REVIEW ARTICLE

Are nanomaterials really safe?

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ABSTRACT

Nanotechnology is not but many nanoscale technologies with powerful engineering to control nanomaterials or matter-building atom-by-atom is gaining speed and focus. Although, the organization and creation of nanotechnology products or materials is not random, but unfortunately a little is done about the mechanisms or rules that govern its assembly and toxicity. As a result, environmental health and safety agencies around the world continue to grapple with how best to regulate these novel materials.

Taken together, the focus must be directed towards approaches and sophisticated tools for risk assessment and management. This review article continues the debate, and offers a unique view perspective from the vantage point of a nanotechnologist. JMS 2018; 21 (2):72-76

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INTRODUCTION

Nanotechnology is not one but many high-throughput technologies^[1-2], enabled with powerful computer and engineering tools^[3], with a capability of building materials “atom-by-atom” that is now increasingly revolutionizing a host of products and services^[4-5]. For millennia, battery-storage capacity, computer-chip minimization, space and cyber security, food processing, facial creams, energy conversion, water purification, and is sparking new fields such as quantum information processing and nanobiotechnology^[6]. The development of nanoengineering standards for biological parts, such as how pieces of DNA snap together, will permit computer-aided design (CAD) at levels of abstraction from atomic to population scales^[7]. Interestingly, across the disciplines, biologists are shifting focus from the micro-towards the nano-and even sub-nano level, and will have access to tools that will allow them to arrange atoms to optimize catalysis, for example, or arrange populations of genetically constructed organisms to cooperate in making a chemical^[8]

Similarly, one could anticipate constructing RNA-only

nanodevices to evaluate complex logic in living cells. Such devices would operate at the post-transcriptional level and use an extended RNA transcript to co-localize all circuit sensing, computation, signal transduction, and output elements in the same self-assembled molecular complex, which reduces diffusion-mediated signal losses, lowers metabolic cost, and improves circuit reliability^[9]. As electronic chips hit conventional limits, they will be replaced by atomically precise and fault-tolerant biological circuits^[10]. Importantly, the integration of nanotechnology with biotechnology, as well as with information technology and cognitive science, is expected to accelerate in the next decade^[11]. Other, spearheading efforts to expedite the clinical applications. For example, new methods and instruments have been added to the Clinician's toolkit-nanosurgical techniques for physically removing diseased tissue and reconfiguring healthy tissue, antibiotics for jamming the molecular machinery of unwanted pathogens, gene chips for rapid identification of genetic complexities, targeted drug delivery or carry out computations inside human body for highthrough-put diagnostic evaluations and the creation of gels that could reduce the risk of HIV/AIDS transmission^[12]. Nevertheless, hundreds of studies using nanotechnologies have been published in the past for more than two decades, shedding light on the importance of understanding the effect and safety of

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unembellished, or 'naked' nanomaterials and profoundly, a number of issues have been described^[13-17].

As nanotechnologies inch closer to the market in which most of the products are nanomaterials, establishing a regulatory road map has the potential to address this pressing need, on what parameters should be used for reporting the testing of multitudinous nanomaterials, their quality needs to be highly standardized and rigorous scientific data must be supplied on their efficacy and safety. The mystique surrounding such a process must give way to a common "international verification on risk assessment" and a proper understanding of those concepts and applications. Hope, all the benefits promised by new technology, the potential to lift the quality of science and technology on global scale might be the most important benefit of all; that could be studied with scientific rigor, however, science is often ill-equipped to address novel risks associated with the emerging technologies.

Toxicity of nanomaterials

Although, nanotechnology add strength to golf clubs, odor resistance to socks, ultraviolet protection to cosmetics and point-of-care devices for measuring electrolytes, cardiac markers, and nanomaterials now reside in nursing stations, surgical suites, emergency rooms, and even at patient bedsides^[18]. Imaging scientists and oncologists are now using Immuno PET, [positron emission tomography (PET)], a technology that uses radioactive tracers to visualize the functions of human tissues, to an antibody's propensity to home in on the cells it's made to recognize^[19]. Nonetheless, toxicity is still a major drawback for researchers who are pursuing ambitious applications such as fluorescence guided surgery, in which nanoparticles are injected into a tumor, for instance, to make it glow and help surgeons to remove all traces of malignant cells^[20]. Other self-assembled nanostructures or newly emerging fields as diverse as protein engineering and nanoelectronics, the emergence of atomic-precision molecular manipulations much like nanocars would provide a key for the controlled fabrication of novel nanoscopic materials and devices^[21]. However, there are growing indications that the anticipated risks of some nanoengineered materials may not be as high as was originally thought, but this does not mean that there are no novel risks or that there will not be potential emergent "nanorisks"^[22].

In 2004, the first widely read report to examine both the

benefits and risks of using nanotechnology products was published by the Royal Society and the Royal Academy of Engineering in the UK. Notably, vital issues discussed at the Organization for Economic Co-operation and Development (OECD) conference "Potential Environmental Benefits of Nanotechnology: Fostering Safe Innovation-Led Growth"^[23], which was held in France in 2009, included the use of scarce materials such as indium, cerium and lithium in nanotechnology, energy consumption in manufacturing nanomaterials and the use of highly hazardous materials in producing various other nanotechnology products. Multiple lines of evidence supports that fullerenes, carbon nanotubes, various metal and metal oxide nanoparticles could affect the physiology of different aquatic organisms such as fish, algae and water fleas^[14, 24-25]. Consequently, in 2010 the following nanomaterial types were pinpointed for testing: for example single-walled and multiwalled carbon nanotubes, C60 fullerenes, zinc oxide, silver, iron, gold, aluminum oxide, cerium oxide, silicon dioxide, titanium dioxide, dendrimers and clays^[23]. But everything is not always bad. In order to improve its pharmacokinetics and applicability, chemically modified fullerenes can be far less cytotoxic: fullerenes with carboxylate or hydroxyl groups attached were much less harmful. Importantly, one of the main concerns about nanotechnology is the potential toxicity of nanoparticles, because many key details of newly emerging particles largely remain elusive, even if new technologies are helping researchers to gain access to them. However, in such kind of comparative studies, state-of-the-art applications not based on nanotechnologies must be included for reference purposes in the comparison.

With regard to clinical science, the potential applications of nanotechnology are huge, and has already generated a range of promising examples, such as conceptually new medical diagnostics, imaging agents and therapeutics (using new drug-delivery platforms) for detecting and treating diseases in the early stages^[18,26-29]. The advantages of early detection are not limited to cancer, and many other disorders such as Alzheimer disease are presumed to cause disruptive changes well before clinical manifestations become obvious, but profoundly nanotechnology provides an unprecedented opportunity to build better detection strategies and tools, and places the rapidly evolving field of 'nanodiagnostics' at the front line in the war on diseases^[19, 30,31]. Although, pharmacogenomics focuses on the

identification of genetic variants that influence drug effects, typically through alterations in pharmacokinetics and new emerging analytical approaches have facilitated the evolution of a discovery model from hitherto promising drug candidates towards agnostic genome-wide analyses of patient populations with specific drug-response phenotypes highlighting “toxicity or desired pharmacological effects”^[32,33]. Specifically, designing nanomedicines to seep out of the bloodstream into tumor blood vessels is only the first in cancer drug delivery. Cisplatin usually has severe kidney toxicity, essentially patients have to drink painfully large amount of water during treatment, but that's not the case using advancing nanoparticles as “nanocarriers” because the carrier's size permits it to move deeper into and accumulate in the pancreatic tumor instead of accumulating in the kidney^[34]. Iron-cobalt alloy are tiny magnets that could enhance the contrast of magnetic-resonance imaging (MRI) — used for medical scans — when injected into the body, but they 'rust' easily and are toxic, so have been of little use for such applications. As nanomedicine has revolutionized the study of drug delivery, so has it emphasized how drugs are assessed for safety? The analysis of gene expression profiles is now actively used alongside conventional toxicology assays to assess drug safety. Recently, an estimated 130 nanotech-based drugs and delivery devices are being developed worldwide, yet a number of outstanding issues related to toxicity and environmental impact of nanomaterials would have to be resolved, before regulatory agencies could approve further products^[35].

One of the key challenges in creating effective nanoscale-particles is targeting them to appropriate target cell types. The ability to make particles to exact specifications, and to control their form at the nanoscale with sizes measured in mere billionths of a meter, nanomaterials have very high surface area relative to their mass, and this could alter their toxicity compared with the same material in bulk as a large percentage of their atoms lie on the surface and could therefore be highly reactive and extremely harmful^[36]. For example, small particles of quartz could lead to lung damage and the potential development of progressive lung-disease, yet the same nanoparticles with a thin coating of clay are less harmful. A report published in 2006, for example, helped to explain how early exposure to bisphenol A (BPA)-(a chemical found in thousands of consumer

products from-can linings to baby bottles) could increase rats susceptibility to prostate cancer^[37]. Other examples, are quantum dots, semiconducting devices that can fluoresce in a wide variety of colors, work as cell spies, shadowing the movements of their molecular mechanics and allowing the investigator to follow in-cell events on camera with an astonishing level of detail, although, “everything is good about quantum dots,” except for one thing: their toxicity, such as, the best-performing dots contain cadmium, which can poison cells. However, the problem could be minimized to some extent by replacing cadmium with lesser toxic zinc or indium or by wrapping cadmium-based quantum dots in polymers that are biocompatible^[38].

Ideally advantages or disadvantages should be uncovered in the trial-by-fire of rigorous testing of nanomaterials. Nanotoxicity studies would arguably require additional standards^[39] and quickly advancing molecular tools^[15,40-41] in the complex process of newly emerging nanoparticle risk assessment and high-precision computerized models would be most helpful for predicting the potential impact of these materials if strategic research is to support nanotechnologies, in which risks are minimized and benefits maximized.

Future Prospective

Nanotechnology is already having an impact beyond its field, and by 2030 this will have increased significantly. Myriad technologies will be possible, such as nano-memory devices that harness the ability of certain bacteria to navigate Earth's weak magnetic field using magnetite nanoparticles. The parallel pursuit of technological advances has already generated a range of promising strides, such as conceptually new quantum devices, drug-delivery agents and novel materials and beyond the edge of our conception, like DNA nanotechnology, with the goal of manipulating the molecule as if it were a building material, rather than a carrier of genetic information, and perhaps in future ahead, new forms of devices and processes may emerge. Will this be a new era of medicine?—an era in which health and long life will be the usual state of affairs while sickness, debility and death will be the mercifully rare exceptions.

However, the question remains, are these nanomaterials really safe? No technology is without caveats. We must have cautionary examples from the never-ending debates about synthetic biology or other genetically modified (GM)

organisms, nuclear power, chemical toxicity and the efficacy of cancer screening should be evidence enough that science does not limit or resolve controversies about risk^[42]. Remarkably, a system approach must be included in teaching various aspects of nanoscale science and engineering^[15]. Making material products and processes that reduce or eliminate the use and generation of hazardous substances is an inherently systems approach, but it is generally accepted that, in principle some materials may have the potential to cause harm. Such approaches will “guide decision making” by convening researchers and other experts “to explore the scientific, ethical and policy issues associated with nanotechnology” and must emphasize the need for more research on risks using advancing molecular tools. Worldwide exports are increasingly likely to carry nanotechnology inside them, better regulation is “essential not only for safeguarding people and environment, but for the public acceptance of nanotechnology at global level”.

Looking ahead, such policies built on mutual understanding and shared knowledge must be working their way into our collective decision making “regulatory bodies” and other initiatives guiding our next steps. “That is a platform that is intrinsically scalable and accessible to people around the globe.” However, advancing research be focused on how best to develop these new technologies, interdisciplinary collaborations are being formed to achieve the goals that we now accept as possible, but people are beginning to grapple with the potential consequences.

BIBLIOGRAPHY

1. Ball P. Europe's X-ray laser fires up. *Nature* 548, 507–508 (2017)
2. Campbell N, Deane C, Murphy P. The sounds of nanotechnology. *Nature Nanotechnology* 12, 606–610 (2017).
3. Barth JV, Costantini G, Kerm K. Engineering atomic and molecular nanostructures at surfaces. *Nature* 437, 671–679 (2005).
4. Wright J. Deliver on a promise. *Sci. Am.* 311(1), S12–3 (2014).
5. Dresselhaus MS. A revolution of nanoscale dimensions. *Nature Review Materials* 1, 15017 (2016).
6. Maine E, Thomas VJ. Raising financing through strategic timing. *Nature Nanotechnology* 12, 93–98 (2017).
7. Carr PA, Church GM. Genome Engineering. *Nature Biotechnology* 27, 1151–1162 (2009).
8. Shiekh FA. Synthetic nanocarriers a new paradigm. *Nanomedicine* 9(15): 2259–2262 (2014)
9. Church GM, Elowitz MB, Smolke CD, Voigt CA et al. Realizing the potential of synthetic biology *Nature Reviews Molecular Cell Biology* 15, 289–294 (2014).
10. Collins JJ. Bring in the biologists. *Nature* 509; 155–157 (2014)
11. Eisenstein M. Teaching nanopores to speak protein. *Nature Methods* 13, 715 (2016)
12. Jones N. Nano-delivery could help tackle HIV. *Nature* doi:10.1038/news.2009.435
13. Tsang MP, Kikuchi-Uehara E, Sonnemann GW, Aymonier C et al. Evaluating nanotechnology opportunities and risks through integration of life-cycle and risk assessment. *Nature Nanotechnology* 12, 734–739 (2017)
14. Sheikh FA, Farooq O, Mian SH, Bautista RL, Arja SB, Andrabi KI Pitfalls of growing nanomaterials. *Nanomedicine*. 11 (13): 1635–8 (2016).
15. Maynard AD, Aitken RJ, Butz T et al. Safe handling of nanotechnology. *Nature* 444 (7117), 267–9 (2006).
16. Service RF. Nanotechnology. Calls rise for more research on toxicology of nanomaterials. *Science* 310(5754), 1609 (2005).
17. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature* 526; 343–350 (2015)
18. Walt DR. Chemistry. Miniature analytical methods for medical diagnostics. *Science* 308(5719), 217–9 (2005).
19. Rolle AM, Hasenberg M, Thornton CR et al. Immuno PET/MR imaging allows specific detection of *Aspergillus fumigatus* lung infection in vivo. *Proc. Natl. Acad. Sci. USA*. (2016).
20. Lim X. The nanoscale rainbow. *Nature* 531; 26–28 (2016)
21. Bubnova O. Plug in your brain. *Nature Nanotechnology* (2017)
22. The power of the tiniest shoot. *Nature*

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23. Morris J, Wills J, Martinis DD Hansen B et al. Science policy considerations for responsible nanotechnology decisions. *Nature Nanotechnology* 6,73–77 (2011)
24. Behra R, Krug H. Nanoecotoxicology: Nanoparticles at large. *Nature Nanotechnology* 3, 253 - 254 (2008).
25. Jeong CB, Kang HM, Lee MC, Kim DH et al. Adverse effects of microplastics and oxidative stress-induced MAPK/Nrf2 pathway- mediated defense mechanisms in the marine copepod *Paracyclopina nana*. *Scientific Reports* 7 (2017)
26. Shiekh FA, Mian SH, Arja SB *et al.* Targeted combination nanotherapeutics in cancer a real promise. *Nanomedicine (Lond)* 10(12), 1855-7 (2015).
27. Wright J. Deliver on a promise. *Sci. Am.* 311(1), S12-3 (2014).
28. Shiekh FA. Highlights from recent advances in nanomedicine. *Nanomedicine (Lond)* 9(9), 1287-9 (2014).
29. Shiekh FA, Abu-Izzah AM, Lee VJ, Mudassar S et al. Editor's choice: recent research highlights from the International Journal of Nanomedicine. *Int. J Nanomedicine* 12; 4505–4508 (2017).
30. Pu K, Chattopadhyay N, Rao J. Recent advances of semiconducting polymer nanoparticles in In vivo molecular imaging. *J Control Release* (2016).
31. Zaimy MA, Saffarzadeh N, Mohammadi A, Pourghadamyari H et al. New methods in the diagnosis of cancer and gene therapy of cancer based on nanoparticles. *Cancer Gene Therapy* 24, 233-243 (2017).
32. Lord PG, Papoian T. Genomics and drug toxicity. *Science* 306(5697), 575 (2004).
33. Gibbs JB. Mechanism-based target identification and drug discovery in cancer research. *Science* 287(5460), 1969–1973 (2000).
34. Bourzac K. Nanotechnology: Carrying drugs. *Nature* 491(7425), S58-60 (2012).
35. Nanomedicine: A matter of rhetoric? *Nature* 5; 243 (2006).
36. Cancer nanotechnology: small, but heading for the big time. *Nature* 6; 174-175 (2007).
37. Brendan Borrell. A big test for bisphenol A. *Nature* 464, 1122-1124 (2010).
38. Service RF. Nanotechnology. Calls rise for more research on toxicology of nanomaterials. *Science* 310(5754), 1609 (2005).
39. Reich ES. Nano rules fall foul of data gap. *Nature* 480; 160-161 (2011).
40. Seisenberger G, Reid MU, Endre T, Buning H et al. Real-time single molecule imaging of the infection pathway of an adeno-associated virus. *Science* 294; 1929-1932 (2001).
41. Lim X. The architecture of structured DNA. *Nature* 546,687–689 (2017)
42. Science can't solve it. *Nature* 522; 413-414 (2015).
43. Shiekh FA. Personalized nanomedicine: future medicine for cancer treatment. *Int J Nanomedicine*. 8; 201–202 (2013)
44. Shiekh FA. Targeted nanotherapeutics in cancer. *Int J Nanomedicine* 9; 1627–1628 (2014).
45. McCarthy JJ, McLeod HL, Ginsburg GS. Genomic medicine: a decade of successes, challenges, and opportunities. *Sci Transl Med*. 5(189); 189sr4 (2013).
46. Riddihough G, Zahn LM. Epigenetics. What is epigenetics? *Science* 330(6004); 611 (2012).
47. Pearce JM. Make nanotechnology research open-source. *Nature* 491, 519–521 (2012).
48. Riego-Sintes J. Regulation: safety-test initiatives for nanomaterials. *Nature* 482(7383), 3 (2012).
49. Muhlebach S, Borchard G, Yildiz S. Regulatory challenges and approaches to characterize nanomedicines and their follow-on similars. *Nanomedicine (Lond.)* 10(4), 659–674 (2015).
50. Nel AE, Nasser E, Godwin H, Avery D et al. A multi-stakeholder perspective on the use of alternative test strategies for nanomaterial safety assessment. *ACS Nano* 7(8); 6422-33 (2013).