Industrial Health 2020, **58**, 492–502

Review Article

Oxidative stress induced by occupational exposure to nanomaterials: a systematic review

Javad GHAFARI[1], Nargess MOGHADASI[2] and Soqrat OMARI SHEKAFTIK[2]*

[1]School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Iran
[2]Department of Occupational Health, Faculty of Public Health, Iran University of Medical Sciences, Iran

Received April 8, 2020 and accepted July 14, 2020
Published online in J-STAGE July 21, 2020

Abstract: The rapid growth of nanotechnology has increased the occupational exposure to nanomaterials. On the other hand, a growing body of evidence considers exposure to these materials to be hazardous. Therefore, it is necessary to examine the effects of occupational exposure to these materials by different methods. Biological monitoring, especially the investigation of oxidative stress induced by exposure to nanomaterials, can provide useful information for researchers. This study systematically reviews studies that have investigated oxidative stress caused by occupational exposure to nanomaterials. The search was conducted on the PubMed, Scopus and Web of Science databases. Of the 266 studies we obtained in our initial search, eventually 11 were included in our study. There is currently no specific biomarker for investigating oxidative stress induced by exposure to nanomaterials. Therefore, the reviewed studies have used different biomarkers in different biological fluids for this purpose. Also, the methods of assessing occupational exposure to nanomaterials in the investigated studies were very diverse. Given the approach of the investigated studies to biomarkers and exposure assessment methods, finding a specific biomarker for investigating exposure to nanomaterials seems unattainable. But reaching a group of biomarkers, to assess exposure to nanomaterials seems more applicable and achievable.

Key words: Nanomaterials, Occupational exposure, Biomarkers, Oxidative stress, Exposure assessment

Introduction

Nanotechnology has emerged, formed and developed rapidly in recent decades[1)]. The advances in this field are primarily due to the small size of nanoparticles, and subsequently to the unique properties of nanoscale materials; physical, chemical, electrical, magnetic, mechanical, thermal, optical, and other properties which distinguish them from other materials; even if they have the same chemical composition[2, 3)]. These new features, in addition to the many applications they have created for nanomaterials in various industries and scientific fields, have raised concerns about the effects of nanomaterials on human health and the environment. These concerns have been driving the design and implementation of numerous research and publication articles since the 1990s on the effects of nanomaterials on the environment, plants, laboratory animals, various human cells, and so on[4, 5)].

Concerns have been raised about nanomaterials when in vitro and in vivo studies showed that nanomaterials have new biological properties in addition to specific physical and chemical properties, including movement toward secondary target organs, poor clearance by macrophages, the ability to transmit through the axons of sensory neurons, and to reach intracellular structures such as mitochondria and the nucleus[6)]. It may be argued that the exposure of

*To whom correspondence should be addressed.
E-mail: omari.s@iums.ac.ir

the workers of the manufacturing and consuming companies of nanomaterials is more important; because in the processes involved in the production or use of nanomaterials or in processes that have nanomaterials as by-products, these employees are the first to be exposed to these materials[7–9]. Forecasts suggest that 6 million workers worldwide will be exposed to nanomaterials by the end of 2020[10].

Therefore, different studies have investigated the different scenarios of occupational exposure to nanomaterials and the effects of these exposures in different methods. Some studies have also used conventional occupational health practices to assess occupational exposure to nanomaterials; many studies, however, do not consider traditional occupational health practices to be appropriate for assessing exposure to nanomaterials and have proposed new approaches, equipment, and methods[11–13]. The reason for the need for new methods to nanomaterial exposure assessment and its potential impacts is that many of the information needed for assessment, such as toxicological information, how to measure and report occupational exposure, and exposure scenarios, is not available for nanomaterials[14, 15]. Therefore, different approaches have been proposed and evaluated by different researchers and organizations, each with their own strengths and weaknesses, which has led to a lack of consensus on the methods of assessment of occupational exposure and effects of nanomaterials[16].

One of the researchers' interests in investigating the effects of nanomaterials is to measure the levels of different biomarkers in different tissues and biological fluids of exposed individuals. A wide range of biomarkers, including Cancer/Fibrosis, Inflammation, Oxidative Stress, Cardiovascular, Coagulation, etc., have been studied in blood, urine, EBC (Exhaled breath condensate), WBC (White blood cell) and...[8]. One of the well-known mechanisms of toxicity of nanomaterials is their ability to produce reactive oxygen species (ROSs) and increase cell oxidative stress[17, 18]. Increased levels of oxidative stress in the cell can affect its function and in some cases lead to cell death; disruption of the function and death of cells can eventually damage the body's organs function[19].

Subjects and Methods

This systematic review study began with the determination of title and search keywords. MeSH (Medical Subject Heading)[A] and mtree[B] were used to determine appropriate search keywords. Next, using them, the search strategy was compiled (Appendix 1) and the search was conducted on the PubMed, Scopus and Web of Science databases. The search was conducted among 2,000–2,020 articles. After an initial search, 266 articles were found; after eliminating duplicate articles, this number reached 227. Most of these studies were related to the toxicology of nanomaterials, then most of the studies were related to occupational exposure to nanomaterials, and finally several studies have examined the environmental effects of nanomaterials. Subsequently, articles were reviewed by title, with 59 articles remaining after this step. By reviewing the abstract of these 59 articles, 29 other articles were removed and the remaining 30 were fully reviewed. Finally, 17 articles were compared with our final criteria for staying in the study (study should be cross-sectional, the exposure should be occupational and biomarkers of oxidative stress should be investigated), and 11 articles were reviewed in this study (Fig. 1).

Results

In the present study, 11 studies that have investigated occupational exposure to nanomaterials and its association with oxidative stress were reviewed. Table 1 provides a summary of the reviewed studies.

Occupational exposure to carbon nanomaterials

Carbon nanomaterials are widely produced and used in large quantities worldwide. These materials are manufactured in various forms of tubular, spherical, rod, fibrous, and are used in various industries. Much research has been done on the possible effects of these nanomaterials on humans and the environment. Especially nanotubes and nanofibers, which are usually considered more dangerous than spherical nanomaterials because of their shape[20]. Some studies have also found them to be asbestos-like and may cause fibrosis and malignancy[21]. Therefore, they are among the few nanomaterials for which exposure limits have been proposed[22]. Among the studies, two studies have examined occupational exposure to carbon nanomaterials. The first study conducted at a multi-walled carbon nanotube manufacturing plant in South Korea[23]. The study involved 14 workers of the factory (9 workers exposed to nanomaterials, 4 non-exposed

[A] https://www.ncbi.nlm.nih.gov/pubmed/
[B] https://www.embase.com/#emtreeSearch/default

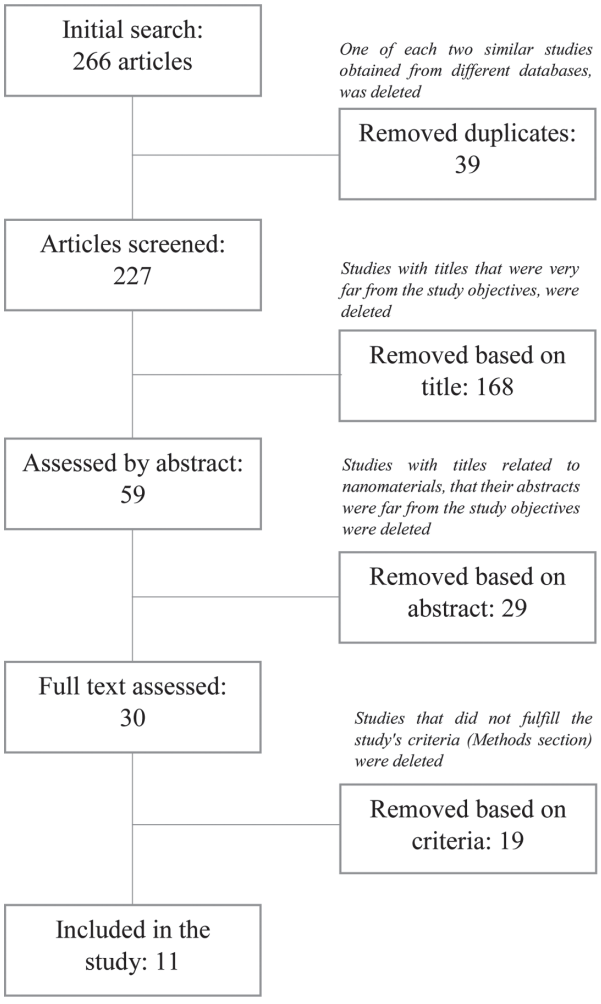

Fig. 1. Flowchart of inclusion studies.

workers). EBC samples were taken from all of them and H_2O_2 (Hydrogen Peroxide), MDA (Malondialdehyde), 4-HHE (4-hydroxy Hexenal), n-Hexanal biomarkers were evaluated in their samples. The results showed that the level of MDA, 4-HHE, n-Hexanal biomarkers in EBC of exposed individuals was significantly higher than non-exposed workers. The second study was conducted in 12 US carbon nanotube/nanofiber manufacturing, consuming, and distributing enterprises[24]. The study involved 108 employees exposed to carbon nanotubes/nanofibers (the study lacked an unexposed group). Sputum and blood samples were taken from these subjects and a total of 37 different biomarkers in their blood and 36 biomarkers in their sputum were examined. The oxidative stress biomarkers were 8-OHdG (8-hydroxy-2′ -deoxyguanosine), MPO (Myeloperoxidase), SOD (Superoxide dismutase) and GPx (Glutathione peroxidase). The results showed that the level of GPx and SOD biomarkers in sputum were significantly associated with exposure to nanotubes/nanofibers. Also, the level of 8-OHdG, GPx and SOD biomarkers in blood were significantly associated with exposure to nanotubes/nanofibers.

Occupational exposure to metal oxide nanomaterials

Studies show that most production and use among nanomaterials is related to metal oxide nanomaterials[25]. Increasing production and use of these materials also increases the number of people exposed to them. Studies have shown that the main mechanisms of toxicity of these substances are the production of metal ions and the production of reactive oxygen species (ROSs), which ultimately leads to increased cellular oxidative stress[26]. Of the 11 studies, 6 have investigated occupational exposure to metal oxide nanoparticles and in particular TiO_2 (titanium dioxide). The first study was conducted at a TiO_2 nanoparticle manufacturing factory in the Czech Republic[27]. Thirty-nine employees (19 with occupational exposure to TiO_2 nanoparticles and 20 non-exposed) participated in this study. EBC samples were taken from all participants and MDA, HNE (4-Hydroxynonenal), HHE, 8-isoprostane, 8-OHdG, 8-OHG (8-hydroxyguanosine), 5-OHMeU (5-hydroxymethyl uracil), o-Tyr (Oxidized tyrosine), 3-Cl-Tyr (3-chloro-tyrosine), NO-Tyr (nitrotyrosine) and LTs (leukotrienes) biomarkers were examined in their EBC samples. The results showed that the level of biomarkers in employees exposed to nanomaterials was significantly higher than non-exposed workers. The second study was conducted at a TiO_2 production plant in the Czech Republic[28]. The study involved 81 staff (36 with occupational exposure to nanomaterials and 45 non-exposed). In this study, the levels of 8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3-ClTyr and 3-NOTyr (3-nitrotyrosine) biomarkers in EBC of workers were evaluated. The results showed that the level of biomarkers studied was higher in the exposed group than the control group. Multiple regression also showed a correlation between TiO_2 production and the level of biomarkers studied. In the third study, 36 office workers of a TiO_2 production plant in the Czech Republic were surveyed[29]. Twenty-two of these employees were occupationally exposed to nano-TiO_2 for less than 30 min daily, and the other 14 were nonexposed to nano-TiO_2 as the control group. The level of 8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3-ClTyr and 3-NOTyr biomarkers in EBC and urine of these subjects were evaluated. The results showed that the level of these biomarkers in the EBC of the exposed staff was significantly higher than that of the control group. On the other hand, the level of urinary

Table 1. Summary of the reviewed studies

Authors	Type of study	Country/Yr	Size of NPs	Subjects	Sample size	Biomarkers	Biological liquid	NPs	Type of NPs	Metrics	Exposure level
Beard *et al.*[24]	Cross-sectional epidemiological study	US/2018	1.5–110 nm × 3.3 μm -1 mn	Workers from 12 U.S. sites	Exposed (108) Nonexposed (0) Total (108)	8-OHdG, GPx, MPO, SOD	Sputum and blood	CNTs/ CNFs	ENPs	Number & Mass Concentrations	Mean particle (10 to 1,000 nm) number concentration (P/cm^3 of air): 540.73 Mean total inhalable CNT/F (structures/cm^3 of air): 1.31E-04
Liou *et al.*[31]	Cross-sectional Exposure-Non-exposure study	Taiwan/2017	<100 nm	Workers with occupational exposure to metal oxide nanomaterials	Exposed (87) Nonexposed (43) Total (130)	8-OHdG & 8-isoprostane	Urine, WBC, EBC	TiO_2, SiO_2, ITO	ENPs	N/A	Qualitative
Pelclova *et al.*[28]	Cross-sectional Exposure-Non-exposure study	Czech Republic/2016	80% of particles <100 nm	Workers exposed to (nano)TiO_2 pigment	Exposed (36) Nonexposed (45) Total (81)	8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3-ClTyr, 3-NOTyr	EBC	TiO_2	ENPs	Number & Mass Concentrations	The median total mass concentrations were 0.65 and 0.40 mg/m^3. The median numbers concentrations were 1.98×10^4 and 2.32×10^4 particles/cm^3
Pelclova *et al.*[29]	Cross-sectional Exposure-Non-exposure study	Czech Republic/2016	80% of particles <100 nm	Office workers exposed to air pollutants including (nano)TiO_2 particles	Exposed (22) Nonexposed (14) Total (36)	8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3-ClTyr, 3-NOTyr	EBC	TiO_2	ENPs	Number & Mass Concentrations	The median respirable TiO_2 mass concentration was 0.40 mg/m^3, median number concentration was 2.32×10^4 particles/cm^3
Lee *et al.*[23]	Cross-sectional Exposure-Non-exposure study	Korea/2015	NA	Workers exposed to MWCNTs	Exposed (9) Nonexposed (5) Total (14)	H_2O_2, MDA, 4-HHE, n-Hexanal	EBC	MW-CNTs	ENPs	Number & Mass Concentrations	The worker exposure to elemental carbon was found to be 6.2–9.3 mg/m^3 in the personal samplings and 5.5–7.3 mg/m^3 in the area samplings
Liou *et al.*[34]	Cross-sectional Exposure-Non-exposure study	Taiwan/2012	<100 nm	Workers handling engineered nanomaterials	Exposed (227) Nonexposed (137) Total (364)	8-OHdG, Isoprostane, SOD, GPx, MPO	Blood, urine, EBC	Various	ENPs	N/A	Qualitative
Pelclova *et al.*[27]	Cross-sectional Exposure-Non-exposure study	Czech Republic/2012	90% of particles <100 nm	Workers exposed to Nanoparticles	Exposed (20) Nonexposed (19) Total (39)	MDA, HNE, HHE, 8-isoprostane, 8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3-Cl-Tyr, NO-Tyr, LTs	EBC	TiO_2	ENPs	Number & Mass Concentrations	Number concentrations 1×10^4–2×10^5 particles/cm^3 and mass concentrations 0.1–30 mg/m^3
Pelclova *et al.*[36]	Cross-sectional Exposure-Non-exposure study	Czech Republic/2018	70–82% of airborne particles were <100 nm	Working in nanocomposites research	Exposed (19) Nonexposed (19) Total (38)	MDA, HNE, HHE, aldehydes C6–C13, 8-isoprostane, 8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3-Cl-Tyr, NO-Tyr	EBC	Various	Incidental	Number & Mass Concentrations	Mass concentrations were 0.120, 1.840, and 0.804 mg/m^3. Median particle number concentrations were 4.8×10^4, 1.3×10^5, and 5.4×10^5 particles/cm^3
Pelclova *et al.*[30]	Cross-sectional Exposure-Non-exposure study	Czech Republic/2017	80% of particles <100 nm	Nano TiO_2 production workers	Exposed (34) Nonexposed (45) Total (79)	MDA, HNE, HHE, aldehydes C6–C13, 8-isoprostane	EBC	TiO_2	ENPs	Number & Mass Concentrations	The median particle number concentration ranged from 1.98×10^4 to 2.32×10^4 particles/cm^3. Mass concentration varied between 0.40–0.65 mg/m^3
Zhao *et al.*[32]	Cross-sectional Exposure-Non-exposure study	China/2018	39% of particles <100 nm	Workers exposed to nano-TiO_2	Exposed (83) Nonexposed (85) Total (168)	SOD & MDA	blood	TiO_2	ENPs	Number, Mass & Surface Area Concentrations	The total mass concentration of particles was 3.17 mg/m^3. The mass concentration of nanoparticles was 1.22 mg/m^3
Graczyk *et al.*[35]	Cross-sectional Exposure-Non-exposure study	Switzerland/2015	92% of particles <100 nm	Workers exposed to welding fume	Exposed (20) Nonexposed (0) Total (20)	H_2O_2, MDA, 8-OHdG	EBC, blood & urine	Various	Incidental	Number & Mass Concentrations	Particle number concentration ranged from 8.69E + 05 to 3.85E + 06 particles/cm^3

8-OHdG: 8-hydroxy-2′-deoxyguanosine; SOD: superoxide dismutase; MPO: myeloperoxidase; GPx: glutathione peroxidase; 8-OHG: 8-Hydroxyguanosine; 5-OHMeU: 5-hydroxymethyl uracil; o-Tyr: o-tyrosine; 3-ClTyr: 3-chlorotyrosine; 3-NOTyr: 3-nitrotyrosine; H_2O_2: Hydrogen peroxide; MDA: Malondialdehyde; HHE: 4-hydroxy Hexanal; HNE: 4-Hydroxynonenal; WBC: white blood cell; EBC: exhaled breath condensate; NPs: Nanoparticles; CNTs: Carbon nanotubes; CNFs: Carbon nanofibers; TiO_2: Titanium dioxide; SiO_2: Silicon dioxide; ITO: Indium Tin Oxide; ENPs: Engineered nanoparticles.

biomarkers did not differ significantly between the two groups. In the fourth study, carried out at one of the TiO_2 producing plants in the Czech Republic, 79 employees of this factory were surveyed[30]. Of these, 34 were exposed to nano-TiO_2 and 45 were unexposed and were evaluated as controls. In this study, malondialdehyde, 4-hydroxy-trans-hexenal, 4-hydroxy-trans-nonenal, 8-isoProstaglandin F2α and aldehydes C6–C12 biomarkers were investigated in their EBC and urine samples. The results showed that the level of all studied biomarkers in EBC samples of exposed individuals was significantly higher than the control group. Urinary biomarkers showed no significant difference. There was also a significant relationship between exposure to TiO_2 nanoparticles and the level of biomarkers studied. The fifth study was conducted in Taiwan and among 130 employees of 14 metal oxide nanoparticle (TiO_2, SiO_2 (Silicon dioxide) and ITO (Indium tin oxide)) manufacturing plants[31]. Of these, 87 were occupationally exposed to nanomaterials (26 exposed to nano-TiO_2, 31 exposed to nano-SiO_2 and 30 exposed to ITO) and 43 participated in the study as control group and had no occupational exposure to nanomaterials. In this study, 8-OHdG in urine and white blood cells and 8-isoprostane in EBC of participants were evaluated as biomarkers of oxidative stress. The results showed that, overall, the level of 8-OHdG in the urine and white blood cells of exposed personnel was significantly higher than that of non-exposed personnel. Also, the level of this biomarker in the urine of exposed workers in each exposure group (TiO_2, SiO_2 and ITO) was significantly higher than the control group; whereas the level of this biomarker in white blood cells was significantly higher only in workers exposed to ITO than the control group. Overall, the level of 8-isoprostane in EBC of exposed workers was significantly higher than non-exposed employees. Also, the level of this biomarker in EBC samples of exposed personnel in each exposure group (TiO_2, SiO_2 and ITO) was significantly higher than the control group. The sixth study was conducted in China among 168 employees of a TiO_2 manufacturing plant[32]. Of the participants, 83 were occupationally exposure to nanomaterials and 85 were non-exposed. Blood samples were taken from all participants and different biomarkers (different cardiovascular, inflammation and oxidative stress biomarkers) in their blood were examined. The results showed that oxidative stress biomarkers (MDA and SOD) were significantly correlated with exposure to nanoparticles.

Occupational exposure to different nanomaterials simultaneously

When studying the effects of exposure to nanomaterials, it is difficult to prove that the observed effects are due to the size and unique properties of nanomaterials or are merely the effects of a chemical. Investigating the effects of exposure to a specific nanomaterial in different sizes or exposure to different nanomaterials simultaneously can provide information in this regard[33]. The first study was conducted among 364 employees of 14 different nanomaterials manufacturing plants in Taiwan[34]. Two hundred twenty seven participants had occupational exposure to nanomaterials and 137 were non-exposed to nanomaterials. Urine, blood, and EBC samples were taken from participants, and oxidative stress biomarkers (8-OHdG in blood and urine and and Isoprostane in EBC) were evaluated; the antioxidant enzymes examined in this study included MPO, SOD and GPx. The results showed that there was no significant difference between the levels of oxidative stress biomarkers in the exposed and unexposed groups. On the other hand, SOD levels in exposed individuals (both at risk level 1 and risk level 2) were significantly lower than those in the control group. GPx levels were also lower in exposed subjects (risk level 1 only) than in controls. The second study was conducted among 20 TIG (Tungsten Inert Gas) welding trainees[35]. The welders were exposed to welding fumes for 60 min. Urine, blood and EBC samples were taken from the participants before welding, immediately after welding, 1 h after welding, and 3 h after welding. In this study, H_2O_2, MDA and 8-OHdG biomarkers were investigated. The results of this study showed that the percentage of studied biomarkers increased significantly three hours after exposure. In the third study, 38 nanocomposite researchers were investigated[36]. Nineteen of them had occupational exposure to nanomaterials and 19 of them had no exposure. In this study, all participants were sampled for EBC; exposed individuals were sampled once before and once after work and MDA, HNE, HHE, 8-isoprostane, 8-OHdG, 8-OHG, 5-OHMeU, o-Tyr, 3- Cl-Tyr and NO-Tyr biomarkers were evaluated in their EBC samples. The results showed that the levels of biomarkers of oxidation of nucleic acids (8-OHG, 8-OHdG, and 5-OHMeU), protein oxidation (o-Tyr, 3-ClTyr, and 3-NOTyr) and lipid oxidation (MDA and aldehydes C6–C13) In the EBC of exposed group, before work, is higher than the control group. After exposure, the levels of lipid oxidation biomarkers (MDA, HHE, HNE, aldehydes C6–C13, and 8-isoprostane) were higher in the exposed staff than in the control group. Finally, there

was a significant relationship between the level of EBC biomarkers and work with nanocomposites.

Exposure assessment

Various methods have been proposed and used so far to assess exposure to nanomaterials. There is currently no standard method with consensus for this purpose. Each of the proposed methods has its own advantages and disadvantages. The methods used in the 11 studies can be divided into two groups:

Qualitative methods

In two of the 11 studies, the NanoTool Control Banding Method was used to assess occupational exposure to nanomaterials[31, 34]. This method is one of the most popular CB-based (control banding) methods used to assess the risk of activities involved with nanomaterials[37]. The NanoTool method uses a combination of information about nanomaterials and exposure scenarios to assess the risk level of activities involving nanomaterials[11, 38]. The reason for using this method was the limitations of using traditional occupational health's quantitative methods to assess exposure to nanomaterials; limitations such as lack of equipment and methods for sampling and analyzing nanomaterials, lack of equipment and methods for personal sampling, and lack of consensus about the metrics for assessing exposure to nanomaterials[34].

Quantitative methods

So far, three metrics have been proposed for quantitative assessment of exposure to nanomaterials; including mass concentration, number concentration, and surface area concentration[39]. Various real-time measurment equipment and sampling methods is available for each of these metrics[40]. In the two studies investigating exposure to carbon nanomaterial, a combination of filter-based sampling methods, real-time measurement devices such as SMPS (scanning mobility particle sizer), DMA (differential mobility analyzer), CPC (condensation particle counter) and LPI (low-pressure impactor) and SEM (Scanning electron microscopy) and TEM (transmission electron microscopy) microscopes were used to assess exposure to carbon nanomaterials. Finally, the mass concentration of elemental carbon and the number concentration of particles were reported[23, 24]. In the other four studies, conducted by Pelclova *et al.*[27–30], only real-time equipment, such as SMPS, APS (aerodynamic particle sizer), portable particle number concentration monitor (P-TRAK) and portable monitor of particle mass concentrations (DustTRAK DRX) was used for exposure assessment. Finally, the mass concentration and the number concentration of nanoparticles were reported. In another study, they used an impactor to investigate mass concentration; they monitored the number concentration using a particle counter and the surface area concentration with a monitor. They also investigated the morphology of the particles using SEM[32]. In another study, real-time equipment such as SMPS, APS, UCPC (ultrafine condensation particle counter) and OPS (optical particle sizer) were used to investigate number concentration and particle size distributions; Impactor was used for mass concentration and SEM and X-ray spectroscopy were used to study particle shape and composition, respectively[36]. The study of Graczyk *et al.* also used a combination of impactor, filter-based sampling, particle counters, and TEM to investigate number concentration, mass concentration, morphology, and particle composition[35].

Biomarkers

The biomarkers investigagted in the studies can be classified into four groups: lipid oxidation, nucleic acid oxidation, protein oxidation and antioxidant enzymes. Lipid oxidation biomarkers include MDA, HHE, n-Hexanal, H_2O_2, HNE, aldehydes C6–C13, and 8-isoprostane. The nucleic acid oxidation biomarkers included 8-OHG, 8-OHdG and 5-OHMeU; protein oxidation was investigated with o-Tyr, 3-ClTyr, and 3-NOTyr biomarkers and the antioxidant enzymes were MPO, SOD and GPx.

Controlled variables

Many variables have been controlled in the studies reviewed. Some studies have used self-report questionnaires for this purpose, some used interviews and others used examinations. The most important controlled variables in these studies were age, gender, race, health status, BMI (Body mass index), smoking status, alcohol consumption, and physical activity.

Type of nanomaterials

Nanomaterials can be classified into three groups in terms of origin: natural, incidental, and engineered. Natural nanomaterials are created by natural processes such as volcanoes; incidental nanomaterials are produced by various industrial processes and tasks, and are by product, such as welding fumes, but engineered nanomaterials are produced deliberately and for specific uses and are the main product[41]. In this study, occupational exposure to incidental and engineered nanomaterials is investigated.

Of the 11 studies, 3 have examined occupational exposure to incidental nanomaterials and the other has considered occupational exposure to engineered nanomaterials.

Discussion

Biological monitoring is one of the most important components of occupational and environmental health survillance; especially when sufficient information on occupational and environmental exposure is not available. Oxidative stress is one of the most important effects caused by exposure to various environmental and occupational factors and has received a lot of attention by researchers. Biological monitoring of oxidative stress is usually performed by examining biomarkers of oxidative stress in biological fluids of the body[42]. Although there are currently no specific biomarkers for assessing oxidative stress induced by exposure to nanomaterials, some researchers have found that known biomarkers of oxidative stress may be appropriate for monitoring workers exposed to nanomaterials; because of the shortage of information about human exposure to nanomaterials, sensitivity of biomarkers are now more important than their specificity[43]. It may be argued that the most important part of the studies reviewed was the methods, equipment, and metrics used to assess occupational exposure to nanomaterials. Many researchers now prefer qualitative risk assessment to assess occupational exposure to nanomaterials; because quantitative information about nanomaterial characteristics and exposure scenarios in nanomaterials' work environments are low, unreliable and in some cases absent[44]. On the other hand, there is still no consensus among researchers about the quantitative methods and equipment for assessing occupational exposure to nanomaterials, and a wide range of filter-based sampling equipment, real-time equipment and microscopic techniques are employed. There is also no agreement among the researchers on the metric used to assess exposure. However, many researchers have found surface area concentration to be appropriate for assessing exposure to nanomaterials in toxicological studies, and consider it better than mass and number concentrations[45]. Among the studies, there was only one study that measured and reported surface area concentration, in addition to mass and number concentrations[32]. Personal protective equipment used by employees during work and the engineering and administrative controls used to reduce exposure are also effective in assessing exposure to nanomaterials and have received less attention in the studies. NIOSH (National Institute for Occupational Safety and Health) and some other national and international agencies have recommended OELs (occupational exposure limit) for some kindes of nanomaterials such as carbon nanotubes and Titanium dioxide[22, 46]. The results of the reviewed articles show that in many cases, exposure to amounts below these occupational exposure levels also increased the level of oxidative stress biomarkers. Two conclusions can be drawn from this: 1) The recommended OELs are not effective enough; so additional/alternative exposure metrics such as inhalable and respirable and total nanostructures, and health outcomes, such as cancer, cardiovascular diseases, respiratory diseases, or outcomes related to oxidative stress and, inflammation, should be considered when establishing an OEL for nanomaterials. NIOSH acknowledged that alternative exposure metrics may be useful for the development of OEL nanomaterials exposure[47]. 2) The biomarkers examined do not have the necessary sensitivity and specificity; so it is better to look for better and more sensetive and specific biomarkers to assess occupational exposure to nanomaterials. Due to the shortage of research, this will be possible by increasing the number of articles in this field. In terms of the number and diversity of biomarkers, some studies have examined a few biomarkers of oxidative stress, some have investigated a large number of oxidative stress biomarkers, and others, have investigate biomarkers such as Cancer, Inflammation, Cardiovascular and ..., in addition to biomarkers of oxidative stress. Researchers recommend that when there is no specific biomarker (for example for nanomaterials), it is best to look for several biomarkers—a biomarker profile—to be able to simultaneously examine exposure and its effects on different parts of the body[42]. On the other hand, some studies have investigated biomarkers only in one biological fluid, and others have investigated biomarkers in several biological fluids. For example, biomarkers in EBC will indicate lung status and will not show whole body condition[30]. Given that the lung is the main organ for occupational exposure to nanomaterials[48], evalution of EBC biomarkers may be useful; but since they do not represent the whole body condition, biomarkers found in other biological fluids in the body should also be examined. Given what has been said, it seems that simultaneous study of a wide range of biomarkers in a variety of body fluids will provide more useful results. But which types of biomarkers (lipid oxidation, nucleic acid oxidation, protein oxidation and antioxidant enzymes), and in which biological fluid or tissue should be examined and their relationship should be considered, will be determined by increasing the number of studies in this area. Because we

are currently facing a shortage of studies in this area. On the other hand, various research methods in existing studies have made it difficult to draw conclusions and identify appropriate biomarkers to investigate occupational exposure to nanomaterials.

Conclusion

Since all the studies reviewed are cross-sectional, the observed effects cannot be fully confirmed and generalized; as a result, these studies only help to identify some intermediate effects. In order to obtain better and more reliable results, long-term and controlled studies need to be designed and implemented, and exposure and effect biomarkers regularly measured and investigated. The studies should be long-term, because nanomaterials may show their effects after years of exposure and accumulation in the body[49]. They need to be controlled, because oxidative stress can be affected by various occupational and environmental factors. On the other hand, we should not consider the studies that are conducted every few years and continuously in a specific work environment as "well-designed long-term studies", they are just "continuous cross-sectional studies"[50]. The design of long-term studies should take into account all necessary considerations; Including workers' charecteristics, invironmental properties, workplace properties, work conditions, nanomaterials, methods, equipment and metrics used in exposure assessment, sample collection and analysis, interpretation of results and all that can affect the results of the study.

Conflict of Interest

None declared.

References

1) Savolainen K (2014) Chapter 1-General Introduction. In: Handbook of Nanosafety, Vogel U, Savolainen K, Wu Q, van Tongeren M, Brouwer D, Berges M, (Eds.), 1–16, Academic Press, San Diego.
2) Horie M, Kato H, Iwahashi H (2013) Cellular effects of manufactured nanoparticles: effect of adsorption ability of nanoparticles. Arch Toxicol **87**, 771–81.
3) Filon FL (2017) Skin exposure to nanoparticles and possible sensitization risk. In: Allergy and Immunotoxicology in Occupational Health, 143–152, Springer, Singapore.
4) Armstead AL, Li B (2016) Nanotoxicity: emerging concerns regarding nanomaterial safety and occupational hard metal (WC-Co) nanoparticle exposure. Int J Nanomedicine **11**, 6421–33.
5) Omari Shekaftik S, Hosseini Shirazi F, Yarahmadi R, Rasouli M, Soleimani Dodaran M, Ashtarinezhad A (2019) Preliminary investigation of the symptoms of nanotechnology companies employees in Tehran, Iran, 2018. J Occup Hyg Eng **6**, 61–70.
6) Pietroiusti A, Magrini A (2015) Engineered nanoparticles at the workplace: current knowledge about workers' risk. Occup Med (Lond) **65**, 171–3.
7) Miller A, Frey G, King G, Sunderman C (2010) A handheld electrostatic precipitator for sampling airborne particles and nanoparticles. Aerosol Sci Technol **44**, 417–27.
8) Iavicoli I, Leso V, Manno M, Schulte PA (2014) Biomarkers of nanomaterial exposure and effect: current status. J Nanopart Res **16**, 2302.
9) Kim J, Yu IJ (2016) National survey of workplaces handling and manufacturing nanomaterials, exposure to and health effects of nanomaterials, and evaluation of nanomaterial safety data sheets. BioMed Res Int **2016**, 8389129.
10) Roco MC (2011) The long view of nanotechnology development: the National Nanotechnology Initiative at 10 yr. J Nanopart Res **13**, 427–45.
11) Zalk DM, Paik SY (2016) Chapter 6-Risk assessment using control banding. In: Ramachandran G, ed. Assessing Nanoparticle Risks to Human Health, 2nd Ed, 121–152, William Andrew Publishing, Oxford.
12) Tsai CJ, Pui DYH (2009) Editorial: Recent advances and new challenges of occupational and environmental health of nanotechnology. J Nanopart Res **11**, 1–4.
13) Ostiguy C, Riediker M, Triolet J, Troisfontaines P, Vernez D (2010) Development of a specific control banding tool for nanomaterials. French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort.
14) Schulte PA, Kuempel ED, Drew NM (2018) Characterizing risk assessments for the development of occupational exposure limits for engineered nanomaterials. Regul Toxicol Pharmacol **95**, 207–19.
15) Omari Shekaftik S, Yarahmadi R, Moghadasi N, Sedghi Noushabadi Z, Hosseini AF, Ashtarinezhad A (2020) Investigation of recommended good practices to reduce exposure to nanomaterials in nanotechnology laboratories in Tehran, Iran. J Nanopart Res **22**, 59.
16) Schulte PA, Leso V, Niang M, Iavicoli I (2019) Current state of knowledge on the health effects of engineered nanomaterials in workers: a systematic review of human studies and epidemiological investigations. Scand J Work Environ Health **45**, 217–38.
17) Castiglioni S, Cazzaniga A, Perrotta C, Maier JA (2015) Silver nanoparticles-induced cytotoxicity requires ERK activation in human bladder carcinoma cells. Toxicol Lett **237**, 237–43.
18) Mendoza RP, Brown JM (2019) Engineered nanomaterials and oxidative stress: current understanding and future challenges. Curr Opin Toxicol **13**, 74–80.

19) Sarkar A, Ghosh M, Sil PC (2014) Nanotoxicity: oxidative stress mediated toxicity of metal and metal oxide nanoparticles. J Nanosci Nanotechnol **14**, 730–43.
20) Castranova V, Schulte PA, Zumwalde RD (2013) Occupational nanosafety considerations for carbon nanotubes and carbon nanofibers. Acc Chem Res **46**, 642–9.
21) Duke KS, Bonner JC (2018) Mechanisms of carbon nanotube-induced pulmonary fibrosis: a physicochemical characteristic perspective. Wiley Interdiscip Rev Nanomed Nanobiotechnol **10**, e1498.
22) ACGIHTLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, 2020.
23) Lee JS, Choi YC, Shin JH, Lee JH, Lee Y, Park SY, Baek JE, Park JD, Ahn K, Yu IJ (2015) Health surveillance study of workers who manufacture multi-walled carbon nanotubes. Nanotoxicology **9**, 802–11.
24) Beard JD, Erdely A, Dahm MM, de Perio MA, Birch ME, Evans DE, Fernback JE, Eye T, Kodali V, Mercer RR, Bertke SJ, Schubauer-Berigan MK (2018) Carbon nanotube and nanofiber exposure and sputum and blood biomarkers of early effect among U.S. workers. Environ Int **116**, 214–28.
25) Wang Y, Ding L, Yao C, Li C, Xing X, Huang Y, Gu T, Wu M (2017) Toxic effects of metal oxide nanoparticles and their underlying mechanisms. Sci China Mater **60**, 93–108.
26) Djurišić AB, Leung YH, Ng AM, Xu XY, Lee PKH, Degger N, Wu RSS (2015) Toxicity of metal oxide nanoparticles: mechanisms, characterization, and avoiding experimental artefacts. Small **11**, 26–44.
27) Pelclova D, Zdimal V, Fenclova Z, Vlckova S, Schwarz J, Pusman J, Zikova N, Syslova K, Kuzma M, Navratil T, Zakharov S, Kacer P (2012) Markers of oxidative stress are elevated in workers exposed to nanoparticles. Paper presented at: NANOCON 2012-Conference Proceedings, 4th International Conference.
28) Pelclova D, Zdimal V, Fenclova Z, Vlckova S, Turci F, Corazzari I, Kacer P, Schwarz J, Zikova N, Makes O, Syslova K, Komarc M, Belacek J, Navratil T, Machajova M, Zakharov S (2016) Markers of oxidative damage of nucleic acids and proteins among workers exposed to TiO2 (nano) particles. Occup Environ Med **73**, 110–8.
29) Pelclova D, Zdimal V, Kacer P, Vlckova S, Fenclova Z, Navratil T, Komarc M, Schwarz J, Zikova N, Makes O, Zakharov S (2016) Markers of nucleic acids and proteins oxidation among office workers exposed to air pollutants including (nano)TiO2 particles. Neuroendocrinol Lett **37** Suppl1, 13–6.
30) Pelclova D, Zdimal V, Kacer P, Zikova N, Komarc M, Fenclova Z, Vlckova S, Schwarz J, Makeš O, Syslova K, Navratil T, Turci F, Corazzari I, Zakharov S, Bello D (2017) Markers of lipid oxidative damage in the exhaled breath condensate of nano TiO_2 production workers. Nanotoxicology **11**, 52–63.
31) Liou SH, Wu WT, Liao HY, Chen CY, Tsai CY, Jung WT, Lee HL (2017) Global DNA methylation and oxidative stress biomarkers in workers exposed to metal oxide nanoparticles. J Hazard Mater **331**, 329–35.
32) Zhao L, Zhu Y, Chen Z, Xu H, Zhou J, Tang S, Xu Z, Kong F, Li X, Zhang Y, Li X, Zhang J, Jia G (2018) Cardiopulmonary effects induced by occupational exposure to titanium dioxide nanoparticles. Nanotoxicology **12**, 169–84.
33) Colognato R, Park MVDZ, Wick P, De Jong WH (2012) Chapter 1-Interactions with the Human Body. In: Adverse Effects of Engineered Nanomaterials, Fadeel B, Pietroiusti A, Shvedova AA (Eds.), 3–24, Academic Press, Boston.
34) Liou SH, Tsou TC, Wang SL, Li LA, Chiang HC, Li WF, Lin PP, Lai CH, Lee HL, Lin MH, Hsu JH, Chen CR, Shih TS, Liao HY, Chung YT (2012) Epidemiological study of health hazards among workers handling engineered nanomaterials. J Nanopart Res **14**.
35) Graczyk H, Lewinski N, Zhao J, Sauvain JJ, Suarez G, Wild P, Danuser B, Riediker M (2016) Increase in oxidative stress levels following welding fume inhalation: a controlled human exposure study. Part Fibre Toxicol **13**, 31.
36) Pelclova D, Zdimal V, Schwarz J, Dvorackova S, Komarc M, Ondracek J, Kostejn M, Kacer P, Vlckova S, Fenclova Z, Popov A, Lischkova L, Zakharov S, Bello D (2018) Markers of oxidative stress in the exhaled breath condensate of workers handling nanocomposites. Nanomaterials (Basel) **8**, 611.
37) Omari Shekaftik S, Ashtarinezhad A, Shirazi FH, Hosseini A, Yarahmadi R (2020) Assessing the risk of main activities of nanotechnology companies by the NanoTool method. Int J Occup Saf Ergon. Epub ahead of print.
38) Zalk DM, Paik SY, Swuste P (2009) Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J Nanopart Res **11**, 1685.
39) Asbach C (2015) Chapter 3.3-Exposure Measurement at Workplaces. In: Nanoengineering, Dolez PI (Ed.), 523–555, Elsevier, Amsterdam.
40) Gensdarmes F (2015) Chapter 1.3-Methods of Detection and Characterization. In: Nanoengineering, Dolez PI (Ed.), 55–84, Elsevier, Amsterdam.
41) Omari Shekaftik S, H. Shirazi F, Yarahmadi R, rasouli M, Solaymani Dodaran M, Ashtarinezhad A (2019) Exploratory study of nanoworkers' symptoms & work-relatedness of these symptoms. Tehran, Iran. Occupational health, Iran University of Medical Sciences.
42) Bergamaschi E, Gulumian M, Kanno J, Savolainen K (2019) Chapter 41-Engineered Nanomaterials: Biomarkers of Exposure and Effect. In: Biomarkers in Toxicology, 2nd Ed, Gupta RC (Ed.), 735–755, Academic Press, Cambridge.
43) Bergamaschi E, Poland C, Canu IG, Prina-Mello A (2015) The role of biological monitoring in nano-safety. Nano Today **10**, 274–7.

44) Landsiedel R, Sauer UG, de Jong WH (2017) Chapter 8-Risk Assessment and Risk Management. In: Adverse Effects of Engineered Nanomaterials, 2nd Ed., Fadeel B, Pietroiusti A, Shvedova AA (Eds.), 189–222, Academic Press, Cambridge.
45) Dusinska M, Rundén-Pran E, Schnekenburger J, Kanno J (2017) Chapter 3-Toxicity Tests: In Vitro and In Vivo. In: Adverse Effects of Engineered Nanomaterials, 2nd Ed., Fadeel B, Pietroiusti A, Shvedova AA, (Eds.) 51–82, Academic Press, Cambridge.
46) Gibbs L, Lamba F, Stoxkmeier B, Kojola W (2012) General safe practices for working with engineered nanomaterials in research laboratories. National Institute for Occupational Safety and Health (NIOSH), Washington, DC.
47) Safety NIfO Health. Current intelligence bulletin 65: occupational exposure to carbon nanotubes and nanofibers. In: US Department of Health and Human Services, Public Health Service, Centers, 2013.
48) Rim KT, Song SW, Kim HY (2013) Oxidative DNA damage from nanoparticle exposure and its application to workers' health: a literature review. Saf Health Work **4**, 177–86.
49) ISIRI Nano technology−Health and safety in nano occupational settings−Code of Practices. In. Tehran, Iran: Institute of Standards and Industrial Research of Iran. 2015.
50) Wu WT, Li LA, Tsou TC, Wang SL, Lee HL, Shih TS, Liou SH (2019) Longitudinal follow-up of health effects among workers handling engineered nanomaterials: A panel study. Environmental Health: A Global Access Science Source. 18(1).

Appendix 1.

Nanomaterial: Nanostructure; Nanostructured Materials; Material, Nanostructured; Materials, Nanostructured; Nanostructured Material; Nanomaterials; Nanomaterial; nanoscale material; nanoscale structure; nanostructures

Nanoparticle: Nanoparticle; Nanocrystalline Materials; Material, Nanocrystalline; Materials, Nanocrystalline; Nanocrystalline Material; Nanocrystals; Nanocrystal; millimicrosphere; nano-particle; nano-scale particle; nanoparticles; nanoscale particle

Occupational exposure: Exposure, Occupational; Exposures, Occupational; Occupational Exposures

Oxidative stress: Oxidative Stresses; Stresses, Oxidative; Stress, Oxidative; oxidant stress; oxidant stresses

PubMed:

((“Oxidative stress”[tiab] OR “Oxidative Stresses”[tiab] OR “oxidant stresses”[tiab] OR (Stresses[tiab] AND Oxidative[tiab]) OR (Stress[tiab] AND Oxidative[tiab]) OR “oxidant stress”[tiab]) AND (“Occupational exposure”[tiab] OR (Exposure[tiab] AND Occupational[tiab]) OR (Exposures[tiab] AND Occupational[tiab]) OR “Occupational Exposures”[tiab]) AND (Nanomaterial[tiab] OR “Nanomaterials”[tiab] OR Nanoparticle[tiab] OR “nanoparticles”[tiab] OR “nano-particle”[tiab] OR nanoobject[tiab] OR “nanoobjects”[tiab] OR “nano object”[tiab] OR “nano-object”[tiab] OR Nanostructure[tiab] OR “Nanostructures”[tiab] OR “Nanostructured Materials”[tiab] OR (Material[tiab] AND Nanostructured[tiab]) OR (Materials[tiab] AND Nanostructured[tiab]) OR “Nanostructured Material”[tiab] OR “nanoscale material”[tiab] OR “nanoscale structure”[tiab] OR “nano-scale particle”[tiab] OR “nanoscale particle”[tiab] OR nanofiber[tiab] OR “nanofibers”[tiab] OR nanocomposite[tiab] OR “nanocomposites”[tiab] OR nanoplate[tiab] OR “nanoplates”[tiab] OR nanorod[tiab] OR “nanorods”[tiab] OR nanotube[tiab] OR “nanotubes”[tiab] OR nanowire[tiab] OR “nanowires”[tiab] OR graphene[tiab] OR “graphenes”[tiab] OR fullerene[tiab] OR “fullerenes”[tiab] OR “CNF”[tiab] OR “CNT”[tiab] OR “SWCNT”[tiab] OR “MWCNT”[tiab] OR “DWCNT”[tiab]))

Scopus:

((TITLE-ABS-KEY (Oxidative stress) OR TITLE-ABS-KEY (Oxidative Stresses) OR TITLE-ABS-KEY (oxidant stresses) OR TITLE-ABS-KEY (oxidant stress)) AND (TITLE-ABS-KEY (Occupational exposure) OR TITLE-ABS-KEY (Occupational Exposures)) AND (TITLE-ABS-KEY (Nanomaterial) OR TITLE-ABS-KEY (Nanomaterials) OR TITLE-ABS-KEY (Nanoparticle) OR TITLE-ABS-KEY (Nanoparticles) OR TITLE-ABS-KEY (nano-particle) OR TITLE-ABS-KEY (nano-scale particle) OR TITLE-ABS-KEY (nanoscale particle) OR TITLE-ABS-KEY (Nanostructure) OR TITLE-ABS-KEY (nanostructures) OR TITLE-ABS-KEY (nanoobject) OR TITLE-ABS-KEY (nanoobjects) OR TITLE-ABS-KEY (nano object) OR TITLE-ABS-KEY (nano-object) OR TITLE-ABS-KEY (Nanostructured Materials) OR TITLE-ABS-KEY (Nanostructured Material) OR TITLE-ABS-KEY (nanoscale material) OR TITLE-ABS-KEY (nanoscale structure) OR TITLE-ABS-KEY (nanofiber) OR TITLE-ABS-KEY (nanocomposite) OR TITLE-ABS-KEY (nanoplate) OR TITLE-ABS-KEY (nanorod) OR TITLE-ABS-KEY (nanotube) OR TITLE-ABS-KEY (nanowire) OR TITLE-ABS-KEY (graphene) OR TITLE-ABS-KEY (fullerene) OR TITLE-ABS-KEY (CNF) OR TITLE-ABS-KEY (CNT) OR TITLE-ABS-KEY (SWCNT) OR TITLE-ABS-KEY (MWCNT) OR TITLE-ABS-KEY (DWCNT)))

Web Of Science:

TI= ((“Oxidative stress” OR “Oxidative Stresses” OR “oxidant stresses” OR “oxidant stress”) AND (“Occupational exposure” OR “Occupational Exposures”) AND (Nanomaterial OR “Nanomaterials” OR Nanoparticle OR “Nanoparticles” OR “nano-particle” OR “nano-scale particle” OR “nanoscale particle” OR Nanostructure OR “Nanostructures” OR nanoobject OR “nanoobjects” OR “nano object” OR “nano-object” OR “Nanostructured Materials” OR “Nanostructured Material” OR “nanoscale material” OR “nanoscale structure” OR nanostructures OR nanofiber OR nanocomposite OR nanoplate OR nanorod OR nanotube OR nanowire OR graphene OR fullerene OR “CNF” OR “CNT” OR “SWCNT” OR “MWCNT” OR “DWCNT”))