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Towards an animal-free regulatory system for industrial chemicals

ECHA New Approach Methodologies Workshop background paper

The NAMs workshop "Towards an animal free regulatory system for industrial chemicals" will provide the space for collecting feedback and commitments from all stakeholders on how to accelerate the transition to a regulatory system with no or minimal reliance on animal testing.

Organised in four main sessions, the workshop aims to discuss the critical needs within the current regulatory system bringing perspectives from different stakeholders. The workshop will also explore opportunities to increase the use of NAMs in the short term, looking at both regulatory and scientific aspects; it will look into how research can support the transition in the longer term and how other considerations, besides the scientific ones, could play a role when introducing changes in the regulatory system. The main objective is to identify next steps in accelerating the transition to non-animal testing.

This document outlines the key elements that should be considered for a transition towards a regulatory system with no reliance on animal testing for hazard assessment of industrial chemicals to enable comprehensive risk management and ensure a similar or higher level of protection as the current system.

1. Introduction

The use of new approach methodologies (NAMs) to evaluate the effects of chemicals on humans and the environment is a topic of increasing interest. Several roadmaps have been developed recently (e.g., US EPA, EFSA) to support the implementation of NAMs and aiming towards a full replacement of animal testing. There is however no consensus on how to best increase the use of NAMs in regulatory decision-making on chemicals. The lack of consensus stems largely from the differences in the regulatory frameworks and requirements under the different legislations and jurisdictions.

In this context and according to ECHA, NAMs denote alternatives to traditional toxicity methods that typically involve animal testing. These alternatives are useful for predicting and assessing chemical risks and hazards, by providing mechanistic information for biologically complex endpoints. They include, e.g. in vitro, in chemico methods and in silico computational models, which may be used alone or in combination with other methods and have the potential to be quicker, cheaper and use less animals.

2. The EU regulatory context

The primary objective of EU legislation regulating industrial chemicals is to ensure a high level of protection of human health and the environment while promoting the use of alternative methods and maintaining competitiveness of the EU chemical sector. It relies on the identification of hazardous properties of substances and has REACH and CLP as the two key horizontal EU Regulations.

Since its entry into force in 2007, REACH is the regulatory framework producing the largest knowledge base on chemicals globally. REACH ensures that industry provides adequate data, if necessary, by means of testing on animals as a last resort, to assess the chemicals' hazardous properties as well as fate, uses and exposure properties. It also provides a horizontal framework for the management of risks to human health and the environment arising from the use of chemicals.

The CLP Regulation enables classification of substances in defined hazard classes for human health, environmental and physico-chemical hazards, based on identification of hazardous properties under REACH. CLP criteria have far-reaching consequences for risk management; they ensure that appropriate classification is consistently applied for most hazardous substances and provide a framework for generic risk management and progressive shift to less hazardous chemicals.

In addition to REACH and CLP, sectorial legislation complements the EU framework on the identification of hazards, risk assessment and management of chemicals. Chemicals management relies on the effective interplay between REACH, CLP and the sectorial legislation. It depends on the cooperation of different actors (industry, authorities, third parties, etc.) according to the roles and responsibilities described by the regulatory frameworks, providing predictability and legal certainty for industry to comply and authorities to enforce.

The current regulatory system achieves its main objectives of protection of human health and the environment while making use of animal testing as a last resort. Therefore, it can be maintained as a framework for transitioning to an animal-free regulatory system. The last review of REACH[1] concluded that "REACH is effective" but still had "opportunities for improvement". Some shortcomings in the current regulatory system have been identified in the Chemicals Strategy for Sustainability (CSS), setting the direction for the imminent revision of this system. The CSS also clearly lays down an expectation to move towards a reduced reliance on animal testing.

A replacement of animal testing in the hazard assessment of chemicals should consider the fundamental elements of the current system which function well, namely:

- defined hazard classes,
- clear criteria to allow consistent classification
- standard information requirements which allow a conclusive outcome for hazard and risk assessment and in turn allow predictability and legal certainty for both industry and regulators
- ensure reliability, comparability, and re-use of data
- avoid duplication of work by authorities and industry as well as support consistency between the regulatory actions under the different legislative frameworks addressing industrial chemicals
- while being prescriptive, it should be based on solid scientific considerations

In addition, the following aspects of the chemicals legislations should be also considered:

- The generic system under REACH and CLP does not require intervention of authorities by default – chemicals are not systematically assessed for safety by the regulators before they are put on the market; this assessment is done solely by industry ("the reversed burden of proof"). Authorities may scrutinise these assessments and take regulatory actions (e.g., request further information or initiate regulatory risk management), where required.
- Adaptations to standard information requirements are allowed and used to a large extent in supporting both hazard and risk assessment.
- It is the responsibility of industry to agree and jointly submit the necessary data including building read-across and category approaches; authorities can use read-across solely for the purpose of risk management (for example, under harmonised classification or restriction proposals).

[1] SWD (2018) 58. Commission general report on the operation of REACH and review of certain elements

3. Challenges for non-animal approaches

NAMs, as defined above, have been developed and used in hazard and risk assessment so far at three different levels within the REACH and CLP context:

- by registrants to replace animal testing in support of hazard identification and classification, while aiming to provide scientifically relevant, fit-for-purpose data to enable better informed decisions,
- by registrants to support read-across and category approaches, to limit the testing requirements for each individual substance,
- by authorities to support screening and priority setting by identifying potential substances of concern for further data gathering and assessment including when the concerns need to be further addressed by animal testing.

The needs or expectations for NAMs are different depending on legislation (sectoral or horizontal), type of chemistry and depending on what the data are used for. NAMs to support the screening, prioritisation and read-across are available, continue to be developed and are already used to some extent by regulators around the globe, in line with the set frameworks and regulatory requirements.

However, there are currently only a few endpoints where full replacement of *in vivo* studies with non-animal methods has been accepted in a way that is suitable for classification and labelling or to conclude on (no) hazard: skin sensitisation, skin and eye irritation and (partially) genotoxicity.

In these cases, a particular adverse effect is investigated and the mechanism(s) leading to it are in general well understood. This is true in particular for skin sensitisation and irritation, where mechanistic knowledge combined with fixed data interpretation procedures developed at the international level (OECD), allows classification according to the CLP criteria. Consequently, the REACH information requirements have been updated accordingly to remove reliance on animal testing.

For the other, more complex toxicological endpoints, such as repeated dose toxicity, reproductive toxicity, carcinogenicity and long term aquatic toxicity or bioaccumulation, the mandatory information requirements still rely on animal testing although, several initiatives are actively exploring opportunities to fulfil standard information requirements through a combination of approaches, including the use of cell transformation assays (CTAs), QSARs, toxicokinetics, and other in vitro assays and computational tools.

There is also now a wider acceptance and understanding of the need to move beyond one-to-one replacements of animal tests for these more complex endpoints due to the complexity of the biological events (going hand in hand with a complex adverse outcome pathway) that need to be considered.

In addition, it was largely assumed, including by the regulatory community, that a full understanding of the underlying toxicological effects is needed to regulate chemicals based solely on mechanistic information from in silico/in vitro systems. This ambition is not achievable in the near future. However, it is possible to develop robust options based on non-animal methods which can provide protection levels comparable or higher than the current ones for many toxicological properties without a full understanding of the underlying toxicological effects. Moreover, it starts to be clear that a single solution that works for all REACH chemicals is not possible, instead multiple solutions able to address different chemistries might be necessary.

Full replacement of animal testing still requires 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 effects and diseases of

concern for the society (e.g., CMR, immunotoxicity, EDs, etc.) and how to ensure a similar or better level of protection for human health and environment.

Finally, it is generally accepted that animal testing has some limitations such as biological diversity, statistical power, dose spacing, subjectivity, reproducibility, lack of full understanding for human relevance. On the other hand, there is limited data on the hazardous properties of industrial chemicals for humans, with few exceptions (e.g., occupational data for some substances and effects). It is therefore expected that, during the transitional period, animal test data will continue to be used together with relevant human data for benchmarking NAM performance through accounting for known limitations, with view to develop a system establishing confidence in NAMs.

4. Identification of the critical elements necessary to transit to a non-animal system

To facilitate a smooth and responsible transition, the first step is to identify what are the critical elements needed to enable hazard and risk assessment without reliance on animal testing. Such identification will allow focusing resources on critical issues and clear communication between policy makers, developers and users about these challenges.

In principle, a new, animal-free system will need to allow conclusions whether a substance does or does not have hazardous properties. In addition, in case that a toxic property has been identified, also the level of its severity should be determined (effect type and its potency). Finally, there is a need to express predicted toxicity values in external doses used in risk assessment and risk management. Therefore, the critical needs to be addressed are, at the minimum:

- **NAMs for hazard identification**: The ability to demonstrate that NAMs, (e.g., an integrated in vitro/in silico system) can be used to allow a conclusive outcome on the (lack of) hazardous properties for given regulatory endpoint; the conclusion that the substance does not have a certain hazardous property should be sound.
- **NAMs for hazard characterisation**: The ability to reliably identify hazard and derive reference values based on changes at the molecular/cellular level instead of observed adversity in an organism. And to inform how severe the toxic effect is for human health or environment.
- **NAMs for extrapolation**: The ability to reliably convert nominal concentrations measured or predicted by NAMs (e.g., concentration in a tissue culture medium) into external doses used to set safety levels (e.g., mg/kg bodyweight), to communicate the hazard and assess the risks.

In addition to the three critical elements described above, the combination of various NAMs will be needed to cover more complex endpoints. Consequently, in addition to the test methods and/or predictive models also the explicit rules for the evidence integration and derivation of the overall outcome also needs to be developed and implemented.

4.1. Standardisation needs at international level

As already stated above, there are several roadmaps and initiatives aiming to gradually replace animal testing. Dynamic developments of NAM testing and risk/hazard assessment strategies by various organisations without standardisation and agreement at the international level can lead to erosion of the Mutual Acceptance of Data (MAD) system and benefits associated to that.

OECD plays a strategic role in harmonising approaches and gaining wider acceptance for NAMs. Ensuring the internationally harmonised application of the NAM methodologies as well as mutual acceptance of NAM data between jurisdictions will be key to bring such methodologies into general use. It is therefore expected that the OECD programmes will evolve in line with the developments of NAMs, including finding appropriate ways of validating their relevance and reliability to increase the confidence of regulators and users in the results from such tests. An appropriate problem formulation for such validation would be however of key importance considering the differences in the legal systems among the OECD member countries.

5. Transition as a shared commitment

The replacement of animal testing for industrial chemicals whilst ensuring a high level of protection is a shared objective by all stakeholders at EU level. Alignment at global level is also a critical factor for success, based on the alignment of the CLP-criteria with the globally harmonised system (GHS). For pursuing such ambition, there is a need for a close and effective cooperation of stakeholders, via open dialogues and concerted actions. All stakeholders will need to play their part to ensure progress in research, standardisation/validation and methods implementation. Platforms like the EPAA provide a forum to monitor progress and alignment and exchange experiences, including with other sectors beyond industrial chemicals.

ECHA is fully committed to play its part 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. The workshop is an opportunity to collect feedback and commitments from all stakeholders on how to accelerate the transition.