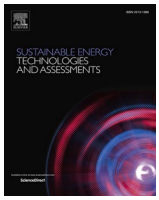
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Review article

Addressing nanotoxicological risks in green hydrogen technologies: a safety by design perspective

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ABSTRACT

Green hydrogen offers a key solution for decarbonizing hard-to-abate industries and heavy-duty transportation, supporting global climate targets and the European Union's Clean Industrial Deal. Its large-scale production and use increasingly rely on nanomaterials, which, while enhancing performance, raise concerns about potential nanotoxicological risks that remain largely unexplored. If not properly addressed, these risks could translate into significant regulatory barriers, slowing the widespread deployment of green hydrogen technologies. This perspective assesses these challenges and proposes strategies to mitigate them through the Safety-by-Design approach. Addressing safety during early material development can help avoid future regulatory obstacles and promote safer, more sustainable technological advancements.

Introduction: the quest for risk assessment in green hydrogen technology

Green hydrogen is an energy vector that can be produced in an environmentally neutral manner, offering a significant opportunity to support the transition to a low-carbon economy and reduce emissions in sectors where direct electrification is challenging [1,2]. It can be used *i*) as a reagent for the chemical industry [3], *ii*) as fuel for combustion for high-temperature thermal treatments and engines [4], *iii*) as a fuel to generate electricity [5], and *iv)* as a substitute for carbon in iron metallurgy [6]. Its large-scale deployment relies primarily on water electrolysis powered by renewable electricity. To get an approximate idea of the challenge, the total deployment of electrolyzers is planned to exceed 3 TWh worldwide by 2050 [7]. In February 2025, the European Union's Clean Industrial Deal [8] envisioned green hydrogen as a key vector to decarbonize Europe [9] (industry, agriculture, transportation) promoting the adoption of a Delegated Act on Low-Carbon Hydrogen to clarify production rules and a third funding call under the Hydrogen Bank with a €1 billion budget to support hydrogen projects, all aimed at scaling up the hydrogen sector and advancing decarbonization efforts. Green hydrogen has also been named a strategic technology within the Draghi Report [10] for increasing EU future competitiveness worldwide.

However, several hurdles must be faced to reach the targets mentioned above. Green hydrogen technologies span a broad value chain, including production (e.g., electrolysers), conversion (e.g., fuel cells), storage, and transport systems, where nanomaterials are increasingly employed in catalysts, membranes, and functional components [11,12]. In this work, we specifically focus on proton exchange membrane (PEM)-based technologies, namely proton exchange membrane water electrolysers (PEMWEs) and proton exchange membrane fuel cells (PEMFCs), which currently represent the most advanced low-temperature systems for hydrogen production and utilization.

PEMWEs enable efficient and flexible hydrogen production, particularly under intermittent renewable energy supply [13], while PEMFCs efficiently convert hydrogen into electricity, supporting applications in transportation and stationary energy systems [14].

If, on one side, PEMWEs and PEMFCs are essential for producing and utilizing hydrogen, they require effective electrocatalysts [15] based on critical raw materials like metals from the platinum group (PGMs), to enable the following four reactions: (1) the hydrogen evolution reaction (HER) that occurs at the cathode of the electrolyzer; (2) the oxygen evolution reaction (OER) that occurs at the anode of the electrolyzer; (3)

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the hydrogen oxidation reaction (HOR) at the anode of the fuel cell; and (4) the oxygen reduction reaction (ORR) taking place at the cathode of the fuel cell.

Enhancing the kinetics of these reactions while minimizing their energy demand is fundamental to driving an efficient hydrogen-based economy. To date, Pt and its alloys, often deposited on a carbon-based support (Pt/C) [16], are extremely efficient for hydrogen evolution, hydrogen oxidation, and oxygen reduction. Iridium Oxide (IrOx) has emerged as an effective electrocatalyst for oxygen evolution [17].

These materials, however, exhibit limited stability under the harsh electrochemical conditions, particularly during oxygen evolution [18,19]. Typically, both Pt and IrOx particle sizes are well below 10 nm, and very often their diameters are smaller than 5 nm [20,21]. Particles within this size range can detach at the electrode–electrolyte interface and, if released into the environment, may interact with biological systems, posing risks to human health and ecosystems [22] (Fig. 1).

Alkaline technologies, including alkaline electrolysis (AWE), alkaline membrane fuel cells (AMFCs), and alkaline membrane water electrolysis (AEMWE), have been explored as potential alternatives to reduce the dependence on precious metals. AWE, however, may suffer from lower performance compared to PEM-based technologies, while AMFCs and AEMWE, are not yet mature enough for large-scale deployment.

In addition, the environmental concerns associated with nanoparticle detachment cannot be separated from the vulnerability arising from PGMs scarcity. The heavy dependence of green hydrogen technologies on PGMs also poses a significant threat to the supply chain [23,24]. These metals are expensive, scarce, and concentrated in a few regions of the world, often marked by geopolitical instability. Therefore, the reliance on limited PGMs resources would still constrain the scalability of PEM-based technologies.

As such, most research efforts have focused on developing "nanostructured electrodes" with extremely high surface-to-volume ratios and dual scale porosity [25], which maximize catalyst exposure while minimizing material usage [26].

Nonetheless, this approach does not prevent nanoparticle detachment or metal leaching during operation, making PGMs' recovery technically challenging while raising additional ecological and health concerns.

Remarkably, despite the increased safety awareness in the development of nanomaterials, the potential risks of nano-structured electrodes used in hydrogen-related technologies have received little to no attention [27]. Existing studies have predominantly focused on improving catalytic activity, durability, and material efficiency, with degradation mechanisms such as Pt dissolution, Ir leaching, and carbon corrosion primarily interpreted as performance-limiting phenomena. In parallel, hydrogen safety studies have traditionally focused on macroscopic risks such as leaks, dispersion, ignition, and explosion across the entire hydrogen value chain (production, storage, transport, and utilization), often supported by computational fluid dynamics (CFD) and quantitative risk assessment (QRA) approaches [28–30].

In parallel, a substantial body of work in nanotoxicology has produced frameworks to assess hazard, exposure, and environmental fate of engineered nanomaterials, including adverse outcome pathways (AOPs), in vitro/in vivo assays, [31].

These frameworks, however, have been largely developed outside the context of hydrogen technologies and do not explicitly account for specific operational conditions and material architecture.

As a result, these two domains remain largely disconnected. In particular, catalyst degradation in PEM-based systems is rarely considered as a potential source of nanoparticle release, and nanosafety approaches have not been systematically applied to electrochemical energy technologies. Even comprehensive hydrogen safety assessments [28] do not explicitly consider nanoparticle release and nano–bio interactions. At the same time, nanosafety methodologies have not been adapted to the operational environments and degradation mechanisms of electrochemical systems.

This lack of cross-fertilization results in an incomplete understanding of risk, where material-level hazards and system-level safety are treated separately rather than as interdependent dimensions.

This gap is particularly critical in PEM-based systems, where catalyst degradation may represent a previously overlooked pathway linking material instability to environmental and health risks.

We argue that the electrocatalysis community remains largely unaware of the potential toxicological implications of the technologies under development.

This Perspective aims to fill this gap, raise awareness, and discuss relevant conceptual approaches emerging from nanosafety research. In this regard, we focus on the Safety-by-Design (SbD) approach [32], a strategy aimed at preventing risks at early stage of product development, ideally before material realization. The implementation of this approach must face two sources of uncertainty: (1) uncertainty regarding the safety of not yet fully developed electrocatalysts, and (2) limited understanding of the toxicity mechanisms of nanoparticles involved in electrocatalysis. If the first source of uncertainty is, by definition, unavoidable, the second may require decades of toxicological assessments to be solved. The SbD approach addresses these uncertainties by providing strategies to assess rather than quantify risk.

Building on this conceptual foundation, we propose, for the first time, an integrated approach that links electrocatalyst degradation mechanisms, nanomaterial release pathways, and SbD principles across the lifecycle of PEM-based hydrogen technologies.

The paper is organized as follows: it introduces the core elements of nanotoxicological risk, followed by an overview of relevant regulatory developments. It then analyzes key materials and components used in PEMWEs and PEMFCs, explicitly linking their synthesis, integration, and

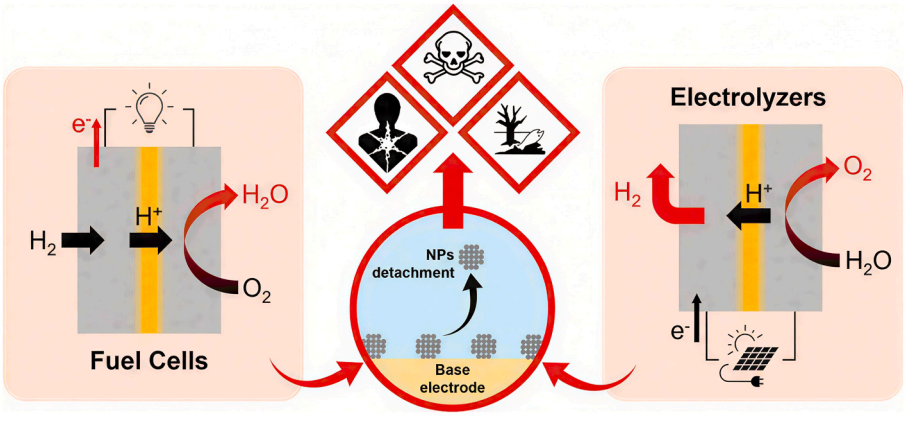


Fig. 1. Potential release of electrocatalysts nanoparticles (NPs) at the electrode/electrolytes interface in fuel cells (PEMFCs) and water electrolyzers (PEMWEs).

degradation mechanisms to potential nanoparticle release and exposure pathways. These aspects are subsequently interpreted through an SbD framework to identify points of intervention for risk minimization. Finally, the paper provides a structured synthesis through a SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis to support implementation-oriented decision-making.

Key aspects of the toxicity of nanomaterials

Generally speaking, risk results from the combination of *hazard*, that is, the type of damage that a nanomaterial can cause, and *exposure*, which accounts for the probability that the hazardous nanomaterial reaches a biological target [33]. To give an idea of the potential risks associated with nanomaterials, we must consider that the cellular membrane has an average thickness of ~7 nm, while the diameter of a whole cell falls in the micrometre range. The dimensions of the most performing nanomaterials used as electrocatalysts for green hydrogen production are comparable to those of biological systems, making size [34] the primary potential source of hazard. The specific type of interaction, however, depends on a vast spectrum of other physical–chemical properties of the nanomaterials, which include morphology and shape (nanotubes, dendrimers etc.), chemical composition, crystalline structure, and chemical reactivity [22,35] (Fig. 2).

These unique properties make nanomaterials highly effective in technology, but also extremely variable in terms of toxicity [22,36]. The assessment of the toxicity of a nanomaterial before it is manufactured represents a key challenge: designing safe nanomaterials from the outset is more effective than mitigating risks at a later stage, although unknown toxicity profiles and the difficulty of measuring exposure in yet-to-be-built facilities complicate the risk management [37]. At the state of the art, experimental methods alongside computational modelling are used to evaluate the damaging potential of nanomaterials. Physics-based tools like molecular dynamics are increasingly integrated into the SbD process [38].

Initiatives towards the regulations of nanomaterials production and use

In the past decades, the EU Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) defined 'nanoscale' as a size that ranges from 1 nm to 100 nm [39]. Following, the EU further defined nanomaterials' characteristics [40], supported by the European Chemicals Agency (ECHA), which established the European Union Observatory on Nanomaterials (EUON). However, these organizations act as information hubs for stakeholders but do not enforce laws, nor regulate or ban nanomaterials.

In 2012, the European Commission Directorate-General for Research and Innovation (DG RTD) established the Network for Safety and Sustainability of Chemicals and Materials [41], which fosters collaboration among European projects about nanosafety. This network explores strategies for the minimization of risks arising from the use of nanomaterials and provides the main groundwork for the regulatory framework. Currently, the initiative counts more than 30 active projects (with 50 already completed) covering toxicology, exposure, risk assessment, and standardization.

Another central regulatory framework in the European context is the REACH regulation (Registration, Evaluation, Authorization and Restriction of Chemicals) [42], which defines the term "nanoform" referring to various products that engage the use of nanomaterials, such as nanoparticles or nanotubes. However, we clarify that, at the broader regulatory level, a formal definition of nanoform has been established within the EU framework, but this terminology has not yet been agreed and adopted at the international level.

Under REACH, manufacturers and importers are required to provide detailed information on physicochemical properties, hazard classification, and exposure scenarios, including nano-specific characteristics such as size distribution, surface area, and reactivity. Nevertheless, the application of REACH to nanomaterials remains challenging [43] due to the high variability of nanoparticles and the limited availability of standardized testing protocols, which often results in significant uncertainty during risk assessment and registration processes. The REACH regulation, however, allows the manufacturer of nanoparticles to submit, in place of experimental evaluations, a well grounded theoretical assessment of risks for which the SbD scheme can be extremely useful. Only in 2022, the Organization for Economic Co-operation and Development (OECD) recommended that, to mitigate potential risks related to nanomaterials, nanoparticles should, whenever possible, be securely embedded in inert supports to minimize their release into the environment [44]. However, fully embedding nanostructures is not feasible in green hydrogen technologies as the exposure of electrocatalysts to the reaction environment is mandatory. Consequently, alternative strategies are needed to manage their potential release.

In this context, the SbD approach can be interpreted as a conceptual tool to anticipate, already at the material development stage, future regulatory requirements. By integrating hazard identification, exposure minimization, and lifecycle considerations into the design process, SbD can reduce uncertainties about risks, facilitate nanoparticles characterization, and support more robust and efficient compliance pathways.

Overview of safety-related risks in PEMWEs and PEMFCs nanotechnologies

Building on the previous regulatory perspective, SbD can be further understood at the technological level as the operational entry point of the Safety and Sustainability by Design (SSbD) framework [45], which, in addition to safety, evaluates economical, social, environmental aspects of the development of new products.

For nanoparticles, the SbD scheme is critical to the Life Cycle

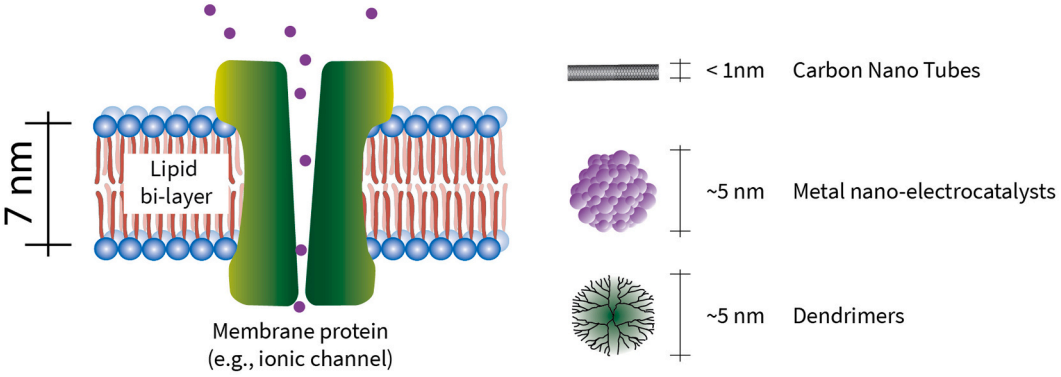


Fig. 2. Comparison of dimensions of a cellular membrane with some examples of nanostructures used in electrocatalysis.

Assessment (LCA) process because it mitigates risks at the source, before they propagate through the entire life cycle. Its primary functions include:

- Hazard Reduction at Synthesis: By modifying intrinsic physicochemical properties (e.g., surface functionalization) during synthesis, SbD reduces the toxicity and environmental release potential that an LCA would quantify as high-impact in later stages.
- Early Identification of "Hotspots": SbD tools identify "red flags" and potential issues during R&D, allowing for design improvements before full-scale production.
- Bridging Data Gaps: Early screening assessments provide the necessary data for more rigorous LCA later in the product's development.
- Integrating Functionality with Safety: SbD ensures that safety measures do not compromise the product's performance, balancing risk reduction with technical utility.

This latter aspect is particularly critical in electrochemical energy technologies such as PEMFCs and PEMWEs, where material design is inherently driven by performance optimization. In these systems, maximizing catalytic activity, conductivity, and mass transport often requires nanoscale engineering strategies that may inadvertently increase hazard potential. Therefore, integrating functionality with safety is not an auxiliary consideration, but a central design challenge.

In PEMFCs, both the anode and cathode utilize carbon nanopowder supports for Pt and Pt alloy nanoparticles [46]. This carbon support introduces dual-scale porosity, enhancing mass transport and providing a uniform dispersion of metallic nanoparticles, typically ranging from 1 nm to 10 nm [47]. The carbon-based structure ensures high electronic conductivity and efficient gas diffusion, essential for the HOR at the anode and the ORR at the cathode [48].

In PEMWEs, while the cathode design is similar to that of PEMFCs, the anode requires a different approach due to the harsh conditions of the OER, which could corrode the carbon support, compromising the electrode efficiency and increasing the risk of nanomaterial dispersion [49].

Beyond electrodes, a critical component common to both technologies is the membrane electrode assembly (MEA). In the MEA, the electrocatalyst-coated electrodes are integrated with the PEM, located at the centre of the sandwich, to facilitate the essential electrochemical reactions [50]. The MEA's design is key to improving performance, and its fabrication involves several precise steps, including the synthesis of nanoparticles, deposition onto supports (integration of the nanoparticles), preparation of electrocatalyst inks, and final assembly [51].

While electrodes and MEAs design, in both PEMFCs and PEMWEs, focuses on technological optimization, such as the maximization of surface area, lowering critical materials content in the electrocatalyst and enhancing chemical transport, the potential risks associated with the handling and fabrication of these materials are often overlooked. To our knowledge, there are no strategies in place to prevent these risks.

Although quantitative exposure data for nano-electrocatalysts in PEM-based hydrogen technologies remain limited, indicative ranges can be inferred from studies on engineered nanomaterials in occupational settings. Airborne nanoparticle concentrations in laboratory and pilot-scale environments have been reported in the range of 10^3–10^6 particles cm^{-3} [52,53] depending on the process and level of containment. Inhalation is therefore considered the primary exposure route during synthesis and ink preparation stages, while dermal exposure may occur during handling of dispersions [54].

From a lifecycle perspective, potential exposure can be categorized into three main stages: (i) manufacturing (nanoparticle synthesis, ink formulation, electrode deposition), where aerosolization and solvent emissions are most relevant [55] (ii) operation, where catalyst leaching and degradation may release dissolved or particulate species [56]; and (iii) end-of-life and recycling, where mechanical processing can reintroduce particulate forms into the environment [57]. We emphasize, however, that standardized occupational exposure limits specific to Pt, Ir, or their nanoparticles have not yet been established, highlighting a critical gap that reinforces the need for preventing, as much as possible, risks by a SbD approach.

The following sections provide a comprehensive overview describing electrocatalyst synthesis, integration with conductive supports of electrocatalyst inks and MEA fabrication (Fig. 3), highlighting the phases where risks emerge.

Synthesis of the electrocatalyst

The fabrication of PEMFC and PEMWE electrodes starts with the synthesis of nano-electrocatalysts, a critical step that directly affects the performance and stability of the MEA [58].

In PEMFCs, both the anode and cathode use carbon-based supports, such as carbon black, graphene, or carbon nanotubes, to anchor Pt and Pt alloy nanoparticles. Vulcan XC 72R, a highly graphitized carbon black, is the most commonly used carbon support for fuel cells due to its large surface area, excellent electrical conductivity, and cost-effectiveness [59]. Carbon black offers a surface area ranging from 200 to 2000 $m^2\,g^{-1}$. Graphene stands out with its exceptional electrical conductivity, remarkable mechanical strength, and surface area of up to 2630 $m^2\,g^{-1}$. Carbon nanotubes also offer excellent electronic properties and large surface areas, exceeding 1000 $m^2\,g^{-1}$ [60].

In PEMWEs, the cathode design is like that of PEMFCs and uses Pt/C nanoparticles for HER. The PEMWE anodes employ unsupported IrO_2 nanoparticles, which are deposited directly onto the PEM, or over a porous transport layer (PTL), typically made of titanium, to ensure stability and durability during water electrolysis [61]. The quest for IrO_2 support is of critical importance as it may reduce the Ir loading, assuring limited use of PGMs [62].

Chemical reduction is the most commonly used commercial method for synthesizing electrocatalysts of noble metals. In this approach, metal precursors, such as hexachloroplatinic acid, react with reducing agents like sodium borohydride to form metal nanoparticles anchored onto carbon supports. This method not only facilitates the simultaneous synthesis and deposition of nanoelectrocatalysts, but also ensures uniform dispersion and strong adhesion [63].

Another popular technique is thermal decomposition, which is widely used for producing IrO_2 nanoparticles. In this process, metal precursors break down at elevated temperatures; for example, heating $IrCl_3$ leads to its decomposition and formation of IrO_2 nanoparticles.

Colloidal synthesis is a further method, which involves the generation of Pt nanoparticles in a solution that contains a stabilizing agent that prevents aggregation (e.g., polyvinyl alcohol or citric acid) [64]. Once the nanoparticles have formed, carbon support is introduced into the colloidal solution, and nanoparticles adsorb onto its surface.

Although this method offers excellent control over nanoparticle size and distribution compared to chemical reduction, it is complex and time-consuming, two limitations for its large-scale adoption.

Electrocatalyst inks

The next step is the preparation of an electrocatalyst ink [65,66] that consists of mixing the electrocatalyst (i.e., the metal nanoparticles over the support) with a solvent (e.g. ethanol, isopropanol, etc.) to ensure a uniform metal dispersion, and an ionomer (e.g. Nafion, Aquivion, etc) that works as a binder and ionic conductor. In particular, Nafion is widely used to provide both ionic conductivity and help adhere the electrocatalyst to the electrode.

The electrocatalyst ink is used to manufacture electrodes for both PEMWEs and PEMFCs cathodes [67]. More details related to the electrocatalyst ink formulation are reported in a recent comprehensive review [65].

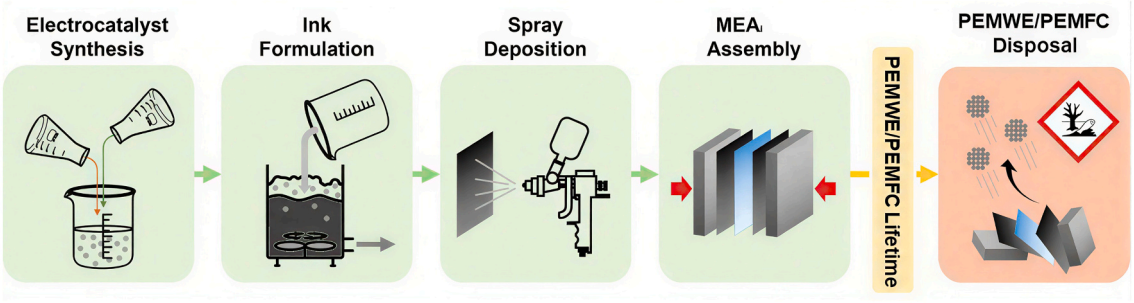


Fig. 3. PEMFCs and PEMWEs assembly, life cycle and end of life.

Membrane electrode assembly (MEA)

The electrocatalyst ink can be deposited directly onto the polymeric membrane to form a catalyst-coated membrane (CCM), or onto an electrode substrate to create a catalyst-coated substrate (CCS). Although both PEMFCs and PEMWEs use the same membrane materials [68], their electrode substrates differ. In PEMWEs, it is the PTL that ensures effective water delivery to the catalyst and facilitates gas release (oxygen and hydrogen) while in PEMFCs, it is the gas diffusion layer (GDL) that allows reactant gases (hydrogen and oxygen/air) to reach the catalyst layer while also facilitating water removal. Despite the differences in function, some materials can be used in both technologies. For instance, at the cathode of both PEMWEs and PEMFCs carbon paper of cloth can be used.

To obtain CCM and CCS, the electrocatalyst ink can be deposited on the membranes using techniques such as spray coating, blade coating, or inkjet printing. Spray coating creates a thin, uniform layer by spraying the ink onto the substrate. In blade coating, a blade is used to evenly spread the ink and control the layer's thickness. Inkjet printing, on the other hand, enables precise deposition of the ink.

Once deposited, the coated electrodes are dried to remove the solvent and then undergo heat treatment to enhance the adhesion and conductivity of the catalyst layer. Drying may occur at room temperature or slightly elevated temperatures (often accelerated in an oven) while the subsequent heat treatment, typically between 80°C and 150°C, improves the mechanical stability and electrical contact of the electrocatalyst.

As mentioned earlier, the PEMWE anode usually consists of IrO_2 nanoparticles anchored directly onto the membrane or on a titanium paper or mesh, which functions as the PTL.

In the final stage of device fabrication, the prepared electrodes are assembled into single cells and then integrated into a complete PEMWE or PEMFC stack [69]. In PEMFCs, the anode and cathode are positioned on opposite sides of PEM and are sandwiched between GDLs, whereas in PEMWEs the electrodes are arranged around the PEM to meet the differing operational demands of HER and OER. This careful assembly is critical to ensure optimal performance throughout the device's operational life.

Each of the previous stages (Fig. 3) presents distinct technical challenges characterized by specific risks. Nanoparticles, ranging from 1 to 10 nm, are easily aerosolized, increasing the likelihood of inhalation and environmental release. Materials like Vulcan XC 72R, being highly dispersible, are particularly prone to becoming airborne. The preparation of electrocatalyst inks also involves volatile solvents and binders that emit harmful vapors. Fluoro-polymers like Nafion are raising health concerns as they belong to the Perfluoroalkyl and polyfluoroalkyl substances (PFAS) [70].

Devices lifetime and disposal

Over the device lifecycle, the risk of nanomaterial release persists, whether during routine operations, accidents, or recycling.

During operation, metals can dissolve through electrochemical corrosion, a process often referred to as "catalyst leaching." Unlike mechanical nanoparticle detachment, this pathway involves the atom-by-atom loss of metal into the electrolyte. Catalyst leaching is a major durability and sustainability challenge in both PEMWEs and PEMFCs, as the release of metal species degrades performance, accelerates structural damage, and complicates end-of-life metal recovery, while also increasing the risk of environmental release.

In PEMFCs, Pt alloys are particularly prone to leaching: metals ions (e.g. Co) dissolve from the alloy surface and migrate into the ionomer, where they competitively occupy sulfonic acid groups, lowering proton conductivity and progressively degrading the integrity of the catalyst layer and MEA [71,72].

Ir-based catalysts, widely deployed for OER in PEMWE, face dissolution under acidic and high-potential conditions, a process that is especially concerning given Ir's scarcity and cost [73,74]. Ru-based OER catalysts exhibit similar vulnerabilities, with Ru dissolution observed at elevated voltages and strongly acidic pH, ultimately limiting their suitability for large-scale PEMWE deployment [75,76].

These phenomena arise from electrochemical instabilities during potential excursions, as well as broader degradation pathways including metal dissolution, particle agglomeration, and carbon-support corrosion that lead to cumulative performance losses and reduced device efficiency [77]. The resulting decline in active surface area manifests as diminished current density and lower overall energy efficiency [78], while the migration of dissolved metals into the membrane or catalyst layer accelerates structural fatigue and raises long-term maintenance requirements.

Building on the considerations outlined above, we follow to give, for the first time, a perspective on the potential application of the SbD approach to integrate safety at the early design stage of the PEMWE and PEMFC technology, for hydrogen production and use.

Nanoparticle release in PEM-based technologies: current evidence and knowledge gaps

Several critical knowledge gaps must be addressed to assess the nanotoxicology risk in PEM-based hydrogen technologies. The most urgent priorities concern the characterization of nanoparticles exposure pathways (manufacturing, operation, and end-of-life), across air, water, and surface compartments. An overview of the interplay between life-cycle stages, nanomaterials behaviour, exposure pathways, and SbD interventions is presented in Table 1.

During the fabrication of membrane electrode assemblies, catalyst inks e.g. containing Pt and IrO_2 nanoparticles are deposited onto substrates by spray coating and blade coating processes that are known to generate airborne aerosols. Studies on analogous spray coating operations with nanoparticle-containing suspensions have documented near-field particle number concentrations spanning several orders of magnitude and nanoparticulate fractions of 10–60% in dried spray aerosols

Table 1
Lifecycle-based overview of nanomaterials integration, transformation, and potential release in PEM-based hydrogen technologies, including associated exposure pathways and safety-by-design strategies across manufacturing, operation, and end-of-life stages.

Lifecycle stage	Focus area	Operational & practical SbD interventions
Manufacturing	Nanoparticle Synthesis	• Control particle size (particles smaller than 30 nm often show higher toxicity). • Favor spherical over anisotropic/non-spherical shapes to reduce cytotoxicity. • Implement process containment and engineering controls to prevent aerosolization
	Catalyst Ink & Integration	• Prefer liquid dispersions over dry powders to minimize inhalation risks from airborne aerosols. • Use spray/blade coating in contained environments to manage nanoparticle fractions in aerosols. • Consider alternatives to fluoro-polymers (like Nafion) due to PFAS-related health concerns
Operation (PEMWE/ PEMFC)	Material Architecture	• Develop stable catalyst architectures to prevent mechanical nanoparticle detachment. • Use corrosion-resistant supports (e.g., TiO_2, Nb-doped SnO_2, or doped oxides) instead of carbon black to minimize catalyst leaching and support corrosion.
	Immobilization	• Implement immobilization strategies to secure nanoparticles to their support, reducing dissolution and migration into the membrane.
End-of-life	Disposal & Recycling	• Design for recyclability to ensure safe disassembly and recovery of critical metals like Pt and Ir. • Design for recyclability to ensure safe disassembly and recovery of critical metals like Pt and Ir.

[79,80], while even routine laboratory handling of nanoparticle dispersions under fume hoods has been shown to elevate sub-60 nm particle counts by up to 10^5 cm^{-3} [81]. Wet processing reduces, but does not eliminate, airborne nanoparticle generation. Remarkably, no published study has yet addressed airborne Pt/C, IrO_2 or other similar catalysts during MEA manufacturing at industrial scale, leaving the primary exposure pathway essentially uncharacterized.

Similar gaps exist with respect to nanoparticles releases during operations. In particular, operando measurements in single-cell PEMWE systems have detected transient peaks of catalyst-derived material in water outlets during conditioning and load transitions [82–84]. In PEMWEs, post-mortem microscopy of degraded MEAs revealed metallic Ir deposits within the membrane bulk [85], confirming that catalyst material migrates beyond the electrode layer during operation. However, most of the existing analytical methods have been optimized for dissolved ionic species rather than for the detection and quantification of intact nanoparticles, leaving unresolved whether and to what extent free nanoparticles may be released. This distinction carries direct toxicological relevance, as the biological activity of particulate forms differs substantially from that of dissolved ions.

Quantitative evidence specifically from the electrochemical literature provides important context for assessing the magnitude of these release processes. Dissolution rates for iridium-based anodic catalysts under PEMWE operating conditions have been reported in the range of 0.1–10 ng $cm^{-2}h^{-1}$ under steady-state polarization, rising by one to two orders of magnitude during transient events such as start-up, shutdown, and load cycling [86,87]. Platinum-based cathodic catalysts in PEMFCs, dissolution is strongly potential-dependent and accelerated during voltage cycling, with cumulative Pt losses reaching several per cent of the initial loading over accelerated stress test protocols [88]. Critically, the propensity for dissolution and particle detachment varies significantly with catalyst architecture: unsupported IrO_2 nanoparticles exhibit higher mass-normalized dissolution rates than rutile-phase IrO_x or Ir-based mixed oxides, while carbon-supported Pt nanoparticles are more susceptible to Ostwald ripening and agglomeration than Pt deposited on corrosion-resistant supports such as TiO_2 or Nb-doped SnO_2 [86,89].

These architecture-dependent differences are directly relevant to SbD: catalyst formulations developed for improved electrochemical durability also represent, by design, lower-release options from a nanosafety perspective, reinforcing the alignment between performance and safety objectives that is central to the SbD framework proposed here.

Addressing the current knowledge gaps requires a coordinated research effort combining industrial hygiene monitoring during MEA manufacturing, standardized methods capable of distinguishing and quantifying particulate release versus dissolved metal species in water and effluents, and targeted toxicological studies on both pristine and transformation-product nanoparticles. Progress in these areas, supported by mechanistic frameworks linking physicochemical properties to biological outcomes, will provide the empirical foundation needed to refine the SbD approach and ensure that the scale-up of PEM-based hydrogen technologies proceeds on a sound nanosafety basis.

The safety-by-design: mitigation of nanotoxicity in PEMWEs and PEMFCs

For nano-enabled products, the SbD process typically starts with the assessment of risks by identifying physical–chemical drivers of potential hazards and by estimating the probability that nanoparticles will be released from the finished product. Details and guidelines are available in several documents, such as OECD series [44] and EU Commission publications [90], as well as recent SbD frameworks that explicitly link material functionality with safety during early-stage design [91].

The SbD approach is already routinely followed by the pharmaceutical and aerospace industries, two sectors which rely on the anticipation of all possible risks before pursuing the road for commercialization and mass-scale production. The SbD of a product has the advantage of reducing the costs of post-production management of risks (including the withdrawal of technology from the market) and minimizing potential harm during the life cycle of the product. In the field of nanomaterials, however, SbD is still evolving and largely implemented through conceptual and decision-support frameworks rather than standardized industrial practices [92,93].

In the context of hydrogen production and conversion by PEMWEs and PEMFCs one of the key aspects of SbD is the control of the size of the nano-electrocatalysts at the manufacturing stage (Table 1): size is the primary characteristic that makes these materials potentially harmful. Some authors have suggested setting the threshold of the transition from nano-specific to non-nano-specific effects at ~30 nm [94]. This threshold, however, should not be regarded as a clear boundary between toxic and non-toxic nanoparticles, since, as discussed later, size is not the sole factor influencing toxicity. It has been observed, however, that smaller nanoparticles, including those of Pt [95,96], often display increased toxicity, particle size remains a readily controllable parameter.

More broadly, the interplay between structure, composition, and surface properties governs both performance [97] and potential hazard, reinforcing the need for integrated SbD strategies [98,99]. This trade-off can be addressed by defining lower bounds on particle size (e.g., the ~30 nm mentioned before), avoiding ultra-small, highly reactive sizes, which increase surface reactivity, dissolution, and toxicity compared with larger particles. Similarly, immobilization of nanoparticles on carbon or alternative supports reduces the likelihood of particle release and exposure, but it may limit the fraction of accessible active surface; this can be compensated through support engineering (e.g., optimizing

porosity or surface functionalization) to preserve catalytic efficiency while minimizing release. Surface modification strategies provide an additional lever, as coatings or functional groups can reduce nanoparticle reactivity and dissolution rates, albeit sometimes at the expense of catalytic activity.

At this point we must emphasize that comprehensive and systematic studies of the toxicity of Pt, and of other PGM, nanoparticles do not exist; it will take decades to get such knowledge. Nonetheless, drivers of risks of these materials can be inferred from their characteristics, and from what is known about other types of nanoparticles. The challenge we are facing in this work is just the design of safe (or, as safe as possible) nanostructured electrocatalysts in a context of high uncertainty.

It has been observed, for example, that anisotropic, non-spherical Pt nanoparticles resulted more cytotoxic than spherical counterparts [100]. A further layer of complexity originates from the versatile behaviour of nanoparticles in biological environments, where their physical–chemical properties change due, for instance, to the adsorption of biomolecules, release of ions, aggregation and agglomeration. For example, the characteristic that makes Pt nanoparticles valuable in hydrogen technologies is their high surface reactivity, an essential property for catalysis but one that may also trigger harmful mechanisms. Biologically active species will interact with the surface of the nanoparticle, activating a cascade of events that include depletion of glutathione (an antioxidant), alteration of protein structure and functions (e.g., through cysteine bonding), and DNA damage [101]. Chemical composition of the surface represents another source of hazard. Pt nanoparticles are prone to be oxidized by exposure to oxygen: there are evidences that Pt(II) might be more toxic than Pt(0) [102]. Finally, biopersistence of Pt nanoparticles may cause accumulation in some organs, inducing a long term toxicity [103–105].

The complex nature of the interactions at the nano/bio interface is the reason why the toxicity of Pt nanoparticles, widely used in electrocatalysts in hydrogen technology, has not yet been thoroughly investigated, except for some preliminary eco-toxicological studies [27,98]. This lack of knowledge is a common trait in the assessment of risks every time a new type of nano-form comes under scrutiny, raising great uncertainty about their safety. In this case, hypotheses about sources of hazard can be formulated with the help of theoretical [106] or statistical models [107].

Experimental or theoretical, these hypotheses are the starting points that will inform the SbD steps to achieve "as-safe-as-possible" nano-enabled technology for hydrogen production and conversion. Hereafter, we present the SbD approach structured around four key steps: (i) defining the technical function of the nano-form, (ii) reducing the potential hazard of nano-electrocatalysts, (iii) minimizing the potential release of nanoparticles, and (iv) integrating safety measures from the manufacturing stage onward.

First step: the definition of the technical function of the nano-form in PEMWEs and PEMFCs

Fig. 4 shows the conceptual scheme of an SbD process for the design of nano-enabled electrodes. The process starts with the definition of the *technical function* of the nano-form, that is, the specific task that the nano-form must perform within the electrode.

For PEMWEs and PEMFCs, the nano-forms are the electrocatalysts, the units responsible respectively for the production of hydrogen driven by an external electrical potential and for the conversion of hydrogen into electricity. Because SbD may involve some modifications of the nanoelectrocatalysts, the preliminary analysis of their behaviour must include the identification of the physical–chemical characteristics that determine their technical function. This step is crucial in order to identify, among all the available redesigns, the one that reduces risks without modifying (or doing it minimally), the *physical–chemical determinants* of the technical function.

Let us observe that nano-electrochemists overlook this type of analysis when developing electrocatalysts. For nano-electrocatalysts, these determinants include *composition, size and electrical conductivity*. After the technical function of the nano-form has been analyzed, the following step is the identification of the suitable nano-forms. At the state of the art, we already discussed that PGMs supported over a carbon matrix are the most suitable for HER, ORR and HOR (especially Pt) and the unsupported IrO2 for the OER. We recall that studies of the multiple aspects of the toxicity of these nanoparticles are not yet available. It is

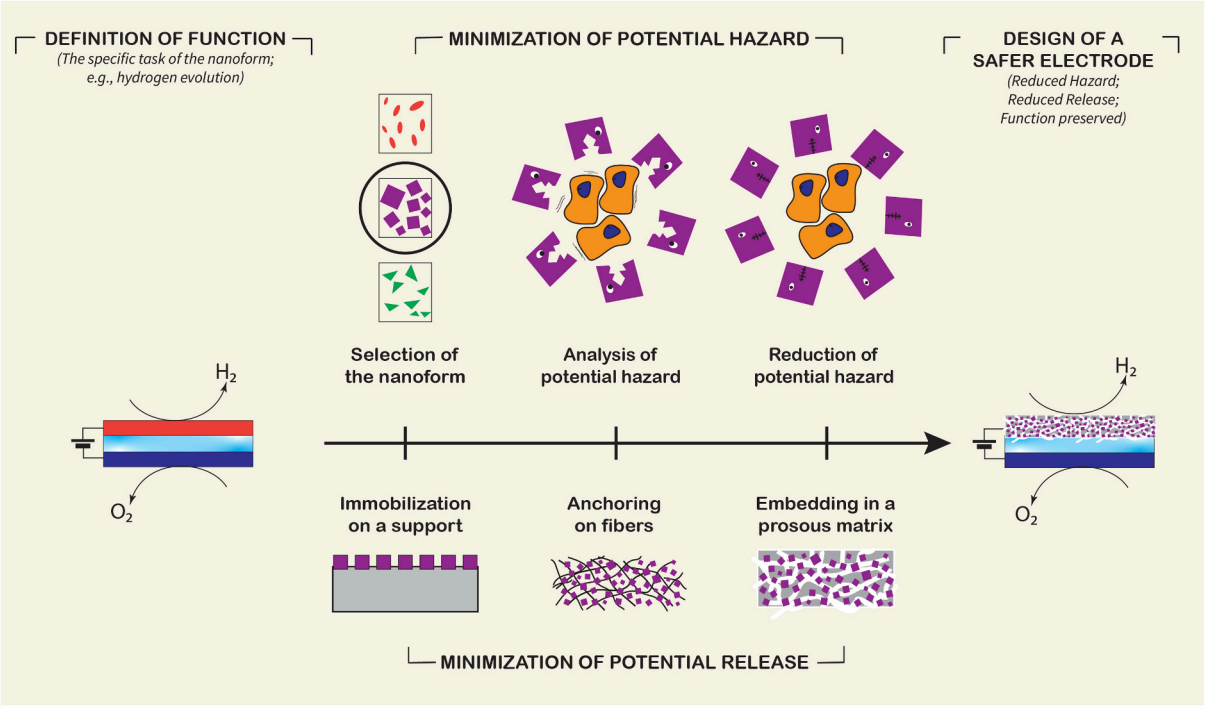


Fig. 4. The safety-by-design process for hydrogen production based on nano-enabled electrodes.

possible, however, to hypothesize hazardous mechanisms: whatever the uncertainty of these hypotheses, they are important because they represent the starting point of any process of control of toxicity.

It is well known that Pt decomposes hydrogen peroxide, a ubiquitous molecule in cells. This reaction generates, catalytically, oxygen-based radicals, the so-called Reactive Oxygen Species (ROS), that are extremely active and damaging. Production of radicals inside a cell can activate a variety of hazardous processes (e.g., oxidative stress) that, if not counterbalanced (e.g., by antioxidants), lead to diseases with different degrees of gravity.

Second step: reduction of the potential hazard of nano-electrocatalysts

It is important to recall that Pt-nanoparticles will not remain naked in a biological environment. Pt is extremely oxophilic; in addition, a series of sulfur-terminated molecules (e.g., glutathione, an antioxidant, or Cysteine, an amino acid) will chemisorb at the metal surface, together with other species, giving rise to what is often called the "bio-corona" [32]. It has been proposed that the complex nanoparticle/bio-corona should be considered as the real species responsible for observed toxicity in-vivo. The formation of this bio-chemical shell on the surface of the Pt nanoparticles will not prevent some catalytic processes from occurring. Nano-electrocatalyst larger than 30 nm should be less toxic than those smaller, which, in turn, result in more effective electrocatalysts for HER, ORR and HOR.

This observation implies that the development of safe nanotechnology may require sacrificing some efficiency, effectiveness and electrocatalytic activity to reduce potential damage of the nano-form. The specific requirements of nano-enabled electrocatalysis, however, fall in the range of sizes well below the threshold of 30 nm. In this case, the minimization of the release of nano-particles becomes crucial for reducing risks.

Third step: minimization of potential release of the nano-electrocatalysts

If it is guaranteed that the nano-electrocatalyst will not be able to leave the electrode (e.g. metal leaching or particle detachment) and reach a biological target, the risk would be negligible regardless of its hazard. Nevertheless, it is very difficult, and often impossible, to ensure that a nanoelectrocatalyst will never be released. For this reason, the design of a safe PEMWE and PEMFC must consider the minimization of the emission of active nanoparticles at any stage of their life cycle by engineering a strong and stable immobilization on the conductive matrix. In practical terms, this corresponds to several mitigation strategies currently explored in PEM technologies such as the development of more stable catalyst formulations (e.g., CuNiMo alloys) [108,109], structural optimization of ionomer distribution to suppress degradation [110], the use of advanced carbon supports or protective coatings to enhance catalyst anchoring [111], and the adoption of corrosion-resistant TiO_2-based supports that suppress Pt dissolution [112–115]: all act as examples of SbD implementation to reduce particle detachment, dissolution, and metals leaching. The choice of the conductive matrix is also critical [116,117]: the key factors that must be considered: i) the strength of adhesion of the nanoparticles (intuitively, the stronger the better) and ii) the rate of degradation, which, obviously, determines the probability of indirect release of nanoparticles [118–121]. These aspects are also crucial for anticipating risks of the after-life fate of the nano-enabled electrolyzers and fuel cells, and their final disposal.

However, while the previous strategies, taken individually, are technically effective, they have been developed primarily to improve performance and durability, rather than as part of an explicit SbD approach. In other words, they correspond to SbD principles ex post, but were not originally conceived within the structured SbD workflow illustrated in Fig. 4, which integrates hazard assessment, release minimization, and functional requirements into a unified design process.

Relying on ex post strategies leaves gaps in risk control, because potential hazards may only be addressed after they occur or are detected, making the release of nanoparticles less predictable and more difficult to manage systematically.

In contrast, formalizing these approaches under an SbD framework allows hazards, release minimisation, and functional requirements to be integrated from the outset, as explained in the following section.

Fourth step: safety-by-design starts at the manufacturing plant

At the state of the art, workers must be trained to recognise hazards related to chemical reactivity and material handling, to use personal protective equipment correctly, and to respond to emergencies. Personal protective equipment plays a central role, with the effectiveness of gloves, masks, and protective clothing depending strongly on their material and design [122–124] and nanoparticle-specific certification must account for particle size, charge, and environmental conditions like humidity [125,126]. Engineering controls further reduce exposure, relying on appropriate ventilation, containment systems, and equipment maintenance, particularly in environments where nanoparticles are produced or handled [127], supported by real-time air-quality monitoring and proper maintenance of protective systems [128].

Effective risk assessment requires applying the hierarchy of controls, prioritising elimination or substitution of hazards before relying on administration and PPE, while compliance with health and safety regulations and collaboration with regulatory bodies ensures alignment with evolving standards [129,130]. Health surveillance and environmental monitoring help identify early signs of exposure and ensure that concentrations remain within acceptable limits [131], enabling preventive actions such as upgrading PPE or improving ventilation [132]. Finally, strong hazard communication programmes ensure workers remain informed and protected [133], and detailed documentation of protocols, training, and incident reports supports continual safety improvement.

However, the previous measures operate by mitigating exposure after hazardous nanomaterials and processes have already been introduced into the manufacturing chain. SbD, instead, embeds risk reduction at the earliest stages by modifying material properties, selecting inherently safer chemistry, and redesigning processes to eliminate or minimise hazards at their source.

Therefore, while conventional approaches protect workers from existing hazards, SbD aims to prevent those hazards from arising in the first place, providing a more robust and sustainable route to worker protection.

As an example, to minimize the exposure of workers to nanoparticles in PEMWEs and PEMFCs construction, liquid formulations of nano-electrocatalyst (e.g., dispersions, liquid solutions, etc) should be preferred to dry powders. Powders linger in the atmosphere for a time related to their dustiness, making inhalation very likely to occur. Points of potential emission within the production chain should be identified to foresee adequate protection. Ideally, the entire production plant should be designed by considering the safety of workers and the environment surrounding the plant.

It would be very controversial to produce a technology for green hydrogen by endangering people and polluting the environment. This would also be a boomerang in terms of public consensus and social acceptance [134].

Conclusion and outlook

To translate the insights emerging from this perspective into implementation-oriented priorities, we summarize the key messages through a SWOT framework (Table 2), distinguishing internal technological factors from external deployment drivers across the PEM-based technologies lifecycle. This structured view highlights where nano-

Table 2
Strengths, weaknesses, opportunities, threats (SWOT) analyses internal technological factors (strengths/weaknesses) and external deployment drivers (opportunities/threats), supporting Safety-by-Design interventions in H_2 Technologies.

Strengths (internal enablers)	**Weaknesses** (internal gaps / limitations)
High catalytic performance enabled by nano-scale properties.	Toxicity is nanoform-specific and variable, limiting generalised safety measures.
Nanoform tunability (size, shape, surface) enables optimisation of activity and stability.	Hazard mechanisms on multiple interacting properties (e.g., size, morphology, surface chemistry, bio-corona formation).
Mature PEM-based electrode designs: porous conductive supports ensure good dispersion and mass transport.	Pre-manufacture risk assessment is difficult, especially during scale-up (limited exposure data).
Established MEA manufacturing chain supports reproducibility and scale-up.	Full embedding is not feasible because catalysts must remain exposed to the reaction environment.
Wide engineering toolbox (supports, coatings, architectures) to improve adhesion and durability.	Safety is not systematically integrated into design and fabrication practices.
Strong focus on performance and durability optimisation accelerates materials innovation.	PEMWE anode OER conditions promote degradation and potential dispersion or release.
Opportunities (external drivers & pathways)	**Threats** (external risks & barriers)
Safe-by-Design as a prevention strategy to reduce risks early, before scale-up and regulation.	Biological-scale hazard: nano sizes overlap with cell interfaces (membrane ~7 nm).
Modelling and experiments (e.g., molecular dynamics) can support safer nanoform design.	Aerosolization during handling: 1–10 nm particles can become airborne, posing inhalation risk.
Innovation in retention and immobilisation strategies (stable supports, coatings, embedding).	Lifecycle release persists: detachment or leaching during operation, accidents, and recycling.
EU/International nanosafety system supports collaboration, risk assessment, and standardisation.	Chemical co-exposures from inks (volatile solvents and binders).
Design-for-circularity to improve retention and recovery of critical metals at end-of-life.	Face increasing regulatory scrutiny (as occurring in fluoropolymers, e.g., Nafion).
Stakeholder-facing guidance to support implementation and scale-up decisions.	Social acceptance risk if occupational or environmental harm is perceived.

enabled electrocatalysts already deliver decisive advantages and where targeted SbD interventions are required to prevent risks from becoming barriers to scale-up.

Regarding the "Strengths" perspective, nanoparticles enable the high performance of PEM-based hydrogen technologies. Their tunable physicochemical properties and high surface reactivity support efficient electrocatalysis and reduced PGM loadings, while mature electrode architectures and established MEA manufacturing workflows provide a robust platform for scale-up and reproducibility.

In contrast, key "Weaknesses" reflect gaps in knowledge and practice rather than in performance. Safety is not yet treated as a design characteristic in electrodes and MEA development. Moreover, hazard characterization remains nanoparticle-specific and exposure quantification is limited under realistic manufacturing and scale-up conditions. As a result, risk management is often addressed ex post, rather than being integrated alongside durability and performance.

The main "Threats" are therefore systemic: as production volumes increase, any nanoparticle release pathway across the lifecycle (manufacturing, operation, recycling, and end-of-life) may translate into occupational and environmental exposure concerns. Even a limited or sporadic release could complicate authorization and market uptake due to potential regulatory reassessment, reduced public trust, and ultimately slowing deployment. These risks are further amplified by co-exposure issues linked to volatile solvents and fluoropolymer binders, which are receiving increasing attention in European policy discussions. Importantly, perceived harm may also reduce social acceptance and weaken public support for hydrogen infrastructures.

"Opportunities" arise from turning these weaknesses and threats into explicit engineering targets. SbD provides a practical workflow to integrate hazard assessment, release minimisation, and functional requirements from the outset, in line with international and European guidance. In this context, SbD can be operationalized as a constraint-based strategy, where performance, durability, and safety are co-optimized through material and process design choices. For PEMWEs/PEMFCs, the core opportunity is to develop "immobilisation strategies" that suppress detachment and leaching while preserving electrochemical accessibility.

Priority research directions include nanofroms immobilization approaches such as atomic layer deposition, physical vapour deposition, electrodeposition, catalyst embedding and hybrid support architectures. Crucially, immobilization must also combine conductivity, mechanical robustness, thermal tolerance, and corrosion resistance under relevant electrochemical conditions. Titanium felts, particularly when modified by anodization to create nanotubular surface structures, offer oxidative stability beyond conventional carbon supports [135–138]. In parallel, nanostructured thin films can improve catalyst adhesion in fuel cells while maintaining access to active sites [139].

Taken together, these advances represent tangible pathways to align durability and performance requirements already envisaged with risk prevention by design, supporting safer scale-up of nano-enabled hydrogen technologies.

To support implementation, the following actionable priorities emerge:

For researchers: develop and benchmark immobilization strategies under realistic operating conditions; establish robust structure–property–hazard relationships; and advance standardized methods for hazard and exposure assessment.

For industry practitioners: integrate SbD criteria into catalyst design, material selection, and manufacturing workflows, focusing on minimizing nanoparticle release while maintaining performance, durability, and scalability.

For policymakers and regulatory bodies: develop clear guidelines and harmonized testing protocols, and align SbD approaches with existing regulatory instruments (e.g., REACH and occupational safety directives) to enable safe scale-up and market uptake.

Successfully implementing these strategies will require close collaboration between material scientists, toxicologists, and policymakers to develop a regulatory framework that supports the safe development and commercialization of nano-enabled electrocatalysts.

This perspective raises the urgent need to integrate nanosafety as a core design and assessment priority, so that the benefits of nanotechnology in hydrogen production are delivered without avoidable occupational, health, or environmental consequences.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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