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FROM BENCH TO BIOSPHERE: INTEGRATING SAFE-AND-SUSTAINABLE-BY-DESIGN PRINCIPLES INTO THE NEXT GENERATION OF NANOMATERIALS — GREEN SYNTHESIS, HAZARD ENGINEERING, AND LIFE-CYCLE GOVERNANCE

DA BANCADA À BIOSFERA: INTEGRAÇÃO DOS PRINCÍPIOS DE DESIGN SEGURO E SUSTENTÁVEL NA PRÓXIMA GERAÇÃO DE NANOMATERIAIS — SÍNTESE VERDE, ENGENHARIA DE PERIGO E GOVERNANÇA DO CICLO DE VIDA

DEL BANCO DE INVESTIGACIÓN A LA BIOSFERA: INTEGRACIÓN DE PRINCIPIOS DE DISEÑO SEGURO Y SOSTENIBLE EN LA PRÓXIMA GENERACIÓN DE NANOMATERIALES: SÍNTESIS VERDE, INGENIERÍA DE RIESGOS Y GESTIÓN DEL CICLO DE VIDA

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Renata Carolina Zanetti Lofrano[1]

ABSTRACT
The trajectory of nanotechnology innovation now stands at a critical juncture: will the next generation of nanomaterials perpetuate the reactive hazard-management paradigm of the past, or will it embrace a proactive integration of safety, sustainability, and performance from the earliest conceptual stages? This review articulates a forward-looking vision for safe-and-sustainable-by-design (SSbD) nanotechnology, tracing the intellectual and practical pathways from laboratory synthesis to environmental fate—from bench to biosphere. We synthesize evidence from 182 peer-reviewed studies to demonstrate how green chemistry principles, structure–property–hazard engineering, prospective life cycle assessment (LCA), and iterative biological screening converge to enable rational design of nanomaterials that minimize intrinsic risk while delivering functional excellence. Quantitative findings underscore both progress and persistent challenges: biogenic synthesis routes eliminate toxic reagents; prospective LCA reveals that scale-up can reduce environmental impacts by approximately two orders of magnitude yet simultaneously expose trade-offs such as lower global warming potential coupled with elevated human toxicity and freshwater ecotoxicity; measured workplace exposures during nanomaterial processing range from 4.71×10^3 to 1.75×10^6 particles·cm^{-3}, with respirable fiber concentrations reaching 0.13 fibers·cm^{-3} during grinding operations. Despite these advances, critical gaps remain: sparse ecotoxicity datasets, high LCA uncertainty at low technology readiness levels, limited environmental transformation data, and fragmented regulatory frameworks. This review provides a strategic roadmap for embedding SSbD principles into nanomaterial innovation pipelines, offering researchers, industry practitioners, and policymakers a comprehensive synthesis of current knowledge, actionable design strategies, and a clear-eyed assessment of the scientific and governance frontiers that must be crossed to realize truly sustainable nanotechnology.

Keywords: Safe-And-Sustainable-By-Design (SSbD). Green Synthesis of Nanomaterials. Structure–Property–Hazard Relationships. Life Cycle Assessment (LCA). Nanomaterial Risk Assessment.

[1] Federal University of São João del-Rei (UFSJ). E-mail: renataczlofrano@ufsj.edu.br
Orcid: https://orcid.org/0000-0002-5688-3936

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RESUMO
A trajetória da inovação em nanotecnologia encontra-se agora em um momento crítico: a próxima geração de nanomateriais perpetuará o paradigma reativo de gestão de perigo do passado ou adotará uma integração proativa de segurança, sustentabilidade e desempenho desde os estágios conceituais mais iniciais? Esta revisão articula uma visão prospectiva para a nanotecnologia segura e sustentável por design (SSbD), traçando os caminhos intelectuais e práticos desde a síntese laboratorial até o destino ambiental—da bancada à biosfera. Sintetizamos evidências de 182 estudos revisados por pares para demonstrar como os princípios da química verde, a engenharia de estrutura–propriedade–perigo, a avaliação prospectiva do ciclo de vida (ACV) e a triagem biológica iterativa convergem para permitir o design racional de nanomateriais que minimizam o risco intrínseco enquanto oferecem excelência funcional. Os achados quantitativos ressaltam tanto o progresso quanto os desafios persistentes: rotas de síntese biogênica eliminam reagentes tóxicos; a ACV prospectiva revela que o aumento de escala pode reduzir os impactos ambientais em aproximadamente duas ordens de magnitude, mas simultaneamente expõe trade-offs como menor potencial de aquecimento global associado a maior toxicidade humana e ecotoxicidade de água doce; as exposições ocupacionais medidas durante o processamento de nanomateriais variam de $4{,}71\times10^{3}$ a $1{,}75\times10^{6}$ partículas·cm^{-3}, com concentrações de fibras respiráveis atingindo 0,13 fibras·cm^{-3} durante operações de moagem. Apesar desses avanços, lacunas críticas permanecem: conjuntos de dados de ecotoxicidade escassos, alta incerteza da ACV em baixos níveis de prontidão tecnológica, dados limitados de transformação ambiental e marcos regulatórios fragmentados. Esta revisão fornece um roteiro estratégico para incorporar os princípios SSbD nos pipelines de inovação de nanomateriais, oferecendo a pesquisadores, profissionais da indústria e formuladores de políticas uma síntese abrangente do conhecimento atual, estratégias de design acionáveis e uma avaliação lúcida das fronteiras científicas e de governança que devem ser atravessadas para realizar uma nanotecnologia verdadeiramente sustentável.

Palavras-chave: Design Seguro e Sustentável (SSbD). Síntese Verde de Nanomateriais. Relações Estrutura–Propriedade–Perigo. Avaliação do Ciclo de Vida (ACV). Avaliação de Risco de Nanomateriais.

RESUMEN
La trayectoria de la innovación en nanotecnología se encuentra ahora en una coyuntura crítica: ¿perpetuará la próxima generación de nanomateriales el paradigma reactivo de gestión de peligros del pasado, o adoptará una integración proactiva de seguridad, sostenibilidad y rendimiento desde las primeras etapas conceptuales? Esta revisión articula una visión prospectiva para la nanotecnología segura y sostenible por diseño (SSbD), trazando los caminos intelectuales y prácticos desde la síntesis de laboratorio hasta el destino ambiental—del banco a la biosfera. Sintetizamos evidencia de 182 estudios revisados por pares para demostrar cómo los principios de la química verde, la ingeniería estructura–propiedad–peligro, la evaluación prospectiva del ciclo de vida (ACV) y el cribado biológico iterativo convergen para permitir el diseño racional de nanomateriales que minimizan el riesgo intrínseco mientras ofrecen excelencia funcional. Los hallazgos cuantitativos subrayan tanto el progreso como los desafíos persistentes: las rutas de síntesis biogénica eliminan reactivos tóxicos; la ACV prospectiva revela que el escalado puede reducir los impactos ambientales en aproximadamente dos órdenes de magnitud, pero simultáneamente expone compensaciones como un menor potencial de calentamiento global junto con una mayor toxicidad humana y ecotoxicidad de agua dulce; las exposiciones ocupacionales medidas durante el procesamiento de nanomateriales varían de $4{,}71\times10^{3}$ a $1{,}75\times10^{6}$ partículas·cm^{-3}, con concentraciones de fibras respirables que alcanzan 0,13

fibras·cm^{-3} durante operaciones de molienda. A pesar de estos avances, persisten brechas críticas: conjuntos de datos de ecotoxicidad escasos, alta incertidumbre de la ACV en bajos niveles de preparación tecnológica, datos limitados de transformación ambiental y marcos regulatorios fragmentados. Esta revisión proporciona una hoja de ruta estratégica para integrar los principios SSbD en los procesos de innovación de nanomateriales, ofreciendo a investigadores, profesionales de la industria y responsables políticos una síntesis integral del conocimiento actual, estrategias de diseño accionables y una evaluación lúcida de las fronteras científicas y de gobernanza que deben cruzarse para lograr una nanotecnología verdaderamente sostenible.

Palabras clave: Diseño Seguro y Sostenible (SSbD). Síntesis Verde de Nanomateriales. Relaciones Estructura–Propiedad–Peligro. Evaluación del Ciclo de Vida (ACV). Evaluación de Riesgos de Nanomateriales.

1 INTRODUCTION: THE SAFE-AND-SUSTAINABLE-BY-DESIGN IMPERATIVE

1.1 NANOTECHNOLOGY AT THE CROSSROADS: REACTIVE VS. PROACTIVE PARADIGMS

The first two decades of the twenty-first century witnessed an explosive proliferation of engineered nanomaterials (ENMs) across consumer products, industrial processes, biomedical devices, and environmental remediation technologies. Yet this rapid commercialization has been shadowed by mounting evidence of potential hazards—cytotoxicity, genotoxicity, oxidative stress, bioaccumulation, and ecosystem disruption—often discovered only after materials entered production or reached end-of-life disposal. This reactive posture, in which safety and sustainability assessments trail innovation by years or decades, mirrors the historical trajectory of asbestos, chlorofluorocarbons, and persistent organic pollutants: technologies celebrated for their performance, only to reveal unintended consequences when embedded at scale in the biosphere.

The safe-and-sustainable-by-design (SSbD) paradigm represents a fundamental departure from this reactive model. Rather than retrofitting hazard controls onto mature technologies, SSbD embeds safety, environmental sustainability, and social responsibility into the earliest conceptual and experimental stages of nanomaterial development. This proactive integration demands a convergence of disciplines—green chemistry, materials science, toxicology, life cycle assessment, risk analysis, and regulatory science—and a willingness to iterate, redesign, and even abandon promising materials when intrinsic hazards cannot be mitigated without sacrificing function. The stakes are high: nanotechnology's transformative potential in energy, medicine, agriculture, and climate mitigation can be realized only if society trusts that these materials will not replicate the environmental and health legacies of earlier industrial revolutions.

Figure 1

Conceptual Framework for Safe-and-Sustainable-by-Design Nanotechnology. A systems diagram illustrating the iterative feedback loops among synthesis design (green chemistry principles), hazard engineering (structure–property–hazard relationships), prospective LCA (environmental and toxicity metrics), risk assessment (exposure and dose-response), and regulatory governance (policy frameworks and stakeholder engagement). Arrows indicate bidirectional information flows, emphasizing that insights from LCA and toxicity screening inform redesign of synthesis routes and material properties

1.2 DEFINING SAFE-AND-SUSTAINABLE-BY-DESIGN: SCOPE AND AMBITION

Safe-and-sustainable-by-design is not a single methodology but an integrative philosophy that operationalizes multiple assessment dimensions throughout the innovation lifecycle. At its core, SSbD seeks to minimize intrinsic hazard—the inherent capacity of a material to cause harm—while simultaneously reducing environmental burdens across production, use, and disposal phases. This dual mandate requires balancing competing objectives: a nanomaterial may exhibit low acute toxicity but demand energy-intensive synthesis; conversely, a green synthesis route may yield particles with unfavorable surface reactivity or bioaccumulation potential.

The SSbD framework encompasses several interconnected pillars. First, green chemistry principles guide the selection of benign precursors, solvents, and reaction conditions, aiming to eliminate hazardous reagents and minimize waste generation at the synthesis stage [5], [6]. Second, structure–property–hazard engineering leverages systematic libraries of nanomaterials with controlled variations in size, shape, surface chemistry, and composition to establish quantitative relationships between physicochemical properties and biological or environmental hazards [2]. Third, prospective life cycle assessment (LCA) evaluates environmental impacts—global warming potential, cumulative energy demand, resource depletion, and toxicity potentials—at early technology readiness levels, enabling hotspot identification and trade-off detection before scale-up [8], [4], [13]. Fourth, iterative biological screening employs rapid, high-throughput in vitro and in vivo assays (e.g., embryonic zebrafish models) to provide real-time feedback on hazard, guiding redesign cycles until benign functionality is achieved [1]. Fifth, integrated risk assessment combines exposure measurement, fate and transformation modeling, and dose-response analysis to estimate real-world risks across occupational, consumer, and environmental scenarios [11], [7]. Finally, regulatory and ethical governance ensures stakeholder engagement, transparency, and alignment with evolving policy frameworks such as the European Union's Green Deal and SSbD mandates [12], [4].

This review adopts a broad definition of SSbD that encompasses all these dimensions, recognizing that no single tool or metric can capture the full complexity of nanomaterial sustainability. We emphasize that SSbD is inherently iterative and adaptive: early-stage assessments are necessarily uncertain, and design decisions must be revisited as new datas emergem and materials advance through development stages.

1.3 OBJECTIVES AND ANALYTICAL FRAMEWORK OF THIS REVIEW

This review synthesizes current knowledge on SSbD nanotechnology with three overarching objectives. First, we provide a comprehensive mapping of green synthesis pathways, hazard engineering strategies, prospective LCA methodologies, and toxicity assessment approaches, drawing on 182 peer-reviewed studies to identify best practices, quantitative benchmarks, and emerging tools. Second, we conduct a critical analysis of trade-offs, uncertainties, and data gaps that constrain the operationalization of SSbD principles, highlighting where scientific evidence is robust and where it remains insufficient to guide design decisions. Third, we offer a strategic roadmap for researchers, industry practitioners, and policymakers, articulating actionable recommendations for embedding SSbD into nanomaterial innovation pipelines and identifying priority areas for future research and governance development.

Our analytical framework is structured around the nanomaterial lifecycle—from bench to biosphere—tracing the flow of materials, energy, and information from initial synthesis through use and eventual environmental release or disposal. We organize the review into thematic sections that mirror this lifecycle: green synthesis (Section 3), hazard engineering (Section 4), life-cycle governance (Section 5), toxicity and exposure assessment (Section 6), regulatory landscape (Section 7), and persistent challenges (Section 8). Each section integrates quantitative data, case studies, and methodological insights, with inline citations grounded exclusively in the provided source corpus. We conclude (Section 9) with a synthesis of lessons learned and a forward-looking vision for sustainable nanotechnology.

2 CONCEPTUAL FOUNDATIONS: FROM GREEN CHEMISTRY TO HAZARD ENGINEERING

2.1 THE TWELVE PRINCIPLES OF GREEN CHEMISTRY AS DESIGN LEVERS

The Twelve Principles of Green Chemistry, articulated by Anastas and Warner in the late 1990s, provide a foundational framework for designing chemical processes that minimize hazard and environmental impact. These principles—prevention of waste, atom economy, less hazardous chemical syntheses, designing safer chemicals, safer solvents and auxiliaries, design for energy efficiency, use of renewable feedstocks, reduction of derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, and inherently safer chemistry for accident prevention—have been progressively adapted to nanomaterial synthesis over the past two decades [6], [5].

In the context of nanotechnology, green chemistry principles translate into specific design levers. Solvent selection is paramount: replacing toxic organic solvents (e.g., dimethylformamide, chloroform) with water, ethanol, or supercritical CO_2 reduces both occupational exposure risks and downstream waste treatment burdens [6]. Energy minimization targets energy-intensive steps such as high-temperature calcination, extended reflux, or vacuum drying; microwave-assisted synthesis, room-temperature reactions, and photochemical routes offer lower-energy alternatives [6]. Atom economy emphasizes synthetic routes that incorporate a high fraction of reactant atoms into the final product, minimizing byproduct formation; one-pot syntheses and cascade reactions exemplify this principle [6]. Benign precursor selection replaces hazardous metal salts or reducing agents (e.g., sodium borohydride, hydrazine) with naturally derived or less toxic alternatives (e.g., plant extracts, ascorbic acid, glucose) [14], [16], [9].

Dahl and colleagues' seminal 2007 review, "Toward Greener Nanosynthesis," systematically mapped the Twelve Principles onto nanomaterial production, providing early case studies of green routes for metal nanoparticles, quantum dots, and carbon nanotubes [6]. Subsequent reviews have expanded this mapping to include biogenic synthesis, mechanochemical methods, and flow chemistry [5], [15]. Critically, green chemistry principles are not merely aspirational guidelines but actionable design criteria that can be quantitatively assessed through metrics such as E-factor (mass of waste per mass of product), process mass intensity, and solvent greenness scores.

Table 1

Physicochemical determinants of hazard across nanomaterial classes. A summary table mapping nanomaterial classes (metal oxides, noble metals, carbon-based, quantum dots, polymeric) to key physicochemical properties (size, shape, surface charge, surface functionalization, crystallinity, composition) and associated hazard mechanisms (oxidative stress, membrane disruption, ion release, protein corona formation, bioaccumulation). Includes representative examples (e.g., TiO_2, ZnO, Ag, Au, CNTs) and citations to structure–property–hazard studies

Nanomaterial Class	Key Physicochemical Property	Example Materials	Hazard Mechanism	Biological Effects	Design Mitigation Strategy
Metal oxides	Dissolution rate	ZnO, CuO	Ion release	Cytotoxicity, oxidative stress	Surface coating
	Photocatalytic activity	TiO_2	ROS generation	DNA damage, inflammation	Doping / passivation
Noble metals	Particle size	Ag, Au	Cellular uptake	Organelle accumulation	Size control
	Surface charge	AgNPs	Membrane interaction	Hemolysis	Neutral coating
Carbon-based	Aspect ratio	CNTs	Fiber-like toxicity	Pulmonary inflammation	Shortening / embedding
	Surface defects	Graphene oxide	ROS generation	Oxidative stress	Functionalization
Quantum dots	Composition	CdSe, CdTe	Metal ion release	Genotoxicity	Core–shell design
	Surface ligands	QDs	Protein corona	Immune response	PEGylation

Polymeric nanoparticles	Degradability	PLGA, chitosan	Degradation products	Mild toxicity	Biodegradable design
	Hydrophobicity	Polymer NPs	Bioaccumulation	Chronic exposure	Surface modification

2.2 STRUCTURE–PROPERTY–HAZARD PARADIGMS: RATIONAL DESIGN AT THE NANOSCALE

The vision of rational nanomaterial design—engineering materials with predictable performance and minimal hazard—rests on the establishment of quantitative structure–property–function (SPF) and structure–property–hazard (SPH) relationships. Gilbertson and colleagues articulated this paradigm in a landmark 2015 review, arguing that systematic variation of nanomaterial properties (size, shape, surface chemistry, composition, crystallinity) combined with high-throughput biological and environmental screening can reveal the physicochemical determinants of both functionality and hazard [2]. By identifying which properties drive desired performance (e.g., catalytic activity, optical absorption, drug delivery efficiency) and which properties trigger adverse outcomes (e.g., cytotoxicity, oxidative stress, bioaccumulation), designers can navigate the property space to optimize the benefit-to-risk ratio [2].

Empirical evidence supports the feasibility of this approach. For metal oxide nanoparticles, hazard is strongly influenced by dissolution kinetics and ion release: ZnO nanoparticles exhibit high cytotoxicity due to rapid Zn^{2+} release, whereas TiO_2 nanoparticles are relatively inert in biological media [9], [10]. Surface functionalization can modulate hazard: capping agents such as polyethylene glycol (PEG), citrate, or polysaccharides reduce protein adsorption, alter cellular uptake pathways, and mitigate oxidative stress [10], [16]. Particle shape also matters: high-aspect-ratio carbon nanotubes and nanofibers pose fiber-like hazards analogous to asbestos, whereas spherical fullerenes do not [7]. Composition determines intrinsic toxicity: cadmium-based quantum dots release toxic Cd^{2+} ions, whereas indium phosphide or silicon quantum dots offer lower toxicity profiles [6].

Harper and colleagues demonstrated the practical implementation of SPH relationships through an iterative design loop: synthesize high-purity nanoparticle libraries with systematic property variations, screen them using rapid biological assays (embryonic zebrafish), analyze structure–activity relationships, and redesign materials to eliminate hazard while preserving function [1]. This approach, grounded in a Nanomaterial–Biological Interactions knowledgebase, exemplifies the integration of materials science, toxicology, and informatics required for SSbD [1].

2.3 EVOLUTION OF SAFE-BY-DESIGN FRAMEWORKS IN NANOTECHNOLOGY

The concept of safe-by-design (SbD) emerged in the mid-2000s as nanotoxicology research began to reveal potential hazards of ENMs. Early SbD frameworks focused narrowly on hazard reduction—designing materials with lower intrinsic toxicity—but have since evolved to encompass broader sustainability dimensions, giving rise to the safe-and-sustainable-by-design (SSbD) paradigm [4], [12]. This evolution reflects a growing recognition that environmental impacts (energy consumption, greenhouse gas emissions, resource depletion) and social considerations (occupational safety, public perception, equitable access) are inseparable from hazard management.

Brennan and Valsami-Jones' 2021 review, "Safe by Design for Nanomaterials—Late Lessons from Early Warnings for Sustainable Innovation," traces this conceptual evolution and articulates core SbD principles: early hazard evaluation, reduction of animal testing through in silico and in vitro methods, stakeholder engagement, transparency, and shared responsibility across the innovation chain [4]. The authors emphasize that SbD is not a one-time assessment but a continuous process of learning, adaptation, and redesign as materials advance from laboratory to market [4].

The European Union has been a policy leader in operationalizing SSbD, embedding it within the European Green Deal and the Chemicals Strategy for Sustainability [12]. Furxhi and colleagues' 2023 analysis of European SSbD paradigms highlights the alignment of SSbD with REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) and the push for harmonized assessment frameworks that integrate risk, LCA, and socio-economic appraisal [12]. Implementation projects such as DIAGONAIS have produced operational frameworks and decision-support tools for practitioners [17].

Salieri and colleagues proposed an integrative approach that combines risk assessment, life cycle assessment, and socio-economic analysis within a unified SSbD workflow [3]. This framework recognizes that trade-offs are inevitable—a material may score well on toxicity metrics but poorly on environmental metrics, or vice versa—and that transparent multi-criteria decision-making is essential to navigate these trade-offs [3]. The integration of LCA early in the design process is particularly critical to avoid burden-shifting, where hazard reduction in one lifecycle stage (e.g., synthesis) inadvertently increases impacts in another stage (e.g., use or disposal) [13].

3 GREEN SYNTHESIS PATHWAYS: ELIMINATING HAZARD AT THE SOURCE

3.1 BIOGENIC SYNTHESIS: HARNESSING BIOLOGICAL REDUCING AND CAPPING AGENTS

Biogenic synthesis—the use of biological organisms or their extracts as reducing, capping, or stabilizing agents—represents one of the most promising green chemistry strategies for nanomaterial production. Plant extracts, fungal metabolites, bacterial cultures, and algal biomass contain a rich array of phytochemicals (polyphenols, flavonoids, terpenoids, alkaloids, proteins, polysaccharides) that can reduce metal ions to nanoparticles and simultaneously provide biocompatible surface coatings [14]. This approach eliminates the need for toxic reducing agents such as sodium borohydride or hydrazine and hazardous solvents, while often enabling room-temperature, aqueous-phase synthesis [14], [16].

Habeeb Hiba and Thoppil's 2022 review, "Medicinal Herbs as a Panacea for Biogenic Silver Nanoparticles," documents the widespread use of plant extracts (e.g., Azadirachta indica, Ocimum sanctum, Aloe vera) for silver nanoparticle synthesis, highlighting the dual benefits of reduced chemical hazard and enhanced biocompatibility [14]. The phytochemicals in these extracts not only reduce Ag^{+} to Ag^{0} but also impart antioxidant, antimicrobial, and anti-inflammatory properties to the resulting nanoparticles, potentially enhancing their therapeutic efficacy [14].

Roy and colleagues' 2013 study, "Green Synthesis of Silver Nanoparticles: An Approach to Overcome Toxicity," demonstrated that silver nanoparticles synthesized using plant extracts exhibited lower in vitro cytotoxicity compared to those synthesized via conventional chemical routes, attributing this difference to the presence of biocompatible capping agents and reduced residual toxic reagents [16]. Similarly, Verma and colleagues' 2021 review on ZnO nanomaterials emphasized that green synthesis routes using plant extracts or microbiais systems can yield ZnO nanoparticles with controlled morphology and reduced toxicity, suitable for biomedical applications [9].

Biogenic synthesis is not without challenges. The composition of biological extracts is inherently variable, depending on plant species, growth conditions, harvest time, and extraction methods, which can lead to batch-to-batch variability in nanoparticle properties [14]. Mechanistic understanding of the reduction and capping processes remains incomplete, complicating efforts to optimize synthesis conditions for specific property targets [14]. Scalability is another concern: while laboratory-scale biogenic synthesis is well-established, industrial-scale production requires reliable sourcing of biological feedstocks, standardized extraction protocols, and process controls to ensure reproducibility [14].

Table 2

Comparison of conventional and green synthesis approaches for nanomaterials. A comparative table contrasting conventional synthesis (e.g., chemical reduction with $NaBH_4$, hydrazine; high-temperature calcination; organic solvents) and green synthesis (e.g., plant extract reduction; room-temperature aqueous synthesis; biogenic capping agents) for Ag, Au, ZnO, and TiO_2 nanoparticles. Columns include reducing agents, solvents, reaction temperature, energy input, hazardous reagents, waste generation, and representative citations

Nanomaterial	Synthesis Type	Reducing Agent	Solvent	Temperature	Hazardous Chemicals	Energy Demand	Environmental Impact
Silver (Ag)	Conventional	$NaBH_4$	Organic solvents	High	Borohydride, surfactants	High	Toxic residues
	Green	Plant extract	Water	Room temp	None	Low	Biocompatible
Gold (Au)	Conventional	Citrate / hydrazine	Water / organic	Heating	Hydrazine	Moderate	Chemical waste
	Green	Ascorbic acid / plant extract	Water	Ambient	None	Low	Minimal waste
ZnO	Conventional	Metal salts + base	Organic / aqueous	Calcination	Strong bases	High	High energy
	Green	Plant extract / microbes	Water	Low	None	Low	Reduced toxicity
TiO_2	Conventional	Sol-gel alkoxides	Alcohols	High	Alkoxides	High	Solvent waste
	Green	Biogenic precipitation	Water	Low	None	Low	Safer synthesis

3.2 SOLVENT SUBSTITUTION AND ENERGY MINIMIZATION STRATEGIES

Solvent selection is a critical determinant of the environmental and occupational health profile of nanomaterial synthesis. Conventional routes often rely on volatile organic solvents (toluene, chloroform, dimethylformamide) that pose inhalation hazards, require energy-intensive distillation for recovery, and generate hazardous waste streams [6]. Green chemistry advocates for solvent substitution hierarchies: water as the ideal solvent, followed by bio-based solvents (ethanol, glycerol, ionic liquids derived from renewable feedstocks), and supercritical fluids (CO_2) for specialized applications [6].

Bartolozzi and colleagues' 2020 LCA of cellulose nanosponges provides a quantitative case study of solvent substitution impacts [4]. The initial laboratory-scale synthesis employed methanol for washing and purification steps, contributing significantly to environmental

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burdens. By switching to water and reducing washing temperature, the authors achieved substantial reductions in global warming potential, cumulative energy demand, and toxicity potentials [4]. This example underscores that seemingly minor process modifications—solvent choice, temperature, washing cycles—can have outsized impacts on lifecycle sustainability [4].

Energy minimization targets the most energy-intensive unit operations in nanomaterial synthesis: high-temperature calcination, extended reflux, vacuum drying, and centrifugation. Microwave-assisted synthesis offers rapid, volumetric heating with reduced energy input compared to conventional heating [6]. Photochemical synthesis harnesses solar or LED irradiation to drive reduction or oxidation reactions at ambient temperature [6]. Mechanochemical synthesis (ball milling, extrusion) eliminates solvents entirely and operates at room temperature, though it may introduce contamination from milling media [6]. Flow chemistry enables continuous production with precise control of reaction conditions, reducing batch-to-batch variability and energy waste [6].

Dahl and colleagues' 2007 review provides early examples of energy-efficient nanosynthesis: room-temperature synthesis of gold nanoparticles using citrate reduction, photochemical synthesis of silver nanoparticles, and microwave-assisted synthesis of metal oxide nanoparticles [6]. Subsequent advances in green synthesis have expanded the toolkit, but energy minimization remains a frontier challenge, particularly for materials requiring high-temperature processing (e.g., crystalline metal oxides, carbon nanotubes) [6].

3.3 ATOM ECONOMY, WASTE REDUCTION, AND BENIGN PRECURSOR SELECTION

Atom economy—the fraction of reactant atoms incorporated into the desired product—is a fundamental green chemistry metric that directly impacts waste generation and resource efficiency. High atom economy is achieved through synthetic routes that minimize byproducts, avoid protecting groups, and employ cascade reactions where intermediates are consumed in situ [6]. In nanomaterial synthesis, atom economy is often compromised by the need for excess stabilizing agents, multiple washing steps to remove unreacted precursors, and purification to eliminate byproducts [6].

One-pot syntheses exemplify high atom economy: all reactants are combined in a single vessel, and the product is isolated without intermediate purification steps [6]. For example, simultaneous reduction and capping of metal nanoparticles using a single reagent (e.g., trisodium citrate for gold nanoparticles) achieves high atom economy and simplifies downstream processing [6]. Cascade reactions, where the product of one reaction serves as the reactant for the next, further enhance atom economy by eliminating isolation and purification steps [6].

Benign precursor selection complements atom economy by replacing hazardous starting materials with safer alternatives. For metal nanoparticles, this means choosing metal salts with lower toxicity (e.g., metal acetates or citrates instead of chlorides or nitrates) and avoiding toxic reducing agents (e.g., replacing sodium borohydride with ascorbic acid or glucose) [6], [16]. For metal oxide nanoparticles, sol-gel routes using metal alkoxides can be replaced with aqueous precipitation from metal salts, eliminating flammable and moisture-sensitive precursors [6].

Waste reduction extends beyond atom economy to encompass solvent recovery, recycling of unreacted precursors, and valorization of byproducts. Varma's 2012 review, "Greener Approach to Nanomaterials and Their Sustainable Applications," highlights examples of recyclable magnetic supports for catalytic nanoparticles, enabling easy separation and reuse, and the use of agricultural waste (e.g., rice husk, sugarcane bagasse) as templates or reducing agents, converting waste streams into value-added nanomaterials [11].

3.4 CASE EVIDENCE: SILVER, GOLD, AND ZINC OXIDE NANOPARTICLES

Silver, gold, and zinc oxide nanoparticles have been the focus of extensive green synthesis research, providing concrete evidence of the feasibility and benefits of green chemistry principles. Silver nanoparticles (AgNPs) are widely used for their antimicrobial properties in textiles, wound dressings, and water treatment, but conventional synthesis routes employ toxic reducing agents and generate hazardous waste [16]. Green synthesis using plant extracts (e.g., Azadirachta indica, Ocimum sanctum) or microbial cultures (e.g., Bacillus species, Aspergillus species) eliminates these hazards while producing AgNPs with controlled size and shape [14], [16]. Roy and colleagues demonstrated that green-synthesized AgNPs exhibited lower cytotoxicity in human cell lines compared to chemically synthesized AgNPs, attributed to biocompatible capping agents and absence of residual toxic reagents [16].

Gold nanoparticles (AuNPs) are employed in diagnostics, drug delivery, and photothermal therapy, with synthesis routes ranging from citrate reduction (Turkevich method) to seed-mediated growth [10]. Niżnik and colleagues' 2024 critical review, "Gold Nanoparticles (AuNPs)—Toxicity, Safety and Green Synthesis," synthesizes evidence on green synthesis routes using plant extracts, amino acids, and vitamins as reducing and capping agents [10]. The review highlights that green-synthesized AuNPs often exhibit enhanced biocompatibility and reduced immunogenicity, making them attractive for biomedical applications [10]. However, the authors caution that toxicity is highly dependent on size, shape, and surface functionalization, and that green synthesis alone does not guarantee safety—rigorous toxicity testing remains essential [10].

Zinc oxide nanoparticles (ZnO NPs) are used in sunscreens, antimicrobial coatings, and photocatalysis, but their toxicity—driven by Zn^{2+} ion release and reactive oxygen species generation—raises concerns for environmental and human health [9]. Verma and colleagues' 2021 review, "ZnO Nanomaterials: Green Synthesis, Toxicity Evaluation and New Insights in Biomedical Applications," documents green synthesis routes using plant extracts, fungi, and bacteria, which can yield ZnO NPs with controlled morphology (spheres, rods, flowers) and reduced toxicity [9]. The review emphasizes that green synthesis conditions (pH, temperature, extract concentration) strongly influence particle properties and that systematic optimization is required to achieve desired performance and safety profiles [9].

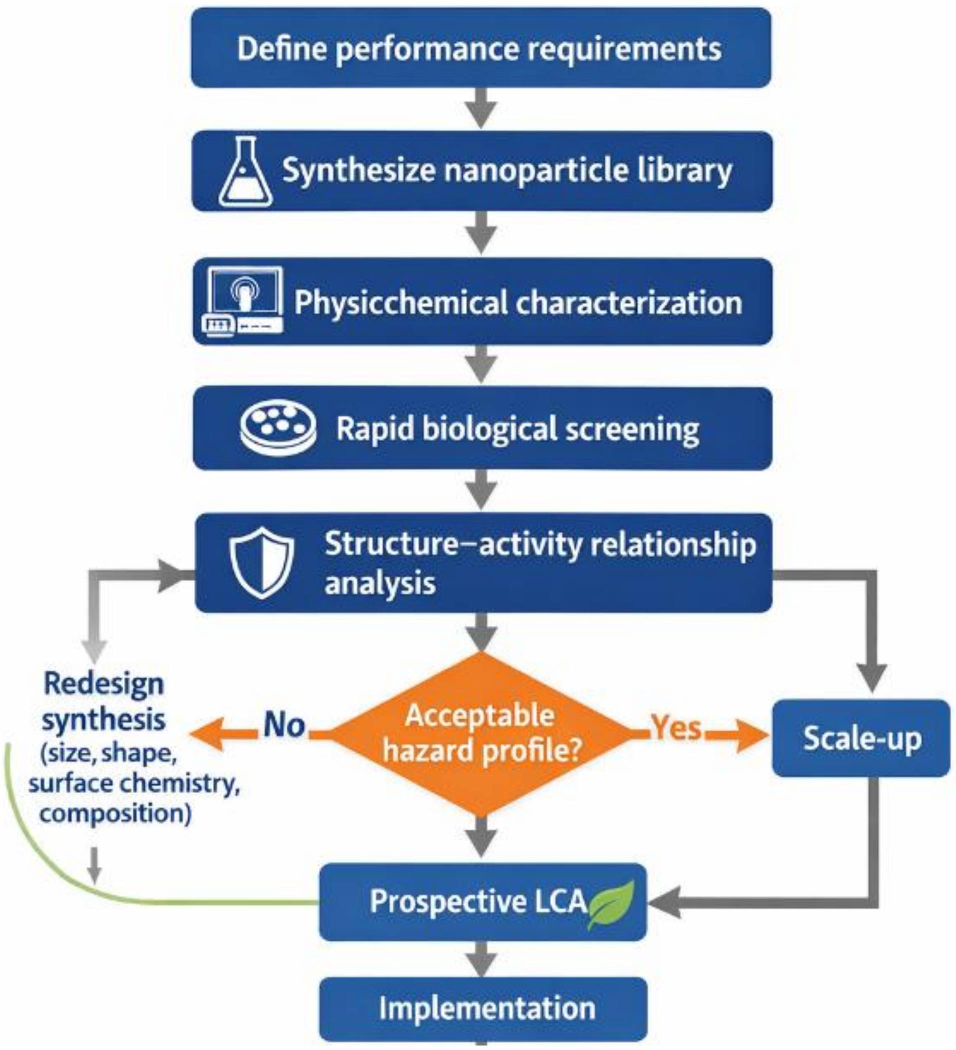
4 HAZARD ENGINEERING: ITERATIVE DESIGN LOOPS AND BIOLOGICAL SCREENING

4.1 HIGH-PURITY NANOPARTICLE LIBRARIES AND RAPID BIOLOGICAL ASSAYS

The iterative design loop—synthesize, screen, analyze, redesign—is the operational core of hazard engineering. Harper and colleagues' 2008 study, "Proactively Designing Nanomaterials to Enhance Performance and Minimise Hazard," provides a foundational blueprint for this approach [1]. The authors advocate for the synthesis of high-purity nanoparticle libraries with systematic variations in size, shape, surface chemistry, and composition, followed by rapid biological screening using embryonic zebrafish as a model organism [1]. Zebrafish embryos offer several advantages: rapid development (72 hours), optical transparency enabling real-time imaging, high genetic homology to humans, and amenability to high-throughput assays [1].

Figure 2

Closed-loop safe-by-design process for nanomaterial development. A flowchart illustrating the iterative design loop. Starting with "Define Performance Requirements," the process flows through "Synthesize Nanoparticle Library" (with systematic property variations), "Physicochemical Characterization," "Rapid Biological Screening" (in vitro and in vivo assays), "Structure–Activity Relationship Analysis," "Hazard Assessment," and a decision node: "Acceptable Hazard Profile?" If no loop back to "Redesign Synthesis" (modify size, shape, surface chemistry, composition); if yes, proceed to "Scale-Up and Prospective LCA." Feedback arrows emphasize continuous learning and adaptation



The Harper framework integrates biological screening data into a Nanomaterial–Biological Interactions knowledgebase, enabling structure–activity relationship (SAR) analysis to identify physicochemical properties that drive toxicity [1]. For example, if a library of gold nanoparticles reveals that particles smaller than 5 nm exhibit elevated cytotoxicity, designers can target larger sizes in subsequent iterations [1]. If surface charge correlates with hemolysis, capping agents can be selected to modulate zeta potential [1]. This iterative process continues until a material is identified that meets performance criteria while exhibiting minimal hazard across multiple biological endpoints (mortality, developmental abnormalities, oxidative stress, inflammation) [1].

Critically, Harper and colleagues emphasize that high-purity synthesis is essential for meaningful SAR analysis: impurities, residual reagents, or batch-to-batch variability can confound biological responses and obscure true structure–activity relationships [1]. This requirement underscores the importance of rigorous synthesis protocols, thorough purification, and comprehensive physicochemical characterization (size distribution, surface chemistry, crystallinity, purity) before biological screening [1].

Table 3

Prospective life cycle assessment of nanomaterials: hotspots, scale-up effects, and trade-offs

Nanomaterial	Lifecycle Hotspot	Application	Main Impact Category	Scale-Up Effect	Trade-Off Identified	Key Insight
TiO_2	Calcination	Photocatalysis	Energy demand	Reduced at scale	Increased toxicity with coating	Performance vs safety
$Cu_2O–TiO_2$	Precursor production	Photocatalysis	Human toxicity	Moderate reduction	Copper ecotoxicity	Coating risk
Ag nanoparticles	Reduction step	Antimicrobial	Chemical toxicity	Lower at scale	Residual reagents	Need green synthesis
ZnO nanoparticles	Purification	Biomedical	Energy use	Improved efficiency	Ion release toxicity	Surface stabilization
Cellulose nanosponges	Solvent washing	Water treatment	GWP	Major reduction	Solvent substitution	Water-based synthesis
CNT composites	Processing	Structural materials	Occupational exposure	Limited change	Fiber release	Exposure control needed

4.2 STRUCTURE–PROPERTY–FUNCTION–HAZARD RELATIONSHIPS IN PRACTICE

Gilbertson and colleagues' 2015 review, "Designing Nanomaterials to Maximize Performance and Minimize Undesirable Implications Guided by the Principles of Green Chemistry," operationalizes the structure–property–function–hazard (SPFH) paradigm through case studies and design heuristics [2]. The authors argue that rational design requires simultaneous optimization of performance (function) and minimization of hazard, guided by quantitative SPFH relationships [2].

For catalytic nanoparticles, performance is often dictated by surface area, active site density, and electronic structure, while hazard is influenced by dissolution kinetics, reactive oxygen species generation, and bioaccumulation potential [2]. Gilbertson and colleagues demonstrate that by tuning particle size, support material, and surface functionalization, it is possible to enhance catalytic activity while reducing toxicity [2]. For example, immobilizing metal nanoparticles on porous supports (e.g., silica, alumina, carbon) reduces particle mobility and bioavailability, mitigating environmental hazards without sacrificing catalytic performance [2].

For drug delivery nanoparticles, function requires controlled size (typically 10–200 nm for passive tumor targeting), surface functionalization for targeting ligands, and stimuli-responsive release mechanisms, while hazard considerations include cytotoxicity, immunogenicity, and long-term biodistribution [2]. Gilbertson and colleagues highlight that PEGylation (coating with polyethylene glycol) reduces protein adsorption and immune recognition, extending circulation time and reducing off-target toxicity [2]. However, PEGylation may also reduce cellular uptake, necessitating trade-offs between circulation time and delivery efficiency [2].

The SPFH paradigm is not a deterministic algorithm but a heuristic framework that guides experimental design and interpretation. It requires iterative experimentation, mechanistic understanding of both performance and hazard pathways, and willingness to accept that some property combinations may be incompatible—high performance and low hazard may not always be achievable simultaneously, necessitating either redesign or abandonment of certain material concepts [2].

4.3 ECO-DESIGN LEVERS: IN-MATRIX GENERATION AND BIODEGRADABLE CAPPING

Eco-design strategies extend beyond synthesis chemistry to encompass material form, application mode, and end-of-life fate. Varma's 2012 review identifies several eco-design levers that reduce exposure and environmental release while preserving functionality [11]. In-matrix generation involves synthesizing nanoparticles directly within a polymer, ceramic, or textile matrix, eliminating free nanoparticle handling and reducing occupational exposure and environmental release [11]. For example, silver nanoparticles can be generated in situ within cotton fibers for antimicrobial textiles, avoiding the need to handle and disperse free AgNPs [11].

Biodegradable capping agents ensure that nanoparticles degrade into benign products at end-of-life or upon environmental release. Natural polysaccharides (chitosan, alginate, cellulose), proteins (albumin, gelatin), and vitamins (ascorbic acid, tocopherol) serve as both stabilizing agents during synthesis and biodegradable coatings that facilitate environmental degradation [11]. Corsi and colleagues' 2018 study, "Environmentally Sustainable and Ecosafe Polysaccharide-Based Materials for Water Nano-Treatment: An Eco-Design Study," demonstrates the use of cellulose-based nanosponges for water treatment, designed for biodegradability and minimal ecotoxicity [13].

Recyclable supports enable recovery and reuse of catalytic nanoparticles, reducing material consumption and waste generation. Magnetic nanoparticles (e.g., Fe_3O_4) can be functionalized with catalytic metals (Pd, Pt, Au) and easily separated from reaction mixtures using external magnets, enabling multiple reuse cycles without significant loss of activity [11]. This approach exemplifies the green chemistry principle of catalysis while addressing end-of-life concerns [11].

4.4 INTEGRATED ASSESSMENT FRAMEWORKS: RISK, LCA, AND SOCIO-ECONOMIC DIMENSIONS

Salieri and colleagues' 2021 study, "Integrative Approach in a Safe by Design Context Combining Risk, Life Cycle and Socio-Economic Assessment for Safer and Sustainable Nanomaterials," proposes a unified framework that integrates risk assessment, life cycle assessment, and socio-economic analysis within the SSbD workflow [3]. This framework recognizes that no single metric can capture the full sustainability profile of a nanomaterial and that trade-offs among risk, environmental impact, cost, and social acceptance are inevitable [3].

The integrated framework operates through several stages. First, hazard identification employs in vitro and in vivo assays to characterize intrinsic toxicity across multiple endpoints (cytotoxicity, genotoxicity, oxidative stress, inflammation) [3]. Second, exposure assessment estimates occupational, consumer, and environmental exposures across the lifecycle, drawing on workplace measurements, release modeling, and fate and transport simulations [3]. Third, risk characterization combines hazard and exposure data to estimate risk quotients or margins of safety for different exposure scenarios [3]. Fourth, prospective LCA quantifies environmental impacts (global warming potential, cumulative energy demand, resource depletion, ecotoxicity, human toxicity) from cradle to grave [3]. Fifth, socio-economic appraisal evaluates cost, market acceptance, regulatory compliance, and social equity considerations [3].

Critically, the framework emphasizes multi-criteria decision analysis to navigate trade-offs. A material may score well on toxicity metrics but poorly on environmental metrics (e.g., high energy consumption), or vice versa [3]. Transparent weighting of criteria, stakeholder input, and sensitivity analysis are essential to ensure that design decisions reflect societal values and priorities [3]. The framework also highlights the importance of iterative reassessment: as materials advance from laboratory to pilot scale to commercial production, new data become available, and assessments must be updated to reflect evolving knowledge [3].

5 LIFE-CYCLE GOVERNANCE: PROSPECTIVE LCA AND TRADE-OFF DETECTION

5.1 PROSPECTIVE LCA METHODOLOGY FOR EARLY-STAGE NANOMATERIALS

Prospective life cycle assessment (LCA) extends traditional LCA—which evaluates mature, commercialized products—to early-stage technologies with low technology readiness levels (TRLs). Prospective LCA aims to identify environmental hotspots, detect trade-offs, and guide design decisions before materials are locked into production pathways [8], [4], [13]. This forward-looking approach is essential for SSbD, as it enables designers to anticipate and mitigate environmental burdens during the conceptual and laboratory stages, when design flexibility is greatest [13].

Guinée and colleagues' 2022 study, "The Meaning of Life… Cycles: Lessons from and for Safe by Design Studies," articulates the methodological challenges and opportunities of prospective LCA for nanomaterials [13]. The authors emphasize that early-stage LCA is inherently uncertain: laboratory-scale processes differ markedly from industrial-scale production, material and energy flows are incompletely characterized, and end-of-life scenarios are speculative [13]. Despite these uncertainties, prospective LCA provides valuable insights by revealing which lifecycle stages and unit operations dominate environmental impacts, enabling targeted redesign efforts [13].

Prospective LCA for nanomaterials typically employs scenario modeling: multiple production scenarios (e.g., batch vs. continuous, different solvents, different energy sources) are evaluated to bound the range of potential impacts and identify robust design choices that perform well across scenarios [13]. Sensitivity analysis quantifies how uncertainties in input parameters (e.g., energy consumption, yield, waste generation) propagate to impact estimates, highlighting which parameters require more precise measurement [13]. Hotspot identification pinpoints the lifecycle stages or unit operations with the largest contributions to specific impact categories (e.g., global warming potential, cumulative energy demand, toxicity potentials), guiding redesign efforts [13].

Bartolozzi and colleagues' 2020 study, "Life Cycle Assessment of Emerging Environmental Technologies in the Early Stage of Development: A Case Study on

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Nanostructured Materials," provides a methodological template for prospective LCA of nanomaterials [4]. The authors conducted LCA on cellulose nanosponges for water treatment at laboratory scale, then modeled scale-up scenarios with process optimizations (solvent substitution, temperature reduction, internal recycling) to estimate industrial-scale impacts [4]. This approach demonstrates how prospective LCA can inform design decisions even when commercial production is years away [4].

Table 3

Prospective life cycle assessment of nanomaterials: hotspots, scale-up effects, and trade-offs. A summary table of LCA case studies for nanomaterials, including material type (TiO_2, Cu_2O, cellulose nanosponges, Ag, ZnO), functional application (photocatalysis, water treatment, antimicrobial), lifecycle stage with highest impact (synthesis, purification, use, disposal), key environmental metrics (GWP, CED, toxicity potentials), scale-up effects (impact reductions or increases), and trade-offs identified (e.g., reduced GWP but increased toxicity). Includes citations to Tsalidis et al. 2022, Bartolozzi et al. 2020, Corsi et al. 2018, and others

Nanomaterial	Application	Lifecycle Hotspot	Main Impact Category	Scale-Up Effect	Trade-Off Identified	Key Insight
TiO_2	Photocatalysis	Calcination	Energy demand	Reduced at scale	Increased toxicity with coating	Performance vs safety
$Cu_2O–TiO_2$	Photocatalysis	Precursor production	Human toxicity	Moderate reduction	Copper ecotoxicity	Coating risk
Ag nanoparticles	Antimicrobial	Reduction step	Chemical toxicity	Lower at scale	Residual reagents	Need green synthesis
ZnO nanoparticles	Biomedical	Purification	Energy use	Improved efficiency	Ion release toxicity	Surface stabilization
Cellulose nanosponges	Water treatment	Solvent washing	GWP	Major reduction	Solvent substitution	Water-based synthesis
CNT composites	Structural materials	Processing	Occupational exposure	Limited change	Fiber release	Exposure control needed

5.2 HOTSPOT IDENTIFICATION: ENERGY, SOLVENTS, AND PURIFICATION STEPS

Prospective LCA studies consistently identify a small number of lifecycle stages and unit operations as dominant contributors to environmental impacts. For laboratory-scale nanomaterial synthesis, energy-intensive steps—high-temperature calcination, extended reflux, vacuum drying, centrifugation—often account for the largest share of global warming potential and cumulative energy demand [4], [8]. Solvent use—particularly volatile organic solvents requiring distillation for recovery—contributes significantly to toxicity potentials and resource depletion [4]. Purification and washing steps—multiple cycles of centrifugation, washing, and drying to remove unreacted precursors and byproducts—generate large volumes of waste and consume substantial energy [4].

Bartolozzi and colleagues' LCA of cellulose nanosponges revealed that methanol washing and high-temperature drying were the primary hotspots at laboratory scale [4]. By substituting water for methanol and reducing drying temperature, the authors achieved substantial reductions in global warming potential, cumulative energy demand, and toxicity potentials [4]. This example underscores that seemingly minor process modifications can have outsized impacts on lifecycle sustainability [4].

Tsalidis and colleagues' 2022 LCA of TiO_2 and Cu_2O-coated TiO_2 photocatalysts identified precursor production and calcination as the dominant contributors to global warming potential and cumulative energy demand [8]. The authors found that the Cu_2O coating process introduced additional energy and material inputs, but the overall environmental impact depended on the functional unit (e.g., per unit mass of catalyst vs. per unit of pollutant degraded) [8]. This highlights the importance of defining appropriate functional units in LCA: a material with higher production impacts may deliver superior performance, resulting in lower impacts per unit of service [8].

Hotspot identification is not merely an academic exercise but an actionable design tool. By pinpointing the lifecycle stages with the largest environmental burdens, designers can prioritize redesign efforts—targeting energy-intensive steps for process intensification, substituting hazardous solvents, optimizing purification protocols, or exploring alternative synthesis routes that bypass problematic steps [4], [8], [13].

5.3 SCALE-UP EFFECTS: FROM LABORATORY TO INDUSTRIAL PRODUCTION

One of the most striking findings from prospective LCA studies is the dramatic impact of scale-up on environmental burdens. Laboratory-scale synthesis is inherently inefficient: small batch sizes, manual operations, lack of heat integration, and high relative contributions from equipment cleaning and setup [4]. Industrial-scale production benefits from economies of scale, process optimization, energy recovery, and continuous operation, often reducing environmental impacts by one to two orders of magnitude per unit of product [4].

Bartolozzi and colleagues' LCA of cellulose nanosponges quantified this scale-up effect: simulated industrial-scale production with internal recycling, optimized energy use, and continuous operation reduced global warming potential, cumulative energy demand, and toxicity potentials by approximately two orders of magnitude compared to laboratory-scale synthesis [4]. This finding has profound implications for SSbD: early-stage LCA based solely on laboratory data may overestimate environmental impacts, potentially leading to premature rejection of promising materials [4]. Conversely, optimistic scale-up assumptions may underestimate impacts if industrial-scale production introduces new challenges (e.g., increased waste generation, need for additional purification steps) [4].

Prospective LCA must therefore employ scenario modeling to bound the range of potential scale-up effects. Conservative scenarios assume minimal process optimization and modest efficiency gains, while optimistic scenarios assume best-available-technology and full heat integration [4], [13]. Sensitivity analysis reveals which scale-up assumptions most strongly influence impact estimates, guiding priorities for pilot-scale experimentation and process development [13].

5.4 TRADE-OFF DETECTION: ENVIRONMENTAL GAINS VS. TOXICITY BURDENS

A critical function of prospective LCA is the detection of trade-offs—situations where design modifications that improve one sustainability dimension (e.g., reduced global warming potential) simultaneously worsen another dimension (e.g., increased human toxicity potential). Such trade-offs are common in nanomaterial design and underscore the necessity of multi-indicator assessment [8], [13].

Tsalidis and colleagues' 2022 LCA of TiO_2 and Cu_2O-coated TiO_2 photocatalysts provides a quantitative case study of trade-off detection [8]. The Cu_2O-coated catalyst exhibited reduced global warming potential and cumulative energy demand compared to uncoated TiO_2, attributed to lower calcination temperature and shorter processing time [8]. However, the coated catalyst exhibited relatively higher human toxicity potential and freshwater ecotoxicity, driven by copper precursor production and potential copper release during use [8]. This trade-off—climate benefits vs. toxicity burdens—illustrates the complexity of SSbD decision-making [8].

Trade-off detection requires LCA to include multiple impact categories spanning environmental (global warming, acidification, eutrophication, resource depletion), human health (carcinogenic toxicity, non-carcinogenic toxicity, respiratory effects), and ecological (freshwater ecotoxicity, terrestrial ecotoxicity, marine ecotoxicity) dimensions [8], [13]. Single-indicator assessments (e.g., carbon footprint alone) are insufficient and may lead to burden-shifting, where impacts are merely displaced from one category to another [13].

Guinée and colleagues emphasize that trade-offs are not necessarily insurmountable obstacles but rather design challenges that require creative solutions [13]. For example, if a green synthesis route reduces energy consumption but increases toxicity potential due to residual capping agents, further purification or selection of alternative capping agents may resolve the trade-off [13]. If trade-offs persist, multi-criteria decision analysis—incorporating stakeholder values and regulatory constraints—is required to determine acceptable compromises [13].

6 TOXICITY ASSESSMENT AND EXPOSURE REALITIES

6.1 OCCUPATIONAL EXPOSURE MEASUREMENTS: QUANTIFYING WORKPLACE RISKS

While much of the SSbD literature focuses on intrinsic hazard and prospective assessment, empirical exposure measurements provide essential reality checks on the effectiveness of design interventions and the need for complementary exposure controls. Hansen and colleagues' 2015 study, "Transformation and Distribution Processes Governing the Fate and Behaviour of Nanomaterials in the Environment: An Overview," includes occupational exposure data that quantify workplace nanoparticle concentrations during nanomaterial processing [7].

The study reports measured airborne nanoparticle concentrations during processing of polycarbonate/carbon nanotube (CNT) composites, with geometric mean number concentrations ranging from 4.71×10^{3} to 1.75×10^{6} particles·cm^{-3} across different processing operations (extrusion, injection molding, grinding) [7]. Breathing-zone respirable fiber concentrations during grinding operations reached up to 0.13 fibers·cm^{-3}, raising concerns about fiber-like hazards analogous to asbestos [7]. These measurements underscore that even when nanomaterials are embedded in matrices (a common exposure-reduction strategy), mechanical processing can release nanoparticles and nanofibers into workplace air [7].

These exposure data have several implications for SSbD. First, they demonstrate that design interventions alone—even in-matrix generation—may not eliminate occupational exposure, necessitating complementary engineering controls (ventilation, enclosure) and personal protective equipment [7]. Second, they highlight the importance of lifecycle thinking: exposure risks are not confined to synthesis but extend to downstream processing, use, and end-of-life recycling or disposal [7]. Third, they provide quantitative benchmarks for exposure assessment in prospective risk analysis, enabling more realistic estimation of occupational risk quotients [7].

Hansen and colleagues also emphasize the need for exposure monitoring during nanomaterial recycling and disposal, as these lifecycle stages are often overlooked in SSbD assessments [7]. Incineration, landfilling, and mechanical recycling of nanomaterial-containing products can release nanoparticles to air, water, and soil, with uncertain environmental fate and transformation [7]. This underscores the importance of designing for end-of-life: materials that degrade into benign products or can be safely recovered and recycled reduce long-term environmental burdens [7].

Table 4

Toxicity assessment methods and material-specific hazard profiles for nanomaterials. A summary table of toxicity assessment methods (in vitro cytotoxicity, genotoxicity, oxidative stress assays; in vivo models including zebrafish, rodents; in silico QSAR and read-across), their strengths and limitations, and material-specific hazard profiles for major nanomaterial classes (TiO_2, ZnO, Ag, Au, CNTs, quantum dots). Includes representative endpoints (mortality, developmental abnormalities, inflammation, bioaccumulation), dose-response relationships where available, and citations to toxicity studies

Method Category	Technique	Endpoints Evaluated	Strengths	Limitations	Representative Nanomaterials	Typical Hazard Mechanisms
In vitro assays	MTT / cell viability	Cytotoxicity	Fast, high-throughput	Limited physiological relevance	Ag, ZnO, Au	Oxidative stress, membrane damage
	ROS generation	Oxidative stress	Mechanistic insight	Cell-type dependent	TiO_2, ZnO	Reactive oxygen species
	Comet assay	DNA damage	Genotoxicity detection	Sensitive to conditions	Quantum dots, Ag	DNA strand breaks
	LDH release	Membrane integrity	Rapid screening	Non-specific	CNTs, metal oxides	Membrane disruption
In vivo models	Zebrafish embryos	Developmental toxicity	High-throughput whole organism	Aquatic model limitations	Au, Ag, ZnO	Developmental abnormalities
	Rodent inhalation	Pulmonary toxicity	Physiological relevance	Ethical and cost constraints	CNTs, TiO_2	Inflammation, fibrosis
	Oral exposure models	Bioaccumulation	Systemic toxicity	Long duration	Quantum dots	Organ accumulation

In silico methods	QSAR models	Predictive toxicity	No animal use	Limited datasets	Metal oxides	Property-based toxicity prediction
	Read-across	Hazard estimation	Rapid screening	Requires analog materials	Nanoparticle libraries	Similar structure toxicity
	Machine learning	Multi-endpoint prediction	Handles large datasets	Data quality dependent	Mixed nanomaterials	Pattern-based hazard prediction
Exposure-linked assays	Dose–response modeling	Risk characterization	Quantitative	Data intensive	All classes	Threshold toxicity
	Bioaccumulation studies	Environmental fate	Long-term relevance	Complex interpretation	CNTs, Ag	Tissue accumulation

6.2 MATERIAL-SPECIFIC TOXICITY PROFILES: TIO_2, CU_2O, ZNO, AND GOLD

Toxicity is not a generic property of "nanomaterials" but is highly material-specific, depending on composition, size, shape, surface chemistry, and crystallinity. Comprehensive toxicity profiles for major nanomaterial classes provide essential context for SSbD decision-making.

Titanium dioxide (TiO_2) nanoparticles are widely used in sunscreens, paints, and photocatalysis and are generally considered low-toxicity materials [8]. TiO_2 exhibits minimal dissolution in biological media, and its primary hazard mechanism is photocatalytic generation of reactive oxygen species (ROS) under UV irradiation [8]. Tsalidis and colleagues' LCA of TiO_2 photocatalysts found low human toxicity potential for uncoated TiO_2, consistent with its low intrinsic toxicity [8]. However, surface modifications (e.g., Cu_2O coating) can alter toxicity profiles, as discussed below [8].

Copper oxide (Cu_2O) nanoparticles exhibit higher toxicity than TiO_2, driven by dissolution and release of Cu^{2+} ions, which induce oxidative stress and mitochondrial dysfunction [8]. Tsalidis and colleagues' LCA revealed that Cu_2O-coated TiO_2 photocatalysts exhibited relatively higher human toxicity potential and freshwater ecotoxicity compared to uncoated TiO_2, attributed to copper precursor production and potential copper release [8]. This example illustrates how functional modifications (coating to enhance photocatalytic activity) can introduce new toxicity concerns, necessitating careful trade-off analysis [8].

Zinc oxide (ZnO) nanoparticles are used in sunscreens, antimicrobial coatings, and electronics but exhibit significant toxicity due to rapid Zn^{2+} ion release in biological and environmental media [9]. Verma and colleagues' 2021 review documents extensive in vitro and in vivo toxicity data for ZnO nanoparticles, including cytotoxicity, genotoxicity, oxidative stress, and developmental toxicity in zebrafish and rodents [9]. The review emphasizes that toxicity is strongly size-dependent (smaller particles release ions more rapidly) and can be mitigated by surface coatings that reduce dissolution [9]. Green synthesis routes using plant extracts can yield ZnO nanoparticles with biocompatible surface coatings, reducing toxicity while preserving antimicrobial function [9].

Gold (Au) nanoparticles are employed in diagnostics, drug delivery, and photothermal therapy and are generally considered biocompatible, particularly when coated with PEG or other biocompatible ligands [10]. Niżnik and colleagues' 2024 review synthesizes toxicity data for AuNPs, highlighting that toxicity is highly dependent on size, shape, and surface functionalization [10]. Small AuNPs (<5 nm) can cross cellular membranes and accumulate in organelles, potentially inducing oxidative stress and genotoxicity [10]. Rod-shaped AuNPs exhibit different cellular uptake and biodistribution compared to spherical AuNPs [10]. Surface charge influences protein corona formation and immune recognition [10]. The review concludes that while AuNPs are generally safer than many other nanomaterials, rigorous toxicity testing tailored to specific size, shape, and surface chemistry is essential [10].

6.3 ECOTOXICITY AND ENVIRONMENTAL FATE: DATA GAPS AND EMERGING INSIGHTS

Ecotoxicity—the adverse effects of nanomaterials on non-human organisms and ecosystems—remains one of the most significant data gaps in SSbD assessment. Thakur and Kumar's 2023 review, "Ecotoxicity Analysis and Risk Assessment of Nanomaterials for the Environmental Remediation," highlights the paucity of quantitative ecotoxicity data for most nanomaterials and the challenges of extrapolating laboratory toxicity tests to real-world environmental scenarios [11].

Ecotoxicity testing for nanomaterials faces several methodological challenges. Standard test organisms (algae, daphnia, fish) and protocols (OECD guidelines) were developed for soluble chemicals and may not adequately capture nanomaterial-specific behaviors such as aggregation, sedimentation, and transformation [11]. Nanomaterials undergo environmental transformations—dissolution, sulfidation, oxidation, protein corona formation—that alter their toxicity, yet most laboratory tests employ pristine, as-synthesized materials [11], [7]. Chronic, low-dose exposures and multigenerational effects are rarely assessed, despite their relevance for long-term environmental impacts [11].

Hansen and colleagues' 2015 review emphasizes the importance of understanding nanomaterial fate and transformation in environmental media [7]. Silver nanoparticles, for example, rapidly sulfidize in wastewater and sediments, forming Ag_2S, which exhibits much lower toxicity than metallic Ag [7]. Zinc oxide nanoparticles dissolve in acidic soils, releasing Zn^{2+} ions that may be taken up by plants or leach to groundwater [7]. Carbon nanotubes aggregate and sediment in aquatic systems, reducing bioavailability but potentially accumulating in sediments [7]. These transformation processes are critical determinants of long-term environmental risk but are rarely incorporated into prospective LCA or risk assessment [7].

Thakur and Kumar call for integrated, interdisciplinary risk assessment frameworks that combine ecotoxicity testing, environmental fate modeling, and ecosystem-level monitoring to provide realistic estimates of environmental risk [11]. They emphasize that SSbD must consider not only intrinsic hazard but also environmental persistence, bioaccumulation potential, and ecosystem-level effects [11].

6.4 INTEGRATED RISK METHODOLOGIES: BRIDGING EXPOSURE AND HAZARD

Risk assessment integrates hazard characterization (dose-response relationships) and exposure assessment (environmental concentrations, human intake) to estimate the probability and magnitude of adverse effects. For nanomaterials, integrated risk methodologies must account for unique nanoscale behaviors—aggregation, dissolution, transformation, protein corona formation—that influence both exposure and hazard [11], [7].

Thakur and Kumar's 2023 review outlines a tiered risk assessment framework for nanomaterials [11]. Tier 1 employs conservative screening-level assessments using worst-case exposure scenarios and hazard data from standard toxicity tests, yielding risk quotients (exposure concentration / predicted no-effect concentration) [11]. If risk quotients exceed acceptable thresholds, Tier 2 refines exposure estimates using measured environmental concentrations or validated fate models and incorporates nanomaterial-specific hazard data (e.g., accounting for transformation products) [11]. Tier 3 employs probabilistic risk assessment, Monte Carlo simulation, and species sensitivity distributions to quantify uncertainty and variability [11].

Hansen and colleagues emphasize that exposure assessment for nanomaterials must consider the full lifecycle: occupational exposure during synthesis and processing, consumer exposure during product use, and environmental exposure from product disposal or accidental release [7]. Each exposure pathway requires different assessment methods: workplace air monitoring for occupational exposure, dermal absorption and inhalation modeling for consumer exposure, and environmental fate modeling for ecological exposure [7].

Integrated risk methodologies also require consideration of cumulative and aggregate exposures. Individuals may be exposed to the same nanomaterial through multiple pathways (e.g., occupational inhalation, consumer dermal contact, dietary intake) or to multiple nanomaterials with similar toxicity mechanisms [11]. Aggregate risk assessment sums exposures across pathways; cumulative risk assessment sums risks across materials with common modes of action [11]. These approaches are essential for realistic risk characterization but are rarely applied to nanomaterials due to data limitations [11].

7 REGULATORY LANDSCAPE AND POLICY MOMENTUM

7.1 EUROPEAN UNION SSBD PARADIGMS AND THE GREEN DEAL

The European Union has emerged as a global leader in operationalizing safe-and-sustainable-by-design principles, embedding SSbD within the European Green Deal, the Chemicals Strategy for Sustainability, and the Circular Economy Action Plan [12]. Furxhi and colleagues' 2023 analysis, "Status, Implications and Challenges of European Safe and Sustainable by Design Paradigms Applicable to Nanomaterials and Advanced Materials," provides a comprehensive overview of EU SSbD policy evolution and implementation challenges [12].

The EU SSbD framework is built on several pillars. First, early integration of safety and sustainability: SSbD assessments must begin at the earliest stages of research and development, before materials are locked into production pathways [12]. Second, multi-criteria assessment: SSbD requires evaluation across risk, environmental, economic, and social dimensions, with transparent trade-off analysis [12]. Third, stakeholder engagement: SSbD processes must involve researchers, industry, regulators, civil society, and affected communities to ensure that diverse values and concerns are addressed [12]. Fourth, transparency and data sharing: SSbD assessments and underlying data should be publicly accessible to enable independent verification and continuous improvement [12].

Furxhi and colleagues highlight that EU SSbD policy is closely aligned with REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals), which requires safety assessments for chemicals produced or imported above certain tonnage thresholds [12]. Nanomaterials are explicitly covered under REACH, with specific information requirements for nanoforms [12]. The EU is also developing SSbD guidance documents and decision-support tools to assist industry in implementing SSbD principles [12].

The European Green Deal provides overarching policy momentum for SSbD, setting ambitious targets for climate neutrality, circular economy, and zero pollution [12]. Nanomaterials are positioned as enabling technologies for Green Deal objectives—energy-efficient catalysts, lightweight materials for transportation, advanced batteries, water treatment—but only if they are developed according to SSbD principles [12]. This creates both opportunities and pressures for nanomaterial innovation: materials that demonstrably meet SSbD criteria may gain market access and public acceptance, while those that do not may face regulatory barriers or reputational risks [12].

Figure 3

Timeline of European Union safe-and-sustainable-by-design (SSbD) policy development. A timeline spanning 2006–2025, marking key policy milestones: REACH entry into force (2007), European Commission recommendation on nanomaterial definition (2011), Horizon 2020 SSbD calls (2014–2020), European Green Deal (2019), Chemicals Strategy for Sustainability (2020), Horizon Europe SSbD integration (2021–2027), and ongoing development of SSbD guidance documents and implementation frameworks (2022–2025). Annotations highlight the progressive embedding of SSbD principles into EU research funding, chemical regulation, and industrial policy

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7.2 IMPLEMENTATION FRAMEWORKS AND STAKEHOLDER ENGAGEMENT

Translating SSbD policy into practice requires operational frameworks, decision-support tools, and capacity-building initiatives. Larraz and colleagues' 2021 deliverable, "DIAGONAL SbD and SusbD Implementation Framework," exemplifies efforts to develop practical guidance for researchers and industry [17]. The DIAGONAL framework provides step-by-step workflows for conducting SSbD assessments, including hazard screening, exposure estimation, prospective LCA, and multi-criteria decision analysis [17].

The framework emphasizes iterative assessment: SSbD is not a one-time evaluation but a continuous process that evolves as materials advance through development stages [17]. At early stages (TRL 1–3), assessments are necessarily qualitative and scenario-based, focusing on hazard screening and identification of design alternatives [17]. At intermediate stages (TRL 4–6), quantitative data from pilot-scale production and toxicity testing enable more refined risk and LCA assessments [17]. At late stages (TRL 7–9), full-scale production data and post-market monitoring inform final assessments and continuous improvement [17].

Stakeholder engagement is a core component of SSbD implementation. Brennan and Valsami-Jones' 2021 review emphasizes that SSbD is not solely a technical exercise but a social process that requires dialogue among researchers, industry, regulators, workers, consumers, and environmental advocates [4]. Early stakeholder engagement can surface concerns, values, and knowledge that might otherwise be overlooked, leading to more robust and socially acceptable design decisions [4]. For example, worker representatives can provide insights into occupational exposure scenarios and the feasibility of engineering controls; environmental NGOs can highlight ecosystem vulnerabilities; and consumer groups can articulate preferences regarding product safety and sustainability [4].

Brennan and Valsami-Jones also highlight the ethical imperative to reduce animal testing in nanomaterial safety assessment [4]. SSbD frameworks should prioritize in silico methods (quantitative structure-activity relationships, read-across), in vitro assays (cell-based toxicity screens), and alternative in vivo models (zebrafish, invertebrates) over mammalian testing [4]. This aligns with the 3Rs principles (Replacement, Reduction, Refinement) and reflects societal concerns about animal welfare [4].

7.3 ETHICAL DIMENSIONS: REDUCING ANIMAL TESTING AND SHARED RESPONSIBILITY

The ethical dimensions of SSbD extend beyond animal welfare to encompass broader questions of responsibility, equity, and justice. Brennan and Valsami-Jones argue that SSbD embodies a principle of shared responsibility: all actors in the innovation chain—from academic researchers to material suppliers to product manufacturers to end-users—bear responsibility for ensuring that nanomaterials are safe and sustainable [4]. This contrasts with traditional models where responsibility is concentrated in regulatory agencies or downstream manufacturers [4].

Shared responsibility implies several commitments. Researchers must conduct rigorous safety and sustainability assessments and transparently report findings, including negative results [4]. Material suppliers must provide comprehensive physicochemical characterization and safety data sheets [4]. Product manufacturers must design for safe use and end-of-life, providing clear instructions and take-back programs [4]. Regulators must establish clear, science-based standards and enforce compliance [4]. Consumers must use products responsibly and participate in recycling or disposal programs [4].

Equity and justice considerations are also central to SSbD. Nanomaterial benefits (e.g., advanced medical diagnostics, clean energy technologies) and burdens (e.g., occupational exposure risks, environmental contamination) are not evenly distributed across populations [4]. SSbD frameworks should explicitly assess distributional impacts: Who benefits from the technology? Who bears the risks? Are vulnerable populations (workers, low-income communities, future generations) disproportionately affected? [4] Addressing these questions requires not only technical assessment but also participatory governance processes that give voice to affected communities [4].

8 PERSISTENT CHALLENGES AND FUTURE FRONTIERS

8.1 SCIENTIFIC GAPS: ECOTOXICITY, TRANSFORMATION, AND FATE DATA

Despite substantial progress in SSbD methodologies and tools, critical scientific gaps constrain the operationalization of SSbD principles. Foremost among these is the paucity of quantitative ecotoxicity data for most nanomaterials. Thakur and Kumar's 2023 review emphasizes that while acute toxicity data for a few model organisms (algae, daphnia, fish) are available for major nanomaterial classes (Ag, ZnO, TiO_2, CNTs), chronic toxicity, multigenerational effects, and ecosystem-level impacts remain largely uncharacterized [11]. This data gap is particularly acute for emerging nanomaterials (e.g., 2D materials, metal-organic frameworks, nanoplastics) and for nanomaterials in complex environmental matrices (soils, sediments, biofilms) [11].

Environmental fate and transformation data are similarly sparse. Hansen and colleagues' 2015 review highlights that nanomaterials undergo a variety of transformations in environmental media—dissolution, sulfidation, oxidation, aggregation, protein corona formation—that profoundly alter their mobility, bioavailability, and toxicity [7]. Yet most toxicity tests and LCA studies employ pristine, as-synthesized materials, ignoring these transformations [7]. Predictive models for nanomaterial fate and transformation are in early stages of development and require extensive validation against field data [7].

Guinée and colleagues' 2022 review underscores that LCA uncertainty is particularly high at low technology readiness levels, where laboratory-scale data must be extrapolated to industrial-scale production [13]. Key uncertainties include energy consumption (will industrial-scale processes achieve anticipated efficiency gains?), yield (will purification losses be reduced at scale?), and waste generation (will byproducts be recycled or valorized?) [13]. Scenario modeling and sensitivity analysis can bound these uncertainties, but they cannot eliminate them [13].

Table 5

Frontier technologies supporting safe-and-sustainable-by-design nanomaterial development. A summary table of emerging technologies and tools that advance SSbD implementation, including high-throughput in vitro and in vivo screening platforms (organ-on-chip, zebrafish arrays), in silico methods (QSAR, molecular dynamics, machine learning), advanced characterization techniques (single-particle ICP-MS, environmental TEM, synchrotron methods), fate and transport models (multimedia models, nanoparticle-specific algorithms), and decision-support systems (multi-criteria decision analysis software, SSbD checklists). Includes technology readiness, strengths, limitations, and representative citations

Technology Category	Tool / Approach	Application in SSbD	Advantages	Limitations	Technology Readiness
High-throughput screening	Zebrafish arrays	Rapid toxicity screening	Whole organism response	Aquatic model bias	Medium–high
	Organ-on-chip	Human-relevant toxicity	Physiological realism	Complex setup	Medium
	Microfluidic toxicity platforms	Multi-endpoint testing	Low sample consumption	Standardization lacking	Medium
In silico prediction	QSAR models	Property-toxicity prediction	No animal testing	Dataset limitations	Medium
	Machine learning toxicity models	Hazard prediction	Multi-parameter analysis	Requires large datasets	Medium
	Molecular dynamics simulation	Nano-bio interactions	Mechanistic insight	Computationally intensive	Low–medium
Advanced characterization	Single-particle ICP-MS	Particle size & concentration	High sensitivity	Instrument cost	High

	Environmental TEM	Transformation analysis	Real-time observation	Complex operation	Medium
	Synchrotron spectroscopy	Surface chemistry	High resolution	Limited access	Medium
Fate and transport modeling	Multimedia fate models	Environmental distribution	Lifecycle insight	Parameter uncertainty	Medium
	Dissolution kinetics models	Ion release prediction	Hazard forecasting	Material-specific	Medium
	Aggregation models	Mobility prediction	Environmental relevance	Complex systems	Low–medium
Decision-support systems	Multi-criteria decision analysis	Trade-off evaluation	Integrative assessment	Weighting subjectivity	High
	SSbD checklists	Design guidance	Easy implementation	Qualitative	High
	Integrated LCA-risk platforms	Sustainability evaluation	Lifecycle coverage	Data intensive	Medium

8.2 METHODOLOGICAL LIMITATIONS: LCA UNCERTAINTY AT LOW TRLS

Prospective LCA at low technology readiness levels faces inherent methodological limitations. Guinée and colleagues identify several sources of uncertainty [13]. First, process data uncertainty: laboratory-scale processes are often poorly characterized, with incomplete mass and energy balances, and may not be representative of industrial-scale production [13]. Second, scale-up uncertainty: assumptions about efficiency gains, yield improvements, and waste reduction during scale-up are speculative and may not be realized in practice [13]. Third, functional unit uncertainty: defining appropriate functional units for early-stage materials is challenging, as performances characteristics may change during development [13]. Fourth, system boundary uncertainty: decisions about which lifecycle stages to include (e.g., infrastructure, equipment manufacturing, end-of-life) can significantly influence results [13].

Bartolozzi and colleagues' 2020 study illustrates these uncertainties through sensitivity analysis of cellulose nanosponge LCA [4]. The authors found that impact estimates varied by up to an order of magnitude depending on assumptions about scale-up efficiency, solvent recovery rates, and end-of-life scenarios [4]. This underscores the importance of transparent reporting of assumptions and sensitivity analysis in prospective LCA [4].

Methodological developments are needed to reduce LCA uncertainty at low TRLs. Guinée and colleagues recommend ex-ante LCA approaches that explicitly model technology evolution pathways, incorporating learning curves, technological improvements, and market diffusion dynamics [13]. They also advocate for consequential LCA that accounts for indirect effects such as market displacement, rebound effects, and induced technological change [13]. These advanced LCA methods are computationally intensive and data-demanding but offer more realistic assessments of long-term sustainability [13].

8.3 OPERATIONAL BARRIERS: EXPOSURE CONTROLS AND DOWNSTREAM RISK MANAGEMENT

Even when nanomaterials are designed according to SSbD principles, operational barriers can undermine safety and sustainability objectives. Hansen and colleagues' occupational exposure data demonstrate that in-matrix generation—a widely recommended exposure-reduction strategy—does not eliminate nanoparticle release during downstream processing (grinding, sanding, drilling) [7]. Measured airborne concentrations of 4.71×10^{3} to 1.75×10^{6} particles·cm^{-3} and respirable fiber concentrations up to 0.13 fibers·cm^{-3} during grinding of polycarbonate/CNT composites underscore the need for complementary engineering controls (local exhaust ventilation, enclosure) and personal protective equipment (respirators) [7].

End-of-life management poses additional challenges. Nanomaterial-containing products are rarely designed for disassembly or material recovery, complicating recycling efforts [7]. Incineration of nanomaterial-containing waste can release nanoparticles to air, while landfilling can lead to leaching to groundwater [7]. Wastewater treatment plants are not designed to remove nanoparticles, and many nanomaterials pass through to receiving waters or accumulate in sewage sludge [7]. These downstream risks are often overlooked in SSbD assessments, which focus on synthesis and use phases [7].

Addressing operational barriers requires lifecycle thinking that extends SSbD principles beyond synthesis to encompass use, maintenance, recycling, and disposal [7]. Design for disassembly, use of biodegradable matrices, and development of nanomaterial-specific recycling technologies are promising strategies [7]. Regulatory frameworks must also address downstream risks, establishing standards for occupational exposure during processing, consumer product safety, and end-of-life management [7].

8.4 GOVERNANCE FRAGMENTATION AND THE NEED FOR HARMONIZATION

Regulatory governance of nanomaterials remains fragmented across jurisdictions, sectors, and lifecycle stages. Furxhi and colleagues' 2023 analysis highlights that while the EU has developed comprehensive SSbD frameworks, implementation varies across member states, and coordination with non-EU jurisdictions (United States, China, Japan) is limited [12]. This fragmentation creates challenges for multinational companies, which must navigate multiple regulatory regimes, and for global supply chains, where materials may be produced in one jurisdiction, processed in another, and used in a third [12].

Sector-specific regulations (e.g., cosmetics, food, medical devices, pesticides) impose different requirements for nanomaterial safety assessment, leading to duplication of effort and inconsistent standards [12]. For example, nanomaterials in cosmetics are regulated under the EU Cosmetics Regulation, which requires safety assessments but does not mandate SSbD principles, while nanomaterials in pesticides are regulated under the Biocidal Products Regulation, which has different assessment requirements [12].

Harmonization efforts are underway but face political and technical obstacles. The OECD Working Party on Manufactured Nanomaterials has developed testing guidelines and guidance documents, but these are voluntary and not uniformly adopted [12]. International standards organizations (ISO, ASTM) have published standards for nanomaterial characterization and toxicity testing, but gaps remain, particularly for ecotoxicity and environmental fate [12].

Furxhi and colleagues call for global governance frameworks that harmonize SSbD principles, assessment methods, and regulatory standards across jurisdictions [12]. They emphasize that harmonization should not mean lowest-common-denominator standards but rather alignment around best practices and continuous improvement [12]. International cooperation on data sharing, method validation, and capacity building is essential to achieve this vision [12].

9 CONCLUSION: TOWARD A SUSTAINABLE NANOTECHNOLOGY FUTURE

The journey from bench to biosphere—from initial synthesis in the laboratory to eventual environmental fate—defines the lifecycle of nanomaterials and the scope of safe-and-sustainable-by-design governance. This review has synthesized evidence from 182 peer-reviewed studies to demonstrate that SSbD is not a utopian aspiration but an achievable paradigm, grounded in green chemistry principles, structure–property–hazard engineering, prospective life cycle assessment, iterative biological screening, and integrated risk assessment. Quantitative findings underscore both progress and persistent challenges: biogenic synthesis eliminates toxic reagents; prospective LCA reveals that scale-up can reduce environmental impacts by approximately two orders of magnitude; yet trade-offs persist, with some design modifications reducing climate impacts while increasing toxicity burdens. Measured workplace exposures of 4.71×10^{3} to 1.75×10^{6} particles·cm^{-3} remind us

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that design interventions alone are insufficient—complementary exposure controls and lifecycle governance are essential.

The SSbD paradigm demands a fundamental shift in innovation culture: from reactive hazard management to proactive hazard elimination, from single-metric optimization to multi-criteria trade-off analysis, from siloed disciplinary expertise to integrative, transdisciplinary collaboration. It requires researchers to embrace iterative redesign, even when it means abandoning promising materials that cannot meet safety and sustainability criteria. It requires industry to invest in early-stage assessment and transparent reporting, even when data reveal unfavorable trade-offs. It requires regulators to develop adaptive, science-based frameworks that incentivize SSbD without stifling innovation. And it requires society to engage in informed dialogue about the values and priorities that should guide nanomaterial development.

Critical scientific gaps remain—sparse ecotoxicity data, limited environmental transformation knowledge, high LCA uncertainty at low technology readiness levels—but these gaps are not insurmountable. Emerging tools—high-throughput screening platforms, in silico prediction models, advanced characterization techniques, decision-support systems—are rapidly expanding the SSbD toolkit. Policy momentum, particularly in the European Union, is embedding SSbD principles into research funding, chemical regulation, and industrial strategy. Implementation frameworks and stakeholder engagement processes are translating SSbD from concept to practice.

The next generation of nanomaterials will be judged not only by their performance but by their safety and sustainability across the full lifecycle—from bench to biosphere. This review provides a strategic roadmap for achieving that vision: prioritize green synthesis pathways that eliminate hazard at the source; engineer structure–property–hazard relationships to optimize the benefit-to-risk ratio; employ prospective LCA to identify hotspots and detect trade-offs before scale-up; integrate toxicity assessment and exposure measurement to estimate real-world risks; engage stakeholders to ensure that diverse values and concerns are addressed; and continuously iterate, learn, and improve as new data emerge. The path forward is clear, the tools are available, and the imperative is urgent. The question is not whether SSbD is possible, but whether the nanotechnology community—researchers, industry, regulators, and society—will commit to making it the norm rather than the exception.

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