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Occupational Exposure to Engineered Nanomaterials: Pathways, Risk Assessment and Regulations

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ABSTRACT: Occupational exposure to engineered nanomaterials (ENMs) has emerged as a critical concern due to their unique physicochemical properties, which influence their behavior, bioavailability, and toxicity. This review synthesizes current knowledge on occupational exposure pathways, risk assessment strategies, regulatory frameworks, and key challenges associated with ENMs. Occupational exposure occurs predominantly during manufacturing and handling processes, with inhalation identified as the primary route, although dermal and incidental ingestion pathways are also relevant. Exposure characterization remains limited, particularly across the full lifecycle of nano-enabled products, as transformation processes such as dissolution, aggregation, and surface modification can alter exposure profiles. Advances in risk assessment have led to the development of control banding tools, Bayesian networks, weight-of-evidence frameworks, and computational models such as nano-quantitative structure–activity relationship (nano-QSAR) models. Grouping and read-across strategies have also been proposed to address data gaps and reduce testing requirements. However, these approaches remain constrained by insufficient standardized data, variability in dose metrics, and limited regulatory acceptance. Existing lifecycle–based decision support systems offer promising integrated frameworks but remain dependent on data availability and methodological harmonization. This review integrates occupational exposure pathways, emerging risk assessment methodologies, and regulatory developments into a unified lifecycle-oriented perspective. It further offers a critical perspective on how predictive modeling, grouping strategies, and safe-by-design concepts can collectively support preventive rather than reactive nanosafety governance. Despite regulatory progress in the European Union, the United States, and the Asia-Pacific regions, inconsistencies in definitions, data requirements, and nanospecific provisions continue to hinder global harmonization and effective risk management of ENMs.

KEYWORDS: Harmonization; inhalation; lifecycle; nanoparticles; occupational; toxicity

1. Introduction

Engineered nanomaterials (ENMs), typically defined as materials with at least one dimension in the range of 1–100 nm, have emerged as a cornerstone of modern technological innovation.

Their rapid development over the past two decades has been driven by their unique physicochemical properties, which differ fundamentally from their bulk counterparts [1]. ENMs are now widely utilized across a broad spectrum of industries, including electronics, energy, medicine, environmental remediation, and advanced manufacturing [2]. For example, metal and metal oxide nanoparticles, such as titanium dioxide and zinc oxide, are extensively used in coatings, catalysts, and personal care products, while carbon-based nanomaterials, such as carbon nanotubes and graphene, have revolutionized applications in electronics and composite materials [3,4]. This accelerated industrial expansion has led to a significant increase in the production, processing, and incorporation of ENMs into commercial products, thereby raising important questions regarding their safety, particularly in occupational settings where exposure is most likely to occur [5].

Occupational exposure to ENMs has become an increasingly relevant concern as workers represent the population with the highest and most consistent levels of contact with these materials [6]. Across various sectors, including nanomaterial synthesis, product manufacturing, healthcare applications, laboratory research, and waste management, workers may be exposed during multiple stages of the nanomaterial lifecycle (Figure 1). In manufacturing environments, exposure can occur during synthesis, handling, mixing, and packaging processes, particularly when operations involve open systems or generate aerosols (Figure 1) [7]. In research laboratories, scientists and technicians frequently handle ENMs in powder or suspension forms, often under conditions that may not fully replicate industrial safety controls [8]. The healthcare sector presents additional exposure scenarios, especially with the growing use of nanomaterials in drug delivery systems, imaging agents, and antimicrobial coatings [9].

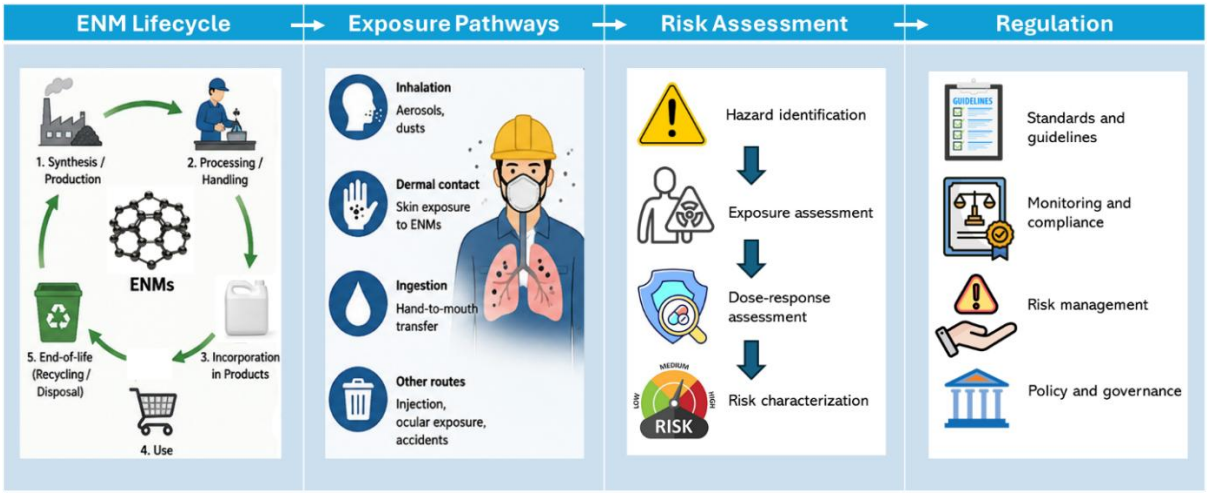

Figure 1. Lifecycle and safety management of ENMs.

Furthermore, as nanotechnology-enabled products reach the end of their lifecycle, workers involved in recycling, disposal, and waste treatment may encounter transformed or degraded nanomaterials. This introduces additional complexity to exposure scenarios [10]. An Italian study reported the detection of In_2O_3 nanoparticles in blood samples from employees at two companies, with a mean concentration of 10,371 particles/mL, absent in the control group [11]. Another study conducted in a laboratory setting found that workers were exposed to 0.046 $\mu g/m^3$ and 0.077 $\mu g/m^3$ of gold and silver nanoparticles during their synthesis, though the levels were below the respective occupational exposure limits [12]. Thanachoksawang et al. [13] highlighted that Fe nanoparticles are a major toxic metal constituent (79%) of welding fumes,

and the blood Fe concentrations of welders corresponded to their occupational exposure to Fe nanoparticles. These diverse and dynamic exposure contexts highlight the need for a comprehensive understanding of occupational risks associated with ENMs.

The unique properties that make ENMs highly valuable for industrial and technological applications are also central to their potential health risks. At the nanoscale, materials exhibit increased surface area-to-volume ratios, enhanced chemical reactivity, and novel optical, electrical, and mechanical properties [14]. These characteristics can influence how ENMs interact with biological systems. For instance, their small size facilitates deep penetration into the respiratory tract upon inhalation, enabling deposition in the alveolar region and potential translocation into systemic circulation [15, 16]. High surface reactivity may lead to the generation of reactive oxygen species, contributing to oxidative stress, inflammation, and cellular damage [17]. Additionally, surface functionalization, aggregation behavior, and solubility further modulate the biological interactions and toxicity profiles of ENMs [18]. Importantly, these properties are highly variable and dependent on material composition and environmental conditions, making it challenging to generalize findings across different types of nanomaterials [14, 18−20]. As a result, traditional paradigms in toxicology and exposure assessment, which are largely based on bulk materials, may not adequately capture the complexities of nanoscale materials.

Conventional occupational health frameworks face significant limitations when applied to ENMs (Figure 1). Existing exposure assessment strategies typically rely on mass concentration as the primary metric. However, for nanomaterials, metrics such as particle number concentration and surface area may be more relevant indicators of exposure and toxicity [21]. Similarly, established occupational exposure limits are often unavailable or insufficient for ENMs due to limited toxicological and epidemiological data [22].

Standard monitoring techniques may lack the sensitivity or specificity required to accurately detect and characterize nanoscale particles in workplace environments, particularly in the presence of background ultrafine particles [6]. Moreover, risk assessment approaches developed for conventional chemicals may not adequately account for the dynamic behavior, transformation, and complex interactions of ENMs in real-world settings [23]. These challenges are further compounded by the rapid pace of nanotechnology development, which often outstrips the evolution of regulatory frameworks and safety guidelines [24, 25].

In response to these challenges, there is a growing need for an integrated and critical evaluation of occupational exposure to ENMs that encompasses exposure pathways, risk assessment methodologies, and regulatory considerations. While a substantial body of research has been devoted to nanotoxicology and environmental impacts, the occupational dimension remains fragmented, with gaps in linking exposure scenarios to health outcomes and regulatory practices [2, 21, 26]. Furthermore, recent reviews focus primarily on the risks and toxicity of specific ENMs, such as silica and semiconductor nanomaterials [19, 27, 28]. Additionally, these reviews seem fragmented, covering regulations and risk assessment separately, which limits their applicability to real-world occupational risk management [29-31]. A comprehensive synthesis of current knowledge is therefore essential to inform evidence-based exposure, risk management, and policy development. It integrates diverse evidence into a coherent, critical, and application-oriented framework.

This review aims to address these needs by providing a structured and critical examination of occupational exposure to engineered nanomaterials. Specifically, it seeks to (i)

synthesize the major exposure pathways and scenarios encountered in workplace environments; (ii) evaluate existing risk assessment approaches, including their strengths, limitations, and emerging advancements tailored to nanomaterials; and (iii) critically examine current regulatory frameworks at international and regional levels, highlighting key gaps and challenges in their implementation. By integrating insights across these domains, this review intends to contribute to a more coherent understanding of occupational nanomaterial safety and to identify priority areas for future research, policy development, and industrial practice.

2. Review Methodology

This review adopts a narrative, integrative approach to synthesize current knowledge on occupational exposure to ENMs, with particular emphasis on exposure pathways, risk assessment strategies, and regulatory frameworks. Unlike systematic reviews that aim for exhaustive inclusion and quantitative aggregation, a narrative review is more suitable for this topic due to the heterogeneous, interdisciplinary, and rapidly evolving nature of the field, which encompasses diverse study designs, materials, exposure scenarios, and regulatory contexts.

A comprehensive literature search was conducted across major academic databases, including Web of Science, Scopus, and PubMed, to capture peer-reviewed journal articles, review papers, and relevant conference proceedings. The search covered publications from approximately 2016 to 2026. Keywords and Boolean combinations were developed to reflect the three core themes of the review: 1) Engineered nanomaterials OR nanoparticles OR nanotechnology; 2) Occupational exposure OR workplace exposure OR inhalation OR dermal exposure; 3) Risk assessment OR hazard identification; and 4) Regulation OR policy OR law.

Given the narrative nature of the review, flexible and purposive inclusion criteria were applied to ensure both breadth and relevance. Studies were selected based on:

a. Direct relevance to occupational exposure to ENMs, including experimental, field-based, modeling, and review studies;
b. Contribution to understanding exposure pathways, risk assessment methodologies, or regulatory frameworks; and
c. Scientific rigor and credibility, prioritizing peer-reviewed research articles and reports from recognized international organizations.

Studies on the toxicology of ENMs are excluded, as the review focuses on risk assessment methodologies rather than the specific toxicity of ENMs. While ENM toxicity is integral to their occupational risks, detailing their in vivo and in vitro toxicological responses across diverse organisms and cell types is beyond the scope of this review. A total of 259 articles were identified, of which 93 were included after screening based on the inclusion criteria. Rather than employing standardized data extraction forms typical of systematic reviews, this study utilized a thematic synthesis approach. Relevant information from selected studies was extracted and organized into key thematic categories aligned with the objectives of the review, namely exposure pathways, risk assessment approaches, regulatory frameworks, and challenges.

3. Occupational Exposure Pathways of Engineered Nanomaterials

Occupational exposure to ENMs is governed by a complex interplay of source and release mechanisms, transport processes within workplace environments, and primary routes of human

exposure [32, 33]. Evidence from real-world occupational settings consistently demonstrates that exposure is highly task-specific, influenced by material properties and process conditions, and often characterized by transient peaks rather than steady-state concentrations. This section synthesizes current knowledge on these interconnected components, integrating findings from field measurements, experimental studies, and epidemiological evidence.

3.1. Sources and release mechanisms.

ENMs may be released in occupational environments through both intentional production-related processes and unintentional or incidental activities. A substantial body of evidence indicates that handling, processing, and post-processing tasks are the dominant sources of release, rather than enclosed synthesis operations alone. A large-scale synthesis of 306 exposure situations across 72 workplaces demonstrated that potential exposure occurred in 233 cases, with particularly high frequencies for carbonaceous (83%), metallic (73%), and nanoclay (100%) materials [34]. Importantly, this study identified handling tasks as the most frequent source of exposure, with workers often encountering micro-sized agglomerates composed of nanoscale primary particles (Figure 2).

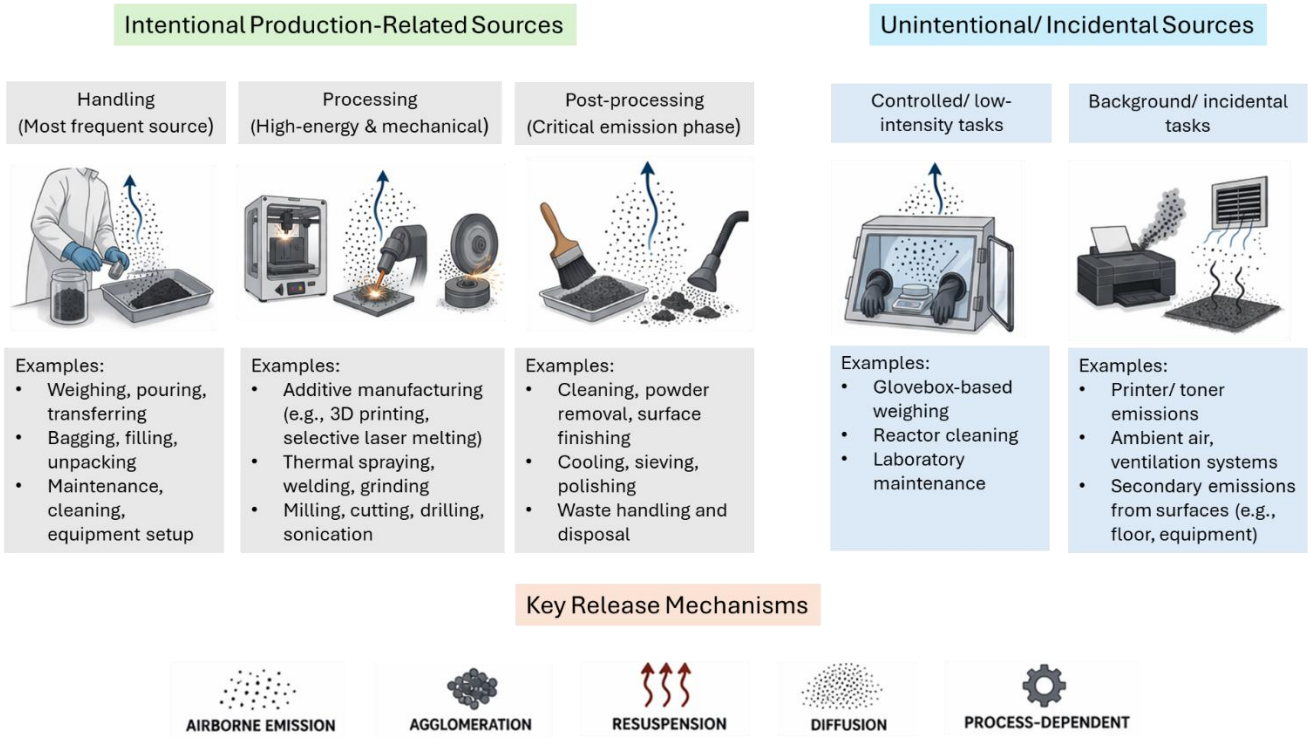

Figure 2. Sources and release mechanisms of engineered nanomaterials in occupational environments.

Real-world measurements further confirm that manual and mechanical processes are critical emission sources. For example, in additive manufacturing environments, the highest particle number concentrations were consistently observed during post-processing activities such as cleaning, powder removal, and finishing, rather than during the printing phase itself (Figure 2) [35,36]. In selective laser melting, concentrations reached up to 1.1×10^6 particles/cm³ during processing and remained elevated during cooling and post-processing, highlighting the persistence of emissions beyond active production [36]. Similarly, Jensen et al. [37] reported that chamber emptying, grinding, and powder removal significantly increased

particle concentrations above background levels, with particles predominantly in the nanoscale (Figure 2) (<200 nm).

High-energy industrial processes represent another major source of ENM release. Thermal spraying, welding, and grinding generate substantial quantities of nanoscale particles, often enriched in metals such as Ni, Cr, and W, with particle number concentrations exceeding 10^6 cm^{-3} (Figure 2) [38,39]. In metalworking environments, nanoparticle concentrations were more than 20-fold higher than in office settings, with ultrafine particles dominating number concentrations despite contributing minimally to mass [40]. These findings underscore the inadequacy of mass-based metrics for capturing nanoparticle exposure.

Unintentional release also occurs during seemingly controlled or low-intensity tasks. Even glovebox-based weighing of nanoparticles can generate detectable emission events, with particle number concentrations increasing threefold and peaks exceeding 3000 particles/cm^3 due to upward diffusion of ultrafine particles (~25 nm) (Figure 2) [41]. Similarly, short-lived emission spikes have been observed during routine laboratory activities such as reactor cleaning or equipment operation, even in well-controlled environments (Figure 2) [8].

The role of process design and engineering controls is critical in modulating release. Enclosed systems, ventilation, and material encapsulation can significantly reduce emissions, as demonstrated in nanocarbon layer production and 3D printing with polymer-bound nanomaterials, where particle concentrations remained near background levels [42]. However, localized emissions during maintenance or cleaning tasks persist even in controlled systems, highlighting the importance of task-based exposure assessment.

In addition to engineered processes, background and incidental sources contribute to nanoparticle presence in workplaces. Printing environments, for instance, exhibit elevated nanoparticle concentrations due to toner emissions, with peaks reaching ~500,000 particles/cm^3 and complex chemical compositions including organic carbon and trace metals (Figure 2) [43]. Ambient air, ventilation systems, and secondary emissions from materials such as carpets or office equipment also contribute to baseline nanoparticle levels [40].

Collectively, these findings demonstrate that ENM release is episodic, task-dependent, and influenced by both engineered and incidental sources, with manual handling and high-energy processes representing the most critical emission scenarios.

3.2. Transport in occupational settings.

Following release, ENMs undergo dynamic transport processes within workplace environments, which determine their spatial distribution, persistence, and eventual human exposure. Airborne transport is the dominant pathway, particularly for ultrafine particles that exhibit low settling velocities and can remain suspended for extended periods. Aerosol dynamics, including diffusion, coagulation, and agglomeration, play a central role in particle behavior. Studies report that ENMs are predominantly present as aggregates or agglomerates, often ranging from tens of nanometers to several micrometers [34, 42]. Agglomeration influences aerodynamic properties, deposition behavior, and biological interactions, complicating exposure assessment.

Workplace ventilation is a key determinant of nanoparticle transport and persistence. Poor ventilation can lead to prolonged airborne residence times, as demonstrated in laser cutting operations where inadequate airflow resulted in slow decay of particle concentrations and extended exposure durations [42]. Conversely, effective engineering controls such as fume

hoods, gloveboxes, and local exhaust ventilation can maintain particle concentrations near background levels [8,44]. However, even in controlled environments, short-term spikes during specific tasks may still occur, indicating that ventilation alone cannot eliminate exposure. Spatial variability in particle distribution is another important consideration. Studies have shown that particle concentrations can vary significantly between near-field and far-field locations, as well as vertically within the workspace. For example, in additive manufacturing environments, higher concentrations of smaller particles were detected near the floor, suggesting downward migration and accumulation despite ceiling-level ventilation [45]. Similarly, sensor positioning influences measured concentrations, with delayed but higher peaks observed in elevated positions due to upward diffusion [41].

Surface deposition and resuspension further contribute to exposure dynamics. Deposited particles on surfaces can be re-entrained into the air through human activity, cleaning, or mechanical disturbances, creating secondary exposure pathways [21]. This is particularly relevant in environments with frequent manual handling or inadequate housekeeping practices. Interactions with background aerosols and co-pollutants also influence transport behavior. In some cases, high background particle concentrations may promote coagulation, reducing the mobility of engineered nanoparticles [42]. However, mixed particle systems complicate exposure characterization and may alter toxicological outcomes. Overall, transport processes are highly dynamic and context-dependent, shaped by the interplay of particle properties, environmental conditions, and workplace practices. These processes ultimately determine the extent to which released ENMs contribute to worker exposure.

3.3. Exposure routes.

The primary routes of occupational exposure to ENMs are inhalation, dermal contact, and ingestion, with inhalation widely recognized as the dominant pathway. Evidence from both epidemiological and experimental studies highlights the central role of inhalation in determining health outcomes. Inhalation exposure occurs when airborne nanoparticles are deposited in the respiratory tract. Due to their small size, ENMs can penetrate deep into the alveolar region, where gas exchange occurs. Biomonitoring studies provide compelling evidence of this pathway. For instance, analysis of bronchoalveolar lavage samples from patients with lung diseases revealed that a majority (>50%) had a high probability of occupational exposure to unintentionally released nanoparticles, with particularly strong associations observed for idiopathic pulmonary fibrosis (88%) [46]. These findings suggest a potential link between inhaled nanoparticles and lung pathophysiology.

Occupational studies further confirm that inhalation is the primary exposure route in industrial settings. In metalworking and thermal spraying environments, high airborne concentrations of ultrafine particles result in substantial respiratory deposition, with up to 70% of inhaled particles depositing in the alveolar region [39]. Similarly, studies on child labor exposure in small-scale industries identified inhalation of industrial dust as the dominant exposure pathway, followed by ingestion and dermal contact [47].

Dermal exposure occurs through direct contact with nanomaterials or contaminated surfaces. While less extensively studied than inhalation, dermal exposure can be significant in tasks involving manual handling, particularly in the absence of protective equipment [48]. The extent of dermal uptake depends on particle properties and skin condition, with damaged or compromised skin increasing permeability [49].

Ingestion is generally considered a secondary pathway but can contribute to overall exposure, particularly through hand-to-mouth transfer. Behavioral studies have demonstrated that workers frequently engage in hand-to-mouth contact, with rates reaching 23.6 contacts per hour during non-task periods [50]. Such behaviors can facilitate the ingestion of nanoparticles deposited on hands or surfaces, especially in environments with poor hygiene practices.

Importantly, these exposure routes are interconnected. Airborne particles may deposit on surfaces, contributing to dermal and ingestion pathways, while resuspension can reintroduce particles into the air, sustaining inhalation exposure. The relative contribution of each route depends on workplace conditions, task characteristics, and individual behaviors. A summary of the exposure pathways is presented in Table 1.

Table 1. Occupational exposure pathways of engineered nanomaterials.

Study	Workplace/ Scenario	Source & Release Mechanisms	Transport Characteristics	Primary Exposure Routes	Key Findings
[46]	Clinical cohort (lung disease patients)	Unintentional release of airborne nanoparticles	Airborne dispersion leading to lung deposition	Inhalation	>50% of patients had high probability of exposure; strong link between inhaled nanoparticles and lung diseases (e.g., 88% in idiopathic pulmonary fibrosis)
[51]	Few-layers graphene & SiO_2 nanoparticle production	Production processes, handling, emissions during synthesis	Higher near-field concentrations vs background	Inhalation	Elevated particle number concentration and lung deposited surface area (LDSA) in production sites; exposure cannot be excluded despite controls
[40]	Office, metalworking, woodworking	Welding, grinding, polishing, office equipment	Metal industry shows highest airborne nanoparticle transport; ultrafine dominance	Inhalation	Metalworking had >20× higher particle concentration than office; nanoparticles dominate number but not mass
[38]	Office, metal, woodworking	Industrial processes (welding, grinding)	Broad particle distribution; high ultrafine fraction	Inhalation	Nanoparticles dominate number concentration; mass metrics underestimate exposure
[42]	Multiple nanotech workplaces	Laser cutting, cleaning, synthesis, manual handling	Poor ventilation prolongs airborne persistence; agglomerates form	Inhalation	Peak emissions up to 1.5×10^6 particles/cm³; manual tasks and poor ventilation increase risk
[36]	Additive manufacturing (Selective Laser Melding, Fused Deposition Modeling, Binder Jetting)	Printing, cooling, post-processing	Elevated airborne particles during all phases; temperature & ventilation influence transport	Inhalation	Selective Laser Melding had highest emissions (1.1×10^6 particles/cm³); post-processing critical exposure stage
[35]	Metal additive manufacturing	Cleaning, powder removal, post-processing	Localized peaks during manual tasks	Inhalation	Cleaning tasks produced highest emissions; worker proximity increases exposure
[37]	3D printing facility	Powder handling, grinding, chamber cleaning	Airborne dispersion of particles <200 nm	Inhalation	Grinding increased concentrations to 2.5×10^5 particles/cm³; post-processing key source
[41]	Glovebox nanoparticle weighing	Handling of nanopowders	Upward diffusion; spatial variability in concentration	Inhalation	Short emission peaks; particle size ~25 nm; LDSA increased significantly

Study	Workplace/ Scenario	Source & Release Mechanisms	Transport Characteristics	Primary Exposure Routes	Key Findings
[8]	Research laboratories	Cleaning, equipment operation	Controlled environments; low background with transient spikes	Inhalation	Overall low exposure; short-term peaks during specific tasks
[43]	Printing centers	Toner use, printing processes	Airborne nanoparticles with complex chemistry	Inhalation	Peaks up to 500,000 particles/cm³; significant exposure from nano-enabled products
[52]	Spray painting with Ag nanoparticles	Spray application	Aerosol droplets containing embedded nanoparticles	Inhalation	Low respirable Ag levels; exposure depends on ventilation and spray characteristics
[44]	Semiconductor facility	Chemical mechanical polishing	Well-controlled transport via ventilation	Inhalation	Low exposure due to engineering controls; nanoparticles detected as agglomerates
[45]	Additive manufacturing	Powder handling, cleaning	Downward migration; accumulation near floor	Inhalation	Peaks during cleaning (~16,000 particles/cm³); nanoscale particles present
[53]	Graphene-related materials	Handling, maintenance, cleaning	Mostly low airborne transport; localized spikes	Inhalation	Generally low exposure; spikes up to 460,000 particles/cm³ during cleaning
[50]	Multiple workplaces	Surface contamination, hand contact	Transfer via surfaces and objects	Ingestion	Hand-to-mouth contact up to 23.6 events/hour; significant ingestion pathway
[47]	Small-scale industries	Cutting, polishing, welding	Dust dispersion in poorly ventilated environments	Inhalation, ingestion, dermal	Inhalation primary route; high heavy metal accumulation in workers
[34]	72 workplaces (meta-analysis)	Handling tasks, secondary processes	Airborne agglomerates dominate	Inhalation	Exposure in 233/306 scenarios; engineering controls reduce exposure significantly

4. Risk Assessments of Engineered Nanomaterials

The risk assessment of ENMs has evolved into a complex, multidisciplinary field due to the unique physicochemical properties that distinguish nanomaterials from their bulk counterparts. These properties, such as high surface area, reactivity, and size-dependent behavior, introduce novel exposure pathways, toxicokinetic profiles, and biological interactions, thereby complicating conventional human health risk assessment (HRA) paradigms [54]. Consequently, a wide array of methodological frameworks has been developed to address uncertainties across hazard identification, exposure assessment, and risk characterization.

4.1. Conceptual foundations of nanomaterial risk assessment.

Risk assessment for ENMs fundamentally follows the classical paradigm where risk is a function of hazard and exposure [55]. However, this relationship is often expanded to incorporate additional parameters such as occurrence likelihood and toxic effects, as demonstrated in the Pythagorean Fuzzy Health Risk Assessment (PFHRA) model [54]. This approach integrates expert judgment through fuzzy logic and multi-criteria decision-making (PF-Analytic Hierarchy Process), allowing for nuanced evaluation under uncertainty. Application of PFHRA to Si and ZnO nanoparticles revealed predominantly major risk classifications for Si nanoparticle production and minor risks for ZnO nanoparticles,

highlighting material-specific variability in occupational risk profiles. Similarly, simplified risk banding approaches (Risk = Hazard × Exposure) provide practical tools for early-stage assessment [56]. Hazard scoring is based on intrinsic properties such as size, dissolution potential, and chemical composition, while exposure is estimated via source-to-receptor models incorporating process conditions, frequency, and handling. This framework underscores a critical insight: highly hazardous nanomaterials may pose low risk under controlled exposure, whereas less toxic materials can present significant risks under high exposure conditions.

4.2. Advanced modeling approaches: Bayesian and weight-of-evidence methods.

To address data gaps and uncertainty, probabilistic and data-driven approaches have gained prominence. Bayesian networks (BNs) and weight-of-evidence (WoE) frameworks enable integration of heterogeneous datasets, including physicochemical properties, toxicological data, and exposure scenarios [57]. Comparative studies show consistent hazard ranking of metal oxide ENMs (ZnO > Ag > TiO_2), although BNs demonstrate superior adaptability and predictive performance due to their capacity for self-learning. BN models further allow the incorporation of causal relationships between exposure routes, material properties, and biological effects [58]. Validation studies report prediction accuracies of approximately 70%, demonstrating their utility for supporting regulatory decision-making under uncertainty. In contrast, WoE approaches rely more heavily on structured expert judgment and iterative evidence integration, offering transparency but less adaptability [59]. The stability of WoE rankings may also be sensitive to variations in input assumptions and weighting criteria, resulting in lower robustness under stressed or incomplete datasets. Furthermore, WoE methods can be influenced by subjectivity in expert elicitation and evidence weighting, potentially affecting reproducibility and consistency across assessments [57, 60]. Consequently, while both BN and WoE approaches provide valuable tools for ENM risk assessment under uncertainty, their effectiveness remains strongly dependent on data quality, methodological standardization, and continuous updating as new nanosafety evidence emerges.

4.3. Computational nanotoxicology and predictive modeling.

The emergence of quantitative structure–activity relationship (QSAR) and Nano-QSAR models represents a significant advancement in predictive toxicology [61−63]. These models correlate physicochemical descriptors, such as particle size, surface charge, and enthalpy of formation, with biological effects, enabling in silico prediction of cytotoxicity. For instance, Nano-QSAR studies have identified key determinants of toxicity, including polarization force (Z/r) and cation formation enthalpy, which influence mechanisms such as oxidative stress and DNA damage [62]. Despite their promise, these models are constrained by limited, non-standardized datasets, hindering regulatory acceptance. Nevertheless, they provide valuable tools for screening and prioritizing nanomaterials for further testing and safer design.

4.4. Grouping and read-across approaches.

A major challenge in nanomaterial risk assessment is the vast diversity of nanoforms, making case-by-case testing impractical. To address this, grouping and read-across strategies have been developed to infer hazard based on similarity. The 2016 proposal by the European Chemicals

Agency, Joint Research Centre, and National Institute for Public Health and the Environment provides a structured framework for read-across of nanomaterials for relative risk assessment [64]. This approach is based on the principle that nanomaterials with similar physicochemical properties, such as composition, size, shape, surface chemistry, and dissolution behavior, will exhibit comparable toxicological profiles. The framework emphasizes 1) Identification of similarity criteria (e.g., surface reactivity, solubility, agglomeration state); 2) Use of multiple descriptors to define similarity domains; 3) Application of WoE approaches to justify read-across; 4) Consideration of toxicokinetics and exposure routes; and 5) Uncertainty analysis to ensure transparency and regulatory robustness.

This proposal supports relative risk ranking rather than absolute risk quantification, making it particularly useful in early-stage screening and prioritization. It also complements computational approaches such as Nano-QSAR and facilitates data-efficient risk assessment by reducing the need for extensive experimental testing. However, grouping and read-across approaches remain constrained by an incomplete understanding of the relationships between physicochemical properties and biological effects. Small variations in particle size, coating, crystallinity, or surface functionalization may substantially alter toxicity, limiting the reliability of similarity-based predictions [65]. Furthermore, the absence of universally accepted grouping criteria, cut-off values, and standardized descriptor sets creates challenges for reproducibility and regulatory acceptance. The predictive accuracy of read-across is also highly dependent on the availability of high-quality reference datasets that adequately capture the diversity of ENMs and exposure conditions [66].

Closely related is the DF4nanoGrouping framework, which classifies nanomaterials into four categories: soluble, high-aspect-ratio, passive, and active [67, 68]. This tiered approach integrates life-cycle considerations, biopersistence, and mode of action, enabling targeted testing strategies and efficient hazard identification. Nevertheless, the framework still relies partly on functional classifications rather than fully established mechanistic relationships between intrinsic material properties and apical toxic outcomes. In addition, some nanomaterials may exhibit overlapping or dynamic behaviors across categories due to environmental transformations, aggregation, or dissolution, complicating classification and reducing predictive certainty. Consequently, while grouping and read-across approaches substantially improve the efficiency of nanosafety assessment, further refinement, harmonization, and validation are required before they can fully support robust regulatory decision-making.

4.5. Control banding and screening-level tools.

Given the lack of established occupational exposure limits for many ENMs, control banding (CB) tools have emerged as practical risk management instruments [69]. These tools provide semi-quantitative or qualitative evaluations of risk by integrating hazard and exposure information into simplified frameworks, enabling decision-making even in data-poor contexts. It is fundamentally different from grouping, which is primarily a hazard/risk assessment strategy and involves classifying nanomaterials into categories based on shared properties [64]. The main purpose of CB is to manage risk by recommending appropriate control measures. CB tools typically classify ENMs into hazard bands based on intrinsic properties such as particle size, surface reactivity, solubility, and known toxicological effects. Exposure bands are derived from task-specific parameters, including material form (e.g., powders vs. suspensions),

quantity handled, frequency and duration of activities, and the presence of engineering controls [70]. The combination of hazard and exposure bands produces a risk level, which is linked to recommended control measures, ranging from general ventilation to containment and advanced personal protective equipment [26].

Widely used tools include the CB Nanotool, Stoffenmanager Nano, NanoSafer, and the ANSES framework, each differing in complexity and scope. For instance, Stoffenmanager Nano incorporates modifying factors such as ventilation efficiency and task duration, while NanoSafer is tailored for small and medium-sized enterprises (SMEs) and laboratory settings [69]. These tools are particularly valuable for early-stage risk screening, task-based assessments, and resource-limited environments, supporting proactive risk management and safe-by-design strategies. However, limitations remain. Variability in input parameters, scoring systems, and underlying assumptions across CB tools can lead to inconsistent risk classifications. Furthermore, their largely qualitative outputs restrict their direct application in regulatory contexts requiring quantitative risk estimates [71]. Despite these challenges, CB tools provide a pragmatic foundation for managing ENM-related risks, particularly when integrated with more advanced risk assessment methodologies.

4.6. Life-cycle and integrated risk assessment frameworks.

Traditional risk assessment often focuses on production stages, neglecting use and end-of-life phases. To address this, integrated tools such as the GUIDEnano (Guidance for Risk Assessment & Mitigation of Nano-enabled Products) Tool and Sustainable Nanotechnology Decision Support System (SUND) have been developed [23, 72]. These platforms enable life-cycle risk assessment, incorporating exposure, hazard, and socio-economic factors. The NANoREG framework further advances this approach by prioritizing nanomaterials based on key risk indicators (e.g., dissolution, bioaccumulation, genotoxicity) and promoting safe-by-design strategies [73]. Similarly, LICARA (Life Cycle Assessment and Risk Assessment of Nanoproducts) nanoSCAN supports early-stage innovation by comparing risks and benefits of nano-enabled products [74].

These frameworks highlight a paradigm shift from risk control to risk prevention, emphasizing early intervention in material design and process development. However, several limitations remain. Many life-cycle frameworks still rely heavily on simplified screening-level assessments and qualitative or semi-quantitative outputs, which may not fully capture the dynamic transformations of ENMs across the use, recycling, and disposal stages. Reliable implementation is also constrained by insufficient physicochemical, toxicological, and exposure data across the entire product life cycle, particularly for long-term environmental fate and end-of-life scenarios [75]. In addition, many frameworks require substantial assumptions regarding exposure conditions, release rates, and material behavior, introducing uncertainty into risk estimations. Tools, such as GUIDEnano, SUND, and LICARA nanoSCAN, also remain conceptual or insufficiently validated through large-scale industrial case studies, limiting their practical applicability and regulatory acceptance [74, 76]. Differences in input parameters, assessment criteria, and scoring systems among frameworks further complicate the comparison and harmonization of results. Furthermore, although these approaches promote safe-by-design and sustainability-oriented innovation, the integration of risk assessment into real-world industrial decision-making and product development workflows remains limited.

4.7. Toxicokinetics and dose metrics.

An important advancement in ENM risk assessment is the integration of toxicokinetic modeling, as demonstrated by Heringa et al. [77]. Their comparison of external dose-based and internal concentration-based approaches revealed that organ accumulation significantly alters risk estimates, underscoring the importance of considering absorption, distribution, and persistence. Moreover, ENMs require multiple dose metrics, including mass, particle number, and surface area, to accurately capture exposure and biological effects. This complexity is further reflected in frameworks for nanopesticides, which track multiple entities (e.g., nanoparticle, released ions, carrier systems) across different exposure stages [78]. The risk assessment approaches are summarized in Table 2.

Table 2. Summary of risk assessment approaches for engineered nanomaterials.

Approach/ Tool	Type	Core Principle	Key Inputs	Outputs	Strengths	Limitations	Ref.
CB Tools (e.g., CB Nanotool, Stoffenmanager Nano)	Qualitative/ semi-quantitative	Combines hazard and exposure bands to recommend controls	Material properties, task characteristics, exposure potential	Risk levels and control measures	Practical, user-friendly, suited for SMEs	Lack of standardization; qualitative outputs	[69]
Bayesian Networks (BNs)	Probabilistic/ quantitative	Uses probabilistic relationships between variables to predict hazard	Physicochemical data, exposure routes, biological effects	Hazard probability and toxicity predictions	Adaptive, handles uncertainty, integrates data	Requires large datasets; variable accuracy	[57]
Weight-of-Evidence	Semi-quantitative	Integrates multiple evidence streams using expert judgment	Experimental studies, literature data	Hazard ranking	Transparent, systematic	Subjectivity; less adaptive than BNs	[57]
Nano-QSAR Models	Computational/ predictive	Predict toxicity from structure–activity relationships	Physicochemical descriptors (size, charge, composition)	Cytotoxicity predictions	Reduces experimental needs; supports design	Limited datasets; regulatory acceptance low	[61-63]
Read-Across Approaches	Predictive/ grouping	Infers toxicity from similar nanomaterials	Physicochemical similarity metrics	Estimated hazard/ toxicity	Efficient; reduces testing burden	Requires robust similarity criteria	[61,64]
DF4nanoGrouping Framework	Tiered hazard grouping	Groups ENMs by mode of action and properties	Solubility, biopersistence, toxicity data	Classification into 4 groups (MG1–MG4)	Reduces testing; lifecycle perspective	Uncertain property–effect relationships	[67,68]
Organization for Economic Co-operation and Development (OECD) Tiered Approach	Tiered framework	Stepwise exposure and hazard assessment	Workplace exposure data, triggers for refinement	Progressive risk characterization	Structured and internationally recognized	Requires detailed standard operating procedures	[79]

Approach/ Tool	Type	Core Principle	Key Inputs	Outputs	Strengths	Limitations	Ref.
NANoREG Framework	Screening-level	Prioritizes nanospecific risks across lifecycle	Exposure, kinetics, hazard indicators	Risk prioritization and data needs	Comprehensive; integrates multiple tools	Limited validation; lacks cut-off values	[72,73]
SUNDS / GUIDEnano Tools	Integrated decision-support	Combines exposure, hazard, and socio-economic analysis	Lifecycle data, exposure scenarios	Quantitative risk + sustainability insights	Lifecycle perspective; decision support	Data-intensive	[23,72]
Risk Banding Framework (Inhalation)	Qualitative	Links deposition, lung burden, and toxicity	Particle size, deposition, clearance	Risk bands for inhalation exposure	Mechanistic basis	Limited to inhalation	[80]
LICARA nanoSCAN	Screening/ comparative	Compares risks and benefits vs. alternatives	Product data, exposure scenarios	Qualitative risk–benefit profile	Supports innovation decisions	Not regulatory-oriented	[74]
Nanopesticide Risk Framework	Tiered/ decision-tree	Tracks nano-specific transformations and exposure	Particle properties, transformation, exposure stage	Refined human health risk assessment	Integrates kinetics and lifecycle	Complex implementation	[78]
Toxicokinetic-Based Risk Assessment	Quantitative	Considers internal dose and accumulation	Absorption, distribution, organ concentrations	Organ-specific risk estimates	More realistic risk estimation	Data-intensive	[77]

4.8. Comparative analysis.

The various ENM risk assessment approaches differ substantially in their objectives, complexity, data requirements, and applicability. Broadly, these methods can be categorized into qualitative screening tools, probabilistic and computational models, grouping approaches, and integrated life-cycle frameworks. Each approach addresses different aspects of nanosafety assessment and therefore possesses distinct strengths and limitations. CB tools, such as CB Nanotool and Stoffenmanager Nano, are among the most practical approaches for occupational settings because they require relatively limited data and provide immediate recommendations for exposure control measures [26, 69, 70]. Their simplicity, accessibility, and suitability for SMEs make them valuable for early-stage risk management. However, their largely qualitative outputs and inconsistent scoring systems limit their regulatory applicability and predictive accuracy [71].

Probabilistic approaches, particularly BNs, provide a more advanced framework by integrating heterogeneous datasets and modeling causal relationships between physicochemical properties, exposure pathways, and biological effects [57, 58]. Compared with WoE approaches, BNs are more adaptive, data-driven, and capable of updating predictions as new evidence becomes available [57]. WoE methods offer greater transparency and systematic integration of evidence but are more dependent on expert judgment and therefore more susceptible to subjectivity and variability [59]. Computational methods such as Nano-QSAR models provide rapid in silico prediction of toxicity and support safer-by-design nanomaterial development [61−63]. These approaches reduce experimental burden and are

highly useful for prioritization and screening. However, their reliability remains constrained by limited standardized datasets and insufficient regulatory acceptance [61].

Grouping and read-across approaches, including DF4nanoGrouping, improve efficiency by reducing the need for extensive case-by-case testing [64,67,68]. These methods are particularly useful for early-stage hazard prioritization and regulatory screening. Nevertheless, they depend heavily on robust similarity criteria and high-quality reference datasets, while small changes in nanomaterial properties may substantially alter toxicity [64].

Integrated life-cycle frameworks such as GUIDEnano, SUNDS, and NANoREG provide the most comprehensive perspective by incorporating exposure, hazard, socio-economic factors, and safe-by-design principles across the entire lifecycle of nano-enabled products [23, 72, 73]. Unlike conventional approaches that focus mainly on production stages, these frameworks address use, recycling, and disposal phases, thereby offering a more holistic understanding of risk. However, they are highly data-intensive, methodologically complex, and still insufficiently validated for widespread industrial and regulatory implementation [72–74].

Overall, no single method is sufficient to comprehensively assess ENM risks because of the complexity and diversity of nanomaterials. However, among current approaches, integrated life-cycle frameworks combined with probabilistic Bayesian modeling appear to represent the most promising strategy. Bayesian approaches provide robust handling of uncertainty and adaptive predictive capability [57, 58], while lifecycle frameworks incorporate broader exposure scenarios, transformation processes, and sustainability considerations [23, 72]. When supplemented with Nano-QSAR, grouping/read-across, and practical CB tools for preliminary screening and workplace management [61–64, 67, 69], this integrated, multi-tiered strategy offers the most balanced, scientifically robust, and future-oriented approach to ENM risk assessment and governance. Figure 3 summarizes the comparison of the overarching risk assessment approaches.

Overarching Approach	Strength	Limitation	Example
CB Tools (Qualitative screening) 	✓ Low data requirements ✓ Immediate workplace recommendations ✓ Practical for small and medium-sized enterprises	❖ Qualitative outputs ❖ Inconsistent scoring ❖ Low predictive accuracy	CB Nanotool, Stoffenmanager Nano
Computational & Grouping (In silico/ read-across) 	✓ Rapid hazard prioritization ✓ Reduces animal/ experimental burden ✓ Supports safer-by-design	❖ Lack of standardized datasets ❖ Low regulatory acceptance ❖ Sensitivity to small property changes	Nano-QSAR, DF4nanoGrouping
Probabilistic Models (Advanced modeling) 	✓ Adaptive & data-driven ✓ Models complex causal relationships ✓ Handles uncertainty robustly	❖ Methodologically complex ❖ Requires heterogeneous data ❖ Higher computational expertise	Bayesian Networks
Integrated Frameworks (Lifecycle) 	✓ Holistic cradle-to-grave scope ✓ Includes socio-economic factors ✓ Addresses recycling/ disposal	❖ Highly data-intensive ❖ Insufficiently validated ❖ Complex industrial implementation	GUIDEnano, SUNDS, NANoREG
Multi-tiered Integration	Combine CB screening + predictive modeling + lifecycle frameworks for robust governance 		

Figure 3. Comparative strengths and limitations of overarching EMN risk assessment approaches.

5. Overview of Major Regulations for Engineered Nanomaterials

The regulation of ENMs has evolved into a multi-jurisdictional landscape, with major regions adopting distinct yet increasingly convergent approaches. While early frameworks relied on adapting conventional chemical regulations, recent developments reflect a transition toward nano-specific requirements, lifecycle-based assessment, and the integration of risk governance.

5.1. European Union (EU).

The EU remains the global leader in ENM regulation, characterized by a precautionary and highly structured approach. The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation has been progressively updated to explicitly address nanoforms, requiring detailed physicochemical characterization, exposure assessment, and nano-specific risk data (Figure 4). The introduction of nanoform-specific registration requirements under Regulation (EU) 2018/1881 marked a critical milestone, ensuring that different nanoforms of the same substance are assessed individually (Figure 4) [81]. Complementing REACH, the EU has advanced harmonized definitions of nanomaterials (updated in 2022), enabling consistency across regulatory sectors [82]. Sector-specific regulations, such as those governing cosmetics, food, and biocides, now incorporate nano-specific provisions, including pre-market authorization, labeling requirements, and restrictions on high-risk nanomaterials [78, 83, 84]. Furthermore, EU-funded initiatives such as GUIDEnano and SUNDS [23, 72] exemplify the integration of lifecycle-based risk assessment and socio-economic analysis into regulatory decision-making. These tools support the shift toward safe-by-design and sustainability-oriented governance, aligning with broader policy strategies such as the EU Chemicals Strategy for Sustainability.

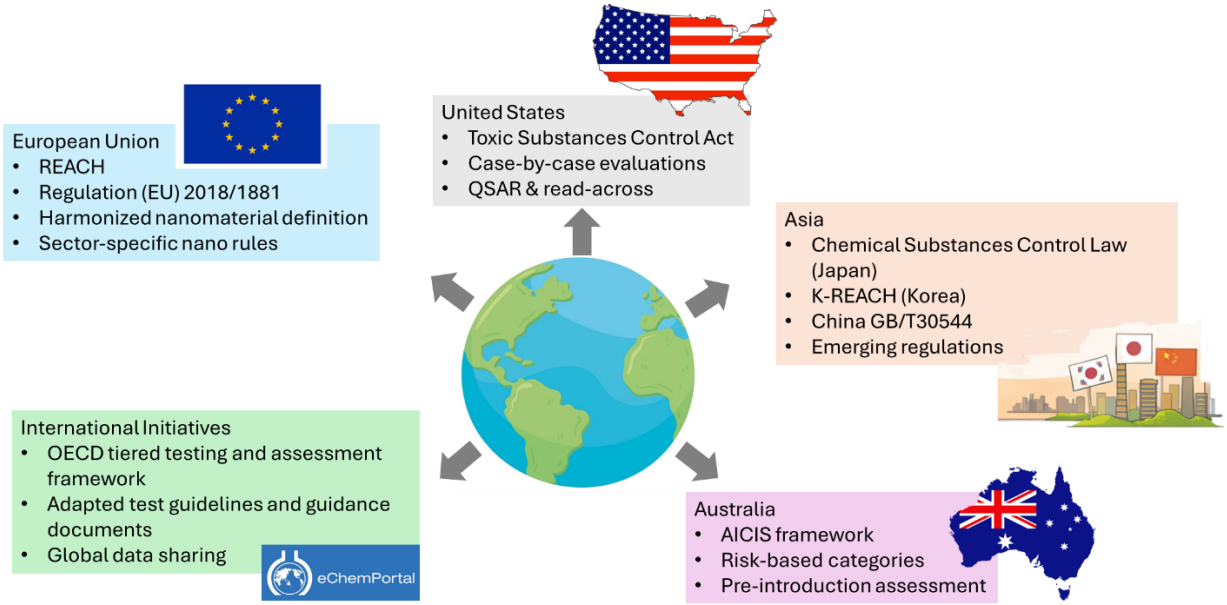

Figure 4. Major global regulations for engineered nanomaterials.

5.2. United States.

In contrast to the EU's precautionary model, the United States adopts a more risk-based and adaptive regulatory approach, primarily under the Toxic Substances Control Act (TSCA)

(Figure 4). The U.S. Environmental Protection Agency (EPA) regulates ENMs largely as chemical substances, with additional reporting requirements introduced through the TSCA Nanoscale Materials Rule. This rule mandates one-time reporting of production volume, manufacturing methods, exposure, and health effects for nanoscale materials [22, 85]. The U.S. framework emphasizes case-by-case evaluation, often relying on existing chemical risk assessment paradigms supplemented by emerging tools such as QSAR models and read-across approaches [61]. While this approach provides flexibility and supports innovation, it has been criticized for limited nano-specific provisions and reliance on post-market data generation.

5.3. Asia.

Regulatory development in Asia is rapid but heterogeneous, reflecting varying levels of industrialization and regulatory capacity. Countries such as Japan and South Korea have integrated nanomaterials into existing chemical management systems (e.g., Chemical Substances Control Law and K-REACH), with increasing emphasis on risk assessment, reporting, and workplace safety (Figure 4) [86, 87]. China has also made significant progress, incorporating nanomaterials into its chemical regulatory framework (e.g., GB/T30544.1) while promoting standardization and testing guidelines (Figure 4) [88]. However, across many Asian jurisdictions, ENM regulation remains largely embedded within conventional chemical legislation, with limited nano-specific requirements. This creates challenges in addressing nanoscale-specific risks, exposure pathways, and lifecycle impacts.

Compared with the EU, Asian regulatory frameworks are generally less precautionary and less harmonized. The EU has implemented comprehensive nano-specific provisions under REACH, including nanoform-specific registration requirements, harmonized definitions, pre-market authorization, and labeling obligations for certain sectors such as cosmetics and food [78, 81−84]. In contrast, most Asian countries continue to rely primarily on adaptations of existing chemical regulations, with fewer legally binding nanospecific assessment requirements and less extensive lifecycle-based governance.

Relative to the U.S., Asian approaches share a reliance on conventional chemical management frameworks and case-by-case assessment strategies [22, 85]. However, the U.S. EPA has introduced dedicated reporting obligations through the TSCA Nanoscale Materials Rule, requiring manufacturers to submit information on production, exposure, and health effects of nanoscale materials [85]. Such reporting systems are still less consistently implemented across many Asian jurisdictions. Overall, while Asia is advancing rapidly in nanomaterial governance, regulatory fragmentation, uneven technical capacity, and limited harmonization continue to constrain the development of comprehensive and consistent ENM oversight across the region.

5.4. Australia

Australia regulates ENMs primarily through the Australian Industrial Chemicals Introduction Scheme (AICIS) (Figure 4), which replaced the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). The framework applies a risk-based categorization system, where introductions are classified as exempted, reported, assessed, or commercial evaluation based on risk level [89]. Nanoforms are explicitly considered, particularly where they exhibit novel properties or increased bioavailability, and may trigger higher regulatory scrutiny. Australia emphasizes pre-introduction assessment and compliance, though nano-specific

guidance remains under development compared to EU standards [90]. Compared with the EU, Australia adopts a less precautionary and less prescriptive regulatory approach. While the EU REACH framework includes detailed nanoform-specific registration requirements, harmonized nanomaterial definitions, and sector-specific obligations such as labeling and pre-market authorization [81−84], Australia primarily integrates ENMs within its broader industrial chemicals management system. Consequently, Australia provides greater regulatory flexibility but fewer explicit nanospecific provisions and lifecycle-based governance mechanisms than the EU.

In comparison with the U.S., Australia shares a generally risk-based regulatory philosophy focused on case-by-case assessment and proportional oversight [22, 85]. However, Australia places greater emphasis on pre-introduction categorization and compliance through AICIS, whereas the U.S. TSCA framework has been criticized for a greater reliance on post-market data generation and comparatively limited pre-market nano-specific requirements [85]. Relative to many Asian jurisdictions, Australia's framework is generally more centralized and structured in explicitly recognizing nanoforms within chemical regulation [86−90]. Nevertheless, like several Asian countries, Australia still relies substantially on adaptations of conventional chemical legislation rather than on a fully dedicated ENM regulatory system. Generally, Australia occupies an intermediate regulatory position between the highly precautionary EU framework and the more adaptive, conventional chemical-based approaches adopted in the U.S. and many Asian countries.

5.5. International and multilateral initiatives.

At the global level, organizations such as the OECD have played a pivotal role in harmonizing ENM risk assessment. The OECD has developed a tiered testing and assessment framework, promoting standardized methodologies for exposure assessment, hazard characterization, and data sharing (Figure 4) [91]. In recent years, these efforts have been further strengthened through the activities of the OECD Working Party on Manufactured Nanomaterials, which has expanded guidance on physicochemical characterization, environmental fate, and toxicokinetics of nanomaterials. Notably, the OECD has advanced the adaptation of existing Test Guidelines (TGs) and Guidance Documents (GDs) to ensure their applicability to nanomaterials, including considerations for dispersion stability, dosimetry, and particle characterization throughout testing (Figure 4) [79].

In parallel, collaborative initiatives have advanced grouping and read-across strategies, enabling more efficient risk assessment by leveraging similarities among nanomaterials [65]. The proposal by European agencies for read-across in relative risk assessment represents a key step toward reducing testing burdens while maintaining scientific robustness [64]. Complementing these developments, the OECD has promoted the concept of "integrated approaches to testing and assessment" and the use of adverse outcome pathways to support mechanistic understanding and regulatory decision-making. Furthermore, the establishment of international databases and data-sharing platforms, such as the OECD eChemPortal, has facilitated transparency and accessibility of nanosafety data [92].

6. Current Challenges

The rapid expansion of ENMs across industrial, commercial, and consumer applications has exposed persistent and interrelated challenges in understanding exposure pathways, conducting robust risk assessments, and developing coherent regulatory frameworks. A central difficulty lies in the complexity and variability of exposure pathways, which depend heavily on material properties, process conditions, and workplace practices. Evidence from occupational settings consistently demonstrates that ENM release is often task-specific and episodic, with the highest emissions occurring during manual handling, cleaning, and post-processing activities rather than during controlled production phases [35, 36, 93].

Similarly, studies across additive manufacturing, metalworking, and nanomaterial synthesis environments show that particle number concentrations and lung-deposited surface area can increase significantly during high-energy processes or inadequate ventilation conditions, while remaining near background levels under enclosed or well-controlled systems [8, 41, 42]. These findings underscore the heterogeneous and transient nature of ENM emissions, complicating exposure characterization and hindering the establishment of representative exposure metrics.

A further challenge is the multi-route nature of exposure, encompassing inhalation, dermal contact, and ingestion. While inhalation remains the dominant pathway in occupational environments, particularly for ultrafine particles (<100 nm), behavioral factors such as hand-to-mouth contact significantly contribute to ingestion exposure [50]. Empirical evidence from industrial settings also indicates that inhalation of airborne particles is often the primary exposure route, followed by ingestion and dermal pathways, particularly in poorly controlled environments [47]. Importantly, the distinction between engineered and incidental nanoparticles remains blurred, as background sources (e.g., ambient air, combustion processes) frequently overlap with process-generated ENMs, complicating source apportionment and exposure attribution [40, 43]. This overlap challenges the development of standardized exposure assessment protocols and raises uncertainty about linking specific ENMs to observed health outcomes, as illustrated by biomonitoring studies that associate inhaled nanoparticles with respiratory diseases [46].

These exposure complexities directly translate into significant limitations in risk assessment methodologies. Traditional risk assessment paradigms, which rely on well-defined hazard and exposure data, are often inadequate for ENMs due to data gaps in toxicity, exposure, and long-term effects. Although simplified frameworks such as hazard–exposure banding [56] and CB tools [69] provide practical solutions, they inherently rely on qualitative or semi-quantitative inputs, limiting their precision and comparability. Advanced approaches, including BN and WoE models, offer improved capacity to integrate diverse datasets and expert judgment, yet their predictive accuracy remains variable and dependent on data quality [57]. Similarly, computational tools such as nano-QSAR models and read-across methods show promise in reducing experimental burdens and enabling predictive toxicology, but their broader application is constrained by the lack of standardized, high-quality datasets and limited regulatory acceptance [61-63].

Another critical challenge is the dynamic behavior and transformation of ENMs across their lifecycle, which complicates both exposure assessment and hazard characterization. Nanomaterials may undergo aggregation, dissolution, or surface modification, leading to changes in bioavailability and toxicity that are not captured by conventional assessments. This

has necessitated the development of more sophisticated frameworks, such as the nanopesticide risk assessment model, which explicitly accounts for multiple exposure-relevant species and transformation processes [78]. Likewise, toxicokinetic-based approaches demonstrate that internal dose metrics may yield substantially different risk estimates compared to external exposure-based assessments, highlighting the importance of incorporating absorption, distribution, and accumulation processes [77]. Despite these advances, integrating such complex dynamics into routine risk assessment remains a significant challenge.

Regulatory frameworks further reflect these scientific uncertainties and are characterized by fragmentation and limited nano-specific provisions. While jurisdictions such as the EU have made substantial progress by incorporating nanoform-specific requirements, harmonized definitions, and lifecycle considerations, many other regions, including the United States, Asia, and Australia, continue to regulate ENMs largely within existing chemical legislation [29, 73, 82, 86]. This results in inconsistent requirements, variable levels of precaution, and gaps in enforcement, particularly regarding nanospecific exposure limits and standardized testing protocols. Even within advanced frameworks, the lack of quantitative occupational exposure limits for most ENMs necessitates reliance on CB and precautionary approaches, reflecting the broader uncertainty in risk characterization [69].

Moreover, regulatory efforts are often constrained by insufficient data across the full lifecycle of ENMs, with most assessments focusing on production and occupational exposure while neglecting use-phase and end-of-life scenarios. Emerging tools such as GUIDEnano and SUNDS aim to address this gap by integrating exposure, hazard, and socio-economic considerations across the lifecycle [72], yet their effectiveness depends heavily on the availability of high-quality input data. The implementation of grouping and read-across strategies, as proposed by regulatory agencies, represents a promising pathway to improve efficiency and reduce testing burdens, but also introduces uncertainties related to material similarity and extrapolation [64]. Table 3 summarizes the key challenges, current solutions, and limitations to be addressed.

Table 3. Key challenges, current solutions, and limitations in the risk assessment and regulations of engineered nanomaterials.

Category	Key Challenges	Current Solutions	Remaining Limitations/ Research Needs
Data availability and quality	Limited toxicological and exposure datasets for ENMs; inconsistent experimental protocols; lack of validated databases	High-throughput screening, databases, read-across methods, Nano-QSAR models, OECD data-sharing initiatives	Need standardized, high-quality datasets and harmonized testing methods for reliable predictive modeling and regulatory acceptance
Hazard characterization	ENMs exhibit highly variable toxicity due to size, shape, surface chemistry, coating, dissolution, and aggregation behavior	BNs, WoE, QSAR, Nano-QSAR, DF4nanoGrouping frameworks	Poor mechanistic understanding of toxicity pathways; insufficient validation across diverse ENMs
Exposure assessment	Difficulty measuring nanoparticle exposure in workplaces; conventional mass-based metrics inadequate; lifecycle exposure poorly addressed	CB tools, source-to-receptor models, exposure banding, lifecycle assessment frameworks	Need standardized exposure metrics incorporating particle number, surface area, and transformation behavior

Risk assessment uncertainty	Limited toxicokinetic and epidemiological data; uncertainty in extrapolating from in vitro to in vivo effects	PFHRA, Bayesian models, probabilistic approaches, tiered assessment schemes	Greater integration of toxicokinetics, omics, and longitudinal health studies required
Lifecycle complexity	Exposure and transformation occur throughout synthesis, use, recycling, and disposal stages; many frameworks focus mainly on production stage	GUIDEnano, SUNDS, lifecycle-based risk assessment tools	End-of-life and consumer exposure remain underexplored
Regulatory adaptation	Conventional chemical regulations insufficient for nanospecific behavior and risks	Nano-specific REACH amendments, TSCA Nanoscale Materials Rule, K-REACH, AICIS	Many jurisdictions still rely heavily on conventional chemical frameworks without nano-specific provisions
Standardization and harmonization	Lack of globally harmonized definitions, testing protocols, and classification systems	OECD Test Guidelines, harmonized EU nanomaterial definitions, international guidance documents	Need globally unified regulatory standards and interoperable databases
Risk governance and policy integration	Fragmented linkage between science, regulation, and industrial practice	SUNDS, GUIDEnano, OECD integrated testing and assessment approaches	Need stronger integration of socio-economic analysis, sustainability, and governance
International regulatory differences	Regulatory approaches vary widely among regions (EU, U.S., Asia, Australia)	EU precautionary nano-specific regulations; U.S. adaptive risk-based approach; OECD harmonization efforts	Greater international coordination and mutual recognition needed
Regulatory implementation gaps	Many frameworks provide conceptual guidance but limited practical implementation pathways	NANoREG, SUNDS, LICARA nanoSCAN	Clear operational criteria, thresholds, and case-study validation are still needed

7. Conclusions

ENMs present complex challenges in exposure characterization, risk assessment, and regulatory governance due to their dynamic physicochemical properties and diverse applications. Exposure pathways remain difficult to quantify across the full lifecycle, particularly during product use and end-of-life stages, where data are scarce and transformation processes such as dissolution, aggregation, and corona formation alter bioavailability and toxicity. Existing occupational exposure assessments are often limited to production environments, and the lack of standardized metrics (mass, number, surface area) further complicates cross-study comparisons. Risk assessment frameworks for ENMs have advanced significantly, incorporating approaches such as control banding, BNs, nano-QSAR, and grouping/read-across methods to address data gaps. However, these approaches remain constrained by insufficient high-quality, harmonized datasets and limited validation for regulatory acceptance. While tools such as the SUNDS and GUIDEnano systems provide integrated, lifecycle–based assessments, their effectiveness remains dependent on data availability and consistent methodological assumptions. Similarly, regulatory frameworks across jurisdictions (e.g., EU REACH, U.S. TSCA) have incorporated nanospecific considerations, yet global harmonization remains limited, and many frameworks rely on

adaptations of conventional chemical risk assessment paradigms. Future research should prioritize generating standardized, high-quality datasets through coordinated international efforts to enable robust model development and validation. Greater emphasis is needed on lifecycle–wide exposure assessment, particularly for occupational pathways at the consumption and disposal stages, supported by advanced monitoring technologies and high-throughput screening. The integration of omics-based biomarkers into routine risk assessment holds promise for improving mechanistic understanding and predictive accuracy. In parallel, the development of universally accepted descriptors and dose metrics is essential to enhance comparability across studies. Regulatory progress will depend on the continued advancement of grouping and read-across methodologies, as well as the implementation of "safe-by-design" principles early in material development. Strengthening collaboration between academia, industry, and regulatory bodies will be critical to achieving a harmonized, science-based framework that ensures both innovation and safety in nanotechnology.

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Author Contribution

Conceptualization, methodology, and writing: K.H.D.T.

Competing Interest

There is no competing interest to declare.

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