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More than a Decade On: Mapping Today's Regulatory and Policy Landscapes Following the Publication of *Nanoscience and Nanotechnologies: Opportunities and Uncertainties*

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Abstract It is now more than a decade since the release of the Royal Society and Royal Academy of Engineering's (RA/RAEng) seminal report on nanosciences and nanotechnologies. The report, for the first time, brought together the spectrum of scientific and societal issues underpinning the emergence of the technology. In articulating 21 recommendations, the RA/RAEng provided the United Kingdom Government—and others—with an agenda on how they could, and should, deal with the disparate aspects of the technology. The report provides a baseline to measure progress against. By focusing on the eight recommendations that dealt specifically with regulation and governance, I reflect on the extent, and nature, of this progress; identify key actors in shaping the evolving governance framework; and, importantly, distinguish areas where progress appears to have lagged.

Keywords Governance · Health and safety · International activities · Nanotechnologies · Regulation · Royal Society and Royal Academy of Engineering · United Kingdom

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> "A slow sort of country!" said the Red Queen. "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"
> - *Lewis Carroll, Alice through the Looking Glass.*

Introduction

29 June 2014 marked the tenth anniversary of the release of the Royal Society and Royal Academy of Engineering's (RS/RAEng) report, *Nanoscience and Nanotechnologies: Opportunities and Uncertainties* [1]. Commissioned by the United Kingdom (UK) Government in 2003, the report was not the first document published by members of the epistemic community on the potential benefits and risks posed by the technology, or of its potential economic, ethical, social, and/or legal dimensions [2–6]. However, its influence on shaping policy across jurisdictions has ensured that it remains one of the preeminent publications in the field. Leading commentators across disciplines continue to draw from the report [7–9], including governments, regulators, academics, and members of the non-governmental community. By providing a comprehensive assessment of the scientific, social, and legal landscape in which the nanosciences and nanotechnologies were emerging, the report provided a baseline from which activities and actions could then be measured against.

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With the report now having been in the public domain for more than 10 years, it is timely to reflect on how far we have come in addressing the concerns articulated in the report. And, in particular, the ways in which governments, regulators, and other actors have sought to address the sets of recommendations[1] set out in the report. Or, put in another way, to identify priority areas that still require attention from relevant stakeholders.

In this article, I focus on assessing the progress been made by the UK Government (HM Government), other governments, EU policy makers and other key stakeholders in addressing the regulatory issues and the recommendations (R) articulated by the RS/RAEng [1]. My reasoning for doing this is simple: the types of activities and actions taken (or even considered) by policy makers and regulators have generally occurred in the public domain and can therefore be more easily identified and mapped; the groups of actors who have helped shape such responses can, for the most part, be identified; and given the contentious nature of some of the regulatory recommendations, have generated noteworthy dialog and debate within the literature.

In order to track and assess the extent to which key bodies, including governments and regulators, had adopted or moved to adopt the RS/RAEng's recommendations, a desktop literature review was undertaken. The start point for the review was the RS/RAEng's [1] report itself, followed by the UK Government's response. Initial database searches focused on the UK, and then the EU. Drawing on the English-language articles, reports and other documents cited within this initial body of literature (including, for example, parliamentary debates, bills, and legislation), I was able to broaden out my initial search. This snowball approach resulted in the creation of an additional body of literature dealing with activities beyond the EU's border; specific jurisdictions of focus were found to be Australia, New Zealand, and the United States of America (USA). Language limitations limited me from undertaking a supplementary literature review that looked specifically at jurisdictions in which English is not an official language. Additional, supplementary, information was supplied by my active participation in some of the activities and processes noted in the article, and my active role more generally in the nanoregulation debate since May 2004.

The article is structured as follows: The first section of the article sets out each of the eight recommendations that dealt with regulatory issues. Each recommendation, the UK Government's response, and key actions and activities within the UK, the EU, and more globally are considered in the subsequent section. In this part of the article, we consider the progress made, if any, since the release of the report in 2004 and reflect on what this new landscape looks like. The final section of the article draws together my concluding thoughts on progress made, the implications of this progress, and suggests what the regulatory path may look like going forward.

The Regulatory Recommendations in Detail

As noted above, the RS/RAEng [1] offered eight recommendations that were directly associated with regulatory matters within the UK and the EU. My interpretation of the recommendations is as follows:

R8. Due to the breadth of agencies and instruments involved in regulating nanotechnology-based products and processes, all relevant agencies should undertake their own regulatory reviews in order to assess their adequacy to deal with such products and processes. The results of such reviews should be made publically available, including details of how they intend to address so-called regulatory gaps.

R9. Regulatory bodies should be proactive in addressing risk and regulatory gaps and include horizon-scanning activities as part of their operational activities.

R10. Nanomaterials should be considered and classified as "new chemicals" for the purposes of triggering industrial chemical legislative regimes. They should not be classified as "existing chemicals" and treated in the same manner as their conventional macroscale chemical counterparts.

[1] The 21 Recommendations were placed into six categories: The industrial application of nanotechnologies (R1–2); Possible adverse health, safety and environmental impacts (R3–7); Regulatory issues (R8–15); Social and ethical issues (R16–17); Stakeholder and public dialog (R18–19) and Ensuring the responsible development of nanotechnologies (R20–21). While distinct for the purposes of the report, many of the recommendations draw from, and build upon, the other multiple domains.

Threshold triggers and risk assessment regimes should be reviewed to determine application and effectiveness.

R11. Due to the potential for inhalation exposure to workers manufacturing nanoparticles, occupation health and safety legislation should be reviewed to assess adequacy to protect the worker population. In the absence of toxicological data, occupational exposure levels should be lowered for nanoparticles as a precautionary measure.

R12. Consumers will increasingly come into contact with nanomaterials through everyday products such as cosmetics and personal care products. Given the potential for increasing exposure, the relevant regulatory regimes should be assessed to determine their adequacy to safeguard human health with respect to nano-based products. This work should be informed by the European Commission's (EC) relevant scientific advisory committees. Consumer products containing nanomaterials should be required to indicate the presence of nanomaterials on their packaging, and industry should be required to disclose safety-testing methodologies.

R13. The Department of Health should review the adequacy of existing regulatory arrangements to address the potential adverse side effects associated with the use of nanomaterials in new medical devices and/or medicines.

R14. Due to the potential for human and environmental exposure to occur at the end of a product's lifecycle, manufacturers should publicize details on how they propose to address end-of-life issues.

R15. In partnership with industry and government, the research community, should work together to develop measurement standards for nanoscale products. Priority areas include measurement standards relevant to the occupational health and safety context, as well as those most relevant to the regulatory community.

As these eight recommendations highlight, potential worker, consumer, and environmental exposures were identified by the RS/RAEng [1] as being of particular importance due to the potential risks associated with near-term, or increased, exposure relative to other products and/or areas. Similarly, the RS/RAEng [1] articulated a need to move away from regulating chemicals solely on the basis of their name (or Chemical Abstract Service, CAS, number). Chemical regulatory schemes traditionally regulate a chemical substance on the basis of its name/CAS number and not in relation to physicochemical characteristics, such as scale and/or surface area to volume ratio, which may give rise to unique properties when compared to their larger scale equivalents. In their report, the RS/RAEng called for a more sophisticated process that takes into account particle size as well as chemical name.

While these recommendations were drawn from the authors' analysis of the UK's and EU's respective regulatory matrices at that time, their findings and implications extend beyond the EU's borders. This is due to the global nature of trade, the ubiquitous nature of nanotechnologies, and the push by many governments, including the USA and China, to incorporate nanotechnologies (and other emerging technologies) into their economic and innovation strategies in the twenty-first century [10, 11]. As such, the issues, challenges, and questions identified by the RS/RAEng can be largely viewed as being horizontal in nature, common in most jurisdictions. This is despite the exact text of their legislative and regulatory instruments varying, as too the institutional design of their regulatory agencies. It is for these reasons that the splash of the report was felt beyond the borders of the UK and EU and is likely to have contributed albeit in varying ways to the actions taken by relevant parties beyond the EU's jurisdictional borders.

The HM Government official response to the RS/RAEng's report was published in February 2005 [12]. In their rejoinder, the Government crafted an overall response to the threads and themes identified by the RS/RAEng before specifically addressing each of the 21 recommendations.

Of particular note was their acknowledgement of the need for additional data on physicochemical characteristics of nanomaterials along with toxicological and ecotoxicological studies. In light of the obvious and substantial gaps in the science and the evolving state of the scientific art, it was stated that they were,

> "supportive of the precautionary stance taken by the RS/RAEng and agree[d] that sensible and pragmatic steps can be taken now to control possible risks to environmental and human health from the manufacture of new free nanoparticles

without the need to halt development activity, and that such steps should be taken alongside action to understand their properties" [12].

In this vein, the UK Government agreed with the RS/RAEng's recommendation that a moratorium on the development and commercialization of nanotechnologies was unnecessary and inappropriate, and that a more nuanced approach that encouraged precaution and responsible innovation was preferable [12].

HM Government went on to systematically address each of the RS/RAEng's 21 recommendations. Looking specifically at those dealing with regulatory issues, the Government agreed with or supported many of the recommendations articulated by the RS/RAEng but stopped short of accepting them all. This would appear to be in recognition of the overarching EU legislative structures and governance.[2]

For example, the Government supported R8 and R9, which called for in-depth regulatory reviews, monitoring, and horizon scanning activities to be undertaken by all relevant regulatory bodies and their advisory committees. Similar sentiments were offered in relation to R11 and R13, with HM Government acknowledging the need for the Health & Safety Executive (HSE), the Department of Environment Food and Rural Affairs (Defra), the Environmental Agency and the Department of Health to take a proactive approach to managing nanotechnologies within the workplace, the environment, and in relation to medicines and medical devices. Their focus was not simply, however, on the enactment of new legislative instruments (i.e., hard law). Rather, it would appear they saw a role for softer instruments to be incorporated into their respective approaches. This included, for example, the development of advice documents, guidance materials, and protocols. The Government also advocated for regulatory agencies to work with other relevant bodies to ensure best practice across the board.

Chemical substances and many consumer products, including cosmetics, are regulated at the EU level through regulations and/or directives. As such, while the Government,

> "accepte[d] that a chemical form of nanoparticles or nanotubes may exhibit different properties to the bulk form of the chemical; sometimes this is beneficial and sometimes it may be potentially hazardous" [12],

and acknowledged that new regulations may be required for chemicals at the nanoscale (R10), they noted that this was not within their regulatory powers. Rather, such changes would fall to the European Parliament and Council. This would also be dependent on the findings of an in-depth regulatory review within the UK.

While the Government similarly accepted that full safety assessments of nanomaterials, disclosure of testing methodologies, and appropriate labeling of consumer products containing nanoparticles would assist in the development of best practice and informed choice by consumers (R12), such action would have to occur at the EU level. As such, the response stressed the need for "working " and "communicat[ing]" with the Commission, relevant Directorates-General (DGs), the scientific committees, other governments, and industry in order to ensure best practice within the framework of EU legislation [12].

The overarching role of EU legislation was similarly stressed in their response to R14. Specifically, the response acknowledged the need for a proactive approach by the Commission to effectively, and adequately, oversee the whole-of-life cycle, including the disposal of products containing nanomaterials [12].

The need for "measurements that underpin regulation and quality control" (R15) was "accepted" as an area of high priority [12]. The response went on to state how they had already begun to address the need for measurement and standardization challenges for nanotechnologies, including through their involvement in the European Standards Organization. The role of, and for, industry in the development of standards was similarly noted; implicit here was the fundamental role that industry has played in creating standards in other areas/sectors, and the continuing role that they would play in standard setting bodies such as the International Organization for Standardization (ISO).

Despite the positive response from HM Government [12], and the acceptance of many of the 21 recommendations, such agreement came without explicit funding to support such activities. Without dedicated funding for regulatory reviews, horizon scanning activities, and stakeholder engagement, one must ask

[2] It should be noted that at the time the UK Government released their response to the RS/RAEng the concept of "Brexit" had not been conceived. As such, the Governance deferred–as and where required–to the overarching legislative regimes established by the European Parliament and Council for member states. At the time of writing (October 2016), it still remains unclear how the Brexit vote will impact on the regulation within the United Kingdom.

whether the RS/RAEng report had the impact, or shaped activities, to the degree to which its authors envisaged.

While such a question is impossible to answer, we can map the ways in which the UK's regulatory landscape has changed for nanotechnology since the report's release in 2004. Progress made in other jurisdictions, including the EU, which looked to debates and discussions playing out in the UK at the time, can similarly be identified. In this way, it is possible to map just how far governments and key policy makers have come in addressing the concerns articulated by the RS/RAEng at the time, the types of activities non-governmental actors have participated in, and the way in which broader actions and activities have contributed to the evolving governance of nanoscience and nanotechnologies.

Progress Made?

In order to fully appreciate the progress that has, or has not been made, since the publication of the RS/RAEng's report on policy and regulatory landscapes, as well as the broader governance framework for nanotechnologies, it is essential to track each of the recommendations separately. As such, this section of the article focused on each of the eight recommendations respectively. In doing so, the article looks first at progress being made in the UK, followed by the EU. Based on the literature review and snowball approach articulated above, the article then turns its attention to activities and progress made beyond the EU. Key actions and initiatives that speak directly to the recommendation are the focus of this article.

Regulatory Issues and Regulatory Gaps

Prior to the release of the RS/RAEng's report, few commentators had focused on the potential legal and regulatory challenges that nanotechnologies may give rise to in the short, medium, and longer term [5, 6, 13–15]. Instead, governments had tended to focus primarily on the economic and commercial aspects of the technology [16]. This is arguably not surprising given the limited number of products and applications that had made their way into the market by 2004, alongside the speculative nature of the technology at that time. Moreover, the potential human and environmental impact of nanomaterials had only begun to be publically discussed, and debated, in academic circles.

In my view, an underlying strength of the RS/RAEng's report was that it coupled the state of the science with the broader legal and regulatory questions and provided real-world examples of how current regulatory regimes may be challenged by current and future applications, especially in relation to potential risks. In doing so, the onus was placed back on safety regulators to test, and ensure, the robustness of current frameworks in light of the evolving state of the scientific art.

Following the acceptance of this recommendation (R8), a number of relevant UK regulatory agencies initiated or commissioned reviews of their regulatory arrangements and/or scientific reviews relating to the products that they would regulate. These included the HSE [17], Defra [18], the Food Standards Agency (FSA) [19], and the Committee on Human Medicines (CHM) [20]. Given the different media on which the reviews were focused, conclusions varied across the reports. For example, while Chaudhry et al. [18] identified a number of "deficiencies and gaps" in relation to how nanomaterials would be dealt with under the UK's environmental regulatory regime, others suggested that the regimes were sufficiently robust to deal with nanotechnologies in the short to medium term [19].

Against this backdrop, the EC initiated their own in-house review of the potential regulatory challenges posed by nanotechnologies in relation to human and environmental health and safety [21, 22]. This review appears to be a direct outcome of the EC's Communication, *Nanosciences and nanotechnologies*: *an action plan for Europe 2005–2009* [23], and suggests a subtle shift by government to consider the broader health and safety dimensions of the technology. And not just the economic potential.

The two-volume report examined a plethora of regulatory instruments and their implementation relating to chemicals, worker protection, consumer products (including, for example, biocides, cosmetic products, food and feed), and the environment [22]. The terrain covered was extensive and illustrative of the many fields and areas that nanotechnologies could be utilized in over the coming decade [21, 22]. The key conclusion stemming from the review was as follows: that "[c]urrent legislation covers in principle the potential health, safety and environmental risks in relation to nanomaterials" [21].

Accordingly, with nanotechnologies captured under the existing regulatory matrix, the Commission

suggested that the challenge moving forward would be more about the implementation of the instruments than coverage and capture per se. The term "regulatory gap" was not used within the context of the review, despite the recognition of "knowledge gaps" [21]. Despite the EC's perceived robustness of the current approach, other relevant stakeholders appear to have been less convinced, including members of the European Parliament.

A number of other governments commissioned their own reviews following the handing down of the RS/RAEng's report. These included the USA, Australia, and New Zealand [24–27]. While the terms of reference, scope, nature, and conclusions of such reviews have varied across agencies and jurisdictions, along with the legislative and regulatory instruments that they sought to review, a common denominator can be said to exist across all of them: their focus on identifying the adequacy of existing regulatory arrangements in both the short and medium term for nano-based products and processes. These reviews represent progress; a comprehensive understanding of the potential strengths and weaknesses of an existing regime to effectively regulate a new technology and its products allow for the development of a more nuanced policy response. Such a process also allows government and key stakeholders to consider not only potential legislative response—where required—but to also consider the ways in which softer instruments, and other actors, may play in shepherding the technology into the market.

Regulatory Gap Identification, Action, and Horizon Scanning Activities

It can be argued that at the very core of this recommendation is the call for policy makers and regulatory agencies to collectively take a proactive approach to manage any potential risks associated with emerging technologies. While directed specifically at nanotechnologies, the recommendation is equally relevant to other emerging technologies, albeit, for example, synthetic biology, additive manufacturing, autonomous vehicles, neurotechnologies and/or CRISPR-Cas 9. Moreover, the recommendation is an explicit acknowledgement of the so-called pacing-problem [28], in which legislation and regulation lags behind the development and commercialization of technologies and their applications [29, 30].

Fulfillment of this recommendation turns on a number of issues. For example, regulatory gap identification is dependent on the agencies and other stakeholders undertaking reviews of regulatory regimes in a timely manner. As noted above, the quality of such reviews will be at least partially dependent on access to state-of-the-art scientific knowledge. There is also a political element at play, where the definition of "regulatory gap" within these systems is, in itself, potentially contestable and will be dependent on the framing of terms of reference for such reviews.

Albeit in relation to a so-called gaps, regulatory action is dependent on the regulatory agency being vested with the necessary legislative power to act. For example, if a regulatory body is vested by the parliament with only those powers to assess, and address, human health and safety issues, then it is not within its remit to implement regulations to deal with environmental or societal issues despite this having been (potentially) perceived as a gap by one or more commentators. Adequate resourcing of agencies or other bodies to undertake these actions, including horizon-scanning activities, underpins the ability for such activities to be undertaken. Without the necessary financial support, the ability to undertake any such action is limited even if the capacity, will, and legislative power are available to do such work.

R9 was "supported" by HM Government [12]. In their response to the RS/RAEng, the Government noted the need for advice and coordination among various bodies, agencies, and specialists, including but not limited to advisory bodies, the HSE, and the EPA [12]. A commitment of additional funds to pay for such work to be undertaken was not, however, provided.

The commissioning of a suite of regulatory reviews (as noted above) is illustrative of the Government's action in relation to this recommendation. A number of advisory committees to the Government subsequently issued statements and/or provided advice on potential human and environmental health risks posed by nanotechnologies [31]. This collective knowledge has progressed the scientific and regulatory debate forward, allowing for more nuanced discussions around the potential benefits and risks of the technology. We have seen, for example, greater specificity on the types/families of nanomaterials that may pose a health risk under certain circumstances [32–35]. Policy makers may then use this information to help formulate tailored solutions.

R9 also stressed the need for a more formalized approach to horizon scanning activities. In line with,

but not directly in response to R9, the Office of Science and Innovation established the Government Office of Horizon Scanning Center [36] in 2005 as part of the Government's Foresight Program. As noted on the HSC's website, the "centre of excellence for strategic futures thinking to encourage longer term thinking and evidence-based analysis throughout Government" [37]. The HSC has, since, merged with the Cabinet Office's Horizon Scanning Secretariat in order to create a new entity: the Horizon Scanning Program (HSP) team [38]. The remit of the HSP is not too dissimilar to that of the HSC: to help "government to analyze whether it is adequately prepared for potential opportunities and threats" [38]. Horizon scanning activities are designed to improve the capacity of government departments to respond to, and prepare for, potential opportunities and threats posed by emerging technologies. A key component of this approach is the development of appropriate and timely policies that incorporate, where appropriate, resilience [39–42].

The establishment of the HSC/HSP was welcomed by organizations such as the RS/RAEng [43]. Systematic evaluation of trends and emerging technologies, including potential benefits and risks, can assist in designing appropriate instruments for stewarding a technology into the market, including the development of softer instruments in partnership with non-state actors [44]. This potential broader governance role would appear to be especially important for rapidly evolving technologies that have a high degree of uncertainty and ambiguity associated with them.

Beyond the UK, scientific advisory bodies have been very active since 2004 and have extensively contributed to the growing volume of literature that examines the potential health and safety implications of nanotechnologies. In particular, the EC's scientific committees have been at the forefront of this work, where the opinions of these bodies helped to shape the regulatory and policy decisions within the EU [45–53]. Regulatory agencies such as, for example, the German Federal Institute for Occupational Safety and Health (BAuA), Australia's Therapeutic Goods Administration (TGA) and SafeWork Australia, and the USA's Food and Drug Administration (FDA) have similarly added to this body of work through the publication of opinion documents, literature reviews, and guidance materials [54–63]. Such work has helped inform regulatory and policy activities, as well as highlight potential shortcomings in the relevant regulatory matrices, implementation landscape, and scientific knowledge.

"Existing" versus "New" Chemical Substance (R10)

At the time of RS/RAEng's report, chemical substances in the UK and the EU more generally were regulated on the basis of their status as being considered as either an "existing substance" or a "new substance." While this distinction between the two categories is historical and arguably arbitrary, it remains important due to the differing requirements, including scientific testing and assessment, associated with the two classes [64–66]. Through this historical distinction, regulatory requirements for new chemicals were significantly more onerous than those for existing substances. Under this approach, chemicals were identified and approved on the basis of their name. More specifically, these chemicals were identified and approved based on their CAS number; a CAS number is specific to a given chemical and does not differentiate a chemical on the basis of its size. For example, titanium dioxide (TiO_2) manufactured at the macroscale will have the same CAS number as nano-TiO_2 despite potentially exhibiting different properties, including toxicity.

Given this, it is not surprising that the focus of R10 was on the way in which chemical regulatory schemes dealt with existing and new chemical substances and the challenges that this may present with nanoscale substances. Under the regime at that time, "existing substances that are produced in the form of nanoparticles are not defined as new chemicals" [1], and as such were not subjected to testing and notification requirements. This approach was viewed by the RS/RAEng as a regulatory gap, and one that should be addressed by defining all nanoparticles/tubes as new chemical substances for the purposes of regulatory approval [1].

At the time that their report was published, the RS/RAEng [1] acknowledged that the chemical regulatory regime was to be superseded by a new regime— Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Regulation (Regulation (EC) no. 1907/2006). Under REACH, this seemingly arbitrary distinction between existing and new would be removed, with the triggers and requirements instead focused on a substance's production and/or importation level. However, uncertainty existed at that time in relation to the exact scope, nature, and triggers that would underpin REACH.

Given this flux, HM's Government's response to R10 can be viewed as being somewhat cautious. For example, they acknowledged that "a chemical in the form of a

nanoparticle or nanotubes may exhibit different properties to the bulk form of the chemical" [1]. Noting the likelihood of a new regulatory regime for chemical substances being realized within the EU in the near future, the Government reiterated the need to examine the appropriateness of REACH and its rules for nanomaterials, including threshold mass-based triggers [1]. However, they noted that any nano-specific criteria for chemicals would need to be introduced at the EU level and was beyond the scope of the UK's legislative powers.

The response provided by the UK Government suggests that the introduction of REACH and its provisions, which sought to remove this somewhat arbitrary distinction and apply the same level of oversight to new and existing chemicals equally, can be seen as progress. But, the response, and indeed REACH, does not address all of them. For example, the Government acknowledged that mass trigger thresholds might be inappropriate for certain types of nanomaterials.

The need to incorporate nano-specific provisions into the text of the REACH Regulation was noted by the RS/RAEng [43] and picked up by certain members of the European Parliament during the final stages of the negotiations [64, 67]. The attempt to include a number of nano-specific provisions into the Regulation's final text during its second reading was unsuccessful. As such, the final text of the REACH Regulation, which was passed in December 2006, was silent on "nano." This remains the case today.

Recognition of the need for the REACH regime to differentiate between nanoparticles and convention chemical substances has been widely discussed since the passage of the legislation [68, 69]. In particular, concerns focused on the applicability of conventional risk assessment methodologies for nanomaterials. In what would seem like a response to this set of concerns, the EC initiated in 2009 the REACH Implementation Project on Nanomaterials, or RIPoN. The purpose of RIPoN is "to provide scientific and technical advice on key aspects of the implementation of REACH with regard to nanomaterials" [70]. To date, three reports—RIPoN1, RIPoN2, and RIPoN3—have been published [71, 72]. These reports appear to go some way in addressing the concerns articulated by the RS/RAEng in 2004.

The so-called regulatory gap identified by the RS/RAEng in R10 is a feature of many national chemical regulatory schemes; oversight is triggered on the basis of new or existing, and regulatory implications arise on the basis of this triage process [7, 65, 66]. It is therefore not surprising that since 2004, similar observation regarding the appropriateness of the regimes for effectively regulating nanoscale substances have been made in relation to, for example, the analogous schemes in the USA, Australia, and New Zealand [26, 27]. Calls to address the gap in ways envisaged by the RS/RAEng have similarly followed. However, unlike the EU which was in the process of recasting, its regulatory regime at the time of the RS/RAEng's report as part of a broader regulatory reform agenda, jurisdictions such as the USA and Australia have not experienced wholesale reform of key regulatory regimes. As such, these jurisdictions have focused on using existing regulatory tools for capturing specific types of nanomaterials. For example, in the USA, the EPA promulgated significant new use rulings (SNURs) for five nanomaterials [72]. Such action does little to overcome the fundamental challenges created by the existing versus new dichotomy but does suggest that regulators may have a variety of tools already at their disposal that could, if deemed necessary and appropriate, be employed in relation to nanoscale substances.

While it is reasonably foreseeable that nano-specific amendments may be incorporated into REACH in some form in the future—based on the European Parliament and Council's move to specifically regulate nanotechnology in cosmetics and food (labeling and novel foods)—the same cannot be said for chemical regulatory regimes outside of the EU. There appears to be less political will among other jurisdictions to make progress in this way.

Protecting Workers Manufacturing Nanoparticles from Potential Exposure, and Precautionary Occupational Health and Safety Measures

The issue of worker exposure to nanomaterials, including in particular carbon nanotubes (CNTs), and the need to monitor any such exposure and the potential risks associated with the exposure of workers to such particles, is a theme that percolates throughout the RS/RAEng's report [1]. It is therefore not surprising that one of the recommendations—R11—focuses on worker exposure. As noted by RS/RAEng's report [1] in relation to the occupational health and safety regime designed to protect such individuals, "it is questionable whether regulation by mass or by another metric reflecting surface

area or number is the more appropriate." In this vein, R11(i)–(iii) focused on the need for Government to review the adequacy of existing regulatory arrangements for workers, current procedures for accidental release, and methods for controlling exposure.

As noted by HM Government [12], progress had already been made in relation to this recommendation by the time that the RS/RAEng's was published, with the HSE having already discharged some of their concerns. This included, for example, the HSE having conducting their own in-house regulatory review [73, 74], as well as engaging in a number of technical activities, including exposure control strategies, reviewing of current procedures, and exploring the potential need to adopt a precautionary approach for controlling worker exposure [12]. It is in relation to this last recommendation (R11(iii)), to ensure that current methods for assessing and controlling exposure, that HM Government [12] acknowledged that "there could be potential weaknesses in existing arrangements." It is suggested by the Government that regulatory reviews, and horizon scanning activities, would be employed to help address these potential gaps.

The regulatory reviews conducted by the HSE and Defra helped to further identify, and refine, the areas of potential concern [18, 75]. Together, they formed a rich body of work relating to crucial knowledge gaps needing to be addressed to ensure appropriate decision-making, as well as the potential weaknesses of the current regulatory regime. While the commissioning of the reports was a key component of accepting R11, as noted by the RS/RAEng [43] in the two years following the release of their report, only limited progress had been made in the first two years.

As noted by HSE [17], the regulatory framework for workplace safety is governed at the EU level by a number of Directives; the UK's Health and Safety at Work Act 1974 is the legislative instrument that creates the legal obligations within the UK. As such, while the UK Government has the capacity to introduce more stringent requirements to protect workers, their ability to overhaul their occupational health and safety regime is limited. In their review of regulatory framework, the EC [21, 22] unequivocally asserted that the instruments were adequate for ensuring a high level of protection to occupational risks that may arise from the manufacturing and/or handling of nanomaterials. And, as such, revisions to the regime—at least at the level of legislative reform—were unnecessary.

It is arguably not surprising that we have seen a lack of inertia at the EU level, or within the UK Government, to amend key legislative instruments so as to specifically incorporate, for example, exposure levels for different classes of nanomaterials. We have instead (and arguably more importantly) seen attention by these bodies on the generation of fundamental data and knowledge to address the gaps identified by the RS/RAEng [76–80].

A growing volume of literature on worker safety, potential health risks, and nanomaterials in the workplace now exists [81–89]. Governments, regulatory agencies, multilateral bodies, industry, and the research community have all contributed to building the evidence base needed to ensure that individuals working with nanomaterials have the highest level of protection needed in order to safeguard their health [66, 90–93]. The work of the International Standards Organization Technical Committee 229 on Nanotechnologies (ISO TC229) in relation to core terms and definitions, as discussed in detail below, has contributed to this growing body of work and enabled substantial progress to be made [94–97].

In the absence of certainty regarding what measures, if any, may be needed, governments have been hesitant to amend OH&S legislative instruments. There has been a preference, instead, to look for solutions under a broader governance framework. One example includes the Dutch government's effort to develop nano-reference values (NRVs) for occupational exposure limits where such limits do not exist for nanomaterials [98]. The NRVs are not legally binding and have instead been designed to assist employers in the country to meet their legal obligations [99]. In this way, they may be best described as a risk management tool for employers [100].

Looking beyond the EU, Safe Work Australia has developed a number of guidance documents and information sheets, as part of a precautionary approach to nanomaterials in the workplace [59, 60, 92, 93, 101, 102]. Such documents, which have been supported through the work of ISO TC229, have been designed to provide employers and employees with information on best-practice approaches and summarize the state of the scientific art (see also the guidance document that has been published by the National Institute for Occupational Safety and Health in the USA [103–105]).

Prior to 2004, the topic of nanomaterials and workplace safety had received little attention from regulators and the broader research community. There were no doubt good reasons for this. Significant work has been done since 2004, with a growing volume of data,

standards, and risk management tools having been produced.

Adequacy of Regulatory Regimes for Consumer Products, Labeling Requirements, and the Public Disclosure of Safety-Testing Methodologies

Consumer products including, in particular, those products that contained nanoscale zinc oxide (nano-ZnO) as an active ingredient were the focus of R12. While the recommendation itself was broad in nature, involving five subcomponents, the crux of R12 appears to be focused on communication and the provision of information to regulators (provisions of full safety assessment data to regulators), consumers (through labeling), the public at large (publication of risk assessment methodologies), and scientific review of the potential risks of nanomaterials in such products. While R12 was focused on all consumer products, the tone of the report suggested that cosmetic products were an area of particular interest for the RS/RAEng.

As with the other recommendations, HM Government appeared to endorse the core facets of R12, including the need for great disclosure and transparency by industry. Such action was seen as been fundamental in "help[ing] build public confidence" [12]. However, in agreeing with the majority of R12, the Government also noted the limitations of the regulatory regime, and the need for feasibility studies in relation to the introduction of nano-specific labeling for certain classes of consumer goods. As such, while the Government had the ability to act on some of the dimensions of R12, it was clear that action at the EU level would also be needed in order to fully address the concerns set out by the RS/RAEng [1].

Significant advances have been made since 2004 in relation to each limb of R12. Such progress has occurred by virtue of actions at both the UK level and at the supranational level. This has included, for example, the publication of a number of scientific reports by the EC's scientific committees that pertain directly to the safety, and/or the risk assessment methodology used in relation to nanomaterials in cosmetic products [45, 106, 107], and two EU regulatory reviews [21, 22], each of which touched upon the issue of consumer products and transparency.

However, it can be argued that the most significant advances have come in relation to consumer information provision in the form of labeling requirements. Pursuant to R12 (iii), the RS/RAEng [1] specifically recommended that, "ingredients lists of consumer products should identify the fact that manufactured nanoparticulate material has been added." While the Government acknowledged the need for consumers to "make informed choices," they went on to state that "the feasibility of labeling needs [would] need[s] to be fully investigated" [12]. They also pointed out that given that many consumer products, including cosmetics and food, are regulated through EU instruments, any such action would be required at the European Parliament and Council.

Despite reluctance of the EC [21, 22] to specifically regulate nanomaterials, such hesitancy was not shown by the European Parliament and Council. In adopting Regulation (EC) No. 1223/2009 on cosmetic products (the Cosmetic Regulation), the EU became the first national or supranational legislative instrument to specifically differentiate between conventional products—in this case cosmetics—and those that contained nanomaterials (as defined in Article 2(k) of the Cosmetic Regulation).

The Cosmetic Regulation contains a number of nano-specific requirements, including labeling requirements. Pursuant to Article 19(1)(g)), as of July 2013, cosmetic products containing nanomaterials must indicate the presence of the nanomaterial(s) in its list of ingredients. This is accomplished through the placement of the word nano in brackets after the ingredient/s that are present in the nano-form [108]. In addition to this labeling requirement, the Cosmetic Regulation also requires, for example, the provisions of safety information on existing and new cosmetic products containing nanomaterials to the EC within designated time periods, as well as the creation of a public catalog that details the use of nanomaterials in cosmetic products (Article 16(10)(a)).

Such action by the Parliament and Council went to the very heart of R12 and can be said to signify significant progress on addressing the concerns articulated by the RS/RAEng. Further progress was made with the passage of the Regulation (EC) No. 1169/2011 on the provision of food information to consumers (the Food Information Regulation), which requires foods that contain nanomaterials (as defined by the Regulation) to be labeled as such. It is important to note, though, that the inclusion of nano-specific labeling requirements for both cosmetics and foods occurred within the context of the broader EU regulatory reform agenda; nanotechnology was not the catalyst for either recast.

This call for greater transparency around the use of nanomaterials in consumer products has been mirrored in numerous jurisdictions. The issue of, or push for, mandatory labeling regimes appears to be the most contentious; this call has often been coupled with a call for mandatory reporting schemes [109]. Despite the high profile nature of some of these debates, including those in Australia and the USA, governments have generally opted to retain the status quo. The exception to this is New Zealand, which has introduced labeling requirements for cosmetic products that mirror that of the EU [110].

The issue of, and call for, enhanced information-sharing and greater transparency—especially in relation to safety data—for consumer products has intensified over the past 10 years as more products have made their way into the market. The RS/RAEng brought attention to many of the key issues that have been subsequently debated over the past 12 years. This in itself should be viewed as progress, albeit somewhat less than that which the RS/RAEng may have wished for.

Reviewing the Adequacy of Regulatory Arrangements for Nanomedicine

R13 focused specifically on the use of nanomaterials in medical devices and drugs, along with the potential adverse consequences of their incorporation into such products [1]. It called on the Department of Health to review the adequacy of existing regulatory arrangements for such products. This recommendation was separate and distinct from their earlier and more general recommendation for an evaluation of relevant regulatory regimes (R8), which would have included therapeutic applications.

This recommendation was supported by the UK Government [12]. However, they went on to note that "UK regulations on medicines and medical devices are based on European legislation" [12], and that any decision to amend relevant regulations would need to be done at the supranational level and would involve active input from the European Medicines Agency (EMA). This response is again illustrative of the tensions that exist within the EU in relation to legislative decision-making.

Despite these limitations, it would appear that the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) have taken a proactive approach to reviewing existing regulatory arrangements. While it does not appear that the regulator undertook, or commissioned, a regulatory review per se, according to the MHRA, "[t]he suitability of existing regulations is continually assessed as the area evolves" [111]. MHRA goes on to state that despite the lack of nano-specific provisions, "current EU regulations for medicines and medical devices are sufficiently stringent and broad in scope to cover theoretically risks associated with nanotechnologies" [111]. These statements would appear to have been informed by a number of science-based reviews and activities, to which the MHRA has been an active contributor to in many instances. These include, for example, a report examining the potential toxicity of nanomaterials in medical devices [112], a general reflections paper the use of nanomaterials in medicinal products [113], as well as several specific reflections papers on the use of specific applications of nanomaterials in nanomedicine [114–118]. Such action would appear to incorporate both elements of potential gap identification and horizon scanning (R8 and R9).

At the EU level, medicinal products were one of the consumer product categories considered by the EC as part of their regulatory review [21, 22]. The Staff's Working Document sets out the key legislative instruments, and the role of guidance documents, for medicinal products in the EU, including the UK. Drawing heavily on the EMA reflections paper [113], the EC notes that the existing framework captures, and indeed foresees, the use of nanomaterials in therapeutic products and that no new legislation is needed. However, recognition is given to the technical challenges that the more sophisticated applications may give rise to, including those that straddle the boundary of device and drug [22]. Accordingly to the EC, such challenges should be addressed through "additional specialized expertise" combined with the creation of "guidance specific to nanomedicinal products, or for the update of existing ones to accommodate for the specific aspects of these products" [22]. Such guidance material was seen as a way to assist industry as they navigate the system in relation to novel products.

As such, no regulatory gaps were identified or foreseen by the EC in relation to this therapeutic product per se, with any potential shortcomings identified in the implementation process as opposed to the legislative architecture [21, 22]. This conclusion is similar to that reached by the USA's FDA and Australia's TGA in relation to analogous nanomedicine products that currently fall under their regulatory regime [25, 26].

That being said, the FDA and Ludlow et al. went on to differentiate between nanomedicine products subject to the premarket authorization approval process, and those that are not [26]. According to Ludlow et al. [26], in relation to the Australian context, nanomedicine products subject to a premarket authorization assessment regime must be assessed for safety and efficacy. This should be sufficient for evaluating potential risks to human health prior to entry onto the market. In contrast, "low risk" or "listed goods" that are not subject to premarket authorization within Australia—such as sunscreens—are only assessed on the basis of quality and safety. Given the number of listed goods that have been reformulated so as to include active ingredients at the nanoscale [119], a number of commentators have expressed their concern about exposure and potential long-term harms associated with repeated dermal application [120–122]. While such concerns may have been framed primarily in relation to the Australian context, debate continues within the scientific literature over these questions more generally [123–126].

Unlike its UK equivalent, the TGA has responded to these specific concerns by undertaking its own review of the published scientific literature on the safety of metal oxide nanoparticles, specifically nano-ZnO and nano-TiO_2, in sunscreens [57, 119]. The primary focus of the 2013 review was on "evidence for ability of these [nanoparticles] to penetrate the skin to reach viable cells and the potential toxicity exerted by them" [57]. Drawing on a number of published studies within the peer-reviewed literature, as well as reports by expert scientific committees such as the EC's Scientific Committee on Consumer Safety (SCCS), the TGA has continued to reaffirm its position that, based on the current state of the scientific art, the inclusion of such nanoparticles as active ingredients in topically applied products is unlikely to cause harm to the user [57]. As such, it appears unlikely that any modifications to Australia's existing regulatory approach will occur in the short to medium term despite this controversy.

This conclusion is likely to hold true for most jurisdictions in relation to the field of nanomedicine, where those regulatory agencies that have reviewed the adequacy of existing arrangements appear to be confident in their ability to effectively regulate such products under existing legislative. The undertaking of the regulatory reviews by the MHRA and analogous bodies should be viewed as progress in itself.

Public Disclosure of Manufacturer's Approach to Dealing with End-of-Life Issues

End-of-life issues, including producer responsibility, are covered by several EU directives. As such, while HM Government acknowledged the need to review the scope of the existing regulatory arrangements and their application to nanomaterials (within the context of their response to R14 and R8), it was acknowledged that any direct legislative action would need to be undertaken at the European level. Any such action would be driven by the evolving science and proportional to the potential health and safety risks posed by nanomaterials [10].

The terms of reference set out by the Government in relation to the Defra scoping study included end-of-life issues [18]. What was clear from their report is that there are numerous avenues by which nanomaterials may intentionally or unintentionally end up in the environment. While a number of EU Directives address issues such as waste management (i.e., landfill, hazardous waste, etc.), and environmental contamination and remediation, many of these instruments will only be triggered upon the entry of the nanomaterial into the environment. Others may be triggered earlier in relation to controlling exposure. The effectiveness of both types of instruments is dependent, however, on regulators and other stakeholders being aware of what the potential risks nanomaterials pose to the environment. At the time of the review, a dearth of information existed in this area [46]. While there is now a growing body of literature that addresses environmental fate of nanomateirals, which can, and should be, viewed as progress, there are still scientific gaps that need to be addressed.

End-of-life issues were similarly considered by the EC in their 2008 regulatory review [21, 22]. The report noted that the general directives and specific legislation already in place "captured" the concerns raised by the RS/RAEng [1]. According to the EC, regulatory challenges existed primarily in relation to the "implementation of legislation" [21], rather than the scope and breadth of the legislation itself. Less attention was given to such issues in the second regulatory review [21, 22], with the EC focused instead on definitional issues and specific nanomaterials, rather than the media in which such materials would be regulated.

It would appear that unlike a number of the RS/RAEng's regulation-based recommendations, R14 has received limited attention and/or response from within the UK and the EU more generally. In short, progress

here has been slow and limited. End-of-life issues and broader environmental exposure questions have been examined within the context of a number of government-initiated reviews and reports [24, 26, 27, 101]. The need for additional scientific data, especially in relation to potential exposure pathways, have also been one and has been one of the drivers behind voluntary data-programs. However, no substantive policy or regulatory action has been taken by any government to address potential end-of-life issues. We would argue that it is likely to be at least partially due to the significant unknowns that still exist in relation to exposure and potential risks to humans and the environment. Moreover, other areas of regulation concern—including consumer exposure to products containing nanomaterials (such as cosmetic products)—appears to have been better at capturing stakeholders' attention, including that of members of parliament and consumer groups.

Development of Measurement Capabilities and Standards for the Nanoscale

The RS/RAEng's recommendation that efforts be direct toward the development of monitoring technologies for airborne nanoparticles, combined with terminology, nomenclature, measurement, and characterization for the nanosciences was, arguably, reflective of a global recognition of the need for capacity and standard development in the field. HM Government [12] accepted this recommendation and acknowledged the need to be at the forefront of supranational and multilateral activities. As a sign of progress on this front, the Government pointed to the establishment of the cross-Governmental Research Co-ordination Group, which they saw as being essential to addressing R15, as well as the potential role that the UK could play in standard setting under the umbrella of CEN. It should be noted, however, that the UK's national standards body, National Standardization Committee (BSI), is a private entity and not an arm of HM Government and that CEN is a non-governmental transnational body [127]. As such, the role of government is somewhat limited here, and that standard setting falls largely into the broader governance landscape.

It would also appear productive to note that significant work on development standards, terminology, characterization, and measurement capacity had already occurred by 2004 [128, 129]. In short, progress was already occurring in the field, with significant momentum behind it. The RS/RAEng's report highlighted the need for continued investment and momentum in this area, but progress would have occurred, so it would seem, regardless of the report and this specific recommendation.

Since 2004 significant work has occurred within the standardization and measurement field, with numerous standards now having been developed and published. The establishment of ISO/TC 229 in 2005 [94], has been a driving force for much of this work [94]. As of October 2016, 37 countries, including the UK under the auspices of BSI, were participants within TC229, with the TC having published some 51 ISO standards [130].

This fundamental work in the area of measurement and standardization has been further supported by the Organization for Economic Co-operation and Development (OECD) [94] and national and supranational standards bodies across the world. As such, measurement and standards development for nanotechnologies should be viewed as a global endeavor that contributes to, and is supported by, a broader governance function.

Concluding Thoughts

Even a cursory review of scientific literature is illustrative of just how far nanosciences and nanotechnology have matured since 2004. One only has to look at the growth in articles, reports, patents, and products to see the innovation that has taken place in a little over a decade. Tracking the developments and progress outside of the laboratory and within the spaces of ethics, law, and the social science is, however, much more difficult. What metrics do you use? What constitutes progress or success? And, how do you reconcile the different voices and views expressed in relation to defining what progress here means? And, even for those who have been active participants and/or observers in the debates and activities framed around, for example, regulation, governance, public engagement, education, and ethics, it can be difficult to see, and articulate, where progress has been made and where progress still needs to be made.

This article sought to illuminate where progress has been made—or has not—in relation to the debates that have focused on regulation of nanotechnology. It did so by drawing upon eight regulation-focused

recommendations articulated by two epistemic communities. These recommendations were used as the baseline to measure progress against. As the article illustrates, meaningful progress has been made across the eight focal areas identified by the RS/RAEng.

Whether this progress is perceived to be sufficient, appropriate, or goes too far will depend on where the viewer sits. It is not unreasonable to suggest, for example, that the Friends of the Earth Nanotechnology Project would argue that while legislation that requires the labeling of cosmetics and foods that contain nanomaterials in the EU market is a good first step toward promoting transparency within the market, much more could, and should, have been done.

What we do know is that as a consequence of the nano-specific labeling requirements of the Cosmetic Regulation, it is now possible to purchase an Australian made (and owned) face moisturizing cream in the USA, which conforms to the requirements set out in Regulation (EC) No. 1223/2009. While this example may seem flippant, it is illustrative of the broader governance framework at play here and the ripple effects that occur across jurisdictional boundaries. This type of diffusion shall only increase as an increasing number of products make their way into the market to meet consumers both at home and overseas.

From the perspective of this article, what is important here is that the types of issues and gaps articulated by the RS/RAEng in their report have not been ignored or dismissed out of hand by the key actors and organizations. Progress has been made in addressing each area of concern, albeit to varying degrees. This work has been undertaken by a range of stakeholders, spanning sectors and borders. It can be argued that this collective, and diffuse, action has helped to advance the science and technology and enabled greater engagement around potential benefits and risks, balancing innovation with health and safety aspects.

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