Commentaries

Recommendations for the EU roadmap to accelerate the transition towards phasing out animal testing for chemical safety assessments

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Animal testing has long been a controversial issue in the European Union (EU), with growing public concern over the ethical and scientific limitations of relying on animal models for chemical safety assessments. Despite being seen as a “gold standard” in research and safety assessment, animal studies have limited applicability to human health [1], and are difficult to replicate due to poor reporting procedures and large variability [2].

A significant majority of surveyed publics across the world and in the EU call for phasing out animal testing or ending it immediately [3]. The EU, where - de jure - animal models are to be used as a last resort [4] but - de facto - are still being used despite alternatives [5], officially aims to fully transition away from animal testing in safety assessment. European Citizens Initiatives [6] along with the European Parliament [7] have urged the European Commission (EC) to do more to address this issue, and to accelerate the transition. In response, the EC has committed to a roadmap to phase out animal studies for chemical safety testing in the coming years.

As the EU strives to become a global leader in ethical and innovative safety assessment methods, it is crucial to develop a clear roadmap [8] for phasing out animal testing and promoting the adoption of New Approach Methodologies (NAMs). The EU is uniquely positioned to lead such a change. With a solid foundation in research and innovation, and strong bonds to the USA where developments are accelerating the transition [9], the EU can foster stronger partnerships to make the regulatory changes needed. The EU has had its chemicals regulation framework adopted worldwide [10], showing what influence it yields in shaping animal testing practices globally.

This commentary outlines key steps the EC can take to accelerate this transition. Despite the technology for developing NAMs having progressed quickly, the international validation/qualification and legal implementation of NAMs is slow (1-4 per year) [11]. Some of the main barriers to adopting NAMs are now social and institutional [12], with regulatory sciences and toxicology deemed particularly conservative to change [13]. The EU suffers from a particularly fragmented governance system of regulatory testing with up to 40 relevant legal acts [14]. EU agencies have furthermore been ill-equipped to deal with their regulatory tasks [15], as evidenced by only 500 out of 100.000 chemicals on the EU market being well characterized for their risk and hazard [16]. Furthermore, the testing of mixtures of chemicals is another immense challenge which is practically impossible to be addressed by animal testing.

Key recommendations by members from the international, transdisciplinary consortium combining biomedical and social sciences backgrounds, 'SAFE' (Safety Assessment through animal-Free Evolution), aimed at accelerating the transition to animal free safety assessment in the EU and USA (SAFE 2024) are:

1. **Develop a Clear and Ambitious Roadmap**: The EC should establish a roadmap with specific, measurable milestones and timelines for phasing out animal testing. Clear goals, both for the short- and medium term, are essential for a successful roadmap [17]. Milestones should especially include clear goals for phasing out animal testing to avoid NAMs being used in parallel to animal tests instead of replacing them.

2. **Amend Legislation and Regulations**: Existing legislation should be harmonized and simplified to remove contradictions and streamline processes that currently mandate animal testing. The use of validated NAMs should be mandated wherever possible, even when animal tests are still required for other countries and recognized across all regulatory frameworks. The Cosmetics Regulation should be strengthened to fully align

with the goals of phasing out animal testing [18]. Such regulatory changes can be best developed by bringing together regulators, representatives of companies who want to phase out animal testing, and NAMs experts in order for regulators to understand current needs and possibilities.

3. **Enhance Governance and Coordination**: A dedicated steering committee comprising experts in NAMs, social sciences, regulatory affairs, and industry representatives should be formed to oversee the roadmap's implementation [19]. This committee could help oversee, coordinate, and accelerate the transition in order to break the current deadlocks, and examine the underlying causes hindering the transition [20]. Annual monitoring of the transition should inform the roadmap activities of the next year, which should be focused on addressing the most pressing barriers. Cross-sectoral and international coordination should be promoted to harmonize policies and practices. New governance structures such as a Human Exposome Project [21] should be considered to complement the Human Genome Project and move safety assessments toward the exposure contribution of disease; whilst current governance systems based on animal testing need to concurrently be phased out [22].

4. **Engage the Public and Increase Transparency**: Transparency in the transition process should be ensured by regularly publishing progress reports, data, and findings related to NAMs. The EC should foster closer engagement with EU citizens, respecting their concerns and opinions on animal testing, in alignment with the European Citizens' Initiative and the European Green Deal [23]. Fostering transparency and involving citizens creates more legitimacy and trust; broader societal engagement is crucial for the transition process to be successful, since acceleration in transitions often comes from outsiders [24].

5. **Take the lead in global harmonization**: The EU should work towards global harmonization of non-animal testing methods by collaborating with international organizations, especially the OECD, and positioning itself as a global leader in animal-free safety assessments.

6. **Address Social and Institutional Barriers**: Insights from social science research should be integrated [25] to understand and address the social and institutional barriers to the transition [26]. Some of the most significant barriers are social and institutional, including values and norms on safety and health, the political economy, and legislative norms, and competencies in social science are crucial to effectively govern the

transition. Moreover, the transition to non-animal testing methods should be inclusive and consider the interests of all stakeholders.

7. **Aim for systems change:** A new more flexible safety assessment paradigm based on scientific evidence is needed, moving from hazards-based to risk-based; to a one substance, one assessment approach; and from attempts to replace a single animal test by a NAM to changing the system of safety assessment, including through Next Generation Risk Assessment (NGRA).

8. **Embrace the ethical debate:** The issue of animal cruelty is often avoided in policy debates, framing them as 'emotions' or 'ethics'. With the relevance of data derived from animal testing for human health increasingly questioned, these ethical questions become even more relevant.

9. **Increase Funding and Incentives**: Dedicated funding opportunities should be increased for the development, validation, and implementation of NAMs. Financial support and career incentives as well as inclusion in curricula should be provided for young researchers specializing in NAMs to build a strong future workforce.

10. **Build Capacity and Provide Training**: A centralized and coordinated effort to offer comprehensive training programs on the use of NAMs should be developed and implemented for regulators, industry professionals, and researchers. Educational initiatives targeting secondary schools, universities, and early professional training should be promoted to instil a commitment to the 3Rs principles [27]. Transdisciplinarity [28], and expertise in the NAMs domain is crucial if the transition is to be sustained.

11. **Develop Knowledge Infrastructure and Promote Data Sharing**: A centralized, publicly accessible database for NAMs should be created (or the current knowledge-sharing role of the Joint Research Centre (JRC) should be strengthened) to facilitate knowledge sharing and reduce duplication of efforts. These should become living documents, given the pace of NAMs developments. The publication of animal test results should be made mandatory after a grace period. Digital innovations such as artificial intelligence (AI) [29] should be leveraged to enhance the development, validation, and implementation of NAMs. This will help reduce the need for animal testing and aid in more effective safety assessment.

12. **Encourage communication, flexibility and transparency in the current safety**

assessment process: By giving registrants the opportunity to dialogue during the safety assessment process with EU agencies such as ECHA and amending registration requirements to encourage the use of NAMs, non-animal methods will be more readily used and integrated into the current system as it transitions whilst fostering mutual cooperation and trust between stakeholders[30].

In conclusion, by adopting these concrete steps, the EC can become the leader in significantly accelerating the transition towards an animal-free regulatory system for chemical safety assessments. With this, safety assessment will become more human-relevant, efficient and cruelty-free.

The current capacity to safely assess chemicals, and mixtures of chemicals is far lower than what could be possible by using NAMs. These measures will enhance the protection of human health and the environment while positioning the EU as a global leader in ethical and innovative safety assessment methods. By incorporating these measures into the EC roadmap, Europe can put its full potential to use and accelerate the transition to an animal-free safety assessment system as it has promised to do. The time for action is now, and the EC must demonstrate its commitment to phasing out animal testing by implementing these recommendations as concretely as possible without delay.

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