PRECISION TOXICOLOGY: NEW APPROACH METHODOLOGIES FOR CHEMICAL SAFETY

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Introduction

Pollution kills three times more people than AIDS, malaria, and tuberculosis combined, accounting for one in four deaths in the poorest countries.[1] In addition to impacts on human health, chemical pollution is a significant contributor to biodiversity loss, as eco-toxins adversely affect the capacity of eco-system functions and services. Under the framework of the European Green Deal,[2] the EU Action Plan on Pollution,[3] supported by the Chemical Strategy for Sustainability,[4] pursues the ambitious aim of zero pollution by 2050, meaning that pollution in air, water, and soil should be reduced to levels no longer considered harmful to health and natural ecosystems.

Alongside this, chemicals regulation in Europe has a long-stated aspiration to comply with the 3Rs principle, namely, to *Replace*, *Reduce* and *Refine* the use of animals for the purposes of scientific testing, with the aim of full replacement.[5] Yet the adoption in 2006 of a regulatory framework for chemical safety, 'Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals' (REACH),[6] based on better scientific information on chemical hazards, always implied likely increases in animal testing. Despite the text of REACH urging industry to avoid unnecessary animal testing (for example, by sharing data) and stating that testing on vertebrate animals should be employed only as a 'last resort',[7] the reality is rather different. For most chemicals with production volumes exceeding 10 tonnes per annum, the Regulation will ordinarily require *in vivo* testing. While some amendments to REACH have allowed progress for testing in areas such as skin sensitisation/irritation or eye irritation/damage, for the most part, testing under REACH will involve animals.[8] Pressure remains to go further; in September 2021, the European Parliament voted for an EU Action Plan on animal testing, which, it demanded, should contain ambitious but achievable targets with accompanying timelines.[9]

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1) PJ Landrigan et al., 'The *Lancet* Commission on Pollution and Health' (2017) *Lancet* 391(10119) 462 to 512.

2) European Green Deal COM(2019) 640 final.

3) Pathway to a Healthy Planet for All EU Action Plan: 'Towards Zero Pollution for Air, Water and Soil', COM(2021) 400 final.

4) Chemicals Strategy for Sustainability Towards a Toxic-Free Environment, COM(2020) 667 final.

5) See the consolidated text of Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes.

6) 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, OJ L 396, 30 December 2006, 1 to 849.

7) REACH, Article 25.

8) F Pistollato et al., 'Current EU Regulatory Requirements for the Assessment of Chemicals and Cosmetic Products: Challenges and Opportunities for Introducing New Approach Methodologies' (2021) *Arch. Toxicol.* 95 at 1867.

9) European Parliament Resolution of 16 September 2021 on plans and

Of late, some progress has been made in this direction on both sides of the Atlantic. In the US, the 'Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products' seeks to motivate federal agencies to gradually replace and, in the meantime, reduce reliance on animal testing by the adoption of new approaches to risk assessment of chemicals and medical products.[10] In guidance issued in 2021, the US Environmental Protection Agency (EPA) waived toxicity tests on animal skin.[11] This follows amendments to the Toxic Substances Control Act, introduced in 2016, which include a requirement to reduce testing on vertebrate animals under section 4(h) of the Act.[12] In 2013, the EU introduced a ban on animal testing for cosmetics,[13] while in 2021 the European Food Safety Authority (EFSA)'s Director emphasised the ambition that 'by 2027, the large majority of European Food Safety Agency (EFSA) requests for additional data will be based on alternative methodologies'.[14] With regards to cosmetics, it is worth noting that certain chemical ingredients of cosmetics will be subject to animal testing and a ban on animal testing in cosmetics does not eliminate such testing in relation to environmental endpoints or worker exposure. Reasons for these policy shifts come partly from certain limitations that animal tests may have in predicting adverse effects on humans,[15] but mainly from economic and ethical considerations associated with animal testing.

Against this background, included in the Horizon 2020 research programme was a call for projects advancing the safety assessment of chemicals without resort to animal testing. This resulted in three awards to projects which form part of the programme labelled 'Animal-free Safety Assessment of Chemicals: Project Cluster for Implementation of Novel Strategies' (ASPIS).[16] ASPIS brings together three funded consortia, ONTOX,[17] PrecisionTox,[18] and Risk Hunt3r.[19] Together, these projects engage 70 institutions across 16 European countries and the US in research, delivering on a €60 million investment.

The goal of the ASPIS cluster is to pool available knowledge across disciplines to improve the accuracy, speed, and affordability of chemical safety testing without reliance on traditional laboratory animals (most commonly, rodents). It focuses on the provision of testing methodologies including: *in vitro* (a means of testing organs, tissues, cells, or sub-cellular aspects);[20] *in silico* methods (computational methods, including artificial intelligence and machine learning, which can analyse other tests or be used as prediction tools);[21] and those based on omics (such as biomolecular data obtained from genomics, transcriptomics, and metabolomics). These 'New Approach Methodologies' (NAMs) draw heavily on data analysis, informed by artificial intelligence, to seek to improve animal-free chemical risk

10) U.S. Department of Health and Human Services, 'A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States' (*National Toxicology Program* 2020) <https://ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy/index.html> accessed 5 May 2022.

11) EPA, 'EPA Finalizes Guidance to Waive Toxicity Tests on Animal Skin' (EPA 2021) <https://www.epa.gov/newsreleases/epa-finalizes-guidance-waive-toxicity-tests-animal-skin#:~:text=WASHINGTON%20(January%2019%2C%202021),whether%20pesticides%20lead%20to%20adverse> accessed 5 May 2022.

12) ST Parish et al. 'An Evaluation Framework for New Approach Methodologies (NAMs) for Human Health Safety Assessment' (2020) *Regul Toxicol Pharmacol*, 112(104592) at 2.

13) European Commission, 'Communication from the Commission to the European Parliament and the Council on the Animal Testing and Marketing Ban and on the State of Play in relation to Alternative Methods in the Field of Cosmetics' COM(2013)0135 final.

14) J Laperrouze, 'The European Parliament must Protect the Animal Testing Ban on Cosmetics' (*The Parliament* 3 May 2021) <The European Parliament must protect the animal testing ban on cosmetics (theparliamentmagazine.eu)> accessed 5 May 2022.

15) Note 12 above.

16) Aspis – Project cluster for Implementation of Novel Strategies (aspis-cluster.eu).

17) https://ontox-project.eu.

18) https://precisiontox.org.

19) https://www.risk-hunt3r.eu.

20) S Singh et al., 'Development of In Vitro Toxicology: A Historic Story' in A Dhawan and S Kwon (eds) *In Vitro Toxicology* (Academic Press 2018).

21) T Hartung and S Hoffmann, 'Food for Thought … on In Silico Methods in Toxicology' (2009) *ALTEX – Alternatives to Animal Experimentation* 26(3) at 155.

assessment in the EU. This article focuses on and explains the research work of the PrecisionTox project, which has three main pillars of work. The first concerns phylotoxicology, which is explained in the next section, but which looks to replace toxicity testing on traditional animal models such as rodents by understanding the evolutionary origins of human toxicity pathways across a suite of alternative non-mammalian species.[22] The second theme relates to variations in susceptibility to help determine safe levels of exposure to chemicals for populations according to genetic variation. The final element of the research programme is labelled 'embedded translation', which the authors help to lead, and which seeks to accelerate the uptake of NAMs in regulatory and commercial applications by directly involving regulatory bodies, industry, and civil society in project design and execution. This is the pillar of the project which is the primary focus of this article.

Precision Toxicology

The label 'precision toxicology' is deliberately resonant of the term 'precision medicine', which has revolutionised approaches to combatting human disease. Building on the sequencing of the human genome in 2001, precision medicine allowed the rapid discovery of a fuller spectrum of disease pathways by examining not how a genetic defect might elevate mortality, but by analysing, in a less targeted approach, how genes might conspire to threaten health.[23] In a similar manner, rather than investigating the health impacts of a single chemical, precision toxicology can examine the impact of chemical compounds in the environment to discover pathways to adverse health outcomes.

The tools that allow this include high-throughput testing methods, which, rather than employing rodents as surrogates for humans because of our shared mammalian biology, focus instead on a broad suite of evolutionarily diverse biomedical model organisms and human cell lines to observe the toxic response in an approach labelled 'phylotoxicology'.[24] This suite of 3Rs-compliant model test species include invertebrate species such as *Drosophila* (fruit flies), *Caenorhabditis* (nematodes), and *Daphnia* (water fleas), and embryos of *Danio* (zebrafish) and *Xenopus* (clawed frog). These model organisms are subject to chemical exposure. Measurements at several time intervals chart toxicological response by measuring the products of metabolism to indicate changes in health state (metabolomics). Genes responsible for these metabolic events are identified by simultaneously measuring changes in their transcription by RNA-sequencing (transcriptomics). This multi-omics approach helps to determine whether the mechanisms of toxicity are shared among organisms by evolutionary descent, which includes humans.[25]

Alongside this evolutionary omics approach to toxicology is a heavy reliance on data science, which introduces a significant capacity to analyse and compare thousands of toxicology samples and their metabolomic and transcriptomic data to locate key molecular events indicative of adverse outcome pathways. The application of quantitative genetics using genetically diverse populations of *Drosophila* and human Lymphoblastoid cell lines, with the profiling of gene expression, helps to identify variations in individual susceptibility allowing the development of exposure safety thresholds based on empirical data. Finally, machine learning is used to identify biomarkers for molecular key events to feed into the regulation of chemical hazards.

It is at this point that the legal input to the project comes to the fore, aiming to work with regulatory agencies and industry to facilitate the uptake of precision toxicology. This involves analysis of existing regulatory structures to assess how

22) 'The Precision Toxicology Initiative' (2023) 383 *Toxicology Letters*, 33–42.

23) J McCarthy et al., 'Genomic Medicine: A Decade of Successes, Challenges, and Opportunities' (2013) *Sci. Transl. Med.* 5(189) 189sr4.

24) JK Colbourne et al., 'Phylotoxicology: Breaking the Artificial Divide between Human- and Eco-toxicology' (2015) *Toxicology Letters* 238(2) at S12.

25) JK Colbourne et al., 'Toxicity by Descent: A Comparative Approach for Chemical Hazard Assessment' (2022) *Environmental Advances* 9 at 100287.

readily these could accommodate the new approach methodologies, suggesting, as necessary, reform of the regulation or enhancement of guidance to the regulated community. It is to this element of the research programme that we now turn.

Regulating for Chemical Safety

Given the prevalence of chemical pollution stemming from a wide range of products and applications, regulation on the testing and marketing of chemicals is vital to the protection of human and environmental health. Of the thousands of chemicals that are being and have been produced, many have become widely dispersed in the environment producing harmful impacts.[26] Unsurprisingly, then, regulation seeks to control the entry of chemicals to the market across various sectors ranging from pesticides to children's toys, and these measures ordinarily involve some process of chemical risk assessment.[27] Alongside the regulation that is product-specific (such as the regulation of food additives), there is overarching regulation of chemicals placed on the EU single market.

The key EU provisions in this respect are Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP)[28] and EU Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). The latter, as we will see, is crucial for the consideration of the employment of NAMs for chemical testing. The main objective of REACH is to '*ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation*'.[29] The Regulation is underpinned by the precautionary principle[30] and manufacturers, importers and downstream users have a duty to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment.

The information requirements for REACH registration dossiers are cumulative by tonnage. Annex VII applies if 1–10 tonnes of a substance is imported or manufactured; Annex VIII for 10–100 tonnes; Annex IX for 100–1000 tonnes; and Annex X for 1000 tonnes or more. The REACH Annexes list 'standard information required,' with varying levels of information and specificity depending on the endpoint, and some 'specific rules for adaptation' are also provided here. For some complex endpoints such as reproductive toxicity, there is no standard information required from registrants for the lower tonnage (Annex VII) substances. Information needs to be submitted in the technical dossier that will contain all physicochemical, toxicological and ecotoxicological information on substances manufactured or imported, depending on their tonnage, to the European Chemicals Agency (ECHA).[31] Despite the fact that most testing involves animals, REACH in principle accommodates and fosters other forms of testing. REACH allows for the generation of information on intrinsic properties of substances by other means of testing other than animal testing,[32] and, as stated above, animal testing should be used as a last resort.[33]

It is clear, therefore, that a route to the adoption of NAMs within the REACH Regulation exists in principle. However, while the technology is increasingly mature, the adoption of new approach methodologies to direct that technology to regulatory imperatives requires more work. We may be looking at an incremental approach in which, over time and as the application of the science develops, NAMs may play an enhanced role in hazard identification and eventually in the assessment of chemical risk. An example of this may assist (see box).

26) Note 1 above.

27) UNEP, 'Benefits of Chemicals Control'. Available at: <https://wedocs.unep.org/bitstream/handle/20.500.11822/28399/ChemControl.pdf?sequence=1&isAllowed=y> (accessed 16 May 2023).

28) OJ L 353, 31 December 2008, at 1 to 1355.

29) REACH, Article 1(1).

30) Ibid., Article 1(3).

31) Ibid., Article 12.

32) Ibid., Article 13.

33) Ibid., Article 25.

Already there is an alternative approach (a NAM) for filling data gaps in the process of dossier submission for REACH registration, widely known as 'grouping and read across'. This allows information from related source substances to predict the properties of other target substances. In other words, regulators may accept information available from existing better-understood substances to be attributed to closely analogous substances in order that experimental animal testing can be reduced. The appropriate application of read-across depends on structural similarities between source and target substances and rests on the assumption that similar structural characteristics are likely to generate similar hazards. Ideally one might wish to test this by reviewing the toxicokinetic and toxicodynamic properties of compounds grouped together. By this is meant that one might assess the rate at which a chemical will enter the body together with what occurs thereafter to excrete and metabolise the compound with a view to understanding the biological effects of the chemical. Resort to NAMs opens up these possibilities, since by generating kinetic and dynamic data based on key event biomarkers, we might lead to greater confidence in the hazard characterisation of compounds grouped together. At this stage, in substantiating a chemical grouping hypothesis for *read across, NAMs are fulfilling a largely informative function which generates some confidence in reading across data from one compound to another. One can envisage, however, progress from this point, perhaps by using biomarkers to identify potential health hazards within certain groups of chemicals in a manner which is indicative rather than merely informative. Even now, omics-based NAMs are sufficiently mature to support (or repudiate) the grouping hypothesis of chemicals (including mixtures) based not merely on chemical structure but on observed molecular bioactivity and substance metabolism indicative of their modes of action.*

Changes in approach, such as that illustrated, may or may not fit into the regulatory flow of existing regulation. Therefore, one task in the work on 'embedded translation' of the PrecisionTox programme is to determine whether the adoption of NAMs will require legislative change. Given the pressures on legislative capacity and the time taken up by legislative reform, formal amendment of the law should be avoided where NAMs could be accommodated within existing frameworks. It may be that there will be opportunities for the adoption of NAMs in assessing and regulating classes of hazard for which there are currently no established examples of animal testing; to some extent we see this in areas such as endocrine disruption. Equally, it might be that chemicals are put to purposes which are unregulated or poorly regulated, in which case legal intervention to control such usage may incorporate NAMs.

For much of current chemicals regulation in Europe, however, testing methods may be prescribed in some detail. In the case of REACH, for example, for the different tonnage bands laid out above, the relevant annexes lay down standard information required from industry when registering a chemical substance being manufactured in or imported into the EU. Although the annexes are in places prescriptive as to the information to be provided (for example, from a form of animal testing) this is not always the case. However, even if the text of REACH does not prescribe a methodology for endpoint assessment in all cases, it might be that soft law provisions, such as guidance issued by ECHA, may indicate preferred methods and as such may need to be updated or revised. Bear in mind that CLP and REACH are only regulating chemicals as such and that these chemicals may be employed in a variety of substances, which will then be placed on the single market. There is a vast array of legislation then dealing with risk relating to chemical ingredients of products such as food additives or packaging, cosmetics, or toys. In these contexts, too, there may be the capacity to employ NAMs. Indeed, in cosmetics regulation, animal testing on cosmetics products has been banned since 2013. It follows that there is considerable work in the research programme on tracking legislation and the requirements for chemical risk assessment to review where and how NAMs might be entertained.

Socio-technical Barriers to NAMs

From both the point of view of those wishing to eliminate animal testing and those pressing for more comprehensive testing of chemicals, the take-up of NAMs into chemicals regulation can offer significant advantages. Yet outside of cosmetics regulation, the formal adoption of NAMs within regulatory frameworks has progressed slowly.[34] Unsurprisingly, new scientific method takes time before it is understood and utilised. Until that point, policymakers, regulators, and other stakeholders may cling to the methods which they have long employed, which may involve extrapolation of harm to human or environmental health from laboratory testing on animals. This raises the interesting question of whether the barriers to take-up of NAMs lie within the domain of the technical or the social.

An immediate observation in addressing this question is that the two domains are inextricably linked to the point that it is quite difficult to separate them. One reason for this is that much agreement on scientific discovery is a social as well as a technical achievement. The formulation of hypotheses in consultation with colleagues and co-researchers, the processes of peer review, and the reaching of a point of closure on a scientific question are all examples of social processes embedded in science. This is no less true for the types of risk assessment conducted as part of chemical risk governance. In the process of characterising risk, the underpinning concerns that we seek to address, and the estimations of likely exposures are the product of social as well as technical know-how. Indeed, often the heuristics employed are somewhat reflex and drawn from social experience, background, and training.[35] Nonetheless, we use the label of 'socio-technical barriers' to the take up of NAMs to illustrate that what stands in the way of their adoption is not merely some formulation of the technical processes but a series of social commitments to existing and well-established processes. This is necessary because regulators will wish to know that a method has regulatory relevance; that it directs them to information about a point of concern that gave rise to the regulation in the first place. A regulator will also be keen to ascertain that the method is reliable. Relevance and reliability of a method is generally confirmed by a process of validation.[36] This is seen as an objective and independent assessment of the method and its performance in the context of its use.[37] Although this could take many forms, and sometimes does so, generally the regulatory communities will place more reliance on methods which gain formal endorsement, such as that offered by the OECD, under Defined Approaches or, in Europe, by the European Centre for the Validation of Alternative Methods (ECVAM).[38]

There are, therefore, some clear technical barriers to NAMs being taken up, especially since suitable *in vitro* test methods within REACH are said to be 'those that are sufficiently well developed according to internationally agreed test development criteria'.[39] In a sense, toxicity testing on animals is relatively standardised in that it involves tests which expose animals to very high doses of chemical substances.[40] Even then it can be difficult to interpret the results of animal toxicity testing for the human population (which often leads to yet more animal testing).[41] In comparison, NAMs take a variety of forms, and these may be employed in combination to produce a weight of evidence approach in relation to toxicity.[42] Perhaps the category of NAMs that have made the greatest headway are quantitative structure-activity relationship (QSAR) models,

34) E Benfenati et al., 'The Acceptance of In Silico Models for REACH: Requirements, Barriers, and Perspectives' (2011) *Chem. Cent. J.* 5(58); G Pain et al, 'Drivers of and Obstacles to the Adoption of Toxicogenomics for Chemical Risk Assessment: Insights from a Social Science Perspective' (2020) *Environ. Health Perspect.* 128(10).

35) JC Hanekamp et al., 'Tradeoffs of Chemicals Regulation – The Science and Tacit Knowledge of Decisions' (2018) *Sci. Total Environ.* 794 (148566).

36) OECD Series on Testing and Assessment, Number 34 'Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment' 2005.

37) EA Patterson et al., 'The Role of Validation in Establishing the Scientific Credibility of Predictive Toxicology Approaches intended for Regulatory Application' (2021) *Comput. Toxicol.* 17 (100144).

38) EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) (europa.eu).

39) European Chemicals Agency, 'Guidance on Information Requirements and Chemical Safety Assessment Chapter R.4: Evaluation of available information' (2011) at 6 and see REACH Annex XI section 1.4.

40) I Fischer et al., 'Toxicity Testing is Evolving!' (2020) *Toxicology Research* 9(2) at 67.

41) Note 8 above.

42) REACH Annex XI section 1.2.

which are regression models that investigate the relationship between properties of chemical substances and biological activities in an attempt to provide a reliable statistical model which can predict the activities of new chemical substances. In contrast, the work within PrecisionTox on omics pursues a much more open-ended enquiry into the impacts of chemical substances on the biological systems represented by the suite of model species. The challenge then becomes one of making the best use of such NAMs within the regulatory context, which raises the question of whether the NAM needs to be adapted to fit the regulation or whether the regulation might need to change to accommodate NAMs. In part, PrecisionTox explores the latter question, but it is a challenging one since any regulatory system will strive for procedural fairness and some certainty of like outcomes in like cases.[43] Traditional toxicity testing, despite its uncertainties, has gained regulatory acceptance and its procedures are widely understood by both industry and regulators, generating a level of confidence which protects regulatory decisions against challenge.[44]

At a social level, there is considerable investment in animal testing, which is often promoted as the 'gold standard' which implicitly restricts the space for alternative testing.[45] This investment by advisers, consultants, and laboratories creates a lock into existing methods and a reluctance to shift from the dominant paradigm of animal-based chemical risk assessment. Although research continues on the utility of NAMs for such assessment, much of this work is university-based and is not directed, ordinarily, to findings of immediate regulatory relevance.[46] Research on and employment of NAMs takes place also within the largest multinational corporations which are keen to gather early insights into products being developed for the market,[47] but much of this work does not appear in dossiers submitted to regulators for product approval. PrecisionTox is unusual, then, in wishing to explore the capacity for regulatory adoption of NAMs, and in seeking to explore the socio-technical barriers to this happening.

Led by a university research team at the University of Birmingham, PrecisionTox has a mission to use relatively recent insights from combining omics, evolutionary biology, and genetics to better understand and gather data on molecular processes that might be influenced by chemical exposure. There are a number of ways in the domain of higher education by which it seeks to advance this process, for example by better training in the use of NAMs and by producing and disseminating F.A.I.R. data – data which meet principles of findability, accessibility, interoperability, and reusability – in a transparent fashion. As part of this endeavour, one of the aims of embedded translation is to provide draft guidance as to how and when NAMs may be employed to advantage in the work of chemical risk assessment.

Conclusion

As shown above, PrecisionTox is a research programme which is part of a wider ASPIS cluster devoted to the advancement of NAMs to produce 3Rs compliant chemical testing. Within PrecisionTox, the work package on embedded translation examines how the scientific findings from the wider research programme might be applied in the policy and law that seeks to identify and minimise hazards emanating from chemical substances. This work involves mapping out the regulatory structures in Europe with a view to identifying opportunities to make the best use of NAMs. Alongside this objective, we seek to identify socio-technical barriers to the take up of NAMs and ask how these might be addressed. Finally, as the embedded translation label suggests, the work package looks to provide methods ready for regulatory take-up by providing accompanying guidance on how these may be employed. This is an ambitious agenda but one that is aimed to facilitate the development of ground-breaking methods to assess chemical safety while avoiding reliance on animal derived testing and data.

43) M Mondou et al, 'Factors affecting the Perception of New Approach Methodologies (NAMs) in the Ecotoxicology Community' (2020) *Integr. Environ. Assess. Manag.* 16(2) 269 at 276.

44) Benfenati, Note 33 above.

45) D Swaters et al., 'History of Regulatory Animal Testing: What Can We Learn?' (2022) *Alternatives to Laboratory Animals* 50(5) 322 to 329.

46) SE Escher et al., 'Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment' (2022) *EFSA Supporting Publications* 19(6) at 153.

47) K Taylor, 'Recent Developments in Alternatives to Animal Testing' in K Herrmann and K Jayne (eds), *Animal Experimentation: Working Towards a Paradigm Change* (BRILL 2019) at 585.