GRESHAM COLLEGE

13 November 2018

Nanomaterials: A Tale of Two Alices

Professor Jaqueline McGlade

Along with synthetic biology and artificial intelligence, there is a new urgency surrounding our entry into the world of nanoengineering and nanomaterials because of the enormous potential that the nanoworld presents for countless applications such as nanobots for delivering drugs and targeting cancer cells, improving resource efficiency, sensing the environment and helping to clean-up pollution. But there are also potential risks to human health and threats to the environment that we need to know about. For example, nano-sizing a material can give it amazing properties, but it can also change its environmental and health impacts.

With so many more nanomaterials in development, there is a serious risk that we will not understand enough about their long-term effects to regulate them or put in place safeguards and appropriate levels of guidance to use them safely. Past lessons from exposure to hazardous materials – such as asbestos, which had deadly consequences – teaches us that "no evidence of harm" is not the same as "evidence of no harm".

Starting Out Small

Human beings have long been fascinated by miniature things. Playing with tiny versions of animals and objects and creating small worlds is an important part of early child development. A whole genre of children's literature exists for just this. *The Borrowers* is a children's fantasy novel by Mary Norton, and features a family of tiny people who live secretly in the walls and floors of an English house and "borrow" from the big people in order to survive. It was one of the top Carnegie Medal-winning books.

Perhaps the most famous small world story, however, is Lewis Carroll's[1] 1865 tale of *Alice in Wonderland*. This was based on a story he told to a party of girls whilst on a boating trip.

> *"Alice was beginning to get very tired of sitting by her sister on the bank and having nothing to do: .. when suddenly a White Rabbit with pink eyes ran close by her… Alice started to her feet .. and burning with curiosity, she ran across the field after it, and fortunately was just in time to see it pop down a large rabbit-hole.. In another moment down went Alice…. thump, thump, down she came upon a heap of sticks and dry leaves, and the fall was over. She found herself in a long, low hall. … Suddenly she came upon a three-legged table, all made of solid glass; there was nothing on it except a tiny golden key. She came upon a low curtain.. and behind it was a little door about fifteen inches high.. Alice opened the door and looked along the passage to the loveliest garden you ever saw. But she could not even get her head through the doorway. .. she went back to the table; this time she found a little bottle on it .. and round the neck of the bottle was a paper label, with the word 'DRINK ME'. It was all very well to say 'Drink me', but the wise little Alice was not going to do that in a hurry.' 'No I'll look first,' she said, 'and see whether it's marked "poison" or not'; for she had never forgotten that, if you drink much from a bottle marked 'poison', it is almost certain to disagree with you, sooner or later. However, this bottle was not marked 'poison', so Alice very soon finished it off. 'What a curious feeling!' said Alice. I must be shutting up like*

[1] Lewis Carroll is the pseudonym of Charles Dodgson, a mathematician working on symbolic logic.

a telescope." And so it was indeed: she was now only ten inches high and her face brightened up at the thought that she was now the right size for going through the door into that lovely garden."

Alice's journey into a miniature world was filled with crazy and wildly improbable animals, none more so than the Mad Hatter's Tea Party attended by the March Hare and the Hatter. An amazing artist Willard Wigan, creator of the world's smallest handmade sculptures, captured the tea party in the eye of needle, painstakingly created in his studio using a tiny diamond cutter and tweezers from his own eyelash. Sadly, as he was putting the finishing touches to the sculpture he lost concentration and breathed, inhaling Alice. He then set about making another. He observes that "when you work at this scale, things change because you are working with the molecules themselves."

Nanoscopic Nature

What does nanoscale mean? Nano is 10^{-9} or one billionth of a metre or a millionth of a millimetre. To give an idea of what we are talking about, think of a strand of hair – which is on average 100 micrometres in diameter – this is the equivalent of one hundred thousand single walled carbon nanotubes of one nanometre in diameter.

Working at the *nanoscopic* scale is at the level where fluctuations in properties, such as the motion and behaviour of individual particles, begin to have a significant effect on the behaviour of a whole system. The properties of a material change and surface area or quantum effects become more apparent – these effects are due to the geometry of the material i.e. how thick it is, how wide it is, which, at these low dimensions, can have a drastic effect on quantized states, and the properties of a material. Above this scale, the properties of a material are caused by bulk or volume effects, namely which atoms are present, how they are bonded, and in what ratios.

Nature is full nanoscopic architectures. They underpin the essential functions of a variety of life forms, from ants to bacteria, insects to whales, going back to structures that are over 500 million years old. The properties and structures are dazzling in their diversity.

Long before engineers thought about developing photonics - microscopic devices that manipulate light for electronics, Nature had developed animals that reflect light with smaller and more complex structures than any manufactured by humans. The colouration of iridescent beetles and butterflies to fish-scales and petals are produced by sets of carefully spaced nanoscopic pillars, made of sugars such as chitosan, or proteins such as keratin, where the widths of slits between the pillars are engineered to manipulate light to achieve certain colours or effects like iridescence.

Pigments tend to bleach with exposure to light, but structural colours are different because they remain stable for long periods of time[2]. Colours can also be changed by varying the size and shape of the slits and by filling the pores with liquids or vapours too. If a specimen is soaked in water and there is a vivid colour change, then it is likely that structural colouration is present. Some wing structures are so sensitive to air density in the slits that colour changes are seen in response to temperature[3]. This has led researchers to understand the important role they play in sexual communication.

As well as deflecting light at an angle to achieve the appearance of colour, some ultra-thin layers of slit panels completely reverse the direction of the travel of light rays. This deflection and blocking of light can work together to create stunning optical effects such as the wings of the *Morpho rhetenor* butterfly which reflect its brilliant blue colors not from pigment but from extremely small scaffolding within the scales of the butterfly's wings[4] with half-a-mile

---

[2] Silvia Vignolini, Paula J. Rudall, Alice V. Rowland, Alison Reed, Edwige Moyroud, Robert B. Faden, Jeremy J. Baumberg, Beverley J. Glover, and Ullrich Steiner (2012) Pointillist structural color in *Pollia* fruit. *PNAS* 109 (39) 15712-15715; https://doi.org/10.1073/pnas.1210105109

[3] Krisztián Kertész, Gábor Piszter, Zsolt Endre Horváth, Zsolt Bálint & László Péter Biró (2017) KChanges in structural and pigmentary colours in response to cold stress in *Polyommatus icarus* butterflies. *Scientific Reports* volume 7 Article number: 1118 https://www.nature.com/articles/s41598-017-01273-7

[4] Sarah Davison (2004) Advanced optics on butterfly wings. *Live Science* November 16

visibility[5], and beetles with brilliant white scales[6], measuring a slim five micrometres. These structures are impressive and represent a sophisticated level of complexity which can outperform artificially engineered structures that are 25 times thicker.

Knowing about these structures has led to innovations in pigments and dyes.

Labs around the world are working on different techniques to understand and mimic the geometry of these light-scattering and reflective natural nanomaterials. The hope is to make sustainable pigments out of non-toxic compounds that won't damage the environment, or reflective coatings to keep interiors cool.

Nature has done it very efficiently. In fact, some plants can make both solid and iridescent colours from one of earth's most abundant polymers – cellulose. Silvia Vignolini at the University of Cambridge and has been exploring how plants use cellulose to make nanostructures. She first got interested when looking at the intense blue of the fruits of an African plant – *Pollia condensata* or marble berry – which maintain their colour for decades. A specimen at the UK's Royal Botanic Gardens in Kew is still bright more than 150 years after it was picked in Kenya, while the chlorophyll pigment in the leaves of the plant faded long ago. Scanning electron microscopy of the berry revealed cellulose nanofibrils, which were arranged in beautiful helical structures, twisting right and left, so they circularly polarise light in either one direction or the other to produce what artists would describe as a 'pointillist' effect. Vignolini and her team wondered if they could design a similar optical appearance with the same polymers. 'If we can use cellulose – especially from food or agricultural waste – then we can obtain sustainable and non-toxic pigments.' But the task is not straightforward, she adds, and much research remains to be done.

Scientists at Toyota's research labs in the US and Japan spent 15 years working out how to recreate the vivid, iridescent blue of the morpho butterfly's wings. The layered scale structure of its wings strongly reflects a narrow wavelength of blue light that can be seen from afar. The nanostructure used in the morpho butterfly scales has been described as like a fir tree. One of the physicists experimented with pairing up materials that in a multi-layered format would reflect the same wavelength of light from all angles. He eventually chose titanium and hafnium oxides but there was a drawback: 31 layers were needed, making it impractical. Working with US pigment specialist Viavi Solutions, the researchers eventually managed to reduce the number of pigment layers to seven, with the addition of aluminium to boost reflectivity. Once they'd made the new pigment, it took a further year to ensure it could be dispersed in a water-based paint, in an automotive paint system. It takes eight months to produce enough pigment for 300 vehicles; each vehicle will have over 300 billion pigment flakes that each act like tiny mirrors to produce the vivid blue.

Paint manufacturer AkzoNobel has been working in the UK with the Natural History Museum in London and researchers at the University of Sheffield to identify which animals and plants have vivid whites and blues, and then to discover the structures which underlie those colours. and bring them to the paint-pot.

Researchers at Lawrence Berkeley National Laboratory in California, US, are starting to work with commercial partners on a polymer coating for windows that reflects back infrared energy, while allowing visible light to pass through. This would reduce the need for air conditioning in warm climates, so cutting the energy bills and carbon dioxide emissions associated with it. The idea is to produce a low-cost DIY coating that, with wide adoption that could cut carbon dioxide emissions by up to 24 billion kilograms a year – the equivalent of taking 5 million cars off the road.

Another impressive area of nanonature is adhesion. Gecko feet can bind firmly to practically any solid surface in milliseconds, and detach with no apparent effort. This adhesion is purely physical with no chemical interaction

[5] Luca Plattner (2004) Optical properties of the scales of *Morpho rhetenor* butterflies: theoretical and experimental investigation of the back-scattering of light in the visible spectrum. *J. Roy Soc. Interface* 22 November 2004.DOI: 10.1098/rsif.2004.0006

[6] Pete Vukusic, Benny Hallam,and Joe Noyes (2007) Brilliant Whiteness in Ultrathin Beetle Scales. *Science* 19 Jan Vol. 315, Issue 5810, pp. 348 DOI: 10.1126/science.1134666

between the feet and surface[7]. The active adhesive layer of the gecko's foot is a branched nanoscopic layer of bristles called "spatulae", which measure about 200 nanometres in length. Several thousand of these spatulae are attached to micron sized "seta". Both are made of very flexible keratin. Though research into the finer details of the spatulae's attachment and detachment mechanism is ongoing, the very fact that they operate with no sticky chemical is an impressive feat of design. Gecko's feet are also self-cleaning, resistant to self-matting and detach by default[8]. These features have prompted suggestions that in the future, glues, screws and rivets could all be made from a single process, casting keratin or similar material into different moulds[9].

The strongest form of any solid is the single crystal state –such as diamonds – in which atoms are present in near perfect order from one end of the object to the other. Steel rods, aircraft bodies and car panels are not single crystalline, but polycrystalline, similar in structure to a mosaic of grains. So, in theory, the strength of these materials could be improved by increasing the grain size, or by making the whole structure single crystalline.

Single crystals can be very heavy, but in nature the solution comes in the form of nanostructured pores. The resultant structure – a meso-crystal – is the strongest form of a given solid for its weight category. Sea urchin spines and mother of pearl [10] are both made of meso-crystalline forms. These creatures have lightweight shells and yet can reside at great depths where the pressure is high; nacre has long puzzled scientists because it is 3,000 times more break-resistant than the mineral that comprises its building blocks, aragonite[11]. But in 2004, Gilbert's team, using synchrotron radiation, revealed that nacre had a brick like construction with organic mortar between the clumps of mineral-crystal bricks. The columns of mineral-crystals interlock like a zip, with each column facing a different direction.

Another example of the power of nanonature, are magnetotactic bacteria. These can sense minute magnetic fields, including the Earth's own, using small chains of nanocrystals called magnetosomes[12]. These are grains sized between 30–50 nanometres, made of either magnetite (a form of iron oxide) or, less commonly, greghite (an iron sulphur combination). Several features of magnetosomes work together to produce a foldable "compass needle", many times more sensitive than man-made counterparts. Though these "sensors" are only used for navigating short distances across ponds, their precision is incredible. Not only can they find their way, but varying grain size means that they can retain information, while growth is restricted to the most magnetically sensitive atomic arrangements. Great skill is required to selectively produce the correct form, and create the magnetosome chains, a skill that is currently beyond our reach but future navigation could be revolutionised if we learnt how to mimic these structures.

The Engineered Nanoworld

In 2016, the Nobel Prize in Chemistry was awarded to Jean Pierre Sauvage, Sir J. Fraser Stoddart and Bernard L. Feringa for their work on learning to design and synthesize molecular machines[13], as shown in a four-nanometre long 'car' with four wheels operated by molecular motors.

Recent advances in nanotechnology and nanoscience have introduced nanoscale materials with emergent physical and chemical properties in many, different forms that have the power to transform our world[14]. They can now be found

---

[7] Kellar Autumn, Metin Sitti, Yiching A. Liang, Anne M. Peattie, Wendy R. Hansen, Simon Sponberg, Thomas W. Kenny, Ronald Fearing, Jacob N. Israelachvili, and Robert J. Full (2002) Evidence for van der Waals adhesion in gecko setae *PNAS* September 17: 99 (19) 12252-12256; https://doi.org/10.1073/pnas.192252799

[8] W. R. Hansen and K. Autumn (2005) Evidence for self-cleaning in gecko setae PNAS January 11, 2005 102 (2) 385-389; https://doi.org/10.1073/pnas.0408304102

[9] Kellar Autumn, Nick Gravish (2008) Gecko adhesion: evolutionary nanotechnology. Phil. Trans Roy Soc A. https://doi: 10.1098/rsta.2007.2173

[10] Corey Binns (2007) Secret to Abalone shell strength revealed. *Live Science* July.

[11] Pupa Gilbert and Susan Coppersmith (2007) *Physical Review Letters*.

[12] Chen, L., Bazylinski, D. A. & Lower, B. H. (2010) Bacteria That Synthesize Nano-sized Compasses to Navigate Using Earth's Geomagnetic Field. *Nature Education Knowledge* 3(10):30

[13] Nobel Media AB (2016). The Nobel Prize in Chemistry 2016 - Popular Information. Nobel Prize website. http://www.nobelprize.org/nobel_ prizes/chemistry/laureates/2016/popular.html

[14] Hochella Jr., M.F., et al. (2015). Nanotechnology: nature's gift or scientists' brainchild? Environmental Science: Nano, 2, 114-119. http://pubs.rsc.org/en/ content/articlepdf/2015/EN/C4EN00145A;

in more than 1,300 commercial products including medical equipment, textiles, fuel additives, cosmetics, plastics and more. They can be created from a variety of products, such as carbon or minerals such as silver and can have unique optical, magnetic, electrical, and other emergent properties with great potential for electronics, medicine, and other fields. They are everywhere in our lives.

Nanoisation is also fundamentally altering manufacturing processes. Electrospinning devices are now being used to create conductive, graphene biopolymer nanofibrous smart fabrics[15] It is impossible to produce fibres with a diameter smaller than a micrometre using conventional fibre spinning, however electrospinning technology which applies a high voltage to a polymer solution, produces materials that are 100 times thinner than hair and extremely strong, tough, flexible, and due to carbon content, also conductive. The material allows efficient energy storage owing to its high surface area. Cellulose can be used as the original raw material of smart fabric to make polymer fabric that is bio-based. Nanofibres are useful for a number of purposes:

- In environmental protection, the non-woven fabric can be used to clean contaminated air or water from fine particulate matter and heavy metals;
- In agriculture, it can be used as a shade cloth for plants to keep away insect pests;
- In medicine, the nanofabric can be used to grow cells and produce antibacterial plasters and bandages. Nanofibers can be used to create cell culture media (stem cells are seeded on a biopolymer mat) and the grown stem cells can then be transplanted to damaged human skin;
- In the clothing industry, nanofibrous materials can be used to produce special protective clothing that stores energy for charging mobile devices. Nanofibrous electrodes with enhanced mechanical properties can be used as components of smart clothing to monitor and affect the health condition of the wearer. Garment sensors provide information about the wearer's needs as well as potential emergency situations (rescuers, fishermen, etc.).

Research suggests that some preparation methods used in traditional medicine, such as calcination, inadvertently produce nanomaterials and their particular attributes[16]. Researchers are examining medieval weapons, such as Damascus steel blades, to test the theory that specific and ritualized forging and annealing techniques exploited production of nanomaterials to enhance strength and suppleness of the steel[17]. At nanoscale, the physical, chemical, optical, magnetic and electrical properties and behaviours of the materials change significantly compared to the same materials at larger sizes[18]. This happens because of the dramatic increase in the surface-to-volume ratio and the appearance of quantum effects as a material gets smaller.

Rendering a nanosized version of a material can thus produce capabilities in materials that are otherwise inert. Another example is bulk gold which is diamagnetic—it responds very weakly to magnetic field—but gold nanoparticles possess unusual magnetic properties[19]

---

[15] Kashif Javed et al, A method for producing conductive graphene biopolymer nanofibrous fabrics by exploitation of an ionic liquid dispersant in electrospinning, ***Carbon* (2018). DOI: 10.1016/j.carbon.2018.08.034**

[16] Pavani, T et al. (2015). Ayurvedic synthesis of γ-Fe2O3 nanoparticles and its Characterization. International Journal of Current Engineering and Technology, 5(1), 321-324. http://inpressco.com/wp-content/ uploads/2015/02/Paper57321-324.pdf; Sumithra, M., Raghavendra, Rao, P., Nagaratnam, A. and Aparna, Y. (2015). Characterization of SnO2 Nanoparticles in the Traditionally Prepared Ayurvedic Medicine. Materials Today: Proceeding, 2(9), Part A., 4636-4639. http://www.sciencedirect.com/science/article/ pii/S2214785315009074

[17] Reibold, M., etal. (2006). Materials: Carbon nanotubes in an ancient Damascus sabre. Nature, 444(7117), 286. https://www.nature.com/ nature/journal/v444/n7117/pdf/444286a.pdf; Sanderson, K. (2006). Sharpest cut from nanotube sword. Nature News, 15 November 2006. http://www.nature.com/ news/2006/061113/full/news061113-11.html

[18] Sharma, V.K., Filip, J., Zboril, R. and Varma, R.S. (2015). Natural inorganic nanoparticles – formation, fate and toxicity in the environment. Chemical Society Reviews, 44, 8410-8423. http://pubs. rsc.org/en/content/articlepdf/2015/CS/C5CS00236B 9. 11.

[19] JASRI (2012). Clarifying the hidden magnetism of gold (Au). Press Release, 23 January 2012. Japan Synchrotron Radiation Research Institute, Kouto. http://www.spring8.or.jp/en/news_publications/ press_release/2012/120123_2/

Just as with their bulk counterparts, nanoforms of metals, such as silver, titanium and zinc and their oxides, are used in sunscreen, toothpaste, cosmetics, food, paints, and clothing[20]. Due to its antimicrobial properties, nanosilver is widely incorporated into many consumer products such as sports textiles, shoes, deodorants, personal care items, washing powder and washing machines. Nanodiamonds demonstrate functional characteristics that enable them to penetrate through the blood-brain barrier, and allow targeted delivery of remedies to multiple types of cancerous tumours[21]. Because of their fluorescence, optical and electrochemical properties, nanodiamonds are used in advanced bioimaging techniques, and promising materials for transmitting signals that indicate the health of brain function[22].

Nanozymes are nanomaterials with intrinsic enzyme-like properties developed for biosensing, bioimaging, tumour diagnosis and therapy[23]. They also find applications in marine anti-fouling, pollutant removal and environmental monitoring. Nanotechnology can be used to design pharmaceuticals that can target specific organs or cells in the body such as cancer cells, and enhance the effectiveness of therapy. Nanomaterials can also be added to cement, cloth and other materials to make them stronger and yet lighter. Their size makes them extremely useful in electronics, and they can also be used in environmental remediation or clean-up to bind with and neutralize toxins.

Carbon nanomaterials are particularly interesting in terms of the different shapes and forms that they can take. Graphene is a single-atom-thick sheet of carbon. Carbon nanotubes are essentially graphene sheets rolled into seamless hollow cylinders with diameters of the order of a nanometre[24]. Carbon nanotubes are a one atom thick layer of carbon rolled up into a seamless cylinder. A carbon nanotube is 117 times stronger than steel of the same diameter and a better conductor than copper, and have higher thermal conductivity than diamonds. Another form is the buckyball, a spherical structure of 60 carbon atoms, named after R. Buckminster Fuller, famous for his design of geodesic domes. Carbon nanotubes are widely used in lithium ion batteries for notebook computers and mobile phones, lightweight wind turbine blades boat hulls, biosensors, medical devices and data cables. Potential applications include tissue engineering and regeneration, and cancer biomarker. The worldwide commercial production capacity of carbon nanotubes now exceeds several thousand tons per year.

More recently, research groups have been making progress on using nanomaterials to absorb carbon dioxide and to mitigate pollution. Nanoparticles offer a promising approach to this because they have a large surface-area-to-volume ratio for interacting with CO_2 and properties that allow them to facilitate the conversion of CO_2 into other things. Another emerging area is in plasmonics, creating light activated nanoparticles of gold and silver and now carbon nanomaterials, for a whole range of applications, such as treating cancer.
Today, nanomaterials are pervasive. Globally the nanomaterials market is projected to grow at 20.7% annually and reach 55 USD billion by 2022.

Developing a scientific foundation to better understand, predict and manage the challenges of nanomaterials

---

20 SCENIHR (2013). Opinion on Nanosilver: safety, health and environmental effects and role in antimicrobial resistance. The Scientific Committee on Emerging and Newly Identified Health Risks of the European Union, Luxembourg. http://ec.europa.eu/ health/scientific_committees/emerging/docs/scenihr_o_039.pdf

21 Mochalin, V.N., et al. (2011). The properties and applications of nanodiamonds. Nature Nanotechnology, 7, 11-23. https://www.nature.com/nnano/ journal/v7/n1/pdf/nnano.2011.209.pdf; Xi, G., et al (2014). Convection-enhanced delivery of nanodiamond drug delivery platforms for intracranial tumor treatment. Nanomedicine: Nanotechnology, Biology and Medicine, 10(2),381-391. https://www.ncbi. nlm.nih.gov/pubmed/23916888

22 Bačáková, L., et al. (2016). The Application of Nanodiamond in Biotechnology and Tissue Engineering. In Diamond and Carbon Composites and Nanocomposites, M. Aliofkhazraei (ed.). InTech, Rijeka. https://www.intechopen.com/ download/pdf/51099; Waddington, D.E.J., et al. (2017). Nanodiamond-enhanced MRI via in situ hyperpolarization. Nature Communications, 15118. http://walsworth.physics.harvard.edu/ publications/2017_Waddington_NatureComm.pdf

23 Gao, L., and Yan, X. (2016). Nanozymes: an emerging field bridging nanotechnology and biology. Science China: Life Science, 59, 400–402. https://link.springer.com/content/pdf/10.1007%2Fs11427-016-5044-3. pdf

24 Aqel, A., et al. (2010). Carbon nanotubes, science and technology part (I) structure, synthesis and characterisation. Arabian Journal of Chemistry, 5, 1–23. http://www. sciencedirect.com/science/article/pii/S1878535210001747; De Volder, et al. (2013). Carbon nanotubes: Present and future commercial applications. Science, 339(6119), 535-539. http://science.sciencemag.org/ content/339/6119/535/tab-pdf

Along with the excitement about opportunities the engineered nanomaterials could present, questions are emerging about the environmental safety of nanomaterials, as well as their production and applications. There are still significant gaps in our knowledge about what nanomaterials could do and what effects they might have. In fact, there is a serious risk that we do not know enough about the long-term effects of these materials on human health or the environment to use them without greater safeguards in place. Even well-known materials, such as silver for example, may pose a hazard when engineered to nano size. Nano-sized particles can enter the human body through inhalation and ingestion and through the skin and fibrous nanomaterials made of carbon have been shown to induce inflammation in the lungs in ways that are similar to asbestos.

Past experience suggests we should proceed on a firmer basis of the evidence of risks and harm[25].
Carbon nanotubes and carbon nanofibres have shown the ability to cause damage to skin, eye, lung and brain tissues, and accumulate in the body[26]. Carbon nanotubes share similar characteristics with asbestos fibres[27]. They have needle-like shape, and both are bio-persistent. They can pierce through lung tissue and cause inflammation[28]. Evidence of the health hazard of working with asbestos came as early as 1898 from Lucy Deane, one of the first women Inspectors of Factories in the UK[29]. She noted that asbestos work was a 'demonstrated danger to the health of workers ... because of ascertained cases of injury to bronchial tubes and lungs medically attributed to the employment of the sufferer'.

What can we learn from asbestos: meeting Alice

In 1982, a TV documentary, Alice, a Fight for Life, featured Alice Jefferson, a 47-year-old woman who contracted mesothelioma, a fatal form of cancer, from working for a few months at a local asbestos plant in the United Kingdom[30]. The story of this Alice had an immediate impact on British public opinion. The government responded by introducing asbestos licensing regulations that lowered asbestos exposure limits. A voluntary labelling scheme soon followed. Pressure continued to build, and so did scientific evidence on the mesothelioma epidemic due to past exposure to asbestos[31]. It took until 1999 for all types of asbestos to be banned in the United Kingdom: 101 years after evidence of harm had begun to accumulate and thousands of people had died of asbestosis or related cancers. Today efforts are still made to minimize the risk of asbestos exposure to workers engaged in renovation and maintenance of buildings containing asbestos.

The question is, "What lessons can we learn from the century of struggle to understand and address the deadly dangers posed by exposure to asbestos when managing and assuring the safety of nanomaterials in the future?"

From our experience with asbestos and other hazardous materials, we know the list of potential threats is long. Environmental exposure of engineered nanomaterials is inevitable. Their adverse effects and persistence could have

---

[25] EEA (2001). Late lessons from early warnings: the precautionary principle 1896-2000. EEA Report No. 22. European Environment Agency, Copenhagen. https://www.eea.europa.eu/publications/ environmental_issue_report_2001_22/Issue_Report_No_22.pdf

[26] NIOSH (2013). Occupational Exposure to Carbon Nanotubes and Nanofibers. Current Intelligence Bulletin 65. The Centers for Disease Control/The National Institute for Occupational Safety and Health, Atlanta. https://www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf; Oberdörster, E. (2004). Manufactured Nanomaterials (Fullerenes, C60) Induce Oxidative Stress in the Brain of Juvenile Largemouth Bass. Environmental Health Perspectives, 112(10), 1058-1062. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1247377/pdf/ehp0112-001058.pdf

[27] Poland, C.A., et al. (2008). Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nature Nanotechnology, 3, 423–428. http://www.nature.com/nnano/journal/v3/n7/pdf/ nnano.2008.111.pdf;

[28] Nagai, H. and Toyokuni, S. (2012). Differences and similarities between carbon nanotubes and asbestos fibers during mesothelial carcionogensis: Shedding light on fiber entry mechanism. Cancer Science, 103(8), 1378-1390. https://www.researchgate.net/publication/224924547_Differences_and_similarities_between_ carbon_nanotubes_and_asbestos_fibers_during_mesothelial_ carcinogenesis_Shedding_light_on_fiber_entry_mechanism;

[29] Deane, L. (1898). Report on the health of workers in asbestos and other dusty trades. In HM Chief Inspector of Factories and Workshops, 1899, Annual Report for 1898, 171–172

[30] EEA (2001) ibid

[31] Peto, J., et al. (1995). Continuing increase in mesothelioma mortality in Britain. The Lancet, 345(8949), 535-539. https://www.ncbi.nlm.nih.gov/pubmed/7776771; HSE (2017). Asbestos health and safety. The Health and Safety Executive website. http://www.hse.gov.uk/asbestos/index.htm

significant consequences on organisms, ecosystems and food chains[32]. Oral, dermal and pulmonary exposure could lead to inflammation and fibrosis, disrupt metabolism and organ's function, and induce DNA damage and genetic instability[33].

The speed of industrial development is far out-stripping the pace of regulatory development. In the absence of long-term monitoring and scientific information of the many aspects of nanomaterial toxicity and toxicology, specific regulations have been slow to emerge, despite mounting indications of potential exposure and risks[34] The increased production and use of engineered nanomaterials by diverse industries will likely result in their unintentional release into the environment at any point along the product's lifecycle[35].

For example, nanosilver from clothing and fabric is released during washing; titanium dioxide nanoparticles in paint and building materials are emitted to the air and water due to weathering; and carbon nanotubes become airborne during production or leach from discarded lithium-ion batteries into soil and groundwater[36].

Assessing the potential human health and environmental risk, it is critical to understand the exposure and adverse effects of engineered nanomaterials is vital[37]. At present, a limited number of studies are available to explain the fate of engineered nanomaterials once released into the atmosphere, soil, sediment, water and biota, including their behaviour, concentration, transport, distribution, transformations, bioavailability, bioaccumulation in food chains, and biochemical interactions with ecological communities[38]. Last year the European Chemicals Agency classified

---

32 Gottschalk, F. and Nowack, B. (2011). The release of engineered nanomaterials to the environment. Journal of Environmental Monitoring, 13, 1145-1155. https://www.researchgate.net/profile/Bernd_Nowack/ publication/50349175_ The_release_of_engineered_nanomaterials_ to_the_environment/links/54c75fc30cf238bb7d0a7d1a/The-releaseof-engineered-nanomaterials-to-the-environment.pdf; Garner, K.L. and Keller, A.A. (2014). Emerging patterns for engineered nanomaterials in the environment: a review of fate and toxicity studies. Journal of Nanoparticle Research, 16, 2503. https://link.springer.com/ content/pdf/10.1007%2Fs11051-014-2503-2.pdf; Delay, M. and Frimmel, F.H. (2012). Nanoparticles in aquatic systems. Analytical and Bioanalytical Chemistry, 402(2), 583-592. https://link. springer.com/content/pdf/10.1007%2Fs00216-011-5443-z.pdf; Du, J., et al. (2013). Understanding the toxicity of carbon nanotubes in the environment is crucial to the control of nanomaterials in producing and processing and the assessment of health risk for human: A review. Environmental Toxicology and Pharmacology, 36, 451-462. https://www.ncbi.nlm.nih.gov/labs/ articles/23770455/

33 Schulte, P.A., et al. (2016). Taking stock of the occupational safety and health challenges of nanotechnology: 2000–2015. Journal of Nanoparticle Research, 18, 1–21. https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC5007006/pdf/nihms812231.pdf; Trouiller, B., et al.(2009). Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice. Cancer Research, 69(22), 8784-8789. https://www.ncbi.nlm.nih.gov/pubmed/19887611

34 Seaton, A., et al. (2010). Nanoparticles, human health hazard and regulation. Journal of The Royal Society Interface, 7, S119-S129. http://rsif.royalsocietypublishing.org/content/7/ Suppl_1/S119.long

35 Lowry,G.V. et al. (2010). Environmental Occurrences, Behavior, Fate, and Ecological Effects of Nanomaterials: An Introduction to the Special Series. Journal of Environmental Quality, 39, 1867–1874. https://www. ncbi.nlm.nih.gov/pubmed/21284284

36 Geranio, L., et al. (2009). The behavior of silver nanotextiles during washing. Environmental Science & Technology, 43(21), 8113-8118. http://pubs.acs.org/doi/abs/10.1021/es9018332; Shandilya, et al. (2015). Emission of Titanium Dioxide Nanoparticles from Building Materials to the Environment by Wear and Weather. Environmental Science & Technology, 49, 2163–2170. http://pubs.acs.org/doi/abs/10.1021/ es504710p

37 Gottschalk, F. and Nowack, B. (2011). The release of engineered nanomaterials to the environment. Journal of Environmental Monitoring, 13, 1145-1155. https://www.researchgate.net/profile/Bernd_Nowack/ publication/50349175_The_release_of_engineered_nanomaterials_ to_the_environment/links/54c75fc30cf238bb7d0a7d1a/The-releaseof-engineered-nanomaterials-to-the-environment.pdf

38 Batley, G.E., et al. (2012). Fate and risks of nanomaterials in aquatic and terrestrial environments. Accounts of Chemical Research, 46(3), 854-862. https://www.researchgate.net/ publication/228113803_Fate_and_Risks_of_Nanomaterials_in_ Aquatic_and_Terrestrial_Environments; Gardea-Torresdey, J.L., et al. (2014). Trophic Transfer, Transformation, and Impact of Engineered Nanomaterials in Terrestrial Environments. Environmental Science & Technology, 48(5), 2526–2540. http://pubs.acs.org/doi/pdf/10.1021/es4050665; Garner, K.L. and Keller, A.A. (2014). Emerging patterns for engineered nanomaterials in the environment: a review of fate and toxicity studies. Journal of Nanoparticle Research, 16, 2503. https://link.springer.com/ content/pdf/10.1007%2Fs11051-014-2503-2.pdf; Peijnenburg, W. J. et al. (2015) A Review of the Properties and Processes Determining the Fate of Engineered Nanomaterials in the Aquatic Environment. Critical Reviews in Environmental Science and Technology, 45, 2084−2134. http://www.tandfonline.com/doi/abs/10.1080/1064338 9.2015.1010430

titanium oxide as a potential carcinogen if inhaled[39]. This has led cosmetics firms to seek alternatives and Vignolini's group is now working with French group L'Oreal as part of its sustainability agenda. The goal is to replace the titanium dioxide it uses in lipsticks, and potentially other pigments in both lipsticks and hair-colouring.

Changing the properties of a material by nanosizing it can intensify its environmental and health impacts. In the case of nanosilver, its toxicity can cause argyria, which turns the skin permanently into a metallic blue colour; pulmonary inflammation; alterations in organ functions and disturbances to the immune system and gene expression[40]. Exposure to silver nanoparticles can produce a stress response and genomic changes in bacteria, which may contribute to the development of antimicrobial resistance genes[41] Silicon and titanium dioxides can cause pulmonary inflammation[42].

Studying the unique chemical and physical features of nanomaterials, such as size, shape, chemical composition, stability, is vital for helping develop predictive models to determine which nanomaterials may pose a higher probability of risk and those expected to have little impact. The problem is that currently, very little is known about the long term impacts of nanoscale materials and how they affect human health and the environment.

One challenge is that nanoscale materials can in theory be engineered from minerals and nearly any chemical substance, and they can differ with respect to composition, primary particle size, shape, surface coatings and strength of particle bonds. Nanocrystals, which are composed of a quantum dot surrounded by semiconductor materials, nano-scale silver, dendrimers, which are repetitively branched molecules, and fullerenes, which are carbon molecules in the form of a hollow sphere, ellipsoid or tube. They represent a two-edged sword.

The properties that make nanomaterials potentially beneficial in product development and drug delivery, such as their size, shape, high reactivity and other unique characteristics, are the same properties that cause concern about the nature of their interaction with biological systems and potential effects in the environment.

For example, nanotechnology can enable sensors to detect very small amounts of chemical vapours, yet often there are no means to detect levels of nanoparticles in the air—a particular concern in workplaces where nanomaterials are being used. Researchers are concerned about whether inhaled carbon nanotubes could lead to certain lung diseases, including pleural fibrosis, which results in the hardening and thickening of the tissue which covers the lungs, impairing breathing. Testing this hypothesis, they exposed laboratory mice to varied doses of pollutants and nanoparticles. Mice exposed to certain doses of carbon nanotubes developed subplural fibrosis just two to six weeks after inhaling carbon nanotubes[43]. The work suggests that minimizing inhalation of nanotubes is prudent until further long-term assessments are conducted.

Low concentrations of carbon nanoparticles had profound effects on cells lining renal tubules—a critical structure in the kidneys[44]. Both barrier cell function and protein expression were impacted. The results indicate that carbon

---

39 Robert Baan (2008) Carcinogenic Hazards from Inhaled Carbon Black, Titanium Dioxide, and Talc not Containing Asbestos or Asbestiform Fibers: Recent Evaluations by an *IARC Monographs* Working Group. J. Inhalation Toxicology 19: 213-228; European chemicals body links titanium oxide to cancer (2017) https://www.chemistryworld.com/news/european-chemicals-body

40 De Jong, et al. (2013). Systemic and immunotoxicity of silver nanoparticles in an intravenous 28 days repeated dose toxicity study in rats. Biomaterials, 34, 8333-8343. http:// www.sciencedirect.com/science/article/pii/S0142961213007631; Johnston, H.J., et al. (2010). A review of the in vivo and in vitro toxicity of silver and gold particulates: Particle attributes and biological mechanisms responsible for the observed toxicity. Critical Reviews in Toxicology, 40(4), 328-346. http://www.tandfonline.com/doi/abs/10.3109/104084409034 53074?journalCode=itxc20

41 Graves Jr., et al. (2015). Rapid evolution of silver nanoparticles resistance in Escherichia coli. Frontiers in Genetics, 6(42), 1-13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4330922/pdf/ fgene-06-00042.pdf

42 Weir, A., et al. (2012). Titanium dioxide nanoparticles in food and personal care products. Environmental Science and Technology, 46(4):2242-2250. http://pubs.acs.org/doi/abs/10.1021/es204168d

43 Ryman-Rasmussen JP,et al. (2009). Inhaled carbon nanotubes reach the subplural tissue in mice. Nature Nanotechnology v. 4 (11): 747-51

44 Blazer-Yost BL, et al. (2011) Effect of carbon nanoparticles on renal epithelial cell structure, barrier function and protein expression. Nanotoxicology v.5 (3):354-71.

nanoparticles impact renal cells at concentrations lower than previously known and suggest caution with regard to increasing carbon nanoparticles levels entering the food chain.

Nanoscale materials are being used in many cosmetics, sunscreen and other consumer products. Possible absorption of the materials through the skin, and potential consequences, have not been determined. NIEHS-funded scientists applied nanosized particles of cadmium selenide, a known carcinogen, on hairless laboratory mice. They found that when the mice's skin had been abraded to remover upper skin layers before the solution was applied, cadmium elevation was detected in the mice's lymph nodes and liver. When the quantum dots of cadmium selenide were applied to the undisturbed skin of mice, no consistent cadmium elevation was detected in the organs. The study concluded that skin absorption of nanomaterials depended on the quality of the skin barrier and that future risk assessments should consider key barrier aspects of skin and its overall integrity.[iii]

Nanosized materials show great promise in drug delivery, with the potential of targeting cancerous cells with a drug but avoiding an attack on healthy cells. One study demonstrated that the ability of two lines of cancer cells to absorb nanosized, rod-shaped particles differed depending on the aspect ratio of the nanoparticles—meaning the proportions between the particles' height and width. The finding could help in achieving more efficient drug delivery[45].

As in the case for asbestos, the first people exposed to nanomaterials are workers. The first few studies conducted in the late 1990s and early 2000s to assess occupational exposure to carbon nanotubes paved the way for further workplace investigations, and later the establishment of a first ISO-guideline on characterizing occupational nanoaerosol exposures in 2007[46].

Based on studies of animals exposed to carbon nanotubes and carbon nanofibres, the US National Institute for Occupational Safety and Health considers findings such as lung inflammation, granulomas and fibrosis in subject animals to be significant enough to warrant action to set a recommended exposure limit. The Organisation for Economic Co-operation and Development undertook multi-year programmes to generate toxicological data on a variety of nanomaterials to amend existing test guidelines for manufacturers[47].

Are Nanomaterials Regulated?

Because of the breadth of applications, regulatory bodies need to rely on existing regulations governing the areas of chemicals, pharmaceuticals, cosmetics, food, pollution, wastes and labelling to seek provisions for nanomaterials[48]. However, there are also challenges in applying existing regulatory frameworks to nanosized materials. For instance, the reduction in size of a material may not initiate any need to revise the existing regulations or legislation if the nanosized and bulk materials are of the same chemical substance. Or, some consumer products are not subject to safety requirements and can enter the market without being tested.

In Europe there is now a strong regulatory regime under REACH[49] and the use of nanomaterials in cosmetics; the U.S. Food and Drug Administration (FDA) regulates a wide range of products, including foods, cosmetics, drugs,

---

[45] Meng H, et al. (2011) Aspect ratio determines the quantity of mesoporous silica nanoparticle uptake by a small GTPase-dependent Macropinocytosis mechanism. ACS nano v. 5 (6): 4434-47

[46] Kuhlbusch, T.A.Jet al. (2011). Nanoparticle exposure at nanotechnology workplaces: A review. Particle and Fibre Toxicology, 8(22), 1-18. https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC3162892/pdf/1743-8977-8-22.pdf 49; ISO (2007). ISO/TR 27628:2007 Workplace atmospheres - Ultrafine, nanoparticle and nano-structured aerosols - Inhalation exposure characterization and assessment. International Organization for Standardization, Geneva. https://www.iso.org/standard/44243.html

[47] OECD (2016). Single walled carbon nanotubes (SWCNTs): Summary of the dossier. OECD Environment, Health and Safety Publications – Series on the safety of manufactured nanomaterials No.70. The Organisation for Economic Co-operation and Development, Paris. http://www.oecd. org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/ mono(2016)22&doclanguage=en

[48] Charitidis, C.A., Trompeta, A.F., Vlachou, N. and Markakis, V. (2016). Risk management of engineered nanomaterials in EU-The case of carbon nanotubes and carbon nanofibers: A review. Transactions of the Materials Research Society of Japan, 41(1), 1-11. https://www.jstage.jst. go.jp/article/tmrsj/41/1/41_1/_pdf

[49] EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

devices, and veterinary products, some of which may utilize nanotechnology or contain nanomaterials. At the U.S. Environmental Protection Agency (EPA) , many nanomaterials are regarded as "chemical substances" under the Toxic Substances Control Act (TSCA). The U.S. Consumer Product Safety Commission (CPSC) is an independent federal regulatory agency that was created in 1972 by Congress in the Consumer Product Safety Act. In that law, Congress directed the CPSC to "protect the public against unreasonable risks of injuries and deaths associated with consumer products."

Going to the Beach?

Let me finish with a final example - the use of sunscreen. For years we've been told to slap on sunscreen to protect against the harmful effects of the sun's UV rays. But you may want to take care, as studies show that many contemporary sunscreens pose a threat to the ocean environment. Oxybenzone is a common chemical found in all types of sunscreen, but particularly in the spray-on variety, that researchers have found harms coral, and is in high concentrations at some of the most world's most popular reefs. In a study published in 2015[50] and in research set for publication later this year, biologists found that oxybenzone contributes to bleaching, has a similar effect on DNA to gasoline, and disrupts reproduction and growth, leaving young corals fatally deformed. The most recent research has found that even small doses, about a drop in six and a half Olympic swimming pools – damages coral. The researchers found concentrations 12 times that rate in popular areas off Hawaii and the US Virgin Islands. On this basis Hawaii banned the use of sunscreen with oxybenzone and octinoate in them from 2021.

What Has This to Do with Nanomaterial?

Mineral sun protection products contain titanium dioxide or zinc oxide or both as active physical ingredient. These do not penetrate the skin but stay on its surface working like a mirror that reflects light. Generally, zinc oxide offers a better protection, more effective against long-wave UVA rays than titanium dioxide as well as it is noncomedogenic and antimicrobial. Titanium dioxide blocks UVB but not the full spectrum of UVA rays. It can be a good choice for those who cannot use zinc containing products due to allergy. However, the most common negative feedback on mineral sunscreen without nanoparticles is the whitish layer that it leaves on the skin. To avoid this and make the product more-user-friendly, companies often use nano zinc in sunscreens to minimize the whitening effect.

But it is not safe for corals. Regional offices of the National Park Services, including in Hawaii, the Virgin Islands and south Florida, advise swimmers use sunscreens made with zinc oxide or titanium oxide, which biodegrade, and several Mexican preserves require visitors to use biodegradable sunscreens. But now consumers need to take extra care not to use sunscreens advertising "nano" zinc oxide or titanium oxide. According to EU definition, non-nano particle means that the size is bigger than 100 nm, the Australian rule indicates that more than 90% of the molecules are above 100 nm in a non-nano product.

Look carefully next time you purchase sunscreen or other products to see which ones have nanomaterials in them. You will be surprised!

---

[50] Down, C.A. et al. (2016) Toxicopathological Effects of the Sunscreen UV Filter, Oxybenzone (Benzophenone-3), on Coral Planulae and Cultured Primary Cells and Its Environmental Contamination in Hawaii and the U.S. Virgin Islands. Archives of Environmental Contamination and Toxicology Volume 70, Issue 2, pp 265–288