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ARTICLE

Occupational Health and Safety: reflection on potential risks and the safety handling of nanomaterials

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ABSTRACT

Every day the nanotechnology, that refers to a field whose theme is the control of matter on an atomic and molecular scale working with nanometric structures (< 100 nm), is more present in the development of products and industrial processes. The particle manipulation of nanometric structures has created opportunities in the development of new products and materials. However, synthesis, handling, storage, stabilization and the incorporation of these materials, with nanometric dimensions, demand a new perspective of analysis and evaluation of old manufacturing processes, procedures and industrial devices, in order to guarantee collective and individual protection to workers and society. With the increasing of scale and production of nanoestrutuctured materials, a big part of labour community starts to be in contact with different nanomaterials (forms and ways). In this work the main aspects and involved risks of manufacture, storage, synthesis, stabilization and incorporation of nanomaterials on new products are evaluated in order to reduce, decrease and eliminate chemical, physical and biological risks for the employees. A bibliographic review was conducted about risk, safety and nanotechnology based on available English literature focusing safety and environmental agencies from different countries such as USA, Canada, EU (France, UK, Germany, Denmark), Australia and Japan.

KEYWORDS: Occupational Safety; Risks; Nanotechnology; Nanoparticles

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Introduction

Occupational diseases and hazards have been known since antiquity. The creation of modern toxicology started with the work of Paracelsus (Philippus Aureolus Theophrastus Bombastus von Hohenheim) in the early 14th century, the work of Mathieu Josep Bonaventura in 1818, and the work of the Italian physician Bernardini Ramazzini in his book titled "As Doenças dos Trabalhadores – De Morbis Artificum Diatriba" published in 1700. These investigations served as the foundation for understanding the relationship between typical occupational diseases and labor and were essential to the creation of occupational medicine in England in the 19th century and occupational safety engineering early in the 20th century[1-4]. Figure 1 shows an illustration demonstrating the underground working risks, published at the book "De Re Metallica"[5].

Technological advancements promoted by the discovery of new materials, chemicals, and the increased development of materials with ever smaller dimensions have posed new challenges to the management of occupational health in environments prone to occupational liabilities involving exposure levels and potential health risks to workers.

In 2008, 36,660,377 inorganic and organic compounds were cataloged in the database from the Chemical Abstract Service (CAS), which is a division of the American Chemical Society (ACS), including 21,867,815 commercially available chemicals. In 2013, this number increased to over 72,841,808 registered compounds and substances, representing an increase of almost 100% in a period of only 5 years. This simple comparison illustrates the dynamics and complexity of safety and risk management aspects associated with the occupational exposure to chemical substances and compounds[6].

Figure 1. Illustration from the book "De Re Metallica," one of the first treatises on mining and metallurgy, published in 1550, with detailed information on the risks of death and suffocation and on the health of workers in underground mines, where miners would use fire obtained through the burning of wood for the explosion of mineral shafts and rocks[5].

However, the 2013 Guide to Occupational Exposure Values compiled by the American Conference of Governmental Industrial Hygienists (ACGIH) indicates only approximately 800 chemical substances[7], and only 147 substances have been listed in the Brazilian Regulatory Norm - NR15[8]. Thus, in the present study, we conducted a literature review focusing on the main risks associated with nanomaterials. We acquired data available in English from health and safety agencies in countries including the USA (United States of America), Canada, Australia, Japan, and European countries. For countries such as France, Germany, Denmark, and England, special attention has been given to publications from the last 5–7 years.

Nanomaterials

The term nanotechnology, coined by the Japanese researcher Norio Taniguchi in 1974, was first used in the microelectronics industry. Currently, the technical scientific definition of the term includes any material that has at least one of its dimensions ranging from 1 nm to 100 nm[9]. However, despite the intense normative work achieved in the last decade, this definition still has cultural and scientific divergences that stem from historical and legal aspects. In principle, nanotechnology is based not only on the reduction of the particle size to the nanometer scale but also on the appearance of new characteristics in the material. In Japan, particles between 50 nm and 100 nm are regarded as ultrathin, whereas only particles <50 nm are considered as nanomaterials. In 2003, the American Act for Research and Development in Nanotechnology defined nanotechnology as the creation of materials, devices, and systems at the atomic and molecular scale[10]. A detailed discussion of the definitions of nanomaterials used worldwide and the complexity of technological evolution for the establishment of monitoring procedures and identification of liabilities can be found in the book titled "Nanotechnology: Health and Environmental Risk"[11].

Technological advancements at the nanoscale level have created many opportunities in distinct science and technology fields, including the development of novel drugs, delivery systems for medications and synthetic cellular tissues, medicinal therapies, and miniaturization of circuits and electromechanical devices (MEMS/NEMS) as well as the development of new materials and products with specific features and functionalities. These advancements also involve the development of sensors, new catalytic processes, paints and coatings, cosmetics, and new sources of energy production and storage and have thus reached the boundaries of the interactions between nanotechnological devices, living organisms, and information systems[12].

Risks of technology in the work environment: Complex processes and incomplete safety information

From the point of view of occupational and population health, a number of studies have indicated that more comprehensive and precise toxicological information on nanoparticulate materials is warranted with an aim of understanding the complex relationship between nanoparticles and living organisms[13,14]. Humans have long lived with nanoparticulate materials in the form of aerosols from natural processes such as fires or volcanic eruptions. However, until recently, this contact did not involve synthetic nanomaterials of enhanced purity, concentration, complexity, or functionalization. Moreover, this intensified interaction has greatly increased the complexity of processes involving the synthesis, manipulation, handling, storage, stabilization, development, and use of nanomaterials and has warranted the adoption of a multidisciplinary approach when addressing risk, safety, and environmental issues at the nanoscale.

Multiple points of views can be considered when reflecting on nanotechnology and should cover topics such as risks, benefits, advantages and disadvantages, ethics, individual and collective freedom, public safety, strategies for industrial and technological development at the national level, regulatory frameworks, education, patents, and public engagement or public access to free and thorough information. Moreover, several questions must be formulated, analyzed, and evaluated to secure safe conditions for workers. Some of these concerns have been outlined below[15]:

1) Is it necessary to use a certain process or nanostructure when developing new products?

2) Are the risks involved in the handling, synthesis, stabilization, and incorporation of nanomaterials known? Can these risks be controlled or mitigated?

3) Is there technical and personnel training to ensure the safe development of activities related to storage, handling, synthesis, stabilization, and incorporation of nanomaterials?

4) Is sufficient and high-quality information available to enable ergonomic analysis of activities that can directly or indirectly expose workers to nanomaterials?

5) Have procedures been updated, discussed, evaluated, implemented, understood, and practiced, and are there adequate facilities for the performance of work involving handling of nanomaterials?

6) What is needed to be known regarding the interactions at the nano and molecular levels to assess the toxicological effects of nanomaterials in the short term, medium term, and long term?

7) How should the generated waste (isolated or incorporated nanomaterials) be managed and what is the best way to recycle or discard it?

8) Are the measurement metrics for exposure and impact assessment suitable for nanomaterials that have large variations in their specific area, low density, high reactivity, and surface properties?

9) How and to what extent can we classify nanomaterials with minor differences in their chemical composition, morphology, and catalytic activity, particularly with regard to their toxicological, environmental, and biological interactions?

10) How should a hierarchical occupational safety system that comprises the processes of elimination, substitution, modification, segregation, ventilation, and filtration of materials and that is capable of protecting the health of workers be developed?

As nanotechnology advances, populations have more contact with nanotechnological products. Thus, the adoption of new strategies related to occupational safety and environmental issues, particularly when assessing risks and understanding processes and interactions of nanomaterials in the workplace, is essential for the development of safer nanotechnology in the workplace.

The first reports on the potential risks and adverse effects of the interaction of nanoparticles and nanoparticulate materials on workers' health, and on living organisms in general, appeared in the early 21st century[16,17]. Currently, the probable routes of contamination and major mechanisms of interaction between humans and nanoparticles are well defined; however, the effects of dose and exposure on human health warrant further investigation.

As an example of the complexity of this issue, we can consider the reports of carbon nanomaterials such as nanotubes[18] described in 1991 by Ijima and carbon nanofibers[19] described in the 1950s by Radushkevich and Lukyanovich. In this respect, studies conducted in 2007 reported the biological toxicity effects associated with the metals used in the synthesis of commercial carbon nanotubes, including a time- and dose-dependent increase in reactive oxygen species and a decrease in the membrane potential of mitochondria[20]. However, only in 2013, in Bulletin number 65, the National Institute for Occupational Safety and Health (NIOSH)[21] published data on the occupational exposure to nanotubes and nanofibers and gave clear recommendations about the need to control exposure, perform environmental and work-related assessments, conduct medical surveillance, monitor particle concentrations in the workplace, and give recommendations on the choice of respiratory protection equipment.

With respect to graphene, an allotropic form of carbon discovered in 2004[22], data regarding its toxicity, physicochemical interactions with biological systems, and potential risks are even scarcer. Nonetheless, the literature available on *in vitro* testing reports that graphene is either inert or toxic to cells, depending on the number of graphene layers, perimeter, hydrophobicity, surface functionalities, and the dose used. Moreover, the hydrophobic character of the surface of graphene may lead to interactions with lipid membranes, causing toxicity or even adsorption of molecules on membrane surfaces[23].

Recent studies have reviewed the biological responses, safety, and potential biomedical applications of graphene[24,25].

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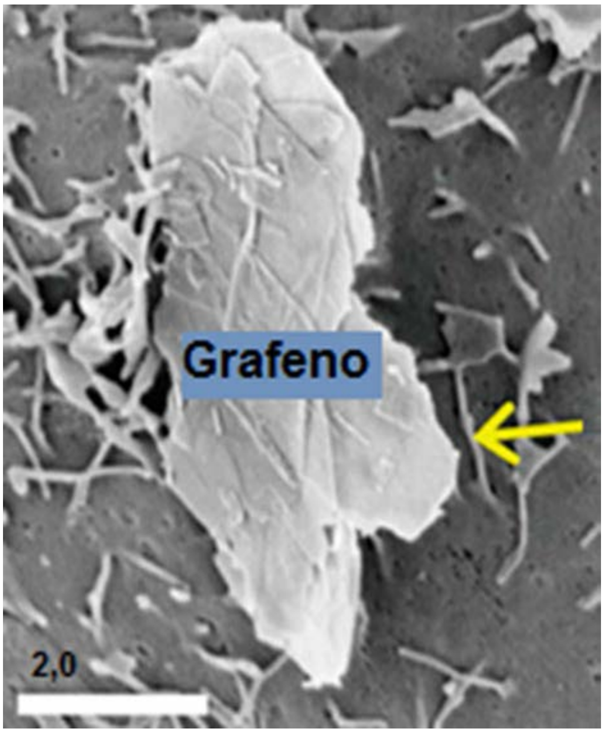

Figure 2. Field-emission scanning electron microscopy in secondary electron imaging mode, showing the interaction of a graphene microsheet (arrow) with the membrane of a human lung epithelial cell, highlighting the penetration of the edge of the graphene sheet. The cells were post-fixed in a 2% aqueous osmium tetroxide solution, followed by dehydration in ethanol[25].

Figure 2 shows the penetration potential of a sheet of graphene (few layers graphene) in a cell membrane.

The increased use of nanotechnological products in daily life and in the workplace underscores the importance of ethical issues, public engagement, education, safety, and environment in society. We have also forecasted an increase in the number of nanotechnology jobs, which should amount to 2 million in 2015, and an expected annual growth of up to 25% by 2020, when a market worth of US$3 trillion is expected[26].

Routes of exposure and protective measures

Many studies[14,27-30] have reported that contamination through the respiratory tract is the main route of entry of nanoparticles in the body, although it can also occur through the skin, mucosae, eyes, ingestion, or injection of nanoparticles. Figure 3 shows the relationship between variables and interactions of nanoparticles and aspects of risk analysis involving such materials.

Prevention and protection

Considering the potential risks of contamination by nanoparticles, the establishment of guidelines and recommendations for labor safety is required, although the effectiveness of these practices still demands further investigation. Best protection practices are given below and indicate the major routes of contamination and exposure.

a) Respiratory protection (inhalation):

With regard to the routes of exposure of workers, it is essential to develop management systems for occupational health that focus on the elimination or minimization of exposure, the use of cleanrooms, biosafety cabinets with filtration systems such as high-efficiency particulate air (HEPA) filters, as well as the adoption of respiratory protection programs where the use of collective and personal protective equipment is corresponds to the labor activities and to the types of nanometric materials

Table 1. Recommended respiratory protection from exposure to carbon nanofibers and nanotubes[21].

Concentration of carbon nanofibers and nanotubes at the workplace	Minimal respiratory protection devices
1-10 µgM^3 (10 x REL) - (a)	Any half-face air-purifying respirator equipped with an appropriate filter system for particulate matter - (b) Any half-face negative-pressure air-purifying respirator with a filter
≤ 25 µgM^3 (25 x REL)	Any powered air-purifying respirator system with a hood or helmet and equipped with a HEPA-type filter - (c) Any compressed-air-driven continuous-flow system with a hood or helmet
≤ 50 µgM^3 (50 x REL)	Any full-face clean air system equipped with filters N-100, R-100, or P-100 - (c) Any powered air-purifying respirator system equipped with a HEPA-type filter and tight-fitting masks Any full-face negative-pressure air-purifying system Any compressed-air-driven continuous-flow system equipped with tight-fitting half-face masks Any full-face negative-pressure air-purifying respirator with a filter
≤ 1.000 µgM^3 (1.000 x REL)	Any full-face compressed-air-driven respirator system.

Notes:

(a) REL (Recomended Exposure Level): Recommended exposure limit. This is a weighted average limit considering a work period of 10 h per day (and 40 h per week).

(b) An appropriate filter means any filter (types N, R, or P) from series 95 or 100, considering the presence of oil in the environment, which precludes the use of filters of the N series.

(c) HEPA is similar to the P3-type filter, and N95 is similar to the P2-type filter (refer to ABNT NBR norms 13698:2011 and 13697:2010 to ensure compatibility between filters and respirators).

(d) For comparison, the concentrations of graphite and carbon black in the workplace, based on NIOSH Permissible Exposure Limit (PEL), are 5,000 µgM^3 and 3,500 µgM^3, respectively. The maximum recommended exposure for all types of carbon nanotubes is <1 ugM^3.

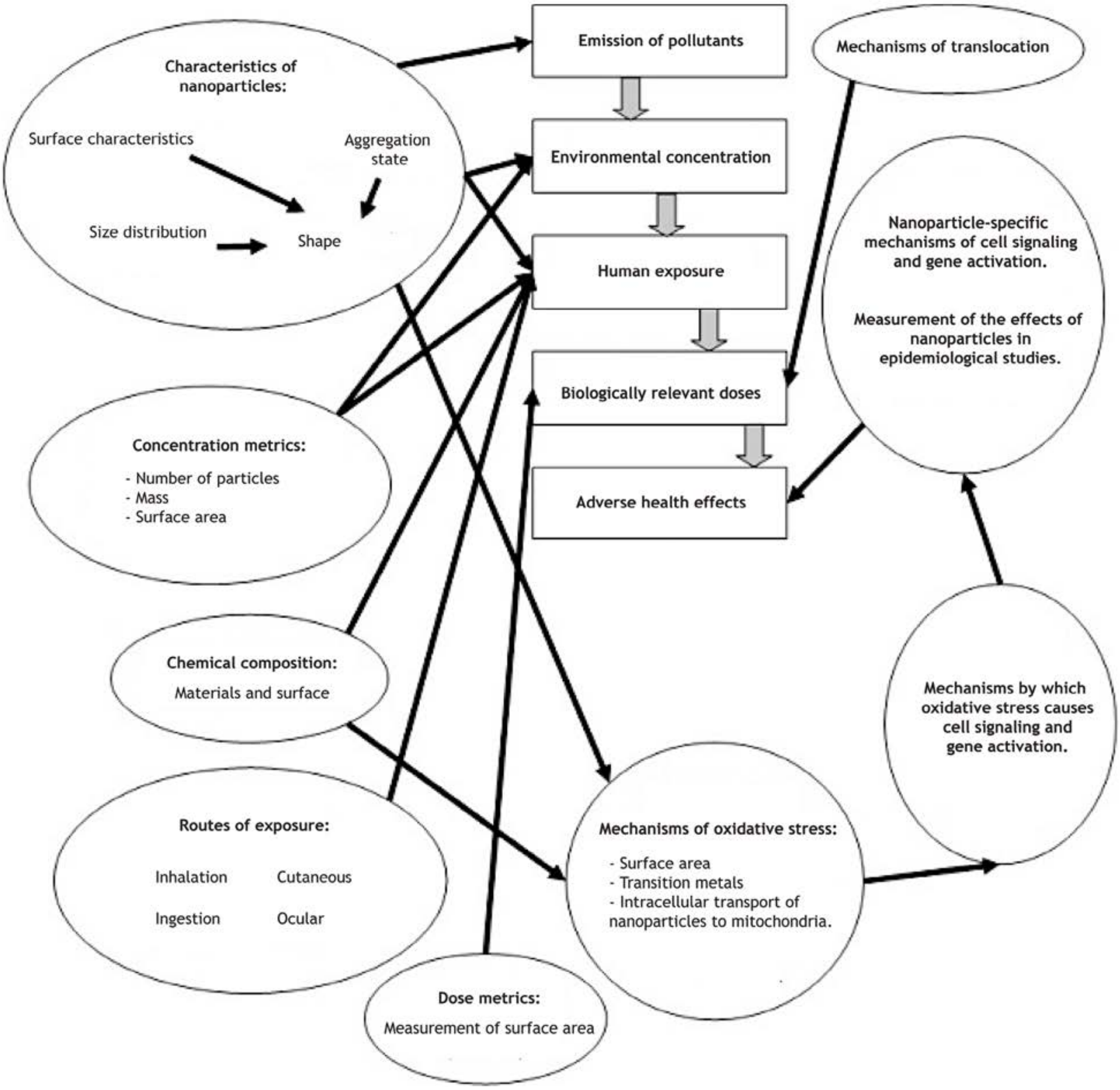

Figure 3. Relationship between interactions, variables, and mechanisms for assessing risks associated with nanoparticles[14].

used. These systems would also include measurements of particle concentration and education and staff training activities. Table 1 presents the NIOSH recommendations for the selection of protection equipment for workers who are exposed to environments containing carbon nanotubes and nanofibers.

b) Skin protection:

The healthy dermal layer of the skin is able to protect against the entry of nanoparticles. However, in a few instances, the presence of cracks, cuts, sores, and even the growth of hair and hair follicles can allow the penetration of nanoparticles. Usually, the use of gloves (vinyl, nitrile, or neoprene) and the use of disposable garments made of high-density polyethylene are sufficient to provide adequate protection against nanoparticle contamination. Figure 4 shows the results of a series of experiments employing nanoparticles with sizes of 40, 750, and 1500 nm and indicates that only 40-nm particles were able to penetrate the skin through the hair follicle and reach the surrounding tissue[31].

c) Ingestion:

Ingestion can be divided into at least 2 conditions: (i) accidental ingestion, resulting from poor hygiene or from contamination of food, utensils, and liquids and (ii) the intentional intake of products containing nanoparticles (food, medicine, therapeutic practices, etc.). For these conditions, the most important measures for contamination control involve professional training, segregation, monitoring of environments that contain nanoparticles, and monitoring of nanoparticles in products that come into

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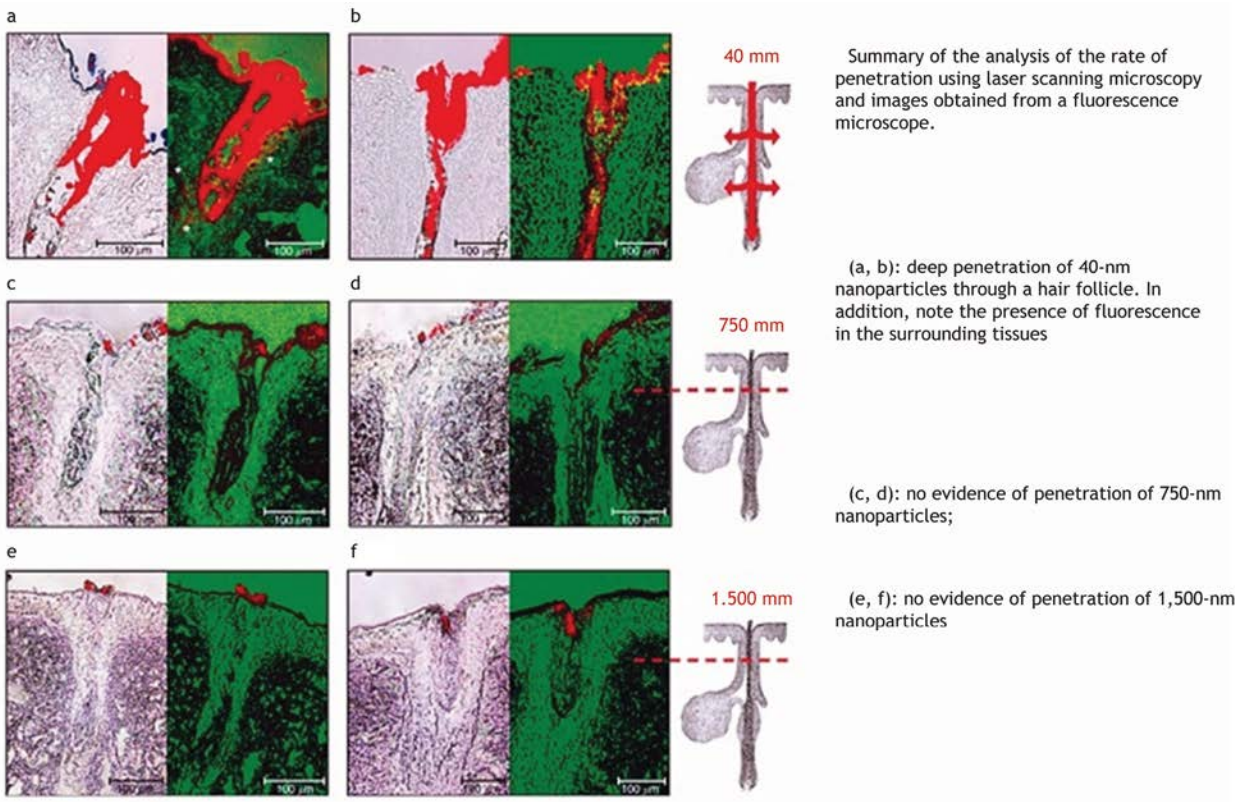

Figure 4. Fluorescence detection in human tissue samples by laser scanning microscopy and digital image processing, showing the penetration of different-sized nanoparticles through hair follicles: (a, b): 40 nm (0.1% solids, 2.84×10^{13} particles/mL, N = 6), (c, d): 750 nm (0.1% solids, 1.08×10^{10} particles/mL), and (e, f): 1,500 nm (0.1% solids, 1.35×10^{9} particles/mL)[31].

contact with food and water. Moreover, environmental issues involving nanotechnology should be addressed in a broader sense and should include analysis of the life cycle of products and the interactions of nanoparticles with the environment.

d) Eye Protection:

		Exposure (emission potential) band for nanoparticles			
		EP1	EP2	EP3	EP4
Hazard Band	HB1	CL1	CL1	CL2	CL3
	HB2	CL1	CL1	CL2	CL3
	HB3	CL1	CL1	CL3	CL4
	HB4	CL2	CL2	CL4	CL5
	HB5	CL5	CL5	CL5	CL5

HB: Hazard band;
EB: Exposure (emission potential) band;
CL: Control level.

Figure 5. Control banding matrix indicating the association between hazard levels and potential exposure levels generated during handling of nanoparticles of different physical states. Control levels with higher indices indicate a higher potential risk of the activity/operation, where: CL5 > CL4 > CL3 > CL2 > CL1[41].

The proper use of eye protection, including full face masks or even PPE (Personal Protective Equipment) & safety systems like hoods equipped with filtration systems, should be recommended after an assessment of labor safety. Importantly, the use of safety glasses is insufficient for eye protection against nanoparticles and the use of collective protection, segregation of operations, and the use of cleanroom systems should be evaluated.

Summary of the analysis of the rate of penetration using laser scanning microscopy and images obtained from a fluorescence microscope.

(a, b): deep penetration of 40-nm nanoparticles through a hair follicle. In addition, note the presence of fluorescence in the surrounding tissues.

(c, d): no evidence of penetration of 750-nm nanoparticles;

(e, f): no evidence of penetration of 1,500-nm nanoparticles

e) Protection against fire and explosion:

The risk of fire and explosion from manual labor is inherent to work involving high-energy storage materials (high-surface-area materials). In the case of nanomaterials, the decrease in particle size considerably increases the surface (and total) energy of the particulate system. However, reliable data on the potential risk for each type of nanomaterial are still lacking, and conventional methods for measuring particulate matter dispersed in the environment are prone to errors[32-34]. Accordingly,

Table 2. Major protocols, standards, and guidelines on the safe handling of nanomaterials and the risks associated with nanoparticles.

Organization (Acronym)/Country	Name	Publication	Year	Website
IRSST (Canada)	Institut de recherche Robert-Sauvé en santé et en sécurité du travail	Health Effects of Nanoparticles, second edition	2008	www.irsst.qc.ca
ILO/ONU (Suíça)	International Labour Office	Emerging Risks and new patterns of prevention in a changing world of work	2010	www.ilo.org
NIOSH (USA)	The National Institute for Occupational Safety and Health	Approaches to Safe Nanotechnology: Managing the health and safety concerns associated with engineered nanomaterials Filling the knowledge gaps for safe nanotechnology in the workplace Occupational exposure to carbon nanotubes and nanofibers	2009 2012 2013	www.cdc.gov/niosh
Cordis (Europe)	Community Research and Development Information Service	Safety aspects	-	www.cordis.europa.eu/ nanotechnology
SWA (Australia)	Safe Work Australia	Engineered nanomaterials: investigating substitution and modification options to reduce potential hazards	2010	www.safeworkaustralia.gov.au
ISO (Switzerland)	International Organization for Standardization	ISO/TR 13121:2011- Nanotechnologies - nanomaterial risk evaluation; ISO/TR 12885:2008 - Nanotechnologies - health and safety practices in occupational settings relevant to nanotechnologies.	2011 and 2008	www.iso.org
HSE & Safenano (UK)	Health and Safety Executive Safenano	Using nanomaterials at work Health effects of particles produced for nanotechnologies Working safely with nanomaterials in research and development	2013 2004 2012	www.hse.g.,ov.uk www.safenano.org
BAuA (Germany)	German Federal Institute for Occupational Safety and Health	Guidance for handling and use of nanomaterials at the workplace	2007	www.baua.de
DTU (Denmark)	Danish Ministry of Environment - EPA	Nanocat: a conceptual decision support tool for nanomaterials	2011	www.mst.dk
ANSES (France)	Agence Nationale de Securité Sanitárie de l'alimentation	Toxité et écotoxité des nanotubes de carbone	2012	www.anses.fr
AIST (Japan)	National Institute of Advanced Industrial Science and Technology	Information portal for the societal implications of nanotechnology	-	unit.aist.go.jp/nri/cie/nanotech_ society
OECD (France)	The Organization for Economic Co-operation and Development	Current Developments: activities on the safety of manufactured nanomaterials	2007	www.oecd.org
ABDI	Brazilian Agency for Industrial Development	Nanotecnologias: subsídios para a problemática dos riscos e regulação	2011.	www.abdi.com.br

some procedures and parameters should be evaluated for preventive purposes, including the following:

- Avoiding the aggregation of nanomaterials in the environment by using filtering and exhaust systems;

- Using anti-spark and anti-static systems or vacuum packaging that is thermally stable;

- Reducing the amount of stored material;

- Decreasing the temperature and pressure of the processes for the synthesis of nanomaterials;

- Installing physical barriers, such as glovebox fire protection systems, as appropriate to each situation;

- Using inert gases such as argon or nitrogen when handling nanometals to prevent oxidation reactions. Oxygen levels in the environment can also be monitored;

- Stabilizing nanomaterials containing metals or semimetals in compatible liquids that can create a surface coating in order to protect these metals against oxidation and combustion reactions (by using protective layers of salts, polymers, oils, or stable emulsions);

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- Using well-defined exclusion zones having restricted access for storage of nanomaterials;

- Installing fire protection systems using cooling agents as appropriate to the chemical nature and amount of stored nanomaterials, and removing combustible materials.

Understanding surface passivation phenomena (formation of oxidized layers that are stable and impermeable) is important for decreasing the reactivity of nanometals. However, the mechanisms of ignition and extent of the reactions are not always the same for nanomaterials and their micrometric counterparts. Thus, individual assessments must be made with regard to the minimum ignition energy, minimum concentration of explosion, maximum pressure of explosion, and the explosion index.

Evolution of safety procedures

In the last 5 years, several institutions and governmental and non-governmental organizations have created protocols, recommendations, and safety handling guidelines[21,27,32,35,36]. Table 2 presents the main institutions and their guidelines and the reports that are available for consultation.

Risk analysis

Analysis of the risks involved in the production, handling, storage, acquisition, use, and disposal of nanomaterials is a complex process because of the gap in the information regarding the limits of exposure for most of the new nanomaterials developed[14,37]. At this point, adoption of the precautionary principle is necessary but not sufficient to guarantee safety for the workers, population, and environment. The use of risk assessment techniques, such as the adoption of control banding methods, is still incipient in case of nanomaterials. In addition, these techniques are often considered too simplistic in high complexity situations, such as those involving nanomaterials, because of their qualitative nature. Notably, there is an effort from several institutions such as ABDI (Brazilian Industrial Development Agency), IRSST (National Research and Safety Institute), ISO (International Organization for Standardization), ANSES (French Agency for Food, Environmental and Occupational Health & Safety), NIOSH (National Institute for Occupational Safety and Health/USA), and ILO (International Labour Organization) to investigate and build enhanced and specific control banding models[38-44]. These models have been adapted to enhance the banding technique for more specific and complex conditions such as those for nanomaterials. Figure 5 shows a control banding matrix for exposure to nanomaterials in different physical states (solid, particulate, liquid, and aerosol). The scaling value of the control indicates the type of control that should be adopted for each of the evaluated conditions.

Conclusions

With regard to the safe handling of nanomaterials and their potential occupational risks, our main conclusions are as follows:

- Terms such as nanotechnology, nanomaterials, nanoparticles, etc. should not be generalized, and individual assessments should be made in each case;

- The different interactions at the nanoscale (chemical, physical, biological, environmental, etc.) should be acknowledged.

- The risks associated with nanomaterials should be completely comprehended and analyzed;

- The shape, morphology, surface area, functionality, surface energy, and surface type are essential for the modification in the properties of products that have been already developed or are under development. Therefore, investigations related to health, safety, and environment should start from the premise of the discovery of novel nanobiological and physical-chemical interactions for these materials;

- Novel technologies require the adoption of novel approaches for the prevention, handling, and storage of materials as well as the establishment of systems and metrics for measurement, control, and individual or collective protection;

- The exposure limits for nanomaterials need to be clearly defined, monitored, and updated according to new developments and findings;

- Low exposure levels do not directly mean a low risk because novel nanosubstances may have different properties and effects, and the effects of dose, exposure, and toxicity over time or the risks associated with each type of material remain to be fully elucidated;

- It is essential to work in groups with the view to seeking opinions and points of view that are diverse, multicultural, multidisciplinary, and hierarchical.

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