New Approach Methodologies (NAMs)

New Approach Methodologies (NAMs) collectively refer to technology-enabled strategies for obtaining information about the toxicity of chemicals without relying on traditional animal testing. These strategies have the potential to supplement, reduce, and eventually replace animal testing by uncovering the fundamental processes, often at the level of biomolecular interactions, that may make certain chemicals toxic to humans. Specific NAMs strategies include computational modeling (see BTS statement on *in silico* approaches), cell and tissue culture assays (see BTS statement on *in vitro* approaches), and the use of alternative model organisms to observe how biology (from cells to whole organisms) is impacted by exposure to chemicals. Looking to the future, knowledge of chemistry will be harnessed through computational approaches and models to simulate and predict the toxic effects of chemicals, enabling more rapid, accurate, ethical and less expensive safety assessment.

The science behind NAMs is not new; many NAMs approaches are in widespread use among academic researchers and in biomedical fields, including pharmaceutical drug development. What is new about NAMs are the proposed regulatory applications of these strategies and technologies for protecting human health and the environment from chemical hazards.

How are NAMs different from traditional approaches to regulatory toxicology?

Regulatory chemical testing has traditionally relied on exposing laboratory animals, typically rodents because of our shared mammalian ancestry, to high concentrations of chemicals. The outcomes of testing focus on observable harm including cancers, organ failure, and problems with the animal's development, behaviour and reproduction.

In addition to being slow, expensive, and raising ethical concerns, this testing approach leaves many questions unanswered. Unlike the high-concentration exposures used in the laboratory, most real-world chemical exposures occur over the long term and at lower concentrations, such as through the air we breathe, the food and water we consume, and through contact with manufactured products, often as complex mixtures. Additionally, observing outward health symptoms provides little insight into what makes a specific chemical toxic to humans or what other chemical formulations could offer less toxic alternatives.

Because NAMs focus on pinpointing changes in biological function that occur before outward symptoms (Figure 1), these strategies allow for a more mechanistic understanding of the biomolecular interactions along the pathway towards harm. Knowledge of these pathways to toxicity allows NAMs to assess exposure concentrations at which toxicity is initiated (a point of toxicological departure), to group chemicals based on their signatures of bioactivity, and to classify toxic substances by their shared modes of action. Using these approaches, NAMs may offer opportunities for chemicals to be regulated more precisely and effectively as groups — for example, according to their specific adverse effects on cellular functions or hormone production — thereby addressing a severe backlog of chemicals requiring safety assessment.

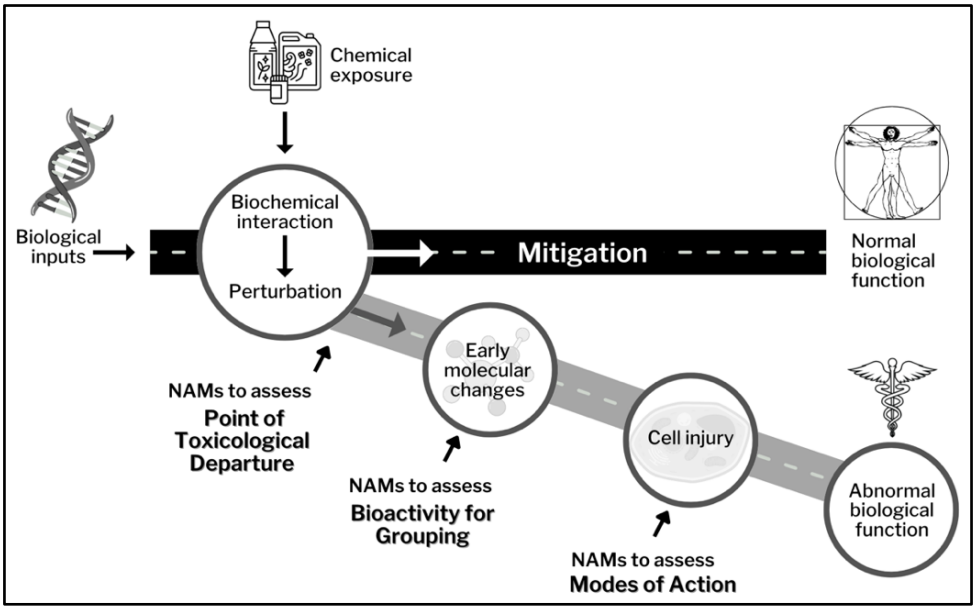

Figure 1 depicts the chain of events when normal biological function is perturbed by exposure to a toxic chemical. At low concentrations, the body may adjust to the presence of a chemical without entering a disease state (adaptation or mitigation). By pinpointing the changes that signal tipping points or cascading 'points of departure' (depicted as early molecular changes or cell injury), NAMs can be used to detect, specify, and assess toxicity at distinct stages in this process to achieve various regulatory functions including grouping and classifying chemicals based on their shared modes of action. *[Image source: PrecisionTox, which is funded by the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 965406]*

How can NAMs pinpoint the toxic properties of chemicals?

Rather than relying on outward symptoms of harm, measurement tools that quantify gene products, metabolites, and cellular interactions can monitor specific biomarkers activated in response to chemical exposures. These tools can also capture how toxic chemicals break down through metabolism and identify interactions among different chemicals. NAMs measurement strategies can produce huge amounts of data that can be analysed using high-performance computing to identify both known and currently unknown linkages between exposure to specific chemical types or structures and the biological reactions that follow. In this way, NAMs can help to categorise chemicals according to their biological effects.

Many of these tests can be performed with lab-cultured cells and tissues without using animals. Additionally, rather than testing on rodents or other mammals, NAMs can use the same model species used in foundational biomedical research for over 125 years and in pharmaceutical research to develop safe and effective medicines (Figure 2). Although these species are more distantly related to humans on the evolutionary tree compared to mammals, most internal systems that are fundamental to growth, maintenance, and reproduction are similar because genes controlling these life processes are ancestrally shared by descent across the animal Tree of Life. Genes related to disease, in particular, appear to be among the most ancient and shared among animals, with even invertebrates appearing to possess between 65-75% of human disease-related genes.

Ongoing research increasingly demonstrates that gene interactions that are most fundamental for proper human development and health have deep evolutionary origins. This means that studying organisms like worms and flies can provide information about how different chemical compounds—whether industrial chemicals or pharmaceutical drugs—systemically affect the health of humans and animals important to our ecosystem.

Figure 2. Although animals exhibit a great diversity of morphological, physiological, behavioural and life history traits, animals also share common genetic ancestry, including in their organ systems and cellular biology, leading to many similar responses to chemical exposure *(https://doi.org/10.1016/j.toxlet.2023.05.004).* Alternative animal models to mammalian species have been used for over a century to understand the human condition in experimental biomedical research (*Drosophila*, *Caenorhabditis*, embryos of *Danio* and *Xenopus*) and to understand ecological processes (*Daphnia*).

What is the status of NAMs in chemical regulation?

Scientists and regulators have been calling for alternatives to animal testing for more than 60 years. The "3Rs" goals of reducing, refining, and replacing animal testing were introduced in 1959. The UK Animals (Scientific Procedures) Act, updated in 2013, aims to restrict research on vertebrates, and the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) has been dedicated to this mission since 2004. Despite this interest, the implementation of NAMs in chemical regulation has been slow for reasons beyond scientific progress (Figure 3). Research identifying barriers to using NAMs in regulatory toxicology highlights several self-reinforcing cycles of resistance to changing test methods used in regulation. These "catch-22" cycles include the reluctance of risk managers to accept NAMs data due to their lack of trust and familiarity with these approaches, with this lack of familiarity reinforced by companies' reluctance to submit NAMs data that will likely be rejected by regulators.

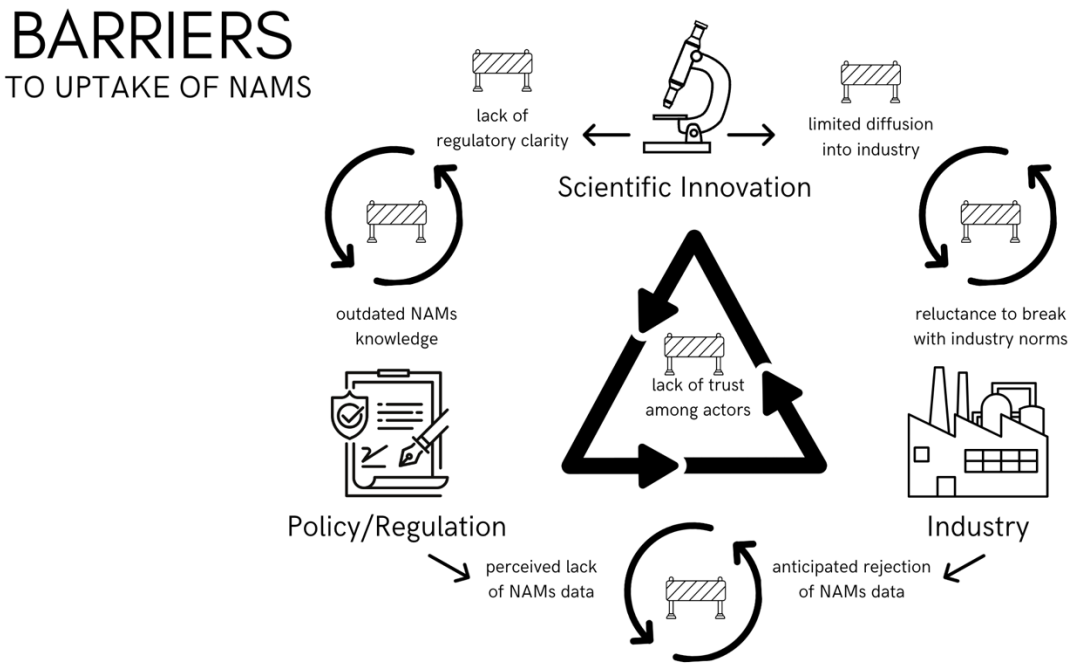

Figure 3 depicts self-reinforcing cycles among social and technical barriers to the uptake of NAMs in chemical regulation. Lack of clarity among all actors regarding the regulatory acceptability of NAMs data limits the ability of scientific innovation to inform chemical safety policy. Decision makers in industry are reluctant to submit data that regulators won't accept, while many regulators remain largely cautious about, and thus unwilling to accept, NAMs data. *[Image source: PrecisionTox]*

Despite these barriers, continued scientific advancements coupled with ongoing public commitments to phasing out traditional animal testing have increased interest in incorporating NAMs in the chemical safety assessment process. The likely path forward is to gradually introduce NAMs, beginning by using these strategies to group chemicals with similar biological effects. This grouping and classification of chemicals based on their shared modes of action could be one means of reducing animal testing: once NAMs substantiate a grouping of chemicals, more in-depth testing using traditional methods (if required) can be conducted using only a smaller number of class-representative substances for these observations to be applied to all other chemicals in that group.

What are the expected long-term benefits of using NAMs in chemical safety testing?

NAMs offer faster and less expensive means of gathering large volumes of data on the biological effects of chemicals. This information can help link specific chemical structures with their resulting biomolecular health outcomes. In time, this knowledge can be used to design safer chemicals rather than testing chemical products for safety after they have already been developed.

Additionally, due to the shared genetic legacy described above, NAMs-based protections safeguard human health and that of wildlife and ecosystems, contributing to ecological resilience and shifting the chemical industry toward greater environmental sustainability.

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