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ARTICLE

Towards Non-Animal Testing in European Regulatory Toxicology: An Introduction to the REACH Framework and Challenges in Implementing the 3Rs

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Abstract

The European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation aims to ensure high levels of human health and environmental protection, while also promoting alternatives to animal testing. REACH permits animal testing as a last resort only and imposes the 3Rs principle (Replacement, Reduction, and Refinement of animal testing). Nevertheless, the current regulatory practices still heavily rely on animal-based methods. This study underscores the scientific limitations of animal models and highlights the ethical and methodological burdens associated with their use. It synthesises the challenges and opportunities associated with integrating New Approach Methodologies (NAMs) into regulatory toxicity testing under REACH, as highlighted by various scientific experts. Key challenges identified include contradictory and inadequate legislative frameworks, slow and restrictive validation processes, low acceptance of NAMs by regulatory authorities, and legislative amendments expected to increase animal testing. To create a more flexible regulatory environment and advance the adoption of NAMs, there is a need for legislative reforms and increased collaboration between academia, industry and regulatory bodies. In this context, it is also necessary that more legal scholars begin to show interest in this field to help tackle the multidisciplinary challenges to non-animal testing for regulatory purposes. This article provides an introduction to the field of regulatory toxicology with a focus on the REACH framework from a legal perspective.

Keywords: 3Rs; last resort requirement; new approach methodologies; REACH; regulatory toxicology

I. Introduction

1. Moving away from animal-based toxicity testing

Currently, around 100,000 substances[1] are produced globally in volumes of up to 400 million tonnes, making the chemicals industry one of the largest industries in the world.[2] Global chemicals production and use are expected to double by 2030 compared to 2017.[3]

[1] Substances will be used as a synonym for chemicals in this paper (see definition of "substances" according to Art. 2 REACH).

[2] Bundesamt für Gesundheit BAG, Bundesamt für Lebensmittelsicherheit und Veterinärwesen BLV, Bundesamt für Umwelt BAFU, Bundesamt für Landwirtschaft BLW Staatssekretariat für Wirtschaft SECO, Strategie Chemikaliensicherheit für den departementsübergreifenden Vollzug des Chemikalienrechts 2023 – 2027 (Version 29.06.2023) p 4.

[3] Cf United Nations Environmental Programme, "Global Chemicals Outlook II, From Legacies to Innovative Solutions: Implementing the 2030 Agenda for Sustainable Development" (2019) (UN Report 2019) p 24.

Chemical substances exist in various forms, such as basic chemicals (eg, petrochemicals), speciality chemicals derived from basic chemicals (eg, plastics, electronic chemicals, catalysts, adhesives etc.) or as components in products like medicines, pesticides, biocides, fertilisers and household products (eg, detergents, soaps, dyes).[4]

Chemicals can be detrimental to human health (eg, negative impact on the reproductive system, carcinogenic or endocrine disrupting properties), and the environment (eg, contamination of soil and water, resulting in reproductive, immunological, and neurological damage or death to wildlife, biodiversity loss and ozone layer damage).[5] Therefore, the production, use and marketing of chemical substances and consumer products are subject to quality standards[6] and safety requirements[7] outlined by various national and international laws, regulations, and guidelines. These regulatory requirements typically involve conducting experimental studies using animals,[8] non-animal methods, or a combination of both. Animal experiments remain integral to safety testing, contributing significantly to the ongoing prevalence of animal testing in Europe: According to current statistics, out of nearly 8 million animals used for scientific purposes[9] in the European Union and Norway in 2020,[10] approximately 1.4 million were used for regulatory purposes.[11]

This situation contrasts with the clear intent of the European Parliament to transition away from animal testing[12] and with the 3Rs principle of Replacement, Reduction and Refinement[13] enshrined in the European legislation on animals used for scientific purposes.[14] This also applies to testing for regulatory purposes.[15] However, there is a persistent reliance on animal testing in the current regulatory testing systems, largely reflecting how (industrialised) societies aim to minimise potential risks to human health

[4] Cf OECD, Environmental Outlook to 2050 (2012) p 304 <https://doi.org/10.1787/9789264122246-en>.

[5] Ibid, pp 145 ff.

[6] For example, batch potency, purity, stability or efficacy of substances.

[7] For example, toxicity testing.

[8] Cf European Commission, "Summary Report on the Statistics on the Use of Animals for Scientific Purposes in the EU and Norway in 2020" (Commission staff working document) SWD (2023) final pp 41 ff; Bundesamt für Lebensmittelsicherheit und Veterinärwesen BLV, "Sicherheitsprüfungen 4.01" (Juli 2011) <https://www.blv.admin.ch/dam/blv/de/dokumente/tiere/tierversuche/toxizitaetsrichtlinie.pdf.download.pdf/fachinformation-4-01-sicherheitsheitspruefung-stoffe-erzeugnisse.pdf> accessed 29 January 2024.

[9] Around 12 million additional animals are bred, killed and never used in animal experiments in the EU, including the UK (Report from the Commission to the European Parliament and the Council on the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes in the Member States of the European Union (SWD(2020)0015) p 7 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0015&from=EN> accessed 12 February 2024.

[10] The most recent statistics available from the European Union and Norway for 2020 exclude figures from the UK (see European Commission (supra, n 9) p 3). In the same year, 3.3 million animals were used in research and testing in the UK (Cf Statista, "Annual Number of Animals Used in Research and Testing in Selected Countries Worldwide as of 2020" (2024) <https://www.statista.com/statistics/639954/animals-used-in-research-experiments-worldwide/> accessed 12 February 2024).

[11] Alures, "Animal Use Reporting System Section 2" <https://webgate.ec.europa.eu/envdataportal/content/alures/section2_number-of-uses.html> accessed 30 January 2024.

[12] Cf recital 10 of the Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes [2010] OJ L276/33 (Directive 2010/63/EU), which refers to the *final goal* of full replacement of procedures on live animals for scientific and educational purposes, and the European Parliament resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education.

[13] Cf Swiss 3R Competence Centre (3RCC), "The 3Rs Principle" <https://swiss3rcc.org/description-on-the-3rs> accessed 12 July 2024.

[14] Art. 4 of Directive 2010/63/EU.

[15] Cf recital 42 of Directive 2010/63/EU, according to which "it is necessary to introduce specific measures in order to increase the use of alternative approaches and to eliminate unnecessary duplication of regulatory testing".

and the environment by adhering to the well-established practice of animal testing. This results in risk-averse legislation and application of the law, particularly concerning non-animal methods and new technologies.[16] Animal models became the established standard for regulatory safety testing following significant health crises in the twentieth century, such as the sulfanilamide elixir poisonings in the 1930s, the discovery of thalidomide causing widespread birth defects in the 1960s, and the health risks associated with diethylstilbestrol use until 1971.[17] In response, governments around the world enacted laws mandating comprehensive animal testing before new substances could be marketed.[18]

Scientists argue that today's regulatory systems represent an emotional rather than scientifically grounded response to past health crises.[19] These systems are founded on the belief that substantial advancements in medical knowledge throughout the twentieth century were made possible primarily through the use of animal models.[20] Consequently, there is a prevailing view that ensuring public safety requires extensive animal testing of substances.[21] Decades-old testing procedures to evaluate substance toxicity were standardised and incorporated into international guidelines to facilitate production and international trade. As a result, animal models became the gold standard, without ever undergoing comprehensive quality control or validation,[22] making it very difficult to move away from animal testing and integrate new scientific advancements in toxicity testing.[23]

The continued adherence to an unsustainable animal-based testing paradigm despite the availability of scientifically sound and potentially better non-animal test methods is increasingly criticised in the scientific community.[24] Not only does this practice contradict the requirements and objectives formulated by legislators, but it also ignores the issue of poor repeatability[25] and translatability[26] of animal test data: Often, toxicity testing outcomes cannot be reproduced between animal species or sexes, or compared to control animals used in previous toxicity testing for the same substance.[27] An analysis of animal testing to predict the toxicity of pharmaceuticals in humans, involving 2,366 different drugs, concluded that the predictive value of animal tests in terms of determining whether

[16] Cf M-J WA Schiffelers and others, "Regulatory Acceptance and Use of 3R Models: A Multilevel Perspective" (2012) 29(3) ALTEX 287, p 298.

[17] Cf D Swaters and others, "A History of Regulatory Animal Testing: What Can We Learn?" (2022) 50(5) ATLA 322, pp 324ff; MF Paine, "Therapeutic Disasters That Hastened Safety Testing of New Drugs" (2017) 101(4) Clinical Pharmacology & Therapeutics 430.

[18] Cf Swaters and others (ibid) p 325.

[19] Ibid, p 324.

[20] Cf M-J Schiffelers, *Animal Testing, 3R Models and Regulatory Acceptance – Technology Transition in a Risk-aversive Context* (Utrecht University 2016) p 25.

[21] Cf Swaters and others (supra, n 17) p 322.

[22] Cf T Hartung, ECVAM, "Food for Thought . . . on Validation" (2007) 24(2) ALTEX 67, p 68.

[23] Cf T Hartung, "Toxicology for the Twenty-First Century" (2009) 460(9) Nature 208, p 323 f; Schiffelers (supra, n 20) p 90.

[24] Cf GM Hilton and others, "A New Paradigm for Regulatory Sciences" (2023) 145(105524) Regulatory Toxicology and Pharmacology 3; I Fischer, C Milton, H Wallace, "Toxicity Testing Is Evolving!" (2020) 9(2) Toxicology Research 67.

[25] Cf S Schmeisser and others, "New Approach Methodologies in Human Regulatory Toxicology – Not if, But How and When!" (2023) 178 Environment International p 2f; T Hartung and AM Tsatsakis, "The State of the Scientific Revolution in Toxicology" (2021) 38(8) ALTEX 379, p 380.

[26] Cf R Ram, "Extrapolation of Animal Research Data to Humans: An Analysis of the Evidence" in K Herrmann and K Jayne (eds), *Animal Experimentation: Working Towards a Paradigm Change* (Human Animal Studies, Volume 22, Brill, Leiden 2019), p 356 ff.; C Leenaars and others, "Animal to Human Translation: A Systematic Scoping Review of Reported Concordance Rates" (2019) 17(223) Journal of Translational Medicine; P Pound and M Ritskes-Hoitinga, "Is It Possible to Overcome Issues of External Validity in Preclinical Animal Research? Why Most Animal Models Are Bound to Fail" (2018) 16(304) Journal of Translational Medicine.

[27] Cf GA Van Norman, "Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach?" (2019) 4(7) JACC: Basic to Translational Science 845, p 846.

a substance will be toxic in humans was "barely greater than that which would result merely by chance."[28] The referenced study noted that "the fact that a compound shows no toxic effects in animals provides essentially no insight into whether the compound will also show no toxic effects in humans'.[29] In a subsequent study, the same authors found that even preclinical tests in monkeys failed to predict toxicity in humans reliably and concluded that the data "suggest strongly that a lack of toxicity in any species cannot be reliably used to imply a probable lack of toxicity in any other species."[30] Toxicologist Thomas Hartung poignantly sums up the issues with translatability between species due to the differences in physiology, life span, and exposure to environmental factors: "We are not 70kg rats."[31]

Consequently, animal testing cannot reliably predict whether a substance will be harmful to humans. In fact, some substances that have been proven safe for animals have resulted in toxic outcomes and sometimes death for humans.[32] At the same time, it is assumed that many substances that had toxic effects in animals and were therefore discontinued before reaching the clinical testing phase in humans would have been effective and beneficial for humans.[33] It has been suggested in the literature that certain widely used drugs, such as paracetamol, aspirin and penicillin, known to be toxic or lethal to various animal species, would not have been developed and made available for human use if they had undergone animal testing.[34] The process of extrapolating results from animals to humans is also highly influenced by policy considerations and it can have varying outcomes depending on the practice of the responsible agency and specific legislative requirements (eg, requirement to balance risk against benefit or to factor in economic considerations), which can lead to diverse safety assessments.[35]

Despite these demonstrable problems with animal-based toxicity testing, the most important legislation for assessing and managing chemicals in Europe,[36] the Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH),[37] along with the Regulation on Classification, Labelling and Packaging of Substances and Mixtures (CLP Regulation),[38] is largely based on an animal testing paradigm. REACH, in

[28] J Bailey and others, "An Analysis of the Use of Animal Models in Predicting Human Toxicology and Drug Safety" (2014) 42(3) ATLA 181, p 187.

[29] Ibid.

[30] J Bailey and others, "Predicting Human Drug Toxicity and Safety via Animal Tests: Can Any One Species Predict Drug Toxicity in Any Other, and Do Monkeys Help?" (2015) 43(6) ATLA 393, p 400.

[31] Hartung, "Toxicology for the Twenty-First Century" (supra, n 23) p 208.

[32] Cf HZ Attarwala and H Attarwala, "TGN1412: From Discovery to Disaster" (2010) 2(3) Journal of Young Pharmacists 332; M Eddleston, AF Cohen and DJ Webb, "Implications of the BIA-102474-101 Study for Review of First-into-Human Clinical Trials" (2016) 81(4) British Journal of Clinical Pharmacology 582.

[33] Cf Van Norman (supra, n 27) p 847.

[34] Ibid 847; Swaters and others (n 17) p 323; T Koppanyi, MA Avery, "Species Differences and the Clinical Trial of New Drugs: A Review" (1966) 7(2) Clinical Pharmacology and Therapeutics 250, p 251.

[35] Cf MA Kamrin, "Toxicology and Regulation" in P Wexler (ed), *Encyclopedia of Toxicology* (fourth edition, Cambridge, MA, Academic Press, 2024) 455, p 456.

[36] European Commission, "Inception Impact Assessment, Revision of EU Legislation on Registration, Evaluation, Authorisation and Restriction of Chemicals" <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12959-Chemicals-legislation-revision-of-REACH-Regulation-to-help-achieve-a-toxic-free-environment_en> 1, accessed 12 July 2024.

[37] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC [2006] OJ L396/1.

[38] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 [2008] OJ L353/1.

force since 2007, aims to ensure a high level of protection for human health and the environment from risks posed by chemicals, and to promote the use of alternative methods for assessing substance hazards to reduce animal testing. REACH applies to all chemical substances, from those in our daily lives to industrial chemicals, requiring companies to gather information on the properties and uses of substances they manufacture or import in quantities of one tonne or more per year and to assess and manage associated risks. For this purpose, REACH contains standard information requirements, which are largely based on standard (animal) tests to assess substances in terms of specific human health and environmental effects.[39,40]

While REACH is not the sole EU legislation regulating chemicals,[41] there appears to be more stagnation within the REACH framework in terms of transitioning away from animal testing and adopting advanced non-animal safety assessment methods compared to other chemical safety legislations, such as those governing food safety or cosmetics.[42]

Because of the thousands of chemicals on the market with either lacking or incomplete toxicity data, toxicology experts see a particular challenge in applying a traditional animal-centric approach to meet REACH requirements. They worry that applying this approach to the existing chemicals and those expected to enter the market in the future will take too much time and resources.[43] In addition, six of the most common animal tests provided for in the OECD guidelines for chemical safety assessments have been shown to produce different outcomes in repeat experiments.[44] Numerous analyses of traditional animal models used to assess systemic toxicity[45] have indicated that animal testing in this area is largely unreliable.[46] There is also growing concern about the suitability of animal testing for assessing the safety of new substances, such as nanomaterials,[47] the potentially harmful effects of combined exposure to multiple substances (mixture risk assessment, MRA),[48] and providing solutions to emerging health questions, eg, the effect of chemicals on neurodevelopment.[49]

For these reasons, scientists are increasingly calling for a new system based on so-called New Approach Methodologies (NAMs) that allow for more human-relevant assessments of the adverse effects of chemicals on human health and the environment, using fewer or no

[39] ECHA, "Understanding REACH" <https://echa.europa.eu/regulations/reach/understanding-reach> accessed 12 July 2024.

[40] For a brief history of REACH, see AM Warhurst, "REACH, A New Approach to Chemicals Regulation in Europe: A Brief History, Key Features, and Expected Outcomes" (2005) 3 EurUP 164.

[41] REACH is among 40 different legislative instruments addressing chemical safety, including the safety of pharmaceuticals, biocides, plant protection products, food, toys etc. (European Commission, 'Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on a Chemicals Strategy for Sustainability Towards a Toxic-Free Environment (Chemicals Strategy for Sustainability)' COM (2020) 667 final p 3).

[42] Cf J Fentem and others, "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" (2021) 49(4) ATLA 122, p 126.

[43] Cf Schmeisser and others (supra, n 25) p 2 f.

[44] T Leuchtefeld and others, "Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR): Outperforming Animal Test Reproducibility" (2018) 165(1) Toxicological Sciences 198, pp 203–204 and 207.

[45] Systemic toxicity includes repeated-dose toxicity (RDT), carcinogenicity, and developmental and reproductive toxicity (DART).

[46] Cf L Smirnova and others, "3S – Sytematic, Systemic, and Systems Biology and Toxicology" (2018) 35(2) ALTEX 139, pp 142 ff.

[47] Cf Hartung and Tsatsakis (supra, n 25) p 382.

[48] Cf Schmeisser and others (supra, n 25) p 3.

[49] D Lupu and others, "The ENDpoiNTs Project: Novel Testing Strategies for Endocrine Disruptors linked to Developmental Neurotoxicity" (2020) 21(11) 3978, pp 6–7.

animals.[50,51] Despite this, REACH remains highly rigid and unadapted to new (non-animal) methodologies, with regulatory authorities still reluctant to accept safety assessments that have not been conducted using animals,[52] maintaining animal testing as the gold standard. Non-animal test methods are still measured against this standard,[53] thereby limiting the potential for the development and validation of new human-relevant non-animal models and methods.[54]

Keeping this situation in mind, the present study provides an overview of the regulation of chemical safety within the scope of REACH as an important example of the challenges to implementing the 3Rs in regulatory safety testing, shedding light on the REACH-specific challenges to the increased implementation of NAMs. The significance of REACH cannot be overstated as it governs chemical safety across Europe. Additionally, because it regulates the import of substances and products from non-EU countries into the EU, it holds crucial importance for countries like Switzerland, which primarily export to the EU and are thus directly affected by EU legislation.[55]

2. *Current situation: numbers on the rise for compliance with REACH despite clear intent to reduce and replace*

The European Commission initially estimated that 2.6 million animals would be needed to comply with REACH after its introduction.[56] However, the number of animals used so far has already doubled,[57] and this figure is expected to keep increasing. For one, this is due to ongoing compliance checks of already registered substances by the European Chemicals Agency (ECHA), which is responsible for overseeing compliance with REACH. Theses checks can result in requests by the Agency to conduct animal testing for registrations deemed non-compliant.[58] Furthermore, it is expected that recent amendments to REACH, as well as the CLP Regulation, will lead to more animal testing: An amendment to Annexes VI to X of REACH,[59] which came into force in 2022, requires several additional animal tests for substances that have either been tested in vitro and the results have come out positive or that are otherwise of a specific concern.[60] It is expected that this amendment will cost

[50] Cf Schmeisser and others (supra, n 25) p 3 ff; Hartung, "Toxicology for the Twenty-First Century" (supra, n 23) pp 211–212; Hartung and Tsatsakis (supra, n 25) pp 382 ff.

[51] For more on NAMs, see below, ch II.3.

[52] Cf Swaters and others (supra, n 17) p 323.

[53] Cf V Gerritsen, *Güterabwägung im Tiervesuchsbewilligungsverfahren* (Schriften zum Tier im Recht, Band 23, Schulthess, Zürich, Basel, Genf 2022) pp 294 f.; Schiffelers (supra, n 20) p 90.

[54] Cf Swaters and others (supra, n 17) p 323.

[55] Cf T Stadler and A Kölliker, "Die neue EU-Chemikalienverordnung REACH: Schweizerische Handlungsoptionen und deren Auswirkungen (2007) Die Volkswirtschaft, p 2 ff.

[56] K van der Jagt and others, "Alternative Approaches Can Reduce the Use of Test Animals under REACH" (EU 21405, European Commission 2004), p 9.

[57] An estimated 4.2 million animals were used in just three test categories for compliance with REACH, which is almost twice as much as the European Commission had originally predicted, namely 2.6 million animals for *all* test categories (J Knight, T Hartung and C Rovida, "4.2 Million and Counting . . . The Animal Toll for REACH Systemic Toxicity Studies" (2023) 40(3) ALTEX 389, p 403).

[58] Cf Art. 41 REACH; ECHA, "Compliance Checks" <https://echa.europa.eu/regulations/reach/evaluation/compliance-checks> accessed 27. November 2024; C Rovida and others, "REACH Out-Numbered! The Future of REACH and Animal Numbers" (2023) 40(3) ALTEX 367, p 369.

[59] Regulation (EU) 2022/477 of 24 March 2022 amending Annexes VI to X to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [2022] OJ L98/38.

[60] Eg, requirement of new animal testing if any in vitro genotoxicity test comes out positive (Section 8.4 of Annexes VII-X of REACH), although the in vitro genotoxicity test has a high rate of false positive results (cf Rovida and others (supra, n 58) p 377).

millions of animal lives for substances that have already been registered.[61] A 2023 amendment to the CLP regulation[62] included several new hazard classes relating to endocrine disruption in humans and the environment, with animal testing being the main method of testing for these endpoints, which is also expected to cost additional animal lives.[63] It also expected that the EU Commission plan to revise REACH as part of its Chemicals Strategy for Sustainability with the aim of tackling information gaps to keep humans and the environment safe from potential hazards will also entail more animal testing if carried out as planned.[64]

At the same time, the purpose of REACH is not just to guarantee a high level of protection for human health and the environment, but also to promote alternative methods for assessing the hazards of substances. Testing on animals[65] to meet the REACH requirements is only permitted as a last resort.[66] These principles and requirements are also in line with the objectives of Directive 2010/63/EU on the protection of animals used for scientific purposes.[67]

The significant disparity between these ambitions and legal goals to move away from animal testing and the actual increase in animal testing is especially pertinent considering that non-animal methods have advanced to the extent that defaulting to animal testing is no longer deemed necessary. A new, more reliable, and efficient regulatory system based on the routine use of non-animal methods is seen as feasible.[68] Hence, the current regulatory system is inadequate, which appears partly due to issues in the formulation and design of the relevant legal bases as well as other factors, warranting further investigation.[69]

The ECHA has faced criticism for showing a significant bias towards animal testing.[70] This perspective is supported by official sources: In 2021, the European Parliament adopted a resolution urging the development of an EU-wide action plan to "accelerate the shift to innovative methods that do not involve animal use in research, regulatory testing, and education."[71] The resolution expresses concern that the number of animals used in

[61] Ibid, p 377 ff; N Foote, "Two Million Animals Stand in Firing Line of EU's New Sustainable Chemical Ambitions" (*Euractiv*, 18 November 2021) <https://www.euractiv.com/section/health-consumers/news/two-million-animals-stand-in-firing-line-of-eus-new-sustainable-chemical-ambitions/> accessed 12 July 2024.

[62] Regulation (EU) 2023/707 of 19 December 2022 amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures [2022] OJ L93/7 (CLP regulation).

[63] Cf Rovida and others (supra, n 58) p 379.

[64] For more on the planned revision of REACH, see text to n 234 ff. in ch III. 4.

[65] "Animals" refers to vertebrate animals. Invertebrates are generally excluded from the scope of animal protection laws. Exceptions exist with regard to invertebrates that have been proven to be sentient and capable of experiencing pain. Art 1(3)b of Directive 2010/63/EU includes cephalopods, and the Swiss animal welfare legislation extends protection to both cephalopods and reptantia (Art 2(1) Animal Welfare Act and Art 1 Animal Welfare Ordinance).

[66] Art 25(1) REACH.

[67] Recital 10, referring to the full replacement of animal testing as the "final goal," and recital 42, deeming it "necessary to introduce specific measures in order to increase the use of alternative approaches and to eliminate unnecessary duplication of regulatory testing."

[68] Cf DS Macmillan and others, "The Last Resort Requirement under REACH: From Principle to Practice" (2024) 147 Regulatory Toxicology and Pharmacology 105557, p 8; Schmeisser and others (supra, n 25); N Ball and others, "A Framework for Chemical Safety Assessment Incorporating New Approach Methodologies within REACH" (2022) 96(3) Archives of Toxicology 743, p 744.

[69] Various technical, political and social obstacles to moving away from animal testing to comply with regulatory requirements in the EU in general were detected and summarized as far back as 2007 (see M-JWA Schiffelers and others, "Factors Stimulating or Obstructing the Implementation of the 3Rs in the Regulatory Process" (2007) 24(4) ALTEX 271).

[70] Cf Macmillan and others (supra, n 68) p 3.

[71] European Parliament resolution (2021/2784(RSP)) of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education (EU Parl resolution 2021).

experiments has not substantially decreased since Directive 2010/63/EU came into effect. It also highlights bureaucratic hurdles in accepting non-animal testing methods, inadequate enforcement of their use, and insufficient funding for their development.[72] Furthermore, it calls on the European Commission to set reduction goals in view of Article 13 of the REACH regulation, which mandates the revision of test methods when non-animal alternatives become available[73] and specifically urges the European Chemicals Agency (ECHA) to formulate a replacement and reduction strategy.[74]

Following a European Citizen's Initiative (ECI) to strengthen the ban on animal testing for cosmetics in January 2023,[75] the European Commission committed to launching a roadmap for phasing out animal testing in chemical safety assessments.[76] So far, there have been two workshops on the roadmap involving EU member states and stakeholders from research, industries, and animal welfare organisations[77] as well as a public consultation.[78] Furthermore, in its strategic plan for 2023–2026, the ECHA included a commitment to "enhance cooperation with the European Commission, other institutional partners, the scientific community and stakeholders to support the development of a roadmap towards full replacement of animal testing".[79] The effectiveness of these measures in reducing animal testing to meet regulatory requirements, specifically for REACH compliance, remains to be seen.

II. The link between natural sciences and law with regard to chemical safety: regulatory toxicology and the implementation of the 3Rs

1. What is regulatory toxicology?

Regulatory toxicology[80] describes the legally mandated collection and use of information on potentially hazardous properties of substances and safe levels of human and environmental exposure to these hazards. This information is used to make decisions about risk and exposure management, hazard communication through classification and labelling, and other regulatory actions, such as imposing restrictions or bans on dangerous substances. The aim is to assess the risks and set management standards to prevent human

[72] EU Parl Resolution 2021, recital A.

[73] Ibid, recital G.

[74] Ibid, recital J.

[75] European Citizens' Initiative, "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing" <https://citizens-initiative.europa.eu/initiatives/details/2021/000006_en> accessed 27. November 2024.

[76] EU Commission, "Communication from the Commission on the European Citizen's Initiative (ECI) "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing" COM (2023) 5041 final.

[77] EU Commission, "Training and Workshops, Roadmap for Phasing Out Animal Testing in Chemical Safety Assessments: Second Workshop" <https://single-market-economy.ec.europa.eu/events/roadmap-phasing-out-animal-testing-chemical-safety-assessments-second-workshop-2024-10-25_en> accessed 27 November 2024.

[78] EU Commission, "Animal Testing in Chemical Safety Assessments – Commission Roadmap to Phase It Out" <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/14281-Animal-testing-in-chemical-safety-assessments-Commission-roadmap-to-phase-it-out_en> accessed 27 November 2024.

[79] ECHA, "ECHA Programming Document 2023–2026" <https://echa.europa.eu/documents/10162/17623970/final_mb_41_2022_echa_pd_2023-2026_en.pdf/dac8bfb4-f7f4-2e4b-7347-76d9d405419a?t=1674827053808> accessed 12 July 2024.

[80] The International Union of Pure and Applied Chemistry defines *toxicology* as the "scientific discipline involving the study of the actual or potential danger presented by the harmful effects of substances on living organisms and ecosystems, of the relationship of such harmful effects to exposure, and of the mechanisms of action, diagnosis, prevention, and treatment of intoxications"; *ecotoxicology* is to be understood as the "study of the toxic effects of chemical and physical agents on all living organisms, especially on populations and communities within defined ecosystems; it includes transfer pathways of these agents and their interactions with the environment" (JH Duffus and others, "Glossary of Terms used in Toxicology, 2nd edition: IUPAC Recommendations 2007" (2007) 79(7) Pure and Applied Chemistry 1153, pp 1210, 1326).

and environmental health hazards from exposure to all kinds of substances, such as industrial chemicals, pharmaceuticals, foods, cosmetics, biocides, plant protection products, etc.[81]

Regulatory toxicology links private industries, the natural sciences, and the law. Regulatory agencies are tasked with managing or carrying out the technical, scientific, and administrative aspects of the relevant regulations.[82] They base their decisions on toxicological evaluations of substances by private industries, scientific institutions, and interdisciplinary committees with toxicological expertise. Both the relevant legislation and the decisions and actions taken by the regulatory agencies are informed by scientific as well as non-scientific criteria. Scientific criteria include everything to do with the physicochemical, toxicological, and ecotoxicological properties of the substances, while non-scientific aspects include considerations regarding costs, compatibility of actions with intersecting laws, liability issues, risk vs. benefits of substances with the potential to harm humans or the environment, public opinion etc.[83]

Due to globalisation, substances are traded across national and international jurisdictions. This necessitates standardisation of chemical safety evaluation and harmonisation of legal requirements to promote international acceptance of national or regional regulatory decisions, and ultimately to guarantee safe exposure to chemicals no matter where they are used. For this purpose, numerous international programs, collaborations, and organisations have been established and many international agreements have been adopted.[84]

Depending on the regulated area and substances in question, different laws can apply and intersect, potentially resulting in repeated testing for the same substance due to varying protection objectives.[85,86] In its 2020 Chemical Strategy for Sustainability, the European Commission vowed to address the inconsistencies and lack of transparency and harmonisation of chemical safety assessments in the current regulatory landscape, explicitly mentioning the goal of avoiding the duplication of work.[87] It is yet to be seen if the corresponding legislative proposals put forward by the European Commission[88] – and recently adopted by the European Council for negotiation with the European Parliament[89] – will help reduce animal testing and avoid repeat testing.

[81] Cf M Schwenk, M Werner and M Younes, "Regulatory Toxicology: Objectives and Tasks Defined by the Working Group of the German Society of Experimental and Clinical Pharmacology and Toxicology" (2002) 126 Toxicology Letters 145, p 146; H Greim, "Aims and Mission of Regulator Toxicology" in F-X Reichl and M Schwenk (eds), *Regulatory Toxicology* (second edition, Cham, Springer 2021) pp 4 ff.; UNECE, "About the GHS" <https://unece.org/about-ghs> accessed 12 July 2024.

[82] See Arts 75 ff. REACH on the establishment, composition, and tasks of the European Chemicals Agency (ECHA).

[83] Cf Schwenk, Werner and Younes (supra, n 81) pp 146 f.

[84] For a comprehensive list of international programs, organisations, and agreements on chemical safety, see A Lampen and KE Appel, "National and International Collaboration in Regulatory Toxicology" in Reichl and Schwenk (supra, n 81) pp 37 ff.

[85] Cf Schwenk, Werner and Younes (supra, n 81) p 151.

[86] For example, the Council Regulation (EC) 1223/2009 on cosmetic products [2009] OJ L342/59 (Cosmetics Regulation) prohibits the testing of substances in cosmetics on animals for end-user protection, while REACH can require animal testing for that very substance to ensure worker safety or environmental health (see text to n 231 ff. in ch III. 5 for more about the regulation of cosmetics and recent case law).

[87] COM (2020) 667 final (supra, n 41) p 15.

[88] The new rules are intended to achieve better coordination among the different regulatory EU agencies, create a common data platform that provides an overview of all studies performed on a substance, and ensure transparency on the studies performed (see European Commission, "Commission Proposes 'One Substance, One Assessment' Chemicals Assessment Reform for Faster, Simplified and Transparent Processes" (2023) <https://ec.europa.eu/commission/presscorner/detail/en/ip_23_6413> accessed 30 July 2024.

[89] European Council, "Chemicals Assessment: Council Adopts Mandate for Forthcoming Negotiations with the European Parliament" (2024) <https://www.consilium.europa.eu/en/press/press-releases/2024/06/14/chemicals-assessment-council-adopts-mandate-for-forthcoming-negotiations-with-the-european-parliament/> accessed 30 July 2024.

Depending on the specific safety needs of the regulatory area, the relevant legislation contains provisions on how to meet these needs.[90] For instance, REACH, the regulation at the centre of this study, mandates the collection of data on the physical, toxicological, and ecotoxicological properties of substances as a basis for hazard and risk assessment to establish how to safely use the substance in question. The necessary information for this purpose is generally acquired by studying existing data and performing tests with animal models, non-animal methods, or a combination of both.[91]

The testing required to assess substance hazards and the risks from exposure to hazards is largely conducted on animals, the core belief being that animal models serve as surrogates for the human organism, allowing an examination of the reactions of the organism to substances or how substances affect specific organs.[92] However, as explained above, this animal testing paradigm is being increasingly called into question for various reasons,[93] one fundamental one being that scientific developments have brought forward a wide array of new methodologies that can replace current animal models or that produce more reliable human-relevant information without even having to mimic the responses of animal test subjects on a method-by-method basis.[94]

In its latest report on global chemicals, the United Nations Environment Programme highlights the 3Rs principle – *replacing*, *reducing*, and *refining* animal testing, first introduced by scientists William Russell and Rex Burch in 1959[95] – as an international priority in the assessment of chemical hazards.[96] It traces the beginning of this prioritisation of the 3Rs in toxicology across countries to a landmark 2007 report by the United States National Academy of Sciences,[97] which provides potential ways forward for more efficient toxicity testing based on modern non-animal methods.

Despite these developments and explicit legal requirements to test with means other than animals wherever possible and to use animals as a last resort only,[98] many scientifically sound and available new approach methodologies (NAMs) face challenges to their implementation. Various reasons have been identified for this impasse, including inflexible legislation and a test method validation system – the process of verifying that methods perform as intended[99] – which has proven inadequate to accommodate new non-animal methods in a timely manner for regulatory approval and acceptance.[100]

2. *Chemical safety assessment as an integral part of regulatory toxicology*

Chemical safety assessments[101] are integral to regulatory toxicology, their purpose being to establish if exposure to a chemical through its use or presence in the environment can

[90] Cf Schwenk, Werner and Younes (supra, n 81) p 147.

[91] Ibid, 147 ff.

[92] Cf Hartung and Tsatsakis (supra, n 25) p 380.

[93] Further reasons include the questionable validity of animal testing and current issues such as political and legislative efforts to move away from animal experimentation. Additionally, a growing number of chemicals require risk assessments for which animal testing is impractical due to cost and time constraints. Traditional toxicity testing, which involves administering high doses of a substance to animals to observe effects, has shown limited predictive capacity for potential risks from long-term exposure to low doses, which is how humans are most commonly exposed to substances (Ibid, 380 ff).

[94] Cf text to n 119 in ch II.3. on the definition of NAMs.

[95] W Russel and R Burch, *The Principles of Humane Experimental Technique* (London, Methuen 1959).

[96] UN Report 2019 (supra, n 3) p 387.

[97] National Research Council, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (Washington, DC, National Academies Press 2007).

[98] For example, Arts 13 and 25 REACH.

[99] Cf Art 47 Directive 2010/63/EU.

[100] See text to n 137 in ch III.3.b for more on test method validation.

[101] Safety assessment is often used interchangeably with risk assessment; however, the terms have slightly different objectives in regulatory toxicology: The safety assessment is focused on preventing harm by setting safe

have adverse effects[102] on human health or other organisms, to determine safe levels of exposure for humans and the environment,[103] and/or to establish risk management measures and operational conditions.[104] To this end, substances are generally assessed according to a multi-stage process consisting of a hazard identification,[105] a dose-response assessment and hazard characterisation,[106] an exposure assessment,[107] and a risk characterisation.[108,109,110]

Note that a hazard stands for the innate properties of a substance and its potential to cause harm, while a risk represents a percentage expressing the likelihood of harm through exposure to the hazard.[111] It is also worth noting that "safe" is not a scientifically defined term. The safety of a substance for human health is still generally determined by extrapolating test results to real life, which depends on a number of extrapolations (ie, from animal to human; from high test dose to low dose; from average to individual human; from short term to long term exposure)[112] and is influenced by policy considerations. This can lead to varying outcomes depending on the assessment practice of the agency responsible and the legislative requirements,[113] resulting in diverse safety assessments even where repeat experiments produce the same results.[114]

Within the scope of the chemical safety assessment, specific studies are performed to identify the hazards of substances depending on the nature and latency[115] of their toxic effects.[116] The most common studies include acute toxicity testing, repeated dose toxicity testing, genotoxicity studies, and reproductive and developmental toxicity tests. Acute toxicity studies, for which there are now a range of internationally accepted non-animal

exposure limits for chemicals. This is done by detecting the levels where no or lowest adverse effects (NOAEL/LOAEL) can be detected to establish safe exposure limits. Risk assessment begins at higher exposure levels and compares these to the dose-response, that is, to the effects of a substance as a function of dose (cf Schwenk, Werner and Younes (supra, n 81) p 148).

[102] For example, acute, chronic, genetic, developmental effects (cf Lampen and Appel (supra, n 84) p 37).

[103] Cf Ball and others (supra, n 68) p 744.

[104] Cf ECHA, "Chemical Safety Report" <https://echa.europa.eu/regulations/reach/registration/information-requirements/chemical-safety-report> accessed 1 July 2024.

[105] Hazard identification consists of identifying the toxic properties, ie, intrinsic potential of a substance to cause harm.

[106] This step consists of evaluating the effects depending on dose to assess the risks from exposure to a substance, which is done by testing varying dose levels to determine safe exposure levels.

[107] During exposure assessment the extent to, regularity, and the way in which humans and other living organisms are exposed to a substance resulting from the intended or actual use during its life cycle are determined (eg, by testing concentrations in the environment or in human urine).

[108] The risk is characterised by relating the outcome of the dose-response assessment to the actual exposure of humans or the environment to the hazard. Exposure scenarios are made and compared to the lowest adverse effect values derived during dose-response assessment to establish if a given exposure will entail health risks. If health risks are to be expected, risk management measures can be applied.

[109] Schwenk, Werner and Younes (supra, n 81) p 148; L Aicher and MF Wilks, "From Risk Assessment to Regulation" in C Colosio and others (ed), *Exposure and Risk Assessment of Pesticide Use in Agriculture: Apporaches, Tools and Advances* (Amsterdam, Academic Press 2020) pp 4 f.; ECHA, "Guidance on Guidance on Information Requirements and Chemical Safety Assessment, Part A: Introduction to the Guidance Document" (2011 Version 1.1) p 3.

[110] For in-depth information on the individual steps in the chemical safety assessment under REACH see the guidance documents Part A-G under ECHA, "Guidance on Information Requirements and Chemical Safety Assessment" <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment> accessed 1 July 2024.

[111] Cf Aicher and Wilks (supra, n 109) p 4.

[112] Schwenk, Werner and Younes (supra, n 81) p 148.

[113] For example, the requirement to balance risk against a benefit or to factor in economic considerations.

[114] Cf MA Kamrin (supra, n 35) p 456.

[115] Latency of effects refers to the period between exposure to a hazard and appearance of effects.

[116] Cf Aicher and Wilks (supra, n 109) p 6.

methods, generally provide information on health hazards from short-term exposure and single-dose tests (eg, acute oral and dermal effects, or eye irritation and corrosion). Testing of a substance can also be performed over a longer period to assess the various risks associated with repeated use. This is called repeated dose toxicity testing, which is done by administering the test substance daily over a specified period. Genotoxicity testing is aimed at acquiring information on the potential of the test substance to interfere with DNA and cause cancer. Reproductive and developmental toxicity tests are performed to establish the effects of a substance on reproductive functions and the health of offspring.[117]

Further studies aimed at addressing specific concerns include developmental neurotoxicity testing and studies on endocrine disruption. The former specifically address neurological effects of repeated exposure of offspring to substances in utero and after birth, while the latter are performed to assess hormonal disruption through exposure to the test substance.[118]

3. *New approach methodologies (NAMs) and the 3Rs in regulatory toxicology*

(a) Definition and purpose

Within the scope of toxicity testing, new approach methodologies (NAMs) are generally understood as alternatives to animal-based testing or other methods, technologies, and approaches that can be used to obtain information about substance hazards and risks without using animals or in combination with animal-based tests.[119,120] NAMs include method-by-method replicas of existing animal tests as well as methods that can deliver human-relevant information without requiring an entire organism.[121] Non-animal strategies can be experimental[122] or non-experimental[123] in nature and can consist of combinations of various non-animal and/or non-testing methods, strategies, and technologies such as integrated testing strategies (ITS) or integrated approaches to testing and assessment (IATA).[124]

NAMs are generally divided into three categories: (1) one-on-one replacement, which describes a non-animal test that entirely replaces an animal test; (2) combining datasets, where a combination of methods and information sources are applied in the absence of a one-on-one replacement (eg, combining in vitro cell cultures with organs-on-a-chip and

[117] Ibid, pp 6 f.

[118] Ibid, p 7.

[119] Cf C Westemoreland, "Use of New Approach Methodologies (NAMs) in Regulatory Decisions for Chemical Safety: Report from an EPAA Deep Dive Workshop" (2022) 135 Regulatory Toxicology and Pharmacology 105261, p 2; Schmeisser and others (supra, n 25) p 4.

[120] There is no officially adopted definition of New Approach Methodologies (NAMs) or comprehensive catalogue of methods and approaches considered as NAMs, which is why the ECHA has stated a need for a taxonomy of methods for NAMs (ECHA, New Approach Methodologies in Regulatory Science, Proceedings of a scientific workshop, Helsinki, 19–20 April 2016, p 47).

[121] Cf Schmeisser and others (supra, n 25) p 3; Ball and others (supra, n 68) p 751.

[122] By testing in vitro.

[123] Such non-testing approaches include grouping and read-across, used to predict the effects of a substance based on information from similar substances; the qualitative structure-activity relationship approach (QSAR), which involves mathematical models to predict biological effects based on chemical structure; and the weight of evidence approach, which integrates multiple sources of information (see Annex XI, Setions 1.2-1.5 REACH; cf J Knight and others, "t4 Report: Continuing Animal Tests on Cosmetic Ingredients for REACH in the EU" (2021) 38(4) ALTEX 653).

[124] The idea behind ITS is that because single non-animal test methods cannot replicate an entire animal organism data must be generated by using various NAMs-based sources to arrive at the necessary information (cf C Rovida and others, "t4 Workshop Report: Integrated Testing Strategies (ITS) for Safety Assessment" (2015) 32(1) ALTEX 25, pp 29 ff.).

computational models); and (3) reformulated research questions, which are not geared towards an animal model but are instead broken down into separate mechanistic steps (eg, through the application of so-called adverse outcome pathways[125]).[126] The various non-animal methods include in vitro methods (eg, using human cell cultures, tissues, organoids etc.), in chemico approaches (ie, chemical reactivity methods), in silico methods (ie, computational tools) and new technologies such as omics.[127,128] Another way to acquire information, not technically a NAM but often used alongside NAMS to replace or reduce animal testing, is to use existing data. This data can originate from animal tests, human data, or NAMs.[129]

The purpose of NAMs is to provide information on substance hazards and exposure in a way that complies with the principle of the 3Rs to replace, reduce, and refine animal testing, and to increase the efficiency of the current chemical safety testing system.[130] Article 13(1) REACH states that, in particular for human toxicity, information must be generated whenever possible by means other than vertebrate animal tests, thereby prioritising replacement. It also constitutes a legal basis for the use of NAMs as a standard for toxicity testing because the technology needed to obtain reliable information to assess the safety of substances is already available, and new methods and strategies are continuously being developed.[131]

Despite this clear legal requirement, NAMs-based information still has a hard time being accepted within the scope of REACH. This has a lot to do with the fact that many NAMs don't fit into the mould of the current animal-based paradigm of chemical safety assessments.[132] This is particularly true for NAMs for complex endpoints such as chronic toxicity, systemic toxicity, reproductive toxicity, and carcinogenicity: Unlike NAMs for less complex endpoints such as skin and eye irritation, they do not result in an apical outcome – ie, in an observable outcome in a whole organism – and thus don't function as one-to-one replacements for animal models.[133] For example, it has been shown that the ECHA often rejects data generated without animal testing, unless NAMS are used that are in international guidelines, and requests the performance of (new) animal tests.[134] However, only a small number of NAMs for simple topical endpoints, such as eye and skin irritation, have been incorporated in the OECD TG and the EU Test Method Regulation so far.[135]

[125] Adverse outcome pathways (AOPs) are defined as "analytical constructs that describe a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect" and are seen as "the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning" (OECD, "Adverse Outcome Pathways" <https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/adverse-outcome-pathways.html> accessed 26 November 2024.

[126] These categories are defined and taught in the EU-52 learning module "Searching for Existing Non-Animal Alternatives" on the European Education and Training Platform for Laboratory Animal Science (ETPLAS), which can be accessed under ETPLAS, "EU-Function Modules" <https://learn.etplas.eu/> accessed 26 November 2024.

[127] For a summary of methods, strategies, and approaches constituting NAMs and reference to sources of information on different NAMs, see, among others, Schmeisser and others (supra, n 25) pp 3 f.

[128] For the sake of simplicity, in the following, the acronym "NAMs" will be used as a general reference to all non-animal forms of obtaining information on intrinsic properties and hazards of substances, unless a test method is explicitly specified, and will not refer to combinations of non-animal and animal-based testing.

[129] Cf Annex XI, Section 1 REACH.

[130] Cf Schmeisser and others (supra, n 25) p 3.

[131] Ibid, pp 3 f.; Fentem and others (supra, n 42) pp 123 f.; Ball and others (supra, n 68) p 744.

[132] Cf Schmeisser and others (supra, n 25) pp 4 f.; A Carusi, "Chemicals Regulation and Non-Animal Methods: Displacing the Gold Standard" (2024) 9(167) Wellcome Open Research 8.

[133] Cf ECHA fifth report on the use of alternatives, p 24; Schmeisser and other (supra, n 25) p 6.

[134] Cf Fentem and others (supra, n 42) p 124; Macmillan and others (supra, n 68) pp 3 ff.

[135] Cf Fentem and others (supra, n 42) p 123.

According to Article 13(3) REACH, where testing is required to comply with the requirements of REACH, it must be conducted according to the test methods laid down in a Commission Regulation, ie, the EU Test Method Regulation,[136] or in accordance with other international test methods recognised by the Commission or the ECHA.

This raises the following questions: How do NAMs end up in international guidelines and why haven't more NAMS been accepted in these guidelines?

(b) Validation of NAMs for regulatory acceptance

The validation of a non-animal test method according to internationally accepted principles and protocols generally facilitates the inclusion of a test method or approach in international test guidelines and regulations such as the OECD Guidelines for the Testing of Chemicals (OECD TG)[137] or the EU Test Method Regulation.[138,139] Validation is a condition for the inclusion of NAMs in the OECD system of Mutual Acceptance of Data in the Assessment of Chemicals (MAD system), which is aimed at harmonising the multitude of national and regional regulatory requirements to promote acceptance of data across countries, and thus avoid duplication of chemical risk assessments.[140]

Validation is generally understood as a process in which a test method[141] is independently and transparently evaluated as to whether it is fit for purpose, in other words, if the test results are reliable – ie, reproducible in different laboratories according to a standardised protocol – and if the test method is relevant – ie, capable of measuring or predicting the sought-after biological effects.[142] A common feature of the different existing

[136] Commission Regulation 440/2008/EC of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [2008] OJ L142/1 (Test Method Regulation).

[137] The OECD TG are internationally recognised as standard methods for chemical safety testing (see OECD, OECD Test Guidelines for Chemicals <https://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm> accessed 20 May 2024). Before the establishment of international guidelines on test method validation, the approaches to the validation process and the individual requirements commonly varied across national or regional organisations and even between regulatory agencies within the same country, resulting in diverging validation outcomes or repeated validation procedures for a given test method. To bring about international standardisation of validation approaches and procedures, the OECD, in cooperation with numerous international organisations, renowned validation bodies, and individual validation experts, set out to establish a globally harmonised framework for the validation and regulatory acceptance of test methods. This resulted in the drafting of internationally recognised validation principles ("Solna Principles") in 1996 and the subsequent development of the OECD Guidance Document on the Validation and International Acceptance of New Test Methods for Hazard Assessment (Guidance Document 34), with multiple revisions to the original draft taking into account expert opinions and ideas from OECD member countries and its ensuing publication in 2005 (cf Leonard M. Schechtman, "Internationally Harmonized Processes for Test Method Evaluation, Validation and Regulatory Acceptance: The Role of OECD Guidance Document 34" (2007) 14(Special Issue) ALTEX 475, pp 475 ff).

[138] Most of the test methods laid down in the Test Method Regulation are based on the OECD TG.

[139] Cf ECHA Report, "Non-Animal Approaches: Current Status of Regulatory Applicability under the REACH, CLP and Biocidal Products Regulations" (2017) pp 46 f.

[140] OECD, Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals of 1981 (2024) OECD/LEGAL/0194. See also OECD, "OECD Test Guidelines for Chemicals" <https://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm> accessed 24 May 2024, and OECD, "OECD Series on Principles of Good Laboratory Practices and Compliance Monitoring 1: OECD Principles of Good Laboratory Practice" (1988, ENV/MC/CHEM(98)17).

[141] A test method is an "experimental system that can be used to obtain a range of information from chemical properties through the adverse effects of a substance" (OECD, "Series on Testing and Assessment, 34: Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment" (2005) (Guidance Document 34) 17.

[142] Cf Guidance Document 34, pp 13 and 17; T Hartung, "Food for Thought . . . on Validation" (2007) 24(2) ALTEX 67; C Griesinger and others, "Validation of Alternative in Vitro Methods to Animal Testing: Concepts, Challenges,

approaches to validation is a multi-step process that takes place after the development or update of a test method: first, a laboratory that is independent from the test developer assesses the test method in terms of its transferability, reproducibility, and relevance (prevalidation), and either proposes further optimisation of the test or, if the test method performance proves to be acceptable, refers it to full inter-laboratory reliability and relevance assessment (validation via ring-trial study).[143] The validation process as set out in the OECD Guidance Document 34 is based on the validation principles of internationally accepted validation bodies, such as the EU Reference Laboratory for alternatives to animal testing (EURL ECVAM)[144] and the US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM),[145] among others.[146]

Even though this formal validation process has strongly contributed to the global harmonisation of test method acceptance,[147] it has proven to be a barrier to the timely validation of NAMs: The validation and uptake of NAMs in international test guidelines can take up to 20 years from the development of a NAM and has thus shown a strong need for a paradigm change in validation concepts.[148] The focus on single-method validation has been inadequate for assessing the validity of NAMs, particularly for complex endpoints such as reproductive toxicity, as it does not allow for new and more flexible concepts of validating NAMs with a performance-based approach.[149,150]

In that sense, during the most recent meeting of the International Cooperation on Alternative Test Methods (ICATM)[151] in 2023, representatives of the member validation organisations concluded that the OECD Guidance Document 34 is no longer suitable to accommodate current scientific developments, and is in need of revision. In particular, concern was expressed about the adequacy of multi-laboratory ring trials in assessing the

Processes and Tools" in C Eskes and M Whelan (eds), *Validation of Alternative Methods for Toxicity Testing* (Advances in Experimental Medicine and Biology, vol 856, Cham, Springer 2016) p 65.

[143] Cf Guidance Document 34, p 27ff; Schechtman (supra, n 137) p 477.

[144] The mandate and duties of the EURL ECVAM are outlined in Article 48 and Annex VII of Directive 2010/63/EU and include, among other things, coordinating and participating in the validation of alternative approaches at Union level as well as promoting dialogue between legislators, regulators, and all relevant stakeholders (industry, scientists, animal welfare groups, etc) with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches. For information on the EURL ECVAM validation process, see European Commission, EU Reference Laboratory for alternatives to animal testing (EURL ECVAM), "Validation and Submission Process" <https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/alternative-methods-toxicity-testing/validation-and-submission-process_en> accessed 28 May 2024.

[145] National Toxicology Program, "About ICCVAM" <https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam> accessed 10 Juni 2024.

[146] Cf Schechtman (supra, n 137) p 478.

[147] Ibid, p 480.

[148] Cf Schmeisser and others (supra, n 25) p 10; T Burgdorf and others, "Workshop on the Validation and Regulatory Acceptance of Innovative 3R Approaches in Regulatory Toxicology – Evolution versus Revolution" (2019) 59 Toxicology in Vitro, pp 5 ff., with various suggestions for new validation paradigms.

[149] For example, so-called mechanistic validations specifically tailored to the data generated by NAMs on a molecular or cellular level as opposed to the whole-organism endpoints typical for animal tests (cf T Hartung, S Hoffman and M Stephen, "Food for Thought . . . Mechanistic Validation" (2013) 30(2) ALTEX 119, 124 ff).

[150] Cf Ball and others (supra, n 68) pp 744 and 752 with further references to current discussions relating to new validation strategies.

[151] In 2009, various national and international validation organisations established the Cooperation on Alternative Test Methods (ICATM) to facilitate collaboration in the development, validation, and regulatory use of non-animal test methods across countries and thus avoid duplication of validation studies and support swifter international adoption of non-animal approaches, among other goals. For a list of member organisations and more information on the ICATM, see European Commission, "International Cooperation on Alternative Test Methods (ICATM)" <https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/alternative-methods-toxicity-testing/advisory-and-consultation-bodies/international-cooperation-alternative-test-methods-icatm_en> accessed 24 May 2024.

transferability and performance of NAMs. Proposals were made to improve the validation procedure, such as a move away from the "gold standard" of the animal model towards human-relevant reference criteria[152] and better coordination of peer reviews to avoid duplicate validation of methods.[153] At the same time, the OECD is currently calling for an "urgent mobilisation of national and regional resources to support the acceleration of new method validation for the safety testing of chemicals."[154]

III. The legal framework for chemical safety in the EU under REACH and the challenges to the implementation of NAMs for compliance with REACH

The acronym REACH stands for **R**egistration, **E**valuation, **A**uthorisation, and **R**estriction of **Ch**emicals. REACH was adopted in 2006 and came into force in 2007 in response to inadequate safety regulations for chemicals in the European Union. Prior to its inception, the regulation of chemicals was deemed inadequate due to its fragmentation, and the view prevailed that there was a general lack of information about the safety of existing substances.[155] Furthermore, the burden of proof to guarantee the safety of chemicals was on the regulators, ie, public authorities were tasked with gathering and evaluating information on substances from chemicals industries.[156] It was therefore decided that a new chemical safety legislation was needed and, in 1999, the European Commission was engaged to draft a document for a new chemicals strategy that would ensure that manufacturing companies and importers of chemicals into the European market would register important data on the substances with a centralized agency so that the data could be used to monitor and restrict substances of very high concern.[157] In 2000, the European Commission published a White Paper with a concrete REACH proposal. Following stakeholder debates and a public consultation process, the European Commission published the final proposal in 2003, which was subsequently debated in the European Parliament,[158] before the Regulation entered into force on 1 June 2007.

Simply put, REACH requires that substances are evaluated for specific human health and environmental effects, which are called endpoints (eg, skin corrosion, reproductive toxicity, short-term toxicity in fish, etc). To obtain information on these endpoints, REACH stipulates, among other things, the generation of information via testing on animals. The

[152] Because information on the toxicological properties of chemicals has been traditionally derived from animal models instead of directly from humans, there are almost no direct human reference points against which an alternative method can be measured. Reference data is still derived from animals that function as surrogates for humans, even though none of the standard animal testing methods have undergone validation themselves (cf Griesinger and others (supra, n 142) p 75).

[153] For more information on the 2023 ICATM meeting, see National Toxicology Program, "International Cooperation on Alternative Test Methods" <https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam/international-partnerships/icatm> accessed 22 May 2024.

[154] OECD, "Testing of Chemicals, Focus" <https://www.oecd.org/chemicalsafety/testing/> and <https://web-archive.oecd.org/2023-01-23/650072-urgent-mobilisation-national-regional-resources-to-support-the-validation-of-new-methods-safety-testing-of-chemicals.pdf> both accessed 15 May 2024.

[155] Although industries were required to report existing substances, the European Commission criticized the insufficient enforcement of the previous Regulation 793/93/EC on the Evaluation and Control of the Risks of Existing Substances (OJ L84/1 1993) (See European Commission Report on the operation of Directive67/548/EEC, Directive 88/379/EEC, Regulation (EEC) 793/93, Directive 76/769/EEC, SEC(1998) 1986 final).

[156] Cf A. M Warhurst, "REACH, a New Approach to Chemicals Regulation in Europe: A Brief History, Key Features, and Expected Outcomes" (2005) 2(3) Journal for European Environmental & Planning Law 164, 166 with reference to further sources of information on the development and inception of REACH.

[157] Cf K Taylor and others, "Food for Thought . . . Experiences of the REACH Testing Proposals System to Reduce Animal Testing" (2014) 31(2) ALTEX 107, p 108.

[158] Warhurst (supra, n 156) pp 166 f.

information requirements depend on how much of a substance is produced or imported annually into the European Economic Area (EEA).[159,160]

In the context of REACH, the Regulation (EC) 1272/2008 on the classification, labelling, and packaging of substances and mixtures (CLP Regulation) plays an important role. The CLP Regulation is based on the United Nations's Globally Harmonised Systems (GHS) and requires manufacturers, importers, and downstream users of substances or mixtures to classify, label, and package their hazardous chemicals appropriately before placing them on the market.[161,162] The CLP Regulation outlines the criteria for the hazard classification of substances.[163] When registering a substance under REACH, one requirement is to provide information regarding the hazard classification of that substance.[164]

1. Aim and scope of REACH: protecting human and environmental health and promoting alternatives to animal testing

The purpose of REACH is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for the assessment of hazards of substances,[165] as well as the free circulation of substances on the internal market of the European Economic Area (EEA), while enhancing competitiveness and innovation (Article 1(1) REACH).

By incorporating the promotion of alternative methods in its purpose Article the Regulation makes clear that the 3Rs are an integral component of REACH. The fact that this is not to be understood as just an empty phrase, is emphasized in Article 13 REACH, which states that all information on intrinsic properties of substances must be generated by other means than testing on vertebrate animals wherever possible (1) and that the methods must be regularly reviewed and improved with a view to reducing testing on vertebrate animals and the number of animals involved (2). Article 25 REACH stipulates that testing on vertebrates for the purpose of the Regulation can only be undertaken as a last resort. Annexes VII to X REACH, which contain the standard information requirements

[159] The EEA consists of the European Union, Iceland, Norway, and Lichtenstein. Switzerland is not part of the EEA and therefore not subject to REACH provisions on Swiss territory. However, Swiss manufacturers of chemicals based in the EEA and manufacturers based in Switzerland that export chemicals to the EEA must comply with REACH requirements (for more information, see Common notification authority for chemicals, "REACH and Switzerland" <https://www.anmeldestelle.admin.ch/chem/en/home/themen/reach-clp-helpdesk/reach-helpdesk/reach-und-die-schweiz.html> accessed 25 June 2024).

[160] Cf Knight, Hartung and Rovida (supra, n 57) p 389.

[161] To this end, all substances placed on the EU market must be assessed to establish if they meet physical, health, environmental and/or additional hazard classification criteria according to the CLP Regulation, regardless of the production or import volumes. Identified hazards of classified substances and information on their proper use and management must be communicated to all users with specified labels such as signal words, pictograms, and standard information about hazards, storage, handling, disposal etc. The CLP Regulation also lays down packaging requirements for classified substances. The Regulation does not require additional testing where information on substances has been gathered according to REACH (Art. 8 CLP), i.e. CLP information requirements are generally based on the testing results according to REACH. However, new testing is permitted if existing data is inadequate for classification and labelling. Because many classification criteria are based on results from animals, new testing for CLP compliance still costs many animal lives (cf Rovida and others (supra, n 58) p 379).

[162] For more information on the CLP Regulation, see ECHA, "Understanding CLP" <https://echa.europa.eu/regulations/clp/understanding-clp> accessed 21 June 2024.

[163] Annex I CLP Regulation.

[164] Article 10(a)(iv) and Annex VI, Section 4 REACH.

[165] Certain substances or activities involving substances fall entirely under other legislation and are therefore fully exempt from the scope and requirements of REACH (eg, radioactive substances, Art 2(1)(a). Other substances are exempt from some of the REACH requirements because, eg, they also fall within the scope of other legislation, such as cosmetic products (Art 2(4)(b)). For more on whether and to what extent cosmetic products are exempt from the scope of REACH, see text to n 249 ff in ch III. 5).

for substances depending on the tonnage levels of production or import, also explicitly state in their introductory sections that all existing data should be consulted first before new tests may be carried out, and in their respective column 2 provide for possible adaptations to the standard information requirements, ie, scenarios in which a specific test listed in column 1 may be omitted.

REACH applies to manufacturers, importers, and downstream users who produce in the EEA, import into the EEA, place on the EEA market, and use substances on their own, in mixtures or articles[166] in the EEA[167] depending on the intended production or import volume[168] and obliges them to do so in a way that does not harm human health and the environment.[169,170]

2. *Basic legal structure of REACH: substance registration, evaluation, authorization, and restriction*

(a) Registration: "No Data, No Market"

Registration is mandatory for the manufacture[171] and placement on the EEA market of a substance on its own, in a mixture, or articles in quantities of one tonne or more per year.[172,173] In other words: Without prior registration, chemicals can neither be produced nor imported (no data, no market). Substance registration is meant to ensure documentation for substances on the market to guarantee their safety for human health and the environment throughout the entire supply chain.[174] To register a substance, the manufacturer or importer into the European Union is required to apply to the European Chemicals Agency (ECHA)[175] by submitting a technical dossier containing specified information.[176,177,178] If the production or import volume surpasses 1 tonne per year,

[166] This means that REACH applies to everyone who trades in any kind of products that contain chemicals, eg, cars, disposable lighters, toys etc. (cf V Heyvaert, "No Data, No Market. The Future of EU Chemicals Control under the Reach Regulation" (2007) 9(3) Environmental Law Review 201, 202).

[167] Art. 1(2) REACH.

[168] Cf Art. 6(1) REACH, which requires registration for substances of one tonne or more per year.

[169] Art. 1(3) REACH.

[170] Art. 3 REACH contains a long list of definitions of terms used in the Regulation, some of which are self-explanatory, such as substance, manufacturer, import, downstream user, placing on the market. Definitions will be provided in this paper only where the terms in question may be ambiguous or are not defined in Art. 3.

[171] The registration obligation explicitly includes the production of substances, which goes a step further than the notification system in place before the introduction of REACH, which only required registration for marketing. This results in a duty to comply with the registration requirements for substances produced in the EU and intended for export (cf V Heyvaert, "No Data, No Market. The Future of EU Chemicals Control under the Reach Regulation" (2007) 9(3) Environmental Law Review 201, p 202).

[172] Arts 5 and 6 REACH.

[173] The annual tonnage level is intended as a surrogate for the substance dose and the number of people exposed to it and suggests that the larger the quantities produced or imported, the larger the exposure (cf Ball and others (supra, n 68) pp 746 f.).

[174] Cf ECHA, "Registration" <https://echa.europa.eu/support/registration> accessed 24 June 2024.

[175] Arts 6 and 7 REACH.

[176] Art. 10 and Annex VI REACH.

[177] The information requirements are for general registration purposes and are mandatory for all substances manufactured or imported in quantities of one tonne or more per year. The technical dossier must include, among other things, general registrant information, information making it possible to identify the substance, information on the intended use and uses advised against, guidance on safe use, hazard classification and labelling according to the CLP Regulation and, for substances produced or imported in quantities of 1–10 tonnes per year, data regarding human and environmental exposure and patterns of exposure to the substance (Sections 1–6 of Annex VI REACH). For substances produced or imported in quantities of 10 tonnes or more per year, Art. 14 REACH requires performing a chemical safety assessment.

[178] Depending on whether the data generated about the substance meets the criteria of the CLP Regulation, the substance may need to be assigned a hazard class and category (Section 4 of Annex VI REACH).

registrants are required to submit additional (eco)toxicological information on the substance and data on its physicochemical properties.[179] With increasing tonnage levels, additional information is required.[180] In addition to the technical dossier, registrants must perform a chemical safety assessment for substances in quantities of 10 tonnes or more per year.[181] To avoid duplication of studies, REACH provides for data-sharing and dispute settlement mechanisms for cases in which previous registrants fail or refuse to provide information on their testing results for the substance in question.[182]

(b) Evaluation: Dossier and substance evaluation

During the evaluation phase, the ECHA performs a mandatory examination of testing proposals for the highest tonnage levels.[183] If an animal test is planned for a substance in the highest tonnage levels (Annexes IX and X REACH), registrants must submit the (animal) testing proposal before carrying it out. The ECHA must publish the proposal on its website and invite public commenting, ie, call on third parties to submit existing scientifically valid information on the substance in question.[184] Based on the information received, the ECHA must then draft a decision and give the registrant 30 days to comment on it.[185] The ECHA – or the Member State authority in cases of substance evaluation (Article 46 REACH) – must then consider the registrant's comments and may amend the draft decision accordingly.[186,187] This mechanism is intended to ensure that existing information is used and to avoid duplicate tests on vertebrate animals. However, evidence suggests that comments made by registrants in support of non-animal approaches are often not considered by the ECHA.[188]

In contrast to its obligation to perform a compliance check for testing proposals for substances in the highest tonnage levels, the ECHA has discretion regarding compliance checks for all other registrations under REACH.[189] If the ECHA establishes insufficient compliance, it may require registrants to submit further information, eg, an (additional)

[179] So-called standard information requirements according to Annexes VII–X REACH.

[180] Art. 12 REACH. The following standard information requirements (SIRs) under REACH apply depending on the tonnage level of the substance produced or imported: Annex VII for 1 to <10 tonnes; Annex VII and VIII for 10 to <100 tonnes; Annexes VII-IX for 100 to <1000 tonnes; Annexes VII-X for 1000 tonnes or more (see Annex VI REACH, Note on Fulfilling the Requirement of Annexes VI to XI).

[181] Art. 14(1) REACH.

[182] Arts 26 and 27 REACH.

[183] Art. 40(1) REACH.

[184] Art. 40(2) REACH.

[185] Art. 40(3) REACH.

[186] Art. 50(1) REACH.

[187] For more on the testing proposal process cf Taylor and others (supra, n 157) pp 109 f.

[188] The ECHA had issued final decisions on 198 out of 681 substances in the registration process with a testing proposal by the end of 2012 and only one testing proposal was rejected following third-party consultation (Taylor and others (supra, n 157) p 113.) According to a follow-up study in 2018, only 10 per cent of third-party comments had resulted in an amendment of the ECHA draft decision or a withdrawal of a test proposal up to that point. The ECHA entirely rejected an animal testing proposal in only six cases. Taylor suspects that the poor success rate of third-party comments also has to do with the very short window of time granted to comment on large amounts of information. Taylor also points to an unjustified shifting of responsibility to registrants and the passive role taken by the ECHA in assessing test proposals. Following a complaint to the Ombudsman by the European Coalition to End Animal Experiments (ECEAE) against the ECHA, which had stated in 2013 that it had a legal basis to reject testing proposals in very limited circumstances, the Ombudsman criticized the ECHA for failing to acknowledge that avoiding animal testing was one of the main principles of REACH (European Ombudsman, Decision in Case 1606/2013/AN (2015)). Subsequently, the ECHA included a requirement for registrants to justify their testing proposal. However, this still placed the responsibility to avoid animal testing almost entirely on registrants (K Taylor, "Ten Years of REACH – An Animal Protection Perspective" (2018) 46(6) ATLA 347, pp 359 f.)

[189] Art. 41(1) REACH. As of 2023, the ECHA has fully checked 21 per cent of all submitted registration dossiers (ECHA, "Progress in evaluation" <https://echa.europa.eu/progress-in-dossier-evaluation> accessed 24 June 2024).

animal test (Article 41 para 3 of REACH) after granting registrants their right to comment within 30 days of receipt (Article 50 para 1 of REACH). The ECHA must examine any additional information submitted by registrants (Article 42(1) REACH). As established by the European Court of Justice, the obligation to examine new information extends to information acquired using NAMs, even when the ECHA has explicitly demanded additional animal tests from the registrant to complete the registration dossier.[190] However, REACH does not provide a deadline after which the ECHA may no longer perform compliance checks. This means the ECHA can revisit a dossier at any time after registration and request new testing.[191]

Under the coordination of the ECHA, the competent authorities of the Member States are responsible for evaluating the substances (not the registration dossiers) to determine if and which substances pose a risk to human health and the environment.[192,193] If there is reason to suspect that the substance poses a threat, the registrants can be obligated to provide additional information, eg, based on animal testing for complex endpoints, such as endocrine disruption properties,[194] but also information not included in the standard information requirements in Annexes VII to X REACH.[195]

In its report on the Integrated Regulatory Strategy to identify substances of concern for 2022, the ECHA stated that it had detected numerous substances that it suspected of having hazardous properties and that had been registered with insufficient data. The Agency concluded that more data was needed to assess compliance with REACH and the need of risk management action. Despite stating that it intended to assess all available data and group chemicals to avoid unnecessary animal testing, it is vague in terms of how many additional animal tests are required.[196] This reflects the concerns expressed by experts in the field of NAMs-based safety testing that the ECHA is requesting new animal tests for substances that are already widely used and that it is thereby not made sufficiently clear that animal testing will effectively only be required as a last resort.[197]

(c) Authorisation and restriction

In the case of substances of very high concern listed under Annex XIV REACH,[198] registrants must apply for authorisation of production and/or import.[199] Annex XVII REACH contains a list of restricted substances, which may not be produced, imported, or

[190] The ECJ ruled that this "possibility (for submission of non-animal data) arises from the relevant general provisions of the REACH Regulation and from the guiding principle of limiting animal testing which those general provisions reflect," thereby emphasizing the significance of the requirement to perform animal testing as a last resort only according to Art. 25(1) REACH and the obligation to generate information by means other than vertebrate animal tests whenever possible as stipulated in Art. 13(1) REACH (Case C-471/18 P *Germany v Esso Raffinage* [2021] ECR I–48, paras 128–129).

[191] The ECHA is only required to check the compliance of at least 20 per cent of all submitted dossiers for substances in tonnage bands of less than 100 tonnes per year until the end of 2027 (Art. 41(5) REACH). This situation could merit further investigation from a legal certainty standpoint.

[192] Arts 44 ff. REACH.

[193] Cf ECHA, "Evaluation" <https://echa.europa.eu/regulations/reach/evaluation> accessed 24 June 2024.

[194] Cf ECHA, "Substance Evaluation" <https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation> accessed 24 June 2024.

[195] Art. 46(1) REACH.

[196] ECHA, "Speeding up the Identification of Chemicals of Concern. Integrated Regulatory Strategy Annual Report" (2023) <https://echa.europa.eu/documents/10162/5641810/irs_annual_report_2022_en.pdf/385b97dc-72ed-1ba0-5a9d-9c85f10bf9eb?t=1688375136656> p 8, accessed 6 July 2024.

[197] Cf Fentem and others (supra, n 42) p 125.

[198] Art. 57 lists substances that may be included in Annex XIV: certain carcinogens, mutagens, reproductive toxins, substances that are (very) persistent and (very) bioaccumulative, or substances like those with endocrine disrupting properties for which there is evidence of probable serious effects to human health or the environment.

[199] Arts 56 and 62 REACH.

used unless the conditions of the restriction in column 2 of Annex XVII REACH specify otherwise. Restrictions can also apply to substances in quantities of less than one tonne per year.[200]

3. Standard information requirements and adaptations: animal testing and NAMs

(a) Standard information requirements according to Annexes VII–X

According to the general information requirements set out in steps 1–4 of Annex VI REACH, which are mandatory for all substances manufactured or imported in quantities of one tonne or more per year, the registrant must consider information needs for compliance with the relevant Annexes VI–X REACH and first gather and share all existing information on the substance. If information gaps are identified, the registrant must generate new data, ie, directly perform new tests according to Article 13 REACH, or in case the production or import volume exceeds 100 tonnes per year and the registrant plans to generate information on the substance with animal tests,[201] propose a testing strategy first before performing a test.[202]

Annexes VII–X REACH each contain a column 1 with standard information requirements on the physicochemical substance properties[203] and toxicological and ecotoxicological information.[204] Column 1 lays down specific endpoints and test methods, which must be conducted according to the Test Method Regulation or in accordance with other international test methods recognised by the European Commission or the ECHA.[205] Column 2 specifies rules for adaptations to the testing requirements, ie, for omission or modification of testing or the need for additional testing.

(b) Chemical safety assessment

If a substance is produced or imported in quantities of 10 tonnes or more per year, the registrant must provide, in addition to the standard information required for the registration dossier set out in Annexes VI–X REACH, a chemical safety report containing a chemical safety assessment as set out in Annex I of REACH.[206] The chemical safety assessment consists of gathering existing information on the intrinsic substance properties, a human health hazard assessment, a physicochemical hazard assessment, an environmental hazard assessment,[207] and an assessment as to the existence of (very) persistent, (very) bioaccumulative and toxic properties (PBT or vPvB).[208] If the outcome of the assessment concludes that the substance fulfils certain hazard class criteria according to the CLP Regulation or is assessed to be have (very) persistent, (very) bioaccumulative and toxic properties, the chemical safety assessment must additionally include an

[200] Cf ECHA, "Restriction" <https://echa.europa.eu/regulations/reach/restriction> accessed 26 June 2024.

[201] Annexes IX and X REACH provide for animal testing as the standard information requirements for the registration of substances in volumes of 100 tonnes or more per year.

[202] Art. 10(a)(ix) and Annexes IX and X REACH.

[203] For example, melting/freezing point, boiling point, relative density, vapour pressure, surface tension, flammability, explosive properties (cf column 1 of Annex VII REACH).

[204] Toxicological and ecotoxicological information for substances produced in the lowest tonnage band (between 1 and 10 tonnes per year) is only required if predictions and evidence suggest that the substance is likely to meet criteria for classification as a human or environmental hazard (eg, carcinogenicity) or that it will have dispersive or diffuse uses. In all other cases, the information requirements are limited to the available physicochemical and (eco)toxicological information and to new testing for physicochemical information requirements according to Annex VII REACH.

[205] Art. 13(3) REACH.

[206] Art. 14 and Annex I REACH.

[207] These three hazard assessments must include the classification of the substance in accordance with the CLP Regulation (cf Sections 1–3, Annex I REACH).

[208] Cf Section 4, Annex I REACH.

exposure assessment and a risk characterization as described in Annex I, Sections 5 and 6 REACH.[209,210]

Note that a comprehensive human health hazard assessment required as part of the chemical safety assessment includes determining human exposure levels that should not be exceeded (Derived No-Effect Level, DNEL).[211] The standard human toxicity tests required in Annex VII, like skin sensitization, eye/skin irritation, and acute toxicity, cannot provide the necessary information to establish a Devired No-Effect Level. Currently, no validated non-animal test methods to determine a DNEL exist; therefore, for substances produced or imported in quantities over 10 tonnes per year, live animal testing remains a standard requirement.[212]

(c) Adaptations to the standard information requirements according to Annex XI

In addition to the adaptations provided for in column 2 of Annexes VII–X, Annex XI REACH gives substance registrants the possibility to adapt their standard testing regime, ie, to waive animal testing. Testing according to the standard information requirements of Annexes VII–X may be omitted if it does not appear scientifically necessary. This can be the case when there is either existing data from previous testing or historical human data, sufficient weight of evidence from several independent sources, adequate results from qualitative or quantitative structure-activity relationship models ((Q)SAR), acceptable results from validated in vitro methods, or sufficient information from grouping or read-across[213] approaches.[214] Testing can also be omitted if it is technically impossible to test[215] or the registrant can demonstrate that humans or the environment will not be exposed to substance hazards (substance-tailored exposure-driven testing[216]).

The ECHA can review dossiers to verify if the adaptations of the standard information requirements, along with the related justifications, comply with the rules for adaptations under Annexes VII to X and the general rules outlined in Annex XI.[217] This is emphasized by the information on the ECHA support page for registrants: "Importantly, omitting testing on animals must not compromise the safe use of substances. Therefore, every adaptation you use instead of submitting the standard information needs a valid and documented justification."[218] The requirement to justify the submission of NAMs-based data highlights the animal-centric nature of the REACH Annexes and contradicts the principle that animal testing should be avoided whenever possible and used only as a last resort.[219]

[209] Art. 14(4) REACH. If the criteria for the hazard classes are not fulfilled and the substance is assessed as not having (very) persistent, (very) bioaccumulative and toxic properties, the chemical safety assessment is limited to a hazard assessment (cf Art. 14(3) REACH).

[210] For detailed information on the different steps of the chemical safety assessment under REACH, see ECHA, "Guidance on Information Requirements and Chemical Safety Assessment" <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment> accessed 7 July 2024.

[211] Annex I, Section 1.0.1. REACH. Similarly, the environmental hazard assessment is aimed at identifying the concentration of the substance below which adverse effects in the environmental sphere of concern are not expected to occur (Predicted No-Effect Concentration, PNEC) (Annex I, Section 3.0.1. REACH).

[212] Cf Rovida and others (supra, n 58) p 380.

[213] Read-across functions by grouping structurally similar substances and using existing studies to make an estimate for the substance in question (See Annex I, Section 0.1, and Annex XI, Section 1.5 REACH).

[214] Annex XI, Section 1 REACH.

[215] Annex XI, Section 2 REACH.

[216] Annex XI, Section 3 REACH. Exposure-based waiving of standard test regimes is also provided for in column 2 of Annexes VIII–X REACH.

[217] Art. 41(1)(b) REACH.

[218] ECHA, "Adaptations to the Standard Information Requirements" <https://echa.europa.eu/support/registration/what-information-you-need/adaptations-to-the-standard-information-requirements> accessed 12 July 2024.

[219] Cf Art. 13(1) and Art. 25(1) REACH.

However, in a recent judgment by the European Court of Justice[220] on the use of adaptations to fulfill standard information requirements after an explicit decision by the ECHA asking registrants to perform an additional animal test, the Court held that "a registrant has, generally and therefore especially where ECHA issues it with a decision asking it to complete its registration dossier with a study involving animal testing, not simply the possibility but the *obligation*[221] to generate information obtained by means other than animal testing ...." According to the Court, this conclusion follows from recital 47 of REACH, according to which "it is necessary to replace, reduce or refine testing on vertebrate animals," the related general provisions of REACH, which require that information be generated whenever possible by means other than animal testing and that animal tests should be performed as a last resort only,[222] and the aim of REACH to promote alternative methods for hazard assessments.[223] This decision provides an important clarification as to what should be considered the standard information source for chemical safety assessments: Registrants have an obligation to use NAMs and may only resort to animal testing when there is truly no other way to obtain the necessary information.

In light of this judgment, there are calls to halt any new animal testing requested by the ECHA following compliance checks to enable a transparent scientific assessment of submitted testing proposals.[224] Others are calling into question the current system under REACH with its "rigidly hazard-focused, tick-box approach" in its entirety.[225]

(d) Legal inconsistencies impeding the use of non-animal methods to adapt the standard information requirements

Article 13(3) REACH stipulates that test methods used for compliance with REACH must be carried out according to internationally accepted test method guidelines or otherwise be internationally accepted. It also states that information on the intrinsic properties of substances may be generated in accordance with *other test methods*[226] as long as the requirements set out in Annex XI REACH are met. For example, the Annex XI weight-of-evidence approach allows for "the use of newly developed test methods, not yet included in the test methods referred to in Article 13(3)" if they provide sufficient "weight of evidence," which may lead to the "conclusion that a substance has or has not a particular property". If this is the case, animal testing must be omitted.[227,228] This wording expressly permits the use of NAMs that have not been validated (yet).

This is where the legal requirements become difficult to follow: The information acquired according to Annex XI of REACH must be adequate for the purpose of classification and labelling under the CLP Regulation. However, the criteria for classification as specified in Annex I of the CLP Regulation require either human or animal data or information based on tests according to test guidelines or other

[220] Case C-471/18 P, *Federal Republic of Germany v Esso Raffinage* [2021] ECR I-48.

[221] Emphasis added by author.

[222] Art. 13(1) and Art. 25(1) REACH.

[223] Case C-471/18 P (supra, n 220) paras 130 ff.

[224] Cf Fentem and others (supra, n 42) p 125.

[225] M Pereira and others, "REACHing for Solutions: Essential Revisions to the EU Chemicals Regulation to Modernise Safety Assessment" (2022) 136 Regulatory Toxicology and Pharmacology 2.

[226] Emphasis added by the author.

[227] Annex XI, Section 1.2 REACH.

[228] Cf recital 47 REACH, which states that animal testing should be replaced by alternative methods "validated by the Commission or international bodies, or *recognised by the Commission or the Agency as appropriate to meet the information requirements* (emphasis added by the author) ...." This serves as a strong indicator that the ECHA and the Commission have the competency to determine the appropriateness of a NAM, irrespective of its validation status.

internationally accepted test methods.[229,230] In turn, these criteria impede the use of non-guideline and/or unvalidated NAMs.[231] This merits further investigation to better understand what legislative amendments are needed to accommodate the uptake of new non-animal methodologies, particularly test methods that have not yet been officially validated but produce sufficient data to satisfy regulatory needs.

Some scientists have proposed alternative interpretations of Annex XI to allow for an increased use of NAMs for REACH compliance.[232] However, the underlying paradigm of animal-based testing remains an obstacle to the acceleration of NAMs acceptance: In practice, the ECHA generally only accepts NAMs-based data when the test method functions as a direct replacement of the standard animal test and has been fully validated.[233]

Therefore, while the urgency of accelerating validation procedures is evident and the benefits of validating test methods are indisputable – such as promoting data acceptance across countries, ensuring regulatory consistency, building public confidence, and facilitating effective risk management, which ultimately reduces duplication in chemical risk assessments – there is also an equally pressing need to amend the relevant laws. The amendments must be designed to allow decision-makers greater flexibility in accepting information derived from innovative, not yet fully validated test methods, thus aligning legislation with the legal obligation to adhere to the 3Rs principle and, specifically, to use non-animal methods whenever possible and conduct animal testing as a last resort only.

[229] Cf Art. 8(3) and Annex I criteria of the CLP Regulation.

[230] There is an exemption for the classification criteria for endocrine disruptors for human health and the environment: The classification criteria specifically allow for the use of "non-animal data providing equivalent predictive capacity as animal data or existing human data" (Annex I, 3.11.1 and 4.2.1 CLP). However, there is a lack of information as to what non-animal data can be considered to have a predictive capacity comparable to the corresponding human or animal data. As a result, this option is not being applied in practice, and/or there is no regulatory recognition of such data to suggest it has been utilised and approved.

[231] This is especially true for the use of non-guideline NAMs in assessing complex endpoints, eg, carcinogenicity, reproductive toxicity or repeated dose toxicity. These endpoints necessitate using multiple NAMs in succession – ie, a battery approach – to recreate a standard animal-based test required for such endpoints (eg, OECD TG 408: repeated dose 90-Day oral toxicity study in rodents) (cf Schmeisser and others (supra, n 25) pp 4 f). Such battery approaches have not (yet) been validated and included in relevant test guidelines. However, it is worth mentioning in this context the significant efforts put by the European Food Safety Authority (EFSA) into the development of a OECD test guideline for a developmental neurotoxicity (DNT) in-vitro testing battery (cf I Cattaneo and others, "Implementing New Approach Methodologies (NAMs) in Food Safety Assessments: Strategic Objectives and Actions Taken by the European Food Safety Authority" (2023) 133 Trends in Food Science & Technology 277, p 282). Furthermore, the scientific report commissioned by EFSA on the development of a roadmap for action on NAMs in risk assessments explicitly states that "the transition to the use of NAMs and the subsequent 3R impact is in general determined by the acceptance of non-guideline studies, ie, not formally validated studies." It points to a pragmatic approach taken by EFSA in this regard, namely by taking into account data from not formally validated testing in a weight-of-evidence approach (SE Escher and others, "Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment" (External Scientific Report, Euopean Food Safety Authirty 2022) p 80). However, the classification criteria of the CLP Regulation will also presumably prove to be a legal barrier where the product or substance to be assessed is to be classified in accordance with CLP or where the information requirements only provide for animal testing without an option for adaptations (eg, regulation of pesticides, cf ibid 80).

[232] Ball and others (supra n 68). The authors offer examples for a tiered approach for assessing the risk associated with a substance by deciding on the use of a substance and the estimated exposure to it, followed by a hazard assessment based on the exposure assessment using a combination of information from in vitro, in silico, and in vivo testing (pp 753 ff). However, the authors see a major difficulty in applying their proposed approach due to the structure of the legislation, particularly the way the CLP Regulation, with its mandated studies, essentially forces the replication of prescribed tests, leaving little room for new approaches that function differently – and potentially in a much more precise manner – than 1:1 replacements of existing studies (p 760).

[233] Cf Macmillan and others (supra, n 68) p 3; Schmeisser and others (supra, n 25) pp 4 f.

4. Planned revision of REACH with negative implications for animals and the 3Rs

In its 2020 Chemicals Strategy for Sustainability, the European Commission announced a revision of REACH and the CLP Regulation, in which it stated its intention to amend EU chemicals legislation to ensure a safer use of chemicals and to simplify the legal framework.[234] In its Inception Impact Assessment of 2021 on the planned revision of REACH and the CLP Regulation, the European Commission held that the revision aims, among other things, to tackle substance information gaps.[235] In its presentation of policy plans,[236] the Commission listed increased information requirements for low tonnages and the identification of the most harmful substances as the main goal of its Chemicals Strategy for Sustainability. While some animal tests are set to be deleted (eg, acute oral toxicity in rats) or replaced (eg, replacing short-term toxicity testing in fish with in vitro testing or fish embryo toxicity), the Commission states that it intends to close the human health information gaps for 5,800 low tonnage substances by subjecting them to information requirements for higher tonnage bands such as repeated dose toxicity and reproductive and developmental toxicity. Furthermore, more animal testing is also planned for endocrine-disrupting chemicals. There is, however, no further illustration of whether and how the last resort requirement of Article 25 REACH will be promoted and ensured as part of the planned amendment.

Scientists estimate that millions of animal lives could be lost if the REACH revision proceeds without transitioning from the animal-based testing standard to a next-generation risk assessment (NGRA) using non-animal methods to meet the increased information requirements for identifying endocrine disruption.[237] The fact that more animal testing is being actively planned is incomprehensible given the global trend towards the use of NAMs[238] and the European Commission's own words that "safety testing and chemical risk assessment need to innovate in order to reduce dependency on animal testing but also to improve the quality, efficiency and speed of chemical hazard and risk assessments".[239]

This is all the more untenable in light of the questionable reliability and relevance of animal testing.[240] It is also seen as a missed opportunity to facilitate the transition to a more modern and efficient chemical safety regulation that would truly be in line with the objectives of REACH to promote innovation and NAMs.[241] The proposed amendments to REACH and the CLP Regulation also contrast with other European regulatory fields, such as food safety, where the competent regulatory bodies, namely the European Food Safety Authority (EFSA), are moving towards less animal testing and more new technologies.[242]

[234] COM (2020) 667 final (supra, n 41) pp 10 ff.

[235] EU Commission, "Inception Impact Assessment, Revision of EU Legislation on Registration, Evaluation, Authorisation and Restriction of Chemicals" (2021) <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12959-Chemicals-legislation-revision-of-REACH-Regulation-to-help-achieve-a-toxic-free-environment_en> p 1, accessed 6 July 2024.

[236] European Commission, "REACH revision, Changes in Standard Information Requirements and Annex XI: Status & Implications" <https://echa.europa.eu/documents/10162/23930482/20230531_nam_workshop_katrin_schutte_com_en.pdf/8b8d968a-ef07-fc21-662d-ad41d86739ae?t=1685511393161> accessed 7 July 2024.

[237] Cf Rovida and others (supra, n 58) p 380; Fentem and others (supra, n 42) p 125; NC3Rs, "Endocrine Disruptor Assessment" <https://nc3rs.org.uk/endocrine-disruptor-assessment#implications-of-new-eu-reach-information-requirements> accessed 7 July 2024; European Commission, "Feedback from: Cruelty Free Europe" <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12959-Chemicals-legislation-revision-of-REACH-Regulation-to-help-achieve-a-toxic-free-environment/F2333087_en> accessed 7 July 2024.

[238] Cf Pereira and others (supra, n 225) p 1.

[239] COM (2020) 667 final (supra, n 41) p 22.

[240] Cf Pereira and others (supra, n 225) p 5.

[241] Ibid, p 2.

[242] Cf EFSA, "Strategy 2027 Science Safe Food Sustainability" <https://op.europa.eu/webpub/efsa/strategy-2027/en/> accessed 27 November 2024.

The final REACH revision proposal was initially planned for 2022 and was then postponed to the end of 2023 by the European Commission, with implementation of the revision initially expected to enter into force between 2025–2027.[243] However, as of now, the proposal has not yet been introduced, and it remains uncertain whether the revision will proceed as planned or when it will be implemented.[244] The delay has raised public and environmental health concerns due to a lack of identification and effective management of hazardous substances.[245] The European commission has been criticised for stalling the revision following lobbying by chemicals industry groups opposed to anticipated restrictions and bans on highly toxic chemicals.[246,247] The Commission has remained vague about the reasons for the delay, emphasizing that quality takes precedence over speed, the need to ensure compatibility with other regulations, and to design a regulation that simplifies the administrative burden for registrants, all of which takes time.[248]

5. Animal testing for cosmetics-only substances continues for compliance with REACH

There has been growing concern and frustration among the public,[249] the scientific community,[250] and manufacturers of chemical products[251] over ongoing animal testing for ingredients in cosmetic products to comply with REACH requirements, even though the

[243] Cf REACH Law, "REACH Revision State of Play 2023" <https://www.reachlaw.fi/reach-revision/> accessed 28 November 2024.

[244] Cf European Parliament, "Legislative Train Schedule, Revision of the Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)" <https://www.europarl.europa.eu/legislative-train/theme-a-european-green-deal/file-reach-revision> accessed 27 November 2024.

[245] Cf European Environmental Bureau (EEB) and CHEMTrust, "Waiting for REACH: The Negative Impacts of Delaying Reform of EU Chemical Laws" (report 2023).

[246] Cf "Big Toxics and Their Lobby Firepower" (*Corporate Europe Observatory*, 25 May 2023) <https://corporateeurope.org/en/big-toxics-firepower> accessed 28 November 2024.

[247] In this regard, in 2023, the EU Ombudsman rebuked the European Commission for its refusal to fully disclose its impact assessment and the opinions of its Regulatory Scrutiny Board (The Regulatory Scrutiny Board is an independent body within the Commission that advises the latter and issues opinions on the impact assessments of legislative proposals by the Commission (Commission, "Regulatory Scrutiny Board" <https://commission.europa.eu/law/law-making-process/regulatory-scrutiny-board_en> accessed 28 November 2024) regarding the planned revision of REACH upon request for public access by a civil society organisation, deeming it maladministration on the part of the Commission and recommending that the latter grant full access to the documents (European Ombudsman, Decision in Case 1053/2023/MIK (2023)). However, the Commission has refused a second request for full disclosure following the decision of the Ombudsman and has not granted access to the documents to date (cf "REACH Regulation – EU Commission's Failure to Share Full Documents Constitutes Double-Maladministration" (*Corporate Europe Observatory*, 18 March 2024) <https://corporateeurope.org/en/2024/03/reach-regulation-eu-commissions-failure-share-full-documents-constitutes-double> accessed 28 Novbember 2024). Following a further complaint concerning individual meetings held by the Regulatory Scrutiny Board with lobby groups, the European Ombudsman raised concerns with regard to the independence of the Board and "undue influence by stakeholders" (European Ombudsman, Decision in Case 439/2023/KR (2024)).

[248] Cf European Parliament, "Multimedia Center" (Committee on Environment, Public health, and Food Safety, 1 March 2023) <https://multimedia.europarl.europa.eu/en/webstreaming/committee-on-environment-public-health-and-food-safety_20230301-1430-COMMITTEE-ENVI> accessed 28 November 2024.

[249] Cf European Citizen's Initiative: Save Cruelty Fee Cosmetics – Commit to a Europe Without Animal Testing (Save Cruelty Fee Cosmetics initiative) <https://citizens-initiative.europa.eu/initiatives/details/2021/000006_en> accessed 11 July 2024.

[250] Cf Macmillan and others (supra, n 68) p 7; J Knight and others, "Continuing Animal Tests on Cosmetic Ingredients for REACH in the EU" (2021) 38(4) ALTEX 653.

[251] Cf S Houlton, "Sustainable Safety Testing" (*Chemistry World*, 1 June 2021) <https://www.chemistryworld.com/industry/sustainable-safety-testing/4013736.article> accessed 11 July 2024; Fentem and others (supra, n 42) pp 124 ff.

Cosmetics Regulation prohibits animal testing for marketing cosmetic products – both final products and ingredients used exclusively in cosmetics (cosmetics-only substances[252]).[253] The European Parliament, in its resolution on a global ban to end animal testing for cosmetics, has also clearly stressed the importance of upholding the EU citizen's will to end animal testing for cosmetics.[254]

There has been an ongoing conflict between the Cosmetics Regulation and REACH since 2014,[255] with the ECHA and ECHA Board of Appeal having thus far interpreted the relevant provisions in favour of animal testing for compliance with REACH: They hold that the Cosmetics Regulation is solely intended to protect end users of cosmetic products – ie, consumers and professionals who work with cosmetic products. Therefore, they consider new animal tests justified if conducted to determine the compliance of a cosmetic ingredient with REACH, specifically to assess the risks associated with worker exposure and environmental health.[256,257]

This interpretation by the ECHA and the ECHA Board of Appeal has now been upheld by a 2023 ruling by the General Court of the European Court of Justice (GC).[258] The Court determined that the relevant provisions do not establish the primacy of one regulation

[252] Substances that are also used in other products, in addition to being used in cosmetic products, are subject to the provisions of other legislation. For example, ingredients used in both cosmetics and detergents fall under the scope of REACH. This is evident from Art 18(1)(a)(b) Cosmetics Regulation, which specifies that the animal testing ban applies to tests carried out to meet the requirements of the Cosmetics Regulation itself. This means that if animal testing is conducted for compliance with other regulations, such as REACH, the ban under the Cosmetics Regulation does not apply. Art 2(1)(a) Cosmetics Regulation, which defines a cosmetic product as "any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours," also indicates that the scope of the Cosmetics Regulation is limited to substances intended for cosmetic purposes. Other purposes are not included in the definition of a "cosmetic product." Thus, products with dual or multiple uses are not included in the scope of the animal testing ban under the Cosmetics Regulation.

[253] Art. 18(1)(a)(b) Cosmetics Regulation.

[254] European Parliament Resolution of 3 May 2018 on a Global Ban to End Animal Testing for Cosmetics [2018] OJ C41/45, paras 4 and 5.

[255] For more on this conflict, cf Knight and others (supra, n 250) p 654 ff.

[256] ECHA, "Factsheet, Interface between REACH and Cosmetics Regulations" <https://echa.europa.eu/de/publications/fact-sheets> accessed 13 July 2024; ECHA Board of Appeal Case A-010-2018 (15 May 2020) <https://echa.europa.eu/about-us/who-we-are/board-of-appeal/decisions> accessed 13 July 2024.

[257] The following provisions form the basis for this interpretation by the ECHA and the ECHA Board of Appeal: Art 2(4)(b) REACH states that REACH applies "without prejudice to the Cosmetics Regulation as regards testing involving vertebrate animals within the scope of that Regulation". According to Art 14(5)(b) REACH, "the chemical safety report need not include consideration of the risks to human health from the end use of cosmetic products within the scope of the Cosmetics Regulation". Furthermore, according to Art. 3 Cosmetics Regulation, cosmetic products made available on the market must be safe for human health when used under normal or reasonably foreseeable conditions of use. Art. 18(1)(a()(b)(c)(d) Cosmetics Regulation prohibits the placing on the market of cosmetic products and ingredients in cosmetics that have been tested on animals as well as testing on animals to meet the requirements of the Cosmetics Regulation. Since "normal or foreseeable conditions of use" are understood to refer to the use of cosmetics by end users (ie, consumers and professionals who work with cosmetic products), the conclusion is therefore drawn that the animal testing ban applies only to testing results intended to assess consumer safety. In this context, animal testing is viewed as being conducted "in order to meet the requirements of the Cosmetics Regulation" as laid down in Art. 18(1) Cosmetics Regulation (cf ECHA Board of Appeal Case A-010-2018 (15 May 2020) paras 106 ff). However, the author contends that the ruling of the European Court of Justice referenced in paragraph 107 (Case C-592/14 *European Federation for Cosmetic Ingredients v Secretary of State for Business, Innovation and Skills and Attorney General* [2016] ECR I-5341) does not support the ECHA Board of Appeal's argument in paragraph 108 that the marketing ban is only triggered if animal testing was performed to establish product safety for end users. The referenced ECJ case does not mention end users – or any type of users, for that matter.

[258] Case T-655/20, *Symrise AG v European Chemicals Agency (ECHA)* [2023] ECR II-736.

over the other.[259] It also concluded that the scope of the animal testing ban under the Cosmetics Regulation is limited to studies performed to assess the safety of end users only, leading to the conclusion that workers involved in the manufacturing of a cosmetic product or its ingredients are excluded from the scope of the Cosmetics Regulation, as they are exposed to the product or ingredient throughout its production cycle and under conditions that differ from those associated with the use of the final product.[260]

As a result of the limited scope of the animal testing ban under the Cosmetics Regulation, over 100 studies on animals have been performed for sixty-three cosmetics-only substances for human-health endpoints after the deadlines for animal testing set by the Cosmetics Regulation. Most of these animal tests are assumed to have been conducted to fulfil REACH requirements.[261]

These developments underscore the urgent need to address the protection goals of the different laws involved to bring the practice of testing substances in line with the political decision to ban animal testing for cosmetic products. For example, manufacturers of cosmetic products have demonstrated how they implement specific risk management measures to ensure worker safety during the production phase, thus rendering animal testing for this purpose unnecessary.[262] Such proposals must be integrated into the legislation to uphold the fundamental commitment to ending animal testing for cosmetics.

6. Summary of current challenges to the implementation of NAMs under REACH

Despite the significant potential of NAMs to replace animals in chemical safety assessments, various obstacles hinder their broader adoption within the current regulatory framework under REACH and impede the shift away from the animal testing paradigm. These obstacles, some of which have been mentioned throughout this study, will be briefly outlined and summarised below.

(a) Inadequate and contradictory legislation

Despite the legal requirement to use animal testing as a last resort only, REACH largely requires guideline animal tests for compliance with the standard information requirements in its Annexes, especially for higher tonnage production or import volumes. Test method guidelines are updated following lengthy validation procedures, thus offering only a very small number of validated NAMs to choose from. At the same time, the option to adapt the standard information requirements by using new, not yet validated non-animal test methods is hampered by contradicting legal requirements that essentially force registrants to perform animal tests. Therefore, suggestions have been made to replace the current system of fixed testing requirements towards a more open and flexible system of assessing chemical safety that does not follow a tick-box approach of mandated tests and leaves room to fulfil the legal requirement of putting safe chemicals on the market in a result-oriented way.[263]

[259] Paras 65–68.

[260] Para 82.

[261] Cf Rovida and others (supra, n 58) p 368; Knight and others (supra, n 250) pp 654 ff.

[262] Cf Fentem and others (supra, n 42) p 127.

[263] For example, by only stipulating information needs without requiring specific studies and by allowing for the use of NAMs in the context of Integrated Approaches to Testing and Assessment (IATA) or next-generation risk assessment (NGRA) both for REACH and CLP compliance (cf ibid, pp 125 f). The latter is defined as "an exposure-led, hypothesis-driven risk assessment approach that integrates in silico, in chemico, and in vitro approaches, translating data obtained with NAMs to derive the threshold level for the safe use of chemicals" (Rovida and others (supra, n 58) p 382).

Furthermore, scientists are criticising the widely unquestioned paradigm of testing on animals with doses that are multiple times higher than that to which humans and the environment are exposed to in reality, with the aim of coming at conservative answers to maximise safety, all the while ignoring the fact that this approach is scientifically questionable and can produce distorted results.[264]

Some stakeholders advocate for the requirement of testing proposals for all substances, not just those produced or imported in volumes of 100 tonnes or more per year.[265] The ECHA must publish the testing proposal on its website and allow third parties to submit existing information on the substance.[266] This process aims to promote transparency and collaboration in the safety assessment, ultimately helping to avoid unnecessary or duplicate animal tests. By extending the duty of registrants to submit testing proposals and the ECHA's obligation to publish these proposals for all planned animal testing, regardless of production or import volume, proponents of this amendment argue that it would encourage the use of NAMs instead of animal studies.[267] Another related demand is to amend the last resort requirement under REACH to specify that animal testing can only be performed if the NAMs-based results are insufficient for risk assessment and risk management.[268]

There is also a conflict between REACH and the Cosmetics Regulation as animal testing is still required to assess the safety of substances intended solely for cosmetics under REACH. A revision of both regulations is needed to ensure that the intentions of the EU Parliament and EU citizens to ban animal testing for cosmetics are respected. It has been proposed that only existing information or data generated using NAMs should be permitted to meet the standard information requirements under REACH for cosmetics-only substances.

(b) Restrictive validation system

To achieve quicker validation and broader acceptance of NAMs the current validation system is in need of an overhaul. So far, only NAMs that function as direct replacements for animal test methods have been validated, while other scientifically sound approaches that ensure human-relevant results are still being met with scepticism. Furthermore, method-by-method replacements have only proven successful for simple endpoints such as eye or skin irritation, while battery approaches to recreate whole organisms for more complex endpoints have not yet been validated and included in regulations.

It currently takes up to 20 years from the development of test methods to their validation, which is untenable and shows that the legal side of toxicity testing is lagging far behind scientific developments. The (largely successful) ban on animal testing for cosmetics was possible not least because of increased technological developments and investments in non-animal test methods.[269] Therefore, the fact that the paradigm shift in chemical safety testing for compliance with REACH is being hampered by a rigid and outdated validation system despite the availability of the necessary technology is becoming increasingly unjustifiable.

Another issue lies in how NAMs are obviously being held to stricter standards than animal models with respect to the variability of test results. As mentioned in the introduction, there is ample evidence of poor transferability of test results from animals to

[264] Cf Ball and others (supra, n 68) p 745.
[265] Cf Art. 12(1)(e) REACH.
[266] Cf Art. 40(2) REACH.
[267] Cf Pereira and others (supra, n 225) p 5.
[268] Ibid, p 6.
[269] H Grimm and others, "Advancing the 3Rs: Innovation, Implementation, Ethics and Society" (2023) 10 Frontiers in Veterinary Science 3.

humans and between species, as well as for the uncertainty and variability of animal test results.[270] Therefore, scientists are calling for the same standard of variability to apply to NAMs as animal methods, and also for the uptake of new approaches to validation that consider the relevance of NAMs for humans (performance-based validation) instead of their ability to replicate animal models.[271]

(c) Low acceptance by the ECHA

The ECHA has pointed to an inadequate use of non-testing approaches by registrants such as read-across and Qualitative or Quantitative structure-activity relationship models ((Q) SAR)[272] and that it has therefore required additional data generation via standard (animal) testing.[273] This has been attributed to an unreasonably high burden of proof required to justify the use of adaptations to the standard information requirements.[274] Given the last resort requirement, it is questionable why the ECHA does not – or is not obligated – to accept NAMs-based information by default if the regulatory needs are adequately addressed, and, where more information is necessary, to require additional NAMs-based data first, before resorting to animal testing as a genuine last resort.

NAMs are also having a hard time because there is a lack of multidisciplinary expertise amongst regulators who have been traditionally trained to interpret results from animal tests and therefore expect information that is directly comparable or equivalent to animal models. Therefore, experts in the field are calling for more collaboration between academia, industry, and regulatory agencies, as well as enhanced knowledge generation in academia to foster knowledge transfer and a better understanding of NAMs and how NAMs-based chemical safety assessments work.[275]

Another concern is that the ECHA often requires testing of substances used solely in cosmetics to comply with REACH, aiming to protect workers and the environment. This occurs despite industries suggesting practical solutions to mitigate worker exposure to these substances without resorting to animal testing. These solutions include utilising consumer-related exposure data, considering various exposure scenarios for workers, and implementing adequate occupational safety measures to safeguard workers from potential exposure.[276]

(d) Recent and planned amendments to REACH and CLP

Some recent amendments to REACH have included further animal testing requirements. A 2022 amendment to Annexes VI to X of REACH requires several additional animal tests for substances that have either been tested in vitro and the results have come out positive, or that are otherwise of a specific concern. It is expected that this amendment will cost

[270] For example, in an evaluation of the noncancer toxicologic outcomes of rodent tests for thirty-seven chemicals, it was concluded that "overall . . . , it appears that if a pathology is observed in an organ in one species (or sex or assay length), it is not very likely, on average, that the same pathology will be observed in another species exposed to the chemical". (B Wang and G Gray, "Concordance of Noncarcinogenic Endpoints in Rodent Chemical Bioassays" (2014) 35(6) Risk Analysis 1154, p 1165).

[271] Cf Schmeisser and others (supra, n 25) p 7.

[272] ECHA, fourth report on the use alternatives, pp 42 ff.

[273] In its latest report on the operation of REACH and CLP of 2021, the ECHA stated that 75 per cent of registrations based on read-across were insufficient (ECHA, "Report on the Operation of REACH and CLP 2021" (n) 36).

[274] Cf Pereira and others (supra, n 225) p 4.

[275] Cf Sebastian Schmeisser and others (supra, n 25) p 11; Fentem and others (supra, n 42) p 129; F Pistollato and others, "Current EU Regulatory Requirements for the Assessment of Chemicals and Cosmetic Products: Challenges and Opportunities for Introducing New Approach Methodologies" (2021) 95 Archives of Toxicology 1867, pp 1868 and 1889 f.

[276] Cf Fentem and others (supra, n 42) p 127.

millions of animal lives for substances that have already been registered. An amendment to the CLP Regulation of 2023 included several new hazard classes relating to endocrine disruption in humans and the environment, with animal testing being the main method of testing for these endpoints, which is also expected to cost additional animal lives.

Furthermore, based on what has been communicated by the European Commission so far, it is also expected that the pending revision of REACH and the CLP Regulation will result in increased animal testing. Consequently, both the recent and the forthcoming amendments, should they be carried out as planned, are incompatible with the requirement to adhere to the 3Rs, specifically, to exhaust all non-animal methods first and use animal testing as a last resort only, and the final goal of moving away from animal testing according to EU Law. This is also in obvious contrast to other regulatory areas, such as food safety, where the European Food Safety Authority (EFSA) is readily adopting new technologies.

(e) Registrant hesitation

For all the stated reasons above, it has been observed that registrants often use animal models pre-emptively as a path of least resistance, and also because of a fear of legal liabilities in case of wrong substance classification.[277]

(f) Summary

The implementation of NAMs under REACH faces significant challenges, including contradictory and inadequate legislation, a slow and restrictive validation system, low acceptance by the ECHA, and legislative amendments that have increased animal testing requirements, with an upcoming revision expected to add even more animal tests to the standard information requirements. Consequently, registrants often resort to animal testing preemptively. To overcome these obstacles, legislative and regulatory reforms are necessary to create a more flexible and adaptive framework. This includes updating validation processes, ensuring equal standards for NAMs and animal tests, enhancing expertise on NAMs among regulators, and aligning contradicting legislations to avoid duplicating animal tests for the same substance or carrying out animal tests for cosmetics-only substances.

IV. Conclusion and outlook

The analysis presented in this paper highlights significant challenges and opportunities associated with the implementation of New Approach Methodologies (NAMs) in regulatory toxicity testing under REACH. Despite the explicitly stipulated final goal of moving away from animal testing in EU law, the legal requirement to replace, reduce, and refine animal testing and to use animals as a last resort only, the current regulatory framework under REACH still heavily relies on animal-based methods due to several entrenched practices and systemic barriers. These include contradictory and inadequate legislation, a slow and restrictive validation system for NAMs, and low acceptance by the European Chemicals Agency (ECHA). Additionally, recent and forthcoming amendments to REACH and the Classification, Labelling and Packaging (CLP) Regulation are poised to increase the requirements for animal testing, further complicating the transition towards non-animal methods.

The persistence of animal testing within REACH can be attributed to historical precedence, risk-averse regulatory practices, and the deeply ingrained belief in the

[277] Cf Schmeisser and others (supra, n 25) p 5.

reliability of animal models for ensuring human safety. However, the scientific community is increasingly critical of the translatability and predictability of animal tests. Evidence suggests that many substances deemed safe in animal studies have proven harmful to humans, and vice versa, raising concerns about the efficacy of animal-based testing. Moreover, the financial and ethical costs associated with animal testing cannot be overlooked, further necessitating the shift towards more humane and scientifically advanced methodologies.

The current system also faces significant practical challenges, such as the vast number of chemicals requiring safety assessments and the limitations of animal testing in addressing complex and emerging health issues, such as the effects of nanomaterials and chemical mixtures. The inability of animal models to adequately mimic human physiology and predict human-specific responses underscores the urgent need for alternative approaches.

Looking ahead, it is imperative to address the aforementioned challenges to foster the broader adoption of NAMs and advance the 3Rs principles. Legislative and regulatory reforms are necessary to create a more flexible and adaptive framework that prioritizes NAMs over animal testing. This includes updating the validation processes to ensure they are more inclusive of NAMs that do not function as 1:1 replacements of animal models, enhancing the expertise on NAMs among regulators, and aligning conflicting legislations to prevent redundant animal testing for the same substance.

Additionally, fostering collaboration between academia, industries, and regulatory agencies will be crucial. Such collaboration can enhance the generation and transfer of knowledge regarding NAMs, thereby improving their acceptance and implementation in regulatory contexts. Moreover, increasing investment in the development and validation of NAMs can provide more reliable and human-relevant data, ultimately leading to safer and more ethical chemical safety assessments.

Promising developments include the European Parliament's resolution calling for an EU-wide action plan to accelerate the shift to non-animal testing methods, the EU Commission roadmap for phasing out animal testing in chemical safety assessments under way, and the strategic plans by the ECHA to enhance cooperation with various stakeholders with regard to NAMS. These initiatives, if effectively implemented, could significantly reduce the reliance on animal testing and promote the use of NAMs.

To conclude, the road to fully integrating NAMs in regulatory toxicity testing under REACH is fraught with obstacles, but urgently needed to benefit human health, environmental safety, and animal welfare. By embracing scientific advancements and regulatory flexibility, a more humane and scientifically robust framework for chemical safety assessment is possible. In this regard, it is also imperative that legal scholars bring their expertise into the field and begin working alongside scientists to assist in overcoming the legislative and regulatory challenges and to facilitate the regulatory acceptance of NAMs.

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