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Safe by Design for Nanomaterials—Late Lessons from Early Warnings for Sustainable Innovation

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Abstract The Safe by Design conceptual initiative being developed for nanomaterials offers a template for a new sustainable innovation approach for advanced materials with four important sustainability characteristics. Firstly, it requires potential toxicity risks to be evaluated earlier in the innovation cycle simultaneously with its chemical functionality and possible commercial applications. Secondly, it offers future options for reducing animal laboratory testing by early assessment using *in silico* predictive toxicological approaches, minimizing the number that reaches *in vitro* and *in vivo* trials. Thirdly, it promotes a culture of shared responsibility for ethical and sustainable outcomes in the innovation process by promoting early dialogue between groups with vested interests. Finally, it offers the prospect of a more democratized innovation process by including civil society actors in decisions on product safety, commercial applications, and social utility. Collectively, these four characteristics offer the prospect for a new social contract between science, technology, and society for the societal alignment and sustainable innovation of advanced materials.

Keywords Safe by Design · Shared responsibility · Social contract · Sustainable innovation

Introduction

Environmental activists have spurred a generational political mobilization that has caught the world's attention by highlighting the prospect of irreversible global socioecological changes, particularly climate change [1, 2]. Poorly regulated industries continue to create unresolved crises such as episodes of ozone depletion, possible irreversible insect biomass loss, micro- and nanoplastic ubiquity in water supplies, and chronic air, water, and land pollution [3]. An alliance of scientists supports the environmental activists' calls for transformable techno-scientific initiatives, combined with a radical transparency of innovation processes, as critical components for the resolution of the supranational crises facing us [4].

The European Union (EU) has responded with its 'Green Deal' policy for sustainable growth [5], with the European Commission (EC) calling for a toxin-free environment by the development of inherently safe and sustainable chemicals from product development to end of life [6]. The question is whether the adoption of the Safe by Design (SbD) conceptual approach, with its emphasis on early safety warnings, shared responsibility for sustainable outcomes, and supported by a new social contract, can assist in preventing future crises. Past mistakes cannot be retracted and erased, but advocates of the SbD evidence-based approach for nanomaterials (NM) believe it offers such a template for novel advanced hybrid and smart materials. SbD can be delivered

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by a control system approach that couples disparate scientific, engineering, regulatory, and deliberative constituents for product safety and design modification [7]. It can strengthen EU regulatory preparedness for unexpected NM future risks, with the additional benefit of developing novel products that are more socially aligned and sustainable, minimizing the repetition of past socioecological mistakes [8]. SbD incorporates within research and development (R&D) practices the methodological integration of sound science, responsible technology innovation, and democratic participation [8, 9]. It underpins the necessity for techno-scientific mechanisms to prevent future novel innovation acting unexpectedly in the way it influences our lives and shapes our futures. This is achieved by providing early warnings of possible adverse environmental and biological outcomes [8, 9].

Early Warnings for Sustainable Innovation

Nanotechnology R&D is providing an ever-expanding techno-economic base for a new generation of smart, nano-enabled products within disparate industry sectors, e.g., aerospace, coatings, and pharma. However, the discovery of novel NM techno-scientific features is accompanied by continuing unresolved concerns regarding potential enhanced toxicity risks; in particular, much smaller NM concentrations might pose risks at exposure levels below those currently tolerated within EU regulations. The EC received criticism in the Vienna Declaration 2017, from a group of EU member states, who believed that environmental health and safety (EHS) risks from novel NM were outpacing and overspilling current EU regulatory boundaries [10, 11, pp. 169–189]. As part of its response, the EC proposed new nanospecific safety regulatory testing protocols enacted on 1 January 2020 [12].

Current industry practice tends towards EHS risk assessments for regulatory approval to be conducted on a timeline close to market in their manufacture of safe products [8, 9]. The intention is that these EU regulatory changes will support SbD decision-making by enabling earlier upstream EHS risk considerations simultaneously with the NM chemical functionality and commercial applications. So, in SbD practice, the NM chemical functionality and its potential (eco-)

toxicity are modelled in an integrated manner and given equal weighting in any decision-making [8, 9]. By making this R&D decision earlier in the innovation process, SbD can act as an exemplary EHS early warning platform by the application of the precautionary principle [9]. So, industry decisions to ‘fail early’ can be made before high levels of R&D investment have occurred and become too substantial to retrace or abandon the new product development. The intention with SbD is that the responsibility for making fail early or design modification decisions will become a shared one (see p. 100166 in [13]).

Shared Responsibility

The promotion of a culture of collective responsibility by disparate partners with different vested interests in the innovation outcome is a central principle. Through shared responsibility for early warnings, modifications can be made to the R&D investment plan, technological design, commercial applications, and the regulatory response. By moving from a reactive to a proactive role, regulators can improve their anticipatory capabilities by an early dialogue with industry on the novel innovation processes and their expected outcomes. In doing so, the regulators can develop a Regulatory Preparedness (RP) plan for adaptable (safety) regulation that keeps pace with knowledge generation and novel innovation applications. SbD and RP can then collectively contribute to a novel Sustainable Innovation Approach (SIA) for industry and regulators alike for the safe and sustainable development of nanoproducts [6, 8, 13, p. 100166]. SIA is designed to be a resilient system that is flexible, responsive, and adaptive as new knowledge is generated, to better anticipate future risks and generate corresponding regulatory modifications (see p. 100166 in [13]).

The development of a culture of shared responsibility will require an early dialogue with actors with diverse vested interests who influence final innovation outcomes. This includes the innovator who must make R&D techno-economic decisions, the risk assessor raising potentially costly EHS critical questions, and the regulator on the ‘if’ and ‘how’ the product comes to market (see p. 100166 in [13]). An additional aspiration is that civil society actors will be invited into this circle for the early stages of this

dialogue. This proposal is predicated on the understanding and acceptance that everybody can make a valued contribution. The expression of this radical transparency can result in an acceleration of the time to market and in the creation of a more value-laden marketable product that is economic, socially aligned, and sustainable.

Transforming the Societal Alignment of Innovation

Product social alignment will require adaptive R&D practices, more open to incorporating social needs, values, and concerns within innovation decisions (see pp. 316–331 in [14]). With this radical transparency, civil society actors can step outside the narrower techno-scientific boundaries to offer differing, sometimes unexpected, insights and perspectives. These do not have to be confined to safety concerns but can include value-adding views on product functionality, viability, and commerciality (see p. 2045 in [15]). They can ask fundamental questions such as ‘should we proceed with this product?’ as well as ‘could we succeed with this product?’ Thus, with this collaboration, SbD can become a part of a template for a new social contract between science, technology, and society for inherently safe and sustainable products. This will require the innovator to relinquish, in a controlled manner, some decision control and commercial confidentiality for their product development [5, 6]. This will be in part exchange for the critical outsiders contributing differing insights and perspectives that could be commercially value-adding to the product and its long-term success (see pp. 316–331 in [14, 15, p. 2045]).

Twenty-first Century Paradigms for Sustainable Safety Testing

Nevertheless, NM sustainable innovation continues to be underpinned by EU nano-specific testing protocols, which can still use animals for chemical testing [6, 12]. This is despite the EU policy commitment to the replacement, reduction and refinement of animal experiments (the ‘3Rs’) [16]. Whilst SbD safety testing can still use animal experiments, the long-term

goal is their minimization or elimination to meet the 3Rs objectives. What SbD offers is future options for reducing animal testing by early assessment using *in silico* predictive toxicological approaches or virtual human platforms, aided by artificial intelligence and machine learning [6, 8, 9]. By this means, there is the evolving prospect of gradually minimizing the number of tests that reach *in vitro* and *in vivo* trials [6]. Only a sufficient weight of evidence, to predict potentially significant EHS risks, would justify laboratory testing on lower-level sentinel organisms or mammals [8, 9, 17, 18, pp. 1321–1331]. Over time, with increasing confidence in the scientific accuracy of the computational modelling, economic efficiencies will emerge due to the reduced need for costly laboratory experimentation. Consequently, this system offers the potential for evaluating a wider range of advanced chemicals across a broader range of adverse biological responses. The challenges for their implementation are achieving this proof of concept and for industry acceptance.

Challenges for Main-Streaming SbD

Whilst the ethical and sustainable outcomes for SbD are apparent, creating a business case for SbD integration for market advantage and economic success is a significant challenge. There is limited evidence that companies are incorporating sustainable innovation policies within their corporate plans (see pp. 316–331 in [14, 15, p. 2045, 19]). Many industries will argue that they are already regulatory compliant, acting in a safe and responsible manner, and that any additional SbD testing costs are difficult to justify. There are particular concerns for small- and medium-sized (SME) enterprises, which may lack the resources to adopt this strategy. But, critically, it is within this SME entrepreneurial space that much novel innovation takes place. The EC suggests that industry incentives may be necessary to encourage adoption of new safe and sustainable product development processes [6]. These could include governmental grant funding or tax breaks, opportunities for fast-track passporting through regulatory regimes, and charter marking/trade-marking certification for product branding (see p. 2045 in [15, 19]). There is also the need for allaying industry concerns regarding loss of commercial confidentiality and intellectual property. Initiatives, such

as providing Trusted Environments within government technology hubs, could act as neutral venues for this democratized collaboration (see p. 100166 in [13, 19]). In these settings, collaborative learning, mutual trust, confidence, and respect can be nurtured between the civil society actors, NM entrepreneurs, and regulatory agencies [19]. In addition, a tracking process for each project could be developed and implemented to record outcomes for system feedback, reflection, and technology and social learning [19].

Conclusions

The proposed SbD conceptual approach for NMs is not a panacea for sustainable futures. It is risk governance at the frontiers of science and innovation where there will always be unpredictability. Yet, it offers a twenty-first century transformable model for the safe and sustainable development of NM, with the prospect to act as a template for the innovation of other novel advanced materials. It provides for early warnings for NM design, and future options to implement alternative *in silico* predictive toxicological paradigms. These approaches could minimize animal-based testing and enhanced regulatory preparedness to anticipate unexpected outcomes. Critically, its setting is within a culture of shared responsibility and radical transparency of the innovation process. It offers a model for other evolving technologies to consider adopting when aiming for a toxin-free environment, and for identifying solutions for the grand socioecological challenges facing all of us today.

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