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International Journal of Occupational Medicine and Environmental Health 2026;39(6)
https://doi.org/10.13075/ijomeh.1896.02877

OCCUPATIONAL EXPOSURE TO ENGINEERED NANOMATERIALS: BIOMONITORING EVIDENCE AND CHALLENGES FOR RISK INTERPRETATION

MAGDALENA MATYSIAK-KUCHAREK[1], KRZYSZTOF BOGUMIŁ SAWICKI[1], MARCIN KRUSZEWSKI[2], and LUCYNA KAPKA-SKRZYPCZAK[1,3]

[1] Institute of Rural Health, Lublin, Poland
Department of Molecular Biology and Translational Research
[2] Institute of Nuclear Chemistry and Technology, Warsaw, Poland
Centre for Radiobiology and Biological Dosimetry
[3] Calisia University, Kalisz, Poland
World Institute for Family Health

Highlights
- Biomonitoring studies show consistent biological responses to engineered nanomaterials.
- Observed biomarker changes are sensitive but largely non-specific.
- Exposure–response relationships remain unclear in occupational settings.
- Uncertainty limits interpretation of biomonitoring data.

Abstract
The increasing use of engineered nanomaterials (ENMs) in industrial settings has raised concerns about potential risks to workers' health; however, occupational risk assessment remains limited despite extensive toxicological evidence. This study aimed to systematically map epidemiological evidence based on biomonitoring data in workers exposed to ENMs and to identify key methodological limitations affecting the interpretation of these data. A scoping review was conducted in accordance with PRISMA-ScR guidelines and included 34 studies reporting biomarkers of exposure or early biological effects in occupational settings. The available evidence was highly heterogeneous, with most studies based on relatively small populations, cross-sectional designs, and variable approaches to exposure assessment. Biomonitoring findings consistently indicated biological responses, particularly related to oxidative stress and inflammation; however, the biomarkers used were generally sensitive but lacked exposure specificity. Overall, the reviewed evidence suggests that occupational biomonitoring provides important indications of biological activity in exposed workers but remains insufficient to establish robust exposure–response relationships or support quantitative occupational risk assessment. These limitations are primarily related to heterogeneous exposure assessment, incomplete exposure characterization, lack of standardized exposure metrics, and the predominance of non-specific biomarkers. To facilitate interpretation of these findings, a conceptual framework is proposed that highlights the main sources of uncertainty across the exposure–dose–effect pathway. Future progress in occupational risk assessment will require improved exposure characterization, more informative and validated biomarkers, and well-designed longitudinal studies. Int J Occup Med Environ Health. 2026;39(6)

Key words:
occupational exposure, biomonitoring, nanoparticles, uncertainty, risk assessment, oxidative stress

Conflict of interest: the authors declare no potential conflicts of interest related to the research, authorship, or publication of this article.
Funding: this work was supported by the Institute of Rural Health in Lublin, Poland, through statutory activity funding (project No. 24040, entitled "Prometastatic potential of silver nanoparticles in an *in vitro* model of A549 lung cancer cells" (2024–2026), project manager: Magdalena Matysiak-Kucharek).
Received: April 9, 2026. Accepted: October 10, 2026.
Corresponding author: Magdalena Matysiak-Kucharek, Institute of Rural Health, Department of Molecular Biology and Translational Research, Jaczewskiego 2, 20-090 Lublin, Poland (e-mail: matysiak.magdalena@imw.lublin.pl).

INTRODUCTION

The rapid development of nanotechnology over recent decades has led to the widespread use of engineered nanomaterials (ENMs) in numerous industrial sectors. However, their unique physicochemical properties, such as large surface area and increased reactivity, which drive their applications, also raise concerns about potential adverse effects on human health [1]. Occupational exposure is becoming increasingly important with the expansion of ENM production and use. Exposure may occur at multiple stages, including production, processing, use, and disposal, and depends on material properties, industrial processes, and workplace conditions[2]. Inhalation is generally considered the predominant route of exposure, although dermal contact and accidental ingestion are also possible [3]. Engineered nanomaterials can deposit in the respiratory tract, translocate across biological barriers, and distribute to secondary organs. However, the relationship between external exposure and internal dose remains poorly defined, limiting the establishment of exposure–response relationships in occupational settings [3–4].

Despite increasing toxicological evidence, a persistent gap remains between hazard identification and reliable occupational risk assessment for ENMs. While experimental studies indicate that ENMs may induce oxidative stress, inflammation, and other biological effects, translating these findings into real-world human risk remains challenging [5–7]. This limitation reflects insufficient exposure characterization, lack of standardized measurement methods, and limited epidemiological evidence, with available biomonitoring studies being heterogeneous, often based on small populations, and relying on largely non-specific biomarkers. Uncertainty arises at multiple stages of the exposure–dose–effect pathway from exposure assessment and internal dose estimation to the interpretation of biological effects and may propagate across the pathway, limiting the reliability of quantitative risk assessment [8–9].

Although these limitations are increasingly recognized, they are typically addressed within individual domains rather than as an integrated property of the entire pathway. Several conceptual approaches have been proposed to support chemical risk assessment, including adverse outcome pathways (AOPs) and uncertainty frameworks developed by European Food Safety Authority (EFSA) and Organisation for Economic Co-operation and Development (OECD). However, these approaches generally address individual components of the hazard-risk pathway and do not fully integrate empirical evidence from occupational exposure studies and human biomonitoring. In particular, they do not explicitly link biomonitoring-based epidemiological evidence with uncertainty arising at the exposure–dose interface, which represents a critical bottleneck for interpreting human data.

The aim of this study was to systematically map epidemiological evidence on occupational exposure to ENMs using a scoping review approach, with a particular focus on biomonitoring data, which represent the primary source of human evidence but remain difficult to interpret in a risk assessment context. In addition, exposure assessment methods were considered to provide context for interpreting this evidence, particularly in relation to methodological limitations and sources of uncertainty. The synthesis of the identified studies was used to examine recurring patterns in biological responses and key limitations affecting their interpretation across the exposure–dose–effect pathway. To support a structured interpretation of this heterogeneous evidence, a conceptual framework is outlined as a complementary tool that reflects the main sources of uncertainty identified in the reviewed studies. The framework should be understood as an interpretative aid rather than a standalone analytical or predictive model.

METHODS

Study design

This study was conducted as a scoping review, following the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [10]. The scoping review approach was chosen due to the heterogeneity of ENMs, exposure scenarios, and biomarker results reported in the literature.

Search strategy

A literature search was conducted in the PubMed and Web of Science databases. The search strategy included terms related to ENMs, occupational exposure, and biomonitoring. The search strategy was developed iteratively. Several combinations of keywords related to ENMs, occupational exposure, and biomarkers were evaluated during preliminary searches. The final search string was selected because it provided the most relevant and comprehensive retrieval of studies consistent with the objectives of the review while minimizing the number of irrelevant records.

The following search string was used: ("engineered nanomaterials" OR nanoparticles OR nanomaterials) AND ("occupational exposure" OR workplace OR workers OR "occupational setting" OR "occupational health") AND ("exposure assessment" OR biomarker* OR epidemiologist*)

The search strategy was adapted to the syntax of each database. No time limit was applied. Only peer-reviewed articles published in English were included. The search was conducted until February 2026.

Study selection

A total of 828 records were identified (Web of Science N = 469, PubMed N = 359). After removal of duplicates, 636 records remained and were screened based on titles and abstracts. Of these, 569 records were excluded after title/abstract screening.

Full texts of 67 articles were assessed for eligibility. At the full-text stage, 33 articles were excluded due to:

- lack of occupational exposure (N = 10),
- inclusion of incidental rather than ENMs (N = 11),
- absence of biomonitoring or health-related outcomes (N = 12).

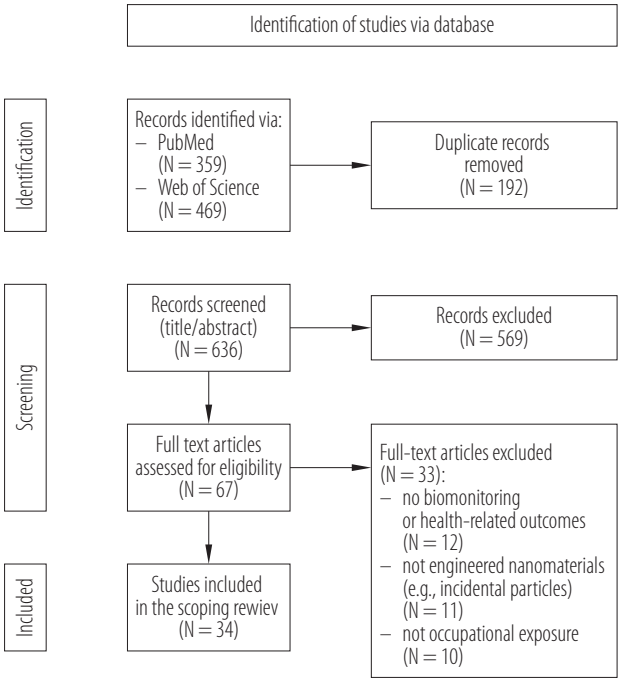


Figure 1. PRISMA flow diagram of the study selection process for the scoping review (publications from 2012–2025), covering studies conducted in Europe, Asia, North America, and Oceania

Two independent reviewers conducted the screening process. Discrepancies were resolved by consensus. The study selection process is presented in Figure 1.

Eligibility criteria

Studies were included if they:

- involved human participants in occupational settings,
- addressed exposure to ENMs,
- reported biomarkers of exposure or early biological effects.

Studies were excluded if they:

- were review articles,
- focused exclusively on *in vitro* or animal studies,
- did not involve occupational exposure scenarios,
- did not report biomonitoring or health-related outcomes,
- involved incidental ultrafine particles not clearly defined as ENMs.

Data extraction and synthesis

Data were extracted using a predefined data charting form. Extracted variables included study characteristics (author and year), type of ENM, exposure assessment approach, study population, biomarkers assessed, analytical methods, key findings, predominant biological domain, and primary interpretation. Exposure assessment methods were further categorized according to the level of exposure characterization reported in the original studies (quantitative, semi-quantitative, or qualitative) to support interpretation of biomonitoring findings in the context of the exposure–dose–effect pathway. The classification of occupational exposure assessment approaches was based on the level of exposure characterization reported in the original studies rather than on the specific sampling or analytical techniques used. Studies were classified as quantitative when exposure was assessed using direct workplace measurements reported as numerical exposure metrics (e.g., particle number concentration, mass concentration, or other quantitative exposure indicators). Semi-quantitative classification was assigned to studies relying on surrogate exposure metrics or structured exposure assessment approaches (e.g., control banding, cumulative exposure indices, or risk-level classifications). Qualitative classification was defined for studies in which exposure characterization was primarily descriptive and no quantitative exposure metrics were reported.

Due to substantial heterogeneity in exposure assessment methods, biomarker selection, and study design, a quantitative synthesis was not considered appropriate. Therefore, the results were synthesized descriptively, focusing on recurring patterns in biological responses and methodological limitations.

No formal assessment of the strength or quality of evidence was performed, in line with scoping review methodology. Instead, an interpretative qualitative categorization based on predefined criteria, including the consistency of findings, frequency of reported effects, biomarker specificity, exposure characterization, and key methodological characteristics, was applied to support structured synthesis and interpretation of the evidence. For the conceptual summary uncertainty levels were assigned qualitatively using these predefined criteria rather than a formal scoring system. Domains supported by more consistent findings, better exposure characterization, and greater biomarker specificity were assigned lower uncertainty, whereas domains characterized by limited evidence, methodological heterogeneity, or exploratory biomarker approaches were assigned higher uncertainty.

The conceptual framework was developed based on the synthesis of the identified evidence and methodological patterns observed across the included studies. It is intended as an interpretative conceptual representation of recurring patterns and sources of uncertainty, rather than a formal analytical or predictive model

Assessment of methodological limitations

In line with the scoping review methodology, a formal risk of bias assessment was not performed. However, selected methodological aspects relevant to the interpretation of the evidence were considered during data extraction and synthesis. These included study design characteristics, exposure assessment approaches, and consideration of potential confounding factors (e.g., smoking, co-exposures). Across the included studies, several recurring methodological features were observed. Many studies were conducted in relatively small and non-random occupational populations, often based on voluntary participation. Exposure assessment approaches varied across studies and included different workplace measurement strategies. However, detailed physicochemical characterization of nanomaterials was often lacking, and many exposure assessment methods had limited ability to distinguish ENMs from background particles. In addition, confounding factors were variably addressed, and cross-sectional designs predom-

Table 1. Measurement approaches for engineered nanomaterials (ENMs) in occupational settings and their implications for exposure–dose interpretation

Method category	Examples	Parameters measured	Strengths	Limitations	Key source of uncertainty for exposure–dose interpretation	Implication for risk assessment
Real-time monitoring	SMPS, CPC	particle number concentration, size distribution	high temporal resolution; identifies emission events and exposure patterns	no chemical composition; cannot distinguish ENMs from background particles	limited specificity due to background interference, uncertainty in attributing signals to ENMs	may lead to exposure misclassification; limited reliability for linking exposure to biological effects
Microscopy	TEM, SEM (with EDS)	morphology, structure, elemental composition	high specificity; direct identification of ENMs	labor-intensive; limited representativeness; no temporal resolution	high specificity but limited representativeness for overall exposure	confirms presence of ENMs but does not reflect exposure intensity or variability
Chemical analysis	ICP-MS	elemental content (mass concentration)	sensitive and quantitative; widely used for metal-based ENMs	cannot distinguish particulate vs. dissolved forms; limited particle information	uncertainty in linking measured mass to biologically effective dose	provides quantitative exposure estimates, but weak relevance for predicting biological responses
Surface area methods	BET, diffusion chargers	particle surface area	potentially more biologically relevant than mass	limited availability; lack of standardization	high variability and poor comparability across studies	promising metric, but limited by methodological inconsistency and low applicability

BET – Brunauer-Emmett-Teller surface area analysis; CPC – condensation particle counter; EDS – energy-dispersive X-ray spectroscopy; ICP-MS – inductively coupled plasma mass spectrometry; SEM – scanning electron microscopy; SMPS – scanning mobility particle sizer; TEM – transmission electron microscopy.

inated, limiting the assessment of temporal relationships between exposure and observed biological responses. These methodological characteristics were taken into account in the qualitative synthesis and interpretation of the evidence.

RESULTS

Measurement and characterization of ENMs in occupational settings

Assessment of occupational exposure to ENMs is methodologically complex, as no single measurement technique can fully capture the relevant characteristics of airborne particles. In practice, studies combine different approaches to obtain information on particle number, size, morphology, and, in some cases, chemical composition [2,9,11]. Measurement approaches used in occupational settings can be broadly grouped into three categories: real-time monitoring, microscopy-based techniques, and chemical analysis. Each of these captures a different aspect of exposure and provides only partial information, which has important implications for interpretation in a biological and risk assessment context (Table 1).

Real-time instruments, such as scanning mobility particle sizers (SMPS) and condensation particle counters (CPC), are commonly used to measure particle number concentration and size distribution. They are particularly useful for identifying emission events and temporal patterns of exposure. However, they do not provide information on particle composition and cannot distinguish ENMs from background ultrafine particles, which limits their specificity [9,12]. Micros-

copy-based methods, including transmission electron microscopy (TEM) and scanning electron microscopy (SEM), allow detailed characterization of particle morphology and structure. When combined with energy-dispersive spectroscopy (EDS), they also enable elemental identification. These techniques are valuable for confirming the presence of ENMs, but they are labor-intensive, require complex sample preparation, and do not provide information on exposure dynamics over time. Chemical analysis methods, such as inductively coupled plasma mass spectrometry (ICP-MS), are used to quantify elemental composition and are often applied to assess total metal content. However, these approaches do not distinguish between particulate and dissolved forms, which limits their relevance for understanding biologically effective exposure and linking external measurements to internal dose [11]

In occupational studies, exposure is therefore typically described using different exposure metrics, such as particle number concentration, mass concentration, or elemental content. These metrics are not interchangeable and reflect different aspects of exposure, which complicates comparisons across studies and limits their interpretation in a risk assessment context [9]. A key challenge is the lack of agreement on which metric best reflects biologically relevant exposure. Traditional measures, such as mass concentration, may not adequately capture nanoscale properties that drive biological interactions [13]. Alternative metrics, including particle number concentration and surface area, have been proposed as more relevant, but each has important limitations. For example, particle number concentration is strongly influenced by background ultrafine particles, while surface area measurements are not routinely available and lack standardization [9,14]. As a result, no single metric can be considered a reliable indicator for internal dose or biological effect [2,15]. This lack of standardization represents a major barrier to developing exposure–response relationships, as findings based on different metrics are difficult to compare.

From a biological perspective, these limitations translate into uncertainty in how exposure data should be interpreted. Individual measurement techniques provide fragmented and method-specific information, while the inability to clearly distinguish ENMs from background particles further complicates assessment. In addition, the absence of standardized measurement protocols contributes to variability across studies [9]. Taken together, current approaches provide incomplete representations of occupational exposure to ENMs. This directly affects dose estimation, as the relationship between external exposure and biologically effective dose remains poorly defined [13,15]. Consequently, exposure assessment does not yet provide a robust basis for quantitative exposure–response relationships or risk characterization.

These methodological limitations are directly reflected in epidemiological studies of occupational exposure to ENMs. As shown in Table 2, exposure assessment approaches varied considerably across studies and included both quantitative workplace measurements and semi-quantitative exposure classification approaches. However, despite the use of different exposure assessment strategies, detailed physicochemical characterization of ENMs was often limited, and many methods had restricted ability to distinguish ENMs from background particles. These limitations contribute to uncertainty in linking external exposure to internal dose and observed biological responses. Consequently, the interpretation of biomonitoring findings remains constrained by the limited specificity, comparability, and biological relevance of the exposure assessment approaches used across studies.

Epidemiological evidence of health effects in workers exposed to ENMs

Characteristics of included studies

Experimental studies indicate that ENMs can induce oxidative stress, inflammation, and other biological responses. However, translating these findings into real-world work

Table 2. Overview of epidemiological studies on occupational exposure to engineered nanomaterials (ENMs) using biomonitoring approaches, scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025[a]

Study	Country	ENMs	Exposure assessment/ characterization[b]	Population	Biomarkers assessed and analytical methods	Key findings	Predominant biological domain[c]	Primary interpretation
Shi et al., 2025 [16]	China	amorphous silica nanoparticles (Si NPs)	quantitative (workplace dust concentration measurements)	workers (N = 15), controls (N = 45)	metabolomics (LC-MS), lung function	↓ lung function; altered serum metabolomic profile	omics	suggests metabolic disruption and early functional effects, but interpretation remains exploratory
Squillacioti et al., 2024 [17]	Italy, Spain, Switzerland	mixed ENMs	quantitative (cumulative exposure based on direct workplace measurements)	workers (N = 136)	cytokines (EBC), lung function (spirometry)	↓ FEV_1 and $FEF_{25-75\%}$, altered inflammatory cytokines	inflammation	suggests an association between airway inflammation and impaired lung function, but causal relationships remain uncertain
Bonetta et al., 2023 [18]	Italy	pigment-grade TiO_2	quantitative (respirable dust and TiO_2 measurements)	workers (N = 15), controls (N = 20)	comet assay (±Fpg), buccal micronucleus assay, oxidative stress/inflammatory biomarkers	↑ direct and oxidative DNA damage; associations with oxidative stress and inflammatory biomarkers	DNA damage	supports early genotoxic effects associated with oxidative stress, although the specificity of the observed biomarkers remains limited
Hemmendinger et al., 2023 [19]	Switzerland, Spain, Italy	mixed ENMs	quantitative (PNC and LDSA measurements)	workers (N = 141)	EBC and urine biomarkers of inflammation and oxidative stress	↑ inflammatory cytokines (IL-10, IL-1β, TNF-α); ↓ urinary total antioxidant power	inflammation	suggests activation of the innate immune response, while evidence of oxidative stress remained limited
Bocca et al., 2023 [20]	Italy	metal ENPs	quantitative (SP-ICP-MS in blood and urine)	workers (N = 6), controls (N = 2)	metal ENPs in blood and urine (SP-ICP-MS)	detection of metal ENPs in biological samples, supporting internal exposure assessment	internal exposure/ biomonitoring	highlights the value of biological monitoring for investigating potential mechanisms, including oxidative stress

Table 2. Overview of epidemiological studies on occupational exposure to engineered nanomaterials (ENMs) using biomonitoring approaches, scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025[a] – cont.

Study	Country	ENMs	Exposure assessment/ characterization[b]	Population	Biomarkers assessed and analytical methods	Key findings	Predominant biological domain[c]	Primary interpretation
Bergamaschi et al., 2022 [21]	Italy	pigment-grade TiO_2	quantitative (air monitoring and biomonitoring)	workers (N = 15), controls (N = 20)	urinary Ti, oxidative stress and inflammatory biomarkers	↑ urinary Ti; ↑ MDA; altered inflammatory and lung injury biomarkers	oxidative stress	supports integrated biomonitoring of exposure and early biological effects associated with oxidative stress
Cavallo et al., 2022 [22]	Italy	graphene	quantitative (workplace particle number monitoring)	workers (N = 6), controls (N = 11)	BMCyt assay, Fpg-comet assay, urinary oxidative damage biomarkers	↓ micronucleus frequency; ↓ oxidative DNA damage after exposure mitigation	DNA damage	supports the reversibility of early biological effects following exposure reduction
Mostovenko et al., 2021 [23]	USA	CNT/F	quantitative (personal breathing zone measurements)	workers (N = 24)	serum peptidomics (mass spectrometry)	altered peptide profiles	omics	provides mechanistic insight into subclinical biological responses and supports the potential of peptidomics for biomonitoring
Chen et al., 2021a [24]	China	TiO_2 NPs	quantitative (airborne TiO_2 measurements)	workers (N = 56), controls (N = 44)	serum metabolomics	altered metabolic pathways	omics	indicates metabolic disruption, but interpretation remains exploratory
Chen et al., 2021b [25]	China	TiO_2 NPs	quantitative (mass concentration measurements)	workers (N = 66), controls (N = 66)	urine metabolomics (HPLC-MS)	altered urine metabolome	omics	consistent metabolic changes, but limited applicability for risk assessment
Wu et al., 2021 [26]	Taiwan	CNTs and metal oxide NPs (TiO_2 and SiO_2 NPs)	semi-quantitative (control banding risk level assessment)	workers (N = 80), controls (N = 69)	lipid peroxidation biomarkers (urine, EBC)	↑ lipid peroxidation biomarkers associated with occupational exposure	oxidative stress	supports oxidative stress as a central response mechanism

Pelclova et al., 2020 [27]	Czech Republic	nanocomposites	quantitative (direct workplace aerosol measurements)	workers (approx. 20)	oxidative stress biomarkers (EBC, plasma, urine)	persistent elevation of oxidative stress biomarkers across biological matrices	oxidative stress	consistent evidence across biological matrices, although biomarker specificity remains limited
Ursini et al., 2021 [28]	Italy	graphene and SiO_2 NPs	quantitative (PNC, LDSA and personal exposure monitoring)	workers (N = 12), controls (N = 11)	BMCyt assay, Fpg-comet assay, urinary oxidized DNA bases, cytokines	↑ DNA damage and inflammation	DNA damage/ inflammation	indicates early genotoxic and inflammatory responses, although confirmation in larger studies is needed
Ghosh et al., 2020 [29]	The Netherlands	MWCNTs	quantitative (air monitoring/elemental carbon measurements)	workers (N = 24), controls (N = 43)	telomere length, mtDNA copy number	↑ telomere length, mtDNA copy number	omics	suggests cellular adaptation, but unclear health relevance
Novotna et al., 2020 [30]	Czech Republic	nanocomposite materials	quantitative (air monitoring: BLPI, SMPS, APS)	workers (N = 20), controls (N = 21)	enzyme-modified comet assay (Fpg/Endo III)	↑ DNA damage; ↑ oxidized DNA bases	DNA damage	supports genotoxic potential, but based on limited populations
Rossnerova et al., 2020 [31]	Czech Republic	nanocomposite materials	quantitative (workplace aerosol monitoring, SMPS/APS)	workers (N = 20), controls (N = 20)	genome-wide DNA methylation (Infinium MethylationEPIC BeadChip [EPIC 850K] array)	altered DNA methylation profile following long-term exposure	omics	indicates epigenetic effects, but long-term relevance unclear
Schubauer-Berigan et al., 2020 [32]	USA	CNT/F	quantitative (personal EC and TEM-based structure count measurements)	workers (N = 102)	*ex vivo* stimulated cytokine response (TruCulture assay)	altered immune response	inflammation/ immune response	suggests altered immune responsiveness, although the clinical significance remains uncertain
Tang et al., 2020 [33]	China	CB NPs	quantitative (environmental air monitoring)	workers (N = 82), controls (N = 106)	endothelial activation assay, inflammatory mediators	↑ endothelial activation; ↑ inflammatory mediators	organ-specific (cardiovascular)	suggests endothelial activation associated with occupational exposure, although long-term clinical implications remain uncertain

Table 2. Overview of epidemiological studies on occupational exposure to engineered nanomaterials (ENMs) using biomonitoring approaches, scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025[a] – cont.

Study	Country	ENMs	Exposure assessment/ characterization[b]	Population	Biomarkers assessed and analytical methods	Key findings	Predominant biological domain[c]	Primary interpretation
Wu et al., 2019 [34]	Taiwan	ENMs	semi-quantitative (control banding-based exposure assessment using surrogate exposure metrics and risk-level classification)	workers (N = 206), controls (N = 108)	comet assay, micronucleus assay, oxidative stress, antioxidant, inflammation and cardiopulmonary biomarkers	↑ antioxidant enzyme activity (SOD, GPx); no significant changes in oxidative damage, inflammation or genotoxicity biomarkers	oxidative stress	suggests adaptive antioxidant responses rather than consistent adverse biological effects under the studied exposure conditions
Pelclova et al., 2018 [35]	Czech Republic	nanocomposite materials	quantitative (direct workplace measurements of particle mass and number concentrations)	workers (N = 20), controls (N = 21)	inflammatory markers (EBC), FENO, lung function (spirometry)	↑ airway inflammation (deep airways); ↓ lung function	inflammation/ functional	indicates airway inflammation and early functional impairment associated with occupational exposure, although based on a small study population
Beard et al., 2018 [36]	USA	CNT/F	quantitative (personal workplace exposure measurements)	workers (cross-sectional, N = 108)	MMP-2, MMP-9, TIMP-1, IL-18, GPx, SOD, 8-OHdG, ICAM-1, VCAM-1, vWF	altered inflammatory, oxidative stress and endothelial biomarkers associated with CNT/F exposure	inflammation	suggests early biological responses, although findings were not consistent across all biomarkers
Schubauer-Berigan et al., 2018 [37]	USA	CNT/F	quantitative (personal workplace exposure measurements)	workers (N = 108)	spirometry, CBC, blood pressure, resting heart rate, induced sputum	↑ respiratory allergies; ↑ resting heart rate; ↑ hematocrit; no consistent changes in lung function	functional/ systemic	suggests limited systemic responses associated with occupational CNT/F exposure, although most health measures were not associated with exposure
Kuijpers et al., 2018 [38]	The Netherlands	MWCNTs	quantitative (personal workplace exposure measurements)	workers (N = 22), controls (N = 42), follow-up: workers (N = 13), controls (N = 6)	endothelial markers (ICAM-1), cardiovascular markers (blood)	↑ ICAM-1; no consistent changes in other cardiovascular biomarkers	organ-specific (cardiovascular)	suggests endothelial activation associated with occupational MWCNT exposure, although evidence for broader cardiovascular effects remains limited

Zhao et al., 2018 [39]	China	nanoTiO_2	quantitative (direct workplace exposure assessment)	workers (N = 83), controls (N = 85)	SP-D, VCAM-1, ICAM-1, SOD, MDA, IL-8, IL-6, IL-1β, TNF-α, IL-10, spirometry	↓ lung function; ↑ SP-D; ↑ MDA; altered inflammatory and cardiovascular biomarkers	functional/ organ-specific	suggests cardiopulmonary effects associated with occupational exposure, although confirmation in longitudinal studies is needed
Ghosh et al., 2017 [40]	The Netherlands	MWCNT	quantitative (direct workplace EC measurements)	workers (N = 24), controls (N = 43)	global DNA methylation (LC-MS/MS), LINE-1, DNMT1, ATM, SKI, HDAC4 (bisulfite pyrosequencing)	no changes in global DNA methylation; altered gene-specific DNA methylation	omics	indicates gene-specific epigenetic alterations associated with occupational exposure, although their biological significance remains uncertain
Glass et al., 2017 [41]	Australia	ENPs	quantitative (personal particle number monitoring)	workers (N = 34), controls (N = 55)	cytokines (sCD40, sTNFR2, sCD62P), FeNO, CRP, blood counts, spirometry	↑ selected cytokines (sCD40, sTNFR2, sCD62P); no changes in FeNO, CRP, or lung function	inflammation	suggests selective inflammatory responses despite the absence of consistent changes in other clinical markers
Liou et al., 2017 [42]	Taiwan	metal oxide NMs	semi-quantitative (control banding/risk level matrix)	workers (N = 87), controls (N = 43)	global DNA methylation, urinary and WBC 8-OHdG, EBC 8-isoprostane	↓ global DNA methylation; ↑ 8-OHdG; ↑ 8-isoprostane	omics/oxidative stress	indicates epigenetic alterations and oxidative DNA damage associated with occupational exposure, although confirmation in longitudinal studies is needed
Vlaanderen et al., 2017 [43]	The Netherlands	MWCNTs	quantitative (personal breathing-zone monitoring)	workers (N = 22), controls (N = 39), follow-up: workers (N = 10), controls (N = 6)	CCL20, sIL-1RII, FGF-basic, CBC, FeNO, CC16, SP-A, SP-D, spirometry	altered immune markers; ↓ FeNO; changes in selected CBC parameters; no changes in lung function or pneumoproteins	inflammation	suggests early immune responses associated with occupational MWCNT exposure, although findings require confirmation in larger longitudinal studies

Table 2. Overview of epidemiological studies on occupational exposure to engineered nanomaterials (ENMs) using biomonitoring approaches, scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025[a] – cont.

Study	Country	ENMs	Exposure assessment/ characterization[b]	Population	Biomarkers assessed and analytical methods	Key findings	Predominant biological domain[c]	Primary interpretation
Pelclova et al., 2017 [44]	Czech Republic	nanoTiO_2	quantitative (real-time workplace particle monitoring)	workers (N = 34), controls (N = 45)	MDA, 4-HHE, 4-HNE, 8-isoprostane, C_6–C_{12} aldehydes (EBC, urine)	↑ lipid peroxidation markers in EBC	oxidative stress	supports airway oxidative stress associated with occupational TiO_2 exposure, although findings are based on cross-sectional biomonitoring
Pelclova et al., 2016a [45]	Czech Republic	nano iron oxide aerosol	quantitative (real-time workplace particle monitoring)	workers (N = 14), controls (N = 14)	MDA, 4-HHE, 4-HNE, 8-isoprostane, aldehydes C_6–C_{12}, 8-OHdG, 8-OHG, 5-OHMeU, o-tyrosine, 3-ClTyr, 3-NOTyr (EBC, urine, LC-MS/MS)	↑ oxidative stress biomarkers in EBC, no increase in urinary biomarkers	oxidative stress	supports airway oxidative stress associated with occupational exposure to iron oxide nanoparticles, although findings are based on a small cross-sectional study
Pelclova et al., 2016b [46]	Czech Republic	nanoTiO_2 pigment	quantitative (real-time workplace particle monitoring)	workers (N = 36), controls (N = 45)	8-OHdG, 8-OHG, 5-OHMeU, o-tyrosine, 3-ClTyr, 3-NOTyr (EBC, LC-MS/MS)	↑ oxidative DNA and protein damage biomarkers in EBC	DNA damage/ oxidative stress	supports oxidative molecular damage associated with occupational TiO_2 exposure, although findings are based on cross-sectional biomonitoring
Pelclova et al., 2016c [47]	Czech Republic	TiO_2 aerosol	quantitative (real-time workplace particle monitoring)	workers (N = 30), office employees (N = 22), controls (N = 45)	LTB_4, LTC_4, LTD_4, LTE_4 (EBC, urine, LC-ESI-MS/MS), FeNO, spirometry	↑ leukotrienes in EBC; no increase in urinary leukotrienes; limited changes in spirometry	inflammation	supports airway inflammation associated with occupational TiO_2 exposure, although findings are based on cross-sectional biomonitoring

Liou et al., 2012 [48]	Taiwan	ENMs	semi-quantitative (control banding/risk level matrix)	workers (N = 227), controls (N = 137)	SOD, GPx, fibrinogen, ICAM-1, IL-6	↓ SOD and GPx; ↑ fibrinogen, ICAM-1 and IL-6	oxidative stress/ inflammation	suggests altered antioxidant defenses and inflammatory responses associated with occupational nanomaterial exposure
Wu et al., 2014 [49]	Taiwan	NMs	semi-quantitative (control banding/risk level matrix)	workers (N = 241), controls (N = 196)	FeNO, NF-κB (EBC), spirometry	↑ FeNO (particularly in RL2 and nanoTiO_2-exposed workers), positive association with NF-κB	inflammation	suggests airway inflammation associated with occupational nanoparticle exposure, although exposure assessment relied on control banding

CB – carbon black; CNT/F – carbon nanotubes and nanofibers; EC – elemental carbon; ENPs – engineered nanoparticles; LDSA – lung-deposited surface area; MWCNTs – multi-walled carbon nanotubes; nanoTiO_2 – nanoscale titanium dioxide; NMs – nanomaterials; NPs – nanoparticles; PNC – particle number concentration; SiO_2 – silicon dioxide (silica); TiO_2 – titanium dioxide.
APS – aerodynamic particle sizer; BLPI – Berner low-pressure impactor; BMCyt – buccal micronucleus cytome assay; HPLC-MS – high-performance liquid chromatography–mass spectrometry; LC-ESI-MS/MS – liquid chromatography-electrospray ionization-tandem mass spectrometry; LC-MS – liquid chromatography-mass spectrometry; LC-MS/MS – liquid chromatography-tandem mass spectrometry; SMPS – scanning mobility particle sizer; SP-ICP-MS – single-particle inductively coupled plasma mass spectrometry; TEM – transmission electron microscopy.
3-ClTyr – 3-chlorotyrosine; 3-NOTyr – 3-nitrotyrosine; 4-HHE – 4-hydroxy-2-hexenal; 4-HNE – 4-hydroxy-2-nonenal; 5-OHMeU – 5-hydroxymethyluracil; 8-OHdG – 8-hydroxy-2′-deoxyguanosine; 8-OHG – 8-hydroxyguanosine; ATM – ATM serine/threonine kinase; CBC – complete blood count; CC16 – club cell secretory protein 16; CCL20 – C-C motif chemokine ligand 20; CRP – C-reactive protein; DNMT1 – DNA methyltransferase 1; EBC – exhaled breath condensate; Endo III – endonuclease III; $FEF_{25–75\%}$ – forced expiratory flow between 25% and 75% of forced vital capacity; FeNO – fractional exhaled nitric oxide; FEV_1 – forced expiratory volume in 1 s; FGF-basic – basic fibroblast growth factor; Fpg – formamidopyrimidine DNA glycosylase; GPx – glutathione peroxidase; HDAC4 – histone deacetylase 4; ICAM-1 – intercellular adhesion molecule 1; IL-1β – interleukin-1β; IL-6 – interleukin-6; IL-8 – interleukin-8; IL-10 – interleukin-10; IL-18 – interleukin-18; LINE-1 – long interspersed nuclear element 1; LTB_4 – leukotriene B_4; LTC_4 – leukotriene C_4; LTD_4 – leukotriene D_4; LTE_4 – leukotriene E_4; MDA – malondialdehyde; mtDNA – mitochondrial deoxyribonucleic acid; MMP-2 – matrix metalloproteinase 2; MMP-9 – matrix metalloproteinase 9; NF-κB – nuclear factor kappa B; sCD40 – soluble cluster of differentiation 40; sCD62P – soluble cluster of differentiation 62P (soluble P-selectin); sIL-1RII – soluble interleukin-1 receptor type II; SKI – Sloan-Kettering Institute proto-oncogene; SOD – superoxide dismutase; SP-A – surfactant protein A; SP-D – surfactant protein D; sTNFR2 – soluble tumor necrosis factor receptor 2; TIMP-1 – tissue inhibitor of metalloproteinases 1; TNF-α – tumor necrosis factor alpha; VCAM-1 – vascular cell adhesion molecule 1; vWF – von Willebrand factor; WBC – white blood cell count.

[a] All included studies investigated occupational inhalation exposure to engineered nanomaterials across different workplace settings. Therefore, exposure type is not presented separately for each study, as it was consistent across all included studies.

[b] Exposure assessment was classified according to the level of exposure characterization reported in the original studies. Quantitative assessment referred to studies using direct workplace exposure measurements, semi-quantitative assessment to studies using surrogate exposure metrics or structured exposure classification approaches (e.g., control banding), and qualitative assessment to studies with descriptive exposure characterization. No studies included in this review were classified as qualitative.

[c] The biological domain reflects the main biological effect reported in each study. When studies assessed more than one biological effect, they were classified according to the predominant finding. This classification was intended to facilitate comparison of the included studies and does not represent a formal assessment of evidence quality.

settings remains difficult, and epidemiological evidence regarding exposed workers remains limited. At the same time, available epidemiological studies provide an important empirical basis for assessing whether these experimentally observed mechanisms are reflected in occupational settings. The studies included in this review (Table 2) range from small exploratory studies to larger occupational cohorts and include various types of nanomaterials, including carbon nanotubes (CNTs), titanium dioxide nanoparticles, and mixed ENMs. Considerable variability is observed between studies in terms of sample size, exposure scenarios, and study design, with a predominance of cross-sectional approaches. In addition, substantial variability was observed in exposure assessment approaches, which included both quantitative workplace measurements and semi-quantitative exposure classification methods. The level of exposure characterization and reporting varied considerably between studies. Despite this variability, the overall body of evidence represents a coherent and informative dataset for evaluating early biological responses associated with occupational exposure to ENMs.

Overall, the evidence suggests relatively consistent indications that occupational exposure to ENMs is associated with detectable biological responses, primarily reflected in oxidative stress and inflammation, although the lack of specificity and standardized exposure metrics limits their interpretation in terms of exposure–response relationships. This limitation is further reinforced by the variability in exposure assessment approaches and the lack of standardized exposure metrics across studies (Table 2).

Biomarker responses and patterns of effects

The synthesis of the included studies indicates that the available evidence remains heterogeneous and constrained by study design, sample size, and exposure characterization. However, this heterogeneity likely reflects methodological differences rather than the absence of biological effects, particularly given the limited specificity and comparability of exposure assessment approaches.

Among the included studies (N = 34), 20 (59%) reported increases in biomarkers of oxidative stress or inflammation, while 12 (35%) showed mixed results. Only 1 study (3%) reported a decrease following exposure reduction, and 1 (3%) showed no clear effect. Most studies reported a biological response; however, these findings should be interpreted with caution due to heterogeneity, potential publication bias, and the limited specificity of the biomarkers used. Despite these limitations, the frequent observation of biological responses suggests a pattern of biological activation across diverse occupational settings, although this does not establish exposure–response relationships.

A consistent pattern across studies indicates activation of oxidative stress-related pathways, with responses varying in magnitude and specificity. Biomonitoring is largely based on non-specific markers of oxidative stress and inflammation, including malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), C-reactive protein (CRP), and pro-inflammatory cytokines (e.g., IL-6, TNF-α) [18,19,48]. Some studies also report organ-specific indicators of endothelial activation and lung injury, such as vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), club cell secretory protein 16 (CC16), and surfactant protein D (SP-D) [33,39]. These biomarkers provide sensitive indicators of early biological responses but lack specificity for ENM exposure.

Overall, biomarkers can be grouped into 3 categories:

– oxidative stress markers,
– inflammatory and immune markers,
– molecular or epigenetic indicators of cellular damage.

Their interpretative value reflects a trade-off between consistency and specificity: widely used markers provide reproducible signals but lack exposure specificity, whereas more specific markers remain insufficiently validated. Emerging approaches, including metabolomics, epigenetics, and mitochondrial markers, offer mechanistic insight but remain exploratory due to limited standardization and uncertain applicability [16,23,24].

Across studies, this trade-off results in a biomarker landscape characterized by high sensitivity but low specificity, limiting causal attribution to ENM exposure. This limitation is further compounded by the heterogeneity and limited standardization of exposure assessment metrics across studies. Nevertheless, the sensitivity of these markers allows detection of biologically relevant changes that may represent early stages of exposure-related effects.

Across the reviewed studies, oxidative stress was the most frequently reported biological response [27,34], together with markers of inflammation [17,43,47], molecular damage [18,28,30], and functional alterations affecting the respiratory and cardiovascular systems [33,38,39]. Although this pattern is broadly consistent with findings from experimental studies, the available epidemiological evidence does not allow firm conclusions regarding the temporal sequence or causal relationships between these biological responses. Their interpretation is further limited by uncertainty in exposure characterization, particularly at the exposure–dose interface, as well as by the predominance of cross-sectional study designs and the use of non-specific biomarkers.

Recent studies have introduced novel biomarkers, including metabolomic, peptidomic, and mitochondrial indices [16,23,24]. While these approaches provide additional mechanistic insight, their reproducibility and applicability remain limited. Some longitudinal and intervention studies suggest partial reversibility of biological responses following exposure reduction [22], supporting a potential exposure–related component.

To facilitate interpretation of heterogeneous evidence, a structured summary of key evidence domains is presented in Table 3. This categorization reflects consistency of findings, methodological characteristics, and levels of uncertainty across studies.

Taken together, the available evidence suggests that occupational exposure to ENMs may be associated with several commonly reported biological responses, including oxidative stress, inflammation, molecular damage, and functional alterations (Figure 2). Although these responses are broadly consistent with findings from experimental studies, the available epidemiological evidence does not allow firm conclusions regarding their temporal sequence or causal relationships.

Interpretation and limitations of biomonitoring evidence

Despite this apparent coherence, important limitations remain. Studies show substantial heterogeneity in exposure assessment, nanomaterial characterization, and biomarker selection. Exposure assessment approaches varied considerably across studies and included both quantitative workplace measurements and semi-quantitative exposure classification approaches. However, differences in exposure metrics, incomplete exposure characterization, and the predominance of cross-sectional study designs continue to limit causal inference and the interpretation of exposure–response relationships. Confounding factors, including smoking and co-exposures, were not consistently controlled, and commonly used biomarkers lack specificity for nanoparticle exposure [41,48].

A key limitation concerns the interpretative value of widely used biomarkers. Markers of oxidative stress and inflammation (e.g., MDA, 8-OHdG, CRP, cytokines) are inherently non-specific and influenced by multiple external factors. Consequently, observed differences between exposed and control groups cannot be unambiguously attributed to ENM exposure, even when consistent patterns are observed. Oxidative stress, should therefore be interpreted cautiously, as increased production of reactive oxygen species (ROS) reflects a general cellular response rather than an ENM-specific effect and does not directly indicate exposure intensity, internal dose, or clinical relevance. These markers should be understood as indicators of biological activity rather than direct evidence of adverse health effects.

These limitations constrain exposure–response interpretation. The use of non-specific biomarkers makes it diffi-

Table 3. Structured summary of uncertainty and frequency of reported effects across evidence domains in studies on occupational exposure to engineered nanomaterials (ENMs), scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025

Evidence domain	Typical characteristics	Level of uncertainty	Frequency of reported effects[a]	Interpretative confidence	Interpretation for exposure–response inference
Oxidative stress biomarkers	sensitive, widely used indicators (e.g., ROS, MDA, 8-OHdG)	moderate	>20 (very frequently reported)	moderate	provides the most consistent evidence of biological response across studies, but lacks specificity, limiting its value for exposure–response attribution
Inflammatory markers	cytokines, FeNO, and other indicators of immune response	moderate	10–20 (frequently reported)	moderate	supports inflammation as a recurrent downstream mechanism, although limited specificity constrains causal interpretation
DNA damage	comet assay, oxidative DNA lesions (e.g., 8-OHdG)	moderate	10–20 (frequently reported)	moderate-to-low	indicates potential molecular-level effects, but evidence remains heterogeneous and insufficient for robust exposure–response inference
Organ-specific biomarkers	endothelial and lung-specific markers (e.g., ICAM, VCAM, CC16, SP-D)	moderate-to-high	5–10 (occasionally reported)	moderate-to-low	offers greater mechanistic relevance, but limited consistency and validation reduce interpretative strength
Molecular/omics approaches	metabolomics, epigenetics, mitochondrial markers	high	<5 (rarely reported)	low	provides mechanistic insight, but currently lacks standardization and applicability for exposure–response assessment
Functional outcomes	lung function, cardiovascular parameters	moderate	10–20 (frequently reported)	moderate-to-low	represents clinically relevant endpoints, but is strongly influenced by confounding and does not allow clear attribution to ENM exposure

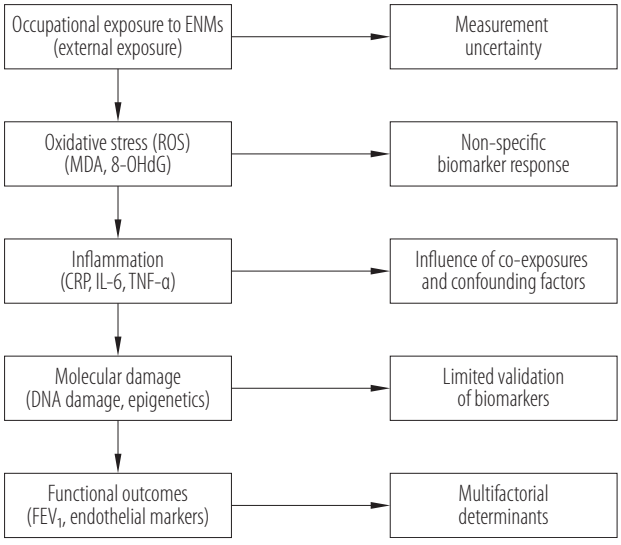
ROS – reactive oxygen species.
Other abbreviations as in Table 2.
[a] Frequency based on 34 included studies; categories are not mutually exclusive and reflect frequency of reporting rather than strength of evidence. Uncertainty levels reflect a qualitative assessment based on the consistency of findings, frequency of reported effects, biomarker specificity, exposure characterization, and methodological robustness across the included studies. They do not represent a formal quality assessment or risk-of-bias score.

cult to distinguish adaptive from adverse responses, while limited exposure characterization weakens the linkage between external exposure, internal dose, and health outcomes. As a result, biomonitoring data provide limited support for quantitative risk assessment but remain valuable for qualitative and mechanistic interpretation. Overall, these findings highlight the need for structured approaches to interpreting biomonitoring data under conditions of uncertainty. Key methodological characteristics and their implications are summarized in Table 4.

Risk assessment and uncertainty framework

Despite substantial advances in nanotoxicology, the authors' review demonstrates that translating human biomonitoring findings into occupational risk assessment remains challenging. The authors' synthesis identified three recurring sources of uncertainty that consistently limit the interpretation of occupational biomonitoring studies: heterogeneous exposure assessment, limited linkage between external exposure and internal dose, and the predominant use of non-specific biomarkers. The available studies are constrained by cross-sectional designs, relatively small populations, and the predominant use of non-specific biomarkers. Consequently, the reported biological responses should be interpreted primarily as indicators of biological activity rather than exposure-specific effects, limiting causal inference and quantitative exposure–response assessment. These observations are consistent with previous systematic reviews, which similarly concluded that the current occupational evidence base is dominated by heterogeneous exposure assessment, limited epidemiological data and insufficient integration between exposure characterization and biomonitoring [50,51].

Importantly, these limitations are interconnected. Rather than occurring independently, these sources of uncertainty accumulate across different stages of exposure assessment and biological response, reducing confidence in the interpretation of biomonitoring findings and limiting



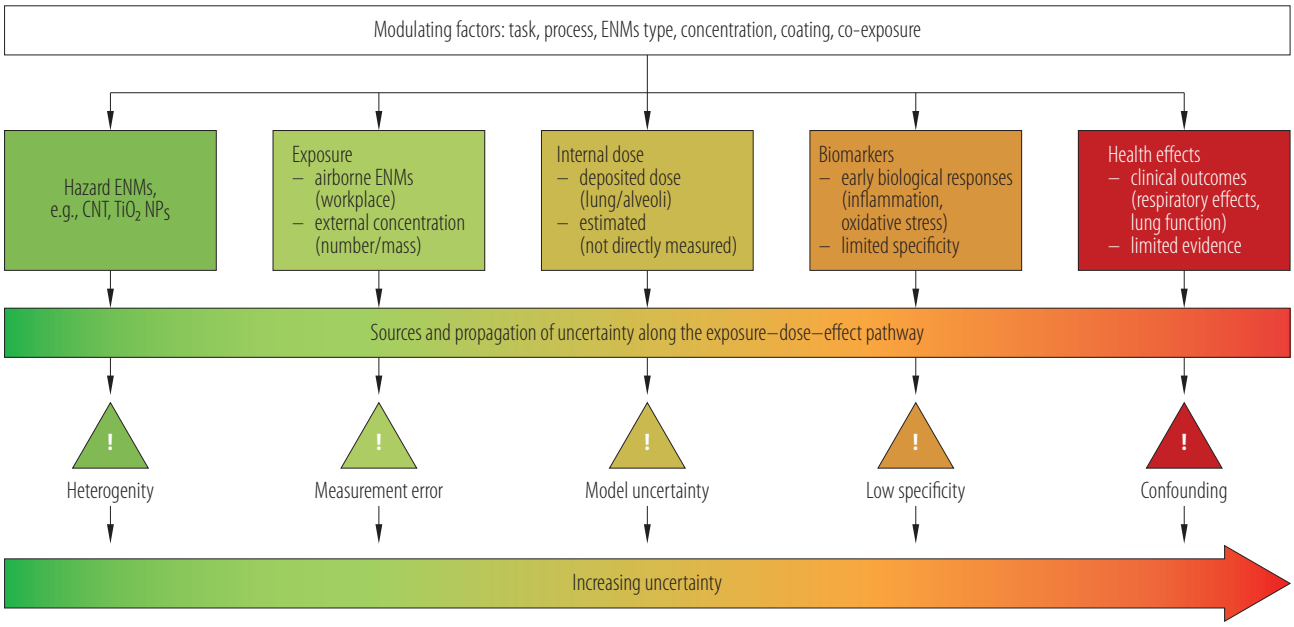
Abbreviations as in Table 2 and 3.

Figure 2. Conceptual representation of commonly reported biological responses associated with occupational exposure to engineered nanomaterials (ENMs), scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025

quantitative risk estimation. As a result, occupational risk assessment for ENMs often relies on qualitative or semi-quantitative approaches, including precautionary strategies [9]. The authors' findings therefore support the need for uncertainty-aware interpretation of occupational biomonitoring data. Based on the recurring patterns identified across the reviewed studies, we developed the conceptual framework presented in Figure 3. Previous reviews have highlighted several methodological and interpretative challenges in occupational biomonitoring of ENMs. Building on these observations, the framework proposed here integrates the recurring sources of uncertainty identified across the reviewed studies into a single conceptual framework for interpreting heterogeneous biomonitoring data. By making key sources of uncertainty explicit, it may facilitate weight-of-evidence approaches and improve the consistency of interpretation across studies, particularly in situations where exposure–response relationships are not well established [8].

Table 4. Structured summary of key methodological characteristics and biomonitoring-related features and their implications for interpretation of evidence in occupational engineered nanomaterials (ENM) studies, scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025

Domain	Empirical pattern observed across included studies	Frequency of occurrence across studies	Implications for interpretation of biomonitoring data
Study population characteristics	studies frequently conducted in relatively small occupational groups, often based on voluntary participation and specific workplace settings	frequently observed	may limit generalizability and introduce variability between study populations
Study design characteristics	predominance of cross-sectional designs, with limited longitudinal or intervention studies	frequently observed	limits assessment of temporal relationships and causal inference
Exposure assessment approaches	exposure commonly characterized using different exposure metrics (e.g., particle number, mass, elemental content), with limited physicochemical characterization and difficulty distinguishing ENMs from background particles	frequently observed	contributes to uncertainty in linking external exposure to internal dose
Consideration of confounding factors	inconsistent adjustment for key determinants such as smoking, co-exposures, and workplace variability	common	limits attribution of observed biological responses specifically to ENM exposure
Biomarker specificity	predominant use of non-specific biomarkers of oxidative stress and inflammation across studies	frequently observed	observed responses reflect general biological activity rather than exposure-specific effects
Consistency of biomarker responses	frequent reporting of increased oxidative stress and inflammatory markers across diverse exposure scenarios	frequently observed	suggests a consistent pattern of biological activation, but not necessarily specific to ENM exposure
Diversity of biomarker approaches	substantial variability in biomarker panels, including oxidative stress, inflammation, DNA damage, and emerging omics methods	common	limits comparability across studies and complicates integration of findings
Exposure–biomarker linkage	limited ability to relate biomarker changes to specific exposure metrics due to incomplete exposure characterization	frequently observed	weakens interpretation of exposure–response relationships
Temporal interpretation of biomarker responses	biomonitoring data largely derived from cross-sectional studies, with limited repeated or longitudinal measurements	frequently observed	prevents assessment of dynamics, reversibility, and causality of observed responses



Abbreviations as in Table 2.

Figure 3. Conceptual framework of occupational exposure to engineered nanomaterials (ENMs), integrating hazard, exposure, internal dose, biological responses, and health outcomes across the exposure–dose–effect continuum, scoping review of studies conducted in Europe, Asia, North America, and Oceania, 2012–2025

Regulatory implications and application of the framework

Current regulatory frameworks, including Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), EFSA and OECD guidance, provide a basis for chemical risk assessment but require exposure characterization and exposure–response relationships that remain insufficiently defined for ENMs [8,9,52]. The studies included in this review consistently showed that occupational biomonitoring provides evidence of biological responses, but these findings are difficult to translate into quantitative estimates of occupational risk. This reflects heterogeneous exposure assessment, limited information on the relationship between external exposure and internal dose, and the predominant use of non-specific biomarkers. Similar limitations have been highlighted in previous reviews of occupational studies [50,51]. As a result, risk management often relies on qualitative or precautionary approaches, including control banding [9]. The framework proposed in this study was developed from the common patterns identified across the reviewed studies. Rather than focusing on individual biomarkers or exposure metrics, it links the main sources of uncertainty to different stages of the exposure–dose–effect pathway, providing a structured approach for interpreting heterogeneous occupational biomonitoring data. Although the framework is not intended to predict risk or establish exposure limits, it may support more transparent and consistent interpretation of biomonitoring evidence, particularly where quantitative exposure–response relationships are lacking.

The findings of this review also point to several priorities for future research and regulatory practice. Biomarker development and validation remain essential, because the biomarkers most frequently used in occupational studies mainly reflect general biological responses rather than exposure-specific effects. Future studies should focus on biomarkers more closely related to internal dose and early adverse effects, while evaluating multi-marker approaches and emerging methods such as metabolomics and epi-

genetics under standardized study protocols. Study design and exposure characterization also require improvement since most available occupational studies remain cross-sectional and include relatively small populations. Longitudinal studies with improved exposure characterization and repeated biomonitoring measurements are needed to better understand temporal relationships and strengthen the evidence linking exposure, internal dose and biological responses. Greater attention should also be paid to major confounding factors, including smoking and co-exposures. Until exposure-specific biomarkers and stronger exposure–response evidence become available, occupational biomonitoring should primarily be interpreted as evidence of biological activity rather than direct evidence of health risk. Regulatory decisions should therefore explicitly consider the main sources of uncertainty identified in this review, while precautionary approaches remain appropriate in poorly characterized occupational settings. In this context, the proposed framework may assist weight-of-evidence evaluation by providing a structured interpretation of heterogeneous biomonitoring findings. Overall, the authors' review indicates that progress in occupational risk assessment of ENMs will depend on better exposure characterization, more informative biomarkers and well-designed longitudinal studies. The framework proposed here is intended to support interpretation of the available human evidence by explicitly identifying the major sources of uncertainty revealed by the reviewed studies.

Illustrative case study:
occupational exposure to carbon nanotubes

To illustrate how the patterns identified in this review may be interpreted in a specific occupational context, exposure to CNTs is presented as an example. Carbon nanotubes are among the most extensively studied ENMs in occupational settings and have been associated with potential respiratory and systemic effects. The aim of this illustrative case study is not to provide a comprehensive review of CNT toxicity, but to demonstrate how uncertainty can be identified and interpreted across the exposure–dose–effect pathway based on the types of evidence described in this review.

Stage 1: External exposure

In occupational environments, exposure to CNTs occurs primarily via inhalation during production, handling, or processing. However, exposure characterization remains challenging. Measurements are typically based on different exposure metrics such as particle number concentration, elemental carbon, or microscopy-based identification, each capturing only part of the exposure. Distinguishing CNTs from background ultrafine particles further contributes to uncertainty. These approaches nevertheless provide useful, albeit partial, information on exposure conditions.

Stage 2: Exposure-dose interface

The relationship between external exposure and internal dose remains poorly understood. Variability in physicochemical properties and limited knowledge of deposition, translocation, and clearance complicate dose estimation. The exposure–dose interface therefore represents a key source of uncertainty. This uncertainty reflects current knowledge gaps rather than the absence of exposure–dose relationships.

Stage 3: Biological response

Studies of CNT-exposed workers frequently report changes in biomarkers related to oxidative stress and inflammation, including lipid peroxidation products, pro-inflammatory cytokines, and markers of airway inflammation [26,43]. Evidence of oxidative DNA damage and alterations in mitochondrial or epigenetic markers has also been described [29]. While these findings are broadly consistent with experimental data, most biomarkers remain non-specific and may be influenced by confounding factors such as co-exposures or lifestyle variables. Consequently, they should be interpreted as indicators of biological activity rather than exposure-specific effects. Their

consistent alteration across studies nevertheless supports the presence of exposure-related biological responses.

Stage 4: Functional outcomes

Studies report functional changes, including reduced lung function and markers of endothelial activation, suggesting potential respiratory and cardiovascular involvement [37,38]. However, these findings are largely based on cross-sectional or small-scale studies, limiting causal inference. These observations are therefore indicative of potential effects but require confirmation in longitudinal studies.

This case study illustrates how uncertainty arises at multiple stages of the exposure–dose–effect pathway and propagates across it, and how these patterns can be interpreted within a specific occupational context. Uncertainty is particularly pronounced at the exposure assessment stage and at the exposure–dose interface, which constrains the interpretation of biomonitoring data and the establishment of exposure–response relationships. These uncertainties can be explicitly identified when the evidence is interpreted within the exposure–dose–effect framework described above. This example reflects the types of limitations and uncertainty patterns consistently observed across the reviewed biomonitoring studies. In practical terms, this implies that biomarker changes observed in CNT-exposed workers should be interpreted with caution and in conjunction with exposure context, rather than as direct indicators of risk. These observations are consistent with the broader pattern identified across the studies summarized in Table 2.

Limitations

This study has several limitations. As a scoping review, it does not include quantitative synthesis or formal assessment of the strength or quality of evidence. However, this approach is appropriate given the heterogeneity of the available studies and allows for a comprehensive mapping of the evidence base, as well as structured interpretation of heterogeneous findings. The analysis was limited to epidemiological studies reporting biomonitoring data in occupational settings, which does not fully capture experimental and toxicological evidence. At the same time, this focus enables direct assessment of human data, which is particularly relevant for the interpretation of occupational exposure. The included studies are heterogeneous in terms of exposure assessment, nanomaterial characteristics, and biomarker selection, which limits comparability across studies. Furthermore, although the search strategy was developed iteratively and several keyword combinations were evaluated during the preliminary search, the heterogeneous terminology used in the field of occupational biomonitoring of ENMs may have resulted in the omission of some relevant studies employing alternative terminology. This represents an inherent limitation of the present scoping review. Most studies are based on cross-sectional designs and relatively small populations, restricting causal inference and the assessment of temporal relationships. In addition, commonly used biomarkers of oxidative stress and inflammation lack specificity and may be influenced by confounding factors such as smoking or co-exposures. As a result, observed biological responses should be interpreted as indicators of biological activity rather than exposure-specific effects. Finally, the conceptual framework presented in this study is based on the synthesis of the reviewed evidence and has not been empirically validated. It should therefore be interpreted as an interpretative conceptual representation intended to support structured interpretation of the evidence, rather than as a formal analytical, predictive, or decision-making model. Its applicability in regulatory and occupational settings requires further evaluation. These limitations should be considered when interpreting both the empirical synthesis and the conceptual framework derived from it.

CONCLUSIONS

Occupational exposure to ENMs is increasing, while the ability to perform robust risk assessment remains limited. Evidence from biomonitoring-based epidemiological studies

highlights a persistent gap between hazard identification and the interpretation of human data in occupational settings. The available evidence suggests that occupational exposure to ENMs is associated with measurable biological responses in workers; however, these responses are largely non-specific and difficult to interpret in a risk assessment context. As a result, biomonitoring findings primarily reflect biological activity rather than exposure-specific effects, which limits their use for exposure–response assessment. This gap reflects multiple sources of uncertainty, including incomplete exposure characterization, lack of standardized metrics, limited understanding of internal dose, and the widespread use of non-specific biomarkers. These uncertainties arise across the exposure–dose–effect pathway and constrain the interpretation of biomonitoring data. Despite these limitations, the available evidence provides consistent indications of biological responses that may inform interpretation when considered in context. In this setting, structured approaches that explicitly account for uncertainty may support a more transparent and consistent interpretation of heterogeneous data. Further progress will require improved exposure characterization, development and validation of more specific biomarkers, integration of multidisciplinary evidence, and well-designed longitudinal studies. Such advances will be essential to strengthen the evidence base and enable more robust risk assessment for ENMs in occupational settings. Until then, explicit consideration of uncertainty remains essential for the interpretation of biomonitoring data and for the protection of workers exposed to ENMs.

AI USE

AI tools were used for minor language editing and stylistic improvements. No AI was used for data analysis, interpretation, or generation of scientific content.

AUTHOR CONTRIBUTIONS

Research concept: Magdalena Matysiak-Kucharek, Marcin Kruszewski, Lucyna Kapka-Skrzypczak

Research methodology: Magdalena Matysiak-Kucharek, Krzysztof Bogumił Sawicki, Marcin Kruszewski

Collecting material: Magdalena Matysiak-Kucharek, Krzysztof Bogumił Sawicki

Interpretation of results: Magdalena Matysiak-Kucharek, Krzysztof Bogumił Sawicki, Marcin Kruszewski, Lucyna Kapka-Skrzypczak

References: Magdalena Matysiak-Kucharek, Krzysztof Bogumił Sawicki

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