AFSA
ANIMAL-FREE SAFETY ASSESSMENT COLLABORATION

DIM testing in REACH: when animal testing is difficult, impossible and meaningless

Abstract

Under the European Union's REACH Regulation, animal testing is intended to be used for providing information on chemical toxicity only if considered that no other testing approaches can be used and therefore as a last resort option. Yet, despite the availability of non-animal approaches and a growing consensus for their scientific validity, testing requirements often default to traditional *in vivo* methods. This position paper explores the concept of Difficult, Impossible and Meaningless (DIM) testing within REACH, focusing on cases where animal testing was performed in situations where testing was difficult, technically unfeasible, or scientifically unjustified. Drawing on insights from the Animal-Free Safety Assessment (AFSA) Collaboration and recent literature, the current potential and the limitations of REACH Annex XI, which has been drafted to enable adaptations and waivers from standard testing requirements, were addressed. Based on the preliminary results, a scientifically driven reinterpretation of regulatory frameworks appears necessary to ensure alignment between regulatory needs and testing strategies, moving beyond checkbox compliance toward robust, substance-tailored, animal-free safety assessments.

Introduction

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EC No. 1907/2006), introduced by the European Union in 2006, aims to ensure a high level of protection for human health and the environment. Central to REACH is the promotion of alternative methods for determining the safety of chemicals, reflected in a fundamental requirement: animal testing must be used only as a last resort, as clearly stated in Article 25.[1] This requirement sets a regulatory foundation for the adoption of non-animal, modern testing methodologies.

In practice, however, aligning regulatory implementation with this intent remains challenging[2]. Despite the legal mandate, traditional animal tests are often still performed, not due to scientific necessity, but in response to rigid regulatory expectations or procedural habits, a "tick-box" approach that undermines innovation and efficiency.

The Animal-Free Safety Assessment (AFSA) Collaboration, a global, multidisciplinary initiative, advocates for a shift toward science-driven, non-animal safety assessment strategies. One of its core priorities is the effective implementation of legislative requirements that support such a shift; this includes increasing enforcement and accountability of REACH's last resort requirement.

In 2024, the analysis by the AFSA Collaboration highlighted the need for scientifically justified decision-making in test selection for a given chemical[2]. This approach ensures not only compliance with legal frameworks but also the generation of relevant and meaningful safety data without unnecessarily relying on animal testing. Meeting REACH obligations should not default to *in vivo* testing; instead, it must involve a critical evaluation of a test's relevance and reliability for a specific chemical toward a specific regulatory purpose.

[1] According to REACH Article 25(1): "In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests."

[2] Macmillan et al. (2024). The last resort requirement under REACH: From principle to practice. Regul Toxicol Pharmacol. doi: 10.1016/j.yrtph.2023.105557 PMID: 38142814

As the European Commission prepares for the long-awaited revision of REACH, now expected by the end of 2025, a fundamental opportunity emerges to better align regulatory practices with the original vision of the regulation. The revision promises to enhance industry competitiveness, reduce administrative burdens, and reinforce the commitment to health and environmental safety, while paving the way for a more modern, streamlined, and animal-free approach to chemical safety assessment.
Therefore, this upcoming revision represents a critical moment to put the last resort requirement into practice and fully activate the potential of Annex XI, which provides the legal basis for adapting and waiving unnecessary animal tests under specific conditions.

REACH and the Last Resort Requirement: Scientific Rationale and Regulatory Gaps

The REACH Regulation mandates that animal testing should be used only as a last resort, reflecting both ethical considerations and scientific advances in alternative testing methods. This requirement is embedded throughout REACH but finds its most explicit procedural expression in Annex XI, which provides the regulatory framework for adapting standard information requirements, including the possibility to waive certain tests, particularly those involving vertebrate animals.
Annex XI is therefore central to operationalising the last resort requirement. It enables registrants to avoid unnecessary testing by justifying their decisions with scientific arguments or technical limitations. However, while the annex sets out theoretically robust pathways for waiving in vivo tests, in practice the interpretive ambiguities often compromise its effectiveness in achieving the intended reduction of animal use.
Currently, Annex XI outlines three primary scenarios for adapting the testing approach or waiving standard information requirements:

- The test is not scientifically necessary;
- The test is technically not possible;
- Substance-tailored exposure-driven adaptations are possible/adequate.

These categories are conceptually sound, but in practice, they are hindered by unclear guidance, inconsistent interpretation, or a lack of harmonisation with other parts of REACH, particularly the standard data requirements in Annexes VII to X.
Widespread use of Annex XI adaptations suffers from practical and interpretative limitations that often undermine its utility.

- Scientific redundancy and irrelevance: The provision for replacing animal tests on the basis of scientific necessity includes strategies such as the use of existing data, Weight of Evidence (WoE) approaches, and non-animal methods (e.g., *in vitro* or *in silico*). However, a critical shortcoming lies in the failure to fully recognise scenarios where testing is not only unnecessary (i.e. other non-animal testing or approaches are suitable and sufficient) but also not toxicologically/biologically relevant or meaningful.
  For instance, testing may be biologically irrelevant from an exposure perspective when a substance's intrinsic properties, such as high volatility, rapid degradation, or low bioavailability, mean it will not occur in the tested environment at harmful concentrations. Similarly, certain test species may be poorly suited to detect the relevant hazards of specific chemical classes; in such cases, more sensitive systems or endpoints might provide the necessary data without resorting to standard animal testing. From a biological perspective, irrelevance can arise when the test system itself (e.g., a particular animal species) is poorly suited to detect meaningful hazards due to fundamental differences in biology or toxicological pathways.
  Therefore, clarity on relevance is crucial, especially considering that the historical *in vivo* methods' applicability domain (AD) and limitations are less questioned or formally addressed, compared to more modern methods[3]. The absence of explicit documentation of such limitations may be misinterpreted to mean that they are broadly applicable and thus reliable. In contrast, modern non-animal methods typically come with clearly delineated conditions for use and may be misinterpreted as being generally less reliable due to their explicit applicability

[3] Browne P. et al. (2019) Regulatory use and acceptance of alternative methods for chemical hazard identification. Current Opinion in Toxicology. Doi: 10.1016/j.cotox.2019.02.003.

limitations. This discrepancy may create a bias in favour of outdated animal tests, undermining the scientific validity of safety evaluations and contradicting the spirit of the last resort requirement.

- Technical impossibility and difficult-to-test guidance: Annex XI also permits waivers on the basis that animal testing is technically not feasible. Yet, the accompanying guidance, particularly as related to Article 13(3), is often vague and does not adequately address the limitations of traditional *in vivo* methods. Similar to the above, the discrepancy in how ADs and specific limitations are described for animal versus non-animal methods continues to present a barrier to the broader acceptance of non-animal alternative approaches.
  In cases where testing is not impossible, but recognised as being difficult, modifications to the standard procedure are often requested. Although there is an OECD document[4] providing guidance on how to address difficult-to-test substances, this guidance document, when followed to the letter, might include many potentially confounding test adaptations that would limit the use of the test results for regulatory purposes. This is mainly due to the fact that scientific nuances and relevant test adaptation details in test reports may be challenging to incorporate into regulatory dossiers. Therefore, these adaptations, which do not necessarily improve test reliability and relevance, can be easily overlooked.
  Under such conditions, alternative methods may actually provide more robust and reliable results than experimental studies. For example, for many difficult-to-test substances, functional chronic fish QSARs (Quantitative Structure-Activity Relationships) are available and, when demonstrably within their AD, should be prioritised. Registrants should be actively encouraged to use these validated alternative methods, since in vivo studies are often repeated several times for difficult-to-test chemicals simply to obtain a result satisfying information requirements.

- Interaction between adaptations in Annex XI and Annexes VII–X: persistent challenge lies in the legal and procedural disconnect between the adaptivity of Annex XI and the prescriptiveness of Annexes VII to X, which list standard information requirements. In cases of conflict, the rigid structure of Annexes VII–X often overrides the adaptive potential of Annex XI. This restricts registrants from submitting scientifically justified, tailored approaches that align more closely with the chemical's properties and the last resort principle.
  Furthermore, while alternative approaches (adaptations) should be considered equivalent if they address the regulatory purpose of the standard study they replace, in practice, this equivalence is difficult to establish. A major barrier to *in vitro* introduction is that most current standard information requirements are not method-agnostic, as they are tied to specific, complex test methods that often address multiple endpoints simultaneously. This lack of flexibility creates a structural obstacle to the practical implementation and regulatory acceptance of scientifically sound adaptations.
  The situation is slightly different for *in silico* methods. These approaches are designed around specific endpoints they predict and, as a result, can sometimes serve as a complete replacement for in vivo studies or can be incorporated within a Weight of Evidence approach, when combined with reliable information from literature.

  Therefore, the apparent contradiction between Annex VII to X and Annex XI (prescriptive vs. substance-tailored approaches) or lack of clarity on which takes precedence leads to inconsistent acceptance of alternative strategies, regulatory uncertainty, and, in many cases, unnecessary animal testing, counteracting both the ethical and scientific mandates of REACH.

The AFSA DIM Testing Project

To address persistent regulatory and scientific shortcomings in the implementation of REACH's last resort requirement, particularly the inconsistent use of provisions under Annex XI and the

[4] **OECD (2019), *Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures*, OECD Series on Testing and Assessment, OECD Publishing, Paris**, https://doi.org/10.1787/0ed2f88e-en

underutilisation of non-animal approaches, a multi-phase project has been launched (Figure 1). This initiative is designed to explore the nature and extent of animal testing practices that may be classified as Difficult, Impossible, or Meaningless (DIM) under REACH, and to develop targeted recommendations for regulatory reform.

The project has two overarching aims:

- ✓ To assess how often and under what conditions DIM testing occurs, thereby clarifying the urgency and scale of the problem;
- ✓ To provide practical, science-based recommendations that better align regulatory practice with the last resort requirement and better utilise robust non-animal alternatives.

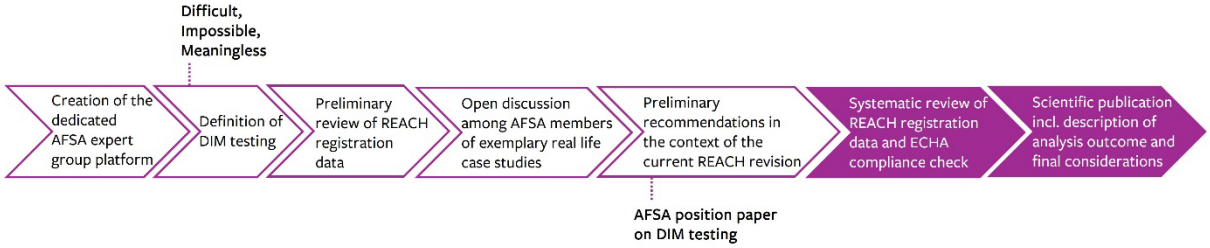

Figure 1. The AFSA DIM testing project timeline and deliverable. The first steps are described in this position paper (empty boxes); the final steps will be described in a final scientific publication (filled boxes)

The project has been initiated with the establishment of a multidisciplinary expert group, under the umbrella of the AFSA Collaboration, composed of experts in regulatory science with direct experience in REACH dossier preparation and compliance, as well as test developers and scientists specialised in non-animal methodologies, including *in vitro*, *in chemico*, and i*n silico* approaches. The group brings together expertise across a wide range of chemical sectors, including pesticides, UVCBs, and other industrial chemicals and provides a structured platform for collaborative evaluation, case study analysis, and consensus building.

A key early milestone was the formal definition of DIM animal testing, which refers to instances where animal testing is scientifically difficult, technically impossible, or meaningless. The definition has been grounded in objective criteria such as: physicochemical properties (e.g., solubility, volatility, reactivity) that invalidate certain animal test methods or lack of biological or mechanistic relevance for specific substance classes.

DIM testing definition:

- Difficult: substances whose physical-chemical properties fall outside the normal AD of the *in vivo* test methods requested under REACH Standard Information Requirements. These substances have characteristics that render animal testing extremely challenging, to such an extent that the results obtained from the studies would be questionable for human or environmental safety assessment. Difficult testing can include studies that require significant deviation or modification of existing testing guidelines to accommodate specific substance characteristics (e.g. use of atypical solvents or carriers, adjusted exposure systems). These modifications may confound test results or require preliminary testing, which results in additional test animals to refine the testing method. These modifications may also have prohibitive implications on the costs and timelines of testing, compromising one of the main tenets of REACH: "to enhance competitiveness and innovation". More importantly, the information obtained at the end of such costly and prolonged testing may be questionable or of no use (i.e. meaningless) to the safety assessment.
  For example, the OECD Guidance Document on Difficult Substances and Mixtures[1] mentions that regulators should decide if an *in vivo* test would be the most suitable for substances that are considered difficult to test (according to the criteria in this guidance document) or that other (non-)testing approaches should already inform the relevant hazards (e.g. read across, categorisation and/or QSAR modelled data in combination with specific *in vitro* tests).

- Impossible: substance characteristics render the test impossible to conduct. The study may still have gone ahead, with observed effects attributed to "chemical" toxicity of the substance; however, effects may have been of non-chemical nature (e.g. corrosivity, physical effects through agglomeration, etc.). Such instances might lead to test results that are meaningless for the safety assessment as the identified hazard cannot be (with low uncertainty) attributed to the toxicity of the tested substance because it might be related to secondary physical hazards due to the test substance specifically under the testing regime followed.

- Meaningless: incorporates both difficult and impossible tests. Any test whereby the conduct of the study is of questionable relevance to safety assessment due to inherent characteristics of the substance in question should be considered to be "Meaningless".
  (Eco)Toxicity testing required for REACH should be conducted to ensure the protection of human health and the environment. Hence, the testing should reflect the potential exposure scenarios for humans and different environmental compartments. If a substance, due to its characteristics, is not an exposure threat, then the (eco)toxicity testing for the substance should be considered meaningless. In this context, Next Generation Risk Assessment (NGRA) plays a critical role. NGRA is an exposure-led, hypothesis-driven approach that integrates *in silico*, *in chemico*, and *in vitro* methodologies to assess risks more effectively and accurately. By focusing on relevant exposure scenarios, NGRA enhances the scientific basis for toxicity testing, ensuring that only tests that contribute meaningful data are carried out. This approach prioritises methods that are scientifically grounded, reducing or eliminating the need for traditional animal testing.

DIM categories	Examples
Difficult	✓ Poorly soluble substances requiring extensive use of solvents or emulsifiers to achieve exposure levels, potentially leading to confounding effects. ✓ Highly viscous or sticky substances that challenge normal dosing and exposure procedures. ✓ Substances with borderline volatility, where exposure levels fluctuate unpredictably despite controlled conditions.
Impossible	✓ Long-term toxicity studies on chelating agents that interfere with essential ions in the test system ✓ Rapidly biodegrading substances where microbial communities (e.g., biofilms) adapt quickly during the study period; ✓ Chronic toxicity testing of highly volatile substances, where maintaining stable exposure concentrations is unachievable
Meaningless	✓ Testing of a substance not expected to reach the target compartment (e.g. a chronic test requested for a highly volatile, rapidly degrading substance) ✓ Testing substances for toxicity when their use and release scenarios indicate no plausible exposure. ✓ Testing of a substance when there is sufficient body of evidence allowing conclusions on toxicity.

Based on preliminary DIM criteria developed through consensus, the project has assessed the extent of DIM testing under REACH. This has been pursued through a systematic analysis of REACH registration dossiers (particularly post-2009) in combination with ECHA compliance check outcomes. By applying the preliminary DIM criteria to these data, the project aims to identify substances and test endpoints where animal testing was performed/requested when:

- Should have been waived;
- Could have been avoided through valid non-animal approaches;
- Was conducted in ways that produced unnecessary and/or irrelevant results.

From preliminary findings, it is clear that DIM testing is more common than expected, particularly in the ecotoxicological space. In several specific cases, hundreds of animals were used per test due to

compliance check challenges from ECHA, even though regulatory conclusions could (and should) have been based on existing *in silico* and *in vitro* evidence. These cases not only raise ethical concerns but also lead to potentially misleading conclusions, increased costs and innovation delays, and no demonstrable improvement in health and environmental safety assessments.

To bring these preliminary findings into practical focus, the expert group has been conducting transparent evaluations of real-life dossiers. These case studies have been selected based on:

- Evidence of DIM testing;
- Missed opportunities for alternative non-animal approaches and scientifically supported waivers;
- Misalignment between scientific reasoning and regulatory outcome.

Exemplary case studies

Case Study #1 -
DIM category(ies): *Difficult/Impossible*
Regulatory area: *Environmental toxicity*
In vivo TGs requested: *OECD TG 203; OECD TG 305*
Chemical(s) tested: *10 substances identified from preliminary DIM screening*
Description: Of 24 substances meeting the DIM criteria that were tested for OECD 203 (acute toxicity to fish), 10 were identified for which this test should have been avoided because these substances met the DIM criteria for low water solubility (<0.1 mg/L) and/or logP values >6. Although the chronic fish (OECD 210) testing would still be required according to REACH (as these DIM criteria could not be applied to avoid chronic fish studies as there is no formal value right now where we can be sure of no toxicity to fish), it is very unlikely that any substance with a logP >9 will show any toxicity and probably such a substance would be difficult/impossible to test anyway.
A similar approach might be recommended for the bioconcentration testing (OECD 305), where substances with a solubility <10 µg/L or log P>6.5 would make it (virtually) impossible to test these substances for this endpoint.

Case study #2:
DIM category(ies): *Meaningless*
Regulatory area: *Environmental toxicity*
In vivo TGs requested: *OECD TG 210 (chronic fish testing)*
Chemical(s) tested: *SXS-Sodium (Xylene and 4-Ethylbenzene) Sulfonates (EC: 701-037-1; CAS: 1300-72-7)*
Description: A read-across and categorisation approach for REACH registration of the target chemical was proposed. The approach was based on information on acute aquatic toxicity ($L(E)C_{50}$) values for the entire category (>100 mg/L) and known mode of action for the category (polar narcotics).
Although the read-across and categorisation approach for REACH registration was acknowledged by ECHA, a chronic (early life stage) fish test (OECD 210) was requested. Due to the requested high dose testing, exact quantification was finally not possible, therefore the testing is meaningless.
The registrant of this substance conducted a QSAR prediction in parallel and the predicted NOEC (>10 mg/L) was below the experimental NOEC for fish early life state (FELS) test (>12 mg/L). This finding shows the robustness and high sensitivity of QSAR prediction for many chemical classes (based on structures and functional moieties) based on substantial empirical databases.

Based on the above preliminary analysis and additional expert discussions, the project has therefore defined a set of preliminary recommendations relevant to the current regulatory context and the ongoing REACH revision, extending also beyond the considerations of the DIM animal tests.

Identified issues and preliminary recommendations

1. Enhance collaborative exchange between registrants and regulators

Issue: Communications from ECHA in the draft decision documents do not clearly indicate that alternative strategies to experimental testing will be accepted, provided they are justified. The feedback from industry is often that non-animal methods are rejected even when proposed. More explicit clarification should be provided by ECHA in their feedback, particularly in cases involving substances with recognised DIM properties.

At present, some registrants may hesitate to rely on non-animal methods, opting instead for traditional animal tests due to the perception that they offer greater legal certainty and expediency.

Recommendation: Structured, transparent dialogue, through mechanisms such as pre-submission meetings, timely and comprehensive written feedback, and testing proposal evaluations, can help address these concerns. When regulatory authorities provide clear feedback on the scientific acceptability of alternative approaches, it builds confidence, supports informed decision-making, and encourages the appropriate use of non-animal methods. Involving interdisciplinary expertise (e.g. toxicologists, exposure scientists, computational modelers) further strengthens the assessment of testing needs and reduces unnecessary animal studies.

2. Encourage substance-tailored testing strategy, science-based justification

Issue: There is a lack of clear scientific justification when additional data is requested, particularly in cases involving animal studies. Regulatory processes sometimes place the burden on registrants to justify deviations from prescribed testing methods, which can create uncertainty, especially when non-animal-based testing methods are proposed. Additionally, there is a current attitude that encourages "checkbox compliance," where the focus is on meeting minimal regulatory requirements rather than pursuing scientifically robust, substance-tailored testing strategies. This approach can lead to unnecessary or redundant animal testing and undermines the adoption of non-animal alternatives, limiting the potential for more scientifically relevant and ethically responsible testing approaches.

Recommendation: To ensure that animal testing remains a measure of last resort, regulatory processes should more consistently rely on clear scientific justification when additional data are requested, particularly in cases involving animal studies. This includes fostering a more balanced approach in which well-defined rationales support requests for further testing. These considerations underscore the importance of adopting a substance-tailored testing strategy, where test requirements are customised based on a comprehensive understanding of the test methods' characteristics and the substance's physicochemical properties, environmental fate, and biological interactions, to ensure that testing is both relevant and scientifically justified.

When a deviation from an *in vivo* TG is proposed by a regulatory body, it would be preferred if (in line with recommendation #1) a structured and transparent dialogue takes place between the regulatory body and the registrant(s) if only to encourage the appropriate use of non-animal methods. Alternatively, the requester should bear the responsibility for scientifically justifying that the deviation is valid. This ensures that the burden of proving the scientific merit of any deviation from the prescribed test methods rests with the party proposing the deviation (usually the regulator), rather than the registrant. This encourages responsible, science-driven decisions while preventing unnecessary burdens on those submitting data. If the registrant were required to justify a deviation, it could lead to uncertainty, especially when new or alternative testing methods are involved

3. Strengthen the role and incorporation of toxicokinetics (TK) and align testing strategies with meaningful exposure scenarios

Issue: There is a continued reliance on arbitrary (high)-dose testing in regulatory frameworks, which does not always reflect realistic internal and external exposure conditions. This approach often leads to misleading conclusions, obscuring actual hazards and inflating risk estimates. This mindset limits the ability to adopt more accurate, modern strategies for risk assessment, such as the use of in vitro

and in silico models for predicting internal exposure levels and supporting more relevant toxicity testing.

Recommendation: Toxicokinetic (TK) data, derived from *in vitro* and *in silico* models of absorption, distribution, metabolism, and excretion (ADME), are essential for interpreting both historical and contemporary toxicity studies. These data enable more accurate predictions of internal exposure levels and support in vitro-to-in vivo extrapolation (IVIVE). This is especially critical when assessing systemic, tissue-specific, or route-dependent effects.
For toxicity testing to be scientifically meaningful, it must reflect realistic internal and external exposure conditions. Risk assessments grounded in plausible exposure scenarios, rather than arbitrary high-dose testing, are more biologically relevant and help avoid over-conservative or misleading conclusions. Excessive reliance on high-dose animal studies can obscure actual hazards, inflate risk estimates, and generate Points of Departure (PoDs) that lack real-world applicability.
Incorporating TK into test strategies enhances the ability to compare *in vitro* bioactivity data with actual exposure levels, offering a scientifically sound basis for determining when testing is needed, what type is most appropriate, and how to interpret results. This improves regulatory relevance and helps prevent unnecessary or uninformative animal testing by ensuring that study designs and outcomes are linked to credible exposure contexts.

4. Define scientific robustness and adequacy across all testing sources, including in vivo tests
Issue: While non-animal methods are often comprehensively characterised in their limitations, many *in vivo* methods currently considered as "standard" were developed decades ago and lack characterisation according to modern validation standards.
Their applicability domains are often poorly defined, which may result in:
- Testing of chemical modifications (e.g. hydrolysis products) rather than the parent compound;
- Ambiguous results due to confounding physiological or systemic factors;
- Misinterpretation of observed effects, particularly when extrapolated to human health or environmental contexts.

Recommendation:
Scientific adequacy of a test method should be explicitly and transparently defined using a structured, criteria-based framework. Key considerations include:
- Relevance to the endpoint of interest;
- Reliability and reproducibility of results;
- Appropriateness of the method for the chemical's properties and exposure scenario;
- Strength of supporting evidence (e.g., peer-reviewed validation, cross-method consistency).

Clear definitions and expectations would reduce regulatory uncertainty and support consistent decision-making.
Modern regulatory science must critically evaluate these legacy methods using up-to-date frameworks to ensure relevance, reproducibility, and domain applicability.

5. Improve transparency in data traceability and for regulatory purpose
Issue: There are currently significant challenges in determining whether specific tests in the ECHA database were conducted to meet REACH requirements or for other purposes. This lack of traceability introduces uncertainties in data analysis and regulatory evaluation.

Recommendation:
Increased transparency, through better metadata tagging, standardised data formats, and clearer documentation, would enhance the ability of regulators, scientists, and relevant experts to interpret data relevance, identify structural issues, and support policy decisions with robust evidence.

Policy-related recommendations
6. Level regulations to the latest state of science and improve the implementation of Annex XI
While Annex XI conceptually enables the use of scientifically justified adaptations and promotes animal testing as a last resort, its practical implementation is hindered by several structural,

interpretative, and procedural challenges. Despite its positive aspects, the annex still reflects a traditional two-tiered approach, where animal testing is implicitly treated as the default or standard, and non-animal methods are considered only as a secondary option. This framing undermines the equal scientific standing of modern, mechanistically informed approaches and continues to limit their full integration into regulatory practice.

Greater clarity around the application of Annex XI, Section 3 on technical infeasibility remains essential. Current guidance could better support consistent decision-making by providing more explicit criteria for evaluating both traditional and alternative test methods, including a balanced assessment of their respective limitations and applicability domains. Additionally, distinguishing more clearly between tests that are unnecessary, because suitable data already exist or validated alternatives are available, and those that lack biological or toxicological relevance to the endpoint would enhance scientific consistency and transparency.
Annexes VII–X also present structural challenges due to their close linkage to specific test methods. Moving toward outcome-focused, method-neutral information requirements, wherever scientifically justified, would help reduce regulatory rigidity and allow greater flexibility in how data are generated. Establishing clear criteria and decision-support tools for demonstrating equivalence between standard studies and scientifically justified adaptations would further enable the fair consideration of modern, non-animal approaches that achieve the same scientific objectives.

7. Support the legal and cultural transition to Next-Generation Risk Assessment
As the regulatory community transitions from a historical animal-centric paradigm toward Next-Generation Risk Assessment (NGRA), stronger legal mandates and policy incentives are needed to embed the use of non-animal approaches. This includes:

- Clear requirements for considering and prioritising non-animal methods before proposing in vivo testing;
- Embedding training programs (such as AFSA Master Class[5]) and improving guidance to build regulatory and industry confidence in alternative approaches;
- Strategic investment in infrastructure, data sharing platforms, and validation efforts.

Such a framework would ensure that REACH remains scientifically sound, ethically responsible, and fit for the future.

Outlook

Beyond the scope of this position paper, the AFSA DIM testing project will continue with a systematic review of REACH registration data and ECHA compliance checks to assess the broader prevalence, patterns, and regulatory enablers of DIM testing. This analysis aims to identify recurring justifications for such testing, evaluate the consistency of regulatory decision-making, and uncover potential opportunities for more efficient, scientifically grounded approaches. The findings will provide an evidence base for refining current practices and advancing the use of non-animal methods within REACH.

The outcomes of this phase will be reported in a peer-reviewed scientific publication that will detail the project's methodology, key insights, and final policy recommendations. By shedding light on how testing decisions are made in practice, and where improvements can be made, this analysis is expected to inform future guidance development, support more targeted regulatory reforms, and contribute to the broader effort of modernising chemical safety assessment in the EU.

[5] https://www.afsacollaboration.org/masterclass/