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PERSPECTIVES

Rhetorical gamesmanship in the nano debates over sunscreens and nanoparticles

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Abstract Communication of risk profiles associated with sunscreens incorporating nanoparticles has been challenging when some communicators shift risk profiles from highly problematic nanoparticles to others, which are much less problematic. This article vets a popular publication from a civic advocacy group that cited scientific research papers to make environmental health and safety claims. The phenomenon of risk profile shifts is demonstrated by re-examining the scientific articles being cited. In addition, the authors for correspondence for each of the articles cited were interviewed via email and their comments about the claims made are included.

Keywords Nanotechnology · Nanoparticles · Sunscreens · Titanium dioxide · Zinc oxide · Background · Literature review · Literature survey · Environmental health and safety (EHS) · Risk communication · Risk profile shifts · Governance · Societal implications

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Introduction

The public debates over the health and safety of nanoparticles are a mess and blame rests nearly everywhere. The confusion started with rhetorical flourishes describing nanoscience as revolutionary and nanotechnology as the next industrial revolution. Nearly simultaneously and in part responding to warnings from environmentalists, we had claims that nanoscience was not particularly dangerous because it was simply evolutionary, the next step in chemistry and material sciences. Next we had a series of metaphors applied to nanotechnology. The public was entertained with broad estimations of nanoscience and nanotechnologies as analogous to genetically modified organisms (GMOs), especially as they pertained to foodstuffs marketed in Western Europe by American-based transnational corporations. Linking nanotechnology to GMOs rhetors intended to transfer the negative valence associated with the GMO fiasco to the bourgeoning field of nanoscience. This was followed closely with claims that should a business or group market products, which may have a high negative risk profile; then the entire industry would collapse under the weight of negative publicity. This phenomenon is a little more sophisticated than transference has been called contagion, sometimes the cascade or bandwagon effect, and is a much denser than a simple correlation. The next major rhetorical jab came in the form of testimony from environmental health and safety (EHS) researchers who argued that nanoparticles functioned differently than particles larger in size and as such their risk profiles may be unique making standard setting especially problematic. Environmental activists and some civil advocacy groups (CAG) grabbed onto this concept and began to ask whether regulators were positioned to protect public safety. Toxicologists crooned that there was insufficient information and much more research on EHS was needed. In response, some environmentalists and CAGs demanded pre-emptive precautionary measures including moratoria. Finally, we need to at least tip our hats to the role media has played in attenuating and amplifying the EHS profiles of some nanoproducts. The media love to portray issues as disaster events, including EHS reports about emerging technologies.

Cumulatively, this level of discord has frustrated the public's capacity to wring something intelligible out of the EHS debate. After examining report after report in the nanosphere while at the University of South Carolina's NanoCenter, my NanoScience and Technology Studies students and I noticed the employment of a rhetorical device we dubbed risk profile shifts. They seem to be employed primarily to bias public opinion about the safety of some nanoparticles. In academia, authors could not get away with such behavior. The review process is simply too vigorous to allow questionable scholarship and violators are punished in dozens of different ways. However, nobody seems intent to police the nanosphere with equal vigilance.

Background

There are many fallacies in scientific debates, risk profile shifting is one such and is derived from the fallacies of division, equivocation, and hasty generalization in symbolic logic and the term shift fallacy in linguistics. The term shift fallacy occurs when a term, which has different contextual meanings is misleadingly used.

Why do you doubt the miracles described in the Bible when you have witnessed miracles like man (sic) landing on the moon? In the first occurrence, miracle means something that defies the laws of nature. In the second occurrence, miracle means something amazing, that you would not have thought could be done. The fact that the second kind of miracle occurred does not make it more likely that the first kind occurred. An argument that commits the fallacy of equivocation would be valid if it were not for the shift in meaning. When meaning shifts in structurally significant ways, the pattern of the argument is destroyed, and the conclusion does not follow the premises. (Cedarbloom 1986).

The term shift fallacy can be intentional and unintentional. Being obscure can be politically advantageous (Vedung 1982). For example, journalists understand that outrageous claims are potential headliners and most editors want headline possibilities within the text of any article. In a rhetorical flourish, a journalist may misuse a term to purposefully draw the attention to a claim being made.

At other times, the vocabulary is blameworthy: the possible grouping of entities far exceeds the possible words or terms in nearly everyone's vocabulary. Some languages simply have fewer words and terms to express complex ideas: compare German or Chinese to English. Some people simply have more limited vocabularies than others.

According to Kaplan (1997), half the problems in the world result from people using the same words with different meanings. While this may be an overclaim, it helps us to move to a phenomenon found in many scientific arguments that has surfaced in some EHS debates over nanoparticles.

Risk-profile shifts

Each event or phenomenon has a risk profile. The profile is a composite of estimates of degree of hazard, dosage variables drawn from studies, and exposure variables often expressed as a probability.

Often, the event or phenomenon under examination belongs to a class or set of phenomena. If we take the risk profile of one phenomenon in a class of phenomena and transfer it to a different phenomenon within the same class, the acceptability of the transfer is clearly a function of how homogenous the class from which the phenomenon was drawn may happen to be. The more heterogeneous the class the higher the likelihood of error and the transference in question may be invalid.

Risk-profile shifting has become much too common in the EHS debates on nanoparticles. While it would be first-class if this shifting was done with pure motivation, this may not be the case in this instance. In too many situations, we have seen presumably good people engaging in behavior, which is highly questionable because of threats or perceived threats to their self-esteem and well-being. This article calls them to task.

Serious risk profile shifts surfaced over a year ago after some effort was made to trace the sources found in a report by a self-proclaimed non-governmental organization, which called for a moratorium on all nanoproducts. The project was frustrating for the student researchers under my supervision because it takes must less time to make an outrageous claim than to rebut the same outrageous claim.

We discovered that when studies were reported the rhetoric chosen to describe the findings was much more totalistic or absolute than the researchers admitted could be drawn from their own research. Efforts on the parts of the researchers who actually did the research to control how their findings would be framed by others were simply ignored. For more information on this experience, I refer to my blog postings (http://www.nanohype.blogspot.com/).

The media attempt to prime public opinion by overclaiming findings when they report tentative findings as conclusive. While it might be excessive to claim the media write the public agenda on EHS, it is not an exaggeration to claim that the media and the community of civil advocacy groups (hereafter referred to as CAGs) together contribute significantly to the public agenda. We expect more so than experts in the field.

Unfortunately, both the media and the CAGs are motivated to hyperbolize the findings on toxicity for many of the same reasons: (1) the public reacts positively to crisis rhetoric and prefers disaster to objective and boring research findings; (2) the public has been weaned on the rhetoric of fear for over a decade and has grown comfortable to claims of foreboding by parties of all sorts; (3) the public assigns prestige value to sources of controversial and unsetting information crediting them for uncovering oftentimes conspiratorial findings; and (4) the public responds with increased readership and membership to those who break a newsworthy message about EHS.

Other stakeholders have different and sometimes similar motives. Some media and CAGs are much more concerned with presenting a balanced approach to reports. Other media and CAGs stay out of debates they are not prepared to engage. Some media and CAGs subject what they publish to a higher level of scrutiny than others. For example, there are many CAGs, including but not limited to Environmental Defense and Greenpeace, who have been valiant in moderating their claims to avoid over dramatization. Unfortunately, this restraint is not embraced by everyone.

Talking about nanotechnology is challenging enough. Not only is the subject highly technical for public audiences, but also nanotechnology is incredibly heterogeneous as a subject field. Broad conclusions about nanotechnology and nanoparticles are difficult to make and sustain.

- There is no single nanotechnology but many nanotechnologies.
- Some industries may use a nanotechnology to produce a finished product but that product may not in itself contain nanoparticles.
- Nanoparticles can be functionalized in many different ways and as such be differentiated from another nanoparticle of the same sort but functionalized in a different way.
- Nanoparticles can be freely mobile in the waste stream or bound within a matrix, such as polymers, though their status at the end of their life cycle remains unknown.
- Nanoparticles aggregate during use and in some instances their characteristics may be enhanced or degraded with use and maybe through disposal as well.

Most of the science world, the media, and CAGs are correct when they claim that we do not know enough about nanotechnology and nanoparticles to claim they are safe. Oxygen and water are not safe when taken in extremes: exposure and dosage matter. In addition, nanoparticles must be compared to the larger sized particles they may replace.

While the public is highly apprehensive about uncertainty, there remains very little that the scientific community can say about nanoparticles with any certainty. Equivocation is the foundation of scientific writing. The statements made by researchers on questions of toxicity remain guarded. Finally, you will be challenged to find any toxicologist to ever admit there is enough information about toxic effects to draw any conclusion whatsoever and this fuels another level of discord. Some argue that uncertainty should be a ground for regulation if not total prohibition (a moratorium), while the majority argue that we need more research to determine the fate of products using nanoparticles. No one seems to have determined how much data is needed to fashion reasonable regulations.

There is much to learn about the toxicology of nanoparticles. The only conclusion to be drawn here is that in some instances we might know enough to make an intelligent assessment and in other instances that is clearly not the case. Beyond the obvious: exposure and dosage will affect the risk profile of nanoparticles. Nanoparticles are very different from particles of larger scale as they are from one another and that discussion is ongoing. Carbon nanotubes are different from nanosized titanium dioxide; some forms (anatase, rutile, and brookite) of nanosized titanium dioxide may be photoactive and other forms are not; coated and nanosized titanium dioxide produces different effects than its uncoated varieties (they are coated with trimethyloctylsilane, Al_2O_3 or SiO_2, for example, to minimize reactivity while maintaining UV diffraction). In addition, how nanoparticles are prepared for use in finished products can produce effects due to the presence of trace materials such as metals. Finally, the forms of the nanoparticles shipped to companies making the final products can produce different effects altogether.

However, using the risk profile from one of the most likely toxic nanoparticle to characterize another nanoparticle with a much more favorable risk profile is simply misleading. To continue to do so when you know better, is fear mongering and that is more than misleading, it is wrong.

Sunscreens and risk profiles

During the summer of 2007, we assembled a team of students to begin to tease out claims and counterclaims in the nano-industry with the goal of publishing brief guides for the general public. After years of complaining about the absence of a public clearinghouse for EHS information on nanoparticles, it was time to step forward. As long as these guides were editable and organic in nature, we felt that they had great potential to raise the quality of the debates on the EHS of nanoparticles. As such, we started "Citizen Guides on Nanotechnology" a joint project involving the University of South Carolina and North Carolina State University. At present, this project remains unfunded by government, industry, and academe.

Nonetheless, our first guide will be on cosmetics and sunscreens and our next two are on food (one on production and the other on specific products and will be available at our web sites). After reading almost everything in print on the subject of cosmetics and especially sunscreens, even we were able to deduce that there were different classes of nanoparticles, such as the nano-titanium oxide being used in sunscreens. For example, we have noted a claim made by a cosmetics company that when they buy titanium oxides as nanopigments from companies, such as BASF or Kobo, for incorporation into a sunscreen, they purchase micronized aggregates (from 100 up to 600 nm in size) of these particles. The suppliers admit the primary particles are typically between 0.2 and 0.3 μm in diameter, although larger aggregates and agglomerates can be formed when coated with inorganic (e.g., alumina, zirconia and silica) and organic (e.g., polyols, esters, siloxanes and silanes) compounds to control and improve surface properties (IARC 2006). This may increase the size of the aggregates. Unfortunately, this report on the size of these aggregates seems to be at odds with claims that ultrafine grades of titanium dioxide (i.e., 10–50 nm) are used in sunscreens and plastics to block ultraviolet light. While this might be described as marketing rhetoric describing ideal conditions, it might explain the findings from Consumer Union on the ineffectiveness of current sunscreens purportedly using nanoparticles.

We know that titanium oxide remains a reference of non-toxicity which is why we find it used widely in foodstuffs as a coloring agent (GSFA Online Food Additive Details 2007) as well as some dental products (WIPO 2002). It is generally insoluble, inert, and coated. There are different types of titanium oxide which are photoreactive nanoparticles proposed to be used to help break down chemical contamination in polluted areas by enhancing sunlight's effects. Of course, these are not the nanopigments used in sunscreens.

The occurrence of skin cancer is growing all over the planet with one American in five likely to develop skin cancer in his lifetime. If the ozone layer continues to decrease, the likelihood increases. And skin cancer can kill you. Sunscreens were designed as one of the many precautions individuals should take when they expose themselves to sunlight. Others include coverings of all sorts, reducing exposure, and avoiding the experience altogether. Companies produce sunscreens with different SPFs from 2 to 60 and more (SPF stands for sun protection factor and is calculated by comparing the amount of time needed to produce a sunburn on protected skin to the amount of time needed to cause a sunburn on unprotected skin).

Companies add titanium dioxide and zinc oxide to sunscreens because of their capacity to reflect and scatter UV radiation. There are studies demonstrating titanium dioxide reduces exposure to UV radiation (Delrieu 2006; Nohynek and Schaefer 2001) as well as studies linking extensive UV exposure to the occurrence of skin cancer (Nohynek and Schaefer 2001; Pagoda and Preston-Martin 1996; Rooney and Bryson 1991). The International Agency for Research on Cancer has gone on record that nano-titanium dioxide sunscreens are effective, the recent claims of Consumer Reports (CR) notwithstanding (Consumer Reports 2007).

In addition, companies use nano-titanium dioxide and zinc oxide because of their increased transparency when applied. The World Health Organization claims that this will facilitate their acceptance and application as well as reapplication, by the consumer.

In August 2007, we witnessed the release of *Nanotechnology & Sunscreens: A consumer guide for avoiding nano-sunscreens* by Friends of the Earth. The intent of the release is obvious. It incorporates a color-coded alert system, like the USA's terrorist alert hierarchical system, to warn consumers against products that use nanoparticles. The companies producing them admit doing so and all the products of companies that chose not to respond to the queries of the team that published the release constitute a suspect class.

Let me begin by congratulating Friends of the Earth (Australia) and the primary author Ian Illuminato, a self-proclaimed health and environmental campaigner with FOE, and those who signed onto and contributed to the report including George Kimbrell of the International Center for Technology Assessment, Georgia Miller of FOE, Jennifer Sass of the Natural Resources Defense Council, Erich Pica of FOE, and Rye Senjen of FOE for maintaining vigilance. What you do is important and this article should not be interpreted as an attack on the general integrity of FOE or these individuals per se. Furthermore, it is serendipitous that a CAG and this publication were selected for this exercise. Indeed, an industrial or regulatory source and one of their statements or publications could have been selected and may happen in the near future.

One of their observations in the FOE release is particularly noteworthy. Too many producers of sunscreens failed to respond to the request for information. Companies producing consumer products need to make a genuine effort to increase their transparency. Some of us have noticed that the business world of nanotechnology is experiencing survey fatigue at this time. Too many people are asking for too much information often without disclosing how the information would be used. Their motives may be no less nefarious than those individuals writing the reports, nonetheless responding to as many queries as possible would be prudent.

In addition, too many people are writing reports who simply should not because they are not qualified to do so. Leave the reports to those with the freedom and willingness to work hard enough to find the best reasons to believe that something is probable true.

That having been said, what follows is a review of page five of the FOE report. Page five was selected because it had the most references and the references are to the scientific literature purportedly relevant to the claims being made. Every single reference to a secondary source material made in the report is examined against the claims made by the authors of the source material. The studies were read in their entirety and the claims made by the scientific researchers are compared to those in the FOE report.

Finally, the lead or designated author for each of the referenced studies was contacted and asked whether the claim made in the report was supported by the study or review referenced. This part of the exercise was instructive for another set of reasons. Some of the authors of the research articles vetted below responded with their opinion regarding whether the claim made in the report examined below legitimately referenced their research, especially Donaldson, Maynard, Maysinger, Gunter Oberdörster, Nel, and Tinkle. One was highly suspicious, and responded that the articles should simply be read (which, of course, was done), but this remark does underscore one reason why the public has such a difficult time vetting scientific rhetoric. One did not respond though he received and opened the email requests. And one could not be located electronically and was sent a snail mail inquiry. We decided to go to press rather than wait any longer for the responses. In general, we want to note that the science community was ungrudgingly cooperative and were genuinely apprehensive about how their findings were used by others.

Examination and vetting

There were 15 claims made on page five and they are vetted below. It was not my intention to pick apart each of these claims against parallel claims made by the authors of the original study as reported in peer-reviewed professional journals. Rather my goal was to contextualize the claims and report any inconsistencies between the FOE claims and those made by the researchers.

As a quick backgrounder, sunscreens are applied to the stratum corneum (SC) not to living skin. (The SC is 10–20 μm thick). Keratin, the inactive protein in hair and fingernails, is the main component of SC. We regularly slough off the SC every two weeks. As such, the presence of a sunscreen and its particles is short-lived. Some of the sunscreen may enter the hair follicle ostium, but sebum flow tends to flush the follicular sink and the follicular channel is covered with a horny layer barrier as well. There is some concern that nanoparticles in sunscreens may reach living skin through breaks in the skin, like acne and psoriasis (see below) and through stressed skin presumably impacted by sun damage (see below). If and once they reach the living skin, there are claims that these nanoparticles can cause DNA damage and cell death.

It is important to note that exposure alone is not sufficient to claim a risk. There must be enough exposure to produce the hazard; hence we need to pay close attention to the dosage of the nanoparticles or some cascading or proliferating event consequence to minimal dosage.

After an exhaustive review of the literature, the majority of the research indicates that titanium oxide nanopigments do not cross the skin barrier, the stratum corneum (Mavon et al. 2007; Nohynek et al. 2007; Bütz et al. 2005: Gamer et al. 2006; Roberts 2006; Dussert et al. 1997; Lademann et al. 1999; Pflücker et al. 1999) transfollicular pathways notwithstanding (Gottbrath and Müller-Goymann 2003; Lekki et al. 2007). Some NANODERM research makes the same claims in the cases of both healthy and skin compromised by acne and psoriasis (Pinheiro et al. 2007). Generally, others report the low hazard potential on particles used in sunscreens (Li et al. 2007; Warheit et al. 2007) even regarding their alleged phototoxicity (Theogaraj et al. 2007). Additionally, the aggregates used in sunscreens simply may not meet the prevailing definition of a nanoparticle (1–100 nm) in one or more dimension. If they are many times larger, then transferring findings from studies on truly nanosized particles of titanium and zinc oxides may be problematic. Finally, we noted that even when injected into the stratum corneum, particles tend to aggregate and are not found in other organs (Umbreit et al. 2007).

Claim 1—“Particles 1,000 nm in size can cross human skin and gain access to the dermis from where they can access the blood stream.” The source is Tinkle et al. (2003). The assumption is that once particles cross the skin and reach the blood stream some negative implication occurs. Tinkle et al. is cited to demonstrate nanoparticles can penetrate stressed skin. In general, we know the skin sections that were flexed were relatively thin, about 400 μm. There is also the observation that the nanoparticles might have become trapped in hair follicles and appeared to have traveled into the skin when they did not. There is a corresponding concern regarding the pressure exerted on the skin, which may have confounded the results. Finally, there is the observation that fluorescent markers detach from nanoparticles and the results followed the markers that leached into the tissue rather than the particles. Next, absolutely missing from this claim is any discussion of the minimum dosage needed to produce some hazard. Clearly a single particle would be insufficient to cause much anticipated damage. Finally, this study is about beryllium which is not used in sunscreens. As Tinkle (2007) observed. “My research showed that 500–1,000 nm particles, in conjunction with flexing, as at the wrist, can translocate across intact stratum corneum in human skin explants (skin recovered from organ donors and attached to a flexing device on a lab bench). We occasionally saw particles in the dermis. And we did not say they could access the blood stream from the dermis. It is, perhaps, a logical extension of our data, but we did not say it. Also, we did not study particles that meet the current National Nanotechnology

Initiative definition (materials with one dimension less than 100 nm). Importantly, these were proof of concept experiments, and we did not show this in living human beings." One source for the bloodstream idea has been Montiero-Riviere et al. (2005) who studied uncoated carbon nanotubes and not nanopigments used in sunscreens. In the discussion of this article, we read: "Evidence of dermal irritation (Eedy 1996) coupled with a report of toxicity to keratinocytes (Shvedova et al. 2003) suggests that particles not optimized for intracellular delivery may enter cells and adversely affect cellular function" (382). As such, we have the findings of these two studies conflated to establish an exposure route for the carbon nanotubes under investigation. Both Eedy and Shvedova also studied carbon and not nanopigments used in sunscreens. Eedy (1996) was a case report about a single case having airborne contact dermatitis. Eedy linked it to carbon fibre composite dust particles released from drilling, cutting, and grinding of carbon fibre components in an aircraft factory at which the case worked (362). Shvedova et al. (2003) treated HaCaT cell culture with single walled carbon nanotubes (SWCNT) and found that exposure to unrefined SWCNT resulted in ultrastructural and morphological changes in cultured human cells (1924).

Claim 2—"Uptake is increased with flexing and massage." Source is Tinkle again. First, see above and then consider there is no discussion of massage in Tinkle et al. (2003) though a hypothetical discussion of flexing such as what occurs about the wrist area could be deduced. However, that observation is moderated by the pressure exerted and that confounding variable is not addressed. Tinkle reported: "We saw a time-dependent increase in the number of skin samples that were positive for particle penetration, that is, with increasing amount of time flexing on the apparatus, starting at 0–15–30–60 min, more samples were positive for particles beneath the stratum corneum. We did not demonstrate an increase in the number of particles/skin sample over time because the experimental method was not quantitative. PLEASE NOTE (emphasis was Tinkle's)—we used FITC-labeled polystyrene spheres and not metal oxide particles. We did not use, nor make any conclusions about, uptake and massage, other than to cite the Tan et al. (1996) article that applied TiO_2 topically to the skin. This was used as background and context only" (2007).

Tan et al. (1996) studied human skin excised from 13 patients. Tan reported in results: "There was no correlation between the duration of sunscreen application and the concentration of titanium in the samples, and no relationship between the site of sunscreen application and concentration of titanium in the samples" (186).

Claim 3—"Broken skin is an ineffective barrier and enables particles up to 7000 nm in size to reach living tissue." Source is the three Oberdörsters (2005b). First, this is not a study; it is a review of the literature. The three Oberdörsters reference Tinkle (see above) when discussing nanosized particles. The quote which seems to be the basis of the claim may be: "dermal translocation will therefore be minimal or nonexistent under normal conditions but increases in areas of skin flexing (Tinkle et al. 2003) and broken skin" (835). An email communication with Prof. Oberdörster verified this claim to a study about podoconiosis premised on the hypothesis that soil particles can reach inguinal lymph nodes in barefoot runners (Corachan et al. 1988; Blundell et al. 1989). The Corachan et al. work involves two cases of field workers and in their discussion they noted "any barefoot population exerting gravity pressure on different types of soil containing microparticles can develop podoconiosis" (363). The role of pressure in this study is simply not addressed in Tinkle's work. The Blundell et al. piece involved a survey of a single Cameroonian woman with elephantiasis and was challenged to explain "why the majority of the populations who are exposed to a similar environment fail to develop the disease" (385).

In addition, how particles go from lymph nodes to the circulatory system comes from a 1988 study on amosite fibers and the lungs (Oberdörster et al. 1988). This is inhalation research not dermal penetration and seems to be dependent on an extrapolation from the Corachan and Blundell research to demonstrate a route of exposure as well. Whether there may be a similar translocation from dermal exposure seems very speculative.

Oberdörsters asked hypothetically: …" how likely is this to occur in the dermis layer of the skin with its dense supply of different types of sensory nerves? It may be conceivable considering data on neuronal uptake and translocation of nanosized particles after intramuscular injection" (835–836). In the very next paragraph, the Obserdörsters add: "Future studies need to determine whether and to what degree such translocation along sensory skin neurons also occurs with nanosized particles penetrating the epidermis" (836).

Claim 4—"Many types of nanoparticles interfere with normal cellular function, and cause oxidative damage and even cell death." Source is Borm and Kreyling (2004). First, this is an inhalation study not a dermal study; hence these implications are wholly dependent on the earlier transport claims. Furthermore, this study lauds the use of polymeric nanoparticles as drug delivery systems with significant reductions in adverse drug reactions; hence risk values may need to be comparative. Second, this claim is highly moderated by dosage considerations. The authors establish that caveat as well (523).Third, they admit the surfaces of titanium oxides are sometimes chemically very active (523) and couch this discussion exclusively to exposure from inhalation (524). Furthermore, they add; "Conflicting studies (in animals and humans) have been reported regarding particle translocation after inhalation…" (526).

Claim 5—"Some nanoparticle types may also be transported within cells and be taken up by cell mitochondria." Source is Oberdörster et al. (2005a). This is a review of research and not original work. The relevant source is Li et al. (2003) and it is an inhalation study (see below under claim 6). "The study used collected ambient nanoparticles (as well as larger ambient particles), and so may not be directly translatable to engineered nanoparticles, or non-carbon based nanoparticles (depending on uptake mechanism). In vitro tests were conducted, using cells either found in the lung, or that mimicked lung cell behavior. Thus the results shed possible light on what happens when incidental nanoparticles are inhaled and deposited in the lungs (with the emphasis on "possible", as the tests were conducted outside the body, under idealized conditions). They also allow us to hypothesize over what might happen if engineered nanoparticles are inhaled, and possibly what could happen if nanoparticles reach similar cells in other parts of the body—for instance, if they penetrated the outer layers of the skin" (Maynard 2007). Professor Maynard continued. "The use of this study in the context of TiO_2/ZnO nanoparticle exposure from topical applications is therefore rather speculative. The assumption-chain is that:

1. Nanoparticles can penetrate to cells that have similar characteristics to lung epithelial cells and macrophages;
2. The carrier/matrix that the nanoparticles are in does not alter their behavior;
3. The particles used in sunscreens have similar physicochemical characteristics to ambient nanoparticles—specifically, characteristics that govern biological transport and uptake; and
4. The data from in vitro tests on ambient nanoparticles related to the lungs can be extended to in vivo impacts of metal oxide particles on the skin WITHOUT FURTHER STUDIES (Emphasis is Maynard's).

There is the further implicit assumption that the presence of the nanoparticles in the mitochondria is important. But without information on dose, and response, this is an assumption that cannot be made."

Maynard concluded "The cited study raises important questions over how nanoparticles might behave in the body, and supports the formulation of a number of hypotheses. Yet while the claim made is technically accurate, how it is used within the context of the FOE is not justified when the limitations of the study are compared to the materials and scenarios being discussed."

Claim 6—"Some nanoparticle types cause cell mutation." Sources are Li et al. (2003) and Savic et al. (2003). We begin with Li et al. (2003). This is an inhalation study of organic particulate matter in the Los Angeles Basin. It remains unclear as to what characteristics of the ultrafines studied by this team are responsible for the findings of oxidative stress. While the ultrafines studied should be attended to in terms of regulating exposure from inhalation, it is unclear whether the nanopigments used in sunscreens would be inhaled at dosage levels sufficient to produce a similar effect and whether the findings associated with the organic particulate matter studied by this team are transferable to the nanopigments used in sunscreens. Next we have Savic et al. (2003). The contact person for the article responded directly to the claim made by FOE. "Our reference (Savic et al. 2003) is not adequately cited to support the claim for two reasons: (1) it does not deal with metallic nanoparticles (TiO) and (2) there is no claim in our article that polycaprolactone-b-polyethylene oxide causes mutations" (Maysinger 2007).

Claim 7—"Some nanoparticle types even result in cell death." Source is Geiser et al. (2005). First, this is as good a place as any to note that we lose

50,000,000 cells every second. Unless nanoparticles can be held responsible for the death of a threshold of cells, it may not be an issue worth our consideration given what we know at this time. No one has suggested that nanoparticles alone would be sufficient to kill enough or the right combination of cells to produce an imminent health hazard. The most condemning research has involved inhalation studies of rodents to date and conclusions related to respirable titanium oxide have been mixed. Geiser's study pertains to high levels of airborne particles (1555) and the subject of the research is air pollution and not titanium oxide. Second, workers have and can be protected. The likelihood a casual application of sunscreen would release sufficient respirable titanium oxide to produce a health hazard has never been supported by evidence.

Claim 8—"Titanium dioxide has been classified as a possible carcinogen for humans, based on rodent data." Source is The World Health Organization's International Agency for Research in Cancer (IARC) (2006). In terms of selective reporting, note that the IARC offers this advice: "Studies on the application of sunscreens containing ultrafine titanium dioxide to healthy skin of human volunteers revealed that titanium dioxide particles only penetrate into the outermost layers of the stratum corneum, suggesting that healthy skin is an effective barrier to titanium dioxide. There are no studies on penetration of titanium dioxide in compromised skin" (3). This group was incredibly hesitant to offer the claim of possible carcinogenicity. Once you discount the inhalation research, this conclusion cannot be sustained. "Oral, subcutaneous, and intraperitoneal administration did not produce a significant increase in the frequency of any type of tumor in mice or rats" (2). Even the conclusion cited above is suspect upon reading the caveats preceding the claim. "There is inadequate evidence in humans for the carcinogenicity of titanium dioxide" (5). Finally, workers in the production of titanium oxides are safer than ever. "Levels of exposure to respirable dust in these occupations ranged between <1 and 5 mg/m^3 (geometric mean) but have declined over time. No data were available that would allow the characterization or quantification of exposure to ultrafine primary particles" (1). Furthermore, isolating titanium oxide as the cause of disease in workers is incredibly problematic given: "Workers in the titanium dioxide manufacturing industry may also be exposed to ore and other dusts, strong acids and asbestos" (1).

Claim 9—"Nanoparticles are much more likely than larger particles to form free radicals." Source is Nel et al. (2006). Nel did offer a brief response: "It does not talk about sunscreens or metal oxides but there are other studies that do show adverse biological responses to metal oxides, including mitochondrial damage." He added, "You will not see quote 9 coming out of that source as stated" (Nel 2007) and see above.

Claim 10—"Free radicals cause damage to DNA and can harm our delicate skin in many ways." Sources are Donaldson et al. (1996) and Dunford et al. (1997). This is a good place to make a comparative risk assessment.

There is an extensive literature that accords to sunscreens the capacity to reduce DNA damage (Gallagher 2005; Lee et al. 2005; Mahroos et al. 2002; Young et al. 2000; Gallagher et al. 2000a; Gallagher et al. 2000b). Gallagher of the Cancer Control Research Program of the British Columbia Cancer Agency (2005) reported that "a number of trials have provided good evidence that, when applied consistently, sunscreens can realistically play a role in reducing the risk of squamous cell carcinoma" (244). Approximately, 1 in 20 develops this type of carcinoma. Gallagher does admit no effect on basal cell carcinoma which is three times more frequent. Lee et al. (2005) studied nevus development among a randomized sample of 300 white children to determine whether nevus density may have increased with increased sunscreen use. Earlier studies did not control for phenotype and prior sun exposure though they discovered a positive association between sunscreen use and new nevi (Autier et al. 1998; Luther et al. 1996). Lee et al. discovered the sunscreen group developed fewer new nevi and nevus density is a predictor of cutaneous malignant melanoma. Mahroos et al. (2002) tested 18 women over a 4-day period, under controlled exposures to UV radiation, and measured thymine dimer formation. They reported "regular use of a broad-spectrum sunscreen is effective in preventing a major form of UV-induced DNA damage" (1480). Young et al. (2000) reported: "Protection by a broad spectrum UVA sunscreen may offer additional protection from oxidative damage to DNA caused by UVA" (40). Gallagher et al. (2000a) studied nearly 700 children and concluded, “that broad-spectrum sunscreens may attenuate the development of nevi in children and perhaps ultimately reduce their risk of developing melanoma” (html, n. pag.). Gallagher et al. (2000b) replying to a letter to the editor in a later issue added: “The true degree of protection afforded by sunscreens against nevi will probably always be underestimated because of ethical concerns and practical considerations surrounding sunscreen trials” (2870). As such, we need to evaluate this claim comparatively.

First, there is the reference to Donaldson et al. (1996). “The article is aimed at showing the link between particle-derived oxidative stress and inflammation. It shows that TiO_2 can damage naked bacterial plasmid DNA. This is emphatically not an assay of genotoxic risk; it is simply using bacterial DNA as a sensor of free radicals. In mammalian cells the DNA is closely associated with histone protein tucked away in the nucleus and surrounded by antioxidants. In order to measure genotoxic potential you would have to expose whole cells not naked bacterial DNA, which is frequently done. There is no skin in my studies just naked bacterial DNA and, although it shows DNA damage, it’s not a ‘fair ‘ estimate of the ability of the particles to cause DNA damage in a whole live cell, since the protective milieu of the cell and nucleus is absent” (Emphasis is Donaldson’s). Donaldson (2007) continued. “In the article I do say ‘...This oxidant burden could cause classical oxidant damage to lipid, protein and DNA...’ so I said it was possible that DNA damage could be caused by such particles—but is it emphatically NOT demonstrated here. I must admit mea culpa in not making it crystal clear in the article that this is not an assay of genotoxicity. I had to make this clear quite often in response to questions after giving talks, around this time. People get mixed up with the use of plasmid DNA, and the demonstration of genotoxicity. In my defence, the whole thrust of the article is towards inflammation and not genotoxicity, and so I probably thought it was obvious” (Donaldson 2007).

Dunford et al. (1997) is another matter since she was unreachable as the article went to press. Primarily, there is an exposure issue here. Dunford et al. admit: “Our results demonstrate that sunscreen TiO_2 and ZnO can catalyze oxidative damage to DNA in vitro and in cultured human fibroblasts. The fate of these materials applied to skin is uncertain” (89). Second, we might be more careful when conflating photocatalytic activity and phototoxic potential.

In addition, Dunford et al. were vetted in a 2006 Australian Review (2006) entitled “A review of the scientific literature on the safety of nanoparticulate titanium dioxide or zinc oxide in sunscreens.” First, there were claims regarding the systems under study included in vivo though none were actually conducted in vivo. Second, it is unclear whether the particles studied were nanoparticles. The TiO_2 samples were extracted from marketed sunscreen products with no reference to size of the particle extracted. Third, the authors indicate absorption of TiO_2 has yet to be adequately demonstrated (7). Generally, the exposure issue is tabled in the text by referencing Dupre et al. (1985), Moran et al. (1991) and Tan et al. (1996).

Dupre et al. (1985) studied a single patient with a penile pigmentation allegedly caused by an ointment called Parkipan containing titanium dioxide. The patient was treating herpetic lesions and they healed. The researchers are hesitant to state unequivocally the titanium oxide in the cream was the cause of the discoloration. Instead, they hypothesize “the erosive lesions may have allowed increased percutaneous penetration” (658). Moran et al. (1991) studied six patients and studied exposure along different modalities: lung, skin, and synovium. In terms of dermal exposure, they referenced research demonstrating allergic reactions in some people when skin lesions have been treated with topical creams including TiO_2 and as a local irritant when forming part of a metal alloy implants. But Moran et al. were unable to isolate the cause of lesions they studied. They admit that it may be a function of a “secondary phenomenon due to contaminants deposited with the titanium dioxide” (352). Tan et al. (1996) is discussed above.

Claim 11—“Titanium dioxide nanoparticles used in sunscreen can form free radicals in skin cells.” Source is Donaldson et al. (1996). “I think this is very obviously an unwarranted extension of what the paper says. The first half of the sentence is true ‘Titanium- dioxide nanoparticles used in sunscreen can form free radicals... .’ It is the second part that is extended by the reviewer of my paper to what he thinks to be the case—‘in skin cells…’. My paper does not use skin cells, I have never published an article that used skin cells and in fact this study does not even use cells, only bacterial plasmid DNA. The kind of TiO2 I used is not used in sunscreen, so there is also an issue about generalising across different samples of particles composed of what is nominally the same material, which can differ a lot, e.g., size and coating, contaminating metals etc." (Donaldson 2007).

Claim 12—"Titanium dioxide nanoparticles used in sunscreen can form free radicals in skin cells, especially when skin is exposed to UV radiation." Source is Dunford et al. (1997). See above and below.

Claim 13—"The process of skin-damaging free radical formation is further propelled when we wear nanoparticle titanium dioxide while in the sun." Source is Dunford et al. (1997) again and see above again. While the Dunford et al. findings are interesting, it might behoove us to heed the conclusion of the Australian Review. "There is evidence from isolated experiments than ZnO and TiO_2 can induce free radical formation in the presence of light and that this many damage these cells. However, this would only be of concern in people using sunscreens if the ZnO and TiO_2 penetrated into viable skin cells. The weight of current evidence is that they remain on the surface of the skin and in the outer dead layer of the skin" (15).

Claim 14—"Nanoparticles can also become toxic vehicles by binding to other foreign materials and piggy-backing on them into organs and sensitive areas that cannot normally be accessed." Source is Lomer et al. (2004). Lomer et al. were studying the roles of particulates (mainly titanium dioxide) and particulate silicates in aggravating Crohn's disease (CD). CD is an inflammatory bowel disease. There is neither an argument in this study nor data produced to support the claim made by this report. This leads us to assume shoddy end notation.

Claim 15—"Personal care products may also be inhaled and are often ingested. Some figures show that over a trillion particles of titanium dioxide are ingested per person per day." Source is Lomer et al. (2004) again. We know titanium oxide particulates are found in toothpaste and some foods and we ingest 10^{12}–10^{14} particles in our standard Western diets. First, the study examined food-additive microparticles and not nanoparticles. There is no evidence that the source is personal care products, such as sunscreens. Production safety protocols tend to significantly mitigate inhalation risks. Second, there is no indication that personal care product sources would significantly increase current exposure. Third, there was no comparison done comparing those with Crohn's disease and those without leading Lomer et al. to offer this caveat: "the cause of CD remains elusive, and whether certain aspects of the diet exacerbate symptoms is difficult to identify due to the nature and complexity of dietary habits (954)." They conclude, "if exposure to microparticles is associated with the inflammation of CD, then the present study rules out excess intake as the problem (947)." The study helped identify microparticle containing foods and was an important first step in assessing dietary variables in the occurrence of CD but it hardly evidences the claim made by the report.

Discussion

If everything said above is true, how then can the August 2007 release be anything more than muck-raking? Surely it would not pass the scrutiny given to most academic publications by colleges of faculty.

One of the causes with this confusion lies in the claim that nanoparticles are different from particles of a larger size and much of the blame for the confusion rests with some of the members of the cosmetics industry itself. Too many companies are overclaiming the effectiveness of their sunscreens and cosmetics. In order to differentiate a new nanoproduct from another non-nanoproduct, advertisers and marketers are stretching the truth and stoking the concern that motivates some people to write reports like the one criticized above.

There are at least four classes of nanoparticles being used in the preparation of sunscreens and cosmetics. Each class has very different risk profiles. What some colleagues have done was to conflate all these classes using the high risks profiles of one class for all four classes.

The first class involves insoluble nanopigments. They are minerals, including titanium and zinc oxides and they are primarily used in sunscreens. They are inert by design and used as a reference of non-toxicity as well as used as a coloring agent in food and dental products as previously mentioned. In sunscreens, nano-sized titanium oxide may be present in large clusters or aggregates up to 600 nm.

The second class includes nanoemulsion products containing oil and water droplets reduced to nanometric size to increase the effectiveness of nutritious oils. Fragile active ingredients, like vitamins, are protected from air inside liposomes that release the ingredient upon contact with the skin at the time of application. These nanoemulsions are designed to allow active ingredients to reach beneath the topmost layer of the skin hence carrying a higher risk profile than nanopigments.

The third class includes cosmetics that use fullerenes or fullersomes as carbon cages for active ingredients. While carbon nanoparticles, such as fullerenes, might be hazardous when inhaled and they may oxidize some cells there is much weaker evidence that they can be absorbed transdermally. On the other hand, there are some concerns that a true life cycle analysis may find them in waste streams entering the environment though there is some suggestion they agglomerate easily and would no longer by nanometric in size. Nonetheless, they would carry a higher risk profile.

The fourth class includes two subclasses. The first subclass can be readily dismissed and involves products claiming to dissolve cellulite, to enhance breast tissues, etc. and there is no evidence they work. There is also no evidence they function on the nanolevel. The second subclass involves some claims made by the pharmaceutical industry and others regarding dermal application of some compounds which would be absorbed through the skin into another system, such as the circulatory or limbic systems. There is interesting research (Kayser and Kiderlen 2003) that confirms the effectiveness of transdermal drug delivery (TDD) systems for a limited set of compounds with precise chemical signatures and to especially invasive devices such as patches festooned with microtubules which pierces the SC to deliver their payload. These TDD systems are quite exploratory at this point in time and would be regulated under the FDA's medical device and drug pre-market review. Nonetheless, their risk profiles are very high and the cosmetics and sunscreen industries will be hard pressed to delineate for the public why their products are not absorbed while the drugs associated with TDDs are (an issue to be addressed at a later time).

What has happened is that the risk profiles of the second, third and especially fourth classes of nanoproducts have been transferred to those in the first class, the nanopigments used in sunscreens. As mentioned above, it is very difficult to discern motivations of the proponents of this false claim. Some has been promulgated by those who benefit from fear and apprehension including but not limited to toxicologists and researchers who are intoxicated by research funding, to some CAGs and individuals who claim to represent the interests of civil society but find prestige, stature, membership, and dues contingent on controversy, and the media who use timidity and trepidation to sell news and advertisements by amplifying over-claims. Unfortunately, they have instigated a heightened level of fear in the general public and that is wrong.

Conclusion

Primarily, this article is not to be read to conclude there are no transdermal risks from all nanoparticles. This work is specifically limited to the use of nanopigments in sunscreens and profiled against a report by the CAG Friends of the Earth (FOE, 2007). This article should not be read to conclude that there are no dermal risks to nanopigments in sunscreens just that the case made in the FOE publication referenced throughout may not have been made satisfactorily. Finally, it is not an apologia for the cosmetics and sunscreen industry.

If this article draws any conclusion, it may be that we need to vet reports from stakeholders in the nanorealm. Whether from the media, CAGs, NGOs, industry, regulators, or academia, we cannot simply believe what we are reading. There is no "Truth in Advocacy" (TIA) team out there that springs to action when a spurious claim is being made. While scientists may debunk research findings at professional meetings and in academic journals, too often that information does not reach the public. While stakeholders of all sorts respond that information of all sorts is available on the World Wide Web, few, if any, of the sites involved are written for public consumption. Maybe, we need a "TIA" team or maybe not, but we do desperately need public information on the risks associated with nanoparticles written in a registry that the public can understand.

The discussion associated with this project included the following set of observations. They are not rank ordered.

- Why not attempt to categorize nanoparticles into classes? This exercise alone would be productive in increasing understanding for many different stakeholders. As long as the classifications were subject to revision as more information became available, it should not be overly problematic. Even if the classes were used for provisional regulations, as long as the regulation had a sunset provision built into them, they could be re-examined against a growing body of toxicology literature
- Scientists need to stop telling the public how uncertain they are. Instead, develop a calculus which allows responsiveness in the absence of certainty. The literature on the precautionary principle and its variants is only burdensome to those who have never tried to work their way through the literature. By and large, "precautionists" are not devolutionists. They are not arguing we return to some form of tribalism or pre-industrial society. They are asking for a calculus for science and technology decision making that incorporates concerns about the lack of certainty. This would be a worthy undertaking in expert risk communication.
- We cannot simply read what we want to believe is true. A common bias in persuasion theory involves our tendency to believe what is most in accordance with our previously held beliefs. CAGs and every other stakeholder must be on guard to compensate for this bias in their claims and reports.
- It behooves all of us to take a very close look at what we are reading and to refrain from endorsing material which while being consistent with what we may want to believe, could be suspect. We cannot reserve our cynicism for only government and business generated claims while giving CAGs and the media a free pass.
- A case can be made for a team of researchers willing to function to insure the accurateness of claims made by stakeholders about nanotechnology. While this article might be considered as an example of the work a Truth in Advocacy team would undertake, it would benefit the stakeholding community if we had more individuals involved in the process. In addition, it might be prudent to establish and maintain a team of this sort under a more articulated organizational structure to increase transparency and assure reliability as well as validity.

Are nanoparticles safe? Nothing is safe, but they may be safer than chemicals we are currently using for both the people producing them and those using them. Without a doubt, more research is required to identify the conditions under which some specific types of nanoparticle may be hazardous. As Prof. Maysinger wrote in one of her emails to me, "It is extremely important that (the) public understands that one can NOT make GENERAL statements for ALL classes of nanoparticles: some nanoparticles could be hazardous under CERTAIN conditions." [Emphases are hers.]

Nanoparticles were included in product lines to kill neither the workers making the products nor the consumers buying them. Furthermore, the development, production, and incorporation of nanoparticles into finished products are not inexpensive. My discussions with colleagues in the business world lead me to believe that nanoparticles may improve product lines in many different ways. Nonetheless, we need to maintain our vigilance.

The phenomenon of risk profile shifting is disconcerting. Stereotyping the class of nanoparticles and products using nanoparticles threatens to retard efforts to use nanoparticles for promising applications, which despite the associated risk profile could have significant benefits. Nanoparticles may be used to bring potable water to those dying of dysentery. Nanoparticles may be used to bring new more humane treatments for cancer. And nanoparticles may even be used to reduce the incidence of skin cancer. Finally, we must examine the EHS risk profile of nanoparticles with the most rigorous science and scientific discipline we can muster and we must craft our arguments well. The public deserves nothing less from us.

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