FINAL REPORT

Project: Facilitate the regulatory acceptance and practical use of new approach methods in next-generation risk assessment

Vertrags-ID: 142005151 / 643-4/1/1

Including

Summary Technical Report D1[1]

Summary of the landscaping exercise assessing the status of integration and use of NAMs across sectorial frameworks

Summary Technical Report D2[1]

Summary of the gaps & needs analysis, barriers, opportunities, drivers for integration and use of NAMs across sectorial frameworks

Workshop Report D3[1]

Action plan for prioritization of regulatory-relevant scenario-based case studies

Technical Report D4[1]

Summary of the scenario-based case studies (initiation)

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[1] according to Vertrags-ID: 142005151 / 643-4/1/1, chapter 7 “Termine”

1 EXECUTIVE SUMMARY

The necessity and relevance of animal experiments for human health risk assessment are increasingly debated, particularly regarding whether they can be replaced entirely. While animal testing remains indispensable for evaluating systemic toxicity following repeated exposure (DFG, 2023), alternative approaches are rapidly advancing.

New Approach Methodologies (NAMs) already provide valuable mechanistic insights into modes of action, especially when integrated into conceptual frameworks such as Adverse Outcome Pathways (AOPs), Integrated Approaches to Testing and Assessment (IATA), and Defined Approaches (DA). These frameworks enable more scientifically robust risk assessments and help reduce animal use. Mechanistic understanding is already informing regulatory decisions, for example, in deriving threshold values or applying read-across methods when substance-specific data are limited.

Despite these advantages, the regulatory uptake of NAMs still lags behind their technical potential, constrained by legal, motivational, and economic factors. This report demonstrates that NAMs have the potential to transform chemical risk assessment, provided there is consensus on their “fit-for-purpose” use. The “fit-for-purpose” principle acknowledges that validation requirements must align with the intended regulatory context, emphasizing flexibility and proportionality in the validation process.

Insights from literature, expert consultations, and NAM case studies across chemical sectors and regulatory settings reveal strong and growing interest in human-relevant NAMs and rapid progress in their development. However, their implementation depends on the adaptability of existing regulatory frameworks and on broader cultural change at individual, institutional, and societal levels. To fully leverage NAMs, greater flexibility in testing requirements is needed, along with continuous education for regulators and stakeholders to clarify when and how specific NAMs can be applied and how their data should be interpreted.

Building scientific and regulatory confidence further requires clear guidance to streamline and accelerate validation processes, coupled with structured opportunities for early dialogue between method developers and regulatory agencies to ensure that data needs are met.

Although successful NAM-based submissions exist, regulatory acceptance remains uneven—frameworks under the US EPA, for instance, appear more accommodating than those implemented by ECHA. Achieving global acceptance will require sustained international collaboration and cross-sector coordination to harmonize standards and advance the best science efficiently.

The Swiss Federal Office for Public Health (FOPH) largely follows European law when it comes to chemical regulations. It also supports Swiss research, for example to strengthening expertise in regulatory toxicology, including NAMs and AOPs, within both the academic and regulatory environments. The Swiss Centre for Applied Human Toxicology (SCAHT) acts as an interface of research, regulation, and education. Supported by FOPH and to fulfil its role of a scientific interface, the SCAHT organized five webinars and an in-person workshop aiming at i) educating Swiss regulatory agencies and academia on next generation risk assessment (NGRA), AOPs and IATAs and ii) developing ideas for Swiss case studies with problem formulations to be tackled with NAMs.

Two case studies are presented to illustrate future directions in applying NAMs: 1. Health consequences of bisphenol TMC (BPTMC) exposure and 2. Metal mixture exposure and the consequences for brain development. These case studies were deliberately selected to represent contrasting scenarios and demonstrate the broad applicability of NAM-based approaches. The BPTMC case study reflects a data-poor situation in which literature review, AOP mapping, and the potential to apply read-across were explored. In contrast, the developmental neurotoxicity of heavy metals is well established; thus, the core challenge in this case study was to determine how an NGRA-like workflow could be adapted to evaluate mixture risks using NAMs.

For each case study, the report examines a workflow tailored to its specific needs and identifies gaps that must be addressed for future data integration. Both case studies require additional development and more robust datasets before regulatory conclusions can be drawn. These efforts will continue in upcoming initiatives, including the PARC project.