MB/34/2022 FINAL
Helsinki, 29 September 2022
PUBLIC

ECHA and the promotion of alternative methods to animal testing

67th Meeting of the Management Board 29 September 2022

Proposal

The Management Board (MB) is invited to take note of an update on ECHA's approach related to its activities to promote alternative methods, or New Approach Methodologies (NAMs).

As explained in the context of the orientation debate on the ECHA Programming Document (see agenda item B.6), the secretariat proposes to include a specific activity in the planning to better explain, focus and target ECHA's work on NAMs in 2023-2026. This will focus on three main areas:

1. invest in the areas where the Agency has relevant scientific-technical competences;
2. enhance the cooperation with the European Commission and other institutional partners to support developments of a European roadmap towards full replacement of animal testing, and
3. increase visibility and stakeholder engagement.

The paper sets out the state of play in this field, including ECHA's current activities and initiatives, and proposes an updated approach. This approach will allow ECHA to increase its impact and visibility in supporting the development and up-take of alternative methods that are suitable for regulatory purposes. This activity will be complementary to the regular work of ECHA, in accordance with the current regulatory framework.

The feedback from the MB will inform the further development of the approach, in cooperation with the incoming Executive Director, with the objective of clarifying ECHA's contribution in this area.

1. Introduction

The promotion of alternatives to animal testing is among the aims of the REACH Regulation and, therefore, part of ECHA's mandate since its establishment. It is a complex topic, both from scientific and regulatory perspectives. It leads to a degree of conflicting expectations from stakeholders and policy makers, which are to ensure a high level of protection for human health and environment, while aiming to follow the 3Rs principle to reduce, replace and refine animal testing.

NAMs are non-animal-based approaches to provide information in assessing risks and hazards of chemicals. There is no agreed definition of NAMs however, in general, it includes all alternatives to traditional animal testing (in vitro assays, in silico computational models, read-across, omics, etc.) which may be used as stand-alone or combined, to predict biologically complex endpoints.

NAMs' development is closely linked with the overall ambition to replace animal testing. While Europe's commitment to fully replace animal testing is irrefutable, there are different views in relation to the means, timelines and readiness to get there.

In September 2021, the European Parliament adopted a resolution to 'Accelerate a Transition to Innovation without the use of Animals in Research, Regulatory Testing and Education[1]' calling for ambitious objectives, reduction targets and replacement timelines. More recently, a European

[1] European Parliament resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education (2021/2784(RSP)).

Citizens' Initiative[2] gathered 1.3. million signatures calling the European Commission to take immediate action to protect and strengthen the EU Cosmetics animal testing ban, transform the EU Chemicals Regulation, and modernise EU safety science through committing to a roadmap that will phase out animal testing.

In parallel, the Commission's Chemical Strategy for Sustainability (CSS) aims to regulate chemicals at a faster pace, by improving the current regulatory framework to ensure appropriate hazard and risk characterisation. The anticipated changes to REACH and CLP, and consequently ECHA's implementation work, may therefore lead to additional animal testing to better protect human health and environment from chemicals with, for example, endocrine disruptive properties. At the same time, the CSS also puts forward less reliance on animal testing, thus aiming to facilitate further scientific developments in the field.

ECHA has been engaged with this topic within its institutional mandate since its setup. There is, however, an increased perception that ECHA does not sufficiently consider the scientific developments in the field and does not devote sufficient attention and resources to the promotion of alternative methods to animal testing. This is articulated in the European Parliament discharge resolutions (for the financial years 2019 and 2020[3]) which call on ECHA to put in place proactive measures and more resources to reduce animal testing and replace existing tests with NAMs.

The MB, therefore, requested during its meeting of March 2022 an update on ECHA's activities devoted to the promotion of alternatives to animal testing and on its approach to address public and institutional concerns.

2. ECHA's activities to promote alternatives to animal testing

ECHA has been active in a wide range of activities related to NAMs which, in general, is structured around three main pillars:

a) Effective implementation of ECHA's integrated regulatory strategy to identify and address risks of chemicals of concern

This work focuses on:

- Selection of chemicals for regulatory work: chemicals are addressed in groups with the aim to prioritise those, where further data generation is needed to conclude on the appropriate risk management measures. This, compared to looking into chemicals individually, reduces the data generation needs.
- Support provided by ECHA to registrants in developing testing strategies for their registration dossiers based on read-across which ultimately aims to reduce animal testing. For instance, ECHA developed and made available a cutting-edge approach for read across, the Read Across Assessment Framework, which supports the regulatory acceptance of read across adaptations.
- Implementation of the mechanisms built in the legislation to reduce unnecessary animal testing, such as obligatory data sharing or the evaluation of testing proposals, where ECHA verifies that the use of alternatives has been considered, runs public consultations and ensures that the proposed testing addresses correctly the information requirements.
- Supporting provided by ECHA to the European Commission on the use of alternatives to animal testing in the EU regulatory context. For example, ECHA is actively involved in the European Partnership for Alternative Approaches to Animal Testing (EPAA), which is a platform representing the European Commission, relevant EU Agencies and Industry, and aiming to progress towards the replacement, reduction and refinement of animal use for regulatory purpose.

[2] Save cruelty free cosmetics - commit to a Europe without animal testing, Commission registration number: ECI(2021)000006.
[3] P9_TA(2021)0194 and P9_TA(2022)0174.

b) Investment in international activities promoting alternatives

This work focuses on:

- Financing and co-managing the development of the OECD QSAR Toolbox, which is one of the most recognised tools at global level for assessing hazards of chemicals based on similarities in toxicological profile and modelling of the biotransformation pathways (the budget amounted to € 1 million Euro over the past two years).
- Contributing, through ECHA's experts, to the development of OECD test guidelines, in line with the requirements of refinement, reduction and replacement. For example, ECHA made significant and widely recognised contributions towards the development and adoption of the new OECD test guidelines for skin and eye irritation and skin sensitisation, which do not rely on animal testing; and
- Steering flagship research projects aiming at developing alternatives suitable for regulatory needs (for example PARC - European Partnership for the Assessment of Risks from Chemicals or other H2020-funded projects). ECHA has also joined efforts with authorities from other regions, such as the US or Canada, within the APCRA initiative (Accelerating the Pace of Chemical Risk Assessment[4]) to work together towards the identification and acceptance of alternatives in regulatory frameworks.

c) Making data available

Investing in making information available to the broad chemicals community, through the dissemination of registered information. As an example, IUCLID datasets are available for download (e.g., REACH studies' results, pharmaceutical industry data contribution). This information is essential to ensure the correct use of alternatives in the regulatory context, but it is also key for developing new alternatives. The ultimate objective is to effectively exchange data in common IUCLID format to further build and improve the chemicals knowledgebase globally.

3. NAMs – Challenges and opportunities

NAMs have been used for priority setting for decades. However, despite significant investment in research, the progress to date is far below the expectations set when, for example, REACH was adopted. While the science has progressed, the regulatory applicability of these new developments remains limited.

The **challenges** related to NAMs' development are both of a regulatory and scientific nature:

- **Regulatory challenges** - The current regulatory system for chemicals management is based on a generic approach reflected at EU level in REACH and CLP and related legislations. REACH ensures that industry provides adequate data, if necessary, by means of testing on animals, to assess the chemicals' hazardous properties. CLP enables the classification of chemicals based on the adverse effects observed in standard testing methods, including tests on animals, which are then used to derive safety levels and provide a framework for generic risk management.

  This system provides predictability and legal certainty to regulators and stakeholders. In general, the regulatory requirements prescribe specific animal tests to assess chemical hazards. Further integrating NAMs data within the existing framework brings an additional layer of complexity for regulators, particularly in the context of decision-making, e.g., concluding on the (lack of) hazardous properties for a substance.
- **Scientific challenges** – Until recently, NAMs have been developed with the aim to fully

[4] Accelerating the Pace of Chemical Risk Assessment (APCRA) | https://apcra.net/

replace animal testing for a specific endpoint. The developments have been successful for the relatively simple endpoints, such as skin and eye irritation and skin sensitisation, where a particular adverse effect is investigated and the mechanism(s) leading to it are well understood.

In these cases, the use of alternatives allows the classification according to the CLP criteria and the setting of appropriate safety levels. However, it has taken considerable time, nearly a decade, to adopt robust, reliable methods to fully replace animal testing for these endpoints.

Development of NAMs for more complex endpoints has been less successful. There is now wider acceptance across the scientific community and regulators that it would be almost impossible to develop one-to-one replacements of animal tests for more complex endpoints (repeated dose toxicity, reproductive toxicity) due to the complexity of the biological events that need to be considered. There are also areas where biology is still poorly understood, (because it is based only on observation of effects, with very little/no understanding of what generates those effects), which makes it even more challenging for NAM development.

Opportunities for better use

However, in the short term, there are opportunities to better integrate NAMs in the current regulatory system by:

- Using high-throughput screening and machine learning tools to prioritise chemicals likely to be hazardous and potentially needing additional animal testing;
- Using NAMs to model the metabolic pathway of a chemical in the body and then substantiate a read-across/category approach; and
- Using data generated under different legislations like REACH, pharmaceuticals, agrochemicals better, to support NAM developments

These measures would support reduction, however would not lead to a full replacement of animal testing.

Towards full replacement of animal testing

A significant/full replacement of animal testing would require advancement in the scientific developments, accompanied by fundamental policy changes, which should address two key questions: how a new approach can cover the most relevant (adverse) effects and diseases of concern for the society (for example, CMR (carcinogenic, mutagenic, or toxic for reproduction), immunotoxicity, Endocrine Disruptors, etc.) and how to ensure a similar or better level of protection for human health and environment.

Such fundamental changes ultimately represent policy options. ECHA has the competence and is ready to support policy makers in developing a suitable, consistent approach for regulating chemicals based on an increased use of NAMs, and eventually phase out animal testing.

4. Next steps

ECHA recognises that the topic of NAMs is very relevant in the current context of policy changes and is committed to contribute to the scientific debate and regulatory work to replace animal testing, while continuing to fully implement the policy lines and the regulatory frameworks adopted by the legislator.

The secretariat proposes to make NAMs a priority area for the upcoming programming period and have a dedicated activity in the Programming Document 2023-2026. ECHA will review its activities around NAMs, focusing on three main areas:

a. Invest in the areas where the Agency has relevant scientific-technical competences

- Continue investing in data availability, which is key for the development of NAMs – the central role foreseen for the Agency in the EU Common Data Platform will provide further opportunities to strengthen its position, and
- Invest in further development of the QSAR toolbox to integrate new information (for example, Biocides or Pharma data).

b. Enhance the cooperation with the European Commission and other institutional partners to support the development of a European roadmap towards full replacement of animal testing

- Increase co-operation across legislation within Europe and outside Europe (US EPA, Health Canada) through platforms such as EPAA and APCRA and

- Strengthen the dialogue between different stakeholders to increase awareness of on-going work and potential synergies and develop a common understanding on what NAMs can achieve in short and longer term. In this context, a workshop is planned in 2023 to contribute to EU efforts towards building an EU roadmap for the replacement of animal testing.

c. Increase visibility and stakeholder engagement

- NAMs Task Force – review and consolidate the internal organisation for supporting NAMs by creating a horizontal taskforce within ECHA, responsible for NAMs/promotion of alternatives; the taskforce will comprise relevant competences, will be responsible for coordinating internal activities, forming ECHA's views, and liaison with the scientific community and stakeholders
- Build internal capacity on NAMs – organise training for ECHA scientists and Committees (MSC, RAC) to increase the level of knowledge on NAMs suitable for the regulatory needs
- Play a more visible and active role in the scientific/regulatory community by steering flagship research projects dedicated to NAMs (via PARC or Horizon Europe)
- Engage in coherent, consistent communication on ECHA's activities on NAMs across all relevant channels[5]. This would include the development of key corporate messages, bespoke communications plans per initiative, coordination of speaking appearances and interaction with stakeholders.

Attachments: N/A

For questions: ofelia.bercaru@echa.europa.eu with copy to mb-secretariat@echa.europa.eu

[5] European Chemicals Agency describes measures to reduce and replace animal tests | Cruelty Free Europe
Data-sharing to reduce animal testing - PETA Science Consortium International e.V. (thepsci.eu)