Upholding the EU’s Commitment to ‘Animal Testing as a Last Resort’ Under REACH Requires a Paradigm Shift in How We Assess Chemical Safety to Close the Gap Between Regulatory Testing and Modern Safety Science

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Abstract
Animal use for testing chemicals under REACH continues to increase, despite advances in non-animal safety science during the past 15 years. The application of modern science and technology, and the use of ‘next generation’ weight-of-evidence assessment approaches, are embedded in EU guidance for establishing the safety of cosmetics and foods – and of the ingredients used in these products. However, this is still not the case for the regulation of chemicals. Under the new Chemicals Strategy for Sustainability, thought leaders in human health and environmental protection are calling on the European Commission to quickly embrace the benefits of modern and innovative non-animal safety science, in place of outdated animal testing, if the EU is to be a leader in safe and sustainable innovation under the European Green Deal transformational change ambitions. The European Commission also needs to enable companies to meet their legal obligation to only conduct animal testing as a last resort, by providing a more flexible, science-based and consistent regulatory framework for assuring chemical safety, which supports the integration of data from different sources. We are at a tipping point for closing the gap between regulatory chemicals testing and modern safety science. It is time to join forces, across policy makers, scientists, regulators and lawyers, to lead the paradigm shift needed to deliver what EU citizens want – namely, chemicals and products that are safe and sustainable, without resorting to animal testing.

Keywords
alternatives, animal testing, chemical safety, new approach methodologies, next generation risk assessment, product safety, REACH, regulatory testing, safety science

Introduction
The European Union Directive 2010/63/EU, on the protection of animals used for scientific purposes, is based on Russell and Burch’s concept of the ‘Three Rs’ which dates back to 1959, that is, the replacement, reduction and refinement of animal use. These principles have been present ‘in spirit’ in the EU’s horizontal legislation since 1986. However, the 2010 Directive made the Three Rs a firm legal requirement: the principles must be considered systematically at all times when animals are used for scientific purposes in the EU, including where animals are used in regulatory testing.

The EU Chemicals REACH Regulation (REACH; Registration, Evaluation, Authorisation and Restriction of Chemicals) came into force in 2007, as the outcome of the EU Commission’s 2001 White Paper on the strategy for a future chemicals policy. REACH places the burden of proof on companies, who must identify and manage the risks linked to the substances they manufacture and market in the EU. They have to demonstrate how the substance can be used safely, and they must communicate the risk.

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management measures to the users. REACH strives to increase our understanding of the possible hazards of chemicals while, at the same time, avoiding unnecessary testing on animals. The European Chemicals Agency (ECHA) is responsible for implementing the EU’s chemical legislation, working for the safe use of chemicals, and contributing to innovation and the competitiveness of European industry.

Article 25 of the REACH legislation states that testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. Recital 37 provides further explanation in this regard: “Implementation of this Regulation should be based on the use of alternative test methods, suitable for the assessment of health and environmental hazards of chemicals, wherever possible. The use of animals should be avoided by recourse to alternative methods validated by the Commission or international bodies, or recognised by the Commission or the Agency as appropriate to meet the information requirements under this Regulation”.

From the standpoint of both principle and law, it appears that there is full alignment between the requirements of Directive 2010/63 and REACH, in that any animal testing should be conducted only as a last resort to meet EU REACH information requirements. However, when it comes to their practical implementation for regulatory testing and assessing the safety of specific chemicals in the EU, there are some big challenges and concerns relating, in particular, to an ever increasing gap between: (i) the technical capabilities and experience now available in applying leading-edge science and using new approach methodologies (NAMs) for assessing the safety of chemicals used in consumer products; and (ii) the methods, mainly animal tests, accepted currently by ECHA for the purpose of regulating chemicals. Greater alignment between companies (who have the burden of proof and a legal requirement to avoid animal testing wherever possible in meeting the information requirements) and ECHA (for acceptance of the data) on the most suitable, relevant and up-to-date scientific assessment approaches for assuring safety is needed urgently, particularly if the legal principle of ‘animal testing as a last resort’ is to be upheld transparently and with integrity.

Despite the pioneering work done over the past 30 years by the Commission’s experts in alternatives to animal testing at the European Centre for the Validation of Alternative Methods (ECVAM), in collaboration with their global partners across different stakeholder groups, the ECHA Director was recently quoted as saying that “we’re currently 40 years away from being able to effectively predict toxicity of chemicals, but with focused investment and regulatory needs driving the work, this could be reduced to 20 years”. It would be a good first step for ECHA to fully enable application of the relevant non-animal scientific capability that already exists for filling information gaps, understand the actual (vs perceived) limitations, and then use these insights to develop and resource an accelerated roadmap for the next 3–5 years to address this challenge. This will likely require considerable investment in building ECHA’s scientific capabilities in modern approaches for assessing chemical safety, with a switch in focus to the regulatory application of NAMs in combination with exposure science.

Future chemical regulations need to be anchored in applying the best methods available to protect people and the environment. Application of leading-edge exposure science capability is critical as the basis of the regulatory approach. This enables regulators to truly prioritise which chemicals require in-depth scientific evaluation across multiple sectors, with the emphasis on industry to provide the information requirements for their applications, based on NAMs and exposure science.

If the fundamentals of the regulatory approach fail to change and the information requirements remain based on tonnage, as a proposed scale of environmental and consumer exposure, and perceived level of concern, then two issues play out. Firstly, the EU will fail to protect consumers and the environment from the chemicals of potentially most concern based on actual exposures; and secondly, industry will be overwhelmed by the volume of data needing to be generated – even if these data are based on modern science and high-throughput approaches. Defining better surrogates than tonnage bands for chemical exposures is a key need that continues to be overlooked in the EU’s plans for improving chemical safety.

**Assessing the safety of consumer products without animal testing**

Considerable progress was made pre-2003 in developing alternatives to animal testing, and in the subsequent adoption of some non-animal methods into the Organisation for Economic Co-operation and Development (OECD) testing guidelines for chemical hazard assessment. This progress was primarily in areas associated with topical toxicity, such as skin and eye irritation. Discussions at that time, on the implementation of an EU ban on animal testing for cosmetic ingredients, highlighted the need for a paradigm shift if companies were to continue to innovate and use new ingredients without reliance on new animal data for demonstrating the safety of consumer products, particularly with respect to potential health effects seen following systemic exposure to chemicals. The Unilever team published a suggested future direction in 2004, and this was the initial basis for re-thinking our approach to assessing consumer safety without new animal testing.

Over the past 15+ years, we have leveraged the best new science and technology and expertise available, in partnership with leading scientists globally, to transform how we apply next generation science and a non-animal toolbox...
(based on NAMs) to make decisions on the safety of products used by billions of consumers across the world every day.\textsuperscript{6,10,15} We have published and presented our research outputs, and made these publicly available via a dedicated Safety Sciences in the 21st Century website,\textsuperscript{16} and have discussed the non-animal science and assessment approaches we now use with scientists working in academia, governments, non-governmental organisations and other companies. Most recently, we published a detailed Unilever case study on a next generation risk assessment (NGRA) based on the use of NAMs.\textsuperscript{6}

Unilever entered into a collaborative research and development agreement (CRADA) with the US Environmental Protection Agency (EPA) in 2015, to develop and implement NAMs to better assess and assure the safety of chemicals in consumer products without using animal data.\textsuperscript{17,18} The US EPA and Unilever intend to show how a defined set of non-animal based NAMs that cover broad biological activity, in conjunction with computational tools that predict exposure, can be brought together to make a safety decision on chemicals that assures the protection of consumers, workers and the environment, rather than predicting the incidence of apical endpoints in animals. A new CRADA (2021–2023) has been initiated recently, as part of the US EPA’s NAMs work plan,\textsuperscript{19} to develop a comprehensive NAMs dataset on a minimum of 40 chemicals. These data will be used to make the scientific case for using NAMs in regulatory decisions. All data generated through this collaboration will be in the public domain, to provide opportunities for corporate, government and other scientists to use NAMs data in their research and decision making.

Through partnerships and open discussions, the application of NAMs within a NGRA framework for assessing the safety of cosmetics ingredients is now an integral part of the principles and guidance published by the International Cooperation on Cosmetics Regulation (ICCR)\textsuperscript{20} and the EU Scientific Committee on Consumer Safety (SCCS).\textsuperscript{21} Alongside the ongoing research programmes led by Cosmetics Europe,\textsuperscript{22} outputs of the EU-funded multi-partner research programmes, Seurat-1 and EUToxRisk, in defining new workflows for assessing chemical safety based on exposure considerations and NAMs,\textsuperscript{23} were important contributions to the scientific progress and broader acceptance. Together with other case studies being discussed and refined across the safety science community, the ICCR and SCCS guidance are enablers for sustainable innovation and competitive growth by the cosmetics industry, whilst ensuring companies can meet the demands of consumers for safe products without animal testing, in compliance with the testing and marketing bans in the EU Cosmetics Regulation.\textsuperscript{24} Approximately 75% of EU citizens say that they do not want to buy consumer products associated with animal testing.\textsuperscript{25}

Legislative bans on animal testing of cosmetics are now in place in many other countries as well as in the EU member states (over 40 countries in total). In May 2018, the European Parliament called on the EU Commission to establish a global ban by 2023.\textsuperscript{26} However, with requests from ECHA for new animal testing on existing ingredients that have been used safely in many consumer products for many years,\textsuperscript{27,28} compliance with the testing ban implemented in March 2009 for cosmetics-only ingredients in the EU is now being questioned. The EU bans in place already fall short of the expectations of consumers, animal protection NGOs and politicians, given the lack of alignment of the EU legislative requirements on animal testing for cosmetics (consumer safety; animal testing bans) and chemicals (worker and environmental safety; ECHA requests for animal testing under REACH).

Failure of ECHA to implement ‘animal testing as a last resort’

At present, there are an increasing number of cases where ECHA, following compliance checks of submitted dossiers, is asking companies to conduct animal testing where, in the original submissions, it was deemed scientifically feasible to use non-animal approaches to protect human health and our environment, and to meet the REACH information requirements. This would seem to contradict what ECHA is stating on its website, that is, that “Registrants may only carry out new tests when they have exhausted all other relevant and available data sources”.\textsuperscript{3,29} Whilst the REACH legislation does allow for adaptation to standard information requirements (i.e. where an animal test is not scientifically necessary, the registrant can provide a justification for an alternative way of addressing the information requirement),\textsuperscript{30} the use of bespoke, scientifically relevant adaptations are often rejected for procedural reasons. In addition, recent amendments to the REACH legislation further restrict the use of non-animal approaches by limiting the occasions when such adaptations may be used.\textsuperscript{31,32}

Most recently, the European Court of Justice (ECJ) found in favour of Esso Raffinage, which was being required by ECHA to conduct a developmental toxicity study on animals to fill a gap in its data.\textsuperscript{33} Esso argued that it could avoid animal tests by demonstrating the safety of its substance by using evidence from other sources, but ECHA refused this option. The Court confirmed that under REACH legislation animal tests must only ever be carried out as a last resort, stressing that the registrant has the obligation to generate information by means other than animal testing whenever possible, and even after ECHA has made a decision that animal tests must be carried out. ECHA also has a duty to consider alternatives put forward by registrants at this stage.\textsuperscript{33}

This case is starting to change how some registrants and chemicals manufacturers respond to requests from ECHA to generate new animal data, since it has further clarified the legal obligations on companies as well as on ECHA. Rather
than registrants having to justify why they have used a non-animal approach for filling an information requirement, the ECIJ judgement confirms that non-animal approaches should be the first consideration, and that justification should be needed if an animal test is the only way to fill that information requirement. To ensure that the implications of the ECJ ruling on this case are fully understood and embedded across registrants and the broader chemicals industry, a pause on any new animal testing requested as a result of ECHA compliance checks, to enable discussion and a transparent scientific review of the requests and testing proposals already issued, may be in order. Under the auspices of the Animal-Free Safety Assessment collaboration, there is an opportunity for knowledge transfer, training and capacity building in the use of suitable non-animal approaches. The European Partnership for Alternative Approaches to animal testing (EPAAs) and the relevant EU trade associations could also play a key role, for example, in working with all relevant groups to ensure compliance with the animal testing as a last resort mandate as clarified by the ECJ ruling.

New animal testing requested for widely used existing chemicals under REACH

The European Commission and industry have pioneered the use of alternative methods to animal testing since 1991 (and earlier for some companies), and invested over one billion euro in the past 20 years in developing non-animal safety science capability and NAMs. Despite this, a large number of new animal studies on widely used existing ingredients, with a history of safe use, are being requested by ECHA as part of their ongoing review of REACH dossiers and compliance checks. For instance, there are requests for new animal tests on common surfactants (e.g. linear alkylbenzene sulphonate) and preservatives (e.g. sodium benzoate), which are used in many different types of consumer products, where large data sets already exist which underpin confidence in their safe use based on extensive scientific weight-of-evidence.

To better protect EU citizens and improve chemical safety, there needs to be a more strategic holistic approach to prioritising for more testing of those chemicals that are of most concern, rather than an administrative tick-box process to filling information gaps through the dossier compliance checks. In this regard, the following excerpt from ECHA’s Integrated Regulatory Strategy report in April 2021 exemplifies our concerns about the approach being taken, and highlights the need for an open forum for stakeholder dialogue with ECHA on the best scientific approaches to be used to ensure any animal testing is as a last resort: “Alcohol ethoxylate sulfates (36 substances as group members) function as surfactants, foaming agents, processing aids and process regulators. They have a large variety of uses by professional workers and consumers, including in washing and cleaning products, textile coating, cosmetics and body care products. These uses have a potential for exposure to humans and releases to the environment and, therefore, ECHA assessed whether the substances could be of concern. Based on available information, all substances appeared to have low human health and environmental hazards. However, the dosiers of these substances were generally data-poor and the proposed read-across adaptations within the group or category were not sufficiently substantiated by data. Therefore, compliance check was opened to confirm the low hazard for human health and the environment. ECHA adopted decisions requesting nearly 100 studies for 11 substances on several endpoints addressing both human health (in vitro mutagenicity, subchronic and pre-natal developmental toxicity) and environmental (short and long-term toxicity to aquatic invertebrates, plants and fish) toxicity. Updated dosiers including new studies are expected to be come by spring 2023.

REACH and the Classification, Labelling & Packaging (CLP) Regulation are the two main instruments of the EU chemicals legislation. They will both be revised over the next 18 months, with the aim of improving the protection of people and the environment, in line with the European Green Deal’s ambitions and the new EU Chemicals Strategy for Sustainability (CSS). Currently, ECHA’s plans do not include a focus on how best to comply with the legal obligation that animal testing is used a last resort, which could be an important omission given the millions of animals that may otherwise be used in regulatory testing of chemicals. With the extension in scope of REACH – for example, the inclusion of polymers and mixtures assessments – this will likewise increase the use of animals, unless data from non-animal approaches are more widely accepted by EU chemicals regulators.

It is critical that EU policy for assuring the safe use of chemicals continues to evolve, and that it strengthens the protection of people and our environment from exposures to chemicals that could cause harm. It appears, however, that rather than considering new, non-animal approaches to generating data for this purpose, the default initial approach for any area where information is needed is to assume that the ‘gold standard’ is automatically a new animal test (e.g. for assessing potential effects on the endocrine, immune and nervous systems).

With the current proposals and roadmaps from ECHA, it is possible that millions of animals could be used in the coming years to address new CSS information requirements on chemicals. Whether and how this will actually translate into better protection of human health and our environment from the potential adverse effects of chemical exposures remains to be demonstrated. Those of us who have been actively involved in progressing the ambitions and
application of next generation safety science capabilities articulated in *Toxicity Testing in the 21st Century: A Vision and a Strategy*.42, find it difficult to believe that thousands of new animal studies are scientifically justifiable these days, and are of the opinion that the regulations urgently need to evolve to better facilitate the use of different types of data relevant for human health and environmental protection.

**Inconsistency in EU approaches for establishing product and ingredient (chemical) safety**

Various initiatives taken by the EU Commission between April and June 2021 demonstrate that the gap continues to widen between the scientific approaches acceptable for assessing the safety of ingredients used widely in consumer products, including cosmetics and foods, versus requests for new animal testing of some of those same ingredients being evaluated under REACH (e.g. common surfactants, preservatives and UV filters).

In April 2021, the European Commission’s SCCS issued revised guidance for the safety evaluation of cosmetics ingredients.21 For the first time, NAMs featured prominently, with attention given to NGRA as a framework for the safety evaluation of cosmetic ingredients.6,7,10,20,23 The SCCS stated: “risk assessment of cosmetics and their ingredients is shifting towards a strategic combination of NAMs and new technology with historical animal data, if available, to come to a weight-of-evidence decision making approach.”21 They also commented on ECHA asking for animal studies even where the chemical was foreseen only for cosmetic use, yet those data cannot be used in the cosmetic product safety report and cannot be submitted to the SCCS for risk assessment purposes.21

Also in April 2021, the European Food Safety Authority (EFSA) released its 2027 Strategy for public consultation,43 with a focus on harnessing new developments in data, technology and science, to improve the safety and sustainability of food and meet its increased responsibilities to EU citizens. It includes key actions to “develop and integrate new approach methodologies (NAMs) and omics for regulatory risk assessment” and to “integrate cheminformatics and bioinformatic approaches, technologies and data into NGRA”.43

In May 2021, the European Commission published two roadmaps for the revisions proposed to the REACH44 and CLP45 regulations under the CSS. Whilst there is little reference to how it will ensure that animal testing is only conducted as a last resort, there is a proposal for a simpler ‘one substance – one assessment’ (OS-OA) process for the risk and hazard assessment of chemicals.39 The registration and risk assessment of chemicals is currently fragmented across different legal frameworks, depending on the use of the chemical. Important differences exist which result in inconsistent assessment outcomes for similar chemicals. Chemicals are also registered under different frameworks due to their multiple uses, and chemicals which are not approved under one framework are, in some instances, allowed on the market under other frameworks.

One substance – one assessment will likely require greater harmonisation in the scientific methodologies used to assess the safety of chemical ingredients used across different product types, including cosmetics and foods. However, in stark contrast to the progressive approaches adopted for assessing cosmetics and food safety by the EU institutions responsible, which are embracing new science and NAMs,21,43 and leveraging relevant developments in data analytics and technology, there appears to be less appetite for doing likewise during the far-reaching revisions to the EU chemicals policy and legislation. If so, this is a missed opportunity to build on the considerable progress made over the past decade in implementing NAMs for chemical safety assessment, in particular, by the US EPA and its partners.19,46

**Assessing chemical safety without animal testing**

In 2007, the US National Academy of Sciences published *Toxicity Testing in the 21st Century: A Vision and a Strategy*,42 initiating a paradigm shift in chemical safety assessment approaches for regulatory purposes by the US EPA to those firmly based on human biology. It triggered: (i) a commitment to change in the North American scientific community and with some influential policy and regulatory leaders; (ii) investment in building and starting to apply new scientific capabilities (e.g. knowledge of biological/toxicity pathway perturbations and pathway assays in humans, computational modelling); (iii) the development and publication of roadmaps for implementing the strategy, and new research collaborations to deliver those roadmaps19; and (iv) some high quality outputs in the published literature, particularly from the US EPA Centre for Computational Toxicology & Exposure.47,48

A promising international governmental collaboration initiative, involving authorities from North America, Europe and Australasia, commenced in 2016 to accelerate the regulatory application of NAMs: APCRA – which stands for ‘accelerating the pace of chemical risk assessment’.49 The aim of APCRA is to promote collaboration and dialogue on the scientific and regulatory needs for the application and acceptance of NAMs in regulatory decision making. Case studies are being compiled that focus on how to modernise quantitative risk assessment, and demonstrate how the data and tools can be incorporated into future risk assessment activities, in particular for chemicals with
Re-thinking the EU’s approach to chemical safety

It appears the time is right to pause and think more critically about the ongoing EU chemicals activities,55 to avoid acceptance of the status quo as the path of least resistance, and to be creative in re-purposing data relevant to the REACH information requirements and supplementing these with new data generated by using NAMs.51,123,56 A different route from that currently being taken in the EU is surely preferable, learning from the ambitions and strategic leadership shown by Wheeler and the US EPA46,52 – that is, a paradigm shift by the European Commission to use NAMs as the default approach for assessing chemical safety under REACH, whilst also defining how to incorporate better surrogates for chemical exposures than tonnage bands. The application of NAMs should also enable higher throughput, faster decision making to protect people and our environment, and scientifically sound data to be generated for the assessment of mixtures (another requirement of the CSS).39

More published examples are needed of how NAM data that are used increasingly to make exposure-driven decisions for consumer safety can be used in the context of worker safety, where exposure scenarios can differ. There are several examples of chemicals which are used only in cosmetics, for which safety for consumers is assured in line with the EU Cosmetics Regulation,24 where new additional animal data have been requested by ECHA relating to worker safety.

To ensure worker safety in Unilever (and other company) operations, all sites implement process and occupational safety management systems involving core elements of risk assessment, risk management and employee training to identify, understand and manage workplace risks. Specifically on occupational safety, worker exposure to these cosmetic-only ingredients in factories is very limited, due to the fact that many factory processes are automated. Where any chemical exposures may occur, workers are primarily protected with a combination of containment measures and local extract ventilation. The use of suitable personal protective equipment may also be employed, aligned to any identified risks. We do not believe therefore that additional use of animals for testing these chemicals would do anything to further assure the safety of people working with them.56

Cronin et al.57 wrote recently that scientific consensus is emerging on how to use NAMs for chemical safety assessment, combining data on biological activity and kinetics comparing the outputs with estimates of human exposure. They stated that the “task which faces us is to adapt this consensus approach for different regulatory frameworks in which chemical safety is assessed”, noting the essential need to include improved approaches to using exposure...
information in REACH beyond the current use of annual production tonnage information.\textsuperscript{57}

The need for an evolution of the regulatory framework is reflected in the Transformational Programme number 4 of the European Centre for Ecotoxicology & Toxicology of Chemicals (ECETOC): “ECETOC believes that much of the technology which is required to provide a 21st century regulatory system for chemicals (including pesticides and biocides) already exists, but that it requires a new framework.”\textsuperscript{58} In 2019, the OECD published principles and key elements for establishing weight-of-evidence for chemicals assessment,\textsuperscript{59} and the EPAA provides an ideal forum to apply these,\textsuperscript{35} bringing together expertise in NAMs from across the European Commission and the EU industry sectors to lead the creative thinking needed to introduce more modern safety science into a re-shaped EU chemicals regulatory framework.\textsuperscript{10,57}

**Concluding comments**

We are at a tipping point – a paradigm shift in how we assess chemical safety in the EU is essential, and the European Commission must quickly embrace the benefits of modern and innovative safety science in place of outdated animal tests, if it wants the EU to be a leader in safe and sustainable innovation under the European Green Deal.\textsuperscript{58,39}

Twenty years ago we were having similar discussions to those of the last 12 months, about the necessity and relevance of a huge amount of new animal testing of chemicals for decisions on their safety for workers and our environment. These were stimulated by the EU Commission’s 2001 White Paper on the strategy for a future chemicals policy.\textsuperscript{5} In the first decade of REACH, the annual average animal use was 275,000.\textsuperscript{60} From ECHA’s 2020 report,\textsuperscript{61} the total number of animals used in testing for REACH appears to have doubled since the previous report in 2016, from 1,119,283 animals to 2,395,056 in 2019. This number is likely to continue to increase with the new testing proposals\textsuperscript{27} and requests for new animal testing from compliance checks, and with new requirements under CSS.\textsuperscript{39}

Since REACH was implemented in June 2007,\textsuperscript{4} there have been huge advances in science and technology, and considerable progress has been made in leveraging these advances to develop NAMs and apply non-animal NGRA approaches for protecting people and our environment from chemical exposures.\textsuperscript{6,10,11,47,48,50,54,57} Therefore, our response as safety scientists to the publication of the EU CSS needs to be very different and more influential than it was in 2001–2007. There is a commitment within REACH to use non-animal approaches which can provide “the same level of information as current animal tests”.\textsuperscript{4} However, it is quite possible that similar (or better) protection of human health could be provided by using modern science and understanding of human biology from NAMs, without necessarily predicting the apical toxicity effects seen in high-dose animal studies. This principle has been core to the evolution in approach to using NAMs in the USA,\textsuperscript{19,46,53} yet has not been given sufficient consideration in the discussion on updating chemicals legislation in the EU.\textsuperscript{44,45}

In a recent article, Gary Marchant\textsuperscript{62} explained how it is law, not science, that is holding us back and impeding the shift to using modern non-animal safety science. He identified three hurdles faced by the US regulatory agencies regarding the replacement of animal tests with NAMs: (i) gaining confidence in the ability of the new methods to accurately predict human safety (work ongoing\textsuperscript{10,50,51}); (ii) the willingness of agency administrators to base regulatory decisions on these new methods\textsuperscript{54}; and (iii) overcoming legal barriers to the use of NAMs (this is the most challenging hurdle, since outdated legal requirements impede new scientific developments). Over decades of mandating animal testing, government agencies have embedded these requirements into their regulations, which have the force of law. Unless these existing regulations are updated, regulators cannot request non-animal methods for product safety, and manufacturers will not have confidence that their non-animal approaches will stand up to regulatory or judicial scrutiny. Marchant\textsuperscript{62} states that agencies such as the US EPA should “act with anticipation now to start revising their own regulations to eliminate the mandatory use of animal tests in safety testing”. This is equally applicable to the European Commission – and the new CSS provides the context and opportunity to start doing so.

It is clear that EU citizens, like many others across the world, want safe and sustainable chemicals without more animal testing. We need to be bold enough to use this mandate, and the associated political support from those listening to the views of the people they represent, to drive a paradigm shift in how we assess chemical safety to meet regulatory requirements. So, this time, taking our learnings from the past 20 years, under the CSS REACH and CLP revisions we should:

- do our utmost to uphold the EU’s commitment to, and legal requirement for, ‘animal testing as a last resort’;\textsuperscript{4,33}
- change the mindset of regulatory compliance being sufficient justification for animal testing, and continue to constructively challenge the scientific basis of ECHA’s requests for new animal testing on existing ingredients, used safely for many years, that could translate into millions more animals being sacrificed.
- be creative in using NAMs and re-purposing existing data to meet information needs, ensuring return on the huge investment made by governments, companies, animal protection organisations and others in developing non-animal approaches over the past 40 years.\textsuperscript{11,57}
— be consistent and more transparent in the assessment approaches used to ensure safety across foods, household products, cosmetics and the chemicals used in those products.
— not allow good science and our new methods to be held back by laws and regulations;62 the scientific community should advocate more strongly for modernising legal and regulatory requirements, thereby facilitating broader acceptance and use of the best scientific evidence and approaches available to protect human health and our environment.
— let go of the idea that NAMs will give the same results as apical endpoints in animal studies, and evolve the regulatory frameworks for chemicals safety to accommodate weight-of-evidence assessments.53,57,59

To close the regulatory testing – modern safety science gap for chemicals safety assessment, there is an urgent need for knowledge transfer to help build up the technical expertise needed by those involved in chemicals regulation across the EU. This could be achieved, for example, through investing in ECHA and strengthening the collaboration between ECHA officials and the EC Joint Research Centre’s scientific experts.11,63

Increasing the number of commercial service providers or contract research laboratories skilled in NAMs, that can generate and help interpret NAMs data, would facilitate their uptake and remove one of the key obstacles – namely, that toxicologists already know where to go to have animal studies conducted, but few would perhaps know where to go for the high-throughput transcriptomics assays, and kinetic and exposure modelling, that are key elements of our new non-animal safety assessment toolbox.6,9,19,23,50

A commitment by the European Commission to follow the lead from the US authorities in investing in effective knowledge transfer between the safety science and regulatory communities toward the development of ‘next generation’ non-animal safety science capacity, and in fully leveraging the new and evolving toolbox we currently have at our disposal, is now essential. This would facilitate the significant modernisation of chemicals safety policy and future chemicals regulations envisaged under the European Green Deal and CSS, ensuring they are firmly rooted in scientific advancement and application of the best methods available to protect people and our planet. In this way, the changes introduced to REACH and CLP in the coming years could act as a key enabler for sustainable innovation, whilst also meeting the demands of EU citizens for safe and sustainable products and ingredients without resorting to animal testing.

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