Nano Today 24 (2019) 10–14

Contents lists available at ScienceDirect

Nano Today

journal homepage: www.elsevier.com/locate/nanotoday

News and opinion

Biomedical nanotechnology: Occupational views

Veruscka Leso [a], Luca Fontana [b], Ivo Iavicoli [a,*]

[a] *Section of Occupational Medicine, Department of Public Health, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy*
[b] *Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, Italian Workers' Compensation Authority (INAIL), Via di Fontana Candida 1, 00040 Monte Porzio Catone, Rome, Italy*

ARTICLE INFO

Article history:
Received 7 September 2018
Received in revised form 24 October 2018
Accepted 16 November 2018
Available online 14 January 2019

Keywords:
Nanotechnology
Biomedical applications
Nanomedicine
Occupational health and safety
Risk assessment and management

ABSTRACT

Nanotechnology is expected to transform biomedical sectors providing more sensitive and specific imaging techniques, nano-devices and nano-robotics for early detection of biochemical changes, targeted and less toxic drug treatments, as well as enhanced supports for regenerative medicine. Although beneficial, some concerns have emerged on the possible adverse impact that nano-enabled applications may have on human health, particularly on workers exposed throughout the product life cycle, due to the still unpredictable toxicological behavior of nano-sized materials. Therefore, for biomedical nano-technological applications to be considered for a "responsible benchtop to the bedside" translation, occupational health implications should be carefully addressed.

Introduction

Nanotechnology refers to one of the most innovative technologies of the twenty-first century [1]. Peculiar physico-chemical properties of nano-sized materials have been exploited in several production and industrial sectors and are expected to transform biotechnology, medicine and pharmaceutical fields as well. Nanotechnology, in fact, may provide solutions to many of modern medicine's unsolved issues regarding the prevention, diagnosis, and treatment of diseases, offering beneficial advantages for healthcare workers, individual patients, and society in general [2]. However, concerns emerged on the possible adverse impact that nano-enabled solutions may have on human health, and particularly on workers exposed throughout the product life-cycle. Therefore, this paper focuses on opportunities as well as occupational health and safety risks possibly derived from nanoscale biomedical applications that should be carefully considered to achieve a responsible nanotechnological development.

Nano-enabled imaging diagnostics

Nanotechnology may increase the sensitivity and specificity of anatomical and functional imaging, engineering nanomaterials (NMs) with targeted and more biocompatible contrast properties. In this regard, super-paramagnetic iron oxide nanoparticles (NPs) have been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) as contrast agents for magnetic resonance. This may support healthcare workers in an early diagnosis, better staging and pathological lesion follow-up, all of which are important determinants of patients' healing and/or survival rate. Nanomaterials may also function as attractive theranostic platforms, activated by tumoral physico-chemical stimuli, to provide diagnosis and therapeutic delivery in a single procedure. The current practice of surgical oncology may be radically changed by the intraoperative use of nano-enabled imaging techniques, i.e. near-infrared optically active NMs are under investigation as imaging agents for the precise mapping of surgical margins, cancer-bearing lymph nodes, and remnant disease [3,4].

Nano-sensing

Nano-sensor platforms for biochemical and molecular sensing, as well as for surface discrimination of cancerous cells and infective agents, are investigated for their potential impact on diagnosis, disease monitoring and genetic screening. Nano-robots may characterize a promising area of future nanotechnological development, combining robotic technology and biological knowledge for a theranostic approach in dental, neurosurgical, cardiovascular, and hematological practice. Enhancing traditional analytical based strategies, these devices may ameliorate primary prevention and

* Corresponding author at: Department of Public Health, Section of Occupational Medicine, University of Naples Federico II, Via S. Pansini 5, 80131, Naples, Italy.
E-mail address: ivo.iavicoli@unina.it (I. Iavicoli).

https://doi.org/10.1016/j.nantod.2018.11.002
1748-0132/

Table 1
Non-exhaustive examples of commercially available nano-enabled solutions for biomedical applications.

Field of application	Nanotechnology systems	Major indications
Nano-therapeutics and drug delivery systems	Nanocrystals	√ Sirolimus: graft rejection; kidney transplantation √ Fenofibrate: hypercholesterolemia √ Aprepitant: postoperative nausea and vomiting √ Olanzapine, paliperidone: schizophrenia
	Drug-free inorganic NPs	√ Iron-hydroxide complexes: iron deficiency in chronic kidney disease √ Iron oxide: glioblastoma thermal therapy
	Polymeric drugs	√ Glatimer: multiple sclerosis √ PEGylated interferon-gamma beta-1a: relapsing multiple sclerosis √ PEGylated GCSF: chemotherapy induced neutropenia √ PEGylated anti-hemophilic factor VIII: bleeding √ PEGylated interferon alpha-2b protein: hepatitis B, hepatitis C
	Liposomes	√ Liposomal daunorubicin: Kaposi's Sarcoma, ovarian cancer √ Liposomal vincristine: acute lymphoblastic leukemia √ Liposomal irinotecan: pancreatic cancer √ Liposomal amphotericin B: fungal/protozoal infections √ Liposomal morphine sulphate: post operative analgesia √ Liposomal verteporfin: macular degeneration, wet age-related myopia, ocular histoplasmosis
	Micelles	√ Micellar estradiol: menopausal therapy
Medical diagnosis	Inorganic and metallic NPs	√ SPION coated with dextran: super-paramagnetic contrast agent for MRI √ SPION coated with silicone: super-paramagnetic contrast agent for MRI
Tissue engineering	Nanocrystals	√ Hydroxyapatite: bone substitute √ Calcium phosphate: bone substitute

GCSF, granulocyte colony stimulating factor; MRI, magnetic resonance imaging; NPs, nanoparticles; SPION, super-paramagnetic iron oxide nanoparticle.

treatment of clinical disorders, while reducing costs of imaging and frequent follow-up visits [5,6].

Nano-therapeutics and drug delivery systems

Nano-therapeutics and nano-enabled drug delivery systems may offer easier access to biological barriers, increased solubility, stability and targeted specificity, providing more effective, controlled, and personalized treatments with fewer side effects [7]. Drugs with a crystal size in the submicron range, i.e. sirolimus, fenofibrate, aprepitant, and olanzapine are commercially available in US and Europe to treat organ rejection following transplantation, hypercholesterolemia, and postoperative nausea and vomiting, as well as schizophrenia, respectively (Table 1) [3,6,8]. Nanocrystal formulations of hydroxyapatite and calcium-phosphate have been approved by FDA as engineered materials for bone structure regeneration. Certain drug-free inorganic NPs, i.e. iron oxide-NPs, are available as iron replacement therapies to treat anemia in Europe and US. *In vitro* and *in vivo* studies demonstrated that i.e. silver, gold, cerium oxide, zinc oxide-NPs possess anti-microbial properties, although their function as pharmaceutically active compounds still needs clinical confirmation. According to the innovative concept of "caging" *vs* "killing" cancer, NPs can be formulated to deliver pro-inflammatory/pro-immune molecules against tumor antigens to make the cancer microenvironment inhospitable for growth. Iron oxide nanocrystals received FDA and EMA approval, while modified silica, gold, or lipoprotein NPs, are under investigation as primary light absorbers for photo-thermal cancer therapy [3,6,9]. Liposomes and polymeric therapeutics, i.e. polyethylene-glycol-protein conjugates, find application in Europe and US as drug nano-carriers for the treatment of cancers, infections, wet macular degeneration, and pain after major surgery. Other nano-formulations, including polymeric micelles, oil in water emulsions, and inorganic NPs have been investigated for the release of different biologically active molecules [10].

Opportunities for healthcare workers

Providing targeting drug performance, nano-medicines may support simplified treatment regimens, in terms of timing, administration frequency, and dosage, therefore enhancing patient compliance to the treatment plans. This may improve response rate, durable therapy effectiveness, while reducing possible development of drug resistance. Nanotechnology may support advances in the "precision medicine" concept, which relies on "patient-centered" healthcare models, and medical management autonomy [6]. Tissue engineering and regenerative medicine may achieve unprecedented performance if NM properties are able to accelerate the healing process and prevent the risk of infection in injured tissues, be biocompatible with and support the growth of several tissues, as well as to interface with electrically active ones [11].

Occupational health and safety concerns

The path of nanotechnology in biomedical application should take into account not only the provided public health advantages (Fig. 1), but also occupational health and safety implications for workers who may become exposed to such innovative materials for extended periods of their working life (Table 2) [12,13].

Laboratory workers involved in the research and synthesis of biomedical nano-products, as well as those employed in preparing, dispensing, and administrating such products in clinical pharmacies, and healthcare delivery settings may all face innovative NM related occupational health risks. Physicians, pharmacy, nursing, as well as shipping, receiving, and maintenance personnel may come into contact with NMs while handling contaminated items, including the disposal of excreta from patients receiving nano-drugs, as well as from cleaning equipment and areas where nano-products or nano-enabled contrast agents have been used and spilled. Dental and/or surgical procedures involving operations on medical products containing NMs may also cause exposure [2,14].

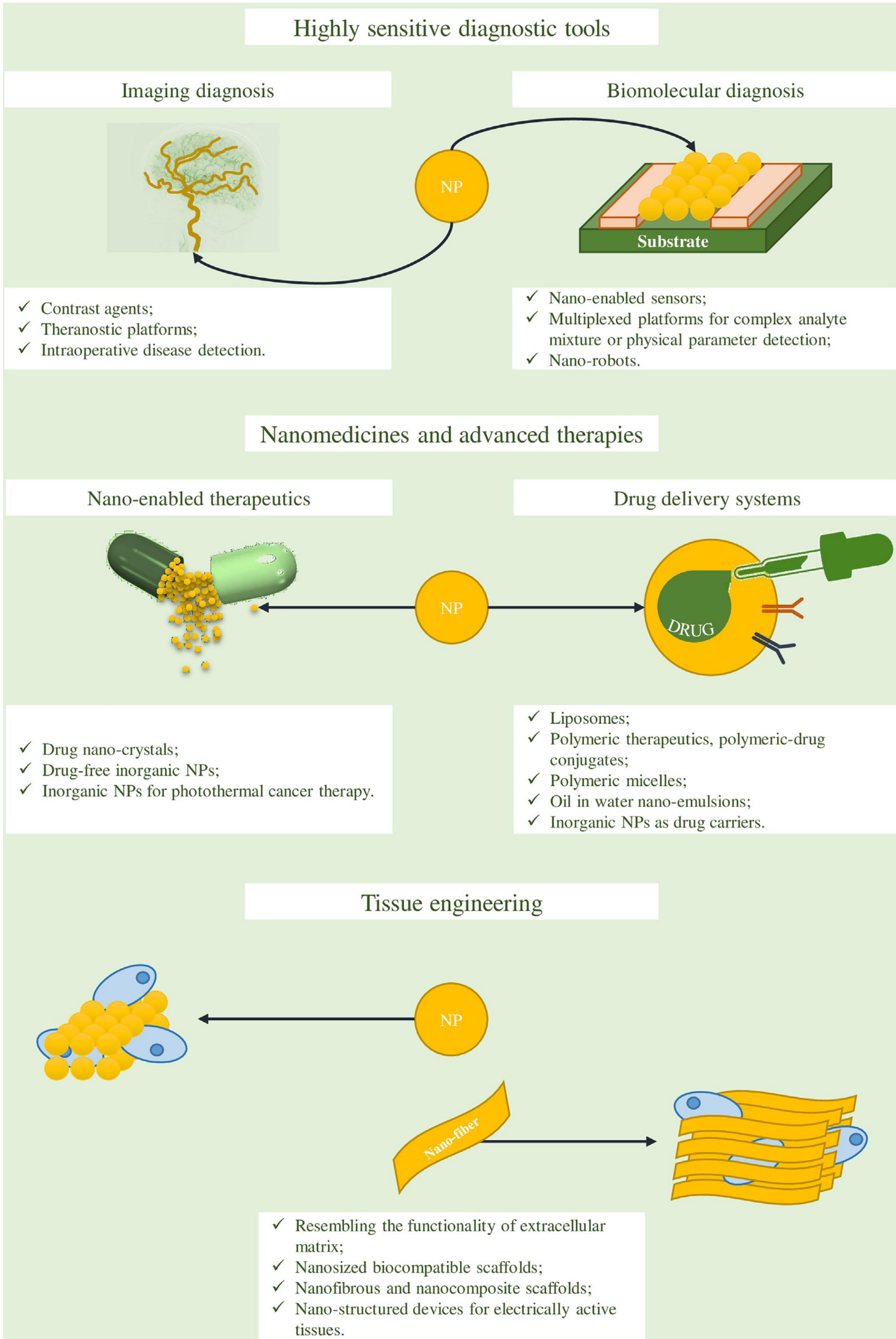


Fig. 1. Applications of nanotechnology in biomedical fields.

However, despite the increasing likelihood of occupational exposure, our knowledge of which NMs may be harmful for the health of workers, particularly concerning the influencing role exerted by their physico-chemical properties, i.e. size, shape, surface chemistry, hydrophobicity/hydrophilicity, aggregation status, degradability and dissolution, is still preliminary. Nanomaterials are not a unified class of compounds, with intrinsically heterogeneous health and safety profiles. Additionally, NMs may have different bio-molecular interactions once introduced into the body that may affect their bio-persistance, bio-accumulation, and toxicodynamic behavior [15].

Currently, human biosafety information from clinical trials is limited and some information concerning toxicity of NMs applied in biomedical fields derives from research carried out in *in vitro*

Table 2
Nanotechnology in healthcare sector: occupational opportunities, and health and safety issues in occupational fields.

OPPORTUNITIES	APPLICATION FIELDS	CHALLENGING ISSUES
↑ Imaging sensitivity and specificity ↑ Early disease detection ↑ Better staging and follow-up ↓ Doses of contrast agents ↓ Acquisition times ↓ Risk of incomplete surgical resection	IMAGING DIAGNOSTICS	BIOSAFETY • Differently characterized nanomaterial (NM) compounds • Limited knowledge on NM toxicological profile • Not fully understood role of NM physico-chemical features • Biomolecular interactions *in vivo* • Limited biosafety information from clinical trials
↑ Multiplexed diagnostic platforms ↑ Advanced biomarker analyses ↑ Primary prevention capabilities ↑ Better disease follow-up ↓ Biological sample manipulation	CHEMICAL BIOLOGY	EXPOSURE ASSESSMENT • Variable conditions of exposure • Lack of reliable exposure metrics • Lack of affordable environmental monitoring strategies • Limited knowledge on NM toxicokinetics and dynamics • Not validated biological monitoring measures
↑ Personalized treatments ↑ Patient compliance to treatment ↑ Improved outcomes ↑ "Precision medicine" ↑ Medical autonomy ↑ Theranostic strategies ↓ Adverse side effects ↓ Health care system costs ↑ Multidisciplinary medicine approach	THERAPEUTICS and DRUG DELIVERY SYSTEMS	RISK ASSESSMENT AND MANAGEMENT • Workforce awareness on NM presence • Multiple risks in occupational settings • Emerging risks due to innovative procedures • Increasing pressure on the workforce • Effectiveness of actual engineering and administrative controls • Ethical dilemmas • Justice principles debate
↑ Accelerate the healing process ↑ Biocompatible substrates ↓ Follow-up surgeries ↑ "Organs-on-a-chip" for experimental settings	REGENERATIVE MEDICINE	

and *in vivo* experiments. Titanium dioxide ultrafine particles and multi-walled carbon nanotubes-7 have been classified as possibly carcinogenic to humans [16,17]. However, a correct extrapolation of animal data to human beings remains a challenging issue due to the species-related differences and methodological design of the studies, which frequently does not adequately resemble the low-dose, long-term conditions of exposure, as those potentially experienced in the workplace. Additionally, the difficulty in defining those exposure metrics better correlating with toxicological outcomes and affordable environmental monitoring technologies may prevent correct exposure assessments for healthcare NM workers. Moreover, some uncertainties remain concerning workforce awareness of the presence of NMs in handled products, and the proper identification of such NMs in safety data sheets or product labeling. To date, no biological monitoring strategies have been validated to assess exposures and early effects of NMs in healthcare sectors [13,18].

Occupational risk assessment and management

Overall, to evaluate the risks associated with occupational exposure to NMs in biomedical fields is a quite challenging issue, considering also the "co-exposure scenarios", in terms of biological, physical, and organizational safety and health hazards that healthcare workers routinely experience during their job tasks [19]. Additionally, advances in nanotechnology may require a forced professional updating for employees to be continuously qualified and skilled to face such changing occupational realities and to deal with multidisciplinary expertise involved in nano-technological biomedical applications [20].

In such developing field, regulatory guidance is needed to provide clarity and legal certainty to manufacturers, policymakers, healthcare providers, and public, as well as to define possible health and safety implications for exposed workers. However, the still uncertain scenario warrants efforts for a precautionary risk management approach for healthcare workers. This means ensuring a less toxic profile for NMs according to a "safety by design approach", as well as adopting reasonable preventive and protective measures that will change, be continuously evaluated, improved, and verified as risk information becomes more substantial. In this context, good practices on work should include transparency and traceability to increase workplace awareness of where nano-enabled products are used and exposure may occur, the adoption/implementation of collective and personal protective equipment to prevent/minimize exposure, and the development of education and training of the staff about measures necessary to face emerging risks. To these aims, the application of pharmaceutical industry good manufacturing procedures, guidance for working with NMs in research laboratories, and guidelines for healthcare workers handling hazardous medicines may be adapted to a nano-enabled healthcare scenario. Occupational health surveillance may serve as a secondary preventive measure to identify biomarkers of exposure and early effect.

In this context, it may be important to effectively engage with stakeholders involved from academia to industry, non-governmental organizations and regulators, workers' representatives, and occupational health and safety professionals into a whole risk assessment and management process [18]. In conclusion, for biomedical nano-technological applications to be considered for a "responsible benchtop to the bedside" translation, implications for the health and safety of workers should be carefully addressed.

Conflicts of interest

The authors declare that there is no conflict of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of organizations to which they are affiliated.

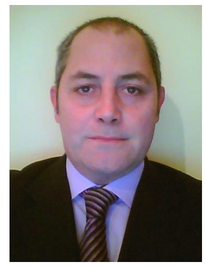
Acknowledgements

The authors thank dr. Paola Gervetti and dr. Sara Mauro for their contribution in the bibliographic search.

References

[1] M. Reese, Health Matrix Clevel. 23 (2013) 537–572.
[2] ECHA, European Chemical Agency, 2012, Accessed on 31 August 2018 https://osha.europa.eu/it/tools-and-publications/publications/e-facts/e-fact-73-nanomaterials-in-the-healthcare-sector-occupational-risks-and-prevention.
[3] D. Bobo, K.J. Robinson, J. Islam, K.J. Thurecht, S.R. Corrie, Pharm. Res. 33 (2016) 2373–2387.
[4] B. Pelaz, C. Alexiou, R.A. Alvarez-Puebla, F. Alves, A.M. Andrews, S. Ashraf, et al., ACS Nano 11 (2017) 2313–2381.
[5] Y. Saadeh, D. Vyas, Am. J. Robot. Surg. 1 (2014) 4–11.
[6] A. Hafner, J. Lovrić, G.P. Lakoš, I. Pepić, Int. J. Nanomed. 9 (2014) 1005–1023.
[7] H. Su, Y. Wang, Y. Gu, L. Bowman, J. Zhao, M. Ding, J. Appl. Toxicol. 38 (2018) 3–24.
[8] M.L. Etheridge, S.A. Campbell, A.G. Erdman, C.L. Haynes, S.M. Wolf, J. McCullough, Nanomedicine 9 (2013) 1–14.
[9] C.M. Hartshorn, M.S. Bradbury, G.M. Lanza, A.E. Nel, J. Rao, A.Z. Wang, et al., ACS Nano 12 (2018) 24–43.
[10] A.Z. Mirza, F. Siddiqui, Int. Nano Lett. 4 (2014) 94.
[11] J.D. Kingsley, S. Ranjan, N. Dasgupta, P. Saha, J. Pharm. Res. 7 (2013) 200–204.
[12] J. Zhao, V. Castranova, J. Toxicol. Environ. Health B Crit. Rev. 14 (2011) 593–632.
[13] V. Murashov, J. Howard, J. Occup. Environ. Hyg. 12 (2015) D75–85.
[14] V. Murashov, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 1 (2009) 203–213.
[15] M.A. Gatoo, S. Naseem, M.Y. Arfat, A.M. Dar, K. Qasim, S. Zubair,Biomed Res. Int. 2014 (2014), 498420.
[16] NIOSH, National Institute for Occupational Safety and Health, 2011, Accessed on 31 August 2018 https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf.
[17] IARC, International Agency for Research on Cancer, 2014, Accessed on 31 August 2018 https://monographs.iarc.fr/wp-content/uploads/2018/06/mono111.pdf.
[18] V. Leso, L. Fontana, M.C. Mauriello, I. Iavicoli, Curr. Nanosci. 13 (2017) 55–78.
[19] US-OSHA, Occupational Safety and Health Administration, (2014), https://www.osha.gov/SLTC/healthcarefacilities/index.html, Accessed on 31 August 2018.
[20] A. Allon, R. Ben-Yehudah, J.H. Dekel, K.M. Solbakk, Weltring G. Siegal, Med. Health Care Philos. 20 (2017) 3–11.

Veruscka Leso, MD, PhD is Assistant Professor of Occupational Medicine at the Department of Public Health of the University of Naples “Federico II”, Italy. She obtained her Medical Degree in 2007, specialization in Occupational Medicine in 2012 and PhD in Environmental, Occupational, and Social Medicine in 2016 at the Catholic University of the Sacred Heart of Rome, Italy. Her research interests include the evaluation of possible toxic effects of nanomaterials on cellular and animal models, the assessment of the impact of nanomaterial exposure on the health of workers, the evaluation of possible strategies to assess and manage nanomaterial risks.



Luca Fontana, MD, PhD is researcher at the Italian Workers' Compensation Authority, Department of Occupational and Environmental Medicine, Epidemiology and Hygiene. He obtained a degree in Medicine, a specialization in Occupational Medicine and a Ph.D. in Occupational, Environmental and Social Medicine at the Catholic University of the Sacred Heart of Rome. He has publications on international journals on topics such as nanotechnology and nanomaterials, endocrine disruptors, hormesis and platinum group metals. His current research activity mainly concerns the risk assessment and management of exposure to nanomaterials and their effects on in vitro and in vivo models.

Ivo Iavicoli, MD, PhD is Full Professor of Occupational Medicine at the Department of Public Health of the University of Naples “Federico II”, Italy. He obtained with honors his Medical Degree in 1998 and specialization in Occupational Medicine in 2002 at the Catholic University of the Sacred Heart of Rome, Italy. He earned his PhD in Occupational Medicine and Industrial Hygiene in 2006 at the University of Milan, Italy. He is the Chairman of the Scientific Committee on Nanomaterial Workers' Health at the International Commission on Occupational Health. He is author of more than 260 scientific publications on occupational health.