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Policy Brief

Achieving zero pollution by 2050 needs regulatory change:

a call for policy support of New Approach Methodologies (NAMs)

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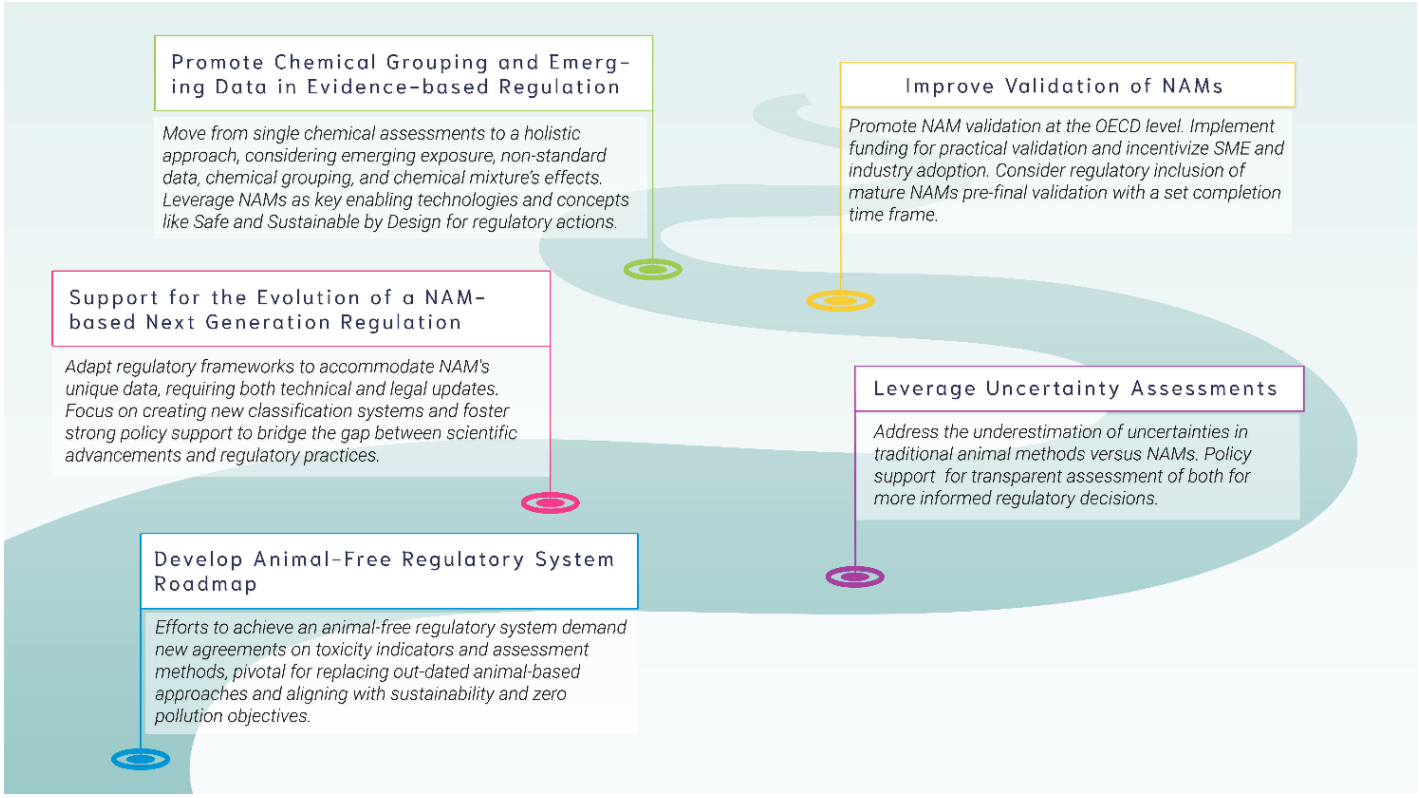

Figure 1: Recommendations for a roadmap towards the zero pollution goal which needs a shift to an animal free regulatory system.

Background

The European Commission is committed to achieving the zero-pollution vision for air, water and soil by 2050. The European Green Deal announced bold action points to achieve a toxic-free environment and a circular economy by 2050, going beyond climate neutrality. The Chemicals Strategy for Sustainability towards a Toxic-Free Environment aims to better protect humans and the environment from hazardous chemicals. The risk posed by hazardous chemicals is a systemic problem, driven by production and consumption patterns, as well as the lack of environmental monitoring techniques and remediation solutions and the limited availability and quality of the (eco)toxicological data, especially for exposure to mixtures, needed for a comprehensive safety assessment.

The six Horizon 2020 research and innovation action projects in the Green Deal Health Cluster – ALTERNATIVE, LIFESAVER, PANORAMIX, PROMISCES, SCENARIOS and ZeroPM, are firmly aligned with the vision and goals of the Green Deal. The projects are establishing new knowledge to support next-generation risk assessment and regulation, explore the feasibility of new or improved environmental remediation technologies and hazard assessment methods, and demonstrate innovative solutions to protect health, the environment and natural resources from hazardous chemicals including persistent, mobile and toxic substances.

This policy brief has been created for policy makers and provides key findings and recommendations from these projects that are deemed essential to achieve the goal of a zero-pollution Europe.

Key findings

PFAS need next generation regulation using emerging exposure, chemical grouping, non-standard data and non-animal methodologies

Per- and Polyfluoroalkyl Substances (PFAS) are a group of manmade substances (comprising at least 10,000 chemicals) with a wide application domain. Known as “forever chemicals”, they can remain in the environment for decades and are very difficult and costly to remove from water, sediment and soil. For several regulated substances in the group (e.g. perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA)), reliable exposure, environmental fate and hazard data are available. However, the lack of data for the vast majority of PFAS prevents comprehensive environmental and human risk assessments relying on estimated persistence, mobility and bioaccumulation data. As knowledge of environmental fate, toxicity pathways and access to datasets for specific PFAS advances, the list of restricted and manufactured PFAS is growing, as structurally similar alternatives continue to be brought to market by the chemicals industry. Preventing the substitution of one harmful PFAS with another for which new data has to be assembled before further regulatory action can be taken, is crucial. However, substitution is complicated by the lack of adequate risk management strategies for these situations in the current regulatory system.

To combat this, the European Commission is considering grouping approaches for PFAS, and the current proposal for a broad restriction of PFAS from five EU Member States highlights the intent that the manufacture, use and emissions of these substances should be reduced. “Chemical grouping” is already an established regulatory approach. Despite this, further evolution of the legislative framework is needed so that emerging contaminants, possibly problematic in terms of environmental exposure, environmental fate and/or toxicity, can be identified, and regulated without delay. The application of New Approach

Methodologies (NAMs)[1] is a promising approach considering the high number of assessments needed. NAMs can support a mechanistic grouping of chemicals, which may facilitate read-across results from data-rich to data-poor chemicals and may support the assessment of mixtures and materials. Utilising adverse outcome pathways to validate the mechanistic relevance of NAMs and applying toxico-kinetic modelling, where possible within high throughput approaches, can extend the use of NAMs to various other regulatory problem formulations including hazard and risk assessment.

The current dependence of chemical regulations on animal testing is the Achilles heel for achieving the Green Deal´s zero-pollution ambition

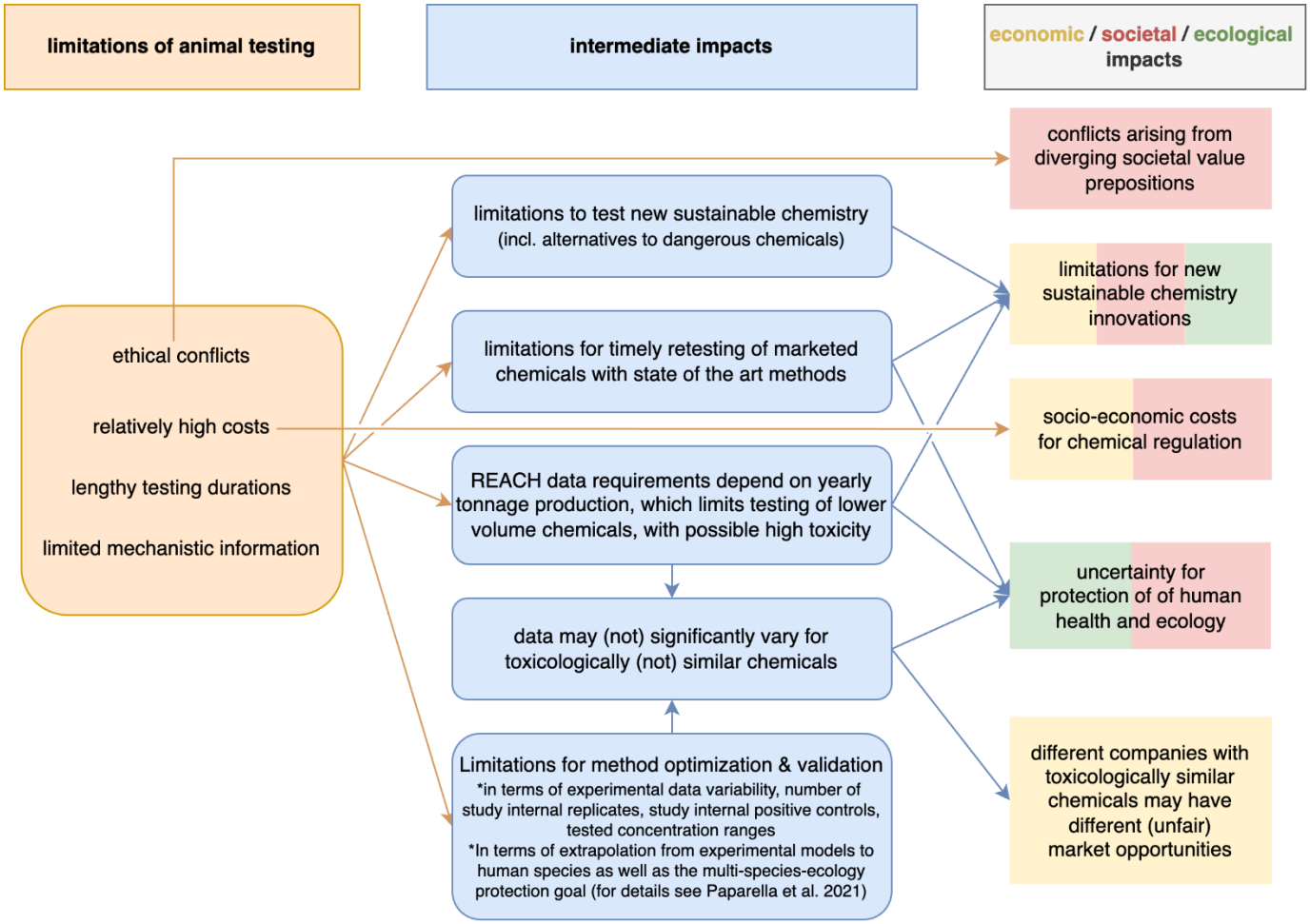

Figure 2: The way in which the limitations of animal testing result in economic, social and ecological impacts.

The current dependency of regulation on animal testing is in direct conflict with all three spheres of sustainability, i.e. social, economic and ecological. This implies ethical conflicts, relatively high costs, lengthy testing times and limited mechanistic information. These result in regulatory limitations related to timely retesting of newly marketed chemicals using the state-of-the-art methods, limitations related to testing the high number of lower volume chemicals and limitations for method optimisation and validation. The latter leads to uncertainty in variability seen in experimental data and uncertainty in extrapolations

[1] *The definition of "New Approach Methodology" varies (see e.g. OECD GD 329 Annex A) . In any case it includes in vitro* assays and computational approaches, but i*n its broadest interpretation it encompasses also in vivo refinement and reduction methods such that it is very similar to the 3R terminology. We note that the definition of "new" is time-dependent and ambiguous. Sometimes NAM is also used as an acronym for "Non-Animal Methods", and, if necessary, the latter could be adjusted to 'Non-(protected) Animal Methods' to encompass, for instance, invertebrate species for in vivo ecotoxicity testing*

from experimental models to the human species as well as to the multi-species and multi-ecology protection goals. Each of these consequences negatively impacts sustainability (see Figure 2).

To address this, the European Commission has begun to develop a roadmap for the transition towards phasing out animal testing from chemical safety assessments within all regulatory sectors (chemicals, biocides, pesticides, human & veterinary medicine, consumer products). This work complements the current Directive for the Protection of Animals used for Scientific Purposes, which already forbids any animal testing wherever adequate non-animal methods are available and requires public transparency for animal testing authorised in Europe.

The Green Deal Health Cluster projects are currently developing various NAM-based methods for regulatory purposes (see Figure 3). It is widely acknowledged that the data obtained from the use of NAMs is fundamentally different to that from animal testing which means that directly exchanging and/or comparing these data, like jigsaw puzzle pieces with identical shapes, is not possible. Scientists, regulators and policy makers must come together to discuss which image shall be ultimately displayed on the completed new jigsaw puzzle and consequently, how the new jigsaw pieces need to be arranged. A profound evolution of the current regulatory system is needed to fully exploit the scientific potential of NAMs.

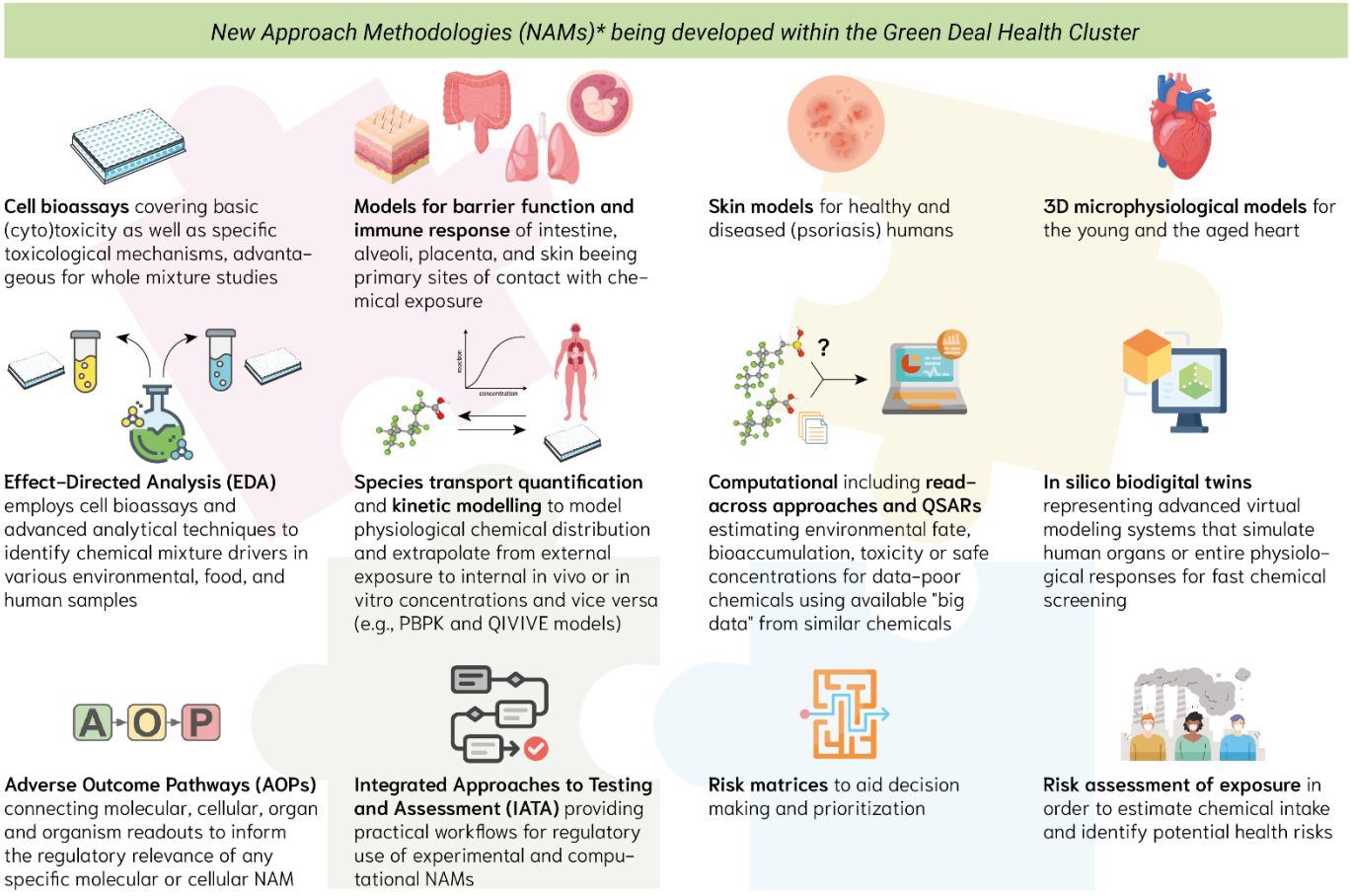

Figure 3: The NAM based methods being developed by the Green Deal Health Cluster projects.

Policy recommendations

1. *Support using exposure, non-standard data and chemical grouping for regulatory action*

Currently, hazardous chemicals are assessed one at a time, which is costly, time-consuming and unsustainable. Moreover, chemicals are tested in isolation and very limited mechanistic information is generated, which hinders the assessment of possibly enhanced effects arising from chemical mixtures within products and in environmental and human media. The broad PFAS restriction proposal as well as the Safe and Sustainable by Design Framework which includes environmental life cycle exposure assessments and essential use are examples of where up to date information can be integrated as a basis for regulatory action. In this regard, **NAMs are key enabling technologies,** since the mechanistic toxicological information they provide can be used to assess the toxicity of chemicals within a larger chemical group. The mechanistic readouts of NAMs may also support the assessment of possible synergistic effects of chemicals within mixtures and ultimately this information may be used to derive safe environmental and human health threshold values. It is paramount that work continues in this direction, especially considering the ambitious targets set by the European Commission.

However, high level policy support is needed to ensure continued progress and a complete transition towards an animal-free regulatory system as follows:

2. *Support the improvement and the validation process of NAMs*

The regulatory validation process for NAMs is currently updated at the OECD level. The process aims to move away from relying on animal test data as the gold standard, to shift focus from resource-intensive ring trials to a comprehensive assessment of the robustness of the method within the developers' laboratory as well as very carefully planned laboratory transferability testing, and to separate technical validation from the regulatory context. These changes are intended to maximize the efficiency, affordability, and sustainability of the validation process. Therefore Europe needs new specific funding schemes with adequate resources for practical NAM validation within specialised institutions and working groups. Additionally, economic incentives for SMEs and industries to invest in establishing new methods in their labs and performing the required interlaboratory transferability assessment should be increased. One option may be to develop a framework that allows scientifically validated, relevant and relatively mature NAMs to be used within regulations before official OECD validation, by means of method quantification schemes and that is based on more differentiated method readiness evaluations for example in Annex XI via the REACH revision. Moreover, the inclusion of recent scientific literature, especially regarding Adverse Outcome Pathways could be utilized and this information included within structured Weight of Evidence Approaches.

3. *Support leveraging uncertainty assessment for NAM recognition*

The underestimation of uncertainties in established animal methods, in comparison to the uncertainties in new approaches, is one of the major hurdles for the regulatory acceptance of NAMs.

A regulatory requirement to make the scientific uncertainties of both animal-based and NAM-based hazard and risk assessments much more transparent, as far as possible by employing quantitative approaches, can help to overcome this hurdle and misconception regarding the certainty provided by the current approach. Guidance from regulatory science for uncertainty assessment is available. However, to realise this paradigm shift, it is necessary to have strong policy support to help free up resources for specialised

training and initiatives to overcome the natural resistance of institutions and working groups that have historically followed established assessment procedures.

4. *Provide support for the evolution of a NAM based next-generation regulation*

NAMs provide completely new types of data, which are not currently compatible, technically, or legally, with the current concepts of hazard and risk assessment used in regulation. To exploit the full regulatory potential of NAMs, both a technical Next Generation Hazard and Risk Assessment (NGRA) framework (such as the one developed by the Horizon 2020 ASPIS cluster) and a legal Next Generation REgulation (NGRE) is needed. Important steps to reach this goal will be the introduction of NAM based classification criteria within the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). Scientific research into this topic is currently ongoing within the Green Deal Health Cluster and the European Partnership for Alternative Approaches to Animal Testing (EPPA) NAM DESIGNATHON initiative. However, the translation of science to regulatory practice and law, needs strong policy support.

The “roadmap for phasing out animal testing in chemical safety assessments” initiated by the European Commission and supported by work in the European Partnership for the Assessment of Risks from Chemicals” (PARC) is regarded as highly relevant in his context. One further option may be to support and legally require “out of the cage” assessments sometimes referring to sandbox exercises within specialised regulatory expert groups that can themselves then become NGRA and NGRE champions and create regulatory science momentum to continue moving the regulation forward.

5. *Support for the initiative to develop a European roadmap to an animal-free regulatory system*

Zero pollution and sustainability are high on the agenda of many governments. Practical implementation of the European Commission’s roadmap towards an animal-free regulatory system will require significant investment at the science-policy interface. Investment will also be needed to support the establishment of new multi-stakeholder agreements on the relevance and regulatory utility of usage of new types of toxicity indicators, safety assessment approaches, and classification schemes, to replace the current animal-based approaches.

As the Green Deal Health Cluster, we fully endorse the promotion of NAMs for regulatory use and strongly support the development of a European roadmap towards achieving an animal-free regulatory system.

Related work

This brief is a part of the actions carried out within the context of the Green Deal Project Support Office (GD-SO). The GD-SO has been developed to facilitate coordination between projects funded under the Horizon 2020 Green Deal Call and maximise their positive impact in the longer term. The Green Deal Projects Support Office started in December 2021 and will operate until November 2026. The key activities include supporting Green Deal projects in effective collaboration, providing networking and knowledge exchange opportunities to develop synergies, and helping projects boost communication efforts of their results. The GD-SO supports networking, knowledge exchange and common capacity-building activities through five working groups: 1) Climate Change and Biodiversity, 2) Clean Energy, 3) Urban Environment and Mobility, 4) Food and Health, and 5) Knowledge and Citizens.

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