Biomonitoring of Nanotechnology Workers: A Scoping Review

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**Abstract**

The production and use of engineered nanomaterials (ENMs) continue to increase, posing a potential health risk to those working in close contact with ENMs. ENMs are particulate materials measuring between 1 and 100 nanometers (nm) in at least one dimension. Some unique properties of nanomaterials have increased their demand in various applications in multiple industries. However, workers' health may be compromised during the production and handling of ENMs. Since no comprehensive details on occupational hazards of nanomaterial are available to date, further research into acute or chronic health effects in ENMs-exposed workers is needed. In this scoping review, we critically assessed the literature on nanoparticle biomonitoring and discussed this approach's utility. The current review explored multiple databases using inclusion and exclusion criteria set by the PRISMA guidelines. From 286 articles reached during the initial search, 24 were shortlisted following the second round of screening by two subject specialists. Our review presented up-to-date information on biomarkers and their use in the timely detection of health hazards associated with several kinds of nanomaterials. Each sensitive, validated biomarker of exposure reported in the literature served as a valuable tool for eliciting health risks associated with workers' exposure to the nanoparticles. This review will be helpful not only in policy decision-making in the field of occupational health but also in regulating and setting occupational exposure limits in workplaces.

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

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**Introduction**

The industrial use of nanotechnology and nanoscale materials is gaining enormous scope and scale. The ENMs, with new physio-chemical properties, are continuously being produced. According to the World Health Organization (WHO), the "increased production of ENMs is putting workers at high risk of exposure to these materials, which is a cause of increasing adverse health effects" (WHO. 2017). Previous studies have provided enough evidence that workers are exposed to ENMs in various tasks they carry out in industries (Debia et al. 2016). Some industrial processes, such as cleaning, packaging, and recycling, may also put consumers at risk of nanoparticle exposure (Kuhlbusch et al. 2011). Some characteristics of ENMs, including their small dimensions, large surface area, high reactivity, charge, crystal formation, and aggregation, are potentially hazardous to human health. It is due to the reason that the biological activity of ENMs and nanoparticles largely depends on their physicochemical properties. According to Liao et al. (2014), these properties are not routinely considered in toxicological screening; therefore, their toxicity and adverse health effects remain largely unknown.

Human biomonitoring is one of the essentially applied tools in occupational health studies and refers to the “repeated, controlled measurement of chemical or biological markers or biomarkers. The markers are often detectable in exposed individuals' body fluids, tissues, or other accessible biological samples. biomonitoring provides reasonable estimates of workplace chemical, physical or biological risk factors" (Manno et al. 2010). Exposure to ENMs, as reported in previous literature, occurs through oral, dermal, and inhalation routes of exposure. Similarly, dermal penetration via injection is another route of exposure (Sahu and Hayes, 2017). Considering the wide range of their biological effects, the potential for biomonitoring of nanoparticles exposure is diverse. For example, inhalation is an important route of exposure in the occupational setting; Nanoparticles lodging in the lungs contributes to the development of idiopathic respiratory diseases. According to Rinaldo et al. (2015), around 10 to 20 percent of insoluble Nanoparticles accumulate in the lungs. However, multiple routes of Nanoparticles exposure allow us to use different methods for the biological monitoring of exposure.

One of the unwanted biological effects of ENMs is the production of reactive species (ROSs) and increased oxidative stress. A report submitted by WHO (2017) admits the scarce availability of data about routes, the fate of exposure, and ENMs' capability of inducing unwanted biological endpoints. In a past review on biological monitoring, the authors found that ENMs' physio-chemical characteristics were the main reason behind the non-availability of data on workers' health risks. The paper further explains that for the same reason, there is a scarce availability of established screening programs or protocols for quantifying biomarkers in exposed individuals (Shulte et al. 2019). A brief objective of the current review was to gain insight into scientific publications concerning biomonitoring data and exposure biomarkers of ENMs and Nanoparticles collected from ENMs manufacturing hotspots. In addition, workers' exposure to engineered materials and Nanoparticles released as a by-product during industrial activities (e.g., welding) was also profoundly studied. In light of published literature, we also discussed the current and prospects of how biological monitoring can help regulate ENMs exposure sites.

**Materials and Methods**

We run a systemic literature search in two renowned databases, i.e., Web of Science and PubMed, following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Tricco et al. 2018). The search strategy was restricted to literature published in the English language, in peer-reviewed journals, between January 1, 2009, and December 31, 2021. The keywords (or terms) used, separately or in combinations, for data extraction included "nanoparticles" or "engineered nanomaterials," "health effects," "biological markers," "biomarkers," and "workers epidemiology" **(Table 1).** The term"nanoparticles" was also used as a spelling variant to "nanomaterials” to increase the chances of reaching the relevant records. All the selected keywords helped secure two hundred eighty-six unique search results in both databases. Before initiating the screening process, all the duplicate entries were removed.

**Table 1.** Search keywords and 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 selection, screening, and eligibility criteria

PRISMA

Eligibility

Included

Screening

Identification

PubMed: n = 199

Web of Science: n = 87

Number of articles shortlisted:

n = 286

duplicate removed:

n = 165

Papers included:

n = 24

Articles excluded: n = 134

1. Review papers: n = 44
2. No occupational exposure: n = 67
3. No nanoparticles: n = 23
4. In Vitro studies: n = 5

**Figure 1** Outlines a flow chart of the selection criteria adopted from the PRISMA-ScR (PRISMA extension for Scoping Reviews) group statement (Tricco et al. 2018). Full texts of the papers meeting eligibility criteria were obtained, and the list of references was searched for articles meeting the inclusion criteria. Publications reporting biomarkers of occupational exposure to nanoparticles were prioritized.

**Screening process**

After removing duplicate entries from the original search, the abstracts of 165 articles were secured, **Fig 1**, and reviewed further by two experts. Next, the pool was narrowed further to relevant articles by excluding review articles and studies concerning non-occupational exposure to Nanoparticles, ENMs ("not occupational"), or not associated with Nanoparticles, ENMs exposure ("not nanoparticles"). Additionally, some non-epidemiological in-vitro studies were also removed during the screening process. Finally, 24 articles meeting the selection criteria were shortlisted for further review and critical analysis.

**Results**

A list of the variables of interest commonly used in biomonitoring and exposure science was summarized in **Table 2**. Variables such as exposure groups, source and health outcomes of exposure, methods for detection and quantification, the biological expression in specific biomarkers, and potential confounding factors were enlisted in separate columns. All these variables were frequently reported in almost every research article. **Table 3** summarizes the more frequently reported biomarkers of effect. Each set of respective biomarkers indicated a biological endpoint, such as cardiovascular effects, lung fibrosis, systemic inflammation, nucleic acids, lipid and protein oxidative stress, antioxidant enzyme activity, genotoxicity, and metabolic markers.

**Table 2.** Summary of the study population, nanomaterial or nanoparticle, health outcome, selected biological markers of the outcome, results, and confounding factors.

| References | NM/ NP | Exposed Population / Study/ Assay | Health effects/ Biological Markers | biospecimens used for screening | Biological Endpoint | 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: non-specific 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, bronchial-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 Nanoparticles | 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 | Nanoparticles:  CNT, TiO2, SiO2, Silver, Gold,  nanoresins, nanoclay, nanoalumina, and metal oxides  20-100 nm | A 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 Nanoparticles 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 the 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 Nanoparticles  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 were first examined cross-sectional 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 are 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-OHG  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. Eco screen 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 | **Increase** 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-OHG,  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 Nanoparticles 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-OHG  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. RedTube 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) 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 Nanoparticles 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:**  Oxidative stress Markers: LTB4 and cysteinyl LTE4 most useful and elevated in nanoTiO2 workers. | Job seniority,  material 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 Nanoparticles (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. SMP 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  PIPE |
| 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 Nanoparticles 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-isoPGF2α, 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 m size  2. silica NP(SiO2Nanoparticles)  50 nm size | Pilot study.  12 FLG (Few Layers Graphene)production (synthesis) workers  11 healthy office workers unexposed controls  Assays:   1. Questionnaire 2. Buccal Micronucleus Cytome (BMCyt) assay 3. Formamide 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, 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 senioritySmoking status  Alcohol consumption  X-ray test  Use of PPE |
| Bello D et al.  Nano sim-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: GMCSF (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 Nanoparticles | 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  Licorice 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 Nanoparticles | Cross-sectional study  66employees ofaTiO2 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 a majority of biomarkers of effect reported in the published litereture

| 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) |
| --- | --- | --- | --- | --- | --- |
| xbp-1 | 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) |  |  |
|  |  |  | IL4 (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**

In this literature review, we categorized nanoparticles into five general types for further discussion, i.e., metal oxides, multi-walled carbon nanotubes, single-walled carbon nanotubes, welding fume Nanoparticles, polyacrylate, and a mixed NP composition. Although, several health implications cause by Nanoparticles are related to their physicochemical properties, such as their shape, size, and particle composition, the impact of each of these Nanoparticles on workers' health was also discussed frequently in the literature.

1. **Metal oxide nanoparticles**. Printer toner is one of the routinely used consumables in offices. Human exposure to nanoparticles released from toner-based printing equipment and photocopiers has been linked to genotoxicity, immunologic and respiratory diseases. According to Khatri et al. (2017), titanium dioxide, iron oxide fumed silica, and several other metals are nanoparticles found in photocopiers and printers' toners. They also reported a link between such nanoparticles' physicochemical and morphological properties and their effects on human health. In a follow-up study, Khatri and colleagues (2017) observed an association between chronic exposure to nanoparticles and upper airway inflammation and systemic oxidative stress in photocopier operators. Similar findings were reported by Khatri et al. (2013) and Pirela et al. (2013, 2014) in their in-vitro and in-vivo investigations. A few epidemiological studies have reported a 2 to 3 times higher prevalence of health-related symptoms in photocopier operators compared to controls. They also developed distinct physiological symptoms, including chronic cough, wheezing, nasal blockage, excessive sputum production, breathing difficulties, and shortness of breath. Respiratory symptoms were particularly intensified in the susceptible individuals and those chronically and repeatedly exposed to ENMs. These studies provide sound evidence of an association between workers’ exposure to ENMs and the onset of immunological, cardiovascular, and other disorders.

There has been much debate about the development of appropriate safety screening methods. One approach is to deepen the understanding of the pathways causing cellular injury and gain more information on the properties of hazardous materials, particularly those posing risks to human health and the environment. George and his colleagues (2010) highlighted this point and described how metal oxides nano-particles affect pulmonary cells. They demonstrated a rapid screening assay helpful in estimating oxidative stress induced by toxic nanoparticles in bronchial epithelial and macrophage cell lines. They also studied the biological oxidative stress generated in response to Titanium dioxide (TiO2), cerium dioxide (CeO2), and zinc oxide (ZnO) using this rapid, throughput multi-parameter cellular assay. The assay highlighted the reactive oxygen species (ROS) generating capability of Zn2+ release on the dissolution of ZnO nanoparticles. As a response, the integrated pathway of cytotoxicity was also activated. This pathway included mitochondrial depolarization, intracellular calcium flux, and plasma membrane leakage. Such parameters could be helpful in deriving estimates of exposure.

Exposure to Iron oxide Nanoparticles is routine in many occupational settings because iron oxide pigments are widely used in paints, ink, rubber and plastic products, cosmetics, and medical devices. As Pelclova et al. (2016c, 2018) reported, iron oxide-Nanoparticles were associated with elevated oxidative stress biomarkers levels in the exhaled breath condensate (EBC) of exposed workers. Similarly, 5-hydroxymethylcytosine (5hmC) signatures were observed by Yu et al. (2020) in manufacturing/handling workers exposed in an iron oxide Nanoparticle manufacturing plant. The airborne concentration of nanoparticles was significantly high in these worksites and was associated with 5hmC, i.e., a biomarker of increased methylation of genomic DNA in workers. This study presented biomarkers as valuable tools for monitoring epigenetic signatures and predicting the onset of diseases at early stages. Zinc oxide, another example of ENM, is widely used in several consumer products, including sunscreens, cosmetics and textiles, self-charging, and electronic devices. According to Chen et al. (2014), increased pulmonary damage and risk of cardiovascular disease are associated with Nanoparticle exposure; however, a valuable estimate of Nanoparticle toxicity is still largely unknown (Chen et al. 2014).

Nanoscale titanium dioxides can induce inflammation and lipid peroxidation. The workers' exposure to nanoscale titanium dioxide has been extensively reported in many past publications (Andujar et al. 2014, Liao et al. 2014, Pelclova et al. 2016a, 201); Liou et al. 2017, and Zhao et al. 2018). Some related biomarkers were also detected in workers exposed to nano-TiO2 while carrying out production and packaging tasks. Such as biomarkers of lung and airway injury, oxidative damage of DNA and protein (observed in EBC specimen), and, to a lesser extent, in bronchoalveolar lavage (BAL). All of the biomarkers mentioned above were remarkably higher in exposed workers compared to a corresponding control group (Zhao et al. 2018). In the case of SP-D, a biomarker of lung damage, a dose-response pattern was also observed within the exposed subjects. Since biomarkers of cardiovascular disease and acute phase, reactants have been detected in blood and, in some cases, in urine samples. Therefore, these samples were considered sensitive and valuable, while urine was also a non-invasive monitoring tool for exposure assessment.

In two of their published studies, Pelclova et al. (2016a, 2017a) investigated short-term exposure of office employees to TiO2 pigments production facility. This study aimed to elicit the implications of nano-TiO2 exposure on the physiological parameters of workers. The results were in line with many past findings. They found evidence of the association between TiO2 exposures and biomarkers for systemic inflammation, oxidative stress, and pulmonary effects. In another investigation, Pelclova et al. (2018) also found elevated biomarkers of oxidative stress in the EBC samples of workers exposed to three different Nanoparticles compared to corresponding controls. However, the biomarkers were slightly higher in concentration in nano-TiO2- exposed workers. They employed similar biomarkers of effect, i.e., lipids, nucleic acids, and proteins oxidation, for comparison among exposure groups. Additionally, there was a strong association between leukotriene B4 (LTB4) and cysteinyl LTE4, biomarkers of inflammation. According to Pelclova and his colleagues, non-invasive biomonitoring using EBC samples and markers of oxidative stress was sensitive enough to estimate exposure to engineered nanoparticles.

A similar finding was concluded in a dose-response relationship study in laboratory animals. Comparing the bio-persistence of NiO and TiO2 nano-particles, the NiO was more persistent in tested animals (burden in lung tissues) than TiO2. This bio-persistence of nanoparticles was directly related to histopathological changes and other biomarkers in BAL fluid BALF (Oyabu et al. 2017). The bio-persistent of Nanoparticles was perceived as a remarkable indicator of hazardous potential associated with Nanoparticles. In addition, some urinary metabolites (potential candidate biomarkers), useful in the early detection of TiO2 exposure, were observed in individuals working at TiO2-NP production sites. According to Zhang Jian and his co-workers, the role of these metabolites in lipid transport, metabolism/peroxidation, and cell damage makes them useful urinary biomarkers (Zhangjian et al. 2021). Indium tin oxide (ITO) is another type of nanoparticle increasingly used in liquid crystal displays and semiconductors. The workers handling such products are, therefore, routinely exposed to nanoparticles.

Moreover, workers are exposed to TiO2, SiO2, and ITO NP granules or indium nano-sized fumes during splashing, pulverization, cutting, and grinding ITO plates. For this reason, Liou et al. (2017) evaluated workers' exposure to ITO using the EBC sampling approach. They found nanoparticles in EBC samples, blood, and urine specimen. The study suggested that exposure to metal oxide Nanoparticles may lead to global methylation and oxidative damage to DNA, and lipid peroxidation.

1. **Multi-walled Carbon Nanotubes** (MWCNT). Another example of ENMs, which can trigger physiological changes in the exposed individual, is MWCNT. Several in vivo and in vitro toxicology studies have provided enough evidence of MWCNT-related inflammation, oxidative stress, pulmonary fibrosis, mesothelioma, and cardiovascular effects (Kim et al. 2015; NIOSH, 2013). Another walkthrough health survey evaluating MWCNT-exposed workers revealed significantly higher levels of malondialdehyde (MDA), 4-hydroxy-2-hexenal, and 4-hydroxy-trans-nonenal in MWCNT manufacturing workers compared to those working in the office. This evaluation was carried out in Blood and EBC samples, while pulmonary function testing (PFT) was used to evaluate the health effect of exposure. In another study, Lee et al. (2015) suggested that elevated MDA and n-hexanal levels may also serve as biomarkers of MWCNT exposure. MWCNT exposure also affected the immune system and lung functions in exposed individuals in MWCNT-producing facilities. This association was observed by Vlaanderen et al. (2017) in a cross-sectional study at an occupational site. The complete blood count and fractional exhaled nitric oxide (FENO) parameters were different in exposed individuals compared to controls. Among the immune markers, increased basic fibroblast growth factor, C-C motif ligand 20, and soluble IL-1 were observed with increasing MWCNT exposure. These results were replicable and robust to sensitivity analysis, confirming the early effects in the study's second phase. The results indicated early effects of MWCNT exposure in the occupational site.

MWCNT aerosols are often very high in some manufacturing sites. The workforce is therefore exposed to MWCNT during packaging, fragmentation, and handling processes. According to Shvedova et al. 2016, MWCNT exposure altered the main regulators of gene expression in such exposure groups in MWCNT manufacturing facilities. The mRNA and ncRNA profile of individuals working in close contact with MWCNT was significantly different compared to controls. The global mRNA (long non-coding RNAs), lncRNA and micro RNAs (miRNAs), and non-coding RNA (ncRNA) expression profiles were also altered in the exposed group, revealing an interference in the gene expression (Shvedova et al. 2016). Other biological endpoints of MWCNT exposure observe in rodents include pulmonary inflammation and fibrosis (Shvedova et al. 2005; Porter 2010, Mercer 2011, Poulsen 2015). However, further research is needed to confirm such health outcomes in humans. Dust is a ubiquitous carrier of many contaminants in some workplaces; exposure to dust-bound Carbon Nanotubes (CNTs) is often unintentional. A case report (Wu et al. 2010) evidenced morbidity in respondents exposed to world trade center dust around 9/11incidence. They reported clinical and pathological findings in the lungs of first responders and rescue and recovery workers following the terrorist attack on World Trade Center (WTC), NYC, on 9/11/2001. The responders were diagnosed with pulmonary fibrosis, chronic bronchiolitis, and granulomas resulting from CNT exposure. The CNT was detected in biopsy specimens and air samples collected at the crash site.

1. **Nanoparticles in welding fume**. To our knowledge, no epidemiological study has investigated the neurotoxicity of manufactured nanoparticles. However, several articles have been published discussing populations exposed to anthropogenic sources of Nanoparticles. Nevertheless, studies on population exposure provide an exciting insight into exposure dynamics and health-related effects of nanoparticles in the human population. Some pollutants are site-specific, such as nanoscale fumes generated at the welding sites and other non-intentional combustion-related releases of mineral or metallic nanoparticles. Such sites can be of paramount interest in exposure science. One of the first confirmatory links between nanoparticles in welding fumes and long-term pulmonary effects was documented by Andujar et al. (2014). Nanoparticles such as Fe, Mn, and Cr oxides were identified in the sections of welders’ lung tissue, macrophages in the alveolar lumen, and fibrous regions of their lungs. Similar results were obtained in an in vitro macrophage exposure to nanoparticles, which increased the synthesis of a pro-inflammatory secretome (i.e., inflammatory markers, chemokines CXCL-8, IL-1ß, TNF-α, CCL-2,−3,−4). Another cross-sectional study was devoted to observing the central nervous system's response when exposed to welding fumes containing nano-particulate fraction. (Graczyk et al. 2016). To this purpose, Graczyk and his co-workers (2016) analyzed nonsmoker trainee welders' blood, urine, and EBC samples. They tested oxidative stress biomarkers, including 8-hydroxy-20-deoxyguanosine, malondialdehyde, and hydrogen peroxide. The samples were collected 60 min before and after work hours, during which the subjects were exposed to Tungsten Inert Gas (TIG) released in the welding fumes. Interestingly, there was an increase in the concentration of biomarkers after 3 hrs of exposure. Similar pulmonary and systemic oxidative stress biomarkers were observed in welders exposed to nanoparticles in two other studies (i.e., Jarvela et al. 2013 and Kauppi et al. 2015). A host of other investigators, together with Andujar et al. (2014), Song et al. (2016), Dierschke et al. (2017), and Rossnerova et al. (2020), concluded the same findings. Welding fumes also increased workers' nasal inflammatory mediators IL-6, C-reactive protein, and serum amyloid A (SAA). The inflammatory response was attributed to the fumes' ultrafine zinc- and copper-containing particles (Baumann et al. 2018). The risk of cardiovascular events resulting from short-term exposures to welding fumes in workers' nasal secretions was also investigated by Baumann et al. (2018). They used nasal secretions to quantify biomarkers of exposure, which could be a promising non-invasive approach for exposure biomonitoring. They also concluded that measuring nasal inflammatory mediators might provide helpful evidence of exposure to ultrafine particles in metallic fume.
2. **Exposure to mixed nanoparticles of different types.**A 6-months long longitudinal study gathered more evidence of cardiovascular and pulmonary disorders associated with ENMs exposure. The investigation conducted by Liou and co-workers (2012) involved ENMs-handling workers from 14 different factories and a control group. However, they also relied on the same biomarkers of effect as used in earlier studies, i.e., the signs of inflammation, oxidative stress, antioxidant enzymes, and genotoxicity. There was a significant association between these biomarkers and ENMs-exposure. The antioxidant enzymes (superoxide dismutase, glutathione peroxidase) and biomarkers of cardiovascular disease (vascular cell adhesion molecule, paraoxonase) were significantly associated with ENMs-handling workers compared to controls (Liou et al. 2012). Liao et al. (2014) confirmed many of these findings, explaining that testing lung function may provide valuable estimates of exposure to ENMs. After observing a marker of minor airway damage, Clara cell protein 16, and other lung function test parameters, Liao and his team reached this conclusion.

Urine and nasal lavage (NL) is another valuable pair of non-invasive matrices for exposure biomonitoring. Both were used by Khatri et al. (2017) to investigate a group of photocopiers. Photocopying is an occupation where workers are exposed to a mixture of organic compounds almost daily. Such organic mixtures also comprise nanoparticles and metallic ENMs. Photocopiers suffered systemic inflammation (as indicated by elevated concentrations of IL-6, IL-8, TNFα, IL-1β, and eotaxin in NL samples) and oxidative stress (increased biomarkers in urine). In another study, a mixture of nanomaterials (containing nano-titanium oxide, nano-silicon dioxide, and carbon nanotubes) was linked to a high risk of lipid peroxidation in exhaled breath condensate (EBC) samples of exposed workers as compared to a corresponding control group (Wu et al. 2021). The confirmatory evidence of lipid peroxidation was a strong association between various prostaglandins (8-isoPGF2α, 2, 3 dinor-8-isoPGF2α, PGF2α) in EBC and total urinary isoprostane. Likewise, urinary 2, 3 dinor-8-isoPGF2α was also significantly correlated with 8-isoPGF2α in EBC samples of exposed workers. All the prostaglandins mentioned above served as biomarkers of lipid peroxidation (Wu et al. 2021). Ursini et al. (2021) expanded their research to multiple human matrices to find sensitive biomarkers and suitable matrices for exposure biomonitoring. To this purpose, a group of workers was recruitted whose job was production and handling graphene nanomaterials (GNMs) and silica nanoparticles (SiO2Nanoparticles). Buccal cells (Buccal Micronucleus Cytome) are the primary targets for nanomaterial exposure. Buccal Micronucleus Cytome (BMCyt) assay and fpg-comet test (lymphocytes) were the most promising biomarkers for exposure assessment. In their opinion, buccal cells were the main target of nanomaterials; therefore, they could be used for the early detection of oxidative damage when the damage, whether oxidative or genotoxic, is still reparable.

1. **Polyacrylates.**Sometimes, nanomaterials exposure gives rise to unusual symptoms, possibly due to the complexity of the nanomaterials mixture in exposure sites. A mixture of such kind, containing polyacrylate and other nanoparticles (zinc oxide, titanium dioxide, nanoscale silver cluster, and other ENMs, was examined by Song and his team (2009), causing unusual symptoms among exposed individuals. They investigated a group of people coating polystyrene boards with the aerosolized mixture in a printing and decorating factory. The symptoms recorded during pathological examination included non-specific pulmonary inflammation in lung tissue, pulmonary fibrosis, and foreign-body granulomas of the pleura. The findings suggested severe lung tissue damage was expected if no personal protective measures were adopted to minimize workers' exposure to nanoparticles. In a later study in 2010 involving laboratory animals, Bai and colleagues (2010) reported almost similar findings. The experimental exposure of animals to the printer toner (containing acrylates) resulted in an elevated inflammatory response, pulmonary lesions, and tissue damage. In general, the results of this particular study were suggestive of grave health implications for indoor workers exposed to printer and toner fumes.
2. **General remarks**. We came across a couple of interesting past reviews of literature worth discussing here. Eliciting occupational ENMs exposure and health consequences, a review of the literature by Debia and his colleagues (Debia et al. 2016) summarized several pieces of evidence of exposure to ENMs in 233 situations. They covered exposure to multi-walled carbon nanotubes, single-walled CNTs, carbon nanofibers, aluminum oxide, and silver Nanoparticles Debia et al. (2016) conclude that during the handling of ENMs, the exposure may be alleviated by engineering controls. Reviewing 424 exposure situations, Basinas and his team et al. (2018) identified a scarcity of reliable and quality data on exposure scenarios, needing more research in low to middle-income countries. Furthermore, the exposure was primarily dependent on the physical state of the substances, industrial process, and operational conditions.

In the current literature review, we endeavored to draw readers' attention toward the most recently available scientific information on epidemiological studies concerning exposure to Nanoparticles and nanomaterials. This review also identified several exposure-related biomarkers of physio-biological effects and their molecular endpoints in some studies. In several past publications, the exposed subjects were demarcated by the presence of a significant amount of biomarkers in various biological matrices. In addition, some lab experiments on nanoparticles exposed animals provided further confirmatory dose-response relation between exposure concentration and physio-biological endpoints. In general, the concentration of the biomarkers was often suggestive of early disease onset or potential morbidity. The most commonly observed metabolic changes were oxidative DNA damage, lipid oxidation, and the activation of inflammatory cells. Moreover, some biomarkers were repeatedly detected in many exposed individuals, such as cardiovascular disease, antioxidant markers, serum pneumoproteins, acute phase proteins, clotting factors, adhesion molecules, and metabolic markers.

The majority of epidemiological studies involved nanoparticles from the manufacturing and printing technologies, mainly single- and multi-walled carbon nanotubes, titanium dioxide, metal oxides, silicon dioxide, and other Nanoparticles, including nano-resins, nano-silver, nano-gold, nano-clay, and nano-alumina; multiple exposures to mixed types of nanoparticles were widespread. Titanium dioxide was the most frequently described nanoparticle, separately or in combination with other Nanoparticles, followed by mixtures of nanoparticles in welding fumes and carbon nanotubes in various industries. Some new markers were also identified in the matrices of nanoparticles-exposed workers, showing statistically significant biological changes in exposure groups, such as miRNAs, fibrogenic markers, micronuclei, and ICAM-1 in macrophages. EBC was the most sensitive and valuable non-invasive medium for monitoring workers exposed to nanoparticles from all human samples collected in the different epidemiology studies. A few biomarkers reflect intrinsic changes in the airway lining fluid and lung inflammation. Once undergoing dissolution in biological media, some metallic nanoparticles release ions detectable with analytical methods, which could serve as valuable markers of occupational exposure. The results described in this scoping review demonstrate a good relationship between the exposure of workers to nanoparticles and physiologically significant biomarkers. However, large-scale testing and use of these biomarkers in routine occupational medical surveillance are still awaited. Moreover, a large-scale epidemiological study among well-defined exposure groups will be required to confirm their usefulness in routine occupational biomonitoring.

**Conclusions and recommendations**

The current review summarized research highlights of significant studies on biomarkers of effect due to acute or chronic exposure to nanomaterials in occupational sites. The review also endeavored to scrutinize the association between biomarkers of exposure and effect. Results of published literature bear excellent prospects for further research into the health-incapacitating potential of nanomaterials. Introducing non-invasive, reliable, and rapid biomonitoring techniques improves occupational safety, medical surveillance, and the health capacity of individuals in a hazardous environment. Improved workers' health can be conveniently achieved by adopting new preventive measures, for instance, by developing biological exposure indices and setting exposure limits in light of current knowledge of ENMs exposure outcomes. Further research should focus on the rapid detection of ENMS exposure and reliable biomarkers of biological effects to facilitate prompt health surveillance of the workers. The review urges proper preventive measures, replacement of nanoparticles with suitable alternatives, and adoption of administrative engineering at workplaces to ensure workers’ health and safety.

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