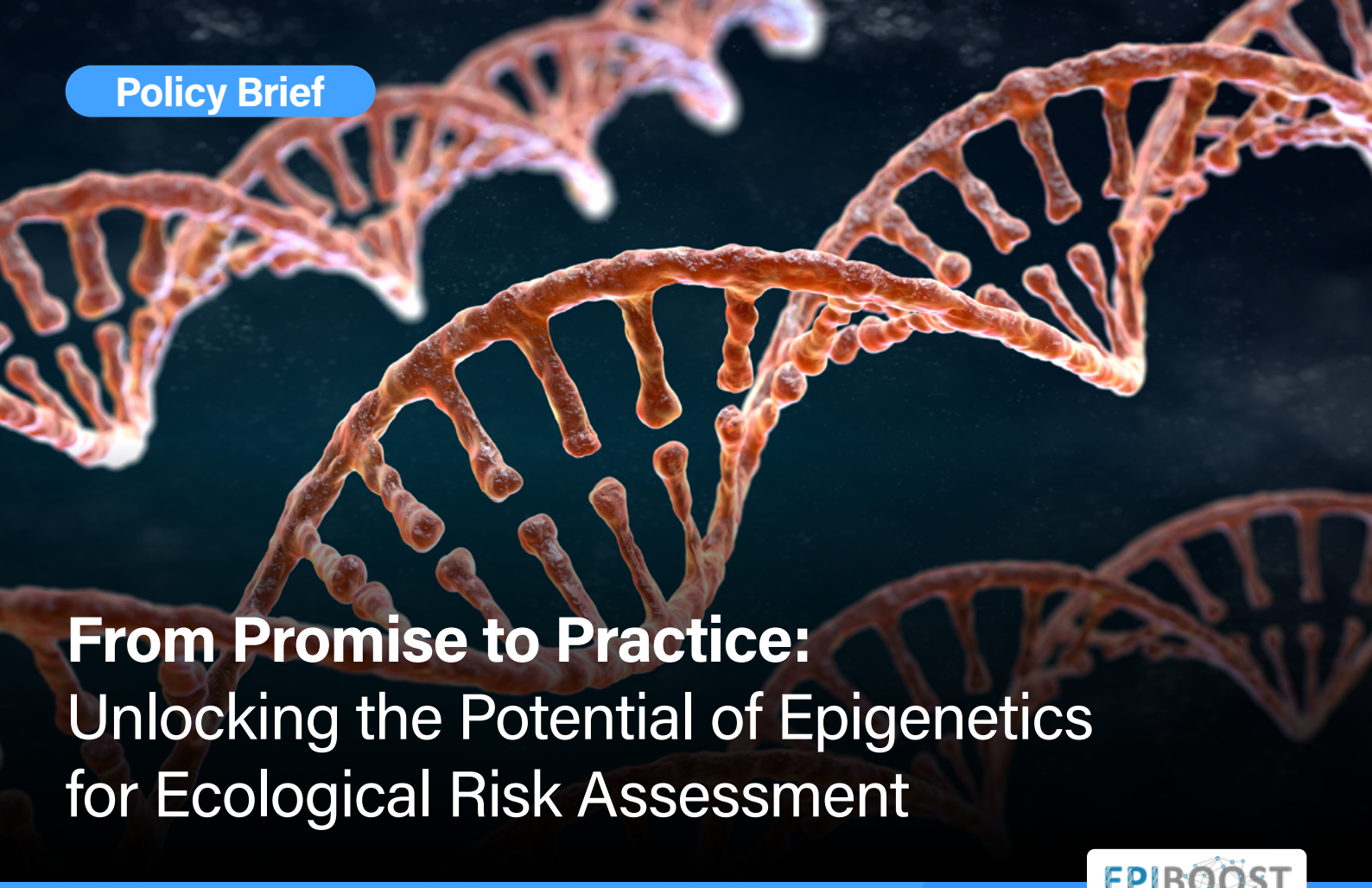
Policy Brief



From Promise to Practice: Unlocking the Potential of Epigenetics for Ecological Risk Assessment

EPIBOOST

Traditional toxicological assessments often fail to capture the delayed consequences and/or subtle toxic effects of an increasing number of chemicals under scrutiny because they focus primarily on overt toxicity endpoints.

Epigenetic responses are changes in gene regulation (e.g., DNA methylation, histone modifications, and non-coding RNAs) that do not alter DNA sequence but can persist over time and, in some cases, across generations. Epigenetic responses provide a powerful means to detect the subtle biological impacts of chemicals of emerging concern, including pharmaceuticals, endocrine disruptors, and per- and polyfluoroalkyl substances (PFAS) — compounds that are rarely acutely toxic but may induce profound long-term and transgenerational effects.

Epigenetic measurements are thus increasingly proposed as innovative tools to improve ecological risk assessment (ERA). In this context, their alignment with related frameworks such as Adverse Outcome Pathways (AOPs) has stimulated interest in identifying epigenetic changes that predict specific health outcomes. However, accumulating scientific evidence highlights that the growth of fundamental genomic and epigenomic knowledge is required for robust, reproducible, and interpretable application of epigenetic responses by non-human model organisms for them to be used in ERA[1].

Realising the potential of epigenetic-based tools to improve ERA requires a solid understanding of species-specific genomes, epigenetic landscapes, and the crosstalk among epigenetic mechanisms. Without this foundation, dismissing these tools altogether, or attempting to embed them in regulation, is premature. Strategic investment in fundamental research is therefore paramount to ensure that epigenetic measurements can be reliably and responsibly incorporated within next generation ERA.

Such investment aligns directly with EU priorities on predictive (eco)toxicology, ecosystem protection and sustainable chemicals management. By integrating epigenetic early-warning signals into risk assessment frameworks, we can strengthen the scientific basis for evaluating the growing number of chemicals that exert severe but delayed and cumulative effects, thereby enabling more proactive and preventive environmental protection strategies.

[1] Pinto et al. Integration of epigenetics into ecotoxicology: insights and fundamental research needs. Biol Rev. DOI 10.1111/brv.70105.

Audience: Funders & Regulators

This policy brief proposes the critical need to strengthen fundamental research on the genomes and epigenetic architecture of ecotoxicologically relevant species. It highlights why solid and comprehensive foundational knowledge is required for a robust regulatory uptake of epigenetic biomarkers in ERA, supporting the need for focused funding programmes.

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The Existent Pitfalls

Epigenetic signals offer promise, but only if mechanistically grounded

It is well demonstrated that epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, are highly responsive to environmental stressors. Importantly, stressor-induced epigenetic changes can persist beyond initial exposure within a generation, constraining developmental trajectories, as well as inter- and transgenerationally. This persistence makes them attractive as early warning and integrative indicators of both immediate and long-term environmental impact. In theory, they can help bridge exposure to downstream biological effects and support the development of mechanistic ERA approaches. However, epigenetic responses are inherently context dependent. Their biological meaning depends on species, tissue, developmental stage, environmental background, dose, time, etc. Without a mechanistic understanding of how specific epigenetic changes relate to adaptive, neutral, transient, or adverse outcomes, these signals cannot be reliably interpreted. As a result, their value for decision-making remains limited.

Lacking essential genomic and epigenomic baselines

Standard species used in ecotoxicology and ecological risk assessment (microalgae, invertebrates, fish) often lack robust genomic and epigenomic resources. Incomplete genome assemblies, limited annotation of regulatory regions, and the absence of reference epigenomes across life stages and tissues constrain the detection and the interpretation of the functional meaning of epigenetic changes. Moreover, the architecture of the epigenetic machinery itself varies widely across taxa. Differences apply to the presence, absence, or function of DNA methyltransferases, demethylation pathways, histone modifiers, and RNA-based regulatory systems. This means that evidence generated in one species cannot be directly transferred to another; different organisms may reach similar health outcomes via fundamentally different (epigenetic) mechanisms. Understanding species-specific pathways is therefore vital for translating findings across biological systems and eventually for assessing relevance to human health.

How stress-driven epigenetic change relate to and report on adverse effects is unclear

Numerous studies report contaminant-associated epigenetic alterations, but (i) upstream and cascading molecular links are poorly resolved; (ii) phenotypic and ecological consequences, across time and dose scales are scarcely established; (iii) concurrent interactions between chemical stressors and the epigenetic machinery (writers, erasers, readers), as well as the crosstalk among different epigenetic mechanisms, towards adverse effects remain largely unexplored. This complicates integration into AOPs and limits confidence in causal interpretation, immediately hampering regulatory uptake - signals that can be scientifically sound become operationally unusable in ERA frameworks.

Why Fundamental Research Matters Now?

Premature regulatory uptake carries scientific and policy risks

The introduction of new molecular endpoints (notably, differential gene expression) in ERA is currently being strongly evaluated by regulators within the so-called Next Generation ERA framework (NGERA). The momentum is hence set for the consideration of epigenetic evidence, expanding the endpoints available for robust regulatory NGERA. However, introducing epigenetic biomarkers into ERA before recognised knowledge gaps are addressed bring important pitfalls rooted in inconsistent results across laboratories and species and misclassification of natural epigenetic variability as contaminant effects. This would obstruct the standardisation and validation needed for robust decision-making, necessarily eroding confidence in molecular tools broadly, and hindering, rather than advancing, innovation in regulatory toxicology.

Fundamental knowledge is an enabler of next-generation environmental regulation

Targeted funding investment in ecotoxicogenomics and ecotoxicoepigenomics should not be viewed as detached basic science, but as enabling infrastructure leveraging next-generation ERA. By strengthening the biological foundations of epigenetic biomarkers, funders and regulators can accelerate their translation into reliable, standardised, and policy-relevant tools.

The chemical landscape is evolving faster than regulatory science

The rapid expansion of documented exposure of the biota to persistent, low-dose, and mixtures of chemicals, including pharmaceuticals, endocrine disruptors, and PFAS, challenges the adequacy of traditional hazard assessment frameworks that are largely designed around acute toxicity endpoints. Many of these substances exert subtle, cumulative, and delayed biological effects that remain undetected until ecological damage becomes visible and often irreversible.

Acting now by fostering funding for fundamental knowledge growth will ensure that epigenetic tools entering regulatory pipelines are robust, interpretable, and fit for purpose, i.e. supporting both environmental protection goals and efficient regulatory decision-making. This approach provides a sustainable path towards EU policy landmarks such as the Chemicals Strategy for Sustainability and the Water Framework Directive, increasingly demanding early, integrative indicators of ecological impact; and the transition towards predictive, mechanism-based, 3R's compliant and economically sustainable regulatory NGERA.

Recommendations: Which are the Priority Funding Targets?

1. **Improving foundational genomic resources.** Support the generation of high-quality, well-annotated genomes for model species used in ecotoxicology and ERA, including regulatory and repetitive regions relevant for epigenetic control.

2. **Developing reference epigenomic roadmaps.** Invest in baseline characterisation of DNA methylation, histone modifications, non-coding RNAs, their crosstalk and players within model species, across tissues, life stages, sexes, genome diversity and natural environmental contexts. This will allow distinguishing epigenetic changes that correspond to natural variability or represent adaptive responses to contaminant exposure from those leading to adverse toxic responses and health outcomes.

3. **Strengthening understanding of epigenetic responses.** Favour the elucidation of causal links between exposure and epigenetic changes broadly covering different mechanisms and players, as well as dose-response approaches enabling safety thresholds determination.

4. **Integrating epigenetics explicitly to AOP frameworks.** Boost the integration of epigenetic evidence in established and developing AOPs, mechanistically linking molecular drivers of sub-individual, individual and supra-individual outcomes potentially linking to ecological effects.

5. **Potentiating the value of epigenetic biomarkers.** Value the clarification of stress priming roles of epigenetic mechanisms, as well as their potential to support prediction of long-term effects (through life, generations and at evolutionary scales) of pulse and chronic exposure to contaminants, based on short-term testing; this is especially relevant for contaminants of emerging concern for which long-term toxicity is poorly known.

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