Biomonitoring of Nanotechnology Workers: A Scoping Review

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**Abstract**

The widespread and increasing use of engineered nanomaterials (i.e., particulate materials measuring 1–100 nanometers (nm) in at least one dimension) poses a potential health and safety risk to exposed workers. Their unique properties have made nanomaterials useful in multiple industries. However, their production and use may compromise worker health, presenting an emerging occupational health hazard, the acute and chronic effects of which have not been fully assessed. In this scoping review, we critically assess the literature focused on the biomonitoring of nanoparticles and discuss the utility of biomonitoring as a means of assessing internal doses and the physiological effects of nanoparticle exposure among nanotechnology workers. Multiple databases were queried based on select inclusion and exclusion criteria according to PRISMA guidelines, and articles were independently screened by two topic experts. Of 286 articles initially retrieved, 24 were included after screening and eligibility. The reviewed articles indicate that sensitive, validated biomarkers of exposure and disease progression, may be useful for monitoring toxicological effects and risks associated with nanoparticle exposure in the workplace. This review will aid policy decision-makers in the occupational health field as they promote regulations and define occupational exposure limits to contribute to worker health and well-being.

**Keywords**: biomonitoring; biomarkers; engineered nanomaterials; nanoparticles

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**Introduction**

The utilization of nanotechnology and nanoscale materials in industry is rapidly increasing in both scope and scale. According to the World Health Organization (WHO), the “increased production of manufactured nanomaterials and their use in consumer and industrial products means that workers in all countries will be at the front line of exposure to these materials, placing them at increased risk for potential adverse health effects” (WHO. 2017). There is high-quality evidence based on exposure assessment studies that workers are exposed to ENMs in a variety of industries and work tasks (Debia et al. 2016). Some industrial processes, such as cleaning, packaging, and recycling, may expose both workers and consumers to nanoparticles (NPs) (Kuhlbusch et al. 2011). Moreover, ENMs with new chemical and physical properties that offer value in specific technological applications, are being produced regularly. The properties of these ENMs and NPs, such as their small dimensions, shape, large surface area, high reactivity, charge, crystal formation, and tendency towards aggregation, determine their biological activity and can thus cause potentially toxic effects in exposed workers. According to Liao et al. (2014), these properties are not routinely considered in toxicity screening studies, and their adverse effects and toxicity remain mostly unknown.

Within the context of occupational health, biomonitoring refers to the “repeated, controlled measurement of chemical or biological markers in fluids, tissues or other accessible samples from subjects exposed to chemical, physical or biological risk factors in the workplace” (Manno et al. 2010). Exposure to nanomaterials has been described via oral, dermal, inhalation, and injection routes, depending on use patterns (Sahu and Hayes, 2017). Consequently, the spectrum of NP-related biological effects is broad, and the opportunities for biological monitoring are diverse. Inhalation is the most biologically significant route of exposure in occupational settings, and NPs that accumulate in the lungs contribute to the development of idiopathic respiratory pathologies. According to Rinaldo et al. (2015), approximately 10−20% of insoluble NPs accumulate in the lungs. However, these multiple routes of NP exposure and bioabsorption highlight the possibility for different approaches to the biological monitoring of exposed workers.

A WHO report (2017) acknowledges the “paucity of precise information about human exposure pathways for manufactured nanomaterials, their fate in the human body and their ability to induce unwanted biological effects such as generation of oxidative stress”. Biomonitoring is useful in the occupational health screening of exposed industrial workers and can be a surrogate strategy used to estimate the internal dose of a given compound or to quantify associated pathophysiological changes. As noted in a previous review on the biological monitoring of workers exposed to engineered nanomaterials, the significant physio-chemical variability of nanomaterials makes it difficult to assess associated occupational risks and may explain why there are no established screening programs or protocols for related biomarkers (Shulte et al. 2019). The present study undertakes a scoping review of published research focused on the use of biological markers associated with NP exposure in the workplace, including both engineered nanomaterials and nanoparticles produced as a byproduct of industrial activities such as welding. Based on the current state of the published toxicological research, we discuss the utility of biological monitoring of NP-exposed workers and directions for future research.

**Materials and Methods**

**Search Strategy and Inclusion Criteria**

We conducted a scoping review to identify and analyze toxicological and epidemiological studies focused on the biomonitoring of nanomaterial-exposed workers. The Web of Science and PubMed search engines were queried utilizing an identification, screening, eligibility, and inclusion algorithm based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Tricco et al. 2018). Subject search terms included “nanoparticles” or “engineered nanomaterials,” “health effects,” “biological markers,” “biomarkers,” and “workers epidemiology.” **(Table 1).** Search restrictions included the English language, years of publication (January 1, 2009–December 31, 2021), and peer-reviewed studies. In order to expand the scope and reduce the probability of missing relevant literature, the term “nanoparticles” was used in addition to “nanomaterials.” Two hundred eighty-six unique search retrievals for each search term were obtained in both databases. Duplicate articles from different search terms were removed prior to the screening process.

**Table 1.** Search terms and query results.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Search terms | PubMed | Web of Science |  |  |
| Nanoparticles AND workers AND biomarkers | 45 | 46 |  |  |
| Biomonitoring AND nanomaterials workers | 27 | 9 |  |  |
| Biomonitoring AND nanoparticles workers | 19 | 16 |  |  |
| Biomonitoring AND engineered nanomaterials workers | 14 | 3 |  |  |
| Biological markers AND engineered nanomaterials AND workers | 27  25 | 2  2 |  |  |
| Biological markers AND exposure to engineered nanomaterials AND workers  Biological markers AND exposure to nanoparticles AND workers | 42 | 9 |  |  |
| **Total** | **199** | **87** |  |  |

**Figure 1**. Flow chart of study selection, screening, and eligibility

PRISMA

Eligibility

Included

Screening

Identification

PubMed: n = 199

Web of Science:n = 87

Total database searches:

n = 286

Records after duplicate removal:

n = 165

Papers included:

n = 24

Excluded: n = 134

1. Reviews: n = 44
2. Not Occupational: n = 67
3. Not Nanoparticles: n = 23
4. In Vitro: n = 5

**Figure 1** A flow chart of the selection process adapted from the PRISMA-ScR (PRISMA extension for Scoping Reviews) group statement (Tricco et al. 2018). The full texts of the papers considered eligible for this review were obtained, and reference lists were searched for additional articles that met the study inclusion criteria. Only publications that measured biological markers of occupational exposure to NP were included.

***Eligibility process***

After the removal of duplicate studies, the abstracts of the 165 remaining articles were reviewed independently by two researchers. We then narrowed the pool of relevant articles by excluding review articles as well as articles that were focused on non-occupational exposure (“not occupational”) or not clearly associated with NP exposure (“not nanoparticles”). Non-epidemiological *in vitro* studies were also removed during the screening. Following this screening for eligibility, 24 articles remained and were included in the review.

**Results**

The study populations, types of exposures, methods used, health outcomes, expression of specific biological markers, and potential confounding factors in the reviewed studies are summarized in **Table 2**.

The most frequently utilized and studied biological markers of nanomaterial-related effects, involving cardiovascular effects, lung fibrosis, lung and systemic inflammation markers, nucleic acids, lipid and protein oxidative stress markers, antioxidant enzyme activity, genotoxicity, and metabolic markers, are summarized in **Table 3**.

**Table 2.** Summary of the study populations, NMs or NPs, health outcomes, selected outcome-related biological markers, results, and confounding factors.

| Author | NM/ NP | Population Exposure/ Study/ Assay | Health Outcomes/ Biological Markers | Tested in humans | Results | Confounding factors |
| --- | --- | --- | --- | --- | --- | --- |
| Y. Song et al. Eur Respir J 2009 | Polyacrylate (polyacrylic ester)  30 nm diameter | 7 females and 1 male (ages 18-47) working in print plant 5-13 months.  Assays:   1. Histopathology STEM 2. HE stain 3. Protein electrophoresis 4. Spirometry 5. Thoracentesis | * Shortness of breath, pleural and pericardial effusions.   Skin exposure, itching on faces and arms   * Biomarkers:   Blood cells monocytes, lymphocytes  Biochemical markers  Fibrosis, granuloma in lung tissue | Samples:  Lung tissue Thoracic exudate Pleural BALF effusion Blood Urine  Functional tests: liver, kidney, and lung | **Increased:**  Blood & serum: Monocytes, ESR, ALT, AST  Exudate: monocytosis  Pleural effusion: glucose  BALF: lymphocytosis.  **Decreased:**  Blood & serum: neutrophils, albumin  Pleural effusion: chloride ion in all patients: very low  BALF: macrophages  Pathological examinations: nonspecific pulmonary inflammation, fibrosis, and foreign-body granulomas of pleura | Nonsmokers  Not exposed to hazardous materials |
| M.Wu  Environ. Health Perspect 2010 | CNT  Aluminum &  magnesium silicates, chrysotile asbestos, calcium phosphate & sulfate | Case Report  7 previously healthy rescue and recovery workers exposed to WTC dust on 09/ 11/ 2001.  Assays:  Histopathology: mineralogic tissue analyses by STEM & EDS | * Severe respiratory impairment- interstitial lung disease, bronchio-parenchymal disease, non-necrotic granuloma, asthma, bronchitis, pneumonia * Unexplained radiologic findings. | Samples:  Lung tissue sections | **Increased:**  Lung tissue: CNT and silicates  Extensive interstitial/ parenchymal abnormalities, Small airways disease | Age Gender Occupation Smoking history Comorbidities  Length of exposure |
| J. H Lee  Nanotoxicology  2012 | Silver NPs | Case study:  Walkthrough evaluation of manufacturing process of 2 workers over 7 years. | No significant findings  Silver concentration | Samples:  Blood  Urine | Silver in urine: not detected  Silver in blood: low conc. | \_ |
| S.H. Liou  J. Nanopart Res 2012 | NPs:  CNT, TiO2, SiO2, Silver, Gold,  nanoresins, nanoclay, nanoalumina, and metal oxides  20-100 nm | Cross-sectional study of  manufacturing & application workers.  227 exposed vs. 137 unexposed controls from 14 NP plants.  Assays:  Questionnaire | * Biomarkers:   Cardiovascular: fibrinogen, ICAM, interleukin-6  Antioxidants: MPO, SOD, GPX | Samples:  Blood Urine EBC  Pulmonary functions (FVC, FEV1, PEFR, MMF, FEF25 %, FEF50 %, FEF75),  Heart rate  Neurobehavioral function (correct rate of 7-digit backward memory) | **Increased**:  fibrinogen, ICAM, and interleukin 6  Significantly higher in part of workers  **Decreased**:  SOD significantly (p < 0.05)  GPX significantly  in part of workers.  Neurobehavioral functions Significantly lower in part of workers.  **No changes** in DNA damage, genotoxicity, and pulmonary markers | Exposure status Demographics  Geographic and socioeconomic status Smoking and alcohol consumption Betel nut chewing habits History of respiratory disease Dusty environment |
| Andujar et al. Part. & Fib. Toxicol.  2014 | Iron 20–25 nm  chromium and /or manganese, titanium, aluminum, silica and nickel in lung tissue | Cross-sectional study  21 welders vs. 21 controls.  Assays:  a. Questionnaires  b. *In vitro* tests on macrophages from BAL  c. Quantification of NPs in tissue: Imaging & material science techniques: STEM; μXRF; EDX.  d.Immunohistochemistry: Lung tissue sections stained HES (hematoxylin-eosin-saffron) or Perls Prussian  CD68 staining.  e. Fibrosis evaluation: Roggli Semi-quantitative score | * Biomarkers   Pulmonary markers of inflammation: CXCL-8, IL-1ß, TNF-α, CCL-2−3, −4 | Samples:  Lung tissue sections BAL macrophages Fibroblasts | **Increased:**  CXCL-8, IL-1ß, TNF-α, CCL-2. **Moderate increase**: IL-6, CCL-7, and −22 in macrophages in alveolar lumen and fibrous regions. No fibroblasts differentiation.  CD68 staining: **High** number of macrophages in lung tissue; Perls stain: **high** iron load; **elevated** count of siderophages (iron-laden macrophages),  **high** number of fibrotic lesions | Gender Smoking habits Occupational seniority |
| H.Y. Liao et al. Nanotoxicology 2014 | Nanosilver, Nanogold,  Fe2O3, TiO2,  CNT, SiO2  Multiple exposures to mixed types of NPs Size < 100nm | Longitudinal study of workers from colors, LED, colorants, air cleaners, CNT, photocatalyst, and textile industries exposed vs. unexposed.  Assays:   1. Questionnaires 2. Outcome biomarkers first examined in a cross-sectional manner and then 6 months later. | * Biomarkers:   Pulmonary, cardiovascular disease, genotoxicity; inflammation and oxidative stress.  Airway damage marker: Clara cell protein 16; lung function test Antioxidant enzymes; | Samples:  EBC Blood Urine | **Increased**:  VCAM, IL-6 ICAM, LF, VLF.  **Decreased**:  SOD, GPX CC16, PON1, Pulmonary function (changes of maximal mid-expiratory flow, PEFR, and FEF 25%) in exposed group. | Age Gender Smoking habits History of respiratory disease Dusty environment |
| Lee et al. Nanotoxicology 2015 | MWCNTs | Health surveillance study: Walkthrough personal and area exposure levels evaluation  9 manufacturing workers and 4 office workers. | * Biomarkers:   Oxidative stress | Samples:  Whole blood EBC  Pulmonary function test | **Increased:**  EBC:  MDA, 4-HHE, and n-hexanal in manufacturing workers significantly higher than in office workers.  Blood:  Normal hematology and biochemistry values  Lung function: normal | Gender, median age, work period, smoking status,  diurnal variation work-shift |
| Shvedova et al. PLoS One  2016 | MWCNTs aerosols | Cross-sectional study.  Exposed (n=8) vs. non-exposed (n=7) workers in a 6-month period.  Assays:   1. Spectrophotometer IPA global mRNAs, ncRNA expression profile blood 2. RT-PCR miRNA sequencing 3. TEM count of CNT from breathing zone. | * Lung inflammation and/or fibrosis; granuloma; lung different type tumors; systemic inflammation; cardiovascular injury * Biomarkers:   IL6, EGFR, TGFβ; ERK, PDGFA, CASP8  KL-6 (MUC 1) | Samples:  Whole blood Particles in personal breathing zones | **Dysregulation:**  mRNA, lncRNA, and miRNA expression profiles of target genes affecting cell cycle regulation IL6, EGFR, TGFβ; ERK, PDGFA, CASP8  KL-6 (MUC 1) | Age Gender Pernicious habits Work experience History of disease |
| Fatkhutdinova et al. Toxicol. & Applied Pharmacol.  2016 | MWCNTs aerosols | Cross-sectional study.  Exposed (n=10) vs. non-exposed (n=12).  22 workers (18 males, 4 females) aged 19–63 working > 1 year.  Assays:   1. TEM count CNT particles 2. EC: elemental carbon analysis 3. ELISA (serum and sputum) 4. Flow cytometry (serum and sputum) | * Biomarkers:   Inflammatory and fibrotic markers | Samples:  Nasal lavage Induced sputum Blood Serum Air samples from specific areas and personal breathing zones | **Increased:** significantly  Sputum: IL-1β, IL6, TNF-α, inflammatory cytokines, KL-6.  Serum: TGF-β1(in young) | Age Gender  Smoking habits  Work experience |
| Graczyk et al. Particle and Fibre Toxicol.  2016 | Welding fumes (Tungsten Inert Gas, TIG) | Cross-sectional study.  welding trainees, 15-24 y (n=10). | * Biomarkers:   Oxidative stress: 8 hydroxy-20 -deoxyguanosine, MDA, hydrogen peroxide, and total reducing capacity | Samples: Exhaled breath condensate (EBC) Blood Urine | **Increased:** significantly  Plasma H2O2 24%;  14% 8-OHdG  urinary H2O2 91%;  45% urinary 8-OhdG | Non smokers,  Trainees,  age  Males  Weight, height, BMI |
| Pelclova et al. Occ. & Env. Med.  2016a | NanoTiO2 pigment | 36 male workers  working with TiO2 pigment for at least 6 months and 45 unexposed controls.  Assays:   1. Questionnaire 2. Ecoscreen Turbo DECCS Jaeger: EBC sampling 3. Crystallography: Gemini 4 circle CCD diffractometer: for Ti in EBC 4. LC-ESI-MS/MS: Markers of oxidative stress in EBC | * Biomarkers:   Titanium  Oxidation of nucleic acids: (8-OhdG), (5-OHMeU)  Proteins: o-tyrosine (o-Tyr), 3-chlorotyrosine (3-ClTyr) and 3-nitrotyrosine (3-NOTyr) | Samples: EBC | **Increased:**  EBC: Titanium and most oxidative stress markers **significantly higher** in production workers (p<0.001) than in research workers and unexposed controls. | Occupational history Medical treatments Lifestyle habits  (e.g., diet, alcohol  intake, smoking,  physical activity) |
| Pelclova et al.  J. Breath Research  2016b | NanoTiO2 aerosol  80% of particles <100 nm diameter | 30 workers exposed to TiO2 aerosol, 22 office employees, and 45 unexposed controls.  Assays:   1. LC-ESI-MS/MS 2. FENO 3. Spirometry | * Potential fibrotic changes in lungs, inflammation * Biomarkers:   EBC: LT B4, C4, E4, D4  Lungs: % VCIN; % PEF | Samples:  EBC  Urine | **Increased** in EBC: LT B4, C4, E4, D4 in workers relative to controls (p < 0.01).  Cysteinyl LTs  Impaired %VCIN and %PEF (both *p* < 0.01). | Allergic diseases  Smoking status |
| Pelclova et al.  J. Breath Research  2016c | Iron oxide aerosol  80% of particles <100 nm diameter | 14 workers aged 43± 7 y. exposed 10±4 y. and 14 controls (aged 39±4 y.)  Dose-dependent.  Assays:   1. LC-ESI-MS/MS 2. SMPS; APS; P-TRAK; DustTRAK DRX: for workplace aerosol | * Asymptomatic with Oxidative stress markers * Biomarkers:   Oxidative stress, oxidation of nucleic acids- and inflammation  Proteins: o-tyrosine, 3-chlorotyrosine, and 3-nitrotyrosine | Samples:  EBC  Urine | **Increased**:  EBC: MDA, HHE  HNE, 8-isoprostane,  aldehydes C6–C12, 8-OHdG,  8-OHG, 5-OHMeU, 3-ClTyr,  3-NOTyr, o-Tyr (all *p* < 0.001)  in workers relative to controls  (p < 0.01).  Urine: no increase | Age BMI Smoking and alcohol consumption |
| Pelclova et al.  Nanotoxicology 2017b | nanoTiO2  80% of particles <100 nm diameter | Cross-sectional study  Production workers and Controls. | * Lung injury, inflammation, * Biomarkers:   Lipid oxidation, oxidative stress, cytotoxicity, and genotoxicity  MDA, 4-hydroxy-trans-hexenal, 4-hydroxy-trans-nonenal, 8-iso Prostaglandin F2α; aldehydes C6–C12 | Samples:  EBC | **Increased**:  11 markers of lipid  oxidation in production  workers relative to  controls  (p < 0.001) | Age Smoking and alcohol consumption  Physical activity \_ |
| Pelclova et al.  Rev. Environ. Health 2017a | Nanoscale titanium dioxide (nanoTiO2)  <100 nm diameter | Cross-sectional study.  Short-term MVA. 22 office workers intermittently exposed to TiO2 vs. 14 unexposed.  Assays:   1. Questionnaires 2. Physical exam 3. Spirometry 4. TiO2 | * Inflammation * Biomarkers: Lipid oxidation MDA, HHE, HNE, 8-isoprostane, aldehydes C6−C12 | Samples:  EBC  Urine | **Increased:**  9 markers of lipid  Oxidation, DNA and  protein oxidative damage in  production workers.  EBC: highly significant difference between production and office workers. (p < 0.001)  Urine: No increase | Age Smoking and alcohol consumption  Physical activity |
| Vlaanderen  et al. Nanotoxicology 2017 | MWCNT | Exposed vs. non-exposed workers.  Assay:  Molecular cross-section | * Pulmonary and immune system damage. * Biomarkers:   Immune markers & pneumoproteins: C-C motif ligand 20, basic fibroblast growth factor, soluble IL1 receptor II | Samples:  Serum  Whole blood (CBC)  FENO  Lung function | **Increased:**  Significant upward trends for immune markers C-C motif ligand 20 (p= 0.005), basic fibroblast growth factor (p= 0.05), and soluble IL-1 receptor II (p= 0004) | Age BMI  Gender Smoking status |
| Liou et al. J. Hazardous Mat. 2017 | TiO2, SiO2, indium tin oxide (ITO) | Cross-sectional study.  130 workers 70% males and 30% females; mean age 35 yr. handling NPs 3.4 ds. / wk. 4.4 h/ day Exposed vs. non-exposed workers. Assays:  Questionnaires | * Biomarkers:   Global methylation, DNA oxidative damage, lipid peroxidation.  Oxidative stress  Urinary and WBC 8-OHdG, EBC 8-isoprostane | Samples:  Blood  Urine  EBC | **Increased:**  WBC; 8-OHdG  8-isoprostane  8-OHdG (negatively correlated with global methylation)  WBC and urinary 8-OHdG positively correlated.  Lower global methylation in ITO handling workers. | Demographic Socioeconomic characteristics Lifestyle (or smoking and alcohol consumption)  Occupational history Personal and family disease |
| Dierschke et al. Int’l. Arc. Occ. & Env. Health 2017 | Welding fumes -mild steel welding (Iron 70% and Mn 30%) | 11 welders with and 10 without work-related symptoms from lower airways and 11 asymptomatic non-welders.  Assays:   1. Questionnaires:   Exposed vs. non-exposed to fumes workers, random double-blind   1. RTube for EBC sampling 2. Cytospin and May-Grüenwald Giemsa for NL 3. Luminex Immunoassay (cytokines) 4. Sysmex XE-5000/1800i counters (neutrophils) 5. Visual analog scale for eyes examining | * Biomarkers:   EBC: leukotrienes LT-B4  NL: IL-6  Neutrophils  IL-8 | Samples:  EBC  Blood  Serum  Nasal lavage (NL)  Lung function | 1. Lung function: No adverse effect.  2. EBC: LT-B4 pre-exposure significantly **increased** (tenfold higher level) in symptomatic sensitive welders with work-related airway symptoms (chronic exposure to welding fumes).  3. NL: IL-6 increased in non-symptomatic groups  4. Blood: rapid elevation of IL-8 and neutrophils after exposure followed by a significant decrease (ongoing neutrophilic low-grade inflammation). | Non-current smokers (5 yr.)  Total welding time Age Exposure Allergies Work-related symptoms from eyes and airways |
| Khatri et al. NanoImpact 2017 | Mixture of organic compounds with metal ENPs | 6 photocopiers workers vs. 11 controls 3 random weeks during 2 years.  Assays:   1. Quantitative airborne NPs 2. Chemistry 3. Lung burden estimates | * Chronic upper airway inflammation and systemic oxidative stress * Biomarkers:   NL: 14 pro-inflammatory cytokines/ chemokines, inflammatory cells, and total protein  8-OH-dG | Samples:  Nasal lavage  Urine: 8-OH-dG | **Increased:**  NL: IL-6, IL-8, TNFα, IL-1β and Eotaxin (significantly p˂0.0001)  inflammatory cell infiltration 2.7-fold  Total Protein: 4-fold  Urine: 8-OH-dG 4.3-fold | Age, gender, Smoking status, job seniority |
| Pelclova et al. Occ. & Env. Med. 2018 | TiO2  Iron oxides  Nanocomposites | 3 groups of workers vs. comparable control groups. 34 nano TiO2 workers over 2 years.  14 nano Iron oxides; and  32 nanocomposites workers 2-year follow up  Assays:   1. Spirometry 2. FENO 3. LC-ESI-MS/MS 4. APS, SMPS, OPS, and CPC (Aerosol exposure) | * Biomarkers:   Lipids oxidation, nucleic acids and proteins: MDA, HHE, HNE, 8-isoProstaglandinF2α, C6-C13, 8-OHdG, 5-hydroxymethyl uracil, o-tyrosine, 3-ClTyr, 3- NOTyr; pro-inflammatory leukotrienes LTB4, LTC4, LTE4, LTD4 | Samples: EBC | **Increased:**  Markers of oxidative stress: LTB4 and cysteinyl LTE4 most useful and elevated in nanoTiO2 workers. | Job seniority,  materials used, Exposure to aerosols > 2 years |
| Zhao et al. Nanotoxicology 2018 | TiO2 | Cross-sectional study  83 exposed workers vs. 85 controls in packaging workshop.  Assays:   1. Questionnaire 2. Spirometer 3. ELISA 4. Cytometric Bead Array 5. BD FACSCalibur flow cytometer | * Significant changes in chest X-ray images * Biomarkers: Pulmonary surfactant protein D (SP-D)   Cardiovascular disease: VCAM-1, ICAM-1, LDL, and TC  Inflammatory and acute phase reactants, oxidative stress | Samples:  Serum  Chest radiography  PFT | **Increased**:  SP-D; VCAM-1 and ICAM-1  LDL  IL-8, IL-6, and TNF-alfa  IL-1beta, IL-10 **Decreased** (significantly): creatinine, triglyceride, and total cholesterol | Demographic Smoking and alcohol consumption Occupational and medical history Use of personal protection equipment (PPE) |
| Baumann et al.  Nanotoxicology 2018 | Zinc- and copper welding fumes  (in vehicle construction & interiors)  50 - 300 nm different shapes | 15 healthy male volunteers (age 26, nonsmokers).  Assays:   1. Lavages nasal strips (Leuco- sorb) 2. Coomassie Plus (Pierce) 3. ECL 4. Spirometry 5. Plethysmography 6. Cycling ergometry 7. ROC curve analysis -Receiver operating characteristic to differentiate welding fume from control exposure 8. Field Emission SEM 9. EDX | * Inflammatory responses Cardiovascular events: elevated risk * Biomarkers:   Systemic: IL-6, CRP, and SAA  ICAM-1, and VCAM-1  Nasal interferon-c (IFN-c)  Total protein | Samples:  Nasal secretion (serial)  Lung function | **Increased:**  Nasal: (IFN-c)  Nasal Total protein, CRP, and SAA: significantly  No significant changes: IL-6, sVCAM-1, sICAM-1 | Non smoking, healthy lung function, non-exposed to metal fumes,  no atopy, cardiac condition or asthma |
| Yu et al.  Toxicology & Industrial Health 2020 | Iron oxide NPs (IONP) | Cross-sectional study.  23 workers aged 23 unexposed to metal. Assays:   1. ELISA 2. PCR | * Biomarkers:   Iron status, oxidation markers, methylation of genomic DNA  5-methylcytosine (5mC), hepcidin, iron, soluble transferrin receptor (sTfR), ferritin, 8-OHdG, and glutathione | Samples:  Blood | **Increased:**  5hmC  No change, the rest  Positive correlation: 5hmC and IONP | Demographics (e.g., gender)  Occupational history |
| A. Rossnerova et al. Int’l. J. Mol. Sci. 2020 | Aerosolized welding fumes 2 fractions  <25 nm  25–100 nm | Cross-sectional study.  20 exposed welding and machining vs. 20 unexposed. (both genders) 14.5± 9.2 years exposure.  No PPE used.  Assays:   1. Infinium Methylation Assay 2. EPIC BeadChips microarray 3. ELISA 4. SMPA 5. APS | * Biomarkers:   Methylation pattern at CpG loci | Samples:  Blood | **Increased:**  Significant CpG in genes of lipid metabolism, immune system, lung functions, signaling pathways, cancer,xenobiotic detoxification. | Age  Gender  BMI  PPE |
| Wu WT et al. Nanotoxicology 2021 | Mixed NM  nano-TiO2, nano-SiO2, CNTs in ceramic coatings, semiconductors production fiber injection | Cross-sectional study  14 factories  80 NM manufacturing/ handling workers  69 unexposed office workers  2 years exposure  Assays:   1. Quantitative airborne NPs 2. SMPS:Particle size distribution and Mass concentration (10-1000nm) 3. LC-MS/ MS analysis 4. Jaffe Method (Creatinine) | * Biomarkers:   Lipid peroxidation: 8-Iso PGF2α  2,3 dinor-8-iso PGF2α, and PGF2α. | Samples:  EBC  Urine | **Increased:**  EBC: 8-Iso PGF2α  Urine: 8-isoPGF2α, 2,3 dinor-8-isoPGF2α and PGF2α, Total Isoprostane (Free+ Conjugated) | Demographic and socioeconomic characteristics; lifestyle  Smoking and alcohol consumption occupational history  personal and family histories of disease. |
| Ursini CL et al. Nanotoxicology 2021 | 2 exposed groups:  1. graphene powder (GNPs) 1.6nm x 1.1 mm size  2. silica NP (SiO2NPs)  50 nm size | Pilot study.  12 FLG (Few Layers Graphene) production (synthesis) workers  11 healthy office workers as unexposed controls  Assays:   1. Questionnaire 2. Buccal Micronucleus Cytome (BMCyt) assay 3. Formamido pyrimidine glycosylase (FPG) protein -comet test (lymphocytes from whole blood), 4. Exposure metrics by Real-time measurements: particle number concentration; average diameter; Lung Deposited Surface Area (LDSA); Size Distribution (SD) at nanoscale; gravimetric, chemical, and morphological analyses | * Biomarkers:   Oxidative stress  8-oxoGua, 8-oxoGuo and 8-oxodGuo (urine)  Cytokines (serm)  BMCyt  FPG protein | Samples:  Buccal cells  Whole blood  EBC  Urine  FENO (fractional exhaled nitric oxide)  Serum | **Increased:**  BMCyt  FPG protein | Age, gender,  Job seniority Smoking status  Alcohol consumption  X-ray test  Use of PPE |
| Bello D et al.  Nanoim-pact  2021 | Mixture of ENM in toner-based printing equipment:  TiO2, MnO2  NiO2, Carbon Black, Iron and copper oxides, amorphous silica; organic and inorganic compounds  Size: PM0.1 and larger | Phase I: Cross-sectional study  Phase II: Longitudinal study  Exposure of 19 healthy copier operators at 6 photocopy centers in Singapore  4 times in 2 weeks  Assays:   1. Standardized Respiratory Questionnaire 2. Immunofluorescence, Multiplex Immunoassays 3. Exposure metrics: particle number concentration; average diameter; LDSA 4. Exposure effect on air and airway microbiome (profiling) | * Biomarkers:   14 inflammatory cytokines | Samples:  nasal lavage (NL)  plasma  urine  saliva and sputum | **Increased:**  NL: Fractalkine, IL-1β, IL-1α  Plasma:Fractalkine, IL-1β, TNF-α, IFN-γ  **Decreased:**  Plasma: GM CSF (Granulocyte Macrophage-Colony Stimulating Factor) | Occupational history, past exposures; full/ part-time employment  Intensity of work  Smoking status  healthy lung function, non-exposed to ENM  Pre-existing diseases (diabetes, myocardial or thyroid disease, etc) |
| Zhangjian Ch et al.  Nanotoxicology 2021 | TiO2 NPs | Cross-sectional study  56 exposed packaging workers  44 unexposed office workers as controls  age: >20 yr  employed > 1 year in present job  healthy subjects  Assays:   1. Questionnaire 2. Metabolomics detection: Ultra- performance Liquid Chromatography time of flight Mass Spectrometry (UPLC) 3. Machine learning methods: Random forest, Support vector machines, and Boruta used for the screening of potential Biomarkers 4. Colorimetric assays | * Biomarkers:   Lipids peroxidation:  Serum metabolite: **liquoric acid** (represents 8 biomarkers metabolites) | Samples:  Serum | **Increased:**  Lipid peroxidation:  MDA  Liquoric acid  Significantly correlated (p<0.05),  **Decreased:**  Antioxidant enzyme SOD | Age  Gender  BMI  Smoking status  Drinking habits  History of respiratory, heart, liver and kidney diseases, diabetes, cancer; recent fever or inflammation; other acute/chronic diseases. |
| Zhangjian Ch et al.  Nanoscale 2021 | TiO2 NPs | Cross-sectional study  66 employees of aTiO2 NP manufacturing plant  66 controls  Assays:   1. Questionnaire 2. HPLC-MS 3. Metabolomics detection: UPLC 4. Machine learning methods: Random forest, Support vector machines, and Boruta used for the screening of potential Biomarkers | * Biomarkers:   Dibenzyl ether  Quassimarin  Tryptophan. | Samples:  Urine | **Increased:**  Dibenzyl ether  Quassimarin  Tryptophan | Age  Gender  BMI  Smoking status  Drinking habits |

**Abbreviations**: CRP: C-reactive protein; SAA: serum amyloid A ;SOD: superoxide dismutase; GPX: glutathione peroxidase; NO: nitric oxide; NL: Nasal lavage; VCAM: vascular cell adhesion molecule; ICAM: intercellular adhesion molecule; IL-6: interleukin-6; Clara cell protein 16: CC16, VLF: very low frequency; LF: low frequency; L/H: tail/head ratio; PFT: Pulmonary Function Test; PEFR: peak expiratory flow rate; FEF25%: forced expiratory flow at 25%; LT: leucotrienes; PMN: polymorphonuclear neutrophils; LDL: Low Density Lipoprotein; BHTs: biological half times; ELISA: Enzyme Linked Immunosorbent Assay; ECL: electrochemiluminescense; ICP-AES: Inductively Coupled Plasma-Atomic Emission Spectrometer ; MMPD: Multiple Path Particle Dosimetry; PCR: Polymerase Chain Reaction; FENO: fractional exhaled nitrogen oxide ; PAI-1: plasminogen activator inhibitor-1; TF: Tissue Factor; MDA: malondialdehyde; 8-OHdG: 8 hydroxydeoxyguanosine; 5-OHMeU: 5-hydroxymethyl uracil; 3-ClTyr: 3-chlorotyrosine; 3-nitrotyrosine: 3-NOTyr; Titanium dioxide: TiO2; Cerium dioxide: CeO2 , MVA: Multi variate analysis; CCL-2, CCL-3, CXCL-8: chemotactic cytokines; TEM/ STEM: Scanning Transmission Electron Microscopy; μXRF: X-ray microfluorescence; EDX: energy dispersive X-ray; EDS: energy dispersive spectroscopy; IPA: Ingenuity Pathway Analysis; APS: Aerodynamic Particle Sizer; SMPS: Scanning Mobility Particle Sizer; CPC: Condensation Particle Counter; OPS: Optical Particle Sizer; LC-ESI-MS/MS: liquid chromatography-electrospray ionization-tandem mass spectrometry; VCin: Inspiratory vital capacity; PEF: Peak Expiratory Flow; Ultra- performance Liquid Chromatography time of flight Mass Spectrometry (UPLC); yr: years

**Table 3.** Summary of most commonly analyzed biological effect markers

| Genotoxicity markers (DNA damage) | Oxidative stress markers | Pulmonary effect markers (tissue damage) | Systemic inflammation markers | Antioxidant markers | Other markers (lipid and food metabolism and transport, cell membrane damage) |
| --- | --- | --- | --- | --- | --- |
| XBP1 | 3-NOTyr (3-nitrotyrosine) | CC16 (Clara cell protein) | hsCRP (Highly sensitive C-reactive protein) | SOD (Superoxide dismutase) | Tryptophane |
| Caspase-12 | 5-OHMeU (5-Hydroxymethyl uracil) | FENO Fractional exhaled nitric oxide | IL-1β (Interleukin1 β); IL-1α | GPX (Glutathione peroxidase) | Quassimarin |
| CHOP | PGF2α | KL-6 (Krebs von den Lungen 6) | IL-8 (Interleukin 8) | PON1 (Paraoxonase 1) | Dibenzyl ether |
|  | 8-isoprostane (8-Iso-prostaglandin F2α) |  | IFN-γ (Interferon-gamma) |  |  |
|  | 2,3 dinor-8- isoPGF2α |  | Fractalkine |  |  |
| GADD34 | 8-OHG (8-Hydroxyguanosine/  8 hydroxy-20-deoxy guanosine) | MIP-1beta (Macrophage inflammatory protein-1b) | IL-6 (Interleukin 6) |  |  |
| miRNAs,  mRNA | C6–C12 (n-alkanes) | PFT (Pulmonary function test) | IL6sR (Interleukin 6 soluble receptor) |  |  |
|  |  |  | IL-4 (Interleukin 4) |  |  |
|  | HNE (4-Hydroxy-trans-nonenal) | FVC (Forced vital capacity) | NF-kb (Nuclear factor-kappa beta) |  |  |
|  | HHE (4-Hydroxy-trans-hexenal) | FEV1 (Forced expiratory volume at 1s) | TNF alpha (Tumor necrosis factor alfa) |  |  |
|  | LTs (Leukotrienes) | MMF (Maximal mid-expiratory flow) | Vascular endothelial function biomarkers: miR-451a |  |  |
|  | MDA (Malondialdehyde) | PEFR (Peak expiratory flow rate) | ICAM (Intercellular adhesion molecule) |  |  |
|  | Liquoric acid metabolites |  | VCAM-1 vascular cell adhesion molecule-1 |  |  |
|  | o-tyr (o-Tyrosine) | FEF 25 / 50 / 75% (Forced expiratory flow at 25/50/75% respectively) | MPO (Myeloperoxidase) |  |  |
|  | 3-Cl-Tyr (3-chloro-tyrosine) | TGF-b1 (Transforming growth factor beta1) | HRV (Heart rate variability) |  |  |
|  |  | LDH (Lactic dehydrogenase) | IFN-c (Nasal interferon-c) |  |  |
|  |  | Total Protein | NOS (Nitric oxide synthase) |  |  |
|  |  | Acid Phosphatase | CCL-2, CCL-3, CXCL-8 |  |  |
|  |  | p-PERK | leukotrienes LTB4, LTC4, LTE4, LTD4 |  |  |
|  |  | MCP-1 | Cysteinyl LT |  |  |
|  |  | GM-CSF | SAA (Serum amyloid A) |  |  |

**Discussion**

The impact that NPs have on human physiology is primarily dependent on their unique composition, shape, size, and other physicochemical properties. The literature reviewed in this study primarily assessed the physiological impact of exposure to five general types of nanoparticles on worker’s health: metal oxides, multiwalled carbon nanotubes, single-walled carbon nanotubes, welding fume NPs, polyacrylate, and mixed composition NPs.

1. **Metal oxide NPs**. Printer toner is one of the most prevalent consumables in daily office work. The NPs released from toner-based printing equipment such as printers and photocopiers have been linked to genotoxicity and to both immunologic and respiratory diseases. Khatri et al. 2017 described the physicochemical and morphological properties of ENMs (e.g., titanium dioxide, iron oxide, fumed silica, and several other metals found in photocopier and printer toners) and their effects on human health in a follow-up study of photocopier operators. These authors observed upper airway inflammation and systemic oxidative stress in photocopier operators chronically exposed to NPs, in accordance with their previous study (Khatri et al. 2013) and similar studies conducted by Pirela et al. (2013, 2014), both of which included earlier results from cellular and animal toxicological studies. In humans, limited epidemiological studies report a 2-3-fold higher prevalence of chronic cough, wheezing, nasal blockage, excessive sputum production, breathing difficulties, and shortness of breath in copier operators relative to controls. Respiratory symptoms were found to be exacerbated during chronic repeated exposures as well as in susceptible individuals. Thus, respiratory, immunological, cardiovascular, and other disorders may develop following exposure to these NPs.

While there is much debate as to what constitutes appropriate safety screening methods, one common approach is the assessment of cellular injury pathways in an effort collect knowledge about hazardous material properties that could harm humans and the environment. George et al. (2010) studied the effects and resultant biomarkers of metal oxide NP-induced damage in pulmonary cells. They demonstrated the utility of using a rapid, throughput multiparameter cellular screening approach to evaluate toxic oxidative stress in bronchial epithelial and macrophage cell lines. Titanium dioxide (TiO2; classified by IARC as a group 2B) cerium dioxide (CeO2), and zinc oxide (ZnO) NPs triggered a biological oxidative stress response in these exposed cell lines. Of these materials, the dissolution of ZnO nanoparticles and Zn2+ release in particular were capable of generating reactive oxygen species (ROS) and activating an integrated cytotoxic pathway that includes intracellular calcium flux, mitochondrial depolarization, and plasma membrane leakage, which could thus be used as parameters to gauge exposure.

Iron oxide pigments are used in paints, ink, rubbers, plastics, cosmetics, and medical devices. Pelclova et al. (2016c, 2018) evaluated occupational exposure to iron oxide NPs, and correlated the elevated levels of oxidative stress markers found in the exhaled breath condensate (EBC) of workers during pigment production. Similarly, Yu et al. (2020) recently evaluated the NP exposure of manufacturing/handling workers in a plant where iron oxide NPs are manufactured These authors found that significantly increased airborne particle levels at the worksite were associated with increased methylation of genomic DNA marker 5hydroxymethylcytosine (5hmC) levels among occupationally exposed workers, suggesting this marker may be used to monitor epigenetic signatures and may have the potential to predict the onset of clinically significant diseases.

Zinc oxide ENMs have also been widely used in cosmetics, sunscreens, advanced textiles, self-charging devices, and other electronic devices. In addition to pulmonary damage, NP exposure is also strongly correlated with an increase in cardiovascular disease incidence; however, their toxic potential remains unclear (Chen et al. 2014).

The exposure of workers to nanoscale TiO2 has been extensively studied. Andujar et al. (2014), Liao et al. (2014), Pelclova et al. (2016a, 2017b), Liou et al. (2017), and Zhao et al. (2018) documented an increase in inflammation and lipid oxidation markers, markers of lung and airway injury, and DNA and protein oxidative damage in EBC and, to a lesser extent, in the bronchoalveolar lavage (BAL) fluid of production and packaging workers exposed to nanoTiO2 relative to appropriate controls (Zhao et al. 2018). A significant dose-dependent association between TiO2 exposure and lipid oxidation markers in EBC samples was established for these workers. Moreover, markers of cardiovascular disease and acute phase reactants were found in their blood samples and some urine samples, providing an opportunity for effective and sensitive noninvasive monitoring.

Two complementary studies performed by Pelclova et al. (2016a, 2017a) assessed the impact of short-term exposure to nanoTiO2 on physiological markers among office employees working in a building where TiO2 pigments were produced. Their findings strengthen previous results linking markers of systemic inflammation, oxidative stress, and pulmonary effect markers with occupational exposure to TiO2. Pelclova et al. (2018) examined EBC samples among three groups of workers exposed to various NP exposure profiles and compared these results to the same markers of lipid, nucleic acid, and protein oxidation. They detected elevated markers of oxidative stress in all workers, especially nanoTiO2 workers. The inflammatory markers leukotriene B4 (LTB4) and cysteinyl LTE4 exhibited the highest association in these workers. The authors thus considered EBC markers to be sensitive targets for the noninvasive monitoring of workers exposed to engineered NPs. Their findings were also partly supported *in vivo* by Oyabu et al. (2017), who examined the dose-response relationships of NiO and TiO2 NPs nanoparticles, each of which exhibited distinct toxicity profiles, through inhalation and intratracheal instillation studies. They observed increased pulmonary inflammation and oxidative stress marker levels alongside NP biopersistence in the lungs as reflected by histopathological changes and other biomarkers in BAL fluid. However, due to the ability of NPs to translocate to other organs, biopersistence, which has previously been established as a useful toxicity indicator for micron-size particles, appears to be a particularly valuable indicator of biological effects in the lungs. More recently, Zhangjian et al. (2021) performed metabolomics screening in serum samples from packaging workers and identified liquoric acid as a new lipid oxidation biomarker of TiO2 NP exposure. In a similar work, Zhangjian et al. (2021) performed metabolic screening in urine samples from TiO2 NP production workers and found several metabolites involved in lipid transport, metabolism, and peroxidation, cell damage, and excretion such as quassimarin, tryptophane, and benzyl-ether. These compounds may thus represent potential biomarkers of the early health effects for occupational exposure to TiO2.

Liou et al. (2017) described the effect of Indium tin oxide (ITO) on NP handling workers. As ITO is increasingly used in liquid crystal display and semiconductor production processes, they examined the exposure of NP manufacturing and handling workers to TiO2, SiO2, and ITO NP granules or indium nano-sized fumes during different processes involved in the splashing, pulverization, cutting, and grinding of the final ITO plates. Using noninvasive evaluation methods, they detected the presence of NPs in EBC, blood, and urine, signaling that exposure to metal oxide NPs may lead to global methylation, DNA oxidative damage, and lipid peroxidation.

1. **Multi-walled Carbon Nanotubes** (MWCNTs). Several *in vivo* and *in vitro* mechanistic toxicology studies have focused on MWCNTs given that they are a commonly used nanomaterial, revealing that MWCNT exposure can potentially induce physiological effects in humans. These studies have shown considerable evidence of inflammatory induction, oxidative stress, pulmonary fibrosis, mesothelioma-like effects, and cardiovascular effects (Kim et al. 2015; NIOSH, 2013). In one occupational health survey of MWCNT-exposed workers, the assessment of personal and area exposure levels to MWCNTs was performed using a walkthrough evaluation approach. Blood and EBCs from manufacturing and office workers were collected, and pulmonary function testing (PFT) was performed. Analyses of the EBC samples from these workers revealed significantly higher levels of oxidative stress markers such as malondialdehyde (MDA), 4-hydroxy-2-hexenal, and 4-hydroxy-trans-nonenal in MWCNT manufacturing workers as compared to office workers. MDA and n-hexanal levels were also found to be elevated in a similar study (J.S. Lee et al. 2015), suggesting that they may represent valuable biomarkers of MWCNT exposure.

Vlaanderena et al. (2017) studied the effects of occupational exposure to MWCNTs through a molecular cross-sectional study in which they evaluated the association between occupational exposure to MWCNTs and the lung health and immunological activity in workers at an MWCNT-producing facility. They observed significant upward trends in the levels of immune markers including C-C motif ligand 20, basic fibroblast growth factor, soluble IL-1 receptor II, and fractional exhaled nitric oxide (FENO), as well as differences in all measured hematological parameters between exposed and non-exposed workers. Their results were found to be robust in sensitivity analyses, confirming the early effects of occupational exposure to MWCNTs on lung health and the immune system. The researchers concluded that some indications of early biological perturbations were associated with exposure to MWCNTs.

In another study, analyses were performed using the blood of manufacturing workers exposed to MWCNT aerosols during fragmentation, packaging, and laboratory handling processes for at least 6 months, with these samples being compared to blood samples from unexposed workers (Shvedova et al. 2016). These analyses revealed altered levels of key regulators of biological processes owing to global changes in mRNA, long non-coding RNA, lncRNA, microRNA (miRNA), and non-coding RNA (ncRNA) expression profiles due to interference with gene expression. Several animal studies have reported pulmonary inflammation and fibrosis in rodents (Shvedova et al. 2005; Porter 2010, Mercer 2011, Poulsen 2015), but the effects reported in animal studies have not yet been confirmed in humans. As such, the potential markers of MWCNT exposure in humans require further study.

A case report regarding unintended occupational exposure to dust-containing CNTs, among many other materials, was published by Wu et al. (2010). In this report, the authors described the clinical and pathological findings in the lungs of first responders and rescue and recovery workers following the September 11th terrorist attack on the World Trade Center (WTC) complex in New York City who had been diagnosed with pulmonary fibrosis, chronic bronchiolitis, and granulomas resulting from CNT exposure. Their findings were detected in biopsy specimens as well as in air samples collected at the WTC attack site.

1. **Welding fume NPs**. To date, there are no epidemiological studies that have specifically investigated the neurotoxic effects of manufactured NPs. However, studies of populations exposed to anthropic NPs provide an interesting perspective on concerns related to the possible effects of NPs on humans. Analyses of workers exposed to occupational pollutants released at the nanoscale (welding fumes and other non-intentional combustion-related mineral or metallic NPs) are of great interest when assessing this evidence. Andujar et al. (2014) provided the first confirmation of a link between human NP exposure and long-term pulmonary effects. They identified welding-related NPs such as Fe, Mn, and Cr oxides in welders’ lung tissue sections, alveolar macrophages, and in fibrous regions of the lungs. Macrophages exposed *in vitro* to those NPs exhibited the increased production of a pro-inflammatory secretome (inflammatory marker and chemokines including CXCL-8, IL-1ß, TNF-α, CCL-2, CCL-3, CCL-4). The effects of the nanoparticulate components of welding fumes on the human central nervous system were examined by Graczyk et al. (2016) in a cross-sectional study. They assessed oxidative stress biomarker concentrations (8-hydroxy-2’-deoxyguanosine, malondialdehyde, hydrogen peroxide, and total reducing capacity) in EBC, blood, and urine collected from non-smoking male welding trainees at different time points before and after a 60-min exposure to Tungsten Inert Gas (TIG). Their findings revealed significant increases in the measured biomarkers 3 hours after exposure. Similar results were obtained by Jarvela et al. (2013), and Kauppi et al. (2015), who found that after investigating the association between NP exposure, inflammation, and oxidative stress in both subject groups, pulmonary and systemic levels of the later biomarkers were significantly elevated in welders. Some of these results were also confirmed by Andujar et al. (2014), Song et al. (2016), Dierschke et al. (2017), and Rossnerova et al. (2020). The risk of cardiovascular events resulting from short exposures to ultrafine zinc- and copper-containing welding fumes was further investigated in analyses of nasal secretions. They detected a significant increase in nasal inflammatory mediators IL-6, C-reactive protein, and serum amyloid A (SAA) in exposed workers; thus, they concluded that measuring nasal inflammatory mediators may provide a useful noninvasive method for the occupational surveillance of workers exposed to ultrafine metal fume particles.
2. **Mixed NP types.** In a longitudinal study of nanomaterial-handling workers recruited from 14 different factories performed by Liou et al. (2012), health hazards and possible exposure surveillance markers were compared between these workers and unexposed workers being monitored six months later. The researchers investigated markers of pulmonary and cardiovascular disease, inflammation, oxidative stress, antioxidant enzymes, and genotoxicity. They found that antioxidant enzymes (superoxide dismutase, glutathione peroxidase) and cardiovascular markers (vascular cell adhesion molecule, paraoxonase) were significantly associated with nanomaterial handling during the follow-up period. In a similar study, Liao et al. (2014) confirmed many of these findings while also noting that a small airway damage marker, Clara cell protein 16, and lung function test parameters were also significantly associated with handling nanomaterials, suggesting that these biomarkers and lung function tests can be used for the surveillance of nanomaterial-handling workers. Khatri et al. (2017) studied the influence of exposure to a mixture of organic compounds on photocopier workers, leading to the detection of metal ENMs in nasal lavage (NL) samples and urine. They observed a significant increase in markers of systemic inflammation (IL-6, IL-8, TNFα, IL-1β, and eotaxin) in NL samples as well as oxidative stress markers in urine, revealing a good correlation with previous results for the tested biomarkers. More recently, Wu et al. (2021) found strong evidence of exposure to NM, after assessing the effects of lipid peroxidation in EBC from workers handling different types of NMs- (nano-titanium oxide, nano-silicon dioxide, and carbon nanotubes) to unexposed workers. Furthermore, significant correlations were found between various prostaglandins (8-iso PGF2α, 2,3 dinor-8-iso PGF2α, PGF2α) in EBC and total isoprostane levels in urine in these workers, with further correlations being detected between EBC 8-iso PGF2α and urinary 2,3 dinor-8-isoPGF2α whether they handled nano-TiO2, nano-SiO2, or CNTs. In a pilot study, Ursini et al. (2021) sought to find sensitive biomarkers of genotoxic and oxidative stress together with the most optimal biological matrices for use in biomonitoring studies. The investigators monitored graphene NMs (GNMs) and silica NPs (SiO2NPs) in production workers, focusing the analyses on buccal cells given that they are among the main targets of NM exposure. They found that the Buccal Micronucleus Cytome (BMCyt) assay and fpg-comet test (lymphocytes) were the most sensitive biomarkers of early and still reparable genotoxic and oxidative effects, with these biomarkers thus being suitable for the biomonitoring of workers exposed to various NPs used in the NM production process.
3. **Polyacrylates.** Song et al. (2009) examined a group of workers presenting unusual symptomatic findings after being exposed to a mixture of polyacrylate and other NPs (ZnO, TiO2, nanoscale silver clusters, and other engineered nanomaterials) in the process of coating polystyrene boards with this aerosolized mixture in a printing and decorating factory. Pathological analyses of lung tissue samples from these workers revealed nonspecific pulmonary inflammation, pulmonary fibrosis, and foreign-body granulomas of the pleura, raising concerns that long-term exposure to NPs without protective measures could severely damage human lungs. Markers of pulmonary lesions, tissue damage, and inflammation after exposure to toner-containing acrylates, among other nanomaterials, were also found by Bai et al. (2010) in their *in vivo* experiments, at least partially corroborating the findings published by Song et al.

Our review follows other landmark reviews that have assessed reported occupational routes and forms of exposure to engineered nanomaterials. Debia et al. (2016) reviewed studies describing 306 exposure situations in 72 work environments and graded the quality of the evidence of exposure to ENMs. They found high-quality evidence of occupational exposure to MWCNTs, single-walled CNTs, carbon nanofibers, aluminum oxide, and silver NPs. The authors also reported high-quality evidence of elevated risk of ENM exposure during “handling tasks” and found that engineering controls substantially reduced such occupational exposures. Basinas et al. (2018) reviewed 424 exposure assessment situations describing an “occupational process or activity during the manufacture, handling, or end-use of particular ENM or product containing ENM”. These authors concluded that there is a lack of measurement data for ENM exposure, although their review suggested that the route and form of occupational exposure is dependent primarily on nano-activities such as industrial processes and operational conditions.

The goal of this review was to draw on the most recent information from epidemiological studies in order to identify the expression of biological markers of physiological and molecular effects resulting from occupational exposure to different nanomaterials and nanoparticles. Studies published to dave have assessed a variety of biological markers, many of them showing statistically significant changes in biomonitoring and respiratory function studies in humans. Experiments using animals exposed to different NPs at varying doses and exposure routes allow for analyses of the effects of doses relevant to physiological human exposures. Increases or decreases in markers of lipid oxidation and inflammatory cell activation, cardiovascular disease markers, markers of oxidative DNA damage, antioxidant markers, serum pneumoproteins, acute phase proteins, clotting factors, adhesion molecules, and metabolic markers have been described.

The majority of epidemiological studies have focused on NPs derived from the manufacturing and printing technologies, mainly single- and multi-walled carbon nanotubes, titanium dioxide, metal oxides, silicon dioxide, and other nanomaterials including nanoresins, nanosilver, nanogold, nanoclay, and nanoalumina. However, multiple exposures to mixed types of NPs are very common. TiO2 was the most frequently described nanomaterial in this context, with exposure occurring either separately or in combination with other NPs. Other common exposures included mixtures of nanomaterials in welding fumes and carbon nanotubes in a variety of industries. Biomarkers exhibiting statistically significant changes in samples from NP-exposed workers such as miRNAs, fibrogenic markers, micronuclei, and macrophage ICAM-1 expression have been reported. Human sample collection efforts in different epidemiological studies have shown EBC to be a sensitive technique for the noninvasive monitoring of workers exposed to NPs, allowing for the assessment of biomarkers that reflect intrinsic changes in the airway lining fluid and lung +inflammation. Upon dissolution in biological media, some metal NPs release ions that are detectable with specific analytical methods th

at could serve as valuable markers of occupational exposure. Although the results described in this scoping review demonstrate a good relationship between exposure of workers to NPs and physiologically significant biomarkers, in order to use these biomarkers in routine occupational medical surveillance, large-scale epidemiological studies among well-defined groups of workers will be required to confirm the utility of routine occupational biomonitoring.

**Conclusions**

This review highlights the adverse physiological effects of occupational exposure to nanomaterials, as demonstrated by the significant association between such exposure and specific effect-related biomarkers. Validated biomarkers will enable the further advancement of knowledge regarding the potential health effects associated with occupational NP exposure, and will contribute to the implementation of reliable, noninvasive occupational medical surveillance of potential health outcomes. The development of biological exposure indices and occupational exposure limits will help to protect workers from emerging exposures. With further research, biomarkers could be recommended for preventive occupational medicine surveillance and to help monitor workers with occupational exposure to NPs. Based on the findings of this review, workplaces with significant NP exposure should implement preventive measures such as the substitution of certain NPs, or administrative, engineering, or personal protective equipment where possible in order to reduce exposure levels and protect workers from potential adverse health effects.

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