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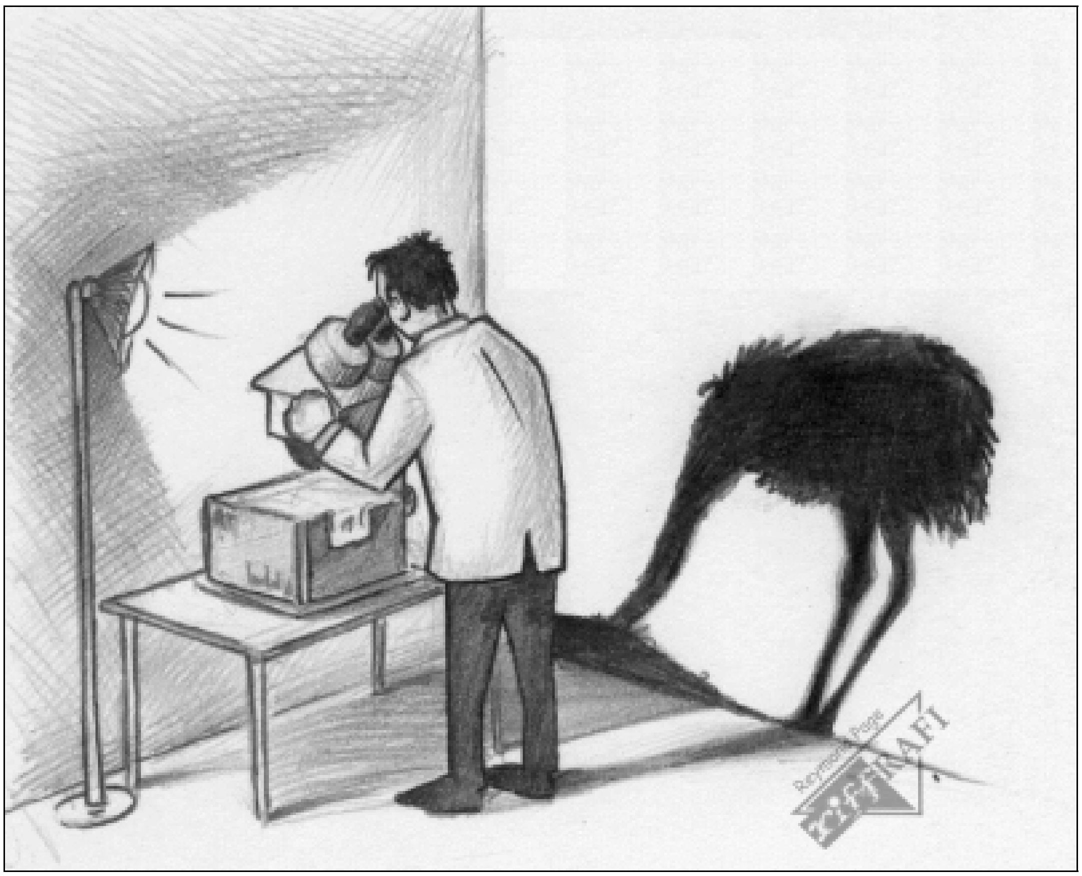
No Small Matter II: The Case for a Global Moratorium
Size Matters!



Industry and government regulators maintain that the unique size and properties of nanoscale materials do not warrant a closer look at the potential health, safety and environmental impacts. In this *Occasional Paper*, ETC Group explains why *size matters!*

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Size Matters

Issue: Decades after their appearance in laboratories and in consumer products, some scientists are beginning to wonder if the nanoscale particles so valued for their chemical reactivity and other quantum characteristics should be investigated for their possibly negative impacts on our health and environment. Even though industry is pushing to scale-up the manufacture of "bulk" nanoparticles and to commercialize even less well-researched carbon nanotubes, there appear to be no government regulations in Europe or North America to ensure the safety of workers or consumers. Yet, nanoparticles already find daily use in sunscreens (including some intended for children, from infancy onwards), cosmetics, and in wound dressings, along with scores of other products and processes. Regulators do not test nano-sized materials for health, safety and environmental impacts if their macro- or micro-sized counterparts have already been approved.

Impact*:* The current market for nanoparticles is small, but analysts predict it will exceed $900 million by 2005. Some of the world's largest companies (DuPont, BASF, L'Oréal, Hewlett-Packard, Mitsubishi, Toyota, and IBM) as well as some of the world's smallest (NanoProducts, Nanophase, Altair) are ratcheting up nanomaterial research quickly. Nanoparticles represent Phase I of a new industrial revolution, which the US National Science Foundation values at $1 trillion by 2015. Atomtech (or nanotech, as the industry prefers to call it) cuts across every industrial sector and will affect every national economy. The potential impact of nanoparticles – for good or ill – on the environment and on human health is enormous. Beyond nanoparticles, impressive strides are being made in the field of nanobiotechnology. Developments that many believed to be either impossible or decades distant, such as molecular manufacturing, now appear more likely and closer at hand. If the industry can't be trusted with the safe development of nanoparticles, it will have no credibility when it comes to atomtech's more sophisticated applications – such as molecular self-assembly (see ETC Group *Communiqué* # 77, "Green Goo: Nanobiotechnology Comes Alive!"). Unless the scientific community gets behind the call for a moratorium, the future of this emerging technology could be irreparably damaged.

Policies**:** No single intergovernmental body is charged with monitoring and regulating atomtechnology. A few national governments are beginning to consider some aspects of atomtech regulation but no government is giving full consideration to the socioeconomic (especially labour), environmental, and health implications. The US National Toxicology Program has not begun to look at nanomaterials as a class.[1] The UK's Better Regulation Taskforce states that "the Government will need to demonstrate it has clear policies in place to ensure the safety of individuals, animals and the environment, whilst permitting [nanotech] research to continue."[2] Some initial studies seem to be underway in Germany and in Brussels. Despite more than a quarter-century of laboratory activity, there are no internationally-accepted scientific standards governing lab research or the introduction of nanomaterials in commercial products. In light of this astonishing negligence and because consumers are already being exposed to synthetic nanoparticles, the call for a mandatory moratorium is the only reasonable policy response.

Fora**:** Ultimately, governments must negotiate a legally-binding International Convention for the Evaluation of New Technologies (ICENT).

Born to be mild: Climbing up the evolutionary ladder, *Homos sapiens* were glad enough to take a deep breath when they clambered onto the seashore and then genetically out-distanced saber-tooth tigers and mammoths. It was only when we were finally able to relax around the fire and we breathed in some of the soot that a minor shortcoming to our hard-won lungs manifested itself: our lungs are not well-equipped to deal with very small particles of matter, such as those found in smoke and, later, in industrial pollutants and car exhausts. When particulate matter is very, very small, it may be more than just our lungs that object. When molecules are small enough, it is possible for them to slip past the guardians in our respiratory systems, skip through our skin into unsuspecting cells, and (sometimes) cross through the blood-brain barrier. Human nature, it seems, grew up assuming that the nanoscale was "unnatural."

Borne again: Noteworthy quantities of air-borne particles less than 100 nm in size came only with the industrial revolution in the form of air pollution, an unintended but largely unavoidable byproduct of high-temperature industrial processes. In the last quarter of the last century, scientists began to explore the idea that not all nanoparticles (also called ultra fine particles or UFPs – particles less than 100 nm in size) belong to the class of polluting "effluent." Nanoparticles can exhibit desirable properties that their bigger relations do not. For example, nanoparticles of titanium dioxide and zinc oxide used in sunscreens have the same chemical composition and formula (TiO_2 and ZnO, respectively) as larger titanium oxide and zinc oxide particles – the white glop that has been slathered on lifeguards' noses for decades – but nanoparticles of TiO_2 and ZnO are transparent. Also, materials that would normally be conductors of electricity can become insulators at the nanoscale, or vice versa.

While carbon black (i.e., soot produced from burning natural gas) has been manufactured in bulk quantities since the early twentieth century (used as a reinforcing agent in car tires), the intentional manufacture of chemically-precise nanoparticles to harness desirable characteristics got underway only in the mid-1970s. A Massachusetts company, Hyperion Catalysis, has been manufacturing carbon fibers since 1983 and another US company, Nanophase, has been selling nanoparticles of various metal oxides since the mid-'80s. In the past, effluent was generally seen as the unintended and undesirable byproduct of industry; in the case of "synthetic nanoparticles," the effluent *is* the industry.

Affluent Effluent: Already more than 140 companies worldwide are engaged in nanoparticle manufacture.[3] By 2005, the global market for nanoparticles will come close to $1 billion.[4] At least 44 elements in the Periodic Table are commercially available in nanoscale form (see below). A small Colorado startup called NanoProducts expects to have another 20 elements for sale in the near future.[5] Earth's remaining fifty or so elements are either radioactive, gaseous, or have a half-life so fleeting that FedEx would be delivering empty packages. The explosion in "bulk nano" means that nanoparticles are now in daily use in everything from popular sunscreens and sunglasses to L'Oréal cosmetics. Burn dressings treated with silver nanoparticles are used in over 100 of the 120 major burn centers in North America.[6] Babolat incorporates carbon nanotubes into their tennis rackets to make them stronger without making them heavier. If the ball you're hitting with your nanotube racket is the Wilson Double Core, it's been treated with a nanoclay that locks in air. The fuel lines of many US and European cars, some Toyota auto bodies, and Renault's plastic side panels all incorporate nanoscale materials. (See table of nanoparticle products on pp. 12-13. Note: The list of products / companies is not intended to indicate safety or risk associated with nanoparticles – it is merely a partial list of some commercial products containing nanoparticles.) Kraft and the US Department of Agriculture (USDA) are researching the use of nanoparticles in food packaging and ultimately in food itself. Is there any reason to be concerned about the "appearance" of invisible nanoparticles in so many consumer goods? Are some applications of nanomaterials safe and others not?

Kraft (and USDA) Might Be Surprised!
"After all, we're not advising that you eat nanotech stuff." – Richard Smalley, Nobel Prize Laureate, 1996, advising that parallels between biotech and nanotech should not be overstated,
The Times Higher Education Supplement, Mar 21, 2003

All Aboard: No one denies that research in the area of nanoparticle toxicity is urgently needed. Vicki Colvin, Director of the Center for Biological and Environmental Nanotechnology at Rice University (Houston, TX, USA) has written, "In a field with more than 12,000 citations a year, we were stunned to discover no prior research in developing nanomaterials risk assessment models and no toxicology studies devoted to synthetic nanomaterials."[7] John Bucher, of the National Institute of Environmental Health Sciences' Environmental Toxicology Program in the USA, recently stated that "we don't know the answers [to the questions related to nanomaterial toxicity]; we've just begun to ask the questions."[8] Unfortunately, Colvin's Center at Rice, one of six National Science Foundation multi-million dollar research facilities dedicated to atomtechnology and the only one focused exclusively on the environment and the interface between biological and material atomtechnology, does not include toxicology as a research area. While it's important for scientists in the field to acknowledge the lack of data, acknowledgement falls short when nanoparticles are already being sold to consumers. Public money devoted to the study of health and environmental impacts also falls short. In the USA, for example, only 2.9% of the $710 million budget for the National Nanotechnology Initiative is devoted to environmental implications, including applications.[9]

Size Wise

Particle Category	Size	
Coarse	Particles with an average diameter of < 10 µm (µm = micron)	
Fine	Particles with an average diameter of < 2.5 µm	
Ultrafine (Nanoparticles)	Particles with an average diameter of < 0.1 µm (<100 nm)	
Ultrafine (Nanoparticles)	**UFP – Approx. size***	**Potential Entry Point**[10]
	70 nm	alveolar surfaces of the lung
	50 nm	cells
	30 nm	central nervous system
	<20 nm	no comprehensive scientific data as yet

*The contribution of size vs. the contribution of material composition to a particle's toxicity has not been clearly established. There are indications that size matters as much as or more than the material of which the particle is composed (see Annex).

Mountains and Molehills? While there is a mountain of data suggesting that nanoscale particles in pollutants such as car exhaust are toxic, some scientists insist that there could be significant differences between the "accidentally-manufactured" particles in pollutants and intentionally-constructed nanoparticles. Conclusions about toxicity cannot and should not, they argue, be extrapolated from past studies of industrial pollutants. So few toxicology studies have been conducted on synthetic nanoparticles, however, that the toxicity distinction between "intentional" and "accidental" nanoparticles remains largely theoretical. Some atomtechnologists point out that humans will not necessarily come into intimate contact with most synthetic nanoparticles – they will not become airborne in the way that car exhaust particles do – so the possibility of their toxicity is not relevant.

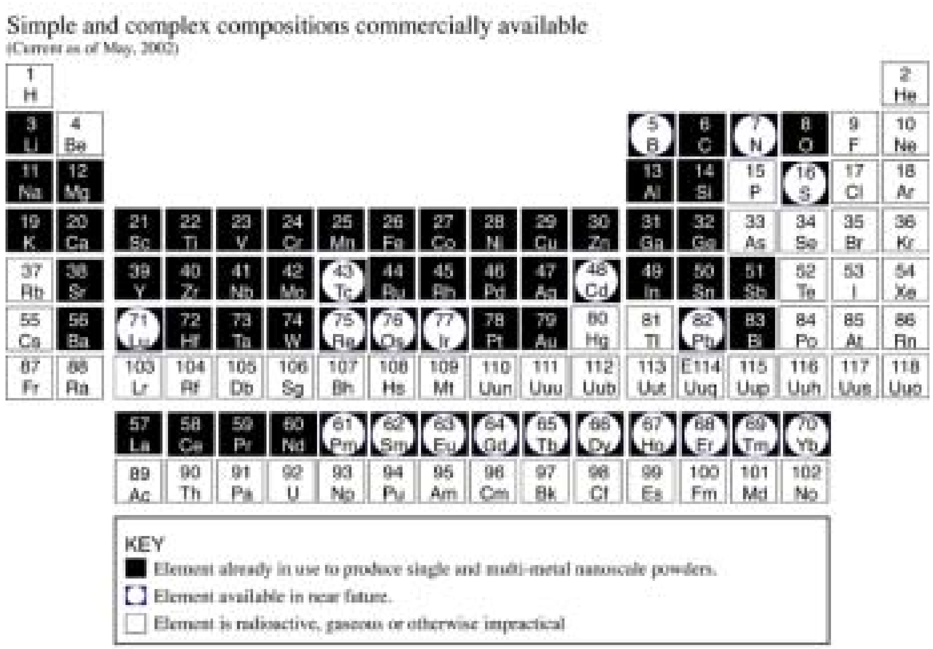
> ***"In a field with more than 12,000 citations a year, we were stunned to discover no prior research in developing nanomaterials risk assessment models and no toxicology studies devoted to synthetic nanomaterials." –*** Vicki Colvin, "Responsible Nanotechnology: Looking Beyond the Good News," www.eurekalert.org

Research is underway, however, to use nanoparticles in drug delivery systems (some are being designed to cross the blood-brain barrier), for *in vivo* cell tracking, in food packaging, even in food products. Titanium dioxide (TiO_2) nanoparticles are, for example, an ingredient in many transparent sunscreens and there are data suggesting that these could be harmful in certain forms. (See discussion below.)

There are two posited differences between unintended UFPs and "intentional" nanoparticles: one, the *surface chemistry* of synthetic nanoparticles is uniform and can be controlled and, two, *particle size* can be controlled to be made homogenous. In other words, if it turns out that the surface chemistry of a particular material is causing health problems (because, for example, the large surface area allows the particle to be so reactive that it becomes toxic), chemists can alter the *surface chemistry* to alleviate the problem. The (potential) ability to control surface chemistry to eliminate problems does no good, of course, until we know what the problems are.

With regards to homogenous *particle size*, scientists have argued that if it turns out that a particular size-range is problematic, atomtechnologists will be able to calibrate their method of manufacture so they get the size that's "just right" to ensure health. It seems that around 70 nm is a problematic size for the lungs, 30 nm spells trouble for the central nervous system and 50 nm gives the green light to enter cells.[11] Again, the (potential) ability to control particle size is only helpful if toxicology studies have been performed on synthetic nanoparticles demonstrating which sizes are problematic and which are not. It could be, in fact, that homogenous particle size will make synthetic nanoparticles *more* dangerous than their non-uniform pollutant UFP cousins if they are all being made the "wrong" size, a size that can potentially cause damage in cells or lungs or the central nervous system. A quick survey of TiO_2 nanoparticles being sold in the US for use in cosmetics, for example, shows that their size is not exactly precision-tuned – the particles fall within a range between about 20 and 50 nanometers, encompassing the particle sizes that may allow entrance to the central nervous system and cells.

Elements Commercially Available as Nanoparticles



Elements already in use to produce single and multi-metal nanoscale particles			Elements available in near future	
Aluminum	Iron	Ruthenium	Boron	Sulfur
Antimony	Lanthanum	Scandium	Cadmium	Technetium
Barium	Lithium	Silicon	Dysprosium	Terbium
Bismuth	Magnesium	Silver	Erbium	Thulium
Calcium	Manganese	Sodium	Europium	Ytterbium
Carbon	Molybdenum	Strontium	Gadolinium	
Cerium	Neodymium	Tantalum	Holmium	
Chromium	Nickel	Tin	Iridium	
Cobalt	Niobium	Titanium	Lead	
Copper	Oxygen	Tungsten	Lutetium	
Gallium	Palladium	Vanadium	Nitrogen	
Germanium	Platinum	Yttrium	Osmium	
Gold	Potassium	Zinc	Promethium	
Hafnium	Praseodymium	Zirconium	Rhenium	
Indium	Rhodium		Samarium	

Source: ETC Group based upon info available from NanoProducts Corp. and other commercial sources

An even more fundamental problem is that, at this point, there is no standardized method for determining particle size. Dr. Robert Shull of the National Institute of Standards and Technology (USA) has recently stated that there are somewhere between five and ten methods used to measure particle size.[12] The results can differ by a factor of two depending on the measuring method used. Dr. Shull acknowledged this to be a "real serious problem" and said that his agency will address it by assessing the various measurement techniques and coming up with a definitive method.[13]

No one expects the scientific community to have all the answers at this early stage; every consumer would expect, however, that scientists and regulators get it right before nanoproducts are sold or released in the environment and before they potentially endanger the health of workers in labs and in manufacturing facilities. ETC Group finds two test cases particularly troubling.

Presumption of Innocence I – The case of carbon nanotubes: Carbon nanotubes are straw-shaped molecules of pure carbon discovered by Sumio Iijima of Japan in 1991. They have been dubbed the "miracle molecule" because they are 100 times stronger than steel and six times lighter. Nanotubes can be as small as 1 nm in diameter and as long as 100,000 nm. They can be single-walled, like straws, or they can be multi-walled, resembling posters in a mailing tube. Depending on how they are configured, they can act as semiconductors or as conductors. There are an estimated sixteen major producers of carbon nanotubes worldwide.[14] The global market for carbon nanotubes was estimated at $12 million in 2002, but is expected to grow to $430 million by 2004.[15] Two Japanese companies have been launched to make nanotubes in bulk quantities: Frontier Carbon Corporation (a joint venture of Mitsubishi Corp. and Mitsubishi Chemical Corp.) plans to produce 40 tons of nanotubes this year and Carbon Nanotech Research Institute aims for an annual production of 120 tons. In the USA, Carbon Nanotechnologies, Inc. has plans for a new plant that will produce between 150 and 300 tons per year of single-walled nanotubes.[16] Electronics giant NEC plans to start selling nanotube fuel cells for laptops and mobile phones within a year and nanotube flat screen displays shortly thereafter.[17]

Because nanotubes have a high aspect ratio (i.e., they are needle-like in shape), there was some speculation initially that they could behave like asbestos fibers if they became airborne and were inhaled.[18] Until this year, there existed only one published study addressing the issue of carbon nanotube toxicity: researchers at the University of Warsaw concluded, after a 4-week trial in which nanotubes had been injected into the tracheas of guinea pigs, that working with nanotubes was "unlikely to be associated with any health risk."[19]

A second nanotube toxicity study at the Johnson Space Center (NASA) got underway last year. Hardly had the NASA researchers begun when the *Financial Times* preemptively (and mistakenly) assured its readers that the soon-to-be-released NASA study would give nanotubes its second clean bill of health.[20] Then, in February, rumours circulated that all was not well. The research team posted an abstract of their study on the American Chemical Society's website.[21] A fuller report was presented at the Society's national meeting in New Orleans on March 24. Rather than declaring carbon nanotubes safe, the researchers warned that the carbon tubes they tested (three different kinds) were more toxic than quartz dust – the material that causes silicosis among miners and railroad workers. One of the researchers recently told *New Scientist*, "The message is clear. People should take precautions. Nanotubes can be highly toxic."[22]

To make matters more complicated, a third study on nanotube toxicity, this one by DuPont Haskell Laboratory for Health & Environmental Sciences, was also presented at the American Chemical Society's meeting in New Orleans, immediately following the presentation of the NASA study.[23] This study concluded that nanotubes are less toxic than quartz dust and that their harmful effects appear to lessen after two months. Like Goldilocks with her three bowls of porridge, we now have "way too toxic," "a little bit toxic," and "just right" to pick from: three studies running the gamut of possible conclusions. None of the studies looked at health effects after 90 days. All three studies used a similar protocol – nanotubes were injected into the rodents (instillation) rather than allowing them to breathe nanotubes (inhalation), a method that both presenters in New Orleans acknowledged to be inferior. Inhalation studies are technologically difficult to perform in any case,[24] but in the case of carbon nanotubes, where prices can reach

$750/gram, even dedicated research scientists will wince at letting mice breathe in nanotubes at their leisure. It's like feeding pearls to swine! A further sobering reality is to consider the limited scope of the three studies: all three considered the toxicity of only single walled nanotubes of carbon, which means that that the possible toxicity of buckyballs, multiwalled carbon nanotubes, nanohorns and nanotubes made from other elements is still an open question. All three studies considered the effects on only one organ, the lungs. The possibility of translocation to the detriment of other organs was not considered, though translocation in the body is a real concern.

The Presumption of Innocence II – the case of nanoparticles of titanium dioxide and zinc oxide: Possibly the most ubiquitous use of nanoparticles to date is in cosmetics. Larger particles of titanium dioxide (TiO_2) and zinc oxide (ZnO) have been used in sunscreens for decades since they both effectively scatter light including harmful UV rays. They act as physical "blockers" or "reflectors" giving sunscreens an opaque, white appearance. However, if the crystals are reduced to the nanoscale, both titanium dioxide and zinc oxide lose their characteristic white colour and become transparent, allowing visible light to pass but still blocking UV rays. Taking advantage of this nanoscale property change, companies including BASF and L'Oréal have created transparent sunscreens and UV-resistant cosmetics incorporating these metal oxide nanoparticles.[25]

Unfortunately, transparency isn't the only change associated with these nanosized metal oxides. While both zinc oxide and titanium dioxide are generally considered inert in their larger form, nanoparticles of both substances can be highly photo-reactive in the presence of UV light, which is partially absorbed into the particle.[26] As a result, nano-titanium dioxide, for example, can exert a "strong oxidizing power that attacks organic molecules"[27] and can produce free radicals (i.e., unstable fragments of molecules that are highly reactive). Many applications of nano-titanium dioxide seek to harness this photo-reactive property, including solar cell research, water cleanup techniques, and even self-cleaning windows that repel dirt in the presence of natural UV light. At Argonne National Laboratory in the USA, scientists have developed a method of using photo-reactive TiO_2 nanocrystals to break DNA strands as a more precise genetic engineering technique. Others have proposed that in some forms, nanoscale TiO_2 could be used to fight cancer or even anthrax.[28]

When Transparency is Problematic

Are transparent sunscreens incorporating nanoparticles safe? In an interview in the April 2003 *Technology Review*, Rice University's Vicki Colvin had this to say:

COLVIN: *"I do know that nanomaterials are already used in sunscreens and also in cosmetics. The fact that they are used in those circumstances is of interest, and I do feel that eventually there will be a regulatory component to this industry."*
TR: *"Have the nanoparticles used in sunscreens and cosmetics been tested? What do you tell people about the risks of these consumer products?"*
COLVIN: *"To my knowledge, they have not been tested. Do I use sunscreens? Yes. Does it make me stay up at night? Actually, it doesn't. Because the kind of diseases —if you look at other larger particulate-based diseases—are ones that usually develop in workers who have acute exposures to the materials over decades. So I don't feel that there is any chance occasional sunscreen use is unhealthy for me or my family. Still, it would be better for everyone to conduct thorough tests."*

The problem, of course, is that pesky hole in the ozone layer. Accelerating awareness that ultraviolet rays cause skin cancer has led to a boon in the sun protection product business. Aussie parents, for example, don't just dab transparent sunscreens on their children "occasionally." From infancy onward, a growing number of people in affluent sunbelt zones lather on sunscreen every day, year-round. Since the leading sunscreen makers are but a modest (though blooming) part of the $90 billion a year cosmetics industry, there is a push to build UV protection into skin moisturizers and other beauty products.[29] Europeans spend more than €1 billion[30] a year on sun protection products, while the US market is expected to exceed $750 million by 2006.[31]

With increased use, invisibility becomes an important sales point. Consumers want transparent creams for their sunscreens. Nanoparticles of titanium dioxide and zinc oxide give that transparency. But is it safe to apply these compounds in their untested nanoparticle form to your skin day after day and year after year? No one knows.

In 1997, scientists from Oxford (UK) and Montreal (Canada) isolated titanium dioxide nanoparticles from over-the-counter sunscreens and observed their behaviour when introduced to human cells. They found that these nanoparticles oxidized to produce hydroxyl radicals, which inflicted substantial damage to the cell's DNA.[32] The concern was that rather than averting skin cancer, the use of these nanoparticles instead threatened to exacerbate it. Although the upper layers of skin are dead, nanosized particles may be able to get into deeper layers of the skin, particularly if the skin is flexed during movement, as well as into hair follicles and wounds.[33]

In research that considers the impact of TiO_2 on the lungs, it has already been established that ultrafine TiO_2 exhibits toxic characteristics. A comprehensive review of titanium dioxide smoke toxicity by the US Army consistently found significant toxic effects associated with inhalation of ultrafine titanium dioxide smoke that did not occur for larger particles. They recommended that safe exposure limits for TiO_2 nanoparticles be set at least eight times lower than exposure limits for normal titanium dioxide particles.[34]

Government regulators and industry players seem to respond to demonstrated risks in different ways. On the one hand, some nanoparticle producers have altered their particles to reduce or eliminate free radical production, either by coating the particles in organic or inorganic ingredients such as silica or by adding antioxidants and vitamins to mop up free-radicals.[35] By contrast, governments have tended to disregard the size-dependent risks associated with nanoparticles. After an off-record meeting with the cosmetics industry, the EU Scientific Committee for Cosmetic Products and Non-Food Products intended for Consumers issued an opinion that titanium dioxide particles are a safe component in sunscreen "whether or not subjected to various treatments (coating, doping, etc.), irrespective of particle size."[36] The US Food and Drug Administration (FDA) was also deliberate in its decision not to distinguish between nanoparticles and their larger relations. In a final monograph on sunscreen ingredients, they ruled: "The agency is aware that sunscreen manufacturers are using micronized titanium dioxide to create high SPF products that are transparent and esthetically pleasing on the skin. The agency does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of the titanium dioxide originally reviewed by the Panel." Pointing out that "fines" have been part of commercially used titanium dioxide powders for decades, they decided that nanoparticles were simply "a refinement of particle size distribution."[37] By taking this approach, both the US government and the European Union may have inadvertently established a principle of "substantial equivalence" (see box, next page), based on dubious assumptions. While the modifications made by some nanoparticle TiO_2 producers to modify their particles may well have rendered them safe for use in sunscreens, there is no independent body to assess this, no requirement for toxicity studies nor any regulations to prevent manufacturers from using unmodified nanoparticles. Furthermore, there are many other commercial uses of photo-reactive titanium dioxide nanoparticles ranging from self-cleaning windows to flat screen display technology that are coming to market unregulated. Could these nanoparticles become ambient in the environment over a product's lifetime or during production or disposal? Do they pose a risk to the health of workers who manufacture them?

Breaking the brain barrier: Confronted with this scientific muddle, ETC Group contacted Dr. Vyvyan Howard of the Developmental Toxico-Pathology unit of the University of Liverpool's Dept. of Human Anatomy and Cell Biology. In 1999, Dr. Howard, as president of the Royal Microscopy Society, co-edited the first collection of papers (1999) to examine the toxicity of nanoparticulates.[38] The papers are authored by leading scientists in the fields of air pollution and particle toxicology. We asked Dr. Howard to undertake a literature search relating to the effects of nano-sized particles on human health and the routes by which nanoparticles can enter the body. His full report is attached.

Substantial Equivalence: Ducking Responsibility Again?

To those in civil society familiar with the debate over the safety of genetically modified organisms (GMOs), the presumption that novel nanoparticles are "substantially equivalent" to their larger-scale relations will seem like "déjà vu all over again."

From Australia to North America to South East Asia, the carefully concocted smoke screen of substantial equivalence has allowed the Gene Giants to legally unleash GM crops into our fields, our food supply and our diet without a full toxicological assessment. In essence, substantial equivalence says that a new food product produced by genetic engineering is usually considered as safe as the equivalent product produced by traditional plant breeding. In GMO regulations worldwide the carefully inserted concept of substantial equivalence requires that, in most cases, little more than a partial chemical analysis be provided to regulators of GM food. Studies comparing only a few key nutrients and toxicants in the modified and unmodified versions of the tomato, corn or soybean are enough to veto the full safety studies that GM medicines are expected to undergo. As a risk assessment tool, 'substantial equivalence' was criticized from the outset by some experts within the US Food and Drug Administration (FDA),[39] and has been condemned in the pages of *Nature* as 'a pseudo-scientific concept…created primarily to provide an excuse for not requiring biochemical or toxicological tests."[40] In 2001, the expert committee of the Royal Society of Canada also dismissed substantial equivalence as a "scientifically unjustifiable" basis for GMO safety regulation.[41] In their report, "Elements of Precaution," the Royal Society characterized the substantial equivalence approach as, "It looks like a duck and it quacks like a duck, therefore we assume that it must be a duck – or at least we will treat it like a duck."[42]

Is the atomtech industry ducking nanosafety issues by embracing the principle of substantial equivalence? Nanoparticles of titanium dioxide may have exactly the same atoms as larger particles of TiO_2 used in paint or food whitener, but that's where the comparison should end. Nanoparticles are smaller, usually more reactive and may have a different colour, strength, shape and conductive properties. Yet the US FDA dismisses nanoparticles as merely a "refinement of particle size distribution."[43] It is clear from ETC Group's enquiries to the European, Canadian and UK authorities responsible for laboratory safety, as well as discussions with companies producing nanoparticles, that neither laboratory guidelines nor national chemicals policies distinguish between handling nano and macro particles.[44] Indeed, so inadequate is the current regulatory approach for nanoscale materials, that the European Union has belatedly commissioned a consortium called Nanosafe to check if they ought to be more discriminating.[45] Until that consortium reports in 2005, however, the interim approach appears to be: "If it's a different colour from a duck, if it doesn't quack like a duck and even if it goes places ducks can't go – let's treat it like a duck anyway!"

Dr. Howard's most important conclusion is that more research is urgently needed and that there are many indications that ultrafine particles could enter the human body and pose a human health hazard. Among his conclusions:

"Research is now showing that when normally harmless bulk materials are made into ultrafine particles they tend to become toxic. Generally, the smaller the particles, the more reactive and toxic their effect. This should come as no surprise, because that is exactly the way in which catalysts are made, to enhance industrial chemical reactions. By making particles of just a few hundred atoms you create an enormous amount of surface, which tends to become electrically charged, and thus chemically reactive."

Beyond concern that nanoparticles could enter the body through the lungs or through the digestive tract, Dr. Howard also notes the risk that ultrafine particles could enter through the skin. "Recent studies have shown that particles of up to 1µm in diameter (i.e. within the category of 'fine' particles) can get deep enough into the skin to be taken up into the lymphatic system, while particles larger than that did not. The implication is that ultrafine particles can and will be assimilated into the body through the skin." Given the extensive use of unregulated titanium dioxide nanoparticles in popular over-the-counter skin care products as well as wide use of nanoparticles in cosmetics and wound dressings, this conclusion is of immediate concern to government agencies and consumers. "*In vitro* studies on living cells have confirmed the increased ability of UFPs to produce free radicals which then cause cellular damage," Dr. Howard adds.

One of the most surprising conclusions of Dr. Howard's survey is that, "It does seem, in the light of current knowledge, that the size effect is considerably more important to UFP toxicity than the actual composition of the material." In other words, whether the nanoparticles are carbon or titanium or even latex may not be as important as their size.

Dr. Howard ends his survey with the following comment, "There is evidence that UFPs can gain entry to the body by a number of routes, including inhalation, ingestion and across the skin. There is considerable evidence that UFPs are toxic and therefore potentially hazardous. The basis of this toxicity is not fully established but a prime candidate for consideration is the increased reactivity associated with very small size. The toxicity of UFPs does not appear to be very closely related to the type of material from which the particles are made, although there is still much research to be done before this question is fully answered."

Mandatory moratorium: Based on our initial research on the safety of nanoparticles (see ETC *Communiqué* "No Small Matter," May/June, 2002), ETC Group called for a mandatory moratorium on the use of synthetic nanoparticles in the lab and in any new commercial products. The move was almost universally condemned by the industry. Some argued that it would be impossible to prove the safety of nanoparticles if laboratories couldn't undertake tests. Others worried that a moratorium would simply drive research underground where it would become more dangerous. On the contrary, ETC Group has stressed that, although a moratorium is the only responsible avenue open at this time, it need not be long-lasting. Researchers should come together immediately to propose the "best practices" possible for laboratory workers within the internationally-recognized concept of the Precautionary Principle. Assuming that agreement can be reached quickly within the scientific community, these "best practices" should be adopted by the governments of countries where research is underway. The "best practices" should include clear monitoring mechanisms and reporting procedures that will allow governments – in conjunction with scientists – to amend lab protocols as new information becomes available. Simultaneously, the international community must begin work on a legally-binding mechanism to govern atomtechnology, based on the Precautionary Principle, one that will look beyond laboratory research to consider the wider health, socio-economic and environmental implications of nanoscale technologies. This protocol should be embedded in one or more of the relevant United Nations agencies such as UNEP, ILO, WHO, or FAO. Ultimately, ETC Group believes that the international regulations for atomtechnology should be incorporated under a new International Convention for the Evaluation of New Technologies (ICENT).

The Bottom-Up Line: The atomtech community has had a quarter-century to come to grips with the obvious health and environmental questions that inevitably arise when dealing with such a powerful set of new technologies. Governments have failed to act responsibly. Lab workers and consumers should not be exposed to nanoparticles in the absence of credible scientific evaluation under government regulation. (Some institutions, for example, have no safety rules for nanoparticle production; others insist their workers wear surgical masks and at least one insists that their workers treat nanoparticles on the same level as they would the HIV/AIDS virus.)[46]

The failure of governments to act now may unnecessarily endanger the future of a powerful and potentially beneficial technology. For the protection of both society and science, the responsible option is to call for an immediate moratorium on the laboratory use of synthetic nanoparticles. In the absence of toxicology studies, ETC Group believes that governments must also urgently consider extending the moratorium to products that place consumers in direct contact with synthetic nanoparticles through their skin, lungs or digestive systems.

Governments seem to agree that atomtechnologies will bring about the next industrial revolution. As though it was a mantra, they are telling themselves they won't make the same mistakes they made with the introduction of biotechnology. Would that they were right! In ignoring the uniqueness of quantum characteristics, governments have allowed atomtech to move much faster than biotech. They have accepted mass manufacture of un-tested nanoparticles and have allowed commercialization of consumer products containing nanoparticles without taking seriously the possible health and environmental effects.

Given that atomtech is still in its infancy, this is an extraordinarily risky way to run a revolution. Is the call for a moratorium a thinly-veiled ploy to squelch nanotech? Hardly. It is crucial that governments think in the long-term while insuring that the foundations of this "bottom up" technology are solid. In the absence of toxicology studies, transparent regulations and widespread public discussion on socio-economic, health and environmental impacts of atomtech, governments must act responsibly by adopting a moratorium on laboratory use of synthetic nanoparticles.

As Small gets Bigger

A partial list of nanoparticle manufacturers and a sampling of commercial products containing nanoparticles

Nanoparticles	Manufacturer	Brand Names / Products
Sunscreens and Cosmetics		
Titanium Dioxide	Altair Nanotechnologies	
	Chengyin Technologies	
	Micronisers	Microsun, Sunsorb, Nanosun
	Nanophase	
	Nanosource	
	Oxonica	
	Particle Sciences, Inc. (T-Cote 031)	Vanicream Sunscreens, Skin Doctrine Sun Protector
	Sachtleben / Merck (Eusolex)	
	Showa Denka (Maxlight FTS)	
Zinc Oxide	Advanced Powder Technologies (ZinClear)	Bare Zone, Bare Zone Nippers, Wet Dreams, Wild Child
	Micronisers	Microsun, Sunsorb, Nanosun
	Nanophase/ BASF "Z-Cote"	All Terrain Terrasport, Australian Gold, Dermatone, SPF To Go, Skin Doctrine Sun Protector, Skinceuticals, Sun Smart, Vanicream Sunscreens, NuCelle Sunsense
	Oxonica	
	Showa Denko (Maxlight ZS)	
"Nanocapsules" filled with various nutrients (130-600 nm)	L'Oréal	Lancôme Flash Bronzer Self-Tanning Face Gel, L'Oréal Plenitude Futur-E Moisturiser
Textiles		
Teflon®	DuPont	Some stain-resistant apparel sold by: Levi Dockers, J. Crew, London Fog, Marks and Spencer, Ralph Lauren, Regatta, Liz Claiborne, Pendleton
Unspecified polymer fibers	Nano-Tex, LLC/Burlington (Nano-Care, Nano-Dry, Nano-Pel, Nano-Touch)	Some stain/wrinkle-resistant apparel sold by: Bremen Trousers, Croft and Barrow, Dreamyland, Eddie Bauer, Elbeco, Gap, Haggar, Kathmandu, Lee Performance Khakis, Levi Dockers, Levi Strauss, Marks Work Warehouse, Savane, Sleepmaker
Titanium Dioxide (500 nm)	BASF - Ultramid BS416N	For use in UV-protected fabrics
Coatings		
Custom-made nanocomposites	Nanogate Technologies, GmbH	Schweizer Optik anti-scratch lenses
Titanium Dioxide	AFG Industries	Radiance Ti self-cleaning glass

Nanoparticles	Manufacturer	Brand Names / Products
Titanium Dioxide	Pilkington	Pilkington Activ self-cleaning glass
Titanium Dioxide	PPG Industries	SunClean self-cleaning glass
Custom-made nanocomposites	Nanogate Technologies, GmbH	WonderGliss anti-stick coating, Sekcid tile coating
Electronics		
Titanium Dioxide	Ntera Ltd.	NanoChromics displays
Carbon Nanotube	NEC	Flat-screen displays (not yet commercialized)
crystalline films	Optiva	Sony Liquid Crystal Displays
Energy storage		
Lithium Titanate nanoparticles	Altair Nanotechnologies, Inc./Ntera Ltd.	For use in rechargeable lithium ion batteries. Not yet commercialized.
Carbon Nanohorns	NEC	Fuel cells for mobile phones and notebook PCs. Not yet commercialized.
Sports goods		
Carbon Nanotube	Nanoledge	Babolat VS nanotube tennis racquet
Nanoclay particles, rubber polymers	InMat, LLC	Wilson Double Core tennis balls
Nanocomposites	Nanogate Technologies, GmbH	Cerax Racing Polymer (ski wax)
Military uses / Decontamination		
Aluminum	Argonide Metal Technologies (Alex)	rocket propellant booster
Titanium Dioxide	KES Science and Technology, Inc.	AiroCide TiO2 Filter to destroy airborne pathogens, such as anthrax
Various metal oxides	NanoScale Materials, Inc.	NanoActive remediation of hazardous chemical waste
Titanium Dioxide	Altair Nanotechnologies / Western Michigan University	Product for nuclear waste remediation and sensors to detect chemical and biological agents under development
Surface Disinfectant		
Lanthanum-based compound (40 nm)	Altair Nanotechnologies	Nanocheck Algae Preventer for pools, aquariums
Nanoemulsions (170 nm)	EnviroSystems, Inc.	Ecotru Surface Disinfectant
Dental uses		
Hydroxyapatite crystals	BASF	Toothpaste with enamel - not yet commercialized
Polyhedral Oligomeric Silsesquioxane	Hybrid Plastics	NanoBond bonding agent
Medical uses		
Silver	Nucryst (division of Westaim)	Smith & Nephew Acticoat Bandages
Silver	Institute for New Materials	Audio Service GmbH, antimicrobial coating on hearing aids
Automobile		
Carbon Nanotube	Hyperion Catalysis	Widely-used in automobile fuel lines and Renault Clio and Megane plastic panels
Nano Tracking Devices		
Various metals	Nanoplex Technologies, Inc.	Nanobarcodes used for bioanalysis, such as protein arrays

ENDNOTES:

[1] The National Toxicology program is not a US government regulatory agency, though Federal and State Regulatory Agencies use the National Toxicology Program study data in considering the need for regulation of specific chemicals to protect human health. See: http://ntp-server.niehs.nih.gov/main_pages/RegAct2001.HTML
[2] Better Regulation Taskforce, "Scientific Research: Innovation with Controls," January 2003; available on the Internet: http://www.brtf.gov.uk/taskforce/reports/Scientificresearch.pdf
[3] According to Scott Mize, "Near-Term Commercial Opportunities in Nanotechnology," comments made during presentation at the Foresight Conference, October 10, 2002.
[4] Business Wire, Inc., "Altair Nanotechnologies Awarded Patent for its Nano-sized Titanium Dioxide," Sept. 4, 2002. The estimate is based on market research by Business Communications Co., Inc.
[5] See www.nanoproducts.com
[6] http://www.smalltimes.com/document_display.cfm?document_id=5019
[7] Vicki Colvin, "Responsible Nanotechnology: Looking Beyond the Good News," available on the Internet, www.eurekalert.org
[8] John Bucher, presentation at the symposium, "Nanotechnology and the Environment," American Chemical Society meeting in New Orleans, LA, March 23, 2003.
[9] Tina Masciangioli and Wei-Xian Zhang, "Environmental Technologies at the Nanoscale," *Environmental Science and Technology*, March 1, 2003, p. 108 A.
[10] See footnote 11.
[11] The critical size assessments come from Vivyan Howard's discussion in the Annex to this document, Vicki Colvin's interview in *Technology Review* (David Rotman, "Measuring the Risks of Nanotechnology," April 2003, p. 72), Günter Oberdörster, "Effects and fate of inhaled ultrafine particles," presentation at the American Chemical Society, New Orleans, LA, March 23, 2003.
[12] Robert D. Shull, remarks made at NNI conference, Washington, DC, April 3, 2003.
[13] Ibid.
[14] Anon. Press Release, Multimedia Research Group, Inc.; available on the Internet: http://www.mrgco.com/Press_Releases_1.html#Carbon%20Nanotubes%202002%20PR
[15] Anon. Press Release, Business Communications Company, February 3, 2003; available on the Internet: http://www.bccresearch.com/editors/RGB-245R.html
[16] News item posted on Nanoinvestor News; available on the Internet: http://www.nanoinvestornews.com/modules.php?name=News&file=article&sid=1345
[17] Paul Kallendar, "NEC Tries to Grab the Fuel Cell Market by the Carbon Nanohorns," *Small Times*, March 25, 2003; available on the Internet: http://www.smalltimes.com/document_display.cfm?document_id=5719
[18] Personal communication with Dr. Richard Siegel via telephone, June 17, 2002.
[19] Andrzej Huczko et al., "Physiological Testing of Carbon Nanotubes: Are They Asbestos-Like?" *Fullerene Nanotubes and Carbon Nanostructures* (formerly *Fullerene Science and Technology*), vol. 9 (2), 2001,p. 253.
[20] Victoria Griffith, "Inside Track: Big Risks on a Microscopic Scale," *Financial Times*, Sept 25, 2002.
[21] ETC Group is limiting its discussion of the NASA study to the information contained in the published abstract (www.chemistry.org) and the published article in *New Scientist* (see note 22). At the New Orleans meeting, chief researcher Chui-wing Lam asked attendees to respect a "media embargo" as the study had not yet been accepted for publication.
[22] Kurt Kleiner, "How Safe is Nanotech?" *New Scientist*, 29 March 2003, pp. 14-15.
[23] David B. Warheit, "Pulmonary-toxicity-screening studies with single-wall carbon nanotubes;" abstract available on the Internet: www.chemistry.org
[24] http://ntp-server.niehs.nih.gov/htdocs/98AP/9tox.html#particle
[25] BASF produces Z-cote for transparent zinc oxide sunscreens and also is intending to use nano-sized TiO_2 in its "Ultramid" UV protected sports fabrics. L'Oréal uses nano-sized TiO_2 in a selection of its products including its Lancôme range of SPF cosmetics.
[26] N. Serpone, A. Salinaro, and A. Emelino, "Deleterious Effects of Sunscreen Titanium Dioxide Nanoparticles on DNA. Efforts to Limit DNA Damage by Particle Surface Modification," *Proceedings of SPIE* vol. 4258 (2001).
[27] Anon., "Argonne Nanotechnology Research May Yield New Sequencing Technology," October 8, 2002; available on the Internet: http://www.genomeweb.com/articles/view-article.asp?Article=2002108145653
[28] Daniel M. Blake, Pin-Ching Maness, Zheng Huang, Edward J. Wolfrum, and Jie Huang, "Application of the Photocatalytic Chemistry of Titanium Dioxide to Disinfection and the Killing of Cancer Cells," *Separation and Purification Methods* Volume 28(1) 1999, pp. 1-50; Emergency Response Technology Programme, Photocatalytic Self-

Cleaning Nano Layer Process for Neutralizing Chemical and Biological Contaminants for Filtration, Cleaning, and other Environmental Applications. See details online: http://www.nttc.edu/ertProgram/photocat.asp

[29] Anon., "The Colour of Money, Unilever and P&G are challenging L'Oréal," *The Economist*, March 6, 2003, p.59.

[30] Marc Berman, *Euromonitor*, March 2001, http://www.in-cosmetics.com/page.cfm/Link=55

[31] Datamonitor Corp. October, 2002, from excerpt of report entitled "US Suncare 2002," available on the Internet: http://www.theinfoshop.com/study/dc11760_suncare_toc.htmlive

[32] Rosemary Dunford, Angela Salinaro, Lezhen Cai, Nick Serpone, Satoshi Horikoshi, Hisao Hidaka and John Knowland, "Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients," *FEBS Letters*, Volume 418, Issues 1-*2*, 24 November 1997, pp. 87-90.

[33] Sally S. Tinkle, James M. Antonini, Brenda A. Rich, Jenny R. Roberts, Rebecca Salmen, Karyn DePree, Eric J. Adkins, "Skin as a Route of Exposure and Sensitization in Chronic Beryllium Disease," *Environmental Health Perspectives, doi:10.1289/ehp.5999* (available at http://dx.doi.org/); Accessed 24 February 2003.

[34] Commission on Life Sciences (CLS), *Toxicity of Military Smokes and Obscurants*, volume 2, National Academies Press, (1999), pp. 68-96.

[35] For example, see Allen Bernard, "Oxonica's Nanopowders Improve Catalysts, Biotags and Sunscreen," July 10, 2002; available on the Internet: http://www.nanoelectronicsplanet.com/nanochannels/profiles/article/0,,10500_1383331_2,00.html

[36] Opinion concerning Titanium Dioxide, Colipa n¡ S75 adopted by the SCCNFP during the 14th plenary meeting of 24 October 2000. In several committee discussions previous to this opinion the question of special toxicity from smaller particles had been raised and a special meeting was arranged between the working group of SCCNFP and industry to resolve toxicology questions over Nano TiO_2.That such a meeting was held on 13 June 2000 is recorded in the minutes of the 13th meeting of the SCCNFP (see http://europa.eu.int/comm/food/fs/sc/sccp/out128_en.html), however, no record of the proceedings of the meeting with industry appears to exist.

[37] US Food and Drug Administration, HHS, "Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph," *Federal Register*, May 21, 1999 (Volume 64, Number 98), pp. 27666-27693.

[38] Howard, C.V. and Maynard, R.L., eds., *Particulate matter: properties and effects upon health*, Oxford: BIOS Scientific Publishers; New York: Springer, 1999.

[39] See, for example, comments from Dr. Linda Kahl, FDA compliance officer, to Dr. James Maryanski, FDA Biotechnology Coordinator, about the *Federal Register* document "Statement of Policy: Foods from Genetically Modified Plants," dated January 8, 1992. (3 pages available from www.biointegrity.org /FDAdocs/01/index.html).

[40] E. Millstone, E. Brunner, and S. Mayer (1999a), "Beyond 'Substantial Equivalence," *Nature*, vol. 401, pp. 525-526.

[41] *Elements of Precaution: Recommendations for the Regulation of Food*, An Expert Panel Report on the Future of Food Biotechnology prepared by The Royal Society of Canada at the request of Health Canada, Canadian Food Inspection Agency and Environment Canada, February 2001; available on the Internet: www.rsc.ca/foodbiotechnology/indexEN.html

[42] *Ibid*., p. 181.

[43] US Food and Drug Administration, HHS, *Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph*, Federal Register: May 21, 1999 (Volume 64, Number 98), pp. 27666-27693.

[44] Personal communication with Maureen Meldrum (16 Jan 2003) and Christine Northage (21 Jan 2003) both of UK Health and Safety Executive, Mark Schmahl - European Commission DG Enterprise (21 Jan 2003), Kevin Matthews of Oxonica, (28 March 2003).

[45] FP6: Expression of Interest for Integrated Project Priority Thematic Area: Nanotechnology Risk Assessment of Airborne Nanoparticles in the Workplace (NANOSAFE). Available on the Internet: www.tau.ac.il/research/EU/europe/nano/EOIvers2.pdf

[46] Representative of South Africa's National Nanotechnology Program, Leslie Petrik of the University of the Western Cape, Dec 2, 2002, in a presentation to an African Regional Meeting on new technologies, organized by Biowatch South Africa and ETC Group.

The Action Group on Erosion, Technology and Concentration, formerly RAFI, is an international civil society organization headquartered in Canada. The ETC group is dedicated to the advancement of cultural and ecological diversity and human rights. www.etcgroup.org. The ETC group is also a member of the Community Biodiversity Development and Conservation Programme (CBDC). The CBDC is a collaborative experimental initiative involving civil society organizations and public research institutions in 14 countries. The CBDC is dedicated to the exploration of community-directed programmes to strengthen the conservation and enhancement of agricultural biodiversity. The CBDC website is www.cbdcprogram.org

Annex

Nano-particles and Toxicity

C. Vyvyan Howard 2 April 2003

The nano-technology industry is commencing the bulk production of ultrafine particles (UFPs) for applications in a range of products.
Examples include:

- the use of UFP titanium dioxide in sunscreens,
- the making of 'bucky balls' – which are 1 nanometre diameter 'footballs' made of 60 carbon atoms, and
- the production of carbon 'nanotubes' which are of 1 nm diameter but may be up to 1 μm in length and are a technological development arising from 'bucky balls'. Manufacturers are moving into production levels in excess of 100 tons per annum.

Particles that can be breathed in (i.e. are respirable) are classified as:

Coarse or PM_{10}:
Particles with an average diameter of < 10 μm

Fine or $PM_{2.5}$:
Particles with an average diameter of < 2.5 μm

Ultrafine or $PM_{0.1}$:
Particles with an average diameter of < 0.1 μm

1 μm (or micron) is one thousandth of a millimetre and is 1,000 nm (or nanometres).

We have two defence mechanisms in the lung: First, a carpet of mucus which lines all but the most peripheral parts of the lung. This carpet moves slowly upwards, carrying any particles that have landed on it, and is then swallowed. Particles that make it beyond this carpet of mucus (they tend to be the fine and ultrafine fractions), then get into the alveolar spaces where gas exchange between the air and the blood takes place. The alveolar surfaces are patrolled by 'macrophages', which are scavenger cells that mop up particles. However, they appear to have difficulty recognising particles of less than 70 nm as being 'foreign' and in addition, they can be easily overwhelmed by too many particles, a condition called 'overload' (Wichmann and Peters, 2000).

Considering the types of particle that we were exposed to throughout our evolution is illuminating. These mainly consisted of suspended sand and soil particles and biological products such as pollens. Most of these are relatively coarse and become trapped before getting to the alveoli. There have always been ultrafine particles, mainly consisting of minute crystals of salt which become airborne through the action of the waves of the sea (Eakins & Lally 1984). These are not toxic because they are soluble salts. What is clear is that, for particles of less than 70 nm, there was nothing much in the air throughout our prehistory which was of particular consequence, until we harnessed fire to our uses.

Research is now showing that when normally harmless bulk materials are made into ultrafine particles they tend to become toxic. Generally, the smaller the particles, the more reactive and toxic their effect. This should come as no surprise, because that is exactly the way in which catalysts are made, to enhance industrial chemical reactions. By making particles of just a few hundred atoms you create an enormous amount of surface, which tends to become electrically charged, and thus chemically reactive. The upper size limit for the toxicity of UFPs is not fully known but is thought to lie between 65 and 200 nm (Donaldson *et al*., 2000).

There is epidemiological evidence showing that chronic exposure to particulate aerosols leads to long term health effects, primarily on the cardiovascular system (Dockery & Pope 1993, Kunzli *et al.* 2000). Most of these studies have measured PM_{10} to assess effects. More studies are now tending to use $PM_{2.5}$, though the question of whether it is more predictive of harm than PM_{10} is still being debated (Anderson 2000). There is also evidence that short term effects from poor air quality is due to particle overloading. The number of studies that have used ultrafine particles ($PM_{0.1}$) is low, but there are indications that they are more hazardous than $PM_{2.5}$ (Wichmann & Peters 2000).

The main questions about UFPs currently facing scientists are:

1)By what routes do UFPs get into the body and then where do they travel to?
2)What is the mechanism of toxic action and how does the reactive surface of UFPs interact with 'wet biochemistry' in the body?
3)What is the relative contribution of particle size versus particle composition in the overall toxicity of UFPs?

Definitive answers to all these questions are currently lacking, though research is underway in a number of different centres. Evidence for the potential harm associated with UFPs comes from a number of sources. Some toxicological studies have been performed *in vivo* on experimental animals. Further studies, mainly looking at mechanisms of toxicity have been performed *in vitro* on cells and tissues. Some studies have addressed absorption and fate of UFPs.

Question 1. Routes of access into, and travel around, the body

Firstly, it should be noted that there appears to be a natural 'passageway' for nanoparticles to get into and then subsequently around the body. This is through the 'caveolar' openings in the natural membranes which separate body compartments. These openings are between 40 and 100 nm in size and are thought to be involved in the transport of 'macromolecules' such as proteins, including on occasion viruses. They also happen to be about the right size for transporting UFPs. Most of the research on that, to date, has been performed by the pharmaceutical industry, which is interested in finding ways of improving drug delivery to target organs. This is particularly so for the brain, which is protected by the 'blood brain barrier' which can be very restrictive. This has been reviewed by Gumbleton (2001). In essence, it appears that chemists are able to design UFPs that can hoodwink certain membranes into allowing 'piggybacking' of novel chemicals across membranes, that would not be possible otherwise. For example Kreuter *et al*. (2001 and 2002) have shown that Poly(butyl cyanoacrylate) nanoparticles precoated with polysorbate 80 can be used to enhance the delivery of apolipoproteins to the brain. Alyaudtin *et al*. (2001) have demonstrated similar UFPs mediate delivery of [3H]-dalargin to the brain.

Although there are clear advantages to the intentional and controlled targeting of 'difficult' organs, such as the brain, with nanoparticles to increase drug delivery, the obverse of this particular coin needs to be considered. When environmental UFPs (such as from traffic pollution) gain unintentional entry to the body, it appears that there is a pre-existing mechanism which can deliver them to vital organs (Gumbleton, 2001). The body is then 'wide open' to any toxic effects that they can exert. The probable reason that we have not built up any defences is that any such environmental toxic UFPs were not part of the prehistoric environment in which we evolved and therefore there was no requirement to develop defensive mechanisms.

There is considerable evidence to show that inhaled UFPs can gain access to the blood stream and are then distributed to other organs in the body (Kreyling *et al.* 2002, Oberdörster *et al.* 2002). This has been shown for synthetically produced UFPs such as bucky-balls (Brown 2002, Rice Conference 2001) which accumulate in the liver.

Another possible portal of entry into the body is via the skin. A number of sunscreen preparations are now available which incorporate nano-particle titanium dioxide (TiO_2). Recent studies (Tinkle *et al*., 2003) have shown that particles of up to 1 µm in diameter (i.e. within the category of "fine" particles) can get deep enough into the skin to be taken up into the lymphatic system, while particles larger than that did not. The implication is that ultrafine particles can and will be assimilated into the body through the skin. The exact proportion of those deposited which will be absorbed remains unknown. Tinkle *et al*. (2003) have studied the penetration of dextran beads into postmortem human skin and demonstrated that 0.5 µm and 1 µm beads can penetrate the stratum corneum of skin being flexed. This process affected over 50% of samples if the process continued for 1 hour. In a small proportion of case the beads got as far as the dermis.

Question 2. The mechanism of toxic action

In vivo studies performed on laboratory animals have looked at the ability of UFPs to produce inflammation in lungs after exposure to UFP aerosols (Donaldson 1999, Donaldson 2000, Donaldson 2001, Oberdörster 2000). The degree to which UFPs appear to be able to produce inflammation is related to the smallness of the particles, the 'age' of the aerosol and the level of previous exposure. It has been hypothesised (Seaton 1995) that the chronic inhalation of particles can set up a low grade inflammatory process that can damage the lining of the blood vessels, leading to arterial disease.

In vitro studies on living cells have confirmed the increased ability of UFPs to produce free radicals which then cause cellular damage (Rahman 2002, Li 2002, Uchino *et al*. 2002). This damage can be manifested in different ways, including genotoxicity (Rahman *et al.* 2002) and altered rates of cell death (including apoptosis) (Rahman *et al.* 2002, Uchino 2002, Kim *et al.* 1999, Afaq *et al.* 1998).

Question 3. Particle size versus particle composition

Early indications were that transitional metals might be more toxic as UFPs than other materials (Donaldson *et al*., 1999). Since then, other studies have shown very similar toxicities between very different materials when presented as UFPs, for example latex and TiO_2 (Oberdörster 2000). UFPs are able to transport transition metals, which have been implicated in the proinflammatory effects and toxicity of PM10 (Gilmour *et al*. 1996). More recently, Donaldson *et al*. have discounted transitional metals as a source of oxidative stress and their researches (Donaldson *et al*. 2001) are concentrating on the effects of ultrafine carbon black. What seems clear from all these papers is that exposure of living systems to UFPs tends to increase oxidative stress. It does seem, in the light of current knowledge, that the size effect is considerably more important to UFP toxicity than the actual composition of the material.

Conclusions

There is evidence that UFPs can gain entry to the body by a number of routes, including inhalation, ingestion and across the skin. There is considerable evidence that UFPs are toxic and therefore potentially hazardous. The basis of this toxicity is not fully established but a prime candidate for consideration is the increased reactivity associated with very small size. The toxicity of UFPs does not appear to be very closely related to the type of material from which the particles are made, although there is still much research to be done before this question is fully answered.

In the meantime, there is already enough evidence extant to demonstrate that UFPs are likely to pose a health hazard and that human exposure in general, and in particular in the workplace, should be minimised on a precautionary basis. We are defenceless against the internalisation of UFPs by ingestion, inhalation or transdermal assimilation. UFPs appear to have a toxicity which is primarily a property of their small size rather than their composition. While it is easy to appreciate how this can be harnessed to positive pharmaceutical purposes, there is an urgent need to curb the generation of unnecessary UFPs, particularly of the insoluble variety. Full hazard assessments should be performed to establish the safety of species of particle before manufacturing is licensed. We are dealing with a potentially hazardous process.

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