The UK as a leader in new approach methods (NAMs) for safety science

An evidence-based proposal using the cosmetic testing bans as a legislative framework.

The UK as a leader in new approach methods for safety science; an evidence-based proposal using the cosmetic testing bans as a legislative framework.

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1. Highlights

- A unique opportunity exists for the UK to become the global leader in animal-free innovation.
- The bans on animal testing for cosmetics provide a legislative 'blueprint' which with required adaptations, can initiate a roadmap for change.
- The cosmetic testing bans pioneered the development and acceptance of new methods which other regulatory industries (e.g. pharmaceuticals, foods) continue to benefit from.
- Animal tests fail to adequately predict human disease and safety in response to chemicals.
- 86–90% of new drugs fail during clinical trials. This failure rate has remained unchanged for three decades.
- 90% of currently marketed chemicals have either limited (20%) or poor (70%) safety data available after decades of a regulatory testing system which has been largely reliant on animal testing and has unassailably demonstrated the need for change.
- Many industry stakeholders are ready to embrace such change. A wealth of new approach opportunities is available to drive scientific and commercial gain in the UK.
- Public health and environmental protection are paramount and an animal-free roadmap to reform regulatory testing can achieve this.
- Without drivers such as the cosmetic testing bans, it is unlikely we would have the innovative animal-free methods and approaches that are available to the regulatory industry now.
- UK public support remains high on phasing out animal testing. 76% want to see existing funding diverted away from animal experiments to improve the development of animal free methods.
- There is a legislative opportunity for a way forward to better science for human health and the environment and there is no reason why the UK Government should not take it.

2. Executive Summary

A unique opportunity exists for the UK to become the global leader in developing and deploying innovative and biologically relevant, animal-free scientific methods for safety testing and research.

The EU bans on animal testing for cosmetics phased in between 2009 and 2013 (referred to hereafter as the 'cosmetics bans') represent an unprecedented – and arguably as yet unsurpassed – legal milestone in the transition towards animal-free safety testing and science.

The purpose of this report is to provide an evidence-based overview of how the cosmetics bans have driven the scientific development and use of a variety of non-animal approaches, now accepted as the way forward in cosmetic safety assessment. Furthermore, in providing this evidence, we describe how the legislative framework of the cosmetics bans can be extended to ensure animal-free safety and protection for human health and the environment across other regulatory sectors, including industrial chemicals, food, pharmaceuticals and more.

The cosmetics bans are widely recognised as 'game-changing' in driving the development of non-animal methods for regulatory safety testing and have *'shaped the landscape of alternative methods dramatically'* [1] both in the cosmetics industry and other chemical sectors.[2]

Extensive work to develop and approve methods to replace the use of live animals was stimulated to be ready for the deadlines which provided a robust legal framework to end regulatory testing for cosmetic products and ingredients, despite numerous postponements and delays including legal challenges to stop the bans altogether.

Ultimately however, the final deadline for the ban on remaining animal testing was implemented regardless of available alternatives.

The bans drove a sea change in innovation of non-animal methods, which to various extents replaced animal tests for cosmetics for several key toxicity endpoints, but also exerted positive influence across other regulatory sectors, including industrial chemicals, food, and pharmaceuticals, which also adopted use of these methods and were described as *'a unique move that cemented the cosmetics industry's place as a propeller for innovation in the field of safety testing.'* [3]

Over the last decade and following implementation of the cosmetics bans, there has been a significant shift in global recognition to develop, adopt and use non-animal methods, often more recently termed 'new approach methodologies' or 'NAMs'.

It is important to specify 'non-animal NAMs' as NAMs are considered by some to include 'new' animal (in vivo) methods. New and existing techniques may be combined as

NAMs as a way forward to answer a specific research question.

Therefore, non-animal NAMs may be comprised of in chemico methods (which provide physicochemical data on the test chemical), in silico (computational) models, human relevant in vitro models as well as existing and new human data from clinical trials or biomonitoring studies.

When different methods are combined it is often considered a *'Weight of Evidence' (WoE)* approach or a *'Defined Approach'* – a specific guideline provided on how to use a combination of methods (in chemico, in vitro, in silico) approved by the OECD; for example to assess skin sensitisation /allergy,[4] relevant to cosmetics testing and many other industries.

Put simply, if we think of any individual method of any kind (e.g. in silico, in vitro, in chemico or existing or new human data) as an 'ingredient' and a NAM as a 'recipe,' there is an urgent need (and virtually limitless opportunities) to improve use of existing ingredients, develop new ones, and *'write more recipes'.*

The scientific and commercial opportunities that NAMs offer for the UK are infinite, especially where current test methods are very poor or lacking, presenting ongoing dilemmas; for example in development of biologicals and vaccines, as emphasised by the recent COVID-19 pandemic.[5]

It is widely acknowledged that NAMs are urgently needed as the way forward, with several political and legislative mandates in place over the last few years in both the EU and the USA to achieve greater flexibility in accepting new safety testing methods and phasing out animal testing to make way for 'new and improved' science.[6]

86–90% of new drug candidates fail during the clinical trial pipeline, having passed preclinical testing stages which remain largely based on animal tests. This rate of attrition has remained the same for decades[7] and is considered a major factor in demonstrating the lack of translation from lab to patient.[8] [9]

Furthermore, of approximately 100,000 currently marketed chemicals, 90% are deemed to have either limited (20%) or poor (70%) characterisation of their hazards and exposures. This is after decades of a regulatory testing system which has been largely reliant on animal testing and has unassailably demonstrated the need for change.[10]

There is a legislative opportunity for a way forward to better science for human health and the environment and there is no reason why the UK Government should not take it.

3. The bans on animal tested cosmetics – a unique landmark in legislation

Though campaigning and scientific initiatives to transition towards modernised and biologically relevant science originate many decades ago, few decisions outweigh the landmark impact of the bans on animal testing for cosmetics, which were implemented in a series of 'phase in' deadlines between 2009 and 2013 in the EU. Under the Seventh Amendment to the Cosmetics Directive, which later became the Cosmetics Regulation.[11]

To correctly convey the impact of the bans, some historical context is provided below.

Challenge and delay, but innovation underway

Development of alternative methods to live animal use has its origins in the 1960s-70s. However, it took until the 1990s to see meaningful shift in legislative dialogue towards recognition of alternatives to animal testing, driven in large part by the 1993 adoption of the EU Directive 93/35/EEC, also widely known as the *'Sixth Amendment to the 1976 Cosmetics Directive'*,[12] which called for a sales ban on animal tested cosmetics from 1998 if scientifically validated methods were available. In any case, the Directive required the Commission to submit a report on progress made in developing alternative methods by then.

By the mid-1990s, collaborative trials to approve the first alternative human skin models were being carried out, led by the European Centre for the Validation of Alternative Methods (ECVAM).[13] [14]

Ultimately, the 1998 EU ban was sadly postponed. However, the sixth amendment had already made its earliest mark in stimulating use of alternative tests beyond the cosmetics sector, for example in medical and biological engineering applications, using reconstructed human skin models, with researchers confident that these 'very useful tools' could be employed in routine toxicity testing.[15]

1998 – the UK takes the lead in decision making

It must be noted that despite the 1998 ban being postponed in the EU, at the time as one of the (then) 15 member states, *the UK did go ahead with a national ban on animal testing for cosmetics. This represented a key example of UK leadership to legislate towards new scientific innovation*.[16]

In 2000, the EU ban was postponed a second time, based on the conclusion that alternatives were still 'not available'. However, three in vitro methods were approved and available from 1997.[17]

A partial ban on animal tests for 'finished cosmetic products' was implemented in the EU in 2004.6 However, as most animal testing is conducted on individual ingredients, a need for greater impact was still to come.

Another reason for the postponement of a full ban was concern over potential World Trade Organisation (WTO) conflicts – The European Parliament referred to this in its subsequent call some years later for a global ban on animal tested cosmetics in 2018 stating it *'calls on the Commission and the Council to make sure that the EU ban on animal testing for cosmetics is not weakened by any ongoing trade negotiations, nor by World Trade Organisation rules; calls on the Commission to exclude cosmetics tested on animals from the scope of any free trade agreements already in force or currently under negotiation'*.[18]

Nevertheless, despite numerous postponements on the basis that 'alternatives weren't ready,' in the background, a significant proportion of the regulatory community was engaged on the need to prepare for the forthcoming bans and international collaboration to innovate was underway. One very notable example, the human skin model EPISKIN was validated and approved in 2007 for skin irritation testing[19] having commenced validation studies for another endpoint, skin corrosion almost a decade earlier.[20]

EPISKIN and other models saw uptake beyond the cosmetics sector, for example in an analysis of the increase of use of in vitro methods in the pharmaceutical industry which noted that the first use of the EPISKIN alternative (among others) was in 2008 with continued increase in use from 2008–2013.[21] This is discussed further later in this report.

Both long before and after the bans came into force, there was firm opposition from within the cosmetics industry that scientific innovation and competitive advantage would be stifled or stopped altogether if the bans went ahead. The French Government mounted a legal challenge to stop the bans going ahead but was defeated and ordered to pay costs at the European Court of Justice in 2005.[22] In parallel however, the forthcoming deadlines continued to stimulate unprecedented innovation, for example as part of the *Sixth and Seventh Framework Programmes for Research and Technological Development*, which ran between 2002–2006 and 2007–2013 respectively.[23] [24]

'The bans are coming' – driving new science for cosmetics and beyond

In its 2008 report on 'Alternative Testing Strategies' under the 6th Framework Programme, the EU Directorate General (DG) for Research and Innovation stated that: *'The need for non-animal alternatives is now all the more important because of existing and pending EU regulations. The 7th Amendment to the Cosmetics Directive (Directive 76/768/EEC) will completely ban all animal testing for cosmetic ingredients by 2009 at the latest. The ban covers skin sensitisation. Conversely, the new EU legislation on chemicals (REACH) will require a great deal of additional chemical testing. It is estimated that skin sensitisation testing is among those human health effects that require large numbers of animals.'*

As a result, 28 groups from academia and industry, as well as special interest organisations, joined a collaborative initiative known as 'Sens-it-iv' to develop non-animal tests and testing strategies to assess allergenic potential. The overall goal of Sens-it-iv was described as *'to develop strategies to replace animal experimentation by in vitro assays for identifying skin and respiratory sensitisers. This is seen in relation to the use of safe ingredients by the chemical, cosmetic and pharmaceutical industry.'* [25]

Legislative history was made on 11 March 2009 when a ban on the testing, import and sale of cosmetic ingredients on animals was applied to several toxicity endpoints (e.g. skin irritation, skin corrosion, phototoxicity, skin absorption/penetration, eye irritation, genotoxicity / mutagenicity, acute toxicity) as well as a testing ban on more complex endpoints (repeat dose toxicity, skin sensitisation, reproductive toxicity, carcinogenicity and toxicokinetics).

Exactly four years later on 11 March 2013, the marketing ban became effective under the 7th amendment for these latter endpoints too, regardless of available alternative methods, effectively underlining the view that animal suffering was no longer justifiable for cosmetics. The bans were unique in this ethical standpoint in that even if replacements were not available, animal testing was forbidden according to the regulation.

In its communication on the marketing ban published on the same day, the Commission confirmed that *between 2007 and 2011, a total of 238 million EUR was invested in research into alternatives to animal testing in the EU*.[26] The fact that such major investment was envisaged for use well beyond the cosmetics industry reaffirms the impact of the bans, especially as animal tests for cosmetic purposes represented 'only' 0.05% of total animal use in the EU. This reflects the fact that most cosmetic ingredients are multi-purpose (used in cosmetics, food, drugs, other chemicals) and therefore 'exclusively cosmetic' substances are relatively small in number. This adds further weight to the fact that other chemical sectors continued to benefit from the development of new methods under the bans.[27]

The SEURAT initiative ('Safety Evaluation Ultimately Replacing Animal Testing') was an initiative under the 7th Framework Programme, funded with €50 million by Cosmetics Europe and the European Commission between 2011 and 2015.[28] The funders described the initiative as *'proof of the active role assumed by the cosmetics industry in the development of alternative testing methods'*. [22]

SEURAT was a collaboration of more than 70 European research teams, with the goal of developing novel methods for predicting repeated dose systemic toxicity to chemical exposure in humans. The project investigated combinations of computational (in silico) and in vitro methods for supporting safety assessment decisions.

The SEURAT project also described how repeated dose systemic toxicity testing is not only relevant for the ingredients of cosmetic products, with impact on many other areas of application such as drug development, food production, and safety assessment of industrial chemicals, plant protection products and biocides.[29]

It would be remiss if this report did not acknowledge the impact of the REACH chemicals legislation on the Cosmetics Regulation.[30] [31] However, though the issues that REACH presents form part of ongoing lobbying and scientific campaigns, the history and milestones of the cosmetics testing bans remain a standalone landmark achievement in initiating the phase out of animal testing towards new scientific methods which is the primary focus of this report.

This has resulted in a sea change in today's cosmetics industry, which has evolved with a consensus voice that animal free safety science is the way forward and must be accepted as a global industry standard for improved protection of human health and the environment.[32] [33] [34]

The ban on animal-tested cosmetics and its influence

1970s – 1980s

The origin of national and international campaigns raising public awareness and the need to end animal testing for cosmetics

1993

First EU proposal of a ban on animal tested cosmetics (under the Sixth Amendment to the 1976 Cosmetics Directive) with a deadline of 1 Jan 1998

1997

The EU ban is postponed for the first time until 2000

1998

Despite the EU ban delay, the UK goes ahead with a ban on animal testing for cosmetics

2000

The EU ban is postponed a second time

2003

The landmark Seventh Amendment first proposes EU bans on animal testing and marketing for both finished cosmetics products and ingredients

2004

11 Sep 2004: The EU ban on animal testing for finished cosmetic products becomes effective

2005

European court challenge by French Government (fails) to prevent forthcoming bans going ahead

History and Timeline

11 Mar 2009:
The EU bans become effective on:

1. Animal testing for cosmetic ingredients*
2. Import and sale of finished cosmetic products tested on animals

**Animal tests still permitted for more complex test 'endpoints'*

2009

2008 REACH chemicals legislation enters into force

2013

11 Mar 2013:
Full EU ban becomes effective. Animal testing for cosmetic purposes is no longer acceptable under the Cosmetics Regulation

2013 onwards

Many bans on animal-tested cosmetics implemented across the world

2018

EU Parliament proposes a global ban on animal tests for cosmetics

2021

EU Parliament votes almost unanimously for a plan to phase out animal testing in research, testing and education

2023

17 May 2023:
UK Government confirms an end to animal testing for ingredients exclusively used in cosmetics including worker safety under REACH

17 Oct 2023:
UK Government confirms that there is no UK legislation that mandates animal testing

4. The Domino Effect:

Bans on animal tested cosmetics beyond the EU

In addition to the final 2013 ban across all EU member states, countries which represented the European Free Trade Association (EFTA) – namely Norway, Switzerland, Iceland, and Liechtenstein – implemented bans too. This was followed by similar bans in India, Taiwan, Israel, Turkey, South Korea, New Zealand and Guatemala.[35]

In 2018, The European Parliament sought to achieve a global ban on cosmetics testing on animals within the next five years, with a parliamentary resolution which noted that *'the animal testing ban has led to increased research efforts to develop alternative testing methods, with effects going far beyond the cosmetics sector; notes that significant progress has also been made on the validation and regulatory acceptance of alternative methods.'* [36]

By 2020, over 40 countries worldwide had partial or full bans on animal testing for cosmetics with many further nations 'in progress' towards bans. [37]

This included some landmark developments in China, with removal of mandatory animal testing for domestic 'non-special use' products (cosmetics are classified as 'special' or 'non-special' use in China). This was followed by bans on selected imported cosmetics and most impactful of all, an animal testing exemption for 'all general cosmetics.' Though this excludes some products which are on the 'cosmetic vs medical' borderline (e.g. some hair products, whiteners and sunscreens) and though there is still a long way to go, the decision had a pioneering impact towards phasing out animal tested cosmetics in China, alongside first acceptance of alternative test methods.[38]

Bans on cosmetics testing in North America (e.g. selected US states and Canada) also continue to be implemented recently.[39] [40]

The European Citizens Initiative to *'Save Cruelty Free Cosmetics – Commit to a Europe Without Animal Testing'* was launched in August 2021 which called on the European Commission to fulfil three main objectives: to protect and strengthen the cosmetics animal testing ban; transform EU chemicals regulation; and modernise science in the EU. The ECI had monumental impact by collecting 1.2 million public signatures across the EU.[41]

The ECI also outlines how *'the advent of the cosmetics testing and marketing bans saw a boom in the development and application of non-animal methods that can be broadly applied across a range of sectors – including the industrial chemicals sector – for safety assessment purposes. By replicating the model for increased investment set to strict objectives and milestones, an animal-free regulatory framework, once perceived as impossible, can be achieved.'*

The ECI also called for greater consistency and harmonisation across all chemical sectors by use of the *'One Substance One Assessment'* initiative set out under the Chemicals Strategy for Sustainability.[42]

Though the UK is no longer an EU member state, national public opinion aligns with EU citizens. **In a recent poll, 76% of the UK public wanted to see existing funding diverted away from animal experiments to improve the development of animal-free methods.**[43]

5. The Ripple Effect:

Political drivers for change and non-animal methods developed for the cosmetics bans and used in other regulatory testing sectors

In parallel to the launch of the ECI, the European Parliament (EP) again used its voting power in September 2021, with a motion for resolution to establish *'plans and actions to accelerate a transition to innovation without the use of animals in research, regulatory testing and education'*. The EP voted almost unanimously in favour of the resolution with 667 votes in favour and only 4 votes against.[44]

The resolution noted that *'the positive impact on animal welfare in the EU of the landmark ban on animal testing for cosmetics* ***has successfully shown that phasing out the use of animal testing is feasible without jeopardising the development of the cosmetics sector****'* however *'there are still regulatory requirements for continued animal testing for effects on workers handling chemical ingredients exclusively used in cosmetics, and their impact on the environment; whereas, nevertheless,* ***the setting of clear deadlines for the phasing out of such testing in the EU has driven innovation in EU companies*** *and has enjoyed public support.'* With the regard to the scientific need for new approaches it noted that *'the* ***replacement of animal testing by advanced non-animal methods will be necessary to achieve the Commission's ambitious health and environmental goals set out in the Next Generation EU recovery plan and the European Green Deal****'* and *'****where validated non-animal alternatives are already available, these must be given priority****'*. [45] [emphasis added]

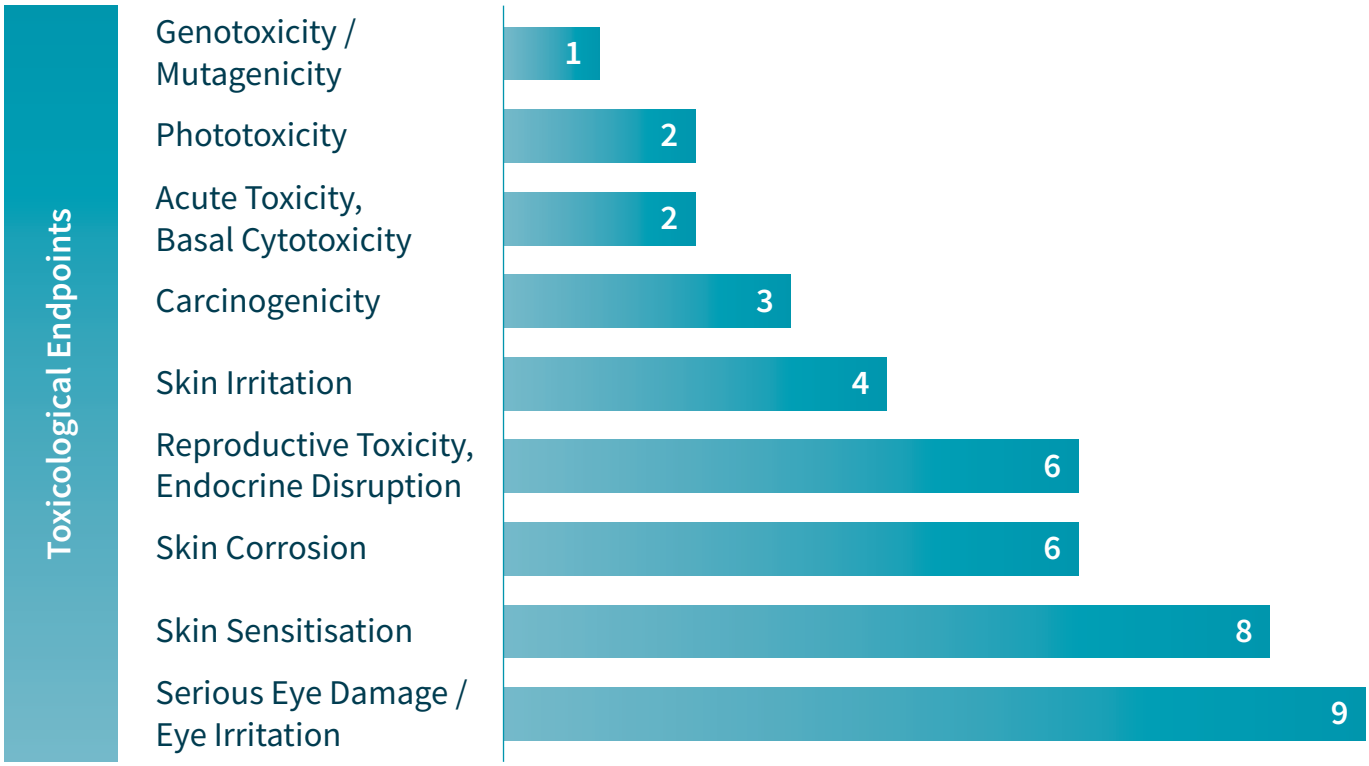
In direct response to both the ECI and EP resolution, in November 2022 the European Commission announced their commitment to *'developing a European roadmap towards the full replacement of animal testing under the chemicals legislation.'* [46] The Commission hosted its first *'Workshop on the Commission roadmap towards phasing out animal testing for chemical safety assessments'* in December 2023.[47]

In the follow up report to the workshop, the Commission describes the impact of the cosmetics testing bans on the regulatory industry: *'The Cosmetics Regulation (EC) No 1223/2009 is the first EU regulatory framework to have completely banned animal testing and marketing of cosmetic products tested on animals since March 2013. This has meant that the use of NAMs became vital and much has been learned.'*

A number of principles were also defined in the report, including *'ensuring a high and transparent level of protection.'* To achieve this, recommendations included in reference to defining a legal framework for elimination of in vivo (animal) testing that *'the use of NGRA (next generation risk assessment) for the safety assessment of cosmetic ingredients could be used to demonstrate what does and does not work successfully.'* [48]

When examining the impact of the cosmetic testing bans, it is important to review some evidence of specific test methods and their development and use both within and beyond the cosmetics industry.

Figure 1:
Toxicological endpoints relevant to human safety of cosmetics
(reproduced from Silva and Tamburic, 2022)



The endpoints relevant to cosmetics testing and alternative approved test methods are represented in the useful visual above (reproduced from Silva and Tamburic, 2022).[3]

The figures represent the number of approved methods available for each cosmetics testing endpoint (e.g. 4 methods for skin irritation). These are mainly in vitro methods, but also include several ex vivo and one in vivo test. For the purposes of this report, we exclude these tests from the discussion as they still involve animals. It is also important to note that there are countless further methods (e.g. in silico, in vitro) in use across industry for example for 'non-regulatory' or 'in house' decision making by cosmetic, pharmaceutical and other companies.

Some further examples on how new approaches are used in other sectors are examined below.

There are many sectors of chemical testing, some examples within pharmaceutical and food industries are provided.

Pharmaceutical Testing

As described earlier, in the years well before, during and since the 2009–2013 EU cosmetics testing bans came into effect, the development and use of a number of alternative methods was stimulated across the regulatory sector.[24]

The availability of new non-animal methods to the pharmaceutical industry as a result of the cosmetics testing bans is apparent for example, for compound 'deselection' to improve the quality of candidate drugs, decrease preclinical failures (attrition), and reduce animal use. The potential of this was noted in a 2013 review with regard to

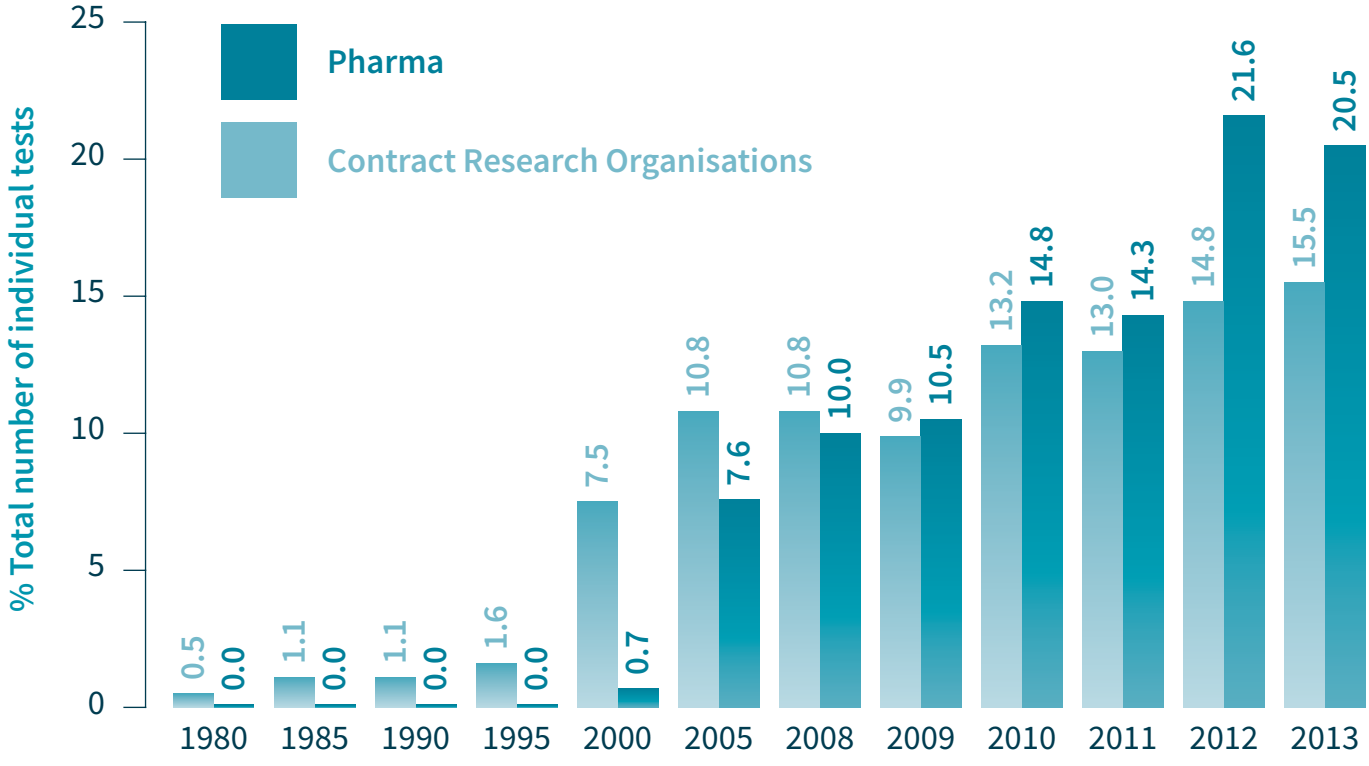
in vitro genotoxicity assays in that *'early detection of genotoxicity in vitro could preclude the further development of these new chemical entities, as is the case with European cosmetics'*. The study also notes that with regard to another endpoint, skin sensitisation, *'considerable progress has recently been made in alternative assays to detect skin sensitization potential'* and the need to incorporate the latest science into safety pharmacology assessments.[49]

Though innovation within the pharmaceutical industry exists in its own right, the industry has benefited from the acceleration of new methods available and the cosmetics framework is regularly cited as a main driver for their development.[45]

The European Medicines Agency (EMA) recognised the increased use of in vitro methods in its 2012 concept paper: *'On the need for revision of the position on the replacement of animal studies by in vitro models'* describing the facilitation of progress in the field by large EU initiatives including the European Centre for the Validation of Alternative Methods (ECVAM) and the European Partnership for Alternative Approaches to Animal Testing (EPAA), noting that *'over the past years a shift has been observed towards the regulatory acceptance of scientifically valid in vitro methods as well as formally validated in vitro methods as part of an integrated testing strategy'*.[50]

This is supported by other evidence, such as an analysis of the development and use of in vitro methods in the UK pharmaceutical industry between 1980 and 2013, which found that more than 20% of all in vitro tests were conducted in the last year of the survey window (2013) and over 70% of tests were conducted since 2010, with relatively low numbers conducted before 2005 (Figure 2).

Figure 2:
Increase in use of in vitro methods in the pharmaceutical industry between 1980–2013
(reproduced from Goh et al., 2015)



The review analysed survey responses from four pharmaceutical companies and three contract research organisations (CROs) in the UK.[16]

The study refers to validation and availability of a number of in vitro tests for pharmaceutical use, for example EPISKIN for skin irritation, following its validation by ECVAM in 2007. The study also highlights the nature of tests predominantly used by pharmaceutical companies compared to 'outsourced' testing to CROs who made diverse use of a range of in vitro test endpoints which had been developed in the lead up to the cosmetics testing bans, including eye irritation, skin irritation and skin absorption.

It is also important to emphasise that aside from 'approved' or 'validated' methods, there are hundreds of methods which have been developed for use within companies without undergoing any official evaluation.[24]

This 'in house' scientific innovation can and must be harnessed and strengthened by a robust legislative framework to deploy consistent and harmonised use of all available non-animal methods and approaches. The large majority of regulatory tests on animals performed in the UK are to meet legislative requirements in the EU and beyond, providing further scope for expansion into the 'non-animal NAMs' market.

It is important to note that if those who lobby to maintain or increase the use of animals in safety testing and research were successful in their objectives, it is arguably very likely that we would not have the innovative animal-free methods and approaches that are available to industry now.

In addition to the scientific and ethical drivers to phase out animal testing, it is important to recognise a 'third factor', which is the business infrastructure and financial interests of the global animal research industry, which extend well beyond researchers to establishments and high profile institutions, large scale international suppliers, breeders and transporters of (genetically modified) animals, cages and experimental equipment, 'laboratory animal' food, treatments and many other products. The global animal testing market was valued at 10.74 billion USD in 2019 and anticipated to have a value of 12.2 billion USD by 2023.[51]

Nevertheless, business opportunities and competitive advantage in the development of NAMs in the pharmaceutical industry has never been better in the UK and beyond, especially since the implementation of the FDA Modernization Act 2.0.

A recent market analysis report describes how *'the number of CRO-type providers offering NAMs boomed over the past 10 years and increased by 31.9%'* and that *'there is a strong market attractiveness for NAMs as large pharmacos are now adopting and investing in these non-animal methods. Because of the complexity of biological systems, the provider landscape is highly fragmented and mainly composed of specialised players with unique technologies'*. [52]

But growth in new technologies is clear, with the organoid market alone expected to grow by 21.7% over the next three years and a projected value of $3.3bn by 2027.[51] This is coupled with new technologies becoming cheaper as their use rises. For example a decrease in the cost of in vitro methods was observed generally between 2010–2018. [26]

The UK is yet to fully exploit these scientific opportunities for economic growth while its reliance on animal use persists.

There is support for NAMs within the pharmaceutical industry citing the influence

of the cosmetic bans. For example, Sanofi recently stated that the roadmap announcement in response to the ECI on Save Cruelty Free Cosmetics *'fits perfectly with the current initiatives and aspirations of the EU pharmaceutical industry, which is "committed to the science-based phase-in of methods to replace the use of animals for scientific purposes and the deletion of animal tests which are obsolete or redundant."'* [53]

Food testing

Many of the alternative methods developed as a result of the cosmetics bans are of benefit to the food testing sector and the integration of NAMS into safety assessments is described as being 'pioneered by the cosmetics industry'.[54]

In analysing new methods and strategies for testing food ingredients as part of a roadmap, tests available for toxicologically relevant endpoints were significantly developed as a result of the cosmetic framework, for example human 3D organotypic models for eye and skin irritation. Food safety researchers note the emphasis on a *'shift from using clinically and / or histopathologically observable … adverse effects of a substance in … animals, towards a more detailed description … of the mechanism of action at the molecular level'* also outlining the opportunities provided by technological innovations which when examined further are closely connected to the cosmetic framework drivers.

In a recent collaborative review, co-authored by international industry stakeholders from the UK, EU and Switzerland entitled: *'Animal-free strategies in food safety and nutrition: What are we waiting for?'* the study findings included that existing non-animal strategies urgently need improved application in food safety assessment, that there is great potential for research strategies that reduce the use of animal tests and action is required by all stakeholders to be more challenging in applying non-animal approaches. Most critically of all, they found that acceptability of non-animal approaches needs to be better reflected in food safety legislation.[55]

Innovation in all sectors continues

The Horizon 2020 (H2020) EU-ToxRisk project: *'An Integrated European "Flagship" Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st Century'* [56] was designed as a follow up of the SEURAT 1 research initiative and as a funding framework for research activities between 2014 and 2020, with focus on repeated dose systemic toxicity, using the lung, kidney, liver, and nervous system as examples of potential target organs; and developmental and reproductive toxicity.

It was described as offering the *'opportunity to continue and expand the Union's commitment to research in alternative, better methods of human safety assessment and capitalize on possible innovation in this field'* also calling on commitment and

engagement from all sectors that would benefit from the development of new alternative methods.[26] Horizon Europe, the latest research and innovation framework began in 2021 and runs until 2027.

RISK-HUNT3R, the successor of EU-ToxRisk and funded under the Horizon Europe initiative, is underway to develop a reliable, efficient, and cost-effective chemical safety assessment approach, based entirely on non-animal methods to deliver improved protection against systemic toxicity caused by (chronic) chemical exposure. The project focus is *'the fundamental need to address all potential health effects relevant and specific to humans. In addition, due to increasing regulatory demands, the limited laboratory capacity and high costs of animal-based testing is becoming a hurdle for the provision of all desired information requirements for chemicals safety assessment.'* [57]

In addition to RISK-HUNT3R, several other initiatives continue under Horizon Europe.

The Virtual Human Platform for Safety Assessment (VHP4Safety) is a project to develop the world's first virtual human platform to determine the safety of chemicals and pharmaceuticals by transitioning from animal-based to human-based approaches and combining innovations in data science, human tissue models and change management initiatives.[58]

ONTOX ('ontology-driven and artificial intelligence-based repeated dose toxicity testing') is a further multinational collaboration which works to provide a functional and sustainable solution for advancing human risk assessment of chemicals to achieve 21st century, animal-free next generation risk assessment.[59]

The cosmetics industry continues to provide large scale funding for all the above projects under the Horizon Europe Framework, to the total of over 40 million EUR.[60]

6. Conclusion:

The UK political and scientific landscape is ready – harnessing innovation, leadership and early Government 'wins' on a UK roadmap

This report has aimed to demonstrate how innovation in regulatory testing in the UK and beyond has been stimulated to great advantage by the bans on animal testing under the Cosmetics Regulation and how the legislative framework the bans provide can be extended across all sectors of chemical safety assessment.

Furthermore, while development of new, more human and environmentally relevant research methods remains crucial, there is also a need to review and revise existing practices; delete duplicative and redundant methods and improve use of methods already available. As described earlier, many methods are used internally within individual organisations which could be harmonised for industry-wide use.

Further to this, there are validated and available methods which are not being used fully.[61] As part of a UK roadmap, these initiatives require no new technologies to be developed, instead requiring review and change of current practices to achieve early-stage government 'wins' to reform regulatory testing.

In response to public concerns over a return to cosmetics testing on animals under the chemicals regulation REACH and abandonment of the cosmetics testing ban[62] in May 2023 the (then) Home Secretary, Suella Braverman announced that '*the Government is taking action to seek alternatives to animal testing for worker and environmental safety of chemicals used exclusively as cosmetic ingredients. We are therefore announcing a licensing ban with immediate effect.*

The Government is committed to replacing animals used in science wherever scientifically possible and is confident that the UK science sector and industry has the talent to provide the solutions.' [63]

Later in 2023, Will Quince MP confirmed in response to questions on testing of pharmaceuticals and steps being taken to promote non-animal methods that *'There is no United Kingdom legislation that mandates animal testing.'* [64]

Though this reflects dialogue from the previous Government, arguably the new Government also considers itself *'committed to replacing animals used in science wherever scientifically possible and is confident that the UK science sector and industry has the talent to provide the solutions.'*

When looking at recent advances in new UK start ups and innovation, there are some exciting method developers who have secured forward thinking industry backing for their work. For example, Newcells Biotech, a spinout from Newcastle University has developed 3D human based models to replace drug testing on animals and is now working with 100 customers across pharma and biotech. Newcells mission is to improve the models available to scientists to overhaul the efficiency of drug development and deliver new therapies to patients.[65]

The research talent within the UK is clear to see and regulations need urgent reform across all sectors in order to keep dynamic pace with scientific progress.

There is a legislative opportunity for a way forward, to enshrine better public health in a modernised, animal-free regulatory framework and there is no reason why the UK Government shouldn't take this opportunity.

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