Is Engineered Nanomaterial Exposure a Myth?

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Posing the question

Here is a question that is asked repeatedly as nanotechnology continues to move from the laboratory to the workplace: will people really be exposed to engineered nanomaterials? Intuitively, you would think that the answer is "yes" - after all, if you are producing and using nanomaterials, surely there must be some likelihood of touching them, breathing them in or ingesting them. Yet a number of people are now arguing that, rather than being inevitable, exposures to these materials are in fact very unlikely. The argument goes something like this:

Nanoparticles - those nanometer-sized pieces of material that are the building blocks of many nanotechnologies - just love to collide and stick together. So much so that when produced in quantity, they will rapidly agglomerate into particles that are much, much larger than the nominal 100 nanometer cutoff point for nanoparticles. What is more, these super-sized agglomerates adhere together so well, that they are unlikely to ever separate back out into the nanoparticles they are made of. So the chances of anyone being exposed to discrete nanoparticles is vanishingly small. And if there is no exposure, there is no risk - even if the material is intrinsically toxic.

This argument is clearly important, as it informs the extent to which time and effort are spent on assessing and minimizing health and environmental risks from engineered nanomaterials. And it does have some basis - it is well known that the small particles agglomerate into large clumps. But to assess whether the process of particle collision and growth is sufficient to prevent significant exposures occurring, we need to go back to basics.

To start with, it is helpful to simplify the problem. Let's put skin and ingestion exposure to one side, and focus on inhalation. To simplify further, let's just concentrate on airborne nanoparticles - otherwise known as aerosols.

When particles collide

Starting from the beginning, we have a simple fact: particles suspended in air move about in a random way. In 1827, the botanist Robert Brown was the first to notice that small particles - grains of pollen in his case - move about when suspended in still water. Around 50 years later, smoke particles were seen to behave in a similar way when suspended in calm air [1]. It took Albert Einstein to work out the physics of what became known as Brownian motion, nearly 100 years after Brown first made his observations [2].

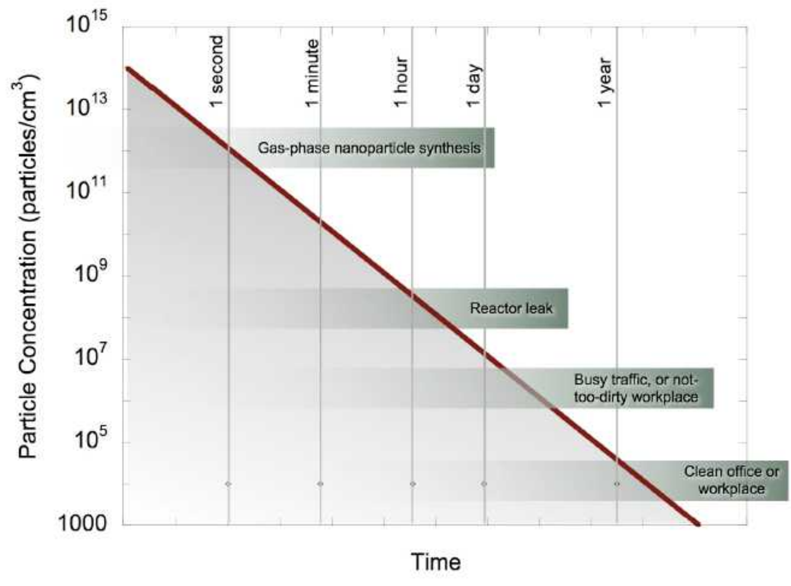
Brownian motion occurs because airborne particles are constantly undergoing random collisions with the surrounding gas molecules. In turn, this motion leads to particles diffusing from areas of high concentration to areas of low concentration.

Smaller particles are generally lighter than larger ones, and so are pushed around more easily by the colliding gas molecules. This results in small particles diffusing far faster than larger ones: for particles smaller than 50 - 100 nm, every time the particle diameter is halved, the rate that they diffuse from one place to another increases by a factor of four.

As you would expect, all this random movement leads to collisions between particles and, by and large, when two particles collide, they stick together. You might anticipate that smaller, faster particles will collide more frequently, and so grow into larger particles more rapidly. But there is a catch - smaller particles also present a smaller target.

The upshot of this is that, as particles get smaller, they move faster but they are harder to hit. These two competing processes roughly balance each other out, meaning that the likelihood of two particles colliding and growing does not depend so much on their size - as long as all the particles in the aerosol are the same size. What does affect the collision rate is the number of particles in the aerosol (the number concentration) - each time the concentration of particles doubles, the chances of one particle colliding with another at any instant increases by a factor of four.

Estimating nanoparticle lifetime



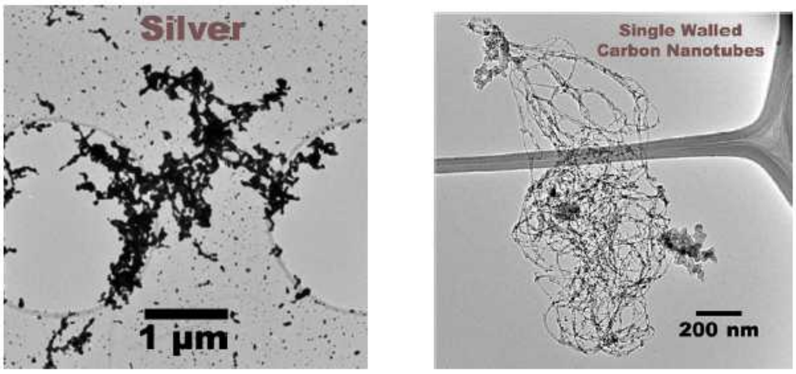
How do your nanoparticles grow?
Simple estimates of how long it takes for particles to grow ten times in diameter through agglomeration. Monodisperse particle agglomeration has been assumed, with a nominal coagulation coefficient of 8.35x10-16 m3/s (representing the mean coagulation coefficient of 10 nanometer and 100 nanometer diameter particles) [1].

Of course, this is a very simple explanation of a complex process, but it does allow us to get an idea of the likelihood that small particles grow into large ones - and how long it takes for them to grow. Assuming that the particles we are interested in are all the same size, are spherical, and stick together when they collide, we can estimate how long it will take for them to grow to ten times their original size [1]. In an environment similar to a relatively clean office, with ten thousand nanoparticles per cubic centimeter, we are looking at over three and a half years for a tenfold increase in size (and a corresponding one thousand-fold decrease in number concentration)! In a not-too-dirty workplace with particle concentrations similar to those found on a busy road - around one million particles per cubic centimeter - it would take 14 days for the particles to grow ten times larger. Increase the concentration to one hundred million particles per cubic centimeter - perhaps associated by a leak in a reactor or a process producing relatively small quantities of nanomaterials, and it takes 3 hours for the particles to grow.

It is only when you reach the relatively high quantities of one trillion particles per cubic centimeter and above that it takes less than a second or so for the initial particles to grow by a factor of ten. Using the same assumptions, it would take 20 minutes for a 10 nanometer particle to grow to 1000 nanometers at such a high concentration. These high concentrations will be found in some production processes, but not all. And in many processes, the aerosol will be intentionally diluted to lower concentrations to prevent particle growth, just milliseconds after the particles have formed.

The trouble with agglomerates

These estimates are somewhat crude, and do not take into account what happens when there is a range of particle sizes in the aerosol - a factor which can significantly increase the rate of agglomeration. But these estimates are good enough to give a rough idea of how rapidly or slowly nanoparticles will agglomerate. And they eloquently demonstrate that, in some cases, people are likely to encounter and inhale airborne nanoparticles, while in other cases they will be exposed to particles that have grown through a process of agglomeration.



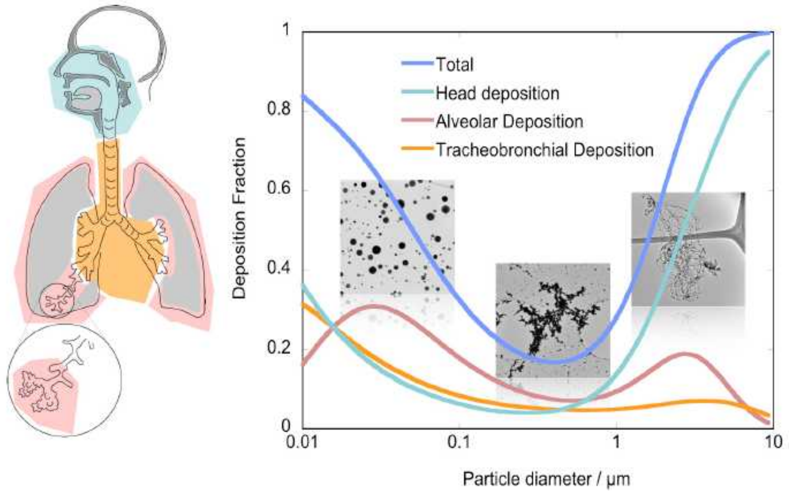
How "nano" is your agglomerate?
Each of these particles was generated as an aerosol. The silver agglomerate was collected from the output of a small silver nanoparticle generator [13], while the single walled carbon nanotube agglomerate was released from nanotube powder by shaking it [9]. Each agglomerate is substantially larger than the nominal cut point for nanoparticles - 100 nanometers. Yet each is small enough to reach and deposit in the deepest part of the lungs when inhaled, and each has an intricate nanostructure that may influence its impact on the body.

Let's focus for a minute on these agglomerates, as a worst-case scenario. If they grew in size rapidly enough, they would settle out of the air before being inhaled - but this is unlikely to happen. Even a 100 micrometer-diameter particles (100,000 nanometers - one thousand times larger than the biggest nanoparticle) would take several seconds to settle to the floor - enough time for someone to inhale it. In reality, most nanoparticles eventually grow to just 300 - 500 nanometers in diameter, at which point they are too large to grow much more through agglomeration, but also too small to settle out of the air. If inhaled, these larger agglomerates are able to penetrate to, and deposit in, the deepest part of the lungs, at the fragile interface between the air and the blood [3].

What happens when these agglomerated particles get to the lungs will depend on the nature of the original nanoparticles. Nanoparticles that began as a liquid will coalesce into larger spherical liquid particles when they collide, which in many cases will dissipate on contact with the lungs, releasing their chemical burden in a non-nano form. If the nanoparticles adhere strongly to each other - perhaps by forming chemical bonds or partially melting together (sintering), they form aggregates in which the individual particles are hard to separate. These are generally complex structures that contain as much open space as solid material, rather similar to a branching tree. Although these particles may be larger than 100 nanometers, they will have nooks and crannies that are at the nanometer scale [4], and in many cases they will have close to the same surface area as the nanoparticles they are made from. Not too much is known about how the intricate structure of these aggregates might affect their behavior in the lungs, but studies have shown the nature of the surface of such particles may be important. In fact, some of the earliest studies on nanoparticle toxicity exposed animals to large nanoparticle aggregates, yet observed effects that seemed to be associated with the individual nanoparticles making up the aggregates [3, 5].

Nanoparticles that do not adhere together so strongly form agglomerates that can, in principle, change shape and even come apart. They form the same open structures as seen with aggregates, but now there is the possibility that when they deposit in the soapy surfactant lining the lungs, they split into smaller particles. There is some evidence that larger agglomerates can break up into smaller ones around 100 nanometers in diameter in in lung surfactant [6], and possibly even into the original particles forming them. And so as well as these agglomerates delivering material with a potentially huge surface area to the lungs, they might also provide an effective way of delivering true nanoparticles into the body.

Non-spherical particles like carbon nanotubes also tend to form aggregates and agglomerates with a lot of open space and complex nanostructures [7]. Studies of single walled carbon nanotube aggregates seem to indicate that they can form particles more akin to spider webs, where each nanometer-scale strand of nanotubes is able to interact with the lungs [8].



Where do the nanoparticles go?
Modeled deposition probability of inhaled particles in the deep lungs (alveolar region), upper respiratory tract (tracheobronchial region) and the upper headways [14]. Silver and single walled carbon nanotubes are shown to give a feel for where these particular agglomerates might deposit. However, deposition probability will depend on their shape and structure as well as physical size, meaning that they could penetrate far deeper into the lungs than indicated (or indeed deposit higher up the respiratory system).

But what about powders liquids and composites

But what about when these nanoparticles have been collected together into a powder, suspended in a liquid or incorporated into a product. Can inhalation exposures still occur? Once these materials are out of the air, it takes some effort to get them airborne again. As a conventional rule of thumb, the smaller the particles are in a powder, the harder it is to re-suspend them. Exposure measurements made while working with nanoparticle powders seem to confirm this [9, 10]. But this does not mean that relevant exposures will not occur. For example, if you shake a container of nano-titanium dioxide particles, you can release agglomerates around 300 nanometers in diameter into the air that can then be inhaled and reach the deep lung. And studies with “as-produced” single walled carbon nanotube powder have shown that if you shake the material hard enough, particles smaller than 10 nanometers can be released into the air [9]. Clearly, the conventional rule of thumb needs updating! This is precisely why research groups around the world are working on how the "dustiness" of various nanoparticle powders might be measured, with the aim of establishing the chances of a nanomaterial releasing particles into the air when handled.

Nanoparticles in a liquid are less likely to become airborne, especially if the liquid is handled carefully. It is possible to think of situations where exposure may occur - for instance, if the liquid forms a spray, through accidental actions or intentional use [3]. While such a scenario might sound unlikely, it is worth remembering that sea spray is an effective generator of salt nanoparticles. Generation of droplets smaller than 5 - 10 micrometers (5,000 - 10,000 nanometers) that contain engineered nanomaterials will provide an excellent way of delivering the materials to the deep lung. But it should be possible to minimize or even avoid totally such exposures with due care and attention.

Once nanoparticles are encapsulated in another material such as a plastic, it would seem that any chance of inhalation exposure has passed. Certainly the chances of individual nanoparticles being released from something like a nanocomposite used on a car or aircraft, or in a food container, are remote. Yet we still do not yet know enough to be comfortable in our assumptions about the safety of such materials. Perhaps the biggest questions are what happens when these materials are machined and ground as part of the production process, and what happens during the wear and tear of everyday use? In these cases, while individual nanoparticles probably will not be released into the air, it is possible that larger - but still inhalable - clumps of material will be released.

Simplifying agglomeration: are the assumptions too simplistic?

The simplifications used to estimate agglomeration rates here are pretty extensive - that all nanoparticles have the same chance of agglomerating, that the particles are all the same size (and remain that way), that they are spheres, and that they always stick together when they collide. Yet the results are surprisingly robust for estimating particle behavior. Changing the size distribution of particles will increase the collision rate, and so the results discussed here represent some of the slowest rates that will be seen. For instance, the collision rate for 100 nanometer diameter particles is around sixty percent higher if the aerosol contains particles ranging in size from 30 nanometers to 300 nanometers [1]. This is due in part to larger particles "mopping up" smaller particles, but also because the probability of collisions changes somewhat with particle size.

As Preining notes in his seminal 1998 paper "The physical nature of very, very small particles and its impact on their behavior", 2 nanometer diameter particles are roughly three times more likely to collide and agglomerate than 20 nanometer diameter particles [12]. But as particles continue to get larger, collision rates begin to come back to similar values seen in the very small particles. So a 200 nanometer diameter particle has a similar probability of colliding with other particles as a 2 nanometer particle has, and a 10 nanometer particle is only twenty five percent more likely to collide with another particle than a 100 nanometer particle.

As a result, errors from the rather simple assumptions made here turn out to be rather small when compared to the effects of, say, changing the particle concentration - where a factor of ten change in the number of particles will lead to a hundred-fold change in how fast the particles agglomerate.

Will these have a nanostructure that affects the lungs if inhaled (imagine one thousand nanometer-diameter particles bristling with nanometer-diameter carbon nanotubes for instance)? We do not yet know.

Summing up

So, back to the original question: will people really be exposed to engineered nanomaterials? Despite protestations to the contrary, the science says yes. There is certainly no reason to believe that exposures will not occur to both individual nanoparticles and agglomerates of nanoparticles that present a nano-specific risk. The magnitude and significance of exposures will depend on the material, the process used to produce it, and how it is handled - including removing, transporting and handling the material, as well as plant maintenance and cleanup of spills and the like. There has not been enough research done yet to state clearly where exposures are more likely, and how they can effectively be avoided. But this is precisely why strategic and targeted research is needed - so that emerging nanotechnology industries can be based on the best possible knowledge. The alternative is to be to rely on speculation, which, even with the best will in the world, is never a substitute for good science.

Postscript

This article addresses nanomaterial exposure and agglomeration, and does not deal with toxicity. Yet exposure is only one half of the equation, and its relevance can only be evaluated if we know how harmful (or benign) the particles are. Nanomaterial hazard is a subject for another day, but here is a sobering thought: In a recent study published in the New England Journal of Medicine, low concentrations of diesel exhaust particulates were found to have a rapid and measurable impact on the cardiovascular system of subjects with stable coronary disease [11]. The particles used had a median diameter of 54 nanometers, and a number concentration of 1.3 million particles per cubic centimeter (with a mass concentration of 300 micrograms per cubic meter). Subjects (all men) were exposed for one hour. Quoting the authors, "brief exposure to dilute diesel exhaust increases myocardial ischemia and impairs endogenous fibrinolytic capacity in men with stable coronary heart disease. Our findings suggest mechanisms for the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events, including acute myocardial infarction".

Assuming for one moment that the mechanisms of action leading to the observed effects could occur with other types of nanoparticles (a reasonable hypothesis, though one that nevertheless still requires further exploration), it is reasonable to ask: how many engineered nanoparticles would need to leak out into a workplace to raise warning flags? A million per cubic centimeter? Ten million per cubic centimeter? A few hundred micrograms per cubic meter? These are all levels where agglomeration is not significant, yet potential health effects might be. Maybe exposures to engineered nanoparticles might turn out to be insignificantly low, but I for one would not want to take the risk without hard evidence.

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