European Animal Research Association

Call for evidence (EARA)

Roadmap to phase out animal testing in chemical safety assessments

The European Animal Research Association (EARA) welcomes the opportunity to provide feedback to the Call for Evidence for the European Commission to build a roadmap to phase out animal testing in chemical safety assessments.

The mission of EARA is to inform its stakeholders about the continued need for, and benefits of, the humane use of animals in scientific research, by providing accurate and evidence-based information. There are more than 190 EARA member organisations, from across the EU and globally, from both public and private research institutions, including some that produce human and animal medicinal products in Europe, and some that routinely conduct chemical safety assessments. As a result, we are strongly driven to provide input to the Commission roadmap, offering our expertise and insights specific to our sector.

The roadmap will aim to reduce and ultimately phase out current animal testing in chemical safety assessment by new approach methodologies (NAMs). This replacement is linked to the availability of scientifically valid alternatives and their regulatory acceptance under different chemical legislations, including for human and animal medicinal products.

The development of NAMs offers researchers the possibility to integrate complementary approaches alongside animal studies when feasible, contributing to more robust and reproducible study outcomes. Today, rapid advances in scientific innovation are enabling accelerated development and adoption of NAMs into safety testing. However, despite this significant progress, the transition from animal studies to NAMs still faces multiple challenges, and the choice of appropriate method or methods, including the use of animals, will in all cases depend on the unique characteristics of the research in question.

Current objectives of chemical safety assessments

To outline milestones and specific actions on the road towards phasing out animal testing in chemical safety assessments, it is important to understand the objectives of current assessment strategies. Chemical safety assessment is concerned with describing the adverse effects of chemicals, both in a qualitative and quantitative sense to determine how much of a chemical is required to produce a given response – the so-called 'dose response information' (Helmut Greim, Robert Snyder. First published:10 August 2018.

Chemical safety assessment, in animals, addresses both aspects in a holistic manner and considers relevant exposure scenarios and accumulation over time. Briefly, chemical safety assessment investigates:

- general toxicity over time, i.e. any dose-dependent adverse effect on any organ system,

- irritation, i.e. local adverse effects at surfaces such as skin*, mucous membranes or eye,
- sensitisation*, i.e. the potential to cause allergic reaction,
- genotoxicity*, i.e. damage to the genetic material in cells that may result in cell death, cancer or developmental defects in offspring,
- carcinogenicity, i.e. the potential to cause or promote cancer,
- reproductive and developmental toxicity, i.e. impairing reproduction or causing harm to the developing embryo or foetus,
- potential to disrupt endocrine signalling *
- toxicokinetics, i.e. investigation of absorption, distribution, and elimination of toxicants and their relevant metabolites as functions of dose and time, and
- mechanisms of action, i.e. understanding how the toxicant damages a cell or tissue.

* OECD Test Guidelines exist for *in vitro* methods in these categories

Current chemical safety assessment is a stepwise procedure, starting with the determination of local effects and systemic effects under short-term exposure. Based on results from these investigations, further characterisation is conducted on a case-by-case basis. Information gathered from these experiments is then used to define acceptable exposure limits and to conduct an appropriate risk assessment for a potential exposure of humans, animals, or the environment.

Chemical safety assessment has evolved over many decades and is an ever-changing and adapting scientific discipline. It is vastly driven by regulation, following isolated events of poisoning, e.g. severe malformations in children after exposure to thalidomide (Contergan) in the 1960s, or life-threatening effects in healthy volunteers participating in an early clinical trial of the antibody TGN1412 in the early 2000s. Each of these setbacks have influenced policies, regulations, procedures and practices in chemical safety assessment globally, regionally, and locally.

NAMs are already used extensively in chemical safety assessment, e.g. to investigate irritation, sensitisation, genotoxicity, and mechanisms of action. They are also used to investigate toxicity on specific types of cells, to produce modelling toxicity based on quantitative structure-activity relationship (Methods Mol Biol. 2025;2834:3-39.), and to predict toxicity based on adverse outcome pathways (AOPs) (Bajard L, *et al*). Application of AOPs to assist regulatory assessment of chemical risks - case studies, needs and recommendations (Environ Res. 2023 Jan 15;217:114650), are concepts that have become firmly embedded in chemical safety assessments.

Despite these scientific and technological advances, characterising some hazards such as those associated with general toxicity, carcinogenicity, or reproductive toxicity still require animal-based methodologies, as non-animal methods, even if multiple cell types are combined in a single micro-physiological system, are not yet capable of addressing the biological complexity and compensatory mechanisms that constitutes a living organism.

NAMs in chemical safety assessments

Further NAMs will certainly continue becoming available, and they will reduce the reliance on and gradually replace animal-based methodologies as they already do today. This process can be further accelerated by a deliberate strategy to address today's challenges, including technological and regulatory. At regulatory level, such a strategy needs to consider existing NAMs and how their use can be expanded in regulatory chemical safety assessments. Explicitly, such as strategy needs to:

1) Focus on specific organ toxicities where NAMs are on the horizon of development, accelerating their validation (by defining and demonstrating context of use or fit-for-purpose approaches) with a supportive programme for implementation.
2) Consider the broad variety of chemicals that humans, animals and the environment are potentially exposed to, covering industrial chemicals, agricultural chemicals, cosmetics and nonpersonal care products, food additives and nutrition supplements, medical devices and human as well as veterinary medicinal products, including small molecule drugs, biotechnology-derived drugs and new modality drugs based on cell and gene therapy - safety assessment procedures differ among those types of chemicals.
3) Allow time to gain experience and confidence with NAMs and technologies to maintain the high level of protection that EU citizens are used to.
4) Include the evolution of the legislative frameworks to facilitate the submission of data from NAMs, including the introduction of improved animal methods, to accelerate the introduction of the best methods available.
5) Consider the international context beyond the boundaries of the European Union, since most chemicals and specifically medicinal products are registered and/or distributed globally and therefore need to obtain international harmonisation. Collaborating with the WHO, OECD, VICH and ICH is of vital importance.
6) Overall the strategy should recognise that the best method available should be selected to ensure the safety of humans, animals and the environment, including animal methods and that a complementary approach should be considered where a variety of methods need to be employed.
7) The strategy needs to consider future legislative developments, in particular possible restrictions of substances necessary for the proper functioning of approved NAMs.

Specific considerations for the animal health sector

Regulation 2019/6 on veterinary medicines requires veterinary clinical trials, as part of the process of authorisation of a veterinary medicinal product. During this phase, a medicine which was developed to prevent, or cure, the disease for a given animal species must be tested on animals of this same species. Veterinary clinical tests cover a huge diversity of cases (e.g. research trials in the field, or in an experimental station, pre-marketing authorisation and post-marketing trials, etc) and as they come late in the approval process, they are generally safe for the tested animals. They are nonetheless a necessary part of the

approval process and aim at avoiding species-specific risks that cannot be detected by other methods such as non-animal methods.

Veterinary medicines manufacturers are committed to enable prevention of, or protection against, any form of pain, suffering, distress and lasting harm caused to the animals it uses in the discovery and development of veterinary medicines, in accordance with EU Directive 2010/63. NAMs are increasingly being developed for these products, however, animal models still remain the only valid method for many specific processes, both technical, legal and regulatory. In many cases, animal-based research therefore currently remains vital to the discovery, innovation and licensing processes which lead to the development, authorisation and improvement of authorised veterinary medicines, with long-term benefits for all animals.

Conclusion

With high ambitions for the protection of humans, animals, and the environment, it is essential that scientists with a deep expertise, in hazard characterisation using animal testing, be included in strategic discussions over the future of chemical safety assessments. Therefore, EARA and its members request to be recognised as key stakeholders in the upcoming targeted consultations as part of the roadmap development.

EARA
October 2024