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ANNEX 4

Theme (Concept) Paper on New Approach Methodologies

Revised theme paper in light of the comments received from the EFSA, European Commission, ENVI Agencies, EU Member States and EFSA's Scientific Committee members in the phases 1 & 2 of EFSA's consultation process

Vision:

By 2027,

- The use of new approach methodologies (NAMs) has become the main approach for addressing data gaps, avoiding animal-based verification studies. The large majority of EFSA requests for additional testing are based on NAMs.
- In agreement with risk managers, mechanistic-based informative risk assessments have been integrated as standard part of EFSA's regulatory assessments for chemicals in food and feed.
- EFSA efforts to minimise animal testing is acknowledged and EFSA is recognised as part of a European (and international) coordination platform, as an important partner for the evolution of the risk assessment paradigm and the use of NAMs in regulatory risk assessments.
- An EFSA Scientific Committee cross-cutting guidance document provides the basis for the use of NAMs in food and feed risk assessment, is implemented across EFSA's domains, and guides EFSA contributions for harmonisation at European (i.e., PARC¹) and international (i.e., OECD and APCRA²) levels.

Scope and objectives:

- The term "NAMs" is used to make reference to any non-animal-based approach that can be used to provide toxicological information in the context of hazard assessments. These new

¹ [European Partnership for the Assessment of Risk from Chemicals \(PARC/EUChemRisk\)](#)

² Accelerating the Pace of Chemical Risk Assessment (APCRA) is an international government-to-government initiative whose aim is to promote collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in regulatory decision making



approaches include integrated approaches to testing and assessment (IATAs), defined approaches for data interpretation, and performance-based evaluation of test methods.

- The main objective is to facilitate the incorporation of NAMs in chemical food and feed risk assessments, contributing to European (PARC) and international (OECD, APCRA) initiatives promoting the implementation of the Farm to Fork Strategy³, reducing the need for animal verification studies and, ultimately, phasing out animal testing.
- The scope is limited to chemical risk assessments, initially aimed to human health, with the intention to extend it at a later stage to animal health and environmental assessments.
- The theme will cover all newly developed NAMs and, where applicable, their integration in EFSA comprehensive regulatory risk assessments, with five complementary areas:
 - 1) understanding the molecular and cellular mechanisms of chemical toxicity leading to adversity: use of *in vitro* mechanistic and -omics data, organoids and microfluidic systems, high throughput screening (HTS), high content screening (HCS), for the identification of Mode of Action (MoA) and inform about Adverse Outcome Pathways (AOP);
 - 2) using existing chemical data and modelling internal dosimetry: *in-silico* tools, enhanced data models, Toxicokinetic and Toxicodynamic (TKTD) modelling and quantitative *in vitro in vivo* extrapolation (QIVIVE);
 - 3) using epidemiological knowledge (e.g. molecular epidemiology and -omics enhanced epidemiological studies) and human data following occupational or environmental exposure, including human inter-individual differences in metabolism and biomonitoring;
 - 4) evolving the risk assessment paradigm towards informative mechanistic-based characterisations, through the integration of hazard and exposure drivers in mechanistically informed risk assessments triggering the identification of susceptible population groups;
 - 5) minimise EFSA requests for conducting new animal studies by supporting Panels and units in the appraisal of NAMs studies.
- The implementation of the use of NAMs in hazard assessment and risk characterisation of chemicals in food and feed will be supported by case studies, covering all domains requiring chemical risk assessment either as regulated products (additives, novel foods, pesticides) or contaminants. The results will be used for developing cross-cutting guidance with an evolved paradigm using NAMs for increasing the mechanistic understanding in the risk characterisation process. The focus will be the integration of new tools with existing data and the use of NAMs to fill data gaps in comprehensive risk assessments.

Opportunities:

- NAMs have not yet been incorporated successfully in regulatory assessments, a main reason is that NAMs offer a different kind of information compared with traditional reference points used for setting reference values such as Health Based Guidance Values (HBGV). While full replacement of animal studies for “new chemistries⁴” is not on the immediate horizon, most EFSA assessments are focused on chemicals or groups of chemicals for which there is already information available, but in some of the cases there are data gaps that might need to be addressed for the risk assessment. The use of NAMs for addressing these gaps can avoid

³ [Farm to Fork strategy – for a fair, healthy and environmentally-friendly food system](#)

⁴ The term “new chemistries” relates to chemicals with new structures, that do not have structural or functional analogues or belong to a family/group of chemicals with available *in vivo* information.



requests for new *in vivo* studies, or for having to repeat existing studies as a result of updated test guidelines, or because the study is considered to be of insufficient quality, hence minimising the need for additional animal testing.

- Several substances falling within EFSA's domain of activity have received significant attention from researchers developing NAMs. A large majority of recent publications on substances with public attention such as bisphenol A, phthalates, glyphosate, etc., as well as nano and advanced materials such as titanium dioxide, include the generation of NAMs data. The pressure from researchers, stakeholders and risk assessors for a transparent assessment of "all" existing scientific information, not just guideline studies, is increasing. This situation offers EFSA and its risk assessment network, the opportunity for contributing to PARC and other initiatives, by developing clear recommendations for facilitating the use of these studies in the regulatory context.
- The use of NAMs for complementing existing animal data and fulfilling data gaps during the risk assessment process offers new opportunities for collaboration between risk assessors and academic researchers. The co-design of NAMs-based Integrated Assessment and Testing Strategies (IATA) and also AOPs for selected case studies of EFSA interest, and the incorporation of the results in EFSA regulatory assessments, will introduce risk assessors to the use of results from new toxicological tools and promote the interest of researchers in regulatory assessments.
- Society requires EFSA to produce more informative human health risk assessments, e.g. addressing vulnerable sub-populations. NAMs can provide mechanistic understanding which can be combined with scientific knowledge on human variability and used to identify the drivers of susceptibility within the population, so providing a more powerful and future-proof scientific assessment.
- While at EU level JRC is leading the validation and 3Rs activities and ECHA the use of NAMs for screening and standardisation, the use of NAMs for mechanistic hazard assessments and informative risk characterisation of chemicals in the regulatory context represents a clear opportunity, and is key for the next generation testing and assessment of chemicals in food and feed.

Cooperation:

- Increase cooperation with key players in Europe, in particular DG JRC, ECHA, EMA, EU Member States, and international regulatory networks such as OECD, APCRA, GCRSR⁵ and ILMERAC⁶. The roadmap will be built on:
 - existing cooperation lines with the organisations mentioned above and with DG SANTE, DG RTD & Innovation, and the European Partnership for Alternative Approaches to Animal Testing (EPAA)
 - further involvements in the activities of international organisations, in particular OECD, FAO and WHO, and
 - extended bilateral collaborations with interested international partners, such as U.S. EPA, U.S. FDA and Health Canada.
- This situation offers an opportunity for EFSA and its partners, connected to the future of chemical risk assessment, to share the work, avoid duplication and jointly prioritise activities for the evolution of the paradigm to incorporate NAMs based mechanistic understanding and

⁵ Global Coalition for Regulatory Science Research

⁶ International Liaison Group on Methods for Risk Assessment of Chemicals in Food



improve the information provided to risk managers and citizens through the risk assessment process.

- Specific cooperation lines will be established with the future European partnerships under Horizon Europe, such as the abovementioned European Partnership for the Assessment of Risk from Chemicals (PARC) which aims to start in 2022. These partnerships may be considered for funding innovative research projects which may support the development of NAMs in the area of IATAs.

Impact for EFSA and partners:

- Prepares the pathway for better and more informative risk assessments; using new toxicological tools and mechanistic information. Chemical risk assessment will be improved through an updated paradigm, allowing risk managers to take informed decisions to protect susceptible subgroups of the EU population.
- Facilitates the application of NAMs in chemical risk assessment by EFSA and at EU level. Significant reduction in the need for using animals for conducting verification studies, by increasing EFSA's scientific capability in the application of NAMs for chemicals in food, particularly for addressing data gaps in the risk assessment instead of requesting additional animal testing. This will include the harmonisation through a cross-cutting guidance on the use of NAMs, and the update of the sectoral guidances in order to adapt the recommendations to the regulatory requirements.
- Positions EFSA as an important partner for the implementation of NAMs in regulatory science for hazard and risk assessment of chemicals in food and feed at EU level, and internationally. The involvement of ECHA and other EU agencies should be also considered in anticipation of the One substance - One assessment approach, that will need inter-agencies alignment on the regulatory use of NAMs. Demonstrates EFSA's contributions to societal needs and reduction of animal testing, with increased visibility of EFSA commitment to stimulate the use of NAMs and to reduce, refine and replace animal testing. Enhancing EFSA's role and position in the area of NAMs internationally through bilateral agreements and multilateral platforms such as APCRA, IFCSLG, GCRSR, WHO's Chemical Risk Assessment Network and ILMERAC.
- Increases researchers' interest in regulatory risk assessment science. Will strengthen EFSA's direct links with research communities working on the new decade of toxicology and EFSA's role as EU knowledge hub, connecting researchers, risk assessors and risk managers, for integrating novel scientific tools and knowledge in comprehensive chemical risk characterisations. By introducing modern methods for risk assessment into its daily work, EFSA becomes an increasingly attractive place for employment for both high level and early career scientists and for external experts recruited to Panels and working groups