"By Design" and Risk Regulation: Insights from Nanotechnologies

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Contemporary risk regulation requires an interdisciplinary approach that integrates science, law and socio-political discourses. This calls for new tools in the risk regulation process that enable regulators to adapt to a constantly changing technological realm and help overcome the interdisciplinarity dilemma. In the field of nanotechnologies, tools proposed in the literature include "by design" approaches. In this article, I analyse how the safe-by-design and benign-by-design concepts, emerging in materials science and drug development, could enhance interdisciplinarity in risk regulation. I suggest that further development and implementation of "by design" from a scientific concept to an adaptive regulatory tool could support progressive risk governance of innovative technological developments and enhance the interdisciplinary approach in risk regulation.

I. Introduction

The umbrella term "nanotechnology" embeds several disciplines, including materials science, biotechnology, physics, chemistry and medicine.[1] Nanotechnology refers to any science and technology at the nanoscale (at the level of atoms and molecules) and to scientific principles and new properties that can be understood and mastered in this domain.[2] Emerging (nano)technologies serve important social and economic purposes today. However, from a regulatory point of view, they are defined as "wicked" public policy problems; in other words, complex areas of policymaking involving a multitude of stakeholders (eg industry, politicians, non-governmental organisations) with competing values and interests.[3] The importance of the

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[1] GA Hodge, DM Bowman and AD Maynard, "Introduction: the regulatory challenges for nanotechnologies" in GA Hodge, DM Bowman and AD Maynard (eds), *International Handbook on Regulating Nanotechnologies* (Cheltenham, Edward Elgar 2010) p 6.

[2] Commission, "Towards a European strategy for nanotechnology" (Communication) COM (2004) 338 final, p 4.

[3] Hodge et al, supra, note 1, pp 3–4. Some of the identified regulatory challenges pertaining to nanotechnologies relate to the heterogeneity and complexity of nanomaterials and applications, the pace of innovation, merging benefits and risks

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interdisciplinary approach has been expressed already in early policy initiatives on nanotechnology. In the USA, the 21st Century Nanotechnology Research and Development Act,[4] enacted in 2003, states that ethical, legal, environmental and societal concerns should be considered, and the emergence of a true interdisciplinary research culture for nanoscale science should be encouraged (eg by effective education and training; 15 U.S.C. § 7501(b)(8–10)). In the European Union (EU), the Commission outlined in 2004 that nanotechnology must be developed in a safe and responsible manner, and the ethical, legal, environmental and societal impacts should be examined and considered.[5] The Commission emphasised that it is essential to address risks upfront as an integral part of the development from conception and research and development (R&D) to commercial exploitation. The fulfilment of these goals requires overcoming disciplinary boundaries. Today, however, nanotechnology risk research is still mostly directed towards understanding the science. Interdisciplinarity, which could improve the attainment of decision-making and regulatory needs, is largely missing.[6] According to Malsch, regulators and risk assessment specialists find it difficult to understand how to integrate emerging technologies into current approaches.[7] A more active role of regulators in the early development phase of emerging technologies and the provision of information between different stakeholders would be helpful.

Because of the wicked nature of nanotechnology regulation, there is great variance and debate surrounding existing regulatory approaches. A recent proposal from a multidisciplinary group, which includes some of the leading experts in nanotechnology risk assessment and regulation, is that a risk governance framework for nanotechnologies should involve: (1) a set of advanced tools to facilitate risk-based decision-making, including evaluation of the needs of users regarding risk assessment, mitigation and transfer; (2) an integrated model of human behaviour and decision-making that influences how the framework is refined, used and interpreted; and (3) an integrated overview of nano-specific and general legal-regulatory requirements, adaptable to an evolving regulatory environment.[8] They push for a more integrative governance approach that goes beyond the legislation and involves a variety of actors from different sectors of society in interdisciplinary dialogue. The suggested criteria for the success of such a framework include leverage of the existing knowledge and tools, protocols to address incomplete knowledge, adaptability, consideration of the

and scientific uncertainty regarding the health and environmental risks of nanomaterials due to insufficient appropriate data. See GE Marchant et al, "Big issues for small stuff: Nanotechnology regulation and risk management" (2012) 52 Jurimetrics 243, 256–65. In addition, there is no universal agreement on the dose, concentration or suitable metrics of nanomaterials in test systems. See V Stone et al, "The Essential Elements of a Risk Governance Framework for Current and Future Nanotechnologies" (2018) 38 Risk Analysis 1321, 1324.

[4] 21st Century Nanotechnology Research and Development Act 15 U.S.C. § 7501 et seq. (2003).

[5] Commission, supra, note 2, pp 3, 6, 15, 18.

[6] K Grieger et al, "Best practices from nano-risk analysis relevant for other emerging technologies" (2019) 14 Nature Nanotechnology 998, 999.

[7] I Malsch, "Nano-education from a European perspective: nano-training for non-R&D jobs" (2014) 3 Nanotechnology Reviews 211, 216, 218.

[8] Stone et al, supra, note 3, pp 1321, 1324–26.

motivations of various users, communication and delivering compliance.[9] These criteria align closely with the characteristics of new governance set in the literature: inclusive and representative participation, collaboration, deliberative decision-making, experimentation, flexibility and revisability, new forms of accountability, learning and adaptation and transparency.[10] The International Risk Governance Council has stated that, in managing emerging risks, adaptability and flexibility are especially crucial.[11]

However, there has been little attention paid to "tools" in the risk regulation process that would help overcome the interdisciplinarity dilemma, which arises from the following: risk regulation requires a range of expertise from different disciplines, and few scholars or policymakers possess the necessary integrated expertise.[12] For example, the focus on scientific methodologies in risk assessment and risk management has hindered other scholars and policymakers from becoming more deeply involved in these debates and developing real legal expertise in this area. Oomen et al and Isigonis et al have reviewed governance frameworks for nanotechnologies and concluded that, currently, tools to support holistic risk governance of nanomaterials are unsatisfactory, and the frameworks are insufficiently detailed to enable actual application either in the regulatory context or in informing decision-making.[13] Oomen et al recognised the need for greater interdisciplinarity in the risk governance of nanotechnologies. Dialogue between stakeholders is necessary to address, and transparently deal with, the uncertainty associated with the state-of-the-art science. One goal of the review by Isigonis et al was to assess the capacity of the existing risk governance frameworks for nanotechnologies to communicate risks to decision-makers. They stated that risk communication and stakeholder engagement are crucial cross-cutting aspects of the risk governance frameworks, but rarely mentioned.

The proposed risk governance tools for nanotechnologies involve "by design" approaches.[14] These include safe(r)-by-design (SbD) and benign-by-design (BbD)

[9] Previously, it has also been stated that nanotechnology governance needs to be transformative, responsible, inclusive and visionary; see MC Roco, B Harthorn, D Guston and P Shapira, "Innovative and responsible governance of nanotechnology for societal development" (2011) 13 Journal of Nanoparticle Research 3557, 3559–60.

[10] See G de Burca and J Scott, "Introduction: New Governance, Law and Constitutionalism" in G de Burca and J Scott (eds), *Law and New Governance in the EU and the US* (Oxford, Hart Publishing 2006) p 3; DM Trubek and LG Trubek, "New Governance & Legal Regulation: Complementarity, Rivalry, and Transformation" (2007) 13 Columbia Journal of European Law 539, 542; D Trubek and L Trubek, "Part I: The World Turned Upside Down: Reflections on New Governance and the Transformation of Law" (2010) Wisconsin Law Review 719, 721–22. C Holley, N Gunningham and C Shearing, *The New Environmental Governance* (London, Earthscan 2012) pp 4–6, 71–72, 101–02.

[11] International Risk Governance Council, "Guidelines for Emerging Risk Governance" (Lausanne, IRGC 2015) p 9.

[12] E Fisher, "Framing risk regulation: A critical reflection" (2013) 2 European Journal of Risk Regulation 125, 126, 131.

[13] AG Oomen et al, "Risk assessment frameworks for nanomaterials: Scope, link to regulations, applicability, and outline for future directions in view of needed increase in efficiency" (2018) 9 Nanoimpact 1, 1–2, 10–11; P Isigonis et al, "Risk Governance of Nanomaterials: Review of Criteria and Tools for Risk Communication, Evaluation, and Mitigation" (2019) 9 Nanomaterials 696, 697, 699, 714–16. Oomen et al reviewed the relevant publications and reports of 23 research and regulatory bodies from the EU, the USA, the Organisation for Economic Co-operation and Development and Germany, as well as references from the open literature. Isigonis et al reviewed peer-reviewed literature from 1990 to 2018 from the Web of Science database for journal articles pertaining to the risk governance of nanotechnologies, as well as relevant EU-funded projects from the Community Research and Development Information Service (CORDIS). They also organised a workshop for a variety of stakeholders to identify evaluation criteria, which they then applied in the analysis of the frameworks.

[14] Stone et al, supra, note 3, p 1327.

concepts that have emerged in the fields of materials science and drug development, respectively. In this paper, I analyse whether the concepts could serve as adaptive network management tools, which would enhance interdisciplinarity in risk regulation. "Network" refers here to various actors (eg academics, politicians, regulators, industry, non-governmental organisations, suppliers, customers, consumers) that may be involved in the innovation life cycle. "Network management tool", in the context of this article, engages relevant actors from different sectors of society in structured decision-making.

The article is organised as follows: Section II introduces the SbD and BbD concepts and depicts their current status. Because inherently value-laden choices are involved in risk regulation (eg how to evaluate future threats and respond to them[15]), discussion in Section III focuses on safety and innovation in order to assess the value of interdisciplinarity included in the by-design concepts in that context. In Section IV, I analyse the applicability of by-design concepts as regulatory tools to enhance interdisciplinarity by using the SbD concept as an example and reflecting on it in relation to the suggested characteristics for the risk governance framework for nanotechnologies and the criteria set in new governance literature: collaboration, participation, deliberation, flexibility, revisability, adaptability, learning and accountability. Finally, conclusions are drawn in Section V.

II. Development and current status of the BbD and SbD concepts

1. BbD concept

The roots of the BbD concept are in the "Green Chemistry Program"[16] and its initiative "Designing Safer Chemicals" of the US Environmental Protection Agency, which was launched on the basis of the Pollution Prevention Act[17] in the 1990s.[18] The "Designing Safer Chemicals" concept includes the structural design of chemicals to meet the needs of both safety and efficacy. The concept does not require zero toxicity or a maximum level of efficacy, but it does require the optimal balance, and it encompasses both human health and the environment throughout the chemical's life cycle.

Since the 1990s, the BbD concept has been developed further by Professor Kümmerer and his research group in the context of innovative pharmaceuticals.[19] According to the

[15] Fisher, supra, note 12, pp 125–26.

[16] US EPA, "Green Chemistry" <www.epa.gov/greenchemistry> (last accessed 18 July 2019). A set of green chemistry principles was codified in 1998 and has been applied in academia and industry worldwide. See PT Anastas and JC Warner, *Green Chemistry: Theory and Practice* (Oxford, Oxford University Press 1998); SE Crawford et al, "Green Toxicology: A Strategy for Sustainable Chemical and Material Development" (2017) 29 Environmental Sciences Europe 16, p 2; PT Anastas and JB Zimmerman, "The United Nations sustainability goals: How can sustainable chemistry contribute?" (2018) 13 Current Opinion in Green and Sustainable Chemistry 150, 150.

[17] Pollution Prevention Act 42 U.S.C. § 13101 et seq. (1990).

[18] RL Garrett, "Pollution Prevention, Green Chemistry, and the Design of Safer Chemicals" in SC DeVito and RL Garrett (eds), *Designing Safer Chemicals* (Washington, DC, American Chemical Society 1996) pp 2–3, 5–6.

[19] K Kümmerer, "Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry" (2007) 9 Green Chemistry 899, 905; C Leder, T Rastogi and K Kümmerer, "Putting benign by design into practice-novel concepts for green and sustainable pharmacy: Designing green drug derivatives by non-targeted synthesis and screening for biodegradability" (2015) 2 Sustainable Chemistry and Pharmacy 31, 32–34; K Kümmerer, "From a problem to a business opportunity – design of pharmaceuticals for environmental biodegradability" (2019) 12 Sustainable Chemistry and Pharmacy 100136.

BbD concept, small alterations in the chemical structure of an active pharmaceutical ingredient may affect its activity, solubility and polarity, as well as its biodegradability, and a set of functionalities exists that can foster both. Properties of molecules can be predicted using modelling tools, and variations for a lead structure can be screened by *in silico* systems to find the best drug candidates in terms of activity and biodegradability. The candidates are subsequently tested experimentally. When combined with systems that allow for the prediction of metabolites, transformation products in the human body and in the environment can be considered in the design phase of pharmaceuticals.

Today, however, the tools and models for sustainable drug design must still be improved and proofs of the concepts established to increase acceptance of the BbD concept in the pharmaceutical industry. Although pharmaceutical companies applying green chemistry principles in manufacturing processes (post-regulatory approval) have reported impressive decreases (70–90%) in waste, incorporating BbD tools in the early design phase is still not common. Industry has stated that designing drugs for degradation in the environment is a major challenge because stability is required under all reasonable manufacturing, storage and use conditions.[20] Because the improvement of tools and models is largely dependent on the availability of experimental high-quality data for the biodegradability of pharmaceuticals – which is mainly produced in-house in pharmaceutical companies – the usability of the BbD concept suffers from an absence of open dialogue between different stakeholders. Key barriers to the implementation of green chemistry in the pharmaceutical industry include the mentality of medicinal chemists, the upfront costs of technology, unawareness of the available methods and regulatory risks.[21] Enhanced dialogue between the experts from different disciplines and the regulators might help to overcome these barriers.

2. SbD concept

The origins of the SbD concept in the nanotechnology context can also be traced to the USA, at RICE University (Houston) in approximately 2004–2005.[22] From the very beginning, the characteristic of safety in the SbD concept has been linked to materials' properties, making safety a concern of engineers and materials scientists. The development of nanomaterials that are safer by design has leaned on the processes used in drug discovery and development.[23]

[20] BW Cue, J Berridge and JB Manley, "PAT and Green Chemistry: The Intersection of Benign by Design and Quality by Design" (2009) 29 Pharmaceutical Engineering 8, 12–14; V Veleva and BW Cue Jr, "Benchmarking green chemistry adoption by 'big pharma' and generic manufacturers" (2017) 24 Benchmarking: An International Journal 1414, 1428; VR Veleva et al, "Benchmarking green chemistry adoption by the Indian pharmaceutical supply chain" (2018) 11 Green Chemistry Letters and Reviews 439, 443.

[21] Veleva and Cue, supra, note 20, pp 1416–17.

[22] C Schwarz-Plaschg, A Kallhoff and I Eisenberger, "Making Nanomaterials Safer by Design?" (2017) 11 Nanoethics 277, 277.

[23] R Hjort, L van Hove and F Wickson, "What can nanosafety learn from drug development? The feasibility of 'safety by design'" (2017) 11 Nanotoxicology 305, 305. See also Crawford et al, supra, note 16, p 29.

The SbD concept appears in risk regulation discourse, especially in the EU, as a boundary object of several EU-funded projects (eg NANoREG[24] and NanoReg2[25]).[26] According to Gottardo et al, the NANoREG SbD is a forward-looking strategy and a voluntary tool for considering innovation requirements and for helping regulatory authorities and industry to keep pace with innovation.[27] Safety information on materials, substances or products is iterated from early R&D phases onwards to search for the best achievable safety conditions. The term "design" is not restricted to the material properties, but applied to the whole innovation process, including production processes and final products.[28] Kraegeloh et al stated that the objective of SbD implementation is to transfer the precautionary principle into practice.[29] However, a combination of regulation and safety research is not an easy task, and implementation of the SbD concept has been difficult.[30] NanoReg2 addressed the difficulties in the practical applicability of the SbD concept by developing the "Safe Innovation Approach" (SIA), which links the SbD with "regulatory preparedness", defined as "The regulators' timely awareness of innovations and the regulator's actions to check whether present legislation covers all safety aspects of each innovation, including initiating revision of the legislation as appropriate".[31] Mutual awareness between regulators and industry, achieved through trusted environments for information sharing, was seen as key to governance of the safety of nanomaterials through the SbD concept and the SIA.[32] This is a clear indication of the demand for interdisciplinarity in the risk regulation of nanotechnologies. Isigonis et al noted that this approach is the first attempt to transition from risk governance to innovation governance.[33] They underlined that the outputs of the applied tools in any risk governance framework must be connected to policymaking and regulatory purposes to have a genuine impact (eg on innovation policy). It is not enough to develop sound risk governance frameworks by the scientific community if stakeholders cannot apply them in their respective societal contexts.

[24] NANoREG <www.nanoreg.eu> (last accessed 22 July 2019).

[25] NanoReg2 <www.nanoreg2.eu> (last accessed 22 July 2019).

[26] Schwarz-Plaschg et al, supra, note 22, p 278; The Austrian Academy of Sciences: Institute of Technology Assessment, "Safe-by-Design – The Early Integration of Safety Aspects in Innovation Processes" (NanoTrust Dossier 50, May 2019) 1, pp 2–4 <http://epub.oeaw.ac.at/ita/nanotrust-dossiers/dossier050en.pdf> (last accessed 17 July 2019). Although many European nanosafety projects refer to the SbD concept, they rarely discuss the meaning or implementation challenges of the concept; see Hjort et al, supra, note 23, p 306.

[27] S Gottardo, H Crutzen and P Jantunen (eds), "NANoREG framework for the safety assessment of nanomaterials" (*Science for Policy Report EUR 28550 EN*, April 2017) 1, pp 100–01.

[28] A Kraegeloh, B Suarez-Merino, T Sluijters and C Micheletti, "Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach" (2018) 8 Nanomaterials 239, 241–42.

[29] ibid, p 243.

[30] The Austrian Academy of Sciences: Institute of Technology Assessment, supra, note 26, pp 2–3.

[31] P Jantunen, A Mech and K Rasmussen (eds), "Workshop on Regulatory Preparedness for Innovation in Nanotechnology" (*JRC Conference and Workshop Reports EUR 29357 EN*, 2018) 1, p 4.

[32] ibid; Kraegeloh et al, supra, note 28, pp 245–47.

[33] Isigonis et al, supra, note 13, pp 697, 714–16. Recently, the "innovation principle", which depicts that new regulatory strategies should include an analysis of the effects on innovation and aims to encourage innovation at all stages of the innovation cycle, has emerged. See Commission, "Towards an Innovation Principle Endorsed by Better Regulation" (EPSC Strategic Notes, 30 June 2016) <https://ec.europa.eu/epsc/sites/epsc/files/strategic_note_issue_14.pdf> (last accessed 17 July 2019).

III. Potential roles of the SbD and BbD concepts in regards to safety and innovation governance

1. Tools for risk assessment, risk management or both?

Safety is the core of both the BbD and SbD concepts, but the definition of safety has not been explicitly articulated.[34] The interface between law, regulation and science is clearly on stage when we consider safety and the BbD and SbD concepts. The definition of "safety" depends on the context in which it is used. For example, Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals[35] does not include a definition of safety, even though the term "safety" is referred to repeatedly. The absence of definitions is because safety is a relational value and absolute safety cannot be achieved. This leads to questions, for example: What is safe enough? Who decides and defines the acceptable level of safety? These are political challenges, embedded with social assumptions, and thus cannot be reduced to a technical dilemma for scientists and innovators.[36] This reveals the unrealistic vision of control included in safety design approaches that could be implemented in the design processes, because of prevalent ignorance and/or uncertainty about the effects of innovative chemicals.[37]

The SbD concept can be considered as multidimensional; in other words, as: (1) an approach to risk assessment; (2) a specific risk management strategy; and (3) a result of the design process.[38] As a risk assessment approach, the SbD concept implies that risks are already assessed in the design phase. As a risk management strategy, it addresses SbD measures (built-in safety). When considered a result of the design process, the SbD concept claims absolute safety and the absence of risk. This last aspect is utopian, and as a point of comparison, it is never aspired to in the context of drug development.[39] On the other hand, the second approach requires the first, and thus they are intertwined.[40] Therefore, the SbD concept is a tool for both risk assessment and management. But how could it enhance the consideration of safety in risk regulation?

The answer is: by creating a structured decision-making platform for a network of stakeholders, which may be involved in the innovation life cycle. This will be performed by defining the innovation project's workflow with specific decision points

[34] Hjort et al, supra, note 23, pp 306, 308.

[35] Regulation (EC) No 1907/2006 of the European parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/105/EC and 2000/21/EC [2006] OJ L136/3.

[36] S Jasanoff, *Designs on Nature. Science and Democracy in Europe and the United States* (Princeton, NJ, Princeton University Press 2007) pp 13–14. For a more in-depth description of the role of science in decision-making, see eg CM Rose, "Environmental Law Grows up (More or Less), and What Science Can Do to Help" (2005) 9 Lewis & Clark Law Review 273.

[37] Schwarz-Plaschg et al, supra, note 22, p 278.

[38] I van de Poel and Z Robaey, "Safe-by-Design: from Safety to Responsibility" (2017) 11 Nanoethics 297, 298.

[39] Hjort et al, supra, note 23, pp 308–309.

[40] van de Poel and Robaey, supra, note 38, p 298.

in each phase of the innovation cycle.[41] Project-specific interdisciplinary dialogue and the possibility of evaluating all of the available information and using it as early as possible in the decision-making process are the benefits of the SbD process. At the national level, Germany has utilised the "NanoDialogue" platform for stakeholder dialogue since 2006 as part of the German government's Nano Action Plan.[42] The NanoDialogue platform was launched by the NanoKommission, "a societal control group" that comprised approximately 20 members as a centralised, national platform.[43] The value of the NanoKommission was that it provided consensual knowledge that was co-produced by all relevant stakeholders from different sectors of society.[44] The NanoKommission as a quasi-external body (external from science and law) was able to make useful decisions in the interdisciplinary dialogue and provide norms for science and the economy in order to cope with scientific uncertainty. The application of the SbD concept means carrying out interdisciplinary dialogue at the project level. This may result in even more concrete effects on science and the economy and help to break the silos between innovators, safety experts, regulators and the public than dialogue at the national level.

Jasanoff noted that technical and social orders are co-produced in each policy regime.[45] Science and Technology Studies have recognised three mechanisms that should be considered in democratising the governance of innovative technological developments, namely the market, regulation and ethical deliberation.[46] While the market emphasises efficiency and regulation emphasises rationality, ethics is concerned with moral values rooted in culture. Consequently, safety should be understood in relation to numerous, often vague entities (eg the environment) that decision-makers encounter during risk regulation. In addition to safety, other values (eg social or ethical acceptance, privacy) come into play at varying degrees under different policy regimes, creating normative

[41] Kraegeloh et al, supra, note 28, p 243. The SbD process is elaborated in more detail in Section III.2.

[42] Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, "The NanoDialogue" <www.bmu.de/en/topics/health-chemical-safety-nanotechnology/nanotechnology/the-nanodialogue> (last accessed 29 April 2020).

[43] The NanoKommission worked in two phases (2006–2008 and 2009–2011). More than 200 experts were engaged on a voluntary basis in the discussion of the responsible use of nanomaterials; ibid.

[44] S-P Pfersdorf, "Governing nanotechnology through stakeholder dialogues: The example of the German NanoKommission" (2012) 10 International Journal of Emerging Technologies and Society 45, pp 47–48, 52, 55–56. Pfersdorf analysed the social conditions that contributed to the NanoKommission's influence on science and the economy. Societal importance describes social processes of constructing norms, and social reality is built through processes of communication between different stakeholders.

[45] Jasanoff, supra, note 36, p 19; S Jasanoff, "Constitutional Moments in Governing Science and Technology" (2011) 17 Science and Engineering Ethics 621, 624. See also B Laurent, *Democratic Experiments. Problematizing Nanotechnology and Democracy in Europe and the United States* (Cambridge, MA, MIT Press 2017) pp 126–34, 200–01. As examples of strategies established to integrate ethical, legal and social aspects with natural science, see DH Guston and D Sarewitz, "Real-time technology assessment" (2002) 24 Technology in Society 93; National Human Genome Research Institute, "Ethical, Legal and Social Implications Research Program" <www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program-ethical-legal-social-implications> (last accessed 20 February 2020).

[46] S Jasanoff, "Governing Innovation: The Social Contract and the Democratic Imagination" Seminar 597 (2009) 1, pp 8–10. See also Roco et al, supra, note 9, pp 3565–66, who have listed international activities related to ethical, legal and social implications of nanotechnology.

ambiguity, a type of uncertainty that the concepts should be able to address.[47] Fisher stated that risk regulation regimes have developed very different means in a jurisdiction.[48] Thus, policymakers seeking to implement the by-design concepts should consider their applicability in different policy regimes. Because the SbD concept will be applied to project-specific data and, connected with the SIA, results in regulation-specific safety dossiers,[49] it is adaptable to different policy regimes. In addition, norms produced in interdisciplinary dialogue are adaptable to diverging societal expectations. However, to be regulatory tools, the rules of behaviour that frame the interaction should be formalised in each policy regime through referring to them in the relevant regulations or through application of the rules by public authorities.[50] Standardisation may assist in the application of the concepts. Currently, the European Committee for Standardization (CEN) is preparing a standard for the SbD concept.[51]

Similarly, BbD encompasses both risk assessment and management dimensions because the material characteristics that affect risk potential (eg solubility, genotoxicity, ecotoxicity) are assessed early as drivers of drug development towards more rational design, focusing on risk mitigation by hazard reduction.[52] The BbD concept could enhance the consideration of safety in risk regulation, for example, so that chemicals that remain in wastewaters are intentionally designed to mineralise rapidly in effluent treatment processes or in surface waters.[53] Although there are limited possibilities to vary the core functional parts of these molecules, other parts can be varied to a much greater extent, and encouraging examples are available even for widely used pharmaceuticals.[54] Today, however, increasingly complex products

[47] van de Poel and Robaey, supra, note 39, pp 299, 300. See also Schwarz-Plaschg et al, supra, note 22, p 278, who argued that the recent focus on SbD and safety in the EU context has narrowed the nanotechnology debate to safety concerns instead of broader innovation governance questions that were on the agenda at the beginning of the debate on nanotechnology.

[48] Fisher, supra, note 12, p 126. See also E Fisher, B Lange, E Scotford and C Carlarne, "Maturity and Methodology: Starting a Debate about Environmental Law Scholarship" (2009) 21 Journal of Environmental Law, 213, 239–243, regarding the multi-jurisdictional nature of environmental law regimes.

[49] Dutch National Institute for Public Health and the Environment (RIVM), "ProSafe Safe-by-Design (SbD) Implementation Concept" 1, p 4 <www.rivm.nl/en/documenten/prosafe-safe-by-design-sbd-implementation-concept-final> (last accessed 1 May 2020). The SbD concept has been tested for different processes in pilot projects. For example, the R2R Biofluidics project has published a SbD report for large-scale micro- and nano-fabrication technologies for bioanalytical devices based on roll-to-roll imprinting. See R2R Biofluidics, "Safe-by-design report. Deliverable 9.3" <www.r2r-biofluidics.eu/images/deliverables/D39_D93_Safe-by-design_report.pdf> (last accessed 1 May 2020).

[50] A Reinchow, "Risk, Uncertainty, and Learning in Nanomaterials Regulation: An Analytical Framework" (2016) 7 European Journal of Risk Regulation 502, 507, 513. Currently, for example, RIVM introduces on its webpages a concept version of the SIA Toolbox developed in the NanoReg2 project. RIVM states that the Toolbox is a set of tools, guidelines and checklists to be used by innovators and regulators along the innovation chain, and that it supports both improved dealing with safety issues and improved regulatory preparedness. See Dutch National Institute for Public Health and the Environment, "NanoReg2" <www.rivm.nl/en/about-rivm/mission-and-strategy/international-affairs/international-projects/nanoregii> (last accessed 1 May 2020).

[51] European Committee for Standardization (CEN), "CNT/TC 352 Work programme" <https://standards.cen.eu/dyn/www/f?p=204:22:0::FSP_ORG_ID,FSP_LANG_ID:508478,25&cs=18E152154F73BA190A16C4D279047F5FD> (last accessed 2 May 2020).

[52] Hjort et al, supra, note 23, pp 310, 317.

[53] K Kümmerer, DD Dionysiou, O Olsson and D Fatta-Kassinos, "A path to clean water" (2018) 361 Science 222, 223.

[54] Such pharmaceuticals include, for example, β-blockers, which are a class of active pharmaceutical ingredients. For example, the β-blocker propranolol has been reported to be a non-biodegradable and highly persistent chemical, which has been detected in effluents of sewage treatment plants. See T Rastogi, C Leder and K Kümmerer, "Re-designing of

with diverse compositions enter the market and end up in the environment. This is largely because of the lack of incentives to develop compounds with fast and complete mineralisation in the environment. In this connection, it must be stressed that the stability of pharmaceuticals is required under all reasonable manufacturing, storage and use conditions, as stated above. Consequently, early screening is always followed by in-depth toxicological testing and regulation. The BbD concept (and the SbD concept) constitutes only a starting point that cannot replace regulatory risk assessment, a prerequisite for market access. However, chemicals that will readily mineralise in the environment will not necessarily need extensive testing regarding their environmental effects.[55]

As an example of how the by-design concepts could be incorporated into the existing legislation, environmental risk assessment (ERA) of medicinal products for human use in the EU and the USA is briefly explored. Article 8(3)(ca) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code related to medicinal products for human use[56] outlines that in order to obtain an authorisation for a medicinal product, the application shall be accompanied by an evaluation of the potential environmental risks posed by the medicinal product (ie an ERA). However, risk–benefit analysis does not consider the ERA. It is solely based on risks relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health (Article 1(1)(28, 28a)). If the ERA points out potential environmental risks, specific safety measures related to the storage of the medicinal product, its administration to patients and for the disposal of waste products to limit the risks case by case shall be envisaged by the applicant (Article 8(3)(ca, g)).

In the Federal Food, Drug and Cosmetic Act,[57] 21 U.S.C. § 355(b)(1)(A) sets only a demand to provide full reports of investigations that have been made to show whether the drug is safe and effective for use. However, the Code of Federal Regulations (CFR) 21 § 25.20(l) determines that approval of a new drug application requires the preparation of an environmental assessment (EA). Contrary to the EU's practice, the US Food and Drug Administration (FDA) can refuse to approve an application if the EA does not contain sufficient information to enable the FDA to determine whether the proposed action may significantly affect the quality of the human environment (21 CFR § 25.15(a)).[58] The FDA can also command the applicant to implement risk-mitigation measures (21 CFR § 25.40(e)). However, because of many categorical exclusions (21 CFR § 25.31), the EA has not been commonly required during the new drug application process, and consequently, the mandate of the FDA to consider environmental risks and to require risk-mitigation measures is limited. In that case,

existing pharmaceuticals for environmental biodegradability: A tiered approach with β-blocker Propranolol as an example" (2015) 49 Environmental Science & Technology 11756, 11757.

[55] Kümmerer et al, supra, note 53, p 223.

[56] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use [2001] L311/67.

[57] Federal Food, Drug and Cosmetic Act 1938 (as amended) 21 U.S.C. § 301 et seq.

[58] For a more detailed analysis of the similarities and differences in the regulative risk assessment procedures of pharmaceuticals in the EU and the USA, see S Walter and K Mitkidis, "The Risk Assessment of Pharmaceuticals in the Environment: EU and US Regulatory Approach" (2018) 9 European Journal of Risk Regulation 527.

the FDA can require the EA only in extraordinary circumstances (ie if the specific proposed action may significantly affect the quality of the human environment; 21 CFR § 25.21).

Both jurisdictions aim to regulate the impacts of pharmaceuticals on the environment by assessing the impact of a product at the market approval phase.[59] It could be reasonable to enforce pre-screening of environmental considerations in the early design phase by applying the BbD concept. This would not replace the ERA or EA at the market approval phase, but, as noted above, it might result in less extensive testing in the future if the approach proves to be feasible. As stated in Section II.1, increased dialogue between the experts from different disciplines and the regulators is needed to enhance the implementation of green chemistry in the pharmaceutical industry. Compulsory application of the BbD concept in the early design phase might make this happen.

2. Supporting radical or incremental innovations?

Defining innovation is far from straightforward because the meaning depends on the context and perspective (eg scientific community, field of industry, customer, society). Regulation is a central factor in the management of the positive and negative societal impacts of innovation.[60] In the past, risk regulatory approaches have allowed harmful innovations and hindered useful innovations, indicating that regulators should find new means of engaging with emerging and evolving technologies. Smismans and Stokes discussed how different innovation types actively shape regulatory responses to new technologies.[61] They showed that the distinction between "radical" and "incremental" innovation may affect the desirability of a new legislative framework, the nature and extent of the evidence base for regulation and the use of the precautionary principle. Defining a technology as incrementally innovative releases policymakers from exploring wider socioeconomic implications. Thus, policymakers are relieved of further understanding of the effects of nanotechnologies on the environment, economy or societies that would require interdisciplinary approach. Smismans and Stokes argued that the distinction, providing possibilities for interpretation, has been used to justify different regulatory strategies adopted towards nanotechnology by the European Commission (incremental) and the European Parliament (radical). Consequently, innovation is an object of governance and an instrument of governance, actively steering regulatory responses in the directions determined by policymakers through interpretations of the type of innovation. Policymakers may describe technology as

[59] An assessment of the impacts of active pharmaceutical ingredients on the environment is currently not required, but a draft guideline on the ERA of medicinal products for human use in the EU considers active pharmaceutical ingredients and metabolism of the active substance may be taken into account as well. See European Medicines Agency, "Guideline on the environmental risk assessment of medicinal products for human use" 1, pp 4, 8 <www.ema.europa.eu/documents/scientific-guideline/draft-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf> (last accessed 29 April 2020).

[60] H Armstrong, C Gorst and J Rae, "Renewing regulation. Anticipatory regulation in an age of disruption" (*NESTA* March 2019) 1, p 11.

[61] S Smismans and E Stokes, "Innovation Types and Regulation: the Regulatory Framing of Nanotechnology as 'Incremental' or 'Radical' Innovation" (2017) 8 European Journal of Risk Regulation 364, 365–66, 370–72.

incrementally innovative to avoid the need for a new legislative framework and broader evidence-based impact assessment that might stifle or delay innovation; namely, they prefer deliberate regulatory ignorance.[62] It must be noted that risk regulation can be conceptualised and understood in a different manner, even in the same jurisdiction, to produce pragmatic frameworks for regulatory decision-making.[63] Practices of regulators, particularly related to innovations, deserve more attention.[64]

The SbD concept in the EU has adhered strongly to the innovation process and economic concerns, raising criticism that safety may become conceptualised as an enabler of innovation, without absolute value.[65] Other points of criticism have been raised with respect to the limitations of existing innovation management frameworks as a basis for the SbD approach. These arguments are, for example, that the models: (1) may not be easily applicable to global networks with diverse interests and safety expectations that are involved in the manufacturing and commerce of innovative nanomaterials; and (2) do not consider that the processes may be better conceptualised as non-linear collective and iterative learning. Jasanoff has stated that as the markets of innovative technological developments expand, democratic processes may not be able to ensure accountability towards all affected parties.[66]

In my opinion, the SbD concept could help to combine techno-scientific and socioeconomic aspects of risk regulation under the same interdisciplinary approach and could support radical innovations by requiring collaborative, transparent interactions between actors throughout the innovation chain.[67] According to Kraegeloh et al, SbD is a bottom-up approach that includes various actors (eg industry, academia, regulators, customers, consumers, society) and covers the whole innovation process.[68] They stated that the concept could be implemented by industry and that regulators could use it as a reference tool that integrates currently used risk assessment practices, innovation management processes, environmental, health and safety assessment, regulatory affairs and data handling. The SbD process can be applied to different processes, products, companies and industries, but the data are project specific. The SbD process is based on the Stage-Gate® innovation process model, in which "stages" represent product development milestones and "gates" provide intervention and adjustment opportunities.[69] Implementation of the SbD concept starts with the definition of the innovation project's workflow, whose structure can be complex, with many actors interacting in different phases of the innovation process.[70] Decision-makers

[62] See also N Cortez, "Regulating Disruptive Innovation" (2014) 29 Berkeley Technology Law Journal 175, 199–227, regarding challenges in decision-making when regulating new technologies.

[63] Fisher, supra, note 12, p 131.

[64] Armstrong et al, supra, note 60, pp 4–5, stated that innovation should be at the centre of regulators' concerns, but public and political discussions on regulation recognise neither it nor the need for new regulatory practices.

[65] Schwarz-Plaschg et al, supra, note 22, p 278.

[66] Jasanoff, supra, note 36, p 28.

[67] Smismans and Stokes, supra, note 61, pp 365–66, 371–72, argued that the European Commission, through its narrow framing of possible regulatory responses for nanotechnology, has avoided engagement with broader questions such as the socioeconomic implications of this technological development. In the EU, integrated impact assessment is the instrument for providing a wider evidence base for policymaking. By framing a technology as only incrementally innovative, it is possible to avoid the need for an integrated impact assessment.

[68] Kraegeloh et al, supra, note 28, pp 241–43.

[69] The Austrian Academy of Sciences: Institute of Technology Assessment, supra, note 30, p 2.

(gatekeepers) at each gate decide on the fate of the innovation project based on balancing expected risks, costs and benefits.[71] The process or product is reviewed before going ahead if the collected information indicates this to be appropriate. Thus, the SbD concept, as a platform for interdisciplinary decision-making, enables iterative learning. Although incorporation of all aspects and actors of global networks involved in the innovation chain is obviously impossible, the SbD concept might enhance transparent dialogue between different stakeholders, which is of the utmost importance in innovation governance.

Although the BbD concept per se has not been closely connected to the innovation process, economic, social and ethical aspects, as well as new business models, have been recognised in the broader context of sustainable chemistry.[72] New business models may create win–win situations between the customer and provider, supporting innovation while reducing the chemical-related environmental burden. Innovative pharmaceuticals, developed according to the BbD concept, are examples of such new business models.[73] Schmutz et al have stated that the efficiency of the innovation process and the collaboration of all involved interdisciplinary actors would be improved if a methodological approach that evaluates the safety of nanomedicines early in the product development phase was available.[74]

In this section, I evaluated how by-design concepts could enhance the consideration of safety in risk regulation and support radical innovations by increasing interdisciplinary dialogue between different stakeholders. In Section IV, I analyse the applicability of the concepts as regulatory tools for enhancing interdisciplinarity by using the SbD concept as an example and reflecting on it in relation to the suggested characteristics for the risk governance framework for nanotechnologies and the criteria set in new governance literature.

IV. From scientific concepts to adaptive regulatory network management tools

Adaptability and flexibility are identified as key characteristics of the frameworks intended to manage emerging risks.[75] These are closely related to learning, revisability and new forms of accountability incorporated into the multiscale collaborative governance arrangements presented in new governance literature.[76] In addition, Holley et al selected two more characteristics for evaluating new (environmental) governance institutions: participation and deliberation.[77] I analyse the

[70] Kraegeloh et al, supra, note 28, pp 243, 248.

[71] Gottardo et al, supra, note 27, p 102.

[72] A Weiser, DJ Lang and K Kümmerer, "Putting Sustainable Chemistry and Resource Use into Context: The Role of Temporal Diversity" (2017) 5 Sustainable Chemistry and Pharmacy 105, 106.

[73] Kümmerer (2019), supra, note 19, pp 3–4.

[74] M Schmutz et al, "A methodological safe-by-design approach for the development of nanomedicines" (2020) 8 Frontiers in Bioengineering and Biotechnology 1, 2. They have developed an approach that is based on the SbD concept in the GoNanoBioMat project <www.empa.ch/web/s403/gonanobiomat> (last accessed 2 May 2020).

[75] IRGC, supra, note 11, p 9.

[76] See eg Holley et al, supra, note 10, pp 5–9.

applicability of by-design concepts as regulatory tools to enhance interdisciplinarity by using the SbD concept as an example and reflecting on it in relation to these characteristics, grouped as (1) collaboration, participation and deliberation; (2) flexibility and revisability; and (3) adaptability, learning and accountability.

1. Collaboration, participation and deliberation

Kraegeloh et al do not explicitly describe how the SbD concept would ensure effective collaboration, participation and deliberation. Holley et al examined how these objectives have been achieved in practice under three new governance programmes.[78] They stated that implementing multi-stakeholder collaboration is demanding and that at least the following should be considered: transaction costs, trust, inclusiveness and representativeness and rules of decision-making. The mechanisms mentioned to address these points include incentives (positive or negative), building trust and a consensus approach. Kraegeloh et al recognised that information sharing is crucial in the implementation of the SbD concept and suggested that an Internet platform should be developed to exchange information between participants.[79] The main objective of such a platform would be to build trust, especially between industry and regulators, but it could also serve as a forum in the SbD process to accumulate and share information with a wider group of participants. The information platform would be one source of information in the SbD process, which also includes the participation of the other actors.

However, how the inclusive and representative participation and deliberative decision-making during the SbD process could be arranged remains unclear, and this may result in imbalances in power during decision-making.[80] Guston and Sarewitz stressed that informed societal responses to innovation depend on how well various societal actors prepare for the impacts of the innovation, and there must be established processes (eg consensus conferences, scenario workshops, focus groups) that help society make actual choices about the progress, direction and application of innovation.[81] Oomen et al proposed that to enhance informed decision-making in the innovation chain, a possible way forward could be the development of a pragmatic, internationally accepted nanomaterial decision framework with only partially scientifically based decision criteria.[82] The adoption of such a framework requires cooperation between policymakers, regulators, scientists and industry. SbD (and BbD in the context of drug development[83]) could enable this type of framework if processes and rules for

[77] ibid, p 10.

[78] Holley et al, supra, note 10, pp 39–42, 70–73.

[79] Kraegeloh et al, supra, note 28, pp 245–46. The major need today is to increase the efficiency in information gathering for risk assessment. See Oomen et al, supra, note 13, p 10; M Miettinen, "Empirical analysis of regulative risk assessment processes of nanomaterials under the Toxic Substances Control Act (TSCA) and European Union regulation concerning the Registration, Evaluation, Authorization and restriction of Chemicals (REACH)" (2019) 1323 Journal of Physics: Conference Series 012023, pp 8–11, 16.

[80] Holley et al, supra, note 10, pp 73, 95–97. Substantial difficulties in achieving the aspirations of participation and deliberation were also observed in their study.

[81] Guston and Sarewitz, supra, note 45, pp 104–05.

[82] Oomen et al, supra, note 13, pp 10–11.

decision-making can be established, because broad collaboration is considered an inherent part of the SbD project. However, realising collaboration is time and resource intensive, and transaction costs may hinder the implementation of the SbD concept if it is based only on voluntary cooperation without incentives.[84]

2. Flexibility and revisability

Because the governance of emerging technologies must manage the low level of knowledge regarding causal or functional relationships between risk sources and their environment, flexibility and revisability are core characteristics of governance frameworks.[85] Kraegeloh et al stated that because regulations and standards applicable to different actors and at different times of an innovation project vary, the SbD approach must be flexible in order to manage (and revise on demand) the safety and regulatory data requirements of each phase of the innovation chain, and it must organise the links between actors that have different roles.[86] When a workflow of an innovation project is determined, the decision points at which the data will be reviewed and decisions about the project status will be taken are defined. Required revisions can arise from safety concerns, functionality shortcomings or feedback from the public or regulators. Consequently, the SbD project includes interdisciplinary decision points in all phases of the project workflow. In addition, flexibility is included in the SbD library (inventory of available tools; eg for risk assessment), which will be constantly updated with the most advanced tools and standards, following the progress in various fora (eg the Organisation for Economic Co-operation and Development, International Organization for Standardization). The use of internationally acknowledged guidance documents (eg on standardised testing) is highly recommended in order to improve the applicability of the by-design approaches in different policy regimes.[87]

3. Adaptability, learning and accountability

New forms of accountability must be considered in dynamic, multiscale, collaborative arrangements in which non-government actors have important roles.[88] Conventional accountability mechanisms (eg authorisation and judicial review) may not have the flexibility to facilitate incremental decision-making. New mechanisms can be roughly divided into two categories: process mechanisms and performance mechanisms. For

[83] BbD has been brought out, for example, in the context of systemic risk governance of pharmaceuticals that leans on the principle of co-responsibility (ie risks that modern societies face are caused by the interplay of a multitude of actors, and a problem solution proves to be a task for many actors); see F Keil, G Bechmann, K Kümmerer and E Schramm, "Systemic Risk Governance for Pharmaceutical Residues in Drinking Water" (2008) 17 GAIA 355, 355–57.

[84] Kraegeloh et al suggested that the implementation of the SbD concept should be, at least initially, based on voluntary cooperation of participants. See Kraegeloh et al, supra, note 28, p 248.

[85] IRGC, supra, note 11, pp 8–9.

[86] Kraegeloh et al, supra, note 28, pp 243–44.

[87] See also Oomen et al, supra, note 13, p 10, who stated that worldwide harmonisation of testing approaches through the Organisation for Economic Co-operation and Development is considered valuable because of their consensus-driven review process and acceptance by regulatory authorities from many countries.

[88] Holley et al, supra, note 10, pp 101–02.

example, risk assessment belongs to process mechanisms, whereas the performance mechanisms focus on outcomes (eg compliance). Learning can be process-based as well; that is, encouraging industries to self-reflect and learn about their environmental impacts. A more advanced mode is systemic learning, in which information is shared between collaborative actors to diffuse innovation and to facilitate continuous adaptation, designed to enhance compliance with policy targets.

The SbD process involves both process- and performance-based accountability mechanisms (eg mutually agreed data requirements, compliance with thresholds and functionality specifications set during the SbD project) and process-based and systemic learning.[89] Process-based learning arises when the needs and the accuracy of data increase during the innovation process. In the early phases, in-depth knowledge of some aspects is necessary, and the process iterates until the collected information allows the industry to proceed to the next phase. Systemic learning emerges in the idea of regulatory preparedness that is included, along with the SbD concept, in the SIA. This makes it possible for regulators to be aware in a timely manner of anticipated implications of innovations and to revise relevant legislation as appropriate.[90] Holley et al stressed that effective monitoring processes are critical for the achievement of accountability and learning goals.[91] In the SbD process, a stage-gate model with specific decision-making points (gates) provides an appropriate frame for the monitoring scheme, if the fulfilment of the mutually agreed data requirements or compliance targets can be achieved.

Armstrong et al introduced an advisory, adaptive, anticipatory model for regulation that emphasises flexibility, collaboration and innovation.[92] Under the model, regulators have a positive, proactive role in shaping how innovations are developed and deployed. They stated that new, more proactive regulatory practices would help the regulators ensure that economic and social benefits are achieved while risks are better understood and managed. Reinchow developed a framework for the analysis of learning in governance networks.[93] She stated that because diverse actor groups (regulators, industry, research institutes) have created a complex game of collaboration, it might be useful to have steering in place to facilitate sound network collaboration. By-design concepts could serve as adaptive network management tools that build trusted relationships between innovators, safety experts, regulators and the public, thus enabling the systemic learning that is necessary for effective regulation of innovative technologies under scientific uncertainty. The networks of actors are dynamic, as Reinchow argued, but in order to be regulatory tools, the rules of behaviour that frame the interaction should be formalised, as discussed in Section III.1.[94]

89 Kraegeloh et al, supra, note 28, pp 243–45.

90 Jantunen et al, supra, note 31, p 4.

91 Holley et al, supra, note 10, pp 138–39.

92 Armstrong et al, supra, note 60, pp 5, 11, 13, 19–20.

93 Reinchow, supra, note 50, pp 505, 515–16.

94 ibid, pp 506, 513.

V. Conclusions

Nanotechnologies serve important social and economic purposes, but for regulators they are wicked public policy problems involving a multitude of stakeholders with competing values and interests. Consequently, the need for greater interdisciplinarity in the risk governance of nanotechnologies has been recognised. This paper analysed how the SbD and BbD concepts, which have emerged in materials science and drug development, could enhance interdisciplinarity in risk regulation.

The analysis showed that the by-design concepts create platforms for interdisciplinary dialogue and decision-making that may also enhance the consideration of safety in risk regulation. The concepts might also support radical innovations and informed decision-making in the innovation chain by requiring collaborative, transparent interactions between actors throughout the innovation chain. In addition, the efficiency of the innovation process may be improved if environmental considerations would be evaluated early in the product development phase. The analysis showed also that by-design concepts might serve as adaptive network management tools that build trusted relationships between innovators, safety experts, regulators and the public, thus enabling the systemic learning that is necessary for effective regulation of innovative technologies under scientific uncertainty. However, to achieve this goal, the rules of behaviour that frame the interaction should be formalised.

The core of the involvement of the SbD or BbD concepts in risk regulation discourse should be a shared responsibility for safety that combines techno-scientific and socioeconomic aspects. Different actors should continuously, in the frames laid out for the interaction, evaluate where responsibility for safety is best addressed. Technologies and regulations should be designed accordingly.[95] Proactive regulatory practices and broad collaboration as inherent parts of the by-design approach would help regulators ensure that economic and social benefits are achieved while risks are better understood and managed. This would enable adaptive risk management and provide democratic opportunities to shape technology, increasing resilience in the risk governance of emerging technologies.

[95] See also van de Poel and Robaey, supra, note 38, pp 297, 300. They argued that adaptive risk management organises a learning process with respect to both what the risks are and how to best manage them, and innovations could be designed to be flexible so that they can be adapted or used differently if new risks emerge. For a more detailed discussion of design for responsibility, see JN Fahlquist, N Doorn and I van de Poel, "Design for the Value of Responsibility" in J van den Hoven, PE Vermaas and I van de Poel (eds) *Handbook of Ethics, Values, and Technological Design* (Berlin, Springer Science+Business Media 2014).