Biomonitoring of Nanotechnology Workers: A Scoping Review

Diana Blank-Porat 1\* and Eric Amster1

***1****Department of Environmental and Occupational Health, University of Haifa School of Public Health, Haifa 31905, Israel*

\*Corresponding Author:*dporat@staff.haifa.ac.il*

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**Abstract**

The production and uses of engineered nanomaterials (ENMs) continues to increase, , posign 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 has increased their demand in multiple industries. however, the worker’s health may be compromised during their production . Since the no comprehensive details on occupational hazards of nanomaterials 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 biomonitoring of nanoparticles and discussed the utility of biomonitoring approach.. In current review of litererure, multiple databases were explored on the basis of the inclusion and exclusion criteria set by the PRISMA guidelines.From 286 articles with matching keyword, 24 were, shortlisted following second round of screening, by two subject specialists..it was concluded that each sensitive, and validated biomarker of exposure and disease progression, may be useful for monitoring health risks associated with worker’s exposure to nanoparticle .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 ganing large scope and scale. According to the World Health Organizarion (WHO), the “increased production of ENMs and their use in is putting workers in all countries at of the risk of potential exposure to these materials, and increasing adverse health effects” (WHO. 2017). prevoius exposure assessment studies have provided enough evidence that workers are exposed to ENMs in a variety of tasks they carry out in industries (Debia et al. 2016). Additionally, some industrial processes, such as cleaning, packaging, and recycling, may also put consumers at risk of exposure to nanoparticles (Kuhlbusch et al. 2011). Novel ENMs, with new physiochemical properties, are continuously being produced. Some characteristics of ENMs, including their small dimensions, large surface area, high reactivity, charge, crystal formation, and aggregation, are potentially hazardous for for workers health, becausethe biological activity of ENMs and nanoparticals (NPs) largely depends on these physicochemical properties. According to Liao et al. (2014), these properties are not routinely considered in toxicological screening, and therefore, their toxicity and adverse health effects remain largely unknown.

Human biomonitoring is one of the essentially applied tool in occupational health studies, and refers to the “repeated, controlled measurement of chemical or biological markers in fluids, tissues or other accessible biological samples of exposed individuals. biomonitoring privides useful estimates of chemical, physical or biological risk factors in the workplace” (Manno et al. 2010). Exposure to ENMs, as reported in previous literature studies, occurs by oral, dermal, inhalation routes of exposure. Similarly, the dermal penetration via injection is another route of potential exposure (Sahu and Hayes, 2017). Considering the wide range of , NPs biological effects, the potential for biological monitoring of NPs exposure is diverse. Inhalation is an important route of exposure in the occupational setting, NPs lodging in the lungs contribute to the development of idiopathic respiratory diseases. According to et al. (2015), aroud to insoluble NPs accumulate in the lungs. However, multiple routes of NPs exposure, alow us to use different methods for biological monitoring of exposured gourps.

As reported submitted by WHO, t (2017) admits that there is scarce infomrioatn about routes, and fate of exposure asa wel as ENMs capability of inducing unwanted biological endpoints. One of unwanted biological effect of ENMs is generation reactive speices and resulting increased onxodative stress, . In a pastreview on biological monitoring, the auathors found that ENMs physio-chemical characteristic main reason behind non-availability of data on worker’s health risks . the paper further explains that for the same reason, there are scarcity of established screening programs or protocols for the quantification of biomarkers among exposure groups (Shulte et al. 2019). The objective ofcurrent review of literature was to gain insight into publications concerning biomonitoring and biomarkers of exposure to ENMs and NPs in potential exposure sites.. workers exposuer to both engineered materials, as wel as NPs released as a by product during industrial activities (e.g. during welding) were considered . In the light of published literature, we also discussed current and future pr ospects of how biological monitoring can be directed in potential ENMs exposues sites.

**Materials and Methods**

**Litereture Search Strategy, and Eligibility Criteria**

We run a systemic litererue search in two of the renowed databases i.e., Web of Science and PubMed, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Tricco et al. 2018). The keywords (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 search strategy was restricted to litereture published in English language, in the peer-reviweed journals, , between the time period of January 1, 2009 andDecember 31, 2021. the term“nanoparticles” was also used as a spelling variat to “nanomaterials to increase the chances of identifying the relevant l records, .” All the selected keywords were helpful in securing two hundred eighty-six unique search results in both databases. Before initiating screeing process, all the duplicate enteries were removed from the relevant records.

**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 | 2725 | 22 |  |  |
| 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

Number of articles shortlisted:

n = 286

duplicates removed:

n = 165

Papers included:

n = 24

Articles excluded: n = 134

1. Review papers: n = 44
2. Not Occupational: n = 67
3. Not 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 reference was also searched for articles meeting the inclusion criteria. publications reporting biomarkers of occupational NP exposure to were prioritized.

***Screening process***

After removing duplicate enteries from the original search, the abstracts of 165 articles as shown in the Fig, were selected and reviewed further by two experts. The pool was narrowed further to relevant articles by excluding review articles and studies concerning non-occupational exposure to NPs, ENMs (“not occupational”) or not clearly associated with NPs, ENMs exposure (“not nanoparticles”). Additionally, non-epidemiological in-vitro studies were also removed during the screening processs. Finally, a total of 24 articles meeting selection criteria, , were shortlisted for further review and critical analysis.

**Results**

Table 2 presents a summary of all the variables of interests, commonly used in the biomonitoring and exposure science. Variables such as exposure groups, souce of exposure, health outcomes of exposure, methods used for detection and quantification, the biological expression in terms of specific biomarkers and potential confounding factors, were frequently considered in all these studies **Table 2**.

**Table 3** summarizes the more frequently usedbiomarkers of effects. Each set of respective biomarkers was indicative of a biological endpoint, such as cardiovascular effects, lung fibrosis, lung and systemic inflammation; nucleic acids, lipid and protein oxidative stress, antioxidant enzyme activity, genotoxicity and metabolic markers, .

**Table 2.** Summary of study population, NM or NP,health outcome, selected biological markers of outcome, results and confounding factors.

| Refernces | NM/ NP  | Exposed Population / Study/ Assay  | Health effects/ Biological Markers | biospecimens used for screening | Health Endpoint | Confounding factors |
| --- | --- | --- | --- | --- | --- | --- |
| Y. Song et al.Eur Respir J2009 | 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, lymphocytesBiochemical markersFibrosis, granuloma in lung tissue | Samples:Lung tissueThoracic exudate PleuralBALF effusionBloodUrineFunctional tests: liver, kidney, and lung  | **Increased:**Blood & serum: Monocytes, ESR, ALT, ASTExudate: monocytosisPleural effusion: glucoseBALF: lymphocytosis. **Decreased:**Blood & serum: neutrophils, albuminPleural effusion: chloride ion in all patients: very lowBALF: macrophagesPathological examinations: nonspecific pulmonary inflammation, fibrosis, and foreign-body granulomas of pleura | NonsmokersNot exposed to hazardous materials |
| M.WuEnviron. Health Perspect2010 | CNTAluminum &magnesium silicates, chrysotile asbestos, calcium phosphate & sulfate | Case Report7 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 silicatesExtensive interstitial/ parenchymal abnormalities, Small airways disease | AgeGenderOccupationSmoking history ComorbiditiesLength of exposure |
|  J. H LeeNanotoxicology 2012 | Silver NPs | Case study:Walkthrough evaluation of manufacturing process of 2 workers over 7 years. | No significant findingsSilver concentration | Samples:BloodUrine | Silver in urine: not detectedSilver in blood: low conc.  | \_ |
| S.H. LiouJ. Nanopart Res2012 | NPs:CNT, TiO2, SiO2, Silver, Gold,nanoresins, nanoclay, nanoalumina, and metal oxides20-100 nm | Cross-sectional study ofmanufacturing & application workers.227 exposed vs. 137 unexposed controls from 14 NP plants.Assays:Questionnaire | * Biomarkers:

Cardiovascular: fibrinogen, ICAM, interleukin-6Antioxidants: MPO, SOD, GPX | Samples:BloodUrineEBCPulmonary functions (FVC, FEV1, PEFR, MMF, FEF25 %, FEF50 %, FEF75),Heart rateNeurobehavioral function (correct rate of 7-digit backward memory)  | **Increased**: fibrinogen, ICAM, and interleukin 6Significantly higher in part of workers**Decreased**:SOD significantly (p < 0.05)GPX significantlyin part of workers.Neurobehavioral functions Significantly lower in part of workers.**No changes** in DNA damage, genotoxicity, and pulmonary markers | Exposure statusDemographicsGeographic and socioeconomic status Smoking and alcohol consumptionBetel nut chewing habitsHistory of respiratory diseaseDusty environment |
| Andujar et al.Part. & Fib.Toxicol.2014 | Iron 20–25 nmchromium and /or manganese, titanium, aluminum, silica and nickel in lung tissue | Cross-sectional study21 welders vs. 21 controls.Assays:a. Questionnairesb. *In vitro* tests on macrophages from BALc. Quantification of NPs in tissue: Imaging & material science techniques: STEM; μXRF; EDX.d.Immunohistochemistry: Lung tissue sections stained HES (hematoxylin-eosin-saffron) or Perls PrussianCD68 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 macrophagesFibroblasts  | **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 | GenderSmoking habitsOccupational seniority |
| H.Y. Liao et al.Nanotoxicology2014 | Nanosilver, Nanogold,Fe2O3, TiO2,CNT, SiO2Multiple exposures to mixed types of NPsSize < 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:EBCBloodUrine  | **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. | AgeGenderSmoking habitsHistory of respiratory diseaseDusty environment |
| Lee et al. Nanotoxicology 2015 | MWCNTs | Health surveillance study: Walkthrough personal and area exposure levels evaluation9 manufacturing workers and 4 office workers. | * Biomarkers:

Oxidative stress  | Samples:Whole bloodEBCPulmonary function test  | **Increased:**EBC:MDA, 4-HHE, and n-hexanal in manufacturing workers significantly higher than in office workers.Blood:Normal hematology and biochemistry valuesLung function: normal | Gender, median age, work period,smoking status,diurnal variationwork-shift |
| Shvedova et al. PLoS One2016 | 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 bloodParticles in personal breathing zones | **Dysregulation:**mRNA, lncRNA, and miRNA expression profiles of target genes affecting cell cycle regulation IL6, EGFR, TGFβ; ERK, PDGFA, CASP8KL-6 (MUC 1) | AgeGenderPernicious habitsWork 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 lavageInduced sputumBloodSerumAir samples from specific areas and personal breathing zones | **Increased:** significantlySputum: IL-1β, IL6, TNF-α, inflammatory cytokines, KL-6.Serum: TGF-β1(in young)  | AgeGenderSmoking habitsWork 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) BloodUrine | **Increased:** significantlyPlasma H2O2 24%;14% 8-OHdGurinary H2O2 91%;45% urinary 8-OhdG | Non smokers,Trainees,ageMales Weight, height, BMI |
| Pelclova et al. Occ. & Env. Med. 2016a | NanoTiO2 pigment | 36 male workersworking 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:

TitaniumOxidation 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 historyMedical treatments Lifestyle habits (e.g., diet, alcohol intake, smoking, physical activity) |
| Pelclova et al.J. Breath Research2016b | NanoTiO2 aerosol80% 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, D4Lungs: % VCIN; % PEF | Samples:EBCUrine | **Increased** in EBC: LT B4, C4, E4, D4 in workers relative to controls (p < 0.01).Cysteinyl LTsImpaired %VCIN and %PEF (both *p* < 0.01). | Allergic diseasesSmoking status |
| Pelclova et al.J. Breath Research2016c | Iron oxide aerosol80% 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 inflammationProteins: o-tyrosine, 3-chlorotyrosine, and 3-nitrotyrosine | Samples:EBCUrine | **Increased**:EBC: MDA, HHEHNE, 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 | AgeBMISmoking and alcohol consumption |
| Pelclova et al. Nanotoxicology 2017b | nanoTiO280% of particles <100 nm diameter | Cross-sectional studyProduction workers and Controls. | * Lung injury, inflammation,
* Biomarkers:

Lipid oxidation, oxidative stress, cytotoxicity, and genotoxicityMDA, 4-hydroxy-trans-hexenal, 4-hydroxy-trans-nonenal, 8-iso Prostaglandin F2α; aldehydes C6–C12 | Samples:EBC | **Increased**:11 markers of lipidoxidation in productionworkers relative tocontrols(p < 0.001)  | AgeSmoking and alcohol consumptionPhysical activity \_ |
| Pelclova et al. Rev. Environ. Health2017a | 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:EBCUrine | **Increased:**9 markers of lipidOxidation, DNA and proteinoxidative damage inproduction workers.EBC: highly significant difference between production and office workers. (p < 0.001) Urine: No increase | AgeSmoking and alcohol consumptionPhysical activity |
| Vlaanderenet 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:SerumWhole blood (CBC)FENOLung 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) | AgeBMIGenderSmoking 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 stressUrinary and WBC 8-OHdG, EBC 8-isoprostane | Samples:BloodUrineEBC  | **Increased:**WBC; 8-OHdG8-isoprostane8-OHdG (negatively correlated with global methylation)WBC and urinary 8-OHdG positively correlated.Lower global methylation in ITO handling workers. | DemographicSocioeconomic characteristicsLifestyle (or smoking and alcohol consumption) Occupational history Personal and family disease |
| Dierschke et al. Int’l. Arc. Occ. & Env. Health2017 | 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-blind1. 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-B4NL: IL-6NeutrophilsIL-8 | Samples:EBCBloodSerumNasal 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 groups4. 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 AgeExposureAllergiesWork-related symptoms from eyes and airways |
| Khatri et al. NanoImpact2017 | 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 protein8-OH-dG | Samples:Nasal lavageUrine: 8-OH-dG  | **Increased:**NL: IL-6, IL-8, TNFα, IL-1β and Eotaxin (significantly p˂0.0001)inflammatory cell infiltration 2.7-foldTotal Protein: 4-foldUrine: 8-OH-dG 4.3-fold  | Age, gender, Smoking status , job seniority |
| Pelclova et al. Occ. & Env. Med. 2018 | TiO2Iron oxidesNanocomposites | 3 groups of workers vs. comparable control groups. 34 nano TiO2 workers over 2 years.14 nano Iron oxides; and32 nanocomposites workers 2-year followupAssays: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,material used Exposure to aerosols > 2 years |
| Zhao et al. Nanotoxicology 2018  | TiO2 | Cross-sectional study83 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 TCInflammatory and acute phase reactants, oxidative stress | Samples:SerumChest radiographyPFT | **Increased**:SP-D; VCAM-1 and ICAM-1LDLIL-8, IL-6, and TNF-alfaIL-1beta, IL-10**Decreased** (significantly): creatinine, triglyceride, and total cholesterol | DemographicSmoking and alcohol consumptionOccupational and medical historyUse 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 SAAICAM-1, and VCAM-1Nasal interferon-c (IFN-c)Total protein | Samples:Nasal secretion (serial)Lung function | **Increased:**Nasal: (IFN-c)Nasal Total protein, CRP, and SAA: significantlyNo 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 DNA5-methylcytosine (5mC), hepcidin, iron, soluble transferrin receptor (sTfR), ferritin, 8-OHdG, and glutathione | Samples:Blood | **Increased:**5hmCNo change, the restPositive 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 nm25–100 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. | AgeGenderBMIPPE |
| Wu WT et al. Nanotoxicology 2021 | Mixed NM nano-TiO2, nano-SiO2, CNTs in ceramic coatings, semiconductors production fiber injetion | Cross-sectional study14 factories80 NM manufacturing/ handling workers69 unexposed office workers2 years exposureAssays: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-isoPGF2α, and PGF2α. | Samples:EBCUrine | **Increased:**EBC: 8-Iso PGF2αUrine: 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 size2. silica NP(SiO2NPs)50 nm size | Pilot study.12 FLG (Few Layers Graphene)production (synthesis) workers11 healthy office workers unexposed controlsAssays: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 numberconcentration;average diameter; Lung Deposited Surface Area (LDSA); Size Distriburion (SD) at nanoscale;gravimetric, chemical, morphological analyses
 | * Biomarkers:

Oxidative stress8-oxoGua, 8-oxoGuo and 8-oxodGuo (urine)Cytokines (serm)BMCytFPG protein | Samples:Buccal cellsWhole bloodEBCUrineFENO (fractional exhaled nitric oxide)Serum | **Increased:**BMCytFPG protein | Age, gender,Job senioritySmoking statusAlcohol consumptionX-ray testUse of PPE |
| Bello D et al.Nanoim-pact 2021 | Mixture of ENM in toner-based printing equipment:TiO2,MnO2NiO2, Carbon Black, Iron and copper oxides, amorphous silica; organic and inorganic compoundsSize: PM0.1 and larger | Phase I: Cross-sectional studyPhase II: Longitudinal studyExposure of 19 healthy copier operators at 6 photocopy centers in Singapore4 times in 2 weeksAssays:1. Standardized Respiratory Questionnaire
2. Immunofluorescence, Multiplex Immunoassays
3. Exposure metrics: particle numberconcentration; average diameter; LDSA
4. Exposure effect on air and airway microbiome (profiling)
 | * Biomarkers:

14 inflammatory cytokines | Samples:nasal lavage (NL) plasmaurinesaliva and sputum  | **Increased:**NL: Fractalkine, IL-1β,IL-1αPlasma:Fractalkine, IL-1β, TNF-α, IFN-γ**Decreased:**Plasma: GMCSF (Granulocyte Macrophage-Colony Stimulating Factor) | Occupational history, past exposures; full/ part time employmentIntensity of workSmoking statushealthy lung function, non exposed to ENMPre-existing diseases (diabetes, myocardial or thyroid disease, etc) |
| Zhangjian Ch et al.Nanotoxicology 2021 | TiO2 NPs | Cross-sectional study56 exposed packaging workers 44 unexposed office workers as controls age: >20 yr employed > 1 year in present jobhealthy subjectsAssays: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: MDALiquoric acid Significantlycorrelated(p<0.05),**Decreased:**Antioxidant enzyme SOD | AgeGenderBMISmoking statusDrinking habitsHistory of respiratory, heart, liver and kidney diseases, dia- betes, cancer; recent fever or inflammation; other acute/chronic diseases. |
| Zhangjian Ch et al.Nanoscale 2021 | TiO2 NPs | Cross-sectional study66employees ofaTiO2 NP manufacturing plant66 controlsAssays: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:

DibenzyletherQuassimarinTryptophan. | Samples:Urine | **Increased:**DibenzyletherQuassimarinTryptophan | AgeGenderBMISmoking statusDrinking 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 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) |
| --- | --- | --- | --- | --- | --- |
| 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) | Dibenzylether |
|  | 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 review of literature, we categorized nanoparticles in five general types for futher discussion i.e., metal oxides, multiwalled carbon nanotubes, single-walled carbon nanotubes,welding fume NPs, polyacrylate, and a mixed NP composition.Since health implications of NPs are largely attributed to their physicochemical properties such as their shape, size and the particle composition . , therefore the impact of each one of these NPs on workers health was also dicussed in the current review,

1. **Metal oxides NPs**. Printer toner is one of the routenly used consumables in offices. Human exposure to nanoparticles released from toner-based printing equipments and and photocopiers,, has been linked to genotoxicity and immunologic and respiratory diseases. According to Khatri et al (2017) titanium dioxide, iron oxide, fumed silica, and several other metals are examples of some nanoparticles found in the toners of photocopiers and printers. They also explored a link between the physicochemical and morphological properties of such nanoparticles and their effects on human health . in this follow-up study, Khatri and colleagues (2017) observed a link betwwen chronic exposure to nanoparticles upper airway inflammation and systemic oxidative stress in photocopier operators ., similar findings were also 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 report from 2 to 3 times higher prevalence of health related symtopms in photocopier operators compared to controls. The distinct symptoms included a chronic cough, wheezing, nasal blockage, excessive sputum production, breathing difficulties, and shortness of breath. Respiratory symptoms were particulary intensified in the susceptible, and those indivisualy who were chronically and repeadtedly exposed to ENMs . these studies provide a sound evidenece for the association between ENMs exposure and the development of immunological, cardiovascular, and other disorders.

While there is much debate on how to develope appropriate safety screening methods, one approach is to to to deepen the understanding of the pathways causing cellular injury and ganing more informtion on the properties of hazardous material, in particular, those affecting both human health and environnment . George et al. (2010) also reported how metal oxides nanoparticles affect pulmonary cells and useful biomarkers of exposure. . George et al. (2010) demonstrated a rapid screening assay helpful in estimating oxidative strees induced by toxic nanoparticles, in bronchial epithelial and macrophage cell lines. They studied the biological oxidative stress response was generated in response to Titanium dioxide (TiO2)— cerium dioxide (CeO2), and zinc oxide (ZnO) using this rapid, throughput multiparameter cellular assay. the assay highlighted the reactive oxygen species (ROS) generating capability of Zn2+ release on dissolution of ZnO nanoparticles, . as a response, the integrated pathway of cytotoxicity was also was also activated. This pathway included the mitochondrial depolarization the intracellular calcium flux, , and plasma membrane leakage. Such parameters could be usful in derving estimates of exposure.

exposure to Iron oxide NPs is also common in many occupational settings, it is because the iron oxide pigments are widely used in paints, ink, rubbers, plastics, cosmetics, and medical devices. since iron oxideNPs, as reportd by , were associated with elevated levels of oxidative stress biomarkers in the exhaled breath condensate (EBC) of exposed workers. Similarly, 5hydroxymethylcytosine (5hmC) signetures were observed by Yu et al. (2020) in manufacturing/handling workers exposed in an iron oxide NPs manufactureingplant . The airborne concentratin of nanoparticles was significantly high in these worksites, and was associated with 5hmC, which is a good biomarkers of increased methylation of genomic DNA. This study provides useful tools to moniting not only epigenetic signatures, but also in predicting diseases at early stages. useful marker ,

Zinc oxide ENMs are also widely used in several consumer products, including sunscreens, cosmetic and textiles products, , and self-charging and electronic devices. According to Chen et al (2014) an increased pulmonary damage, and risk of cardiovascular disease are associated with NP exposed ; however,a potential estimate of NP’s toxicity is still unknown (Chen et al. 2014).

nanoscale titanium dioxide are capable of inducing inflammation and lipid oxidation markers The workers exposure to nanoscale titanium dioxide is extensively reported in many past publications ( Andujar et al. (2014), Liao et al. (2014), Pelclova et al. (2016a, 2017b), Liou et al. (2017), and Zhao et al. (2018). , some other bioamers were also observed in workers exposed to nanoTiO2 while carrying out production and packaging tasks. Such biomarkers of lung and airway injury, those of DNA and protein oxidative damage in EBC samples, and, to a lesser extent, in bronchoalveolar lavage (BAL) were higher in workers compare to a corresponding control group (Zhao et al. 2018). A significant dose-dependent association between TiO2 exposure and EBC-biomarkers of lipid oxidation was established. since biomarkers of cardiovascular disease and acute phase reactants have been detected in blood and in some cases, inurine samples. therefore, these samples were considered sensitive and useful noninvasive monitoring of biomarkers of exposure.

In two of their research studies, Pelclova et al. (2016a, 2017a) investigated short-term exposure of office employees to nanoTiO2 where TiO2 pigments were produced. this study aimed at evaluating the impact of such exposure on physiological markers in the samples of exposed workers . The results were in line with many past finings, and came up with strengthening evidence ofassociation between theTiO2 exposure and resulting biomarkers for systemic inflammation, oxidative stress, and those of pulmonary effect . In another investigation, Pelclova et al. (2018) found elevated biomarkers of oxidative stress in the EBC samples of workers exposed to three different NP compared with conrresponding controls. However, the biomarkers were slightly higher in nanoTiO2- exposed workers. they employed similar biomarkers of effect i.e. lipids , nucleic acids, and proteins oxidation for comapirson among exposure goroups.. Additoinaaly, there was a strongly association between leukotriene B4 (LTB4) and cysteinyl LTE4, which are biomarkers of inflammation, . According to Pelclova and colleagues non-invasive biomonitoring using EBC samplels and markers of oxidative stress was sensitive enought for evaluation of exposure toengineered nanoparticles. A similar finding was concluded in a dose-response relationship study in laboratory animals. Comparing the persisnce of, NiO and TiO2 nanoparticles, the NiO was more persistant in tested anaimals ( burden in lungs tissues ) than TiO2. This biopersistance of nanoparticles was directed related with

 resulting in histopathological changes and other biomarkers in BAL fluid (BALF)(Oyabu et al 2017),

. the biopersistant was of NPs was percieved as a remarkable indicator of hazard associated with NPs . Some urinary metabolites (candidate biomarkers), useful in early detection of TiO2-exposure were observed in subjects working at TiO2-NPs production site. Zhangjian and his colleagues in 2021. including quassimarin, tryptophane, and benzyl-ether. According to this group of researchers, role of these metabolites in lipid transport, metabolism / peroxidation, cell damage makes them useful urinary biomarkers (Zhangjian and colleagues 2021). like .

Liou et al. (2017) Indium tin oxide (ITO) is another type of NP which is increasingly used in liquid crystal display and semiconductor production. The workers handling such products are therefore routinely exposed to NP. these workers are are exposed to TiO2, SiO2, and ITO NP granules or indium nano-sized fumes during different processes of splashing, pulverization, cutting, and grinding of ITO plates (Liou et al 2017) the. Liou et al. (2017) for this reason evaluated worker’s exposure to ITOo using EBC sampling approach. they found NPs in EBC samples, blood, and urine specimen. they study suggested that exposure to metal oxide NPs may lead to global methylation and oxidative damage to DNA, and lipid peroxidation.

1. , **Multi-walled Carbon Nanotubes** (MWCNT), is another example of ENMs, which have capability of triggrering physiological changes in exposed indivisual. 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 office. This evaluation was carried out in Blood and EBCs samples, while pulmonary function testing (PFT) was used for evaluating the health effect of exposure. .in another study, Lee et al (2015) have suggested that the elevated levels of MDA and n-hexanal levels may also serve as biomarkers of MWCNT-exposure .

MWCNTexposure in also affected immune system and lung functions in exposed individuals in MWCNT-producing facility. This association was observed by Vlaanderen et al. (2017) in a cross-sectional study at occupational site. t The complete blood count and fractional exhaled nitric oxide (FENO), parameters, were different in exposed individuals compared to controls. Among the immune markers significant increase in basic fibroblast growth factor, C-C motif ligand 20 , , and soluble IL-1 was observed with increasing MWCNTexposure , . These results were replicable and robust to sensitivity analyses, confirming the early effects in second phase of the study. . The results were indicating early effects of MWCNTs exposure in occupational site .

MWCNT aerosols are often very high in some manufacturing site. Workforce is therefore exposed to MWCNT during packaging, fragmentation, and handling processes. According to Shvedova et al. 2016, MWCNT exposure alterd the main regulators of gene expression, in such exposure groups in MWCNT manufacturing fascility. The mRNA and ncRNA profile of individuals working in close contact with MWCNT was significnaly different compared to controls. The, global mRNA (long non-coding RNAs, lncRNA and micro RNAs (miRNAs) and non-coding RNA (ncRNA) expression profiles was also altered in exposed group, revealing an interference in the gene expression Other health endpoints of MWCNT-exposure observe in redents include the 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 human . Dust is a ubiquitous carrier of many contaminants, in some workplace, 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 were detected in biopsy specimens as well as in air samples collected at the crash site.

1. **Welding fumes NPs**. To the best of our knowledge, no epidemiological study has so farinvestigated the neurotoxicity ofs of manufactured NPs. However, several articles are published discussing populations exposed to anthropogenic sources of NPs. such studies on population exposure provide interesting insight into exposure dynamics, and health related effects of nanoparticles in human population. some pollutants are sites-specific, such as nanoscale fumes generated at the welding sites as wel as other non-intentional combustion-related release of mineral or metallic NPs. such sites can be of paramount interest in exposure studies. One of the first confirmatory link between NPs in welding fumes, and long-term pulmonary effects was documented by Andujar et al. (2014). NPs such as Fe, Mn, 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 obtaine in an *in vitro* macrophage exposureto NPs, which increased the production 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 even devoted to observe response of central nervous system when exposed to nanoparticulate fraction welding fumes . (Graczyk et al 2016). To ths purpose, blood urine and EBC sampes of non-smoker trainee welders were analyzed by Graczyk and co-workers (2016) for oxidative stress biomarkers. They tested oxidative stress biomarker included 8-hydroxy-20 -deoxyguanosine, malondialdehyde, hydrogen peroxide, i . The samples were collected 60 min before and after work hours, during which the subjects were exposed to Tungsten Inert Gas (TIG) relesased in the welding fumes.interestingly, there was an increase in the concentration of biomarkers post 3 hrs of exposure. Almost similar pulmonary and systemic biomarkers of oxidative stress were observed in welder exposed to nanoparticles in two other studies (),. A host of other investiagators 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 nasal inflammatory mediators IL-6, C-reactive protein, and serum amyloid A (SAA) in workers. The inflammatory response was attributed to the ultrafine zinc- and copper-containing particles in the fumes. (Baumann et al 2018). The risk of cardiovascular events resulting from short term exposures to welding fumes was investigated in worker’s nasal secretions, by Baumann et al. (2018). They used nasal secretions to quantify biomarks of exposure, which could be a promising non-invase approach for exposure biomonitirng. They also concluded that measuring nasal inflammatory mediators may also provide a useful evidece of exposure to ultrafine particles of metallic fume.
2. **Exposure to mixed NPs of different types.** a 6-months long longitudinal study, doumented more evidence of cardiovascular and pulmonary disorders associated with ENMs exposure while handling such materials. The investigation conducted by Liou and co-workers (2012), involved ENMs-handling workers from 14 different factories, and a control group ) . Interestingly, they also relied on the same biomarkers of effect, as used in earlier studies, including the signs of, inflammation, oxidative stress, antioxidant enzymes, and genotoxicity. The antioxidant enzymes (superoxide dismutase, glutathione peroxidase) and biomarkers cardiovascular disease (vascular cell adhesion molecule, paraoxonase) were particularly and significantly associated with ENMs handling work compared to a controls (Liou et al 2012). -exposure. Many of these findings were confirme by Liao et al. (2014), explaing that testing lung function may provide useful estimates of exposure to ENMs. . Liao and his team. , reached this conclusion studying a marker of small airway damage, Clara cell protein 16, and other parameters of lung function test. There was a significant association between these biomarkers and ENMs-exposure , , -.

Urine and nasal lavage (NL) another useful pair of non invasive matrices for exposure assessment. These matrices were used by Khatri et al. 2017 styding a group of photocopiers. Photocopying is another example of occupation where workers are exposed tomixture of organic compounds on daily basis.esuch organic mixtures also commprises NPs and metallic ENMs. photocopiers suffered systemic inflammation (as indicated by elevated concentration of IL-6, IL-8, TNFα, IL-1β, and eotaxin in NL samples) as well as oxidative stress (increased biomarkers in urine)., In another study, a mixture of NMs (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 handling workers as compard 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 significnaly correlated with 8-isoPGF2α in EBC samples. of exposed workers,. All the above mentioned prostaglandins served as biomarkers of lipid peroxidataon (Wu et al 2021). Ursini et al. (2021), expanded their research to multiple human matrices, to find sensitive biomarkers and suitable matrics for exposure biomoniroing. To this purpose, a group of graphene nano materials (GNMs) and silica nano particles (SiO2NPs) production and handling workers was recruited. buccal cells (Buccal Micronucleus Cytome), considered to be among the main targets for NM exposure. They found that Buccal Micronucleus Cytome (BMCyt) assay and fpg-comet test (lymphocytes) were the most promising biomarkes for exposure assessment. In their opinion, buccel cells were the main target of nano materials, therefore they could serve in early detection of oxidative damage, when the damage, whether oxidative or genotic, is still reparable. s.

1. **Polyacrylates.** Sometimes, NMs exposure give rise to unusual symptoms, possibly due to composition of mixture of NMs in exposure sites. A mixture of polyacrylate and other nanoparticles (zinc oxide, titanium dioxide, nanoscale silver cluster, and other ENMs, for instance, was examined by Song and his team (2009) causing unusal symptoms among exposed individuals. They investigated a group of people ) involved in coating polystyrene boards with the aerosolized mixture in a printing and decorating factory. the symptoms recorded during pathological examination included a nons-pecific pulmonary inflammation in lung tissue, pulmonary fibrosis, and foreign-body granulomas of the pleura. The findings were suggestive of a possible severe damage to lung tissues in the long run, if no personal protective measures were adopted to minimize worker’s exposure to nanoparticles. In a later study in 2010 involving laboratory animals, almost similar findings were reported by Bai and colleagues (2010). The experimental exposure of animals to the printer toner (containing acrylates), resulted in elevated inflammatory response, pulmonary lesions, and tissue damage, ENMs, in generala, the results of this particular study were suggestive of grave helath implications for indoor workers exposed to printer and tonner fumes.
2. **General Remarks**. We came across a couple of interesting past reviews of literature, eliciting occupational ENMs exposure and health consequences. A review of literature by Debia and his colleagues (Debia et al 2016) sammarized several evidences of exposure to ENMs in 233 situations. The review covered exposure to multiwalled carbon nanotubles, single-walled CNTs, carbon nanofibers, aluminumim oxide, and silver NPs Debia et al (2016) concludes that during handling of ENMs, the exposure, may be alleviated by engeneering controls.

. reviewing of 424 exposure situations, Basinas and his team et al (2018) identified scarcity of reliable and quality data on exposure scenatios, needing more research in low to middle income countries. furthermore, the exposure was mostly depedent on, physical state of the substances, industrial process and operational conditions. occupational exposure is dependent primarily on nano-activity such as i

in current review of litereure, we edavoured to o draw readers attention towards the most recentlt available scientific information on epidemiological studies concerning exposure to NPs and NMs. the review also identified several exposre-related bioamarkers of pysio-biological effect, and and their molecular endpoint in some studies. .in many published studies, the exposed subjecst were clearaly demarcated by the presence of signifinct amount of biomarkers in a variety of biologica matrices. . Some lab experiments on NPs-animals provoded confirmatory dosrer-response realtion between exposure concentration and physio-biological enpoinnts.. In general, the fluctuating biomarkers concentration was suggestive of early disease onset or probable morbitidy. The most commonly observed metabolic changes were, oxidative DNA damage lipid oxidationand, and the activation of inflammatory cell. moreover, some biomarkers were repeatedly observed in many exposed individuals, such as those of 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 either described nanoparticles, 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. From all human samples collected in the different epidemiology studies, EBC was the most sensitive and valuable non-invasive medium for monitoring of workers exposed to nanoparticles. A few of 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 curret review presented highlights of major biomarkers of effect, results as consequence of acute or chronic exposure to nano-materials in occupational sites. The review also edaveared to scrutinize association between biomarkers of exposure and effect. resutlts of published litereure bear great prospects for further research into health incapacitataing potential of nanomaterials, side by side with their auspices. introducing non-invasie, reliable and rapid biomonitorign techniques not only impove occupational safety, and medical surveillance, but also health capacity of individuasl in occupational environnemt . This can be conveniently achieved by adopting noval preventive measures. For instance by developing indeices of biological exposure, and setting exposure limites in the light of current knowlge of ENMs exposures studies,.further research should be focusing rapid detection of ENMS-exposure and reliable biomarkers of biological effects, to fascilitate prompt health survisllence of the workers. The review urges the need for proper preventive measures, replacement of nanoparticles with alternatives, and adoption of administrative engineering at workplaces to ensure health and safety.

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