

UNIVERSITY OF BIRMINGHAM

Research at Birmingham

Long-term monitoring for nanomedicine implants and drugs

Kendall, Michaela; Lynch, Iseult

DOI:

[10.1038/nnano.2015.341](https://doi.org/10.1038/nnano.2015.341)

License:

None: All rights reserved

Document Version

Peer reviewed version

Citation for published version (Harvard):

Kendall, M & Lynch, I 2016, 'Long-term monitoring for nanomedicine implants and drugs', *Nature Nanotechnology*, vol. 11, pp. 206-210. <https://doi.org/10.1038/nnano.2015.341>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Long-term surveillance for nanomedicine implants and drugs

Michaela Kendall and Iseult Lynch

Increasing globalization means that traditional occupational epidemiological approaches may no longer apply, suggesting a need for an alternative model to assess the long term impact of nanomaterial exposure on health.

The Royal Society conference “*Bionano Interactions: new tools, insights and impacts*” (30 April – 1 May 2014) discussed translating potential nanobiotechnologies into clinical applications, and assessed their safety and science-based regulatory regimes¹. A key topic of debate was whether nanomaterials and nanostructures require additional or alternative risk assessment approaches, and what form these might take. In exposure assessment, it was suggested that occupational epidemiology approaches may no longer apply because of increased globalization, where material production has become geographically dispersed and consumer purchasing patterns have changed. Instead, exposure to nanomedicines (e.g. diagnostics such as contrast agents or therapeutics such as drug delivery agents) and nano-structured implants may represent a significant new exposure route or cohort for epidemiological studies of nano-related health effects².

Traditionally, occupation-centric epidemiology – where worker populations are studied over decades - is used to assess the impact of material exposure on health. Accumulated evidence from such studies in specific industries (such as mining, agriculture, radiation workers and others) have alerted observers to common, damaging occupational material exposures, mechanisms and effects. In cases of extreme exposure to a work-related contaminant, it was possible to quantify the level of exposure and the effects on health. Worker cohorts were key to identifying the damaging health effects from inhalation of the crocidolite form of asbestos, which is linked to pleural mesothelioma, a form of lung cancer². Building on these studies, environmental exposures in non-occupational settings became possible. For example, lung and cardiovascular related health impacts from anthropogenic airborne particles have been correlated with exposure via measures such as closeness to busy roads or traffic³, and assessment of health effects from exposure to airborne nanomaterials has also been tested.

In the case of nanomaterials, safety assessment is approached from a responsible governance of innovation viewpoint, to prevent large-scale human health impact, such as that from asbestos⁴. The field of nanotoxicology emerged from the study of fine (0.1-2.5 microns in diameter) and ultrafine (diameters <100nm) combustion or air-pollution particles (also called incidental particles) in the early-2000s, and it focuses specifically on health impacts from engineered or manufactured nanomaterials.⁵ Donaldson et al. recently rejected the idea that engineered nanomaterials may induce specific health effects beyond those already known for combustion-derived particles, such as inflammation and oxidative stress⁶. However, novel features of some engineered nanomaterials, such as an energy bandgap that overlaps with that of cells, or very high surface strain resulting from high temperature synthesis methods, may result in enhanced toxicities compared to ultrafine particles from combustion or air pollution¹. Because health impacts linked to incidental or occupational exposures to engineered nanomaterials are minimal at current usage levels, few nano-specific health effects have been determined by epidemiology, to date⁷. However, from a regulatory viewpoint, in addition to acute effects, cumulative exposures that result in increased incidence of diseases are also important considerations. Indeed, many diseases are increasingly linked to environmental factors⁸ but only manifest after several decades (e.g. dementia, or asbestos-related mesothelioma).

Although practices vary considerably between countries and in industries of different scales (e.g. small and medium enterprises versus corporations), decades of advances in legal protection and increased worker awareness have effectively reduced occupational exposures to materials such as airborne particles to low risk levels. Most of the protective practices developed for powder handling are applicable to nanomaterials, and if adhered to, will protect workers against occupational nano-health effects^{9,10}.

At the recent Safety of Engineering Nanomaterials and Nanotechnologies (SENN2015) conference, Paul Schulte from the US National Institute for Occupational Safety and Health stated that worker populations in individual companies handling nanomaterials are too small to monitor, and that even fewer workers are registered in medical surveillance or epidemiological studies (see Figure 1a). Furthermore, changes in production methods and the globalisation of businesses mean that the nature of exposures is also changing. Because the manufacturing, release and distribution of products to global markets now operate on more compressed timelines than before, long term exposures amongst workers are diminishing. Moreover, as material supply, handling and manufacturing facilities become more geographically dispersed (over various different continents),

the intensity of exposure is reduced. All these point to the fact that workers may no longer represent the highest exposure group for epidemiological studies, including those related to nanomaterials. Schulte concluded that even after 15 years of dedicated nano-industry activities, it has not yet been possible to make decisions regarding the risks faced by workers handling nanomaterials.

Globalisation also makes data gathering much more complex. Exposure to nanomaterials is particularly interesting because evidence of health consequences of occupational exposures is emerging slower than the commercialisation of mass-marketed nano-containing consumer products. Occupational safety and health criteria defining what constitutes responsible development of nanotechnology are missing¹¹. The economic positives of nanomaterial deployment have trumped almost all human health concerns over new materials entering products, markets, humans and the environment¹². Nanomaterials are now included in a wide range of consumer products (>1,600 according to the Woodrow Wilson consumer product inventory¹³), and have been particularly taken up by cosmetics manufacturers^{14,15}. This has led to a flurry of regulatory-related activity in Europe, the US, and elsewhere. For example, in 2014, the US Food and Drug Administration issued guidance for the cosmetics industry¹⁶ that requires manufacturers or distributors to identify and appropriately address new or altered physicochemical properties exhibited by nanomaterials that affect biological interactions, or raise questions about product safety. Specifically, this requires assessing the suitability of traditional methods for testing the toxicity of cosmetic products containing nanomaterials.¹⁶ In Europe (effective since July 2013, with other jurisdictions likely to follow suit in the near future), it is required to include (nano) in front of nanoscale ingredients on cosmetics labels and packaging.

Another area of very rapid growth, with significantly higher market value and much tighter regulation, is the use of nanomaterials in medicine. This extends from nanostructured scaffolds and biomaterials for growth and repair of tissue in regenerative medicine, through use of nanoscale carriers for improving drug solubility and enhancing target specificity of drug molecules, to imaging and diagnostic applications of nanomaterials as contrast agents or as combined diagnostic and theranostic agents.¹⁷ We propose here that the intentional use of nanomedical products provides a new route to monitor the health impacts from exposure to nanomaterials, both intentional (the patient) and potentially occupational (clinical staff), and provide some specific examples below.

The biomaterials market for implantable devices was valued at US\$25.3 billion in 2012 and is estimated to reach US\$33.6 billion globally in 2019, driven by the rising need for medical implants in key growth markets including the U.S., U.K., Canada, Germany, France, Japan, Australia, South Korea and New Zealand.¹⁸ Among the factors that are driving the increased implantation of materials into the human body is the aging global population which is pushing up demand for e.g. hip and knee replacements. Longer lifespans mean that implant recipients can coexist with their implant for increasingly long durations; although designed to last 15-20 years, some implants last as long as 30-40 years. The rapid rise in implant procedures globally has occurred without understanding potential long-term effects of the materials, and there remains strong concern about wear (both abrasion and leakage) and autoimmunity¹⁹. Evidence is mounting that, over time, nanoscale “wear particles”, which are formed as a result of wear to load-bearing implants such as hip-joints, can migrate from the implant site, signal across the blood-foetal barrier and cause damage to DNA^{20,21}. This, along with evidence of short-term complications and high failure rates leading to additional surgeries, led to the UK National Health Service banning the use of metal-on-metal hip implants in October 2013, with the United States and Canada later recommending they not be used²². Events at the implant surface can also affect implant function. Analysis of the so-called foreign body reaction (FBR), one of the major routes of failure of medical implants, demonstrated that disease mechanisms were often related protein adhesion and subsequent interaction of phagocytes with the surface-adsorbed proteins¹⁹. The use of nanostructured surfaces offers a strategy to enhance acceptance of implant materials (see Figure 2) through mediation of protein binding. Other nano-enabled approaches under development include cell encapsulation in injectable multifunctional hydrogels for cell delivery and nanostructured scaffolds for complex tissues generation.¹⁷

The nanomedicine and nanodiagnostics markets are also expanding, driven by the demand for earlier diagnosis (via increased sensitivity and/or improved spatial resolution of contrast agents) and/or improved efficacy and specificity of therapies for widespread diseases such as cancer. Recent market reports have valued the nanomedicine market at US\$72.8 billion in 2011 and it is expected to grow to \$130.9 billion by 2016²³. The pharma patent gap – arising from the lack of new patented drugs and expiry of patented drugs - has pushed the commercialization of nano-enabled innovations. Nanoformulation creates new hope for drug candidates that failed to reach the market previously, because nanomaterials, which are at the same size scale as molecular biology, offer enormous potential to improve the delivery and efficacy of existing drug formulations. For example, poorly soluble or highly toxic drugs can be encapsulated into nanocarriers (in the form of liposomes

or polymeric nanoparticles) to improve their specificity and safety profiles.²⁴ Drugs with poor target specificity can be delivered directly to the target cells, thus reducing the dose required and the side-effects.²⁴ Numerous FDA-approved nanotherapeutics and nanodiagnostics are available for clinical use (see Table 1 for a subset as examples), as well as many more in clinical trials²⁵. However, several nano-diagnostic products that have undergone extensive clinical trials were later withdrawn from the market or denied marketing authorisation (e.g. superparamagnetic iron oxide formulations Resovist® and SINEREM®) as a result of poor specificity and/or poor contrast leading to a high proportion of false negatives.

Given the uncertainty regarding the safety of nanomaterials, longer term surveillance of patients (e.g. weeks, months and years following exposure) during early and advanced clinical trial phases is needed. Close monitoring of patients is important for identifying any long-term consequences, which could be used in product development. Better products are likely to reduce the number of recalls. An important area of development is delivery systems for the respiratory tract, including nasal, tracheobronchial and pulmonary regions, for less invasive treatment of chronic illnesses such as diabetes (see also Figure 2)^{26 27}. While these are not yet in clinical use, tracking both patient and medical worker exposures to inhalable nanomedicines as they come onto the market could provide important links to occupational exposure monitoring, where inhalation is the primary exposure route.

The use of nanomaterials and other advanced materials in contemporary clinical practice could be a particular concern because of the unpredictable effects of cumulative nanoparticle exposures from many sources, including those from medical procedures and general consumer exposure to nanomaterials-containing products. Thus, humans are likely to experience high exposures – and potentially doses – of certain nanomaterials from implantation and/or use of nano-enhanced medicinal products. Clinically prescribed doses of nanomedicines or nanodiagnostic agents are likely to be higher than occupational exposures. Additionally, medical exposures will occur against a background of anthropogenic atmospheric exposures (e.g. from combustion) and from other sources such as food (typical exposure for a US adult may be ~1 mg Ti per kilogram body weight per day).²⁸ Indeed, a more comprehensive approach that assesses the "exposome", i.e. "the totality of exposures throughout a person's life, from chemicals, diet, stress, drugs, infection, and the individual response", has been called for²⁹. The highly specific composition of medical implants (e.g. the CoCr debris particles from metal-on-metal hip implants²⁰) is advantageous in terms of identification and tracking nanomaterials in patients. Similarly, nanodiagnostic tools such as gold or iron oxide

particles used as contrast agents should be easily detectable, and their long-term fate could be tracked following administration. For difficult to detect nanomedical carriers such as polymeric particles, or where no significant accumulation occurs in the body, approaches to monitoring exposure using treatment dose are feasible. Such approaches are currently used to track patient exposure to X-rays for example, as well as monitoring immunisation throughout childhood via national immunisation programmes. Using increasingly sophisticated patient tracking systems like patient accessible electronic health records (PAEHRs),³⁰ public health professionals may monitor the exposure of patients to nanomedicine, and analyse the health implications of nanomedicines or implants over years or decades³¹. With proper due diligence and collaboration, the fields of nanomedicine and public health have the potential to accelerate each other to improve human health more efficiently than either could do individually³¹.

The toxicological study of nanomedicines and implants is critically important, yet it remains difficult to detect chronic effects since there are few long-term studies in toxicology, and only (occupational) epidemiology tends to demonstrate chronic effects. However, evidence for the success or otherwise of implants is emerging from medical practice via clinical trials data, and as a result of product recalls or bans. Patients treated with nanomedicines and nanodiagnostics continue to face a knowledge gap regarding epidemiology studies, unless some specific action is taken to monitor the use of nano-enabled theranostic approaches, and to implement medical surveillance following nano-related treatment. Clearly, such approaches cannot account for self-mediation, whereby the internet has reduced geographical boundaries in terms of availability of products, including medicines and dietary supplements, even where regulation regarding specific products and their safety exists. Thus, patient self-reporting of exposure might supplement surveillance. Importantly, the potential of nanomedicine is not limited to developed countries: public health applications of nanomedicine, such as rapid and portable diagnostics and more effective vaccinations, have the potential to revolutionize global health.³¹ Thus, global best practice for monitoring the use and long-term post-treatment consequences of nanomedicines needs to be established urgently.

As our previous reliance on worker exposure data is undermined by globalisation, advances in industrial production and changes in consumer purchasing patterns, nano-exposure related effects are challenging to detect and define. Along with voluntary or mandatory registries of products containing nanomaterials, mandatory hospital and clinical registries that record the use of nano-enabled or nano-containing medicines and devices for longitudinal epidemiological studies may be necessary in order to facilitate the necessary epidemiological studies. Such registries can identify

issues early on and mobilise a rapid response should product failures or adverse patient responses arise later on. As utilisation of nanomedicines increase, such medical surveillance registries will demonstrate the importance of data collection in assessing both treatment success as well as potential unintended health consequences resulting from nanomedicine exposure. There is precedent for medical surveillance following cancer diagnosis and/or treatment,³² and health-care related infections,³³ which could be extended to nano-based diagnostic or treatment interventions (see Figure 1b). Indeed, advances in classification and multivariable algorithms to analyse patient records and outcomes is improving the predictive capacity of the algorithms in terms of determining whether follow-up care is required and thus, improving the cost effectiveness of post-operative patient care³³. The role of public health professionals in achieving this is vital, and indeed there has already been a suggestion to form a science, technology, medicine law-healthcare policy (STML) center, to support the translation of nanotechnology across medical disciplines³¹. This could provide a legal underpinning to support long-term (decades) surveillance and global sharing of data regarding long-term patient outcomes following treatment with nanomedicines. Longitudinal studies of patients following implant treatment are common (e.g. over 25 years) and should be implemented more broadly for nanomedicines. Coordinated approaches of this nature would also facilitate timely and coordinated responsive action should the need arise.

Given the enormous scope of nanotechnologies, the reinsurance industry was among the first to publish reports on the potential risks of nanomaterials^{34,35}. In addition to employer liability and product liability losses, there could potentially be losses and/or lawsuits arising out of environmental liability,³⁶ e.g. costs of repairing environmental damage arising from both common law claims, and claims arising from national, EU and international legislation. For example, the principle of the polluter pays is enshrined in the Treaty on the Functioning of the European Union (Article 191(2) TFEU) and in the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) of 1980 in the USA. One potential route towards a nanomedical surveillance programme is the use of health insurance records. However, this would not be without legal challenges and data privacy issues. An alternative model could be oversight partnerships between regulators, nanomedicine companies and hospital trusts to extend clinical trials into longer-term surveillance of patient outcomes for a number of years post regulatory approval, such that early warnings of undesirable impacts can be addressed rapidly and effectively. [This could be coupled with monitoring of patient responses to more traditional implant materials, such as metal-on-metal implants, which are increasingly understood to generate nanoparticles during extended use as a consequence of wear-and-tear, to additionally monitor responses to unintentional exposure to nanomaterials.](#)

Additionally, the doctors and nurses routinely handling nanomedicines could provide a parallel occupational exposure cohort. Combined, these three groups (nanomedicine patients, nanomedicine hospital workers and traditional implant patients whose implants generated “wear-induced nanoparticles”) would ensure large cohort sizes for epidemiological studies of impacts of exposure to nanoscale materials.

Michaela Kendall¹ and Iseult Lynch² are at ¹School of Metallurgy and Materials, University of Birmingham, Edgbaston, B15 2TT and ²School of Geography, Earth and Environmental Sciences, University of Birmingham, Edgbaston, B15 2TT, United Kingdom
email: i.lynch@bham.ac.uk

REFERENCES

- 1 Lynch, I., Feitshans, I.L., Kendall, M. Bionano interactions, new tools insights and impacts’’: Summary of the Royal Society Discussion Meeting. *Phil Trans Roy Soc B*, **370**, 20140162 (2015).
- 2 Kendall, M., Holgate, S. Health impact and toxicological effects of nanomaterials in the lung. *Respirology* **17**, 743–758 (2012).
- 3 Künzli, N. Air pollution: from lung to heart. *Swiss Med Wkly* **135**, 697–702 (2005).
- 4 Foss Hansen, S. M., A., Baun, A., Tickner, J.A. Late lessons from early warnings for nanotechnology. *Nat Nanotechnology* **3**, 444-447 (2008).
- 5 Oberdörster, G., Oberdörster, E., Oberdörster, J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* **113**, 823-839 (2005).
- 6 Donaldson, K., Poland, C.A. Nanotoxicity: challenging the myth of nano-specific toxicity. *Curr Opin Biotechnol* **24**, 724-734 (2013).
- 7 Kuempel, E. D., Geraci, C.L., Schulte, P.A. Risk assessment and risk management of nanomaterials in the workplace: translating research to practice. *Ann Occup Hyg* **56**, 491-505 (2012).
- 8 Migliore, L., Coppedè, F. Genetic and environmental factors in cancer and neurodegenerative diseases. *Mutat Research/Rev Mutat Res* **512**, 135–153 (2002).
- 9 NIOSH. Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide; <http://www.cdc.gov/niosh/nppm/upd-04-18-11.html>. (2011).
- 10 Woskie, S. Workplace practices for engineered nanomaterial manufacturers. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* **2**, 685-692 (2010).
- 11 Schulte, P. A., Geraci, C.L., Murashov, V., Kuempel, E.D., Zumwalde, R.D., Castranova, V., Hoover, M.D., Hodson, L., Martinez, K.F. Occupational safety and health criteria for responsible development of nanotechnology. *J Nanopart Res* **16**, 2153 (2014).
- 12 Maine, E., Thomas, V.J., Bliemel, M., A Murira, A., Utterback, J. The emergence of the nanobiotechnology industry. *Nat. Nanotechnol* **9**, 2–5 (2014).
- 13 Woodrow Wilson. (<http://www.nanotechproject.org/cpi/>).

- 14 Nohynek, G. J., Lademann, J., Ribaud, C., Roberts, M.S. Grey Goo on the Skin? Nanotechnology, Cosmetic and Sunscreen Safety. *Crit. Rev. Toxicol.* **3** 251-277 (2007).
- 15 Bowman, D. M., van Calster, C., Steffi Friedrichs, S. Nanomaterials and regulation of cosmetics. *Nat Nanotechnol* **5**, 92 (2010).
- 16 FDA. Guidance for Industry: Safety of Nanomaterials in Cosmetic Products. FDA-2011-D-0489 (2014).
- 17 European Commission and ETP Nanomedicine. Roadmaps in nanomedicine: towards 2020. http://www.etp-nanomedicine.eu/public/press-documents/publications/etpn-publications/091022_ETPN_Report_2009.pdf (2009).
- 18 Transparency Market Research. Biomaterials Market for Implantable Devices (Material Type - Metals, Polymers, Ceramics and Natural, Applications - Cardiology, Orthopedics, Dental, Ophthalmology and Others) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast 2013 - 2019. (2012).
- 19 Hartmann, A., Hannemann, F., Lützner, J., Seidler, A., Drexler, H., Günther, K.P., Schmitt, J. Metal Ion Concentrations in Body Fluids after Implantation of Hip Replacements with Metal-on-Metal Bearing – Systematic Review of Clinical and Epidemiological Studies. *PLoS One* **8**, e70359 (2013).
- 20 Bhabra, G., Sood, A., Fisher, B., Cartwright, L., Saunders, M., Evans, W., Surprenant, A., Lopez-Castejon, G., Mann, S., Davis, S., Hails, L., Ingham, E., Verkade, P., Lane, J., Heesom, K., Newson, R., Case, C.P. . Nanoparticles can cause DNA damage across a cellular barrier. *Nat. Nanotechnol* **4**, 876 – 883 (2009).
- 21 Cogan, N., Baird, B, Caldwell, M, Crompton, L, Phillips, R, Rubio, M, Newson, R, Lyng, F., Case, C. DNA damaging bystander signalling from stem cells, cancer cells and fibroblasts after Cr(VI) exposure and its dependence on telomerase. *Mutat Res/Fund Mol Mechan Mutagen* **683**, 1-8 (2010).
- 22 Hannemann, F. H. A., Schmitt, J., Lützner, J., Seidler, A., Campbell, P., Delaunay, C.P., Drexler, H., Ettema, H.B., García-Cimbrelo, E., Huberti, H., Knahr, K., Kunze, J., Langton, D.J., Lauer, W., Learmonth, I., Lohmann, C.H., Morlock, M., Wimmer, M.A., Zagra, L., Günther, K.P. . European multidisciplinary consensus statement on the use and monitoring of metal-on-metal bearings for total hip replacement and hip resurfacing. *Orthop Traumatol Surg Res* **99**, 263-271 (2013).
- 23 Transparency Market Research. Biomaterials Market for Implantable Devices (Material Type - Metals, Polymers, Ceramics and Natural, Applications - Cardiology, Orthopedics, Dental, Ophthalmology and Others) - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 - 2019. (2012).
- 24 Ventola, C. L. The nanomedicine revolution: part 1: emerging concepts. *P.T.* **37**, 512-525 (2012).
- 25 Schütz, C. A., Juillerat-Jeanneret, L., Mueller, H., Lynch, I., Riediker, M. Therapeutic nanoparticles in clinics and under clinical evaluation. *Nanomedicine (Lond)*. **8**, 449-467 (2013).
- 26 Andrade, F., Neves, J.D., Gener, P., Schwartz, S. Jr, Ferreira, D., Oliva, M., Sarmiento, B. Biological assessment of self-assembled polymeric micelles for pulmonary administration of insulin. *Nanomedicine* **S1549-9634**, 00121-00125 (2015).
- 27 Li, X., Xue, M., Raabe, O.G., Aaron, H.L., Eisen, E.A., Evans, J.E., Hayes, F.A., Inaga, S., Tagmout, A., Takeuchi, M., Vulpe, C., Zink, J.I., Risbud, S.H., Pinkerton, K.E.. Aerosol droplet

- delivery of mesoporous silica nanoparticles: A strategy for respiratory-based therapeutics. *Nanomedicine* **S1549-9634**, 00081-00087 (2015).
- 28 Weir, A., Paul Westerhoff, P., Fabricius, L., von Goetz, N. Titanium Dioxide Nanoparticles in Food and Personal Care Products. *Environ Sci Technol* **46**, 2242–2250 (2012).
- 29 Harper, M., Weis, C., Pleil, J.D., Blount, B.C., Miller, A., Hoover, M.D., Jahn, S. Commentary on the contributions and future role of occupational exposure science in a vision and strategy for the discipline of exposure science. *J Expo Sci Environ Epidemiol* doi: **10.1038/jes.2014.91** (2015).
- 30 Jilka, S. R., Callahan, R., Sevdalis, N., Mayer, E.K., Darzi, A. "Nothing About Me Without Me": An Interpretative Review of Patient Accessible Electronic Health Records. *J Med Internet Res* **17**, e161 (2015).
- 31 Pautler, M., Brenner, S. Nanomedicine: promises and challenges for the future of public health. *Int J Nanomedicine* **5**, 803–809 (2010).
- 32 Kattlove, H., Winn, R.J. . Ongoing Care of Patients After Primary Treatment for Their Cancer. *CA*, **53**, 172-196 (2003).
- 33 Klompas, M., Yokoe, D.S., Weinstein, R.A. . Automated Surveillance of Health Care–Associated Infections. *Clin Infect Dis* **48**, 1268-1275 (2009).
- 34 SwissRe. Nanotechnology: Small matter, many unknowns. (2004).
- 35 Lloyd's Emerging Risks Team. Nanotechnology. recent developments, risks and opportunities. (2007).
- 36 Mullins, M., Murphy, F., Baublyte, L., McAlea, E.M., Tofail, S.A. The insurability of nanomaterial production risk. *Nat Nanotechnol* **8**, 222-224 (2013).
- 37 Ventola, C. L. The Nanomedicine Revolution Part 2: Current and Future Clinical Applications. *P.T.* **37**, 582-91 (2012).
- 38 Loubaton, B. Exploring the quantitative dimensions of the economic impact of nanomedicine, presented at International Symposium on Assessing the Economic Impact of Nanotechnology. (2012).

Table 1: Examples of applications of nanomaterials in medicine, including diagnostics and implants and the relative market value of different areas

Medical area	Nanomaterials used	Example products ¹	Market Value ²
Nanomedicines <ul style="list-style-type: none"> - Anticancer - Central nervous system - Anti-infective - Anti-inflammatory - Occular ageing - Cardiovascular 	Paclitaxel-loaded polymer micelle Polymer–drug conjugates Liposomal amphotericin B Polymer–protein conjugate PEG-anti-VEGF aptamer SPIONs (clinical trials)	Genexol-PM® (Samyang Co., 2007) Copaxone® (Teva, 1996) Abelcet® (Sigma Tau, 1995) PEGINTRON® (Schering Plough, 2000) Macugen® (Eyetechnology, 2004)	28 US\$Billion 14 US\$Billion 9.3 US\$Billion 7.3 US\$Billion - 4 US\$Billion
Nanodiagnostics <ul style="list-style-type: none"> - MRI contrast agent - Circulating tumour cell detection - Lab-on-a-chip - Diagnostics - biomarkers 	Silicone-coated ferumoxsil SPIONs Antibodies bound to Iron Oxide NPs DNA-based tests Functionalized gold NPs	Gastromark (AMAG Pharmaceuticals, 1996) CellSearch (Veridex, 2004) DNAarray (CombiMatrix, 2005) Verigene (Nanosphere, 2007)	7.9 US\$Billion ³ - - -
Implants and prosthetics <ul style="list-style-type: none"> - orthopaedic - wound management - dental / dental care products - cardiac implants - bone-replacement scaffold 	Nano hydroxyapatite Silver NP solution Nano hydroxyapatite Nanoporous hydroxyapatite Ultraporous beta-Tri-calcium phosphate NPs	BoneSource (Lebinger) Silvagard (AcryMed Inc., 2005) UltraDEX® Recalcifying (Periproducts Ltd) Vestasync (MIV Therapeutics, Inc.) Vitoss (Orthovita, 2000)	10.2 US\$Billion ³ - - - -

¹ Selected from references ³⁷ and ²⁵ or identified via web searches. Detailed lists available in these reviews.

² 2011 values for Global nanomedicine market (US\$Billions), from ³⁸. All predicted to double by 2016. – breakdown by class not available.

³ Breakdown into sub-categories not available.

Abbreviations in Table: DNA - deoxyribonucleic acid; NP – nanoparticle; PEG - Poly(ethylene glycol); SPIONs – super-paramagnetic iron oxide nanoparticles; VEGF - Vascular endothelial growth factor.

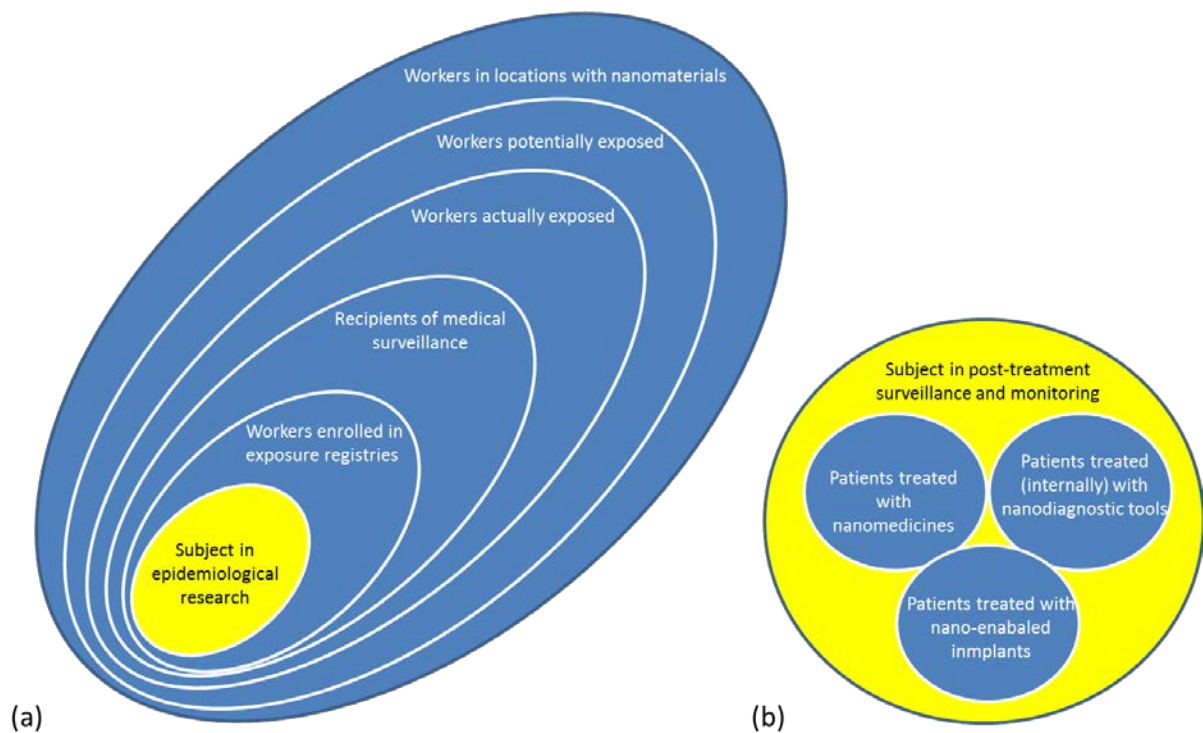


Figure 1: Illustration of the challenge in identifying suitable nanomaterial-exposed cohorts using the traditional occupational exposure paradigm. (a) Functional categories of workers involved with nanomaterials are illustrated for a typical company (figure courtesy P. Schultz, NIOSH, presented at SENN 2015). Since only those workers that are exposed to nanomaterials, and enrolled in exposure registries including participating in an epidemiological research study (i.e. the sub-set of total workers indicated in yellow) are suitable for determination of exposure-related health impacts. The tiny proportion of employees in this category means that it is difficult to perform any meaningful occupational exposure-based risk assessment. (b) As a result of the challenges described in (a), alternative approaches for surveillance and epidemiological assessment of the potential health impacts resulting from exposure to nanomaterials are needed. The potential for a public health approach, via long-term post-treatment monitoring of patients treated with nanomedicines (therapies, diagnostics or implants), is proposed as one new model. This could be coupled with occupational monitoring of doctors and surgical teams involved in administration of nanomedicines.

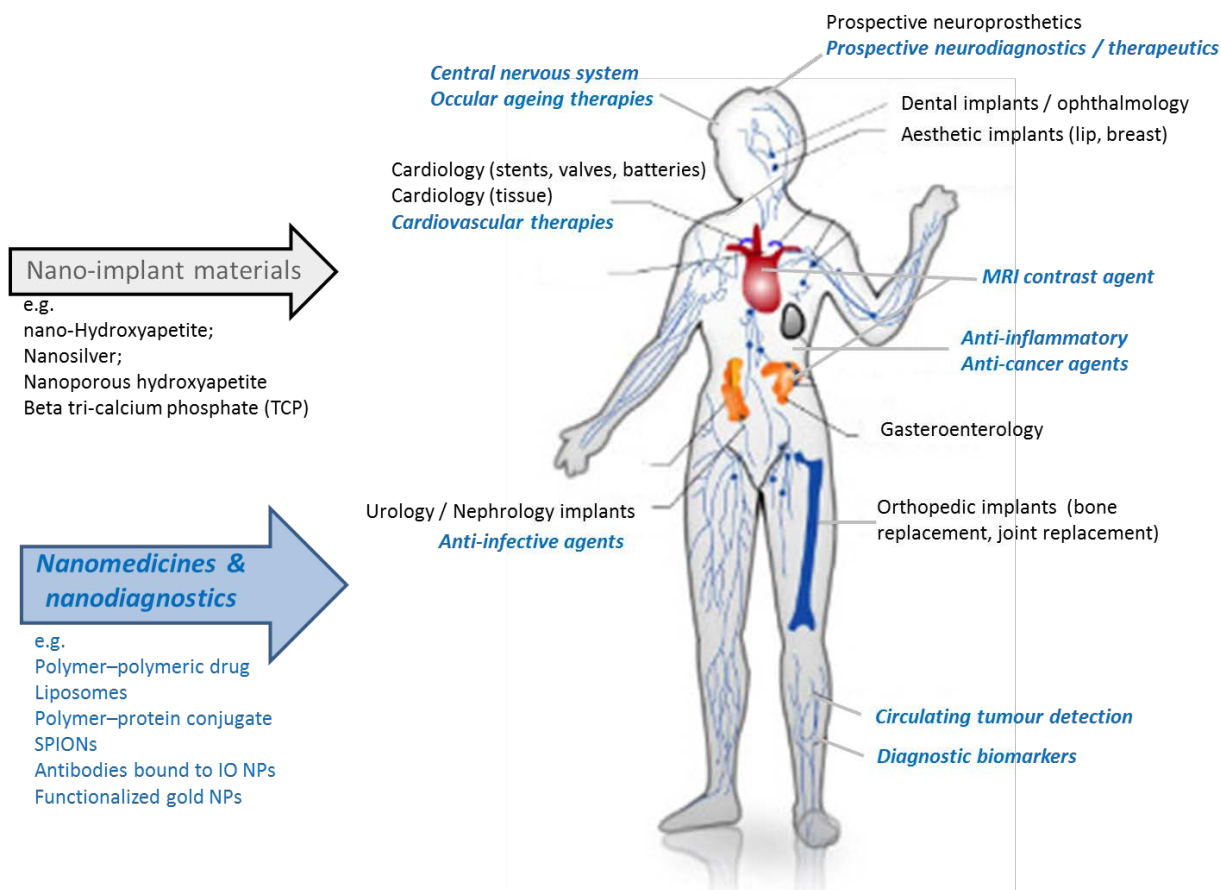


Figure 2: Illustration of the range of application areas of nanomedicines. Nano-implants, nanomedicines and nanodiagnosics are composed of a variety of materials. They can be metals, polymers, ceramics and naturally occurring biopolymer-derived materials that are either nanoporous or contain nanostructured surfaces, or formulated as nanoparticles for use as drug carriers or as contrast agents. These nanomedicines are used to treat a range of diseases including cancer, cardiovascular, ocular ageing, and inflammatory and infective diseases (shown in blue italics in the figure). Nano-structured implants are used in several healthcare applications including cardiology, orthopaedics, dental, ophthalmology, aesthetic surgery, urology, neurology and gastroenterology (black text). The structural and chemical bionano-interface of nanomedicines and nanodiagnostic tools determine their biodistribution to the target site, and is especially important for implants because the interfacial area is the site of greatest stresses in terms of mechanical wear, immune response and potential for infection.